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Lessons on fruiting body morphogenesis from genomes and transcriptomes of Agaricomycetes

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Abstract

24 Fruiting bodies of mushroom-forming fungi (Agaricomycetes) are among the most complex
25 structures produced by fungi. Unlike vegetative hyphae, fruiting bodies grow determinately
26 and follow a genetically encoded developmental program that orchestrates tissue
27 differentiation, growth and sexual sporulation. In spite of more than a century of research,
28 our understanding of the molecular details of fruiting body morphogenesis is limited and a
29 general synthesis on the genetics of this complex process is lacking. In this paper, we aim to
30 comprehensively identify conserved genes related to fruiting body morphogenesis and distill
31 novel functional hypotheses for functionally poorly characterized genes. As a result of this
32 analysis, we report 921 conserved developmentally expressed gene families, only a few
33 dozens of which have previously been reported in fruiting body development. Based on
34 literature data, conserved expression patterns and functional annotations, we provide
35 informed hypotheses on the potential role of these gene families in fruiting body
36 development, yielding the most complete description of molecular processes in fruiting body
37 morphogenesis to date. We discuss genes related to the initiation of fruiting, differentiation,
38 growth, cell surface and cell wall, defense, transcriptional regulation as well as signal
39 transduction. Based on these data we derive a general model of fruiting body development,
40 which includes an early, proliferative phase that is mostly concerned with laying out the
41 mushroom body plan (via cell division and differentiation), and a second phase of growth via
42 cell expansion as well as meiotic events and sporulation. Altogether, our discussions cover
43 1480 genes of *Coprinopsis cinerea*, and their orthologs in *Agaricus bisporus, Cyclocybe
44 aegerita, Armillaria ostoyae, Auriculariopsis ampla, Laccaria bicolor, Lentinula edodes,
45 Lentinus tigrinus, Mycena kentingensis, Phanerochaete chrysosporium, Pleurotus ostreatus,*

46 and *Schizophyllum commune*, providing functional hypotheses for ~10% of genes in the
47 genomes of these species. Although experimental evidence for the role of these genes will
48 need to be established in the future, our data provide a roadmap for guiding functional
49 analyses of fruiting related genes in the Agaricomycetes. We anticipate that the gene
50 compendium presented here, combined with developments in functional genomics
51 approaches will contribute to uncovering the genetic bases of one of the most spectacular
52 multicellular developmental processes in fungi.
53
54 Key words: functional annotation; comparative genomics; cell wall remodeling; development;
55 fruiting body morphogenesis; mushroom; transcriptome
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1. Introduction

Fungi are one of the five main extant lineages in which complex macroscopic structures emerged over the course of evolution. The best known macroscopic structures of fungi are sexual fruiting bodies, which enclose spore-producing cells into a 3-dimensional, protective environment and facilitate spore dispersal(Nagy et al. 2018). Sexual fruiting bodies are complex multicellular structures based on the definition of Knoll(Knoll 2011) and show evidence for repeated evolution across the fungal tree of life(Stajich et al. 2009; Merényi et al. 2020a). They are found in at least 8 lineages, with best known representatives belonging to the Pezizomycotina (e.g. morels, truffles), Agaricomycotina (e.g. agarics, boletes), however, spectacular examples evolved in several other lineages, such as *Endogone* spp. in the Mucoromycota(Chang et al. 2019b) or the enigmatic *Neolecta* genus in the Taphrinomycotina(Nagy 2017; Nguyen et al. 2017). Fruiting bodies reached highest complexity in the Agaricomycetes, which include developmentally integrated morphologies that follow a spatially and temporally tightly regulated developmental program(Hibbett 2004; Virágh et al. 2021). In terms of complexity level, certain Agaricomycete fruiting bodies approach the complexity of simple animals and plants(Taylor and Ellison 2010; Nagy et al. 2018).

160   Fruiting body morphogenesis has been a subject of intense research, however,
161 despite tremendous efforts in this field, morphogenesis of Basidiomycota fruiting bodies is
162 quite poorly known. In comparison, fruiting body development and its underlying genetics are
163 considerably better explored in the Ascomycota (see e.g.(Pöggeler et al. 2006a)). This may
164 be due to a mixture of factors, including the complexity of Basidiomycota developmental
165 programs, the lack of easy-to-use model systems or the relative difficulty of hypothesis
166 testing via genetic manipulation (e.g. due to low frequency of homologous recombination(De
167 Jong et al. 2010)). Research on Basidiomycete fruiting body morphogenesis has recently
168 been relying largely on comparative -omics techniques, which provided insights into the
169 gene repertoires and the regulation of gene expression during fruiting body development.
170 This complements the rich body of literature on functionally characterized genes in
171 *Coprinopsis cinerea* (summarized in Kües(Kües 2000)), *Schizophyllum commune* and other
172 species. There are several recent milestones in fruiting body research such as the
173 publication of key genome sequences(Ohm et al. 2010; Stajich et al. 2010; Morin et al. 2012)
174 or comparative transcriptomic datasets (e.g. (Morin et al. 2012; Plaza et al. 2014a; Kües and
175 Navarro-González 2015; Almási et al. 2019; Krizsán et al. 2019; Merényi et al. 2021)). An
176 emerging driving force of research on fruiting body morphogenesis is the mushroom
177 industry, which produces sexual fruiting bodies for food or as sources of bioactive
178 compounds(Royse et al. 2017; Ma et al. 2018). Fruiting body development has been a
179 subject of several excellent reviews, surprisingly, however, the last gene-centric review of
180 fruiting body development in mushroom-forming fungi was published in 2000(Whiteford and
181 Thurston 2000). This paper aims to complement recent reviews on the morphogenesis of
182 vegetative hyphae(Riquelme et al. 2018), and on the genome of *Neurospora*
183 *crassa*(Borkovich et al. 2004) with knowledge on fruiting body morphogenesis in the
184 Agaricomycetes.
185   The aim of this paper is to systematically catalog genes and genetic processes
186 related to fruiting body morphogenesis in the Agaricomycetes, based on both literature
187 reviews and a meta-analysis of published developmental transcriptomes. We provide a
188 handbook-like inventory of gene families and their putative functions based on expression
189 data and functional annotations borrowed from well-researched model systems. Because a
190 negligible proportion of morphogenesis genes has so far been functionally characterized in
191 the Agaricomycetes, it is currently impossible to build a comprehensive picture based on
192 mechanistic studies alone, as has recently been done for hypha morphogenesis(Riquelme et
193 al. 2018). Instead, we derive functional hypotheses for genes based on comparative
194 expression data across multiple species. Our starting point is that genes which are
195 developmentally regulated in the majority of species for which transcriptome data are
196 available, should belong to the core pathways of fruiting body morphogenesis, whereas
197 genes that show species-specific expression patterns should be responsible for sculpting
198 species-specific morphologies or represent transcriptional or technical noise. Finally, we
199 incorporate novel and previous observations into a new synthesis on processes active
200 during fruiting body morphogenesis.
201

202 ## 1.1. What are fruiting bodies and how do they develop

203 Fruiting bodies, also called basidiomes, basidiocarps or simply 'mushrooms' in lay language,
204 may be some of the best known structures of fungi. They are sexual reproductive organs
205 that facilitate spore dispersal. While in simple Basidiomycota spores are born on naked

206 basidia, mushroom-forming fungi evolved complex 3-dimensional structures that offer
207 tremendous advantages in spore dispersal efficiency.
208   Developmental events that take place in fruiting bodies have been investigated
209 previously in several species, of which *Coprinopsis/Coprinellus* spp. and *S. commune* are
210 the two most widely used groups of models. The development of fruiting bodies in these
211 species has been described in previous reviews(Kües 2000; Kües and Liu 2000; Palmer and
212 Horton 2006; Kües and Navarro-González 2015), therefore, we here only provide a short
213 introduction, and describe the process in more detail (combining new results) in Chapter 5.
214 Briefly, fruiting body development is initiated on sexually competent mycelia as the
215 reprogramming of hyphal branching patterns, which results in the interlacing of hyphae to
216 form a 3-dimensional fruiting body initial(Kües and Liu 2000; Kües and Navarro-González
217 2015). Rather than relying on zygotic (e.g. maternal) mRNA cargo as animals and plants do,
218 fungal hyphae undergo transcriptional reprogramming during fruiting body initiation. This
219 reprogramming is influenced and triggered by a mixture of - often species-specific - factors,
220 such as starvation, light or temperature changes (reviewed by(Sakamoto 2018)). Once
221 appropriate internal and external signals converge on the initiation of fruiting, morphogenesis
222 starts with an undifferentiated initial (hyphal knot, aggregate), which undergoes tissue
223 differentiation to form primordia. In subsequent late primordium and young fruiting body
224 stages rapid growth (stipe elongation and cap expansion) and meiosis happen in a
225 coordinated manner, which ultimately results in species-specific mature morphologies and
226 culminates in spore formation and release.
227   Development of the fruiting bodies is a tightly regulated process that has a high
228 degree of autonomy. That is, once started, the developmental program is not interrupted by
229 even large perturbations, such as injuries, or removal of the fruiting body from the supporting
230 colony at or after certain stages(Moore 2013). In fruiting bodies not only morphogenetic
231 events, but also several internal processes (e.g. nutritional and sexual) are developmentally
232 regulated. For example, in *C. cinerea*, stipe elongation starts immediately after meiosis takes
233 place, after which spore production, maturation and cap expansion follow in a tightly
234 choreographed chronology(Kües 2000; Moore 2013). For detailed description of the process
235 and molecular summaries of current knowledge on fruiting body morphogenesis the reader
236 is referred to recent reviews(Kües 2000; Kües and Navarro-González 2015; Virágh et al.
237 2021) and the following detailed chapters of this paper.

238 1.2. The evolution of Agaricomycete fruiting bodies: from simple to complex
239 morphogenesis

240 How fruiting body complexity evolved has interested mycologists for decades and has
241 received considerable attention recently. Therefore we provide only a brief introduction here
242 and refer the reader to recent reviews on the topic (e.g.(Kües and Navarro-González 2015;
243 Nagy et al. 2018; Virágh et al. 2021)). Phylogenetic studies have made tremendous progress
244 in uncovering broad patterns of morphological transformation and trends in fruiting body
245 evolution (e.g. (Hibbett 2004; Varga et al. 2019; Sánchez-García et al. 2020)). Fruiting body
246 morphologies show a great diversity in the Basidiomycota, from naked lawns of basidia, to
247 resupinate, coralloid or highly complex, or the so called pileate-stipitate fruiting bodies of
248 well-known agarics (e.g. *C. cinerea*) (Fig. 1).
249   Agaricomycete fruiting bodies might have emerged in or around the last common
250 ancestor of Dacrymycetes and Agaricomycetes over 400 million years ago(Varga et al.
251 2019; Prasanna et al. 2020), although there is some uncertainty around ancestral states.

252   This is partly due to the presence of jelly-like telia reminiscent of fruiting bodies in the
253   Pucciniomycotina, uncertainties in the branching order of Basidiomycota subphyla and
254   reductive evolution in early-diverging clades (Bartheletiomycetes, Wallemiomycetes) of the
255   Agaricomycotina subphylum (reviewed in (Prasanna et al. 2020)). Nevertheless, all
256   Agaricomycetes share a single, fruiting body-forming ancestor, which suggests there should
257   be a core, deeply conserved genetic toolkit of fruiting body development. Phylogenetic
258   comparative studies have provided sound evidence that this ancestor had
259   corticioid/resupinate/jelly like fruiting bodies (e.g. *Phanerochaete chrysosporium*) and that
260   more complex forms derived from such morphologies repeatedly(Hibbett 2004; Varga et al.
261   2019). Within the Agaricomycetes, tissues that protect and enclose basidia became thicker
262   and more complex, eventually leading to the mushroom fruiting body structures we know
263   today. From the perspective of this paper, it is important to mention that phylogenetic studies
264   have also established that fruiting body evolution is highly convergent, that is, many of the
265   characteristic traits (e.g. cap, gills) evolved independently several times. Therefore, an
266   evolutionary framework is important for understanding how fruiting bodies evolved and for
267   establishing homologies among tissues. Gills, caps and stipes, for example, although
268   superficially similar, are not homologous across Polyporales and Agaricales. This implies
269   that such, convergent forms (e.g. gills of *Lentinus tigrinus* in the Polyporales and that of *C.*
270   *cinerea* in the Agaricales) are not homologous across lineages and their development should
271   not be expected to follow the same genetic principles. On the other hand, basidia, the sexual
272   processes that happen therein and the development of 3-dimensional fruiting body tissue,
273   are homologous across all mushroom-forming fungi (i.e. they have a single origin in the
274   Basidiomycota), providing an reliable framework for analysis.
275   These examples illustrate how the diversity of fruiting bodies can complicate the
276   identification of core components of their morphogenesis. Ideally, we are interested in
277   developmental processes and underlying genetic components that uniformly characterize
278   fruiting bodies of all mushroom-forming fungi, i.e. those that can be traced back to the first
279   fruiting body-forming Agaricomycete ancestor.
280   Therefore, building 'minimal models', which encompass the minimum set of genes
281   necessary to build a fruiting body are highly relevant. Such minimal models could be, among
282   others, species that produce resupinate fruiting bodies (e.g. *Ph. chrysosporium*)(Krizsán et
283   al. 2019). Recently, *Cryptococcus neoformans* (Tremellomycetes, Basidiomycota) proved to
284   be a useful model organism, because it produces simple lawns of basidia, sometimes
285   referred to as fruiting bodies, in which basidium differentiation, meiosis and spore formation
286   take place(Liu et al. 2018). Therefore, *C. neoformans* 'fruiting bodies' encompass all
287   processes needed for Basidiomycota sexual reproduction but lack features essential to the
288   definition of fruiting bodies such as three-dimensional organization, tissue differentiation and
289   others. Merenyi et al recently sorted developmental genes of *Pleurotus ostreatus* and seven
290   other complex species into groups that were developmentally regulated both in *C.*
291   *neoformans* and mushroom-forming fungi and those in which developmental expression was
292   observed only in mushroom-forming fungi(Merényi et al. 2021). 'Shared' orthogroups
293   comprised most mitosis/meiosis related genes, but also some previously thought to be
294   specific for complex morphogenesis (e.g. fasciclins). This indicates that sexual
295   morphogenesis, even at the very simple forms that exist in *C. neoformans*, involves a
296   morphogenetic program. Comparing genes that are developmentally regulated in fruiting
297   bodies to those regulated in *C. neoformans,* thus, can help constructing more precise
298   genetic models of complex fruiting body morphogenesis.

299 1.3. Cellular and regulatory processes involved in fruiting body development

300 Fruiting body development is an incredibly complex process and this complexity is reflected
301 in the underlying cellular and genetic processes. Several cellular processes are emerging as
302 important regulatory mechanisms underlying fruiting body morphogenesis, whereas some
303 others that proved developmentally relevant in animals and plants seem to be of limited
304 importance in fungi (e.g. gene body methylation(A et al. 2018; Wen et al. 2019)). This
305 chapter summarizes the most important - mostly transcription related - processes described
306 in fruiting bodies recently. Splicing and RNA interference are discussed below under
307 chapters 4.5.3 and 4.6, respectively.
308   Probably the most influential and most commonly assayed mechanisms of fruiting
309 body development are transcriptional reprogramming and gene expression changes. Gene
310 expression changes naturally associate with developmental processes and are informative
311 regarding the cellular processes that take place during fruiting. *In silico* functional analyses
312 of differentially or developmentally expressed genes have been a primary tool for
313 mycologists to understand fruiting body functions. Developmentally dynamic gene
314 expression patterns form the primary data source for this paper and the main part of the
315 paper (Chapter 4) is devoted to discussing genes with conserved expression patterns. A
316 significant unresolved question is how gene expression changes are regulated in various
317 stages of fruiting body development. It is not known currently if transcriptional
318 reprogramming events (e.g. during fruiting body initiation) are mediated by broad regulation
319 of chromatin accessibility, by regulating the expression and activity of regulatory genes (e.g.
320 transcription factors), or a mixture of these. A potentially significant regulatory mechanism is
321 post-translational modification of transcription factors or molecular switches in intracellular
322 signaling pathways, as demonstrated for the *Hom2* or the *Ras1* gene of *S. commune*(Knabe
323 et al. 2013; Pelkmans et al. 2017b). Another exciting avenue of future research is the
324 regulatory potential of selective post-translational protein modification by the
325 ubiquitin/proteasome system. Although direct evidence for its role in fruiting body
326 development has not yet been published, indirect evidence was provided by the remarkable
327 expansion of genes encoding F-box, BTB/POZ and RING-type zinc finger proteins in the
328 genomes of mushroom-forming fungi(Krizsán et al. 2019). These gene families provide the
329 substrate-specificity of ubiquitin ligases and have been shown, in other lineages, to be
330 involved in transcriptional regulation(Kipreos and Pagano 2000).
331 **Natural antisense transcripts (NATs)** are RNA transcripts that show complementarity to
332 transcripts of protein coding genes. NATs occur ubiquitously across eukaryotes and have
333 been detected in mushroom-forming fungi too(Ohm et al. 2010; Muraguchi et al. 2015;
334 Merényi et al. 2021). Because NATs do not encode proteins, they often evolve very fast and
335 are hard to link to specific functions. Nevertheless, their expression is developmentally
336 dynamic in all species examined to date, suggesting that they may be involved in regulating
337 development. Muraguchi et al reported that an antisense transcript of the stipe elongation
338 related AspE gene is transcribed just before stipe elongation(Muraguchi et al. 2015).
339 However, it should also be kept in mind that many NATs may result from random
340 transcription initiation and may therefore be transcriptional noise in fruiting body
341 transcriptomes(Merényi et al. 2021).
342 **Allele-specific expression (ASE)** refers to the imbalance of gene expression from two
343 divergent alleles in diploid or dikaryotic organisms. Fungal dikaryons almost always harbor
344 two allelically different monokaryons (heterokaryons), which can lead to intermediate, A- or
345 B-dominated expression. ASE has so far been detected in fruiting body transcriptomes of *A.*

346   *bisporus*(Gehrmann et al. 2018) and *P. ostreatus*(Merényi et al. 2021), but may be
347   widespread in the Agaricomycetes. In *A. bisporus*, Gehrmann et al suggested that ASE may
348   facilitate the division of labor between nuclei in a dikaryon(Gehrmann et al. 2018). Another
349   study, based on *P. ostreatus*, suggested that, at macroevolutionary timescales, ASE may be
350   a neutrally arising phenomenon that can nevertheless generate adaptive gene expression
351   variation(Merényi et al. 2021). It was found to be mostly characteristic of evolutionarily young
352   genes, consistent with neutral evolution. Allele-specific expression has agriculturally broad
353   consequences in hybrid genetics of plants(Bartoš et al. 2019) and could become a similarly
354   central question in the mushroom industry.
355   **RNA editing** has recently been detected in fruiting body transcriptomes of several
356   Ascomycota species(H et al. 2016; Liu et al. 2017; Teichert et al. 2017) and subsequently
357   reported in Basidiomycota also(Zhu et al. 2014; Wu et al. 2019). Like alternative splicing,
358   RNA editing provides a (post-)transcriptional mechanism for diversifying transcripts encoded
359   by a single gene, by enzymatically modifying certain bases of the primary RNA transcript. A
360   critical analysis recently found no evidence for RNA editing in fruiting body transcriptomes of
361   *P. ostreatus*(Merényi et al. 2021). This study raised the possibility that, because allele-
362   specific expression and RNA editing can generate similar signatures in RNA-Seq data, ASE
363   may have been mistaken for RNA editing in some prior Basidiomycota analyses and that
364   more research is needed to prove a role of RNA editing in mushroom development.
365   Several other exciting phenomena may be involved in the morphogenesis of
366   Basidiomycota fruiting bodies, including regulatory processes that may yet to be discovered.
367   For example, epigenetic regulation represents a potentially widespread but largely
368   underexplored regulatory mechanism for fruiting body morphogenesis(Vonk and Ohm 2021).
369   Similarly, upstream open reading frames (uORFs), which are open reading frames located in
370   the 5' untranslated region of an mRNA, can regulate (e.g. via encoded peptides) or interfere
371   with the transcription of the gene(HM et al. 2009). uORFs are known to be important in the
372   asexual development of Ascomycota(Han and Adams 2001) [and have recently been
373   detected in developmental genes of *C. cinerea* (Hegedus et al in prep)].

374   1.4. Genomic and transcriptomic resources

375   Genomic resources are also available for most model species of fruiting body development
376   (e.g. *C. cinerea* (Schaeff.) Redhead, Vilgalys & Moncalvo*, S. commune* Fr.*, Cyclocybe*
377   *aegerita* (V. Brig.) Vizzini)(Ohm et al. 2010; Stajich et al. 2010; Muraguchi et al. 2015; Gupta
378   et al. 2018; Almási et al. 2019) and those used by the mushroom industry, including
379   *Hericium erinaceus* (Bull.) Pers.(Gong et al. 2020; W et al. 2020)*, Ganoderma spp.*(Chen et
380   al. 2012)*, Flammulina spp.*(Park et al. 2014, 2019; Chen et al. 2020)*, L. edodes* (Berk.)
381   Pegler(Chen et al. 2016; Shim et al. 2016; Sakamoto et al. 2017a)*, Pleurotus spp*(A et al.
382   2018; Wang et al. 2018a; Dai et al. 2019; Lee et al. 2021)*, Agaricus spp*(Morin et al. 2012;
383   O'Connor et al. 2019; Sonnenberg et al. 2020)*, Tricholoma matsutake* (S. Ito & S. Imai)
384   Singer(Min et al. 2020)*, Sparassis crispa* (Wulfen) Fr.(Kiyama et al. 2018)*, Hypsizygus*
385   *marmoreus* (Peck) H.E. Bigelow(Min et al. 2018), among others. More broadly, in the
386   Agaricomycetes, draft genome sequences have been proliferating at a steady pace, due to
387   interest in biodiversity, lignocellulose decomposition(Martinez et al. 2004, 2009a; Floudas et
388   al. 2012; Riley et al. 2014) and mycorrhiza-formation(Martin et al. 2008; Kohler et al. 2015;
389   Miyauchi et al. 2020). This trend has virtually eliminated genome data being the bottleneck in
390   biological discovery in fungi. This is further supported by the spread of third generation
391   sequencing techniques, long-read sequencing data, which allow more and more complete

392 (telomere-to-telomere) assemblies and a range of analyses that draft genomes did not
393 permit.
394   The continuous development of technologies has also influenced the identification of
395 genes related to fruiting body morphogenesis. While early studies isolated fruiting body-
396 specific proteins/genes using mutant analyses, hybridization techniques (among others),
397 these were later substituted by RT-PCR and microarray studies, then by high throughput
398 sequencing analyses, such as 5'-serial analysis of gene expression (SAGE(WW et al. 2008;
399 Cheng et al. 2013a)) and most recently RNA-Seq. As of today, RNA-Seq datasets are
400 available for a wide range of species and conditions. These include *C. cinerea*(Plaza et al.
401 2014a; Muraguchi et al. 2015; Krizsán et al. 2019; Xie et al. 2020), *Flammulina spp*(Yan et
402 al. 2019; Liu et al. 2020b), *L. edodes*(Park et al. 2017; Sakamoto et al. 2017b; Song et al.
403 2018b; Y et al. 2018; Yoo et al. 2019; Kim et al. 2020), *Agaricus spp*(Gehrmann et al. 2018;
404 Lu et al. 2020; O'Connor et al. 2021), *Pleurotus ostreatus* (Jacq.) P. Kumm.(Wen et al. 2019;
405 Merényi et al. 2021), *H. marmoreus*(Zhang et al. 2015b), *C. aegerita*(Orban et al. 2021),
406 *Phanerochaete chrysosporium* Burds.(Krizsán et al. 2019), *Lentinus tigrinus* (Bull.)
407 Fr.(Krizsán et al. 2019), *Mycena kentingensis* Y.S. Shih, Chi Y. Chen, W.W. Lin & H.W.
408 Kao(Ke et al. 2020a), *Rickenella mellea* (Singer & Clémençon) Lamoure(Krizsán et al.
409 2019), *Armillaria ostoyae (*Romagn.) Herink(Sipos et al. 2017a), *Pisolithus microcarpus*
410 (Cooke & Massee) G. Cunn (Pereira et al. 2017), *Laccaria bicolor* (Maire) P.D. Orton
411 (Ruytinx et al in prep), *S. commune*(Ohm et al. 2010) and *Auriculariopsis ampla* (Lév.)
412 Maire(Almási et al. 2019). Many of these datasets build the foundation of this study, by
413 providing windows into developmentally expressed genes in different fungal species.
414   A general observation we made during the analyses we present hereafter is that the
415 resolution of the transcriptomic data is key to identifying expression dynamics and patterns.
416 Both tissue-wise and temporal resolution of the data allowed the discovery of more
417 developmentally relevant expression patterns. We found several cases where tissue-
418 resolved transcriptomes provided clear signal for conserved, tissue-specific expression of a
419 gene, whereas in non-resolved transcriptomes the same gene showed a more or less flat
420 expression curve. This is an inherent nature of bulk RNA-Seq data: spatial expression
421 patterns average out in samples that contain large populations of multiple cell types.
422   Beyond gene expression, a broad array of other types of information could be
423 leveraged for understanding fruiting body development. Notable recent examples include
424 assays of the overrepresentation of certain gene families in the genomes of focal
425 species(Krizsán et al. 2019), a population genomics study combined with selection analyses
426 and gene expression profiling in *L. edodes*(Zhang et al. 2021c) to identify genes involved in
427 fruiting body development(Zhang et al. 2021c), or ChIP-Seq analyses for assaying promoter
428 occupancy and thus transcriptional activity(Vonk and Ohm 2021).

429   2. Description of the approach used in this paper

430 In this study, we address the puzzle of how a fruiting body develops and what novel insight
431 can be gleaned from systematic comparisons of developmental transcriptomes. We aim at
432 providing a comprehensive listing of putatively development-related gene families in the
433 Agaricomycetes. We provide, for each discussed functional group or gene family,
434 information on their expression, orthology to well-established model organisms
435 (*Saccharomyces cerevisiae, Schizosaccharomyces pombe, Aspergillus nidulans*,
436 *Neurospora crassa*) and to key mushroom-forming fungi as tables. We also annotate several

437 conserved pathways in *C. cinerea*, based on strict 1-to-1 orthology to known pathway
438 members in well-researched model systems (see Methods for details).
439   Each chapter is structured so that it starts with a literature review of the given gene
440 family followed by a discussion of novel findings (if any) based on our meta-analysis of
441 transcriptomes. Our main units of investigation are **conserved developmentally expressed**
442 **(CDE)** orthogroups, which are groups of single-copy genes in which the majority (>65%[1]) of
443 the genes were developmentally expressed (see Methods and Merenyi et al 2021(Merényi et
444 al. 2021)). For simplicity CDE orthogroups are considered to be groups of genes sharing
445 similar functions (see limitations below) in fruiting body development.
446   We performed a meta-analysis of 12 developmental transcriptomes (*Agaricus*
447 *bisporus*(Gehrmann et al. 2018)*, C. aegerita*(Orban et al. 2021)*, A. ostoyae*(Sipos et al.
448 2017a)*, A. ampla*(Almási et al. 2019)*, C. cinerea*(Krizsán et al. 2019)*, L. bicolor* (Ruytinx et al
449 in prep)*, L. edodes*(Zhang et al. 2021d)*, L. tigrinus*(Krizsán et al. 2019)*, M. kentingensis*(Ke
450 et al. 2020a)*, Ph. chrysosporium*(Krizsán et al. 2019)*, P. ostreatus*(Krizsán et al. 2019)*, S.*
451 *commune*(Almási et al. 2019)) (Fig. 1). These species belong to two orders (Agaricales,
452 Polyporales), which span an estimated 200 million years of evolution(Varga et al. 2019), and
453 represent diverse ecologies and morphological adaptations, such as simple resupinate (*Ph.*
454 *chrysosporium*), coralloid (*Pterula gracilis*), pileate-stipitate (e.g. *C. cinerea*) and cyphelloid
455 (*A. ampla, S. commune*) forms. Each of these species and their ecological adaptations show
456 several unique aspects (e.g. fruiting body ecotypes) which could be related to gene
457 expression data. However, we are here interested in only the shared aspects of fruiting body
458 development, and therefore use the diversity of the compared species in focusing our
459 attention to widely conserved fruiting body genes which should help define the core building
460 blocks required for fruiting body morphogenesis.
461   The comparative approach we follow is paramount to separate 'wheat from chaff', i.e.
462 developmentally regulated genes that are relevant for the development of fruiting bodies in
463 general from genes with taxonomically restricted or species-specific developmental roles.
464 This builds on the assumption that a gene involved in core fruiting body functions should be
465 conserved across Agaricomycetes and should show similar expression dynamics in all
466 species. Therefore, in our approach we focus on conservation of both sequence and
467 expression. A comparative approach is also desirable because it is now well-known that
468 gene expression is associated with 'biological noise', which may influence the detection of
469 differentially expressed or developmentally regulated genes(Merényi et al. 2021) in any
470 single species, whereas across-species comparisons effectively cancel the effects of gene
471 expression noise.
472   This study, like all others, has limitations. First, it should be noted that evidence for
473 gene function remains, in an overwhelming majority of cases, circumstantial, inferred from
474 expression patterns or extrapolated from the functions of orthologous genes in model fungi.
475 At the moment we rely on these types of evidence due to the scarcity of developmental
476 genetic and in-depth functional studies in most Agaricomycetes. Despite the inferential
477 nature of the study, many orthologs display very conserved expression patterns across
478 Agaricomycetes species (e.g. aquaporins in stipe tissues, see below), allowing us to make
479 confident predictions on the function of such genes. Second, a perfect comparative
480 transcriptomic study would compare corresponding developmental stages across species. In
481 the Agaricomycetes establishing homology relationships among individual species is

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[1] We deviaed from this rule where justified.

482 complicated (see above). Furthermore, the developmental transcriptomes we used differ in
483 the sampled time points and resolution (e.g. tissue-wise or bulk) and do not follow a unified
484 nomenclature for developmental stages (e.g. aggregate in *S. commune* vs. hyphal knot in *C.*
485 *cinerea*). Therefore, we here focused broadly on comparing expression dynamics and the
486 shape of the expression curve, rather than attempting to find 1-to-1 correspondence
487 between stages of different species. Finally, in the present study, we focus on genes with
488 developmentally dynamic expression. However, not all morphogenetically relevant genes
489 show expression dynamics; constantly expressed genes can often be important for
490 development, for example, if regulated post-transcriptionally (e.g. alternative splicing
491 isoforms(Gehrmann et al. 2016; Krizsán et al. 2019)) or post-translationally (e.g.
492 phosphorylation, ubiquitylation etc.(Knabe et al. 2013; Pelkmans et al. 2017a)).
493

494   3. Methods

495   Bioinformatic analyses of RNA-Seq data
496 The raw RNA-Seq data of 12 previously published Basidiomycota species were reanalysed
497 following Merenyi et al(Merényi et al. 2021). The following reference genomes were used: *C.*
498 *cinerea* (AmutBmut pab1-1 v1.0(Muraguchi et al. 2015))*, A. ostoyae* (C18/9(Sipos et al.
499 2017b))*, A. ampla* (NL-1724 v1.0(Almási et al. 2019)), *S. commune* (H4-8a and H4-8b(Ohm
500 et al. 2010))*, L. bicolor* (v2.0(Martin et al. 2008))*, L. edodes* (Le(Bin) 0899 ss11 v1.0(Zhang
501 et al. 2021c))*, L. tigrinus* (RLP-9953-sp(Wu et al. 2018)), *Ph. chrysosporium* (RP-78
502 v2.2(Ohm et al. 2014)), *P. ostreatus* (PC15 v2.0(Riley et al. 2014))*, M. kentingensis*(Ke et al.
503 2020a)*, A. bisporus* (var. bisporus H97(Morin et al. 2012))*, C. aegerita* (AAE-3(Gupta et al.
504 2018))*. To remove adaptors, ambiguous nucleotides and any low quality read ends, reads
505 were trimmed using bbduk.sh and overlapping read pairs were merged with bbmerge.sh
506 (part of BBMap/BBTools; http://sourceforge.net/projects/bbmap/) with the following
507 parameters: qtrim=rl trimq=25 minlen=40. A two-pass STAR alignment(Veeneman et al.
508 2016) was performed against reference genomes with the same parameters as in our
509 previous study(Krizsán et al. 2019) except that the maximal intron length was reduced to
510 3000 nt. Reads were counted and summarized for each exon with FeatureCounts(Liao et al.
511 2014) taking into account the mode of sequencing (paired-end, single-end). Since the
512 *Cyclocybe* transcriptome was obtained with the Quantseq method, reads were counted only
513 in the -100 - +400 region of the 3' ends of the genes. Read count data were normalized
514 using EdgeR(Robinson et al. 2010). Expression levels were calculated as fragments per
515 kilobase of transcript per million mapped reads (FPKM).
516   Developmentally regulated genes were identified as before(Krizsán et al. 2019;
517 Merényi et al. 2021), based on a stricter four-fold or a more permissive two-fold change
518 cutoff between adjacent developmental stages or tissue types. Genes showing a 4-fold
519 upregulation in the first primordium stage relative to vegetative mycelium were termed 'FB-
520 init', and considered regulated during fruiting body initiation. It should be noted that the data
521 we analyze is noisy, based on different chemistries, different labs and protocols, etc., which
522 introduces a certain amount of data loss in our analyses. Nevertheless, the transition to
523 fruiting body development is such a dramatic change that we expect similar gene expression
524 changes to be discoverable across species, despite the heterogeneity of the data. This is
525 supported by previous comparative transcriptomic studies(Plaza et al. 2014b; Krizsán et al.

526 2019; Merényi et al. 2020b, 2021) as well as the biologically meaningful conclusions
527 obtained here.
528
529 **Orthology based on reciprocal best hits**
530 Proteins of each species were searched against the proteomes of other species using the
531 reciprocal best hit (RBH) module of MMSeqs2(Steinegger and Söding 2017). To remove
532 spurious RBHs, a bidirectional 50% coverage and at least 1e-6 e-value were required.
533 Proteins were clustered into single copy clusters using a connected component clustering
534 algorithm in the igraph package([CSL STYLE ERROR: reference with no printed form.]),
535 based on reciprocal best hits. This step clustered 74.3% of the proteins in the examined
536 species. The other 25.7% of proteins form clusters with duplication in any or more species.
537 For these 1:1 orthogroups were circumscribed using the 'ortholog coding' algorithm of the
538 COMPARE pipeline(Nagy et al. 2014). In the case of terminal duplications, orthogroup
539 membership was decided based on connectivity; the protein which showed more hits to
540 other members of the orthogroup was selected while the other(s) moved to separate
541 orthogroup(s). Complete orthology relationships of genes across all 12 species are given in
542 this paper are presented in Supplementary Table 1.
543   This approach is suitable for identifying moderately to very conserved gene groups,
544 whereas for highly volatile genes (i.e those that show frequent duplication/loss), a more
545 liberal approach building on orthologous groups (like(Krizsán et al. 2019)) is more
546 appropriate. For fast-evolving genes, approaches looking at sequence conservation might
547 not work. Therefore, in the case of certain gene families, such as defense genes or cell wall
548 remodeling CAZymes, we relied on primary gene family classification instead of reciprocal
549 best hit based orthogroups. In the case of CAZymes, we followed the cazy.org
550 classification(Levasseur et al. 2013).
551
552 **Identification of CDE orthogroups**
553 The central unit of discussion in this paper is referred to as 'conserved developmentally
554 expressed (CDE) orthogroup', which refers to groups of single-copy genes (one gene per
555 species) in which the majority of genes is developmentally regulated either at fold change >2
556 or >4. As a principal rule, we considered an orthogroup to be a CDE orthogroup if >65% of
557 the genes in it were developmentally regulated, and at least 8 species were represented.
558 Deviations from this rule were allowed in unique cases (e.g. taxonomically restricted but
559 important gene family) and are transparently presented in tables and supplementary tables
560 under each of the following chapters.

561 # 4. Results: developmentally expressed gene classes in the
562 # Agaricomycetes

563 In this paper we synthesized literature reviews with a meta-analysis of developmental
564 transcriptomes to identify conserved gene families involved in fruiting body development. For
565 the latter we reanalysed data for 12 species and identified developmentally regulated genes,
566 i.e. those that showed >2 or >4-fold changes between successive developmental stages or
567 adjacent tissue types (Supplementary Table 2). Statistics on developmentally expressed
568 genes are provided in Supplementary Table 2/b. Numbers of developmentally regulated
569 genes were similar to those reported by previous studies,(Almási et al. 2019; Krizsán et al.

570   2019; Merényi et al. 2020b, 2021) therefore, we here do not discuss these in detail, rather
571   focus on those that are conserved across species.
572   We organized developmentally regulated genes into strict 1-to-1 orthogroups
573   following the logic of Merenyi et al(Merényi et al. 2021). Orthogroups in which >65% of the
574   genes were developmentally regulated were designated as conserved developmentally
575   expressed (CDE) orthogroups at fold change values of >2 or >4. We identified 921 CDE
576   orthogroups across the twelve Agaricomycetes species; these form the basis of the
577   discussion presented in the rest of this paper. Statistics on the number of species which had
578   developmentally regulated genes in these orthogroups are shown on Fig. 2/A. The
579   transcriptome data of *A. bisporus* was an outlier in several aspects. We currently do not
580   know if this is due to biological differences of this species or technical reasons, nevertheless
581   this transcriptome was assigned lower weight and discussed rarely in the following chapters.
582   By relying on conserved developmentally expressed orthogroups, we here take shared
583   expression dynamics as a proxy for conservation of function. It should be mentioned that this
584   approach may be, in several cases, only a crude approximation of real conservation of
585   function, but facilitates comparative discussion of gene families and their speculated
586   functions in fruiting body morphogenesis.
587   We functionally characterized CDE orthogroups and arranged them into broader
588   groups based on function inferred by orthology to genes in well-known model systems (*S.*
589   *cerevisiae, Schizosaccharomyces pombe, A. nidulans, N. crassa*) and/or their Gene
590   ontology and InterPro annotations. We defined 17 broader functional groups, cell
591   division/proliferation, defense, transcriptional regulators, signal transduction, cell wall
592   biosynthesis and remodeling, cell surface proteins, secondary metabolism, cytoskeleton,
593   basic metabolism and acetyl-CoA production, lipid metabolism, storage carbohydrate
594   metabolism, ubiquitin/proteasome system, transporters, functionally poorly known genes,
595   unannotated genes, stress response related genes and ferric reductases (Fig. 2/B). The
596   main categories were further subdivided into finer groups to facilitate discussions of putative
597   functions. We categorized developmental genes manually to the best of our knowledge
598   based on inferred gene function, though the subdivision is probably not impeccable. For
599   example, overlaps exist between chromatin remodeling and DNA replication related
600   regulatory factors or between the latter and cytoskeleton related genes (e.g. kinesins
601   involved in moving chromatids during mitosis).
602   The two largest categories were functionally poorly characterized and unannotated
603   genes, these contained 182 and 176 CDE orthogroups, respectively (Fig. 2/B). The first,
604   'functionally poorly characterized genes' contains orthogroups which we could not
605   confidently link to any fruiting body functions. It is possible that this category could be
606   subdivided and with further manual annotation more orthogroups could be explained in the
607   context of fruiting body development. On the other hand, unannotated genes are those that
608   contain no existing Pfam or InterPro domain signatures and lack all kinds of functional
609   annotation. The largest functional group for which a function could be determined was
610   related to cell proliferation (DNA replication, DNA repair, mitosis, meiosis) followed by cell
611   wall biosynthesis and remodeling. Transcriptional regulators (including transcription factors,
612   chromatin-related and RNA-binding regulatory proteins), transporters and Acetyl-CoA
613   production related genes were also represented by a considerable number of genes. Certain
614   functional categories, such as 'defense' and 'secondary metabolism' contained only a small
615   number of CDE orthogroups. In these cases, these low numbers reflect the lack of
616   conservation of gene sequences, rather than the lack of a role of these gene families in
617   fruiting bodies.

618 Our discussion is guided here by conservation of developmentally regulated families.
619 However, there are gene families that do not form conserved orthogroups, but are
620 nevertheless very important for fruiting body development. These can be either multigene
621 families that undergo frequent duplication and thus orthology relationships are intricate (e.g.
622 hydrophobins), or fast-evolving families in which divergence quickly erases orthology
623 relationships (e.g. F-Box proteins, defense-related proteins). Therefore, in addition to gene
624 families/pathways identified through CDE orthogroups, we discuss broader, fast-evolving
625 gene families based on annotations at the gene family level only (i.e. without orthogroups)
626 and performed manual annotations to identify broader containing gene families or cellular
627 pathways. Accordingly, in addition to the 921 CDE orthogroups, we discuss further 558 gene
628 groups which belong to broad functionalities involved in fruiting body development. For some
629 processes we were able to reconstruct (nearly) complete pathways, such as in the case of
630 mitosis/meiosis related genes or fatty acid biosynthesis, whereas in other cases we only
631 document the widespread developmental regulation and expression profile conservation of a
632 gene family, but without information on the containing pathway of broader cellular function.
633 For some gene groups, such as cytoskeletal genes, GPCRs or MAP kinase pathways, we
634 provide annotations despite their limited expression dynamics during fruiting body
635 development. Such gene families may be important in fruiting body development despite
636 their low expression dynamics, therefore, we decided to annotate them in order to facilitate
637 comparative discussion across mushroom-forming fungi and more thoroughly investigated
638 Ascomycota model systems.
639 In the following chapters we discuss each of the more important gene groups in
640 detail, with emphasis on expression profiles, putative function and role in fruiting body
641 development. Besides well-known ones, we intentionally focus on lesser-known gene
642 families with widespread developmental expression, to potentially distill new insights into
643 fruiting body development. We provide catalogues and references to recent reviews for well-
644 researched gene families as well (e.g. hydrophobins or laccases).
645

4.1. Cell division, proliferation and growth

4.1.1. Meiotic and mitotic gene expression show two distinct expression peaks

648 Mitosis and meiosis are key to the development and growth of multicellular organisms.
649 Mushroom fruiting bodies are no exception: mitosis leads to cell proliferation early in fruiting
650 body development, whereas meiosis happens in basidia, which are localized to gills, to
651 produce spores.
652 Transcriptomic data provided clear evidence for expression peaks of genes related to
653 mitotic or meiotic cell division, as well as associated processes in DNA replication, repair,
654 chromosome dynamics/movement etc., during fruiting body development. The enrichment of
655 meiotic/mitotic genes during fruiting body development and sporulation was noted in *C.*
656 *cinerea*(Burns et al. 2010; Muraguchi et al. 2015; X et al. 2015; Krizsán et al. 2019),
657 *Pisolithus microcarpus*(Pereira et al. 2017)*, Tricholoma matsutake*(Tang et al. 2020) and *L.*
658 *edodes*(Song et al. 2018b), *Agaricus blazei*(Lu et al. 2020) as well as in a six-species
659 comparison published by Krizsan et al(Krizsán et al. 2019), among others. Similar signal for
660 meiotic gene upregulation has been detected in Ascomycota fruiting bodies as
661 well(Rodenburg et al. 2018). *C. cinerea* has been used as a model system of Basidiomycota
662 meiosis, in particular in so called white cap mutants that have meiosis-associated defects(Lu

663   et al. 2003). These works revealed many conserved and some unique aspects of the meiotic
664   process as well as resulted in meiosis being one of the best understood processes in this
665   species(Seitz et al. 1996; NY et al. 1997; L et al. 1999; Gerecke and Zolan 2000; Nara et al.
666   2001; Cummings et al. 2002; Lu et al. 2003; SH et al. 2004; Muraguchi et al. 2008a; AM et
667   al. 2009).
668   Probably the most detailed such study was performed by Burns et al(Burns et al.
669   2010), who investigated by microarray the transcriptional events that happen in *C. cinerea*
670   gills during a time course that encompasses the meiotic events. They found that 2,721
671   genes exhibited changing probe intensity during the six time points around meiosis. Using
672   dikaryotic mycelium as reference, they identified 886 genes that were expressed in gill tissue
673   only; these genes included core meiotic components. Like in other species, genes were
674   induced in successive waves during the meiotic process; these waves were arranged into 9
675   clusters based on expression trajectories. The clusters separated genes into functional
676   groups, e.g. those required for prophase I or sporulation in early and late in the time series,
677   respectively. Early genes further included ones related to DNA replication, cytoskeleton
678   organization and regulation. Late induced genes in their study are mostly related to spore
679   formation and show overlaps with genes related to ascospore formation in *S. cerevisiae*(S et
680   al. 1998a; Primig et al. 2000) and *Sch. pombe*(Mata et al. 2002). Ribosomal protein coding
681   gene expression was found to be high up to karyogamy, at which point it starts to decrease
682   and does not lift up again. This might reflect the shutting down of protein synthesis as the
683   fruiting body enters the sporulating phase.
684   Freitas Pereira et al examined sporogenesis in *Pisolithus*, an ectomycorrhizal fungus
685   in the Boletales, and found that meiotic genes (annotated by KEGG) showed dynamics
686   throughout the development of basidiospore-containing peridioles(Pereira et al. 2017). In this
687   species spores are produced in peridioles, lentil-shaped to globular compartments within the
688   fruiting body. Several genes that were differentially expressed in peridioles of different
689   maturation stages were annotated as meiotic/cell cycle or cell division related, most of which
690   showed an expression peak in unconsolidated, young, and mature peridioles. These
691   observations are consistent with microscopic observations on the sporogenesis of *P.*
692   *microsporus*(AN and MD 2010).
693   We annotated 180 conserved orthogroups as involved in cell proliferation, such as
694   mitosis, meiosis, DNA replication, DNA repair or the cell cycle, based on expression
695   conservation 141 of these qualified as CDE orthogroup (Table 1). These included previously
696   functionally characterized genes such as *ku70*, *rad50* and *Mre11* of *C. cinerea*(AM et al.
697   2009; Nakazawa et al. 2011), DMC1 (=Lenedo1_1211634) of *L. edodes*(Sakamoto et al.
698   2009)*, ku80* of *S. commune*(De Jong et al. 2010) and *Msh4* of *P. ostreatus*(Lavrijssen et al.
699   2020). Most of these genes showed developmental regulation and similar expression profiles
700   in most of the species. This is not surprising, given that both mitosis and meiosis have well-
701   documented roles in sculpting fruiting bodies. Nevertheless, to our knowledge, these genes
702   represent the most comprehensive, although surely not complete, list of cell proliferation
703   related genes to date. We tentatively subdivided CDE orthogroups into ones related to DNA
704   replication, DNA repair, meiosis as well as both mitosis and meiosis; these contained 87, 26,
705   13, 54 genes, respectively (Table 1). These include members of several well-characterized
706   protein complexes described from S. cerevisiae, such as Ku, SMC, MCM, Ndc80, Gins and
707   cohesin complexes (Table 1). Orthologs of *C. cinerea* arp9, which was described as a
708   putative actin-related protein involved in chromatin remodeling(Nakazawa et al. 2016), were
709   also found to follow similar expression profiles, although at moderate dynamics (Table 1).

710   These genes showed characteristic expression profiles in most species. The
711   expression of meiotic genes shows a distinct peak in gill tissues (Fig. 3, Supplementary Fig.
712   1) or in stages that contain meiotic tissue. Meiotic gene expression precedes early phases of
713   sporulation and was clearly discernible in *C. neoformans* or *P. ostreatus* in previous
714   transcriptomic studies(Liu et al. 2018; Merényi et al. 2021). Because the onset of meiosis is
715   tightly regulated in most species (among mushrooms best known in *C. cinerea*(Kües 2000))
716   meiotic gene expression also provides a landmark to calibrate developmental chronologies
717   among species where this may be hard to do because of morphological divergence. It
718   should be noted that some species develop in ways so that we do not expect a clear peak.
719   For example, cell proliferation and spore production is not synchronized in *S. commune*,
720   where it appears that sporulation progresses from the basal, older parts and progresses
721   towards the edges of the fruiting body(Kües and Liu 2000). In *S. commune*, this may be
722   explained by the highly derived morphology of the fruiting bodies, consisting of an
723   assemblage of cyphelloid fruiting bodies. Therefore, we would not expect one clear peak of
724   meiotic gene expression, unless we sample different zones of the fruiting body separately.
725   On the other hand, mitotic, DNA replication and repair genes showed a clear peak
726   associated with primordium stages, and their expression leveled off in mature fruiting bodies
727   (Fig. 3, Supplementary Fig. 1). This probably reflects intense cell proliferation in primordia,
728   which establishes the main tissues and developmental modules of the mushroom. The
729   expression of these genes later decreases to low levels in young fruiting body stipes and
730   caps (also high in meiotic tissues where one round of mitosis happens) and in mature fruiting
731   bodies. This peak was also detected in previous studies on *Agaricus blazei*(Lu et al. 2020)
732   and *P. ostreatus*(Merényi et al. 2021) and probably relates to the biphasic development of
733   fruiting bodies, where the first phase is concerned with cell proliferation and tissue formation
734   whereas the second with growth by cell expansion without much change in cell numbers.
735   Our data suggest that this pattern should be conserved across agarics, but potentially
736   missing or less clear in species that follow different developmental patterns (e.g. polypores).
737   *Cryptococcus neoformans* recently proved to be a particularly useful model for
738   teasing apart morphogenetic processes(Merényi et al. 2021). This species forms simple
739   fruiting bodies composed of lawns of aerial hyphae bearing basidia. Liu et al pointed out in
740   *Cryptococcus*, that genes co-induced with meiotic genes might be related to basidium
741   morphogenesis, a process that greatly overlaps with meiosis(Liu et al. 2018). Based on
742   transcriptome data it may be hard to separate such genes from meiotic genes, because of
743   the temporal and spatial overlap of their expected expression. Nevertheless, one of the
744   genes reported by Liu et al, *C. neoformans* Csa1 (*C. cinerea* protein ID: 471238, see Table
745   TRA below), which has been implicated in basidium development (and to a lesser extent
746   meiosis(Liu et al. 2018)), is developmentally expressed in 10/10 species in our data and
747   shows expression peaks that overlap with that of meiotic genes.
748   An orthogroup that includes the serine-threonine kinases *Sch. pombe* Ran1 and *S.*
749   *cerevisiae* Sks1 (represented by *C. cinerea* 456276, Table 1) showed marked peaks in gills
750   of mature fruiting bodies in all agaricoid species (except *C. cinerea*) and in mature fruiting
751   bodies in species with no separable gills or caps (*S. commune, A. ampla*). Ran1 is a
752   negative regulator of *Sch. pombe* meiosis (with Mei2 as target(Caligiuri et al. 1997)),
753   whereas Sks1 is involved in the adaptation to low glucose concentrations and pseudohyphal
754   growth in yeast. Despite this apparent strong contradiction, the characteristic expression
755   peaks in meiotic tissues and developmental stages in mushroom-forming fungi suggest roles
756   in sporulation-related processes, possibly the repression of meiotic processes during spore
757   morphogenesis.

758   In summary, mitotic and meiotic (including associated processes such as DNA
759 replication and repair) gene expression showed conserved patterns across the examined
760 mushroom-forming fungi. This probably reflects, on one hand, intense cell proliferation
761 during primordium development and, on the other hand, meiosis that precedes sporulation in
762 basidia. These gene expression patterns are easily recognizable in transcriptomic data and
763 provide landmarks for calibrating developmental series. The downregulation of mitosis
764 related genes in the second half of fruiting body development coincides with ceasing cell
765 proliferation and the transition of the mushroom to growth by cell expansion.

4.1.2. Ribosomal genes

767 Ribosomes produce proteins, the necessary building blocks for living cells. They are
768 composed of four RNA subunits and up to 80 different proteins. The amount of ribosomes,
769 and thus ribosomal protein expression, in a cell is proportional to its protein synthesis
770 demand(Kraakman et al. 1993; Jorgensen et al. 2002). Therefore, ribosomal protein
771 expression has been used as a proxy for the proliferative activity of a cell or a tissue and we
772 expect it can be similarly informative in mushrooms too.
773   We observed a preponderance of ribosomal protein genes among CDE orthogroups,
774 especially at FC>2 and to a lesser extent at FC>4. To look globally at structural proteins of
775 ribosomes, we identified ribosomal protein genes based on previously reported ribosomal
776 compositions, excluding mitochondrial ribosomal proteins and ribosome biogenesis-related
777 genes. The 74 orthogroups identified this way (Table RIB) showed very characteristic
778 expression dynamics, albeit at low fold change values, in most species. Ribosomal genes
779 were highly expressed in the early developmental stages of most species followed by
780 gradual shutting down in young and mature fruiting bodies. A second, sharp expression peak
781 was observed in gill tissues of *P. ostreatus, A. ostoyae, A. bisporus* and *C. cinerea (*Fig. 4,
782 Supplementary Fig. 2). Like in the case of mitotic and meiotic genes, we hypothesize that
783 these two peaks correspond to an early, proliferative stage of development and the protein
784 synthesis demand of spore production/meiosis. Ribosomal genes seem to be co-expressed
785 with genes involved in cell division and proliferation (meiotic, DNA replication and repair, see
786 above) in both primordia and in the gills. This could signify the need for increased protein
787 production for cell proliferation in primordia and for meiosis and spore production, although
788 other processes happening in gills requiring a large amount of protein cannot be ruled out.
789 The characteristic expression of ribosomal genes is a conspicuous pattern and was detected
790 in partial or complete form in several transcriptomic papers in both Basidiomycota(Cheng et
791 al. 2013b; Zhou et al. 2014; Zhang et al. 2015b; Song et al. 2018b; Krizsán et al. 2019; Liu
792 et al. 2020a; Lu et al. 2020) and Ascomycota(Rodenburg et al. 2018; Tong et al. 2020).
793   The vegetative mycelium generally showed high ribosomal protein-coding gene
794 expression, though not in all species, which we hypothesize depended on whether samples
795 for RNA-Seq were harvested from older, inactive or actively growing (e.g. colony edge) parts
796 of the mycelium.
797   A ribosome-bound Hsp70 chaperone protein formed a CDE orthogroup
798 developmentally regulated in 9 species (FC>2) (*C. cinerea* protein ID: 438977) (Table 2).
799 This gene was also detected previously as upregulated in primordia of *C. cinerea*(Cheng et
800 al. 2013b). It is orthologous to *S. cerevisiae* Ssb2, a Hsp70-family chaperone that is bound
801 by the ribosome and escorts the folding of nascent polypeptides(Peisker et al. 2010).
802   In summary, a characteristic expression trajectory of ribosomal genes is
803 characteristic of most mushroom-forming fungi, which likely reflects high protein demands of

804 intensely growing tissue in primordial stages and gills and supports a bi-phasic model of
805 fruiting body development (see below).

4.1.3. Growth by cell expansion and turgor manipulation - a biphasic model of fruiting body development

808 A key difference in fruiting bodies and hyphae is that in the latter growth and expansion
809 takes place at the tip, whereas in the former, cell expansion can vary between apical and
810 isotropic. Already de Bary established, by studying *Mycena vulgaris*, that mushroom fruiting
811 bodies grow mostly by cell expansion not by cell proliferation(Bary et al. 1887). This appears
812 to be a rather widespread feature of fruiting bodies and shows broad similarity to growth by
813 cell expansion in plant fruits(Krizsán et al. 2019). More precisely, fruiting body development
814 seems to be divided into a first proliferative stage, during which cell division, differentiation
815 as well as tissue formation takes place, and a growth phase, which is primarily concerned
816 with cell expansion to achieve the mature shapes and sizes of the fruiting bodies(MOORE et
817 al. 1979; Kües 2000; G et al. 2013; Kües and Navarro-González 2015; Krizsán et al. 2019;
818 Liu et al. 2021). Of the better investigated species, this two-phased development is probably
819 most spectacular in *C. cinerea*, which is adapted to very rapidly lifting cap above ground and
820 expanding it for spore dispersal(Kües 2000).
821 It should be noted that the two-phase development is not fully universal among fungi
822 and does not always mean a complete separation of proliferative and expansive phases. For
823 example, Craig et al(Craig et al. 1977) showed that the top regions of *A. bisporus* stipes
824 elongated up to 9-fold, whereas cell lengths increased up to 2.2-fold, and from these data
825 derived that cell division also occurs to achieve this elongation rate. In *S. commune*, it
826 appears that outer parts of the fruiting body are still growing (by cell proliferation) while older
827 parts are already sporulating(Kues and Liu 2000).
828 Whether for the entire fruiting body or only parts of it, growth by cell expansion
829 seems to be a widespread trait during the second half of development of mushrooms. How
830 cell expansion is achieved, in general, is poorly known, but it probably requires water supply,
831 turgor manipulation (by osmolytes), cell wall elasticity and new cell wall material deposition.
832 Water supply may be realized by the regulated expression of aquaporin genes (see below).
833 On the other hand, the identity of the osmolytes has not been resolved yet. In the
834 Ascomycota ions, ion channels, glycerol and sugars were reported as main players of turgor
835 manipulation(Fischer et al. 2004). In Basidiomycota fruiting bodies, sugars (mannitol,
836 trehalose) offer themselves as straightforward candidates, but Moore([CSL STYLE ERROR:
837 reference with no printed form.]) speculated that high molecular weight sugars are unlikely to
838 be the osmolytes that drive stipe expansion. Trehalose and polyols have been excluded as
839 osmolytes(Kües 2000; F et al. 2005), whereas potassium oxaloacetate has been
840 hypothesized, which would be consistent with the upregulation of oxalate metabolism (see
841 below), but not confirmed(Knoll; Kües 2000). On the other hand, ions would either need to
842 be transported to the fruiting body from the mycelium, or released locally.
843 Factors modulating cell wall elasticity and remodeling are better known. During
844 fruiting body growth, cell wall deposition occurs throughout the cell surface, and not only in
845 the tip region as in hyphae, which was termed diffuse extension(Kües 2000). In *Agaricus*
846 *bisporus* larger proportion of β-1,6-linked glucose side branches in a β-1,3-glucan backbone
847 was observed in the rapidly elongating top segment of the stipe(Mol and Wessels 1990).
848 This causes hydrogen-bonds among glucan chains to be weaker in rapidly elongating stipe
849 compared with mature stipe and vegetative hyphae. It has been hypothesized that these

850 weak bonds are disrupted and reformed by turgor pressure rather than hydrolysing
851 enzymes(Mol et al. 1990). The architecture of cell wall also regulates stipe elongation; in
852 primordial stages chitin microfibrils are arranged isotropically which is remodeled to helical
853 arrangement during development(Kamada et al. 1991). The turgor pressure acting on the
854 cell wall and insertion of new chitin microfibrils allow elongation and in that dynamic
855 rearranges of microfibrils chitin synthases, chitinases and glucanases play the major role in
856 *C. cinerea*(Kamada et al. 1991). Niu et al observed differences in structure of chitin
857 microfibrils in elongating and mature stipe regions(Niu et al. 2015). Extension of the cell wall
858 happens by insertion of newly synthesized microfibrils. In contrast, studies in *Flammulina*
859 and *Coprinopsis* suggested that stipe cell wall extension is mediated by endogenous
860 expansin-like proteins, not turgor pressure or cell wall glycoside hydrolases(Fang et al. 2014;
861 W et al. 2014). Plant expansins mediate Turgor-mediated cell expansion(Baccelli 2015) and
862 several other morphogenetic processes (e.g. organ abscission, fruit softening(Sampedro and
863 Cosgrove 2005)). The auxin-driven expansion of plant cells without changes in cell number
864 is known as acid growth(Rayle and Cleland 1992; Arsuffi and Braybrook 2018), because low
865 pH is required by cell wall modifying proteins (e.g. expansins) to loosen the cell wall. In fungi,
866 it is not known if an analogous process exists, but the acidifying effect of external CO_2 has
867 been hypothesized as a factor in stipe cell elongation(Liu et al. 2021) and there is evidence
868 for expansins participating in the process (see below). Accordingly, high external CO_2 during
869 mushroom cultivation was speculated to cause malformed, long-stipe fruiting bodies by
870 acidifying the extracellular space and activating cell wall modifying proteins(Liu et al. 2021).

871 4.2. Acetyl-CoA production by central carbon metabolism

872 We found evidence for widespread developmental expression of multiple acetyl-coenzyme A
873 (Ac-CoA) producing enzyme families. Ac-CoA is a key intermediate in central carbon
874 metabolism as well as other processes (biosynthesis of lipids and certain amino acids(Chen
875 et al. 2015)). Under normal carbon metabolic conditions, the generated Ac-CoA, which
876 comes from either glycolysis or fatty acid beta-oxidation enters the TCA cycle, where it is
877 oxidized to CO_2 for energy (ATP) production. However, Ac-CoA is required also for the
878 production of biological membranes(Strijbis and Distel 2010; Chen et al. 2015), and our
879 results point in the direction of multiple basic metabolic pathways converging on excess Ac-
880 CoA production for membrane biosynthesis. Combined with gene expression profiles of
881 these genes, we hypothesize that excess Ac-CoA is being channeled into ergosterol and
882 fatty acid production during fruiting body development, as detailed below.
883   For this work we started from Ac-CoA related CDE orthogroups detected in the
884 transcriptomes of the examined species and developmental stages, which belonged to
885 several pathways. We reasoned that if there is an increased demand for Ac-CoA at certain
886 developmental stages of fruiting bodies, then this should be reflected in the regulation of Ac-
887 CoA-producing pathways. Thus, we annotated the TCA cycle, the glyoxal cycle, the fatty
888 acid beta-oxidation, ethanol utilization, glycolytic as well as pyruvate decarboxylation
889 pathways of *C. cinerea*, based on protein orthology to corresponding pathways of *S.*
890 *cerevisiae* (Fig. 5, Supplementary Fig. 3, Table 3). These led to a model we put forth on Fig.
891 5, with the additional note that it reflects one possible synthesis of the observations into a
892 mechanistic model compatible with what we know about fruiting body development, but that
893 other interpretation may also be viable.
894   First of all, we found that oxaloacetase (oxaloacetate lyase) genes were
895 developmentally expressed in 11 species (FC>4, *C. cinerea* 499734). Oxaloacetases

896 produce oxalate and acetate from oxaloacetate, which is an intermediate of both the TCA
897 and the Glyoxylate cycles. In *S. cerevisiae* acetate is converted to Ac-CoA by acetyl-CoA
898 synthases (Acs1), orthologs of which were developmentally regulated in 11 and 4 species at
899 fold change of 2 and 4, respectively (represented by *C. cinerea* 500719). We also found a
900 CDE orthogroup comprising putative orthologs of the *S. cerevisiae* Ac-CoA hydrolase Ach1
901 (represented by *C. cinerea* 442787, FC>2/4: 7/5). Ach1 is a relatively poorly known gene,
902 which was recently shown to be responsible for the conversion of Ac-CoA to acetate, which
903 can then be easily transferred from the mitochondrion to the cytoplasm(Chen et al. 2015).
904 Cytoplasmic acetate is then converted to cytoplasmic Ac-CoA, a starting material for lipid
905 synthesis, suggesting that Ach1 mediated Ac-CoA supply for lipid synthesis. Remarkably,
906 Ach1 orthologs are present in only 8 species and completely missing in *A. bisporus* (missing
907 even in telomere-to-telomere assemblies(ASM et al. 2020)), *M. kentingensis, Ph.*
908 *chrysosporium, L. tigrinus, Pt. gracilis.* This patchiness might indicate that the role of these
909 genes is dispensable and probably others can take over their roles.
910   Acetate is also an intermediate of the ethanol utilization pathway, in which two
911 enzymes form a linear pathway that terminates in the production of Acetyl-CoA(M et al.
912 2003). Aldehyde dehydrogenases orthologous to AldA of *A. nidulans* and Ald4 of *S.*
913 *cerevisiae* formed a CDE orthogroup (*C. cinerea* protein ID: 500663, 9/7); the encoded
914 enzymes also contribute to acetate production and, in *C. cinerea*, showed peak expression
915 in young fruiting body caps. Ald4/AldA converts the toxic compound acetaldehyde to
916 acetate(B et al. 2001). Although the ethanol utilization pathway is mostly discussed in the
917 context of extracellular ethanol (a nonfermentable carbon source) uptake and degradation,
918 as well as anaerobic fermentation, acetaldehyde can also be converted to ethanol (Fig. 5), if
919 it is present in excess amounts in the cells. This may explain the developmental regulation of
920 orthologs of *S. cerevisiae* Adh3 and *A. nidulans* AlcA/AlcC (represented by *C. cinerea*
921 500663), which were developmentally expressed in 11/7 species (FC>2/4, Table 3).
922 Enzymes of the alcohol utilization pathway were recently detected in proteomics data of
923 fruiting bodies of *Guyanagaster necrorhiza*, where their presence was interpreted as
924 evidence for anaerobic fermentation within the fruiting body, as part of an intriguing
925 mutualism with N_2 fixing bacteria(Koch et al. 2021).
926   The last step of glycolysis is catalyzed by the pyruvate decarboxylase Pdc1 in *S.*
927 *cerevisiae,* which converts pyruvate to acetaldehyde. Pdc1 generates cytoplasmic Ac-CoA,
928 which is essential for the biosynthesis of lipids(Chen et al. 2015). Pdc1 orthologs
929 (represented by *C. cinerea* 422402) were developmentally expressed in 11/8 species
930 (FC>2/4), whereas genes encoding other enzymes in glycolysis showed much smaller
931 dynamics (Supplementary Fig. 3). Together, these observations suggest a widespread
932 upregulation of acetaldehyde and from that either acetate or ethanol producing enzyme
933 genes in fruiting bodies.
934   Upstream of oxaloacetases, enzymes responsible for oxaloacetate production in the
935 TCA (yeast Mdh1, *C. cinerea* 500663, 11/3) and glyoxylate cycles (yeast Mdh2, *C. cinerea*
936 449845, 9/3) were also quite widely developmentally regulated. In the glyoxylate cycle we
937 found orthologs of *S. cerevisiae* Mls1 (malate synthase, *C. cinerea* 530292) and Icl1
938 (isocitrate lyase, *C. cinerea* 495730) to form CDE orthogroups developmentally regulated in
939 12/11 and 12/7 species (FC>2/4), respectively. This suggests that the glyoxylate cycle is
940 strongly induced in fruiting bodies. On the other hand, members of the TCA cycle showed
941 lower developmental dynamics (Fig. 5).
942   What happens to the oxalate that is produced by oxaloacetases? It is possible that
943 the resulting oxalate is a waste product, but it may also be used somehow by the fungus,

944 e.g. as a developmental signal molecule(Palmieri et al. 2019) or as an electron donor, as
945 has been observed in wood-decay(Hastrup et al. 2012; Zhu et al. 2016; Grąz et al. 2017),
946 where it acts as an electron donor for oxidative enzymes. One hypothesis for the role of
947 oxalate is that oxidative enzymes, which might participate in the modification of the fungal
948 cell wall during development (see above), utilize it as an electron donor, as do enzymes
949 involved in wood-decay. On the other hand, if oxalate is a by-product, excess amounts may
950 need to be broken down actively. We found evidence for the upregulation of oxalate
951 catabolism in the compared species. The two oxalate degradation pathway in fungi
952 comprises oxalate decarboxylase, which converts oxalate to formate and CO_2 and formate
953 dehydrogenase, which breaks formate down to CO_2(Mäkelä et al. 2014). We detected two
954 CDE orthogroups of oxalate decarboxylases (*C. cinerea* protein ID: 361522, 8/6,
955 Schco3_2751877, 7/6) and one of formate dehydrogenases (*C. cinerea* protein ID: 452378,
956 7/6, orthologous to Fdh1 of *S. cerevisiae*)(Table 3), which were upregulated in fruiting bodies
957 widely, suggesting that fruiting bodies utilize enzymatic mechanisms for the neutralization of
958 oxalate. An alternative route of oxalate degradation in *S. cerevisiae* is catalyzed by PCS60,
959 an oxalyl-CoA synthetase(Foster and Nakata 2014). Orthologs of this gene were found in
960 only a subset of species (represented by *C. cinerea* 474928), but were developmentally
961 regulated in most of them. In addition, a CDE orthogroup of formate transporters,
962 orthologous to the *Postia placenta* gene reported in Martinez et al(Martinez et al. 2009b),
963 was developmentally expressed in 8/5 species (FC>2/4, represented by Schco3_2738153,
964 missing in *C. cinerea*).
965 　　　　Building on the evidence for intense Ac-CoA production, we annotated and analyzed
966 the Coenzyme-A producing pathway as well as two other sources of Ac-CoA, the fatty acid
967 beta-oxidation pathway and the cellular cycle for pyruvate decarboxylation to Ac-CoA. These
968 pathways were reconstructed and annotated based on corresponding pathways in *S.
969 cerevisiae*(JM et al. 2012). Members of these pathways did not show remarkable
970 developmental dynamics (Table 3).
971 　　　　Several genes connected to acetate metabolism and transport also formed CDE
972 orthogroups. Orthologs of *S. cerevisiae* Ady2, an acetate transporter(S et al. 2004), are
973 widely developmentally regulated (represented by *C. cinerea* 441597, 7/6), and were
974 strongly induced in young fruiting body caps of *C. cinerea*. A CDE orthogroup of putative
975 monocarboxylate (lactate, acetate, succinate, etc.) transporters (*C. cinerea* protein ID:
976 375404 [7/5])(Table 3) orthologous to *S. cerevisiae* Jen1(M et al. 1999) were also highly
977 induced in YFB-caps in *C. cinerea*. We also identified putative orthologs of *S. cerevisiae*
978 Yat1 (represented by *C. cinerea* 443703, 10/5), a carnitine acetyltransferase that shuttles
979 Ac-CoA across the mitochondrial membrane. A CDE orthogroup of aquaglyceroporins
980 orthologous to *S. cerevisiae* Fps1, which is involved in the uptake of acetate (*C. cinerea*
981 protein ID: 373141 7/6), were developmentally regulated in 7/6 species. This gene encodes
982 a protein that has been associated with either glycerol influx/efflux(Luyten et al. 1995) or
983 acetate uptake(Mollapour and Piper 2007; Watcharawipas et al. 2018), which leaves some
984 uncertainty on which role it fulfills in fruiting bodies. Orthologues of *S. cerevisiae* Sym1 also
985 formed a CDE orthogroup, although only at a fold change cutoff of 2 (*C. cinerea* protein ID:
986 147126, 9/3) (Table 3). This gene is said to be involved in ethanol utilization and stress
987 response, but mechanistic details are not known(Reinhold et al. 2012; Gilberti et al. 2018).
988 Similarly, orthologs of yeast Sfc1, a succinate/fumarate antiporter that transports C4
989 succinate (which is produced from acetate(Bojunga et al. 1998)), to the mitochondria, are
990 developmentally regulated in several species (represented by *C. cinerea* 374148, 12/7). The
991 Sfc1 ortholog is also strongly induced late in the development of *C. neoformans*(Liu et al.

992   2018). Finally, a CDE orthogroup of putative malate symporters orthologous to *Sch. pombe*
993   Mae1, which is involved in the uptake of extracellular malic acid was detected as
994   developmentally regulated in 9/5 species (FC>2/4, represented by *C. cinerea* 534888, Table
995   3). Whether these genes are related to the above discussed observation of acetate/Ac-CoA
996   related gene upregulation, or how cell surface transporters may be related remains to be
997   determined. The induction of these genes does not happen in the same or similar
998   developmental stage in all species (although there is consistency within species, see the
999   upregulation of several genes in YFB-caps of *C. cinerea*), nevertheless, their induction
1000   suggests differential acetate concentrations and an important role for acetate during in
1001   fruiting body development.
1002 CO_2 produced by the TCA cycle may be fixed into oxaloacetate by the conversion of
1003 CO_2 to hydrogencarbonate by carbonic anhydrases, then conversion of HCO_3^- and pyruvate
1004   into oxaloacetate by pyruvate carboxylases(Elleuche and Pöggeler 2010) (Pyc1 in *S.*
1005   *cerevisiae*). We found that several carbonic anhydrases (2-9 genes in Agaricomycetes
1006   genomes) are developmentally regulated in mushroom forming fungi and they form at least
1007   one CDE orthogroup (represented by *C. cinerea* 450047)(Table 3). *C. cinerea* 450047
1008   shows an upregulation in young fruiting bodies, coincident with the induction of Ac-CoA
1009   producing enzymes. This observation raises the possibility that CO_2 produced by the TCA
1010   cycle in fruiting bodies may be fixed into oxaloacetate, which can further be converted to Ac-
1011   CoA (Fig. 5). Of note, carbonic anhydrases are involved in the regulation of sexual
1012   development in the Ascomycota(Elleuche and Pöggeler 2010).
1013   Taken together, we observed developmental regulation of key enzymes in several
1014   pathways that seem to converge on increased acetyl-CoA production, either directly, or
1015   indirectly (through acetate or oxaloacetate). Several connected pathways, including oxalate
1016   degradation, the ethanol degradation pathway, the terminal reaction of glycolysis as well as
1017   evidence from the TCA and glyoxylate cycles were pointing in this direction. The expression
1018   of these genes tended to be upregulated late during development and showed good
1019   consistency within, but not necessarily across, species. A possible interpretation of these
1020   data is that increased Ac-CoA production is needed for growth by cell expansion late in
1021   development, as a starting material for lipid and sterol biosynthesis. This is underpinned by
1022   the fact that biosynthetic pathways of ergosterol and other membrane components are also
1023   upregulated during late developmental stages (e.g. the young fruiting body stage in *C.*
1024   *cinerea*), probably for membrane assembly needed for rapid cell growth. This interpretation
1025   would be consistent with the two-phased development of several mushroom-forming
1026   species, which consists of a first stage of cell division and differentiation and a second,
1027   during which cell numbers hardly change but their volumes increase considerably via
1028   Turgor-mediated expansion. Such a reprogramming of the fungus's basic metabolism from
1029   using Ac-CoA for energy production (when citrate is in the mitochondrion) to using it for lipid
1030   metabolism (when citrate is in the cytoplasm) seems particularly well-suited for fruiting body
1031   formation, which requires tight regulation of lipid metabolism. It should be mentioned that Ac-
1032   CoA is also required for melanin production(Lee et al. 2019), although it is unlikely to be the
1033   driving force of our observation, because pigment production is not conserved across the
1034   examined species. A previously reported reprogramming of the glyoxylate cycle in
1035   *Fomitopsis palustris* for the production of oxalate(Munir et al. 2001) seems related, however,
1036   in that case, the main product in demand was hypothesized to be oxalate that facilitates
1037   wood-decay, whereas in our case we hypothesize the product in demand is acetate and
1038   finally Ac-CoA. Both variants of the metabolic pathways nevertheless pass through
1039   oxaloacetate(Munir et al. 2001). The excess Ac-CoA production may rely on, or be

1040   connected to carbohydrate reserves that are deposited in the subhymenial part of the cap of
1041   the mushroom(Ji and Moore 1993; Muraguchi et al. 2015) during primordium development.
1042   However, there may be alternative interpretations and the topic is certainly of interest for
1043   detailed, further research, that integrates more functional data beyond gene expression
1044   observations.
1045

4.3. Lipid metabolism

1046

1047   Lipid metabolism is pivotal to very basic organismal processes such as growth,
1048   differentiation, cell division, energy storage and cell membrane composition, to name a few.
1049   Therefore, in depth understanding of gene expression changes associated with lipid
1050   metabolism, catabolism and transport can be expected to provide novel insights into fruiting
1051   body development. Indeed, our meta-analysis of Agaricomycete transcriptomes revealed
1052   several CDE orthogroups related to lipid metabolism. We discuss these below,
1053   complemented with annotations of major related pathways (but no attempt is made to
1054   comprehensively annotate all pathways) and processes. We base our annotations on data
1055   from well-studied model organisms, such as *S. cerevisiae, A. nidulans* and *Sch. pombe*, with
1056   orthology relationships to Agaricomycetes genes established on the basis of 1-to-1
1057   reciprocal best Blast hits.

4.3.1. Yeast beta oxidation

1058

1059   We reconstructed the beta-oxidation pathway (Table 4) in *C. cinerea* based on the yeast
1060   beta-oxidation pathway(van Roermund et al. 2003) (Fig. 5). The expression of genes
1061   comprising the beta-oxidation pathway in general does not appear to be widely dynamic in
1062   fruiting bodies. We found orthologs of yeast CTA1, a catalase A, to form a CDE orthogroup.
1063   However, this catalase in yeast is only a marginal component of the beta-oxidation pathway,
1064   and may be involved in a wide range of other functions (e.g. signaling). The more
1065   widespread developmental expression of ACS1 orthologs is remarkable (11/4 species at
1066   FC=2/4), for a possible connection with sterol biosynthesis (see above). ACS1 produces
1067   Acetyl-CoA, which is the starting point for ergosterol and membrane lipid biosynthesis.

4.3.2. Ergosterol biosynthesis

1068

1069   We reconstructed the ergosterol biosynthesis pathway based on orthology to known
1070   pathway member genes in *S. cerevisiae*(JM et al. 2012) (Table 5). ERG pathway genes of
1071   Agaricomycetes are generally higher expressed in fruiting bodies than in vegetative mycelia
1072   (VM/P1>1 in 20 out of 21 genes in *C. cinerea*), with expression peaking in young fruiting
1073   bodies of *C. cinerea* (Fig. 6, Table 5). Expression peaks at similar stages in other species
1074   too, in primordium 3/young fruiting body in *P. ostreatus* and young fruiting bodies/mature
1075   fruiting bodies stages in *A. ostoyae* (Supplementary Fig. 4). Similar pictures were obtained
1076   for other species. It should be noted that although the ergosterol biosynthesis pathway
1077   shows clear expression trends, the dynamics of expression is relatively low, mostly between
1078   2<FC<4. Therefore, ergosterol biosynthesis genes mostly do not form CDE orthogroups,
1079   nevertheless, the expression patterns are distinctive so they warrant discussion here.
1080   In these species expression peaks seem to coincide with intense growth by cell
1081   expansion in fruiting bodies. Above we showed that mitotic, ribosomal and histone gene
1082   expression level off in late primordium stages (P2 in *C. cinerea*, see Fig. 3), after which

1083   growth by cell expansion takes place. This might create an increased demand for membrane
1084   constituents during rapid cell expansion/growth by turgor, which is what we might see in the
1085   expression patterns of genes in the ergosterol biosynthesis pathway (Fig. 6, Supplementary
1086   Fig. 4). This hypothesis would also explain why there is no clear peak in *C. neoformans* and
1087   *Pt. gracilis*, where sudden growth by cell expansion is lacking.
1088   Similarly, a homolog of the Sterol-Regulatory Element Binding Proteins (SREBP(CM
1089   and PJ 2010)), similar to the *S. cerevisiae* transcription factor HMS1 shows a very similar
1090   expression pattern: in *C. cinerea* (*C. cinerea* protein ID: 488426) expression peak in YFB-S
1091   and YFB-C (Fig. 6), whereas in *P. ostreatus* it peaks in mature fruiting body tissues
1092   (PleosPC15_2_174910). This suggests, based on expression data, that these putative
1093   SREBPs might be regulating ergosterol biosynthesis genes also in the Agaricomycetes.
1094   A connection with the above-mentioned Ac-CoA producing basic metabolic
1095   pathways, where certain, but not all, components were found widely upregulated, is possible
1096   here. These pathways produce Acetyl-CoA, which is the starting point of ergosterol
1097   biosynthesis. This raises the possibility that the upregulation of the ethanol utilization
1098   pathway components (see above, Fig. 5) and certain components of the glyoxylate cycle
1099   reflect increased Ac-CoA production which is required as input to ergosterol biosynthesis
1100   and eventually membrane assembly. A competing hypothesis was put forth in *P.*
1101   *microcarpus*, where upregulation of glyoxylate shunt genes was observed and suggested
1102   that it underlies the production of storage materials for spores(Pereira et al. 2017). Using our
1103   more resolved transcriptome data and based on the observation of ergosterol pathway
1104   expression dynamics, we propose that the connection to the glyoxylate shunt might
1105   represent a link to membrane constituent synthesis, although more data would be needed to
1106   verify this hypothesis.
1107   The upregulation of the ergosterol synthesis pathway was observed in *F. velutipes*,
1108   where most ergosterol biosynthesis genes were upregulated in the young fruiting body
1109   stage(Wang et al. 2019) (approximately in agreement with our definition of young fruiting
1110   bodies) and showing intense growth. Sterol metabolism genes were also found to be more
1111   abundant in fruiting bodies of *H. erinaceus* compared to vegetative mycelia(Zeng et al.
1112   2018). It was reported that orthologs of the lanosterol-alpha-demethylase Erg11 of *S.*
1113   *cerevisiae*, a component of the ergosterol biosynthesis pathway (corresponding *C. cinerea*
1114   ortholog: 397292), was upregulated in fruiting bodies of *Antrodia cinnamomea*(Lu et al.
1115   2014) and *P. ostreatu*s(Sunagawa and Magae 2005). This is consistent with the
1116   observations made in this study.
1117   We also checked the sphingolipid biosynthesis pathway based on orthology to
1118   pathway members in *S. cerevisiae*. Sphingolipids, along with sterols are important in
1119   membrane rafts and microdomains and form key components of fungal cell membranes.
1120   Although some yeast genes did not have clear orthologs in Agaricomycetes, genes involved
1121   in sphingolipid biosynthesis showed a similar expression profile in *C. cinerea* (Fig. 6, Table
1122   5). This may underscore our hypothesis on the link between growth by cell expansion and
1123   membrane assembly.
1124   A characteristic CDE orthogroup of putative C14-sterol reductase genes was
1125   developmentally expressed in 12/7 species (represented by *C. cinerea* 539004)(Table 5, Fig.
1126   6). These proteins are not part of the ergosterol biosynthesis pathway, but show a high
1127   similarity to *A. nidulans* and *C. albicans* membrane phospholipid metabolism proteins
1128   AN2040 and Erg24, respectively, which are involved in ergosterol metabolism. Genes in this
1129   orthogroup show peak expression in late development, coincident with rapid expansion of
1130   fruiting bodies. In several species they were also upregulated in primordia relative to

1131 vegetative mycelium samples. These expression patterns resemble that of ergosterol
1132 biosynthesis genes, and suggest that this orthogroup may be linked to ergosterol
1133 metabolism.

4.3.3. Sterol transport

1135 We detected several CDE orthogroups that were annotated as related to ergosterol transport
1136 and showed similar upregulation in late development as ergosterol biosynthesis genes did.
1137 We therefore inventoried sterol transport related genes of the families Niemann-Pick type C
1138 protein family (*S. cerevisiae* Npc2), the yeast Ncr1 family, the nonspecific sterol transport
1139 protein (Scp2) family, StAR-related lipid-transfer (START) proteins as well as members of
1140 the Oxysterol Binding Protein Homologue (OSH) protein family(Schulz and Prinz 2007).
1141   Of these, the Ncr1, Npc2, Scp2 and START gene families are single-copy families in
1142 mushroom-forming fungi, whereas the OSH family is represented by 5 members in all
1143 mushroom-forming fungi (except *S. commune* which has 6, Table 6). Npc2 (ortholog *C.*
1144 *cinerea* 475807), Scp2 (ortholog *C. cinerea* 478741) and START proteins as well as one
1145 member of the OSH family were (*C. cinerea* protein ID: 427232)(Table 6) upregulated during
1146 the second half of development, at or after the young fruiting body stage. This is similar to
1147 the expression patterns seen in ergosterol biosynthesis genes. One member of the OSH
1148 family orthogroup (*C. cinerea* protein ID: 378276) showed a clearly stipe-specific expression,
1149 with peaks in stipes of young fruiting bodies or fruiting bodies of *C. cinerea, A. ostoyae, M.*
1150 *kentingensis, A. bisporus and P. ostreatus,* albeit mostly with low fold change values
1151 (2<FC<4). Interestingly, the corresponding gene was cap-upregulated in *L. bicolor*
1152 (Lacbi2_456536), whereas in simpler species (*S. commune, A. ampla*), it showed diverse
1153 expression peaks. Ncr1 orthologs (represented by *C. cinerea* 494709) showed consistently
1154 higher expression in fruiting bodies than in vegetative mycelia. Fold changes were generally
1155 low in these gene families, but nevertheless the patterns are phylogenetically very
1156 consistent.
1157   These expression patterns resemble those of ergosterol biosynthesis genes, which
1158 also showed upregulation in mid- to late development, coincident with cell expansion and
1159 growth. This suggests that ergosterol transport, in addition to biosynthesis, is an important
1160 process in the second half of the development of mushroom fruiting bodies. Like synthesis,
1161 transport of sterols might be required to fulfill the needs of rapid cell expansion, which
1162 obviously coincides with cell- and membrane surface expansion too.
1163   Although marginally related, we mention here the CAP domain/Pry1 protein family,
1164 which includes known sterol-binding proteins. The family has been associated with diverse
1165 functionalities, including cell adhesion, pathogenicity (pathogenicity-related PR proteins
1166 belong here), morphogenesis, endocrine and paracrine functions, among others(GM et al.
1167 2008; Schneiter and Pietro 2013). This protein family includes *S. cerevisiae* Pry1, a lipid and
1168 sterol binding protein involved in sterol export(Darwiche et al. 2017). To our best knowledge,
1169 there are no previous reports of this family in fruiting body development, whereas, their role
1170 in morphogenesis in mammals is well-established(GM et al. 2008). We detected, on average
1171 2-5 copies of CAP proteins in the Agaricomycetes, with expansions up to 9 in *Pt. gracilis, L.*
1172 *bicolor* and *A. ostoyae* as well as a CDE orthogroup of Pry1-related CAP-domain proteins
1173 (represented by *C. cinerea* 470387, FC2/4: 7/6, Table 6, Fig. 6). Members of this orthogroup
1174 showed peak expression late in development, at or after the young fruiting body stage in
1175 most species. The sterol transporting ability and expression patterns suggest that this family
1176 may have a role in sterol transport during the second half of development in Agaricomycetes

Running head: fruiting body genomics

1177   fruiting bodies. It should be noted that neither Polyporales species (*Ph. chrysosporium* and
1178   *L. tigrinus*) had developmentally regulated genes in this family, indicating that their role, if
1179   any, may not be universal.

1180   ### 4.3.4. Phospholipid and fatty acid biosynthesis

1181   The phospholipid and fatty acid biosynthesis pathways are conserved in Agaricomycetes,
1182   with most genes showing clear 1-to-1 orthologs to described pathway members of *S.*
1183   *cerevisiae (*Table 7). Because active cell growth and expansion requires an excess amount
1184   of membrane components (ergosterol, phospholipids), we examined pathways involved in
1185   membrane phospholipid and triacylglycerol synthesis. We reconstructed these pathways
1186   based on well-known reaction steps in *S. cerevisiae* and *Yarrowia lipolytica*(Carman and
1187   Han 2011; Fakas 2017). The first half of the pathway, which starts from glycerol-3-phosphate
1188   and leads to the production of phosphatidic acid, shows upregulation in young and mature
1189   fruiting bodies of *C. cinerea* and *A. ostoyae* (Fig. 7). Phosphatidic acid sits in a branching
1190   point of the pathway, with one branch leading to membrane phospholipids (CDP-DAG
1191   pathway), whereas the other leads to triacylglycerol (TAG), a major storage material. The
1192   CDP-DAG pathway shows a general upregulation in the second half of development (young
1193   and mature fruiting bodies) in *C. cinerea, A. ostoyae, M. kentingensis, A. bisporus*
1194   (Supplementary Fig. 5). These patterns are consistent with increased membrane lipid
1195   biosynthesis in these stages, possibly serving the needs of increasing cell volumes during
1196   rapid growth. On the other hand, TAG pathway members appear upregulated somewhat
1197   later, mostly in mature fruiting bodies in most species (Fig. 7, Supplementary Fig. 5), which
1198   coincides with spore formation and could be related to storage material synthesis in spores.
1199   In *P. ostreatus*, both the CDP-DAG and TAG pathways show remarkably uniform
1200   upregulation in primordium stages (Fig. 7), which is quite different from the pattern seen in
1201   other species. This pattern in *P. ostreatus* is also observable in fatty acid biosynthesis
1202   pathways (see below).
1203   Similar to the CDP-DAG and TAG pathways, fatty acid biosynthesis (Table 7) shows
1204   a signal for upregulation in young fruiting body tissues, with *C. cinerea* orthologs of *S.*
1205   *cerevisiae* Acc1, Fas2, Elo2 and Faa1 showing peak expression in the YFB stage. Similar
1206   patterns exist in *A. ostoyae, M. kentingensis* and to some extent in *A. bisporus* (Fig. 7). In *P.*
1207   *ostreatus*, fatty acid biosynthesis genes are co-expressed with the other phospholipid
1208   biosynthesis genes, showing an upregulation in primordia.
1209   Both phospholipid synthesis and fatty acid biosynthesis require Acetyl-CoA as a
1210   starting point. For the former, it is needed for acylation reactions in the conversion of
1211   lysophosphatidic acid to phosphatidic acid (last element of the shared part of the pathway)
1212   whereas in the latter, Ac-CoA is the starting point of fatty acid synthesis(Fakas 2017). This
1213   provides another link with the dynamics of Ac-CoA biosynthesis genes noted above. As in
1214   the case of ergosterol biosynthesis pathway members, phospholipid and fatty acid
1215   metabolism genes showed low expression dynamics (and hence did not form CDE
1216   orthogroups), but their expression patterns were consistent across stages and species.
1217   The expression of mitochondrial membrane components (cardiolipin and
1218   phosphatidylglycerol) is also peaking in young fruiting bodies, mostly in stipe, but not very
1219   characteristic (Fig. 7).

1220 ### 4.3.5. Linoleic acid producing fatty acid desaturases

1221 Several CDE orthogroups of fatty acid desaturases (FAD) were detected among conserved
1222 developmentally expressed genes. Members of these orthogroups show high similarity to *C.*
1223 *albicans* Fad2 and Fad3 and *A. nidulans* OdeA, which are involved in the synthesis of alpha-
1224 linoleic acid. Linoleic acid is a major membrane component in fungi, which, as an
1225 unsaturated fatty acid, regulates membrane fluidity. It has also been speculated to be the
1226 starting point for the biosynthesis of volatiles, such as 1-octen-3-ol(A et al. 2020). Linoleic
1227 acid showed increased proportions in fruiting bodies and reproductive structures in general
1228 in both the Asco- and Basidiomycota(SHAW 1967; Goodrich-Tanrikulu et al. 1998; H and S
1229 2003; Gessler et al. 2017; Song et al. 2018a). Linoleic acid is also a precursor of oxylipins,
1230 key developmental signaling molecules that are actively produced by reproductive
1231 cells(Combet et al. 2006; Gessler et al. 2017; Orban et al. 2021). Accordingly, in the
1232 Ascomycota, several fatty acid desaturase gene mutations were reported to asexual/sexual
1233 defects(Pöggeler et al. 2006b). The higher proportion of linoleic acid in fruiting bodies of
1234 Agaricomycetes was already noted in 1967(SHAW 1967) with several similar reports(H and
1235 S 2003; Song et al. 2018a) later. The proportion of unsaturated fatty acid (which include
1236 linoleic acid) increases during fruiting body formation(H and S 2003) in *L. edodes*. Three
1237 fatty acid desaturases, two in *L. edodes* (Le.Fad1 and Le.Fad2(H and S 2005)) and one in
1238 *C. cinerea* (*Cc.odeA*(H and S 2003, 2005; S et al. 2007b)) have been shown to be capable
1239 of producing linoleic acid. Fad genes were found to be differentially expressed in fruiting
1240 bodies of *A. bisporus* previously(Morin et al. 2012).
1241 We found 7-16 fatty acid desaturase genes in the examined Agaricomycetes, many
1242 of which were developmentally regulated, although clear orthology of these genes to
1243 experimentally characterized Ascomycota genes is missing. Each species had at least 2-3
1244 FAD encoding genes upregulated in primordia relative to vegetative mycelium, suggesting
1245 that their functions are key to the initiation of fruiting body development. FAD genes formed
1246 five CDE orthogroups (Table 8). One of these (*C. cinerea* protein ID: 363743) was FB-init in
1247 most species (*C. cinerea, A. ostoyae, A. ampla, M. kentingensis, P. ostreatus, S. commune,*
1248 *C. aegerita, L. bicolor*), showed high expression in primordium stages, then expression
1249 levels dropped significantly in later developmental stages. The CDE orthogroup containing
1250 Le.FAD1 (Lenedo1_1050661) was upregulated in primordia of most species relative to
1251 mycelium samples (*C. aegerita, A. ampla, S. commune, L. edodes. L. bicolor, L. tigrinus, M.*
1252 *kentingensis,* but not *A. ostoyae, P. ostreatus* and *A. bisporus,* ortholog missing in *C.*
1253 *cinerea)*, although only slightly (fold change = 1.5-2x, except in *L. edodes* and *Pt. gracilis*
1254 which showed >4-fold upregulation). The orthogroup encompassing *Cc.odeA* (*C. cinerea*
1255 protein ID: 422393) and Le.Fad2 (orthogroup represented by *S. commune* 2511002) was
1256 upregulated in primordia relative to vegetative mycelia of several species (*A. ampla, C.*
1257 *aegerita, S. commune, C. cinerea, L. edodes, L. tigrinus* and *P. ostreatus,* but not in *A.*
1258 *ostoyae, M. kentingensis, Pt. gracilis* and *A. bisporus*). Our expression data are consistent
1259 with previous reports of transcripts/protein abundance in case of both Le.FAD1 and Le.FAD2
1260 in *L. edodes*(H and S 2003, 2005). The other two FAD orthogroups showed less
1261 conservation in expression (*C. cinerea* protein ID: 471478, 422976, Fig. 8), including peaks
1262 in later developmental stages, such as young fruiting body caps.
1263 The linoleic acid-producing ability of the proteins encoded by these genes suggests
1264 that the detected CDE orthogroups and expression dynamics relate to linoleic acid
1265 production. It follows from our observations of expression dynamics that linoleic acid
1266 production is upregulated in the primordia of several species. This is consistent with previous

1267 reports of higher linoleic and unsaturated fatty acid proportions in fruiting bodies of
1268 Agaricomycetes (see above). There may be at least three explanations for this observation,
1269 including (i) regulation of membrane fluidity in response to temperature changes, (ii) the
1270 same being genetically encoded in fruiting body development, or (iii) fulfilling the
1271 requirements of oxylipin production. We argue that hypothesis (i) is unlikely, however, we
1272 can't speculate on hypotheses (ii) and (iii).
1273   Regulation of membrane fluidity by increasing the proportion of unsaturated fatty
1274 acids is a common mechanism across organisms(H and S 2005). Therefore, a question
1275 arises whether the higher inferred proportion of linoleic acid and corresponding changes in
1276 gene expression are genetically coded traits of fruiting bodies or simply a consequence of
1277 lower temperature required by several species for fruiting. At least for the transcriptomes we
1278 produced(Sipos et al. 2017a; Almási et al. 2019; Krizsán et al. 2019) we know that
1279 vegetative mycelium samples were harvested at the same temperature as fruiting body
1280 samples for all species, which rules out the possibility that higher linoleic acid proportion is
1281 simply a response to lower fruiting temperatures. Rather, this suggests that higher linoleic
1282 acid concentration is a genetically encoded trait in fruiting bodies. Similar conclusions were
1283 reached in the context of unsaturated fatty acids in *L. edodes*(H and S 2003). From an
1284 evolutionary point of view, such a genetic adaptation could go back to the exposed nature of
1285 fruiting bodies; in the natural environments (soil, wood) the vegetative mycelium is in more
1286 stable conditions than fruiting bodies are, which might therefore need to be adapted to colder
1287 temperatures by increasing the proportion of unsaturated fatty acids in fruiting body tissues.
1288 At the same time, due to their large surfaces and continuous evaporation, fruiting bodies
1289 cool themselves (on average ~2.5C colder than their environments(Dressaire et al. 2016)),
1290 which may explain why genetic encoding of higher linoleic acid proportions is beneficial for
1291 their development. It should be noted that linoleic acid production is also required for the
1292 synthesis of several oxylipin species(Combet et al. 2006), which might be involved in cell-to-
1293 cell communication.

1294 ### 4.3.6. Other potentially membrane lipid related genes

1295 We detected several CDE orthogroups which are not parts of the above-mentioned
1296 pathways, yet might be related to lipid metabolism, membrane organization or assembly. In
1297 many cases the functions of these orthogroups is not clear, but their widespread
1298 developmental expression suggests they might be interesting players in fruiting body
1299 development. Therefore, we discuss them below, with details on potential functions where
1300 available.
1301   **Glycerophosphodiester phosphodiesterases** - A CDE orthogroup of
1302 glycerophosphodiester phosphodiesterases (represented by *C. cinerea* 20997)(Table 9) was
1303 developmentally expressed in 11 species (FC>4), which makes it one of the most widely
1304 developmentally expressed families. However, it is hard to make functional inferences as
1305 these proteins show only limited similarity to experimentally characterized fungal proteins
1306 (highest to Pgc1 of *S. cerevisiae*). *S. cerevisiae* Pgc1 (Phosphatidylglycerol phospholipase
1307 C) negatively regulates phosphatidylglycerol degradation, leading to increased
1308 concentrations in deletion mutants(Šimočková et al. 2008). The glycerophosphodiester
1309 phosphodiesterase family (IPR030395), is represented by three copies in most examined
1310 Agaricomycetes (some species have 4), of which only one is developmentally expressed in
1311 all species. These form a CDE orthogroup in which most genes are FB-init (*C. aegerita, A.*
1312 *ostoyae, A. ampla L. bicolor, L. tigrinus, P. ostreatus, S. commune),* whereas expression had

1313   different dynamics in *C. cinerea, L. edodes, M. kentingensis, Ph. chrysosporium*). These

1314   expression patterns suggest that the role of this orthogroup, although unknown at the

1315   moment, may be key to the initiation of fruiting body formation.

1316   We noticed that the detected glycerophosphodiester phosphodiesterases showed

1317   strongly correlated expression with members of another CDE orthogroup (represented by *C.*

1318   *cinerea* 380149, Fig. 7) in six species (data not shown). This contains putative orthologs of

1319   *S. cerevisiae* Cpt1, a choline/ethanolamine phosphotransferase that catalyzes the last step

1320   (formation of phosphatidylcholine) of the CPD-choline (Kennedy) pathway in *S. cerevisiae*.

1321   The strongly correlated expression in the case of six species (Pearson r >0.8) suggests that

1322   the two genes are linked and possibly form a linear pathway. However, their role in the

1323   context of fruiting body formation requires further research.

1324   **Marvel protein family -** We also detected two CDE orthogroups (represented by *C.*

1325   *cinerea* 444998, 462849) (Table 9) of Marvel proteins showing low similarity to *A. nidulans*

1326   mrvA, *C. albicans* Mrv2 and *S. cerevisiae* Fhn1. The gene family seems to be generally

1327   poorly characterized. In *S. cerevisiae*, it may be involved in nonclassical protein secretion,

1328   might act as a sensor of sphingolipids or be related to membrane organization(M et al.

1329   2010). In metazoans, marvel proteins are related to sterol-rich membrane region

1330   positioning(Sánchez-Pulido et al. 2002). Members of the first orthogroup (*C. cinerea* protein

1331   ID: 444998) were FB-init in several species *(A. ostoyae, M. kentingensis, P. ostreatus, S.*

1332   *commune, L. edodes)*, suggesting that they fulfill key functions in fruiting body initiation. The

1333   second orthogroup (*C. cinerea* protein ID: 462849) showed less characteristic expression

1334   patterns, with upregulation mostly late in development in most species.

1335   **Sphingolipid C9-methyltransferases -** We found two CDE orthogroups of

1336   sphingolipid C9-methyltransferases (*C. cinerea* protein ID: 395241, 365330)(Table 9) that

1337   were FB-init in nearly all species. One of the orthogroups (*C. cinerea* protein ID: 395241)

1338   contains orthologs of Mts1 of *C. albicans,* which is involved in glucosylceramide

1339   biosynthesis*.* Glucosylceramides are glycosphingolipids that form structural components of

1340   the fungal cell membrane, with diverse roles (cell division, spore germination, pathogenicity,

1341   lipid rafts(Poeta et al. 2014)), although little mechanistic detail to date.

1342   **PAP2 enzyme family -** A CDE orthogroup of diacylglycerol pyrophosphate

1343   phosphatases (*C. cinerea* protein ID: 380219)(Table 9) was FB-init in most species in which

1344   the gene was present. The encoded proteins show high similarity (but not 1-to-1 orthology)

1345   to *A. nidulans* and *C. albicans* membrane phospholipid metabolism proteins AN1671 and

1346   Dpp3, respectively. The latter is required also for farnesol biosynthesis(Nickerson et al.

1347   2006). These genes belong to the broader *PAP2* family, which produce diacylglycerol and

1348   are key in the synthesis of phospholipids, triacylglycerol and the generation of signaling

1349   molecules with a lipid nature. The upregulation of these genes in fruiting bodies might be

1350   related to increased membrane material production associated with cell proliferation during

1351   early development.

1352   **Caleosins -** Caleosins are well-characterized in plants and indirect data indicate they

1353   may be involved in oxylipin signaling, lipid metabolism, reproduction(Rahman et al. 2018),

1354   though exact functional knowledge seems to be missing. In fungi, caleosins are involved in

1355   sporulation, pathogenicity and lipid storage(Y et al. 2015). A previous study found that the

1356   caleosin family is present in ~30% of fungal genomes(Rahman et al. 2018), whereas we

1357   found that it is present in most of the examined Agaricomycetes, mostly as a single-copy

1358   gene. Members of a detected caleosin CDE orthogroup (*C. cinerea* protein ID:

1359   376602)(Table 9) were FB-init in most species and consistently had peak expression late in

1360 development, which is compatible with presumed roles in fruiting body initiation and
1361 sporulation, respectively.

4.4. Storage carbohydrate metabolism

1363 Fungal colonies accumulate and mobilize various carbohydrates as reserve material and for
1364 energy storage. Previous research has revealed that there are very specific and tightly
1365 regulated accumulation and mobilization patterns of glycogen, trehalose and mannitol within
1366 fungal fruiting bodies(U et al. 2000). Storage carbohydrate metabolism and distributions in
1367 the mycelium and fruiting bodies have been studied in a number of economically important
1368 mushroom-forming species, including *F. velutipes*(Kitamoto et al. 2001)*, Pleurotus spp.*(Han
1369 et al. 2003; Zhou et al. 2016a; Zhu et al. 2019)*, Pisolithus microcarpus*(AN and MD 2010)*, A.
1370 bisporus*(WELLS et al. 1987; TM et al. 2008; Patyshakuliyeva et al. 2013)*, L. bicolor*(Deveau
1371 et al. 2008) and described to a high precision/resolution in *C. cinerea* in a series of papers
1372 by Moore et al(Kuhad et al. 1987; Ji and Moore 1993; Moore 2013), including links with
1373 cAMP levels (summarized by (U et al. 2000)). Briefly, these studies provided evidence on
1374 tightly regulated glycogen, trehalose and mannitol levels in mycelia and various tissues and
1375 developmental stages of fruiting bodies. They also revealed that the identity and quantities of
1376 major sugars in fruiting bodies differ from species to species; trehalose dominates in *L.
1377 bicolor*(Deveau et al. 2008) and *C. cinerea*(Kues 2000), mannitol in *A. bisporus*(Morton et al.
1378 1985) and *L. edodes*(Tan and Moore), and both present in similar quantities in *P.
1379 ostreatus*(Hong Jai-Sik;Kim 1988; Zhou et al. 2016a).
1380   More recently, genome sequences allowed the reconstruction of carbohydrate
1381 metabolism pathways based on gene orthology information to better studied model systems
1382 such as *S. cerevisiae*. Deveau et al found that most of the genes in known fungal pathways
1383 related to glycogen, trehalose and mannitol metabolism were found in the genome of the
1384 ectomycorrhizal *L. bicolor*(Deveau et al. 2008) and similar patterns can be expected in these
1385 very conserved pathways upon examination of other Agaricomycetes genomes.
1386 Transcriptomic studies further allowed previous biochemical observations to be interpreted in
1387 the light of gene expression patterns, although this has not yet been systematically
1388 performed in any species. In the following sections we review information on the metabolism
1389 of glycogen, trehalose and mannitol gleaned from transcriptomic studies of mushroom
1390 development. Many of these studies highlighted that shared patterns of gene expression
1391 related to storage carbohydrate metabolism exist among mushroom-forming species. For
1392 example, Merenyi et al showed that dynamic glycogen accumulation/breakdown is shared
1393 between *C. neoformans* basidium development and complex fruiting body morphogenesis,
1394 two extremes of Basidiomycota development along the complexity gradient(Merényi et al.
1395 2021). On the other hand, trehalose concentrations were found to react to heat shock in
1396 fruiting bodies of *Flammulina filiformis*(Liu et al. 2016). Our discussion hereafter is based on
1397 well-described pathways of storage carbohydrate metabolism in yeast(François and Parrou
1398 2001; JM et al. 2012).
1399 **Glycogen metabolism** - Glycogen production and mobilization takes place in various
1400 tissues and developmental stages and follows tight regulation that may differ from species to
1401 species (reviewed in (Ji and Moore 1993; Kues 2000; Xie et al. 2020), see also (Ceccaroli et
1402 al. 2011) for Ascomycota). In the Agaricomycetes, this is best known in *C. cinerea* and *A.
1403 bisporus,* whereas mechanistically glycogen metabolism is best known in *S.
1404 cerevisiae*(François and Parrou 2001), which can be used to reconstruct corresponding
1405 pathways in mushroom-forming fungi. Glycogen synthesis encompasses nucleation by

1406 glycogenins and elongation and branching by glycogen synthases. Glycogenins (orthologs of
1407 *S. cerevisiae* Glg1) are upregulated in young fruiting body gills and/or mature fruiting body
1408 gills of most compared species (Table 10), respectively. This likely corresponds to intense
1409 glycogen synthesis during basidiospore maturation(Kües 2000). Consistent with this,
1410 orthologs of yeast Gac1, a phosphatase that positively regulates the activity of glycogen
1411 synthases, is upregulated in gills and mature fruiting bodies of multiple species. Gac1 in *S.*
1412 *cerevisiae* regulates glycogen synthases together with Glc7. The latter has orthologs in
1413 mushroom-forming fungi, but these are not developmentally regulated. In *S. cerevisiae*, a
1414 number of other CBM21 domain proteins (Pig1, Pig2) also participate in the regulation of
1415 glycogen synthase activity, however, these have no clear orthologs in mushroom-forming
1416 fungi. On the other hand, the glycogen branching enzyme Glc3 orthologs (represented by *C.*
1417 *cinerea* 365699) show more diverse expression peaks, and orthologs are upregulated mostly
1418 in stipe tissues (in *C. cinerea, L. bicolor, P. ostreatus* and *A. ostoyae*) (Fig. 9, Supplementary
1419 Fig. 6), indicating that linear glycogen chain production is transcriptionally decoupled from
1420 the addition of branched side chains to the glycogen backbone.
1421   Genes that encode proteins upstream of glycogen synthesis, for example orthologs
1422 of the uridinephosphoglucose pyrophosphorylase Ugp1 (*C. cinerea* protein ID: 359312) and
1423 the phosphoglucomutase PGM1 (*C. cinerea* protein ID: 497782) of *S. cerevisiae*, are
1424 developmentally regulated in multiple species (Table 10). They show some overlap in
1425 expression patterns, in particular, a tendency for upregulation late in development, but their
1426 pattern of expression is quite unique and show lower expression fold changes.
1427   It should be noted that the glycogen synthase kinase 3 (GSK-3)(Chang et al. 2019a)
1428 gene in *C. cinerea* (*C. cinerea* protein ID: 362899), despite its name, it functionally not
1429 relevant to glycogen metabolism, it is an orthologue of *S. cerevisiae* Rim11, a pleiotropic
1430 kinase involved in cell cycle regulation.
1431   **Glycogen mobilization** happens through three primary genes in *S.*
1432 *cerevisiae*(François and Parrou 2001) - all these have orthologs in mushroom-forming fungi
1433 (Table 10). Orthologs of the yeast glycogen phosphorylase Gph1 (represented by *C. cinerea*
1434 495987) mostly show high expression in vegetative mycelia or early development, whereas
1435 those of the glycogen debranching enzyme Gdb1 are upregulated also in mature fruiting
1436 bodies in all species (Fig. 9). This probably indicates differential usage of phosphorolysis
1437 and debranching activities in different stages of development. Sga1 is a sporulation specific
1438 glucoamylase in *S. cerevisiae*. In our species orthologs (represented by *C. cinerea* 473268)
1439 of this gene do not show expression peaks in gills, the tissues in which spore development
1440 takes place. Rather, in *C. cinerea*, this gene is upregulated in young fruiting body cap
1441 tissues. How this upregulation corresponds to patterns of glycogen metabolism remains to
1442 be understood. Large-scale postmeiotic utilization of glycogen accumulated in subhymenial
1443 tissues was reported in *C. cinerea*(Kües 2000), however, subhymenial tissues were part of
1444 gill samples in previous RNA-Seq experiments, which excludes the possibility that Sga1
1445 orthologs were involved in that process. In other species, expression patterns were different,
1446 ranging from upregulation in mature fruiting bodies in *A. ampla*, to peak expression in
1447 vegetative mycelium (*P. ostreatus* and *M. kentingensis*). We also detected a CDE
1448 orthogroup of alpha-amylases (represented by *C. cinerea* 495249), which find *A. nidulans*
1449 AmyA as best hit and are probably involved in glycogen catabolism. In *C. cinerea*, this gene
1450 showed upregulation in primordia and peak expression in young fruiting body caps, similar to
1451 other genes related to glycogen mobilization.
1452   In addition to known members of the glycogen catabolism pathways, we identified
1453 two CBM21 domain containing CDE orthogroups that were developmentally regulated in

1454 11/7 and 11/6 species (*C. cinerea* protein ID: 544130 and 455149) (Table 10). In most
1455 species, this gene had the highest expression in vegetative mycelia, but showed significant
1456 expression dynamics also during fruiting body morphogenesis. This seems to be a
1457 Basidiomycota-specific orthogroup, with no significantly similar proteins in model
1458 Ascomycota. The CBM21 domain mostly occurs in starch-binding proteins (glucoamylase
1459 and α-amylase(Ashikari et al. 1986)) whereas in this orthogroup, the CBM21 domain occurs
1460 alone, providing no specific clues to function. Therefore, our placement of this CDE
1461 orthogroup under this chapter should be viewed tentatively until functional studies prove or
1462 disprove the role of the family in glycogen metabolism.
1463 Beyond these gene families, glycogen utilization patterns in fruiting bodies raise a
1464 number of exciting research avenues, such as the mode of transport within the fruiting body
1465 and the identity of transporters involved in that process.
1466 **Trehalose metabolism** - Out of the at least five pathways known to be involved in trehalose
1467 synthesis, two have been found in Agaricomycetes(Deveau et al. 2008). The first, canonical
1468 pathway comprises the action of a protein complex formed by four proteins in *S. cerevisiae*
1469 (Tps1 - *C. cinerea* 478544, Tps2 - 473004, Tsl1 and Tps3 - no ortholog(François and Parrou
1470 2001)). Of these, Tsl1 (*C. cinerea* protein ID: 503099) and Tps3 are paralogs that arose from
1471 a recent whole genome duplication and thus there is only one corresponding gene in
1472 filamentous fungi. The three genes showed widespread developmentally regulated
1473 expression in examined Agaricomycetes (Table 10), with upregulation mostly late in
1474 development with notable co-regulation between the three genes, as expected for members
1475 of a protein complex (Fig. 9).
1476 A second, noncanonical pathway involving trehalose phosphorylase (TP) exists in
1477 fungi and was detected in multiple mushroom-forming species(K et al. 1998; Eis and
1478 Nidetzky 1999; Wannet et al. 1999; Deveau et al. 2008; Thammahong et al. 2017).
1479 Trehalose phosphorylase gene formed a CDE orthogroup (*C. cinerea* protein ID: 540817) in
1480 the Agaricomycetes we examined(Merényi et al. 2021) and show upregulation in stipes and
1481 in late stages of development in most species (Table 10), although deviations from this
1482 pattern exist (e.g in *C. cinerea*). For example, the gene showed peak expression in
1483 primordium stages of *A. ampla, S. commune* and *M. kentingensis*(Almási et al. 2019;
1484 Krizsán et al. 2019; Ke et al. 2020b).
1485 For **catabolizing trehalose**, fungi exhibit two types of trehalose hydrolyzing
1486 activities, one termed acid trehalase and the other called neutral trehalase(François and
1487 Parrou 2001). Agaricomycetes species possess clear orthologs of neutral trehalases
1488 orthologous to Nth1 of *S. cerevisiae*. On the other hand, and in contrast to Deveau et al
1489 (Deveau et al. 2008), we did not find proteins in the genomes of Agaricomycetes showing
1490 significant sequence similarity (based on BLAST) to acid trehalase. A single neutral
1491 trehalase gene was found in Agaricomycetes, this formed a CDE orthogroup at FC>2 (*C.
1492 cinerea* protein ID: 437212, Table 10) and showed varied expression patterns in the species
1493 examined.
1494 Orthologs of previously described fungal trehalose transporters were not detectable
1495 in Agaricomycetes genomes, based on sequence similarity, in agreement with a previous
1496 study on *L. bicolor*(Deveau et al. 2008). However, it should be noted that fungal trehalose
1497 transporters are poorly known and current knowledge likely misses a large proportion of
1498 genes with this activity(Thammahong et al. 2017).
1499 **Mannitol metabolism** - Mannitol accumulates in high concentrations in fruiting
1500 bodies of certain species, possibly as an osmolyte assisting fruiting body
1501 growth(Chakraborty et al. 2004; Zhou et al. 2016b) (see also opposing evidence above). A

Running head: fruiting body genomics

1502 NADP-dependent mannitol 2-dehydrogenase was reported from *A. bisporus*(JM and H 1998;
1503 S et al. 2001). In agreement, in *L. bicolor* Deveau et al reported a single mannitol
1504 2-dehydrogenase-dependent pathway of mannitol biosynthesis(Deveau et al. 2008), which
1505 works via the direct reduction of fructose. Using the *A. bisporus* NADP-dependent mannitol
1506 2-dehydrogenase gene(JM and H 1998) as a query, we identified an orthogroup
1507 (represented by *C. cinerea* 429272) of short-chain dehydrogenase/reductase genes that
1508 contained only *A. bisporus, L. bicolor, C. cinerea,* and *P. ostreatus*, but was missing from
1509 other species (formed multiple orthogroups probably due to duplications in *A. bisporus*).
1510 However, members of this orthogroup were developmentally regulated in all species (Table
1511 10); they were upregulated at the initiation of fruiting and showed expression peaks in gills of
1512 *C. cinerea* and *P. ostreatus*, young and mature caps of *L. bicolor*, as well as a marked
1513 upregulation in the stipe tissues of *A. bisporus*. These observation agree with mannitol
1514 metabolism being enhanced in fruiting bodies of *L. bicolor* (Deveau et al. 2008).
1515 In summary, the genomes of Agaricomycetes contain clear orthologs of
1516 experimentally characterized members of glycogen, trehalose and mannitol metabolism
1517 pathways. Many of the genes in these pathways are developmentally regulated in fruiting
1518 bodies, often showing conserved expression peaks in multiple species, reflecting a
1519 conservation of storage carbohydrate mobilization strategies within fruiting bodies.
1520 Interestingly, in *L. bicolor* trehalose and glycogen metabolism was upregulated in *both*
1521 fruiting bodies and mycorrhizae, providing links between fruiting bodies and ECM(Deveau et
1522 al. 2008; Martin et al. 2008).
1523

1524 4.5. Transcriptional regulators

1525 4.5.1. Transcription factors

1526 Transcription factors are proteins that modulate gene expression by binding to specific DNA
1527 sequences and subsequently activating or inhibiting transcription. Transcription factors play
1528 a major role in the regulation of development across the tree of life, and mushroom-forming
1529 fungi are no exception. They are involved in many stages of development, ranging from the
1530 establishment of a dikaryon to various aspects of mushroom development.
1531 The best studied are the homeodomain transcription factors of the *MatA* mating-type
1532 locus that are essential for the establishment of a fertile dikaryon, which is required for
1533 fruiting body formation in heterothallic basidiomycetes(Raudaskoski and Kothe 2010; Vonk
1534 and Ohm 2018). During mating the homeodomain transcription factors expressed from
1535 compatible *MatA* loci dimerize and activate dikaryon-specific transcriptional pathways,
1536 including the formation of clamp connections. The mechanism of mate recognition is very
1537 similar to that found in the yeast *S. cerevisiae*(Haber 2012) and is present across the fungal
1538 kingdom, although many ascomycetes do not use homeodomain transcription factors for
1539 mating(Houbraken and Dyer 2015). In some Agaricales, like *C. cinerea* and *S. commune*,
1540 the *MatA* locus has undergone expansion, improving the chances of finding a compatible
1541 mate(Freihorst et al. 2016).
1542 Several transcription factors have been identified that act downstream of the *MatA*
1543 homeodomain transcription factors. Deletion of the transcription factors *hom2, tea1* and *wc2*
1544 in *S. commune* resulted in strains that did not show dikaryotic development beyond clamp
1545 formation(Ohm et al. 2011, 2013; Pelkmans et al. 2017a). Generally, the resulting colonies
1546 remained symmetrical and showed no sign of mushroom development. Hom2 is highly

1547   conserved in mushroom-forming fungi and features four putative phosphorylation sites.
1548   Disruption of these phosphorylation sites leads to a constitutively active Hom2 and the
1549   inhibition of vegetative growth and monokaryotic fruiting, indicating that Hom2 is post-
1550   translationally regulated(Pelkmans et al. 2017a). WC2 is part of the blue light sensing white
1551   collar complex first identified in *N. crassa*. In *N. crassa*, WC1 and WC2 interact through PAS
1552   domains and WC1 contains a LOV domain that binds a FAD chromophore when exposed to
1553   blue light. This results in conformation changes in the white collar complex and activates
1554   transcription factor domains on both WC1 and WC2(Corrochano 2019). Orthologs of WC1
1555   (dst1 in *C. cinerea*) and WC2 (Cc.wc2 in *C. cinerea*) in *S. commune* and *C. cinerea* fulfil a
1556   similar role and deletion (*S. commune wc1* and *wc2*, *C. cinerea wc2*) or mutation (*C. cinerea*
1557   *wc1*) of either *wc1* or *wc2* prevents the formation of mature fruiting bodies and is called a
1558   blind phenotype(Terashima et al. 2005; Kuratani et al. 2010; Nakazawa et al. 2011; Ohm et
1559   al. 2013). In *S. commune* this results in a phenotype where no dikaryotic development is
1560   observed and in increased sensitivity to intense light. However, in *C. cinerea* a blind
1561   phenotype leads to the so called 'dark stipe' phenotype(Kamada et al. 2010). In this
1562   phenotype, the primordial shaft is elongated, but pileus and stipe development cannot be
1563   completed. In *S. commune*, WC1 does not contain a DNA-binding domain, unlike WC1 in *N.*
1564   *crassa*, making transcriptional activity dependent on WC2(Ohm et al. 2010). Orthologs of
1565   white collar complex members with the same function have been reported in *L. edodes*(Sano
1566   et al. 2009) and *P. ostreatus*(Qi et al. 2020). Furthermore, developmental expression of wc
1567   members was reported for *F. filiformis*(Liu et al. 2020b). Mutants of the gene tea1, which is
1568   downregulated in *Δwc1, Δwc2, Δhom2, Δbri1* and *Δfst4* dikaryons, also did not form
1569   mushrooms(Pelkmans et al. 2017a). It should be noted that in *tea1* deletion mutants,
1570   dikaryotic colonies sporadically produced clusters of mushrooms, indicating that Tea1 is not
1571   essential for fruiting body formation and may act as a "switch" that can be bypassed. The
1572   ARID/BRIGHT DNA binding domain transcription factor Bri1 was initially also thought to play
1573   a major role in fruiting development(Ohm et al. 2011). However, later characterization of *bri1*
1574   deletion strains revealed that inactivation leads to significant growth defects that result in a
1575   delay in fruiting(Pelkmans et al. 2017a). The fungal specific transcription factor *fst4* has a
1576   very similar phenotype where no mushrooms are formed, but deletion strains of this
1577   transcription factor do form asymmetrical colonies after mating, which is the first step in
1578   mushroom development(Kües and Liu 2000; Ohm et al. 2010). In *P. ostreatus*, mutations in
1579   *gat1* resulted in a strain that did not fruit(Nakazawa et al. 2019). The missense mutation
1580   inside the zinc-finger binding domain resulted in a dominant gain of function mutation, which
1581   suggests that the mutated transcription factor has an altered DNA-binding specificity. This is
1582   in line with disruption of the ortholog *gat1* in *S. commune*, where the phenotype was not
1583   dominant and resulted in the formation of more, but smaller mushrooms(Ohm et al. 2011). A
1584   general overview of Zn(II)2Cys6 zinc cluster transcription factors, including expression
1585   patterns in *P. ostreatus* fruiting bodies, was published by Hou et al(Hou et al. 2020). In
1586   *Ganoderma lucidum*, silencing of the c_2h_2-type transcription factor *pacC* also resulted in the
1587   absence of fruiting bodies, as well as altered mycelial growth(Wu et al. 2016). Interestingly,
1588   PacC is conserved across the fungal kingdom and activates genes under alkaline conditions,
1589   and inhibits genes under acidic conditions(Peñalva et al. 2008). Therefore, it is unclear if the
1590   absence of fruiting can be attributed to fruiting-specific transcription or general homeostasis.
1591   In *L. edodes*, PriB was described as a primordium-upregulated transcription factor(Endo et
1592   al. 1994). Finally, silencing of *hada-1* resulted in delayed fruiting, as well as multiple growth
1593   defects, in *Hypsizygus marmoreus*(Zhang et al. 2021b).

1594   Downstream in development, *S. commune c2h2, fst1* and *zfc7* gene disruption
1595   resulted in arrested fruiting body formation, where primordia were formed that did not
1596   develop further into mature fruiting bodies(Ohm et al. 2011; Vonk and Ohm 2021).
1597   Interestingly, overexpression of *c2h2* could increase the rate of fruiting in *A. bisporus*,
1598   indicating that *c2h2* expression is a limiting step in fruiting body development(Pelkmans et
1599   al. 2016). The transcription factors Fst1 and Zfc7 were identified due to enrichment of
1600   histone 3 lysine 4 (H3K4) dimethylation in their genes during fruiting body development after
1601   4 days, which indicates increased genetic accessibility and transcription during this
1602   developmental stage(Vonk and Ohm 2021). Further downstream, the *C. cinerea* high-
1603   mobility group transcription factor Exp1 regulates pileus expansion and autolysis to complete
1604   fruiting(Muraguchi et al. 2008b). Notably, this transcription factor is conserved and
1605   developmentally regulated in all studied mushroom-forming fungi, except for *A. ampla, Pt.*
1606   *gracilis* and *S. commune*, whose fruiting bodies do not feature a pileus.
1607   Instead of promoting fruiting body development, several transcription factors are
1608   involved in promoting vegetative growth or repressing fruiting. These include *F. velutipes lfc1*
1609   and *hmg1*, where silencing increased the rate of fruiting(Wu et al. 2020a; Meng et al. 2021).
1610   Additional transcription factors are *P. ostreatus Pofst3* and *S. commune fst3, gat1* and
1611   *hom1*(Ohm et al. 2011; Qi et al. 2019). These genes are differentially regulated in the
1612   majority of mushroom forming species, and conserved in all of them. When the genes are
1613   deleted (*S. commune*) or silenced (*P. ostreatus)* it results in the formation of more, smaller
1614   mushrooms. Finally, premature stop codons in *pcc1* in *C. cinerea* (natural variation,
1615   truncated from 561 to 210 amino acids, HMG-box not disrupted) and *P. ostreatus*
1616   (CRISPR/Cas9-assisted gene mutagenesis, truncated from 471 to 58 amino acids, HMG-
1617   box disrupted) resulted in monokaryotic fruiting and the formation of pseudoclamps(Murata
1618   et al. 1998; Boontawon et al. 2021). In *C. cinerea* these pseudoclamps were formed during
1619   monokaryotic growth, indicating a relation between the *MatA* homeodomain transcription
1620   factors and Pcc1. In *P. ostreatus* however, dikaryotic strains formed pseudoclamps,
1621   suggesting a role in clamp formation.
1622   Many transcription factors are conserved across fungi or specifically in mushroom-
1623   forming fungi. Both *wc2* and *pacC* are conserved in both ascomycetes and basidiomycetes
1624   and except for *hmg1 (F. velutipes), lfc1 (F. velutipes), pdd1 (F. velutipes), pcc1 (C. cinerea*
1625   and *P. ostreatus)* and *zfc7 (S. commune)* all characterized transcription factors are at least
1626   conserved in mushroom-forming fungi. *Cag1* (*C. cinerea* protein ID: 466216) and *Cc.Tup1*
1627   (*C. cinerea* protein ID: 369655) of *C. cinerea* are further examples of highly conserved
1628   transcription factors(Masuda et al. 2016). They are homologs of the highly conserved
1629   general transcriptional co-repressor Tup1 of *S. cerevisiae*, which can form repressive
1630   complexes with a wide range of sequence-specific transcription factors. Deletion of Cag1
1631   resulted in a cap-growthless phenotype, which, upon closer inspection turned out to be
1632   caused by developmental defects of gills(Masuda et al. 2016). However, the expression
1633   patterns are generally not conserved during fruiting body development(Almási et al. 2019;
1634   Krizsán et al. 2019). For example, the developmental stage with the highest expression level
1635   of the ortholog can vary greatly between species. This can indicate either that transcriptional
1636   regulation of fruiting body development is poorly conserved between species, or that
1637   transcription factors are regulated post-translationally. The *MatA* mating type genes are an
1638   example of post-translational regulation, where the transcription factors are constitutively
1639   expressed, but only become activated when heterodimers are formed between compatible
1640   homeodomain transcription factors. Similarly, in *N. crassa* WC2 is activated by structural
1641   changes in its interaction partner WC1 when blue light is detected. Furthermore, Hom2 in *S.*

1642 *commune* is constitutively expressed, but post-translationally phosphorylated to become
1643 inactive.
1644   While many expression patterns of transcription factors are not conserved in
1645 mushroom-forming fungi, there are several interesting and conserved transcription factors.
1646 We identified 51 orthogroups of TFs that were developmentally regulated in a significant
1647 number of species (Table 11). Among the functionally characterized transcription factors,
1648 orthologs of dst1 (=WC1, *C. cinerea* protein ID: 369621) and Cc.wc2 (*C. cinerea* protein ID:
1649 8610) of *C. cinerea* formed CDE orthogroups developmentally regulated in 10/4 and 10/6
1650 (FC>2/4) species, respectively. Orthologs of dst1 and Cc.wc2 showed varied expression
1651 profiles in the examined species. An orthogroup of homeodomain transcription factors (*C.*
1652 *cinerea* protein ID: 497620) is developmentally regulated during fruiting body formation in all
1653 mushroom forming fungi, except for *Pt. gracilis*, which is known for its simplified fruiting body
1654 structure. The detected CDE orthogroups also included exp1 of *C. cinerea* (represented by
1655 *C. cinerea* 421729), which were developmentally regulated in 9/5 species (FC>2/4). In
1656 accordance with its reported function in *C. cinerea*(Muraguchi et al. 2008b), it showed peak
1657 expression in young fruiting body caps. However, the *A. ostoyae, L. bicolor* and *M.*
1658 *kentingensis* orthologs were upregulated in stipe tissues. In *P. ostreatus* we found the
1659 highest expression in cap cuticle. Furthermore, a C_2H_2-type transcription factor (*C. cinerea*
1660 protein ID: 494418) is conserved and expressed in all mushrooms except for *A. ampla*, *Pt.*
1661 *gracilis* and *S. commune*. It may therefore play a similar role to Exp1 in *C.*
1662 *cinerea*(Muraguchi et al. 2008b)*,* which is also conserved and developmentally regulated in
1663 most fungi except for *A. ampla, Pt. gracilis* and *S. commune*. While many other transcription
1664 factor orthogroups are conserved in all studied mushroom-forming fungi, their expression
1665 patterns are not strongly conserved. Therefore, proteomics or functional analyses are
1666 required to further elucidate the role of transcription factors in fruiting body formation.

1667 4.5.2. RNA binding proteins

1668   **Pumilio family** – This family comprises evolutionarily conserved sequence-specific
1669 RNA-binding proteins that bind 3' UTR regions of specific mRNAs. This family has diverse
1670 roles in fungi, including the regulation of meiotic and sexual processes (e.g. Mcp2 of *S.*
1671 *pombe*)(Wilinski et al. 2017; Liu et al. 2018). Pumilio proteins were found to be active during
1672 fruiting body formation in both the Asco- and Basidiomycota(Krizsán et al. 2019; Merényi et
1673 al. 2020b). With a few exceptions, all Agaricomycetes contain six Pumilio protein encoding
1674 genes. These formed two CDE orthogroups (Table 12), one of which (*C. cinerea* protein ID:
1675 378537) contains orthologs of the *Sch. pombe* meiotic coiled-coil protein Mcp2 and shows
1676 expression dynamics reminiscent of mitotic and meiotic genes (see Chapter 4.1.1), and
1677 another, comprising orthologs of *Sch. pombe* Puf3 and *C. neoformans* Pum1 (*C. cinerea*
1678 protein ID: 354109). Both orthogroups are developmentally regulated in a large number of
1679 species (8/7 and 7/6 at FC2/4, respectively). In *C. neoformans*, pum1 has been associated
1680 with basidium development and morphogenesis, suggesting that its orthologs may have
1681 similar roles in Agaricomycetes too.
1682   **RRM family** - We identified five very conserved CDE orthogroups of RNA recognition
1683 motif (RRM) family proteins. One of these (*C. cinerea* protein ID: 471238) were annotated as
1684 related to mitosis and meiosis and is discussed under that chapter. The RRM family
1685 comprises proteins that bind diverse RNA types and shows considerable diversity in fungi,
1686 with 68-88 genes in the Agaricomycetes. Overall, relatively few members of the family were
1687 developmentally expressed, however, the orthogroups we detected showed a conserved

1688   expression pattern. One of them (*C. cinerea* protein ID: 357717) was developmentally
1689   regulated in all 12 species (Table 12) and was upregulated in the second half of fruiting body
1690   development (young fruiting body and mature fruiting body in *C. cinerea*), in particular in gills
1691   (*A. ostoyae, P. ostreatus, M. kentingensis, C. cinerea*) where gill tissue was sampled
1692   separately, or caps (*L. bicolor, L. edodes*). It was also upregulated considerably in primordia
1693   relative to vegetative mycelia. A less characteristic, but similar and very conserved late
1694   upregulation was observed also in the second CDE orthogroup (*C. cinerea* protein ID:
1695   356106), which contains reciprocal best hits of *Sch. pombe* Vip1.
1696   The third CDE orthogroup (*C. cinerea* protein ID: 193545, 11/11 species at FC=2/4)
1697   contains *C. neoformans* Csa2. Members of this orthogroup showed strong induction in the
1698   first primordium stage in *C. cinerea, A. ostoyae, C. aegerita, L. bicolor, L. edodes, P.*
1699   *ostreatus, S. commune, A. ampla, M. kentingensis*. In *C. neoformans* it shows a strong peak
1700   24h after the induction of sexual development, which, combined with evidence for regulation
1701   by pum1, led Liu et al to conclude it is involved in basidium development and sporulation(Liu
1702   et al. 2018). It's an orthologue of *Sch. pombe* Mei2, which is related to meiosis. The other
1703   three basidium-related genes reported by Liu et al (Fad1, Fas1, CNA00260)(Liu et al. 2018)
1704   do not have clear orthologs in *Coprinopsis*.
1705   The CDE orthogroup represented by *C. cinerea* 424800 (Table 12) was consistently
1706   upregulated in gills and sporulating stages (in *A. ampla, S. commune*) in all species,
1707   suggesting roles in hymenium and/or spore formation. In model Ascomycota, proteins in this
1708   orthogroup find Pab1 of both *Sch. pombe* and *S. cerevisiae* as their best Blast hits, which
1709   are related to mRNA export and the control of poly(A) tail length.
1710   Finally, the CDE orthogroup comprising *C. cinerea* 368527 includes best reciprocal
1711   hosts of *S. cerevisiae* Nam8, a meiosis-specific splicing factor. Our expression data are
1712   consistent with a meiosis-specific role: the gene is developmentally regulated in 6/4 species
1713   (FC2/4, see above, Table 1) and shows a peak expression in meiotic tissues in all species
1714   (gills, cap+gills or mature fruiting bodies). Based on these data, we hypothesize that this
1715   gene also participates in meiosis-specific splicing events in the basidia during fruiting body
1716   formation.

1717   4.5.3. RNA interference, Small RNA

1718   RNA interference is a conserved eukaryotic gene-silencing mechanism that acts via base
1719   pairing of small noncoding RNAs of ~20-30 nucleotides to DNA/RNA targets. RNAi is key to
1720   developmental and differentiation processes, genome defense against viruses or
1721   transposons. There is very limited knowledge on the role of RNAi in mushroom-forming fungi
1722   (but see(Lau et al. 2018)), whereas the processes are extensively studied in the Ascomycota
1723   (in particular *N. crassa* and *Sch. pombe*(Dang et al. 2011)), where RNAi has well-
1724   documented roles in defense against viruses, transposons, meiotic silencing of unpaired
1725   DNA, translational repression and even inter-organismal pathogenic interactions(Weiberg et
1726   al. 2013).
1727   A fully functional RNAi machinery exists in the Basidiomycota. Based on orthology to
1728   *Neurospora* proteins, Lau et al annotated dicer-like proteins as Dcl-1 (*C. cinerea* protein ID:
1729   444647), Dcl-2 (*C. cinerea* protein ID: 366047) and Dcl-3 (*C. cinerea* protein ID:
1730   438955)(Lau et al. 2018), whereas Stajich et al annotated the argonaute family proteins
1731   AGO (*C. cinerea* protein ID: 355234), an AGO-like protein (*C. cinerea* protein ID: 473372)
1732   and Qde-2 (*C. cinerea* protein ID: 363313)(Stajich et al. 2010) (Table 13). We identified 3-16
1733   genes encoding argonaute and argonaute-like proteins in the examined Agaricomycetes.

1734 Furthermore, fungal RNA interference involves RNA-dependent RNA polymerases, which
1735 are required for generating double-stranded RNA or for amplifying sRNA signals(Dang et al.
1736 2011). The genomes of the examined Agaricomycetes contain 5-13 RNA-dependent RNA
1737 polymerases; of these, the orthogroup represented by *C. cinerea* 498671 is most similar to
1738 the RDP1 protein of *S. pombe*, which was shown to be integral to RNA
1739 interference(Carmichael et al. 2004). Other RNA-dependent RNA polymerases (Table 11)
1740 might participate in alternative RNAi pathways or signal amplification(S et al. 2012b).
1741 Interestingly, we found no clear orthologs of SAD-1, a meiotic silencing protein(Borkovich et
1742 al. 2004), in the examined genomes.
1743   RNAi components show some expression dynamics during fruiting body
1744 development. Genes encoding Dcl-2, Dcl-3 and AGO-like proteins were upregulated in *C.*
1745 *cinerea* primordia relative to vegetative mycelium(Lau et al. 2018). Similarly, AGO-like and
1746 Qde-2 were found developmentally regulated in *C. cinerea* by Krizsan et al(Krizsán et al.
1747 2019), although Dcl-1-3 genes were not. All of the seven RNA-dependent RNA polymerases
1748 were developmentally regulated in the data of Krizsan et al. In our meta-analysis, the above-
1749 listed components did not show significant developmental expression dynamics (Table 13).
1750 The only noteworthy orthogroup (represented by *C. cinerea* 502116), was developmentally
1751 regulated in 9/6 species (FC>2/4) and contains Argonaute-like proteins that share highest
1752 similarity with *A nidulans* RsdA and *Sch. pombe* Ago1, the first of which is involved in RNA-
1753 silencing(TM et al. 2008) whereas the second has a large suite of described functions, from
1754 RNA silencing to chromosome segregation and cell cycle arrest(Carmichael et al. 2004). We
1755 found no conserved expression pattern in this orthogroup across the examined species.
1756   The most direct evidence for the role of microRNA-like RNAs (milRNA) in mushroom
1757 development was reported by Lau et al(Lau et al. 2018), who compared small RNA
1758 transcriptome profiles of vegetative mycelium and primordium stages and detected 22
1759 milRNA in *C. cinerea*, several of which were differentially expressed between vegetative
1760 mycelia and primordia. These results point to the potential roles of milRNA in mushroom
1761 development, although more studies are needed to understand its roles.
1762   RNA interference has been exploited as a tool of genetic manipulation in mushroom-
1763 forming fungi, often to compensate for the lack of reliable reverse genetics tools in these
1764 organisms. Gene knockdown has been demonstrated in *S. commune*(de Jong et al. 2006)*,*
1765 *C. cinerea*(Namekawa et al. 2005; MA et al. 2006; Heneghan et al. 2007)*, L. bicolor*(M et al.
1766 2009a)*, Ph. chrysosporium*(Matityahu et al. 2008)*, P. ostreatus, A. bisporus*(Costa Ana
1767 S.M.B.;Thomas 2009)*, Grifola frondosa*(Sato et al. 2015) and *L. edodes*(Nakade et al. 2011),
1768 among others, demonstrating the utility of knockdown techniques in cases/species when
1769 gene knockout was not feasible (particularly in the pre-CRISPR times).

1770 ## 4.5.4. Chromatin regulators

1771 Chromatin remodeling is a fundamental and general mode of epigenetic gene expression
1772 regulation. Dynamic chromatin states are generated primarily via chromatin remodeling
1773 complexes and histone modifications in fungi, in response to environmental or internal
1774 signals. Importantly, chromatin remodeling often provides the basis for broad changes in
1775 gene expression, by modulating the accessibility of DNA for transcription, as opposed to
1776 sequence-specific transcription factors, which regulate only specific genes. Epigenetic
1777 changes often associate with developmental processes; these receive increasing attention in
1778 multiple lineages, including fungi. Accordingly, studies addressing the role of chromatin
1779 remodeling in mushroom development, although quite few at the moment, revealed

1780 fundamental roles of chromatin states in fruiting-related gene transcription. For example,
1781 deleting *Cc.snf5* (*C. cinerea* protein ID: 365798, see Table 14), a member of the SWI/SNF
1782 chromatin remodeling complex, leads to the failure to initiate fruiting body development in *C.*
1783 *cinerea* (in addition to defects in dikaryon formation)(Ando et al. 2013). In *C. cinerea* two
1784 further genes identified in mutant analyses, *ich1*(Muraguchi and Kamada 1998) and *Cc.*
1785 *rmt1*(Nakazawa et al. 2010), may be related to chromatin regulation. Recent ChIP-Seq
1786 analyses of epigenetic states revealed substantial changes in transcriptional activity (with
1787 H3K4me2 as a proxy) during the transition to fruiting(Vonk and Ohm 2021), whereas histone
1788 acetyltransferase complex members were found in quantitative trait loci in *L. edodes*(Zhang
1789 et al. 2021d). The presence of SET domain methyltransferases in the Basidiomycota is also
1790 worth mentioning(Freitag 2017). Although evidence at the moment is scanty, the few
1791 available studies and extrapolation from other organisms suggests that chromatin
1792 remodeling may be a significant factor in fruiting body formation. Therefore, in the following
1793 chapters we annotate and discuss expression patterns of genes related to chromatin
1794 maintenance and remodeling based on homology to known chromatin remodeling
1795 components in *S. cerevisiae* and *N. crassa.*

1796 4.5.4.1. Histone gene expression correlates with fruiting body initiation and sporulation

1797 **Histones** - Histones are highly conserved proteins that assemble into octameric
1798 nucleosomes and condense DNA into chromatin in a tightly regulated manner. Shuffling of
1799 histone variants can generate nucleosome variants, which, combined with diverse
1800 posttranslational modifications of histones (acetylation, methylation, phosphorylation) can
1801 generate a finely diversified histone code contributing to fine-tuned regulation of chromatin
1802 states, which, in turn, impact transcriptional patterns of genes(Borkovich et al. 2004).
1803 Histone modifications are often used to make readouts of transcriptional states associated
1804 with development(Vonk and Ohm 2021). Agaricomycetes have 14-40 histone and histone-
1805 variant encoding genes. They show a very similar overall expression pattern in all species
1806 that resembles the expression of meiotic/mitotic and ribosomal genes: upregulation in
1807 primordium stages as well as meiotic tissues (gills or caps+gills) coincident with sporulation
1808 (Fig. 10, Supplementary Fig. 7). Though overall very conserved, there are slight variations to
1809 this general pattern: *A. ampla* shows a peak only in primordia, whereas in *C. cinerea* and *L.*
1810 *tigrinus* a meiosis/sporulation associated peak is better visible, while the primordium-peak is
1811 modest. We detected four CDE orthogroups of histones and histone variants (Table 14).
1812 These include a basidiomycetes-specific histone H2A component (*C. cinerea* protein ID:
1813 363625), which is developmentally expressed in 8/6 species (FC2/4) and show considerable
1814 upregulation in primordia relative to vegetative mycelium in most species. Other CDE
1815 orthogroups also showed primordium- and gill- upregulation. A straightforward interpretation
1816 of the similar expression patterns of histones and cell proliferation related genes is a mutual
1817 link to DNA repair. H2A histone phosphorylation is associated with DNA repair(JA et al.
1818 2000; Borkovich et al. 2004), providing a potential mechanistic explanation for the observed
1819 expression patterns. Somewhat contradicting this is the fact that relatives of the Mec1 kinase
1820 (*C. cinerea* protein ID: 19106), which phosphorylates H2A.Z in *S. cerevisiae*(JA et al. 2000),
1821 are not developmentally regulated in Agaricomycetes. On the other hand, histone
1822 upregulation in primordia and meiotic tissues may also be interpreted as evidence for
1823 intense transcriptional reprogramming, which has been hypothesized for the mycelium-
1824 fruiting body transition(Krizsán et al. 2019; Vonk and Ohm 2021). Alternatively, intense DNA
1825 replication may require increased supply of histones in proliferating tissues.

1826   **Histone chaperone** - We detected a histone chaperone CDE orthogroup containing
1827   homologs of *S. cerevisiae* Chz1 (represented by *C. cinerea* 498885)(Table 14), which forms
1828   a single-copy gene family in the Agaricomycetes. Members of this orthogroup are involved in
1829   histone replacement during transcription and showed the same expression pattern as
1830   histones (peaking in primordia and meiotic tissues), so we speculate they are involved in the
1831   same cellular processes during fruiting body initiation and sporulation.
1832   We next inventoried histone acetyltransferases, histone deacetylases, histone
1833   methyltransferases, histone ubiquitylases, histone kinases and histone ADP-ribosylases
1834   based on homology to corresponding *N. crassa* genes described by Borkovich et
1835   al(Borkovich et al. 2004) as well as diagnostic conserved domains.
1836   **Histone acetyltransferase** (HAT) - We found one HAT gene per species in the
1837   examined Agaricomycetes (represented by *C. cinerea* 420113), in contrast to Ascomycota,
1838   that have multiple histone acetyltransferase genes(Borkovich et al. 2004). This family
1839   showed no developmental expression dynamics in our species. However, we detected
1840   several protein N-acetyltransferases, which resemble HATs, but lack orthology to known
1841   HATs and do not contain diagnostic conserved domains of HATs. They share an identical
1842   domain composition with *Sch. pombe* Ard1, a Gcn5-related N-acetyltransferase (GNAT),
1843   which acetylates diverse proteins, including transcriptional regulators. A CDE orthogroup of
1844   GNATs (*C. cinerea* protein ID: 457726) was developmentally expressed in 8/4 species
1845   (FC2/4, Table 14), however, given the lack of clear histone link we only tentatively discuss
1846   this family here, noting that functional analysis is needed to confirm their functional
1847   annotation.
1848   **Histone deacetylases (HDACs) -** we distinguished two groups of HDACs, one
1849   related to *S. cerevisiae* Hda1 and the Sirtuin family, which were detected in 6-7 (11 in *A.*
1850   *ostoyae*) and 4-9 copies in the examined Agaricomycetes, respectively. Neither groups
1851   showed considerable developmental expression dynamics, except for one CDE orthogroup
1852   comprising sirtuins (represented by *C. cinerea* 455597), which was developmentally
1853   expressed in 9/9 species (FC2/4, Table 14). This family is orthologous to Hst4 of *Sch.*
1854   *pombe* and Hst3 of *S. cerevisiae*, which regulate DNA damage response and repair by
1855   regulating histone H3K56 acetylation(Konada et al. 2018). Consistent with their presumed
1856   role, the expression of this gene family followed closely that of mitosis/meiosis and DNA
1857   repair related genes in all species: they showed a small expression peak in primordia and a
1858   larger one in meiotic tissues coinciding with sporulation (Fig. 10).
1859   Histone ADP-ribosylases are poly(ADP-ribose) polymerases (PARPs) and are
1860   among the least understood factors in epigenetic regulation; they attach (poly-)ADP-ribose
1861   moieties to proteins, including histones and are thought to regulate histone turnover and
1862   DNA damage response. In *N. crassa* the family is represented by a single gene,
1863   *parp*(Borkovich et al. 2004). The examined Agaricomycetes' genomes harbor 3-9 copies of
1864   PARPs, of which two formed CDE orthogroups (*C. cinerea* protein ID: 459336, 384835),
1865   which were developmentally expressed in 8/4 and 6/5 species (FC2/4, Table 14),
1866   respectively. Their expression patterns did not follow that of histones, suggesting that their
1867   actions are independent of those.
1868   Histone methyltransferases and histone kinases showed no noticeable expression
1869   dynamics in fruiting bodies (Table 14), suggesting that they are equally important in fruiting
1870   bodies and vegetative mycelia.
1871

1872 4.5.4.2. Other chromatin related genes

1873 ***Ich1* gene family -** The only methyltransferase that might be connected to chromatin
1874 regulation was the gene underlying the 'Ichijiku' mutant, which was first identified by
1875 Muraguchi and Kamada(Muraguchi and Kamada 1998), as a mutant that produced
1876 malformed, barrel-shaped primordia, in which cap development fails. The corresponding *ich1*
1877 gene encodes a nuclear methyltransferase that contains a winged-helix DNA binding domain
1878 and was reported to be upregulated in primordia(Muraguchi et al. 2015). Our results agree
1879 and extend these observations: Ich1 orthologs form a CDE orthogroup (represented by *C.*
1880 *cinerea* 545797) that is developmentally expressed in 8/6 species (FC2/4)(Table 14) and
1881 shows a marked upregulation in primordia relative to vegetative mycelium in *C. cinerea, A.*
1882 *ostoyae* (weakly)*, A. ampla, S. commune, A. bisporus, M. kentingensis* and *P. ostreatus*.
1883 The exact mechanism of how Ich1 regulates tissue formation is not known, however, this
1884 gene represents a very interesting target for detailed studies, especially given its putative
1885 role in chromatin regulation and/or methylation. On a related note, *Cc.rmt1*, an arginine
1886 methyltransferase which was suggested to participate in histone methylation and to be
1887 required for hyphal knot and fruiting body formation(Nakazawa et al. 2010), forms an
1888 orthogroup which is developmentally regulated in nine species (at FC>2) (Table 14). The
1889 exact role of *Cc.rmt1* is not known so its role in histone methylation remains preliminary.

1890 **Histone isomerases** - We found a CDE orthogroup that was widely developmentally
1891 expressed (represented by *C. cinerea* 493226)(Table 14). Ascomycota orthologs of these
1892 genes are histone proline isomerases in the peptidyl-prolyl cis-trans isomerase family, which
1893 contribute to nucleosome assembly and thus regulate gene expression. This orthogroup
1894 shows upregulation in gills of *C. cinerea, A. ostoyae* and *P. ostreatus* (all species in which
1895 gills were sampled separate) and in cap tissues of *L. edodes, M. kentingensis, L. tigrinus*.
1896 These expression patterns are consistent with a role in sporulation. Genes in this orthogroup
1897 also show upregulation in primordia relative to vegetative mycelia, although this is usually
1898 modest (2-3x, 10x in *P. ostreatus*).

1899 **HMGA and AT-hook protein -** We detected a CDE orthogroup (*C. cinerea* protein
1900 ID: 473747)(Table 14) that includes primarily stipe-upregulated genes (in *C. cinerea, A.*
1901 *ostoyae, L. tigrinus, P. ostreatus, M. kentingensis,* but not *L. bicolor*) that shows expression
1902 peaks also in YFB cap of *C. cinerea* and FB cap of *P. ostreatus*. We found no expression
1903 dynamics in Schizophyllaceae species, which lack stipes. The orthogroup belongs to the
1904 High mobility group A family, which comprises AT-rich DNA binding proteins with an
1905 important role in chromatin organization. This family appears to be patchily distributed in the
1906 examined species, but nevertheless seems to be important for fruiting body development.

1907 **SRA-YDG domain proteins** - We detected a CDE orthogroup (*C. cinerea* protein ID:
1908 511209)(Table 14) of proteins containing an SRA-YDG (IPR003105) domain, which occurs
1909 in histone and chromatin binding proteins and may be associated with the cell cycle.
1910 Proteins with this domain seem to be missing in Ascomycota model species (results not
1911 shown), but show expression patterns similar to those of histones. They are upregulated in
1912 primordia and in meiotic stages (gills, caps with gills) in *C. cinerea, A. ostoyae, P. ostreatus*
1913 and *L. edodes*. In the Schizophyllaceae as well as *P. ostreatus*, the gene family is
1914 upregulated in primordia relative to vegetative mycelium samples. Based on their expression
1915 patterns, we hypothesize they are related to cell proliferation, the cell cycle or chromatin
1916 modification, but available data do not allow us to further narrow down their putative function
1917 among these categories.

4.6. Alternative splicing and spliceosome components

Alternative splicing is a post-transcriptional mechanism for regulating transcript identity and abundances. mRNA variants generated by splicing can increase the diversity of proteins transcribed from a single gene, but can also destine transcripts to the nonsense-mediated decay pathway and thus reduce transcript abundance posttranscriptionally(Krizsán et al. 2019). Transcriptomes allow us to describe alternative splicing complexity of organisms at an unprecedented depth. Several studies looked at alternative splicing in fungi(Zhao et al. 2013; Grützmann et al. 2014; Jin et al. 2017), including Agaricomycetes model systems(Lugones et al. 1999a; Gehrmann et al. 2016; Krizsán et al. 2019). The Basidiomycota and, in particular, the Agaricomycetes displayed a higher percentage of spliced genes than did other groups of fungi(Grützmann et al. 2014; Krizsán et al. 2019). Results of these studies highlighted that, of the several possible splicing events, intron retention (IR) is the most common in fungi while exon-skipping, which most amply contributes to generating protein isoforms, accounts for only 0.5-2.5% of fungal splicing events. Most research on splicing focuses on the latter, however, it appears that exon skipping-rich transcriptomes represent an animal innovation(Grau-Bové et al. 2018). IR events have been considered either as transcriptional noise or as a regulatory mechanism(Middleton et al. 2017). IR can introduce premature stop codons in transcripts or new functional elements for RNA binding proteins. Premature stop codons can activate nonsense-mediated decay, a surveillance mechanism that results in the degradation of the mRNA transcript. Recent results suggest that IR may not only regulate transcript levels, but can be a key driver of posttranscriptional processes(Middleton et al. 2017). There is evidence that in the Basidiomycota IR exerts its effect on transcripts independent of the nonsense-mediated decay pathway(Gonzalez-Hilarion et al. 2016).

Functionally characterized examples of developmentally relevant splicing events are known in the Ascomycota. For example, alternative splicing of the blue light receptor wc-1 gene was observed in *Phaeosphaeria* spp. and it was hypothesized that AS may control various light-dependent reactions(Chiu et al. 2010). In *Neurospora wc-1* transcription is controlled by multiple distinct cis-regulatory regions (termed different promoters), which responded differently (not, weakly or strongly) to light and resulted in alternative protein isoforms(Káldi et al. 2006). These observations, although probably just scratching the surface, implicate AS as an important contributor to the development of fruiting bodies.

Alternative transcript isoforms affect a considerable portion of genes during fruiting body development. IR-generated transcript isoforms with a dynamic expression are abundant in fruiting bodies(Gehrmann et al. 2016; Krizsán et al. 2019), affecting 20-46% of expressed genes, pointing towards potential important regulatory roles. In *S. commune*, 69% of the alternative spliced transcripts had altered predicted functional properties or subcellular localization(Gehrmann et al. 2016). Gehrmann et al reported the largest number of splicing events at the fruiting body initiation stage in *S. commune*, whereas Krizsan et al did not find substantial differences in the number of splicing events across developmental stages.

Splicing can influence transcript levels significantly during fruiting body development. A recent study found 425 genes in *S. commune* for which an alternative transcript replaced the highest expressed transcript in some stage of development. Many such events happened at fruiting body initiation (referred to as the aggregate stage), pinpointing the magnitude of transcriptome reprogramming at this developmental transition. A conceptually similar scenario, genes whose expression do not vary considerably during fruiting body

43

1964 development, but have splicing isoforms that vary in their expression significantly, was
1965 detected for ~160-1300 genes in six Agaricomycetes (Krizsán et al. 2019).
1966   Taken together, recent studies on Agaricomycetes suggest that splicing, in particular
1967 intron retention, is an important process in fruiting body development, contributing to
1968 posttranscriptional regulation of transcript levels or generates functional diversity in proteins
1969 translated from alternative transcripts. The prevalence of IR in fungal transcriptomes
1970 suggests that the main role of splicing in fungi might be posttranscriptional transcript level
1971 regulation rather than the expansion of the proteome space, although mechanistic or
1972 proteome-level studies are missing at the moment.
1973   We here annotated spliceosome components and splicing-associated proteins in *C.*
1974 *cinerea* based on knowledge in *S. cerevisiae* and *Sch. pombe*(Käufer and Potashkin 2000;
1975 JM et al. 2012). We annotated 50 orthogroups associated with splicing, however, none of
1976 them showed remarkable expression dynamics in fruiting bodies (Supplementary Table 3).
1977 These included the gene described as *Le.cdc5* and *Cc.cdc5* in *L. edodes* and *C. cinerea*,
1978 respectively(Miyazaki et al. 2004), a pre-mRNA splicing factor.
1979

1980   4.7. Signal transduction systems and communication

1981 One of the most important multicellular processes.

1982   4.7.1. Oxylipins

1983 In fungi, oxylipins are responsible for a range of signaling functionalities and act as paracrine
1984 hormone-like substances or as so-called 'infochemicals'(Combet et al. 2006; Holighaus and
1985 Rohlfs 2019). Ascomycota species produce diverse oxylipin compounds (reviewed
1986 in(Gessler et al. 2017)) and changes in their levels influence development. For example,
1987 oxylipins can regulate the yeast-to-hypha transition in dimorphic fungi, as well as immune
1988 evasion(Rennemeier et al. 2011) and communication with the host in pathogens, while a
1989 well-known group of oxylipins called psi (precocious sexual inducer) factors regulates sexual
1990 and asexual development in Ascomycota(Tsitsigiannis and Keller 2007). Basidiomycota
1991 oxylipins are less known. The best-known oxylipin of mushroom-forming fungi is 1-octen-3-
1992 ol, an enantiomeric compound that is mainly produced as (R)-(–)-1-octen-3-ol by widely-
1993 known species(Zawirska-Wojtasiak 2004). On the one hand, it acts as an interkingdom-
1994 signaling molecule. It may attract or repel fungivorous arthropods(Fäldt et al. 1999;
1995 Holighaus and Rohlfs 2019) or derogate insect larval development. In combination with the
1996 equally prominent octan-3-one that may attract specialist fungivores, it has also been shown
1997 to attract predators of such fungivores(Fäldt et al. 1999). Furthermore, 1-octen-3-ol has been
1998 shown to retard plant seed germination and vegetative growth(Hung et al. 2014). On the
1999 other hand, 1-octen-3-ol shows a quorum-sensing like action as it inhibits colony growth(Yin
2000 et al. 2015; Kües et al. 2018), conidiation(Fäldt et al. 1999; Yin et al. 2015), fruiting
2001 initiation(Noble et al. 2009; Eastwood et al. 2013) and germination where spores are
2002 crowded(Chitarra et al. 2004; Combet et al. 2006).
2003   The composition of the oxylipin cocktail emitted by intact mushroom tissue changes
2004 in the course of mushroom development while measurement of the most abundant oxylipins
2005 during that process crucially depends on the sampling method: disruption of fungal tissue
2006 has been shown to trigger the release of oxylipins that are not emitted when fungal material
2007 is intact(Fäldt et al. 1999). The changing specific oxylipin bouquet emitted by a developing
2008 mushroom may not solely reflect adaptation to insect attraction for spore dispersal and

2009   repellence of fungivores. It is also possible that, e.g. octan-3-one and 1-octen-3-ol are
2010   produced by the fruiting body to inhibit on-colony spore germination(Combet et al. 2006) or
2011   colonization by mycoparasites(Berendsen et al. 2013). During fruiting body development,
2012   octan-3-one emission either positively(Combet et al. 2009) or negatively(Zhang et al. 2008;
2013   A et al. 2020; Orban et al. 2021) correlates with the amount of 1-octen-3-ol produced by (not
2014   yet) sporulating tissue samples of certain species.

2015   The biosynthesis pathway of 1-octen-3-ol has interested mycologists for a long
2016   time(Combet et al. 2006; Kües et al. 2018; Orban et al. 2021), but remained unresolved to
2017   date. The process starts by oxygenation of polyunsaturated fatty acids (PUFAs) with linoleic
2018   acid as the predominant PUFA in Asco- and Basidiomycota(Combet et al. 2006; Brodhun
2019   and Feussner 2011). It was suggested that lipoxygenases (LOXs), linoleate diol synthases
2020   (LDSs that combine a dioxygenase – DOX – and an isomerase activity), hydroperoxide
2021   lyases (HPLs) and alcohol dehydrogenases (ADHs) participate in 1-octen-3-ol
2022   biosynthesis(Combet et al. 2006). Still, it is possible that 1-octen-3-ol can be produced by
2023   incomplete beta-oxidation or by multiple pathways(Combet et al. 2006; Brodhun and
2024   Feussner 2011). Orban et al. recently attempted to identify genes involved in oxylipin
2025   production based on correlations between 1-octen-3-ol concentrations and gene expression
2026   patterns(Orban et al. 2021) including a gene of an ene-reductase for octan-3-one formation
2027   from ADH-mediated conversion of 1-octen-3-ol.

2028   Two main enzyme classes have been implicated in fungal oxylipin production, LOXs
2029   and LDSs(Combet et al. 2006; Orban et al. 2021). Both act on linoleic acid as the starting
2030   point, from which various compounds are produced by first an oxidation reaction, then by
2031   further modification(Combet et al. 2006). We found LOXs to be highly patchy in
2032   Agaricomycetes, whereas LDSs (basically the Ppo family of proteins) are widely conserved.
2033   Incomplete beta-oxidation has also been suggested as a possible source of oxylipins(Venter
2034   et al. 1997; Brodhun and Feussner 2011), this hypothesis is compatible with the lack of
2035   certain enzymes in many species.

2036   **Lipoxygenases (LOXs) -** Out of the examined species, we only found lipoxygenases
2037   in *C. aegerita*, *P. ostreatus*, *L. bicolor* and *L. edodes*, which have 1-5 copies. These did not
2038   form conserved orthogroups and their expression patterns mostly did not vary substantially
2039   during development. Exceptions include the gene previously described as
2040   *PoLOX1*(Plagemann et al. 2013; Y et al. 2013) (PleosPC15_2_1068582). *PoLOX1* displays
2041   a remarkable upregulation (1880 fold, FPKM 94.000) in fruiting bodies relative to vegetative
2042   mycelium. The gene showed consistently higher expression in stipes compared to caps,
2043   which confirms the previous report on the gene(Y et al. 2013). A lipoxygenase gene
2044   (*CaeLOX4*, gene ID AAE3_04864/Genbank accession no. CAA7262624) of *C. aegerita* also
2045   showed a strong upregulation (~150-fold) during late development (post sporulation stage) in
2046   this species, as noted by Orban et al (Orban et al. 2021). Notably, two other LOXs show
2047   strong phase-specific expression increase in fruiting stage tissue: on the one hand,
2048   *CaeLOX5* (AAE3_07753) shows an expression pattern quite congruent with the maturation-
2049   associated increase of the 1-octen-3-ol levels in the headspace of the *C. aegerita* culture.
2050   On the other hand, Cae*LOX1* (AAE3_00896) shows transcriptional upregulation before
2051   fruiting body maturation sets in. Such patterns may imply stage-specific action or (partial)
2052   functional redundancy among these genes that must, prospectively, be tested by functional
2053   characterization studies.

2054   **Linoleate diol synthases (LDSs) -** The other well-known gene family involved in the
2055   production of oxylipins is the one of linoleate diol synthases, which makes up to PpoA-C
2056   family in *A. nidulans*. The main products of the Ppo family are the so-called psi factors,

2057 which regulate diverse developmental processes from yeast-to-hypha transition and cell
2058 aggregation (reviewed in ref(Tsitsigiannis and Keller 2007)). We identified 1-4 LDS genes in
2059 Agaricomycetes with most species having two copies. Although several genes have
2060 reciprocal best hits among Ascomycota (e.g. *C. cinerea* 423716 to PpoC of *A. nidulans*), a
2061 gene tree analysis showed that these are not true orthologs (results not shown) but likely
2062 resulted from a duplication event that predated the split of Asco- and Basidiomycota.
2063 Therefore, it is likely that Basidiomycota linoleate diol synthases do not have the psi factor
2064 producing activity that *A. nidulans* PpoA-C genes and their homologs have(Tsitsigiannis and
2065 Keller 2007).

2066 Linoleate diol synthases grouped into three conserved orthogroups (Table 15), of
2067 which two (*C. cinerea* protein ID: 398037, 423716) were developmentally expressed in a
2068 considerable number of species. One of these (*C. cinerea* protein ID: 423716) includes *U.*
2069 *maydis* Ssp1 (Ustma2_2_11710), which was found to be specifically expressed in
2070 teliospores(Huber et al. 2002). Genes within these orthogroups seem to show diverse
2071 expression patterns, without noticeable conservation of expression across species. In the
2072 absence of functional information of these genes in Basidiomycota, it is impossible to
2073 speculate on their mechanistic role in fruiting body formation. They are likely to be involved
2074 in oxylipin production(Orban et al. 2021), but further studies are necessary to elucidate their
2075 functions.

2076 **Alcohol dehydrogenases** – the alcohol dehydrogenase family participates in a
2077 broad range of cellular processes, including oxylipin biosynthesis(Orban et al. 2021). We
2078 identified a CDE orthogroup containing *C. aegerita* Adh1-1 (represented by *C. cinerea*
2079 363127), which showed partial conservation of expression: in most species it was
2080 upregulated during late development (*C. aegerita, A. ostoyae, L. edodes, L. tigrinus, C.*
2081 *cinerea*). In addition, in *S. commune, Ph. chrysosporium, A. ostoyae* and *L. edodes* it was
2082 also upregulated >4x in primordia relative to vegetative mycelium. In *M. kentingensis* and *A.*
2083 *ampla* the gene was not developmentally regulated, whereas *L. bicolor* and *P. ostreatus* did
2084 not have orthologs. Based on a previous report of *C. aegerita* Adh1-1(Orban et al. 2021), it is
2085 possible that this orthogroup of alcohol dehydrogenases participate in oxylipin production.
2086

2087 4.7.2. Pheromone and pheromone receptor pathways

2088 The structure and evolution of mating systems, including HD transcription factors (A locus),
2089 pheromone receptors and pheromone precursor genes (B locus) is among the best known
2090 aspects of Agaricomycete biology (e.g.(Kües 2000, 2015; James 2015) refs). The primary
2091 role of pheromone/receptor systems is regulating dikaryotization, i.e. the compatibility of
2092 monokaryons, nuclear movement and other downstream events. Hyphal fusion is believed to
2093 occur ubiquitously in the Basidiomycota, therefore, pheromone/receptor systems may
2094 regulate post-fusion behavior(Raudaskoski and Kothe 2010; Jones and Bennett 2011).
2095 However, pheromone/receptor systems are involved in the regulation of sexual events too.
2096 For example, mating type loci are involved in fruiting body formation in *C. cinerea*(Kues et al.
2097 1998, 2002). Basidiomycete mating systems, pheromone and pheromone receptor genes
2098 have been reviewed recently in detail (e.g.(Raudaskoski and Kothe 2010; Jones and Bennett
2099 2011; James 2015; Kuees 2015)). We here annotate components of the Agaricomycete
2100 mating systems, with special emphasis on copy number variation across the twelve species
2101 examined in this paper and expression dynamics during fruiting body development.

2102   **Pheromone precursor genes** - Basidiomycetes produce mating pheromones that
2103 are structurally analogous to *S. cerevisiae* a-factor(Jones and Bennett 2011). Mating
2104 pheromones are short peptides that undergo a multi-step maturation process and regulate
2105 intercellular communication and sexual development in a wide range of fungi(Jones and
2106 Bennett 2011). Copy numbers of pheromone precursor genes vary across the
2107 Agaricomycetes and are often found in the vicinity of corresponding pheromone
2108 GPCRs(Raudaskoski and Kothe 2010). Four pheromone precursor genes were found in *L.*
2109 *edodes*(Wu et al. 2013)*, P. eryngii*(Kim et al. 2014)*, A. bisporus*(Foulongne-Oriol et al.
2110 2021)*, Moniliopthora roreri*(Díaz-Valderrama and Aime 2016)*,* five in *Ph.*
2111 *chrysosporium*(James et al. 2011)*,* seven in *Pycnoporus cinnabarinus*(Levasseur et al.
2112 2014)*,* two in *P. touliensis*(Gao et al. 2018) and several genes (up to 20) in *C.*
2113 *cinerea*(Riquelme et al. 2005) and *S. commune*(Specht 1995). Synthetic pheromone
2114 administration affected PriA (a primordium-expressed gene) expression in *L. edodes*,
2115 indicating the involvement of mating pheromones in fruiting body formation(Ha et al. 2018).
2116 One of the pheromone precursor genes was expressed in glucose-limited conditions
2117 following blue light induction of fruiting in *C. cinerea*(Sakamoto et al. 2018).
2118   In our dataset, we found up to nine pheromone-precursor encoding genes, however,
2119 we did not find any in *A. ostoyae, A. bisporus, M. kentingensis, Ph. chrysosporium* and *L.*
2120 *tigrinus*. The explanation for this may be that they are simply missing from the genome
2121 annotations. Pheromone precursors are short ~50 amino acid peptides and several genome
2122 annotation protocols omit predicted proteins that are <50 or <100 amino acids long. For this
2123 same reason, it is likely that our inventories of pheromone-precursor genes in other
2124 examined species is incomplete. Nevertheless, we found pheromone precursors in *C.*
2125 *cinerea, A. ampla, L. bicolor, L. edodes, S. commune* and *P. ostreatus*; these genes were
2126 often developmentally regulated, implying that they may participate in developmental
2127 processes, possibly as signal molecules. While knowledge on the role of pheromones in
2128 mating and dikaryon formation is abundant, whether and how they participate in fruiting body
2129 development requires further research.
2130   **Pheromone modification -** pheromone precursor proteins are post-translationally
2131 modified during their maturation process. This involves prenylated, carboxymethylation as
2132 well as proteolytic cleavage to remove N-terminal sequence fragments(Jones and Bennett
2133 2011).
2134   Post-translational prenylation (mostly farnesylation) on CAAX motifs is performed by
2135 RAM proteins in *S. cerevisiae*(Caldwell et al. 1995). Based on orthology with *S. cerevisiae*
2136 pheromone prenylating enzymes, we identified two genes as putatively involved in
2137 pheromone prenylation. The first is orthologous to *S. cerevisiae RAM1* (*C. cinerea* protein
2138 ID: 491483) and shows very modest expression dynamics (Table 16), whereas the second is
2139 an ortholog of *RAM2* (*C. cinerea* protein ID: 473005), encoding a general prenylation
2140 enzyme that also modifies other peptides, including proteins related to cell wall glucan
2141 biosynthesis. Following prenylation, the *S. cerevisiae* a-factor is cleaved by Rce1 (ortholog:
2142 *C. cinerea* 377901) and Ste24 (ortholog: *C. cinerea* 419650). Orthologs of these genes
2143 showed constant expression during fruiting body development (Table 16).
2144   On the other hand, we found evidence for the developmental expression of
2145 carboxymethylating enzymes. Two CDE orthogroups of protein-S-isoprenylcysteine O-
2146 methyltransferases (homologous to *S. cerevisiae* Ste14) were detected among conserved
2147 developmentally expressed genes. Ste14 mediates methylation of the isoprenylated C-
2148 terminal CAAX motif in the mating pheromone a-factor(Romano and Michaelis 2001).
2149 Whether these homologs are related to mating pheromone maturation in mushroom-forming

2150 fungi remains unclear, therefore, we only tentatively classified these as signal transduction-
2151 related genes. Two Ste14 homologs of *C. cinerea* were previously found to be expressed
2152 after blue light exposure(Sakamoto et al. 2018). We detected two CDE orthogroups of Ste14
2153 homologs (Table 16). One of the orthogroups (represented by *C. cinerea* 152667) is present
2154 only in five species and upregulated in primordia of *C. cinerea, A. ostoyae, A. bisporus* and
2155 *P. ostreatus* but interestingly shows the reverse pattern, high in vegetative mycelium and no
2156 expression in any fruiting body stage in *M. kentingensis*. The other orthogroup (represented
2157 by *C. cinerea* 354499) was upregulated in primordia of *C. cinerea, A. ostoyae, Pt. gracilis*
2158 and *S. commune (*but not in *A. ampla* and *P. ostreatus).* More broadly, members of this gene
2159 family were developmentally regulated in several species, although they were not conserved
2160 across species. On the other hand, 1-to-1 orthologs of *S. cerevisiae* Ste14 (represented by
2161 *C. cinerea* 153902), show constant expression in all species.
2162   As a final step of a-factor maturation, Ste24 and Axl1/Ste23 proteolytically cleave the
2163 N-terminus in two steps(Jones and Bennett 2011). The corresponding Agaricomycete
2164 orthologs did not show developmentally dynamics expression (*C. cinerea* protein ID: 419650
2165 and 358206, respectively)(Table 16).
2166   **Pheromone sensing GPCRs -** Seven-transmembrane domain G-protein coupled
2167 receptors have been studied in multiple Agaricomycetes(Kües 2000; Raudaskoski and Kothe
2168 2010; Jones and Bennett 2011; Wirth et al. 2021). Pheromone-sensing GPCRs are located
2169 in the B mating type locus in Basidiomycota, together with pheromone precursor genes.
2170 Pheromone sensing GPCRs transduce signals intracellularly to a mitogen-activated protein
2171 kinase (MAPK) cascade (see next chapter). Homology relationships and copy numbers of
2172 Basidiomycete pheromone-sensing GPCRs vary significantly across species, but all
2173 Basidiomycete pheromone GPCRs are homologous to yeast Ste3, which is involved in
2174 mating (reviewed recently(Raudaskoski and Kothe 2010; Fraser et al. 2014)). For example,
2175 four pheromone-like GPCR genes have recently been annotated in *S. commune*, of which
2176 one was suggested to participate in mating, whereas the others were proposed to have a
2177 role in directing growth in vegetative mycelia(Wirth et al. 2021).
2178   We identified 4-19 pheromone GPCR-encoding genes in the examined species.
2179 These genes in general showed low expression dynamics in fruiting bodies (Table 16),
2180 although several genes were upregulated slightly (FC<4) in stipes in certain species.
2181   **A-factor export proteins** - We identified a CDE orthogroup (represented by *C.*
2182 *cinerea* 540181)(Table 16) of plasma membrane ATPases which are othologous to *S.*
2183 *cerevisiae* Ste6, the protein that exports farnesylated a-factor from the cell. This orthogroup
2184 showed partial conservation of expression across the examined species. In *A. ostoyae, L.*
2185 *bicolor, L. edodes* and *M. kentingensis* it was upregulated in stipe tissues relative to caps,
2186 whereas in *C. cinerea, S. commune, A. ampla* (FC>4) and *C. aegerita* (though only at FC>2)
2187 the gene was upregulated in primordia relative to vegetative mycelium.
2188

2189 4.7.3. MAPK, TOR and cAMP pathways

2190 **MAP kinase pathways -** The mitogen-activated protein kinase (MAPK) cascades are
2191 evolutionary conserved intracellular signal transduction pathways, which regulate important
2192 cellular processes(Román et al. 2007). The extracellular signal is sensed by membrane
2193 proteins or receptors, which is relayed by sequential phosphorylation and activation of three
2194 kinases (MAPKKK, MAPKK, MAPK) to transcription factors that induce or repress specific
2195 target genes. MAPK cascades usually consist of further components, like various adaptors,

2196 docking and scaffold proteins which are implicated in the spatial and temporal regulation of
2197 MAP kinase signaling(Frawley and Bayram 2020).
2198   While in Ascomycota MAPK members have been extensively examined
2199 (e.g.(Teichert et al. 2014)), relatively little information is available on the expression and role
2200 of MAPK pathways (except the pheromone, see above) in Agaricomycetes. In *Pleurotus*
2201 *tuoliensis* pheromone-dependent and starvation-dependent MAPK signaling pathway
2202 members were reported to be up-regulated during fruiting(Fu et al. 2017). Le.MAPK, a MAP
2203 kinase of *L. edodes* (Lenedo1_1058304) was reported to be developmentally regulated and
2204 one of its interacting partners was characterized(Szeto et al. 2007). In this paper, we
2205 annotated Agaricomycetes MAPK signaling pathways based on the four main MAPK
2206 pathways known in *S. cerevisiae*: the peptide pheromone pathway (Fus3), the starvation
2207 responding pathway (Kss1), the high osmolarity glycerol stress pathway (Hog1) and the cell
2208 wall integrity (Slt2/Mpk1) pathway (Table 17). We found relatively few clear orthologs in *C.*
2209 *cinerea* (Table 17). We performed transitive ortholog and domain-based search to find
2210 further putative *S. cerevisiae* orthologs in *C. cinerea*. MAPK pathway components do not
2211 show dynamic expression patterns during fruiting body development.
2212 **TOR pathway -** The target of rapamycin (TOR) is an evolutionary conserved
2213 serine/threonine kinase that is a key regulator in multiple cellular events(Tatebe and
2214 Shiozaki 2017). In fungi, the TOR pathway plays role in the response to nutrients (especially
2215 sugar and nitrogen) but also involved in stress responses, such as osmotic and oxidative
2216 stresses. TOR signaling pathways are well-studied in yeasts, but data about their functional
2217 analysis in multicellular agaricomycetes is rare. In *G. lucidum* TOR signaling was reported to
2218 play a role in the regulation of chitin and β-1,3-glucan synthesis and hence of cell wall
2219 thickness in an SLT2-MAPK dependent manner(Chen et al. 2019). Orthologs of *Ph.*
2220 *chrysosporium* were previously annotated(Nguyen et al. 2020). According to a 5'-SAGE
2221 study of *C. cinerea,* TOR pathway members are constantly expressed during the fruiting
2222 body formation, except Rheb (*C. cinerea* protein ID: 493094) a Ras-like small GTPase,
2223 which is able to prevent FKBP12 inhibition of TOR(Cheng et al. 2013a).
2224   Here we annotated TOR pathway components in mushroom-forming fungi and could
2225 find orthologs for all but three yeast genes reported to participate in the pathway (Table 17).
2226 Consistent with previous reports, TOR pathway components showed modest expression
2227 dynamics during fruiting body development. Nevertheless, based on the broad role of the
2228 pathway in fungal physiology it will be interesting to investigate its connection with fruiting
2229 body morphogenesis in the future.
2230 **cAMP pathway -** Adenylyl cyclase dependent pathway (cAMP-pathway) has diverse roles in
2231 fungi, including cell growth, metabolism, stress resistance and nutrient-sensing (especially
2232 glucose) or starvation in fungi(D'Souza and Heitman 2001). Accordingly, the cAMP pathway
2233 has been intensely researched in mushroom-forming fungi(D'Souza and Heitman 2001;
2234 Tamaki 2007). Genetic manipulation of several cAMP and connected pathway components
2235 in *S. commune* resulted in altered fruiting characteristics, either repression or complete lack
2236 of fruiting body formation(Yamagishi et al. 2002, 2004; Knabe et al. 2013; Pelkmans 2016).
2237 The cAMP pathway has also been linked to morphogenesis in *F. velutipes:* the deletion of a
2238 Gβ-like protein CPC-2 completely impaired fruiting body formation, but the addition of cAMP
2239 or it analog 8-Bromo-cAMP (also a PKA-activator) into the medium restored fruiting in
2240 *Fv.cpc2* knockdown mutants(Wu et al. 2020b). Ras and G-protein □ subunits and their
2241 regulators (e.g. *Thn1*) might also be connected to the cAMP pathway(Yamagishi et al. 2002;
2242 Palmer and Horton 2006; Knabe et al. 2013) and were repeatedly reported to affect
2243 morphogenesis of fruiting bodies (e.g.(Schubert et al. 2006)).

2244   In general, cAMP is a known inducer of fruiting in several basidiomycetes, such as *C.*
2245 *macrorhizus*(Uno and Ishikawa 1973), *C. cinerea*(Swamy et al. 1985)*, S. commune*(Schwalb
2246 1974) and *Ph. chrysosporium*(Gold and Cheng 1979)*.* In the latter, cAMP was speculated to
2247 induce fruiting by overriding the repressive effect of glucose (i.e. mimicked starvation in the
2248 fungus(Gold and Cheng 1979))*.* More recent studies in *S. commune* reported a repressing
2249 effect of cAMP on fruiting, and suggested this was because cAMP is able to mimic high CO_2
2250 levels(Pelkmans 2016). Genes of the cAMP pathway were annotated in *S. commune* and
2251 the pde2 phosphodiesterase (Schco3_2636760), which can degrade cAMP was functionally
2252 analyzed(Pelkmans 2016). The overexpression of pde2 results in fruiting body development
2253 even at elevated CO_2 levels. These results were interpreted as evidence for CO_2 being
2254 sensed via the cAMP pathway(Pelkmans 2016).
2255   We annotated members of the cAMP pathway with *C. cinerea* as reference (Table
2256 17). Consistent with data in *S. commune*(Pelkmans 2016), we could identify most members
2257 of the cAMP pathway in the examined species. Our expression data revealed that cAMP
2258 pathway members show relatively little expression dynamics in mushroom-forming fungi
2259 (Table 17). Nevertheless, this does not preclude an important role of cAMP signaling in
2260 fruiting body formation.
2261

2262 ### 4.7.4. G-protein coupled receptors

2263 G-protein coupled receptors (GPCRs) comprise the largest receptor family in fungi. GPCRs
2264 are seven transmembrane cell surface receptors, which transduce signals from a wide range
2265 of external stimuli by a G-protein heterotrimer(Xue et al. 2008). Fungal GPCRs originally
2266 divided into six classes based on their structural similarity and homology(Xue et al. 2008),
2267 however, this classification was later expanded with additional classes (reviewed in (Brown
2268 et al. 2018)).
2269   Pheromone sensing GPCRs are among the most widely studied in connection with
2270 fruiting body development. In *Flammulina filiformis* six pheromone receptor-like genes were
2271 characterized whereby four were highly expressed in the fruiting body, while two exhibited
2272 the maximal expression level in the mycelia(Meng et al. 2020). Six pheromone-like GPCRs
2273 were characterized also in *S. commune* (*bar3, bbr2, brl1*, *brl2*, *brl3* and *brl4*); it was reported
2274 that the overexpression of *brl2, brl3* and *brl4* enhanced mating or fruiting body formation in
2275 this species(Wirth et al. 2021). We annotated 7 mating-type pheromone receptors in *C.*
2276 *cinerea* (Table 16). Most of the pheromone receptors are highly expressed during the
2277 fruiting, but do not have orthologs in other species. In addition, five further GPCR genes
2278 were detected, which, similarly to pheromone-sensing GPCRs mostly did not have orthologs
2279 in other species (Table 18). This may suggest that fungal species have a specialised GPCR
2280 repertoire, that is hard to examine using orthology-based approaches.
2281   While GPCRs are not conserved, we detected three CDE orthogroups that may be
2282 related to GPCR signaling and were developmentally regulated across several species. An
2283 RGS (regulator of G-protein signaling) domain containing protein family (*C. cinerea* protein
2284 ID: 479562) was developmentally regulated in 11/7 species (FC>2/4)(Table 18). RGS
2285 proteins are involved in signal transduction by regulating G-protein activity and rapidly
2286 switching on or off G-protein coupled receptors pathways. We also found a CDE orthogroup
2287 containing putative Ran-binding proteins (*C. cinerea* protein ID: 472370), which are
2288 members of the Ras superfamily that regulates all receptor-mediated transport between the
2289 nucleus and the cytoplasm. Finally, we detected two arrestin superfamily orthogroups (*C.*

2290   *cinerea* protein ID: 473465, *S. commune:* Schco3_2490312) (Table 18). Arrestins are
2291   involved in signal transduction through the inactivation of G protein-coupled receptors, but
2292   some members of the superfamily have been reported in receptor endocytosis, cell cycle
2293   progression and pH sensing as well also(Herranz et al. 2005; Telzrow et al. 2019).

2294   4.7.5. Other signal transduction related families

2295   **Kinases -** The majority of CDE orthogroups classified as signal transduction were kinases
2296   (Table 15). We found 13 conserved and developmentally expressed kinase orthogroups,
2297   however, most of these proved difficult to functionally characterize, likely due to the high rate
2298   of evolution in kinases and the lack of orthology to well-known genes in model species. One
2299   exception is the CDE orthogroup (*C. cinerea* protein ID: 451611) that contains orthologs of
2300   *S. cerevisiae* Rck2, which is a member of the high osmolarity glycerol (HOG) MAPK
2301   pathway. The HOG pathway is involved in responding to oxidative and osmotic stress. In
2302   most species, Rck2 orthologs showed early upregulation, with highest expression values in
2303   primordia, though its functional significance is not known. Rck2 orthologs were differentially
2304   expressed between dikaryons and A and B type monokaryons of *C. cinerea* as well(Stajich
2305   et al. 2010), and it was concluded that RCK2 genes in *C. cinerea* must serve different
2306   functions from that of *S. cerevisiae* orthologs. The remaining kinase orthogroups are
2307   functionally uncharacterized and may be interesting targets for functional studies, their
2308   dynamic expression patterns indicate potentially conserved and important functions in
2309   fruiting body development.
2310   **Velvet complex** - The velvet complex has been identified as a central regulatory hub in
2311   fungal development and secondary metabolism(Bayram et al. 2008). The complex was
2312   characterized in the Ascomycota, where it consists of VeA, LaeA, VelB as well as VelC and
2313   VosA, which assemble into condition-specific (including light-responsive) complexes. It has
2314   been shown that the velvet domain, an ~200 amino acid fold, binds DNA and resembles the
2315   structure of the metazoan transcription factors NF-κB(Ahmed et al. 2013). Proteins
2316   containing a velvet domain exist outside the Pezizomycotina as well, however, these
2317   proteins did not appear to be orthologous to members of the Velvet complex in the
2318   aspergilli(Ojeda-López et al. 2018); accordingly, how they function and whether they form
2319   complexes also in the Basidiomycota and early-diverging fungi is not known.
2320   The first evidence on a potential role of Velvet proteins in Basidiomycota fruiting body
2321   development was provided by Plaza et al(Plaza et al. 2014b). They detected the
2322   upregulation of a velvet domain containing protein in primordia of *C. cinerea* relative to
2323   vegetative mycelia. Following these trails and combining detailed mechanistic knowledge
2324   from the velvet regulon of *A. nidulans*(Krijgsheld et al. 2013), they could show that some,
2325   albeit a minor proportion, of orthologs of the *A. nidulans* velvet-regulated genes are
2326   upregulated in fruiting bodies in *C. cinerea, L. bicolor* and *S. commune*(Plaza et al. 2014b)
2327   also. This suggested some extent of conservation of function in the Dikarya, although the
2328   lack of orthology between Asco- and Basidiomycota proteins casts some uncertainty on how
2329   these data should be interpreted. Velvet protein-encoding genes were reported to be
2330   developmentally regulated in multiple Agaricomycetes species in the comparative analyses
2331   of Krizsan et al(Krizsán et al. 2019).
2332   Our current analysis indicated that the velvet domain occurs in 5-6 proteins (only 4 in
2333   *P. ostreatus*) encoded in the genomes of mushroom-forming fungi. Surprisingly, the yeast-
2334   like *C. neoformans* also possess 6 genes with a velvet domain, in contrast to Ascomycota
2335   yeasts, which have lost velvet genes(Nagy et al. 2014). Interestingly, Ascomycota on

2336 average have 4 genes that encode velvet-domain containing proteins, indicating an
2337 expansion in the Basidiomycota. Consistent with results of Ojeda-Lopez et al(Ojeda-López
2338 et al. 2018), we found that Basidiomycota velvet proteins lack clear orthology to Ascomycota
2339 genes. Only VelB and VosA of *A. nidulans* have reciprocal best hits in *C. cinerea* (*C. cinerea*
2340 protein ID: 365674 and 374867, respectively).

2341 In terms of expression, observed patterns vary widely among species. For example,
2342 all six genes are developmentally regulated in *C. cinerea*, but none in *A. ostoyae* (both
2343 FC>4), indicating considerable expression plasticity through evolution. We identified three
2344 orthogroups whose members were developmentally regulated in a notable number of
2345 species (Table 19). Of these, genes in one orthogroup (represented by *C. cinerea* 385561)
2346 were mostly upregulated in stipe tissues in the pileate-stipitate species *C. cinerea, A.*
2347 *ostoyae, M. kentingensis*, *L. edodes* (but only in mature FBs of *L. bicolor*). The gene was not
2348 developmentally regulated in *L. tigrinus* and *P. ostreatus*, possibly indicating the distant
2349 relationship of these species from ones in which the gene is stipe-upregulated. The second
2350 most interesting CDE orthogroup (*C. cinerea* protein ID: 496341) was developmentally
2351 regulated in 10 species (FC>2), but expression peaks varied from primordia (*A. ampla, S.*
2352 *commune, A. ostoyae*), to young fruiting body caps (*C. cinerea*) and stipes (*M. kentingensis*).

2353 Based on the above data, velvet protein-encoding genes represent an interesting
2354 target for phylogenetic and functional studies of sexual fruiting bodies in the Agaricomycetes;
2355 we expect their analyses will reveal interesting insights into fruiting body development.

2356

2357 **STRIPAK complex -** The striatin-interacting phosphatase and kinase, STRIPAK (known as
2358 Far complex in(Kück et al. 2019)), is a widely conserved multi-protein complex that can be
2359 found from yeast to metazoans(Reschka et al. 2018). Its function in metazoans is unknown,
2360 whereas in Ascomycota model systems (e.g. *Sordaria macrospora*) it is involved in hyphal
2361 fusion and fruiting body development. It was first discovered in 2004 in fungi(S and U 2004)
2362 and its function has been increasingly clarified in a series of papers since then (see
2363 in(Reschka et al. 2018; Riquelme et al. 2018)). Mechanistically, the STRIPAK complex
2364 provides links between multiple signaling pathways in eukaryotic cells (reviewed in(Kück et
2365 al. 2019)), although many of the details of its interactions with other proteins are not known.
2366 Its role in fruiting body formation in the Basidiomycota has not yet been investigated.

2367 We queried the *C. cinerea* genome with members of the STRIPAK complex
2368 described from *Sordaria* and *S. cerevisiae* (listed in(Reschka et al. 2018)). *C. cinerea* seems
2369 to have a fully functional STRIPAK complex, with all genes having clear orthologs, except for
2370 Far3/7 which only had weak hits. Further, the *C. cinerea* proteins were members of
2371 conserved single-copy Agaricomycetes orthogroups, which indicated that the complex is
2372 conserved in all the examined Agaricomycetes species. Members of this complex did not
2373 show significant expression dynamics (Table 20). The conservation of the complex in the
2374 Agaricomycetes suggests it might have important functions, however, its role in fruiting body
2375 development remains unclear at the moment and requires further research.

2376 4.7.6. Light sensing systems and light receptors

2377 Fungi adapt developmental processes to light signals in time and space to ensure that
2378 sporulating cells can maximize spore dispersal efficiency(Yu and Fischer 2018). The
2379 photobiology and its connection to developmental events are quite well-known in both the
2380 Asco- and Basidiomycota. In the last decade, the molecular architectures and regulatory
2381 networks of sensing and responding to blue, red and green light have been uncovered in

2382 multiple species(Corrochano 2011; Fuller et al. 2015). In this chapter we discuss light
2383 sensing systems in Agaricomycetes and analyze their expression patterns in fruiting bodies.
2384 We note that the best known such system, the white collar complex has transcription factor
2385 activity and is discussed under chapter 4.5.1.
2386   **Cryptochromes** - Fungal genomes include DASH-type cryptochromes, photolyase
2387 genes that function as blue light photoreceptors and are involved in DNA repair(Fuller et al.
2388 2015). Cryptochromes are regulated by the white collar complex in *N. crassa*(Froehlich et al.
2389 2010) and regulate fruiting body development in certain Ascomycota (e.g. *Cordyceps*
2390 *militaris*(F et al. 2017)), but to our best knowledge, no such information is available in the
2391 Basidiomycota. Our analysis suggests that cryptochromes are single copy genes in the
2392 Agaricomycetes, except in *L. edodes*, which has two genes. The CDE orthogroup containing
2393 Agaricomycetes cryptochromes (represented by *C. cinerea* 492962)(Table 21) was
2394 developmentally regulated in 9/7 species (FC>2/4), and showed strong induction in
2395 primordia relative to vegetative mycelium in *A. ostoyae, M. kentingensis, L. edodes, P.*
2396 *ostreatus, Ph. chrysosporium* and at FC>2 in *C. aegerita* and *C. cinerea*. The gene was
2397 constantly expressed in *A. ampla* and *S. commune* and was missing in *L. bicolor.* Based on
2398 these data, cryptochromes may be relevant to fruiting body formation in the Agaricomycetes.
2399   **Phytochromes** are red- and far-red receptors that influence sexual and asexual
2400 sporulation in fungi. The first circumscribed fungal phytochrome was the *fphA* gene in *A.*
2401 *nidulans*, which represses sexual development under red light(A et al. 2005). Since then, the
2402 repression of sexual development has been proven for *N. crassa* too and several details of
2403 the process (e.g. interaction with WCC and velvet factors) have been clarified(A and J 2005;
2404 Wang et al. 2016; Yu et al. 2016). In the Basidiomycota, the few reports of phytochromes
2405 include a systematic mutant library in *C. neoformans*, which circumscribed the gene
2406 encoding *TCO3* (Lee et al. 2016), as well as observations of phytochrome upregulation in
2407 browning mycelium of *L. edodes*(Tang et al. 2013) and in rhizomorphs of *A. ostoyae*(Sipos
2408 et al. 2017b). In *U. maydis* red and blue light receptors have been shown to be required for
2409 the development of fruiting body-like structures(Sánchez-Arreguin et al. 2020).
2410   Phytochromes seem to be single-copy genes in the Agaricomycetes examined here.
2411 They formed a conserved orthogroup (represented by *C. cinerea* 470504, Table 21),
2412 however, genes in this orthogroup did not show significant expression dynamics during
2413 fruiting body formation, except in *A. ostoyae* and *C. cinerea*. In *A. ostoyae* the expression of
2414 the phytochrome gene was ~10x higher in stipes than caps in stage 2 primordia and young
2415 fruiting bodies. Similarly, in *C. cinerea* peak expression was observed in elongating stipes in
2416 the young fruiting body stage. However, other species did not display this expression profile,
2417 indicating that phytochrome expression is not conserved across mushroom-forming fungi.
2418 Although expression patterns did not seem to be conserved in fruiting bodies, it is possible
2419 that red light sensing phytochromes are part of a photoreceptor system that signals position
2420 in open air, which is required for sporulation and fruiting body formation for the majority of
2421 species(J et al. 2010; Fuller et al. 2015).
2422   Fungal light sensing systems also include rhodopsins, seven-transmembrane domain
2423 proteins involved in sensing green light(Bieszke et al. 1999). We detected rhodopsins only in
2424 *L. tigrinus* and *Ph. chrysosporium*, but none of the Agaricales in our dataset.
2425   **Genes related to blue light receptors -** Blue light is one of the most important
2426 signals for fungi and responses as well as molecular aspects of the fungal blue light
2427 response are among the best known aspects of fungal photobiology in both the Asco- and
2428 Basidiomycota. The most important receptors of blue light are the white collar complex
2429 (WCC), which comprises the photoreceptors/transcription factors WC2 and WC1. These

2430 have been discussed under the chapter on transcription factors (see above). We here only
2431 discuss putative accessory proteins similar to VIVID of *N. crassa*. These proteins harbor a
2432 single PAS domain and act as repressors of the WCC in *N. crassa* and were suggested to
2433 provide a mechanism for adapting to changing light intensities during the day(Fuller et al.
2434 2015). Although evidence for that is missing in the Agaricomycetes, a CDE orthogroup of
2435 PAS domain proteins (represented by *C. cinerea* 500409) was developmentally regulated in
2436 9/7 species (FC>2/4) and showed strong induction in primordia relative to vegetative mycelia
2437 in *A. ostoyae, C. aegerita, C. cinerea, L. bicolor, L. tigrinus, M, kentingensis, Ph.*
2438 *chrysosporium* but not in *A. ampla* and *P. ostreatus* (and missing from *L. edodes* and *S.*
2439 *commune*). It will be interesting to see if this or similar genes are involved in light responses
2440 in the Agaricomycetes.
2441   **Dst2 family -** We found that orthologs of the dst2 gene of *C. cinerea* formed a CDE
2442 orthogroup (represented by *C. cinerea* 361584). Dst2 has been described as a FAD-binding
2443 and Berberine-like domain containing protein that, if mutated, results in a blind dark stipe
2444 phenotype similar to what is observed in mutations on the white collar complex(Kamada et
2445 al. 2010; Kuratani et al. 2010). Based on these observations, it has been hypothesized that
2446 dst2 represents a novel photoreceptor(Kuratani et al. 2010). The typical expression profile of
2447 these genes (seen in *A. ostoyae, C. aegerita, C. cinerea, L. edodes* and *P. ostreatus*)
2448 involved upregulation in primordia relative to mycelium and, in later stages, higher
2449 expression in stipes compared to caps. Variations to this pattern exist, such as only being
2450 FB-init in *L. bicolor* and *S. commune*, or being only stipe upregulated but not FB-init in *M.*
2451 *kentingensis* and *L. tigrinus*. We hypothesize that dst2 genes might be related to stipe
2452 development and, potentially, photomorphogenesis.
2453

4.8. Cell wall biosynthesis and modification

2455 The cell wall is an organelle that functions as an extracellular matrix in fungi. It provides
2456 integrity, rigidity to cells, defines cell shape, harbors extracellular proteins, represents a
2457 channel of communication with the environment, and provides the first line of physical
2458 defense, to name just a few of its major roles in fungal physiology. Structural roles are
2459 particularly important for the Agaricomycetes that form above ground fruiting bodies that
2460 should be rigid yet plastic enough to withstand environmental forces and support spore
2461 dispersal. In fruiting bodies, the cell wall must serve structural and defense roles but must
2462 also be sufficiently plastic to allow changes in shape and size during development. Although
2463 mechanisms of cell shape determination are not known in mushroom-forming fungi,
2464 regulated cell wall deposition and remodeling by hydrolytic enzymes residing in the wall
2465 itself(Verdín et al. 2019), are undoubtedly of key importance.
2466   There is plenty of evidence for cell wall remodeling and differential cell wall
2467 compositions in fruiting bodies of various species (e.g. (Buser et al. 2010a; Almási et al.
2468 2019; Krizsán et al. 2019; Zhou et al. 2019)), although most of that is based on
2469 transcriptome rather than functional studies. For example, stipe growth may be realized by
2470 the breaking of chitin-glucan cross-links by hydrolytic enzymes(Liu et al. 2021). Similarly,
2471 there are cross-linking (transglycosidases) and lytic (e.g. glycoside hydrolases) enzymes
2472 that rigidify and make the cell wall more plastic, respectively(Verdín et al. 2019).
2473 Mannosylation might also rigidify the cell wall and mannoproteins are often N-glycosylated,
2474 which contributes to water retention and adhesion(Lesage and Bussey 2006). In the
2475 Agaricomycetes, Buser et al reported a fruiting body-specific N-glycan from *C. cinerea*(Buser

2476   et al. 2010b). The regulated interplay of these enzymes might result in the formation of
2477   stage-, tissue-, and species-specific cell wall architectures in fruiting bodies.
2478   In this chapter we review current knowledge on cell wall related genes in mushroom-
2479   forming fungi and analyze CDE orthogroups that are likely linked to cell wall synthesis or
2480   modification. We will not review cell wall composition in fruiting bodies, but refer to earlier
2481   reviews(Kües 2000). Cell wall functioning is quite well-researched in the Ascomycota (e.g. in
2482   *S. cerevisiae* and *N. crassa*), and to a much smaller extent in the Basidiomycota. We
2483   therefore base much of our functional hypotheses on knowledge in the Ascomycota, noting
2484   that the process may be different and/or significantly more complex in the Basidiomycota.
2485   For example, while some chitin-glucan cross linking enzyme families appear similarly
2486   important both in Asco- and Basidiomycota (e.g. GH16/GH17), there are some (e.g. GH72
2487   and GH76) which are involved in cell wall remodeling in the Ascomycota, but apparently not
2488   in the Basidiomycota. Hereafter we discuss cell wall related CDE orthogroups broken down
2489   into synthetic and remodeling enzymes as well as by substrate (chitin/glucan).
2490   From these analyses a few broad observations emerge, which we discuss here. Most
2491   importantly, the diversity of enzymes that show developmental regulation in fruiting bodies
2492   suggests that the fruiting body cell wall may be significantly more complex than we think,
2493   and we still know quite little about its exact structure and composition. A general pattern that
2494   also arises is that more tissue- and stage-resolved transcriptomes reveal proportionately
2495   more developmentally expressed genes, which indicates that cell wall remodeling and,
2496   consequently, cell wall architectures, likely show high tissue-specificity in fruiting bodies.
2497   Based on our results, it appears that fungal cell wall (FCW) remodeling and crosslinking
2498   genes show significantly more expression dynamics than genes encoding chitin and glucan
2499   synthases. In line with this observation, we found that intracellular components of cell wall
2500   biosynthesis (chaperones, glucan synthase complex, pathways involved in glucan monomer
2501   synthesis) also show little expression dynamics.
2502   Comparisons across species revealed limited conservation in FCW related gene
2503   expression patterns across species, which suggests it diverges rapidly during evolution. This
2504   lends support to the quick evolution of cell wall architectures and corresponding enzyme
2505   profiles in fruiting bodies. Another observation related to this is that FCW-related genes
2506   show complex gene duplication/loss patterns, which complicates the inference of well-
2507   conserved groups of 1-to-1 orthologous genes. Thus, these genes might be more
2508   appropriately analyzed in the context of broader orthogroups (e.g. based on
2509   Orthofinder(Emms and Kelly 2015)) than based on the strict 1-to-1 orthogroups we used.
2510   However, for the sake of uniformity, we stick to the latter, with notes on overall prevalence of
2511   developmental expression in a given family.
2512   An interesting observation is that several FCW active genes upregulated in fruiting
2513   bodies are also expressed during mycorrhiza establishment in ECM fungi such as *L.
2514   bicolor*(Martin et al. 2008; C et al. 2014). Such signals provide clues to shared
2515   morphogenetic mechanisms between ectomycorrhizal development and fruiting bodies.
2516   Finally, an important consideration for cell wall biosynthesis/remodeling genes is
2517   whether they are upregulated in fruiting bodies is the vegetative mycelium sample that was
2518   used as control in the RNA-Seq. Non-growing inactive hyphae (where cell wall synthesis rate
2519   is low) as control of actively growing fruiting bodies can yield more gene expression
2520   differences than an actively growing mycelium sample. Although we do not think this has
2521   significantly influenced our comparisons, because we do not know the sampling conditions
2522   for all species, this possibility should be kept in mind in the interpretation of results.

2523   We attempted to as comprehensively analyze cell wall related gene expression as
2524 possible, at least with consideration of genes that show some expression conservation at the
2525 gene family level. Nevertheless, it is certain that several important, especially species-
2526 specific genes are left out from our inventory. For example, mannosylation, a potentially
2527 interesting process contributing to cell wall functioning, is not discussed here due to the lack
2528 of orthology to experimentally characterized mannosylation components in the Ascomycota.
2529 These aspects will need to be covered in future studies.
2530

2531 4.8.1. Cell wall biosynthesis

2532 4.8.1.1. Chitin biosynthesis (GT2)

2533 Chitin is one of the most important, although usually not the most abundant structural
2534 polymer of the fungal cell wall. This is true for fruiting bodies as well, in which, although cell
2535 wall composition is altered relative to vegetative mycelia(M and C 1981; Mol and Wessels
2536 1990; Kües 2000), chitin is an important component that confers rigidity. Chitin is also a
2537 scaffold for the modification of cell wall structure either by cross-linking, incorporation of
2538 glycoproteins or chemical modifications to the chitin polymers, among others(Verdín et al.
2539 2019). Cell wall chitin assembly involves the action of the UDP-N-acetylglucosamine
2540 biosynthesis pathway (in *S. cerevisiae* Gfa1p, Gna1p, Pcm1p, Qri1p), chitin synthases
2541 (Chs1-3) which elongate the growing chitin polymer as well as chitin deacetylases, which
2542 modify the chitin on the cell surface(Shahinian and Bussey 2000; Klis et al. 2006; Verdín et
2543 al. 2019) (the latter is discussed in chapter 4.8.2.1). While yeasts have up to three chitin
2544 synthases, filamentous fungi have additional chitin synthase genes (on average up to
2545 seven(Verdín et al. 2019)), including highly processive ones that harbor a myosin motor
2546 domain and that were lost in yeasts(N et al. 2006).
2547   We examined chitin synthesis and modification related genes based primarily on
2548 functional annotations and recent reviews(Shahinian and Bussey 2000; Klis et al. 2006;
2549 Verdín et al. 2019). Clear orthologs of the *S. cerevisiae* UDP-N-acetylglucosamine
2550 biosynthesis pathway could be identified in all examined Agaricomycetes species (Table 22).
2551 We identified 8-13 (17 in *L. bicolor*) chitin synthases of the GT2 family, 2-3 chitin synthase
2552 export chaperones as well as orthologs of *S. cerevisiae* SKT5 (activator of chitin synthase 3)
2553 in the examined Agaricomycetes. Interestingly, UDP-N-acetylglucosamine biosynthesis
2554 pathway genes showed more expression dynamics than most chitin synthase genes (Table
2555 22). Among chitin synthases, although many formed conserved orthogroups, only a single
2556 appeared developmentally regulated in a wide array of species. Nevertheless, each species
2557 had developmentally regulated and/or FB-init (sensu Krizsan et al 2019) chitin synthases,
2558 though these did not always belong in conserved orthogroups. The most interesting
2559 orthogroup (represented by *C. cinerea* 359180) was developmentally regulated in 7/6 (at fold
2560 change 2/4) species and showed upregulation and high expression in primordia relative to
2561 vegetative mycelium in several species (*C. cinerea, A. ampla, P. ostreatus, S. commune, C.
2562 aegerita* and *L. edodes*). Comparative genomic data suggests that this orthogroup of chitin
2563 synthases is specific to mushroom-forming fungi or the Basidiomycota, suggesting that it
2564 may be a fruiting body-specific chitin synthase. A second CDE orthogroup of GT2 chitin
2565 synthases (*C. cinerea* protein ID: 519767) was also detected (Table 22).
2566   A chitin synthase regulator described as Csr2 from *C. neoformans*(Banks et al. 2005)
2567 and Skt5 from *S. cerevisiae*(S et al. 1993), is conserved in the Agaricomycetes (orthogroup

2568 represented by *C. cinerea* 538650), but did not show significant expression dynamics (Table
2569 22).

2570 4.8.1.2. *β*-glucan biosynthesis

2571 *4.8.1.2.1. β-1,6-glucan (Kre9/Knh1, GH16, GH63)*

2572 In addition to β-1,3-glucan, β-1,6-glucan is also found in fungal cell walls and is
2573 hypothesized to serve gluing purposes by covalently linking β-1,3-glucan to chitin and
2574 mannoproteins(Lesage and Bussey 2006). Its synthesis builds on UDP-glucose produced by
2575 the corresponding pathway in *S. cerevisiae*. We find that most members of the yeast beta-
2576 1,6-glucan biosynthesis pathway have no clear 1-to-1 ortholog in the Agaricomycetes (Kre9,
2577 Knh1, Dfg5, Dcw1, Kre5, Kre1). Only Kre6 (*C. cinerea* protein ID: 447635), Rot1 (*C. cinerea*
2578 protein ID: 241938), Rot2 (*C. cinerea* protein ID: 359282) and CWH41 (*C. cinerea* protein ID:
2579 486333) had clear orthologs. However, at the family level, all known members of the β-1,6-
2580 glucan synthesis machinery are represented in the Agaricomycetes (Table 23), except Kre1,
2581 which seems missing.
2582 **Kre9/Knh1 -** In yeasts and filamentous Ascomycota, the Kre9/Knh1 and GH16 families
2583 include the main glucan synthases(Lesage and Bussey 2006). Several additional well-
2584 characterized proteins in the endoplasmic reticulum are necessary for β-1,6-glucan
2585 synthesis *(e.g. Big1, Rot1, Rot2, Cwh41).* It should be noted that there is a strong overlap
2586 between genes participating in β-1,6-glucan synthesis and remodeling, therefore, separating
2587 these two processes is harder than it is in the case of chitin or β-1,3-glucan.
2588   The Kre9/Knh1 family of cell surface proteins are involved in β-1,6-glucan assembly
2589 in the cell wall of fungi and have been characterized in a number of Ascomycota
2590 species(Brown and Bussey 1993; Dijkgraaf et al. 1996; S et al. 1998b; Costachel et al.
2591 2005), predominantly yeasts. A member of this family has been independently reported as a
2592 developmentally regulated gene, DRMIP, of *L. edodes*(Szeto et al. 2007)*,* which was
2593 reported to be primarily expressed in primordia. Reports of this family in fruiting body
2594 transcriptomes just started to emerge recently(Almási et al. 2019; Krizsán et al. 2019; Liu et
2595 al. 2020b), and no mechanistic study proved yet a link to cell wall in fruiting bodies. The
2596 family is overrepresented in Agaricomycetes(Krizsán et al. 2019), suggesting it might have
2597 experienced duplications specific to mushroom-forming fungi.
2598   We identified 5-15 Kre9/Knh1 genes in mushroom-forming fungi. Of these 3-4 are
2599 developmentally regulated in each species. Notably, each species has 2-3 genes in this
2600 family that show a considerably higher expression in all fruiting body tissues than in
2601 vegetative mycelia, suggesting that these genes are involved in generating fruiting-body
2602 specific cell walls. For example, in *C. cinerea* we found three FB-init Kre9/Knh1 genes (*C.*
2603 *cinerea* protein ID: 470185, 359649, 465604), whereas in *L. edodes*, there was one FB-init
2604 gene, in addition to DRMIP, which was highly expressed and two-fold upregulated in all
2605 fruiting body tissues compared to vegetative mycelium. The family displayed more
2606 expression dynamics in more resolved transcriptomes (e.g. *A. ostoyae, C. cinerea*),
2607 suggesting that it has considerable tissue-specificity. In addition, each species showed for
2608 some genes an expression peak in vegetative mycelium, which is consistent with a
2609 partitioning of fruiting body and mycelium-specific roles. Taken together, the Kre9/Knh1
2610 family is likely involved in β-1,6-glucan assembly in the cell wall, with several genes showing
2611 fruiting body-specific expression. We detected five CDE orthogroups of Kre9/Knh1 genes
2612 (represented by *C. cinerea* 359649, 465604, 470186, 417746, *S. commune* 2557059)(Table
2613 23).

2614   **GH16 -** The other major β-1,6-glucan synthase family is GH16, which includes both glucan
2615   synthases (e.g. Kre6 of *S. cerevisiae*, = *C. cinerea* 447635) and glucan-chitin cross-linking
2616   enzymes that participate in cell wall remodeling(Patel and Free 2019). We discuss this family
2617   in detail under the 'Cell wall remodeling' chapter.
2618   Several ER-localized β-1,6-glucan synthesis related proteins have been described in
2619   yeasts and filamentous Ascomycota(Lesage and Bussey 2006; Orlean 2012; Essen et al.
2620   2020), including Kre5, Big1, Rot1, Rot2 and Cwh41. Rot2 and Cwh41 are also involved in
2621   protein N-glycosylation(Lesage and Bussey 2006). These are conserved in the
2622   Agaricomycetes, mostly forming single-copy families with low expression dynamics during
2623   fruiting body development. The GT24 (glycoprotein α-glucosyltransferase) family includes
2624   the Kre5 gene in *S. cerevisiae* and *C. albicans.* Kre5 has an indirect role in β-1,6-glucan
2625   synthesis and may be involved in the refolding of misfolded N-glycoproteins in the ER, in
2626   particular β-1,6-glucan synthases(Lesage and Bussey 2006). GT24 is present as a single-
2627   copy family in Agaricomycetes (Table 23); their expression is approximately constant in
2628   fruiting bodies. Big1 is an ER membrane protein of unknown function that is required for β-
2629   1,6-glucan synthesis in *S. cerevisiae*(Lesage and Bussey 2006). It is a single-copy gene
2630   family (represented by *C. cinerea* 432992) in the Agaricomycetes, without developmentally
2631   relevant expression patterns (Table 23). Rot1 is a chaperone involved in protein folding (in
2632   general) located in the ER. It is required for cell wall synthesis and N-glycosylation and O-
2633   mannosylation in *S. cerevisiae*(Lesage and Bussey 2006). Rot1 orthologs are single copy
2634   genes (*C. cinerea* protein ID: 241938) in the Agaricomycetes that showed no developmental
2635   dynamics in the species we examined (Table 23). Rot2 is an ER-localized alpha-glucosidase
2636   involved in protein N-glycosylation, required for normal levels of β-1,6-glucan in the cell wall
2637   of *S. cerevisiae*(Lesage and Bussey 2006). It belongs to the GH31 family, which is present in
2638   3-8 copies in Agaricomycetes. They form two CDE orthogroup (FC2/4: 8/6 species,
2639   represented by *C. cinerea* 499280 and FC2/4: 6/5 species, represented by *S. commune*
2640   2543909)(Table 23), which were developmentally regulated in 6/5 and 5/4 species, however,
2641   expression patterns of these orthogroups did not show marked conservation. 1-to-1
2642   orthologs of *S. cerevisiae* Rot2 (represented by *C. cinerea* 359282) showed very small gene
2643   expression dynamics.
2644   The GH63 family includes alpha-glucosidases, such as Cwh41 of *S. cerevisiae,*
2645   involved in cell wall beta-1,6-glucan assembly in the ER. The family is represented by 2
2646   copies in all but one of the examined species (*L. edodes* has 5 genes). GH63 genes form
2647   two conserved orthogroups, of which one (*C. cinerea* protein ID: 486333), containing
2648   orthologs of *S. cerevisiae* Cwh41) did not appear to be interesting, whereas members of the
2649   other (*C. cinerea* protein ID: 494484) showed marked expression peaks coinciding with
2650   spore formation in all species (Table 23). In *C. neoformans*, the gene showed upregulation
2651   at 72h, also coinciding with sporulation. Whether this GH63 orthogroup is needed for spore
2652   wall assembly or other processes that temporally overlap with sporulation cannot be
2653   determined based on these data, nevertheless, the family seems to be interesting in the
2654   context of fruiting body development.

2655   *4.8.1.2.2. β-1,3-glucan (GT48)*

2656   In *S. cerevisiae* β-1,3-glucan is synthesized by the FKS (Fks1-3) and the GAS (Gas1-4
2657   families as well as a few accessory proteins, such as Smi1 (*C. cinerea* protein ID: 181364)
2658   and Rho1 (*C. cinerea* protein ID: 528086)(Lesage and Bussey 2006; Verdín et al. 2019). Of
2659   the glucan synthases only FKS1 and Gas1 had clear 1-to-1 orthologs is the Agaricomycetes
2660   (*C. cinerea* protein ID: 446030 and 543646, respectively). The glucan synthase complex,

2661 which is formed by FKS1, Rho1, Smi1(Verdín et al. 2019), seems to be conserved in the
2662 Agaricomycetes.
2663   Most Agaricomycetes species have two beta-1,3-glucan synthase genes of the GT48
2664 family (except *M. kentingensis* and *L. tigrinus*, which have 5 and 7 respectively). Somewhat
2665 surprisingly, GT48 genes showed very modest expression dynamics and were mostly not
2666 developmentally regulated. Similarly, the Gas1 family of glucanosyltransferases is present in
2667 1-2 copies in the examined species (*L. bicolor* has 7 and *M. kentingensis* has 4) and they
2668 were not developmentally regulated. Accessory members of the glucan synthase complex
2669 (Smi1, Rho1) showed constant expression in fruiting bodies. Collectively, these data suggest
2670 that β-1,3-glucan synthesis is present, but it is not dynamically regulated in fruiting bodies.
2671

2672 ### 4.8.2. Cell wall remodeling

2673 #### 4.8.2.1. Chitin-active enzyme families (GH18, GH20, X325, AA9, AA14, CBM5/12, CBM50,
2674 CE4)

2675 **GH18 -** Glycoside hydrolase family 18 contains chitinases (both endo- and exochitinases).
2676 Chitinases remodel the chitin structure by cleaving β-1,4 linkage of chitin or modify
2677 oligosaccharide(Verdín et al. 2019) (e.g. cleaving chitobiose from the cell wall). Chitinases
2678 are one of the most straightforward players in fruiting body development and accordingly
2679 have been reported in several previous genomic(Chen et al. 2012; Park et al. 2014),
2680 transcriptomic(Patyshakuliyeva et al. 2013; Sakamoto et al. 2017b; Xie et al. 2018; Krizsán
2681 et al. 2019) and mechanistic(Niu et al. 2016; Zhou et al. 2016c) studies. Despite the clear
2682 prediction of their role in morphogenesis, this has not been mechanistically shown in the
2683 Basidio- or Ascomycota(L et al. 2011), possibly because multiple paralogous genes in each
2684 species' genome complicate functional studies.
2685   In the Basidiomycota, Zhou et al reported chiB1 (*C. cinerea* protein ID: 368217)
2686 (Table 24), a class V exochitinase purified from *C. cinerea* and suggested to be involved in
2687 cap autolysis(Zhou et al. 2016c). Expression data agree with this, the corresponding gene
2688 shows a very strong induction in mature fruiting body caps. Similarly, ChiIII(Niu et al. 2016)
2689 of *C. cinerea* (C. cinerea protein ID: 354859) was reported to have both endo- and
2690 exochitinase activity, and to be expressed mostly in fruiting bodies, with peak expression in
2691 mature fruiting bodies (which is confirmed by our expression data). Most recently, Zhou et al
2692 assayed the role of chitinases in stipe cell wall extension(Zhou et al. 2019) and named six
2693 further chitinases in *C. cinerea*, ChiE1, (*C. cinerea* protein ID: 543586), ChiE2 (*C. cinerea*
2694 protein ID: 520359), ChiEn1 (*C. cinerea* protein ID: 91051), ChiEn2 (*C. cinerea* protein ID:
2695 90984), ChiEn3 (*C. cinerea* protein ID: 470416), and ChiEn4 (*C. cinerea* protein ID: 358869).
2696 Chitinases have also been examined in the context of autolysis of the model mushrooms *C.*
2697 *cinerea* and *Coprinellus congregatus*(H and HT 2009).
2698   GH18 genes are found in 8-12 copies in Agaricomycetes (up to 20 in Polyporales,
2699 see (Chen et al. 2012)), some of which harbor carbohydrate binding modules (CBMs), but
2700 their function has not been examined. Most chitinases are developmentally expressed in
2701 fruiting bodies. Mycelium-upregulated chitinases are also found in most species; these,
2702 although display peak expression in vegetative mycelia (often ~10x that of fruiting bodies),
2703 often also show >4fold expression dynamics within fruiting bodies. We detected seven CDE
2704 orthogroups *(Table 24), which* included *C. cinerea* ChiB1, ChiE2, ChiEn1 and ChiEn3. In
2705 general, although, the detected chitinase orthogroups were developmentally regulated in
2706 many species, they did not show conserved expression patterns across species, which could

2707 indicate quick divergence of function or the failure of our reciprocal-best-hit based approach
2708 to detect functionally related genes (in the latter case phylogenetic analyses might help).
2709 One orthogroup (represented by *C. cinerea* 520359) shows gill-specific expression peaks in
2710 the species in which separate RNA-Seq data are available for gills (*A. ostoyae, P. ostreatus*)
2711 or late upregulation in *Pt. gracilis, C. aegerita, L. edodes, L. bicolor, Ph. chrysosporium, A.*
2712 *ampla* and *S. commune*, suggesting it may have something to do with processes that take
2713 place in the hymenium late in development, possibly sporulation.
2714 **GH20 and chitin degradation products** - A chitin-connected GH family is GH20, which has
2715 β-1,6-N-acetylglucosaminidase activity and thus can cleave chitobiose released by
2716 chitinases further into N-acetylglucosamine (GlcNac). GlcNac may be taken up by the cell for
2717 repurposing of cleaved cell wall components as nutrient source(López-Mondéjar et al. 2009;
2718 de Oliveira et al. 2018) or, to trigger upregulation of chitinolytic genes in a transcriptional
2719 feedback-loop(Langner and Göhre 2015). The latter hypothesis seems more plausible for
2720 cases when the fungus feeds on chitin rather than modifies it for developmental purposes. In
2721 previous reports, GH20 genes have been identified in the post-harvest transcriptome of *L.*
2722 *edodes*(Sakamoto et al. 2017b). We identified 2-8 GH20 genes in the examined
2723 Agaricomycetes, some of which were developmentally regulated (including the single gene
2724 in *C. neoformans*), but did not form conserved CDE orthogroups. The role of this gene family
2725 in fruiting body development may be worth examining further.
2726 　　　　If GlcNac is indeed taken up and metabolized in the cell, then two of the detected
2727 CDE orthogroups may provide clues to its mechanistic bases. An orthogroup of GlcNac
2728 transporters, which contains reciprocal best hits of *C. albicans* NGT1, was developmentally
2729 regulated in 5/4 species (*C. cinerea* protein ID: 464567, Table 24). *C. albicans* NGT1
2730 encodes a specific transporter of GlcNac(FJ and JB 2007; Q et al. 2020). We speculate that
2731 this orthogroup may be involved in the uptake of GlcNac monomers generated by GH20
2732 enzymes extracellularly.
2733 　　　　In fungi, the GlcNac catabolic pathway is best described in *C. albicans*(Kumar et al.
2734 2000; Yamada-Okabe et al. 2001), however, only a few of the corresponding genes are
2735 conserved in Agaricomycetes. Only the GlcN6P deaminase (Nag1, *C. cinerea* 356467
2736 FC2/4: 7/4 species) and a GlcNac permease Nag4 (*C. cinerea* protein ID: 544873, FC2/4:
2737 6/4)(Table 24) genes have clear reciprocal best hits in Agaricomycetes, whereas we could
2738 not identify clear orthologs of N-acetylglucosamine kinase (Nag5) or N-acetylglucosamine
2739 deacetylase (Nag2). Our annotations identified a different gene as N-acetylglucosamine
2740 deacetylase, however (*C. cinerea* protein ID: 446427), which was developmentally regulated
2741 in 8/6 species (FC=2/4). We also detected a GlcNac deacetylase orthogroup (*C. cinerea*
2742 protein ID: 446427), which may be involved in intracellular GlcNac catabolism.
2743 　　　　In summary, the evidence presented here on GlcNac uptake and catabolism in
2744 mushroom forming-fungi is circumstantial, at best, however, provides clues for further
2745 research on this topic. GlcNac (and any other breakdown intermediate) produced during cell
2746 wall modification may be precious compounds in the fruiting body, which is otherwise
2747 dependent on distal supply of nutrients from the mycelium. This might have prompted the
2748 evolution of efficient repurposing mechanisms in fruiting bodies to mitigate its dependence
2749 on mycelial nutrient supply.
2750 **CE4 chitin deacethylases -** Chitin deacetylases (CDA) are involved in chitosan production,
2751 a minor but key constituent of the cell wall. Chitosan, a more soluble polymer than chitin,
2752 occurs in both mycelia and fruiting bodies of basidiomycetes, although its role in fruiting body
2753 formation is thought to be limited(M and C 1981; Crestini et al. 1996; Baker et al. 2007). It is
2754 produced by the synergistic activities of chitin synthases and CDAs, where the former

2755 synthesize and the latter deacetylate chitin in various spatial or temporal patterns and to
2756 varying degrees(Sebastian et al. 2020). CDAs belong to the carbohydrate esterase 4 family
2757 (CE4) in the CAZy classification and are homologous to bacterial nodB factors that produce
2758 signal molecules in the rhizobia-legume symbiosis(Buhian and Bensmihen 2018).
2759 Deacetylation of chitin to chitosan makes it resistant to chitinases, which might provide a
2760 mechanism for regulating the extent of chitinase-mediated wall plasticity and thus cell
2761 expansion (e.g. in stipe elongation(Liu et al. 2021)). Fungal CDAs have a potential in
2762 biotechnology, as chitosan is an additive in food, cosmetic and pharmaceutical
2763 products(Morin-Crini et al. 2019). CDAs have poorly known roles in Ascomycota fruiting
2764 body development, with both *N. crassa* CDAs, nevertheless, being highly expressed during
2765 perithecium development, suggesting roles in sexual morphogenesis(Patel and Free 2019).
2766 It should be noted that CE4 also contains acetyl xylan esterases, which are able to break
2767 down the xylan backbone of hemicellulose during wood decay(X and S 2009). Therefore,
2768 some genes of the family in the Agaricomycetes may be related to wood decay too.
2769 　　　CDA genes have been detected in several RNA-Seq studies focusing on fruiting
2770 body development(Morin et al. 2012; Sipos et al. 2017b; Xie et al. 2018; Krizsán et al. 2019).
2771 Three chitin deacetylases have been experimentally characterized in *C. cinerea*, CDA1 (*C.*
2772 *cinerea* protein ID: 42776), CDA2 (*C. cinerea* protein ID: 502602), and CDA3 (*C. cinerea*
2773 protein ID: 464952)(Table 24), all of which were reported to have high expression in the
2774 elongating region of the stipe(Wang et al. 2018b; Bai et al. 2020). Another chitin
2775 deacetylase, primarily expressed in the fruiting bodies, was investigated in *F. velutipes*(M et
2776 al. 2008).
2777 　　　Searching the genomes of fruiting body forming fungi reveals 5-18 chitin deacetylase
2778 genes, several of which formed conserved single-copy orthogroups. The previously
2779 investigated CDA1-3 genes of *C. cinerea* formed species-specific orthogroups. The majority
2780 of CDA genes in the examined species were developmentally regulated in fruiting bodies,
2781 indicating key functions in fruiting body development. Six out of 17 *C. cinerea* CDA genes
2782 (Table 24) formed CDE orthogroups. These showed diverse expression peaks with no
2783 apparent trend in their expression. However, several genes were upregulated in stipes of
2784 young or mature fruiting bodies. One of them (*C. cinerea* protein ID: 355445) comprise
2785 proteins representing reciprocal best hits of *S. cerevisiae* CDA1, which is involved in the
2786 biosynthesis of the ascospore wall, required for spore wall rigidity. Expression of genes in
2787 this orthogroup did not peak during spore development, suggesting that this specific gene
2788 orthogroup is not involved in basidiospore wall synthesis. On the other hand, the expression
2789 of one and three genes were highest in young fruiting body gills and mature fruiting body
2790 gills and caps, respectively, which might be involved in producing chitosan in spore walls.
2791 　　　On a related note, we could not detect chitosanases, which degrade chitosan, in the
2792 genomes of mushroom-forming fungi, suggesting that chitosan is a terminal cell wall
2793 carbohydrate, not modified or cleaved further.
2794 **Carbohydrate binding modules (CBMs) -** Carbohydrate binding modules, as their name
2795 suggests, bind various carbohydrates, and thus can frequently be attached to cell wall
2796 modifying enzymes. Chitin binding ability has been shown for at least 9 CBM
2797 families(Sánchez-Vallet et al. 2015). Of the most widely known chitin-binding CBMs (1, 5/12,
2798 14, 18, 19, 50), only CBM1, 5/12, 18 and 50 families are conserved in the Agaricomycetes
2799 we examined. The CBM1 family, which primarily binds cellulose and according to some
2800 reports chitin, does not appear to be involved in fruiting body development: most genes that
2801 encode CBM1 containing proteins have virtually no expression in fruiting bodies. Some such
2802 proteins show significant expression dynamics (e.g. *C. cinerea* 363583, 499390), but are not

2803 conserved across species. The CBM18 family occurs in GH16 proteins, which have been
2804 described above.

2805 **CBM5/12** - The CBM5/12 family comprises chitin-binding modules, which assist the
2806 action of cell wall modifying enzymes in fungal development(Hartl et al. 2011). The CBM5
2807 family is sometimes considered a lectin due to its carbohydrate binding ability(Ismaya et al.
2808 2020). Most CBM5/12 modules occur in combination with GH18 domains, where their chitin
2809 binding ability is believed to increase the efficiency of the chitinase(Hartl et al. 2011). We
2810 identified 3-6 CBM5/12 domains in the examined Agaricomycetes. All but one CBM5/12
2811 modules are attached to GH18 chitinases and have thus been discussed above. The single
2812 CBM5/12 module that is not attached to a chitinase occurs on proteins that also harbor a
2813 domain of unknown function (DUF3421) and a DM9 repeat as well. Such proteins occur in
2814 single copy in Agaricomycetes genomes and comprise a CDE orthogroup (*C. cinerea* protein
2815 ID: 413423) that show high expression in vegetative mycelia and mature stipe tissues of
2816 most species (*A. ostoyae, P. ostreatus, M. kentingensis, C. cinerea, L. tigrinus, L. bicolor, L.*
2817 *edodes*) (Table 24). The protein is functionally uncharacterized. Both the DUF3421 and the
2818 DM9 repeat occur primarily in insects and other animals (but are found also in early-
2819 diverging fungi), but their activity is not known. Their developmental expression and the
2820 presence of a CBM5/12 domain suggests they may be linked to the chitin content in the cell
2821 wall, however, how exactly they function remains unclear.

2822 **CBM50** - also known as LysM domain, this family binds chitin and can occur in a
2823 number of chitin-active proteins or on its own(GB et al. 2015). It has been reported to show
2824 developmentally dynamic expression in previous studies of fruiting body
2825 development(Sakamoto et al. 2017b; Sipos et al. 2017b; Krizsán et al. 2019; Huang et al.
2826 2020). LysM domain proteins are widely known as effectors of plant pathogenic fungi, in
2827 which solitary secreted CBM50 modules can mask chitin residues and thus can dampen the
2828 immune response of plants(GB et al. 2015). Solitary CBM50 modules expressed in fruiting
2829 bodies could be involved in defense against insects(Kunzler 2015).

2830 The examined Agaricomycetes contain 3-9 CBM50/LysM domain encoding genes
2831 (except *A. ostoyae,* which has 18, but its expansion may be related to the pathogenic nature
2832 of *Armillaria*(Sipos et al. 2017b)). The CBM50 module occurs almost exclusively on its own
2833 in the examined Agaricomycetes, only *C. aegerita* has proteins that harbored combinations
2834 of CBM50 and chitinase domain signatures. Interestingly, CBM50 encoding genes showed
2835 relatively little expression dynamics within fruiting bodies with 0-2 developmentally
2836 expressed genes per species. This, and reports on the induction of one of the CBM50 genes
2837 of *C. cinerea* in response to bacterial and nematode challenge(Kombrink et al. 2018;
2838 Tayyrov et al. 2018, 2019) could indirectly support a role in defense. However, some genes
2839 had high and constant expression during fruiting body development (e.g. *C. cinerea*
2840 448942), suggesting chitin-linked functions.

2841 **AA9 family (Lytic polysaccharide monooxygenases) -** The family has been
2842 reported only recently to have fruiting body specific expression patterns(Almási et al. 2019;
2843 Krizsán et al. 2019). AA9 proteins were initially considered to be endoglucanases and
2844 classified in glycoside hydrolase family 61, but turned out to be lytic polysaccharide
2845 monooxygenases (LPMOs) that cleave polysaccharide chains using a distinct oxidative
2846 mechanism(G et al. 2010).

2847 The examined Agaricomycetes possess 7-34 AA9 encoding genes, of which 1-10
2848 were developmentally regulated. A part of this copy number variation can be explained by
2849 lifestyle, as wood-decay species are known to have expanded, while biotrophic or
2850 mycorrhizal species have contracted aAA9 repertoires(Miyauchi et al. 2020). AA9 LPMOs

2851 might be active on β-glucan or on both glucan and cellulose as well, providing them with the
2852 activity required to remodel the fungal cell wall(Krizsán et al. 2019). The identified AA9
2853 genes hardly formed conserved orthogroups, which may be a consequence of high
2854 duplication/loss rates.
2855 Several species showed interesting LPMO expression patterns, which were quite
2856 consistent within, but different between species. For example, in *C. cinerea* several genes
2857 had a late upregulation, suggesting that LPMOs might be involved in autolysis. On the other
2858 hand, in *Ph. chrysosporium* many genes showed high expression in vegetative mycelium
2859 and mature fruiting bodies but low in young fruiting bodies, creating U-shaped expression
2860 curves. In *L. tigrinus* several genes showed a marked peak in cap and gill samples of mature
2861 fruiting bodies. The single AA9 gene (Cryne_JEC21_1_562) of *C. neoformans* had a strong
2862 (45-fold) induction in 24h samples, coincident with basidium formation(Liu et al. 2018). In
2863 general, all species displayed several genes with high expression in vegetative mycelium,
2864 but negligible (<5 FPKM) expression in any of the fruiting body tissues, suggesting the
2865 existence of separate vegetative mycelium-specific and fruiting body-specific AA9
2866 subgroups. Yet other AA9 genes displayed uniformly low (<5 FPKM) expression; these
2867 LPMO-s might be specific for the plant cell wall, and thus not induced during development.
2868 Nevertheless, the developmentally dynamic expression of several AA9 genes suggests that
2869 this family is involved in fungal cell wall remodeling during fruiting body development.
2870 **AA14 family -** We found a conserved orthogroup (represented by *C. cinerea*
2871 362412) that contained members of the recently circumscribed AA14 family of lytic xylan
2872 oxidases(Couturier et al. 2018). These proteins require copper as their native cofactor and
2873 were speculated to unlock xylan-coated cellulose fibers in the plant cell wall. We identified
2874 members of the AA14 family based on BlastP (query *Pycnoporus coccineus* AUM86167 and
2875 AUM86166): we find that blastp with e-value cutoff of 10^{-10} yielded copy numbers that match
2876 perfectly those reported by Couturier et al (Suppl Data Set 1)(Couturier et al. 2018). Fruiting
2877 body forming fungi contained 2-5 copies of the family, whereas yeast-like fungi (*U. maydis*
2878 and *C. neoformans*) contained none. Gene belonging to this family did not display
2879 characteristic expression peaks across species. However, as with other GH and AA families,
2880 their developmental expression in fruiting bodies suggests they may be active on some
2881 component of the fungal cell wall as well or have other extracellular roles.
2882 **X325 family -** We also detected the recently described X325 family of copper-
2883 containing, LPMO-like proteins(Labourel et al. 2020). As a new gene family, the only
2884 functional knowledge available currently is that it displays a fold similar to fungal LPMOs,
2885 may be involved in copper homeostasis(Garcia-Santamarina et al. 2020), is upregulated in
2886 several mycorrhizal fungi and resides on the surface (via a GPI anchor) of the fungal cell
2887 wall(Labourel et al. 2020). A morphogenetic role for the family has been speculated. We
2888 here report that members of this family form a CDE orthogroup (represented by *C. cinerea*
2889 454418) and are developmentally regulated in a wide range of species (9/6 at FC4/2),
2890 although expression patterns differ between species. Additional developmentally regulated
2891 X325 genes from other species were segregated into other orthogroups. The *L. bicolor* gene
2892 is slightly upregulated in primordia relative to free living mycelium (FC=1,8) and has a peak
2893 expression in young fruiting body stipes.
2894 AA10 and AA11, two well-known chitinolytic LPMO families(Langner and Göhre
2895 2015; Polonio et al. 2021), are missing in the examined Agaricomycetes, so they are unlikely
2896 to be contributors to fruiting body development.

2897 4.8.2.2. Glucan-linked families (GH3, GH5, GH16, GH17, GH30, GH55, GH71, GH128,
2898 GH152, Cdc43, WSC)

2899 **Cdc43 -** We detected orthologs of *S. cerevisiae* Cdc43 (*C. cinerea* protein ID: 376392) as a
2900 CDE orthogroup in this study (Table 25). Cdc43, together with Ram2, forms the type I
2901 geranylgeranyl transferase of *S. cerevisiae*, which transfers a geranyl-geranyl moiety to
2902 proteins having a CaaX sequence on their C-terminal(AA et al. 1991). One of the targets in
2903 *S. cerevisiae* is Rho1p, a rho-type GTPase, which is the regulatory subunit of beta-1,3-
2904 glucan synthase(SB et al. 1999). Cdc43 orthologs were developmentally expressed in 11/6
2905 (FC=2/4) (Table 25) species as well as *C. neoformans*. They showed a marked upregulation
2906 from vegetative mycelium to primordia in *A. ampla, A. ostoyae, C. aegerita, L. bicolor, L.*
2907 *edodes, C. cinerea, S. commune*, and more or less constant expression in *M. kentingensis,*
2908 *Pt. gracilis* and *P. ostreatus*. On the other hand, orthologs of Ram2 (*C. cinerea* protein ID:
2909 473005) as well as those of the main substrate, Rho1 (*C. cinerea* protein ID: 528086) did not
2910 show strong expression dynamics. We hypothesize that the expression dynamics of Cdc43
2911 mirrors the dynamics of cell wall glucan biosynthesis in fruiting bodies.
2912 **GH17 -** Enzymes belonging to the GH17 family are known to crosslink β-1,3-glucan in the
2913 cell wall of yeast species and presumably *N. crassa* too(Patel and Free 2019). The family
2914 has been reported in a transcriptomic study of mushroom development(Krizsán et al. 2019)
2915 (as endo-β-1,3-glucanosyltransferase), and it was suggested to be involved in β-1,3-glucan
2916 crosslinking, although direct evidence for this is lacking at the moment. The examined
2917 Agaricomycetes possess 1-4 GH17 encoding genes. *C. cinerea* has four GH17 genes, of
2918 which only one appear to be clear orthologs of Ascomycota genes: *C. cinerea* 389921 is
2919 reciprocal best hit to SCW10 of *S. cerevisiae* a soluble cell wall protein with a poorly known
2920 function. GH17-s formed 2 CDE orthogroups (Table 25). One of the CDE orthogroups
2921 (represented by *C. cinerea* 476698) showed clear tissue-specific expression (cap- or stipe
2922 upregulation), but interestingly, this was not fully consistent across species.
2923 **GH16 -** The GH16 family shows glycosylhydrolase and glycosyltransferase activity and
2924 contain glucan synthase and crosslinking enzymes, which are active in cell wall synthesis
2925 (e.g. Kre6 and Skn1 of *S. cerevisiae*) and remodeling. GH16s were shown to crosslink β-1,3-
2926 glucan and β-1,6-glucan to chitin fibers in *Candida* spp and *N. crassa*(Patel and Free 2019).
2927 Chitin-glucan crosslinking is key to morphogenesis in fungi(Arroyo et al. 2016). GH16s
2928 comprise the CRH (Congo Red Hypersensitive) family, three members of which (Crh1p,
2929 Crh2p and Crr1p) were originally circumscribed in *S. cerevisiae.* Of these, only Crr1 has a
2930 clear 1-to-1 ortholog in Agaricomycetes (*C. cinerea* protein ID: 449960), the other two do
2931 not. At the transcriptome level, the upregulation of GH16 genes have been reported before
2932 in a comparative study(Krizsán et al. 2019), in *A. bisporus*(Morin et al. 2012;
2933 Patyshakuliyeva et al. 2013)*, Leucocalocybe mongolica*(Duan et al. 2021)*, Pleurotus spp*(Xie
2934 et al. 2018; Ye et al. 2021) as well as during post-harvest development on *L.*
2935 *edodes*(Sakamoto et al. 2009, 2017b). Mlg1 is a functionally characterized member of the
2936 GH16 family in *L. edodes* assayed for its glucanase activity during postharvest
2937 senescence(Sakamoto et al. 2009).
2938   The species in this study have 21-36 GH16 encoding genes, which is consistent with
2939 a previous report on *L. edodes*(Sakamoto et al. 2017b). About half of the GH16 genes in
2940 each species also carry a 'Beta-glucan synthesis-associated Skn1' domain, which signifies
2941 relationship with the Kre6/Skn1 family, which is involved in β-1,6-glucan synthesis(Garcia-
2942 Rubio et al. 2020). We found five GH16 CDE orthogroups (*C. cinerea* protein ID: 502321,
2943 381870, 411452, 169822, *S. commune* 2686544) (Table 25), that are not orthologous to

2944 functionally characterized GH16 genes in the Ascomycota. Although most genes do not form
2945 conserved orthogroups, possibly because of volatility (frequent duplication/loss), it is
2946 noteworthy that each species has 1-3 genes which show a marked upregulation in the
2947 primordium stage and remain highly expressed in the fruiting body relative to vegetative
2948 mycelium. These might be involved in the formation of 3-dimensional fungal tissues. Another
2949 interesting observation is that eight out of 21 GH16 genes in *C. neoformans* are also
2950 developmentally regulated, with several of them showing peak expression at 24h, coincident
2951 with basidium development.
2952 **GH30 -** Glycoside hydrolase family 30 (GH30) includes enzymes with diverse activities,
2953 which have been mostly discussed for their role as endo-xylanases in wood decay in the
2954 fungal literature(Wymelenberg et al. 2009; Katsimpouras et al. 2019). However, GH30 also
2955 includes β-1,6-glucanases, which were found to be upregulated in *L. bicolor*
2956 ectomycorrhizae(C et al. 2014), raising the possibility of morphogenetic roles. GH30
2957 members were also upregulated during postharvest development of *L. edodes*(Sakamoto et
2958 al. 2017b). Of the 1-3 (6 in *L. bicolor*) GH30 genes in the examined Agaricomycetes, at most
2959 1-2 are developmentally expressed in fruiting bodies and only a single orthogroup
2960 (represented by *C. cinerea* 381637) was so in several species (Table 25). Genes in this
2961 orthogroup were most often upregulated in stipe tissues relative to pileus in fruiting bodies.
2962 GH30 genes of *C. cinerea* have been proposed to facilitate stipe elongation by in the stipe
2963 base may contribute to replacing β-1,6-glucan to β-1,3-glucan crosslinking in the stipe base,
2964 which may reduce wall extensibility, leading to the cessation of growth(Liu et al. 2021).
2965 Further, the shared upregulation of GH30 genes in multiple fruiting body transcriptomes and
2966 in ectomycorrhizae provide strong evidence for its role in FCW remodeling during
2967 morphogenesis in the Basidiomycota.
2968 **GH3 -** The GH3 family comprises enzymes with diverse activities, including exo-β-1,3-
2969 glucanase activity, and has been suggested to participate in cell wall remodeling in
2970 Ascomycetes(Patel and Free 2019). The upregulation of GH3 genes in fruiting bodies has
2971 previously been noted in a number of species(Zhou et al. 2018; Krizsán et al. 2019), raising
2972 the possibility that they participate in cell wall remodeling during fruiting body development.
2973 A GH3 family member, that was upregulated in fruiting bodies of *Auricularia heimuer*, was
2974 recently cloned and characterized(Sun et al. 2020). GH3 encoding genes are present in 7-20
2975 copies in examined Agaricomycetes. Three CDE orthogroups belonging to the GH3 family
2976 (*C. cinerea* protein ID: 369876, 373418, *S. commune* Schco3_2629974,) were detected
2977 (Table 25), genes in these orthogroups showed diverse expression patterns in the fruiting
2978 bodies of different species. It should be mentioned that some GH3 enzymes, mostly in
2979 bacteria, possess β-N-acetylhexosaminidase activity, which allows the encoded enzymes to
2980 be involved in chitin utilization, by cleaving N-acetylglucosamine dimers into monomeric
2981 GlcNac(de Oliveira et al. 2018). Most such enzymes are bacterial, with sporadic reports of β-
2982 N-acetylhexosaminidase activity in fungi(S et al. 2014). Therefore, whether GH3
2983 upregulation is linked to chitin utilization or glucan remodeling cannot be determined here.
2984 **GH5 -** The GH5 family is a very diverse group that includes β-1,4-glucanases, as well as
2985 several other activities. It includes classic cellulases involved in wood decay(Floudas et al.
2986 2012), whereas Ascomycota GH5 genes, such as Exg1, Exg2 and Exg3 of *S. pombe*, or
2987 Exg1 of *S. cerevisiae*, are well-known components of the cell wall glucan remodeling
2988 machinery(Dueñas-Santero et al. 2010). GH5s were shown to not only hydrolyze β-1,3-
2989 glucan, but also to act as transglycosylases, and thus contribute to cell wall
2990 crosslinking(Arroyo et al. 2016). Based on expression patterns, GH5s were speculated to be
2991 active on beta-glucan in fruiting body cell walls also(Y et al. 2005; C et al. 2014; Almási et al.

2992   2019; Krizsán et al. 2019). Krizsan et al reported multiple subfamilies (GH5_7, GH5_9,
2993   GH5_15, GH5_49) with endo-β-1,4-mannanase, endo-β-1,6- and exo-β-1,3-glucanase
2994   activities to be upregulated in fruiting bodies(Krizsán et al. 2019). The family includes the
2995   exo-beta-1,3-glucanase Exg1 from *L. edodes*, which was reported to be fruiting body
2996   specific(Y et al. 2005). Our re-analysis confirms that Exg1 (Lenedo1_1176007) has
2997   consistently higher expression in stipe than in cap tissues.
2998   GH5 is a large family with 16-20(25) copies in the examined Agaricomycetes.
2999   Consistent with their diversity, we detected six CDE orthogroups in our data (*C. cinerea*
3000   protein ID: 546300, 405828, 505989, 496411, 414471, 373700) (Table 25). One of these (*C.*
3001   *cinerea* protein ID: 546300), contains reciprocal best hits of *Sch. pombe* Exg3, a cytoplasmic
3002   β-1,6-glucanase with unknown cellular function. All species in which this orthogroup is
3003   developmentally regulated showed upregulation in mature fruiting bodies. This could indicate
3004   a link to sporulation, or other late developmental events. Another orthogroup (*C. cinerea*
3005   protein ID: 414471) contains 1-to-1 orthologs of *Sch. pombe* and *S. cerevisiae* Exg1, which
3006   is involved in cell expansion and sporulation, picturing potentially similar roles in
3007   Agaricomycetes too. Members of yet another orthogroup (*C. cinerea* protein ID: 373700), are
3008   consistently higher expressed in all fruiting stages (primordia to mature FB) than in
3009   vegetative mycelia in *A. ostoyae, C. aegerita, A. ampla, C. cinerea, P. ostreatus, S.*
3010   *commune* and to some extent in *L. bicolor* and *L. edodes* (but not in *A. bisporus* and *Pt.*
3011   *gracilis*).
3012   **GH55 -** This family contains exo- or endo-β-1,3-glucanases that have been characterized
3013   functionally in fruiting bodies of two Agaricomycetes. Exg2 was found to be expressed higher
3014   in the stipe than in the cap of *L. edodes*(Sakamoto et al. 2005). The GH55 family has also
3015   been reported to be upregulated during cap expansion of *Volvariella volvacea* and the
3016   corresponding gene was named Exg2(Tao et al. 2013). We detected on average two GH55
3017   genes in the examined Agaricomycetes (5 in *A. ostoyae*). One of these formed a CDE
3018   orthogroup (represented by *C. cinerea* 492834), which included *L. edodes* Exg2 and showed
3019   very strong induction in young fruiting body caps and stipes of *C. cinerea*, caps of *A. ostoyae*
3020   and stipes of *M. kentingensis*. Overall, these data are consistent with the suggested role of
3021   GH55 in cap expansion in *V. volvacea*. In *L. edodes*, the expression of Exg2 was higher in
3022   stipes than in cap tissues. Interestingly, the second GH55 gene of *C. cinerea* (*C. cinerea*
3023   protein ID: 454337) (Table 25) also shows this characteristic induction and high expression
3024   in young fruiting body caps and stipes. In species with simpler morphology (*S. commune, A.*
3025   *ampla*) the family did not show characteristic expression dynamics. A third GH55 gene
3026   (Armosto1_267056) in *A. ostoyae* showed an induction in primordia relative to vegetative
3027   mycelium.
3028   **GH128 -** GH128 has been first circumscribed in the context of fruiting body development,
3029   based on a fruiting body expressed β-1,3-glucanase, Glu1, in *L. edodes*(Y et al. 2011).
3030   Since its discovery, some reports have mentioned upregulation of GH128 genes in fruiting
3031   bodies(Krizsán et al. 2019; Duan et al. 2021; Merényi et al. 2021), with a single report also in
3032   connection with wood decay(Mäkinen et al. 2019). On average, the GH128 family has 2-8
3033   members in Agaricomycetes. We detected two CDE orthogroups (represented by *C. cinerea*
3034   463000, 413757) which were expressed in the majority of species (Table 25) and several
3035   GH128 genes which were developmentally expressed in a species-specific way. In *C.*
3036   *cinerea*, protein 413757 represents the best hit of *L. edodes* GLU1. Available data here and
3037   in previous publications suggest that GH128 might be a primarily fruiting body-related gene
3038   family, worthy of further functional examination.

3039 **GH71 -** Four orthogroups containing developmentally regulated GH71 alpha-1,3-glucanases
3040 and beta-glucuronidases were detected (*C. cinerea* protein ID: 22054, 464399, 456054,
3041 492754)(Table 25). GH71 genes (also called mutanases) are involved in fungal cell wall
3042 remodeling in a wide range of species, both yeasts and filamentous fungi(Dekker et al. 2004;
3043 C et al. 2014; H et al. 2015). A well-characterized member of this family is the *Sch. pombe*
3044 endo-1,3-alpha-glucanase Agn1, which facilitates cell fission via the degradation of the
3045 septum material(Dekker et al. 2004). In previous studies of mushroom development, this
3046 family was reported only by Krizsan et al(Krizsán et al. 2019), Park et al(Park et al. 2014),
3047 and Morin et al(Morin et al. 2012). In *Pleurotus eryngii*, GH71 genes were found
3048 downregulated in primordia after blue light stimuli(Xie et al. 2018). GH71 genes are present
3049 in 3-12 copies in the examined Agaricomycetes. One of the CDE orthogroups (represented
3050 by *C. cinerea* 456054) is upregulated in primordia relative to vegetative mycelium in 7 of the
3051 10 species (*C. cinerea, A. ostoyae, C. aegerita, L. tigrinus, L. bicolor, Ph. chrysosporium, P.*
3052 *ostreatus*) in which it is present.

3053 **GH152 -** The GH152 family, also known as thaumatin-like proteins, which include both
3054 putatively defense-related antimicrobial peptides and β-1,3-glucanases. They show
3055 homology to plant thaumatin-like proteins. Because the literature reports both antimicrobial
3056 and glucanase activity for this family(Kunzler 2015), we do not attempt to subdivide them
3057 and refer to them as GH152/thaumatin proteins. The GH152/thaumatins include an
3058 experimentally characterized gene, Tlg1 in *L. edodes* (Lenedo1_561169), which was
3059 detected in a post-harvest screen of cell wall and lentinan degrading genes(Sakamoto et al.
3060 2006). Lentinan is a glucan-like cell wall component with important medicinal properties in *L.*
3061 *edodes*. The expression of the gene was detected only after harvest, raising questions as to
3062 what the physiological role of the gene might be under natural circumstances. Our analysis
3063 of the data from Zhang et al did not reveal developmentally dynamic expression for Tlg1
3064 using RNA-Seq data(Zhang et al. 2021c). Structure prediction for an *A. ostoyae*
3065 developmentally expressed protein indicated an acidic cleft in the 3D structure, characteristic
3066 of antimicrobial members of the family(Krizsán et al. 2019). A new report of antifungal
3067 activity of the thaumatin-like protein Le.TLP1 in *L. edodes* further supports putative defense
3068 roles for the GH152 family(Ma et al. 2021).

3069 The family comprises 2-8 (19 in *Pt. gracilis*) copies in examined Agaricomycetes,
3070 many of which are poorly conserved. Therefore, while several genes are developmentally
3071 expressed in each species, only a single CDE orthogroup was detected (represented by *C.*
3072 *cinerea* 496344)(Table 25). The role of GH152/thaumatins in fruiting body development is
3073 unclear at the moment, it could be involved in defense against microbes, cell wall glucan
3074 remodeling, or both(Kunzler 2015).

3075 Additional beta-glucan active families (GH1, GH6, GH12) were detected in the
3076 broader orthology-based approach of Krizsan et al(Krizsán et al. 2019), which were not
3077 detected in this study, probably because of the strict orthology definition we use.

3078 **WSC family** - this family of lectin-like proteins comprises a widely conserved but poorly
3079 known group of fungal proteins. The family was originally described as a putative stress
3080 receptor in *S. cerevisiae*(AL et al. 1999) and as a domain in an extracellular β-1,3-
3081 exoglucanase in *Trichoderma harzianum*(Cohen-Kupiec et al. 1999), and later demonstrated
3082 to be a carbohydrate binding module, similar to CBMs(S et al. 2019). The best-characterized
3083 member in the Basidiomycota seems to be involved in beta-glucan binding/FCW remodeling
3084 during plant-fungal interaction in *Serendipita indica*(Wawra et al. 2019). Whether this is true
3085 for other WSC family members too, is not known, but is indicative of a potential role in
3086 adhesion/remodeling at the cell surface.

3087   The examined Agaricomycetes harbored 2-12 copies of WSC-domain encoding
3088   genes. Of these, several showed strong induction in primordia and fruiting bodies in *A.*
3089   *ostoyae, C. aegerita, C. cinerea, L. bicolor, L. edodes, L. tigrinus, Ph. chrysosporium, P.*
3090   *ostreatus* and *S. commune* (but not in *A. ampla* and *M. kentingensis*). Genes with a
3091   predicted WSC domain in their encoded proteins were typically primordium-upregulated in all
3092   species. In *C. cinerea* these genes had high expression in early (proliferative) development
3093   (hyphal knots to stage 2 primordia), followed by very low expression in most genes in late
3094   developmental stages. The WSC domain can occur on its own or in combination with other
3095   enzymes (most often GH71 and glyoxal oxidase) and uncharacterized domains, indicating
3096   that it often fulfills a binding role in larger proteins. For example, WSC domain is present on
3097   GH71 proteins that form a 10/8 orthogroup (represented by *C. cinerea* 464399), which we
3098   discussed above.
3099

3100   4.8.2.3. Miscellaneous cell wall remodeling (GH27, GH72, GH76, GH79, GH88, GT18,
3101   pectinesterases)

3102   In addition to chitin- and glucan-active families, several further CAZyme groups showed
3103   widespread developmental regulation in fruiting bodies, for which the substrates in fruiting
3104   bodies are less clear. These make very interesting groups indicating potentially novel cell
3105   wall components, however, they are hard to place in context of fruiting body development as
3106   of now.
3107   **GH79 and 88 -** An orthogroup containing GH79 β-glucuronidases (*C. cinerea* protein ID:
3108   470689) (Table 26), showed developmental expression in several species, consistent with
3109   reports of Krizsan et al(Krizsán et al. 2019). Low amounts of glucuronic acid was reported in
3110   *N. crassa* cell walls(Verdín et al. 2019), but the role of GH79 enzymes in cell wall
3111   biosynthesis or remodeling are unknown. On a related note, an orthogroup of GH88
3112   glucuronyl hydrolases was detected (*C. cinerea* protein ID: 384105)(Table 26). GH88 genes
3113   are generally linked to pectin degradation by wood-decay fungi(van den Brink and de Vries
3114   2011); their potential role in fruiting bodies is not known.
3115   **GH27 -** Similarly, two CDE orthogroups (represented by Armosto1_254810 and
3116   Armosto1_269656) of GH27 enzymes with alpha-galactosidase or α-*N*-
3117   acetylgalactosaminidase activity were detected (Table 26). This family is discussed mostly in
3118   the context of lignocellulose degradation(Kabel et al. 2017), to our knowledge it has not
3119   been reported in fruiting body transcriptomes before. As a tendency, GH27 encoding genes
3120   were often upregulated late in the development of the containing species. Their role in
3121   fruiting body formation is not known.
3122   **GT18 -** The GT18 family, which contains α-1,3(6)-mannosylglycoprotein β-1,6-N-acetyl-
3123   glucosaminyltransferases showed a patchy distribution in the examined species, being
3124   completely missing from the genomes of *C. cinerea* and *A. ostoyae*. However, it showed a
3125   strong upregulation in primordia relative to vegetative mycelium and constant high
3126   expression in fruiting bodies of *A. bisporus, A. ampla, S. commune, C. aegerita* and *P.*
3127   *ostreatus* (not in *M. kentingensis and L. bicolor*)(Table 26, *S. commune* protein ID:
3128   Schco3_2633734). This indicates fruiting body specific functions for this family, possibly in
3129   chitin synthesis, although its exact role remains unknown. To our best knowledge, the role of
3130   the GT18 family in modifying the fungal cell wall has not been described in any species.
3131   **GH72 -** Contrary to our expectations, members of the GH72 family did not appear to be
3132   developmentally relevant in Agaricomycetes. This family contains cell wall transglycosylases

3133 that crosslink glycoproteins to cell wall components in the Ascomycota(Kar et al. 2019), and
3134 therefore we expected it to be developmentally expressed in Basidiomycota as well. Their
3135 expression is considerable but largely constant in Agaricomycetes fruiting bodies. This could
3136 indicate a difference between Asco- and Basidiomycota cell wall composition, or that they
3137 act during fruiting body development irrespective of their constant expression.
3138 **GH76 -** In the Ascomycota, GH76 endo-1,6-alpha-mannosidases (Dfg5 and Dcw1 in *S.*
3139 *cerevisiae*) are required for normal cell wall synthesis. Their exact role may not be known
3140 with certainty, but they were hypothesized to be involved in the proper positioning of
3141 glycosylphosphatidylinositol-anchored cell wall proteins(Orlean 2012). To our best
3142 knowledge, the GH76 family has not yet been suggested to participate in fruiting body
3143 development in the Agaricomycetes. It is present 0-10 copies in the Agaricomycetes and
3144 shows predominantly mycelium-specific expression. We only found scattered expression
3145 dynamics in fruiting bodies, such as a peak in stipes of *P. ostreatus*
3146 (PleosPC15_2_1064904), but most genes are not developmentally regulated. Given that the
3147 family is missing in some species completely and the predominantly vegetative mycelium-
3148 specific expression, we hypothesize that the GH76 family does not participate, or only to a
3149 small extent, in cell wall assembly in Agaricomycete fruiting bodies.
3150 **Pectinesterases -** We detected a CDE orthogroup (represented by Schco3_2614029) that
3151 contains genes generally linked to pectin degradation. It contains pectinesterases that are
3152 developmentally regulated in 6/5 species (FC 2/4) (Table 26). Because pectin is not a known
3153 cell wall component in Agaricomycetes, speculating about the function of these genes is
3154 hard and may require more research.

3155 4.8.2.4. Multicopper oxidases and cupredoxins

3156 Laccases catalyze the oxidation of diverse phenolic and non-phenolic compounds, which
3157 makes them suited to diverse (extra)cellular roles, from lignin degradation, pigment
3158 production to dye decolorization or fruiting body related functions(P 2006). Their biochemical
3159 properties provide laccases with significant potential in industrial applications. Despite very
3160 intense research on laccases (mostly in the context of lignocellulose decomposition), we still
3161 have very limited information on the precise role of laccases in fruiting body development.
3162 Several reports of upregulation of laccase, or multicopper oxidase (MCO, the broader
3163 family in which laccases belong) genes or laccase activity in fruiting bodies of
3164 Agaricomycetes(Zhao and Kwan 1999; Ohga et al. 2000; Chen et al. 2003; Wang and Ng
3165 2005; Madhavan et al. 2014; Sakamoto et al. 2015; Sipos et al. 2017b; Nagy et al. 2018) are
3166 available (reviewed in detail by(Kües et al. 2011)). *Schizophyllum commune* was reported to
3167 have 6 MCO genes (two of which are laccases), of which 3 were reported to be upregulated
3168 in fruiting bodies(Madhavan et al. 2014) (Mco2, Mco3, Lcc1) by RT-PCR, which is consistent
3169 with later RNA-Seq data(Krizsán et al. 2019). Of these, Lcc1 showed the highest similarity to
3170 Fet3-type ferroxidases. Similarly, *P. ostreatus* laccases were reported to be expressed in a
3171 developmental stage-specific manner, with Lacc5 and Lacc12 specifically expressed in
3172 fruiting bodies and primordia, respectively, while other laccases had even or mycelium-
3173 biased expression patterns(Park et al. 2015; Jiao et al. 2018). Stage-specific MCO
3174 expression was reported in *L. bicolor* with specific laccase genes induced in fruiting bodies
3175 (Lcc2), ectomycorrhizae and free-living mycelium(Courty et al. 2009). These studies have
3176 linked laccase expression to two major functions, pigment production in either spores or
3177 fruiting bodies and fungal cell wall modification or cell-cell adhesion(Kües et al. 2011).
3178 Laccases were speculated to polymerize polyphenols in the intercellular spaces and thus
3179 contribute to the binding of neighboring hyphae to each other. The hypothesis of laccases

3180 being related to adhesion comes from Leatham and Stahmann(Leatham and Stahmann
3181 1981), but, to our knowledge, was never experimentally verified. Although not relevant to
3182 fruiting body formation, an interesting inverse relationship between mycelial laccase
3183 expression and flushes of fruiting body development was reported in several species,
3184 possibly related to stopping mycelium growth or nutrient acquisition when nutritional
3185 competence for fruiting is achieved (reviewed in(Kües et al. 2011)).

3186   Developmental studies indicated laccase function in fruiting body formation in
3187 *Pleurotus spp*(Das et al. 1997). and *L. edodes*(Nakade et al. 2011). In *P. florida* laccase
3188 gene silencing abolished fruiting body development and caused slower vegetative growth,
3189 whereas in *L. edodes* aerial hyphae formation was also reduced and hyphae developed
3190 thinner, non-layered cell walls upon the silencing of the Lcc1 laccase gene. Zhang et al
3191 reported faster vegetative growth and earlier fruiting in laccase (Lcc1) overexpressing strains
3192 of *H. marmoreus* compared to wild type strains(Zhang et al. 2015a), although no clear
3193 hypothesis on how overexpression of a single structural gene could result in these
3194 phenotypes was presented.

3195   We here present annotations for multicopper oxidases, which include laccases,
3196 ascorbate oxidases and ferroxidases(Kües et al. 2011). The 11 genomes of Agaricomycetes
3197 examined here had 5-26 multicopper oxidases, a considerable proportion of which were
3198 developmentally regulated, for example, 13 out of 17 in *C. cinerea* (Table 27). We found
3199 three CDE laccase orthogroups; these comprised *C. cinerea* Lcc8, Lcc2 and their orthologs
3200 as well as reciprocal best hits of the *S. cerevisiae* ferroxidase Fet3. [Of note, we detected
3201 reciprocal best hits of the ferroxidase Fet3 in *C. cinerea*, whereas a previous report, based
3202 on phylogenetic analyses did not identify Fet3-type MCOs in this species(Kües et al. 2011);
3203 we note that this may arise from the limitations of our reciprocal best hit based search and
3204 that accurate classification of MCOs requires the examination of specific catalytic residues.
3205 Orthologs of *C. cinerea* Lcc2 (*C. cinerea* protein ID: 368135) are also involved in
3206 morphogenesis in *L. edodes (as Lcc1)*, and differentially expressed during *Cryptococcus*
3207 basidium formation(Liu et al. 2018; Merényi et al. 2021). We found that Lac4 from *Volvariella*
3208 *volvacea*, which was implicated in fruiting body development(Chen et al. 2003) showed
3209 highest similarity to the CDE orthogroup that comprised *L. edodes* Lcc1 (represented by *C.*
3210 *cinerea* 368135). In the examined Agaricomycetes, this group of genes is upregulated in
3211 caps (*P. ostreatus, C. cinerea*), stipes (*M. kentingensis*) or primordia (*A. ampla*), or shows
3212 flat expression curves (other species). The detected ferroxidase orthogroup was present in 7
3213 species, of which it was developmentally regulated in *A. bisporus, A. ostoyae, C. cinerea, L.*
3214 *edodes* and *P. ostreatus* (FC>2). A Fet3-like gene was also upregulated in *S.*
3215 *commune*(Madhavan et al. 2014), but this gene did not group into the detected orthogroup in
3216 our analysis. Ferroxidases are membrane proteins that catalyze the oxidation of Fe^{2+} to Fe^{3+}
3217 for iron uptake and have only weak laccase activities(Larrondo et al. 2003). Finally, *C.*
3218 *cinerea* 440170 is the orthologs of *C. neoformans* Lac1, which has been shown to be
3219 involved in melanin biosynthesis(Lee et al. 2019). This gene shows a strong expression
3220 peak in young fruiting body gills, suggesting that it is involved in producing spore pigments in
3221 *C. cinerea*.

3222   In summary, experimental and gene expression evidence on the role of multicopper
3223 oxidases in fruiting body development is abundant and -omics data reveal marked
3224 developmental stage-specific expression of laccases. Hypotheses on their role either in
3225 pigment production or cell wall crosslinking/adhesion have been put forth, however, the
3226 available data do not allow us at the moment to select between these hypotheses, until more
3227 developmental studies and gene knockout phenotypes become available.

70

3228   In addition to *bona fide* MCOs, we identified four CDE orthogroup of proteins which
3229 belong to the Cupredoxin family, like laccases, but do not contain the typical multicopper
3230 oxidase domain. These might be highly diverged MCO genes or distant relatives of true
3231 MCOs with unknown functions. The five orthogroups are conserved across Agaricomycetes
3232 (*C. cinerea* protein ID: 356026, 451850, 441442, 353997, 497434) (Table 27). One of these
3233 (*C. cinerea* protein ID: 356026) is FB-init is *A. ostoyae, C. cinerea* and *P. ostreatus* (not in *A.*
3234 *ampla, S. commune* and *M. kentingensis*), whereas a second (*C. cinerea* protein ID:
3235 451850) was characteristically late upregulated in most species (*A. ampla, M. kentingensis,*
3236 *P. ostreatus, Pt. gracilis*). Currently, it is impossible to speculate about the role of these
3237 proteins in fruiting body development.
3238

3239 ### 4.8.2.5. Expansins and cerato-platanins

3240 Fungal expansins (or expansin-like proteins) show similarity to plant expansins, proteins that
3241 modify the plant cell wall but do not show hydrolytic activity towards its polymers. Rather,
3242 they exert their action by loosening the cell wall structure, hence the name loosenins(Quiroz-
3243 Castañeda et al. 2011) and swollenins(M et al. 2002a) for some members of the family.
3244 Fungal expansins with activities towards either the plant or fungal cell wall have been
3245 reported. Certain fungal expansins can bind chitin and facilitating the action of hydrolytic
3246 enzymes by separating cell wall chitin microfibrils. Two experimentally characterized
3247 Basidiomycota expansins are Loos1 from *Bjerkandera adusta*(Quiroz-Castañeda et al. 2011)
3248 and ScExlx1 from *S. commune*(Tovar-Herrera et al. 2015). Both were shown to bind chitin
3249 and facilitate the action of chitinases, therefore, it was concluded that they modify, but not
3250 hydrolyze the chitin polymer structure. Recent studies suggested that expansin-like proteins
3251 are involved in stipe cell elongation in *F. velutipes*(Q et al. 2018) and *C. cinerea*(Niu et al.
3252 2015) and were shown to have a role in stipe elongation, by loosening the chitin polymer
3253 structure (reviewed by(Liu et al. 2021)).
3254   Several expansins show expression patterns compatible with a role in fruiting body
3255 development in previous transcriptome-based studies(Barsottini et al. 2013; Sipos et al.
3256 2017b; Q et al. 2018; Almási et al. 2019; Krizsán et al. 2019). Based on analyses of 201
3257 fungal genomes, Krizsan et al reported that expansins are enriched in the genomes of
3258 Agaricomycetes(Krizsán et al. 2019). The examined mushroom-forming fungi possess 9-27
3259 expansin genes, with *C. cinerea* having 13. Given the dual specificity of expansins, it is likely
3260 that several of these are involved in cellulose degradation. However, a significant proportion
3261 (19-85%) of expansin genes are developmentally regulated in fruiting bodies, indicating roles
3262 in morphogenesis too. Expansins are a highly volatile group of genes that did not group into
3263 conserved orthogroups in our analysis (except two CDE orthogroups, see below), therefore,
3264 comparative analysis of their expression patterns across species is hardly possible. Within
3265 *C. cinerea* expansins show diverse expression peaks, in gills, cap or stipes with some genes
3266 highest expressed in vegetative mycelia too (Fig. 11). This could indicate tissue- and stage-
3267 specific roles for expansins in fruiting body formation. For example, four genes had a strong
3268 induction in stipes (*C. cinerea* protein ID: 451456, 464389, 359952, 461698), which is
3269 consistent with previous reports of their participation in stipe elongation(Liu et al. 2021).
3270 Three *C. cinerea* genes showed significant increase in expression from the vegetative
3271 mycelium to hyphal knots (*C. cinerea* protein ID: 461698, 286849, 496836). Despite the
3272 volatility of the family, we detected three putative expansin orthogroups (represented by *C.*
3273 *cinerea* 496836, 467907 and 461698) which were developmentally regulated in 12/10, 11/10
3274 and 10/5 species (at FC>2/4) (Table 28).

3275   **Cerato-platanins** - Although initially thought to be related to hydrophobins, cerato-
3276 platanins share a common origin with expansins(Barsottini et al. 2013; Gaderer et al. 2014;
3277 Baccelli 2015; Luti et al. 2020). First described from the ascomycete *Ceratocystis platani*,
3278 they were initially and generally considered to be related to pathogenesis(Gaderer et al.
3279 2014; Baccelli 2015; Chen et al. 2017; Luti et al. 2020), however, there is piling evidence, so
3280 far only from transcriptome studies, that they might be important in fruiting body
3281 development as well. In such studies, cerato-platanin genes showed extensive expression
3282 dynamics in fruiting bodies, suggesting an activity on the fungal cell wall(Plaza et al. 2014b;
3283 Sipos et al. 2017b; Almási et al. 2019; Krizsán et al. 2019; Liu et al. 2020b), or in
3284 defense(Kunzler 2015). Structure-based biochemistry studies in *Moniliophthora perniciosa*
3285 showed that certain cerato-platanins are able to bind chitin and are active on the fungal cell
3286 wall(Barsottini et al. 2013). Like expansins, cerato-platanins are strongly enriched in the
3287 genomes of mushroom-forming fungi(Chen et al. 2017; Krizsán et al. 2019). There is,
3288 unfortunately, little information on their mechanistic role in fruiting body development, except
3289 a the study by de Barsottini(Barsottini et al. 2013), which provides proof that cerato-platanins
3290 can be active on chitin and the fungal cell wall, providing a biochemical link to their potential
3291 role in fruiting body development.
3292   Our analyses identified 1-8 cerato-platanins in the genomes of examined mushroom-
3293 forming fungi, which is in line with copy numbers reported recently(Chen et al. 2017). Like
3294 expansins, cerato-platanins are quite volatile and we identified only two conserved CDE
3295 orthogroups (*C. cinerea* protein ID: 439071, 544218) (Table 28), with most genes scattered
3296 in species-specific or smaller groups. The first showed opposing expression patterns in
3297 different species: in *C. cinerea* (protein ID: 544218) it was upregulated in caps relative to
3298 stipes, whereas in *A. ostoyae* and *M. kentingensis* it was upregulated in stipes relative to
3299 caps. In *P. ostreatus* and *M. kentingensis* it showed the highest expression in vegetative
3300 mycelia. In *A. ampla* and *S. commune* it showed a very strong induction (>1000-fold) in
3301 mature fruiting bodies.
3302   Expression data across species indicates that developmentally dynamic cerato-
3303 platanin expression was observed only in certain species, while not in others. For example,
3304 no developmentally regulated cerato-platanins were found in *Ph. chrysosporium, A.*
3305 *bisporus*, only a single in *M. kentingensis*, but several in *A. ostoyae, C. cinerea, L. tigrinus,*
3306 etc. This indicates that developmental expression of cerato-platanins may be a species-
3307 specific, rather than a conserved feature in mushroom-forming fungi.
3308

3309 4.8.3. Miscellaneous cell wall related families (HTP, DyP, AA3, AA5, GH76, GT8,
3310 Slt2, Cfs1, Eln3, peptidases)
3311 We identified several CDE gene families which are potentially linked to the fungal cell wall,
3312 however, evidence is lacking on their mechanistic roles and/or they could not be confidently
3313 ascribed to either chitin or glucan, and/or are not enzymatic proteins. These are discussed in
3314 this chapter, with noting that the widely observed developmental expression makes these
3315 protein families interesting, however, their assignment to the cell wall is preliminary.
3316 **HTPs -** Heme-thiolate peroxidases (HTPs) are fungal-specific proteins that were first
3317 described in *C. aegerita* (as haloperoxidase) and use H_2O_2 to modify substrates(R et al.
3318 2004). While their enzymatic properties have been quite thoroughly studied(M et al. 2015a),
3319 their biological roles are poorly known. A remarkable expansion of the family was noted in *A.*
3320 *bisporus* which, combined with the upregulation of HTPs in *Agaricus* substrates led to the

3321   hypothesis that HTPs are linked to the litter decomposer lifestyle(Morin et al. 2012). In the

3322   context of fruiting bodies, HTPs were reported only in *A. ostoyae*(Sipos et al. 2017b) so far.

3323   We detected two CDE orthogroups of HTPs (represented by *C. cinerea* 479688,

3324   442333)(Table 29) as well as several other species-specific developmentally regulated HTP

3325   genes. The examined Agaricomycetes have 2-10 genes with an expansion to 23 genes in

3326   both *M. kentingensis* and *A. bisporus* as reported earlier(Morin et al. 2012). Most of the

3327   species had at least one HTP encoding gene that is strongly upregulated (up to 50-fold) from

3328   vegetative mycelium to the first primordium stage. These observations establish HTPs as a

3329   potentially important morphogenetic gene family in fruiting body development with currently

3330   unknown function. We tentatively discuss this gene family under the chapter on cell wall

3331   modification, however, it should be mentioned that this is based on an assumption of a

3332   potential role of this family.

3333   **DyPs -** Dye decolorizing peroxidases (DyPs) are a group of fungal peroxidases that belong

3334   to the broader heme-containing peroxidase family. They are mostly discussed in the context

3335   of plant cell wall degradation by fungi(Floudas et al. 2012); to our knowledge, this is the first

3336   report of its potential role in fruiting body morphogenesis. We detected 0-5 copies (missing in

3337   *A. ampla, S. commune* and *A. bisporus*) and a patchy distribution in Agaricomycetes.

3338   However, in species that have DyP genes, these are often developmentally expressed. DyP

3339   genes show significant upregulation from vegetative mycelium to the first primordium stages

3340   in *A. ostoyae, C. cinerea, C. aegerita, L. bicolor* and *P. ostreatus*. In *M. kentingensis* all DyP

3341   genes show a marked stipe expression peak, whereas in *Pt. gracilis*, expression curves are

3342   flat. DyP genes grouped into a single CDE orthogroup (represented by *C. cinerea* 407604,

3343   Table 29). While some of the copy number variation is explained by the lignin-degrading

3344   ability of fungi(Almási et al. 2019), the developmental expression of DyP genes suggests

3345   morphogenetic roles as well, possibly in remodeling the cell wall, although this is based on

3346   assumptions distilled from the general activity of the family. It would be interesting to

3347   investigate if, similar to observations during lignin degradation, H_2O_2-generating enzyme

3348   gene expression is co-regulated with peroxidase expression patterns.

3349   **AA5_1 (GLOX) -** Glyoxal oxidases (GLOX) in the AA5_1 family of auxiliary activities are

3350 H_2O_2 generating enzymes that facilitate the oxidative cleavage of lignin by

3351   peroxidases(Floudas et al. 2012). Surprisingly, GLOXs have also been reported to be

3352   upregulated in fruiting bodies in 6 species of Agaricomycetes(Krizsán et al. 2019) and were

3353   detected in fruiting bodies of *Auricularia polytricha* by protein mass spectrometry(Jia et al.

3354   2017). Since lignin is obviously missing from fruiting bodies, they were speculated to

3355   contribute to cell wall remodeling(Krizsán et al. 2019). We found 1-22 GLOX genes in the

3356   examined Agaricomycetes, the fewest in the Schizophyllaceae (*A. ampla, S. commune*)

3357   possibly because of their reduced morphology or reduced lignin-degrading ability(Almási et

3358   al. 2019). Two CDE orthogroups (*C. cinerea* protein ID: 263775 and 440836 Table 29), and

3359   several species-specific developmentally regulated GLOX genes were found in our data. We

3360   found GLOX genes significantly upregulated in primordia relative to vegetative mycelium

3361   (FB-init) in *A. ostoyae, A. ampla, C. cinerea, L. tigrinus, L. bicolor, S. commune, Ph.*

3362   *chrysosporium, P. ostreatus* and *C. aegerita* (not in *M. kentingensis, L. edodes* and *A.*

3363   *bisporus*). Two of the three *C. neoformans* GLOX genes also showed significant

3364   upregulation during basidium development. These data indicate that GLOXs may be

3365   important morphogenetic factors in the Basidiomycota.

3366   **AA3_1 -** cellobiose dehydrogenases in the AA3_1 family (GMC oxidoreductases) are known

3367   to donate electrons to LPMOs during lignocellulolysis in wood-decay fungi(Floudas et al.

3368   2012). There are only two reports on the potential role of CDHs in fruiting body development,

73

3369 one is a comparative transcriptomics study(Krizsán et al. 2019) and the other is a report of
3370 the interaction between CDH and laccases in the formation of cinnabarinic acid, the red
3371 fruiting body pigment of *Pycnoporus cinnabarinus*(Temp and Eggert 1999). A CDE
3372 orthogroup of cellobiose dehydrogenase (CDH) genes (*C. cinerea* protein ID: 469460)(Table
3373 29) was developmentally regulated in all species in which it was present. Additional CDH
3374 genes (2-8 genes in Agaricomycetes) were developmentally regulated in a species-specific
3375 manner in several species, although expression levels were low in many cases. The
3376 biological significance of CDH in fruiting body development is currently unknown; based on
3377 previous studies it may be related to cell wall remodeling or pigment production.
3378 **Slt2 kinase family -** A serine-threonine kinase orthologous to the MAP kinase involved in
3379 the cell wall integrity pathway of *S. cerevisiae* (Slt2) was detected as a CDE orthogroup (*C.*
3380 *cinerea* protein ID: 413665). Slt2 is a terminal kinase in the pathway that phosphorylates
3381 downstream transcription factors (Rlm1 and Swi4/6 in yeast)(Levin 2005). Although the gene
3382 is developmentally regulated in several species (Table 29), expression patterns are not
3383 consistent across taxa. Given the potentially pleiotropic role of this kinase, it is hard to guess
3384 its role in fruiting bodies, but extrapolations from its role in *S. cerevisiae* would suggest links
3385 to cell wall integrity, morphogenesis or the cell cycle.
3386 **Cfs1 family -** The orthogroup containing *C. cinerea* Cfs1 (*C. cinerea* protein ID: 447925), a
3387 cyclopropane fatty acid synthase, was developmentally regulated in 10/7 (FC>2/4) species
3388 (Table 29). Cfs1 was identified in a mutant screen of strains with developmental defects; its
3389 mutation leads to failures in the progression of hyphal knot development(Liu 2005) in *C.*
3390 *cinerea* (stalled at primary hyphal knot). The corresponding gene is highly induced 1h after
3391 blue light exposure(Sakamoto et al. 2018). We discuss this gene under the cell wall,
3392 although some evidence suggests it may be more closely related to plasma membrane
3393 assembly. Structurally, Cfs1 and related proteins are mycolic acid cyclopropane synthases,
3394 a family that occurs in 1-6 copies in the examined Agaricomycetes. Their function is not
3395 known, but presumably they are involved in the synthesis of long fatty acids (mycolic acid is
3396 not known to occur in fungi). In most examined species (*A. ampla, M. kentingensis, C.*
3397 *cinerea, P. ostreatus, S. commune*), the gene is upregulated in primordia relative to
3398 vegetative mycelium, consistent with its phenotypic role in hyphal knot development.
3399 **Eln3 family -** This family is based on the *Eln3* gene of *C. cinerea*, which was found in a
3400 REMI mutagenesis screen. The mutant strain displayed defects in stipe elongation and
3401 mutant stipe cells were disorganized and there were large gaps among stipe cells, whereas
3402 in the wild type strain stipe cells align closely with each other(Liu 2005). It has been
3403 hypothesized that *Eln3* is involved in cell-cell connections, possibly adhesion.
3404 We found that *C. cinerea Eln3* (*C. cinerea* protein ID: 380322) formed a small CDE
3405 orthogroup present in 7 species and was developmentally regulated in 6 species (Table 29).
3406 In these species the gene was predominantly FB-init and stipe upregulated, in agreement
3407 with a previously reported role in stipe elongation(Arima et al. 2004). It should be noted that,
3408 in many species, upregulation in primordia is easy to confuse with stipe-specific
3409 upregulation, because primordia often comprise predominantly stipe tissue. In general, we
3410 found 7-8 genes the examined Agaricomycetes (only 4 in *A. bisporus*) with identical domain
3411 composition to *Eln3*. This does not guarantee identical function, nevertheless is indicative of
3412 the diversity of this family in mushrooms. These genes were often FB-init and showed stipe
3413 or cap-specific upregulation depending on the gene and the species. For example, in *C.*
3414 *cinerea* we found that 5 out of 6 genes were stipe-upregulated. In *A. ostoyae* we found four
3415 cap- and two stipe-upregulated, whereas in *L. bicolor* two cap- and one stipe-upregulated
3416 gene. The widespread developmental regulation of *Eln3* and its homologs suggest

3417 morphogenetic functions, possibly in association with the cell wall. Based on its domain
3418 composition, we hypothesize it represents a cell wall active, possibly new CAZyme family
3419 not yet recognized by Cazy.org.
3420 **GT8 -** The GT8 family has 1-7 (most frequently 5) copies in the Agaricomycetes. The GT8
3421 family includes both N-acetylglucosaminyltransferases linked to the modification of N-linked
3422 glycans in the Golgi, and glycogenins involved in glycogen metabolism. Buser et al
3423 hypothesized that fruiting body-specific N-glycans generated by GT8 enzymes may
3424 contribute to adhesion in *C. cinerea*(Buser et al. 2010a). GT8 genes formed one CDE
3425 orthogroup, represented by *C. cinerea* 461263 FC2/4: 7/3 species), which is closest to *S.*
3426 *cerevisiae* Glg1 glycogenin (discussed under carbohydrate metabolism). Of the other GT8
3427 genes *C. cinerea* (*C. cinerea protein ID:* 453097, =*CcGnt1*)(Buser et al. 2010a)*, A. ostoyae,*
3428 *L. tigrinus, P. ostreatus, A. ampla* and *S. commune* had one FB-init gene each, however,
3429 these did not form CDE orthogroups. CcGnt2 (*C. cinerea* protein ID: 412828) was not
3430 expressed. Other species did not have developmentally regulated genes. Due to the
3431 variability of the family, it is hard to determine whether these are closer to glycogenins or N-
3432 acetylglucosaminyltransferases.
3433 **N-glycosylation -** Mannosylation and N-glycosylation of proteins in the ER is a key process
3434 for cell wall synthesis. Berends et al provided a detailed view of the N-glycosylation
3435 machinery in *S. commune, C. cinerea* and *L. bicolor* based on orthology to the *S. cerevisiae*
3436 N-glycosylation pathway members and expression data in *S. commune* fruiting bodies and
3437 monokaryotic mycelium(Berends et al. 2009). They conclude that Agaricomycetes have the
3438 gene repertoire to produce oligomannose structures only, in contrast to some Ascomycota
3439 which can produce very complex modifications to proteins. Our expression results broadly
3440 agree with theirs in that we detected very low dynamics of corresponding genes (not shown)
3441 in the fruiting body transcriptomes analyzed here.
3442

3443 ## 4.9. Cell surface and cell wall proteins

3444 Secreted cell surface proteins fulfill diverse functions in the life of fungi, ranging from
3445 signaling, interactions with the environment, adhesion, cell wall modifications, but also
3446 communication with hosts in mutualistic or pathogenic interactions(Pellegrin et al. 2015;
3447 Essen et al. 2020). The fungal cell surface proteome and secretome profile of each species
3448 in a given environment is unique, making constituents of fungal communities recognizable by
3449 their extracellular protein profiles(Campbell et al. 2015). Secreted proteins have been the
3450 subject of intense research, mostly in the context of interactions between fungi and other
3451 organisms, adhesion (e.g. via GPI-anchored adhesins) of fungal cells to various
3452 surfaces(Essen et al. 2020; M et al. 2020b). Fruiting bodies, as environmentally exposed, 3-
3453 dimensional multicellular structures, can be expected to display unique cell-surface
3454 attributes. In fact, cell surface proteins include some of the best-known fruiting body-
3455 associated proteins (e.g. hydrophobins, lectins, see below) or proteins related to defense
3456 (see these in a separate chapter). Conceivably, adhesion and/or cell-to-cell communication,
3457 two of the most important multicellular functions(Knoll 2011), could be realized via the action
3458 of secreted cell surface proteins in fruiting bodies, to just name a few of the diverse ways
3459 mushroom-forming fungi might make use of their cell surface protein repertoire. A significant
3460 open question in fruiting body biology is the nature and role of the extracellular matrix and
3461 the biochemical and communication events that take place in the interhyphal space. Cell

3462 surface proteins are undoubtedly important players in these processes, and therefore
3463 represent interesting targets of future research.
3464   While some cell surface proteins are the best examined fruiting body proteins (e.g.
3465 hydrophobins), the following inventory of conserved developmentally expressed genes
3466 shows that there is plenty of new insight to be learned about the cell surface proteome of
3467 Agaricomycetes fruiting bodies. In this chapter we discuss cell surface protein families in the
3468 context of CDE orthogroups detected in our meta-analysis of fruiting body transcriptomes.
3469

3470 ### 4.9.1. Hydrophobins

3471 Hydrophobins are some of the best-known proteins in fruiting bodies. They confer
3472 hydrophobicity to hyphae, which they achieve by self-assembling into a water-repellent
3473 rodlet layer on the cell surface. Hydrophobins were hypothesized to line air channels in
3474 fruiting bodies(Lugones et al. 1999b), but also contribute to water sealing, which is important
3475 in fruiting bodies as they rely on water transported to them from the vegetative
3476 mycelium(Nehls and Dietz 2014). The family has extensively literature, in general(Wösten
3477 2003; Linder et al. 2005; Bayry et al. 2012), in relation to fruiting body development(Ohm et
3478 al. 2010; Kües and Navarro-González 2015; Kim et al. 2016; Sammer et al. 2016; Y et al.
3479 2019) or on potential uses in bioengineering(Wösten and Scholtmeijer 2015). We therefore
3480 concentrate on novel aspects detected in our data that have not or only rarely been reported
3481 before.
3482   Basidiomycota hydrophobins mostly belong to class I hydrophobins(Sammer et al.
3483 2016). On average 11-44 hydrophobin genes (only 6 in *M. kentingensis*) were detected in
3484 the examined Agaricomycetes, a significant proportion of which were developmentally
3485 regulated. They can be arranged into distinct groups based on expression patterns. Previous
3486 studies reported a near complete turnover of hydrophobin genes from vegetative mycelium
3487 to fruiting body, indicating that two distinct sets of hydrophobins exist(Ma et al. 2007; WW et
3488 al. 2008; Cheng et al. 2013a). We also observed that mycelium-expressed and fruiting body-
3489 expressed hydrophobins form distinct groups. For example, the numbers of hydrophobins
3490 showing mycelium- vs fruiting body specific expression was 6/5, 1/9, 10/4, 23/3 and 5/20 (at
3491 fold change 4/2) in *Ph. chrysosporium, S. commune, P. ostreatus, A. ostoyae* and *C.
3492 cinerea*, respectively. *A. ostoyae* further has two rhizomorph-specifically expressed
3493 hydrophobins, indicating morphogenesis-related diversification of the family. This is in line
3494 with observations in *F. velutipes,* where most hydrophobin genes were found to be
3495 primordium-upregulated(Kim et al. 2016). We also detected hydrophobin genes expressed
3496 during early development, but not later, indicating functions linked to primordium
3497 development, which are turned off during later development. These observations further
3498 substantiate the functional diversification, probably driven by morphogenesis and complexity.
3499   Despite the large diversity and developmental expression of hydrophobins, only 2
3500 CDE orthogroups were detected (*C. cinerea* protein ID: 99661, 419467) (Table 30), which
3501 were present in only a subset (11 and 8 species, respectively) of the examined species. This
3502 is due to the frequent duplication of hydrophobin genes(Mgbeahuruike et al. 2017), which
3503 quickly erases clear orthology relationships. CDE orthogroups did not show conserved
3504 expression patterns. Interestingly, *M. kentingensis* has only 6 hydrophobin genes, none of
3505 which were developmentally expressed in our reanalysis of data from Ke et al(Ke et al.
3506 2020a). A possible explanation for this is that this species produces hygrophanous, rather
3507 than hydrophobic fruiting bodies, which absorb rather than repel water. The relatively low

3508 number of developmentally regulated hydrophobin genes in *A. ostoyae* may also be
3509 explained by the hygrophanous caps of this species. Hygrophanicity is a widespread trait in
3510 the Agaricales and might explain some of the differences in hydrophobin diversity and
3511 expression.
3512 Taken together, hydrophobins, as already established by previous research, are one
3513 of the best-known fruiting body-related structural cell surface proteins in the Agaricomycetes,
3514 with almost all species expressing developmental stage-specific suites of hydrophobin
3515 genes.
3516

4.9.2. Lectins

3518 Lectins will be also discussed in Chapter 10 on defense-related proteins, however, a role in
3519 defense has been proven for only a subset of the diverse lectin repertoires of mushroom-
3520 forming fungi; the remaining non-defense, or functionally unknown lectins are discussed in
3521 this chapter (even though not all lectins may be secreted or their secretion status is unclear
3522 at the moment, (Boulianne et al. 2000)). Lectins are proteins that specifically recognize and
3523 bind various carbohydrate moieties, mostly on the cell surface. This ability makes them
3524 suitable for multiple biological roles, from bacterial agglutination and cytotoxicity against
3525 mushroom grazers(Bleuler-MartÍnez et al. 2011; Kunzler 2015) to carbohydrate binding
3526 modules that fulfill roles related to the fungal cell wall (e.g. remodeling), adhesion, cell-to-cell
3527 communication or other functions in the extracellular matrix. Their carbohydrate binding
3528 ability makes them interesting in a wide range of biomedical fields(Hassan et al. 2015),
3529 including cancer research, which led to the broader lectin family rapidly expanding.
3530 Mushroom fruiting bodies remain one of the richest sources of lectins for applied research.
3531 However, regarding their physiological role for the fungi, boundaries between defense-
3532 related and other lectins are far from clear at the moment(Bleuler-MartÍnez et al. 2011).
3533 Due to interest in their practical applications, there is often more information on the structure
3534 of mushroom lectins than on their roles in the fungus' life. Fruiting bodies express a diverse
3535 set of lectins (reviewed by(A et al. 2013; Kobayashi et al. 2014; Y and H 2014)) and several
3536 of the well-known lectin families were first isolated from mushrooms. For example, the fungal
3537 fruit body lectin family was established based on the *Xerocomus chrysenteron* XCL protein,
3538 which was suggested to have insecticidal activity(C et al. 2004). Besides interest in their
3539 biotechnological applications, lectins have been in the focus of research on fruiting bodies.
3540 Early reports identified specific hyphal knot and primordium upregulated galectins (Cgl1 and
3541 Cgl2) in *C. cinerea*(Boulianne et al. 2000; Bertossa et al. 2004), which were initially
3542 postulated to be cell-cell adhesive or communication related molecules that may bind
3543 basidiolipids(Walser et al. 2005). Simultaneous silencing of the *cgl1* and *cgl2* genes did,
3544 however, not disturb fruiting, arguing against his hypothesis(MA et al. 2006). The lectins
3545 were rather shown to inhibit the development of insect and nematode larvae, in nematodes
3546 via binding to a specific N-glycan epitope, suggesting a function in defense against
3547 predators(Butschi et al. 2010; Bleuler-MartÍnez et al. 2011). Both genes were found
3548 upregulated in primordia, relative to vegetative mycelium in recent RNA-Seq based studies
3549 (cgl1 = *C. cinerea* 473274, cgl2 = *C. cinerea* 488611). Later, Wälti et al described cgl3 (=*C.*
3550 *cinerea* 539794), which resembles galectins, but binds chitooligosaccharides and had no
3551 effect on larval development of insects and nematodes(Wälti et al. 2008). Beta-glucan
3552 binding lectins of *Serepindita indica* may be involved in fungal cell wall remodeling at the
3553 plant-fungal interface(Wawra et al. 2019). Several other recent reports of individual lectins

3554   from a diverse set of medicinal or edible mushrooms is available but their detailed discussion
3555   is beyond the scope of this paper. Lectins are also involved in Ascomycota fruiting body
3556   (perithecium) formation and interestingly, the gene recently described in *Podospora anserina*
3557   showed highest similarity to *Xerocomus* lectins(Nowrousian and Cebula 2005). Several
3558   lectin families are overrepresented in mushroom-forming fungi(Krizsán et al. 2019),
3559   suggesting key roles in their life cycle.
3560   'Lectomes' evolve fast (like other defense genes) both in terms of sequence and
3561   gene content. Most lectin families a phylogenetically patchily distributed in mushroom
3562   forming fungi, with the probable sole exception of ricin-B lectins, which occur in all examined
3563   species. It has been suggested that the fast gene turnover can contribute to the expression
3564   of defense gene cocktails by the fungus, which is advantageous and that horizontal gene
3565   transfer from bacteria can provide a mechanistic explanation for the phylogenetic patchiness
3566   of several lectin families(Moran et al. 2012; Kunzler 2015).
3567   We here provide an overview of lectin copy numbers in the examined
3568   Agaricomycetes in the context of 8 main families, but note that more recent
3569   classifications(Lebreton et al. 2021) significantly reorganized lectin families and may provide
3570   a more nuanced view on lectin repertoires. Lectin copy numbers and expression patterns
3571   were summarized in the context of 6 Agaricomycetes species by Krizsan et al(Krizsán et al.
3572   2019) with lectins showing the RicinB fold (which includes protease inhibitors too, see above
3573   and(J et al. 2016)) being most diverse and present in all species, whereas other families are
3574   more patchy. Nevertheless, all lectin families had developmentally regulated genes, often
3575   showing strong induction in primordium stages.
3576   As noted earlier (e.g. (Kunzler 2015)), lectins are poorly conserved and hence mostly
3577   did not form conserved orthogroups in our analysis. Only two CDE orthogroups, all
3578   belonging to the RicinB family were detected (*C. cinerea* protein ID: 495335, 353931)(Table
3579   31). Both orthogroups contained secreted proteins. Expression patterns were poorly
3580   conserved within these orthogroups, but we note that each had FB-init genes in several
3581   species, indicating that these secreted Ricin-B family members are involved in the initiation
3582   of fruiting body development.

3583   4.9.3. Other cell surface proteins (HsbA, Con6, PriA, AA7, CFEM, wax synthases,
3584   fasciclins, peptidases, intradiol ring cleavage dioxygenase)

3585   **The HsbA family** comprises poorly known cell wall galactomannoproteins that includes
3586   HsbA from *Aspergillus oryzae*(S et al. 2006b), a *Magnaporthe* homolog(Soanes et al. 2012)
3587   as well as genes named Mp1 in *Talaromyces marneffei*(Cao et al. 1998) and in *Aspergillus*
3588   *fumigatus*(KY et al. 2001). Detailed functional information is not available for either of these
3589   genes. The family contains GPI-anchored cell surface proteins that can bind to various
3590   surfaces and was circumscribed in the context of appressorium attachment and
3591   lignocellulose degradation in Ascomycetes. The common denominator between these
3592   circumstances may be the need for adhesion of hyphae to various surfaces, enabling
3593   secreted lytic enzymes to exert their action. In the context of fruiting bodies, the family was
3594   first reported in fruiting bodies of *A. ostoyae*(Sipos et al. 2017b). In our current analysis, we
3595   detected 0-3 members of the family in Agaricomycetes (missing from *L. tigrinus, Ph.*
3596   *chrysosporium, A. ampla. S. commune*), all of which were developmentally expressed. The
3597   family did not form CDE orthogroups. Expression of members of this family showed
3598   significant dynamics (>100-fold), mostly with gill- or cap-specific expression peaks late
3599   during development. Functional analysis of this gene family in mushroom-forming fungi

3600 would be very interesting. If, as speculated above, the family is related to adhesion, then it
3601 may provide a missing link to adhesion in complex multicellularity in mushrooms.
3602 **The Con6 protein family** include small hydrophilic peptides that were first discovered as
3603 conidium-specific proteins in *N. crassa* and later shown in *A. nidulans* (ConF and ConJ) to
3604 be responsible for desiccation resistance of asexual spores(Suzuki et al. 2013). The family
3605 also includes the meiotically expressed *Sch. pombe* gene *cum1*. The Con6 family is
3606 conserved in Agaricomycetes, with 1-7 copies in the examined genomes, most of which are
3607 developmentally regulated. They showed two major expression patterns in all species: (i)
3608 strong induction in mature gills or combined gill+cap samples and/or (ii) upregulation in
3609 primordia relative to vegetative mycelia (Fig. 12, Supplementary Fig. 8). For some genes
3610 both for others only one of these expression patterns were observable. The family seems
3611 poorly conserved, nevertheless, they formed three CDE orthogroups (represented by *C.*
3612 *cinerea* 470234, 186809, *S. commune* 2624349)(Table 32). The gill-specific upregulation,
3613 combined with the conidium-specific expression of the gene family in filamentous
3614 Ascomycota, suggests that Con6 proteins may be involved in producing a spore-specific
3615 protein coating in these species. The orthogroup represented by *C. cinerea* 186809 showed
3616 upregulation in primordia of most species and has low expression in vegetative mycelia and
3617 later developmental stages. The strong upregulation of several Con6-encoding genes in
3618 primordia relative to vegetative mycelia in virtually all species suggests that it has general
3619 roles in fruiting bodies as well, possibly in regulating hydrophobicity/hydrophilicity of the cell
3620 surface, although this requires further research.
3621 **Wax synthases** are long-chain alcohol O-fatty-acyltransferases that synthesize wax esters,
3622 a typical constituent of the cuticula of plants or the sebum of the animals(Li et al. 2008). To
3623 our best knowledge, only Krizsan et al(Krizsán et al. 2019) indicated developmental
3624 expression for this family previously.
3625 We detected 4-16 wax synthases in the examined Agaricomycetes, the fewest in *A.*
3626 *bisporus*, but found no CDE orthogroups, suggesting a high duplication rate in the family.
3627 However, each species (except *Pt. gracilis* and *A. bisporus*) had 1-2 FB-init wax synthase
3628 genes, which suggests fruiting body specific roles for these genes. We observed
3629 considerable (>100-fold) upregulation compared to vegetative mycelia in many cases (Fig.
3630 13, Supplementary Fig. 9). Given the widespread upregulation of wax synthases in
3631 mushroom-forming fungi, it is possible that they produce a wax-like layer on the surface of
3632 fruiting body cells. On plants, wax-coating of leaves serves as a defense system that inhibits
3633 penetration of pathogenic fungi and water-sealing(Lewandowska et al. 2020). Products of
3634 fungal wax synthases, although unknown at the moment, could have similar properties in
3635 fruiting bodies, worth investigating in the future.
3636 **PriA family** - this family comprises secreted cell surface proteins first described as a
3637 primordium-induced protein in *L. edodes* (hence its name)(S et al. 1992). The gene has
3638 been quite extensively studied in *L. edodes*(T and K 2000; T et al. 2004a)*,* where a link to
3639 zinc homeostasis has been suggested. It was also detected as developmentally regulated in
3640 *F. velutipes*(Liu et al. 2020b)*, P. eryngii*(Fu et al. 2017), *L. edodes*(S et al. 1992) and in six
3641 species by Krizsan et al(Krizsán et al. 2019). The family also includes the virulence-related
3642 secreted adhesin Cfl1 of *C. neoformans*, which is highly induced during sexual development
3643 and has been thoroughly researched in *C. neoformans*(Wang et al. 2012, 2013). Cfl1 has
3644 been suggested to act as a morphogen that induces neighboring cells to phenocopy the
3645 producing cells' morphology(Wang et al. 2013). Cfl1 has 4 homologs in *C. neoformans*,
3646 which have stage-specific expression including Dha1, which is primarily expressed in
3647 basidia(Gyawali et al. 2017). The family is present in 0-4 copies in the Agaricomycetes and

3648 formed two CDE orthogroups. The first of these (*C. cinerea* protein ID: 359866)(Table 32)
3649 showed a very conserved, mycelium biased expression; it was highly expressed in
3650 vegetative mycelia and the first primordium stage, then virtually unexpressed in all later
3651 stages in *A. ampla S. commune, M. kentingensis* and *P. ostreatus*. In *A. ostoyae* expression
3652 dropped immediately after the mycelium sample. The second CDE orthogroup (represented
3653 by *C. cinerea* 419688) contains best hits of *C. neoformans* Dha1 and showed a peak
3654 expression in gills and caps of *C. cinerea, A. bisporus, C. aegerita*, *L. edodes* and late
3655 stages of *S. commune* and *A. ampla.* At the same time, these genes were significantly
3656 upregulated (up to 50-100x) in primordia relative to vegetative mycelium. In *L. edodes*, our
3657 RNA-Seq based observations are consistent with the first reports of the PriA gene as a
3658 primordium-upregulated one(S et al. 1992). The third orthogroup (represented by *S.
3659 commune* 2681702), was present in only 8 species, and was FB-init in *A. ampla, A. ostoyae,
3660 P. ostreatus, M. kentingensis* and *S. commune* (Table 32). In summary, the PriA family
3661 appears to be a very interesting family from the perspective of fruiting body development. In
3662 *C. neoformans* adhesive and signaling roles have been suggested for the family, although
3663 exact mechanisms of function are still unknown.
3664 **Aspartic peptidase A1** - This family is a versatile group of endopeptidases that has
3665 undergone a characteristic expansion in fungi(Revuelta et al. 2014). They were reported to
3666 be involved in pathogenesis, nutrition, cell wall maintenance and a range of other functions.
3667 The best researched family of A1 aspartic peptidases are yapsins, which are involved in cell
3668 wall assembly and remodeling, although their function is not clear; limited evidence suggests
3669 they proteolytically process secreted (cell wall) proteins(Gagnon-Arsenault et al. 2006; Gow
3670 et al. 2017; M et al. 2021). Based on functional knowledge on yapsins, and the abundance
3671 of GPI-anchored A1 aspartic peptidases in fungi, we discuss this family in the cell surface
3672 section, despite almost certainly not all of them are related to the cell wall. The family has
3673 been reported to be upregulated in fruiting bodies by several studies previously(Rahmad et
3674 al. 2014; Song et al. 2018b; Krizsán et al. 2019). Aspartic peptidase A1 family was found as
3675 15-60 copies in Agaricomycetes genomes. We detected 3 CDE orthogroups and several
3676 species-specifically developmentally expressed genes (Table 32), though these did not
3677 display strong expression conservation in the examined species. Nevertheless, the
3678 developmental expression of several members of this family, combined with evidence on
3679 yeast yapsins(Gagnon-Arsenault et al. 2006) and the secreted nature of these proteins
3680 suggest a cell wall related role for aspartic peptidases which may be worth investigating. Of
3681 note, we detected further CDE orthogroups of various peptidase families (M20, M28, M16,
3682 S10), which may also be involved in fruiting body development (Table 32), but our functional
3683 knowledge at the moment is too limited to speculate about their roles. Other peptidase
3684 families that were reported in mushroom-forming fungi include the metalloprotease M43
3685 family, which was reported from *P. ostreatus*(Joh et al. 2004) and has a strong (>700x)
3686 induction upon fruiting in the data published by Merenyi et al(Merényi et al. 2021).
3687 **AA7 family** - One of the CDE orthogroups (represented by *C. cinerea* 501135)(Table 32)
3688 were top hits of *Fusarium graminearum* ChitO, the only experimentally examined member of
3689 the family known to us(Heuts et al. 2007), which oxidises chitooligosaccharide species. AA7
3690 comprises oligosaccharide oxidising flavo-enzymes which also contain a Berberine-like
3691 domain and produce H_2O_2 during their action. They have been speculated to be involved in
3692 the detoxification of lignocellulose degradation intermediates and in the production of various
3693 secondary metabolites(Levasseur et al. 2013). Based on the activity of their homologs and
3694 their expression in fruiting bodies, it is likely that these AA7 family members are active on
3695 chitin, although their exact roles remain obscure for now.

3696 **CFEM domain proteins** - We detected 2 CDE orthogroups of CFEM domain containing
3697 proteins (Table 32). Homologous CFEM domain proteins may be involved in defense,
3698 pathogenicity, host-pathogen interactions or iron uptake, as is the rbt5 family of *Candida*
3699 *spp.*(Gaurav Bairwa et al. 2017) In *C. cinerea* certain mycelium expressed CFEM domain
3700 proteins were reported to be involved in defense(Plaza et al. 2014b). The detected CDE
3701 orthogroups comprise cell surface proteins with unknown functions, though they might be
3702 involved in defense, however, evidence for that is missing at the moment.
3703 **Fasciclins** are adhesive cell surface proteins that facilitate the attachment of cells to various
3704 surfaces. The few fungal mentions include a report of a role in the adhesion of *Magnaporthe*
3705 *oryzae* to host surfaces(Liu et al. 2009) as well as a primordium-upregulated gene in *L.*
3706 *edodes* (*Le.flp1*)(Y et al. 2007). Recently, fasciclins were hypothesized to have been co-
3707 opted for fruiting body development independently in both the Agarico- and
3708 Pezizomycotina(Merényi et al. 2020b). We identified 2-8 fasciclin-encoding genes in the
3709 examined Agaricomycetes. All examined species have developmentally expressed fascicling
3710 genes, although these formed only small CDE orthogroups (Table 32). Several genes
3711 showed an upregulation in primordia relative to vegetative mycelium (as reported in *L.*
3712 *edodes*), suggesting that this family has widespread roles in mushroom formation, possibly
3713 by facilitating adhesion. We found that the sequence deposited by(Y et al. 2007) (Accession
3714 number: AB287432) as well as ascomycete homologs to which they analyzed are
3715 cupredoxins, not fasciclins, leaving doubts as to the identity of Le.flp1. Nevertheless, this
3716 does not undermine the observation that fasciclin encoding genes are widespread
3717 developmentally expressed genes in mushroom-forming fungi, probably with roles in fruiting
3718 body development.
3719 **Intradiol ring cleavage dioxygenases** catalyze a ring-opening step in the degradation of
3720 aromatic compounds, and were hypothesized to be involved in xenobiotic detoxification or
3721 the utilization of aromatic compounds as carbon sources(Semana and Powlowski 2019).
3722 However, the physiological role of intradiol ring cleavage dioxygenases in fungi is not known.
3723 The only previous mention of a potential relationship to fruiting bodies reported
3724 developmental regulation in 4 out of 6 species(Krizsán et al. 2019). We identified 2-7 copies
3725 (28 in *A. ostoyae*) in the examined Agaricomycetes, with 1-3 developmentally expressed
3726 genes in most of the species that, however, did not form conserved orthogroups. Members
3727 of the family showed a significant upregulation in primordia relative to vegetative mycelium in
3728 *A. ampla, S. commune, C. cinerea, A. ostoyae* as well as a strong upregulation (>100fold)
3729 during late development of *C. neoformans*. Two genes show a very distinct upregulation in
3730 young fruiting body caps of *C. cinerea*. No developmentally expressed genes were found in
3731 *Ph. chrysosporium* and *M. kentingensis.* In summary, intradiol ring cleavage dioxygenases
3732 might be important genes during fruiting body development of several species; they might
3733 degrade aromatic compounds during fruiting, however, the identity of those compounds are
3734 unknown at the moment.
3735

4.10. Defense

3737 Agaricomycete fruiting bodies (mushrooms) are, due to the concentration of biomass,
3738 attractive targets of predators, parasites and pathogens. Accordingly, these structures are
3739 known to be subject to grazing by slugs, to infestations with larvae of phorid and sciarid flies
3740 and to infections by bacteria and molds(Wood et al. 2004; Krivosheina 2008; Lakkireddy et
3741 al. 2020; M et al. 2020a). Since mushrooms are the sexual reproduction organs and a

3742 considerable investment in terms of resources and energy, Agaricomycetes have evolved
3743 several strategies for the protection and defense of these structures(Künzler 2018). Such
3744 strategies include physical barriers(Varga et al. 2021) and chemical defense i.e. the
3745 production of molecules (toxins) impairing the growth, development and/or viability of
3746 antagonists(P 2008; FY and NP 2014; Stadler and Hoffmeister 2015).
3747 Using saprobic Agaricomycete species, whose sexual cycles can be completed
3748 under laboratory conditions, it could be demonstrated that the production of these toxins
3749 occurs axenically i.e. in the absence of the antagonist(Plaza et al. 2014b; Tayyrov et al.
3750 2019). This axenic toxin production is spatiotemporally regulated in that the toxin-encoding
3751 genes are expressed solely during fruiting body formation and in the fruiting body tissue.
3752 Some of these genes belong to the most highly upregulated genes of the entire genome
3753 during fruiting body formation. This expression pattern results in an efficient, constitutive
3754 protection of the fruiting body because at least some toxins are already in place in case the
3755 structure is attacked by an antagonist. It is unclear whether the chemical defense of the
3756 Agaricomycete fruiting body can be fortified by the induction of toxin production in response
3757 to environmental factors e.g. the presence of antagonists. Antagonist-specific induction of
3758 antibacterial and nematotoxic proteins upon challenge with bacteria and fungivorous
3759 nematodes, respectively, has recently been reported for the vegetative mycelium of C.
3760 cinerea(Kombrink et al. 2018; Tayyrov et al. 2019).
3761 Toxins of Agaricomycete fruiting bodies include small molecules (secondary
3762 metabolites)(Kües et al. 2018), peptides (ribosomally or non-ribosomally synthesized) and
3763 proteins, all of which act by binding to and (in case of toxins with enzymatic activity)
3764 converting specific target molecules in the antagonists. In the following, we will summarize
3765 the current knowledge about the structure, function, biosynthesis, regulation and distribution
3766 of Agaricomycete fruiting body toxins. In accordance with the focus of this review on
3767 genomics, we restrict our summary to compounds where the biosynthetic genes have been
3768 identified. We also make references to available gene expression data, but it must be noted
3769 that most toxin-encoding genes evolve fast and thus they do not easily conform to orthology-
3770 based categorizations that are central to the rest of this paper.
3771 **Small molecules** - The structurally related alkaloids ibotenic acid and muscimol of
3772 the fly agaric *Amanita muscaria* are two well-known examples of defensive secondary
3773 metabolites of Agaricomycete fruiting bodies(Michelot and Melendez-Howell 2003). The
3774 toxicity of these compounds toward flies gave rise to the name of the producer fungus. Their
3775 bioactivity is due to their structural similarity to the neurotransmitters glutamate and GABA
3776 and their binding to respective receptors in the brains of both invertebrates and vertebrates.
3777 The recent discovery of the biosynthetic gene cluster for the compounds revealed that their
3778 biosynthesis initiates from glutamate and makes it possible to identify additional *Amanita*
3779 species producing these compounds on a genetic basis(Obermaier and Müller 2020).
3780 Another psychotropic alkaloid produced by Agaricomycete fruiting bodies is psilocybin
3781 produced by several *Psilocybe* species(J et al. 2017; Torrens-Spence et al. 2018). This
3782 tryptophan derivative is an agonist of serotonergic receptors and is currently tested for
3783 treatment of depressions(Tullis 2021). The transcriptional analysis of the recently identified
3784 biosynthetic genes confirms its fruiting body-specific production(R et al. 2020). The blueing
3785 reaction of psilocybin-producing fruiting bodies upon injury has recently been demonstrated
3786 to be due to enzyme-mediated oxidative oligomerization of psilocybin suggesting that at
3787 least part of the defense function of this compound may be based on optical
3788 deterrence(Lenz et al. 2020). Wound-activation by injury (oxidation) has been reported for

3789 other secondary metabolites of Agaricomycete fruiting bodies(Stadler and Sterner 1998; P

3790 2008) but the genetic basis of these compounds and reactions is often not known.

3791   **Defense peptides** - The bicyclic octapeptide α-amanitin produced by some *Amanita*,

3792 *Galerina*, *Conocybe* and *Lepiota* species is probably the most famous toxin of

3793 Agaricomycete fruiting bodies(Walton 2018). The thermal stability and the very low lethal

3794 dose (0.1 mg/kg body weight) of the peptide have led to the common names 'death cap'

3795 (*Amanita phalloides*) or 'destroying angel' (*Amanita bisporigera*) of α-amanitin producers.

3796 Upon ingestion, the peptide is released from the fruiting body tissue and able to passively

3797 enter the intestinal epithelial cells where it binds and inactivates the essential enzyme RNA

3798 polymerase II in the nucleus(X et al. 2018). The fungus protects itself from the toxin by

3799 expressing an insensitive variant of the target enzyme(PA et al. 1978). In 2007, Walton and

3800 coworkers demonstrated that α-amanitin and its relative phallacidin are derived from

3801 ribosomally synthesized precursor peptides with common flanking sequences (MSDIN) by

3802 the action of a dual function prolyloligopeptidase-macrocyclase (POPB)(Hallen et al. 2007; H

3803 et al. 2012). Genome surveys of above Agaricomycete species revealed a large family of

3804 peptide precursor genes differing in the core peptide sequence and, thus, coding for α-

3805 amanitin- and phallacidin-related, but structurally different peptides, referred to as

3806 cycloamanides, whose function is unknown(Pulman et al. 2016; H et al. 2018; He et al.

3807 2020; Zhou et al. 2021). Localization of POPB expression confirmed the fruiting body-

3808 specific expression of α-amanitin and phallacidin(Luo et al. 2010; CH et al. 2018).

3809 Above described secondary metabolites and peptides have received considerable attention,

3810 mainly due to their activity towards humans. During the last two decades of research on

3811 fungal defense, it has become evident, however, that a large part of the chemical defense of

3812 Agaricomycete fruiting bodies, in particular against invertebrate predators and parasites, is

3813 based on protein toxins(M et al. 2002b; J et al. 2016; Tayyrov et al. 2018). These toxins

3814 have received less attention because their activity is usually lost upon boiling and is specific

3815 for a particular group of invertebrates. In addition, based on their fruiting body-specific

3816 expression, some of these proteins have been implicated in fruiting body formation rather

3817 than defense (see the example of *C. cinerea* galectins CGL1 and CGL2 mentioned above),

3818 which has delayed their recognition and functional analysis as toxins(S et al. 2007a; A et al.

3819 2019a). Most of these protein toxins are stored intracellularly and released upon ingestion of

3820 the fruiting body tissue by fungivores(Kunzler 2015; Künzler 2018). Once released, they

3821 interact with the digestive tract of the fungivore. Characterized classes of protein toxins from

3822 Agaricomycete fruiting bodies include lectins(Goldstein and Winter 2007; Bleuler-Martĺnez et

3823 al. 2011; A et al. 2013), protease inhibitors(S et al. 2015; Sabotič et al. 2019), pore-forming

3824 toxins (PFTs)(Anderluh and Maček 2003; JM et al. 2010; Panevska et al. 2020),

3825 ribotoxins(Tayyrov et al. 2019; Ragucci et al. 2021) and biotin-binding proteins(Y et al. 2009;

3826 S et al. 2012a).

3827   **Defense related lectins** - Fruiting body lectins have long been used as tools in

3828 glycobiology without addressing their biological function(Y and H 2014). In the meantime, it

3829 has been established that these proteins bind to specific glycoepitopes on the epithelial cells

3830 of the digestive tract of the fungivore which can ultimately lead to disruption of the structure

3831 and function of this tissue(Stutz et al. 2015). The mechanism of lectin-mediated toxicity is not

3832 clear yet but, in case of lectins without additional functional domain (hololectins), the

3833 bioactivity appears to depend on the crosslinking of protein-bound glycoepitopes on the

3834 epithelial cell surface(S et al. 2017), whereas in case of lectins with additional functional

3835 domains (chimerolectins), the bioactivity appears to depend on binding to lipid-bound

3836 glycoepitopes and endocytosis(T et al. 2011; Juillot et al. 2016). Fruiting body lectins can

3837 adopt various folds and carbohydrate specificities amongst which the RicinB-like (β-trefoil)
3838 fold and fucoside-binding, respectively, are most common. A prototypic example for such a
3839 fruiting body lectin is the hololectin CCL2 (*C. cinerea* protein ID: 408852) from the model
3840 Agaricomycete *Coprinopsis cinerea* which is present in other Agaricomycete species, adopts
3841 a RicinB-like fold, forms a dimer, binds to a specific fucoside present on nematode N-glycan
3842 cores and is toxic towards bacterivorous and fungivorous nematodes(Schubert et al. 2012; S
3843 et al. 2017; Tayyrov et al. 2018). A summary of diverse entomo- and nematotoxic lectin have
3844 been described from fruiting bodies has been given by Sabotic et al (J et al. 2016). Our data
3845 confirm previous reports on the upregulation (>150-fold) of CCL1 (*C. cinerea* protein ID:
3846 456849) and CCL2 (*C. cinerea* protein ID: 408852) in primordia (Table 33).
3847 The RicinB-like (beta-trefoil) fold is also adopted by protease-inhibitors isolated from
3848 Agaricomycete fruiting bodies(J et al. 2016). These proteins were shown to inhibit serine and
3849 cysteine proteases of various insect larvae. A prototypic example for this type of fruiting body
3850 toxin is Clitocypin, an insecticidal cysteine-protease inhibitor isolated from the
3851 Agaricomycete *Clitocybe nebularis*(J et al. 2011; Šmid et al. 2015). Of the examined
3852 species, the genomes of *C. aegerita* and *L. bicolor* encode 1 and 20 putative clitocypins,
3853 respectively. Our data identified a putatively defense-related RicinB protein orthogroup
3854 (represented by *C. cinerea* 485770)(Table 33). Another example is the six-bladed beta-
3855 propeller lectin Tectonin2 from L. bicolor whose production is induced in fruiting bodies and
3856 ectomycorrhizae(Martin et al. 2008). This lectin forms tetramers harboring 24 binding sites
3857 for O-methylated glycoepitopes and exhibits toxicity towards nematodes and agglutination of
3858 bacteria displaying respective glycoepitopes on their cell surfaces(Wohlschlager et al. 2014;
3859 Sommer et al. 2018). We detected tectonin homologs in the genomes of *L. bicolor* and *C.
3860 aegerita*.
3861 **Pore-forming toxins** - A common and probably very ancient class of protein toxins
3862 of Agaricomycete fruiting bodies are pore-forming toxins (PFTs)(Peraro and van der Goot
3863 2015). These toxins are divided into α- and β-PFTs depending on whether the predominant
3864 secondary structure motif is an α-helix or β-sheet. Within the producing cell, these proteins
3865 are usually monomeric and soluble, but upon release and binding to a target cell membrane,
3866 they undergo a dramatic conformational change. This change in conformation leads to
3867 oligomerization and insertion of the protein into the membrane. The result of this complex
3868 process is a proteinaceous pore that leads to lysis of the target cell. Among PFTs occurring
3869 in Agaricomycete fruiting bodies, members of the aerolysin and Membrane Attack Complex
3870 PerForin/Cholesterol Dependent Cytolysin (MACPF/CDC) β-PFT superfamilies have been
3871 characterized most extensively(Reboul et al. 2016; Cirauqui et al. 2017). Examples for
3872 aerolysins are the hemolytic *Laetiporus sulphureus* lectin (LSL)(JM et al. 2010), a
3873 homologous and recently identified nematotoxic protein, CC1G_11805 (*C. cinerea* protein
3874 ID: 546868) and its two paralogs, from *C. cinerea*(Plaza et al. 2014b) and the hemolytic
3875 flammutoxin from *F. velutipes*(T et al. 2004b). Pri1, a primordium-expressed gene in *C.
3876 aegerita* (Agrae_CAA7262647) also belongs to pore-forming toxins(Fernandez Espinar and
3877 Labarère 1997). The MACPF/CDC superfamily is represented by the insecticidal
3878 pleurotolysin complex, consisting of PlyA and PlyB, from the edible mushroom *P.
3879 ostreatus*(K et al. 2014; M et al. 2015b; N et al. 2015; A et al. 2019a). The main
3880 representatives of the two β-PFT superfamilies differ in the specificity determinant of the
3881 target membrane and the dimensions of the formed membrane pore. Whereas LSL likely
3882 binds to lactose-containing glycoepitopes (as part of glycolipids or GPI-anchored
3883 glycoproteins) on the target membrane via an N-terminal RicinB-type(β-trefoil) lectin domain
3884 and forms homomeric transmembrane β-barrels (pores) of seven or eight protomers with an

3885 inner diameter of ~4 nm(I et al. 2011; Szczesny et al. 2011), pleurotolysin PlyA binds to
3886 sphingophospholipids (sphingomyelins) of cholesterol-rich membranes and directs PlyB to
3887 the formation of transmembrane β-barrels (pores) consisting of 13 heteromeric protomers
3888 and an inner diameter of ~ 8 nm(Novak et al. 2020).
3889   **Ribotoxins** are ribonucleases cleaving a single phosphodiester bond in the
3890 universally conserved sarcin/ricin loop (SRL) of 23S or 28S rRNA in intact prokaryotic or
3891 eukaryotic ribosomes, respectively(M et al. 2017b). Upon this action, the ribosome is unable
3892 to interact with translation elongation factors and translation is stalled. The SRL is named
3893 after α-sarcin, one of the best characterized ribotoxins secreted by the ascomycetous mold
3894 *Aspergillus giganteus*(M et al. 2017b). Other fungal ribotoxins have been isolated from
3895 ascomycetous entomopathogens and are generally highly active against insects(A et al.
3896 2009; M et al. 2017a). Recently, the first basidiomycetous ribotoxin, ageritin (Agt1), from
3897 fruiting bodies of the edible mushroom *C. aegerita* was isolated(Landi et al. 2017).
3898 Heterologous expression of the respective cDNA in *Escherichia coli* and phylogenetic
3899 analysis showed that the protein is widespread but patchy among Agaricomycetes and
3900 displays entomotoxic activity similar to its ascomycetous counterparts(A et al. 2019b). In
3901 contrast to its ascomycetous counterparts, however, ageritin does not contain a canonical
3902 signal peptide for secretion suggesting that the protein, as most protein toxins of
3903 Agaricomycete fruiting bodies, is stored intracellularly(Baglivo et al. 2020). In order to avoid
3904 damage to the ribosomes of the producing fungal cell, the protein might be sequestered into
3905 a specific subcellular compartment which might involve N-terminal truncation of the
3906 protein(Ragucci et al. 2021). The agt1 gene (*C. aegerita* CAA7259527) was induced
3907 considerably in primordia relative to vegetative mycelium in *C. aegerita*, based on data
3908 produced by Orban et al (Orban et al. 2021).
3909   **Tamavadins** - Finally, defense proteins of some Agaricomycete fruiting bodies,
3910 similar to animals and bacteria, include proteins that are able to avidly bind and thus
3911 sequester biotin at equimolar concentrations(Michael Green 1990). The prototype of these
3912 proteins, avidin, is thought to protect the eggs of birds from bacterial infections, but the
3913 protein and its relatives also exhibit broad and strong insecticidal activity(JT et al. 2010). A
3914 family of avidin-related biotin-binding proteins, tamavidin (called Tam1 and Tam2), was
3915 isolated from the edible mushroom *Pleurotus cornucopiae* (Tamogitake mushroom) and
3916 shown to possess very strong entomotoxic and nematotoxic activity(Y et al. 2009; S et al.
3917 2012a). Amongst the fruiting body protein toxins tested against two fungivorous nematode
3918 species, tamavidin was the most effective one(Tayyrov et al. 2018). It is unclear how the
3919 producing cells shield their own biotin against this cytoplasmic protein.
3920   Taken together, this data shows that the chemical armory of Agaricomycete fruiting
3921 bodies is very diverse, in terms of compound classes, molecular targets and antagonist
3922 specificity of the toxins, but three common themes can be recognized: (1) Toxin-encoding
3923 genes are phylogenetically patchy, with each family present in only a subset of species (2)
3924 protein toxins provide a large part of the chemical defense of these structures; and (3)
3925 intracellularly stored toxins directed against nematodes and arthropods are predominant.
3926 Latter finding may reflect the use of Agaricomycete fruiting bodies as habitat by these
3927 organisms(Ruess and Lussenhop 2005; Krivosheina 2008). It has even been postulated that
3928 some mycophagous Drosophila flies exploit fruiting body nematotoxins to purge themselves
3929 from insect-parasitic nematodes(JA et al. 2017).
3930

4.11. Secondary metabolism and natural product biosynthesis

Secondary metabolites are one of the most important classes of molecules in chemical warfare and developmental signaling in fungi(Spiteller 2015; Keller 2019; Gressler et al. 2021). Based on recent genome surveys it appears that the fungal secondary metabolome is extremely diverse and is a largely untapped resource of natural products and bioactive molecules(Keller 2019). This may be particularly true for the Agaricomycetes, despite several lines of evidence for a large diversity of secondary metabolites produced by Agaricomycetes(Spiteller 2015; Gressler et al. 2021). From the perspective of fruiting body formation, it is important to note that secondary metabolites can serve defense or repellent purposes in fruiting bodies (see chapter on Defense) but can also influence developmental processes. For example, the deletion of a polyketide synthase gene resulted in malformed perithecia of *Sordaria macrospora*(D and M 2014). The lack of coprinoferrin production in *C. cinerea* resulted in the loss of fruiting body formation(Tsunematsu et al. 2019).

Due to differences in basic genome organization between Asco- and Basidiomycota, the latter possess fewer secondary metabolism gene clusters, yet, according to a recent study some developmentally regulated genes formed 'clusters' in the genomes of 8 species and some of these 'clusters' overlapped with predicted biosynthetic gene clusters that might encode secondary metabolism genes(Merényi et al. 2021).

The number of functionally characterized secondary metabolism genes and linked natural products of Agaricomycetes is rapidly increasing. For example, *ArmB* and orsellinic acid in *Armillaria* spp(Lackner et al. 2013), *LpaA* and laetiporic acid in *Laetiporus* sp(Seibold et al. 2020), or *St.pks1* and strobilurin in *Strobilurus tenacellus*(Nofiani et al. 2018) as well as numerous terpene synthases have been circumscribed in the past decade (reviewed in more detail by(Gressler et al. 2021)). Strobilurin derivatives are available commercially and are the world's most sold fungicides(DW et al. 2002). Siderophore-type secondary metabolites, coprinoferrin, ferrichrome A and basidioferrin in *C. cinerea, Omphalotus olearius* and *Ceriporiopsis subvermispora*, respectively, and their putative synthesizing genes were also identified. In *C. cinerea cfp1* (*C. cinerea* protein ID: *354233*) was reported to be responsible for coprinoferrin production(Tsunematsu et al. 2019), whereas in *O. olearius* a cluster composed of *fso1, omo1* and *ato1*(K et al. 2005). Coprinoferrin proved necessary for fruiting body development, as the cfp1 mutant did not, only in the presence of exogenously administered coprinoferrin produce fruiting bodies. Contrary to expectations based on Ascomycota knowledge, deleting a homolog (*C. cinerea* protein ID: 357031) of *A. nidulans LaeA* did not compromise coprinoferrin production(Tsunematsu et al. 2019). Despite recent advances in understanding Agaricomycetes secondary metabolism, given the number of putative secondary metabolism genes encoded by fungal genomes, we are likely hardly scratching the surface of natural product diversity in mushroom-forming fungi.

Since many secondary metabolites specifically occur in fruiting bodies of Agaricomycetes, it is expected that their biosynthetic gene clusters may be developmentally regulated. However, secondary metabolism related genes evolve fast, which does not make them easily detectable in the orthology-based framework we use here. Nevertheless, we identified several secondary metabolism related genes that showed shared and conserved developmental expression profiles in the examined Agaricomycetes, although the natural products they produce are unknown in most cases.

Polyketide synthases (PKS) are large (often >1500 amino acid) multi-domain enzymes that produce diverse secondary metabolites. They are widely distributed in fungi and are subject to intense research, mostly in the Ascomycota. Polyketide synthases and

3978   the few examples of known natural products of the Basidiomycota have recently been
3979   reviewed(Gressler et al. 2021). Basidiomycete PKSs mostly belong to type 1, which is
3980   divided into highly-, partially- and non-reducing PKSs. Hybrid nonribosomal peptide
3981   synthase-PKS genes have been shown to underlie fungal bioluminescence(Ke et al. 2020a;
3982   Gressler et al. 2021).

3983   We identified orthologs of previously described siderophore biosynthesis related
3984   genes in the examined Agaricomycetes. Members of the biosynthetic cluster described from
3985   *O. olearius*(K et al. 2005) seem to be conserved, with fso1 being orthologous to *C. cinerea*
3986   cfp1 (*C. cinerea* protein ID: 354233), whereas L-ornithine N(5)-monooxygenase omo1 and
3987   the N-acyltransferase ato1 seem single-copy in Agaricomycetes genomes (represented by
3988   *C. cinerea* 492586 and 161175). These genes were not developmentally regulated and had
3989   highest expression in vegetative mycelia. We further identified a single CDE orthogroup of
3990   polyketide synthases (represented by *C. cinerea* 446258, Table 34), which was
3991   developmentally regulated in 11/8 species (FC>2/4). These genes were stipe upregulated
3992   (albeit weakly) in most species (*C. cinerea, P. ostreatus, M. kentingensis, A. ostoyae*),
3993   although their expression also increased in mature caps of *P. ostreatus, A. ostoyae, M.*
3994   *kentingensis* relative to younger cap stages and in mature fruiting bodies of *C. aegerita*, *A.*
3995   *ampla* and *S. commune* relative to earlier stages. The *C. cinerea* gene shows peak
3996   expression in meiotic gill tissues, whereas in *P. ostreatus* and *A. ostoyae*, where gills and
3997   caps were sampled separately like in *C. cinerea*, highest expression was observed in caps
3998   but not in gills.

3999   **Terpene synthases** have been a focus of secondary metabolism studies in
4000   mushroom-forming fungi. They encode highly promiscuous enzymes that can generate a
4001   large diversity of metabolites(Slot and Gluck-Thaler 2019) and thus provide the basis for fast
4002   adaptive evolution. Slot and Gluck-Thaler showed that morphologically complex fungi harbor
4003   more terpene synthases than simpler counterparts(Slot and Gluck-Thaler 2019). Similarly,
4004   terpene synthases were found to be strongly overrepresented in the genomes of
4005   Agaricomycetes compared to other fungi (FDR corrected p-value < 10^{-125})(Krizsán et al.
4006   2019). Twelve sesquiterpene synthases (Fla1-12) were identified in *F. velutipes*(Tao et al.
4007   2016), eleven in *C. aegerita* (Agr1-Agr11)(Zhang et al. 2020, 2021a) and in *Omphalotus*
4008   *olearius* (Omp1-10)(GT et al. 2012) and five (Cop1-Cop6) in *C. cinerea*(Agger et al. 2009)*,*
4009   with information on the potential metabolite products in many cases (e.g.
4010   viridiflorene/viridiflorol, Δ^{6-}protoilludene, γ-cadinene, germacrene).

4011   Agger et al identified six genes, Cop1 to Cop6, related to terpene biosynthesis in *C.*
4012   *cinerea*(Agger et al. 2009). Of the genes reported by Agger et al, orthologs of Cop2 and
4013   Cop4 appear interesting from the perspective of mushroom development. Orthologs of Cop1
4014   show an upregulation in primordia relative to vegetative mycelium in *C. aegerita, A. ampla*
4015   (only FC>2), *L. bicolor, Ph. chrysosporium* and were cap-upregulated in *A. ostoyae, P.*
4016   *ostreatus, L. edodes* and *M. kentingensis*. On the other hand, orthologs of Cop4 (*C. cinerea*
4017   protein ID: 30510) were FB-init in *C. cinerea, C. aegerita, A. ampla, L. bicolor, L. edodes* and
4018   *P. ostreatus* (Table 34). Cop2 (*C. cinerea* protein ID: 443805) is only present in *C. cinerea,*
4019   *A. bisporus* and *P. ostreatus* and is upregulated in primordia relative to vegetative mycelium
4020   in all species, suggesting it functions during fruiting body initiation. Products of these genes
4021   were reported to as δ-cadinene and germacrene A, but the functions of these natural
4022   products remain unknown.

4023   We found 13-28 (63 in *A. ostoyae*) putative terpene synthases in the examined
4024   Agaricomycetes genomes. Of these, several were developmentally regulated, showing one
4025   of two most typical expression profiles: (i) highest expression in vegetative mycelium or (ii) a

4026   strong induction in primordia and other fruiting stages relative to vegetative mycelium. The
4027   latter expression profile is reminiscent of that of typical defense genes (e.g. pore-forming
4028   toxins, see above), but it is compatible with several other putative functions as well. Terpene
4029   synthases formed three CDE orthogroups (Table 34), two of these correspond to *C. cinerea*
4030   Cop1 (*C. cinerea* protein ID: 469738) and Cop4 (*C. cinerea* protein ID: 30510, contains *C.*
4031   *aegerita* Agr4 also), discussed above. The third CDE orthogroup (represented by *C. cinerea*
4032   488324) is developmentally regulated in 8/6 species, but shows mixed expression profiles.
4033   Taken together, terpene synthases might participate in important fruiting body
4034   functions, including events around the initiation of primordium development, yet their exact
4035   functions, whether the production of defense/repellent metabolites and/or compounds for
4036   communication, remain unknown for the moment.
4037   **Phenylalanine ammonia-lyases** - We detected two highly conserved CDE
4038   orthogroups of phenylalanine ammonia-lyases (PAL), one of which (*C. cinerea* protein ID:
4039   386671, ortholog of pal1 of *Pleurotus*) is developmentally regulated in 11/9 species, the
4040   other (*C. cinerea* protein ID: 361541, ortholog of pal2 of *Pleurotus*(Hou et al. 2019)) is in 8/5
4041   (out of 9 species in which present) (Table 34). PAL enzymes are best known from plants,
4042   where they are part of the phenylpropanoid pathway, which is involved in the production of
4043   diverse secondary metabolites, associated with defense, lignin and flavonoid
4044   biosynthesis(Dixon et al. 2002). In fungi, phenylalanine ammonia-lyases are discussed
4045   mostly in the context of catabolism of phenylalanine to cinnamic acid(Hyun et al. 2011),
4046   although some reports of the production of diverse compounds have been published(Hyun et
4047   al. 2011). Recently, an association with fruiting body formation has been reported in *F.*
4048   *velutipes*(Yun et al. 2015) and *P. ostreatus* (Hou et al. 2019).
4049   Our analyses revealed two PAL-encoding genes in most of the examined
4050   Agaricomycetes (up to 4 in *A. ostoyae*). Expression profiles of genes within the two CDE
4051   orthogroups were not conserved, although several genes showed an upregulation in
4052   primordia (e.g. both genes in *C. cinerea*). At the moment the physiological role of PALs is
4053   unknown, to our best knowledge, in any fungus. They could be involved in the production of
4054   defense-related metabolites, as in plants, or other fruiting body related functionalities.
4055

4.12. Cytoskeleton

4056

4057   A plastic cytoskeleton is a key factor for eukaryotic cell shape regulation and has been
4058   named one of the prerequisites for diversification of size, form and function in multicellular
4059   eukaryotes(Knoll 2011). It is involved in the regulation of diverse morphogenetic processes
4060   in fungi, including hyphal growth, conidiation, biofilm formation, dimorphic switching, to name
4061   a few(Riquelme et al. 2018). In line with this, although at a somewhat limited scale, evidence
4062   is available for the role of cytoskeleton rearrangement in fruiting body development.
4063   Evidence from Gene Ontology analyses pointed at differential cytoskeletal gene expression
4064   in *P. microcarpus*(Pereira et al. 2017). Microscopy observations provided evidence for a key
4065   role of cytoskeletal elements during the development of mushroom-forming fungi. For
4066   example, longitudinally oriented microtubules were observed in the sterigmata during spore
4067   formation in *C. cinerea*, along which Golgi vesicles carry carbohydrates to the developing
4068   spore and spore wall(Kües and Liu 2000).
4069   In terms of expression levels, we found only limited dynamics in cytoskeletal proteins,
4070   likely reflecting the need for continuous supply of its components for the cell. Cheng et al
4071   reported an upregulation of tubulin and tubulin-specific chaperone genes in primordium

4072   stages of *C. cinerea*(Cheng et al. 2013a) using 5'-SAGE technology. Although newer data
4073   did not confirm these observations(Muraguchi et al. 2015; Krizsán et al. 2019), both recent
4074   RNA-Seq studies reported upregulation of these genes in stipes of *C. cinerea*.
4075   Following these lines of evidence, we annotated the main cytoskeletal protein groups
4076   in *C. cinerea* based on homology and domain composition and checked their orthologs'
4077   expression patterns across mushroom-forming fungi. We grouped 67 cytoskeletal and
4078   associated protein coding genes into the following categories (Table 35): actin, actin
4079   nucleation, actin filament organization, actin-based motor protein, microtubule, microtubule
4080   heterodimerization, microtubule-based motor protein, regulation of microtubule-based motor
4081   proteins. Copy numbers in these categories agreed with previous annotations, including 2
4082   copies of formins per species and a tubulin gene duplication in the common ancestor of
4083   Basidiomycota(Zhao et al. 2014). Of cytoskeletal genes, only kinesin genes and the
4084   Dynactin complex showed consistent expression dynamics. In both cases, expression peaks
4085   were observed in young fruiting body gills and stipes in *C. cinerea* (Fig. 14, Supplementary
4086   Fig. 10).
4087   Tubulin gene expression (alpha1-, alpha2-, beta-tubulin and tubulin chaperone) was
4088   previously reported to be regulated during early fruiting events of *C. cinerea*, with
4089   upregulation in stage 1 primordia based on 5'-SAGE data(Cheng et al. 2013a). Our data on
4090   the corresponding genes revealed that the three of these, alpha1- (*C. cinerea* protein ID:
4091   176636), beta-tubulin (*C. cinerea* protein ID: 393528) and tubulin chaperone (*C. cinerea*
4092   protein ID: 413977) had constant expression in primordia, but show expression peak in
4093   young fruiting body stipes, whereas alpha2-tubulin (*C. cinerea* protein ID: 359665) was
4094   upregulated in young fruiting body caps. These expression patterns were not consistent
4095   across species (Table 35) and possibly reflect the fast stipe elongation of *C. cinerea*.
4096   **Septins** - Septins form a highly conserved family of proteins involved in morphogenesis,
4097   development and in generating cell asymmetries in fungi and in eukaryotes in
4098   general(Gladfelter 2006; Khan et al. 2015). They have been shown to be responsible for
4099   morphogenesis in a number of model fungi, such as bud emergence in *S. cerevisiae*,
4100   septum formation in hyphae or appressorium formation in *Magnaporthe oryzae*, among
4101   others(Gladfelter 2006). Their broad involvement in morphogenesis and limited evidence
4102   from fruiting body forming fungi suggest that septins have important, although to date
4103   underappreciated, roles in fruiting body development. For example, they have been reported
4104   in stipe elongation in *C. cinerea*(Shioya et al. 2013).
4105   We annotated septins based on their domain composition: the combination of two
4106   IPR domain terms (IPR030379, IPR016491) are diagnostic for fungal septins. Most
4107   mushroom-forming fungi have 7 septin genes (*C. cinerea* protein ID: 367587, 416864 [*cdc3*,
4108   = *A. nidulans* AspE, =AspB], 103773, 415573 [top hit of *A. nidulans* AspE], 103809, 455217,
4109   481878), with some having only 6 while a few having 8, which is similar to the septin
4110   repertoires seen in filamentous fungi and yeasts(Douglas et al. 2005).
4111   Septins are highly variable genes, and did not form conserved orthogroups, but
4112   nevertheless maintain some functional conservation in mushroom-forming fungi. Two
4113   orthogroups of septins showed consistent upregulation at the initiation of fruiting body
4114   development, in the very first primordium stages in all species in which they are
4115   present(Krizsán et al. 2019; Merényi et al. 2021). One of these is the top hit of AspE of *A.*
4116   *nidulans*, which is involved in conidiation and spore production(Hernández-Rodríguez et al.
4117   2014). Septin expression seems to be highly induced in stipes in *C. cinerea, M.*
4118   *kentingensis, A. ostoyae*, but following a different expression tendency in *P. ostreatus*
4119   (mostly in primordia) and *A. bisporus* (mostly in young fruiting bodies). The stipe induced

4120 septins included *Cc.cdc3* of *C. cinerea*, which has been shown to be involved in stipe
4121 elongation(Shioya et al. 2013). The ortholog of *C. cinerea cdc3* was also mostly stipe-
4122 induced in *A. bisporus*(卢园萍 et al. 2019). Muraguchi et al reported a downregulation of
4123 septin expression from the 4_0hrPri primordia (approximately coinciding with stage 2
4124 primordia of Krizsan et al and Kues 2000(Kües 2000; Krizsán et al. 2019)) to the 5_12hrPri
4125 stage of *C. cinerea*(Muraguchi et al. 2015).
4126 The limited diversity of septins raises the question how they can fulfill the diverse
4127 roles they have in fungal morphogenesis. Although most septins had peak expression in
4128 stipes of mushroom-forming fungi (except in certain species) their expression level was
4129 dynamically changing in other tissues and from one developmental stage to the other as
4130 well, suggesting that there is still a long way to uncover their roles in fruiting body
4131 development. Understanding their protein-protein interaction networks is a promising future
4132 avenue of research.

4.13. Ubiquitin-proteasome system

4.13.1. Cop9 signalosome

4135 The Cop9 signalosome is a protein complex conserved across all eukaryotes, which
4136 catalyzes the deactivation of cullin-RING ubiquitin ligase (CRL) complexes by removing the
4137 Nedd8 protein from the cullin subunit of the complex (deneddylation reaction). As such, it is
4138 an important component of various signal transduction pathways and is involved primarily in
4139 multicellular developmental processes. In fungi, it was found dispensable for vegetative
4140 growth, but necessary for sexual fruiting body formation(Busch et al. 2003; Braus et al.
4141 2010), secondary metabolism and it was reported to interact with the Velvet complex(Kress
4142 et al. 2012; Meister et al. 2019). Recognition of the COP9 signalosome (CSN) as an
4143 important player in fruiting body formation started with genetic screens that identified CsnE
4144 and CsnD, which displayed identical defects in fruiting body initiation in *A. nidulans*(Busch et
4145 al. 2003, 2007). The *A. nidulans* Cop9 complex represents an 8-subunit, stereotypical
4146 complex, whereas that of other model fungi (*N. crassa, S. cerevisiae* or *S. pombe*) possess
4147 fewer subunits and are not typical(Braus et al. 2010). Agaricomycetes genomes appear to
4148 encode a typical 8-subunit CSN (Table 36). Neither we nor previous studies found significant
4149 expression dynamics of any subunit of the CSN in mushroom-forming fungi. It is not known
4150 whether the complex is involved in fruiting body development as it is in Ascomycota,
4151 nevertheless, it will be an interesting target for future experiments, especially because it is
4152 involved in light regulation in *N. crassa* and can interact with the Velvet complex, two key
4153 factors that regulate Basidiomycota development also.

4.13.2. Protein ubiquitination

4155 Covalent protein modification by the ubiquitin-proteasome system is a widely conserved
4156 regulatory machinery that functions in several essential processes in eukaryotes and was
4157 recently detected as a potentially very interesting function during fruiting body
4158 development(Krizsán et al. 2019). The regulatory potential of the ubiquitin-proteasome
4159 system stems from its ability to attach the 76-amino acid ubiquitin protein to lysines of target
4160 proteins, which either destines them for degradation by the proteasome or modifies their
4161 activity, cellular localization or DNA-binding ability(LC et al. 2007; Liu and Xue 2011; Finley

4162 et al. 2012). Ubiquitination can modify the activity of transcription factors, which provides an
4163 additional layer of transcriptional regulation(Freiman and Tjian 2003).
4164   The protein ubiquitination machinery is composed of E1 ubiquitin-activating, E2
4165 ubiquitin-conjugating enzymes and E3 ubiquitin ligases, which attach the ubiquitin to target
4166 proteins. While E1 and E2 enzymes are generic components of the system and are present
4167 in limited numbers in eukaryotic genomes (Table 37), ubiquitin ligases provide the substrate
4168 specificity and come in many subtypes and display considerable diversity due to
4169 interchangeable protein components, of which hundreds may exist in the genomes of some
4170 species(Hutchins et al. 2013; Zheng and Shabek 2017). The most diverse such parts are F-
4171 box and BTB/POZ domain proteins, both of which can confer substrate-specificity to the E3
4172 complexes(R et al. 2003) and RING-type zinc finger proteins, which are scaffold proteins
4173 linking target proteins with E2 enzymes(Metzger et al. 2012). These three gene families
4174 were found to be strongly expanded in mushroom-forming fungi, with frequent tissue-specific
4175 developmental regulation seen in RNA-Seq data(Almási et al. 2019; Krizsán et al. 2019)
4176 (see also Table 37). The expansion stems from Agaricomycetes-specific duplication events
4177 and a correlation between fruiting body complexity and F-Box, BTB/POZ and RING-type zinc
4178 finger copy number and expression has been suggested(Krizsán et al. 2019), which could
4179 explain the evolution of increasingly complex mushroom morphologies in the class.
4180   The widespread cellular roles of ubiquitination suggests that it should be instrumental
4181 during fruiting body morphogenesis too. In line with this, the protein ubiquitination system
4182 was found differentially expressed in *F. velutipes* fruiting bodies(M et al. 2006; Liu et al.
4183 2020b) and in caps of the same species subjected to differential CO_2 treatments(Yan et al.
4184 2019). In recent comparative transcriptomics analyses, we provided evidence for the
4185 developmental regulation of several components, mostly those that confer substrate
4186 specificity to E3 ligase complexes, in multiple Agaricomycetes species, including *C. cinerea,*
4187 *A. ostoyae, A. ampla, S. commune* or *P. ostreatus*, among others(Almási et al. 2019; Krizsán
4188 et al. 2019; Merényi et al. 2021). BTB domain-containing proteins, a family of E3 proteins,
4189 were reported to be upregulated in fruiting bodies in *Antrodia cinnamomea* (Lu et al. 2014).
4190 The combination of a remarkable gene family expansion with developmental regulation
4191 suggests that the ubiquitin-proteasome system could play a pivotal role in fruiting body
4192 development, although mechanistic details of the process remain to be understood.
4193 Ubiquitylation is key in developmental processes of the Ascomycota also, including fruiting
4194 body formation, and in some cases more mechanistic details have been uncovered
4195 (reviewed in(Riquelme et al. 2018)). However, a similar expansion of F-Box domains, as
4196 seen in Agaricomycetes, has not been reported.
4197   Hereafter, we present an annotation of components of the protein ubiquitination
4198 machinery in selected mushroom-forming fungi, with particular emphasis on *C. cinerea*
4199 genes and comparisons across species. In this presentation, we follow the classification of
4200 E3 ubiquitin ligases used by Hutchins et al(Hutchins et al. 2013) and identify protein diversity
4201 of each protein family based on Interpro domain HMM-s. Results of the annotation along
4202 with orthologous genes and conservation levels are shown in Supplementary table 4. A
4203 limitation of this approach is that the presence of a defining domain in the protein does not in
4204 all the cases, indicate a function in the ubiquitination machinery. For example, BTB/POZ
4205 domains, which contribute to expanding the diversity of E3 ligase complexes(R et al. 2003)
4206 can, in rare cases, also occur in proteins not related to ubiquitination (e.g. cytoskeleton or
4207 transcription regulating proteins(Stogios et al. 2005)).
4208   Several components of the ubiquitination machinery are very conserved in
4209 Agaricomycetes genomes, including E1 (on average 3 genes) and E2 enzymes (19-24

4210 genes), Cullin genes (4-10 genes) and deubiquitinating enzyme-encoding genes (23-27
4211 genes) (Supplementary table 4). Most of these genes show no or modest expression
4212 dynamics, which is not surprising given that the ubiquitination machinery is needed
4213 constantly in the cell. Of the E1 enzymes, only *S. cerevisiae* Uba3 orthologs (*C. cinerea*
4214 protein ID: 485679), which belong to the neddylation pathway, are developmentally
4215 regulated to some extent (8/3 species at FC=2/4). In *C. cinerea* 14 of the 23 E2 enzymes
4216 and half (13 of 26) of deubiquitinating enzymes are developmentally regulated, potentially
4217 indicating functional diversification of E2 enzymes and deubiquitinating enzymes during
4218 development (Supplementary table 5). We found that none of the cullin genes in *C. cinerea*
4219 are developmentally regulated. Significantly larger dynamics can be observed in E3 ligase
4220 components, which are discussed in detail below.
4221   **RING-type Zinc finger proteins** - RING-domain containing proteins, named after
4222 RING (really interesting new gene), are E3 ubiquitin ligases that confer interchangeability to
4223 the ligase complexes(Deshaies and Joazeiro 2009). Eukaryotic genomes contain large
4224 numbers of RING-domain proteins, which, along with other E3 ligases, enable the ubiquitin
4225 system to selectively ubiquitinate proteins. RING-domain proteins are generally poorly
4226 known in filamentous fungi, though it was recently noticed that they are strongly
4227 overrepresented in Agaricomycetes(Krizsán et al. 2019). The *mfbAc* (=Le.MFB1) gene of *L.
4228 edodes* (Lenedo1_1172639) described as a protein with adhesive properties by Kondoh et
4229 al(Kondoh et al. 1995) also belongs to this gene family.
4230   The examined Agaricomycetes possess 81-148 RING-domain containing proteins
4231 (Table 37), consistent with a previous broader sampling across 200 species. On average,
4232 30-50 RING-domain proteins were developmentally regulated in the examined
4233 species(Almási et al. 2019; Krizsán et al. 2019), representing a significant pool of potentially
4234 important regulators. RING-domain proteins are highly variable, with most of them not
4235 showing clear orthology across species. Nevertheless, we found eight CDE orthogroups
4236 which displayed conserved developmental expression, mostly at FC>2 (Table 37). For
4237 example, one of these (represented by *C. cinerea* 378120) showed a very distinct peak in
4238 gills of *C. cinerea, A. ostoyae, P. ostreatus* and caps (containing gills) of *M. kentingensis, L.
4239 edodes* as well as mature fruiting bodies of *S. commune* and *A. ampla*. Another CDE
4240 orthogroup (represented by *C. cinerea* 440772) was upregulated in gill tissues of mature
4241 fruiting bodies in *P. ostreatus, A. ostoyae, M. kentingensis*, *L. bicolor* and mature fruiting
4242 bodies of *S. commune* and *A. ampla*, but not in *A. bisporus, L. edodes* or *C. cinerea*. These
4243 two orthogroups coincide (partly) with meiosis and sporulation, so they could be involved in
4244 these, or other gill-specific processes. Genes in another CDE orthogroup (C. cinerea protein
4245 ID: 543850) showed an abrupt, although modest upregulation at the initiation of fruiting body
4246 development and expression peak in mature fruiting bodies or gills therein in *C. cinerea, A.
4247 ostoyae, C. aegerita, A. ampla, L. bicolor, L. tigrinus, Ph. chrysosporium, P. ostreatus* and *S.
4248 commune* (not in *L. edodes*).
4249   **F-box proteins -** F-box proteins were recently identified as a potentially key group of
4250 proteins in fruiting body development(Krizsán et al. 2019). They are generally responsible for
4251 providing target specificity to the ubiquitination machinery, by binding and docking substrate
4252 proteins to Cullin E3 ubiquitin ligase complexes. Some F-box proteins interact with multiple
4253 target proteins while others only with a single protein(Jonkers and Rep 2009). Similarly,
4254 some F-Box proteins function independently of the SCF complex(Jonkers and Rep 2009),
4255 allowing for additional, yet poorly known regulatory functions to emerge. For example, F-box
4256 proteins can act as transcriptional co-regulators in plants(Chae et al. 2008) and are present

4257 in large numbers in plant genomes (up to 700-1000 genes(Xu et al. 2009)), providing the
4258 possibility to assemble an enormous diversity of alternative ubiquitin ligase complexes.
4259 The F-box family is highly expanded in mushroom-forming fungi and is composed of
4260 fast-evolving proteins with little similarity to each other. Agaricomycetes possess 69 to
4261 ~1200 F-box proteins in their genomes, whereas other filamentous fungi and yeasts possess
4262 up to 90 and 20 such genes(Krizsán et al. 2019), respectively. This represents a strong
4263 enrichment in Agaricomycetes genomes (P<10^{-140}), considering that the number of other
4264 proteins is not proportionately higher in this group than in other fungi. F-box protein encoding
4265 genes often showed tissue-specific expression and their numbers showed a positive
4266 correlation with the complexity level of the fruiting bodies(Krizsán et al. 2019).
4267 F-Box proteins are highly variable and form few conserved orthogroups, compared to
4268 their diversity in fungal genomes. However, we found eleven orthogroups that showed some
4269 level of conservation and consistent developmental regulation across species (Table 37).
4270 These included orthologs of *A. nidulans* GrrA (*C. cinerea* protein ID: 358351), which is
4271 needed for meiosis and ascospore maturation(S et al. 2006a; Riquelme et al. 2018), are
4272 conserved across Agaricomycetes and developmentally regulated in five species (FC>2),
4273 indicating that some F-Box proteins are conserved despite the general volatility of the family.
4274 Due to this high variability, F-box proteins are hard to examine systematically using a
4275 comparative transcriptomics approach. Rather, they likely often fulfill species- or clade-
4276 specific roles, which could be studied either with more densely sampled transcriptomic data,
4277 or reverse genetics approaches.
4278 **BTB/POZ domain proteins** - Proteins that contain the BTB/POZ motif, a protein-
4279 protein interaction (homodimerization) domain, can possess diverse cellular functions, the
4280 most frequent of which are regulation of chromatin structure (thus, transcription) and protein
4281 ubiquitination, as members of E3 ubiquitin ligase complexes(S et al. 1994; R et al. 2003).
4282 They are poorly known in fungi.
4283 In animals, plants as well as fungi outside the Agaricomycetes, BTB domains are
4284 mostly fused to other conserved protein domains(Stogios et al. 2005) (in animals, mostly to
4285 zinc fingers(S et al. 1994)). In contrast, we observed that in the Agaricomycetes, less than
4286 10% of BTB/POZ domain proteins associate with any other domains and virtually never with
4287 DNA binding transcription factor domains, indicating that the gene family expansion in
4288 mushroom-forming fungi is concerned with proteins that only contain the BTB/POZ domain.
4289 This domain composition suggests that the BTB/POZ family is primarily involved in E3
4290 ligases in Agaricomycetes, therefore we discuss this family under the chapter on protein
4291 ubiquitination.
4292 We found 8 CDE orthogroups with some level of conserved developmental
4293 expression in Agaricomycetes (Table 37). Members of two (*C. cinerea* protein ID: 379603,
4294 449824) of these orthogroups are co-expressed in stages or tissues in which meiosis and
4295 sporulation occurs: gills of *A. ostoyae* and *P. ostreatus*, mature fruiting bodies of *Ph.*
4296 *chrysosporium, A. ampla* and *S. commune,* mature caps of *M. kentingensis, L. bicolor, L.*
4297 *edodes* (but not developmentally regulated in *C. cinerea*). Another CDE orthogroup (*C.*
4298 *cinerea* protein ID: 459680) was upregulated in stipes of *C. cinerea, A. ostoyae, M.*
4299 *kentingensis, L. edodes* (but not in *P. ostreatus* and *A. bisporus*), primordium stages of *A.*
4300 *ampla* and *S. commune* and during early development (primordia + young fruiting bodies) of
4301 *L. bicolor*. A fourth CDE orthogroup, which contains reciprocal best hits to the putative E3
4302 ubiquitin ligase protein *btb1* of *Sch. pombe* (*C. cinerea* protein ID: 545078), but contains also
4303 domains that suggest it regulates chromatin condensation and thus gene expression.
4304 Members of this orthogroup were upregulated typically late during development.

4.14. Other gene groups

4.14.1. Transporters

Among the conserved developmentally expressed genes (CDE orthogroups) we detected 49 putatively transport-related gene families. Many of these genes belong to the Major Facilitator Superfamily or ABC transporters, fast-evolving gene families that are represented by hundreds of genes in fungal genomes. Transporters have been reported in transcriptomic studies of several mushroom-forming species, both in fruiting body(Song et al. 2018b; Krizsán et al. 2019) and ectomycorrhiza formation(Xu et al. 2015). Due to the fast evolution of these families, orthology to genes of Ascomycota model systems and even within the Agaricomycetes is lacking in most cases, making it hard to infer their functions. Nevertheless, some conserved transporter genes were detected, including orthologs of *S. cerevisiae* Pns1 (choline transporter, *C. cinerea* 355745), *A. nidulans* MepA (ammonium permease, *C. cinerea* 538158), *Sch. pombe* Kha1 (plasma membrane potassium ion/proton symporter, *C. cinerea* 449705), *S. cerevisiae* Emp70 (endosomal transport protein, *C. cinerea* 495380), *S. cerevisiae* Opt1 (plasma membrane oligopeptide transporter, *C. cinerea* 496395), among others (see Table 38). In the absence of functional annotations for the vast majority of these genes, we list the genes in Table 38, but do not go into detailed analyses, because it is unlikely that we can arrive at any reasonable speculation about their function.

Notable CDE orthogroups include an MFS transporter *C. cinerea* 465489, which was developmentally regulated in 9/5 species (FC>2/4) and FB-init in *C. cinerea, A. ostoyae, P. ostreatus, S. commune* (in the latter at FC>2 only). A phosphate transporter CDE orthogroup (*C. cinerea* protein ID: 30849) was FB-init in *C. cinerea, C. aegerita, A. ostoyae, A. ampla, S. commune, M. kentingensis* and, at FC>2 in *L. bicolor (*not in *L. edodes*) (Table 38). A group of zinc-regulated transceptors (transporter + receptor, *C. cinerea* protein ID: 455616) orthologous to *S. cerevisiae* Zrt1 was also detected. In summary, transporters can be expected to fulfill key functions in fruiting bodies, in moving around goods, signal molecules, modulating osmolarity to name a few, however, information about these in fruiting bodies is still limited.

Aquaporins are water and solute-transporting membrane channels that are integral to several different aspects of the fungal lifestyle. They were reported to be overexpressed in primordia and stipes of *F. filiformis*, relative to other tissues and developmental stages(Liu et al. 2020b). They were also reported to be upregulated in *L. bicolor* fruiting bodies and ectomycorrhizae(Xu et al. 2015).

We found 2-11 aquaporin genes in the examined Agaricomycetes and observed conserved aquaporin expression in two aquaporin orthogroups. One of these (*C. cinerea* protein ID: 373141) contains putative orthologs of yeast Fps1, an aquaglyceroporin that has suggested roles in acetate uptake or glycerol transport(Nehls and Dietz 2014), not water uptake (see under chapter on Acetyl CoA). It is worth noting that aquaglyceroporins were also differentially regulated in *L. bicolor* fruiting bodies(Xu et al. 2015) and that these proteins were shown to have a capacity to transport various solutes, including NH_3 and glycerol. This led Xu et al to hypothesize that these genes could be involved in osmosis regulation or signaling(Xu et al. 2015), which is different from the conclusion we make above on acetate transport.

The other orthogroup (represented by *S. commune* 2501677) comprises stipe-specific aquaporin genes, which show similar expression trajectories in *A. bisporus, A. ostoyae, M kentingensis* and *P. ostreatus*, as well as in an external *F. filiformis* dataset(Liu et

4351 al. 2020b). In all of these species, the genes showed expression peaks in stipes, mostly in
4352 young and mature fruiting bodies. It is notable that this pattern is seen in pileate-stipitate
4353 species and has been noted in a previous 3-species comparison of transcriptomes(Plaza et
4354 al. 2014b). Species without separate cap and stipe tissues either do not have this gene (*Pt.*
4355 *gracilis*) or they do, but the gene is not developmentally regulated (*S. commune, Ph.*
4356 *chrysosporium*). The current genome assembly of *C. cinerea* does not contain an orthologue
4357 in this group, which might be because it became dispensable for the unique developmental
4358 trajectory of this species or because the genome assembly is incomplete at this genomic
4359 region. The marked stipe expression peak suggests a widespread role of water transport
4360 during mushroom development. Further, the increasing expression parallel with
4361 developmental progression could indicate a role in water supply needed for cellular
4362 expansion. On a related note, *C. neoformans* also shows an upregulation of an aquaporin
4363 gene (Cryne_JEC21_1_3081) late in its development.
4364   A consequence of growth by cell expansion is that growth rate is limited by the speed
4365 of water transport, not cell division and CW material deposition(Roper and Seminara 2019).
4366 Therefore, aquaporin-facilitated water transport might be a selected trait in many mushroom-
4367 forming fungi that undergo fast growth. Although unknown at this moment, if fruiting body
4368 expansion is mediated by locally produced osmolytes (e.g. by breaking down glycogen),
4369 then that could produce a gradient that draws water towards the expanding tissues. This
4370 may be further facilitated by water channels formed by aquaporins. Finally, it is possible that
4371 other physical solutions, e.g. inter-hyphal water passageways also help transporting (e.g. via
4372 surface tension) water in the fruiting body.
4373   The shared stipe upregulation of aquaporins can shed light on the origins of the
4374 typical mushroom (pileate-stipitate) morphology. All examined stipitate Agaricales species
4375 showed a stipe-specific aquaporin expression, which supports a single origin of pileate-
4376 stipitate fruiting bodies in the Agaricales. On the other hand, *L. tigrinus,* which evolved
4377 pileate-stipitate fruiting bodies independently in the Polyporales, does not show stipe-specific
4378 aquaporin expression.

4.14.2. Stress response genes

4380 Diverse stress-related genes were detected among CDE orthogroups. Based on functional
4381 annotations and orthology relationships, many of these seem to be related to protection from
4382 oxidative stress, either through direct protection by their protein products (peroxiredoxins) or
4383 via the produced metabolites (ergothioneine) that protect from oxidative stress. We found
4384 evidence for all three pathways of reactive oxygen detoxification, the peroxiredoxin pathway,
4385 cytoplasmic catalases and glutathione peroxidases(Breitenbach et al. 2015), being active in
4386 fruiting bodies. The dynamic expression of these genes may point to the existence of an
4387 oxidative environment in fruiting bodies. However, it is currently unknown in which
4388 tissues/stages and in what cellular contexts this may arise. One possibility is that the action
4389 of cell wall modifying enzymes (e.g. peroxidases), which require an oxidative environment
4390 (H_2O_2), results in excess reactive oxygen species, though this has not been confirmed yet
4391 and remains a hypothesis for now. Below we discuss the main stress-related CDE
4392 orthogroups which we detected in the developmental transcriptomes of Agaricomycetes.
4393   **Peroxiredoxins** - Peroxiredoxins are antioxidant proteins that can reduce diverse
4394 reactive oxygen species (ROS), including H_2O_2, and are one of the three cellular pathways
4395 of ROS detoxification in fungi. They have also been reported to be involved in signal
4396 transduction. The function of peroxiredoxins are not known in fruiting bodies and we

4397   identified a single report of peroxiredoxin upregulation in fruiting bodies, in
4398   *Termitomyces*(Rahmad et al. 2014). Another gene from *Antrodia camphorata* was cloned
4399   and biochemically characterized(Wen et al. 2007). We found orthologs of peroxiredoxin Tpx1
4400   of *Sch. pombe* and Tsa1 of *S. cerevisiae* (*C. cinerea* protein ID: 468305) to be
4401   developmentally regulated in 12/8 species (FC>2/4) (Table 39). Tpx1 has been
4402   characterized as the H_2O_2 sensor that relays the redox signal to the transcription factor Pap1
4403   by inducing the formation of intramolecular disulfide bonds in Pap1(Jara et al. 2007).
4404   Orthologs of Tpx1 are upregulated mostly in gill and cap tissues of mature fruiting bodies in
4405   the examined species. Orthologs of the Pap1 transcription factor (represented by *C. cinerea*
4406   378471) are expressed constantly in mushroom-forming fungi. Orthologs of yeast Ahp1
4407   peroxiredoxin (*C. cinerea* protein ID: 444300) were also developmentally regulated in the
4408   majority of species (10/4 species at FC=2/4, Table 39). This gene preferentially eliminates
4409   organic peroxides, rather than H_2O_2 and relays signal to the Cad1 transcription factor in *S.
4410   cerevisiae*(Iwai et al. 2010). In *C. cinerea* this gene shows a very strong induction in young
4411   fruiting body gills, whereas in other species no evidence for a transcript enrichment in gill
4412   tissues was found. Finally, we detected orthologs of *S. cerevisiae* Dot5 (*C. cinerea* protein
4413   ID: 379600) (Table 39), a thioredoxin (thiol-specific peroxidase) that is involved in the
4414   detoxification of peroxides(Cha et al. 2003; Izawa et al. 2003), but was also reported to be
4415   involved in the regulation of telomere length. Thioredoxins, together with peroxiredoxins
4416   (thioredoxin peroxidase) make up the thioredoxin system, which acts similarly to the
4417   glutaredoxin system in ROS scavenging. This orthogroup showed a characteristic
4418   upregulation in primordia relative to vegetative mycelium, then lower expression in late
4419   developmental stages in *C. cinerea, L. edodes, C. aegerita, A. ostoyae* and *A. ampla*, but
4420   not in other species.
4421   **Ergothionine biosynthesis** - We also detected orthologs of the ergothioneine
4422   biosynthesis protein Egt1 of *S. pombe*. Ergothioneine is a histidine-derived antioxidant
4423   metabolite known to confer beneficial health effects to mushroom fruiting bodies(Weigand-
4424   Heller et al. 2012; Kalaras et al. 2017). For eukaryotic cells, it might be needed for growth
4425   and survival under oxidative stress conditions, for example during conidial survival and
4426   germination(MH et al. 2012; Sheridan et al. 2016). Ergothioneine is produced via a two-step
4427   reaction pathway in *S. pombe*(Pluskal et al. 2014)*,* comprising Egt1 then Egt2. Both are
4428   conserved in *C. cinerea* (*C. cinerea* protein ID: 356399 and 258252, respectively, Table 39),
4429   however, only the first gene is developmentally regulated in the majority of the species, the
4430   other is not. Expression patterns of the Egt1 orthologs varied, in certain species they are FB-
4431   init, while in others it showed stipe-upregulation (*A. ostoyae, L. bicolor, L. edodes, L. tigrinus,
4432   M. kentingensis*, but not *C. cinerea*). How this can be explained is not clear, nevertheless,
4433   our data provide some evidence for the upregulation of ergothioneine biosynthesis in fruiting
4434   bodies. Orthologs of *Sch. pombe* Egt2, which catalyzes the second step of ergothioneine
4435   production (*C. cinerea* protein ID: 258252) were developmentally regulated in a more
4436   restricted set of species.
4437   **Dehydro-D-arabinono-1;4-lactone** - Two orthogroups that make up the
4438   biosynthesis pathway of dehydro-D-arabinono-1;4-lactone were developmentally expressed
4439   in several species. Dehydro-D-arabinono-1;4-lactone (previously known as D-
4440   erythroascorbate) is a protective metabolite against oxidative stress and is produced by a
4441   pathway comprising Ara1, Ara2 and Alo1 in *S. cerevisiae*(K et al. 2006). Of these, Ara2 and
4442   Alo1 have clear orthologs in Agaricomycetes (represented by *C. cinerea* 365550 and
4443   432313, respectively)(Table 39), whereas Ara1 does not. Both Ara2 and Alo1 orthologs are
4444   strongly upregulated in fruiting bodies. ALO1 orthologs showed a clear upregulation in stipe

4445 tissues of *C. cinerea, A. ostoyae* and *P. ostreatus* (but not in *L. bicolor or L. edodes*),
4446 whereas in *S. commune, A. ampla and L. edodes* it is upregulated in primordia and stays
4447 high throughout fruiting body development. In *C. aegerita*, the gene is strongly upregulated
4448 in the first primordium stage, then expression drops to low levels.
4449   **Catalases -** Two catalase orthogroups (represented by *C. cinerea* 472224 and
4450 420157)(Table 39) were developmentally regulated in the majority of species. Catalases are
4451 involved in H_2O_2 scavenging and thus protection against reactive oxygen species, but also in
4452 other pathways (such as beta-oxidation, see above), so their assignment to oxidative stress
4453 response is less certain than that of the above-mentioned genes.
4454   **Glutathione system -** The glutathione system is composed of (i) glutathione, a 3-
4455 amino acid redox-active metabolite(Pócsi et al. 2004; Sato et al. 2009); (ii) glutathione
4456 peroxidases, which reduce H_2O_2; (iii) glutathione reductases, which convert oxidized
4457 glutathione back to its non-oxidized form; as well as (iv) glutaredoxins, which repair
4458 oxidatively damaged proteins. In *S. cerevisiae* glutathione is produced by a two-step reaction
4459 from L-cysteine and L-glutamate by the enzymes GSH1 and GSH2(CM 2001). We
4460 annotated members of this pipeline in *C. cinerea* based on orthology information to
4461 components of the glutathione system in *S. cerevisiae*(Pócsi et al. 2004; Sato et al. 2009)(
4462 Table 39). We identified single-copy orthologs of two proteins in the glutathione synthesis
4463 pathway, glutathione reductase, glutathione peroxidase. Glutaredoxins are present, on
4464 average, as 5-6 distinct genes in Agaricomycetes genomes, except for *Pt. gracilis* and *M.*
4465 *kentingensis*, which harbor 9 and 11 glutaredoxin genes in their genomes, respectively.
4466 Unlike the other antioxidant systems, the expression patterns in the glutathione system show
4467 only moderate conservation across species, being developmentally regulated in 3-6 species
4468 (Table 39).
4469   **Glutathione-S-transferases** are also involved in defense against oxidative damage.
4470 They represent a diverse gene family also involved in other cellular detoxification tasks, such
4471 as the neutralization of xenobiotics, drugs or pesticides(M et al. 2009b). Leon-Ramirez et al
4472 hypothesized that in *U. maydis* 'basidiocarps' glutathione-S-transferases are involved in the
4473 protection against oxidizing intracellular conditions generated by some enzymes, such as
4474 NAPDH oxidases(CG et al. 2017).Therefore, we only marginally treat them under this
4475 chapter, noting that any glutathione-S-transferase orthogroup, also by virtue of the lack of
4476 clear orthology to functionally characterized genes from model species, could be related to
4477 any of the possible functions of this family, not necessarily protection from oxidative damage.
4478 Glutathione S-transferases are a diverse gene family in fungi, with 20-49 genes (on average
4479 32) in the genomes of Agaricomycetes. In each of the species, ~50% of glutathione S-
4480 transferase encoding genes (up to 70% in *Coprinopsis*) were developmentally regulated,
4481 indicating that these play important roles in fruiting body development, however, due to the
4482 general lack of conservation of these genes, these did not form CDE orthogroups.
4483 Interestingly, each species had genes that showed a marked upregulation (FC>4) at the
4484 initiation of fruiting body development.

4485 ### 4.14.3. Unannotated genes

4486 Genes that encode proteins with no known conserved domain (Pfam or InterPro) signatures,
4487 referred to as unannotated genes here, are abundant in fungal genomes and represent
4488 some of the most exciting gene families. At the same time, they represent a challenge to link
4489 to fruiting body development, due to the complete lack of functional clues. In general, few
4490 literature reports are available on unannotated genes, possibly due to the difficulty of tackling

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4491   their functions. An exception from this is a report of the enrichment of unannotated genes in
4492   mature peridioles of *Pisolithus microcarpus* fruiting bodies(Pereira et al. 2017). An example
4493   of unannotated genes that turn out to be developmentally relevant is the LPMO-like X325
4494   gene family(Labourel et al. 2020), which was circumscribed just recently and appears to be
4495   related to the cell wall (see chapter 4.8.2.1).
4496   We identified 176 CDE orthogroups of unannotated genes (Supplementary Table 6).
4497   These included, for example, *Spc14* and *Spc33* of *S. commune*, which are involved in the
4498   formation of the septal pore cap(Van Peer et al. 2010), are unannotated proteins but form
4499   conserved, single-copy gene families in the Agaricomycetes (represented by *C. cinerea*
4500   419716 and 473658) that was developmentally regulated in 10/6 and 12/5 species,
4501   respectively. In *C. cinerea* alone, we identified 32 FB-init unannotated genes, several of
4502   which showed very significant fold changes (up to 150-200x).
4503   This category of genes included *Ctg1* of *L. edodes* and *Cc.Ctg1* of *C. cinerea*. Ctg1
4504   was originally identified in *L. edodes* as a target of the pre-mRNA splicing factor Cdc5 and
4505   was later shown to influence stipe elongation in *C. cinerea*(Nakazawa et al. 2008). In the
4506   latter study knockdown experiments were unsuccessful, whereas overexpression *C. cinerea*
4507   mutants showed accelerated stipe elongation(Nakazawa et al. 2009). In our data *Ctg1*
4508   orthologs formed a CDE orthogroup (represented by *C. cinerea* 528942) which was
4509   developmentally regulated in 10/8 species (FC>2/4)(Supplementary Table 6). Despite the
4510   conservation of developmental regulation, expression profiles were only partially conserved
4511   across species. For example, the gene was upregulated in mature fruiting bodies in *C.
4512   aegerita, A. ampla, C. cinerea, L. edodes, P. ostreatus*, whereas in other species (e.g. *A.
4513   ostoyae*), it showed upregulation in primordia relative to vegetative mycelium. Overall, CTG1
4514   orthologs seem to be a very exciting group of developmental genes, with no conserved
4515   domains and no mechanistic information on how they might contribute to fruiting body
4516   formation. Its role in stipe elongation needs to be conserved in other species, if expression
4517   profile conservation correlates with phenotype, we may expect other phenotypic effects in
4518   other species.
4519   In summary, unannotated genes may contain very interesting, novel gene families
4520   involved in fruiting body development, yet circumscribing their functions remains challenging
4521   at the moment and will require extensive genetic manipulation techniques.

4522   ### 4.14.4. Functionally poorly known genes

4523   In this group of genes we placed ones that had some (mostly automatic) annotations, but we
4524   could not clearly link them to cellular or fruiting-related processes. Thus, this category differs
4525   from unannotated genes in that unannotated genes are completely devoid of all (even
4526   automated) annotations. Altogether, we assigned 182 CDE orthogroups to this category
4527   (Supplementary Table 7). Some of these genes are discussed briefly below, but we note that
4528   many more interesting, fruiting-related genes are potentially hidden among the 182
4529   orthogroups, however, clarifying their roles is left for future studies.
4530
4531   **Cytochrome p450 family** - We discuss cytochrome p450s in this category, because
4532   they participate in diverse functions, from secondary metabolite biosynthesis (as part of gene
4533   clusters, e.g.(Nofiani et al. 2018)) to unknown cellular pathways mediating stipe
4534   elongation(Muraguchi and Kamada 2000). We detected 8 CDE orthogroups of cytochrome
4535   p450s, most of which are functionally unknown. Among the cytochrome p450s, *C. cinerea*
4536   Eln2 should be mentioned. This gene was identified associated with a dominant mutation

4537   that confers an elongationless stipe phenotype(Muraguchi and Kamada 2000). Eln2 was
4538   reported to be a constitutively expressed cytochrome p450. In accordance with this, we did
4539   not find considerable expression dynamics on the orthogroup containing eln2 (represented
4540   by *C. cinerea* 381558). However, the developmentally regulated orthogroups may be worthy
4541   targets of functional analyses in the future.
4542   **GT25 family** - This family includes enzymes with diverse activities
4543   (lipopolysaccharide β-1,4-galactosyltransferase, β-1,3- or β-1,2-glucosyltransferase). In
4544   bacteria, GT25 are responsible for the biosynthesis of the membrane component
4545   lipopolysaccharides(Bertani and Ruiz 2018) ('endotoxins'). Most known GT25 enzymes are
4546   of bacterial origin, we found no functional study of fungal genes to date. The examined
4547   Agaricomycetes had mostly a single gene encoding GT25, which showed sporulation-
4548   associated expression peaks in most species: young fruiting body gills in *C. cinerea*, fruiting
4549   body gills in *P. ostreatus*, fruiting body cap in *L. edodes* and *C. aegerita*, mature fruiting
4550   bodies in *A. ampla* and *S. commune*, etc.. GT25 encoding genes showed very low
4551   expression in general, in many cases only detectable in the peak expressing stage/tissue.
4552   The broader orthogroup (*C. cinerea* protein ID: 501720) that contains the detected GT25
4553   genes is specific to the Basidiomycota (result not shown), which could indicate bacterial
4554   origin into the phylum. The function of these proteins in fruiting bodies is currently unknown,
4555   however, expression peaks coincident with sporulation suggest they are related to late
4556   developmental events.
4557   **UstYa-like mycotoxin biosynthesis proteins** - this gene family was first reported to
4558   be involved in the synthesis of the ribosomally synthesised peptide toxin ustiloxin in the
4559   ascomycete *Ustilaginoidea virens*(T et al. 2015). This family of genes was found to
4560   participate in the production of other toxic cyclic peptides, collectively named 'dikaritins', in
4561   plant pathogenic fungi (Ding et al. 2016; Vogt and Künzler 2019). Biochemically, they are
4562   oxidases of ribosomally produced peptides, including ustiloxins but also alpha-pheromones
4563   of *S. cerevisiae* (collectively Kex2-processed repeat proteins, KEPs)(Umemura 2020). Using
4564   a simple domain-based search, we detected 2-16 (28 in *A. ostoyae*) genes in the examined
4565   Agaricomycetes. Of these, each species had one to multiple genes that showed an induction
4566   (>4fold) in primordia relative to vegetative mycelia (except *C. cinerea*, in which two genes
4567   were induced in young fruiting body caps), and high expression in all subsequent fruiting
4568   body stages, suggesting that their protein product has an increased abundance in fruiting
4569   bodies. Although the role of these genes in the Basidiomycota remains unknown for now, we
4570   speculate they may be responsible for the production of toxic compounds, possibly with a
4571   role in defense.
4572   **Carbonic anhydrases** (CA) - convert CO_2 to HCO_3^- which is then used in various
4573   ways by eukaryotic cells. CAs have been shown to be involved in fruiting body formation: CA
4574   knockout strains of the ascomycete *S. macrospora* showed slower vegetative growth and
4575   delayed fruiting body formation or defects in ascospore germination(Elleuche and Pöggeler
4576   2009, 2010). The delay in fruiting body formation suggests a lower rate of HCO_3^- buildup
4577   necessary for some as yet unknown downstream processes, that, however, can be made up
4578   in longer time. Similar roles of CAs have not yet been reported in Basidiomycota, however,
4579   they would be worth investigating as many CAs appeared developmentally regulated in
4580   fruiting bodies. We found 2-9 CA encoding gene in the examined Agaricomycetes and that
4581   each species had at least one developmentally regulated carbonic anhydrase gene,
4582   although clear patterns of expression conservation were not noticeable. We found one CDE
4583   orthogroup (*C. cinerea* protein ID: 450047) that was widely developmentally regulated in
4584   mushroom-forming fungi (8/5 species at FC2/4), showing diverse expression peaks in

4585 different species. It should be noted that CA expression levels potentially react also to
4586 ambient CO_2 concentrations, so some of the expression variation we encountered may be
4587 due to the growth conditions used during fruiting.
4588   **CipB gene family -** This category of genes included the *cipB* gene reported from *C.*
4589 *cinerea*(Nakazawa et al. 2009). The *cipB* gene was first identified as an interacting partner of
4590 the splicing factor cdc5 in *L. edodes*(Nakazawa et al. 2008). We found that the orthogroup
4591 that contained *cipB* orthologs (represented by *C. cinerea* 401749) was developmentally
4592 regulated in 10/2 species (FC>2/4), indicating that these genes have widespread although
4593 moderate expression dynamics (Supplementary Table 7). Based on conserved domain
4594 annotations, *cipB* genes are transmembrane ATP synthases located in the mitochondria; its
4595 contribution to fruiting body formation is not known at the moment.

4596 ### 4.14.5. Ferric reductase superfamily proteins and iron metabolism

4597 The Ferric Reductase Domain Superfamily comprises a conserved group of proteins that
4598 include ferric reductases and NAPDH oxidases, both of which are located in the plasma
4599 membrane(Zhang et al. 2013). Ferric reductases are part of a reductive iron uptake system
4600 which, in many model fungi, are involved in maintaining iron and potentially also copper
4601 homeostasis(Gaurav Bairwa et al. 2017). These genes have mostly been studied in the
4602 context of iron acquisition of pathogenic fungi from their hosts. Agaricomycetes don't share
4603 clear orthology with experimentally characterized ferric reductases of the Ascomycota
4604 (reviewed in(Gaurav Bairwa et al. 2017))(cite Hegedus et al 2021). Nevertheless, we
4605 identified eight ferric reductase orthogroups, of which two were developmentally regulated in
4606 multiple species (Table 40), suggesting that ferric reductases have conserved roles in
4607 fruiting body development, although their function in the process is unknown. One of these
4608 was developmentally expressed in 9/5 species (represented by *C. cinerea* 354442, FC>2/4)
4609 contains genes orthologous to *S. cerevisiae* FRE7, which might be involved in copper
4610 homeostasis in *S. cerevisiae*(C et al. 2000). Another orthogroup, which contains orthologs of
4611 *A. nidulans* NoxA and *N. crassa* nox-1 (represented by *C. cinerea* 260659), was
4612 developmentally regulated in 5/1 species. This gene is a NADPH oxidase, which has been
4613 shown to be involved in developmental signaling and tissue differentiation(Nguyen et al.
4614 2017).
4615   The Ferric reductase superfamily also includes NADPH oxidases (NOXs)(Zhang et
4616 al. 2013), which are reactive oxygen-generating cell membrane proteins involved in
4617 differentiation-related signaling processes and tissue patterning(Blackstone). NOX genes
4618 and their regulator NoxR were reported to have been lost repeatedly in yeast lineages,
4619 underscoring their role in multicellularity(Nguyen et al. 2017). There is evidence for NOXs
4620 regulating sexual, but not asexual or vegetative development in *A. nidulans*(T et al. 2003)
4621 and *G. lucidum* and there is expression evidence in *H. marmoreus*(Zhang et al. 2015b). We
4622 identified two putative NOX orthogroups in Agaricomycetes (*C. cinerea* protein ID: 461481,
4623 260659). A third (represented by *C. cinerea* 152927) was interpreted as a NOX by León-
4624 Ramírez et al(CG et al. 2017), but appears to be a ferric reductase. Despite clear reports of
4625 NOXs being induced in sexual structures of Ascomycota(T et al. 2003), we did not find
4626 evidence for consistent induction of these genes in fruiting bodies, rather, expression
4627 patterns vary among fruiting body forming fungi. NOX genes show modest expression
4628 dynamics in mushroom forming fungi (2<FC<4, Table 40). *C. cinerea* 448679 appears to be
4629 a single-copy homolog of noxR that is conserved among mushroom-forming fungi. Members
4630 of this orthogroup are not developmentally expressed.

4631

5. A synoptic model of fruiting body development

4633   This study aimed to provide a catalog of conserved fruiting body development genes based
4634   on a literature review and a meta-analysis of developmental transcriptomes of 12
4635   mushroom-forming fungi. Based on sequence analyses of genes showing developmentally
4636   expression during fruiting body morphogenesis in these 12 species, we identified 921
4637   conserved developmentally expressed orthogroups and several gene families. To more
4638   broadly explore pathways linked to these genes, as well as genes that are known to be
4639   involved in fruiting but do not show significant expression dynamics, we analyzed further 558
4640   gene families. As a result, altogether 1479 genes of *C. cinerea*, and the orthologs of these in
4641   11 other species are treated in this paper. These allowed us to identify developmental
4642   expression patterns that are shared across species. For most of the conserved
4643   developmental orthogroups, we provided broad functional classifications and speculations
4644   on their probable role in fruiting body development, although elucidating their exact function
4645   and molecular mechanisms of their action remains for future studies. In this chapter we
4646   synthesize these data into an updated, synoptic model of fruiting body development in the
4647   Agaricomycetes (Fig. 15). This model strongly builds on work by previous scholars, who
4648   attempted to provide overviews of developmental and/or molecular mechanisms of
4649   mushroom formation. In a series of papers Moore provided detailed descriptions of
4650   developmental events based on morphological and biochemical analyses(Moore 2005).
4651   Later, Kues summarized knowledge on the life history of *C. cinerea* and details of its
4652   developmental biology(Kües 2000; Kües and Liu 2000). More recently, de Plaza et al, Ohm
4653   et al and Muraguchi et al provided examples of transcription networks active during
4654   development and a molecular overview of *C. cinerea* development based on gene ontology,
4655   respectively(Ohm et al. 2011; Plaza et al. 2014b; Muraguchi et al. 2015). This paper further
4656   elaborates these models with more detail, and a selective presentation of only those
4657   processes that, based on gene expression patterns are conserved across twelve
4658   Agaricomycetes species. We hereafter discuss developmental events in three phases: early
4659   events (primordium formation and cell proliferation), growth by cell expansion and late
4660   events (sexual processes, sporogenesis).

5.1. Early events: primordium formation and cell proliferation

4662   Expression patterns of developmentally regulated gene groups outline several distinct
4663   processes and a temporal sequence of cellular events in fruiting bodies. The first in this
4664   sequence and probably the most interesting is the initiation of fruiting body development,
4665   which involves the rearrangement of hyphal branching patterns, and the light-dependent
4666   formation of a primary, then a compact, secondary hyphal knot(Kües 2000; Liu 2005;
4667   Sakamoto et al. 2018). Hyphal knot formation represents a transition from loosely arranged
4668   hyphae with fractal dimensions to true complex multicellular structures(Nagy et al. 2018).
4669   Fruiting body initiation has been a subject of intense research. Several gene expression
4670   changes have been described in this transition, including light-regulated(Sakamoto et al.
4671   2018), defense (e.g. galectins, pore-forming toxins(Plaza et al. 2014b), lectins(Boulianne et
4672   al. 2000; Walser et al. 2005)), fatty acid biosynthesis(Liu 2005), transcriptional regulation
4673   (TFs, velvet proteins(Ohm et al. 2011; Plaza et al. 2014b)), cell surface (hydrophobins, PriA,
4674   fasciclins(S et al. 1992; Y et al. 2007)), cell wall (Kre9/Knh1, laccases(Kües et al. 2011)) as

4675 well as others(Liu 2005; Hou et al. 2019). We update these observations by several
4676 functionalities in this work.
4677 　　　The largest gene group that shows an upregulation in primordium samples is related
4678 to mitotic cell division (See Fig. 3 in chapter 4.1.1 above), which coincides with tissue
4679 differentiation in the primordium and produces the final number of cells that makes up the
4680 fruiting body. Ribosomal and chromatin-remodeling related gene (e.g. histones) expression
4681 show very similar expression profiles in primordia (see Fig. 4 and 10 in chapter 4.1.2 and
4682 4.5.4.1), suggesting that novel protein synthesis and chromatin remodeling are required cell
4683 proliferation/division in primordia. Chromatin remodeling might be required for mitotic
4684 chromosome condensation and/or for rearranging chromatin accessibility for fruiting-specific
4685 trans regulatory factors. We term this the proliferative phase of development, which, in *C.*
4686 *cinerea,* encompasses hyphal knots to stage 2 primordia (Fig. 15). This pattern of mitotic,
4687 histone and ribosomal gene expression has been observed in most species, suggesting that
4688 fruiting body development can, in general, be divided into proliferative phase and growth by
4689 cell division. However, some species (e.g. *A. bisporus*(Craig et al. 1977)*,* see chapter 4.1.3)
4690 might not fully conform to this pattern and we expect non-Agaricales species (e.g.
4691 Polyporales, bracket fungi) to not follow this rule.
4692 　　　While the vegetative mycelium is entangled in the substrate and sensitive to bacterial
4693 and fungal competitors, fruiting bodies grow above ground and are, thus, more exposed to
4694 more extreme environmental conditions and biotic stress (animals grazers or infections).
4695 Accordingly, It has been reported that mycelial- and fruiting body-expressed defense gene
4696 repertoires show little overlap, indicating a dramatic switch in defense strategy upon
4697 fruiting(Plaza et al. 2014b). Defense genes generally show little conservation and high
4698 phylogenetic patchiness and did not form conserved orthogroups in our analyses. We,
4699 therefore, discussed them in the context of broader gene families (for detailed reviews
4700 see(Kunzler 2015; Künzler 2018)). Putative secondary metabolism and oxylipin-related
4701 genes might also serve defense and/or antimicrobial purposes.
4702 　　　Probably as a response to differences in environment compared to the substrate,
4703 such as higher temperature or humidity fluctuations, several cell surface protein-encoding
4704 and fatty acid metabolism genes showed induction in primordia. These included
4705 hydrophobins, cerato-platanins, wax synthases and the Con6 family, among others.
4706 Hydrophobins probably help retaining water or provide protection from excess water above-
4707 ground(Lugones et al. 1999b). Wax synthases and Con6 proteins, although haven't been
4708 examined to date, might act in a similar way. We infer changes in cell membrane
4709 composition in primordia from expression changes in genes influencing membrane
4710 composition. For example, fatty acid desaturases related to linoleic acid biosynthesis are
4711 upregulated in fruiting bodies, probably contributing to the higher linoleic acid contents of
4712 fruiting bodies reported before(SHAW 1967; Song et al. 2018a), with potentially to oxylipin
4713 synthesis too(A et al. 2020)). Putative stress-related gene expression changes
4714 (peroxiredoxins and ergothioneine-biosynthesis genes) might also correspond to genetically
4715 encoded mechanisms for coping with adverse above-ground conditions.
4716 　　　Cell wall remodeling emerges as a potentially important process in fruiting body
4717 initiation both in this study and previous ones (e.g.(Liu et al. 2021)). Fruiting body-specific
4718 cell wall architectures exist and are probably produced by a diverse suite of lytic and cell wall
4719 remodeling enzymes that are induced in primordia (Fig. 15). From the array of conserved
4720 orthogroups, it appears that glucan remodeling is more important than chitin modification.
4721 Additionally, oxidative enzyme genes (HTPs, DyP, MCOs, AA5_1) seem to be important in
4722 primordium development, although their functions have not been elucidated, yet. Cell wall

4723 related gene families show conservation at the gene family level, not always at the level of
4724 strict CDE orthogroups. Therefore, the complete array of cell wall remodeling enzymes
4725 induced in primordia is much broader in any species than shown on Fig. 15. Several cell wall
4726 remodeling related gene families described from the Ascomycota were developmentally
4727 regulated in the Agaricomycetes as well (e.g. GH16/17, Kre9/Knh1), whereas some, that are
4728 central to Ascomycota cell wall remodeling showed constant expression (e.g. GH72) or are
4729 missing in the Agaricomycetes (e.g. GH76). Further, it appears that dynamic expression is
4730 mostly observed in cell wall-active enzyme genes, not in upstream (e.g. ER-localized)
4731 components of the cell wall assembly line.
4732   Although the light-dependency of fruiting body initiation differs from species to
4733 species(Sakamoto 2018), we detected some orthogroups that probably correspond to light
4734 reception. These include phytochromes, the *C. cinerea* Dst2 family and potentially PAS
4735 domain containing proteins. The latter is particularly interesting, given that homologs in *N.*
4736 *crassa* regulate the white collar complex and mediate adaptation to changing light intensities
4737 during the day(Fuller et al. 2015).
4738   The initiation of fruiting body development represents a transition from fractal-like to
4739 complex multicellularity. Accordingly, several complex multicellular processes, such as cell-
4740 to-cell communication, adhesion and the regulation of differentiation(Knoll 2011; Nagy et al.
4741 2018) should turn on in primordia. Like for previous studies, decoding these aspects proved
4742 difficult for us too. We expect regulatory factors, such as transcription factors, kinases,
4743 phosphatases, potentially F-box proteins or non-proteinogenic factors (e.g. small RNA) to
4744 participate in cellular differentiation. We and previous work detected some transcription
4745 factor, kinase, NOX, pheromone, F-box orthogroups upregulated in primordia. However,
4746 these generally did not show significant conservation of expression, so the main regulatory
4747 mechanisms of cellular differentiation in fruiting bodies remain an enigma. It further remains
4748 to be established if differentiation mechanisms described from plants and animals, such as
4749 morphogens, hormone-like substances (e.g. oxylipins) or highly conserved gene regulatory
4750 circuits exist in fungi. Similarly, adhesion-related proteins are mostly unknown at the
4751 moment. Fasciclins and cell wall modification (e.g. by laccases) have been speculated to be
4752 related to adhesion(Nagy et al. 2018; Merényi et al. 2020b), though glucan remodeling
4753 enzymes, wax synthases, the carbohydrate-binding properties of lectins or species-specific
4754 mechanisms could also be key and more research is needed to elucidate what genes glue
4755 hyphae together in 3-dimension fruiting bodies.

4756 ## 5.2. Transition to growth by expansion

4757 At the stage 2 primordium stage (following nomenclature in *C. cinerea*, Fig. 15), cell and
4758 tissue differentiation, cell proliferation has largely completed. This is reflected in the
4759 downregulation of mitotic, ribosomal and chromatin-remodeling genes. At this point, the
4760 fruiting body transitions to a different developmental mechanism, which we term 'growth by
4761 cell expansion'. Growth by cell expansion is a well-known fungal trait and was already noted
4762 by de Bary in 1887(Bary et al. 1887), however, the molecular details have remained
4763 unknown. The phenomenon is marginally similar to fruit ripening in plants, but the
4764 mechanisms are probably completely different, though both involve cell wall loosening,
4765 remodeling and cell expansion.
4766   Based on analyses of developmental transcriptomes, we detected what we believe is
4767 a plausible molecular mechanism for growth by expansion. This involves the upregulation of
4768 membrane biosynthesis genes and the rewiring of basic metabolic pathways for the

4769   production of excess Acetyl-CoA (see chapter 4.2), which is the starting point of the
4770   biosynthesis of membrane components (e.g. ergosterol). Upregulation of genes involved in
4771   sterol transport, ergosterol biosynthesis correlates with the rewiring of basic metabolism. At
4772   the same time, aquaporin gene expression increases in stipes, which probably supports
4773   water transport driving the expansion of cells via turgor. Turgor manipulation requires an
4774   osmolyte, however, despite speculations of trehalose or mannitol serving as osmolytes, its
4775   identity remain unresolved; the expression data analyzed here did not provide unequivocal
4776   evidence for any given osmotically active molecule in fruiting bodies. Trehalose, glycogen
4777   and mannitol metabolism genes are upregulated at this stage, but many of them in gills,
4778   which suggest an involvement in spore storage material production, rather than turgor
4779   manipulation.
4780   For enabling cell volume increases, the fungus deploys a diverse and mostly
4781   species-specific array of cell wall remodeling enzymes. Cell expansion also probably follows
4782   different mechanisms in each tissue. For example, according to the model of stipe
4783   elongation in *C. cinerea* proposed by Liu et al(Liu et al. 2021), CE4 and GH30 genes may
4784   contribute to the rigidification of the cell wall in the stipe base, causing it to be more resistant
4785   to loosening by lytic enzymes than the stipe apex, thereby reducing its elongation potential.
4786   It is reasonable to assume that similar mechanisms underlie the differential expansion
4787   potential of different tissues within the fruiting body. We detected a large suite of conserved
4788   CAZyme orthogroups upregulated in elongating stipes (Fig. 15), whereas only one
4789   conserved orthogroup (GH55) was found in expanding caps. Since caps are composed of
4790   multiple tissues, it is possible that RNA-Seq techniques with higher resolution (e.g. single-
4791   cell RNA-Seq) are needed to uncover conserved tissue-specific cell wall remodeling gene
4792   expression.
4793   What regulatory genes underlie growth by cell expansion will need to be determined
4794   in future studies. We detected conserved orthogroups of several developmentally expressed
4795   regulators (transcription factors, RING-type zinc fingers, F-box, BTB and RNA-binding
4796   proteins) but most showed tissue-specific expression patterns and no expression profile
4797   clearly suggested involvement in regulating cell expansion in general. Interestingly, the Exp1
4798   transcription factor reported to be responsible for cap expansion in *C. cinerea*(Muraguchi et
4799   al. 2008b) was more frequently upregulated in stipes than in caps across the examined
4800   species. We detected a red light-sensing phytochrome orthogroup upregulated in stipes,
4801   which we hypothesize is responsible directing stipe growth away from closed spaces
4802   towards the open air.

5.3. Late events: meiosis and spore production

4804   The young and mature fruiting body (in *C. cinerea* nomenclature) stages are the scene for
4805   most sexual events, including meiosis and spore production. Accordingly, meiotic genes as
4806   well as several genes involved in DNA replication/repair, chromatin remodeling, ribosome
4807   assembly, which showed a peak in the proliferative phase in primordia, show a very sharp
4808   expression peak associated with meiosis (see chapter 4.1.1, 4.1.2 and 4.5.4). We found
4809   several conserved orthogroups of BTB/POZ proteins and RING-type zinc fingers with
4810   expression peaks in gills; these might regulate key events associated with meiosis. A
4811   conserved transcriptional co-repressor, *Cag1* of *C. cinerea* should be mentioned here.
4812   Although this gene and its orthologs did not show significant expression dynamics, its
4813   deletion caused abnormalities in gill development(Masuda et al. 2016).

4814   Genes associated with storage carbohydrate metabolism were upregulated in gills in
4815   most species, which is consistent with a rich body of literature reporting glycogen fluxes in
4816   fruiting bodies(Ji and Moore 1993; Kües 2000). These genes included ones related to
4817   glycogen mobilization, trehalose and mannitol metabolism. We found evidence for glycogen
4818   synthesis (*Gsy1* orthologs), suggesting that this carbohydrate is packaged into spores.

6. Outstanding questions related to fruiting body morphogenesis

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4821   Despite the advances in understanding cellular events of fruiting body morphogenesis,
4822   several significant questions remain open and await further research. We below outline eight
4823   key questions that we think are instrumental to develop a better understanding of fungal
4824   fruiting body formation and complex multicellularity. This represents a subjective assessment
4825   of significant challenges of fruiting body research, there may be other perspectives on
4826   remaining key challenges to be solved.
4827   1. Although new information on fruiting body morphogenesis accumulates at a steady
4828   pace, several questions related to multicellular organization remain open. Fruiting bodies are
4829   complex multicellular structures and thus display complex developmental programs involving
4830   tissue differentiation and cell type specification. Besides a developmental program, adhesion
4831   and cell-to-cell communication are two key traits for complex multicellularity(Knoll 2011).
4832   While we are starting to understand transcriptional networks governing tissue differentiation
4833   (see chapter 4.5.1), we still know very little about the genes/proteins mediating hypha-hypha
4834   adhesion, communication or whether an extracellular matrix (other than the cell wall) exists
4835   in mushroom-forming fungi. Hypotheses have been put forth on adhesion (via laccases or
4836   fasciclins), however, these have not yet been tested experimentally. Tissue differentiation
4837   results in distinct cell types within the fruiting body, however, our current understanding of
4838   cell type diversity in mushroom-forming fungi is limited. All current estimates for cell type
4839   diversity are based on morphology, which probably represent underestimates; technologies
4840   like single-cell RNA-Seq might provide more insights into cell type classification.
4841   2. Regarding regulatory genes, it is an open question whether 'master' regulators of
4842   fruiting body development or tissue differentiation exists, similarly to animal and plant
4843   developmental regulator systems(Meyerowitz 2002). Developmental processes are often
4844   organized modularly and hierarchically so that the resulting modules have a high level of
4845   autonomy. Such autonomy of mushroom development, to our best knowledge, has rarely
4846   been documented. An exception from this is monokaryotic fruiting, the process of forming
4847   basidiocarps on monokaryotic cultures without mating in certain species (e.g. (Herzog et al.
4848   2016)). The fact that fruiting body initiation can bypass mating suggests that the process has
4849   a certain degree of autonomy, which might be reflected as modularity or hierarchy in the
4850   underlying regulatory networks. Moore et al characterized fruiting body morphogenesis as
4851   being made up of developmental subroutines that are somewhat independent of each other
4852   and that makes the whole process resilient to a certain degree of developmental
4853   imprecision(Loftus et al. 2020).
4854   3. Transcriptional changes during the initiation of fruiting are significant. Most studies
4855   with a sufficient number of time points sampled (e.g.(Plaza et al. 2014b; Muraguchi et al.
4856   2015; Sipos et al. 2017b; Almási et al. 2019; Krizsán et al. 2019; Merényi et al. 2021; Zhang
4857   et al. 2021d)) (Ruytinx et al in prep) found the largest number of differentially expressed
4858   genes at the transition from vegetative mycelium to the hyphal knot/primordium stage.

4859   However, whether this transcriptional rewiring event is purely a result of transcription factor
4860   activity or whether there are more general changes, for example, in chromatin accessibility
4861   or epigenetics, is unknown at the moment. Assays such as ATAC-Seq(Buenrostro et al.
4862   2015) or ChIP-Seq (see e.g.(Vonk and Ohm 2021)) could provide insight into the magnitude
4863   of transcriptional versus chromatin-related rearrangement during fruiting body initiation.
4864   Similarly, posttranslational modification of proteins may be a significant regulatory
4865   mechanism in fruiting body morphogenesis(Pelkmans et al. 2017a). Gene methylation, an
4866   important developmental mechanism in animals, seems to be missing in fungi, on the other
4867   hand(Bewick et al. 2019).

4868   4. Understanding tissue specificity of genes and encoded proteins is key to
4869   uncovering mechanisms of tissue differentiation and predicting gene function. The bulk
4870   expression studies and a few studies involving fluorescent protein tagging revealed
4871   numerous examples of tissue-specifically expressed genes; however, more systematic
4872   studies will be needed to understand tissue-specific expression and the mechanisms that
4873   generate it.

4874   5. We identified altogether 176 conserved developmentally expressed orthogroups of
4875   unannotated genes. These genes encode proteins that contain no known protein domains,
4876   therefore, they lack even automated functional annotations. Unannotated genes are
4877   common in fungal genomes and represent an enigma for mycology. Their conservation
4878   implies that they have important functions these are, however, unknown in the vast majority
4879   of cases (see Spc genes of *S. commune* for an exception, chapter 4.14.3). Therefore,
4880   unannotated genes might represent a future treasure trove for developmental biology.

4881   6. Growth by cell expansion is a widely conserved trait of mushroom-forming fungi.
4882   Above we provided evidence for this process involving excess Ac-CoA production, the
4883   upregulation of membrane biosynthetic processes and cell wall remodeling genes (chapter
4884   4.2, 4.3). However, the identity of the osmolyte that drives turgor increase in fruiting bodies
4885   remains unknown and its identification represents a significant challenge for future research.

4886   7. Although not strictly morphogenetic, how the fruiting body is supported by the
4887   mycelium is a question with important practical implications in mushroom industry. It is
4888   known that the directionality of the transport of goods in the mycelium switches as fruiting
4889   body development is initiated(Herman et al. 2020). Also, it has recently been suggested that
4890   secondary metabolite biosynthesis during fruiting body development depends also on the
4891   mycelium(Orban et al. 2021). Thus, transcriptional and metabolic reprogramming has to
4892   affect the entire fungal colony and not only the part where primordia emerge. The feeding
4893   and nutrient transport mechanisms as well as regulation of fruiting in relation to nutrient
4894   availability are exciting avenues of research, but beyond the primarily morphogenetic scope
4895   of the present paper.

4896   8. While useful for discovering shared aspects of fruiting body morphogenesis, the
4897   comparative approach used by us, ignores species-specific aspects of morphology,
4898   ecological adaptation, gene repertoires and expression dynamics. Non-conserved aspects of
4899   development are certainly important, particularly for understanding the biology of individual
4900   cultivated species and will deserve further study in the future. However, given the available
4901   information, making functional inferences for taxonomically restricted or species-specific
4902   genes is even harder than for conserved genes, therefore, we here restrict ourselves to the
4903   discussion of the latter.

7. Conclusions

The development of mushroom fruiting bodies is one of the most complex morphogenetic processes in fungi. A significant body of previous research has focused on understanding the underlying genetics and has made significant progress in cataloging genes related to the initiation, morphogenesis, defense, pigmentation of fruiting bodies, among others. However, available knowledge is still patchy and lacks key details in multiple aspects, such as conserved events in fruiting body morphogenesis and corresponding genes or key regulators of major differentiation steps.

This study aimed at providing a catalog of conserved fruiting body development genes based on a literature review and a meta-analysis of developmental transcriptomes of 12 mushroom-forming fungi. We identified gene orthogroups that show conserved developmental expression across multiple species. Despite some limitations of the genomic and transcriptomic approach used here, this study provided novel insights (such as gene families, orthogroups, conserved expression profiles) into the morphogenesis of mushroom fruiting bodies. We hope these data reveal some aspects of the core genetic program of agaricomycete fruiting body morphogenesis and will provide a roadmap for functional analyses of fruiting body development. We are aware that the summary provided here is still an incomplete survey of developmental genes in fruiting body forming fungi. Comparisons at finer scales, such as within economically relevant genera, denser sampling of time points during development or at better spatial resolution (e.g. single-cell RNA-Seq) could yield additional insights. Joint analyses of gene expression patterns with gene phylogenies or with gene family copy number dynamics, functional genomics assays, the inference of gene co-expression networks or population genomics (e.g. GWAS analyses) among others, could all provide more detailed views on the synergy between evolutionary changes in gene content, expression regulation and morphogenesis. We anticipate that with advances in functional genomics of Agaricomycetes, it will become easier to conduct such studies and shed light on conserved and species-specific aspects of fruiting body morphogenesis.

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Figures

Fig. 1. Species used in this study. Top row left to right: *Agaricus bisporus, Cyclocybe aegerita, Armillaria ostoyae, Auriculariopsis ampla;* Middle row: *Coprinopsis cinerea, Laccaria bicolor, Lentinula edodes, Lentinus tigrinus;* Bottom row: *Mycena kentingensis, Phanerochaete chrysosporium, Pleurotus ostreatus, Schizophyllum commune*
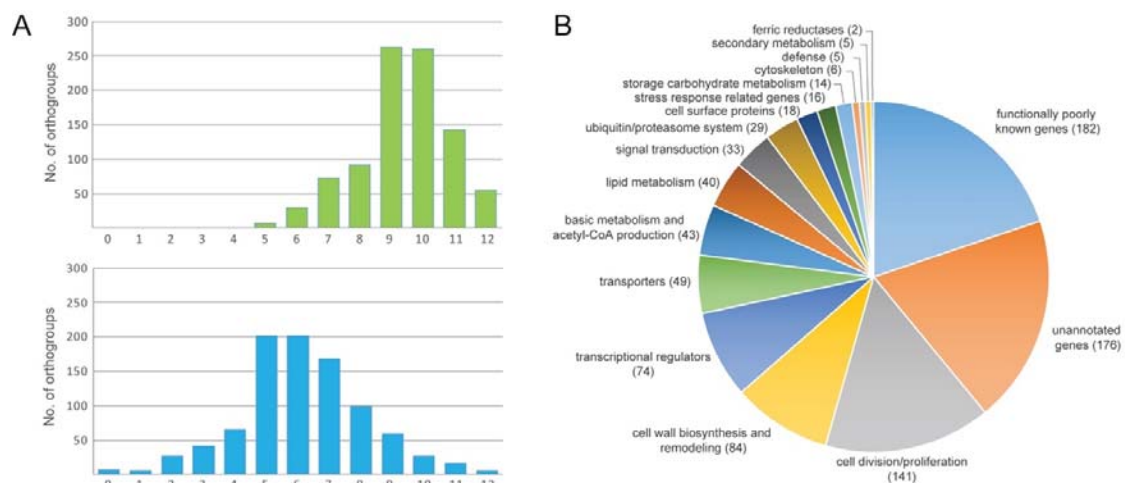
7045 **Fig. 2.** The distribution of conserved developmentally regulated orthogroups across species.
7046 A The number of orthogroups as a function of the number of species in which the orthogroup
7047 is developmentally regulated at fold change >2 (top) and fold change >4 (bottom). Horizontal
7048 axis represent the number of species. B Numbers of genes in each of the functional
7049 categories discussed in the paper.
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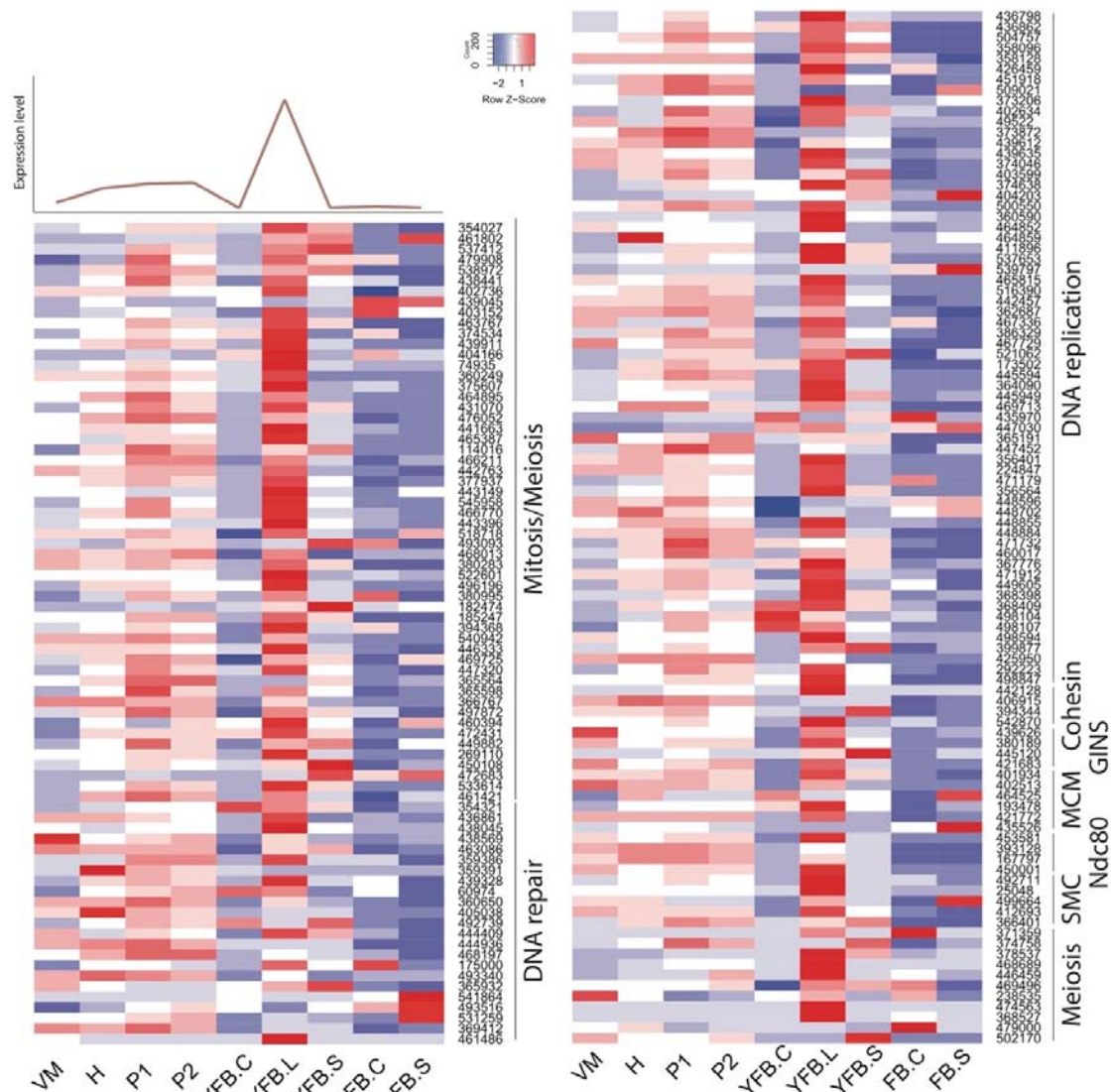
7051
7052 **Fig. 3** Expression heatmap of DNA replication, repair, mitosis and meiosis related genes in
7053 *C. cinerea*. A model expression trajectory, illustrating the two peaks characteristic of most
7054 examined species, is shown above the left panel. Well-delimited complexes mentioned in the
7055 paper are shown separately. Genes are denoted by Protein IDs. Blue and red colors
7056 represent low and high expression, respectively. Developmental stages are abbreviated as
7057 follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2
7058 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S –
7059 young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature
7060 fruiting body stipe.
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Fig. 4. Expression heatmap of ribosomal protein encoding genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal

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7066   knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap,
7067   YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting
7068   body cap (including gills), FB.S – mature fruiting body stipe.
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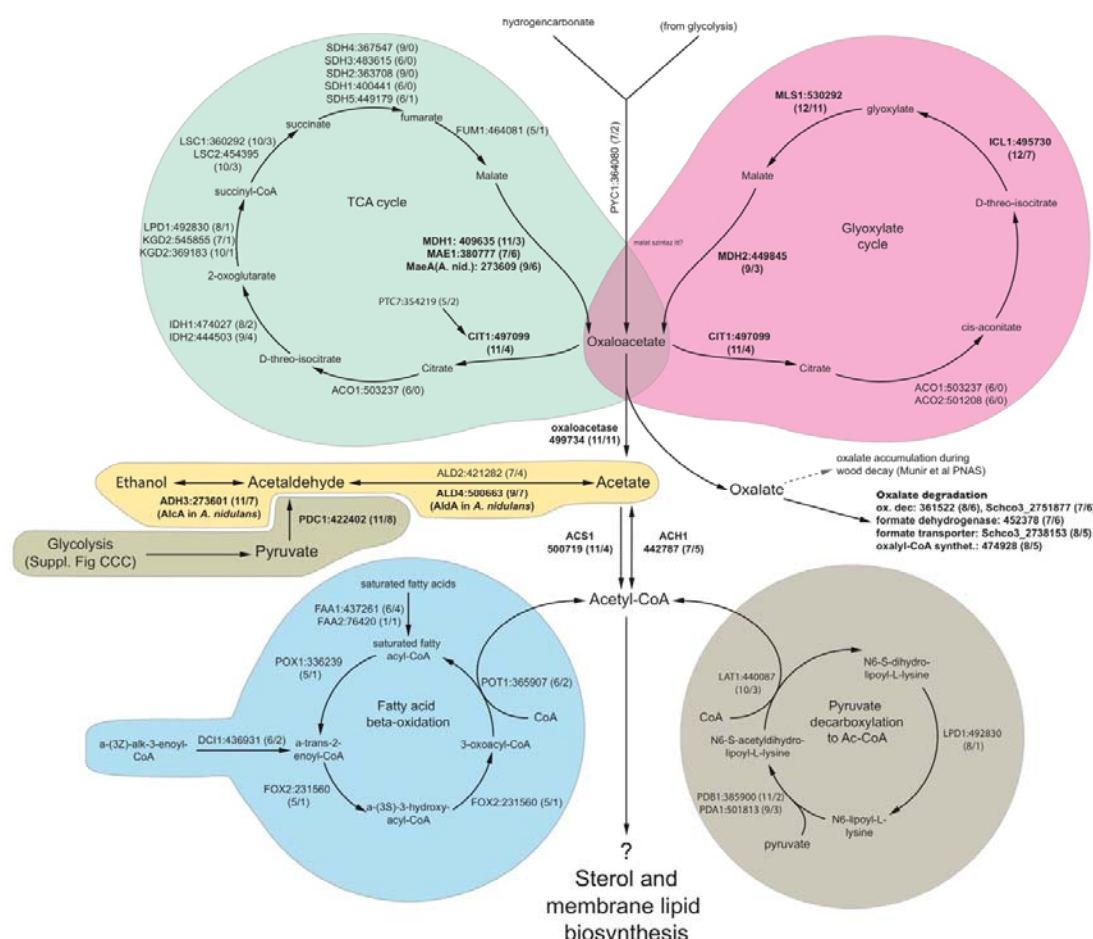
7071
7072   **Fig. 5.** Basic metabolic pathways of *C. cinerea.* Genes in the pathways are denoted by the
7073   *S. cerevisiae* gene name, followed by the protein ID of the *C. cinerea* ortholog and, in
7074   parentheses the number of species in which the gene was developmentally regulated at fold
7075   change >2/>4. Pathways are colored differently for clarity.
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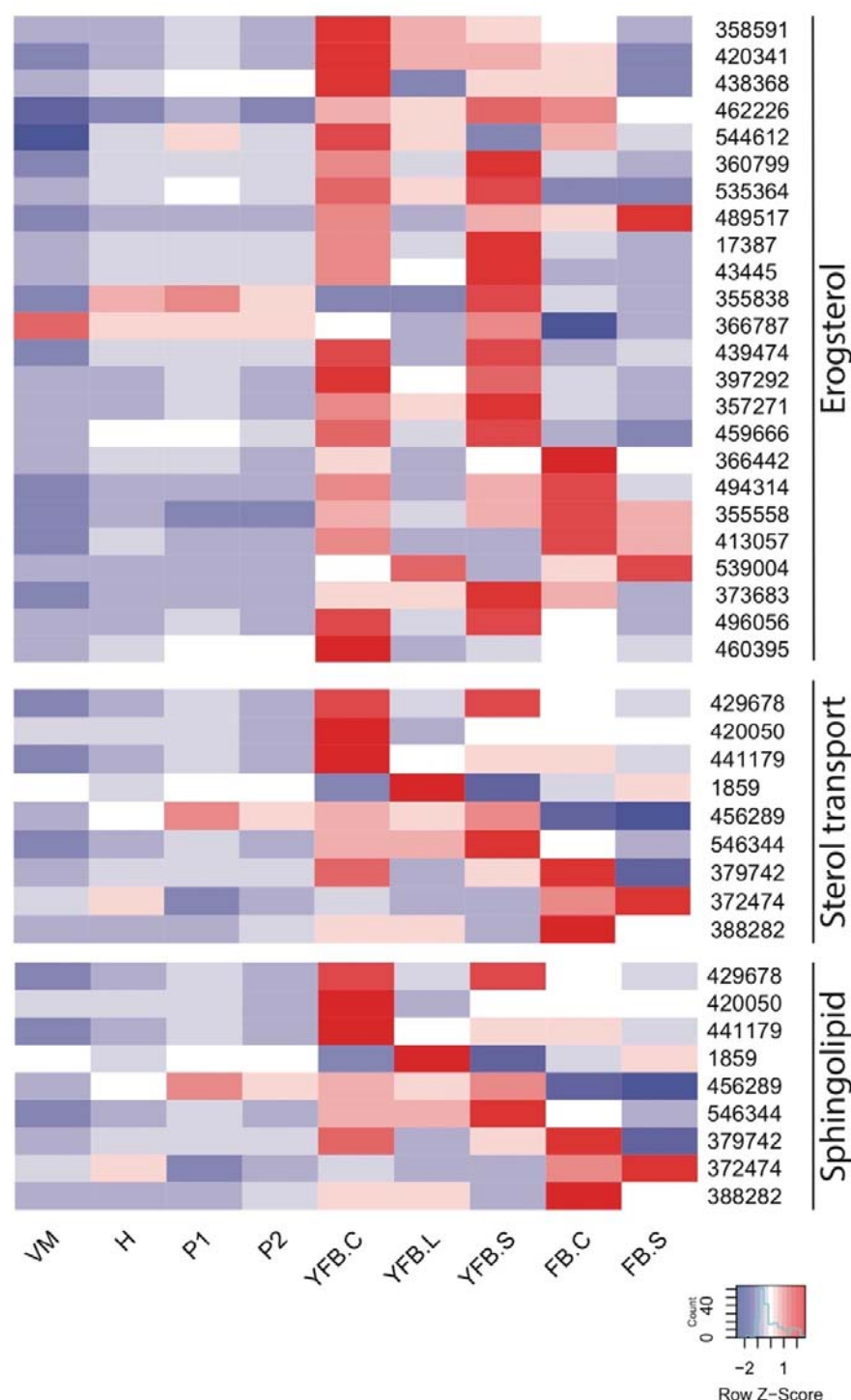
Fig. 6. Expression heatmap of ergosterol and sphingolipid biosynthesis related genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.

Running head: fruiting body genomics

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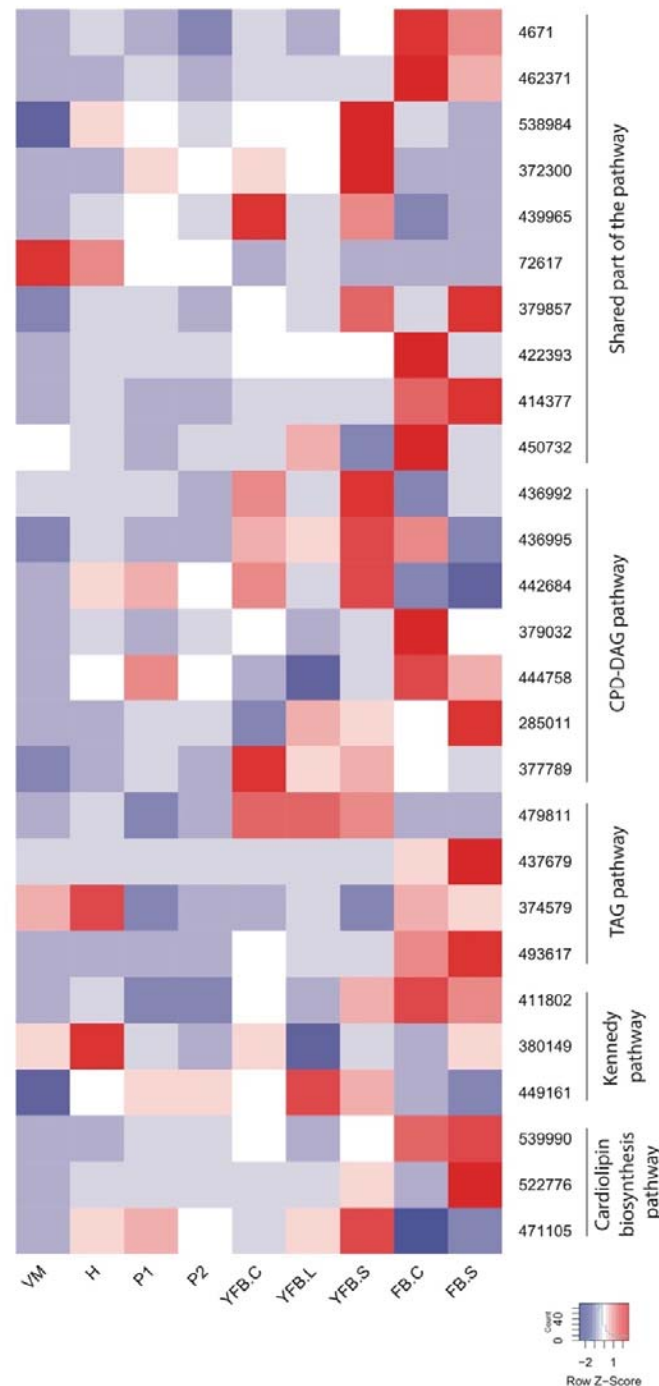
7085
7086 **Fig. 7.** Expression heatmap of membrane phospholipid and fatty acid biosynthetic genes in
7087 *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high
7088 expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative
7089 mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C –
7090 young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe,
7091 FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.
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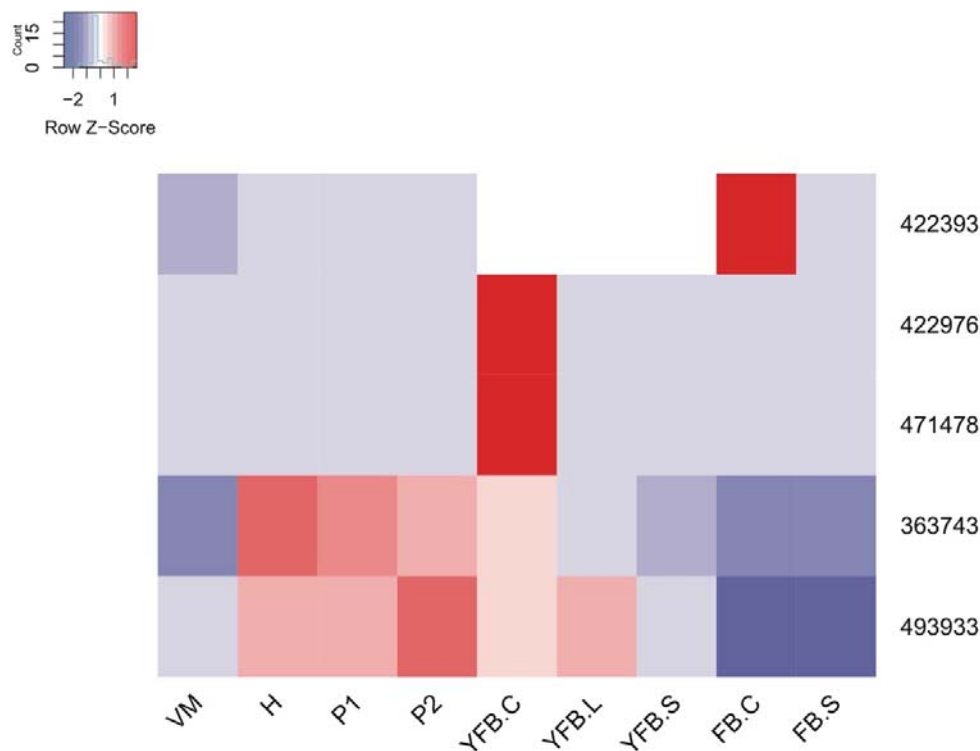
7094
7095 **Fig. 8** Expression heatmap of putatively linoleic acid biosynthesis related fatty acid
7096 desaturase genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors
7097 represent low and high expression, respectively. Developmental stages are abbreviated as
7098 follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2
7099 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S –
7100 young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature
7101 fruiting body stipe.
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Fig. 9. Expression heatmap of storage carbohydrate metabolism genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.

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Fig. 10 Expression heatmap of chromatin remodeling related genes (histones, histone chaperones, histone deacethylases) in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.
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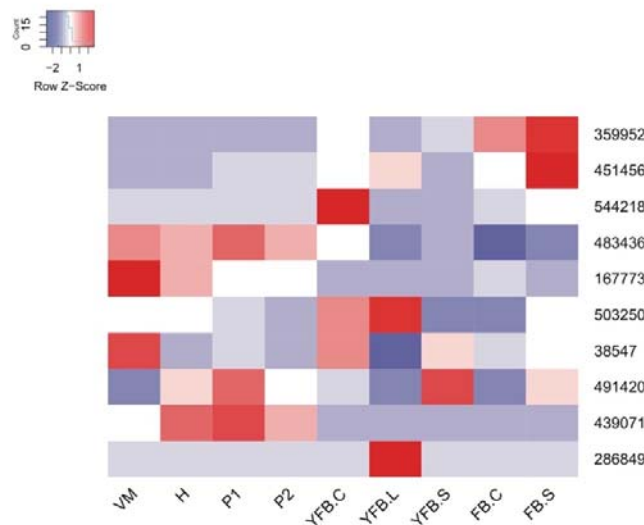
Fig. 11. Expression heatmap of expansin-encoding genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.
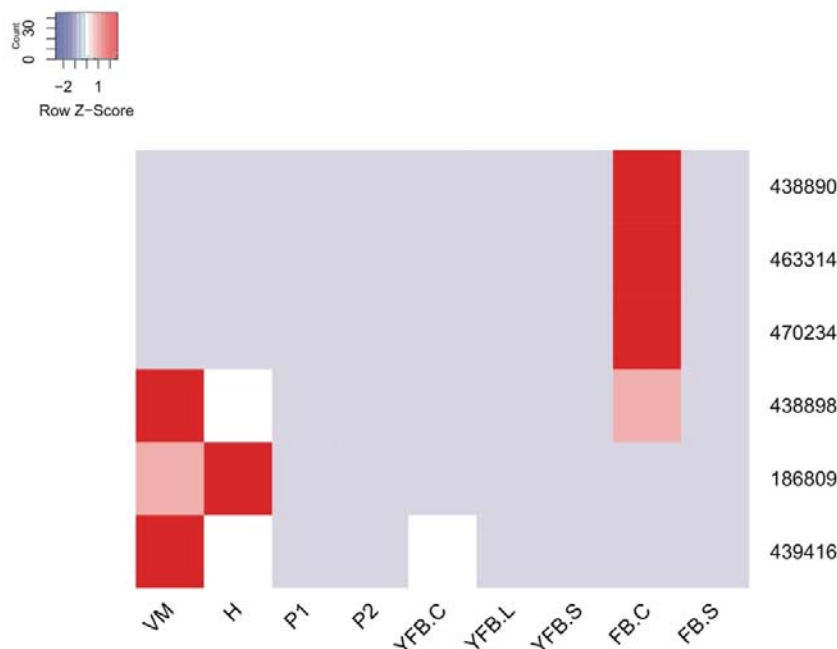
Fig. 12. Expression heatmap of Con6 family cell surface protein-encoding genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.

7135
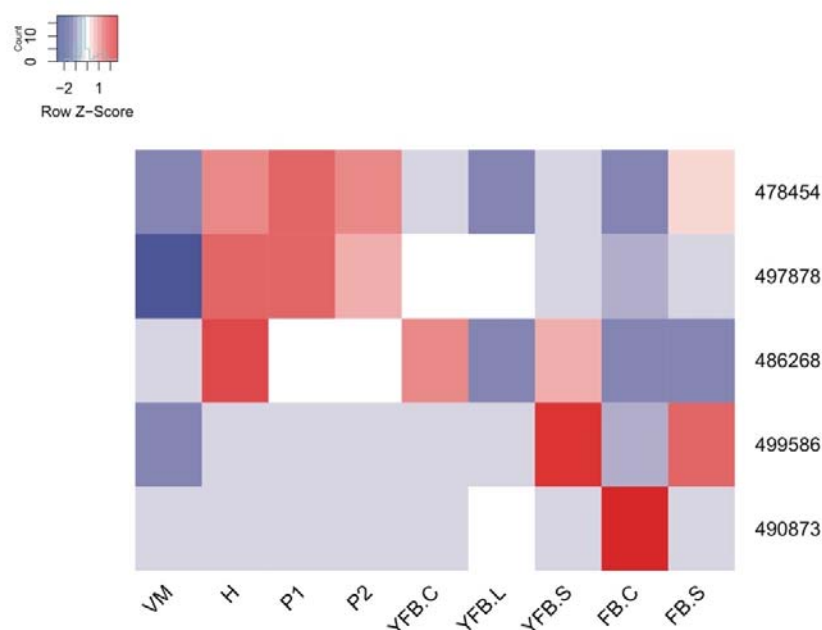
7136
Fig. 13. Expression heatmap of putative wax synthase encoding genes in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.
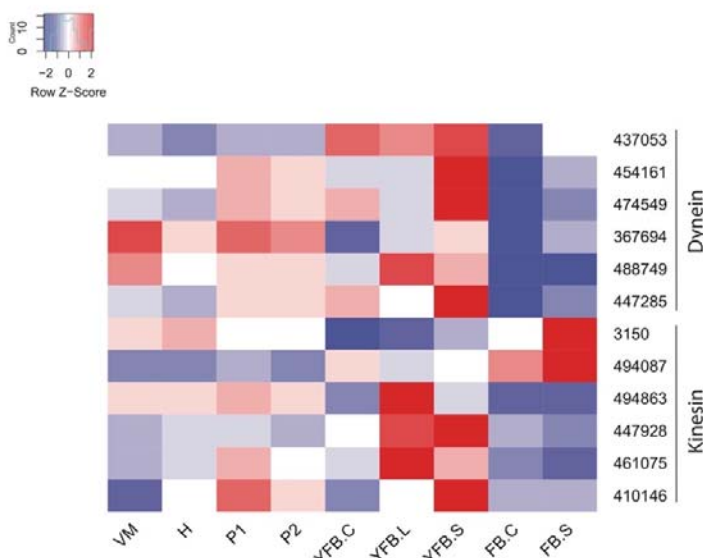
7143
Fig. 14. Expression heatmap of kinesin genes and members of the Dynactin complex in *C. cinerea*. Genes are denoted by Protein IDs. Blue and red colors represent low and high expression, respectively. Developmental stages are abbreviated as follows: VM – vegetative mycelium, H – hyphal knot, P1 – stage 1 primordium, P2 – stage 2 primordium, YFB.C – young fruiting body cap, YFB.L – young fruiting body gills, YFB.S – young fruiting body stipe, FB.C – mature fruiting body cap (including gills), FB.S – mature fruiting body stipe.

7150
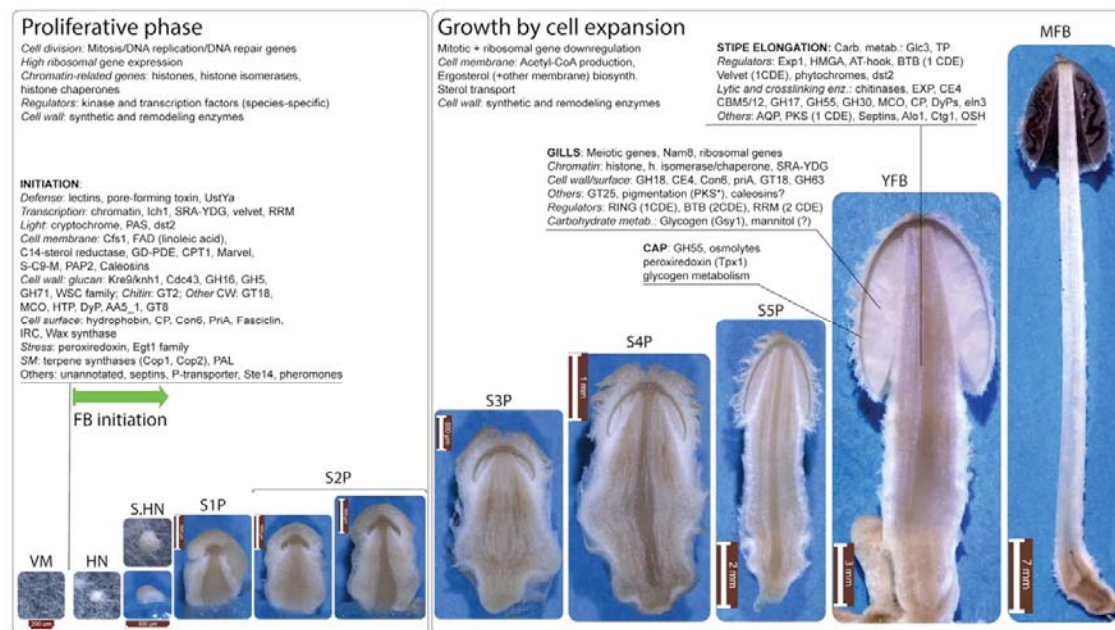
7151
Fig. 15: The most important, conserved genes belonging to each phase are shown - genes with limited expression conservation or species-specific expression are not depicted. [footnote: *pigment patterns vary by species] TP: trehalose phosphorylase, PKS: pyloketide synthase; OSH: Oxysterol Binding Protein Homologue; AQP: aquaporins; EXP: expansins; MCO: multicopper oxidase; RRM: RNA recognition motif family proteins; PAP2: diacylglycerol pyrophosphate phosphatases; FAD: fatty acid desaturase; GD-PDE: Glycerophosphodiester phosphodiesterases; S-C9-M: sphingolipid C9-methyltransferases; IRC: intradiol ring cleavage dioxygenase; PAL: phenylalanine ammonia-lyase; SM: secondary metabolism; HTP: heme-thiolate peroxidase; CP: cerato-platanin. genes associated with cap autolysis are not shown on this Figure, because it is a species-specific trait of *C. cinerea*. Note that light induction schemes are not shown on this Figure, as this varies from species to species.

7164

Table Legends

Supplementary Table 1. Table summarizing ortholog protein ID for all discussed orthogroups in twelve Agaricomycetes.

Supplementary Table 2. Summary of read numbers and alignments in the analyzed fruiting body transcriptomes.

Supplementary Table 3. Summary of developmental expression dynamics of CDE orthogroups of genes related to alternative splicing across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4.

7179

7180 Supplementary table 4. Copy number distributions of genes related to protein ubiquitination
7181 and the proteasome in twelve examined Agaricomycetes.

7182

7183 Supplementary table 5. Genes related to protein ubiquitination and the proteasome in *C.*
7184 *cinerea.*

7185

7186 Supplementary Table 6. Summary of developmental expression dynamics of CDE
7187 orthogroups of unannotated genes across 12 species. Protein ID of a representative protein
7188 is given follows by the number of species in which the orthogroup is developmentally
7189 regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and
7190 ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene
7191 present but not developmentally regulated, 2 - developmentally regulated at fold change >2,
7192 4 - developmentally regulated at fold change >4.

7193

7194 Supplementary Table 7. Summary of developmental expression dynamics of CDE
7195 orthogroups of functionally poorly known genes across 12 species. Protein ID of a
7196 representative protein is given follows by the number of species in which the orthogroup is
7197 developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative
7198 function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent,
7199 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold
7200 change >2, 4- developmentally regulated at fold change >4.

Table 1. Summary of developmental expression dynamics of CDE orthogroups of cell division-related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
S.c. 2052819	6	5	DNA endonuclease involved in DNA excision repair	–	0	4	4	0	0	1	2	4	0	0	4	4
A.o. 268345	7	5	DNA recombination and repair protein Rad51-like	–	0	4	0	4	2	0	4	0	4	2	4	0
365932	11	3	DNA recombination and repair protein Rad51-like	–	2	1	4	2	2	2	2	4	2	2	2	4
S.c. 2463645	7	4	DNA repair protein Rad52/59/22	–	0	4	2	0	0	2	4	2	0	0	4	4
468197	7	4	Postreplication repair E3 ubiquitin-protein ligase RAD18	–	2	1	0	4	1	1	1	4	2	2	4	4
493516	9	6	DNA repair and recombination protein RDH54	YBR073W	4	1	1	4	1	4	4	4	4	2	2	2
439328	5	3	DNA repair protein RAD59	YDL059C	4	0	0	4	2	0	2	0	4	1	0	0
175000	10	4	DNA mismatch repair protein MSH6	YDR097C	4	2	2	4	1	1	2	4	4	2	2	2
354321	10	5	DNA repair and recombination protein RAD54	YGL163C	2	2	1	4	1	2	4	4	4	2	4	2
60974	9	6	ATP-dependent DNA helicase SRS2	YJL092W	4	1	2	4	1	1	4	4	4	4	2	2
438569	8	5	Nucleoside diphosphate kinase	YKL067W	4	1	4	4	2	1	4	2	2	1	4	1
405038	11	6	Flap endonuclease 1	YKL113C	4	2	4	2	2	2	4	4	4	1	2	4
531259	10	5	DNA repair protein RAD5	YLR032W	4	4	2	2	2	1	4	2	4	1	2	4
492739	11	7	Double-strand break repair protein MRE11	YMR224C	2	2	4	4	4	1	4	4	4	2	4	2
438045	12	5	Ribonuclease H2 subunit A	YNL072W	4	2	2	4	2	2	2	4	4	2	4	2
444936	7	3	DNA repair protein RAD50	YNL250W	2	0	4	4	1	1	2	2	1	1	4	2
541864	11	7	DNA mismatch repair protein MSH2	YOL090W	4	4	4	4	1	2	4	2	4	2	4	2
493340	8	3	Serine/threonine-protein kinase RAD53	YPL153C	4	2	1	4	1	2	2	2	4	1	2	1
360650	11	6	AP endonuclease 1	–	4	4	2	2	4	2	4	2	1	4	4	2
444409	9	5	BRCT domain containing protein	–	4	1	1	2	0	2	2	2	4	4	4	4
463086	9	5	DNA damage checkpoint protein 1	–	2	4	4	2	1	2	4	1	4	1	4	2
461486	8	2	DNA repair metallo-beta-lactamase	–	4	1	2	2	0	1	4	2	2	2	2	1
436861	8	2	DNA repair protein crb2	–	4	0	2	4	2	1	2	2	2	1	2	1
369412	8	3	Kinetochore-associated protein DSN1	–	2	2	1	4	1	0	2	2	0	2	4	4
359386	9	6	Ribonuclease H2 subunit B	–	4	2	4	0	1	1	2	4	4	2	4	4

ID			Protein	Code												
359391	11	7	UV-damage endonuclease	–	4	2	4	4	4	4	4	2	1	2	4	2
498107	10	9	Cell division control protein 6	–	4	2	4	4	1	4	4	4	4	1	4	4
442457	10	4	Checkpoint protein hus1	–	2	1	2	2	2	1	4	4	4	2	4	2
402634	12	5	Chromatin assembly factor 1 subunit A	–	2	4	2	4	2	2	4	4	4	2	2	2
504757	10	5	Chromosome segregation in meiosis protein 3	–	2	4	2	2	2	1	1	4	4	2	4	4
451918	12	7	Kinesin	–	2	2	2	2	2	4	4	4	4	4	4	4
404203	9	7	N-acetyltransferase ECO1	–	2	4	1	4	2	1	4	4	4	1	4	4
509021	6	3	DNA helicase	–	4	1	2	4	1	1	2	0	2	1	4	1
498847	8	4	Origin recognition complex associated protein	–	2	1	4	2	1	1	4	2	4	2	4	1
465815	7	3	Polynucleotide 3'-phosphatase	–	4	1	2	2	2	1	2	1	4	1	4	1
373872	10	6	Topoisomerase 1-associated factor 1	–	4	2	1	4	2	2	4	4	4	2	1	4
358128	7	2	Replication factor A protein 1	YAR007C	4	1	1	2	1	1	2	2	2	2	4	1
435970	11	5	Serine/threonine-protein kinase KIN3	YAR018C	2	4	2	2	1	2	4	4	2	4	2	4
362687	9	3	DNA polymerase alpha subunit B	YBL035C	2	2	1	2	2	1	2	4	2	1	4	4
436862	9	5	Kinesin-like protein KIP1	YBL063W	2	4	4	2	1	1	4	4	2	1	2	4
364090	10	6	Condensin complex subunit 2	YBL097W	4	1	2	4	0	2	4	2	4	2	4	4
224847	11	7	Replication factor C subunit 5	YBR087W	4	4	4	2	1	2	4	4	4	2	4	2
374046	11	8	Proliferating cell nuclear antigen	YBR088C	4	4	4	4	2	2	4	4	4	1	4	2
439635	10	8	Pachytene checkpoint protein 2	YBR186W	4	4	1	4	2	1	4	4	4	2	4	4
439612	12	10	Deoxyuridine 5'-triphosphate nucleotidohydrolase	YBR252W	4	4	2	4	4	4	4	4	4	2	4	4
445594	11	4	Cell division control protein 7	YDL017W	4	2	2	2	2	2	2	4	4	1	4	2
445949	7	4	DNA polymerase delta catalytic subunit	YDL102W	4	1	2	2	0	1	4	4	1	1	4	2
467336	12	8	MutS protein homolog 5	YDL154W	4	4	4	4	4	2	4	2	2	2	4	4
368409	10	5	DNA ligase 1	YDL164C	2	2	2	4	2	1	4	4	4	1	4	2
356564	10	7	DDK kinase regulatory subunit DBF4	YDR052C	4	2	0	4	2	4	4	4	4	1	4	2
469713	11	6	Condensin complex subunit 3	YDR325W	1	4	2	4	2	2	4	4	2	2	4	4
425950	11	6	Ribonucleoside-diphosphate reductase large chain 1	YER070W	4	2	2	4	2	1	4	4	4	2	2	4
436798	12	8	Uncharacterized ATP-dependent helicase IRC5	YFR038W	4	2	4	4	2	4	4	4	4	2	4	2
358096	12	9	ATP-dependent DNA helicase MER3	YGL251C	2	4	4	4	2	4	2	4	4	4	4	4
521062	11	4	Minichromosome maintenance protein 10	YIL150C	2	2	2	4	2	2	4	2	2	1	4	4
411896	8	3	ATP-dependent DNA helicase MPH1	YIR002C	4	4	0	2	1	2	4	2	2	1	2	0
448596	10	4	DNA primase small subunit	YIR008C	2	4	2	2	2	1	4	4	2	1	2	4
386329	12	10	Ribonucleoside-diphosphate reductase small chain 1	YJL026W	2	4	4	4	4	4	4	4	4	2	4	4
368398	11	7	Mitotic spindle checkpoint component MAD2	YJL030W	4	4	2	2	2	2	4	4	0	4	4	4
373206	12	9	Replication factor C subunit 2	YJR068W	4	4	4	4	2	2	4	4	4	2	4	4
516390	7	3	Structural maintenance of chromosomes protein 4	YLR086W	4	0	2	2	1	2	0	4	4	0	2	1
500550	9	7	Cell division control protein 45	YLR103C	4	4	2	4	1	1	4	4	2	1	4	4

ID			Protein	Systematic												
471179	12	9	G2/mitotic-specific cyclin-4	YLR210W	4	4	2	4	4	2	4	4	4	2	4	4
448884	9	6	DNA topoisomerase 3	YLR234W	4	4	1	4	1	2	4	2	4	2	4	1
399877	8	1	FACT complex subunit POB3	YML069W	2	1	2	2	2	2	2	2	1	1	4	1
360590	11	8	Chromosome transmission fidelity protein 18	YMR078C	4	4	4	2	4	2	4	4	4	1	2	4
173502	11	7	ATP-dependent helicase SGS1	YMR190C	2	4	2	4	2	2	4	4	4	1	4	4
449605	10	2	DNA polymerase epsilon catalytic subunit A	YNL262W	2	2	2	2	1	1	4	2	2	2	2	4
471912	11	6	Replication factor C subunit 3	YNL290W	4	2	4	4	2	2	4	2	4	1	4	2
498594	12	6	Thymidylate synthase	YOR074C	4	4	4	2	2	4	4	2	4	2	2	2
403599	10	3	ATP-dependent helicase ULS1	YOR191W	4	2	2	2	2	2	4	4	2	1	2	1
448855	6	3	Replication factor C subunit 1	YOR217W	4	1	2	2	1	1	1	2	4	1	4	1
356401	10	7	ATP-dependent DNA helicase CHL1	YPL008W	4	4	2	4	2	1	4	4	4	2	1	4
498104	11	7	DNA polymerase alpha-binding protein	YPR135W	4	4	2	1	2	2	4	4	4	2	4	4
467729	12	0	DNA polymerase epsilon subunit B	YPR175W	2	2	2	2	2	2	2	2	2	2	2	2
448702	7	2	ATP-dependent DNA ligase	–	2	2	4	4	1	0	2	1	0	1	2	2
537653	10	3	E3 ubiquitin-protein ligase substrate receptor MMS22	–	2	4	4	2	0	2	2	4	2	1	2	2
49522	10	5	Mitochondrial morphogenesis protein SLD7	–	4	1	2	2	2	4	2	1	4	4	4	2
292223	11	5	Alpha-actinin-binding protein	–	4	4	2	4	2	2	4	2	4	1	2	2
426459	9	2	Chromosome transmission fidelity protein 8	–	4	2	2	2	2	1	1	4	2	1	2	2
367776	10	5	DNA helicase	–	4	4	2	2	0	2	4	4	4	1	2	2
374638	10	5	DNA helicase	–	4	4	2	4	2	2	2	1	4	0	4	2
447030	10	6	DNA helicase	–	4	4	2	2	4	1	4	2	1	2	4	4
460017	10	5	DNA polymerase delta subunit 3	–	4	2	2	4	0	2	4	2	4	2	4	1
464859	12	10	DNA replication associated protein	–	4	4	2	4	2	4	4	4	4	4	4	4
447452	10	6	DNA replication factor	–	2	2	2	4	1	2	4	4	4	1	4	4
471732	11	8	Formin	–	4	4	4	2	2	4	4	4	2	1	4	4
365191	11	5	Replication factor A protein 3	–	2	2	1	2	2	4	4	4	4	2	4	2
464852	9	4	Telomere binding protein	–	4	4	0	4	2	1	2	2	2	1	2	4
539797	10	7	TPX2 domain-containing protein	–	4	4	2	1	4	2	2	4	4	0	4	4
394344	10	1	Cohesin subunit SCC3	–	2	2	2	2	2	1	2	2	2	1	4	2
442128	7	1	Sister chromatid cohesion protein 1	–	4	1	2	2	1	1	2	2	2	1	2	1
542870	8	3	Structural maintenance of chromosomes protein 1	YFL008W	4	0	0	2	1	1	4	2	2	2	4	2
406915	11	2	Structural maintenance of chromosomes protein 3	YJL074C	2	2	2	2	1	2	2	4	2	2	4	2
445120	10	1	DNA replication complex GINS protein SLD5	–	4	2	1	2	2	2	2	2	2	2	2	1
380189	8	3	DNA replication complex GINS protein PSF1	YDR013W	4	4	2	2	0	2	1	4	1	2	2	1
421683	10	4	DNA replication complex GINS protein PSF2	YJL072C	4	2	2	2	1	1	2	4	4	2	2	4
439626	9	5	DNA replication complex GINS protein PSF3	YOL146W	4	2	2	2	1	1	4	1	4	2	4	4
193478	9	3	DNA replication licensing factor MCM2	YBL023C	2	2	1	2	2	1	4	4	2	1	2	4

ID			Protein	Gene												
435526	11	5	DNA replication licensing factor MCM7	YBR202W	2	2	4	2	2	1	4	4	2	2	4	4
464525	9	5	DNA replication licensing factor MCM3	YEL032W	2	4	2	2	2	1	4	4	1	1	4	4
421772	10	4	DNA replication licensing factor MCM6	YGL201C	2	2	1	4	1	2	4	4	2	2	4	2
401934	10	6	Minichromosome maintenance protein 5	YLR274W	4	4	1	2	2	2	4	4	2	1	4	4
402513	9	3	DNA replication licensing factor MCM4	YPR019W	4	2	0	4	2	1	2	4	2	1	2	2
450001	11	5	Kinetochore protein NUF2	–	4	2	2	4	2	2	4	4	2	1	4	2
393128	11	2	Kinetochore protein NDC80	YIL144W	2	2	2	4	2	1	2	4	2	2	2	2
167797	10	2	Kinetochore protein SPC24	–	2	4	2	2	2	1	2	2	4	1	2	2
453581	9	6	Kinetochore protein SPC25	–	4	2	2	4	1	1	4	4	4	1	4	2
366401	12	5	E3 SUMO-protein ligase MMS21	–	2	4	2	2	2	2	4	4	2	2	4	2
492711	10	6	Non-structural maintenance of chromosomes element 1	–	4	4	0	4	2	1	2	2	4	2	4	4
412693	9	2	Non-structural maintenance of chromosome element 4	YDL105W	2	2	2	0	2	1	2	4	2	1	4	2
25048	8	5	Structural maintenance of chromosomes protein 5	YOL034W	4	2	0	4	1	2	1	2	4	1	4	4
499664	10	4	Non-structural maintenance of chromosome element 3	–	2	2	1	4	2	4	2	2	4	2	4	1
446459	9	6	Meiotic nuclear division protein 1	–	4	1	2	4	0	2	4	2	4	1	4	4
A.o. 269495	7	7	Meiotic recombination protein DMC1	–	0	4	0	4	4	4	4	0	4	4	0	0
468689	10	8	DNA helicase	–	4	2	0	4	4	4	4	0	4	2	4	4
371359	12	12	PHO85 cyclin-2	YDL127W	4	4	4	4	4	4	4	4	4	4	4	4
502170	12	11	MutS protein homolog 4	YFL003C	4	4	2	4	4	4	4	4	4	4	4	4
238535	12	10	Homologous-pairing protein 2	YGL033W	2	4	2	4	4	4	4	4	4	4	4	4
368527	10	7	Protein NAM8	YHR086W	4	2	1	4	4	4	4	2	4	2	4	1
479000	11	8	Meiotic sister chromatid recombination protein 1	YML128C	4	2	2	4	4	4	4	2	4	1	4	4
374758	9	4	Spindle assembly checkpoint kinase	YPL209C	2	2	4	4	1	2	4	4	1	2	2	1
S.c. 85873	9	7	Nuclear fusion protein KAR5	–	0	4	2	4	1	2	4	4	0	4	4	4
474563	6	4	Holliday junction resolvase	–	4	0	0	4	2	2	0	1	0	4	4	0
469496	6	2	Meiosis specific protein	–	4	1	2	1	2	1	1	2	4	1	2	1
378537	12	12	Meiotic coiled-coil protein	–	4	4	4	4	4	4	4	4	4	4	4	4
185247	7	0	Actin-like protein ARP9	–	2	1	2	2	0	1	2	2	1	2	2	1
447320	10	7	Altered inheritance of mitochondria protein 44	–	4	4	2	4	1	2	1	4	4	2	4	4
465387	8	4	Checkpoint protein RAD24	–	4	2	1	4	0	2	2	4	4	1	2	1
S.c. 2570476	4	1	DNA polymerase IV	–	2	1	0	2	2	1	1	0	0	1	4	1
461421	8	2	G1/S-specific cyclin CLN3	–	1	2	2	4	1	1	2	2	4	1	2	2
404166	11	7	Holliday junction resolvase YEN1	–	4	4	2	2	4	2	2	4	4	4	4	1
182474	10	7	M-phase inducer phosphatase	–	4	4	2	2	1	2	4	4	4	1	4	4
215276	11	6	Mediator of replication checkpoint protein 1	–	4	2	2	4	4	2	2	4	4	2	4	0
472431	9	7	Meiosis-specific protein SPO11	–	4	4	1	4	2	4	4	1	0	2	4	4

ID	n1	n2	Protein	Systematic												
461802	11	2	Protein SFI1	–	2	2	2	4	1	2	2	2	2	2	4	2
269110	5	4	DNA helicase	–	4	4	0	4	0	0	4	0	0	0	0	2
365598	11	5	Serine/threonine-protein kinase Haspin homolog ALK1	–	2	4	2	2	2	1	4	4	4	2	2	4
466770	10	4	Serine/threonine-protein kinase MPS1	–	4	2	2	2	2	2	4	4	2	1	4	1
469725	10	4	Spindle assembly checkpoint component MAD3	–	2	4	2	2	2	1	4	4	2	2	4	1
S.c. 2503158	8	7	Uracil-DNA glycosylase	–	0	4	4	4	2	4	4	0	4	0	0	4
442763	9	3	Kinetochore-associated protein MTW1	YAL034W-A	4	1	2	1	2	1	2	4	4	2	2	2
476052	8	3	Origin recognition complex subunit 2	YBR060C	4	1	1	2	2	2	4	4	1	2	2	1
377937	7	5	Anaphase-promoting complex subunit 11	YDL008W	4	1	4	4	0	2	4	1	2	1	4	1
518718	5	0	General transcription and DNA repair factor IIH subunit TFB1	YDR311W	2	1	2	1	2	1	1	1	1	1	2	2
479908	8	2	Tyrosine-protein phosphatase CDC14	YFR028C	2	2	2	4	1	1	2	1	2	1	4	2
394368	9	5	Structural maintenance of chromosomes protein 2	YFR031C	4	0	2	2	1	2	4	4	4	1	2	4
74935	8	5	Spindle pole body component SPC105	YGL093W	4	2	2	4	2	1	0	4	4	1	4	1
545958	12	7	APC/C activator protein CDC20	YGL116W	2	4	2	2	2	4	4	4	4	4	4	2
538972	9	3	Checkpoint serine/threonine-protein kinase BUB1	YGR188C	2	4	2	2	1	1	4	4	1	2	2	2
439189	10	5	Cell division control protein 6	YJL194W	2	4	2	4	2	1	2	4	4	2	4	1
497872	5	0	Anaphase-promoting complex subunit CDC16	YKL022C	2	2	1	2	1	1	2	1	2	1	1	1
354027	9	3	DNA primase large subunit	YKL045W	2	4	1	2	1	1	2	4	4	2	2	2
402736	5	1	Inner kinetochore subunit MIF2	YKL089W	1	1	1	2	2	1	1	1	4	1	2	2
439911	8	4	Condensin complex subunit 1	YLR272C	4	1	2	2	1	1	4	4	2	2	4	1
360249	8	6	Uracil-DNA glycosylase	YML021C	4	1	4	2	4	1	4	2	4	0	4	1
403152	10	6	Cell cycle serine/threonine-protein kinase CDC5/MSD2	YMR001C	4	2	1	2	1	2	4	4	4	4	4	2
449882	11	4	DNA topoisomerase 2	YNL088W	2	2	4	2	2	2	4	4	2	1	4	2
441663	9	5	DNA polymerase alpha catalytic subunit A	YNL102W	4	4	1	2	0	1	4	4	2	2	4	2
439045	11	8	PHO85 cyclin-1	YNL289W	4	4	4	4	4	4	4	2	1	2	4	2
375607	11	6	Cell division control protein 31	YOR257W	4	2	2	2	1	4	4	4	4	2	4	2
533614	12	11	G2/mitotic-specific cyclin-2	YPR119W	4	4	2	4	4	4	4	4	4	4	4	4
380995	10	8	Kinesin-like protein KAR3	YPR141C	4	2	4	4	0	4	4	4	4	2	4	1
438441	10	6	Anaphase spindle elongation protein 1	–	2	2	1	2	0	4	4	4	4	2	4	4
114016	9	6	Chromo/chromo shadow domain	–	4	2	4	4	2	1	2	1	4	1	4	4
522601	7	3	DASH complex subunit Dam1	–	4	1	1	4	2	2	2	4	2	1	0	1
472683	7	3	DNA replication regulator SLD2	–	4	1	0	2	1	2	4	2	0	1	4	2
380283	7	4	DNA replication regulator SLD3	–	2	1	2	4	0	2	4	1	4	1	4	0
463767	7	1	Dynactin subunit 3	–	2	1	1	2	2	2	0	2	4	1	2	1
466211	10	5	Kinetochore protein	–	2	1	2	2	2	2	4	4	4	1	4	4
468013	3	2	Mitotic-spindle organizing protein 1	–	4	1	0	2	0	1	1	0	0	1	4	1

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
537412	9	1	Nuclear rim protein 1	–	2	2	2	1	1	1	2	2	2	2	4	2
431070	12	10	Anaphase-promoting complex subunit 4	–	4	4	2	4	4	4	4	4	4	2	4	4
365564	9	7	CCCh-type zinc finger protein	–	4	4	2	4	4	4	4	0	0	0	4	2
540942	8	1	DNA damage response (DDR) and DNA repair protein	–	4	1	2	2	1	1	2	2	2	2	2	1
A.o. 259630	4	3	DNA helicase	–	0	0	0	4	0	0	4	0	0	2	4	0
446333	9	4	DNA helicase	–	2	4	0	4	4	1	4	2	0	2	2	2
450108	7	0	DNA helicase	–	2	1	2	2	1	1	2	2	1	2	2	1
460394	12	10	Rad21/Rec8-like protein	–	2	4	2	4	4	4	4	4	4	4	4	4
A.o. 254302	8	5	Ribonuclease H2; subunit C	–	0	4	0	2	2	1	4	4	0	2	4	4
374534	9	1	Separase	–	2	1	1	2	2	1	4	2	2	2	2	2
496196	5	4	SET domain protein	–	4	1	1	4	4	1	1	1	4	1	2	0
366767	10	5	RecQ genome instability protein	–	4	2	1	4	2	1	4	2	4	2	4	2
493093	12	6	Sporulation-specific protein 12	–	2	4	4	2	2	2	4	4	4	2	4	2
443396	10	3	Ku80 protein	YMR106C	4	2	2	1	2	1	4	2	4	2	2	2
443149	7	3	Ku70 protein	YMR284W	4	1	4	2	1	1	2	2	2	1	4	1

Table 2. Summary of developmental expression dynamics of CDE orthogroups of ribosomal genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
423325	10	3	60S ribosomal protein L28e	–	4	2	2	2	2	4	2	2	4	1	2	1
405648	10	2	60S ribosomal protein L19-B	YBL027W	4	2	2	2	2	4	2	2	2	1	2	1
412936	10	2	40S ribosomal protein S8-A	YBL072C	4	2	2	2	1	2	2	2	2	2	4	1
478794	11	3	60S ribosomal protein L23-A	YBL087C	4	2	2	2	2	4	2	2	4	2	2	1
366589	9	5	60S ribosomal protein L4-A	YBR031W	4	2	4	2	0	4	4	2	4	1	2	1
497971	7	5	40S ribosomal protein S11-B	YBR048W	4	2	4	0	2	4	0	1	4	1	4	1
464129	8	4	40S ribosomal protein S6-B	YBR181C	4	2	4	2	1	4	2	1	4	1	2	1
430785	8	2	60S ribosomal protein L21-A	YBR191W	4	2	2	2	2	1	4	1	0	2	2	1
467322	9	5	40S ribosomal protein S14-A	YCR031C	4	2	4	2	2	4	2	1	4	1	4	1
493413	9	1	Putatively involved intra-nuclear transport of pre-60S ribosomal subunits	YCR072C	4	2	2	2	1	2	2	2	2	1	2	1
403137	11	4	60S ribosomal protein L31-A	YDL075W	4	2	4	2	2	4	2	2	4	2	2	1
398174	9	3	40S ribosomal protein S16-B	YDL083C	4	2	2	2	2	2	2	1	4	1	4	1
412254	8	2	60S ribosomal protein L35-B	YDL136W	4	2	2	2	2	4	2	1	0	1	2	1
493053	10	4	Putatively involved in	YDL208W	4	2	2	4	2	2	2	2	4	1	4	1

pseudouridylation of rRNA

ID			Description	Systematic												
64051	9	4	40S ribosomal protein S13	YDR064W	4	2	4	2	1	4	2	2	2	1	4	1
381793	10	4	60S acidic ribosomal protein P2-beta	YDR382W	4	2	2	2	2	4	2	2	4	1	4	1
459549	8	2	60S ribosomal protein L12-B	YDR418W	4	2	2	2	1	4	2	1	2	1	2	0
404670	11	4	40S ribosomal protein S17-B	YDR447C	4	2	4	2	2	4	2	1	4	2	2	2
442748	8	2	40S ribosomal protein S18-A	YDR450W	4	2	2	2	0	4	2	1	0	1	2	2
499692	10	5	60S ribosomal protein L27-B	YDR471W	4	2	2	2	2	4	4	1	4	2	4	1
429262	9	4	60S ribosomal protein L34-A	YER056C-A	4	2	2	2	2	4	4	1	0	2	4	1
439980	9	3	40S ribosomal protein S24-A	YER074W	4	0	0	2	2	4	2	2	2	1	4	2
329287	10	5	40S ribosomal protein S26-B	YER131W	4	2	4	2	2	4	2	2	4	1	4	1
426937	9	2	60S ribosomal protein L2-A	YFR031C-A	4	2	2	2	2	4	2	1	0	2	2	1
S.c. 2742667	10	4	60S ribosomal protein L7A	YGL076C	0	2	4	2	2	4	4	2	4	2	2	1
441325	10	3	60S ribosomal protein L28	YGL103W	4	2	2	2	2	4	2	1	4	2	2	1
475518	10	4	40S ribosomal protein S2	YGL123W	4	2	4	2	2	4	2	2	4	1	2	1
437986	9	4	60S ribosomal protein L1-B	YGL135W	4	2	2	2	2	4	2	1	4	1	4	1
480276	8	3	40S ribosomal protein S25-A	YGR027C	4	2	4	2	2	4	2	1	0	1	2	1
475978	10	3	60S ribosomal protein L26-B	YGR034W	4	2	2	0	2	4	4	2	2	2	2	1
130885	9	3	60S ribosomal protein L11-B	YGR085C	4	2	4	2	2	4	2	2	0	1	2	1
495378	5	0	40S ribosomal protein S23-A	YGR118W	2	1	2	2	1	2	1	1	0	2	1	1
379934	9	3	60S ribosomal protein L24-B	YGR148C	4	2	2	2	2	4	2	0	4	1	2	1
494449	10	4	40S ribosomal protein S0-A	YGR214W	4	2	4	2	2	4	2	2	4	1	2	1
467085	10	3	60S ribosomal protein L14-B	YHL001W	4	2	2	2	2	4	2	2	4	1	2	1
165767	9	3	40S ribosomal protein S20	YHL015W	4	2	2	2	2	4	2	2	0	1	4	1
438384	6	1	40S ribosomal protein S27-B	YHR021C	4	1	1	2	0	2	2	1	2	1	2	1
214528	6	6	Protein involved in rRNA-processing	YHR087W	4	1	4	4	1	1	4	4	1	1	4	0
441187	9	4	60S ribosomal protein L42-B	YHR141C	4	2	1	2	2	4	2	1	4	2	4	1
441652	7	3	40S ribosomal protein S4-B	YHR203C	4	2	0	2	0	4	2	1	4	1	2	1
497565	8	2	60S ribosomal protein L39	YJL189W	4	1	2	2	0	4	2	2	0	2	2	1
375577	9	5	40S ribosomal protein S22-A	YJL190C	4	2	4	2	2	4	4	1	4	1	2	1
385517	8	4	60S ribosomal protein L43-B	YJR094W-A	4	2	0	0	0	4	2	2	4	2	4	1
446338	10	3	40S ribosomal protein S5	YJR123W	4	2	4	2	2	4	2	1	2	2	2	1
472703	8	2	60S ribosomal protein L8-B	YLL045C	2	2	4	2	2	2	2	1	0	1	4	1
374411	7	2	60S ribosomal protein L22-A	YLR061W	2	2	4	2	2	1	2	1	0	1	4	1
471911	7	4	Ubiquitin-40S ribosomal protein S31	YLR167W	4	0	4	2	1	4	2	1	4	1	2	1
447700	7	3	60S ribosomal protein L37-A	YLR185W	4	0	2	2	0	4	2	1	4	1	2	1
353298	7	2	40S ribosomal protein S28-B	YLR264W	4	2	2	2	0	4	2	1	0	2	0	0
398047	7	3	60S ribosomal protein L38	YLR325C	4	2	2	0	0	4	2	1	0	2	4	1
367451	7	3	60S acidic ribosomal protein P0	YLR340W	4	2	1	2	1	2	4	1	2	1	4	1
398594	9	3	40S ribosomal protein S29-A	YLR388W	4	2	2	2	0	4	2	2	0	2	4	1
385868	10	4	60S ribosomal protein L6-B	YLR448W	4	2	4	2	2	4	2	2	0	2	4	1

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
474164	9	5	40S ribosomal protein S1-B	YML063W	4	2	4	2	2	4	4	1	2	1	4	1
424304	8	4	60S ribosomal protein L13-B	YMR142C	4	2	0	2	2	4	0	4	2	1	4	1
456295	8	2	60S ribosomal protein L36-A	YMR194W	4	2	2	2	0	4	2	2	0	1	2	1
375811	8	3	60S ribosomal protein L20-A	YMR242C	4	2	4	2	0	4	2	1	2	1	2	1
412005	9	3	60S ribosomal protein L9-B	YNL067W	4	2	2	2	2	4	2	1	2	1	4	1
416494	5	2	40S ribosomal protein S3	YNL178W	4	2	0	0	1	4	2	1	2	1	0	1
438977	9	0	Ribosome-bound, Hsp70-type chaperone	YNL209W	2	2	2	2	2	1	2	2	2	1	2	1
462840	8	4	60S ribosomal protein L18-B	YNL301C	4	2	4	2	1	4	2	1	2	1	4	1
21836	6	0	Putatively involved in nucleolar processing of pre-18S ribosomal RNA	YNL308C	2	1	2	2	2	1	1	1	2	1	2	1
381804	8	2	40S ribosomal protein S15	YOL040C	4	2	2	2	0	4	2	1	2	1	2	1
465651	10	4	40S ribosomal protein S19-A	YOL121C	4	2	4	2	2	4	2	2	4	1	2	1
426850	7	4	60S ribosomal protein L3	YOR063W	4	2	2	0	2	4	0	1	4	1	4	1
401275	9	6	40S ribosomal protein S12	YOR369C	4	2	1	4	0	4	4	2	4	2	4	1
430789	10	4	40S ribosomal protein S9-A	YPL081W	4	2	4	2	2	4	2	2	4	1	2	1
467768	8	5	60S ribosomal protein L5	YPL131W	4	2	4	2	2	4	4	1	0	1	4	1
356089	10	4	60S ribosomal protein L33-A	YPL143W	4	2	2	0	2	4	2	2	4	2	4	1
539347	5	3	60S ribosomal protein L29	YFR032C-A	4	2	0	0	0	4	4	1	0	2	0	1
394207	7	3	60S ribosomal protein L30	YGL030W	4	2	0	2	0	4	2	1	4	1	2	1
539473	7	2	60S ribosomal protein L16-A	YIL133C	4	2	2	0	2	4	2	1	0	1	2	1

Table 3. Summary of developmental expression dynamics of CDE orthogroups of genes related to Acetyl-CoA production and basic metabolism across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
500663	9	7	Aldehyde dehydrogenase 5, mitochondrial	YER073W	4	4	4	4	1	1	2	4	2	1	4	4
500719	11	4	Acetyl-coenzyme A synthetase 2	YLR153C	2	2	4	4	1	2	2	4	2	2	2	4
273601	11	7	Alcohol dehydrogenase 3, mitochondrial	YMR083W	4	2	4	4	4	4	2	4	2	1	4	2
421282	7	4	Aldehyde dehydrogenase	YMR170C	4	0	2	4	1	2	4	0	4	1	2	0
450047	8	5	Carbonic anhydrase	–	4	2	4	2	1	0	1	2	4	1	4	4
355051	9	5	Ceramide synthase	–	4	2	4	2	2	1	4	2	1	1	4	1
82352	9	6	Uncharacterized TLC domain-containing protein YPR114W	YPR114W	4	1	2	4	4	2	1	4	4	1	4	2
503618	9	3	3-methyl-2-oxobutanoate hydroxymethyltransferase	YBR176W	4	2	2	2	4	2	2	2	0	1	4	1
443766	8	1	Dephospho-CoA kinase CAB5	YDR196C	2	2	1	0	2	2	2	1	4	2	2	1

ID			Protein	Gene												
474787	6	1	Pantothenate kinase CAB1	YDR531W	4	1	2	0	0	2	2	1	1	1	2	2
461914	6	2	Phosphopantetheine adenylyltransferase	YGR277C	1	1	0	2	4	0	2	1	2	1	4	2
282840	5	2	2-dehydropantoate 2-reductase	YHR063C	4	1	1	2	2	1	1	1	2	1	4	1
500145	6	3	Pantoate--beta-alanine ligase	YIL145C	4	1	0	1	4	1	2	1	2	1	2	4
374749	8	1	Coenzyme A biosynthesis protein 3	YKL088W	2	2	4	2	1	2	2	2	0	1	2	1
453548	8	4	Pyruvate kinase 1	YAL038W	4	2	4	4	1	1	2	2	1	1	4	2
499160	9	5	Glucose-6-phosphate isomerase	YBR196C	4	1	4	2	2	4	2	2	4	1	4	1
365495	5	2	Glucokinase-1	YCL040W	4	2	1	1	2	2	1	1	1	1	4	1
442066	7	4	Phosphoglycerate kinase	YCR012W	4	1	2	4	1	1	2	4	2	1	4	1
173684	9	5	Triosephosphate isomerase	YDR050C	4	1	4	2	2	2	4	4	2	1	4	1
402119	8	3	Hexokinase-2	YGL253W	2	2	4	4	1	2	2	1	2	1	4	1
245737	9	4	Enolase 1	YGR254W	4	1	4	2	2	2	2	4	2	1	4	1
264276	7	5	Glyceraldehyde-3-phosphate dehydrogenase 1	YJL052W	4	1	4	2	0	2	4	4	1	1	4	1
546961	8	4	Fructose-bisphosphate aldolase	YKL060C	4	1	4	2	2	1	4	2	2	1	4	1
422402	11	8	Pyruvate decarboxylase isozyme 1	YLR044C	4	2	4	4	4	2	4	4	4	1	4	2
436876	9	6	Fructose-1,6-bisphosphatase	YLR377C	4	1	4	4	2	2	2	4	0	1	4	4
462738	8	1	ATP-dependent 6-phosphofructokinase subunit beta	YMR205C	2	1	4	2	2	1	2	2	2	1	2	1
495730	12	7	Isocitrate lyase	YER065C	2	4	2	4	4	2	2	4	4	4	2	4
530292	12	11	Malate synthase 2	YIR031C	4	4	4	4	4	2	4	4	4	4	4	4
501208	6	0	Homocitrate dehydratase, mitochondrial	YJL200C	2	2	2	0	2	1	2	2	1	1	0	1
374148	12	7	Succinate/fumarate mitochondrial transporter	YJR095W	4	4	2	4	4	2	2	4	2	2	2	4
493553	10	5	Phosphoenolpyruvate carboxykinase	YKR097W	4	2	0	4	2	2	1	4	2	2	4	4
449845	9	3	Malate dehydrogenase	–	1	1	4	2	2	2	2	4	2	1	4	2
442593	10	4	ATP citrate synthase	–	4	2	2	4	2	4	2	2	2	1	4	1
443703	10	5	Mitochondrial carnitine O-acetyltransferase	YAR035W	4	1	4	4	2	2	1	4	4	2	2	2
442787	7	5	Acetyl-CoA hydrolase	YBL015W	4	4	0	4	1	4	2	0	0	0	2	4
441597	7	6	Accumulation of dyads protein 2	YCR010C	4	1	4	4	0	4	4	1	2	1	4	1
373141	10	8	Aquaglycerol porin AQY3	YFL054C	4	4	4	4	2	2	4	0	4	0	4	4
357888	10	2	Mitochondrial oxaloacetate transport protein	YKL120W	2	1	2	2	4	2	2	1	2	2	4	2
375404	11	6	Carboxylic acid transporter protein homolog	YKL217W	4	2	4	4	2	4	2	2	4	1	4	2
147126	9	3	Protein SYM1	YLR251W	2	2	4	2	1	1	4	4	2	1	2	2
470219	9	3	Carnitine O-acetyltransferase, mitochondrial	YML042W	2	1	0	2	4	4	2	2	1	2	4	2
474886	9	3	Citrate/oxoglutarate carrier protein	YMR241W	4	1	4	2	0	2	2	2	2	1	4	2
543155	7	6	Acetate kinase	–	4	2	0	4	4	0	0	4	0	1	4	4
534888	9	5	Malate transporter	–	2	4	4	4	2	0	2	2	0	1	4	4
S.c. 2738153	8	5	Formate transporter	–	0	1	4	4	4	0	4	2	2	1	4	2
474928	8	5	Oxalate-CoA ligase	–	4	0	2	4	2	1	4	4	2	1	4	1
452378	9	7	Formate dehydrogenase 1	YOR388C	4	4	1	4	4	0	4	2	4	1	4	2

ID	FC>2	FC>4	Function	S.c.												
361522 S.c.	10	8	Oxalate decarboxylase	–	4	4	4	2	2	4	4	4	1	1	4	4
2751877	6	5	Oxalate decarboxylase	–	0	4	4	0	0	0	0	2	0	4	4	4
499734	11	11	Oxaloacetase	–	4	4	4	4	4	0	4	4	4	4	4	4
385900	11	2	Pyruvate dehydrogenase E1 component subunit beta, mitochondrial	YBR221C	4	2	2	2	2	2	2	2	2	2	4	1
501813	9	3	Pyruvate dehydrogenase E1 component subunit alpha, mitochondrial	YER178W	4	1	4	2	4	2	2	2	2	1	2	1
440087	10	3	Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	YNL071W	4	2	4	2	2	2	2	2	2	1	4	1
273609	9	6	NADP-dependent malic enzyme	–	4	4	4	4	2	2	2	0	4	0	4	1
364080	7	2	Pyruvate carboxylase 2	YBR218C	4	1	2	2	1	2	2	2	1	1	4	1
369183	10	1	Dihydrolipoyllysine-residue succinyltransferase, mitochondrial	YDR148C	2	2	2	2	1	2	2	2	2	1	4	2
492830	8	1	Dihydrolipoyl dehydrogenase, mitochondrial	YFL018C	2	2	2	2	1	2	2	2	1	1	4	1
454395	10	3	Succinate--CoA ligase subunit beta, mitochondrial	YGR244C	4	2	2	1	2	2	2	2	2	1	4	4
354219	5	2	Protein phosphatase 2C homolog 7, mitochondrial	YHR076W	1	1	2	1	2	1	1	1	2	1	4	4
545855	7	1	2-oxoglutarate dehydrogenase, mitochondrial	YIL125W	2	2	1	2	0	2	1	1	2	1	2	4
380777	7	6	NAD-dependent malic enzyme, mitochondrial	YKL029C	4	1	4	4	4	4	2	1	1	1	4	1
409635	11	3	Malate dehydrogenase, mitochondrial	YKL085W	2	2	4	2	2	4	2	2	2	2	4	1
483615	6	0	Succinate dehydrogenase cytochrome b subunit, mitochondrial	YKL141W	1	1	2	0	1	2	2	1	2	2	2	1
400441	6	0	Succinate dehydrogenase flavoprotein subunit, mitochondrial	YKL148C	2	2	2	2	1	1	1	1	1	2	2	1
363708	8	0	Succinate dehydrogenase iron-sulfur subunit, mitochondrial	YLL041C	2	1	2	2	2	2	2	1	2	1	2	1
367547	9	0	Mitochondrial inner membrane protein SHH4	YLR164W	2	1	2	2	1	2	2	2	2	2	2	1
503237	6	0	Aconitate hydratase, mitochondrial	YLR304C	2	2	2	2	0	1	1	2	2	1	1	1
474027	8	2	Isocitrate dehydrogenase subunit 1, mitochondrial	YNL037C	2	2	4	2	4	1	2	1	1	1	2	2
497099	11	4	Citrate synthase, mitochondrial	YNR001C	2	2	4	4	2	2	2	2	4	1	4	2
449179	6	1	Succinate dehydrogenase assembly factor 2, mitochondrial	YOL071W	2	1	0	1	1	2	2	4	0	2	2	1
444503	9	4	Isocitrate dehydrogenase subunit 2, mitochondrial	YOR136W	4	2	4	2	4	2	2	2	0	1	4	1
360292	10	3	Succinate--CoA ligase subunit alpha, mitochondrial	YOR142W	4	2	2	2	2	2	1	2	2	1	4	4
464081	6	2	Fumarate hydratase, mitochondrial	YPL262W	1	1	2	2	2	1	4	2	1	1	4	1

Table 4. Summary of developmental expression dynamics of CDE orthogroups of fatty acid beta-oxidation related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also

given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
437115	7	4	General amino acid permease AGP2	YBR132C	4	2	4	1	4	2	4	0	1	0	1	2
336239	6	1	Acyl-coenzyme A oxidase	YGL205W	1	1	1	2	2	1	2	2	1	1	4	2
438072	10	5	Acyl-CoA-binding protein	YGR037C	4	2	4	4	2	2	2	4	2	1	4	1
365907	6	2	3-ketoacyl-CoA thiolase, peroxisomal	YIL160C	4	1	2	2	4	2	0	1	2	1	1	1
231560	5	1	Peroxisomal hydratase-dehydrogenase-epimerase	YKR009C	2	1	1	4	2	1	2	1	2	1	1	1
354296	6	2	Aspartate aminotransferase	YLR027C	2	2	4	0	0	2	1	1	1	1	4	2
433737	8	3	Peroxisomal 2,4-dienoyl-CoA reductase SPS19 [(3E)-enoyl-CoA-producing]	YNL202W	4	1	4	2	2	4	1	1	2	1	2	2
374386	7	1	Peroxisomal membrane protein PMP27	YOL147C	2	1	2	2	2	2	1	1	2	1	4	1
436931	6	2	Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase	YOR180C	2	1	2	1	0	4	1	2	0	1	4	2
401814	5	2	Peroxisomal long-chain fatty acid import protein 2	YPL147W	4	1	1	2	4	1	1	1	2	1	2	1
395825	8	3	Peroxisomal adenine nucleotide transporter 1	YPR128C	4	1	2	2	1	4	2	2	2	1	4	1
437261	6	4	Long-chain-fatty-acid--CoA ligase 1	YOR317W	2	1	4	4	2	1	4	1	0	1	4	1

Table 5. Summary of developmental expression dynamics of CDE orthogroups of ergosterol and sphingolipid biosynthesis related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
488426	9	3	Transcription factor	–	4	1	0	4	2	2	4	2	2	2	2	1
Late pathway																
366787	9	4	Ergosterol biosynthetic protein 28	YER044C	2	1	2	2	4	2	4	4	2	1	4	1
366442	11	6	Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	YGL001C	4	2	4	4	2	4	2	4	2	2	4	1
544612	10	7	Delta(24(24(1)))-sterol reductase	YGL012W	4	2	4	2	0	4	4	4	2	4	4	1
496056	10	7	Methylsterol monooxygenase	YGR060W	4	1	4	2	4	4	2	4	2	4	4	1
489517	9	6	Squalene monooxygenase	YGR175C	4	1	2	2	0	4	4	4	4	2	4	1

ID	FC>2	FC>4	Function	Sc	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
397292	11	7	Lanosterol 14-alpha demethylase	YHR007C	4	2	4	2	2	4	4	4	2	4	4	1
413057	6	3	NADPH--cytochrome P450 reductase	YHR042W	4	1	4	2	4	1	1	2	1	1	2	1
420341	8	5	Lanosterol synthase	YHR072W	4	2	4	2	0	1	4	4	1	2	4	1
494314	7	4	Delta(7)-sterol 5(6)-desaturase	YLR056W	4	2	4	1	2	2	4	1	1	4	1	1
462226	8	4	3-keto-steroid reductase	YLR100W	4	1	4	2	0	1	4	2	2	1	4	2
373683	10	7	Sterol 24-C-methyltransferase	YML008C	4	1	4	2	4	4	2	4	4	4	2	1
357271	10	6	Cytochrome P450 61	YMR015C	4	0	4	2	2	4	4	2	4	4	4	1
17387	11	7	C-8 sterol isomerase	YMR202W	4	2	4	2	2	4	2	4	4	4	4	1
535364	10	3	Delta(14)-sterol reductase	YNL280C	4	2	2	2	1	2	4	2	2	2	4	1

Mevalonate pathway

ID	FC>2	FC>4	Function	Sc	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
358591	7	2	Cystathionine beta-lyase	YGL184C	4	4	1	1	1	1	2	2	2	2	2	1
43445	9	6	Squalene synthase	YHR190W	4	2	4	4	0	4	2	4	2	1	4	1
459666	9	5	Farnesyl pyrophosphate synthase	YJL167W	4	2	2	1	2	2	4	4	4	1	4	1
360799	8	2	3-hydroxy-3-methylglutaryl-coenzyme A reductase 2	YLR450W	4	1	2	2	2	2	1	2	1	2	4	1
439474	12	5	Hydroxymethylglutaryl-CoA synthase	YML126C	4	2	4	2	4	4	2	4	2	2	2	2
355838	12	10	Phosphomevalonate kinase	YMR220W	4	4	4	4	4	4	4	4	2	4	4	2
438368	8	2	Diphosphomevalonate decarboxylase	YNR043W	2	2	2	1	2	1	2	2	1	4	4	1
355558	7	0	Acetyl-CoA acetyltransferase	YPL028W	2	2	1	2	1	2	1	2	1	2	2	1
460395	6	2	Isopentenyl-diphosphate Delta-isomerase	YPL117C	4	1	1	2	1	1	2	4	1	2	2	1
539004	12	7	3-oxo-5-alpha-steroid 4-dehydrogenase	–	4	4	2	4	2	4	4	2	2	2	4	4

Sphingolipid biosynthesis

ID	FC>2	FC>4	Function	Sc	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
388282	9	5	Alkaline ceramidase YPC1	YBR183W	4	2	4	4	2	2	1	4	2	1	4	1
429678	6	1	Serine palmitoyltransferase 2	YDR062W	4	1	2	1	2	2	1	2	1	1	2	1
372474	7	1	Sphingosine-1-phosphate lyase	YDR294C	2	1	2	4	2	1	2	2	1	1	2	1
379742	7	0	Sphingolipid C4-hydroxylase SUR2	YDR297W	2	1	1	2	0	2	2	1	2	1	2	2
456289	8	0	Ceramide synthase LAG1	YHL003C	1	2	0	2	2	1	2	2	2	1	2	2
420050	6	3	Dihydrosphingosine 1-phosphate phosphatase LCB3	YJL134W	4	1	1	4	1	2	2	1	1	1	4	2
441179	7	2	Ceramide very long chain fatty acid hydroxylase SCS7	YMR272C	4	1	2	2	2	4	2	1	1	1	2	1
546344	6	3	Serine palmitoyltransferase 1	YMR296C	4	1	2	1	4	1	2	1	2	1	4	1
1859	6	2	Sphingoid long chain base kinase 4	YOR171C	4	1	1	1	1	2	4	2	2	1	2	1

Table 6. Summary of developmental expression dynamics of CDE orthogroups of sterol transport related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	Fold change >4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
470387	7	6	Prefoldin subunit 2	–	4	4	4	4	1	2	4	0	1	0	4	0
475807	7	5	Phosphatidylglycerol/phosphatidylinositol transfer protein	YDL046W	2	1	4	4	0	4	1	1	4	1	4	2
378276	6	1	Oxysterol-binding protein homolog 7	YHR001W	4	1	2	2	1	1	1	1	2	1	2	2
494709	7	1	NPC intracellular sterol transporter 1-related protein 1	YPL006W	4	2	1	2	2	1	2	1	1	1	2	2
427232	10	2	Oxysterol-binding protein homolog 4	YPL145C	4	2	2	4	2	1	2	2	2	1	2	2
478741	6	2	SCP2 sterol transport protein family	–	2	1	2	4	1	2	0	1	2	1	4	1

Table 7. Summary of developmental expression dynamics of CDE orthogroups of membrane phoshpolipid and fatty acid biosynthesis genes genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	Fold change >4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
Cardiolipin biosynthesis pathway																
539990	4	0	Phosphatidylglycerophosphatase GEP4, mitochondrial	YHR100C	2	2	1	0	1	1	1	2	0	1	2	1
471105	9	3	CDP-diacylglycerol--glycerol-3-phosphate 3-phosphatidyltransferase	YCL004W	2	1	2	2	2	1	2	1	4	4	4	2
522776	6	1	Cardiolipin synthase	YDL142C	4	2	1	0	1	2	2	1	0	1	2	2
CPD-DAG pathway																
442684	8	1	Phosphatidate cytidylyltransferase	YBR029C	2	2	2	1	2	2	1	1	2	1	4	2
436995	8	1	CDP-diacylglycerol-serine O-phosphatidyltransferase	YER026C	4	1	2	2	0	2	2	2	1	1	2	2
444758	11	4	Phosphatidylethanolamine N-methyltransferase	YGR157W	4	2	2	4	2	2	2	4	1	2	4	2
379032	7	1	Phosphatidylserine decarboxylase proenzyme 2	YGR170W	2	1	2	2	2	1	1	2	2	1	4	1
285011	9	6	Phosphatidyl-N-methylethanolamine N-methyltransferase	YJR073C	4	1	4	0	4	2	2	4	4	2	4	1
377789	7	2	Phosphatidylserine decarboxylase proenzyme 1, mitochondrial	YNL169C	4	1	2	4	0	1	2	2	1	1	2	2
436992	6	2	CDP-diacylglycerol-inositol 3-phosphatidyltransferase	YPR113W	4	1	2	2	2	2	1	1	1	1	4	1
Kennedy pathway																
449161	7	3	Choline-phosphate cytidylyltransferase	YGR202C	4	1	0	4	0	1	4	2	0	2	2	2
411802	3	1	Choline kinase	YLR133W	4	1	1	1	1	1	1	1	0	1	2	2
380149	10	5	Cholinephosphotransferase 1	YNL130C	4	2	4	2	2	4	2	2	1	1	4	4

Shared part of the pathway

76420	1	1	Long-chain-fatty-acid--CoA ligase 2	YER015W	4	0	0	0	0	0	0	0	0	0	0	0
439965	6	4	Elongation of fatty acids protein 2	YCR034W	4	1	4	1	4	2	1	2	0	1	4	1
462371	5	0	1-acyl-sn-glycerol-3-phosphate acyltransferase	YDL052C	2	1	1	1	2	1	2	1	2	1	2	1
379857	9	3	Acetyl-CoA carboxylase	YNR016C	4	2	1	4	0	2	2	4	1	2	2	2
414377	7	6	Glycerol-3-phosphate dehydrogenase [NAD(+)] 2, mitochondrial	YOL059W	4	1	4	4	2	1	4	1	4	1	4	1
372300	9	4	Lysophospholipid acyltransferase	YOR175C	4	2	4	2	2	2	2	1	4	1	4	1
538984	9	5	Fatty acid synthase subunit alpha	YPL231W	4	2	1	4	2	2	4	4	1	1	4	2
72617	4	4	Fatty acid desaturase	–	4	1	1	4	0	1	1	4	0	0	0	4
4671	6	0	Glycerol-3-phosphate O-acyltransferase 1	YBL011W	2	1	2	2	1	1	2	1	2	1	2	1
450732	8	3	NADPH-dependent 1-acyldihydroxyacetone phosphate reductase	YIL124W	2	1	2	4	2	1	4	1	2	2	4	1
422393	10	6	Fatty acid desaturase	–	4	2	4	2	4	4	2	4	1	1	2	4
437261	6	4	Long-chain-fatty-acid--CoA ligase 1	YOR317W	2	1	4	4	2	1	4	1	0	1	4	1

TAG pathway

437679	4	0	Phosphatidic acid phosphohydrolase 1	–	2	1	1	2	1	1	1	2	1	1	1	2
493617	3	1	Phospholipid:diacylglycerol acyltransferase	YNR008W	4	1	1	2	1	1	1	1	1	1	2	1
374579	7	2	Sterol O-acyltransferase 2	–	2	1	2	2	0	2	1	1	4	1	4	2
479811	6	2	Diacylglycerol O-acyltransferase 1	YOR245C	1	1	1	4	1	2	2	1	2	1	4	2

Table 8. Summary of developmental expression dynamics of CDE orthogroups of linoleic acid biosynthesis related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change		Putative function	S. cerevisiae ortholog	Species											
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
S.c. 2511002	10	3	Fatty acid desaturase	–	0	2	4	2	2	2	4	4	1	2	2	2
363743	9	7	Fatty acid desaturase	–	4	4	2	4	4	4	0	4	0	0	2	4
422976	8	8	Fatty acid desaturase	–	4	0	4	4	4	4	4	0	4	0	4	0
471478	9	7	Fatty acid desaturase	–	4	2	4	4	4	0	4	2	1	0	4	4
493933	11	9	Fatty acid desaturase	–	2	4	4	4	4	1	4	4	4	4	2	4
422393	10	6	Fatty acid desaturase	–	4	2	4	2	4	4	2	4	1	1	2	4

Table 9. Summary of developmental expression dynamics of CDE orthogroups of other lipid metabolism related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| ID | Fold change | | Putative function | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
20997	12	11	Glycerophosphodiester phosphodiesterase	–	4	4	4	4	4	4	4	4	4	2	4	4
380219	6	6	Diacylglycerol pyrophosphate phosphatases	–	4	4	0	4	0	0	0	0	4	0	4	4
376602	9	9	Caleosin	–	4	4	1	0	4	4	0	4	4	4	4	4
365330	12	9	Sphingolipid C9-methyltransferase	–	4	2	2	4	4	4	4	4	2	4	4	4
395241	11	8	Sphingolipid C9-methyltransferase	–	4	2	4	4	2	4	4	4	2	4	4	1
444998	8	6	Marvel domain protein	–	4	1	0	4	1	1	4	2	4	2	4	4
462849	10	5	Marvel domain protein	–	4	1	0	2	2	2	4	2	4	4	2	4

Table 10. Summary of developmental expression dynamics of CDE orthogroups of storage carbohydrate metabolism genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| ID | Fold change | | Putative function | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
360850	9	8	Alcohol dehydrogenase	–	4	1	4	4	4	4	4	2	4	1	4	1
369180	10	7	Sorbitol dehydrogenase	–	2	4	4	4	0	4	2	4	4	1	2	4
455149	11	6	CBM21 domain containing protein	–	4	2	2	4	4	2	2	2	4	1	4	4
441344	7	2	Glucoamylase	–	2	4	0	2	1	0	0	2	4	2	2	1
365699	8	5	1,4-alpha-glucan-branching enzyme	YEL011W	4	1	2	4	2	4	4	1	0	1	4	2
496146	2	0	Serine/threonine-protein phosphatase controlling glycogen metabolism	YER133W	2	1	1	0	1	2	1	1	1	1	1	1
457685	9	5	Glycogen synthase	YFR015C	4	2	2	4	1	2	4	1	4	1	4	2
473268	6	3	Glucoamylase	YIL099W	4	0	2	4	0	1	2	0	4	0	2	0
461263	7	3	Glycogenin	YJL137C	4	1	2	4	2	1	2	1	1	1	4	2
359312	9	5	UTP-glucose-1-phosphate uridylyltransferase	YKL035W	4	2	2	4	2	4	4	1	2	1	4	1

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
497782	7	5	Phosphoglucomutase 2	YMR105C	4	1	4	4	0	2	4	2	0	1	4	1
538513	2	1	Cyclin-dependent protein kinase	YPL031C	2	1	1	1	1	1	1	1	1	1	4	1
495987	9	7	Glycogen phosphorylase	YPR160W	4	1	4	4	2	4	4	4	2	1	4	1
405214	10	6	Glycogen debranching enzyme	YPR184W	2	2	2	4	4	1	4	4	4	1	4	2
495249	10	7	Glycoside hydrolase family 13 alpha-amylase	–	4	4	4	4	4	4	2	2	0	2	4	1
544130	11	7	CBM21 domain containing protein	–	4	2	4	4	4	2	4	4	2	1	4	2
429272	4	4	Mannitol dehydrogenase	–	4	0	4	0	0	4	0	0	0	0	4	0
478544	8	2	Alpha,alpha-trehalose-phosphate synthase	YBR126C	2	1	2	2	1	2	2	2	4	1	4	1
437212	10	2	Neutral alpha-trehalase	YDR001C	2	2	2	2	4	2	1	2	2	1	2	4
473004	8	4	Trehalose-phosphatase	YDR074W	4	1	2	2	4	2	1	4	2	1	4	1
503099	7	3	Trehalose synthase complex regulatory subunit TSL1	YML100W	4	1	2	2	1	4	1	2	2	1	4	1
376383	9	6	Trehalase	–	4	2	2	0	4	4	1	4	4	1	4	2
540817	11	6	Trehalose phosphorylase	–	4	4	2	4	4	1	2	2	2	2	4	4

Table 11. Summary of developmental expression dynamics of CDE orthogroups of transcriptional regulator genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	Fold change >4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
421729	9	5	Transcription factor, *C. cinerea* exp1	–	4	1	4	4	4	2	2	2	4	1	2	1
395717	7	7	Transcription factor	–	4	1	0	4	4	4	4	4	4	1	0	1
404567	9	7	Transcription factor	–	4	2	0	0	0	4	4	4	4	2	4	4
437393	11	9	Transcription factor	–	4	4	4	4	4	4	4	2	4	4	0	2
446227	9	8	Transcription factor	–	4	4	4	4	4	1	4	4	1	2	1	4
491825	10	4	Transcription factor	–	4	2	2	4	2	1	2	2	4	1	4	2
494418	10	8	Transcription factor	–	4	0	4	4	4	2	4	4	4	2	4	0
497620	12	9	Transcription factor	–	4	4	2	2	4	4	4	4	4	2	4	4
S.c. 2520583	7	6	Transcription factor	–	0	4	2	4	4	4	0	0	4	0	0	4
8610	10	6	Transcription factor, *C. cinerea* Cc.wc2	–	4	2	4	4	2	2	4	2	4	1	0	4
148855	10	6	Transcription factor, *L. edodes* PriB	–	4	4	1	2	2	2	4	2	4	1	4	4
493627	10	9	Transcription factor, *S. commune* Hom1	–	4	4	4	4	1	2	4	4	4	1	4	4
449111	7	6	Transcription factor	YDR043C	4	1	4	0	4	0	4	4	0	2	4	1
495715	12	12	Transcription factor, *S. commune* Tea1	YEL007W	4	4	4	4	4	4	4	4	4	4	4	4

	ID			Description	Ortholog												
458586	10	3	Transcription-related RNA-binding protein	YGR159C	2	2	2	4	2	2	4	2	2	1	4	1
482097	10	7	Transcription factor	YPR015C	2	4	4	2	4	4	0	2	4	1	4	4
155160	9	6	Transcription initiation factor	–	4	2	2	4	4	4	4	2	4	1	0	0
449345	9	5	Transcription factor	–	4	2	1	4	4	4	2	2	2	1	4	1
463573	9	5	Transcription factor, *S. commune* Fst3	–	4	1	2	4	2	4	2	2	4	1	4	1
365344	9	6	Transcription factor, *S. commune* Fst4	–	4	2	2	4	4	4	2	1	4	1	4	1
211795	10	5	Transcription factor	–	4	4	2	4	2	4	2	2	4	1	2	1
498166	10	6	Possibly related to transcription elongation factors	–	2	4	4	2	1	1	4	4	4	2	2	4
508285	11	4	Potentially involved in in pre-mRNA 3' end processing	–	4	2	2	4	0	2	2	2	4	2	2	4
497197	7	6	Rho termination factor	–	4	1	0	4	0	2	4	4	4	4	0	0
142396	10	7	Transcription factor	–	4	1	4	2	4	4	4	4	4	2	0	2
351135	7	5	Transcription factor	–	4	2	4	4	0	4	2	1	0	1	4	1
357193	9	7	Transcription factor	–	4	1	4	4	2	1	4	4	4	1	4	2
359157	10	6	Transcription factor	–	4	2	2	4	4	2	2	4	4	1	4	1
360688	11	9	Transcription factor	–	4	4	4	4	2	4	4	4	4	1	2	4
367840	8	7	Transcription factor	–	4	1	4	4	1	4	4	2	4	1	4	1
374546	8	5	Transcription factor	–	4	2	4	4	0	4	0	2	2	1	4	1
411205	9	7	Transcription factor	–	4	4	4	4	2	4	1	2	4	1	4	1
416057	10	4	Transcription factor	–	2	2	2	4	2	1	4	4	2	2	0	4
440363	12	7	Transcription factor	–	4	2	2	4	4	4	4	2	4	2	4	2
441820	6	5	Transcription factor	–	4	1	4	4	2	4	1	1	1	1	4	1
442154	10	7	Transcription factor	–	4	4	4	4	2	1	2	4	2	4	0	4
443979	10	8	Transcription factor	–	4	4	4	4	0	2	4	4	0	2	4	4
451915	7	6	Transcription factor	–	4	0	2	0	4	4	0	4	4	4	0	0
452897	9	8	Transcription factor	–	4	4	2	4	4	4	0	0	1	4	4	4
465631	7	6	Transcription factor	–	4	2	4	4	0	4	4	0	4	0	0	1
492675	7	4	Transcription factor	–	4	2	4	2	1	4	1	0	1	1	4	2
500056	10	6	Transcription factor	–	4	2	2	4	2	4	1	4	4	1	4	2
S.c. 2614371	7	7	Transcription factor	–	0	4	0	4	0	0	4	0	4	4	4	4
S.c. 2705300	6	5	Transcription factor	–	0	4	0	4	0	2	4	4	0	4	0	1
438877	9	5	Transcription related protein	–	2	4	2	4	4	2	4	2	1	1	4	1
471238	10	10	RNA binding protein; distantly related to yeast PAB1	–	4	4	0	4	4	0	4	4	4	4	4	4
369621	10	4	Transcription factor, *C. cinerea* dst1	–	4	2	4	4	2	1	2	2	2	1	4	2
538904	8	6	Transcription factor, *S. commune* Gat1	–	4	2	4	4	1	4	4	1	4	1	2	1
355613	9	3	Transcription factor, *S. commune* Hom2	–	4	1	4	2	4	2	2	2	2	1	1	2
413307	7	5	Transcription related Mynd-type zinc finger	–	4	4	4	4	0	4	1	2	0	1	2	1

Table 12. Summary of developmental expression dynamics of CDE orthogroups of RNA-binding protein encoding genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
357717	12	12	RNA binding domain protein	–	4	4	4	4	4	4	4	4	4	4	4	4
354109	8	6	mRNA-binding Pumilio protein	YLL013C	4	4	1	4	0	2	2	4	0	1	4	4
444698	10	3	RNA binding domain protein	–	2	2	2	2	0	2	4	1	4	2	4	2
541323	11	10	Armadillo domain containing RNA binding protein	–	4	4	4	4	4	2	4	4	4	1	4	4
356106	10	5	RNA binding domain protein	–	4	2	2	4	4	2	2	2	4	1	4	1
424800	12	11	RNA binding domain protein	–	4	4	2	4	4	4	4	4	4	4	4	4
193545	11	11	RNA binding domain protein	–	4	4	4	4	4	4	4	4	4	4	0	4

Table 13. Summary of developmental expression dynamics of CDE orthogroups of RNA interference related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
155983	6	2	RNA-dependent RNA polymerase	–	4	1	2	2	1	2	4	2	1	1	1	1
498671	4	1	RNA-dependent RNA polymerase	–	4	1	1	1	2	1	2	1	2	1	0	1
438955	4	2	Dicer-like protein	–	2	1	1	2	4	4	1	1	1	1	1	1
464843	2	1	RNA-dependent RNA polymerase	YDL128W	4	0	0	0	0	2	0	0	0	0	0	0
366047	6	1	Dicer-like protein	YLR332W	1	1	1	2	2	4	2	1	2	1	2	1
473372	8	0	AGO-like protein	–	2	2	1	2	1	2	2	2	2	1	2	1
495272	6	4	Argonaute-like protein	–	4	1	0	2	2	1	4	1	4	1	4	1
502116	9	6	Argonaute-like proteins with high similarity to *A. nidulans* rsdA and *S. pombe* ago1	–	4	2	1	4	2	4	4	4	4	1	2	1
363313	7	1	Orthologs of QDE-2	–	2	2	1	2	1	1	2	2	4	1	2	1
440860	5	1	RNA-dependent RNA polymerase	–	4	1	2	2	1	1	1	1	2	1	2	1
496192	5	1	RNA-dependent RNA polymerase	–	2	0	0	2	2	4	2	1	0	1	1	0
498410	5	1	RNA-dependent RNA polymerase	–	4	1	2	2	1	0	2	1	1	1	2	1

ID	>2	>4	Putative function	Sc. ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
355234	1	1	AGO ortholog	–	4	0	0	0	0	0	0	0	0	0	0	0
368472	1	0	Argonaute-like protein	–	2	0	0	0	0	0	0	0	0	0	0	0
465906	1	0	Argonaute-like protein	–	2	0	0	0	0	0	0	0	0	0	0	0
444647	3	0	Dicer-like protein	–	2	1	1	1	1	1	1	1	2	1	2	1
124704	1	1	RNA-dependent RNA polymerase	–	4	0	0	0	0	0	0	0	0	0	0	0
444494	1	1	RNA-dependent RNA polymerase	–	4	0	0	0	0	0	0	0	0	0	0	0

Table 14. Summary of developmental expression dynamics of CDE orthogroups of chromatin-related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change		Putative function	*S. cerevisiae* ortholog	Species											
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
58294	10	0	Actin-related protein 4	–	2	2	2	2	2	1	2	2	2	2	2	1
485296	9	0	Protein arginine N-methyltransferase 1	YBR034C	2	1	2	2	2	2	2	2	2	1	2	1
498885	11	8	Histone H2A.Z-specific chaperone CHZ1	YER030W	4	0	2	4	2	2	4	4	4	4	4	4
493226	10	7	Histone isomerase	YML074C	4	2	4	4	4	2	2	4	4	1	4	1
455597	9	9	NAD-dependent histone deacetylase HST3	YOR025W	4	4	4	4	4	1	0	4	4	1	4	4
545797	11	9	*C. cinerea* Ich1 gene	–	4	4	4	4	1	2	4	4	4	4	2	4
392307	11	5	HIRA-interacting protein 3	–	2	2	4	4	2	2	4	2	4	1	4	2
384835	8	6	Poly(ADP-ribose) polymerase	–	4	2	0	4	0	0	2	4	4	1	4	4
459336	9	5	Poly(ADP-ribose) polymerase	–	2	2	2	4	1	4	4	0	4	1	4	2
473747	8	6	High mobility group protein	–	4	1	4	4	2	2	0	4	4	1	4	0
66389	10	4	Suppressor protein STM1	YLR150W	4	2	4	2	1	4	2	2	4	2	2	1
264120	2	0	SET domain protein	YJL168C	1	1	1	1	1	1	2	1	1	1	2	1
170659	1	0	SET domain protein	–	2	0	0	0	0	0	0	0	0	0	0	0
456684	3	0	SET domain protein	–	2	1	1	1	0	2	0	2	0	0	1	1
497003	1	0	SET domain protein	–	2	1	0	1	1	0	1	1	1	1	0	1
365798	2	0	*C. cinerea* Snf5 family chromatin remodeling protein	–	2	1	1	1	2	1	1	1	1	1	1	1
252667	8	2	Histone acetyltransferase type B subunit 2	YEL056W	2	2	4	2	1	1	2	2	4	1	2	1
518613	10	4	Histone acetyltransferase complex member	YLL022C	2	2	2	2	0	2	4	4	4	1	4	2
420113	7	4	Histone acetyltransferase type B catalytic subunit	YPL001W	4	1	2	1	1	2	4	1	4	1	4	2
457726	8	4	Histone acethytransferase	–	4	1	4	4	2	1	2	0	2	0	4	2
430366	6	0	Histone deacetylase	YGL194C	2	1	1	2	2	1	1	2	2	1	2	1
415916	4	0	Histone deacethylase	YNL021W	2	1	1	2	2	1	2	1	1	1	1	1

ID	Fold change >2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
354601	6	2	Histone deacetylase	YNL330C	4	2	2	2	1	1	2	1	1	1	4	1
52602	5	3	Histone deacetylase	YPL116W	4	1	1	4	1	1	4	2	0	2	1	1
364572	5	0	Histone deacetylase	–	1	1	2	2	1	1	2	1	2	1	2	1
465141	8	2	Histone deacetylase	–	2	4	4	2	2	1	2	1	2	1	1	2
363625	8	6	Agaricales-specific histone group	–	4	0	0	0	4	4	2	4	4	2	4	0
154410	11	6	Centromere-specific histone variant	–	2	4	2	2	2	4	2	4	4	1	4	4
182362	11	5	Histone	–	4	4	2	2	2	2	2	2	4	0	4	4
473916	8	6	Histone	–	2	0	4	4	1	4	0	2	4	0	4	4
393767	9	5	Histone H2B	–	1	1	4	4	2	2	4	4	0	2	2	4
361866	5	4	Histone H2B.2	YBL002W	2	0	0	4	0	0	4	4	4	0	0	0
418275	10	7	Histone H2A.2	YBL003C	2	4	4	4	2	4	4	0	0	2	4	4
401831	9	6	Histone H4	YBR009C	1	4	4	2	1	4	2	4	4	1	2	4
546355	4	1	Histone H3	YBR010W	2	0	1	2	1	1	1	2	4	1	1	1
284515	11	2	Histone H2A.Z	YOL012C	2	2	4	2	2	2	2	2	4	2	2	1
467558	10	9	Histone H1	YPL127C	4	4	4	4	4	4	4	4	1	2	0	4
320458	0	0	Histone	–	1	0	0	0	0	0	0	0	0	0	0	0
324852	0	0	Histone	–	1	0	0	0	0	0	0	0	0	0	0	0
380437	1	1	Histone	–	4	0	0	0	0	0	0	0	0	0	0	0
385598	1	1	Histone	–	4	0	0	0	0	0	0	0	0	0	0	0
446837	1	0	Histone	–	2	0	0	0	0	0	0	0	0	0	0	0
492876	1	0	Histone	–	2	0	0	0	0	0	0	0	0	0	0	0
503008	1	0	Histone	–	2	0	0	0	0	0	0	0	0	0	0	0
452576	4	0	AMP-activated protein serine/threonine kinase alpha subunit Ssp2	YDR477W	2	1	1	2	1	1	2	1	2	1	1	1
360033	4	1	5'-AMP-activated protein kinase subunit gamma	YGL115W	1	1	4	1	1	1	2	2	1	1	2	1
377394	8	1	Histone-lysine N-methyltransferase, H3 lysine-79 specific	YDR440W	2	1	1	4	2	1	2	2	2	1	2	2
511209	9	8	SRA-YDG domain protein	–	2	4	4	4	4	4	4	0	0	0	4	4

Table 15. Summary of developmental expression dynamics of CDE orthogroups of signal transduction related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
S.c. 2643671	7	6	Protein kinase related to mating	–	1	2	4	2	4	4	4	1	1	1	4	4
363127	8	7	Alcohol dehydrogenase	YMR318C	4	1	0	4	4	0	4	4	2	4	0	4

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
398037	9	7	Linoleate diol synthase	–	4	1	4	2	2	4	4	0	4	4	0	4
423716	10	5	Linoleate diol synthase	–	4	4	2	4	0	2	4	2	1	2	4	2

kinase

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
357261	8	7	Serine-threonine kinase	–	4	4	0	4	0	2	0	4	0	4	4	4
397547	7	5	Serine-threonine kinase	–	4	0	0	4	4	0	0	2	4	2	0	4
405337	12	11	Serine-threonine kinase	–	4	4	2	4	4	4	4	4	4	4	4	4
441896	10	8	Serine-threonine kinase	–	4	0	2	4	4	4	4	2	4	4	4	0
456276	10	8	Serine-threonine kinase	–	2	4	2	4	4	4	4	1	4	1	4	4
493180	9	4	Serine-threonine kinase	–	4	2	2	4	1	2	1	2	2	1	4	4
538093	11	8	Serine-threonine kinase	–	2	4	2	4	2	4	4	4	0	4	4	4
462137	11	9	Serine-threonine kinase	YDR247W	2	2	4	4	4	4	4	4	4	1	4	4
449305	10	4	P38 mitogen-activated protein kinase HOG1	YLR113W	4	1	2	2	2	4	4	2	2	1	4	2
451611	10	6	Serine-threonine kinase	YLR248W	4	2	1	4	4	4	2	2	2	1	4	4
448193	10	6	Serine-threonine kinase	–	2	4	1	4	1	2	4	4	4	2	4	2
359429	6	5	Serine-threonine kinase	–	4	0	0	4	1	4	2	0	4	0	4	0
448807	6	5	Serine-threonine kinase	–	4	0	4	2	4	0	0	4	4	1	0	0
470972	8	6	Serine-threonine kinase	–	4	4	0	2	0	4	1	4	2	4	0	4

Table 16. Summary of developmental expression dynamics of CDE orthogroups of pheromone precursor genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog *in S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
153902	2	0	Protein-S-isoprenylcysteine O-methyltransferase	YDR410C	2	1	0	1	2	1	1	1	1	1	1	1
116060	1	1	Mating pheromone precursor	–	4	0	0	0	0	0	0	0	0	0	0	0
446846	1	1	Mating pheromone precursor	–	4	0	0	0	0	0	0	0	0	0	0	0
446955	1	1	Mating pheromone precursor	–	4	0	0	0	0	0	0	0	0	0	0	0
446956	1	1	Mating pheromone precursor	–	4	0	0	0	0	0	0	0	0	0	0	0
446958	0	0	Mating pheromone precursor	–	1	0	0	0	0	0	0	0	0	0	0	0
446959	1	1	Mating pheromone precursor	–	4	0	0	0	0	0	0	0	0	0	0	0
446966	0	0	Mating pheromone precursor	–	1	0	0	0	0	0	0	0	0	0	0	0
356637	1	1	Pheromone sensing GPCR Ste3 homolog	–	4	0	0	0	0	0	0	0	0	0	0	0
394943	4	2	Pheromone sensing GPCR Ste3 homolog	–	4	0	0	4	2	1	0	0	0	0	2	0
477564	5	3	Pheromone sensing GPCR Ste3 homolog	–	4	0	2	0	4	0	0	2	0	0	4	0
377901	7	3	CAAX prenyl protease 2	–	4	1	2	1	1	2	4	1	4	1	2	2

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
203704	6	3	Pheromone sensing GPCR Ste3 homolog	–	4	2	0	4	4	2	1	0	1	1	0	2
465723	8	4	Pheromone sensing GPCR Ste3 homolog	–	2	1	4	4	2	1	4	2	1	1	4	2
486965	5	3	Pheromone sensing GPCR Ste3 homolog	–	2	0	0	4	0	4	0	2	1	1	4	0
491483	3	2	Protein farnesyltransferase subunit beta	YDL090C	4	1	1	1	4	1	1	1	1	1	2	1
437675	5	0	Pheromone-processing carboxypeptidase KEX1	YGL203C	2	1	1	1	2	2	2	1	1	1	2	1
545529	5	1	Dipeptidyl aminopeptidase B	YHR028C	1	1	4	2	1	1	1	2	2	1	2	1
419650	6	1	CAAX prenyl protease 1 ste24	YJR117W	4	2	2	1	2	1	1	2	1	1	2	1
473005	8	2	Protein farnesyltransferase/geranylgeranyltransferase type-1 subunit alpha	YKL019W	4	2	1	4	2	2	2	2	1	1	2	1
540181	10	4	Alpha-factor-transporting ATPase	YKL209C	4	4	2	2	2	4	2	2	4	1	1	2
358206	8	2	A-factor-processing enzyme	YLR389C	2	1	1	2	2	4	4	1	2	1	2	2
448165	5	2	Putative kexin	YNL238W	1	2	2	4	1	1	1	1	4	1	1	2
106286	7	2	Pheromone sensing GPCR Ste3 homolog	–	4	1	2	4	2	0	2	2	2	0	0	1
152667	9	9	Homolog of *S. cerevisiae* Ste14	–	4	0	4	4	4	4	4	4	1	4	4	0

Table 17. Summary of developmental expression dynamics of CDE orthogroups of conserved signal transduction pathway genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
cAMP																
465055	4	0	Phosphatidylinositol phosphate phosphatase	–	2	1	2	1	1	1	2	1	2	1	1	1
462760	6	0	GTPase involved in G-protein signaling in adenylate cyclase activation	–	2	1	2	2	1	2	1	2	1	1	2	1
539854	10	3	Low-affinity cyclic AMP phosphodiesterase	YGL248W	4	4	2	2	1	2	4	2	2	1	2	2
494851	7	2	Phosphatidylinositol phosphate phosphatase	YKL212W	2	2	4	2	1	1	2	1	2	1	4	1
175104	5	1	High-affinity cyclic AMP phosphodiesterase	YOR360C	1	1	4	2	1	2	1	1	1	1	2	2
45965	7	2	Protein kinase A catalytic subunit 2	YPL203W	4	2	2	2	1	1	1	2	2	1	4	1
361063	6	1	Protein kinase A catalytic subunit 1	–	2	1	4	1	2	1	1	2	2	1	2	1
497554	2	0	Adenylate cyclase	–	1	1	1	2	1	1	1	1	2	1	1	1
449966	1	1	Carbonic anhydrase	–	4	0	0	0	0	0	0	0	0	0	0	0
Cell wall stress																
453815	1	0	1-phosphatidylinositol 4-kinase	–	2	1	1	1	1	1	1	1	1	1	1	1

ID	a	b	Description	Gene												
			STT4													
464132	4	2	1-phosphatidylinositol-4-phosphate 5-kinase	–	4	1	1	1	2	2	1	1	1	1	4	1
494847	2	0	Mitogen-activated protein kinase kinase kinase BCK1	–	1	0	0	1	1	2	1	0	2	1	0	1
186221	4	0	Mitogen-activated protein kinase kinase MKK1	–	1	1	2	2	1	1	1	1	1	1	2	2
466997	3	0	Rho family guanine nucleotide exchange factor ROM2	–	2	1	1	1	0	1	2	1	2	1	1	1
419097	5	1	Classical protein kinase C alpha type	YBL105C	2	1	2	1	1	2	1	1	2	1	4	1
373470	7	2	Cyclin-dependent serine/threonine-protein kinase CDC28	YBR160W	2	1	1	0	1	4	2	2	2	1	4	2
418410	5	1	3-phosphoinositide dependent protein kinase-3	YDR490C	2	2	1	1	2	1	1	1	2	1	4	1
528086	6	0	Rho family GTPase RHO1, Ras homolog gene family, member A	YPR165W	2	1	2	2	1	2	1	1	2	1	2	1
446030	7	1	1,3-beta-D-glucan synthase	YGR032W	2	1	2	4	1	2	2	1	2	1	2	1
498153	6	2	Tyrosine protein phosphatase PTP3	YER075C	2	2	1	4	1	1	2	1	2	1	4	1
413665	8	5	Mitogen-activated serine/threonine-protein kinase SLT2	YHR030C	2	1	4	4	1	4	2	2	4	1	4	1

High osmolarity pathway

ID	a	b	Description	Gene												
474858	4	0	Mitogen-activated protein kinase kinase kinase, osomolarity two-component system, response regulator SSK2	–	1	1	1	2	2	2	1	1	1	1	2	1
494483	4	0	Rho family guanine nucleotide exchange factor CDC24, cell division control protein 24	–	2	1	1	2	1	2	1	1	2	1	1	1
446453	6	0	Type 2C protein phosphatase PTC1	YDL006W	2	1	2	2	1	1	2	1	2	1	0	2
356186	6	1	High osmolarity two-component System, phosphorelay intermediate protein YPD1	YDL235C	4	0	0	2	0	1	2	2	2	1	0	2
484600	10	4	G-protein beta-like WD40 protein	YMR116C	4	2	4	2	2	1	2	2	4	2	4	1
498153	6	2	Tyrosine protein phosphatase PTP3	YER075C	2	2	1	4	1	1	2	1	2	1	4	1
419006	5	0	Pheromone receptor transcription factor	YMR043W	2	1	1	2	1	2	2	2	0	1	1	0

Pheromone pathway

ID	a	b	Description	Gene												
16197	1	0	GTPase-activating protein SST2	–	2	1	1	1	1	1	1	1	1	1	1	1
370279	4	0	Mitogen-activated protein kinase kinase	–	1	2	2	1	2	1	1	2	1	1	1	1
353910	1	0	Mitogen-activated protein kinase kinase kinase STE11	–	1	1	0	2	1	1	1	1	1	1	0	1
446910	3	0	Serine/threonine protein kinase SKM1/CLA4, Serine/threonine-protein kinase CLA4	–	1	1	1	2	2	1	1	1	0	1	2	1
416655	3	0	Rho family GTPase CDC42	–	2	1	1	0	1	1	2	1	1	1	2	1
437458	3	0	Scaffold protein BEM1; phosphatidylinositol-3-phosphate-binding protein BEM1, bud emergence protein 1	–	2	1	2	1	1	1	1	1	2	1	1	1
455590	2	0	The RA domain of Ste50 adaptor protein is required for delivery of Ste11 to the plasma membrane in the filamentous growth signaling pathway (???)	–	2	1	1	1	0	1	1	1	1	1	2	1

ID			Description	Gene												
370180	4	0	Tyrosine/serine/threonine protein phosphatase MSG5	–	2	1	1	1	2	1	1	1	2	1	2	1
445505	5	1	Mitogen-activated serine/threonine-protein kinase FUS3	YBL016W	1	2	2	1	1	1	2	4	1	1	2	1
429295	6	0	Mitogen-activated protein kinase kinase kinase kinase STE20, p21-activated kinase 1	YHL007C	2	1	2	2	0	2	1	1	2	1	2	1
84056	4	2	Guanine nucleotide-binding protein subunit gamma	YJR086W	2	1	2	0	1	1	1	1	4	1	4	1
449416	5	0	Guanine nucleotide-binding protein GI/GS/GT subunit beta-1	YOR212W	2	1	2	2	1	1	1	1	2	1	2	1
498153	6	2	Tyrosine protein phosphatase PTP3	YER075C	2	2	1	4	1	1	2	1	2	1	4	1
419006	5	0	Pheromone receptor transcription factor	YMR043W	2	1	1	2	1	2	2	2	0	1	1	0
376911	8	1	Homeodomain family transcription factor STE12	–	4	1	2	2	1	2	2	2	2	1	0	2

Starvation pathway

ID			Description	Gene												
356859	4	2	SHO1 osmosensor	–	4	1	2	1	1	2	1	1	1	1	4	1
197636	2	1	Signaling mucin MSB2	–	2	0	1	0	1	0	0	1	4	0	0	0
389009	7	0	14-3-3 family protein BMH1	YDR099W	1	2	2	1	2	2	1	2	2	1	2	1
498153	6	2	Tyrosine protein phosphatase PTP3	YER075C	2	2	1	4	1	1	2	1	2	1	4	1
376911	8	1	Homeodomain family transcription factor STE12	–	4	1	2	2	1	2	2	2	2	1	0	2

TOR

ID			Description	Gene												
407528	6	3	SEA complex subunit Seh1	YGL100W	4	1	2	2	1	1	1	4	4	1	2	1
365555	4	0	Protein kinase A regulatory subunit	YIL033C	2	1	2	2	1	1	1	2	1	1	1	1
434690	10	4	Phosphoinositide PI4,5P(2) binding Protein, forms a complex with Slm2p	YIL105C	2	1	4	4	2	2	4	2	2	1	4	2
502431	5	1	COPII-coated vesicle component Sec13	YLR208W	1	1	2	1	2	2	1	2	0	1	4	1
466474	8	6	FK506-binding protein 1	YNL135C	2	4	4	0	4	2	4	4	1	1	4	1
81628	6	0	Gtr1/RagA G protein Gtr1	–	2	1	2	2	1	2	2	1	1	1	2	1
417412	2	0	Component of a membrane-bound complex containing the Tor2p kinase	–	2	1	1	1	1	1	1	1	1	1	2	1
498449	1	0	DEP domain containing 5; subunit of SEACIT (GATOR1)	–	2	1	1	1	0	1	1	1	1	1	1	1
438057	4	1	Gtr1/RagA G protein Gtr2	–	2	1	1	2	1	1	1	1	1	1	4	2
467184	4	1	Guanyl-nucleotide exchange factor, HOPS complex subunit Vam6	–	1	1	2	0	1	1	4	1	2	1	2	1
440799	4	0	Nitrogen permease regulator 2-like protein; subunit of SEACIT (GATOR1)	–	1	1	1	1	1	2	2	1	2	1	2	1
366098	2	0	Nitrogen permease regulator 3-like protein; subunit of SEACIT (GATOR1)	–	2	1	1	1	1	2	1	1	1	1	1	1
374354	4	1	Protein required for the transport of Gap1p	–	4	2	1	2	1	1	1	1	1	1	2	1
493094	1	1	Ras homolog	–	4	0	0	0	0	0	0	0	0	0	0	0
517273	3	0	Subunit of SEACAT, a subcomplex of the SEA complex; Mtc1p	–	1	1	1	2	1	2	1	1	1	1	2	1
367284	0	0	Subunit of SEACAT, a subcomplex of the SEA complex; Sea4p	–	1	1	1	1	1	1	1	1	1	1	1	1
440869	2	0	Subunit of TORC1	–	1	1	1	1	1	2	1	1	2	1	1	1

495775	3	1	Subunit of TORC2, RICTOR homolog	–	4	1	1	2	1	1	1	1	0	1	2	1
439934	2	0	Target of rapamycin	–	2	1	1	2	0	1	1	1	1	1	1	1
23387	3	0	Tuberous sclerosis 2 protein homolog	–	2	1	1	2	1	1	1	1	1	1	2	1

Table 18. Summary of developmental expression dynamics of CDE orthogroups of G-protein coupled receptor genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| | Fold change | | | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
283463	6	0	G-protein coupled receptor	YKL039W	2	1	2	2	1	1	2	1	2	1	2	1
263790	4	3	G-protein coupled receptor	–	4	1	0	4	1	4	0	0	0	0	0	2
485193	6	0	G-protein coupled receptor	–	2	2	1	2	2	1	1	2	1	1	2	1
379008	0	0	G-protein coupled receptor	–	1	0	0	0	0	0	0	0	0	0	0	0
489342	1	1	G-protein coupled receptor	–	4	0	0	0	0	0	0	0	0	0	0	0
229833	11	4	G-protein involved in signal transduction	–	2	1	4	2	2	4	2	2	4	2	4	2
479562	11	7	Regulator of G-protein signaling	–	4	4	4	4	2	2	4	1	2	2	4	4
S.c. 2490312	9	6	Putative arrestin	–	0	4	2	4	4	4	1	2	0	4	4	2
473465	10	5	Putative arrestin	–	4	4	4	2	1	2	2	2	4	1	4	2
472370	11	7	Ras superfamily protein	–	4	2	2	4	4	4	1	4	4	2	4	2

Table 19. Summary of developmental expression dynamics of CDE orthogroups of velvet protein encoding genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| | Fold change | | | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
365674	4	1	Velvet factor	–	4	1	1	1	1	1	2	1	2	1	2	1
355684	3	3	Velvet factor	–	4	0	1	0	4	4	0	0	0	0	0	0
374867	6	1	Velvet factor	–	2	1	2	1	2	2	2	1	4	0	1	1
385561	8	5	Velvet factor	–	4	4	1	0	0	4	2	4	4	1	2	2

ID					Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
496341	10	4	Velvet factor	–	4	2	0	2	2	4	2	1	4	2	4	2

Table 20. Summary of developmental expression dynamics of CDE orthogroups of STRIPAK complex protein genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| | Fold change | | | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
51761	1	0	Forkhead-associated domain	–	2	1	1	1	1	1	1	1	1	1	1	1
439971	1	0	Protein phosphatase PP2A regulatory subunit A	YAL016W	1	1	1	1	1	1	1	1	1	1	2	1
280222	5	0	Serine/threonine-protein kinase KIC1	YHR102W	1	1	1	2	2	2	1	2	1	1	2	1
375927	4	0	Factor arrest protein 11	YNL127W	2	1	1	2	1	1	2	1	1	1	2	1
463106	5	2	Serine/threonine-protein phosphatase PP2A-like PPG1	YNR032W	4	1	4	1	1	1	2	2	1	1	2	1
499433	8	2	MOB kinase activator	–	4	2	2	1	2	1	1	4	2	2	2	1
108726	5	0	Striatin	–	2	1	2	2	1	1	1	2	1	1	2	1

Table 21. Summary of developmental expression dynamics of CDE orthogroups of light sensing related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| | Fold change | | | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
492962	9	7	DASH-type cryptochrome	YOR386W	4	1	2	4	4	0	4	2	4	4	4	1
470504	7	2	Phytochrome	–	4	1	0	4	2	0	2	1	2	1	2	2
361584	11	9	*C. cinerea* dst2, putative AA7 family member	–	4	2	4	4	4	4	4	4	4	1	4	2

Table 22. Summary of developmental expression dynamics of CDE orthogroups of chitin biosynthesis genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4.

Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	Fold change >4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
371191	9	4	Glucosamine 6-phosphate N-acetyltransferase	–	4	2	4	4	1	2	2	2	2	1	4	1
538650	6	0	Chitin synthase regulator SKT5	YBL061C	2	1	2	2	2	1	1	2	2	1	1	1
542039	8	1	Chitin synthase 3	YBR023C	2	2	2	4	2	2	1	1	2	1	2	1
357695	7	5	UDP-N-acetylglucosamine pyrophosphorylase	YDL103C	4	2	4	4	4	1	1	2	1	1	4	1
478844	4	1	Phosphoacetylglucosamine mutase involved in chitin precursor synthesis	YEL058W	4	1	1	2	2	1	1	1	1	1	2	1
440525	9	4	Glutamine-fructose-6-phosphate aminotransferase	YKL104C	4	1	4	4	2	2	2	2	2	1	4	1
439486	3	1	Chitin synthase 1	YNL192W	4	1	1	1	1	2	1	1	1	1	2	1
473500	4	2	Cell wall related glycosyltransferase	YPL227C	2	1	4	1	1	1	1	2	1	1	4	1
382141	7	1	Dolichol-phosphate mannosyltransferase	YPR183W	2	1	2	1	1	4	1	2	2	1	2	2
372414	4	2	Cell wall related glycosyltransferase	–	2	4	0	1	2	0	4	1	0	1	0	1
15443	1	1	Chitin synthase	–	4	0	0	0	0	0	0	0	0	0	0	0
234699	3	0	Chitin synthase	–	1	1	2	0	1	1	1	1	2	1	1	2
357091	5	1	Chitin synthase	–	1	1	1	2	2	2	1	1	2	1	4	1
359180	12	10	Chitin synthase	–	4	4	4	4	2	4	4	4	2	4	4	4
493091	8	2	Chitin synthase	–	2	1	4	2	2	2	2	1	2	1	4	1
374670	3	0	Chitin synthase with myosin motor domain	–	2	1	0	2	1	1	1	1	1	1	2	1
497826	5	0	Chitin synthase with myosin motor domain	–	2	1	2	2	1	2	1	1	2	1	1	1
519767	11	6	Glycosyltransferase 2 family protein	–	4	2	4	4	2	4	2	4	2	1	4	2

Table 23. Summary of developmental expression dynamics of CDE orthogroups of glucan biosynthesis related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	Fold change >4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
417746	12	4	Kre9/Knh1 family putative beta-1,6-glucan assembly protein	–	4	2	2	4	2	2	2	2	4	2	4	2
181364	4	0	Smi1 family protein regulating chitin deposition and cell wall assembly	–	2	1	0	2	2	1	1	1	1	1	2	1

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
359282	9	2	Glucosidase 2 subunit alpha	YBR229C	2	1	4	4	2	2	2	2	2	1	2	1
486333	7	0	Mannosyl-oligosaccharide glucosidase	YGL027C	2	1	2	2	2	1	1	2	1	1	2	2
494484	8	6	Glycoside hydrolase 63 family alpha-glucosidase	YMR196W	4	1	4	4	2	1	4	1	4	1	4	2
241938	5	1	Protein ROT1 involvedin regulating cell wall 1,6-beta-glucan level	YMR200W	4	1	2	2	1	1	1	1	2	1	1	2
543646	1	0	1,3-beta-glucanosyltransferase GAS1	YMR307W	2	0	0	0	0	0	0	0	0	0	0	0
447635	3	0	Beta-glucan synthesis-associated protein KRE6	YPR159W	2	1	1	2	1	1	1	1	0	1	2	1
S.c. 2584405	7	6	Beta-1,6-glucan synthase, GH16 family protein	–	0	4	0	2	0	0	4	4	4	1	4	4
432992	6	1	Big1 family protein putetivaly required for beta-1,6-glucan synthesis	–	4	1	2	2	2	2	1	1	2	1	1	1
499280	8	6	Glycoside hydrolase 31 family alpha-glucosidase	–	4	0	1	4	0	4	2	4	4	2	4	0
S.c. 2543909	6	5	Glycoside hydrolase 31 family alpha-glucosidase	–	0	4	2	4	0	0	4	4	0	1	4	1
526754	10	3	Glycoside hydrolase 9 family protein	–	2	2	2	2	1	1	4	4	4	2	2	2
359649	5	4	Kre9/Knh1 family putative beta-1,6-glucan assembly protein	–	4	1	4	4	1	4	2	1	0	1	0	1
465604	10	3	Kre9/Knh1 family putative beta-1,6-glucan assembly protein	–	4	1	2	2	2	4	2	2	2	1	4	2
470186	12	10	Kre9/Knh1 family putative beta-1,6-glucan assembly protein	–	4	2	4	4	4	4	4	2	4	4	4	4
S.c. 2557059	9	9	Kre9/Knh1 family putative beta-1,6-glucan assembly protein	–	0	4	0	4	4	0	4	4	4	4	4	4
528086	6	0	Rho family GTPase RHO1, Ras homolog gene family, member A	YPR165W	2	1	2	2	1	2	1	1	2	1	2	1
446030	7	1	1,3-beta-D-glucan synthase	YGR032W	2	1	2	4	1	2	2	1	2	1	2	1

Table 24. Summary of developmental expression dynamics of CDE orthogroups of chitin remodeling genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			S. cerevisiae ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
360173	7	2	CE4 chitin deacetylase	–	4	1	2	4	0	1	2	2	0	1	2	2
368217	10	9	Glycoside hydrolase 18, chitinase	–	4	4	4	4	4	0	4	4	2	4	0	4
S.c. 85210	9	7	Glycoside hydrolase 18, chitinase	–	0	4	4	2	4	0	4	4	4	2	4	1
543586	7	2	Glycoside hydrolase 18, chitinase	YDR371W	4	1	2	2	2	1	2	2	1	1	4	1

ID	FC>2	FC>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
544873	6	4	Polyamine transporter 2	YGR138C	4	1	0	4	0	2	4	2	0	1	4	1
354859	10	4	Endochitinase	YLR286C	4	2	1	2	4	2	2	4	4	2	2	1
355445	11	8	CE4 chitin deacetylase 1	YLR307W	4	2	2	4	4	1	4	4	4	4	4	2
413423	11	7	CBM5/12 domain protein	–	4	2	4	4	4	2	2	4	4	1	4	2
375733	7	6	CE4 chitin deacetylase	–	4	1	4	4	2	4	1	1	4	1	4	1
377259	10	4	CE4 chitin deacetylase	–	4	4	4	1	4	2	0	2	2	2	2	2
379321	7	5	CE4 chitin deacetylase	–	4	0	4	0	4	2	2	0	4	0	4	0
42776	2	1	CE4 chitin deacetylase	–	4	0	0	0	2	0	0	0	0	0	0	0
440521	7	7	CE4 chitin deacetylase	–	4	4	4	4	4	4	0	0	0	0	4	1
464952	1	1	CE4 chitin deacetylase	–	4	0	0	0	0	0	0	0	0	0	0	0
502602	1	1	CE4 chitin deacetylase	–	4	0	0	0	0	0	0	0	0	0	0	0
358869	8	3	Glycoside hydrolase 18, chitinase	–	4	2	2	0	2	2	4	0	0	1	4	2
470416	9	6	Glycoside hydrolase 18, chitinase	–	4	2	4	4	2	4	0	2	4	0	4	1
488885	10	7	Glycoside hydrolase 18, chitinase	–	4	4	4	4	4	1	4	2	1	4	2	2
90984	1	1	Glycoside hydrolase 18, chitinase	–	4	0	0	0	0	0	0	0	0	0	0	0
91051	9	8	Glycoside hydrolase 18, chitinase	–	4	1	4	4	0	4	4	4	2	4	4	1
446427	8	6	Glycoside hydrolase 20 family putative β-1,6-N-acetylglucosaminidase	–	4	1	4	4	4	0	4	2	0	2	4	1
464567	9	6	Glycoside hydrolase 20 family putative β-1,6-N-acetylglucosaminidase	–	4	1	4	4	4	2	2	4	2	1	4	1
520359	10	7	Glycoside hydrolase family 18 chitinase	–	4	4	0	4	2	4	4	2	0	2	4	4
356467	7	4	GlcN6P deaminase (Nag1 family) involved in cell wall biogenesis	–	4	1	4	0	4	0	2	4	2	2	1	1
454418	9	6	X325 family LPMO-like protein	–	1	2	4	1	2	4	4	4	4	1	4	2

Table 25. Summary of developmental expression dynamics of CDE orthogroups of glucan remodeling related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change				*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
S.c. 2686544	9	9	Beta-1,6-glucan synthase, GH16 family protein		–	0	4	0	4	0	4	4	4	4	4	4	4
546300	10	10	Beta-glucanase; GH5 family		–	1	4	4	4	0	4	4	4	4	4	4	4
464399	10	8	GH71 alpha-1,3-glucanase/beta glucuronidase family protein		–	4	4	4	4	4	4	2	0	4	0	4	2
373418	9	7	Glycoside hydrolase 3 family protein		–	4	1	4	4	4	2	4	0	4	0	2	4
449960	6	2	Probable glycosidase CRH2		YEL040W	4	2	2	1	2	1	1	1	4	2	1	1

Protein ID	FC>2	FC>4	Function	S. cerevisiae	Cc	Aa	Ab	Ao								
376392	11	6	Geranylgeranyl transferase type-1 subunit beta	YGL155W	4	4	4	4	2	4	4	2	2	1	2	2
414471	11	8	Glucan 1,3-beta-glucosidase I/II	YLR300W	4	1	2	4	4	4	4	2	4	4	4	2
389921	10	4	Family 17 glucosidase SCW10	YMR305C	4	4	2	4	4	2	2	2	2	1	2	1
169822	5	5	Beta-1,6-glucan synthase, GH16 family protein	–	4	0	4	4	1	4	1	0	4	0	0	0
381870	5	5	Beta-1,6-glucan synthase, GH16 family protein	–	4	4	1	4	4	1	0	0	0	4	1	0
411452	6	5	Beta-1,6-glucan synthase, GH16 family protein	–	4	1	0	4	0	4	4	4	2	1	0	1
502321	11	9	Beta-1,6-glucan synthase, GH16 family protein	–	4	4	4	4	2	4	4	4	4	1	4	2
373700	9	5	Beta-glucanase; GH5 family	–	4	2	4	4	2	2	2	0	0	0	4	4
496411	7	7	Beta-glucanase; GH5 family	–	4	4	4	1	4	0	4	4	1	1	4	1
505989	11	8	Beta-glucanase; GH5 family	–	4	2	4	4	1	4	4	4	2	4	4	2
22054	9	6	GH71 alpha-1,3-glucanase/beta glucuronidase family protein	–	4	4	2	4	1	2	4	2	0	0	4	4
492754	6	5	GH71 alpha-1,3-glucanase/beta glucuronidase family protein	–	4	0	0	4	0	4	0	1	4	2	4	0
463000	6	5	Glycoside hydrolase 128 family protein, putative β-1,3-glucanase	–	4	1	0	4	1	1	4	1	4	1	2	4
413757	7	5	Glycoside hydrolase 128 family, putative β-1,3-glucanase	–	4	1	4	0	2	4	2	0	4	0	4	1
476698	8	7	Glycoside hydrolase 17 family protein with putative β-1,3-glucan crosslinking activity	–	4	1	4	2	4	4	4	4	4	1	1	1
369876	10	4	Glycoside hydrolase 3 family protein	–	4	2	4	4	2	2	2	4	2	1	1	2
405828	9	8	Glycoside hydrolase 3 family protein	–	4	4	4	4	4	0	2	4	4	1	4	1
S.c. 2629974	8	6	Glycoside hydrolase 3 family protein	–	0	4	2	4	4	0	4	4	2	1	4	1
454337	1	1	Glycoside hydrolase family 55 putative β-1,3-glucanase	–	4	0	0	0	0	0	0	0	0	0	0	0
381637	11	9	Glycoside hydrolase family protein with putative glucan crosslinking activity	–	4	4	4	4	4	4	2	4	4	4	2	1
494762	10	3	PL8 family chondroitin lyase	–	4	2	2	0	2	2	0	4	2	2	4	2
543210	6	6	Alginate lyase	–	4	0	4	0	4	0	0	4	4	1	4	0
492834	11	9	Pectate lyase family protein	–	4	2	4	4	4	4	4	4	4	4	2	1
496344	7	7	Thaumatin/GH152 family protein	–	4	1	0	4	0	4	4	4	1	4	0	4
456054	10	8	WSC family protein , putative b-1,3-exoglucanase	–	4	0	4	4	4	4	4	2	4	2	4	0
528086	6	0	Rho family GTPase RHO1, Ras homolog gene family, member A	YPR165W	2	1	2	2	1	2	1	1	2	1	2	1

Table 26. Summary of developmental expression dynamics of CDE orthogroups of miscellaneous cell wall remodeling genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A.*

ostoyae, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
384105	9	6	Glucunoryl hydrolase; GH88	–	2	4	4	4	4	2	1	4	2	1	4	1
A.o. 254810	7	5	Glycoside hydrolase; family 27	–	0	4	0	4	2	0	4	0	4	2	4	0
A.o. 269656	8	6	Glycoside hydrolase; family 27	–	0	4	4	1	4	2	4	4	4	0	0	2
S.c. 2614029	7	6	Pectinesterase	–	0	4	4	1	1	2	1	4	1	4	4	4
470689	9	8	Beta-glucuronidase	–	4	0	4	4	2	4	4	4	4	1	4	0
S.c. 2633734	5	4	GT18 α-1,3(6)-mannosylglycoprotein β-1,6-N-acetyl-glucosaminyltransferase	–	0	4	4	0	1	2	0	0	1	0	4	4

Table 27. Summary of developmental expression dynamics of CDE orthogroups of multicopper oxidase genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
408308	0	0	*C. cinerea* laccase lcc1	–	1	0	0	0	0	0	0	0	0	0	0	0
378517	0	0	*C. cinerea* laccase lcc15	–	1	0	0	0	0	0	0	0	0	0	0	0
443425	1	1	*C. cinerea* laccase lcc5	–	4	0	0	0	0	0	0	0	0	0	0	0
467038	0	0	*C. cinerea* laccase lcc6	–	1	0	0	0	0	0	0	0	0	0	0	0
89107	0	0	*C. cinerea* laccase lcc7	–	1	0	0	0	0	0	0	0	0	0	0	0
368135	10	4	*C. cinerea* laccase lcc15	–	4	4	4	2	2	2	0	2	2	0	4	2
353997	9	4	Cupredoxin	–	4	1	4	4	2	2	1	2	4	1	2	2
501548	5	3	Iron transport multicopper oxidase FET3	YMR058W	4	0	4	4	1	0	2	0	0	1	2	0
266892	2	1	*C. cinerea* laccase lcc3	–	2	0	0	0	0	0	4	0	0	0	0	0
440170	2	2	*C. cinerea* laccase lcc8	–	4	0	4	0	0	0	0	0	0	0	0	0
A.o. 257754	7	7	Cupredoxin	–	0	0	1	4	4	1	4	4	4	4	4	0
356026	9	7	Cupredoxin	–	4	1	0	4	4	4	4	2	4	2	4	1
409847	5	3	Cupredoxin	–	4	4	0	0	2	4	0	0	0	0	1	2
441442	9	4	Cupredoxin	–	4	1	1	4	0	2	4	2	4	2	2	2
451850	6	5	Cupredoxin	–	4	2	4	4	1	0	0	0	4	1	4	0
497434	6	5	Cupredoxin	–	4	0	0	1	4	4	4	0	4	0	2	0

Table 28. Summary of developmental expression dynamics of CDE orthogroups of expansin genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune.*

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
439071	6	5	Cerato-platanin	–	4	4	0	4	4	0	2	0	0	0	0	4
544218	8	8	Cerato-platanin	–	4	0	0	4	0	4	4	4	4	1	4	4
461698	10	5	Expansin	–	4	2	4	2	4	4	4	1	0	2	2	2
467907	11	10	Expansin	–	4	4	2	4	0	4	4	4	4	4	4	4
496836	12	10	Expansin	–	4	4	4	4	4	2	4	4	4	2	4	4

Table 29. Summary of developmental expression dynamics of CDE orthogroups of miscellaneous cell wall related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune.*

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
380322	6	4	*C. cinerea* Eln3	–	4	0	4	4	1	4	2	0	2	0	0	0
407604	5	5	Dye decolorising peroxidase	–	4	0	0	4	4	4	0	0	0	0	4	0
447925	10	7	*C. cinerea* Cfs1	–	4	4	4	2	1	1	4	4	4	2	4	2
469460	8	6	Cellobiose dehydrogenase	–	4	0	0	4	2	1	4	4	4	2	4	0
442333	11	7	Chloroperoxidase	–	4	2	4	4	4	2	4	2	4	1	4	2
479688	10	7	Chloroperoxidase	–	4	4	0	4	2	2	4	2	4	1	4	4
263775	9	7	Glyoxal oxidase	–	4	0	2	4	4	2	0	4	4	4	4	0
440836	10	10	Glyoxal oxidase	–	4	4	1	4	4	0	4	4	4	4	4	4
413665	8	5	Mitogen-activated serine/threonine-protein kinase SLT2	YHR030C	2	1	4	4	1	4	2	2	4	1	4	1

Table 30. Summary of developmental expression dynamics of CDE orthogroups of hydrophobin genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 -

developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
99661	7	7	Hydrophobin	–	1	4	0	0	4	1	4	4	0	4	4	4
419467	6	6	Hydrophobin	–	4	4	4	4	0	4	1	0	0	1	0	4

Table 31. Summary of developmental expression dynamics of genes belonging to conserved lectin orthogroups across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
353931	8	7	RicinB lectin protein	–	4	4	0	4	4	0	4	0	0	2	4	4
495335	9	9	RicinB lectin protein	–	4	1	4	4	4	4	0	4	4	1	4	4

Table 32. Summary of developmental expression dynamics of CDE orthogroups of cell surface protein encoding genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
493867	6	1	Fasciclin	YOR100C	2	2	2	2	1	1	1	1	1	1	2	4
186809 S.c.	6	5	Con6 family cell surface protein	–	4	2	0	4	0	0	4	1	0	1	4	4
2624349	5	5	Con6 family cell surface protein	–	0	4	0	0	0	0	4	0	4	0	4	4
361136	7	4	Fasciclin	–	4	1	2	4	2	2	0	4	0	1	4	1
437384	7	5	Fasciclin	–	1	4	4	1	4	2	4	4	0	1	2	0
419688	7	5	PriA family protein	–	4	2	4	0	4	1	4	1	0	2	0	4
470234	6	6	Con6 family cell surface protein	–	1	4	4	0	0	0	4	0	4	0	4	4

ID	>2	>4	Putative function	S.c. ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
359866	9	7	PriA family protein	–	1	4	4	2	4	2	4	4	4	1	4	1
S.c. 2681702	8	7	PriA family protein	–	0	4	2	4	0	4	4	0	4	0	4	4
501135	9	9	AA7 chitooligosaccharide oxidase	–	4	1	4	4	1	4	4	4	4	0	4	4
513409	9	7	AA7 chitooligosaccharide oxidase	–	4	1	4	4	4	4	4	1	2	1	4	2
A.o. 269613	6	5	Aspartic peptidase	–	0	0	1	4	4	4	0	4	0	2	4	0
442743	10	10	Aspartic peptidase	–	4	4	4	4	4	0	4	4	0	4	4	4
S.c. 75642	9	9	Aspartic peptidase	–	0	4	0	4	4	4	4	4	4	4	0	4
367835	10	8	Peptidase M20	–	4	2	4	4	0	2	4	4	4	0	4	4
S.c. 2547616	8	7	Serine carboxypeptidase	–	0	2	1	4	4	4	4	4	4	0	4	1
S.c. 2645761	8	7	Serine carboxypeptidase	–	0	4	4	4	4	1	2	4	4	4	1	1
462300	10	7	Serine carboxypeptidase S28	–	4	2	4	4	2	4	1	2	4	4	4	1

Table 33. Summary of developmental expression dynamics of CDE orthogroups of defense-related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| ID | Fold change | | Putative function | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
185637	9	5	CFEM domain containing protein	–	4	1	4	4	2	2	2	2	4	1	4	1
439390	9	6	CFEM domain containing protein	–	4	4	4	4	2	2	2	4	0	1	1	4
485770	7	5	RicinB lectin protein	–	4	2	4	0	0	1	4	2	0	0	4	4

Table 34. Summary of developmental expression dynamics of CDE orthogroups of terpene synthase genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| ID | Fold change | | Putative function | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc

ID	>2	>4	Function	S. cerevisiae	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
361541	8	5	Phenylalanine ammonia-lyase	–	4	1	4	2	4	4	0	0	2	0	4	2
386671	11	9	Phenylalanine ammonia-lyase	–	4	2	4	4	4	4	2	4	4	4	4	1
446258	11	8	Putative polyketide synthase	YER061C	4	4	4	4	4	1	2	2	2	4	4	4
394772	4	2	Putative terpene synthase	–	4	0	1	4	1	2	1	1	1	1	2	0
443805	3	2	Putative terpene synthase	–	4	0	2	0	0	0	0	1	0	0	4	0
495900	1	1	Putative terpene synthase	–	1	0	0	0	4	0	0	1	1	0	1	0
124670	5	2	Putative terpene synthase	–	4	0	1	4	1	2	0	2	1	0	2	0
30510	9	8	Putative terpene synthase	–	4	4	4	4	4	4	4	2	0	1	4	1
469738	10	8	Putative terpene synthase	–	1	1	4	4	4	4	4	2	4	4	4	2
201523	1	1	Putative terpene synthase	–	4	0	0	0	0	0	0	0	0	0	0	0

Table 35. Summary of developmental expression dynamics of CDE orthogroups of cytoskeleton-related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
130811	3	1	LisH domain protein	–	4	1	1	2	0	2	1	1	0	1	0	1
504216	9	1	Misato tubulin	–	2	4	2	2	2	1	2	1	2	1	2	2
455153	4	0	Actin cytoskeleton-regulatory complex protein PAN1	YIR006C	2	1	2	1	1	2	1	1	1	1	2	1
496271	3	0	Adenyl cyclase associated protein	YNL138W	2	1	1	1	1	1	1	2	1	1	2	1
356686	6	1	Predicted Rho GTPase	–	2	1	2	1	1	2	2	1	4	1	2	1
381381	11	8	Agaricales-specific Rho GTPase Activating Protein	–	4	4	2	4	4	4	2	2	4	1	4	4
472493	4	0	Potential dynactin complex member	–	2	1	1	2	1	1	1	2	2	1	1	1
61699	5	1	Actin	YFL039C	1	2	2	2	2	1	1	1	1	1	4	1
258718	5	1	Myosin	YHR023W	2	1	1	1	1	2	2	2	1	1	4	1
473079	4	2	Myosin	YMR109W	4	1	2	1	1	2	1	1	1	1	4	1
419142	2	0	Myosin	YOR326W	2	1	1	1	1	1	1	1	1	1	2	1
461274	2	0	Protein SLA2	–	1	1	2	1	1	1	2	1	1	1	1	1
13965	2	0	Actin depolymerization related protein	YCR088W	2	1	1	1	1	1	1	1	1	1	2	1
505644	6	2	Cofilin-homolog protein	YDR063W	2	1	4	0	2	1	2	2	1	1	4	1
448482	6	3	Fimbrin	YDR129C	4	1	4	0	2	1	1	2	2	1	4	1
59959	3	0	Twinfilin	YGR080W	2	1	1	2	1	1	1	1	1	1	2	1
366601	4	0	F-actin capping protein	YIL034C	2	1	2	2	1	1	1	1	0	1	2	1
466954	1	0	Tropomyosin	YIL138C	2	0	0	0	0	0	0	0	0	0	0	0
443986	4	1	Actin capping protein	YKL007W	4	1	2	1	1	1	1	1	2	1	2	1
370292	2	0	Cofilin	YLL050C	1	1	1	2	1	1	1	1	0	1	2	1

484047	8	5	Profilin	YOR122C	4	1	4	4	2	1	2	4	2	1	4	0
444584	5	0	Actin filament binding protein	YPL242C	2	1	2	2	1	2	1	1	2	1	1	1
126636	3	0	Coactosin	–	2	1	1	2	1	1	1	1	0	1	2	1
355823	0	0	Villin/Gelsolin	–	1	0	0	0	0	0	0	0	0	0	0	0
376343	4	0	Villin/Gelsolin	–	1	1	2	2	1	2	1	2	1	1	0	1
358108	3	1	Arp2/3 complex member	YBR234C	4	1	2	1	1	1	1	1	1	1	2	1
130742	3	0	Arp2/3 complex member	YDL029W	2	1	2	1	0	1	2	1	1	1	1	1
498732	4	1	Arp2/3 complex regulating protein	YDL146W	4	1	1	1	1	1	2	1	1	2	2	1
114966	6	1	Arp2/3 complex member	YIL062C	2	1	4	1	2	2	2	1	0	1	2	1
57120	6	0	Formin	YIL159W	2	1	2	2	1	2	1	1	2	1	2	1
415488	3	0	Arp2/3 complex member	YJR065C	1	2	2	0	1	1	1	1	1	1	2	1
192562	2	0	Arp2/3 complex member	YKL013C	1	1	2	1	1	1	1	1	0	1	2	1
493018	2	0	Verprolin	YLR337C	2	1	0	1	0	1	1	1	0	0	2	1
421678	4	1	Arp2/3 complex member	YLR370C	1	1	2	1	1	1	2	1	2	1	4	1
148867	2	0	Formin	YNL271C	2	1	1	1	1	1	2	1	0	1	1	1
546441	1	0	Arp2/3 complex member	YNR035C	2	1	1	1	0	1	1	1	1	1	1	1
465398	6	0	WASP protein	YOR181W	2	1	1	2	0	2	1	1	2	1	2	2
544540	8	4	WASP protein	–	4	1	2	4	2	2	4	4	2	1	0	1
176636	5	2	Alpha tubulin	–	4	1	2	0	1	1	1	2	0	2	1	4
393528	6	1	Beta-tubulin	YFL037W	2	2	2	1	1	1	2	2	0	4	1	1
359665	4	1	Alpha tubulin	YML085C	4	2	0	0	1	1	2	1	1	1	2	1
519006	3	1	Beta tubulin	–	2	1	4	1	1	1	2	1	1	1	1	1
494087	3	1	Kinesin	–	4	1	1	1	1	1	2	1	2	1	1	1
3150	6	0	Kinesin	–	2	1	2	1	2	2	1	1	2	1	2	1
447928	3	0	Kinesin	–	2	1	1	1	1	1	1	1	2	1	2	1
461075	12	9	Kinesin	–	4	4	4	4	2	4	4	4	4	2	2	4
367694	9	5	Kinesin	YDR424C	4	2	2	0	2	4	2	4	1	1	4	4
410146	12	7	Kinesin	YPL155C	2	4	4	2	2	4	4	4	4	2	2	4
494863	10	4	Kinesin	–	4	2	2	4	2	2	4	4	2	1	2	1
113001	6	0	Microtubule plus end tracking protein	YER016W	2	1	1	2	1	1	2	2	2	1	2	1
527694	4	1	Tubulin specific chaperone.	–	2	1	2	2	1	1	1	1	1	1	4	1
441578	6	1	Gamma-tubulin comlex member	YHR172W	2	1	1	2	0	2	2	1	2	1	4	1
361158	7	1	Gamma tubulin	YLR212C	4	1	1	2	2	1	2	2	2	1	2	1
156038	5	2	Gamma-tubulin comlex member	YNL126W	4	1	1	2	1	1	2	2	1	1	4	1
357668	5	0	Gamma-tubulin comlex member	–	1	2	1	2	1	1	1	1	2	2	2	1
358462	6	1	Gamma-tubulin comlex member	–	4	2	1	2	2	1	2	2	1	1	1	1
463163	4	1	Gamma-tubulin comlex member	–	2	1	1	1	1	2	4	1	1	1	2	1
474549	4	0	Dynactin complex member protein	–	2	1	1	1	1	1	2	2	1	1	2	1
447285	9	2	Dynactin complex member protein	–	2	1	1	2	2	2	4	2	4	1	2	2
454161	4	0	Dynactin complex member protein	–	2	1	1	2	1	1	2	1	0	1	2	1
488749	3	0	Dynactin complex member protein	–	2	1	1	1	1	1	1	1	1	1	2	2
437053	3	1	Dynactin complex member protein	YOR269W	2	1	1	1	1	1	1	1	4	1	2	1
415573	9	8	Septin	–	4	4	4	4	4	4	0	4	4	1	0	2

ID	>2	>4	Putative function	S. cerevisiae ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
455217	10	7	Septin	YCR002C	4	2	4	4	4	2	4	4	1	1	4	2
367587	10	6	Septin	YHR107C	4	2	4	4	4	2	4	2	2	1	4	1
481878	6	3	Septin	YJR076C	2	1	4	4	2	1	2	0	0	0	4	1
416864	8	4	Septin	YLR314C	4	2	4	4	2	1	2	2	1	1	4	1
103773	5	1	Septin	–	4	1	1	2	1	1	2	2	2	1	1	1
103809	5	2	Septin	–	4	1	2	1	1	2	2	1	4	1	1	1
413977	4	2	Tubulin binding cofactor A	–	2	1	1	1	1	1	1	2	4	1	4	1
362068	4	0	Tubulin binding cofactor D	–	2	1	1	2	1	1	2	1	2	1	1	1

Table 36. Summary of developmental expression dynamics of CDE orthogroups of Cop9 signalosome genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

	Fold change			*S. cerevisiae* ortholog	Species											
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
357329	9	5	Proteasome component	–	4	2	4	2	1	2	4	4	1	1	4	2
502637	6	0	Defective-in-cullin neddylation protein	–	1	0	1	2	2	2	1	1	2	1	2	2
496080	4	2	Nedd8-like ubiquitin	–	2	1	4	1	0	2	1	1	0	1	4	1
438017	7	1	COP9 signalosome complex subunit 5	YDL216C	4	1	2	2	1	2	2	2	2	1	1	1
497773	3	0	Ubiquitin carboxyl-terminal hydrolase 12	YJL197W	1	1	1	1	0	2	2	1	1	1	2	1
494197	4	0	Cop9 signalosome complex subunit 12	YJR084W	2	2	1	1	1	1	1	1	1	1	2	2
450685	3	0	NEDD8-conjugating enzyme UBC12	YLR306W	2	1	1	1	1	2	1	1	2	1	1	1
503638	7	0	NEDD8-activating enzyme E1 regulatory subunit	YPL003W	2	2	2	2	1	1	1	2	2	1	2	1
485679	8	3	NEDD8-activating enzyme E1 catalytic subunit	YPR066W	4	2	4	2	1	1	2	2	4	1	2	1
237692	9	4	Ubiquitin carboxyl-terminal hydrolase	–	4	1	4	2	1	2	4	2	2	2	4	1
439373	5	0	COP9 signalosome complex subunit 1	–	2	1	1	2	1	1	1	2	2	1	2	1
204652	3	0	COP9 signalosome complex subunit 3	–	2	1	1	1	1	1	2	1	2	1	1	1
444512	3	0	COP9 signalosome complex subunit 4	–	2	1	2	1	1	1	1	2	1	1	0	1
390754	4	0	COP9 signalosome protein	–	1	1	2	2	1	1	2	1	1	1	2	1
35248	4	0	COP9 signalosome subunit 6 protein	–	1	1	1	2	1	1	2	2	1	1	2	1
437024	4	1	Csn8 subunit protein	–	2	1	1	1	1	1	2	1	2	1	4	1
442909	2	0	Proteasome component	–	1	1	1	1	2	1	2	1	1	1	1	1
255029	2	0	COP9 signalosome complex subunit 2	–	2	0	1	1	1	1	1	1	2	1	1	1

Table 37. Summary of developmental expression dynamics of CDE orthogroups of protein ubiquitination and the proteasome related genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| | Fold change | | | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
354939	11	5	BTB/POZ domain containing protein	–	4	1	2	4	4	2	2	4	2	2	4	2
379603	9	8	BTB/POZ domain containing protein	–	4	4	1	4	0	4	4	2	0	4	4	4
383774	7	5	BTB/POZ domain containing protein	–	4	2	0	4	4	2	0	0	0	0	4	4
405851	7	5	BTB/POZ domain containing protein	–	4	0	0	2	2	4	4	0	4	0	4	0
446662	5	5	BTB/POZ domain containing protein	–	4	0	4	1	4	4	0	1	1	1	4	0
449824	8	8	BTB/POZ domain containing protein	–	4	4	1	4	0	4	4	1	4	1	4	4
451372	9	4	BTB/POZ domain containing protein	–	2	4	4	2	1	1	2	2	4	1	2	4
459680	11	8	BTB/POZ domain containing protein	–	4	2	4	4	4	4	4	4	4	1	2	2
374447	10	7	BTB/POZ domain containing protein	–	4	4	4	4	2	1	0	2	2	4	4	4
545078	5	1	BTB/POZ domain containing protein	–	2	2	1	2	0	2	1	1	4	1	1	1
358351	5	0	Orthologs of *A. nidulans* GrrA	–	2	1	1	2	2	1	1	1	2	1	2	1
447658	10	5	F-box protein	–	4	4	1	4	1	2	4	2	4	2	2	2
503496	9	5	F-box protein	–	4	1	4	4	2	2	4	4	2	1	2	1
145676	10	6	F-box protein	–	4	2	4	4	2	4	4	2	4	1	2	1
359613	10	6	F-box protein	–	2	2	4	4	4	2	4	4	4	1	2	1
470790	10	6	F-box protein	–	4	2	4	4	2	4	4	2	4	1	1	2
166096	9	7	F-box protein	–	4	0	0	4	2	4	4	4	4	2	4	0
356986	9	6	F-box protein	–	4	1	4	4	2	4	2	2	4	1	4	1
377171	7	2	F-box protein	–	2	2	2	4	1	1	1	2	4	1	1	2
382134	7	4	F-box protein	–	4	1	1	4	2	1	4	2	0	1	4	2
438595	7	7	F-box protein	–	4	1	0	4	1	4	4	0	4	1	4	4
445665	8	7	F-box protein	–	4	1	4	4	4	4	4	2	4	1	0	1
451935	7	6	F-box protein	–	1	4	1	4	0	4	0	4	0	4	4	2
471789	6	6	F-box protein	–	4	1	4	4	4	4	4	0	1	0	0	1
490594	7	3	F-box protein	–	4	1	1	2	2	1	4	1	2	1	4	2
501200	12	9	F-box protein	–	4	4	4	4	4	4	4	2	2	2	4	4
440772	11	7	RING-type zinc finger domain containing protein	–	4	4	2	4	2	2	2	0	4	4	4	4

ID	FC>2	FC>4	Function	S.c.	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
364816	10	3	RING-type zinc finger domain containing protein	–	2	1	4	2	2	2	4	2	2	4	2	1
378120	8	8	RING-type zinc finger domain containing protein	–	4	4	0	4	4	1	4	1	4	0	4	4
455937	9	2	RING-type zinc finger domain containing protein	–	4	2	2	2	0	4	2	2	2	1	2	0
466739	10	7	RING-type zinc finger domain containing protein	–	4	2	2	4	4	1	4	4	4	2	4	1
467805	10	7	RING-type zinc finger domain containing protein	–	2	1	4	4	4	2	4	2	4	4	4	1
543850	11	9	RING-type zinc finger domain containing protein	–	4	4	2	4	4	2	4	4	0	4	4	4

Table 38. Summary of developmental expression dynamics of CDE orthogroups of transporter encoding genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| | Fold change | | | *S. cerevisiae* ortholog | Species | | | | | | | | | | | |
ID	>2	>4	Putative function		Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
538158	8	5	Ammonium/urea transporter	–	4	1	0	4	0	4	2	2	4	1	4	2
404532	9	5	Major facilitator superfamily protein	–	4	1	0	2	4	2	4	0	4	2	4	2
492885	9	5	Major facilitator superfamily protein	–	4	1	2	2	1	1	2	4	4	2	4	4
S.c. 2537163	9	5	Multi antimicrobial extrusion protein	–	0	2	0	4	4	2	2	4	4	1	4	2
233439	9	6	Tetrapeptide transporter; OPT1/isp4 family	–	2	4	2	4	4	1	4	4	1	2	4	1
30849	11	6	10TM phosphate transporter	–	4	4	2	4	4	2	2	2	4	1	4	2
371400	11	9	Major facilitator superfamily protein	–	4	1	4	4	4	4	4	4	2	4	4	2
464027	7	6	Major facilitator superfamily protein	–	4	1	4	0	4	4	2	0	4	1	4	1
468563	6	6	Major facilitator superfamily protein	–	4	4	0	4	1	0	4	1	0	4	4	1
501434	9	9	Major facilitator superfamily protein	–	4	0	4	4	4	4	4	4	1	4	1	1
436779	10	0	Nuclear pore protein 84/107	–	2	2	2	2	1	1	2	2	2	2	2	2
S.c. 2283957	8	6	Sugar/inositol transporter	–	0	2	0	4	4	4	4	4	0	1	4	2
355160	10	9	Threonine/Serine exporter; ThrE	–	4	4	1	4	4	4	2	4	2	1	4	4
432854	10	6	Membrane transport protein family	YBR287W	4	2	2	4	4	2	4	4	1	1	2	4
449861	10	4	GABA-specific permease	YDL210W	2	1	4	2	4	1	2	4	4	2	2	2
428934	10	6	Sugar transporter STL1	YDR536W	4	2	4	4	4	4	4	1	2	1	2	2
422892	10	2	Purine-cytosine permease FCY2	YER056C	2	2	4	2	4	2	1	2	2	2	2	1
455616	5	5	Zinc-regulated transporter 1	YGL255W	4	1	4	4	0	4	4	1	1	1	1	1

ID			Name	Gene												
465413	9	6	Urea transporter	YHL016C	4	1	0	4	4	4	4	2	4	1	2	2
496395	9	7	Oligopeptide transporter 1	YJL212C	4	4	2	4	4	1	4	2	4	1	4	0
502591	9	6	Polyamine transporter 1	YLL028W	4	2	4	1	1	2	4	4	4	0	2	4
360410	9	8	Thiamine pathway transporter THI73	YLR004C	4	1	4	4	1	4	4	4	4	1	4	2
495380	7	1	Transmembrane 9 superfamily member 1	YLR083C	4	2	2	2	1	1	2	1	0	1	2	2
223186	11	3	Inorganic phosphate transporter PHO84	YML123C	4	1	2	2	2	4	2	2	2	2	4	2
393558	10	6	Vacuolar basic amino acid transporter 1	YMR088C	4	4	2	4	2	1	4	2	1	4	2	4
502991	10	6	Major facilitator superfamily protein	YMR279C	4	4	4	4	2	2	4	2	0	1	4	2
421680	7	3	Calcium channel YVC1	YOR087W	2	2	2	4	1	1	4	1	1	1	2	4
542873	10	5	ATP-dependent permease PDR12	YPL058C	2	2	2	4	2	4	1	2	4	1	4	4
462297	10	2	Sulfate transporter YPR003C	YPR003C	2	1	2	4	2	2	2	2	4	1	2	2
S.c. 2501677	9	6	Aquaporin	–	0	4	4	4	2	1	4	2	4	1	4	2
A.o. 253413	6	6	Major facilitator superfamily protein	–	0	0	4	4	0	4	4	4	0	0	4	0
493842	9	6	Major facilitator superfamily protein	–	4	1	4	4	4	2	2	1	4	1	4	2
495288	8	6	Major facilitator superfamily protein	–	4	4	2	4	4	4	0	4	1	1	2	1
496145	9	7	Sugar/inositol transporter	–	4	4	1	4	2	1	4	4	4	2	4	1
498282	10	6	Major facilitator superfamily protein	–	4	2	2	4	1	4	4	2	2	4	4	1
474705	10	6	ABC transporter	–	4	2	0	4	2	4	4	1	2	2	4	4
357414	6	5	Major facilitator superfamily protein	–	4	1	4	4	1	0	0	4	2	1	4	1
420930	8	7	Major facilitator superfamily protein	–	4	4	4	4	2	4	4	1	0	1	4	1
463045	9	6	Major facilitator superfamily protein	–	4	2	4	4	2	4	0	2	0	1	4	4
465489	9	5	Major facilitator superfamily protein	–	4	1	4	4	0	1	2	2	4	2	4	2
488859	9	5	Mitochondrial substrate/solute carrier	–	4	2	4	2	4	1	2	1	4	1	4	2
451236	10	2	Secretory carrier membrane proteins (SCAMP)	–	2	2	1	4	2	2	4	2	2	1	2	2
374240	10	8	Sodium/calcium exchanger	–	4	1	0	4	2	4	4	2	4	4	4	4
450674	9	7	Sugar phosphate transporter	–	4	2	4	4	2	1	4	4	4	1	4	1
537526	10	7	Sugar phosphate transporter	–	4	4	2	4	4	2	2	1	4	1	4	4
358584	7	5	Sugar/inositol transporter	–	4	4	2	4	1	0	1	4	1	1	4	2
487841	11	8	Sugar/inositol transporter	–	4	4	4	4	2	4	4	4	2	2	1	4
502428	7	5	Sugar/inositol transporter	–	4	2	2	4	1	1	1	4	4	1	4	1
S.c. 2627703	6	5	Sugar/inositol transporter	–	0	2	4	4	0	0	4	0	4	0	0	4
397645	9	6	High glucose sensor RGT2	YDL138W	4	4	4	2	0	1	2	2	4	1	4	4
463015	8	7	Hexose transporter HXT10	YFL011W	4	4	0	4	4	0	4	4	0	1	4	2

Table 39. Summary of developmental expression dynamics of CDE orthogroups of stress response genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

ID	Fold change >2	>4	Putative function	*S. cerevisiae* ortholog	Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
475934	7	7	12 kDa heat shock protein	YFL014W	4	4	0	4	0	0	4	4	1	1	4	4
457314	8	5	ATP-dependent molecular chaperone HSC82	YMR186W	4	1	4	4	2	1	4	1	2	1	4	2
492695	6	5	Highly conserved plasma membrane protein	–	4	1	4	4	0	4	0	2	0	0	0	4
496981	9	7	Small heat shock protein HSP20	–	4	2	2	4	1	4	4	4	4	1	4	1
23471	11	5	Endoplasmic reticulum chaperone BiP	YJL034W	4	2	4	2	4	2	2	4	2	2	4	1
367102	11	6	Small heat shock protein HSP20	–	2	2	4	4	2	4	4	4	4	2	2	1
420157	8	5	Catalase	–	4	2	2	2	4	0	0	4	0	4	4	1
472224	11	7	Peroxisomal catalase A	YDR256C	4	2	4	4	2	2	2	4	4	1	4	4
432313	11	11	D-arabinono-1;4-lactone oxidase	YML086C	4	4	4	4	4	4	4	4	4	1	4	4
365550	7	2	D-arabinono-1;4-lactone oxidase	YMR041C	2	2	2	4	0	1	2	2	0	1	4	1
356399	11	8	Ergothioneine biosynthesis protein Egt1	–	4	2	4	4	4	4	4	2	2	1	4	4
355021	9	7	Peroxiredoxin	YBL064C	4	2	0	4	2	4	4	4	4	1	4	1
258252	5	4	Ergothioneine biosynthesis protein Egt2	–	4	1	4	1	4	2	1	4	1	1	1	1
28769	8	2	Glutathione peroxidase-like peroxiredoxin 2	YBR244W	4	1	4	2	2	2	2	2	0	1	2	1
415694	7	0	Monothiol glutaredoxin-6	YDL010W	2	1	2	1	1	1	1	2	2	2	2	2
441808	7	3	Glutaredoxin	YDR513W	2	2	2	4	1	4	4	1	1	1	2	1
378207	5	1	Monothiol glutaredoxin-4	YER174C	1	1	1	2	4	2	1	1	2	1	1	2
412620	5	2	Glutamate--cysteine ligase	YJL101C	4	1	4	2	1	2	2	1	1	1	1	1
370027	5	1	Glutathione synthetase	YOL049W	4	1	1	2	1	1	2	2	1	1	2	1
356216	7	1	Monothiol glutaredoxin-5, mitochondrial	YPL059W	2	1	2	1	0	2	2	2	2	1	4	1
499716	5	3	Gluthatione reductase	YPL091W	1	1	4	2	1	4	1	2	0	1	4	1
39451	7	3	Glutaredoxin	–	4	2	4	2	1	1	2	2	4	1	0	1
378471	4	0	Peroxiredoxin	–	1	1	1	2	2	1	1	2	0	1	2	1
379600	9	6	Peroxiredoxin DOT5	YIL010W	4	4	1	4	4	2	4	2	1	1	4	2
444300	10	4	Peroxiredoxin AHP1	YLR109W	4	1	4	4	2	2	2	2	2	1	4	2
468305	12	8	Peroxiredoxin TSA1	YML028W	4	2	4	4	2	4	2	4	4	4	4	2
437202	8	6	Peroxiredoxin	–	4	1	2	4	2	4	4	0	4	0	4	1
449056	9	7	Peroxiredoxin	–	4	2	4	4	2	1	4	4	1	1	4	4
S.c. 263240	5	3	Peroxiredoxin	–	0	2	0	0	0	0	4	4	0	0	4	2

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Table 40. Summary of developmental expression dynamics of CDE orthogroups of ferric reductase genes across 12 species. Protein ID of a representative protein is given follows by the number of species in which the orthogroup is developmentally regulated at fold change 2 and 4 (FC>2 and FC>4, respectively). Putative function and ortholog in *S. cerevisiae* (if any) are also given. Abbreviations: 0-gene absent, 1-gene present but not developmentally regulated, 2 - developmentally regulated at fold change >2, 4- developmentally regulated at fold change >4. Species names are abbreviated as: Cc – *C. cinerea*, Aa – *A. ampla*, Ab – *A. bisporus*, Ao – *A. ostoyae*, Ca – *C. aegerita*, Lb – *L. bicolor*, Le – *L. edodes*, Lt – *L. tigrinus*, Mk – *M. kentingensis*, Pc – *Ph. chrysosporium*, Po – *P. ostreatus*, Sc – *S. commune*.

| ID | Fold change | | Putative function | S. cerevisiae ortholog | Species | | | | | | | | | | | |
	>2	>4			Cc	Aa	Ab	Ao	Ca	Lb	Le	Lt	Mk	Pc	Po	Sc
354442	9	5	Ferric reductase	–	4	0	4	4	0	4	4	2	2	2	2	1
152927	9	5	Ferric reductase	YOR384W	4	1	1	2	4	2	4	2	4	4	2	1
260659	5	1	Ferric reductase	–	1	1	4	2	2	1	1	1	2	1	2	1
448679	3	1	Ferric reductase	–	1	1	2	1	1	1	1	1	4	1	2	1
461481	4	0	Ferric reductase	–	2	1	2	2	2	1	1	1	0	1	1	1