1 **iHypoxia: an integrative database of the expression** 2 **dynamics of proteins in response to hypoxia in animals**

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17

18 **Running title**

19 *Liu Z et al / iHypoxia: a database of expression dynamics of proteins in*
20 *response to hypoxia*

21

22 This paper has a total of 5875 words, 56 references, 1 table, 7 figures, and 2
23 supplementary tables.

24 **Abstract**

25 Decreased oxygen concentrations (hypoxia) outside of the physiological range
 26 may severely subvert cell, tissue, and organism survival. Mammals have
 27 evolved mechanisms to sense hypoxia and induce a series of hypoxic
 28 responses. In recent years, high-throughput techniques have greatly promoted
 29 global perturbation studies of protein expression during hypoxia, and these
 30 studies have contributed to the understanding of the complex regulatory
 31 networks of hypoxia. In this study, we developed an integrated resource for the
 32 expression dynamics of proteins in response to hypoxia (iHypoxia), which
 33 contains 1,629 expression events of 1,215 proteins identified by
 34 low-throughput experiments (LTEs) and 154,953 quantitative expression
 35 events of 36,194 proteins identified by high-throughput experiments (HTEs)
 36 from five mammals that exhibit a response to hypoxia. Various experimental
 37 details such as the hypoxic experimental conditions, expression patterns, and
 38 samples were carefully collected and integrated. In addition, we conducted an
 39 orthologous search and identified 581,763 proteins that may respond to
 40 hypoxia among 50 animals. An enrichment analysis of human proteins
 41 identified from LTEs showed that these proteins were enriched in certain drug
 42 targets and cancer genes. The annotation of known posttranslational
 43 modification (PTM) sites to proteins identified by LTEs revealed that these
 44 proteins underwent extensive PTMs, particularly phosphorylation,
 45 ubiquitination and acetylation. Based on the results, iHypoxia provides a
 46 convenient and user-friendly method for users to obtain hypoxia-related
 47 information of interest. We anticipate that iHypoxia, which is freely accessible
 48 at <http://ihypoxia.omicsbio.info>, will advance the understanding of hypoxia and
 49 serve as a valuable data resource.

50

51 **Introduction**

52 Oxygen is an essential element for the survival of aerobic organisms, and
53 a decreased oxygen concentration (hypoxia) may threaten the survival of cells,
54 tissues and individuals. To cope with hypoxia, mammals have evolved
55 sophisticated oxygen-sensing systems and adaptive mechanisms [1],
56 including erythropoiesis [2], mitochondrial respiration [3], angiogenesis [4] and
57 metabolic adaptations [5]. In 1995, Wang *et al.* identified hypoxia-inducible
58 factor 1 (HIF-1), which is a heterodimer consisting of a constitutively expressed
59 HIF-1 β subunit and a HIF-1 α subunit that is regulated and expressed in an
60 oxygen-dependent manner [6]. Under normoxic conditions, HIF-1 α is
61 hydroxylated by prolyl hydroxylases and then targeted for proteasomal
62 degradation through Hippel-Lindau (VHL)-mediated ubiquitination [7-9]. During
63 hypoxia, accumulating HIF-1 α dimerizes with HIF-1 β and then binds to
64 hypoxia response elements to trigger the hypoxic response [10]. In addition to
65 HIF-1, many proteins and pathways are involved in hypoxia signaling [11] and
66 thus play important roles in various physiological and pathological processes,
67 such as the regulation of immunity [12], embryonic development [13], cancer
68 [14], cardiovascular diseases [15], and anemia [16]. The use of
69 hypoxia-related strategies for the treatment of disease is being investigated.
70 For example, Chen *et al.* found that roxadustat, an oral inhibitor of HIF prolyl
71 hydroxylase, is useful for treating patients with anemia and chronic kidney
72 disease [17]. Therefore, the dissection of hypoxia signaling is critical, and an
73 exploration of the expression dynamics of proteins in response to hypoxia is
74 the first step.

75 Several databases related to hypoxia are currently available. In 2012,
76 Pankaj *et al.* compiled HypoxiaDB, a database of hypoxia-regulated proteins
77 containing 3,500 human proteins with detailed annotations that were identified
78 from high-throughput experiments [18]. However, HypoxiaDB has not been

79 updated since then. In 2017, Rashid *et al.* developed the HRGFish database,
80 which contains 818 hypoxia-responsive genes collected from 38 fishes [19].
81 During the last decade, massive studies have contributed to dissecting the
82 protein expression dynamics in cellular/animal models in response to hypoxia
83 under various experimental/physiological conditions. Therefore, a
84 comprehensive database that integrates the quantitative events of protein
85 expression in response to hypoxia will boost the reutilization of previous
86 investigations and provide helpful data resources for studying the molecular
87 mechanism of hypoxia-related biology.

88 Herein, we present iHypoxia, an integrative database for the expression
89 dynamics of proteins in response to hypoxia in animals. At present, the
90 iHypoxia database has been curated and hosts 156,582 quantitative
91 expression events of 36,408 proteins in five mammals in response to hypoxia
92 and 581,763 orthologous proteins in 50 animals. Detailed annotations,
93 including posttranslational modifications (PTMs), subcellular locations,
94 protein-protein interactions and drug-target relations, are also provided.
95 Search and browsing services were also implemented for user convenience.
96 An enrichment analysis of human proteins identified in low-throughput
97 experiments (LTEs) showed that proteins that respond hypoxia were
98 significantly enriched in certain drug targets and oncogenes. By mapping
99 known PTM sites to proteins identified in LTEs, we confirmed that these
100 proteins can undergo extensive PTMs, particularly phosphorylation,
101 ubiquitination and acetylation. We anticipate that the iHypoxia database will be
102 beneficial to the research community, and this online service is freely available
103 at <http://ihypoxia.omicsbio.info>.

104 Results

105 Data statistics of iHypoxia

106 The flow chart of the construction of iHypoxia is depicted in **Figure 1**. Through
107 literature curation and public database integration, we obtained 156,582
108 quantitative expression events of 36,408 proteins that respond to hypoxia in
109 five mammals, including *Homo sapiens* (human), *Mus musculus* (mouse),
110 *Rattus norvegicus* (rat), *Sus scrofa* (pig) and *Bos taurus* (cow). Based on the
111 expression alterations of the proteins in hypoxia compared with normoxia,
112 proteins were divided into the upregulation and downregulation categories
113 (**Figures 2A and 2B**). Because proteins that respond to hypoxia present
114 different expression patterns in various tissues/cells or under various hypoxic
115 conditions, some proteins may be upregulated and downregulated as
116 conditions change and were annotated “up/down” (**Figures 2A and 2B**). In
117 general, the protein expression quantifications obtained in LTEs were reliable,
118 and those obtained in high-throughput experiments (HTEs) needed further
119 validation; therefore, we curated the expression quantifications from LTEs and
120 HTEs separately. In this study, for five mammals, we obtained 1,215 unique
121 proteins whose expression levels showed changes in response to hypoxia
122 detected in LTEs (**Figure 2A**) and 36,194 proteins identified by HTEs (**Figure**
123 **2B**). Regardless of whether the proteins were obtained from HTEs or LTEs, the
124 proteins detected in humans, mice, and rats accounted for the vast majority of
125 the proteins, and few proteins were found in cows and pigs. Furthermore, we
126 observed that 82.39% (1001/1215) of the proteins identified in LTEs were also
127 detected in HTEs (**Figure 2C**), and 12,290 proteins showed altered expression
128 at both the protein and transcription levels (**Figure 2D**). The distributions of
129 different experimental types for protein expression detection in LTEs and HTEs
130 are shown in **Figures 2E and 2F**, respectively. Western blotting (WB) and
131 microarrays (arrays) were the most commonly used techniques for the

132 detection of hypoxia-related protein expression. In addition, considering the
133 data for one species should be helpful for studies in another species because
134 cells might utilize the same or similar mechanisms across species, we further
135 expanded our data to 618,171 proteins in 50 animals based on an orthologous
136 search (Supplementary Table S1), and this expansion could provide helpful
137 information for nonmodel animals that scientists might be interested in.

138

139 **Query function and result presentation in iHypoxia**

140 To rapidly access the detailed information on a protein of interest, we
141 recommend that users apply the search function, which is available on both
142 the home and search pages (**Figure 3A**). We also provide examples for each
143 keyword option and allow users to easily experience the search process.
144 Examples include 'ENSG00000100644', 'Q16665', 'HIF1A', and 'hypoxia
145 inducible factor 1 subunit alpha', which are specific for the Ensembl ID, UniProt
146 ID, gene name, and protein name, respectively (**Figure 3A**). The database
147 uses a fuzzy query function, and all matched results are listed and displayed in
148 a table at the bottom of the search page, whereas the matched content is
149 highlighted in red (**Figure 3B**). The table showing the results contains basic
150 information, i.e., Ensembl ID, UniProt ID, gene name, protein name and
151 organism, and detailed information for the searched protein can be viewed in
152 the result page by clicking the 'More' link (**Figure 3B**).

153 Because the iHypoxia data were integrated from LTEs, HTEs and an
154 orthologous search, the browser sections are displayed according to these
155 three categories. We first counted the number of proteins in each species
156 identified in LTEs and displayed the result in 'Statistics for LTE proteins'
157 (**Figure 4A**). To view the proteins in each organism, users can click the
158 corresponding bar, and a table with the basic information of the Ensembl ID
159 and gene name will be shown on the right (**Figure 4B**). Additionally, users can

160 click the 'More' link to view detailed information. For proteins identified in HTEs,
 161 because a series of proteins was identified in a single experiment, we
 162 preferred to first obtain statistics on the experimental conditions for every
 163 organism. The results are displayed in 'Statistics for HTE conditions', and
 164 users can click one bar to view all the experiments that have been performed
 165 with the selected organism (**Figure 4C**). The experimental conditions are
 166 shown in a table on the right, which also contains the protein numbers for each
 167 condition (**Figure 4D**). Moreover, all proteins obtained under certain conditions
 168 in certain organisms are shown at the bottom when users click the 'View'
 169 button. The table of proteins identified in HTEs includes the Ensembl ID, gene
 170 name, log2 ratio, *P*-value and sample type, and detailed information can be
 171 accessed through the 'More' link (**Figure 4E**). Furthermore, to conveniently
 172 browse orthologous proteins, a "Data browse for all organisms" strategy was
 173 implemented. In this part, an evolutionary tree showing the phylogenetic
 174 relationships of these 50 animals is diagrammed on the right side, and the
 175 animals are listed on the left side (**Figure 4F**). Users can click the animal of
 176 interest to view orthologs of experimentally identified proteins (**Figure 4G**).

177 The result page for a protein consists of nine parts. The first part shows the
 178 basic related information of the protein, including the organism, Ensembl ID,
 179 UniProt ID, gene name, protein name, protein function and sequence (**Figure**
 180 **5A**). The other four parts are the expression dynamics of the proteins in
 181 response to hypoxia identified in LTEs and HTEs and those obtained from an
 182 orthologous search of proteins identified in LTEs and HTEs (**Figures 5B to 5E**).
 183 The table of evidence from LTEs contains the experimental conditions,
 184 regulation under hypoxic conditions, brief descriptions of the experiments,
 185 sample types, evidence level, and detection methods (**Figure 5B**), and the
 186 table of HTEs includes the experimental conditions, regulation under hypoxic
 187 conditions, log2 ratios, *P*-values, FDRs, sample types, evidence levels, and

188 detection methods (**Figure 5C**). The tables for proteins obtained from an
 189 orthologous search showing the evidence from LTEs and HTEs are similar to
 190 the tables of evidence from LTEs and HTEs, respectively (**Figures 5D and 5E**).
 191 The remaining four parts are 'Post-translational modification(s)',
 192 'Protein-protein interaction(s)', 'Subcellular location(s)' and 'Drug-target
 193 relation(s)', and these parts correspond to all PTMs we have collected for the
 194 searched protein, a network in which the protein interacts with other LTE
 195 proteins, subcellular location information and potential inhibitors, respectively
 196 (**Figures 5F to 5I**).

197

198 **Functional analyses of collected proteins**

199 To further understand the biological and functional properties of LTE proteins
 200 that are differentially expressed in hypoxia, we performed GO [20] and Kyoto
 201 Encyclopedia of Genes and Genomes (KEGG) [21] pathway enrichment
 202 analyses. For simplicity, only the top 10 significant GO terms of biological
 203 processes (P -value $< 1.73\text{E-}32$), cellular components (P -value $< 1.78\text{E-}13$)
 204 and molecular functions (P -value $< 6.19\text{E-}10$) and KEGG terms (P -value $<$
 205 $3.94\text{E-}12$) are shown in **Figure 6**. The biological processes were enriched in
 206 the regulation of the apoptotic signaling pathway (GO:2001233), response to
 207 oxidative stress (GO:0006979), regulation of vasculature development
 208 (GO:1901342) and GO terms related to oxygen levels such as response to
 209 decreased oxygen levels (GO:0036293), response to hypoxia (GO:0001666),
 210 and cellular response to hypoxia (GO:0071456). (**Figure 6**). Many studies
 211 have found that the levels of reactive oxygen species (ROS) increase during
 212 hypoxia [22], and hypoxia gives rise to apoptotic responses or apoptosis
 213 resistance in tumors [23-25]. Systemically, organisms have evolved many vital
 214 mechanisms to adapt to hypoxia, and these mechanisms include blood vessel
 215 growth, which delivers as much oxygen and nutrients as possible to meet the

216 metabolic demand [4, 26]. With respect to cellular components, most proteins
217 originate from the platelet alpha-granule lumen (GO:0031093),
218 collagen-containing extracellular matrix (GO:0062023), and membrane raft
219 (GO:0045121). The representative molecular functions were
220 2-oxoglutarate-dependent dioxygenase activity (GO:0016706),
221 monosaccharide binding (GO:0048029), protease binding (GO:0002020) and
222 others. The majority of 'binding' terms suggest that proteins that respond to
223 hypoxia play extremely important roles in complex protein interactions. In
224 addition, '2-oxoglutarate-dependent dioxygenase activity' was identified as the
225 most enriched GO molecular function, and dioxygenase can mediate the
226 interaction between HIF-1 α and VHL by hydroxylating HIF-1 α [8, 9, 27].

227 Hypoxia is a complex condition and a feature of physiological and
228 pathological states. Organisms sense and adapt to hypoxic stress via various
229 and intricate pathways [1]. In addition to the classical and well-known HIF-1
230 signaling pathway (hsa04066), the top enriched KEGG pathways include renal
231 cell carcinoma (hsa05211) [28], AGE-RAGE signaling pathway in diabetic
232 complications (hsa04933) [29], central carbon metabolism in cancer
233 (hsa05230) [30], colorectal cancer (hsa05210) [31], prostate cancer
234 (hsa05215) [32], apoptosis (hsa04210) [25], proteoglycans in cancer
235 (hsa05205) [33], and the PI3K-Akt signaling pathway (hsa04151) [34]. In
236 particular, many cancer-related pathways are enriched in human proteins
237 identified from LTEs.

238 We then performed an enrichment analysis with a hypergeometric test by
239 mapping the human proteins identified from LTEs to the druggable proteins
240 acquired from the DrugBank database [35] and oncogenes acquired from the
241 Cancer Gene Census in the Catalog Of Somatic Mutations in Cancer
242 (COSMIC) [36]. As a result, 228 and 54 proteins identified in LTEs were found
243 to be significantly overrepresented in drug targets and cancer genes,

244 respectively (**Table 1**). Therefore, the dysregulation of proteins identified in
245 LTEs may be an essential process in tumorigenesis and development and can
246 be a potential therapeutic target.

247 PTMs play vitally important roles in regulating a wide range of biological
248 processes. In our KEGG analysis results, one of the remarkably enriched
249 KEGG pathways, the PI3K-Akt signaling pathway, was mainly regulated by
250 phosphorylation. In the iHypoxia database, we provide abundant annotations
251 by taking advantage of the knowledge from several PTM resources (**Figure 1**).
252 We then performed a PTM analysis by mapping known PTM sites from six
253 databases to proteins identified in LTEs. In total, we obtained 35,958 PTM
254 sites on 1,097 substrates, which accounted for 90.29% (1097/1215) of the
255 proteins identified in LTEs (**Figure 7A**). More than 30 modifications were
256 involved, and these included 24,018 phosphorylation sites of 1,056 proteins,
257 7,124 ubiquitination sites of 637 proteins and 4,662 acetylation sites of 619
258 proteins (**Figure 7B** and Supplementary Table S2). Different PTMs can
259 engage in crosstalk with each other to synergistically orchestrate specific
260 biological processes, and we found that a fairly large number of proteins
261 identified in LTEs can be regulated by multiple PTMs (**Figure 7C**). Numerous
262 studies have shown that PTMs can be regulated by hypoxia and can also
263 regulate the relevant pathways to respond to hypoxia [37-39].

264 Discussion

265 Oxygen is vital to life on earth. However, hypoxia is a common stress
 266 frequently encountered by aerobic species, such as at high altitudes and in
 267 aquatic habitats, and underground burrows, and cells/tissues within the body
 268 are also exposed to a hypoxic microenvironment. Therefore, mammals have
 269 evolved adaptive mechanisms to cope with hypoxia [2-5]. Hypoxia is also
 270 associated with human diseases such as cancers, cardiovascular diseases
 271 and anemia [15, 16, 40]. The development of high-throughput technologies
 272 has greatly enhanced the large-scale identification of proteins whose
 273 expression at the transcript or protein levels is modified during hypoxia, and an
 274 increasing number of proteins involved in regulating hypoxia have been
 275 verified. Considering that the data from these studies are scattered throughout
 276 the literature and are difficult to obtain and utilize, a resource for the
 277 expression dynamics of proteins in response to hypoxia is needed.

278 In this study, we developed iHypoxia, an integrated database for the
 279 expression dynamics of proteins that respond to hypoxia in animals. At present,
 280 iHypoxia contains 1,629 expression events of 1,215 proteins identified in LTEs,
 281 154,953 quantitative expression events of 36,194 proteins identified in HTEs,
 282 and 581,763 orthologous proteins. Compared with previous databases,
 283 iHypoxia not only contains more data but also has several advanced features.
 284 First, iHypoxia is the first integrated animal database focused on the
 285 expression dynamics of proteins in response to hypoxia and provides evidence
 286 from high- and low-throughput experiments and the transcript and protein
 287 levels of five mammals. Moreover, this resource is well annotated and can
 288 provide abundant information on proteins, including the hypoxic experimental
 289 conditions, expression patterns, samples and other information from the
 290 original studies, as well as PTMs, protein-protein interactions, drug-target
 291 relations and other information from public databases. Furthermore, the

292 iHypoxia website is convenient and user-friendly, and users can rapidly and
293 accurately find the information of interest or download datasets.

294 In the future, iHypoxia will be regularly maintained and updated when new
295 hypoxia data are published. In addition, hypoxia not only transcriptionally and
296 translationally activates genes to modulate cellular adaptations but also
297 influences many other processes, such as protein PTMs and the expression of
298 noncoding RNAs [34, 41, 42]. Therefore, data at other expression levels and
299 more species will be integrated to provide a more comprehensive and useful
300 resource to facilitate related research.

301 **Materials and methods**

302 To develop a comprehensive resource for the expression dynamics of proteins
303 in response to hypoxia in animals, we collected and integrated published
304 (through January 2020) datasets from various sources, such as PubMed,
305 Gene Expression Omnibus (GEO), HypoxiaDB [18], and GO [20]. A workflow
306 of the construction of iHypoxia is depicted in **Figure 1**.

307

308 **Curation of protein expression dynamics in response to hypoxia** 309 **identified in low-throughput experiments and other databases**

310 To obtain the highest quality and validated proteins and their expression
311 patterns in response to hypoxia, we searched for hypoxia-related scientific
312 literature in PubMed using the keyword 'hypoxia', and 572 studies ultimately
313 passed our screening process. By carefully reading the literature, we manually
314 extracted the hypoxic expression of proteins identified from LTEs, such as
315 Western blot (WB), Northern blot (NB), PCR, and other experiments.
316 Considering that proteins show different expression patterns in various
317 tissues/cells, in the presence of different oxygen concentrations and in
318 response to different durations of hypoxia, we retrieved as many details as
319 possible, including the hypoxic experimental conditions, expression patterns
320 (upregulation or downregulation), samples (tissues or cells), evidence levels
321 (proteins or transcripts), experimental methods (e.g., WB and NB) and a brief
322 description of the proteins from the original articles. All the protein expression
323 experiments were checked by two data curators. In addition, we integrated
324 data from HypoxiaDB [18] and GO resources [20]. From GO resources, we
325 collected only the proteins whose GO terms were related to hypoxia, as
326 marked by experimental evidence codes, which indicated that the annotation
327 of the gene was directly supported by evidence from an experiment. We then
328 traced the original literature to obtain the expression pattern of the protein, the

hypoxic conditions and other information. For the data in HypoxiaDB, detailed information was adopted without further changes.

Collection of quantitative expression events of proteins in response to hypoxia in high-throughput experiments

Proteomics is a highly effective approach for identifying alterations in protein levels. To identify the expression at the protein level of genes that respond to hypoxia, we searched PubMed with various keywords such as 'hypoxia AND (proteome OR proteomic)' and 'anoxia AND (proteome OR proteomic)'. To control the quality of the data, we manually examined all the literature retrieved and the corresponding supplemental materials. Information pertaining to the hypoxic condition, regulation pattern, *P*-value, sample type and other details was then extracted.

Transcriptomic approaches have been widely used to research transcriptional expression during the process of hypoxic responses, and GEO hosts many expression samples related to processes of hypoxic responses. Therefore, we searched the GEO database with the keywords 'hypoxia' and 'anoxia'. Hypoxia-related microarray expression datasets were then downloaded and analyzed using the limma package [43]. If the fold change of mRNA expression in hypoxic cells/tissues compared with control (normoxia) cells/tissues was greater than 2 and had an adjusted *P*-value <0.05, the protein was included in the iHypoxia database. Detailed information, including the hypoxic experimental conditions, samples, and other details, was also retrieved from the original studies.

After completing the above data collection, the "Retrieve/ID mapping" tool in the UniProt database was used to convert the different identifiers of the collected proteins to obtain a unified Ensembl ID and UniProt ID [44].

355

356 **Orthologous detection**

357 To identify the proteins in other animals that may respond to hypoxia, the
 358 "Pairwise orthologs" data were downloaded from the OMA database
 359 (<https://omabrowser.org/oma/current/>) [45]. Through screening, we obtained
 360 50 animal ortholog datasets, and the Ensembl ID and UniProt ID were used as
 361 identifiers. The proteins were then mapped to the OMA dataset to obtain their
 362 orthologs.

363

364 **Data obtained from annotation with public databases**

365 To provide abundant annotations for collected proteins, the knowledge
 366 obtained from several public databases, including essential information, PTMs,
 367 subcellular locations, protein-protein interactions and drug-target information,
 368 was integrated.

369 First, essential information on the proteins, such as the gene name, protein
 370 name and sequence, was downloaded from UniProt [46]. PTMs play vital roles
 371 in regulating the structure and function of proteins; thus, PTM data from
 372 BioGRID [47], dbPTM [48], EPSD [49], PhosphoBase [50], PhosphoSitePlus
 373 [51], and PLMD [52] were mapped to the collected proteins. Proteins function
 374 in specific subcellular locations, and these locations provide a particular
 375 environment and a set of interacting chaperone proteins that are necessary for
 376 protein function. Knowledge of the subcellular localization of proteins is
 377 important for understanding cellular processes. Therefore, we acquired the
 378 subcellular locations from UniProt [46] and protein-protein interactions from
 379 BioGRID [47], BioPlex [53], IID [54], IntAct [55], and HuRI [56]. Based on
 380 expression studies, some proteins have also been proposed as potential
 381 diagnostic or therapeutic biomarkers for human hypoxic diseases. To
 382 determine whether the proteins we collected can be used as drug targets, we
 383 downloaded the data from DrugBank and matched them [35].

384

385 **Implementation of the webserver**

386 All the data in iHypoxia were stored in a MySQL database, and the website
 387 was deployed with an Apache server. In the front end, BootStrap, an
 388 open-source user interface framework based on HTML, CSS and JavaScript,
 389 was used to build the basic layout of the website. JavaScript and its tool library
 390 JQuery were used to implement the interactive functions. The visualization of
 391 the data statistics and PTMs was achieved with Echarts, whereas the network
 392 of protein-protein interactions was displayed using Cytoscape.js. Data
 393 processing in the back end was performed through PHP, and the interaction
 394 between the front and back ends was achieved through AJAX. Moreover, to
 395 provide a stable and adaptive service, we tested the iHypoxia website using
 396 various web browsers, including Mozilla Firefox, Google Chrome, and Internet
 397 Explorer.

398 **Competing interests**

399 The authors declare no conflict of financial interests.

400

401 **Data availability**

402 The data in this study is available at <http://ihypoxia.omicsbio.info>.

403

404 **CRedit authorship contribution statement**

405 **Ze-Xian Liu**: Conceptualization, Methodology, Investigation, Writing - review &
 406 editing, Project administration, Funding acquisition. **Panqin Wang**: Data
 407 Curation, Investigation, Writing - original draft. **Qingfeng Zhang**: Data
 408 Curation, Software, Writing - original draft. **Shihua Li**: Data Curation,
 409 Validation. **Yuxin Zhang**: Data Curation, Validation. **Yutong Guo**: Data
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 411 Data Curation, Validation. **Lin Li**: Validation. **Han Cheng**: Conceptualization,
 412 Writing - review & editing, Funding acquisition. **Zhenlong Wang**:
 413 Conceptualization, Writing - review & editing, Funding acquisition.

414

415 **Acknowledgements**

416 This work was supported by grants from the Natural Science Foundation of
 417 China [U2004152 to ZL.W., 81972239 and 91953123 to ZX.L., 31601067 to
 418 H.C.], Program for Guangdong Introducing Innovative and Entrepreneurial
 419 Teams [2017ZT07S096 to ZX.L.], and Tip-Top Scientific and Technical
 420 Innovative Youth Talents of Guangdong special support program
 421 [2019TQ05Y351 to ZX.L.].

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562

563 **Figure legends**

564 **Figure 1 Workflow of the construction of the iHypoxia database**

565 First, we collected and integrated expression data of proteins in response to
566 hypoxia from the literature, HypoxiaDB, GO resources and GEO. We then
567 performed ortholog detection using the OMA dataset. In addition to collecting
568 basic information, we annotated proteins in four aspects: PTMs, subcellular
569 locations, protein-protein interactions, and drug-target relations. Ultimately, the
570 iHypoxia website was constructed.

571 **Figure 2 Data statistics of iHypoxia**

572 **A.** Distribution of proteins identified from LTEs. **B.** Distribution of proteins
573 identified from HTEs. **C.** Overlap between proteins identified from LTEs and
574 HTEs. **D.** Overlap between collected proteins identified at the transcript and
575 protein levels. **E.** Number of proteins identified by different LTEs. IDA, IEP, and
576 IMP are the experimental evidence codes in the GO database. **F.** Number of
577 proteins identified by different HTEs. Smaller amounts of data are not shown in
578 the figure.

579 **Figure 3 Search option in iHypoxia**

580 **A.** Search options on the home page and search page. **B.** Results returned
581 from a search for a protein.

582 **Figure 4 Browsing options in iHypoxia**

583 **A.** Browsing for collected proteins with evidence from LTEs with different
584 organisms. **B.** Search results in a table for proteins identified from LTEs with
585 the chosen organism. **C.** Browsing for proteins with evidence from HTEs with
586 different organisms. **D.** Results in a table obtained with the chosen organism
587 under hypoxic conditions. **E.** Results in a table obtained for proteins identified
588 from HTEs with the chosen organism under the chosen condition. **F.** Browse
589 results by species. **G.** Results in a table for all proteins of the chosen
590 organism.

591 **Figure 5 Results page obtained for a searched protein**

592 **A.** Fundamental annotations of a searched protein. **B.** LTE evidence for a
593 searched protein. **C.** HTE evidence for a searched protein. **D.** LTE evidence for
594 an orthologous search for a searched protein. **E.** HTE evidence for an
595 orthologous search for a searched protein. **F.** PTMs for a searched protein. **G.**
596 Protein-protein interactions of a searched protein. **H.** Subcellular location of a
597 searched protein. **I.** Drug-target relationship of a searched protein.

598 **Figure 6 Enrichment of GO and KEGG terms for human LTE proteins**

599 The results were visualized with WocEA (Word cloud for the Enrichment
600 Analysis, version 1.0). The font size denotes the enrichment ratio of each term,
601 and the color denotes the approximate *P*-value.

602 **Figure 7 PTM analyses of proteins identified from LTEs**

603 **A.** Distribution of modified proteins and sites. **B.** Distribution of the mapped
604 proteins and sites in terms of phosphorylation, ubiquitination, acetylation and
605 others (sites with fewer than 100 sites are not shown). **C.** Overlap of five major
606 types of PTMs of proteins identified in LTEs.

607

608

609 **Tables**

610 **Table 1** Enrichment analyses of drug targets and cancer genes for human LTE
611 proteins.

612

613

614 **Supplementary material**

615 **Supplementary Table S1** Numbers of experimentally or computationally
616 identified proteins in 50 animals in the iHypoxia database.

617 **Supplementary Table S2** Distribution of substrates and different PTM sites of
618 collected proteins identified from LTEs.

1. Dataset curation

Literature collection

hypoxia

we investigated differential plasma proteomes of **high altitude natives** and lowland normal controls by a **TMT**-based proteomic approach. A total of 818 proteins were identified, of which **137 were differentially altered**. **Validation** results demonstrated that CCL18, C9, PF4, MPO, and S100A9 were notably up-regulated, and HRG and F11 were down-regulated in high altitude natives.

Databases integration

HypO₂xiaDB

DataSets analysis

matrix

limma

DEPs

Information extraction

protein	condition	regulation	description
fold	p value	sample	evidence level
method	PMID		

2. Orthology

50 animals

3. Annotation

EPSON

PLMO

PhosphoSitePlus®

dbPTM

PhosphoBase

BioGRID

UniProt

eEnsembl

DRUGBANK

BioGRID

BIOPLEX

IntAct

The Human Reference Protein Interactome Mapping Project

IID Integrated Interactions Database

4. Database construction

Front-end

Basic website construction
HTML, CSS, Bootstrap

Interactive functions
JavaScript, jQuery

Visualization
Echarts, Cytoscape.js

AJAX

Back-end

Web server
Apache

Data management
MySQL

Receive and process
the input
PHP

iHypoxia

<http://ihypoxia.omicsbio.info/>

Integrative database for Hypoxia associated proteins in animals

iHypoxia

Home Browse Search Download Help About Citation LZJ Lab

Welcome to iHypoxia

Oxygen is vital to life on earth. Hypoxia is a condition or state in which insufficient levels of oxygen are supplied to cells or tissues, while it is associated with a wide range of conditions in human health and diseases such as cancers, cardiovascular diseases and anemia, among others. The recent development of high-throughput sequencing based omics technologies greatly advanced the large-scale identification of hypoxia-regulated proteins and the detection of candidate reference markers for diseases diagnosis and therapy. Here, we provide a database of **iHypoxia (integrative database for Hypoxia associated proteins in mammals)**, which host the results of hypoxia regulatory proteins based on low-throughput and high-throughput identification.

In total, **158,615** quantification events on **41,482** hypoxia-regulated proteins for **5** mammals under **390** conditions were collected and integrated in the database, while the details about the samples, hypoxia experiments were also manually curated. We further expanded our data to **618,171** proteins in **50** animals by orthologous search. The iHypoxia database provides simple and user-friendly interface to browse and search data, and the detailed information is organized and visualized for queries.

#1. Ensembl ID : ENSG00000100644, #2. UniProt ID : Q16665, #3. Gene name : HIF1A, #4. Protein name : Hypoxia-inducible factor 1-
alpha

Homo sapiens

Ensembl ID

Please select a type and enter keyword

Submit

A

#1. Ensembl ID : ENSG00000100644, #2. UniProt ID : Q16665, #3. Gene name : HIF1A, #4. Protein name : Hypoxia-inducible factor 1-alpha

All organisms ▾

Gene name ▾

HIF1A

Submit

B

Search content: Gene name = 'HIF1A'

There are 32 entries with your keyword(s).

Ensembl ID	UniProt ID	Gene name	Protein name	Organism	More
ENSPANG00000003899	A0A096NVI7	HIF1A	Hypoxia-inducible factor 1-alpha	<i>Papio anubis</i>	↗
ENSCSAG000000014072	A0A0D9RNL7	HIF1A	Hypoxia-inducible factor 1-alpha	<i>Chlorocebus sabaeus</i>	↗
ENSRNOG000000008292	A0A0G2JX87	Hif1a	Hypoxia-inducible factor 1-alpha	<i>Rattus norvegicus</i>	↗

B All proteins with **LTE** in **Homo sapiens**

Tip: The table below shows all the LTE-associated proteins of the chosen organism. You can click the 'More' button to see the detailed information of a certain protein.

Ensembl ID	Gene name	More
ENSG00000001626	CFTR	More
ENSG00000002330	BAD	More
ENSG00000004455	AK2	More
ENSG00000004799	PDK4	More
ENSG00000005381	MPO	More
ENSG00000005421	PON1	More

D All conditions with **HTE** in **Homo sapiens**

Tip: The table below shows all the HTE-associated conditions of the chosen organism. You can click the 'View' button to see all the significantly different proteins of the chosen condition, and the results are shown at the bottom.

Condition	Protein number	View
0%/24h vs normoxia	3239	View
0%/48h vs normoxia	1317	View
0%/6h vs normoxia	16	View
0.01%/16h vs normoxia	2	View
0.1%/18h vs normoxia	1217	View
0.1%/24h vs normoxia	176	View

E All proteins of **HTE** under **0%/24h vs normoxia** in **Homo sapiens**

Tip: The table below shows all the HTE-associated proteins under the chosen condition of the chosen organism. You can click the 'More' button to see the detailed information of a certain protein.

Ensembl ID	Gene name	Log2 ratio	P value	Sample type	More
ENSG00000000419	DPM1	-1.295	N/A	A431 cells	More

F

All organisms

- Homo sapiens (18,246)
- Pan troglodytes (17,989)**
- Sus scrofa (16,609)
- Bos taurus (16,391)

G

Search content: Organism = **Pan troglodytes**

There are 17150 entries with your keyword(s).

Ensembl ID	UniProt ID	Gene name	Protein name	Organism	More
ENSPTRG000000044347	A0A075B7H5	SEMG1	Semenogelin 1	Pan troglodytes	More

A

Organism	Homo sapiens
Ensembl ID	ENSG00000100644
UniProt ID	Q16665
Gene name	HIF1A
Protein name	Hypoxia-inducible factor 1-alpha
Function	Functions as a master transcriptional regulator of the adaptive response to hypoxia. Under hypoxic conditions, activates the transcription of over 40 genes, including erythropoietin, glucose transporters, glycolytic enzymes, vascular endothelial growth factor, HILPDA, and other genes whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia. Plays an essential role in embryonic vascularization, tumor angiogenesis and pathophysiology of ischemic disease. Heterodimerizes with ARNT; heterodimer binds to core DNA sequence 5'-TACGTG-3' within the hypoxia response element (HRE) of target gene promoters (By similarity). Activation requires recruitment of transcriptional coactivators such as CREBBP and EP300. Activity is enhanced by interaction with both, NCOA1 or NCOA2. Interaction with redox regulatory protein APEX seems to activate CTAD and potentiates activation by NCOA1 and CREBBP. Involved in the axonal distribution and transport of mitochondria in neurons during hypoxia. (Microbial infection) Upon infection by human coronavirus SARS-CoV-2, is required for induction of glycolysis in monocytes and the consequent proinflammatory state ^{1} . In monocytes, induces expression of ACE2 and cytokines such as IL1B, TNF, IL6, and interferons ^{1} . Promotes human coronavirus SARS-CoV-2 replication and monocyte inflammatory response ^{1} .
Sequence	MEGAGGANDKKKISSERRKEKSRDAARRSRSESEVFYELAHQLPLPHNVSSHLDKASVMRLTISYL RVRKLLDAGDLIEDDMKAQMNCFYLKALDGFVMVLTDDGDMYISDNVNKYMGLTQFELTGHSVFD FTHPCDHEEMREMLTHRNGLVKKGKEQNTQRSFFLRMKCTLTSRGRTMNIKSATWVKVLHCTGHIHVY DTNSNQPCQCGYKKPPMTCLVLICEPIPHPSNIEIPLDSKTFLSRHSLDMKFYSYCDERITELMGYEPEEL LGRSIYEYYHALDSHDLTHTHDMFTKGQVTTGQYRMLAKRGGYVWVETQATVIYNTKNSQPQCIVC VNYVVGIIQHDLIFSLQQTECVLKPVESSDMKMTQLFTKVESEDTSFLFDKLKKEPDALTLLAPAAGD TIISLDFGSNDTETDDQQLLEEVPLYNDVMLPSPNEKLQININLAMSPLPTAETPKPLRSSADPALNQEVA LKLEPNPESLELSFTMPQIQDQTPSPSDGSTRQSSPEPNSPSEYCFYVDSDMVNEFKLELVEKLFAED

F

G

H

I

DB01136	DB01275	DB02342	DB05959
DB06082	DB08687		

B

Condition	Regulaion	Description	Sample type	Evidence level	Method
1%/4h vs normoxia	↑	under hypoxic condition synchronously with accumulation of HIF-1alpha into the nucleus, where it interacts with other cofactors to assemble the HIF-1 transcriptional complex, leading to transcriptional activation.	HUVEC	protein	WB
2%/24h vs normoxia	↑	HIF-1alpha is a key factor modulating the angiogenesis induced by hypoxia. HIF-1alpha expression and protein synthesis in MSCs is helpful to be resistant against hypoxic, oxidative, and serum-deprived stress conditions.	DPSC	transcript	PCR

C

Condition	Regulaion	Log2 ratio	P value	FDR	Sample type	Evidence level	Method
1%/10d vs normoxia	↑	3.301	0.003	0.023	hESC	transcript	array

D

Organism	Ort. gene	Condition	Reg.	Description	Sample type	Evidence level	Method
Rattus norvegicus	Hif1a	0.5%/12h vs normoxia	↑	hypoxia preconditioned MSCs were regulated by the transcription factor HIF-1alpha, which produced alterations in Ca2+ homeostasis	MSCs (secreted proteins)	protein	WB

E

Organism	Ort. gene	Condition	Reg.	Log2 ratio	P value	FDR	Sample type	Evidence level	Method
Mus musculus	Hif1a	CCH/4w vs normoxia	↓	-1.179	0.001	0.003	kidneys	transcript	array

A **B**

Number of proteins

C

Number of sites