Genetic, transcriptome, proteomic and epidemiological evidence for blood brain barrier disruption and polymicrobial brain invasion as determinant factors in Alzheimer's disease.

C.J.Carter, PolygenicPathways, Flat 2, 40 Baldslow Road, Hastings, East Sussex, TN34 2EY, UK

Key words: virus, bacteria, fungi, microbes, Alzheimer's disease, immune system, inflammation, blood brain barrier, gene/environment

Running title: Alzheimer's disease relationship with multiple pathogens

Abstract

Multiple pathogens have been detected in Alzheimer's disease (AD) brains. A bioinformatics approach was used to assess relationships between pathogens and AD genes (GWAS), the AD hippocampal transcriptome and plaque or tangle proteins. Host/pathogen interactomes (*C.albicans*, *C.Neoformans*, Bornavirus, *B.Burgdorferi*, cytomegalovirus, Ebola virus, HSV-1, HERV-W, HIV-1, Epstein-Barr, hepatitis C, influenza, *C.Pneumoniae*, *P.Gingivalis*, *H.Pylori, T.Gondii, T.Cruzi*) significantly overlap with misregulated AD hippocampal genes , with plaque and tangle proteins and, except Bornavirus, Ebola and HERV-W, with AD genes. Upregulated AD hippocampal genes match those upregulated by multiple bacteria, viruses, fungi or protozoa in immunocompetent blood cells. AD genes are enriched in bone marrow and immune locations and in GWAS datasets reflecting pathogen diversity, suggesting selection for pathogen resistance. The age of AD patients implies resistance to infections afflicting the younger. APOE4 protects against malaria and hepatitis C, and immune/inflammatory gain of function applies to APOE4, CR1, TREM2 and presenilin variants. 30/78 AD genes are expressed in the blood brain barrier (BBB), which is disrupted by AD risk factors (ageing, alcohol, aluminium, concussion, cerebral hypoperfusion, diabetes, homocysteine, hypercholesterolaemia, hypertension, obesity, pesticides, pollution, physical inactivity, sleep disruption and smoking). The BBB and AD benefit from statins, NSAIDs, oestrogen, melatonin and the Mediterranean diet. Polymicrobial involvement is supported by the upregulation of pathogen

sensors/defenders (bacterial, fungal, viral) in the AD brain, blood or CSF. Cerebral pathogen invasion permitted by BBB inadequacy, activating a hyper-efficient immune/inflammatory system, beta-amyloid and other antimicrobial defence may be responsible for AD which may respond to antibiotic, antifungal or antiviral therapy.

Introduction

Multiple pathogens have been implicated in Alzheimer's disease (AD) either via detection in the AD brain, or in epidemiological studies relating to serum antibodies. Pathological burden (cytomegalovirus, Herpes simplex (HSV-1), *Borrelia burgdorferi*, *Chlamydia pneumoniae* and *Helicobacter pylori*) rather than any individual pathogen may also be associated with AD [1]. Many pathogens are able to increase beta-amyloid deposition and tau phosphorylation in animal models, *in vitro* or *in vivo* and beta-amyloid itself is an antimicrobial peptide active against bacteria and fungi [2,3]and the influenza[4] and herpes simplex viruses [5,6]. These effects are summarised in Table 1 for a number of pathogens and for beta-amyloid.

Previous studies have shown that the life cycles of several pathogens implicated in AD relate to AD susceptibility genes [7]. The proteins found in AD plaques and tangles are also enriched in those used by HSV-1 during its life cycle [8] and the HSV-1 or *Toxoplasma Gondii* host interactomes are also enriched in AD susceptibility genes [9,10]

Similar studies have noted significant overlaps between the Epstein-Barr viral/host interactome and diseases in which the virus is implicated, including B cell lymphoma [11]or multiple sclerosis [12] . The interactomes of oncogenic viruses also relate to cancer genes [13] suggesting important gene/environment interactions that may condition disease susceptilbility.

In this study, the host pathogen interactomes of 17 fungal, bacterial, viral and parasite pathogens were analysed in relation to 78 AD genes derived from genome-wide association studies (GWAS). The anatomical location of these genes was also queried against proteomic /genomic datasets from multiple tissues.

The host genes of the pathogen interactomes were also compared with the combined up and down-regulated genes from a study of the AD hippocampus, post-mortem [14] and to the proteins found in plaques or neurofibrillary tangles. The upregulated genes from this AD hippocampal study were also

compared with upregulated genes from numerous infection microarray datasets (viral, bacterial, fungal and protozoan) housed at the Molecular signatures database [15] or the Gene Expression Omnibus [16].

Pathogens have shaped human evolution, as the survivors of dangerous infections are endowed, via natural selection, with genes conveying resistance. The AD genes were also compared against a series of genome-wide association datasets related to general pathogen or protozoan diversity, viral diversity and the immune response to parasitic worms, across multiple human populations in different geographical locations. Such genes are likely to have been selected for pathogen resistance. [17-20].

The results show that host genes related to pathogens are enriched in all these AD parameters and that many AD susceptibility genes also relate to pathogens, but more likely to pathogen resistance than susceptibility. The anatomical data point to an immune function of many AD genes, while others are localised in the blood-brain barrier, which is disrupted by other environmental risk factors associated with AD.

Methods

The host/pathogen interactomes of two fungal species (*Candida albicans, Cryptococcus Neoformans*) , the Borna virus, human cytomegalovirus, Ebola virus, Herpes simplex (HSV-1), human endogenous retroviruses HERV-W, the human immunodeficiency virus (HIV-1) (the latter from the HIV-1, human interaction database [21] http://www.ncbi.nlm.nih.gov/genome/viruses/retroviruses/hiv-1/interactions , Epstein-Barr , hepatitis C and influenza A viruses, 3 bacterial species (*Chlamydia Pneumoniae, Porphyromonas Gingivalis, Helicobacter Pylori)* and 2 protozoans *(Toxoplasma Gondii* and *Trypanosoma Cruzi)* were obtained by literature survey and from extant databases. These referenced interactomes can be accessed at http://www.polygenicpathways.co.uk/HPI.htm .

Genes misregulated in the AD hippocampus are those reported from a post-mortem microarray study [14]. Up- and downregulated genes (N=2879) were combined for comparison with the pathogen interactomes. These interactomes contain multiple types of interaction (protein/protein, viral microRNA, and effects on transcription etc.) and it is not possible to compare like with like for this aspect.

The upregulated genes (N= 1690) from this AD hippocampal study contain the pathways relevant to pathogens and immune activation (inflammation, complement activation and the defence response) [14] and these were chosen for comparison with upregulated genes from infection datasets at the Molecular signatures database (MSigDB) http://software.broadinstitute.org/gsea/msigdb/index.jsp . MSigDB contains several thousand microarray gene sets which can be compared against the AD input [15]. Infection related datasets, and those related to Toll-like receptor ligands, were identified using search terms (e.g. infection, virus, bacteria, TLR1, lipopolysaccharide, etc.). Microarray viral infection datasets (upregulated gene sets) from the gene expression omnibus (GEO) [22] were also downloaded from the Harmonizome database http://amp.pharm.mssm.edu/Harmonizome/ from the Ma'ayan laboratory of computational systems. [23]. For the searched gene sets, most of the data outputs were restricted at source (by MSigDb or GEO) to the top upregulated genes (usually ~ 200-300).

The proteins found in plaques or neurofibrillary tangles are from two proteomics studies yielding 488 proteins in plaques [24] and 90 in tangles [25].

Seventy eight genes associated with Alzheimer's disease (Reported genes) were obtained from the NHGRI-EBI Catalog of published genome-wide association studies (GWAS) [26], Available at: www.ebi.ac.uk/gwas . Accessed January, 2016, version 1.0 using studies labelled as "Alzheimer's disease" or "Alzheimer's disease late-onset". These genes and their relationships with pathogens or the immune system are catalogued in Supplementary Table 1.These genes are highlighted in **bold** throughout the text.

Genes related to general pathogen diversity , protozoan and viral diversity and to the immune response to parasitic worms are from a series of papers concerning evolutionary selection pressure relevant to pathogen resistance [17-20].

The tissue and cellular distribution of the 78 AD genes were analysed using the functional enrichment analysis tool (FUNRICH) [27]. http://funrich.org/index.html . This tool derives proteomic and genomic distribution data from >1.5 million annotations. It provides the total number of genes in datasets from each region sampled and returns the significance of any enrichment for members of the uploaded AD genes, using the hypergeometric probability test, with p values corrected using the the Storey and Tibshirani method (Q values) [27]. AD gene enrichment was also analysed in a published blood brain barrier proteome dataset of mouse cerebral arteries (6620 proteins) [28].

The presence of the AD genes in exosomes, a means of transit through cells allowing intercellular communication[29,30], was assessed using ExoCarta (http://www.exocarta.org) a manually curated database of exosomal proteins, RNA and lipids [31].The exosomal pathway is hijacked by several viruses, contributing to intercellular spread and immune evasion [32,33] .

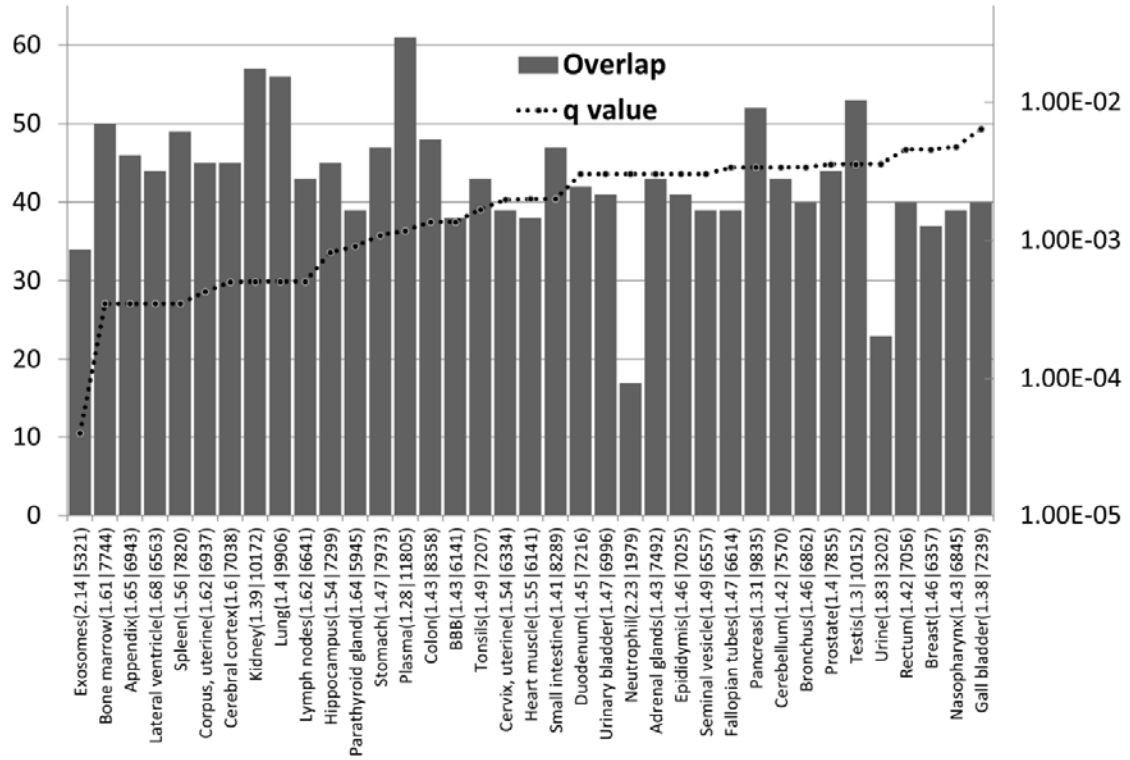
Assuming a human genome of 26846 coding genes and an interactome or other gene set of N genes one would expect N/26846 to exist in the comparator dataset. For example, when comparing 2879 misregulated AD hippocampal genes against any pathogen interactome one would expect 2879/26846 (10.7%) to figure in the pathogen interactome. This calculation was used to define expected values and the enrichment values (observed/expected) in relation to other datasets. Significance of the enrichment was calculated using the hypergeometric probability test. The resultant p values from each analysis series were corrected for false discovery (FDR) [34]. Nominally significant FDR corrected values are considered at $P < 0.05$ and a corrected Bonferroni p value threshold is illustrated on each set of graphs. (Bonferroni $P = 0.05/N$, where N is the maximum number of possible comparisons for each situation (e.g. 78 AD genes or 1690 upregulated genes in the AD hippocampus).

Results

The anatomical location of the AD genes (Fig 1)

Fig 1: The distribution and enrichment of 78 AD genes in diverse proteomic and genomic datasets (Funrich and Exocarta data). The bars indicate the number of genes (from 78) in each tissue and the dotted line the corrected p value (q value). The maximum on this axis is set to q = 0.05. Observed/expected values, followed by the total number of genes expressed are appended after the identities of each sample. BBB refers to a separate blood brain barrier proteomics dataset. Cancer or cell line datasets are omitted and the data are limited to anatomical datasets containg more than 10 AD genes (Not all data are shown).

Figure 1



The AD genes are most significantly enriched in the exosome and bone marrow datasets. As noted above, exosomes are hijacked by many viruses for intercellular spread. Exosomes are prevalent in plasma [35](also enriched in AD genes) and are also the means by which intracellulary generated beta-amyloid is conveyed to the extracellular space [36]. In this context, and in relation to the antimicrobial effects of beta-amyloid, APP and gamma-secretase are highly expressed in the immune dendritic cells that scout for invading pathogens [7]. The bone marrow is the hematopoietic source of red and white blood cells and platelets [37]. B cells in the bone marrow rapidly respond to infection [38] and the bone marrow is also a source of angiogenic cells that are involved in vascular endothelial repair, a process that is disrupted in Alzheimer's disease [39,40]. The parathyroid gland expresses many AD genes and also plays a role in hematopoesis [41,42]. Other immune related areas enriched in AD genes include the appendix, spleen, tonsils, the lymph nodes and the bronchus and neutrophils. The appendix is an important component of mucosal immune function, particularly B cell-mediated immune responses and extrathymically derived T-lymphocytes [43]. The tonsils and nasopharynx, also enriched in AD genes, play an important role in the initial defence against respiratory pathogens [44].

AD genes are enriched in the lateral ventricle, a site of the choroid plexus [45]. This provides cerebrospinal fluid (CSF) and is the location of the blood-CSF barrier, which is exploited by pathogens to gain access to the brain. The choroid plexus plays an important role in pathogen defence [46]. Post-mortem gene expression studies of the choroid plexus epithelium in AD patients show changes indicative of increased permeability of the blood-cerebrospinal fluid barrierand a reduction of macrophage recruitment [47], factors that woud favour pathogen entry and reduce their phagocytosis by macrophages. The hippocampus bulges into the temporal horn of the lateral ventricle [48] and this area, a keystone of AD pathology, is thus in close proximity to a major site of

cerebral pathogen entry. AD genes are also enriched in a separate BBB dataset from mouse cerebral arteries. This is discussed in greater detail below. Other barriers in intestinal and pulmonary tissues, also enriched in AD genes (Fig 1), might also be considered as potential sites of pathogen entry. Immune systems play an important role at barrier interfaces [49].

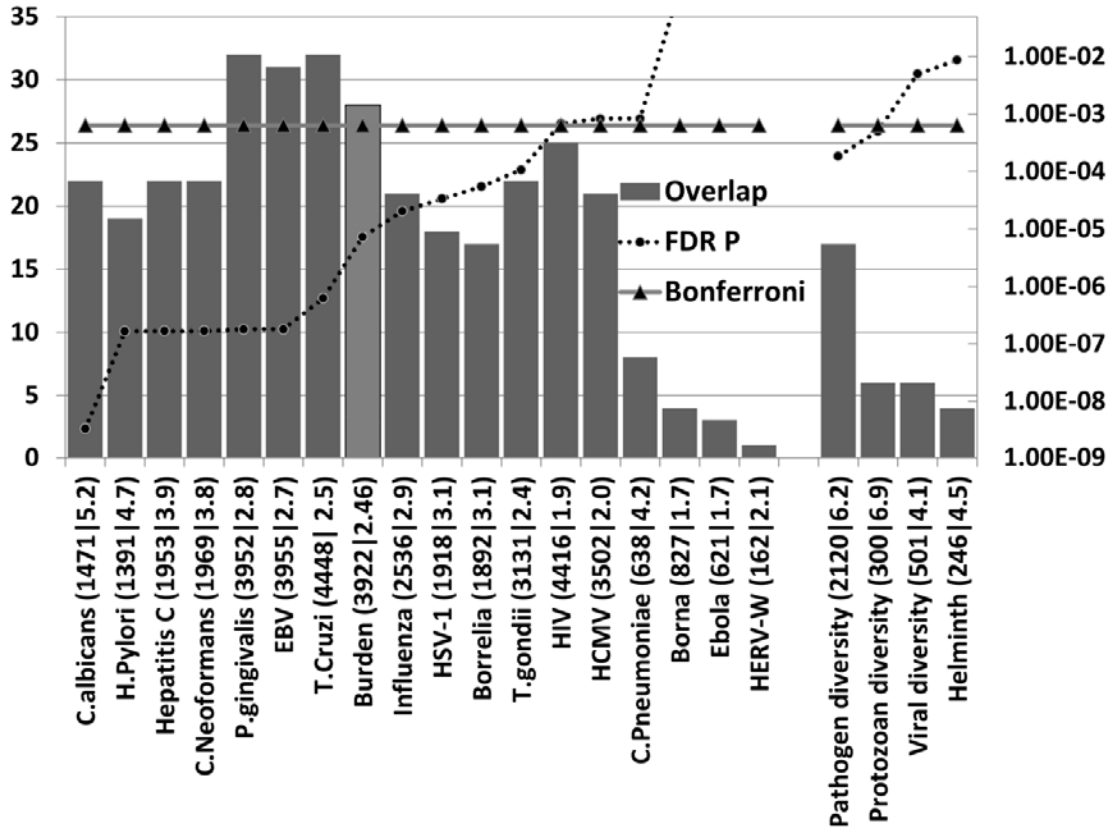
Although AD genes are expressed in other sites, the main focus, in terms of enrichment, relates to immune and barrier systems.

A number of the 78 AD genes (referenced in supplementary Table 1) are primarily concerned with immune function (**HLA-DRB1, HLA-DRB5, HMHA1, IGH**) while many others with diverse primary effects also possess relevant properties in relation to the immune system (**ACE, ADAMTS20, AP2A2, BCL3, BIN1, CR1, CLU , CUGBP2 , DISC1, EPHA1, GAB2, INPP5D, MEF2C. MS4A3, MS4A4A, RIN3, SCIMP, SPPL2A, STK24, TREM2, TREML2, ZNF224**) or pathogen defence (e.g. phagocytosis or autophagy) (**ABCA7, APOC1, APOE, BCAM, CD2AP, CD33, CDON, CELF1, PAX2, PTK2B, SASH1, SQSTM1**). A number of the AD genes also act as primary receptors for pathogens. These include the poliovirus receptor **PVR**, the HSV-1 receptor **PVRL2**, and complement receptor (**CR1**), which binds to many opsonised pathogens but which may also act as an entry receptor for *Plasmodium falciparum*, *Legionella pneumophila and Mycobacterium tuberculosis.* **CD33** binds to the HIV-1 gp120 protein and to diverse forms of sialic acid which coats many pathogens. Others bind bacterial lipopolysaccharides (**APOC1** and **TREM2**) or the Escherichia coli cytotoxic necrotizing factor 1 (**BCAM**). Others (**AP2A2**, **BIN1, CD2AP,** and **PICALM**) are involved in endocytosis, an obligate requirement for pathogen entry following binding to cognate receptors (see supplementary Table 1 for references).

Host/pathogen interactomes are enriched in AD genes (Fig 2).

Fig 2. The number of AD genes (of 78) overlapping with diverse host/pathogen interactomes, or with those implicated in pathogen, protozoan or viral diversity or with the immune response to parasitic worms (Helminth) (Bars). The identities on the X-axis (e.g. *C. albicans* (1471|5.2) are appended with the total number of genes in each interactome (1471 in this case) or genetics dataset followed by the enrichment ratio (5.2 fold). The FDR-corrected p value for enrichment, derived from the hypergeometric distribution, is shown on the right hand axis (log scale) which is set to a maximum of 0.05. Invisible points are above this value. The Bonferroni cut-off level (p=0.05/78) is also shown.The Burden data (lighter shaded bar) correspond to the combined interactomes and AD gene overlaps of the human cytomegalovirus (HCMV), HSV-1, *Borrelia burgdorferi*, *Chlamydia pneumoniae* and *Helicobacter pylori.* EBV= Epstein-Barr virus.

Figure 2



All host/pathogen interactomes, with the exception of those of the Borna virus, Ebola virus and the HERV-W retrovirus were significantly enriched in AD genes (FDR p <0.05) with all but HIV-1, the cytomegalovirus and *C. pneumoniae* below the Bonferroni corrected value (P=6.41E-4). Pathogen burden (cytomegalovirus, HSV-1, *B. burgdorferi*, *C. Pneumoniae* and *H. Pylori)* has been associated with Alzheimer's disease [1] and the pooled interactomes of these five pathogens (3922 host genes) were significantly enriched in AD genes (p= 7.3E-6). Given the variety of pathogens reported in AD brains (Table 1) other cumulative effects might be expected for various permutations.

The most significant pathogens related to fungi (*C. albicans* and *C. Neoformans*), the gum disease pathogen *P. Gingivalis* and the Epstein-Barr and hepatitis C viruses. Numerous fungal species, including *C.albicans*, have been detected in the AD brain (Table 1), although *C. Neoformans* was not one of the species studied. Two case reports have demonstrated virtually complete recovery from long-term (3 years) mis-diagnosed dementia/Alzheimer's disease following antifungal treatment for *C. Neoformans* infection [50,51].

The Epstein-Barr virus has been associated with AD and hepatitis C associated with dementia (table 1). *In vivo* studies for the Epstein-Barr and Hepatitis C viruses are however limited by their inability to infect rats or mice. Several of these pathogens including *C. pneumoniae* , HSV-1, cytomegalovirus and the Epstein-Barr and hepatitis C viruses or *H. pylori* and *B. Burgdorferri* [52-59], periodontitis and P.Gingivalis [57]have also been associated wiith atherosclerosis, an important endophenotype in AD [60].

Apart from **APOE4** no AD genetic variants seem to have been studied in relation to effects on pathogens and it is impossible to note whether the variants favour or oppose their destructive potential. The apolipoprotein E (**APOE4**) variant protects against hepatitis C [61], but favours the cerebral entry of HSV-1 [62]and enhances the attachment of *C. pneumoniae* elementary bodies to host cells [63].

AD genes overlap with those implicated in pathogen, protozoan or viral diversity or with the immune response to parasitic worms (Fig 2).

The AD genes are enriched in a series of genome-wide and global-wide datasets related to general pathogen diversity , protozoan or viral diversity (the number of different pathogens in a geographic region) or with the immune response to parasitic worms, most significantly so for general pathogen and protozoan diversity (FDR $p < 0.05$). The overlaps in relation to viral diversity or the response to parasitic worms exceeded the Bonferroni cut-off.

In evolutionary terms, these pathogen-related genes likely reflect pathogen resistance rather than susceptibility [17-20].

It has also been noted that genes related to inflammatory diseases [64] or to the AD gene network [65]are subject to positive selection pressure. While many pathogens have been implicated in AD, the selection of AD genes for pathogen resistance rather than susceptibility seems logical in relation to several considerations, as already proposed [66,67]. Firstly, the old age of AD patients indicates survival from the many infectious diseases that are among the principal causes of death in adults and children. In the USA, the leading non-accidental causes of death in adults (2013 figures) include heart disease; cancers; chronic lower respiratory diseases; cerebrovascular diseases; Diabetes mellitus; Influenza and pneumonia; nephritis, nephrotic syndrome and nephrosis [68].

Certain viruses, helminths and bacteria are oncogenic and it has been estimated that 15-20% of cancers are due to infections [69]. The inverse association between the incidence of cancer and Alzheimer's disease [70] suggests that AD genes might well be cancer protective (but also that death due to cancer precludes AD). Inflammatory heart diseases [71] and atherosclerosis, cerebrovascular disorders and stroke have also been linked to infection [72,73]. Enteroviruses have been implicated in Type 1 diabetes mellitus [74].

The leading non-accidental causes of infant deaths were congenital malformations, deformations and chromosomal abnormalities; disorders related to short gestation and low birth weight, not elsewhere classified; newborn affected by maternal complications of pregnancy; sudden infant death syndrome; newborn affected by complications of placenta, cord and membranes; bacterial sepsis of newborn; respiratory distress of newborn; diseases of the circulatory system; and neonatal haemorrhage. Again, many of these relate to infections. In evolutionary terms, pandemics and infectious diseases have been, and in poorer countries still are, associated with high mortality.

In relation to Alzheimer's disease, the apolipoprotein E (**APOE4**) variant protects against malaria [75] and hepatitis C [61], although **APOE4** favours cerebral entry of the herpes simplex virus [62]and enhances the attachment of Chlamydia pneumoniae elementary bodies to host cells [63] . Malaria and hepatitis C are both associated with high mortality [76,77] and the protective effects of **APOE4** would encourage its maintenance in the population, to the detriment of infection by the less virulent agents.

The **APOE4** variant is also associated with enhanced immune/inflammatory responses. For example, Toll-like receptor activation (TLR3, 4) in microglia induces cyclooxygenase-2 (PTGS2), microsomal prostaglandin E synthase (PTGES), and prostaglandin E2, an effect exaggerated in **APOE4**/**APOE4** mice [78]. **APOE4** is also associated with enhanced *in vivo* innate immune responses in human subjects. Whole blood from healthy APOE3/**APOE4** volunteers induced higher cytokine levels on ex vivo stimulation with Toll-like receptor (TLR2, 4 or 5) ligands than blood from APOE3/APOE3 patients [79]. Gain of function also applies to AD variant forms of complement receptor **CR1**, which are better able to bind complement component C1q or C3B [80] . C1q and C3B are opsonins that interact with complement cell-surface receptors (C1qRp, **CR1**, CR3 and CR4) to promote phagocytosis (including that of infectious agents) and a local pro-inflammatory response [81] . **TREM2** variants in AD are also associated with enhanced inflammatory responses (upregulation of proinflammatory cytokines) [82]. In presenilin (**PSEN1**) mutant knockin mice, microglial challenge with bacterial lipopolysaccharide

results in enhanced nitric oxide and inflammatory cytokine responses, relative to normal mice [83]. For these genes at least, this gain of immune/inflammatory function concords with selection for pathogen resistance.

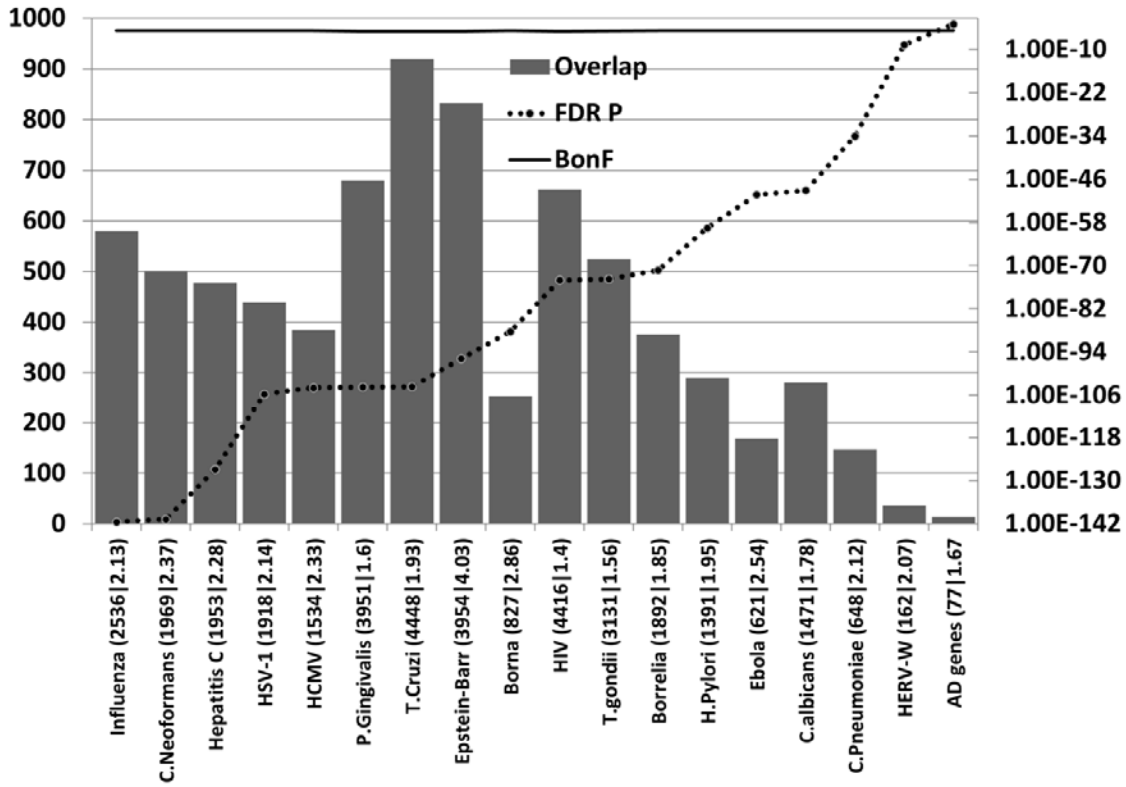
It has also been noted that unaffected offspring with a parental history of AD have an enhanced inflammatory response in lipopolysaccharide -stimulated whole blood samples, producing higher levels of interleukin 1beta, tumor necrosis factor alpha and interferon gamma in response to LPS. This effect was independent of the **APOE4** variant [84] suggesting that other AD genes are also endowed with gain of function in relation to the immune/inflammatory system. Monocyte-derived dendritic cells from Alzheimer's disease patients also produce more interleukin 6 than those from healthy controls. AD monocytes stimulated with LPS also show a higher induced expression of the pro-inflammatory ICAM-1 adhesion molecule than controls [85]. Beta-amyloid also stimulates cytokine production in peripheral blood mononuclear cells (PBMC) and the production of the chemokines, RANTES, MIP-1beta, and eotaxin as well as that of CSF2 (colony stimulating factor 2 (granulocyte-macrophage)) and CSF3 (colony stimulating factor 3) is greater than controls in AD-derived PBMC stimulated with beta-amyloid [86].

Given the antimicrobial properties of beta-amyloid, any genetic variant that increase its production, at least in the periphery, might also be considered as desirable, in evolutionary terms, in relation to pathogen defence. A high percentage of AD GWAS genes are involved in APP processing [87]. The AD genetic variant of **ABCA7** results in increased secretion of beta amyloid and raised beta-secretase activity in CHO- and HEK cells with the Swedish APP mutation [88], but the effects of late-onset AD variant genes on the beta-amyloid response to pathogens remain to be determined.

Host/pathogen interactome enrichment in misregulated genes of the Alzheimer's disease hippocampal transcriptome (Fig 3).

Fig 3. The number of genes misregulated (combined up and down) in a microarray study of the AD hippocampus overlapping with diverse host/pathogen interactomes. The identities on the X-axis (e.g.

C. albicans (1471|5.2) are appended with the total number of genes in each interactome (1471 in this case) or genetics dataset followed by the enrichment ratio (5.2 fold). The p value for enrichment, derived from the hypergeometric distribution, is shown on the right hand axis (log scale) which is set to a maximum of 0.05. The Bonferroni cut off (1.74E-05) is also shown.



All pathogen interactomes, most notably relating to influenza, *C. Neoformans* and Hepatitis C were highly enriched in genes relating to this microarray dataset (combined up and downregulated genes). The significance level of the interactome enrichment for most pathogens was several orders of magnitude below the Bonferroni cut off (p=1.74E-05) (Fig 3). 14/78 AD genes appear in this microarray dataset (FDR p = 0.001). Two case reports have demonstrated virtually complete recovery

from long-term (3 years) mis-diagnosed dementia/Alzheimer's disease following antifungal treatment for *C. Neoformans* infection [50,51]. Regarding the influenza data, bronchopneumonia, often caused by influenza, is a common final cause of death in dementia patients [89] and such recent infections close to death may well influence the data.

Regardless of the rank order, it is clear that many diverse pathogen interactomes affect several hundred genes of the 2879 misregulated in the AD hippocampus and/or that these misregulated AD genes represent a substantial percentage of the individual pathogens' interactomes (Fig 3).

Kegg pathway analysis of these misregulated hippocampal genes using the consensus path database [90] showed that many infection-related pathways were also significantly enriched (FDR $p < 0.05$). These included (pathogen with N genes followed by the FDR corrected p value): Epstein-Barr virus infection (74,5.5E-7); Salmonella infection (36,0.0001); Tuberculosis (57,0.0009); Epithelial cell signaling in Helicobacter pylori infection (28,0.00097); Shigellosis (27,0.001); Influenza A (54,0.003); Herpes simplex infection (56,0.0036); Vibrio cholerae infection (21,0.0089) ;HTLV-I infection (71,0.0096); Toxoplasmosis (37,0.013); Hepatitis B (43,0.018); Pathogenic Escherichia coli infection (20,0.02); Bacterial invasion of epithelial cells (26,0.02); Measles (38,0.04).

Upregulated genes in the AD hippocampus are enriched in genes upregulated by multiple viral, bacterial and fungal pathogens or Toll-like receptor ligands.

Numerous infection-related microarray datasets exist in the Molecular signatures database or in the Gene expression omnibus (see methods), using blood cells taken from infected patients, or cells or tissues infected under laboratory conditions.

Figure 4: The number of upregulated genes (bars) from the AD hippocampal transcriptome that overlap with upregulated genes in viral infection datasets from the Molecular signatures database or the Gene expression omnibus (see methods). The effects of the mimic poly(I:C) are also shown, as is the effect of interferon gamma on gene expression in microglial cells. For each datapoint, the name

of the virus is shown, followed by the cell type and the total number of upregulated genes in the viral datasets (limited by MSigDb or GEO). The significance of enrichment (right axis) represents the FDR corrected p value from the hypergeometric test. All values are below the Bonferroni corection (0.05/300 = 1.67E-04). Because the number of downloaded genes is mostly limited to 300, this is the maximum number of possible overlaps. The pale bar represents the microglial response to interferon gamma.

Tissue/cell abbreviations; A549= adenocarcinomic human alveolar basal epithelial cells; ABL = Akata Burkitt's lymphoma cells; B2B/16HBE, BE(2)C or BEAS-2B = human bronchial epithelial cells; BroLav = human bronchial lavage; Calu-3 = Cultured Human Airway Epithelial Cells; DC = dendritic cells; GRE = glioma cell line; HAE = human airway epithelial cells; HBEC = Human Bronchial Epithelial Cells; HEK = human embryonic kidney cells; HeLa = cervical cancer cell line; HuH-7 = hepatocarcinoma cell line; Macro = macrophage; Mgli = microglia; Mono =monocytes; NES = human nasal epithelial scrapings; NK = natural killer cells; PBMC = peripheral blood mononuclear cells; PLC/PRF/5 cells = human liver hepatoma cells; Trach epi = Tracheal epithelial cells

Viral abbreviations (Reading from the left): HIV= human immunodeficiency virus, Cox B3 =Coxsackie B3 virus; RSV = respiratory syncytial virus; LCMV= Lymphocytic Choriomeningitis Virus; HMPV= Human metapneumovirus; Ebola= Ebola virus; Influenza = Influenza A virus; Sendai = Sendai virus, HCoV = human coronavirus; IFNG = interferon gamma; SARS = severe acute respiratory syndrome coronavirus; HCMV = human cytomegalovirus; MCMV = mouse cytomegalovirus; Dhori = Dhori virus; EBV = Epstein-Barr virus; HepC = hepatitis C virus; KSHV= Kaposi's sarcoma-associated herpesvirus; HSV-1 = herpes simplex; Norwalk = Norwalk virus (Norovirus); Ad5 = adenovirus 5; SIV= Simian immunodeficiency virus; poly(I:C)= Polyinosinic:polycytidylic acid (a viral mimic stimulating Toll-like TLR3 receptors); NDV = Newcastle disease virus; WestEq = Western equine encephalomyelitis virus; LASV = Lassa virus; dsRNA = double stranded RNA; HEV = hepatitis E virus.

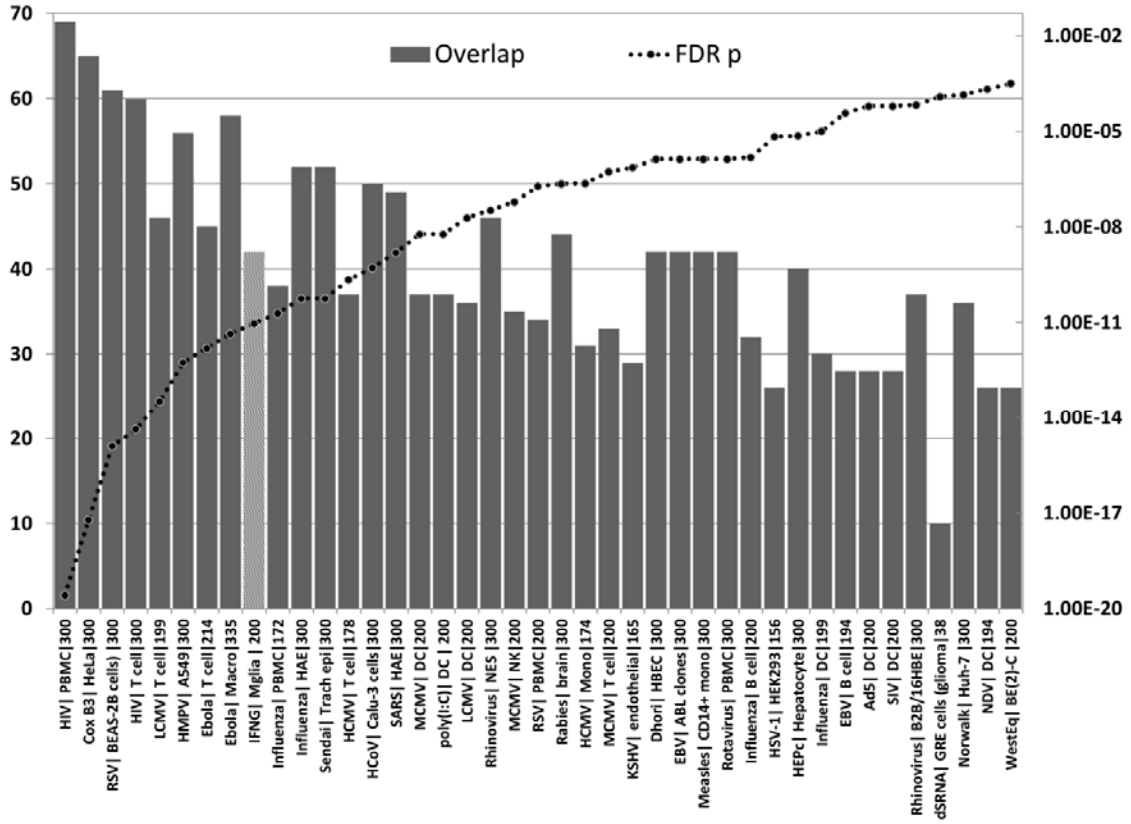


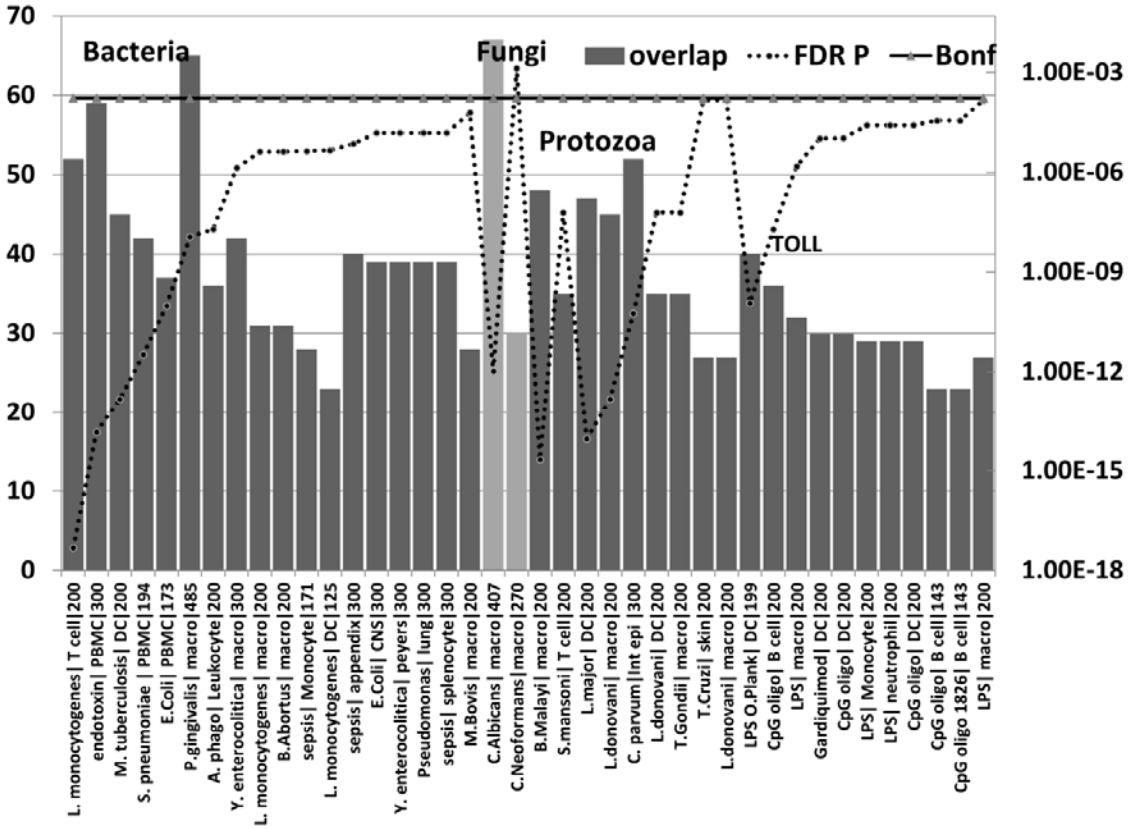
Fig 5

The number of upregulated genes (bars) from the AD hippocampal transcriptome that overlap with upregulated genes in bacterial (first batch), fungal (pale bar =*C.albicans* , C.Neoformans), nematode (B.Malayi) /trematode (S.Mansoni) , or protozoan microarray datasets (see methods). The effects Lipopolysaccharides and other Toll receptor ligands are also shown.

For each datapoint, the name of the pathogen or ligand is shown, followed by the cell type and the total number of upregulated genes in the comparator datasets (limited by MSigDb or GEO). The significance of enrichment (right axis) represents the FDR corrected p value from the hypergeometric test. All values except for *C.Neoformans* are below the Bonferroni correction level.

Pathogen or ligand abbreviations (from left) *L. monocytogenes = Listeria monocytogenes*; endotoxin = gram-negative bacterial wall component; *S.pneumoniae = Streptococcus pneumoniae; E.Coli = Escherichia coli; P. gingivalis = Porphyromonas gingivalis; A .phago = Anaplasma phagocytophilum; Y. enterocolitica = Yersinia enterocolitica; M.Bovis = mycobacterium bovis; C.albicans = Candida albicans, C.Neoformans = Cryptococcus neoformans, B.Malayi = Brugia malay*i (filarial parasite causing elephantiasis); *S.mansoni = Schistosoma mansoni; L. donovani = Leishmania donovani; C. parvum = Cryptosporidium parvum; L. Major = Leishmania major; T.Gondii = Toxoplasma Gondii; T. Cruzi = Trypanosoma Cruzi*; LPS = lipopolysaccharide; LPS O.Plank = Oscillatoria Planktothrix (cyanobacteria lipopolysaccharide) CpG oligo = CpG Oligodeoxynucleotide (TLR9 ligand); Gardiquimod = TLR7 ligand;

Cell type abbreviations as for Fig 4. CNS = central nervous system; peyers = peyers patch; Int epi = intestinal epithelial cells;



The hippocampal genes upregulated in Alzheimer's disease were significantly enriched in upregulated genes in datasets from multiple viral species and to double stranded RNA and the viral mimic/TLR3 agonist, Polyinosinic:polycytidylic acid (poly I:C) (Fig 4). The viruses ranged from the benign (e.g. the rhinovirus that causes the common cold) to the highly malignant (e.g. the ebolavirus, rabies virus or HIV-1). They include common human infectious agents (e.g. adenovirus 5, influenza, Epstein-Barr virus, herpes simplex virus (HSV-1), measles or the Norwalk virus). Apart from HSV-1, the human cytomegalovirus, HIV-1 or hepatitis C (See Table 1) none of these have been implicated in Alzheimer's disease or dementia. Most microarray experiments related to immunocompetent blood cells (B cells, T cells, dendritic cells, monocytes and macrophages) or to cultured cell lines. No infection-related datasets were found for microglia, the brain resident immunocompetent cells, but significant enrichment of the AD upregulated genes was observed for genes upregulated by interferon gamma in microglial cells (Fig 4). Interferon gamma plays an important role in the response to viral, bacterial and parasitic infections [91].

The upregulated hippocampal genes in AD were also enriched in infection datasets for numerous bacteria as well as to fungal species (*C. albicans* and *C.neoformans)* and in those related to bacterial endotoxin or sepsis and to nematode/trematode or protozoan infection datasets (FDR $p < 0.05$) (Fig 5). This also applied to diverse lipopolysaccharide datasets and responses to Toll-like receptor ligands, CpG oligonucleotide (a ligand for TLR9, which mediates cellular response to unmethylated CpG dinucleotides in bacterial DNA (definition from Refseq)) and R848 (a ligand for TLR7/TLR8 both of which recognize RNA released from pathogens that enter the cell by endocytosis [92]) (Fig). With the exception of *H.Pylori, P.Gingivalis* and *Borrelia burgdorferi* and *C.albicans* or *C.Neoformans,* none have been implicated in AD.

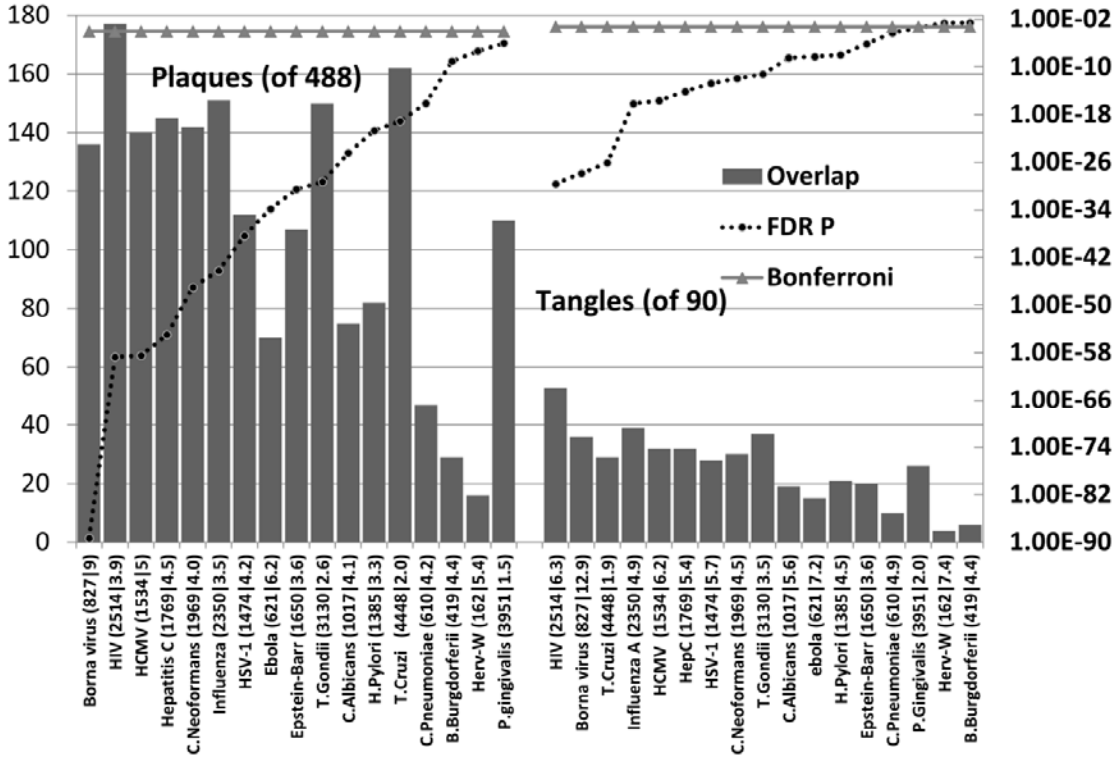
Together these data suggest a significant parallel between the upregulated genes in the AD hippocampus and the responses to multiple and diverse infectious agents with little overall

discrimination between viral, bacterial, fungal or protozoan types of infection. Multiple pathogens have been detected in the AD brain (see Table 1) and the diversity of these infection related overlaps with the AD hippocampal transcriptome suggests that many other pathogens could induce similar pathological transcriptome changes. Microbiome studies in the AD brain and periphery will help to elucidate the role of multiple pathogens.

Pathogen interactomes are enriched in the proteins found in AD amyloid plaques and neurofibrillary tangles (Fig 6).

Fig 6. Host pathogen interactome enrichment in a set of 488 proteins isolated from amyloid plaques in the AD brain or from 90 proteins isolated from neurofibrillary tangles. The identities on the X-axis are appended with the total number of genes in each interactome followed by the enrichment ratio. The FDR p value for enrichment, derived from the hypergeometric distribution, is shown on the right hand axis (log scale) which is set to a maximum of 0.05.

Figure 6



All pathogen interactomes were significantly enriched in proteins found in plaques and all except HERV-W and *B.Burgdorferi* interactomes significantly enriched in tangle proteins (below the Bonferroni cut-off level). The Borna virus and HIV-1 ranked highly in both cases. There is only one publication relating to Borna virus effects on beta-amyloid and none could be found for tangles. The microglial activation produced by the virus reduced brain parenchymal, but increased cerebral vascular beta-amyloid deposition, in APP transgenic mice [93]. The top agents relating to plaques were predominantly viral, while those relating to tangles were mostly viral, but included the parasites, *T. Cruzi* and *T.Gondii*.

Beta-amyloid is an antibacterial, antifungal and antiviral agent (Table 1). It has been shown that it binds to *C.albicans* and *S.Typhimurium* [2] and presumably to other microbes. Such microbes may well have sequestered host proteins specific to their particular life cycles during their passage to the cell, and this would partly explain the interactome enrichment. In addition to the plaque proteins relating to pathogen life cycles (for example receptor binding , endocytosis and transport between intracellular compartments or nuclear entry and subsequent translation in the case of HSV-1) , the proteins found in plaques and tangles contain many related to the immune system, inflammation and autophagy, all of which play a general role in pathogen defence [8,24,25] as does beta-amyloid.

Viruses are transported via the microtubule network [94], which is also exploited by *C.Pneumoniae*, *T.Cruz*i and *T.Gondii* to reorganise cellular organelles to the pathogens' advantage [95,96]. Phosphorylated *tau* is a hallmark of neurofibrillary tangles and is induced by many pathogens (Table 1). Tau phosphorylation can also be induced by interferon gamma, an effect related to disinhibition of glycogen synthase kinase [97]. It is not clear whether or how such effects could influence the pathogens.

AD genes are localised in the Blood brain barrier

30/78 AD genes are expressed in the BBB proteome dataset of mouse cerebral arteries [28] (Fig 1). The list below indicates the 30 BBB genes, annotated with the number of pathogen interactomes

with which they overlap. Most BBB expressed genes interact with none or few pathogens (5 or less of the 17 studied), suggesting a subdivision of mainly BBB and mainly pathogen related. This could of course be confounded by missing data, as several of these genes are poorly characterised in terms of function. These 30 genes (N interactomes in brackets) are:- **PCNX (0), ABCA7 (1), ADAMTS20 (1), ATXN7L1 (1), TREML2 (1), AP2A2 (2), BCAM (2), CNTNAP2 (2), ECHDC3 (2), FRMD4A (2), GRIN3B (2), PAX2 (2), PICALM (2), DISC1 (3), LUZP2 (3), RELN (3), TTLL7 (3), FERMT2 (4), HMHA1 (4), MSRA (4), PPP1R3B (4), SASH1 (4), BIN1 (5), SORL1 (5), PVRL2 (7), MMP12 (8), CLU (9), PTK2B (10), BCL3 (13), SQSTM1 (13).**

The BBB location of a high proportion of AD genes indicates an important function in relation to AD. Several studies have reported that disruption of the blood brain barrier is an important feature of AD [98-101]. Cerebral microbleeds and cortical siderosis (an increase in blood-derived iron deposition) are a feature related to BBB disruption in AD patients [102-104]. Many bacteria depend upon the availability of free iron and such effects may contribute to their sucessful colonisation in AD [105].

Other environmental risk factors in AD disrupt the blood-brain barrier and BBB integrity is maintained by beneficial factors.

AD susceptibility genes might have been selected for pathogen resistance rather than susceptibility (see above). In which case, what are the factors, in the aged, that nevertheless permit the cerebral invasion of a large variety of pathogens? (See Table 1) Certain viruses (e.g. HSV-1) can enter the brain via the olfactory or other neural routes, exploiting an ability to use the axonal transport system [106] . Some parasites [107] and bacteria (e.g. *C. Pneumoniae* [108,109]) have also found ways to circumvent the barrier systems that usually protect the brain.

Aging itself leads to blood brain barrier dysfunction [110] and immunosenescence is also a feature of ageing and AD. However, while immunosenescence can increase susceptibility to pathogens due to immunodefficiency, it is also accompanied by an increase in the pro-inflammatory activity of monocytes and macrophages which can lead to chronic low grade inflammation, termed 'inflamm-

ageing"[111,112]. This increased inflammatory function also applies to microglia, the macrophage-like cells in the brain [113]. Certain AD gene variants are associated with enhanced pro-inflammatory responses (see above) and cerebral pathogen entry would thus be met with a doubly vigorous inflammatory response related to both immunosenescence and genetic variation. Persistently activated monocyte/macrophages have been observed in the blood of patients with early AD [114] and increased activation of microglia/macrophages, colocalized with the area of heavy beta-amyloid concentration, is also observed in the brains of AD patients [115].

Apart from pathogens, many other environmental risk factors have been reported in AD. These include diabetes, midlife hypertension or obesity, smoking and physical inactivity [116]. Other contributory factors include previous head injury [117], exposure to toxic metals (aluminium [118,119] or copper[120]), pesticides (organochlorine and organophosphate insecticides) [121,122], industrial chemicals (flame retardants) and air pollutants (particulate matter and ozone [123-126]). High levels of cholesterol or homocysteine [127-130]and low levels of folic acid [131,132] have also been associated with AD. In relation to cholesterol, atherosclerosis of the carotid arteries or of leptomeningeal vessels and in the circle of Willis has also been observed in AD. Such atherosclerotic effects can lead to chronic cerebral hypoperfusion [60,133,134].Sleep disruption or obstructive sleep apnoea are also associated with AD risk [135,136].

Factors reported to be of benefit, or that reduce the incidence of AD include the use of non-steroidal anti-inflammatories (NSAIDs) [137,138], and the early use of statins [139-141] . Statins also have antimicrobial effects against oral microorganisms including *Aggregatibacter actinomycetemcomitans* and *P. Gingivalis*, and against most dental plaque bacteria, including *Streptococcus mutans*. They possess antiviral properties against the human cytomegalovirus, HSV-1, hepatitis B and C viruses, and antifungal properties against *Candida albicans, Aspergillus fumigatus*, and Zygomycetes species [142].

Beneficial dietary factors in AD include caffeine [130], chocolate (versus cognitive decline in the non-demented aged)[143]) and the Mediterranean diet [144-146] . Melatonin [147,148], estrogen [149-151]and memantine [152,153] also have reported benefits in AD.

The environmental risk factors associated with AD disrupt the BBB, and BBB integrity is maintained by the beneficial factors (Table 2). While infections are random uncontrollable events, many of the other environmental risk factors are modifiable by lifestyle changes, for example diet, obesity, smoking and exercise, and it has been estimated that addressing such modifiable risk factors might result in a significant reduction in the incidence of AD [116]. Amelioration of BBB disruption has already been proposed as a potential therapy in AD, and several drugs including angiotensin receptor blockers, etodolac (NSAID), granisetron (5HT3 serotonin receptor antagonist) or beclomethasone (corticosteroid) [154,155] as well as other NSAIDS, statins and other drugs referenced in Table 2 might be considered as suitable candidates.

Diverse pathogen sensors and defenders relating to bacteria, viruses, parasites and fungi are upregulated in the AD brain, blood or CSF.

We have evolved numerous pathogen detectors whose activation leads to stimulation of the immune system and to the production of defensive mechanisms, including inflammation and free radical attack. Multiple pattern recognition receptors including Toll-like receptors , C-type lectin receptors and nucleotide-binding oligomerization domain-like receptors (NOD-like) sense motifs in bacterial, viral, fungal and parasite proteins or other compounds or respond to foreign bacterial or viral DNA or RNA in cellular locations where host DNA or RNA should not exist [156-159].

Infection also activates inflammasomes, which trigger the maturation of proinflammatory cytokines, activating innate immune defences [160].

In addition to this, a large number of defensins and other antimicrobial peptides exist, targeting bacteria, fungi, parasites and viruses [161]. Beta-amyloid is one such [3].

EIF2AK2 (eukaryotic translation initiation factor 2 alpha kinase 2) better known as pkr, is activated by viral double stranded RNA and to bacterial RNA. This phosphorylates eif2alpha, leading to the arrest of the protein translation that is needed for viral replication. Pkr stimulation also leads to the production of interferon and to activation of the inflammasome [162-165]. Other viral RNA-sensors include RIG-I (coded by retinoic acid-inducible gene 1= DDX58) , MDA5 (Melanoma Differentiation-Associated protein ; coded by IFIH1) and LGP2 (coded by DEXH-box helicase 58= DHX58) [92].

Indoleamine 2,3-dioxygenase 1 (IDO1) diverts tryptophan metabolism to N-formyl-kynurenine, (away from serotonin production) .IDO1 upregulation is an important defence mechanism against pathogenic bacteria, many of which rely on host tryptophan. It is involved in antimicrobial defence and immune regulation, and its effects are not restricted to bacteria This IDO1 response is also deleterious to other pathogens and parasites, including T.Gondii, and to a number of viruses, including herpes simplex virus and other herpes viruses [166]. Kynurenine and kynurenic acid produced by IDO1 activation, are ligands for the aryl hydrocarbon receptor (AHR), which plays an important role in antimicrobial defence and immune regulation [167].

The function of these players with respect to the main pathogens studied above is reviewed in Supplementary Table 2, which also reports expression data in the Alzheimer's disease brain, blood or CSF. Data derived from this table are illustrated in Figs 7 (viral) and 8 (bacteria, fungi and parasites).

Fig 7 and 8. Viral (Fig 7) and fungal or bacterial (Fig 8) defenders and sensors and their expression (^ = upregulated; down = downregulated) in the brain, blood or cerebrospinal fluid of Alzheimer's disease patients. CP = choroid plexus; CSF= cerebrospinal fluid; GVS= granulovacuolar degeneration; HPC = hippocampus; lympho = lymphocytes; macro = macrophages; mcyt=monocytes; mgli = microglia; PBMC = peripheral blood mononuclear cells; Plaq = amyloid plaques; Ser = serum; tang = tangles;

αdefs or βdefs= unspecified alpha or beta defensins: AGER= advanced glycosylation end product-specific receptor (also known as RAGE); APCS= amyloid P component, serum ; CAMP = cathelicidin

antimicrobial peptide (LL-37); Calpro= Calprotectin (S100A8/S100A9 dimer);CHI3L1 = chitinase 3 like 1 (aka YKL-40); C-type lectin = CLEC's; CRP = C-reactive protein; DEAD box proteins = DDX's; Defensins = DEFA's, DEFB's: EIF2AK2 = eukaryotic translation initiation factor 2 alpha kinase 2 (pkr); ELANE = elastase, neutrophil expressed ; IAPP = islet amyloid polypeptide (Amylin); IDO1= indoleamine 2,3-dioxygenase 1; Interferons = IFNA1, IFNA5, IFNB1, IFNG; LCN2 = lipocalin 2; LGALS3 = lectin, galactoside binding soluble 3; LTF = lactotransferrin; MAC = membrane attack complex (complement components C5b-C9); MRC1 = mannose receptor, C type 1; NAIP = NLR family, apoptosis inhibitory protein ; NLRP1 and 3 = NLR family pyrin domain containing 1 and 3; NOD1 and NOD2 = nucleotide binding oligomerization domain containing (1 and 2) ; RARRES2 and 3 = retinoic acid receptor responder (2 and 3) : S100's= S100 calcium binding protein ;Toll-like receptors = TLR1 to 10; ZBP1 Z-DNA binding protein 1. Gene = gene related to the respective pathogen in association studies or with Alzheimer's disease (Gene AD). mod sens = modified senstitivity; The strikethrough's (e.g. ~~TLR1~~) represent a pathogen's ability to inhibit or overcome the combative effects of the defensive or sensor protein. ? = unknown

Borna = Borna virus; CMV = human cytomegalovirus; EBV = Epstein-Barr virus; HepC = Hepatitis C; HSV-1= Herpes simplex; Influ= Influenza A virus; Borrel= *Borrelia burgdorferi*; C.Alb= *Candida albicans*; C.Neo = *Cryptococcus neoformans*; C. Pneu = *Chlamydia pneumoniae*; H.Pyl= *Helicobacter pylori*; P.Ging = *Porphyrymonas gingivalis*; T.Gon = *Toxoplasma Gondii*

Those shaded in black are those most implicated in Alzheimer's disease (Table 1)

Figure 7: Viruses:

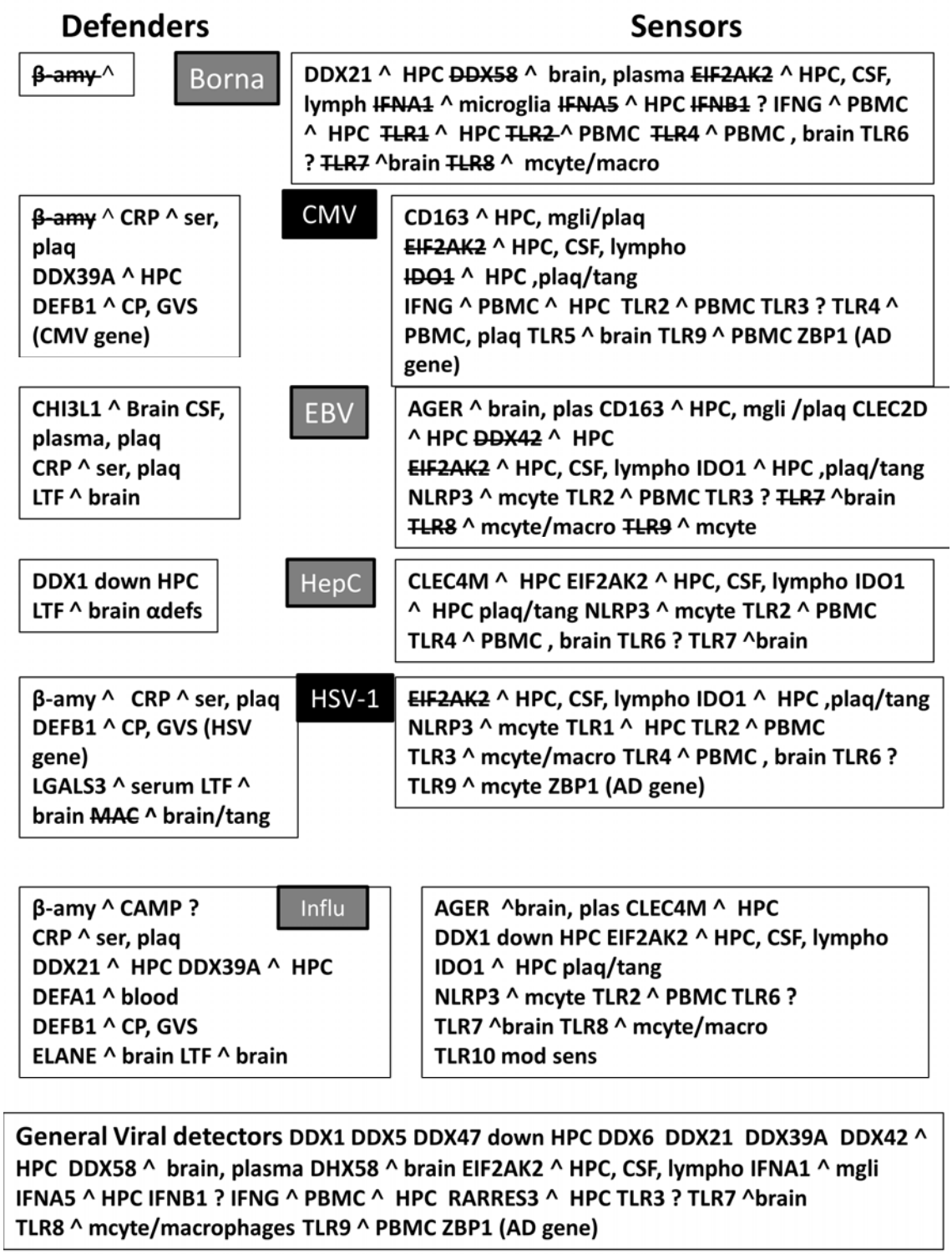
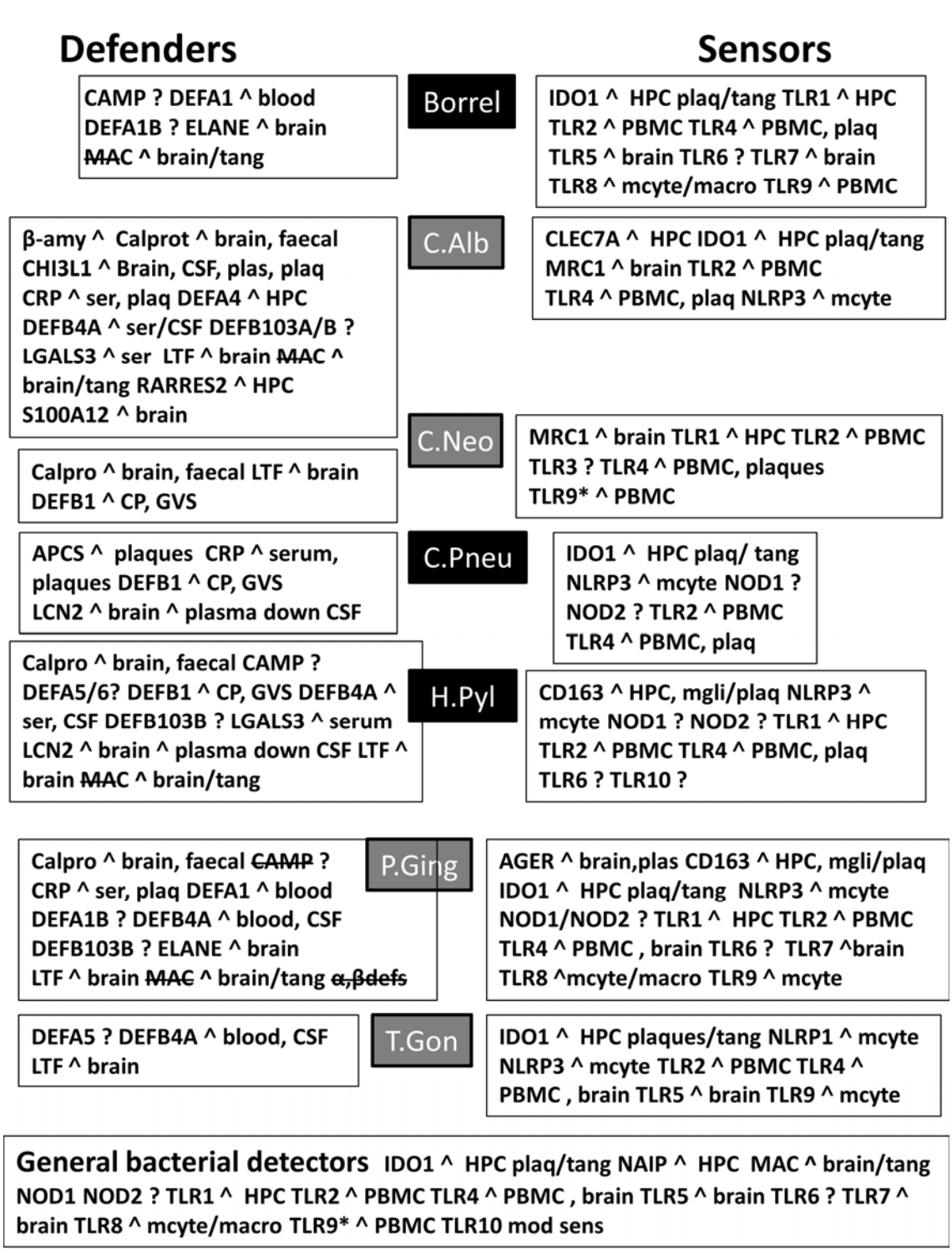


Figure 8: Bacteria, fungi and *T.Gondii*



These figures show that sensors and defenders relating to multiple pathogens are upregulated in the AD brain, blood or CSF. These involve reactions to many different classes (bacteria, viruses, fungi and parasites) and there appears to be no discrimination, or focus on any particular type. This would concord with the multiple and diverse pathogen species that have been detected in the AD brain (Table 1) and with the relationship between the AD genes or the hippocampal transcriptome with multiple pathogen species.

Caveats:

This analysis is based on overlapping gene symbols rather than on specific polymorphisms. There is thus no indication of the physiological weight or importance of any gene/pathogen interaction, some of which will be more important than others. Pathogen effects may also be strain-dependent, and the size of the interactomes also varies widely. Within any large interactome there will be deleterious, neutral and beneficial effects. While HSV-1 infection causes beta-amyloid deposition and neurodegeneration [168], in its latent form, the virus can have neuroprotective effects. For example the viral latency transcript inhibits apoptosis and promotes neurite sprouting in neuroblastoma cells [169], protects neuronal C1300 and Neuro2A cells from granzyme B-induced apoptosis and CD8 T-Cell killing [170] and also protects trigeminal neurones from apoptosis [171] . The Bornavirus is capable of promoting hippocampal degeneration in Man [172]. In rats Borna virus infection decreases choline acetyltransferase activity in the cerebral cortex, horizontal diagonal band of Broca , hippocampus and amygdala [173] a situation similar to that observed in Alzheimer's disease [174] but the inflammation and microglial activation it produces can also reduce beta-amyloid immunoreactivity in the brain parenchyma of Tg2576 mutant beta-amyloid mice [93]. Chronic, adult acquired *T. Gondii* infection causes neurologic and behavioural abnormalities secondary to inflammation and neuronal loss, in a strain-dependent manner [175]. T.Gondii infection in BALB/C mice induces neuroinflamation and learning and memory deficits. It also potentiates the toxic effects

of low doses of intracerebrally administered beta-amyloid[176], but chronic infection can also increase beta-amyloid phagocytosis and clearance by recruited monocytes [177].

Dementia or neurodegeneration, in the absence of amyloid plaques is, by current clinical definition, not considered as Alzheimer's disease, but as already noted, there is no inherent biological reason for this [178,179]. Such divergent effects might also be relevant to findings relating to the presence of amyloid plaques in the absence of dementia, as observed in the Nun study [180,181] or to diagnosed Alzheimer's disease in the absence of beta-amyloid. A recent report showed that ~15% of patients clinically diagnosed with AD do not have amyloid deposits as indexed by positron emission tomography [182]. While some amyloid-negative patients could be re-diagnosed (~50%), the clinical follow-up using other criteria in other amyloid-negative patients continued to support the definition of Alzheimer's disease.

There are also many inter-pathogen interactions relevant to this relatively small sample of the potential microbiome. For example HSV-1 infection activates replication of the Epstein-Barr virus, [183]. Gingipains or other proteases secreted by *P. Gingivalis* degrade multiple complement components [184] as well as alpha- and beta defensins [185],immunoglobulins, IgG1 and IgG3 [186] and interleukin-12, preventing its ability to stimulate interferon production [187]. Such effects enable the pathogen to counteract immune defence and would also impinge on the viability of many other pathogens.

HIV-1 is immunosuppressant and has been associated with many opportunistic pathogens including tuberculosis, toxoplasmosis, cytomegalovirus encephalitis and Cryptococcal brain invasion [188,189]. The human cytomegalovirus is also immunosuppressant via an ability to target MHC class I molecules for degradation [190]and to inhibit MHC class II antigen presentation [191]. Parasites, which maintain a long-term, if unwelcome presence in the host have also developed immunosuppressant and anti-defensive strategies[192,193]. In addition, the success of most pathogens depends upon their ability to subvert the defensive armoury of the host in some way.

The AD genes affect human processes relevant to the disease itself, but given that they are also part of pathogen interactomes, polymorphisms therein are also likely to affect pathogen life cycles or the ability of pathogens to promote diverse effects within the host. Apart from **APOE4** there are no studies relating to the effects of the AD gene variants on pathogens or their effects.

For these and many other reasons, it is perhaps unwise to rank the pathogens by order of importance in relation to their enrichment or p value in any of the data described above. Suffice it to say that diverse pathogens have been detected in the AD brain and all of the bioinformatics data presented above, whether related to genes, transcriptomes, plaques or tangles implicate multiple species of pathogens across viral, bacterial, fungal and protozoan classes.

While there are statistical limitations to this type of analysis, correction for false discovery followed by the Bonferroni correction has been conservatively applied. The relationship of AD to pathogens is supported by experimental observation (Table 1) and by the antimicrobial effects of beta-amyloid. This study also relies on multiple and diverse *in silico* bioinformatic analyses linking AD GWAS genes, plaques and tangles as well as the hippocampal transcriptome to multiple pathogen interactomes, and the upregulated AD hippocampal genes to multiple infection datasets from diverse pathogen species. Polymicrobial involvement is also supported by the diversity of bacterial, viral and fungal sensors and defenders that are upregulated in the AD brain, blood or CSF. Each comparison relates to single pathogens but given the diversity of pathogens detected in AD such effects are likely to be cumulative.

Discussion

Multiple and diverse pathogens (bacteria, viruses, fungi and spirochetes) have been detected in the AD brain and many cause neurodegeneration, increase beta-amyloid deposition and tau phosphorylation or are killed/incapacitated by beta-amyloid, an antimicrobial peptide that is part of the innate immune defence system. Representatives of these pathogens target multiple AD GWAS genes, and their interactomes are enriched in genes related to the AD hippocampal transcriptome

and to the proteins found in AD plaques and tangles. The upregulated genes of the AD hippocampal transcriptome also correspond to those upregulated by multiple species of viral, bacterial, fungal and protozoan pathogens or by interferon gamma and Toll-like receptor ligands.

The AD genes are preferentially localised in the bone marrow and other immunocompetent tissues, and in exosomes that are hijacked by pathogens for intercellular spread. They are also localised in the lateral ventricle and the hippocampus which abuts this area, a prime site of pathogen invasion via the choroid plexus and the blood/csf barrier.

The AD genes are enriched in global GWAS datasets relating to pathogen diversity, suggesting that some have been selected for pathogen resistance rather that susceptibility. This is supported by the old age of AD patients, indicating survival from the many infections that contribute to mortality in the younger population. **APOE4** variants protect against malaria and hepatitis C, and immune/inflammatory gain of function applies to **APOE4**, **CR1**, **TREM2** and presenilin variants, supporting this contention. Logically, any gene variant increasing the production of the anti-microbial peptide beta-amyloid in response to pathogens might also be considered as beneficial in these evolutionary terms. Apart from APOE4, there is however little data examining the effects of AD gene variants on pathogen life cycles or that relate specifically to pathogen responses.

Many AD genes are also localised in the blood brain barrier. This should provide an effective shield against many infections but it is disrupted by multiple environmental risk factors implicated in Alzheimer's disease and protected by several factors reported to be beneficial in relation to Alzheimer's disease, including NSAIDs, statins, oestrogen, memantine, melatonin, and components of the Mediterranean diet.

The relationship between pathogens and Alzheimer's disease has a long history coupled with a degree of scepticism, perhaps related to an inability to fulfil Koch's postulate. For example, the same pathogen is not always found in all AD brains, or in different laboratories. Laboratory confirmation in animal models may be impossible for certain pathogens, for example the Epstein-Barr or hepatitis C

virus, that do not infect rodents. Nevertheless, the diversity of pathogens able to promote neurodegeneration, beta-amyloid deposition or to mimic the effects observed in the hippocampal AD transcriptome suggests that many candidates, alone or severally, could be involved in the pathogenesis of AD. A polymicrobial involvement seems likely given the multiple species detected in the AD brain. Evidently, this could be assessed by microbiome studies in the periphery or in post-mortem brains.

Recent work suggests that the production of the antimicrobial/antiviral peptide beta-amyloid is an expected consequence of infection in general [2,3]. In the context of the amyloid hypothesis [194], this places pathogens upstream of the production of this toxic peptide, and logically as causal, both in terms of beta-amyloid production and in relation to Alzheimer's disease.

Two separate case reports have shown remission from dementia or mis-diagnosed Alzheimer's disease in patients subsequently diagnosed with and treated for *Cryptococcus neoformans* infection [50,51].

In a Greek study, *H. Pylori*-infected AD patients receiving the triple eradication regime (omeprazole, clarithromycin and amoxicillin) showed improved cognitive and functional status parameters where bacterial eradication was successful [195].*H. Pylori* eradication in AD patients with peptic ulcer was also associated with a decreased risk of AD progression in a Taiwanese study [196].

Taking all of the above into consideration the combined data suggest that polymicrobial brain invasion, enabled by environmentally-induced blood-brain barrier defects may be responsible for Alzheimer's disease. This could essentially be mediated via activation of a hyper-efficient inflammatory network, including the call-up of beta-amyloid that, as a consequence, causes massive neuronal destruction in a tissue incapable of regeneration. The role of the innate immune system and the inflammatory response in neurotoxicity has recently been reviewed, and innate surveillance mediated cell death has been suggested as a plausible common pathogenic pathway responsible for many neurodegenerative diseases, including AD [197].

It is therefore not unreasonable to suggest that antibiotic, antifungal and antiviral agents, possibly in combination, tailored to the individual, might be able to halt, delay or perhaps even provide remission in patients with Alzheimer's disease.

Acknowledgements.

Thanks are due to the many authors who have sent reprints and supplementary datasets that made this work possible. Thanks also to David Eby from the Broad Institute of MIT and Harvard for his help with the structure of the Molecular Signatures database.

The author reports no funding and no conflict of interest.

References

[1] Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, Liang CR, Wang QH, Wang X, Cao HY, Yi X, Deng B, Liu CH, Xu J, Zhang LL, Gao CY, Xu ZQ, Zhang M, Wang L, Tan XL, Xu X, Zhou HD, Wang YJ (2015) A study on the association between infectious burden and Alzheimer's disease. *Eur J Neurol* **22**, 1519-1525.

[2] Kumar DK, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE, Moir RD (2016) Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. *Sci Transl Med* **8**, 340ra72-

[3] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, Moir RD (2010) The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* **5**, e9505-

[4] White MR, Kandel R, Tripathi S, Condon D, Qi L, Taubenberger J, Hartshorn KL (2014) Alzheimer's Associated beta-Amyloid Protein Inhibits Influenza A Virus and Modulates Viral Interactions with Phagocytes. *PLoS One* **9**, e101364-

[5] Bourgade K, Garneau H, Giroux G, Le Page AY, Bocti C, Dupuis G, Frost EH, Fulop T, Jr. (2015) beta-Amyloid peptides display protective activity against the human Alzheimer's disease-associated herpes simplex virus-1. *Biogerontology* **16**, 85-98.

[6] Bourgade K, Le Page A, Bocti C, Witkowski JM, Dupuis G, Frost EH, Fulop T (2016) Protective Effect of Amyloid-beta Peptides Against Herpes Simplex Virus-1 Infection in a Neuronal Cell Culture Model. *J Alzheimers Dis* **50**, 1227-1241.

[7] Carter CJ (2011) Alzheimer's Disease: APP, Gamma Secretase, APOE, CLU, CR1, PICALM, ABCA7, BIN1, CD2AP, CD33, EPHA1, and MS4A2, and Their Relationships with Herpes Simplex, C. Pneumoniae, Other Suspect Pathogens, and the Immune System. *Int J Alzheimers Dis* **2011**, 501862-

[8] Carter CJ (2010) Alzheimer's disease plaques and tangles: Cemeteries of a Pyrrhic victory of the immune defence network against herpes simplex infection at the expense of complement and inflammation-mediated neuronal destruction. *Neurochem Int* **58**, 301-320.

[9] Carter CJ (2013) Susceptibility genes are enriched in those of the HSV-1/host interactome in psychiatric and neurological disorders. *Pathog Dis*

[10] Carter CJ (2013) Toxoplasmosis and Polygenic Disease Susceptibility Genes: Extensive Toxoplasma gondii Host/Pathogen Interactome Enrichment in Nine Psychiatric or Neurological Disorders. *J Pathog* **2013**, 965046-

[11] Gulbahce N, Yan H, Dricot A, Padi M, Byrdsong D, Franchi R, Lee DS, Rozenblatt-Rosen O, Mar JC, Calderwood MA, Baldwin A, Zhao B, Santhanam B, Braun P, Simonis N, Huh KW, Hellner K, Grace M, Chen A, Rubio R, Marto JA, Christakis NA, Kieff E, Roth FP, Roecklein-Canfield J, Decaprio JA, Cusick ME, Quackenbush J, Hill DE, Munger K, Vidal M, Barabasi AL (2012) Viral perturbations of host networks reflect disease etiology. *PLoS Comput Biol*, e1002531-

[12] Mechelli R, Umeton R, Policano C, Annibali V, Coarelli G, Ricigliano VA, Vittori D, Fornasiero A, Buscarinu MC, Romano S, Salvetti M, Ristori G (2013) A "candidate-interactome" aggregate analysis of genome-wide association data in multiple sclerosis. *PLoS One* **8**, e63300-

[13] Rozenblatt-Rosen O, Deo RC, Padi M, Adelmant G, Calderwood MA, Rolland T, Grace M, Dricot A, Askenazi M, Tavares M, Pevzner SJ, Abderazzaq F, Byrdsong D, Carvunis AR, Chen AA, Cheng J, Correll M, Duarte M, Fan C, Feltkamp MC, Ficarro SB, Franchi R, Garg BK, Gulbahce N, Hao T, Holthaus AM, James R, Korkhin A, Litovchick L, Mar JC, Pak TR, Rabello S, Rubio R, Shen Y, Singh S, Spangle JM, Tasan M, Wanamaker S, Webber JT, Roecklein-Canfield J, Johannsen E, Barabasi AL, Beroukhim R, Kieff E, Cusick ME, Hill DE, Munger K, Marto JA, Quackenbush J, Roth FP, Decaprio JA, Vidal M - Interpreting cancer genomes using systematic host network perturbations by tumour virus proteins.5.

[14] Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, Landfield PW (2004) Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proc Natl Acad Sci U S A* **101**, 2173-2178.

[15] Liberzon A, Birger C, Thorvaldsdottir H, Ghandi M, Mesirov JP, Tamayo P (2015) The Molecular Signatures Database (MSigDB) hallmark gene set collection. *Cell Syst* **1**, 417-425.

[16] Edgar R, Domrachev M, Lash AE (2002) Gene Expression Omnibus: NCBI gene expression and hybridization array data repository. *Nucleic Acids Res* **30**, 207-210.

[17] Fumagalli M, Pozzoli U, Cagliani R, Comi GP, Bresolin N, Clerici M, Sironi M (2010) The landscape of human genes involved in the immune response to parasitic worms. *BMC Evol Biol* **10**, 264-

[18] Fumagalli M, Pozzoli U, Cagliani R, Comi GP, Bresolin N, Clerici M, Sironi M (2010) Genome-wide identification of susceptibility alleles for viral infections through a population genetics approach. *Plos Genet* **6**, e1000849-

[19] Fumagalli M, Sironi M, Pozzoli U, Ferrer-Admetlla A, Pattini L, Nielsen R (2011) Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. *Plos Genet* **7**, e1002355-

[20] Pozzoli U, Fumagalli M, Cagliani R, Comi GP, Bresolin N, Clerici M, Sironi M (2010) The role of protozoa-driven selection in shaping human genetic variability. *Trends Genet* **26**, 95-99.

[21] Ako-Adjei D, Fu W, Wallin C, Katz KS, Song G, Darji D, Brister JR, Ptak RG, Pruitt KD (2015) HIV-1, human interaction database: current status and new features. *Nucleic Acids Res* **43**, D566-D570.

[22] Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, Marshall KA, Phillippy KH, Sherman PM, Holko M, Yefanov A, Lee H, Zhang N, Robertson CL, Serova N, Davis S, Soboleva A (2013) NCBI GEO: archive for functional genomics data sets--update. *Nucleic Acids Res* **41**, D991-D995.

[23] Rouillard AD, Gundersen GW, Fernandez NF, Wang Z, Monteiro CD, McDermott MG, Ma'ayan A (2016) The harmonizome: a collection of processed datasets gathered to serve and mine knowledge about genes and proteins. *Database (Oxford)* **2016**

[24] Liao L, Cheng D, Wang J, Duong DM, Losik TG, Gearing M, Rees HD, Lah JJ, Levey AI, Peng J (2004) Proteomic characterization of postmortem amyloid plaques isolated by laser capture microdissection. *J Biol Chem* **279**, 37061-37068.

[25] Wang Q, Woltjer RL, Cimino PJ, Pan C, Montine KS, Zhang J, Montine TJ (2005) Proteomic analysis of neurofibrillary tangles in Alzheimer disease identifies GAPDH as a detergent-insoluble paired helical filament tau binding protein. *FASEB J* **19**, 869-871.

[26] Welter D, MacArthur J, Morales J, Burdett T, Hall P, Junkins H, Klemm A, Flicek P, Manolio T, Hindorff L, Parkinson H (2014) The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic Acids Res* **42**, D1001-D1006.

[27] Pathan M, Keerthikumar S, Ang CS, Gangoda L, Quek CY, Williamson NA, Mouradov D, Sieber OM, Simpson RJ, Salim A, Bacic A, Hill AF, Stroud DA, Ryan MT, Agbinya JI, Mariadason JM, Burgess AW, Mathivanan S (2015) FunRich: An open access standalone functional enrichment and interaction network analysis tool. *Proteomics* **15**, 2597-2601.

[28] Badhwar A, Stanimirovic DB, Hamel E, Haqqani AS (2014) The proteome of mouse cerebral arteries. *J Cereb Blood Flow Metab* **34**, 1033-1046.

[29] Mathivanan S, Ji H, Simpson RJ (2010) Exosomes: extracellular organelles important in intercellular communication. *J Proteomics* **73**, 1907-1920.

[30] Sun D, Zhuang X, Zhang S, Deng ZB, Grizzle W, Miller D, Zhang HG (2013) Exosomes are endogenous nanoparticles that can deliver biological information between cells. *Adv Drug Deliv Rev* **65**, 342-347.

[31] Simpson RJ, Kalra H, Mathivanan S (2012) ExoCarta as a resource for exosomal research. *J Extracell Vesicles* **1**

[32] Kalamvoki M , Deschamps T (2016) Extracellular vesicles during Herpes Simplex Virus type 1 infection: an inquire. *Virol J* **13**, 63-

[33] Meckes DG, Jr. (2015) Exosomal communication goes viral. *J Virol* **89**, 5200-5203.

[34] Benjamini Y , Hochberg Y (1995) Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological)* **57**, 289-300.

[35] Baranyai T, Herczeg K, Onodi Z, Voszka I, Modos K, Marton N, Nagy G, Mager I, Wood MJ, El Andaloussi S, Palinkas Z, Kumar V, Nagy P, Kittel A, Buzas EI, Ferdinandy P, Giricz Z (2015) Isolation of Exosomes from Blood Plasma: Qualitative and Quantitative Comparison of Ultracentrifugation and Size Exclusion Chromatography Methods. *PLoS One* **10**, e0145686-

[36] Rajendran L, Honsho M, Zahn TR, Keller P, Geiger KD, Verkade P, Simons K (2006) Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc Natl Acad Sci U S A* **103**, 11172-11177.

[37] Smith SP , Yee GC (1992) Hematopoiesis. *Pharmacotherapy* **12**, 11S-19S.

[38] Baumgarth N (2013) Innate-like B cells and their rules of engagement. *Adv Exp Med Biol* **785**, 57-66.

[39] Lee ST, Chu K, Jung KH, Jeon D, Bahn JJ, Kim JH, Kun LS, Kim M, Roh JK (2010) Dysfunctional characteristics of circulating angiogenic cells in Alzheimer's disease. *J Alzheimers Dis* **19**, 1231-1240.

[40] Sadowski MJ (2010) Circulating angiogenic cells and Alzheimer's disease: contribution of the bone marrow to the pathogenesis of the disease. *J Alzheimers Dis* **19**, 1241-1243.

[41] Cho SW, Pirih FQ, Koh AJ, Michalski M, Eber MR, Ritchie K, Sinder B, Oh S, Al Dujaili SA, Lee J, Kozloff K, Danciu T, Wronski TJ, McCauley LK (2013) The soluble interleukin-6 receptor is a mediator of hematopoietic and skeletal actions of parathyroid hormone. *J Biol Chem* **288**, 6814-6825.

[42] Lee JH, Hwang KJ, Kim MY, Lim YJ, Seol IJ, Jin HJ, Jang YK, Choi SJ, Oh W, Cho YH, Lee YH (2012) Human parathyroid hormone increases the mRNA expression of the IGF system and hematopoietic growth factors in osteoblasts, but does not influence expression in mesenchymal stem cells. *J Pediatr Hematol Oncol* **34**, 491-496.

[43] Zahid A (2004) The vermiform appendix: not a useless organ. *J Coll Physicians Surg Pak* **14**, 256-258.

[44] Nadal D , Ogra PL (1990) Development of local immunity: role in mechanisms of protection against or pathogenesis of respiratory syncytial viral infections. *Lung* **168 Suppl**, 379-387.

[45] Kusuhara H , Sugiyama Y (2004) Efflux transport systems for organic anions and cations at the blood-CSF barrier. *Adv Drug Deliv Rev* **56**, 1741-1763.

[46] Schwerk C, Tenenbaum T, Kim KS, Schroten H (2015) The choroid plexus-a multi-role player during infectious diseases of the CNS. *Front Cell Neurosci* **9**, 80-

[47] Bergen AA, Kaing S, Ten Brink JB, Gorgels TG, Janssen SF (2015) Gene expression and functional annotation of human choroid plexus epithelium failure in Alzheimer's disease. *BMC Genomics* **16**, 956-

[48] Kiernan JA (2012) Anatomy of the temporal lobe. *Epilepsy Res Treat* **2012**, 176157-

[49] Veiga-Fernandes H , Mucida D (2016) Neuro-Immune Interactions at Barrier Surfaces. *Cell* **165**, 801-811.

[50] Ala TA, Doss RC, Sullivan CJ (2004) Reversible dementia: a case of cryptococcal meningitis masquerading as Alzheimer's disease. *J Alzheimers Dis* **6**, 503-508.

[51] Hoffmann M, Muniz J, Carroll E, De Villasante J (2009) Cryptococcal meningitis misdiagnosed as Alzheimer's disease: complete neurological and cognitive recovery with treatment. *J Alzheimers Dis* **16**, 517-520.

[52] Chiu B, Viira E, Tucker W, Fong IW (1997) Chlamydia pneumoniae, cytomegalovirus, and herpes simplex virus in atherosclerosis of the carotid artery. *Circulation* **96**, 2144-2148.

[53] Deniset JF , Pierce GN (2010) Possibilities for therapeutic interventions in disrupting Chlamydophila pneumoniae involvement in atherosclerosis. *Fundam Clin Pharmacol* **24**, 607-617.

[54] Mayr M, Kiechl S, Willeit J, Wick G, Xu Q (2000) Infections, immunity, and atherosclerosis: associations of antibodies to Chlamydia pneumoniae, Helicobacter pylori, and cytomegalovirus with immune reactions to heat-shock protein 60 and carotid or femoral atherosclerosis. *Circulation* **102**, 833-839.

[55] Volzke H, Wolff B, Ludemann J, Guertler L, Kramer A, John U, Felix SB (2006) Seropositivity for anti-Borrelia IgG antibody is independently associated with carotid atherosclerosis. *Atherosclerosis* **184**, 108-112.

[56] Voulgaris T , Sevastianos VA (2016) Atherosclerosis as Extrahepatic Manifestation of Chronic Infection with Hepatitis C Virus. *Hepat Res Treat* **2016**, 7629318-

[57] Hussain M, Stover CM, Dupont A (2015) P. gingivalis in Periodontal Disease and Atherosclerosis - Scenes of Action for Antimicrobial Peptides and Complement. *Front Immunol* **6**, 45-

[58] Apostolou F, Gazi IF, Lagos K, Tellis CC, Tselepis AD, Liberopoulos EN, Elisaf M (2010) Acute infection with Epstein-Barr virus is associated with atherogenic lipid changes. *Atherosclerosis* **212**, 607-613.

[59] Wu YP, Sun DD, Wang Y, Liu W, Yang J (2016) Herpes Simplex Virus Type 1 and Type 2 Infection Increases Atherosclerosis Risk: Evidence Based on a Meta-Analysis. *Biomed Res Int* **2016**, 2630865-

[60] de la Torre JC (2010) The vascular hypothesis of Alzheimer's disease: bench to bedside and beyond. *Neurodegener Dis* **7**, 116-121.

[61] Kuhlmann I, Minihane AM, Huebbe P, Nebel A, Rimbach G (2010) Apolipoprotein E genotype and hepatitis C, HIV and herpes simplex disease risk: a literature review. *Lipids Health Dis* **9**, 8-

[62] Burgos JS, Ramirez C, Sastre I, Bullido MJ, Valdivieso F (2003) ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. *Neuroreport* **14** , 1825-1827.

[63] Gerard HC, Fomicheva E, Whittum-Hudson JA, Hudson AP (2008) Apolipoprotein E4 enhances attachment of Chlamydophila (Chlamydia) pneumoniae elementary bodies to host cells. *Microb Pathog* **44**, 279-285.

[64] Raj T, Kuchroo M, Replogle JM, Raychaudhuri S, Stranger BE, De Jager PL (2013) Common risk alleles for inflammatory diseases are targets of recent positive selection. *Am J Hum Genet* **92**, 517-529.

[65] Raj T, Shulman JM, Keenan BT, Chibnik LB, Evans DA, Bennett DA, Stranger BE, De Jager PL (2012) Alzheimer disease susceptibility loci: evidence for a protein network under natural selection. *Am J Hum Genet* **90**, 720-726.

[66] Finch CE , Morgan TE (2007) Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position paper. *Curr Alzheimer Res* **4**, 185-189.

[67] Finch CE, Martin Gm (2016) Dementias of the Alzheimer Type: Views Through the Lens of Evolutionary Biology Suggest Amyloid-Driven Brain Aging Is Balanced Against Host Defense. In *Evolutionary Thinking in Medicine*, Springer International Publishing, pp. 277-295

[68] Heron M (2016) Deaths: Leading Causes for 2013. *Natl Vital Stat Rep* **65**, 1-95.

[69] Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB (2008) Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res* **25**, 2097-2116.

[70] Zhang Q, Guo S, Zhang X, Tang S, Shao W, Han X, Wang L, Du Y (2015) Inverse relationship between cancer and Alzheimer's disease: a systemic review meta-analysis. *Neurol Sci* **36**, 1987-1994.

[71] Lu L, Sun R, Liu M, Zheng Y, Zhang P (2015) The Inflammatory Heart Diseases: Causes, Symptoms, and Treatments. *Cell Biochem Biophys*

[72] Elkind MS (2010) Infectious burden: a new risk factor and treatment target for atherosclerosis. *Infect Disord Drug Targets* **10**, 84-90.

[73] Miller EC , Elkind MS (2016) Infection and Stroke: an Update on Recent Progress. *Curr Neurol Neurosci Rep* **16**, 2-

[74] de Beeck AO , Eizirik DL (2016) Viral infections in type 1 diabetes mellitus - why the beta cells? *Nat Rev Endocrinol* **12**, 263-273.

[75] Fujioka H, Phelix CF, Friedland RP, Zhu X, Perry EA, Castellani RJ, Perry G (2013) Apolipoprotein E4 prevents growth of malaria at the intraerythrocyte stage: implications for differences in racial susceptibility to Alzheimer's disease. *J Health Care Poor Underserved* **24**, 70-78.

[76] Saraswat V, Norris S, de Knegt RJ, Sanchez Avila JF, Sonderup M, Zuckerman E, Arkkila P, Stedman C, Acharya S, Aho I, Anand AC, Andersson MI, Arendt V, Baatarkhuu O, Barclay K, Ben Ari Z, Bergin C, Bessone F, Blach S, Blokhina N, Brunton CR, Choudhuri G, Chulanov V, Cisneros L, Croes EA, Dahgwahdorj YA, Dalgard O, Daruich JR, Dashdorj NR, Davaadorj D, de Vree M, Estes C, Flisiak R, Gadano AC, Gane E, Halota W, Hatzakis A, Henderson C, Hoffmann P, Hornell J, Houlihan D, Hrusovsky S, Jarcuska P, Kershenobich D, Kostrzewska K, Kristian P, Leshno M, Lurie Y, Mahomed A, Mamonova N, Mendez-Sanchez N, Mossong J, Nurmukhametova E, Nymadawa P, Oltman M, Oyunbileg J, Oyunsuren T, Papatheodoridis G, Pimenov N, Prabdial-Sing N, Prins M, Puri P, Radke S, Rakhmanova A, Razavi H, Razavi-Shearer K, Reesink HW, Ridruejo E, Safadi R, Sagalova O, Sanduijav R, Schreter I, Seguin-Devaux C, Shah SR, Shestakova I, Shevaldin A, Shibolet O, Sokolov S, Souliotis K, Spearman CW, Staub T, Strebkova EA, Struck D, Tomasiewicz K, Undram L, van der Meer AJ, van Santen D, Veldhuijzen I, Villamil FG, Willemse S, Zuure FR, Silva MO, Sypsa V, Gower E (2015) Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 2. *J Viral Hepat* **22 Suppl 1**, 6-25.

[77] Custodio H (2016) Protozoan Parasites. *Pediatr Rev* **37**, 59-69.

[78] Li X, Montine KS, Keene CD, Montine TJ (2015) Different mechanisms of apolipoprotein E isoform-dependent modulation of prostaglandin E2 production and triggering receptor expressed on myeloid cells 2 (TREM2) expression after innate immune activation of microglia. *FASEB J* **29**, 1754-1762.

[79] Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray DT, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB (2014) APOepsilon4 is associated with enhanced in vivo innate immune responses in human subjects. *J Allergy Clin Immunol* **134**, 127-134.

[80] Fonseca MI, Chu S, Pierce AL, Brubaker WD, Hauhart RE, Mastroeni D, Clarke EV, Rogers J, Atkinson JP, Tenner AJ (2016) Analysis of the Putative Role of CR1 in Alzheimer's Disease: Genetic Association, Expression and Function. *PLoS One* **11**, e0149792-

[81] Gasque P (2004) Complement: a unique innate immune sensor for danger signals. *Mol Immunol* **41**, 1089-1098.

[82] Roussos P, Katsel P, Fam P, Tan W, Purohit DP, Haroutunian V (2015) The triggering receptor expressed on myeloid cells 2 (TREM2) is associated with enhanced inflammation, neuropathological lesions and increased risk for Alzheimer's dementia. *Alzheimers Dement* **11**, 1163-1170.

[83] Lee J, Chan SL, Mattson MP (2002) Adverse effect of a presenilin-1 mutation in microglia results in enhanced nitric oxide and inflammatory cytokine responses to immune challenge in the brain. *Neuromolecular Med* **2**, 29-45.

[84] van Exel E, Eikelenboom P, Comijs H, Frolich M, Smit JH, Stek ML, Scheltens P, Eefsting JE, Westendorp RG (2009) Vascular factors and markers of inflammation in offspring with a parental history of late-onset Alzheimer disease. *Arch Gen Psychiatry* **66**, 1263-1270.

[85] Ciaramella A, Bizzoni F, Salani F, Vanni D, Spalletta G, Sanarico N, Vendetti S, Caltagirone C, Bossu P (2010) Increased pro-inflammatory response by dendritic cells from patients with Alzheimer's disease. *J Alzheimers Dis* **19**, 559-572.

[86] Pellicano M, Bulati M, Buffa S, Barbagallo M, Di Prima A, Misiano G, Picone P, Di Carlo M, Nuzzo D, Candore G, Vasto S, Lio D, Caruso C, Colonna-Romano G (2010) Systemic immune responses in Alzheimer's disease: in vitro mononuclear cell activation and cytokine production. *J Alzheimers Dis* **21**, 181-192.

[87] Camargo LM, Zhang XD, Loerch P, Caceres RM, Marine SD, Uva P, Ferrer M, de Rinaldis E, Stone DJ, Majercak J, Ray WJ, Yi-An C, Shearman MS, Mizuguchi K (2015) Pathway-based analysis of genome-wide siRNA screens reveals the regulatory landscape of APP processing. *PLoS One* **10**, e0115369-

[88] Bamji-Mirza M, Li Y, Najem D, Liu QY, Walker D, Lue LF, Stupak J, Chan K, Li J, Ghani M, Yang Z, Rogaeva E, Zhang W (2016) Genetic Variations in ABCA7 Can Increase Secreted Levels of Amyloid-beta40 and Amyloid-beta42 Peptides and ABCA7 Transcription in Cell Culture Models. *J Alzheimers Dis* **53**, 875-892.

[89] Brunnstrom HR , Englund EM (2009) Cause of death in patients with dementia disorders. *Eur J Neurol* **16**, 488-492.

[90] Kamburov A, Pentchev K, Galicka H, Wierling C, Lehrach H, Herwig R (2011) ConsensusPathDB: toward a more complete picture of cell biology. *Nucleic Acids Res* **39**, D712-D717.

[91] Janeway CA, Travers P, Walport M, Schlonchik MJ (2011) *The Immune System in Health and Disease*, Garland Science, New York.

[92] Reniewicz P, Zyzak J, Siednienko J (2016) The cellular receptors of exogenous RNA. *Postepy Hig Med Dosw (Online)* **70**, 337-348.

[93] Stahl T, Reimers C, Johne R, Schliebs R, Seeger J (2006) Viral-induced inflammation is accompanied by beta-amyloid plaque reduction in brains of amyloid precursor protein transgenic Tg2576 mice. *Eur J Neurosci* **24**, 1923-1934.

[94] Slonska A, Polowy R, Golke A, Cymerys J (2012) Role of cytoskeletal motor proteins in viral infection. *Postepy Hig Med Dosw (Online)* **66**, 810-817.

[95] Romano JD, de Beaumont C, Carrasco JA, Ehrenman K, Bavoil PM, Coppens I (2013) Fierce competition between Toxoplasma and Chlamydia for host cell structures in dually infected cells. *Eukaryot Cell* **12**, 265-277.

[96] Tyler KM, Luxton GW, Applewhite DA, Murphy SC, Engman DM (2005) Responsive microtubule dynamics promote cell invasion by Trypanosoma cruzi. *Cell Microbiol* **7**, 1579-1591.

[97] Li A, Ceballos-Diaz C, DiNunno N, Levites Y, Cruz PE, Lewis J, Golde TE, Chakrabarty P (2015) IFN-gamma promotes tau phosphorylation without affecting mature tangles. *FASEB J* **29**, 4384-4398.

[98] van de Haar HJ, Jansen JF, van Osch MJ, van Buchem MA, Muller M, Wong SM, Hofman PA, Burgmans S, Verhey FR, Backes WH (2016) Neurovascular unit impairment in early Alzheimer's disease measured with magnetic resonance imaging. *Neurobiol Aging* **45**, 190-196.

[99] Zenaro E, Piacentino G, Constantin G (2016) The blood-brain barrier in Alzheimer's disease. *Neurobiol Dis*

[100] Montagne A, Nation DA, Pa J, Sweeney MD, Toga AW, Zlokovic BV (2016) Brain imaging of neurovascular dysfunction in Alzheimer's disease. *Acta Neuropathol* **131**, 687-707.

[101] Zlokovic BV (2011) Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci* **12**, 723-738.

[102] Yates PA, Desmond PM, Phal PM, Steward C, Szoeke C, Salvado O, Ellis KA, Martins RN, Masters CL, Ames D, Villemagne VL, Rowe CC (2014) Incidence of cerebral microbleeds in preclinical Alzheimer disease. *Neurology* **82**, 1266-1273.

[103] Inoue Y, Nakajima M, Uetani H, Hirai T, Ueda M, Kitajima M, Utsunomiya D, Watanabe M, Hashimoto M, Ikeda M, Yamashita Y, Ando Y (2016) Diagnostic Significance of Cortical Superficial Siderosis for Alzheimer Disease in Patients with Cognitive Impairment. *AJNR Am J Neuroradiol* **37**, 223-227.

[104] Feldman HH, Maia LF, Mackenzie IR, Forster BB, Martzke J, Woolfenden A (2008) Superficial siderosis: a potential diagnostic marker of cerebral amyloid angiopathy in Alzheimer disease. *Stroke* **39**, 2894-2897.

[105] Pretorius E, Bester J, Kell DB (2016) A Bacterial Component to Alzheimer's-Type Dementia Seen via a Systems Biology Approach that Links Iron Dysregulation and Inflammagen Shedding to Disease. *J Alzheimers Dis*

[106] Kalinke U, Bechmann I, Detje CN (2011) Host strategies against virus entry via the olfactory system. *Virulence* **2**, 367-370.

[107] Kristensson K, Masocha W, Bentivoglio M (2013) Mechanisms of CNS invasion and damage by parasites. *Handb Clin Neurol* **114**, 11-22.

[108] MacIntyre A, Abramov R, Hammond CJ, Hudson AP, Arking EJ, Little CS, Appelt DM, Balin BJ (2003) Chlamydia pneumoniae infection promotes the transmigration of monocytes through human brain endothelial cells. *J Neurosci Res* **71**, 740-750.

[109] Itzhaki RF, Wozniak MA, Appelt DM, Balin BJ (2004) Infiltration of the brain by pathogens causes Alzheimer's disease. *Neurobiol Aging* **25**, 619-627.

[110] Oakley R , Tharakan B (2014) Vascular hyperpermeability and aging. *Aging Dis* **5**, 114-125.

[111] Fulop T, Witkowski JM, Le Page A, Fortin C, Pawelec G, Larbi A (2016) Intracellular signalling pathways: targets to reverse immunosenescence. *Clin Exp Immunol*

[112] Fulop T, Dupuis G, Baehl S, Le Page A, Bourgade K, Frost E, Witkowski JM, Pawelec G, Larbi A, Cunnane S (2016) From inflamm-aging to immune-paralysis: a slippery slope during aging for immune-adaptation. *Biogerontology* **17**, 147-157.

[113] Rawji KS, Mishra MK, Michaels NJ, Rivest S, Stys PK, Yong VW (2016) Immunosenescence of microglia and macrophages: impact on the ageing central nervous system. *Brain* **139**, 653-661.

[114] Zhang R, Miller RG, Madison C, Jin X, Honrada R, Harris W, Katz J, Forshew DA, McGrath MS (2013) Systemic immune system alterations in early stages of Alzheimer's disease. *J Neuroimmunol* **256**, 38-42.

[115] Edison P, Archer HA, Gerhard A, Hinz R, Pavese N, Turkheimer FE, Hammers A, Tai YF, Fox N, Kennedy A, Rossor M, Brooks DJ (2008) Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiol Dis* **32**, 412-419.

[116] Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* **Early Online Publication, 19 July 2011**.

[117] Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A (2003) Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J Neurol Neurosurg Psychiatry* **74**, 857-862.

[118] Ferreira PC, Piai KA, Takayanagui AM, Segura-Munoz SI (2008) Aluminum as a risk factor for Alzheimer's disease. *Rev Lat Am Enfermagem* **16**, 151-157.

[119] Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF (2009) Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. *Am J Epidemiol* **169**, 489-496.

[120] Loef M , Walach H (2012) Copper and iron in Alzheimer's disease: a systematic review and its dietary implications. *Br J Nutr* **107**, 7-19.

[121] Parron T, Requena M, Hernandez AF, Alarcon R (2011) Association between environmental exposure to pesticides and neurodegenerative diseases. *Toxicol Appl Pharmacol* **256**, 379-385.

[122] Richardson JR, Roy A, Shalat SL, von Stein RT, Hossain MM, Buckley B, Gearing M, Levey AI, German DC (2014) Elevated serum pesticide levels and risk for Alzheimer disease. *JAMA Neurol* **71**, 284-290.

[123] Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, Villarreal-Calderon R, Osnaya N, Stone I, Garcia R, Brooks DM, Gonzalez-Maciel A, Reynoso-Robles R, Delgado-Chavez R, Reed W (2008) Long-term air pollution exposure is associated with

neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol* **36**, 289-310.

[124] Wu YC, Lin YC, Yu HL, Chen JH, Chen TF, Sun Y, Wen LL, Yip PK, Chu YM, Chen YC (2015) Association between air pollutants and dementia risk in the elderly. *Alzheimers Dement (Amst)* **1**, 220-228.

[125] Calderon-Garciduenas L, Mora-Tiscareno A, Melo-Sanchez G, Rodriguez-Diaz J, Torres-Jardon R, Styner M, Mukherjee PS, Lin W, Jewells V (2015) A Critical Proton MR Spectroscopy Marker of Alzheimer's Disease Early Neurodegenerative Change: Low Hippocampal NAA/Cr Ratio Impacts APOE varepsilon4 Mexico City Children and Their Parents. *J Alzheimers Dis* **48**, 1065-1075.

[126] Yegambaram M, Manivannan B, Beach TG, Halden RU (2015) Role of environmental contaminants in the etiology of Alzheimer's disease: a review. *Curr Alzheimer Res* **12**, 116-146.

[127] de Chaves EP , Narayanaswami V (2008) Apolipoprotein E and cholesterol in aging and disease in the brain. *Future Lipidol* **3**, 505-530.

[128] Mielke MM, Zandi PP, Shao H, Waern M, Ostling S, Guo X, Bjorkelund C, Lissner L, Skoog I, Gustafson DR (2010) The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology* **75**, 1888-1895.

[129] Martins IJ, Berger T, Sharman MJ, Verdile G, Fuller SJ, Martins RN (2009) Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. *J Neurochem* **111**, 1275-1308.

[130] Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y (2014) Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health* **14**, 643-

[131] Kageyama M, Hiraoka M, Kagawa Y (2008) Relationship between genetic polymorphism, serum folate and homocysteine in Alzheimer's disease. *Asia Pac J Public Health* **20 Suppl**, 111-117.

[132] Reynolds EH (2014) The neurology of folic acid deficiency. *Handb Clin Neurol* **120**, 927-943.

[133] Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, van Duijn CN, van Broeckhoven C, Grobbee DE (1997) Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* **349**, 151-154.

[134] Roher AE, Esh C, Kokjohn TA, Kalback W, Luehrs DC, Seward JD, Sue LI, Beach TG (2003) Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler Thromb Vasc Biol* **23**, 2055-2062.

[135] Branger P, Arenaza-Urquijo EM, Tomadesso C, Mezenge F, Andre C, de Flores R, Mutlu J, de LS, V, Eustache F, Chetelat G, Rauchs G (2016) Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. *Neurobiol Aging* **41**, 107-114.

[136] Emamian F, Khazaie H, Tahmasian M, Leschziner GD, Morrell MJ, Hsiung GY, Rosenzweig I, Sepehry AA (2016) The Association Between Obstructive Sleep Apnea and Alzheimer's Disease: A Meta-Analysis Perspective. *Front Aging Neurosci* **8**, 78-

[137] McGeer PL, Schulzer M, McGeer EG (1996) Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology* **47**, 425-432.

[138] McGeer PL, Rogers J, McGeer EG (2006) Inflammation, anti-inflammatory agents and Alzheimer disease: the last 12 years. *J Alzheimers Dis* **9**, 271-276.

[139] Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G (2000) Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch Neurol* **57**, 1439-1443.

[140] Hendrie HC, Hake A, Lane K, Purnell C, Unverzagt F, Smith-Gamble V, Murrell J, Ogunniyi A, Baiyewu O, Callahan C, Saykin A, Taylor S, Hall K, Gao S (2015) Statin Use, Incident Dementia and Alzheimer Disease in Elderly African Americans. *Ethn Dis* **25**, 345-354.

[141] Lin FC, Chuang YS, Hsieh HM, Lee TC, Chiu KF, Liu CK, Wu MT (2015) Early Statin Use and the Progression of Alzheimer Disease: A Total Population-Based Case-Control Study. *Medicine (Baltimore)* **94**, e2143-

[142] Ting M, Whitaker EJ, Albandar JM (2016) Systematic review of the in vitro effects of statins on oral and perioral microorganisms. *Eur J Oral Sci* **124**, 4-10.

[143] Moreira A, Diogenes MJ, de Mendonca A, Lunet N, Barros H (2016) Chocolate Consumption is Associated with a Lower Risk of Cognitive Decline. *J Alzheimers Dis*

[144] Cooper C, Sommerlad A, Lyketsos CG, Livingston G (2015) Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry* **172**, 323-334.

[145] Feart C, Samieri C, Barberger-Gateau P (2015) Mediterranean diet and cognitive health: an update of available knowledge. *Curr Opin Clin Nutr Metab Care* **18**, 51-62.

[146] Safouris A, Tsivgoulis G, Sergentanis TN, Psaltopoulou T (2015) Mediterranean Diet and Risk of Dementia. *Curr Alzheimer Res* **12**, 736-744.

[147] Cardinali DP, Vigo DE, Olivar N, Vidal MF, Brusco LI (2014) Melatonin Therapy in Patients with Alzheimer's Disease. *Antioxidants (Basel)* **3**, 245-277.

[148] Sanchez-Barcelo EJ, Mediavilla MD, Tan DX, Reiter RJ (2010) Clinical Uses of Melatonin: Evaluation of Human Trials. *Curr Med Chem*

[149] Engler-Chiurazzi EB, Singh M, Simpkins JW (2016) From the 90s to now: A brief historical perspective on more than two decades of estrogen neuroprotection. *Brain Res* **1633**, 96-100.

[150] Pike CJ, Carroll JC, Rosario ER, Barron AM (2009) Protective actions of sex steroid hormones in Alzheimer's disease. *Front Neuroendocrinol* **30**, 239-258.

[151] Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT (2015) Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **86**, 1299-1306.

[152] Wong CW (2016) Pharmacotherapy for Dementia: A Practical Approach to the Use of Cholinesterase Inhibitors and Memantine. *Drugs Aging*

[153] Zhang N, Wei C, Du H, Shi FD, Cheng Y (2015) The Effect of Memantine on Cognitive Function and Behavioral and Psychological Symptoms in Mild-to-Moderate Alzheimer's Disease Patients. *Dement Geriatr Cogn Disord* **40**, 85-93.

[154] Saavedra JM (2016) Evidence to Consider Angiotensin II Receptor Blockers for the Treatment of Early Alzheimer's Disease. *Cell Mol Neurobiol* **36**, 259-279.

[155] Qosa H, Mohamed LA, Al Rihani SB, Batarseh YS, Duong QV, Keller JN, Kaddoumi A (2016) High-Throughput Screening for Identification of Blood-Brain Barrier Integrity Enhancers: A Drug Repurposing Opportunity to Rectify Vascular Amyloid Toxicity. *J Alzheimers Dis*

[156] Kim YK, Shin JS, Nahm MH (2016) NOD-Like Receptors in Infection, Immunity, and Diseases. *Yonsei Med J* **57**, 5-14.

[157] Motta V, Soares F, Sun T, Philpott DJ (2015) NOD-like receptors: versatile cytosolic sentinels. *Physiol Rev* **95**, 149-178.

[158] Oviedo-Boyso J, Bravo-Patino A, Baizabal-Aguirre VM (2014) Collaborative action of Toll-like and NOD-like receptors as modulators of the inflammatory response to pathogenic bacteria. *Mediators Inflamm* **2014**, 432785-

[159] Plato A, Hardison SE, Brown GD (2015) Pattern recognition receptors in antifungal immunity. *Semin Immunopathol* **37**, 97-106.

[160] Schroder K , Tschopp J (2010) The inflammasomes. *Cell* **140**, 821-832.

[161] Wang G, Li X, Wang Z (2016) APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Res* **44**, D1087-D1093.

[162] de Haro C, Mendez R, Santoyo J (1996) The eIF-2alpha kinases and the control of protein synthesis. *FASEB J* **10**, 1378-1387.

[163] Kang R , Tang D (2012) PKR-dependent inflammatory signals. *Sci Signal* **5**, e47-

[164] Lu B, Nakamura T, Inouye K, Li J, Tang Y, Lundback P, Valdes-Ferrer SI, Olofsson PS, Kalb T, Roth J, Zou Y, Erlandsson-Harris H, Yang H, Ting JP, Wang H, Andersson U, Antoine DJ, Chavan

SS, Hotamisligil GS, Tracey KJ (2012) Novel role of PKR in inflammasome activation and HMGB1 release. *Nature* **488**, 670-674.

[165] Munir M , Berg M (2013) The multiple faces of proteinkinase R in antiviral defense. *Virulence* **4**, 85-89.

[166] MacKenzie CR, Heseler K, Muller A, Daubener W (2007) Role of indoleamine 2,3-dioxygenase in antimicrobial defence and immuno-regulation: tryptophan depletion versus production of toxic kynurenines. *Curr Drug Metab* **8**, 237-244.

[167] Mehraj V , Routy JP (2015) Tryptophan Catabolism in Chronic Viral Infections: Handling Uninvited Guests. *Int J Tryptophan Res* **8**, 41-48.

[168] Harris SA , Harris EA (2015) Herpes Simplex Virus Type 1 and Other Pathogens are Key Causative Factors in Sporadic Alzheimer's Disease. *J Alzheimers Dis* **48**, 319-353.

[169] Li S, Carpenter D, Hsiang C, Wechsler SL, Jones C (2010) Herpes simplex virus type 1 latency-associated transcript inhibits apoptosis and promotes neurite sprouting in neuroblastoma cells following serum starvation by maintaining protein kinase B (AKT) levels. *J Gen Virol* **91**, 858-866.

[170] Jiang X, Alami CA, Hsiang C, Carpenter D, Osorio N, Benmohamed L, Fraser NW, Jones C, Wechsler SL (2011) The Herpes Simplex Virus Type 1 Latency-Associated Transcript Can Protect Neuron-Derived C1300 and Neuro2A Cells from Granzyme B-Induced Apoptosis and CD8 T-Cell Killing. *J Virol* **85**, 2325-2332.

[171] Branco FJ , Fraser NW (2005) Herpes simplex virus type 1 latency-associated transcript expression protects trigeminal ganglion neurons from apoptosis. *J Virol* **79**, 9019-9025.

[172] Czygan M, Hallensleben W, Hofer M, Pollak S, Sauder C, Bilzer T, Blumcke I, Riederer P, Bogerts B, Falkai P, Schwarz MJ, Masliah E, Staeheli P, Hufert FT, Lieb K (1999) Borna disease virus in human brains with a rare form of hippocampal degeneration but not in brains of patients with common neuropsychiatric disorders. *J Infect Dis* **180**, 1695-1699.

[173] Gies U, Gorcs TJ, Mulder J, Planz O, Stitz L, Bilzer T, Luiten PG, Harkany T (2001) Cortical cholinergic decline parallels the progression of Borna virus encephalitis. *Neuroreport* **12**, 3767-3772.

[174] Henke H , Lang W (1983) Cholinergic enzymes in neocortex, hippocampus and basal forebrain of non-neurological and senile dementia of Alzheimer-type patients. *Brain Res* **267**, 281-291.

[175] Hermes G, Ajioka JW, Kelly KA, Mui E, Roberts F, Kasza K, Mayr T, Kirisits MJ, Wollmann R, Ferguson DJ, Roberts CW, Hwang JH, Trendler T, Kennan RP, Suzuki Y, Reardon C, Hickey WF, Chen L, McLeod R (2008) Neurological and behavioral abnormalities, ventricular dilatation, altered cellular functions, inflammation, and neuronal injury in brains of mice due to common, persistent, parasitic infection. *J Neuroinflammation* **5**, 48-

[176] Mahmoudvand H, Sheibani V, Esmaeelpour K, Mirbadie SR, Shojaee S, Daneshvar H, Keyhani AR, Ziaali N (2016) TOXOPLASMA GONDII INFECTION POTENTIATES COGNITIVE IMPAIRMENTS OF ALZHEIMER'S DISEASE IN THE BALB/C MICE. *J Parasitol*

[177] Mohle L, Israel N, Paarmann K, Krohn M, Pietkiewicz S, Muller A, Lavrik IN, Buguliskis JS, Schott BH, Schluter D, Gundelfinger ED, Montag D, Seifert U, Pahnke J, Dunay IR (2016) Chronic Toxoplasma gondii infection enhances beta-amyloid phagocytosis and clearance by recruited monocytes. *Acta Neuropathol Commun* **4**, 25-

[178] Herrup K (2010) Reimagining Alzheimer's disease--an age-based hypothesis. *J Neurosci* **30**, 16755-16762.

[179] Herrup K (2015) The case for rejecting the amyloid cascade hypothesis. *Nat Neurosci* **18**, 794-799.

[180] Iacono D, Markesbery WR, Gross M, Pletnikova O, Rudow G, Zandi P, Troncoso JC (2009) The Nun study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. *Neurology* **73**, 665-673.

[181] Snowdon DA (2003) Healthy aging and dementia: findings from the Nun Study. *Ann Intern Med* **139**, 450-454.

[182] Chetelat G, Ossenkoppele R, Villemagne VL, Perrotin A, Landeau B, Mezenge F, Jagust WJ, Dore V, Miller BL, Egret S, Seeley WW, van der Flier WM, La Joie R, Ames D, van Berckel BN, Scheltens P, Barkhof F, Rowe CC, Masters CL, de LS, V, Bouwman F, Rabinovici GD (2016) Atrophy, hypometabolism and clinical trajectories in patients with amyloid-negative Alzheimer's disease. *Brain*

[183] Wu H, Li T, Zeng M, Peng T (2012) Herpes simplex virus type 1 infection activates the Epstein-Barr virus replicative cycle via a CREB-dependent mechanism. *Cell Microbiol* **14**, 546-559.

[184] Popadiak K, Potempa J, Riesbeck K, Blom AM (2007) Biphasic effect of gingipains from Porphyromonas gingivalis on the human complement system. *J Immunol* **178**, 7242-7250.

[185] Carlisle MD, Srikantha RN, Brogden KA (2009) Degradation of human alpha- and beta-defensins by culture supernatants of Porphyromonas gingivalis strain 381. *J Innate Immun* **1**, 118-122.

[186] Vincents B, Guentsch A, Kostolowska D, Pawel-Rammingen U, Eick S, Potempa J, Abrahamson M (2011) Cleavage of IgG1 and IgG3 by gingipain K from Porphyromonas gingivalis may compromise host defense in progressive periodontitis. *FASEB J* **25**, 3741-3750.

[187] Yun PL, Decarlo AA, Collyer C, Hunter N (2001) Hydrolysis of interleukin-12 by Porphyromonas gingivalis major cysteine proteinases may affect local gamma interferon accumulation and the Th1 or Th2 T-cell phenotype in periodontitis. *Infect Immun* **69**, 5650-5660.

[188] Liu TB, Perlin DS, Xue C (2012) Molecular mechanisms of cryptococcal meningitis. *Virulence* **3**, 173-181.

[189] Tan IL , McArthur JC (2012) HIV-associated neurological disorders: a guide to pharmacotherapy. *CNS Drugs* **26**, 123-134.

[190] van der Wal FJ, Kikkert M, Wiertz E (2002) The HCMV gene products US2 and US11 target MHC class I molecules for degradation in the cytosol. *Curr Top Microbiol Immunol* **269**, 37-55.

[191] Johnson DC , Hegde NR (2002) Inhibition of the MHC class II antigen presentation pathway by human cytomegalovirus. *Curr Top Microbiol Immunol* **269**, 101-115.

[192] Elliott DE , Weinstock JV (2012) Helminth-host immunological interactions: prevention and control of immune-mediated diseases. *Ann N Y Acad Sci* **1247**, 83-96.

[193] Maizels RM, McSorley HJ, Smyth DJ (2014) Helminths in the hygiene hypothesis: sooner or later? *Clin Exp Immunol* **177**, 38-46.

[194] Hardy J (2006) Has the amyloid cascade hypothesis for Alzheimer's disease been proved? *Curr Alzheimer Res* **3**, 71-73.

[195] Kountouras J, Boziki M, Gavalas E, Zavos C, Grigoriadis N, Deretzi G, Tzilves D, Katsinelos P, Tsolaki M, Chatzopoulos D, Venizelos I (2009) Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. *J Neurol* **256**, 758-767.

[196] Chang YP, Chiu GF, Kuo FC, Lai CL, Yang YH, Hu HM, Chang PY, Chen CY, Wu DC, Yu FJ (2013) Eradication of Helicobacter pylori Is Associated with the Progression of Dementia: A Population-Based Study. *Gastroenterol Res Pract* **2013**, 175729-

[197] Richards RI, Robertson SA, O'Keefe LV, Fornarino D, Scott A, Lardelli M, Baune BT (2016) The Enemy within: Innate Surveillance-Mediated Cell Death, the Common Mechanism of Neurodegenerative Disease. *Front Neurosci* **10**, 193-

[198] Carbone I, Lazzarotto T, Ianni M, Porcellini E, Forti P, Masliah E, Gabrielli L, Licastro F (2014) Herpes virus in Alzheimer's disease: relation to progression of the disease. *Neurobiol Aging* **35**, 122-129.

[199] Licastro F, Raschi E, Carbone I, Porcellini E (2015) Variants in Antiviral Genes are Risk Factors for Cognitive Decline and Dementia. *J Alzheimers Dis* **46**, 655-663.

[200] Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, Bullido MJ, Carter C, Clerici M, Cosby SL, Del Tredici K, Field H, Fulop T, Grassi C, Griffin WS, Haas J, Hudson AP, Kamer AR, Kell DB, Licastro F, Letenneur L, Lovheim H, Mancuso R, Miklossy J, Otth C, Palamara AT, Perry G, Preston C, Pretorius E, Strandberg T, Tabet N, Taylor-Robinson SD, Whittum-Hudson JA (2016) Microbes and Alzheimer's Disease. *J Alzheimers Dis*

[201] Kristen H, Santana S, Sastre I, Recuero M, Bullido MJ, Aldudo J (2015) Herpes simplex virus type 2 infection induces AD-like neurodegeneration markers in human neuroblastoma cells. *Neurobiol Aging* **36**, 2737-2747.

[202] Lin WR, Wozniak MA, Cooper RJ, Wilcock GK, Itzhaki RF (2002) Herpesviruses in brain and Alzheimer's disease. *J Pathol* **197**, 395-402.

[203] Lurain NS, Hanson BA, Martinson J, Leurgans SE, Landay AL, Bennett DA, Schneider JA (2013) Virological and Immunological Characteristics of Human Cytomegalovirus Infection Associated with Alzheimer's Disease. *J Infect Dis*

[204] Barnes LL, Capuano AW, Aiello AE, Turner AD, Yolken RH, Torrey EF, Bennett DA (2015) Cytomegalovirus infection and risk of Alzheimer disease in older black and white individuals. *J Infect Dis* **211**, 230-237.

[205] Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF (2005) Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. *J Med Virol* **75**, 300-306.

[206] Chiu WC, Tsan YT, Tsai SL, Chang CJ, Wang JD, Chen PC (2014) Hepatitis C viral infection and the risk of dementia. *Eur J Neurol* **21**, 1068-1e59.

[207] Imfeld P, Toovey S, Jick SS, Meier CR (2016) Influenza infections and risk of Alzheimer's disease. *Brain Behav Immun*

[208] Verreault R, Laurin D, Lindsay J, De Serres G (2001) Past exposure to vaccines and subsequent risk of Alzheimer's disease. *CMAJ* **165**, 1495-1498.

[209] Jang H, Boltz D, Sturm-Ramirez K, Shepherd KR, Jiao Y, Webster R, Smeyne RJ (2009) Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. *Proc Natl Acad Sci U S A* **106**, 14063-14068.

[210] Esiri MM, Biddolph SC, Morris CS (1998) Prevalence of Alzheimer plaques in AIDS. *J Neurol Neurosurg Psychiatry* **65**, 29-33.

[211] Soontornniyomkij V, Moore DJ, Gouaux B, Soontornniyomkij B, Tatro ET, Umlauf A, Masliah E, Levine AJ, Singer EJ, Vinters HV, Gelman BB, Morgello S, Cherner M, Grant I, Achim CL (2012) Cerebral beta-amyloid deposition predicts HIV-associated neurocognitive disorders in APOE epsilon4 carriers. *AIDS* **26**, 2327-2335.

[212] Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L (2005) CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. *Neurology* **65**, 1490-1492.

[213] Hellmuth J, Milanini B, Valcour V (2014) Interactions between ageing and NeuroAIDS. *Curr Opin HIV AIDS* **9**, 527-532.

[214] Joseph J, Achim CL, Boivin MJ, Brew BJ, Clifford DB, Colosi DA, Ellis RJ, Heaton RK, Gallo-Diop A, Grant I, Kanmogne GD, Kumar M, Letendre S, Marcotte TD, Nath A, Pardo CA, Paul RH, Pulliam L, Robertson K, Royal W, III, Sacktor N, Sithinamsuwan P, Smith DM, Valcour V, Wigdahl B, Wood C (2013) Global NeuroAIDS roundtable. *J Neurovirol* **19**, 1-9.

[215] Little CS, Joyce TA, Hammond CJ, Matta H, Cahn D, Appelt DM, Balin BJ (2014) Detection of bacterial antigens and Alzheimer's disease-like pathology in the central nervous system of BALB/c mice following intranasal infection with a laboratory isolate of Chlamydia pneumoniae. *Front Aging Neurosci* **6**, 304-

[216] Little CS, Hammond CJ, MacIntyre A, Balin BJ, Appelt DM (2004) Chlamydia pneumoniae induces Alzheimer-like amyloid plaques in brains of BALB/c mice. *Neurobiol Aging* **25**, 419-429.

[217] Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ (2010) Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. *BMC Neurosci* **11**, 121-

[218] Dreses-Werringloer U, Bhuiyan M, Zhao Y, Gerard HC, Whittum-Hudson JA, Hudson AP (2009) Initial characterization of Chlamydophila (Chlamydia) pneumoniae cultured from the late-onset Alzheimer brain. *Int J Med Microbiol* **299**, 187-201.

[219] Gerard HC, Dreses-Werringloer U, Wildt KS, Deka S, Oszust C, Balin BJ, Frey WH, Bordayo EZ, Whittum-Hudson JA, Hudson AP (2006) Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain. *FEMS Immunol Med Microbiol* **48**, 355-366.

[220] Gerard HC, Wildt KL, Whittum-Hudson JA, Lai Z, Ager J, Hudson AP (2005) The load of Chlamydia pneumoniae in the Alzheimer's brain varies with APOE genotype. *Microb Pathog* **39**, 19-26.

[221] Arking EJ, Appelt DM, Abrams JT, Kolbe S, Hudson AP, Balin BJ (1999) Ultrastructural Analysis of Chlamydia Pneumoniae in the Alzheimer's Brain. *Pathogenesis (Amst)* **1**, 201-211.

[222] Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP (1998) Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. *Med Microbiol Immunol* **187**, 23-42.

[223] Maheshwari P , Eslick GD (2015) Bacterial infection and Alzheimer's disease: a meta-analysis. *J Alzheimers Dis* **43**, 957-966.

[224] Wang XL, Zeng J, Feng J, Tian YT, Liu YJ, Qiu M, Yan X, Yang Y, Xiong Y, Zhang ZH, Wang Q, Wang JZ, Liu R (2014) Helicobacter pylori filtrate impairs spatial learning and memory in rats and increases beta-amyloid by enhancing expression of presenilin-2. *Front Aging Neurosci* **6**, 66-

[225] Wang XL, Zeng J, Yang Y, Xiong Y, Zhang ZH, Qiu M, Yan X, Sun XY, Tuo QZ, Liu R, Wang JZ (2015) Helicobacter pylori filtrate induces Alzheimer-like tau hyperphosphorylation by activating glycogen synthase kinase-3beta. *J Alzheimers Dis* **43**, 153-165.

[226] Shindler-Itskovitch T, Ravona-Springer R, Leibovitz A, Muhsen K (2016) A Systematic Review and Meta-Analysis of the Association between Helicobacterpylori Infection and Dementia. *J Alzheimers Dis*

[227] Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Chatzigeorgiou S, Katsinelos P, Grigoriadis N, Giartza-Taxidou E, Venizelos I (2010) Five-year survival after Helicobacter pylori eradication in Alzheimer disease patients. *Cogn Behav Neurol* **23**, 199-204.

[228] Kornhuber HH (1996) Propionibacterium acnes in the cortex of patients with Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci* **246**, 108-109.

[229] Bauer J, Gottfries GG, Forstl H (1996) Critical comments on "Propionibacterium acnes in the cortex of patients with Alzheimer's disease" by H.H. Kornhuber (Eur Arch Psychiatry Clin Neurosci, 1996, 246:108-109). *Eur Arch Psychiatry Clin Neurosci* **246**, 224-226.

[230] Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, Reiss K, Darbinian N, Darekar P, Mihaly L, Khalili K (2006) Beta-amyloid deposition and Alzheimer's type changes induced by Borrelia spirochetes. *Neurobiol Aging* **27**, 228-236.

[231] MacDonald AB , Miranda JM (1987) Concurrent neocortical borreliosis and Alzheimer 's disease. *Human Pathology* **18**, 759-761.

[232] Miklossy J (1993) Alzheimer's disease--a spirochetosis? *Neuroreport* **4**, 841-848.

[233] Miklossy J (2016) Bacterial Amyloid and DNA are Important Constituents of Senile Plaques: Further Evidence of the Spirochetal and Biofilm Nature of Senile Plaques. *J Alzheimers Dis*

[234] Miklossy J (2011) Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. *J Neuroinflammation* **8**, 90-96.

[235] Alonso R, Pisa D, Marina AI, Morato E, Rabano A, Carrasco L (2014) Fungal infection in patients with Alzheimer's disease. *J Alzheimers Dis* **41**, 301-311.

[236] Pisa D, Alonso R, Rabano A, Rodal I, Carrasco L (2015) Different Brain Regions are Infected with Fungi in Alzheimer's Disease. *Sci Rep* **5**, 15015-

[237] Howard J , Pilkington GJ (1992) Fibronectin staining detects micro-organisms in aged and Alzheimer's disease brain. *Neuroreport* **3**, 615-618.

[238] Alonso R, Pisa D, Rabano A, Rodal I, Carrasco L (2015) Cerebrospinal Fluid from Alzheimer's Disease Patients Contains Fungal Proteins and DNA. *J Alzheimers Dis* **47**, 873-876.

[239] Pisa D, Alonso R, Rabano A, Carrasco L (2016) Corpora Amylacea of Brain Tissue from Neurodegenerative Diseases Are Stained with Specific Antifungal Antibodies. *Front Neurosci* **10**, 86-

[240] Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Culliford D, Fuller J, Ibbett P, Raybould R, Thomas R, Puenter U, Teeling J, Perry VH, Holmes C (2016) Periodontitis and Cognitive Decline in Alzheimer's Disease. *PLoS One* **11**, e0151081-

[241] Abbayya K, Puthanakar NY, Naduwinmani S, Chidambar YS (2015) Association between Periodontitis and Alzheimer's Disease. *N Am J Med Sci* **7**, 241-246.

[242] Cerajewska TL, Davies M, West NX (2015) Periodontitis: a potential risk factor for Alzheimer's disease. *Br Dent J* **218**, 29-34.

[243] Kamer AR, Pirraglia E, Tsui W, Rusinek H, Vallabhajosula S, Mosconi L, Yi L, McHugh P, Craig RG, Svetcov S, Linker R, Shi C, Glodzik L, Williams S, Corby P, Saxena D, de Leon MJ (2015) Periodontal disease associates with higher brain amyloid load in normal elderly. *Neurobiol Aging* **36**, 627-633.

[244] Noble JM, Scarmeas N, Celenti RS, Elkind MS, Wright CB, Schupf N, Papapanou PN (2014) Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. *PLoS One* **9**, e114959-

[245] Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S (2013) Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. *J Alzheimers Dis* **36**, 665-677.

[246] Sparks SP, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, Dawson D, III (2012) Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. *Alzheimers Dement* **8**, 196-203.

[247] Riviere GR, Riviere KH, Smith KS (2002) Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. *Oral Microbiol Immunol* **17**, 113-118.

[248] Miklossy J (2015) Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease. *Front Aging Neurosci* **7**, 46-

[249] Jung BK, Pyo KH, Shin KY, Hwang YS, Lim H, Lee SJ, Moon JH, Lee SH, Suh YH, Chai JY, Shin EH (2012) Toxoplasma gondii infection in the brain inhibits neuronal degeneration and learning and memory impairments in a murine model of Alzheimer's disease. *PLoS One* **7**, e33312-

[250] Kusbeci OY, Miman O, Yaman M, Aktepe OC, Yazar S (2011) Could Toxoplasma gondii have any role in Alzheimer disease? *Alzheimer Dis Assoc Disord* **25**, 1-3.

[251] Perry CE, Gale SD, Erickson L, Wilson E, Nielsen B, Kauwe J, Hedges DW (2015) Seroprevalence and Serointensity of Latent Toxoplasma gondii in a Sample of Elderly Adults With and Without Alzheimer Disease. *Alzheimer Dis Assoc Disord*

[252] Mahami-Oskouei M, Hamidi F, Talebi M, Farhoudi M, Taheraghdam AA, Kazemi T, Sadeghi-Bazargani H, Fallah E (2016) Toxoplasmosis and Alzheimer: can Toxoplasma gondii really be introduced as a risk factor in etiology of Alzheimer? *Parasitol Res*

[253] Gasparotto J, Senger MR, Kunzler A, Degrossoli A, de Simone SG, Bortolin RC, Somensi N, Girardi CS, de Souza CS, Calabrese KS, Dal Pizzol F, Moreira JC, Silva-Jr FP, Gelain DP (2015) Increased tau phosphorylation and receptor for advanced glycation endproducts (RAGE) in the brain of mice infected with Leishmania amazonensis. *Brain Behav Immun* **43**, 37-45.

[254] Cordova E, Maiolo E, Corti M, Orduna T (2010) Neurological manifestations of Chagas' disease. *Neurol Res* **32**, 238-244.

[255] Delahaye NF, Coltel N, Puthier D, Barbier M, Benech P, Joly F, Iraqi FA, Grau GE, Nguyen C, Rihet P (2007) Gene expression analysis reveals early changes in several molecular pathways in cerebral malaria-susceptible mice versus cerebral malaria-resistant mice. *BMC Genomics* **8**, 452-

[256] Wojtowicz WM, Farzan M, Joyal JL, Carter K, Babcock GJ, Israel DI, Sodroski J, Mirzabekov T (2002) Stimulation of enveloped virus infection by beta-amyloid fibrils. *J Biol Chem* **277**, 35019-35024.

[257] Banks WA (1999) Physiology and pathology of the blood-brain barrier: implications for microbial pathogenesis, drug delivery and neurodegenerative disorders. *J Neurovirol* **5**, 538-555.

[258] Persidsky Y, Ho W, Ramirez SH, Potula R, Abood ME, Unterwald E, Tuma R (2011) HIV-1 infection and alcohol abuse: neurocognitive impairment, mechanisms of neurodegeneration and therapeutic interventions. *Brain Behav Immun* **25 Suppl 1**, S61-S70.

[259] Song Y, Xue Y, Liu X, Wang P, Liu L (2008) Effects of acute exposure to aluminum on blood-brain barrier and the protection of zinc. *Neurosci Lett* **445**, 42-46.

[260] Brkic M, Balusu S, Van Wonterghem E, Gorle N, Benilova I, Kremer A, Van H, I, Moons L, De Strooper B, Kanazir S, Libert C, Vandenbroucke RE (2015) Amyloid beta Oligomers Disrupt Blood-CSF Barrier Integrity by Activating Matrix Metalloproteinases. *J Neurosci* **35**, 12766-12778.

[261] Perez-Polo JR, Rea HC, Johnson KM, Parsley MA, Unabia GC, Xu G, Infante SK, Dewitt DS, Hulsebosch CE (2013) Inflammatory consequences in a rodent model of mild traumatic brain injury. *J Neurotrauma* **30**, 727-740.

[262] Marchi N, Bazarian JJ, Puvenna V, Janigro M, Ghosh C, Zhong J, Zhu T, Blackman E, Stewart D, Ellis J, Butler R, Janigro D (2013) Consequences of repeated blood-brain barrier disruption in football players. *PLoS One* **8**, e56805-

[263] Di Marco LY, Venneri A, Farkas E, Evans PC, Marzo A, Frangi AF (2015) Vascular dysfunction in the pathogenesis of Alzheimer's disease--A review of endothelium-mediated mechanisms and ensuing vicious circles. *Neurobiol Dis* **82**, 593-606.

[264] Menon PK, Muresanu DF, Sharma A, Mossler H, Sharma HS (2012) Cerebrolysin, a mixture of neurotrophic factors induces marked neuroprotection in spinal cord injury following intoxication of engineered nanoparticles from metals. *CNS Neurol Disord Drug Targets* **11**, 40-49.

[265] Prasad S, Sajja RK, Naik P, Cucullo L (2014) Diabetes Mellitus and Blood-Brain Barrier Dysfunction: An Overview. *J Pharmacovigil* **2**, 125-

[266] Beard RS, Jr., Reynolds JJ, Bearden SE (2011) Hyperhomocysteinemia increases permeability of the blood-brain barrier by NMDA receptor-dependent regulation of adherens and tight junctions. *Blood* **118**, 2007-2014.

[267] Jiang X, Guo M, Su J, Lu B, Ma D, Zhang R, Yang L, Wang Q, Ma Y, Fan Y (2012) Simvastatin blocks blood-brain barrier disruptions induced by elevated cholesterol both in vivo and in vitro. *Int J Alzheimers Dis* **2012**, 109324-

[268] Pires PW, Dams Ramos CM, Matin N, Dorrance AM (2013) The effects of hypertension on the cerebral circulation. *Am J Physiol Heart Circ Physiol* **304**, H1598-H1614.

[269] Tucsek Z, Toth P, Sosnowska D, Gautam T, Mitschelen M, Koller A, Szalai G, Sonntag WE, Ungvari Z, Csiszar A (2014) Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* **69**, 1212-1226.

[270] Balbuena P, Li W, Ehrich M (2011) Assessments of tight junction proteins occludin, claudin 5 and scaffold proteins ZO1 and ZO2 in endothelial cells of the rat blood-brain barrier: cellular responses to neurotoxicants malathion and lead acetate. *Neurotoxicology* **32**, 58-67.

[271] Parran DK, Magnin G, Li W, Jortner BS, Ehrich M (2005) Chlorpyrifos alters functional integrity and structure of an in vitro BBB model: co-cultures of bovine endothelial cells and neonatal rat astrocytes. *Neurotoxicology* **26**, 77-88.

[272] Abu-Qare AW , Abou-Donia MB (2003) Combined exposure to DEET (N,N-diethyl-m-toluamide) and permethrin: pharmacokinetics and toxicological effects. *J Toxicol Environ Health B Crit Rev* **6**, 41-53.

[273] Wolff G, Davidson SJ, Wrobel JK, Toborek M (2015) Exercise maintains blood-brain barrier integrity during early stages of brain metastasis formation. *Biochem Biophys Res Commun* **463**, 811-817.

[274] Ferencz B, Laukka EJ, Welmer AK, Kalpouzos G, Angleman S, Keller L, Graff C, Lovden M, Backman L (2014) The benefits of staying active in old age: physical activity counteracts the negative influence of PICALM, BIN1, and CLU risk alleles on episodic memory functioning. *Psychol Aging* **29**, 440-449.

[275] Zhang P, Xianglei J, Hongbo Y, Zhang J, Xu C (2015) Neuroprotection of Early Locomotor Exercise Poststroke: Evidence From Animal Studies. *Can J Neurol Sci* **42** , 213-220.

[276] de Senna PN, Xavier LL, Bagatini PB, Saur L, Galland F, Zanotto C, Bernardi C, Nardin P, Goncalves CA, Achaval M (2015) Physical training improves non-spatial memory, locomotor skills and the blood brain barrier in diabetic rats. *Brain Res* **1618**, 75-82.

[277] Wang X, Zhang M, Feng R, Li WB, Ren SQ, Zhang J, Zhang F (2014) Physical exercise training and neurovascular unit in ischemic stroke. *Neuroscience* **271**, 99-107.

[278] He J, Hsuchou H, He Y, Kastin AJ, Wang Y, Pan W (2014) Sleep restriction impairs blood-brain barrier function. *J Neurosci* **34**, 14697-14706.

[279] Palomares JA, Tummala S, Wang DJ, Park B, Woo MA, Kang DW, St Lawrence KS, Harper RM, Kumar R (2015) Water Exchange across the Blood-Brain Barrier in Obstructive Sleep Apnea: An MRI Diffusion-Weighted Pseudo-Continuous Arterial Spin Labeling Study. *J Neuroimaging* **25**, 900-905.

[280] Sajja RK, Rahman S, Cucullo L (2016) Drugs of abuse and blood-brain barrier endothelial dysfunction: A focus on the role of oxidative stress. *J Cereb Blood Flow Metab* **36**, 539-554.

[281] Spindler KR , Hsu TH (2012) Viral disruption of the blood-brain barrier. *Trends Microbiol* **20**, 282-290.

[282] Patrick D, Betts J, Frey EA, Prameya R, Dorovini-Zis K, Finlay BB (1992) Haemophilus influenzae lipopolysaccharide disrupts confluent monolayers of bovine brain endothelial cells via a serum-dependent cytotoxic pathway. *J Infect Dis* **165**, 865-872.

[283] Chen N, Warner JL, Reiss CS (2000) NSAID treatment suppresses VSV propagation in mouse CNS. *Virology* **276**, 44-51.

[284] Reichman HR, Farrell CL, Del Maestro RF (1986) Effects of steroids and nonsteroid anti-inflammatory agents on vascular permeability in a rat glioma model. *J Neurosurg* **65**, 233-237.

[285] Candelario-Jalil E (2008) Nimesulide as a promising neuroprotectant in brain ischemia: new experimental evidences. *Pharmacol Res* **57**, 266-273.

[286] Chen X, Ghribi O, Geiger JD (2010) Caffeine protects against disruptions of the blood-brain barrier in animal models of Alzheimer's and Parkinson's diseases. *J Alzheimers Dis* **20 Suppl 1**, S127-S141.

[287] Sugimoto N, Miwa S, Hitomi Y, Nakamura H, Tsuchiya H, Yachie A (2014) Theobromine, the primary methylxanthine found in Theobroma cacao, prevents malignant glioblastoma proliferation by negatively regulating phosphodiesterase-4, extracellular signal-regulated kinase, Akt/mammalian target of rapamycin kinase, and nuclear factor-kappa B. *Nutr Cancer* **66**, 419-423.

[288] Kraft P, Schwarz T, Gob E, Heydenreich N, Brede M, Meuth SG, Kleinschnitz C (2013) The phosphodiesterase-4 inhibitor rolipram protects from ischemic stroke in mice by reducing blood-brain-barrier damage, inflammation and thrombosis. *Exp Neurol* **247**, 80-90.

[289] Martinez-Pinilla E, Onatibia-Astibia A, Franco R (2015) The relevance of theobromine for the beneficial effects of cocoa consumption. *Front Pharmacol* **6**, 30-

[290] Bynoe MS, Viret C, Yan A, Kim DG (2015) Adenosine receptor signaling: a key to opening the blood-brain door. *Fluids Barriers CNS* **12**, 20-

[291] Lehmann M, Regland B, Blennow K, Gottfries CG (2003) Vitamin B12-B6-folate treatment improves blood-brain barrier function in patients with hyperhomocysteinaemia and mild cognitive impairment. *Dement Geriatr Cogn Disord* **16**, 145-150.

[292] Seker FB, Yorulmaz H, Kaptan E, Caglayan B, Oztas B (2016) Gestational treatment of folic acid attenuates blood-brain barrier leakage in pregnant- and prepubertal rats after pentylenetetrazole-induced seizure. *Nutr Neurosci* **19**, 55-62.

[293] Alluri H, Wilson RL, Anasooya SC, Wiggins-Dohlvik K, Patel S, Liu Y, Peng X, Beeram MR, Davis ML, Huang JH, Tharakan B (2016) Melatonin Preserves Blood-Brain Barrier Integrity and Permeability via Matrix Metalloproteinase-9 Inhibition. *PLoS One* **11**, e0154427-

[294] Maggioli E, McArthur S, Mauro C, Kieswich J, Kusters DH, Reutelingsperger CP, Yaqoob M, Solito E (2016) Estrogen protects the blood-brain barrier from inflammation-induced disruption and increased lymphocyte trafficking. *Brain Behav Immun* **51**, 212-222.

[295] Naderi V, Khaksari M, Abbasi R, Maghool F (2015) Estrogen provides neuroprotection against brain edema and blood brain barrier disruption through both estrogen receptors alpha and beta following traumatic brain injury. *Iran J Basic Med Sci* **18**, 138-144.

[296] Witt KA , Sandoval KE (2014) Steroids and the blood-brain barrier: therapeutic implications. *Adv Pharmacol* **71**, 361-390.

[297] Shin JA, Yoon JC, Kim M, Park EM (2016) Activation of classical estrogen receptor subtypes reduces tight junction disruption of brain endothelial cells under ischemia/reperfusion injury. *Free Radic Biol Med* **92**, 78-89.

[298] Zhang W, Zhang H, Mu H, Zhu W, Jiang X, Hu X, Shi Y, Leak RK, Dong Q, Chen J, Gao Y (2016) Omega-3 polyunsaturated fatty acids mitigate blood-brain barrier disruption after hypoxic-ischemic brain injury. *Neurobiol Dis* **91**, 37-46.

[299] Russell KL, Berman NE, Gregg PR, Levant B (2014) Fish oil improves motor function, limits blood-brain barrier disruption, and reduces Mmp9 gene expression in a rat model of juvenile traumatic brain injury. *Prostaglandins Leukot Essent Fatty Acids* **90**, 5-11.

[300] Mohagheghi F, Bigdeli MR, Rasoulian B, Zeinanloo AA, Khoshbaten A (2010) Dietary virgin olive oil reduces blood brain barrier permeability, brain edema, and brain injury in rats subjected to ischemia-reperfusion. *ScientificWorldJournal* **10**, 1180-1191.

[301] Takechi R, Pallebage-Gamarallage MM, Lam V, Giles C, Mamo JC (2013) Nutraceutical agents with anti-inflammatory properties prevent dietary saturated-fat induced disturbances in blood-brain barrier function in wild-type mice. *J Neuroinflammation* **10**, 73-

[302] Latruffe N , Rifler JP (2013) Bioactive polyphenols from grapes and wine emphasized with resveratrol. *Curr Pharm Des* **19**, 6053-6063.

[303] Wei H, Wang S, Zhen L, Yang Q, Wu Z, Lei X, Lv J, Xiong L, Xue R (2015) Resveratrol attenuates the blood-brain barrier dysfunction by regulation of the MMP-9/TIMP-1 balance after cerebral ischemia reperfusion in rats. *J Mol Neurosci* **55**, 872-879.

[304] Griffiths H, Irundika D, Lip G, Spickett C, Polidori C (2014) Oxidised LDL lipids, statins and a blood-brain barrier. *Free Radic Biol Med* **75 Suppl 1**, S15-S16.

[305] Yang CH, Kao MC, Shih PC, Li KY, Tsai PS, Huang CJ (2015) Simvastatin attenuates sepsis-induced blood-brain barrier integrity loss. *J Surg Res* **194**, 591-598.

[306] Yang D, Knight RA, Han Y, Karki K, Zhang J, Chopp M, Seyfried DM (2013) Statins Protect the Blood Brain Barrier Acutely after Experimental Intracerebral Hemorrhage. *J Behav Brain Sci* **3**, 100-106.

[307] Reis PA, Estato V, da Silva TI, d'Avila JC, Siqueira LD, Assis EF, Bozza PT, Bozza FA, Tibirica EV, Zimmerman GA, Castro-Faria-Neto HC (2012) Statins decrease neuroinflammation and prevent cognitive impairment after cerebral malaria. *PLoS Pathog* **8**, e1003099-

Table 1: The effects of diverse pathogens on beta-amyloid deposition, tau phosphorylation and their relationships with Alzheimer's disease.

	Effects on beta-amyloid deposition or Tau phosphorylation	**Presence in Alzheimer's disease brain**	**Antibodies in Alzheimer's disease blood and other analyses**
Viruses			
Borna virus	In transgenic mice expressing an APP mutant (Tg2576) infection of cortical and limbic brain areas is characterized by T-cell infiltrates, high cytokine expression and a massive microglial activation in the hippocampus and neocortex.The inflammatory effects and microglial	?	Associates with a rare form of hippocampal degeneration but not specifically with Alzheimer's disease [172]

	activation were linked to a decrease of parenchymal beta-amyloid deposits but an increase of beta-amyloid deposits in the walls of cerebral vessels [93].		
Epstein-Barr virus: human herpesvirus 4	No reports	The virus has been detected in a small percentage of AD brains (6%). In aged individuals followed for 5 years EBV-positive or HHV-6-positive peripheral blood leukocytes increased in those who developed clinical AD [198]	Viral IgG levels are increased in Alzheimer's patients with the IRF7 GG genotype (interferon regulatory factor7) [199]
HSV-1 (herpes simplex)	HSV-1 induces beta-amyloid and tau phosphorylation in cell culture or in mice, effects that can be attenuated by acyclovir in cell	Numerous studies have reported the presence of HSV-1 in Alzheimer's disease brains or an association with HSV-1 seropositivity (reviewed in [200]).	

	culture [200]		
HSV-2 Herpes simplex virus 2	Increases beta-amyloid deposition and tau phosphorylation in human SK-N-MC neuroblastoma cells[201]	Present at relatively low frequency in brains of both control (20%) and Alzheimer's patients (13%) [202]	?
Human cytomegalovirus : human herpesvirus-5	Beta-amyloid production is increased by cytomegalovirus infection in human foreskin fibroblasts : Seropositivity associated with the presence of brain neurofibrillary tangles in post-mortem human brain [203]	?	Seropositivity associated with Azheimer's disease and with cognitive decline in the aged [204]. Infectious burden consisting of cytomegalovirus , HSV-1, *B. burgdorferi*, *C. Pneumoniae* and *H. Pylori* is associated with Alzheimer's disease [1]
HHV-6 Human herpesvirus 6	No reports found	Present in a higher proportion of the AD than of age-matched normal brain(70 vs 40%) [202]	Viral DNA detected in a higher proportion of

			Alzheimer's disease peripheral blood leukocytes [198] and high seropositivity observed in some Alzheimer's patients [205] . The Epstein-Barr virus and HHV-6 were noted as risk factors for Alzheimer's disease in genetically susceptible elderly patients [199]
Hepatitis C	No reports found	?	Infection associated with dementia [206]

Influenza A	No reports found	?	No association between past infections and Alzheimer's disease in a large study [207] Previous vaccination against influenza, diphtheria, tetanus or the poliovirus has been associated with a lower risk for Alzheimer's disease [208]. A particular strain (A/Vietnam/1203/04 H5N1 virus) can enter the mouse brain from the periphery, causing neurodegeneration and alpha-synuclein (SNCA) accumulation: Cell death primarily

	affects the substantia nigra but aggregated alpha-synuclein was observed in the hippocampus ,cortex and brainstem [209]

HIV-1: human immunodeficiency virus	Amyloid plaques found in the brains of HIV-1 patients and beta-amyloid deposition predicts neurocognitive disorders in HIV-1 infected **APOE4** carriers [210,211].CSF beta-amyloid and tau levels correlate with AIDS associated dementia[212]		As treatment for AIDS has improved dementia associated with AIDS (NeuroAIDS) has increased in the ageing population [213,214]
Bacteria			
Chlamydia pneumoniae	*C. Pneumoniae* infection produces beta-amyloid deposition in the brains of BALB/C mice which resolves as the bacterial antibody titre decreases [215,216].	Detected in the Alzheimer's brain in apposition to plaques and tangles [217-222]	Meta-analysis : Evidence for *C. Pneumoniae* infection (Odds ratio = 5.66) [223]
Helicobacter pylori	*H. pylori* infection in rats increases cerebral beta-amyloid deposition via upregulation of	?	A recent meta-analysis has reported a significant association between

	presenilin 2 , and impairs learning and memory [224] and increases tau phosphorylation in cell culture (mouse neuroblastoma N2a cells) or *in vivo* (rats) via glycogen synthase kinase beta[225].		*H. Pylori* infection and dementia (Odds ratio= 1.71) [226] . Cognitive function and survival rates have been reported to be improved following *H. Pylori* eradication in Alzheimer's disease patients [195,227]. Progression of dementia has also been reported to be reduced in Alzheimer's patients with peptic ulcer following *H. Pylori* eradication [196]
Propionibacterium acnes	?	Propionibacterium acnes was identified in frontal cortex biopsy specimens in three of four AD patients. The bacterium was cultivated from frontal cortical biopsy specimens [228,229].	

Spirochetes

Borrelia burgdorferi	Beta-amyloid deposition and tau phosphorylation induced by the spirochete in cocultured mammalian glial/neuronal cells [230]	Detected in the Alzheimer's disease brain[231]. Detected in 14 AD brains and not in any of 13 control brains. Spirochetes were also found in AD blood and CSF [232]. Beta-amyloid and bacterial DNA are components of pure bacterial biofilms and of senile plaques in AD [233,234]	Meta-analysis : Evidence for Spirochetal infection associated with Alzheimer's disease (Odds ratio = 10.61) [223]

Fungal/yeast species detected in the AD brain include: - *Saccharomyces cerevisiae; Malassezia globosa; Malassezia restricta; Penicillium Phoma, Candida albicans, Candida orthopsis, Candida tropicalis, Cladosporium, Neosartorya hiratsukae, Sclerotinia borealis* [235,236]. Filamentous micro-organisms, possibly relating to actinomycetes have been found in control and AD brains with a four to five-fold higher frequency in Alzheimer's disease [237]. *C. famata, C. albicans* or *C. glabrata* antigens have been found in AD cerebrospinal fluid[238].

Antibodies to *Candida famata, Candida albicans. Syncephalastrum racemosum* and *Phoma betae* stain corpora amylacea in the brains of Alzheimer's disease patients [239].

Two case reports indicated virtually complete recovery from long-term (3 years) mis-diagnosed dementia/Alzheimer's disease following antifungal treatment for *C. Neoformans* infection [50,51].

Periodontal pathogens: Periodontitis has been associated with Alzheimer's disease and with cognitive decline in AD patients [240-242]. Periodontal disease has been associated with increased beta-amyloid load in patients *in vivo* [243].

Actinomyces naeslundii	?	?	Serum IgG levels associated with

			increased risk of AD [244]
Porphyromonas gingivalis	?	*P. Gingivalis* lipopolysaccharide detected in 4/10 Alzheimer's brains post-mortem [245]	?
Fusobacterium nucleatum	?	?	Antibody levels to *F. nucleatum* and *P. intermedia* increased in Alzheimer's disease serum [246]
Prevotella intermedia	?	?	

Treponemes (oral pathogens) detected in the brains of AD patients using species specific PCR

T. pectinovorum, T. amylovorum, T. lecithinolyticum, T. maltophilum, T. medium, T. socranskii, T. denticola, T. vincenti [234,247].

Treponema pallidum causes syphilis. Syphilitic dementia is associated with the pathological features of AD [248]

Parasites

Toxoplasma gondii	*T. Gondii* infection has been reported to inhibit neurodegeneration in transgenic mice (Tg2576) expressing the Swedish APP mutation [249] and to reduce amyloid plaque deposition in 5xFAD mice, effects attributed to immune activation, via recruitment of Ly6C(hi) monocytes and by enhancement of phagocytosis and degradation of soluble beta-amyloid [177]. Chronic infection in mice does produce neuroinflammation and neuronal injury , including	? [80]	A high seroprevalence for the Toxoplasma gondii parasite has also been reported in one study of Alzheimer's disease patients [250], but not confirmed in others [251,252]

Leishmania amazonensis	Increased tau phosphorylation in the brains of infected mice [253].	?	?	
Trypanosoma Cruzi (causes Chagas disease)	?	?		Isolated cases of central nervous system involvement can include dementia, confusion, chronic encephalopathy and sensory and motor deficits [254]
Plasmodium berghei (causes malaria in rodents)	Cerebral accumulation of beta-amyloid in infected malaria-susceptible mice (CBA/J and C57BL/6) [255].			Not applicable

Beta-amyloid:

Antimicrobial effects of beta-amyloid have been noted against *Candida albicans, Escherichia coli; Staphylococcus epidermidis; Streptococcus pneumoniae; Staphylococcus aureus; Listeria monocytogenes ;Enterococcus faecalis ; Streptococcus agalactia* . It also protects against *Salmonella typhinurim* meningitis in transgenic (5XFAD) mice expressing human beta-amyloid and in nematodes (*C. elegans*). Beta-amyloid binds to *C. albicans* and *S. typhimurium*. In transgenic (5XFAD) mice, *S. typhimurium* infection increases beta-amyloid deposition and bacteria are embedded within beta-amyloid deposits in the brain [2,3]. Beta-amyloid has antiviral effects against the influenza[4] and herpes simplex [5,6]viruses.

However, beta-amyloid can stimulate the infection of target cells expressing CD4 and an appropriate coreceptor by HIV-1, not allowing infection in cells lacking these receptors. It also stimulated infection by amphotrophic Moloney leukemia virus, herpes simplex virus, and vesicular stomatitis virus, a phenomenon also observed with other synthetic fibril-forming peptides [256].

Table 2. The effects of Alzheimer's disease environmental risk factors and beneficial agents on blood brain barrier function.

Alzheimer's disease risk factor	Effects on blood brain barrier
Ageing	Aging leads to barrier dysfunction and vascular hyperpermeability in peripheral and blood-brain barriers [110]
Air pollution	Long-term air pollution disrupts the BBB in children and young adults and causes neuroinflammation, an altered brain innate immune response, and accumulation of beta-amyloid and alpha-synuclein starting in childhood [123]
Alcohol abuse	Alcohol(ism) has deleterious effects on the BBB[257,257,258]
Aluminium	Aluminium increases BBB permeability in rats [259]
Beta-amyloid	Beta-amyloid disrupts BBB integrity in mice [260]
Brain trauma (concussion)	Mild traumatic brain injury produces early disruption of the BBB in animal models and in Man [261,262].
Cerebral hypoperfusion/ischaemia (carotid/leptomeningeal.circle of Willis atherosclerosis)	Cerebral hypoperfusion reduces oxygen, glucose and other nutrient supply to the brain, damaging parenchymal cells, and the blood-brain barrier [263].
Copper/aluminium	Nanoparticles from aluminium, silver or copper increase spinal cord pathology after trauma, an effect correlated with breakdown of the blood-spinal cord barrier [264]
Diabetes mellitus	BBB dysfunction plays a role in diabetes-associated neurological complications (stroke, vascular dementia and cognitive deficits) [265]
Homocysteine	Hyperhomocysteinemia increases permeability of the blood-

	brain barrier via N-methyl-D-aspartate (NMDA) receptor activation [266]
Hypercholesterolaemia	High cholesterol disrupts the blood brain barrier, an effect blocked by simvastatin [267]
Hypertension	Hypertension causes blood-brain barrier breakdown via mechanisms involving inflammation, oxidative stress, and vasoactive circulating molecules [268]
Obesity	Obesity induces systemic inflammation and blood-brain barrier disruption in mice, an effect augmented by age [269]
Pesticides	Several pesticides are able to disrupt the BBB in animal models [270-272]
Physical inactivity	Exercise in animal models of cerebral ischaemia/stroke , diabetes, and brain metastasis has been shown to improve BBB function [273]. Physical activity counters the negative influence of PICALM, BIN1, and CLU risk alleles on episodic memory functioning in a dementia-free population [274](all of these are expressed in the BBB proteome dataset)[275-277]
Poor sleep	Sleep disruption or sleep apnoea are both associated with impaired blood-brain barrier function [278,279].
Smoking	Nicotine and smoking disrupt brain microvasculature and the blood brain barrier[280]
Viruses capable of disrupting the blood brain barrier	Viruses infecting humans known to cause disruption of the BBB or endothelial junctions include HIV-1, human T-cell leukemia virus, lymphocytic choriomeningitis virus and the West Nile virus [281]. Bacterial lipopolysaccharide is disruptive in BBB models

	[282].
Beneficial effects	
Anti-inflammatories	Aspirin and celecoxib prevent disruption of the BBB in Vesicular Stomatitis Virus-infected mice [283]. Dexamethasone and methylprednisolone as well as NSAID's (ibuprofen and indomethacin) reduce vascular permeability in a rat glioma model [284]. Nimesulide (a selective cyclooxygenase-2 inhibitor) attenuates blood-brain barrier disruption in animal models of cerebral ischaemia [285]
Caffeine	Caffeine is effective against BBB disruption in animal models of Alzheimer's or Parkinson's disease [286].
Chocolate (caffeine, theobromine and resveratrol)	Theobromine is a phosphodiesterase inhibitor and downregulates PDE4 in a glioma cell line [287]. PDE4 inhibition (rolipram) reduces BBB damage in ischaemic stroke in mice [288]. Caffeine and theobromine are adenosine receptor antagonists [289]. Extracellular adenosine increases BBB permeability and adenosine receptor antagonism blocks the entry of inflammatory cells and soluble factors into the brain [290].
Folic acid	Vitamin B12-B6-folate treatment improves BBB function in patients with hyperhomocysteinaemia and mild cognitive impairment [291] . Folic acid decreases BBB leakage and reactive astrogliosis following seizures in pregnant and prepubertal rats [292].
Melatonin	Melatonin protects BBB integrity by downregulating matrix

	metalloprotease activity (MMP9) [293]
Memantine	Memantine (approved for use in dementia patients) [152] blocks the deleterious effects of homocysteine on the blood-brain barrier [266].
Oestrogen	Oestrogen protects against BBB breakdown in animal models of stroke or following lipopolysaccharide challenge and maintains barrier integrity [294-297]
Components of the Mediterranean diet	Omega-3 fatty acids reduce BBB disruption in hypoxic/ischaemic brain injury [298].Fish oil reduces BBB disruption in a rat model of juvenile traumatic brain injury [299]. Virgin olive oil reduces BBB permeability following middle cerebral artery occlusion in rats [300]. Aged garlic extract protects against BBB disruption caused by a high saturated fatty acid diet in mice [301] . Resveratrol, a component of grape and red fruit skins, and red wine[302], maintains the integrity of the BBB after cerebral ischemia reperfusion in rats [303].
Statins	Statins have been reported to ameliorate BBB dysfunction produced by high cholesterol [267] , oxidised low-density lipoprotein [304], sepsis, intracerebral haemorrhage [305,306] or cerebral malaria [307]

Supplementary table 1:

Definitions of the Alzheimer's disease susceptibility genes studied. While many other functions are recognised, for example relating to beta-amyloid, cholesterol, lipid and glucose metabolism or diabetes, *inter alia* [1-4], the properties isolated in this table focus specifically on immune and pathogen-related effects. The relationship between AD genes, the immune system and inflammation has also previously emphasised [5] and in a recent study from the Alzheimer's Disease Neuroimaging Initiative, another subset of Alzheimer's disease genes showed genetic overlap between Alzheimer's disease and immune-mediated diseases [6] .

Gene Symbol	Name	Immune or pathogen related properties
ABCA7	ATP-binding cassette, sub-family A (ABC1), member 7	Plays a prominent role in phagocytosis by macrophages (demonstrated with Staphylococcus aureus). This is an important line of general host defence against pathogens [7]. Overexpression of ABCA7 in HeLa cells resulted increases intracellular and cell surface ceramide and intracellular phosphatidylserine levels [8]. Ceramide reactivates the herpes simplex virus from latency [9] and is also incorporated into *C.Pneumoniae* inclusions [10]. APOA1 and APOE are substrates for ABCA7, and in cultured

		HEK-293 cells, plasma membrane-situated ABCA7 increases the efflux of phosphatidylcholine and sphingomyelin efflux to APOA1 and APOE, with no effect on cholesterol efflux[11] . Sphingomyelin is enriched in extracellular herpes simplex viral membranes [12] . It is a receptor for the Helicobacter toxin VacA [13] and is also incorporated into inclusion bodies in *C.Pneumoniae* infected cells [14]. Phosphatidylcholine plays an important role in the fusion of herpes simplex glycoproteins B and H with the host cell lipid membrane, a process used in viral entry [15]. Phosphatidylcholine is also able to trigger capsular enlargement in *C.Neoformans* infection [16]. Cholesterol efflux to lipid-laden APOE, but not to lipid free APOE, is increased by ABCA7 expression in HEK-293 cells [17].
ACE	angiotensin I converting enzyme	Modifies the C termini of peptides for

		presentation by major histocompatibility complex class I molecules, which increases the efficiency of antigen-specific CD8+ T cell priming [18].
ADAMTS20	ADAM metallopeptidase with thrombospondin type 1 motif, 20	Cleaves the chondroitin sulfate proteoglycan, versican[19] which interacts with myeloid and lymphoid cells promoting their adhesion and the production of inflammatory cytokines: Inflammatory agents, such as double-stranded viral RNA mimetics, stimulate stromal cells, smooth muscle cells and fibroblasts, to produce fibrillar extracellular matrices enriched in versican and hyaluronan that promote the adhesion of leukocytes [20]
AP2A2	adaptor-related protein complex 2, alpha 2 subunit	Induces the renewal and maintenance of hematopoietic stem cells [21]. Required for binding of human immunodeficiency virus type 1 Nef and cooperative assembly of a CD4-Nef-

		AP-2 complex [22].
APOC1	apolipoprotein C-I	APOC1 binds to lipopolysaccharide (LPS), an outer-membrane component of gram-negative bacteria and is involved in the presentation of LPS to macrophages. This improves the inflammatory response , thus protecting against infection [23]. **APOC1** is a component of high density lipoprotein: Herpes simplex is present in all lipoprotein blood fractions in blood (VLDL, LDL and HDL) and the lipid component of these lipoproteins binds to viral glycoprotein B [24]
APOE	apolipoprotein E	APOE4 favours cerebral access of HSV-1 in mice [25] and enhances C.pneumoniae adherence to host cells [26] and HIV-1 cell entry in vitro [27], but is protective against chronic hepatitis C virus infection [28]. The allele relates to increased viral load in HHV-6 infected epilepsy patients [29]. Hepatitis B pathology has a more benign course in ApoE2-E4 carriers

		[30].
ATXN7L1	ataxin 7-like 1	None found
BCAM	basal cell adhesion molecule (Lutheran blood group)	Adhesion molecule involved in red blood cell adhesion to the vascular endothelium [31] Also plays a role in abnormal red blood cell adhesion in sickle cell disease (c.f. malaria) [32]. Acts as a receptor for Escherichia coli cytotoxic necrotizing factor 1, a toxin found in E.coli strains causing meningitis [33]
BCL3	B-cell CLL/lymphoma 3	BCL3 is essential for the development, survival and activity of adaptive immune cells. BCL3-deficient mice are more susceptible to bacterial and parasitic infection [34].
BIN1	bridging integrator 1	BIN1 negatively controls the expression of indoleamine 2,3-dioxygenase IDO1 in cancer cells [35]. IDO1 activation diverts tryptophan metabolism to N-formyl-kynurenine, (away from serotonin production) .IDO1 upregulation is an important

		defence mechanism against pathogenic bacteria, many of which rely on host tryptophan. It is involved in antimicrobial defence and immune regulation, and its effects are not restricted to bacteria This IDO1 response is also deleterious to other pathogens and parasites, including T.Gondii, and to a number of viruses, including herpes simplex virus and other herpes viruses [166]. Kynurenine and kynurenic acid produced by IDO1 activation, are ligands for the aryl hydrocarbon receptor (AHR), which plays an important role in antimicrobial defence and immune regulation [167]. A BIN1isoform is required for macrophage phagocytosis, a key mechanism in the destruction of many pathogens [36]
CASS4	Cas scaffolding protein family member 4	One of a member of scaffold proteins are regulated by and mediating cell attachment, growth factor, and chemokine signalling [37]

CD2AP	CD2-associated protein	CD2AP and other endocytosis-associated proteins play a role in enteropathogenic Escherichia coli pedestal formation [38]: Also required for late endosomal trafficking of the H. pylori VacA toxin [39]. Clathrin and related proteins including CD2AP are involved in the recruitment of proteins that promote actin polymerization at the interface of T cells and antigen presenting cells [40]. Decreased CD2AP expression enhances the production of type I interferons in human plasmacytoid dendritic cells which secrete type I interferons in response to microbial stimuli [41]
CD33	CD33 molecule	A member of the sialic acid binding Immunoglobulin g-like lectin (SIGLEC) family. CD33-related SIGLEC's regulate adaptive immune responses and are also important as macrophage pattern recognition receptors for sialylated pathogens, including enveloped viruses [42].

		CD33 binds to alpha 2-3- or alpha2-6-linked sialic acids (N-acetyl neuranimic acid) [43]. These residues bind to the influenza virus and the reovirus [44] and these particular sialic acids are expressed on the surface envelope glycoproteins (B, D and H) of the herpes simplex virion, and are required for viral entry into cells [45]. N-acetyl neuranimic acid is expressed by *C.Neoformans* and is involved in fungal adhesion to macrophages [46] and is also a component of the cell wall of *B.Burgdorferi* [47] while *Helicobacter pylori* adhesins also bind to this particular form of sialic acid [48,49] as does *P.Gingivalis*[50]. CD33 binds to sialic acid acquired by P. aeruginosa and to the HIV-1 gp120 protein [51] .
CDON	cell adhesion associated, oncogene regulated	A gene associated with the acquisition of Staphylococcus aureus bacteraemia [52]
CEACAM16	carcinoembryonic antigen-related	The CEACAM family are docking sites

	cell adhesion molecule 16	for pathogenic bacteria [53] but this particular protein has not been characterised in relation to this effect
CELF1	CUGBP, Elav-like family member 1	A downstream effector of interferon beta signalling in macrophages [54].
CLU	clusterin	Inhibits the membrane attack complex, composed of complement components C5 to C9. This is deposed on the bacterial surface forming channels that cause bacterial lysis [55,56] .
CNTNAP2	contactin associated protein-like 2	None found
CR1	complement component (3b/4b) receptor 1 (Knops blood group)	Many pathogens are recognised by the complement system and coated with complement components C1q, C3b and iC3b. This "opsonisation" prepares the microbe for phagocytosis via binding of the complement components to complement receptors, including CR1 [57]. Receptor for the malaria pathogen *Plasmodium falciparum [58], Legionella pneumophila [59], Mycobacterium tuberculosis[60]* and *Cryptococcus neoformans*

CUGBP2 (changed to CELF2)	CUGBP, Elav-like family member 2	CUGBP2 silences the expression of cyclo-oxygenase 2 (PTGS2), thus regulating inflammatory processes [61] CUGBP2 is regulated in response to T-cell signalling and increased CELF2 expression drives a network of activation-induced alternative splicing events in Jurkat cells [62].
DISC1	disrupted in schizophrenia 1	DISC1 has many functions relevant to the psychiatric diseases in which it is implicated, among which is control of the intracellular traffic of mRNAs, neurotransmitter receptors, vesicles and mitochondria along the microtubule network [63,64] . Although DISC1 has not been related to any particular virus or pathogen, the microtubule network provides a set of railway tracks used by many viruses during their life cycles [65-67]. Such traffic is also important in the regulation of the immunological synapse and in the building of functional phagosomes [68]
ECHDC3	enoyl CoA hydratase domain	Expressed in whole blood cells and

	containing 3	platelets, but no functional data available [69,70] .One of several genes downregulated by Trypanosoma Cruzi in mouse macrophages [71]
EPHA1	EPH receptor A1	Suppresses T cell activation and Th2 cytokine expression, while preventing activation-induced cell death in the lung [72]. Upregulated in dendritic antigen-presenting cells in response to the human papillomavirus E7 peptide [73] . Mice infected with M. tuberculosis displayed higher expression of EPHA1 and EPHA2 in monocytes as well as ephrinA1[74]
EXOC3L2	exocyst complex component 3-like 2	None found
FAM113B (now C5orf64)	chromosome 5 open reading frame 64	This locus is considered non-coding by other groups due to a lack of experimental support for the protein, but NCBI annotates the protein because it meets minimal RefSeq quality criteria for representation. The coding status remains uncertain. [19 Nov

		2014](Refseq)
FANCD2OS	FANCD2 opposite strand	No functional publications
FERMT2	fermitin family member 2	None found
FLJ37543 (now C5orf64)	chromosome 5 open reading frame 64	None found
FRMD4A	FERM domain containing 4A	None found
GAB2	GRB2-associated binding protein 2	An adaptor protein involved in multiple receptor tyrosine kinase signalling pathways: phosphorylated by stimulation with growth factors-, cytokines-, Immunoglobulin Fc- and antigen receptors [75] Gab2 knockout mice show reduced inflammatory cytokine levels in, and are relatively protected against Mycobacterium tuberculosis infection[76].
GRIN3B	glutamate receptor, ionotropic, N-methyl-D-aspartate 3B	None found
HLA-DRB1	major histocompatibility complex, class II, DR beta 1	Bind to pathogen antigens and present them to T-cells [77].

HLA-DRB5	major histocompatibility complex, class II, DR beta 5	
HMHA1	histocompatibility (minor) HA-1	When HA-1 peptide was added to mixtures of plasmacytoid DC dendritic cells and T cells, bystander suppression of the response to a colocalized recall Epstein-barr viral antigen occurred primarily via indolamine-2,3-dioxygenase (IDO1) production. Bystander suppression is a process whereby Antigen-specific (adaptive) T regulatory cells inhibit the T effector cell response both to specific antigen and to a colocalized third-party antigen [78]: minor histocompatibility antigens refer to immunogenic peptides which, when complexed with MHC, can generate an immune response after recognition by specific T-cells. The peptides are derived from polymorphic intracellular proteins, which are cleaved by normal pathways of antigen processing (Definition from Uniprot).
HS3ST1	heparan sulfate (glucosamine) 3-O-	Heparan sulfate biosynthetic enzymes

	sulfotransferase 1	are key components in generating a myriad of distinct heparan sulfate fine structures that carry out multiple biologic activities. The enzyme encoded by this gene is a member of the heparan sulfate biosynthetic enzyme family. It possesses both heparan sulfate glucosaminyl 3-O-sulfotransferase activity, anticoagulant heparan sulfate conversion activity, and is a rate limiting enzyme for synthesis of anticoagulant heparan. This enzyme is an intraluminal Golgi resident protein. [provided by RefSeq, Jul 2008]. Heparan sulphates act as attachment sites for many viruses [79,80]
IGH	immunoglobulin heavy locus	Forms the heavy chain of multiple antibodies [77].
INPP5D	inositol polyphosphate-5-phosphatase, 145kDa	Phosphatidylinositol (PtdIns) phosphatase that specifically hydrolyses the 5-phosphate of phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3) to

		produce PtdIns(3,4)P2, thereby negatively regulating the PI3K (phosphoinositide 3-kinase) pathways. Acts as a negative regulator of B-cell antigen receptor signalling. Mediates signalling from the FC-gamma-RIIB receptor (FCGR2B), playing a central role in terminating signal transduction from activating immune/hematopoietic cell receptor systems. Acts as a negative regulator of myeloid cell proliferation/survival and chemotaxis, mast cell degranulation, immune cells homeostasis, integrin alpha-IIb/beta-3 signalling in platelets and JNK signalling in B-cells. Regulates proliferation of osteoclast precursors, macrophage programming, phagocytosis and activation and is required for endotoxin tolerance. Involved in the control of cell-cell junctions, CD32a signalling in neutrophils and modulation of EGF-induced phospholipase C activity. Key regulator of neutrophil migration, by

		governing the formation of the leading edge and polarization required for chemotaxis. Modulates FCGR3/CD16-mediated cytotoxicity in NK cells. Mediates the activin/TGF-beta-induced apoptosis through its Smad-dependent expression. May also hydrolyse PtdIns(1,3,4,5)P4, and could thus affect the levels of the higher inositol polyphosphates like InsP6.2 (Definition from Uniprot)
LUZP2	leucine zipper protein 2	None found
MEF2C	myocyte enhancer factor 2C	MEF2C orchestrates early B-cell development [81] and is also involved in the activation induced cell death of macrophages after priming with Salmonella typhimurium, type 5 adenovirus or Interferon-gamma [82]. Also a risk gene for periodontitis [83], a known risk factor for Alzheimer's disease [84]
MMP12	matrix metallopeptidase 12 (macrophage elastase)	Degrades elastin, a matrikine derived from extracellular matrix proteins: These are implicated in inflammation,

		immune responses, organ development, wound repair, angiogenesis, atherosclerosis, tumor progression and metastasis due to their ability to alter cellular migration, chemotaxis, and mitogenesis.[85] . Aging and various inflammatory diseases such as atherosclerosis, abdominal aortic aneurysms, chronic obstructive pulmonary diseases, cancer and type 2 diabetes are characterized by the destruction of elastin fibres [86]
MMP3	matrix metallopeptidase 3 (stromelysin 1, progelatinase)	PolyI:C treatment (viral DNA mimic) increases the expression levels of Mmp3 mRNA and protein in astrocytes, but not microglia [87].
MPZL1	myelin protein zero-like 1	Present in CD133(+) precursors (CD133= hematopoietic precursor antigen) and endothelial cells, and mainly in mesenchymal and committed myelomonocytic progenitor cells, and in erythroid precursor cell lines [88].

MS4A3	membrane-spanning 4-domains, subfamily A, member 3 (hematopoietic cell-specific)	Modulates cell cycle progression in hematopoietic cells [89]
MS4A4A	membrane-spanning 4-domains, subfamily A, member 4A	Localised in Hematopoietic cells [89]: Expressed in lung mast cells Silencing MS4A4 promotes mast cell proliferation and migration. Mast cells express Toll receptors and play an important role in pathogen recognition and in acquired immunity against parasitic infections [90,91].
MS4A4E	membrane-spanning 4-domains, subfamily A, member 4E	None found
MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	Localised in Lymphoid tissues, Kidney Colon and Wilm's tumor cells [89]
MSRA	methionine sulfoxide reductase A Catalyses two reactions (from KEGG) (1) peptide-L-methionine + thioredoxin disulfide + H2O = peptide-L-methionine (S)-S-oxide + thioredoxin;	Could have an important function as a repair enzyme for proteins that have been inactivated by oxidation. Catalyzes the reversible oxidation-reduction of methionine sulfoxide in proteins to methionine (From Uniprot).

	(2) L-methionine + thioredoxin disulfide + H2O = L-methionine (S)-S-oxide + thioredoxin	
MTHFD1L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like Catalyses the reaction (KEGG) ATP + formate + tetrahydrofolate = ADP + phosphate + 10-formyltetrahydrofolate	The protein encoded by this gene is involved in the synthesis of tetrahydrofolate (THF) in the mitochondrion. THF is important in the de novo synthesis of purines and thymidylate and in the regeneration of methionine from homocysteine (Refseq)
NDUFAF6	NADH dehydrogenase (ubiquinone) complex I, assembly factor 6	None found
NME8	NME/NM23 family member 8	The NME8 locus has been associated in a genome-wide study with the bacterial disease periodontitis [92] also a known risk factor for Alzheimer's disease [84].
PAX2	paired box 2	PAX2 negatively regulates beta defensin-1, an antimicrobial peptide implicated in the resistance of epithelial surfaces to microbial colonization [93].

PCDH11X	protocadherin 11 X-linked	None found
PCNX1	pecanex homolog (Drosophila)	None found
PICALM	phosphatidylinositol binding clathrin assembly protein	Involved in clathrin-mediated endocytosis, a process used by many viruses to gain entry to the cell [94] (AP2A2 and BIN1 are also involved in this process)see KEGG pathway (red text genes) http://www.genome.jp/kegg-bin/show_pathway?hsa04144+274+161
POLN	polymerase (DNA directed) nu	POLN can perform translesion synthesis past thymine glycol, a common endogenous and radiation-induced product of reactive oxygen species damage to DNA. Thymine glycol blocks DNA synthesis by most DNA polymerases, but POLN was particularly adept at efficient and accurate translesion synthesis past a 5S-thymine glycol [95].
PPP1R37	protein phosphatase 1, regulatory subunit 37	No publications

PPP1R3B	protein phosphatase 1, regulatory subunit 3B	None found
PTK2B	protein tyrosine kinase 2 beta	Involved in Toll-like receptor signalling (pathogen recognition receptors)(TLR2, TLR4) in macrophages [96]. Involved in the natural killer cell cytotoxic pathway [97] and in the microglial production of nitric oxide produced by lipopolysaccharide and interferon gamma [98]
PVR	poliovirus receptor	Mediates entry of the poliovirus and binds to NECTIN1 (a receptor for HSV-1 and 2) [99] and NECTIN3 (a receptor for HSV-1) [100] [101,102]
PVRL2	poliovirus receptor-related 2 (herpesvirus entry mediator B)	Entry receptor for HSV-1 [103].
RELN	reelin	Reelin plays a prominent role in the brain but also in the intestine where the reeler mutation down-regulates genes related to the immune response, inflammation, and tumor development [104] . Reelin deposits in the

		hippocampus are a conserved neuropathological feature of aging, and such deposits are accelerated in adult wild-type mice prenatally exposed to a viral-like infection [105].
RFC3	replication factor C (activator 1) 3, 38kDa	The elongation of primed DNA templates by DNA polymerase delta and DNA polymerase epsilon requires the accessory proteins proliferating cell nuclear antigen (PCNA) and replication factor C (RFC).RFC3 is one of 5 subunits of this complex (Refseq). Host nuclear DNA processing factors are also recruited to viral genomes, RFC3 is one of many recruited to the HSV-1 viral genome [106]
RIN3	Ras and Rab interactor 3	RIN 3 inhibits mast cell migration toward stem cell factor, which recruits mast cells to sites of infection or injury, where they release pro-inflammatory substances [107].
SASH1	SAM and SH3 domain containing 1	Scaffold molecule involved in Toll receptor (TLR4) signalling, a receptor involved in the recognition of bacterial

		lipopolysaccharides[108].
SCIMP	SLP adaptor and CSK interacting membrane protein	SCIMP is expressed in B cells and other antigen-presenting cells and is involved in major histocompatibility complex class II signalling [109].
SLC24A4	solute carrier family 24 (sodium/potassium/calcium exchanger), member 4	None found
SLC4A1AP	solute carrier family 4 (anion exchanger), member 1, adaptor protein	None found
SORL1	sortilin-related receptor, L(DLR class) A repeats containing	None found
SPPL2A	signal peptide peptidase like 2A	SPPL2A is a protease that cleaves CD74, the invariant chain of the MHCII complex, and an important chaperone regulating antigen presentation for the immune response. [110].
SQSTM1	sequestosome 1	Autophagy can either promote or restrict viral replication. SQSTM1is an autophagy receptor involved in the life

		cycles of the Chikungunya virus[111], Coxsackievirus[112], Dengue virus [113], the encephalomyocarditis virus [114], enterovirus 71[115], hepatitis B [116] , HIV-1[117], Herpes simplex (HSV-1) [118], Kaposi's sarcoma virus [119], measles [120], Varicella zoster [121] and the West Nile virus [122]
STK24	serine/threonine kinase 24	Important regulator of neutrophil degranulation which results in the releases of proteases and other cytotoxic agents, including matrix metalloproteinases and myeloperoxidase These granule contents are antimicrobial, but can also cause tissue damage [123]
TOMM40	translocase of outer mitochondrial membrane 40 homolog (yeast)	The influenza viral protein PB1-F2 translocates into mitochondria via TOMM40 channels and impairs innate immunity [124]. TOMM40 is required for replication of the African swine fever virus [125]
TREM2	triggering receptor expressed on	A receptor for bacterial lipopolysaccharide that acts as a

	myeloid cells 2	phagocytic receptor for bacteria. It also inhibits the production of inflammatory cytokines induced by Toll like receptors [126-128].
TREML2	triggering receptor expressed on myeloid cells-like 2	TREML2 (Triggering receptor expressed on myeloid cells (TREM)-like transcript 2) is expressed on T cells and regulates interleukin-2 and interferon-gamma production [129].
TRIP4	thyroid hormone receptor interactor 4:	None found: This protein is localized in the nucleus and contains an E1A-type zinc finger domain, which mediates interaction with transcriptional coactivators and ligand-bound nuclear receptors, such as thyroid hormone receptor and retinoid X receptor alpha, but not glucocorticoid receptor (Refseq).
TTLL7	tubulin tyrosine ligase-like family, member 7	None found
ZCWPW1	zinc finger, CW type with PWWP domain 1	None found

ZNF224	zinc finger protein 224	Wilms tumor 1 (WT1) recruits ZNF224 to the interferon regulatory factor 8 (IRF8) promoter [130] The IRF family proteins bind to the IFN-stimulated response element (ISRE) and regulate expression of genes stimulated by type I IFNs, namely IFN-alpha and IFN-beta. IRF family proteins also control expression of IFN-alpha and IFN-beta-regulated genes that are induced by viral infection. [provided by RefSeq, Jul 2008]

Reference List

[1] Sato N , Morishita R (2015) The roles of lipid and glucose metabolism in modulation of beta-amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. *Front Aging Neurosci* **7**, 199-

[2] Karch CM , Goate AM (2015) Alzheimer's disease risk genes and mechanisms of disease pathogenesis. *Biol Psychiatry* **77**, 43-51.

[3] Hao K, Di Narzo AF, Ho L, Luo W, Li S, Chen R, Li T, Dubner L, Pasinetti GM (2015) Shared genetic etiology underlying Alzheimer's disease and type 2 diabetes. *Mol Aspects Med* **43-44**, 66-76.

[4] Guerreiro R , Hardy J (2014) Genetics of Alzheimer's disease. *Neurotherapeutics* **11**, 732-737.

[5] Zhang ZG, Li Y, Ng CT, Song YQ (2015) Inflammation in Alzheimer's Disease and Molecular Genetics: Recent Update. *Arch Immunol Ther Exp (Warsz)* **63**, 333-344.

[6] Yokoyama JS, Wang Y, Schork AJ, Thompson WK, Karch CM, Cruchaga C, McEvoy LK, Witoelar A, Chen CH, Holland D, Brewer JB, Franke A, Dillon WP, Wilson DM, Mukherjee P, Hess CP, Miller Z, Bonham LW, Shen J, Rabinovici GD, Rosen HJ, Miller BL, Hyman BT, Schellenberg GD, Karlsen TH, Andreassen OA, Dale AM, Desikan RS (2016) Association Between Genetic Traits for Immune-Mediated Diseases and Alzheimer Disease. *JAMA Neurol*

[7] Tanaka N, Abe-Dohmae S, Iwamoto N, Fitzgerald ML, Yokoyama S (2010) Helical apolipoproteins of high-density lipoprotein enhance phagocytosis by stabilizing ATP-binding cassette transporter A7. *J Lipid Res* **51**, 2591-2599.

[8] Kielar D, Kaminski WE, Liebisch G, Piehler A, Wenzel JJ, Mohle C, Heimerl S, Langmann T, Friedrich SO, Bottcher A, Barlage S, Drobnik W, Schmitz G (2003) Adenosine triphosphate binding cassette (ABC) transporters are expressed and regulated during terminal keratinocyte differentiation: a

potential role for ABCA7 in epidermal lipid reorganization. *J Invest Dermatol* **121**, 465-474.

[9] Hunsperger EA , Wilcox CL (2003) Caspase-3-dependent reactivation of latent herpes simplex virus type 1 in sensory neuronal cultures. *J Neurovirol* **9**, 390-398.

[10] Marino J, Stoeckli I, Walch M, Latinovic-Golic S, Sundstroem H, Groscurth P, Ziegler U, Dumrese C (2008) Chlamydophila pneumoniae derived from inclusions late in the infectious cycle induce aponecrosis in human aortic endothelial cells. *BMC Microbiol* **8**, 32-

[11] Wang N, Lan D, Gerbod-Giannone M, Linsel-Nitschke P, Jehle AW, Chen W, Martinez LO, Tall AR (2003) ATP-binding cassette transporter A7 (ABCA7) binds apolipoprotein A-I and mediates cellular phospholipid but not cholesterol efflux. *J Biol Chem* **278**, 42906-42912.

[12] van Genderen IL, Brandimarti R, Torrisi MR, Campadelli G, van Meer G (1994) The phospholipid composition of extracellular herpes simplex virions differs from that of host cell nuclei. *Virology* **200**, 831-836.

[13] Gupta VR, Wilson BA, Blanke SR (2010) Sphingomyelin is important for the cellular entry and intracellular localization of Helicobacter pylori VacA. *Cell Microbiol* **12**, 1517-1533.

[14] Wolf K , Hackstadt T (2001) Sphingomyelin trafficking in Chlamydia pneumoniae-infected cells. *Cell Microbiol* **3**, 145-152.

[15] Galdiero S, Falanga A, Vitiello G, Vitiello M, Pedone C, D'Errico G, Galdiero M (2010) Role of membranotropic sequences from herpes simplex virus type I

glycoproteins B and H in the fusion process. *Biochim Biophys Acta* **1798**, 579-591.

[16] Chrisman CJ, Albuquerque P, Guimaraes AJ, Nieves E, Casadevall A (2011) Phospholipids Trigger Cryptococcus neoformans Capsular Enlargement during Interactions with Amoebae and Macrophages. *PLoS Pathog* **7**, e1002047-

[17] Chan SL, Kim WS, Kwok JB, Hill AF, Cappai R, Rye KA, Garner B (2008) ATP-binding cassette transporter A7 regulates processing of amyloid precursor protein in vitro. *J Neurochem* **106**, 793-804.

[18] Shen XZ, Lukacher AE, Billet S, Williams IR, Bernstein KE (2008) Expression of angiotensin-converting enzyme changes major histocompatibility complex class I peptide presentation by modifying C termini of peptide precursors. *J Biol Chem* **283**, 9957-9965.

[19] Silver DL, Hou L, Somerville R, Young ME, Apte SS, Pavan WJ (2008) The secreted metalloprotease ADAMTS20 is required for melanoblast survival. *Plos Genet* **4**, e1000003-

[20] Wight TN, Kang I, Merrilees MJ (2014) Versican and the control of inflammation. *Matrix Biol* **35**, 152-161.

[21] Ting SB, Deneault E, Hope K, Cellot S, Chagraoui J, Mayotte N, Dorn JF, Laverdure JP, Harvey M, Hawkins ED, Russell SM, Maddox PS, Iscove NN, Sauvageau G (2012) Asymmetric segregation and self-renewal of hematopoietic stem and progenitor cells with endocytic Ap2a2. *Blood* **119**, 2510-2522.

[22] Chaudhuri R, Mattera R, Lindwasser OW, Robinson MS, Bonifacino JS (2009) A basic patch on alpha-adaptin is required for binding of human immunodeficiency virus type 1 Nef and cooperative assembly of a CD4-Nef-AP-2 complex. *J Virol* **83**, 2518-2530.

[23] Berbee JF, van der Hoogt CC, Kleemann R, Schippers EF, Kitchens RL, van Dissel JT, Bakker-Woudenberg IA, Havekes LM, Rensen PC (2006) Apolipoprotein CI stimulates the response to lipopolysaccharide and reduces mortality in gram-negative sepsis. *FASEB J* **20**, 2162-2164.

[24] Huemer HP, Menzel HJ, Potratz D, Brake B, Falke D, Utermann G, Dierich MP (1988) Herpes simplex virus binds to human serum lipoprotein. *Intervirology* **29**, 68-76.

[25] Burgos JS, Ramirez C, Sastre I, Bullido MJ, Valdivieso F (2003) ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. *Neuroreport* **14** , 1825-1827.

[26] Gerard HC, Fomicheva E, Whittum-Hudson JA, Hudson AP (2008) Apolipoprotein E4 enhances attachment of Chlamydophila (Chlamydia) pneumoniae elementary bodies to host cells. *Microb Pathog* **44**, 279-285.

[27] Burt TD, Agan BK, Marconi VC, He W, Kulkarni H, Mold JE, Cavrois M, Huang Y, Mahley RW, Dolan MJ, McCune JM, Ahuja SK (2008) Apolipoprotein (apo) E4 enhances HIV-1 cell entry in vitro, and the APOE epsilon4/epsilon4 genotype accelerates HIV disease progression. *Proc Natl Acad Sci U S A* **105**, 8718-8723.

[28] Kuhlmann I, Minihane AM, Huebbe P, Nebel A, Rimbach G (2010) Apolipoprotein E genotype and hepatitis C, HIV and herpes simplex disease risk: a literature review. *Lipids Health Dis* **9**, 8-

[29] Huang C, Yan B, Lei D, Si Y, Li H, Chen MW, Li L, Chen F, Zhou Q, Zhou D, Li JM (2015) Apolipoprotein 4 may increase viral load and seizure frequency in mesial temporal lobe epilepsy patients with positive human herpes virus 6B. *Neurosci Lett* **593**, 29-34.

[30] Toniutto P, Fattovich G, Fabris C, Minisini R, Burlone M, Pravadelli C, Peraro L, Falleti E, Caldera F, Bitetto D, Pirisi M (2010) Genetic polymorphism at the apolipoprotein E locus affects the outcome of chronic hepatitis B. *J Med Virol* **82**, 224-331.

[31] Wautier JL , Wautier MP (2011) Molecular basis of red blood cell adhesion to endothelium. *Ann Pharm Fr* **69**, 3-6.

[32] El Nemer W, Colin Y, Le Van KC (2010) Role of Lu/BCAM glycoproteins in red cell diseases. *Transfus Clin Biol* **17**, 143-147.

[33] Piteau M, Papatheodorou P, Schwan C, Schlosser A, Aktories K, Schmidt G (2014) Lu/BCAM adhesion glycoprotein is a receptor for Escherichia coli Cytotoxic Necrotizing Factor 1 (CNF1). *PLoS Pathog* **10**, e1003884-

[34] Herrington FD , Nibbs RJ (2016) Regulation of the Adaptive Immune Response by the IkappaB Family Protein Bcl-3. *Cells* **5**

[35] Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC (2005) Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the

cancer suppression gene Bin1, potentiates cancer chemotherapy. *Nat Med* **11**, 312-319.

[36] Gold ES, Morrissette NS, Underhill DM, Guo J, Bassetti M, Aderem A (2000) Amphiphysin IIm, a novel amphiphysin II isoform, is required for macrophage phagocytosis. *Immunity* **12**, 285-292.

[37] Nikonova AS, Gaponova AV, Kudinov AE, Golemis EA (2014) CAS proteins in health and disease: an update. *IUBMB Life* **66**, 387-395.

[38] Guttman JA, Lin AE, Veiga E, Cossart P, Finlay BB (2010) Role for CD2AP and other endocytosis-associated proteins in enteropathogenic Escherichia coli pedestal formation. *Infect Immun* **78**, 3316-3322.

[39] Gauthier NC, Monzo P, Gonzalez T, Doye A, Oldani A, Gounon P, Ricci V, Cormont M, Boquet P (2007) Early endosomes associated with dynamic F-actin structures are required for late trafficking of H. pylori VacA toxin. *J Cell Biol* **177**, 343-354.

[40] Calabia-Linares C, Robles-Valero J, de la FH, Perez-Martinez M, Martin-Cofreces N, Alfonso-Perez M, Gutierrez-Vazquez C, Mittelbrunn M, Ibiza S, Urbano-Olmos FR, Aguado-Ballano C, Sanchez-Sorzano CO, Sanchez-Madrid F, Veiga E (2011) Endosomal clathrin drives actin accumulation at the immunological synapse. *J Cell Sci* **124**, 820-830.

[41] Srivatsan S, Swiecki M, Otero K, Cella M, Shaw AS (2013) CD2-associated protein regulates plasmacytoid dendritic cell migration, but is dispensable for their development and cytokine production. *J Immunol* **191**, 5933-5940.

[42] Crocker PR , Redelinghuys P (2008) Siglecs as positive and negative regulators of the immune system. *Biochem Soc Trans* **36**, 1467-1471.

[43] Brinkman-Van der Linden EC , Varki A (2000) New aspects of siglec binding specificities, including the significance of fucosylation and of the sialyl-Tn epitope. Sialic acid-binding immunoglobulin superfamily lectins. *J Biol Chem* **275**, 8625-8632.

[44] Stencel-Baerenwald JE, Reiss K, Reiter DM, Stehle T, Dermody TS (2014) The sweet spot: defining virus-sialic acid interactions. *Nat Rev Microbiol* **12**, 739-749.

[45] Teuton JR , Brandt CR (2007) Sialic acid on herpes simplex virus type 1 envelope glycoproteins is required for efficient infection of cells. *J Virol* **81**, 3731-3739.

[46] Rodrigues ML, Rozental S, Couceiro JN, Angluster J, Alviano CS, Travassos LR (1997) Identification of N-acetylneuraminic acid and its 9-O-acetylated derivative on the cell surface of Cryptococcus neoformans: influence on fungal phagocytosis. *Infect Immun* **65**, 4937-4942.

[47] Hulinska D, Volf P, Grubhoffer L (1992) Characterization of Borrelia burgdorferi glycoconjugates and surface carbohydrates. *Zentralbl Bakteriol* **276**, 473-480.

[48] Aspholm M, Olfat FO, Norden J, Sonden B, Lundberg C, Sjostrom R, Altraja S, Odenbreit S, Haas R, Wadstrom T, Engstrand L, Semino-Mora C, Liu H, Dubois A, Teneberg S, Arnqvist A, Boren T (2006) SabA is the H. pylori hemagglutinin and is polymorphic in binding to sialylated glycans. *PLoS Pathog* **2**, e110-

[49] Bennett HJ , Roberts IS (2005) Identification of a new sialic acid-binding protein in Helicobacter pylori. *FEMS Immunol Med Microbiol* **44**, 163-169.

[50] Hallen U, Bjorkner AE, Hallberg EC (2008) Binding of the periodontitis associated bacterium Porphyromonas gingivalis to glycoproteins from human epithelial cells. *Oral Microbiol Immunol* **23**, 367-371.

[51] Chang YC , Nizet V (2014) The interplay between Siglecs and sialylated pathogens. *Glycobiology* **24**, 818-825.

[52] Nelson CL, Pelak K, Podgoreanu MV, Ahn SH, Scott WK, Allen AS, Cowell LG, Rude TH, Zhang Y, Tong A, Ruffin F, Sharma-Kuinkel BK, Fowler VG, Jr. (2014) A genome-wide association study of variants associated with acquisition of Staphylococcus aureus bacteremia in a healthcare setting. *BMC Infect Dis* **14**, 83-

[53] Tchoupa AK, Schuhmacher T, Hauck CR (2014) Signaling by epithelial members of the CEACAM family - mucosal docking sites for pathogenic bacteria. *Cell Commun Signal* **12**, 27-

[54] Dudaronek JM, Barber SA, Clements JE (2007) CUGBP1 is required for IFNbeta-mediated induction of dominant-negative CEBPbeta and suppression of SIV replication in macrophages. *J Immunol* **179**, 7262-7269.

[55] Yorulmaz S, Jackman JA, Hunziker W, Cho NJ (2015) Supported Lipid Bilayer Platform To Test Inhibitors of the Membrane Attack Complex: Insights into Biomacromolecular Assembly and Regulation. *Biomacromolecules* **16**, 3594-3602.

[56] Peitsch MC , Tschopp J (1991) Assembly of macromolecular pores by immune defense systems. *Curr Opin Cell Biol* **3**, 710-716.

[57] Gasque P (2004) Complement: a unique innate immune sensor for danger signals. *Mol Immunol* **41**, 1089-1098.

[58] Lim NT, Harder MJ, Kennedy AT, Lin CS, Weir C, Cowman AF, Call MJ, Schmidt CQ, Tham WH (2015) Characterization of Inhibitors and Monoclonal Antibodies That Modulate the Interaction between Plasmodium falciparum Adhesin PfRh4 with Its Erythrocyte Receptor Complement Receptor 1. *J Biol Chem* **290**, 25307-25321.

[59] Venkataraman C, Haack BJ, Bondada S, Abu KY (1997) Identification of a Gal/GalNAc lectin in the protozoan Hartmannella vermiformis as a potential receptor for attachment and invasion by the Legionnaires' disease bacterium. *J Exp Med* **186**, 537-547.

[60] Schlesinger LS (1993) Macrophage phagocytosis of virulent but not attenuated strains of Mycobacterium tuberculosis is mediated by mannose receptors in addition to complement receptors. *J Immunol* **150**, 2920-2930.

[61] Mukhopadhyay D, Houchen CW, Kennedy S, Dieckgraefe BK, Anant S (2003) Coupled mRNA stabilization and translational silencing of cyclooxygenase-2 by a novel RNA binding protein, CUGBP2. *Mol Cell* **11**, 113-126.

[62] Mallory MJ, Allon SJ, Qiu J, Gazzara MR, Tapescu I, Martinez NM, Fu XD, Lynch KW (2015) Induced transcription and stability of CELF2 mRNA drives widespread alternative splicing during T-cell signaling. *Proc Natl Acad Sci U S A* **112**, E2139-E2148.

[63] Ogawa F, Malavasi EL, Crummie DK, Eykelenboom JE, Soares DC, Mackie S, Porteous DJ, Millar JK (2014) DISC1 complexes with TRAK1 and Miro1 to modulate anterograde axonal mitochondrial trafficking. *Hum Mol Genet* **23**, 906-919.

[64] Devine MJ, Norkett R, Kittler JT (2016) DISC1 is a coordinator of intracellular trafficking to shape neuronal development and connectivity. *J Physiol*

[65] Carter CJ (2009) Schizophrenia susceptibility genes directly implicated in the life cycles of pathogens: cytomegalovirus, influenza, herpes simplex, rubella, and Toxoplasma gondii. *Schizophr Bull* **35**, 1163-1182.

[66] Afonso PV, Zamborlini A, Saib A, Mahieux R (2007) Centrosome and retroviruses: the dangerous liaisons. *Retrovirology* **4**, 27-

[67] Leopold PL , Pfister KK (2006) Viral strategies for intracellular trafficking: motors and microtubules. *Traffic* **7**, 516-523.

[68] Niedergang F, Di B, V, Alcover A (2016) Comparative Anatomy of Phagocytic and Immunological Synapses. *Front Immunol* **7**, 18-

[69] Eicher JD, Wakabayashi Y, Vitseva O, Esa N, Yang Y, Zhu J, Freedman JE, McManus DD, Johnson AD (2016) Characterization of the platelet transcriptome by RNA sequencing in patients with acute myocardial infarction. *Platelets* **27**, 230-239.

[70] Silbiger VN, Luchessi AD, Hirata RD, Lima-Neto LG, Cavichioli D, Carracedo A, Brion M, Dopazo J, Garcia-Garcia F, dos Santos ES, Ramos RF, Sampaio MF, Armaganijan D, Sousa AG, Hirata MH (2013) Novel genes detected by

transcriptional profiling from whole-blood cells in patients with early onset of acute coronary syndrome. *Clin Chim Acta* **421**, 184-190.

[71] Zhang S, Kim CC, Batra S, McKerrow JH, Loke P (2010) Delineation of diverse macrophage activation programs in response to intracellular parasites and cytokines. *PLoS Negl Trop Dis* **4**, e648-

[72] Wohlfahrt JG, Karagiannidis C, Kunzmann S, Epstein MM, Kempf W, Blaser K, Schmidt-Weber CB (2004) Ephrin-A1 suppresses Th2 cell activation and provides a regulatory link to lung epithelial cells. *J Immunol* **172**, 843-850.

[73] Yang AX, Chong N, Jiang Y, Catalano J, Puri RK, Khleif SN (2014) Molecular characterization of antigen-peptide pulsed dendritic cells: immature dendritic cells develop a distinct molecular profile when pulsed with antigen peptide. *PLoS One* **9**, e86306-

[74] Khounlotham M, Subbian S, Smith R, III, Cirillo SL, Cirillo JD (2009) Mycobacterium tuberculosis interferes with the response to infection by inducing the host EphA2 receptor. *J Infect Dis* **199**, 1797-1806.

[75] Sarmay G, Angyal A, Kertesz A, Maus M, Medgyesi D (2006) The multiple function of Grb2 associated binder (Gab) adaptor/scaffolding protein in immune cell signaling. *Immunol Lett* **104**, 76-82.

[76] Hu S, Zhang Y, Yu Y, Jin D, Zhang X, Gu S, Jia H, Chen X, Zhang Z, Jin Q, Ke Y, Liu H (2014) Growth factor receptor bound protein 2-associated binder 2, a scaffolding adaptor protein, negatively regulates host immunity against tuberculosis. *Am J Respir Cell Mol Biol* **51**, 575-585.

[77] Janeway CA, Travers P, Walport M, Schlonchik MJ (2011) *The Immune System in Health and Disease*, Garland Science, New York.

[78] Derks RA, Jankowska-Gan E, Xu Q, Burlingham WJ (2007) Dendritic cell type determines the mechanism of bystander suppression by adaptive T regulatory cells specific for the minor antigen HA-1. *J Immunol* **179**, 3443-3451.

[79] Vives RR, Lortat-Jacob H, Fender P (2006) Heparan sulphate proteoglycans and viral vectors : ally or foe? *Curr Gene Ther* **6**, 35-44.

[80] Liu J , Thorp SC (2002) Cell surface heparan sulfate and its roles in assisting viral infections. *Med Res Rev* **22**, 1-25.

[81] Herglotz J, Unrau L, Hauschildt F, Fischer M, Kriebitzsch N, Alawi M, Indenbirken D, Spohn M, Muller U, Ziegler M, Schuh W, Jack HM, Stocking C (2016) Essential control of early B-cell development by Mef2 transcription factors. *Blood* **127**, 572-581.

[82] Fu W, Wei J, Gu J (2006) MEF2C mediates the activation induced cell death (AICD) of macrophages. *Cell Res* **16**, 559-565.

[83] Zhan Y, Zhang R, Lv H, Song X, Xu X, Chai L, Lv W, Shang Z, Jiang Y, Zhang R (2014) Prioritization of candidate genes for periodontitis using multiple computational tools. *J Periodontol* **85**, 1059-1069.

[84] Abbayya K, Puthanakar NY, Naduwinmani S, Chidambar YS (2015) Association between Periodontitis and Alzheimer's Disease. *N Am J Med Sci* **7**, 241-246.

[85] Wells JM, Gaggar A, Blalock JE (2015) MMP generated matrikines. *Matrix Biol* **44-46**, 122-129.

[86] Fulop T, Khalil A, Larbi A (2012) The role of elastin peptides in modulating the immune response in aging and age-related diseases. *Pathol Biol (Paris)* **60**, 28-33.

[87] Yamada S, Nagai T, Nakai T, Ibi D, Nakajima A, Yamada K (2014) Matrix metalloproteinase-3 is a possible mediator of neurodevelopmental impairment due to polyI:C-induced innate immune activation of astrocytes. *Brain Behav Immun* **38**, 272-282.

[88] Zannettino AC, Roubelakis M, Welldon KJ, Jackson DE, Simmons PJ, Bendall LJ, Henniker A, Harrison KL, Niutta S, Bradstock KF, Watt SM (2003) Novel mesenchymal and haematopoietic cell isoforms of the SHP-2 docking receptor, PZR: identification, molecular cloning and effects on cell migration. *Biochem J* **370**, 537-549.

[89] Eon KL, Leffler M, Mackay GA, Hulett MD (2016) The MS4A family: counting past 1, 2 and 3. *Immunol Cell Biol* **94**, 11-23.

[90] da Silva EZ, Jamur MC, Oliver C (2014) Mast cell function: a new vision of an old cell. *J Histochem Cytochem* **62**, 698-738.

[91] Taylor ML , Metcalfe DD (2001) Mast cells in allergy and host defense. *Allergy Asthma Proc* **22**, 115-119.

[92] Shimizu S, Momozawa Y, Takahashi A, Nagasawa T, Ashikawa K, Terada Y, Izumi Y, Kobayashi H, Tsuji M, Kubo M, Furuichi Y (2015) A genome-wide association study of periodontitis in a Japanese population. *J Dent Res* **94**, 555-561.

[93] Bose SK, Gibson W, Bullard RS, Donald CD (2009) PAX2 oncogene negatively regulates the expression of the host defense peptide human beta defensin-1 in prostate cancer. *Mol Immunol* **46**, 1140-1148.

[94] Banerjee A, Berezhkovskii A, Nossal R (2016) Kinetics of cellular uptake of viruses and nanoparticles via clathrin-mediated endocytosis. *Phys Biol* **13**, 016005-

[95] Takata K, Shimizu T, Iwai S, Wood RD (2006) Human DNA polymerase N (POLN) is a low fidelity enzyme capable of error-free bypass of 5S-thymine glycol. *J Biol Chem* **281**, 23445-23455.

[96] Hazeki K, Masuda N, Funami K, Sukenobu N, Matsumoto M, Akira S, Takeda K, Seya T, Hazeki O (2003) Toll-like receptor-mediated tyrosine phosphorylation of paxillin via MyD88-dependent and -independent pathways. *Eur J Immunol* **33**, 740-747.

[97] Hinterseher I, Schworer CM, Lillvis JH, Stahl E, Erdman R, Gatalica Z, Tromp G, Kuivaniemi H (2015) Immunohistochemical analysis of the natural killer cell cytotoxicity pathway in human abdominal aortic aneurysms. *Int J Mol Sci* **16**, 11196-11212.

[98] Miyake T, Shirakawa H, Kusano A, Sakimoto S, Konno M, Nakagawa T, Mori Y, Kaneko S (2014) TRPM2 contributes to LPS/IFNgamma-induced production of nitric oxide via the p38/JNK pathway in microglia. *Biochem Biophys Res Commun* **444**, 212-217.

[99] Lu G, Zhang N, Qi J, Li Y, Chen Z, Zheng C, Gao GF, Yan J (2014) Crystal structure of herpes simplex virus 2 gD bound to nectin-1 reveals a conserved mode of receptor recognition. *J Virol* **88**, 13678-13688.

[100] Cocchi F, Menotti L, Di N, V, Lopez M, Campadelli-Fiume G (2004) The herpes simplex virus JMP mutant enters receptor-negative J cells through a novel pathway independent of the known receptors nectin1, HveA, and nectin2. *J Virol* **78**, 4720-4729.

[101] Fabre S, Reymond N, Cocchi F, Menotti L, Dubreuil P, Campadelli-Fiume G, Lopez M (2002) Prominent role of the Ig-like V domain in trans-interactions of nectins. Nectin3 and nectin 4 bind to the predicted C-C'-C''-D beta-strands of the nectin1 V domain. *J Biol Chem* **277**, 27006-27013.

[102] Mueller S , Wimmer E (2003) Recruitment of nectin-3 to cell-cell junctions through trans-heterophilic interaction with CD155, a vitronectin and poliovirus receptor that localizes to alpha(v)beta3 integrin-containing membrane microdomains. *J Biol Chem* **278**, 31251-31260.

[103] Martinez WM , Spear PG (2001) Structural features of nectin-2 (HveB) required for herpes simplex virus entry. *J Virol* **75**, 11185-11195.

[104] Garcia-Miranda P, Vazquez-Carretero MD, Gutierrez G, Peral MJ, Ilundain AA (2012) Lack of reelin modifies the gene expression in the small intestine of mice. *J Physiol Biochem* **68**, 205-218.

[105] Doehner J, Genoud C, Imhof C, Krstic D, Knuesel I (2012) Extrusion of misfolded and aggregated proteins--a protective strategy of aging neurons? *Eur J Neurosci* **35**, 1938-1950.

[106] Dembowski JA , DeLuca NA (2015) Selective recruitment of nuclear factors to productively replicating herpes simplex virus genomes. *PLoS Pathog* **11**, e1004939-

[107] Janson C, Kasahara N, Prendergast GC, Colicelli J (2012) RIN3 is a negative regulator of mast cell responses to SCF. *PLoS One* **7**, e49615-

[108] Dauphinee SM, Clayton A, Hussainkhel A, Yang C, Park YJ, Fuller ME, Blonder J, Veenstra TD, Karsan A (2013) SASH1 is a scaffold molecule in endothelial TLR4 signaling. *J Immunol* **191**, 892-901.

[109] Draber P, Vonkova I, Stepanek O, Hrdinka M, Kucova M, Skopcova T, Otahal P, Angelisova P, Horejsi V, Yeung M, Weiss A, Brdicka T (2011) SCIMP, a transmembrane adaptor protein involved in major histocompatibility complex class II signaling. *Mol Cell Biol* **31**, 4550-4562.

[110] Huttl S, Helfrich F, Mentrup T, Held S, Fukumori A, Steiner H, Saftig P, Fluhrer R, Schroder B (2016) Substrate determinants of Signal peptide peptidase-like 2a (SPPL2a)-mediated Intramembrane Proteolysis of the Invariant chain CD74. *Biochem J*

[111] Judith D, Mostowy S, Bourai M, Gangneux N, Lelek M, Lucas-Hourani M, Cayet N, Jacob Y, Prevost MC, Pierre P, Tangy F, Zimmer C, Vidalain PO, Couderc T, Lecuit M (2013) Species-specific impact of the autophagy machinery on Chikungunya virus infection. *EMBO Rep* **14**, 534-544.

[112] Shi J, Fung G, Piesik P, Zhang J, Luo H (2014) Dominant-negative function of the C-terminal fragments of NBR1 and SQSTM1 generated during enteroviral infection. *Cell Death Differ* **21**, 1432-1441.

[113] Metz P, Chiramel A, Chatel-Chaix L, Alvisi G, Bankhead P, Mora-Rodriguez R, Long G, Hamacher-Brady A, Brady NR, Bartenschlager R (2015) Dengue Virus Inhibition of Autophagic Flux and Dependency of Viral Replication on

Proteasomal Degradation of the Autophagy Receptor p62. *J Virol* **89**, 8026-8041.

[114] Zhang Y, Li Z, Ge X, Guo X, Yang H (2011) Autophagy promotes the replication of encephalomyocarditis virus in host cells. *Autophagy* **7**, 613-628.

[115] Xi X, Zhang X, Wang B, Wang T, Wang J, Huang H, Wang J, Jin Q, Zhao Z (2013) The interplays between autophagy and apoptosis induced by enterovirus 71. *PLoS One* **8**, e56966-

[116] Yang H, Fu Q, Liu C, Li T, Wang Y, Zhang H, Lu X, Sang X, Zhong S, Huang J, Mao Y (2015) Hepatitis B virus promotes autophagic degradation but not replication in autophagosome. *Biosci Trends* **9**, 111-116.

[117] Sagnier S, Daussy CF, Borel S, Robert-Hebmann V, Faure M, Blanchet FP, Beaumelle B, Biard-Piechaczyk M, Espert L (2015) Autophagy restricts HIV-1 infection by selectively degrading Tat in CD4+ T lymphocytes. *J Virol* **89**, 615-625.

[118] Gobeil PA , Leib DA (2012) Herpes simplex virus gamma34.5 interferes with autophagosome maturation and antigen presentation in dendritic cells. *MBio* **3**, e00267-12.

[119] Gjyshi O, Flaherty S, Veettil MV, Johnson KE, Chandran B, Bottero V (2015) Kaposi's sarcoma-associated herpesvirus induces Nrf2 activation in latently infected endothelial cells through SQSTM1 phosphorylation and interaction with polyubiquitinated Keap1. *J Virol* **89**, 2268-2286.

[120] Xia M, Gonzalez P, Li C, Meng G, Jiang A, Wang H, Gao Q, Debatin KM, Beltinger C, Wei J (2014) Mitophagy enhances oncolytic measles virus replication by mitigating DDX58/RIG-I-like receptor signaling. *J Virol* **88**, 5152-5164.

[121] Takahashi MN, Jackson W, Laird DT, Culp TD, Grose C, Haynes JI, Benetti L (2009) Varicella-zoster virus infection induces autophagy in both cultured cells and human skin vesicles. *J Virol* **83**, 5466-5476.

[122] Beatman E, Oyer R, Shives KD, Hedman K, Brault AC, Tyler KL, Beckham JD (2012) West Nile virus growth is independent of autophagy activation. *Virology* **433**, 262-272.

[123] Zhang Y, Tang W, Zhang H, Niu X, Xu Y, Zhang J, Gao K, Pan W, Boggon TJ, Toomre D, Min W, Wu D (2013) A network of interactions enables CCM3 and STK24 to coordinate UNC13D-driven vesicle exocytosis in neutrophils. *Dev Cell* **27**, 215-226.

[124] Yoshizumi T, Ichinohe T, Sasaki O, Otera H, Kawabata S, Mihara K, Koshiba T (2014) Influenza A virus protein PB1-F2 translocates into mitochondria via Tom40 channels and impairs innate immunity. *Nat Commun* **5**, 4713-

[125] Chang AC, Zsak L, Feng Y, Mosseri R, Lu Q, Kowalski P, Zsak A, Burrage TG, Neilan JG, Kutish GF, Lu Z, Laegreid W, Rock DL, Cohen SN (2006) Phenotype-based identification of host genes required for replication of African swine fever virus. *J Virol* **80**, 8705-8717.

[126] Wei P, Lu Q, Cui G, Guan Z, Yang L, Sun C, Sun W, Peng Q (2015) The role of TREM-2 in internalization and intracellular survival of Brucella abortus in murine macrophages. *Vet Immunol Immunopathol* **163**, 194-201.

[127] Gawish R, Martins R, Bohm B, Wimberger T, Sharif O, Lakovits K, Schmidt M, Knapp S (2015) Triggering receptor expressed on myeloid cells-2 fine-tunes inflammatory responses in murine Gram-negative sepsis. *FASEB J* **29**, 1247-1257.

[128] Gao X, Dong Y, Liu Z, Niu B (2013) Silencing of triggering receptor expressed on myeloid cells-2 enhances the inflammatory responses of alveolar macrophages to lipopolysaccharide. *Mol Med Rep* **7**, 921-926.

[129] Hashiguchi M, Kobori H, Ritprajak P, Kamimura Y, Kozono H, Azuma M (2008) Triggering receptor expressed on myeloid cell-like transcript 2 (TLT-2) is a counter-receptor for B7-H3 and enhances T cell responses. *Proc Natl Acad Sci U S A* **105**, 10495-10500.

[130] Montano G, Ullmark T, Jernmark-Nilsson H, Sodaro G, Drott K, Costanzo P, Vidovic K, Gullberg U (2016) The hematopoietic tumor suppressor interferon regulatory factor 8 (IRF8) is upregulated by the antimetabolite cytarabine in leukemic cells involving the zinc finger protein ZNF224, acting as a cofactor of the Wilms' tumor gene 1 (WT1) protein. *Leuk Res* **40**, 60-67.

Supplementary Table 2: A survey of the roles of diverse microbial sensors and defensive proteins. Their expression levels in the Alzheimer's disease brain, blood, cerebrospinal fluid or other defined cells etc. are also reviewed.

Gene	Function	Alzheimer's disease
AGER advanced	Recognizes advanced	Increases in protein levels

glycosylation end product-specific receptor (more commonly known as RAGE)	glycosylation end products, members of the S100 protein family, beta-amyloid and amyloid fibrils, HMGB1, and β-integrin macrophage 1 antigen (Mac-1) [1]. Receptor for S100B , S100A4, 6,11,12,13, S100P [2], Expressed on endothelial cells macrophages, neutrophils, dendritic cells, T cells, B cells, alveolar type II cells and alveolar epithelial cells[3]. AGER(-/-) mice were relatively protected from influenza virus induced mortality showing improved viral clearance , enhanced cellular T cell response and activation of neutrophils [4]. AGER activation enhances the ability of neutrophils to eradicate bacteria (E.Coli) in vitro and in vivo via activation of NADPH	and in the percentage of AGER expressing microglia in the Alzheimer's disease brain linked with disease severity[10].Plasma protein levels increased in Alzheimer's disease [11] but decreased levels of a soluble isoform [12,13]

	oxidase[5]. Involved in the adhesion of Helicobacter pylori to gastric epithelial cells [6]. P. gingivalis infection enhances AGER expression in Murine aortic endothelial cells [7]. Bacteria produce, metabolize and accumulate AGEs .Escherichia coli cells secret AGEs [8]. Influenza A viral pneumonia is associated with enhanced AGER expression on endothelium and de novo expression on bronchial epithelium in mice[4]. The Epstein Barr viral protein LMP1 binds to the AGER promoter [9]	
βAmyloid	Antimicrobial peptide with broad spectrum activity against bacterial (Enterococci, E.Coli, streptococci, staphylococci, pseudomonas, listeria) and	Key component of amyloid plaques

	fungal (Candida albicans) species {Soscia, Kirby, et al. 2010 1912 /id} . It also has antiviral effects against Herpes simplex (HSV-1) {Bourgade, Le Page, et al. 2016 10595 /id}{Bourgade, Garneau, et al. 2015 10596 /id} and the influenza virus {White, Kandel, et al. 2014 8740 /id}. Borna virus infection induced microglial activation can reduce plaque formation in Tg2576 APP mutant transgenic mice [14]	
APCS amyloid P component, serum (commonly known as SAP)	Binds to several bacterial lipopolysaccharides (S. pyrogens and rough strains of E. coli) preventing complement activation[15]. Increased levels of APCS in the atherotic plaques of C.Pneumoniae infected mice fed an atherogenic diet [16] . Binds avidly to C. Albicans	Protein levels elevated in the AD brain and associated with plaques, but low levels in plaques were seen in individuals with AD pathology without dementia [18] .

	when amyloid is formed in fungal cell walls [17]	
CAMP cathelicidin antimicrobial peptide (LL-37)	In addition to its antibacterial, antifungal, and antiviral activities, the encoded protein functions in cell chemotaxis, immune mediator induction, and inflammatory response regulation. [provided by RefSeq, Sep 2014]. [19]Antiviral versus influenza Kills P.Gingivalis [20] but degraded by a P.gingivalis secreted protease (gingipain) [21]. DEFB1 and CAMP (cathelicidin/LL-37) kill H.pylori [22]. Borrelia burgdorferi is killed by human polymorphonuclear leukocyte granule components (elastase ELANE, CAMP, bactericidal/permeability-	None found

	increasing protein (BPI), and human neutrophil peptide-1)[23].	
CD163 CD163 molecule	Functions as an acute phase-regulated receptor involved in the clearance and endocytosis of hemoglobin/haptoglobin complexes by macrophages, and may thereby protect tissues from free hemoglobin-mediated oxidative damage. This protein may also function as an innate immune sensor for bacteria and inducer of local inflammation. [provided by RefSeq, Aug 2011] Upregulated in the gastric mucosa of H. pylori infected children [24]. Upregulated by P.Gingivalis in periodontal ligament cells [25]. Kupffer cell/macrophage activation indicated by increased	Upregulated in the AD hippocampus [29]. Parenchymal microglia were immunoreactive for CD163 in all of 31 AD cases often associated with amyloid plaques [30]

	CD163 is found in the livers of hepatitis C infected patients [26]. The cytomegalovirus encoded IL10 chemokine mimic upregulates CD163 in macrophages [27]. serum levels of soluble CD163 in Epstein-Barr virus positive children positively correlate with EBV-DNA copies [28]	
CHI3L1 chitinase 3 like 1 (aka YKL-40)	Chitinases catalyze the hydrolysis of chitin, which is an abundant glycopolymer found in insect exoskeletons and fungal cell walls. The protein lacks chitinase activity and is secreted by activated macrophages, chondrocytes, neutrophils and synovial cells. The protein is thought to play a role in the process of inflammation and tissue remodeling. [provided by	CSF levels of CHI3L1 are associated with Alzheimer's disease [33-35]. Plasma levels are also increased and the protein is found in astrocytes near a subset of amyloid plaques (immunohistochemistry) [36]

	RefSeq, Sep 2009] CHI3L1 is induced by fungal infection (Candida albicans) and induces the antimicrobial peptides beta-defensin 3 and cathelicidin (CAMP) [31]. In transgenic mice expressing the Epstein-Barr virus LMP1 protein CHI3L1is induced in the epidermis and is secreted and autoantibodies to CHI3L1 are generated [32]	
CLEC2B C-type lectin domain family 2 member B	CLEC-2 is a HIV-1 attachment factor and platelets capture and transfer infectious HIV-1 via DC-SIGN and CLEC-2 [37]. Expression induced by infection of Akata cells [38]	Upregulated in the AD hippocampus [29]
CLEC2D C-type lectin domain family 2 member D	Expression upregulated by respiratory syncytial virus (RSV) infection, in the BEAS-2B respiratory epithelial cell line and	Upregulated in the AD hippocampus [29]

	primary human bronchial epithelial cells [39]. Expression is induced in B cells and inflamed tonsils following viral infection (Epstein-Barr virus or HIV infection) and in inflamed tonsils [40].	
CLEC4M C-type lectin domain family 4 member M (L-SIGN)	……recognizes numerous evolutionarily divergent pathogens ranging from parasites to viruses, with a large impact on public health……..[provided by RefSeq, Feb 2009] CD209 (DC-SIGN) and CLEC4M (L-SIGN) are endocytic receptors for influenza A virus entry and infection, and for the Hepatitis C virus , HIV-1, Sindbis virus, and act as cofactors for cellular entry by Ebola virus. CLEC4M also a receptor for Mycobacterium tuberculosis,	Upregulated in the AD hippocampus [29]

	Schistosomes and Leishmania infant [41-46]	
CLEC7A C-type lectin domain family 7 member A (Dectin 1)	Functions as a pattern-recognition receptor that recognizes a variety of beta-1,3-linked and beta-1,6-linked glucans from fungi and plants, and in this way plays a role in innate immune response……. [provided by RefSeq, Jul 2008].Activated by C.albicans, and Mycobacterium bovis [47]	Upregulated in the AD hippocampus [29]
CRP C-reactive protein, pentraxin-related	Involved in several host defence related functions based on its ability to recognize foreign pathogens and damaged cells of the host and to initiate their elimination by interacting with humoral and cellular effector systems in the blood. Consequently, the level of	High serum levels associated with AD (dependent on methodology) [54], but levels of CRP in a mild and moderate dementia subgroup were significantly lower than that in the control group [55]. A recently developed high-sensitivity (Hs) test reported high serum levels of Hs-CRP

	this protein in plasma increases greatly during acute phase response to tissue injury, infection, or other inflammatory stimuli. [provided by RefSeq, Sep 2009]. Chlamydial lipopolysaccharide serum levels in coronary syndrome correlate with CRP levels [48].High CRP levels observed in H.Pylori and C.Pneumoniae infection [49]. High antibody response to multiple pathogens (cytomegalovirus, herpes simplex virus-1, Hepatitis A virus, Helicobacter pylori and Chlamydia pneumoniae) associated with CRP in atherosclerosis patients [50]. Antibodies to P. gingivalis associate with high levels of SAA and high concentrations of CRP in periodontitis	in AD patients[56]. CRP staining of the hippocampal CA1/2 region correlates with Aβ staining in the AD brain [57].

	patients[51]. Serum CRP elevated in fungal esophagitis or enterocolitis due to C.albicans [52]. High serum levels of CRP found in numerous bacterial or viral infections : (Dengue virus , Cytomegalovirus , Epstein Barr virus, Parvovirus B19 , HSV-1 and -2 and Influenza A and B: [53]	
DDX1 DEAD/H-box helicase 1	DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense double stranded viral RNA, including Influenza and Poly-IC in dendritic cells [58].Binds to hepatitis C biotinylated RNA [59]	Down regulated in the AD hippocampus [29]
DDX18 DEAD-box helicase 18	Few publications	Upregulated in the AD hippocampus [29]
DDX21 DEAD-box helicase 21	DDX1, DDX21, and DHX36 helicases form a complex	Upregulated in the AD hippocampus [29]

	with the adaptor molecule TRIF to sense double stranded viral RNA a in dendritic cells [58]. DDX21 inhibits replication of the influenza virus [60].Interacts with a Borna virus protein [61]	
DDX27 DEAD-box helicase 27	?	Upregulated in the AD hippocampus [29]
DDX39A DEAD-box helicase 39A	Needed for the expression of Kaposi sarcoma-associated herpesvirus ORF57 [62]. The UL69 gene product of the human cytomegalovirus belongs to a family of regulatory proteins conserved among all herpesviruses and binds to DDX39A [63]. Mx proteins exert their antiviral activity against the influenza virus by interfering with the function of the RNA helicases DDX39B and DDX39A [64] .	Upregulated in the AD hippocampus [29]

DDX42 DEAD-box helicase 42	The expression of N-terminal DDX42 binds to the NS4A protein of the Japanese encephalitis virus and DDX42 is able to overcome antagonism of interferon responses by the virus [65]. Also a potential target of an Epstein-Barr viral microRNA [66] . The Japanese encephalitis virus encodes for interferon antagonist proteins, one of which , NS4A, binds to DDX42 [65]	Upregulated in the AD hippocampus [29]
DDX47 DEAD-box helicase 47	Interacts with the E1E4 protein of human papillomavirus type 16 [67]	Down regulated in the AD hippocampus [29]
DDX5 DEAD-box helicase 5	This gene encodes a DEAD box protein, which is a RNA-dependent ATPase, and also a proliferation-associated nuclear antigen, specifically reacting with the simian virus 40 tumor antigen…….	Down regulated in the AD hippocampus [29]

	[provided by RefSeq, Feb 2016] DDX3,5 and 6 play a role in hepatitis C viral replication [68]. DDX5 interacts with the SARS coronavirus [69]	
DDX58 DEXD/H-box helicase 58 ()commonly known as RIG-1)	DEAD box proteins, characterized by the conserved motif Asp-Glu-Ala-Asp (DEAD), are putative RNA helicases which are implicated in a number of cellular processes involving RNA binding and alteration of RNA secondary structure. This gene encodes a protein containing RNA helicase-DEAD box protein motifs and a caspase recruitment domain (CARD). It is involved in viral double-stranded (ds) RNA recognition and the regulation of immune response. [provided by	Expression increased in the temporal cortex and plasma of mild cognitive impairment patients with pathologic evidence of senile plaques and neurofibrillary tangles [71]

	RefSeq, Jul 2008] The DDX58 -activating 5' triphosphate group is removed post-transcriptionally by a viral function and modified DDX58 does not bind the RNAs of Hantaan virus, Crimean-Congo hemorrhagic fever virus or the Borna disease virus [70].	
DDX6 DEAD-box helicase 6	The protein is an RNA helicase found in P-bodies and stress granules, and functions in translation suppression and mRNA degradation. It is required for microRNA-induced gene silencing. Multiple alternatively spliced variants, encoding the same protein, have been identified. [provided by RefSeq, Mar 2012]. It also controls gene expression in RNA viruses	Upregulated in the AD hippocampus [29]

	[72]. DDX3,5 and 6 play a role in hepatitis C viral replication [68]. Binds to a Dengue virus RNA [73]	
DEFA1 defensin alpha 1	Found in the microbicidal granules of neutrophils and likely plays a role in phagocyte-mediated host defence. (from Refseq) Defends against S. aureus , E. coli and E. aerogenes [74] anthrax toxin, C,Difficile toxin B, diphtheria toxin, and Pseudomonas exotoxin A [75-77] and also inhibit the adenovirus, BK polyoma virus and HIV-1 [78-80]. Binds to P.Gingivalis [81].	Defensins alpha1 and 2 (now coded only by DEFA1) are upregulated in Alzheimer's disease blood cells [84]; DEFA1/DEFA1B , DEFA3 and DEFB4A increased in sera and CSF of AD patients [85]

	Antiviral versus Influenza A [82].Alpha-defensin transcription activated by the hepatitis C core protein (specific gene symbol not possible) [83]	
DEFA1B defensin alpha 1B	The protein encoded by this gene, defensin, alpha 1, is found in the microbicidal granules of neutrophils and likely plays a role in phagocyte-mediated host defense. Several alpha defensin genes are clustered on chromosome 8. This gene differs from defensin, alpha 3 by only one amino acid (from Refseq). Binds to P.Gingivalis [81]. Release induced by H.Pylori [86]. Borrelia burgdorferi is killed by human polymorphonuclear leukocyte granule components (elastase	DEFA1/DEFA1B , DEFA3 and DEFB4A increased in sera and CSF of AD patients [85]

	ELANE, CAMP, bactericidal/permeability-increasing protein (BPI), and human neutrophil peptide-1(DEFA1))[23]	
DEFA3 defensin alpha 3	Found in the microbicidal granules of neutrophils and likely plays a role in phagocyte-mediated host defense. (from Refseq) Defends (relatively weakly) against S. aureus , E. coli and E. aerogenes [74]	DEFA1/DEFA3/ DEFB4A elevated in the serum and cerebrospinal fluid of AD patients [84]
DEFA4 defensin alpha 4	Found in neutrophils; it exhibits corticostatic activity and inhibits corticotropin stimulated corticosterone production. [provided by RefSeq, Oct 2014]. Potent killer of Escherichia coli, Streptococcus faecalis, and Candida albicans [87].	Upregulated in the hippocampus [29]
DEFA5 defensin alpha 5	The protein encoded by this gene, defensin, alpha 5, is highly expressed in the	?

	secretory granules of Paneth cells of the ileum. [provided by RefSeq, Oct 2014]Kills H.Pylori [88]. Unmethylated CpG motifs in Toxoplasma gondii DNA induce TLR9- and IFN-β-dependent expression of DEFA5 in intestinal epithelial cells.[89]	
DEFA6 defensin alpha 6	The protein encoded by this gene, defensin, alpha 6, is highly expressed in the secretory granules of Paneth cells of the small intestine, and likely plays a role in host defense of human bowel. [provided by RefSeq, Oct 2014] Kills H.Pylori [88]	?
DEFB1 defensin beta 1	A gene associated with HSV-1 and cytomegalovirus seropositivity in children with acute lymphoblastic leukaemia [90] ,as well as with *H.Pylori* or chlamydial infections [91,92], also	Upregulated in the Alzheimer's disease choroid plexus and in granulovacuolar degeneration structures [95]

	endowed with antimicrobial activity against *C.Neoformans* and other pathogens [93].DEFB1 and CAMP (cathelicidin/LL-37) kill H.pylori [22]. Protects mice from influenza pathogenesis with a mechanism other than inhibition of viral replication. plasmacytoid dendritic cells and monocytes increased production of DEFB1 peptide and mRNA as early as 2 h following infection of purified cells and peripheral blood mononuclear cells with influenza , HSV-1, and Sendai virus[94].	
DEFB103A defensin beta 103A	An antibiotic peptide which is induced by bacteria and interferon gamma, and which displays antimicrobial activity against S. aureus, S. pyogenes, P. aeruginosa, E.	?

	coli, and C. albicans. [provided by RefSeq, Oct 2014] .	
DEFB103B defensin beta 103B	This gene encodes defensin, beta 103, which has broad spectrum antimicrobial activity and may play an important role in innate epithelial defense. [provided by RefSeq, Oct 2014]Kills H.Pylori [96].Binds to P.Gingivalis [81]. Antiviral versus Influenza A [97]	?
DEFB4A defensin beta 4A	This gene encodes defensin, beta 4, an antibiotic peptide which is locally regulated by inflammation. [provided by RefSeq, Jul 2008]. Has potent antimicrobial activity against Gram-negative bacteria and Candida, but not Gram-positive Staphylococcus aureus [98].kills H.Pylori [99] Also involved in defence against	DEFA1/DEFA3/ DEFB4A elevated in the serum and cerebrospinal fluid of AD patients [84]

	Varicella zoster, human respiratory syncytial virus, HIV-1 and the Human papillomavirus [100-103]. Binds to P.Gingivalis [81]. slow-replicating type II and III T.Gonidii induce high levels of DEFB4A gene expression in human intestinal epithelial cells [104]	
Defensins	A large number of antimicrobial peptides (almost 2000 animal derived peptides, 112 from Homo Sapiens) target bacteria, parasites, fungi or viruses [105]. Beta-amyloid can be considered as one such [106] .	
DHX58 DEXH-box helicase 58	Detects double stranded viral RNA and activates antiviral reponses [107,108].	Upregulated in total brain and frontal lobe of AD patients [109]
EIF2AK2 eukaryotic translation initiation factor 2 alpha kinase 2 (commonly known as PKR)	Several stimuli including TNF and other cytokines, double stranded viral RNA or bacterial ligands acting via Toll receptors activate EIF2AK2 resulting in the	Upregulated in the AD hippocampus [29] and CSF [121] and activated in AD lymphocytes [122]

	inhibition of protein synthesis necessary for viral replication. Activation also results in the production of interferons alpha and beta [110]. Activated by lipopolysaccharide or bacterial RNA or by the mycotoxin deoxynivalenol, shiga toxin, and ricin [111-115]. Activated by HCMV, but the virus possesses proteins able to antagonise EIF2AK2 [116]. Activated by HSV-1 which is also able to evade EIF2AK2 activation [117]and by hepatitis C and influenza viruses [118]. Epstein-Barr virus-encoded small RNAs bind the protein PKR and inhibit its activation [119]. Not activated by the Borna virus, suggesting an evasive strategy to abolish antiviral activities [120]	

ELANE elastase, neutrophil expressed	Following activation, this protease hydrolyzes proteins within specialized neutrophil lysosomes, called azurophil granules, as well as proteins of the extracellular matrix. The enzyme may play a role in degenerative and inflammatory diseases through proteolysis of collagen-IV and elastin. This protein also degrades the outer membrane protein A (OmpA) of E. coli as well as the virulence factors of such bacteria as Shigella, Salmonella and Yersinia. [provided by RefSeq, Jan 2016] . Kills Borrelia burgdorferi [23]. H. pylori extract-activated human neutrophils result in endothelial cell detachment from human umbilical vein endothelial cells monolayers	Increased expression in the vessel wall of leptomeningeal vessels in AD . Arterial elastin degradation was observed from Braak stage III onward and correlated with Braak tau pathology [126]. In the brain parenchyma elastase immunoreactivity is restricted to neurons and is markedly elevated in a proportion of neurofibrillary tangle-bearing neurons [127].

	which can be blocked by an elastase antibody. The bacterium also inhibits elastase [123]. Elevated serum levels in patients with influenza virus-associated encephalopathy [124]. Periodontain, a protease secreted by P.Gingivalis, inactivates the human serpin, alpha1-proteinase inhibitor, the primary endogenous regulator of human neutrophil elastase, which may be responsible for increased elastase activity in periodontitis [125] .	
Gamma-secretase	Localised in dendritic cells that scout for invading pathogens. Cleaves receptors for many pathogens including those for adenoviruses, C.Neoformans, cytomegalovirus, Epstein-Barr virus, Hendra virus, hepatitis C, HHV-6, HIV-1, HSV-1, influenza, rhinovirus, measles, Nipah virus, Papilloma virus, P.Gingivalis, rabies, S.Aureus and streptococci, Vaccinia and other pox viruses [128].	
IAPP islet amyloid	Commonly found in	Accumulates intraneuronally

polypeptide (Amylin)	pancreatic islets of patients suffering diabetes mellitus type II, or harboring an insulinoma. Studies suggest that this protein, like the related beta-amyloid (Abeta) associated with Alzheimer's disease, can induce apoptotic cell-death in particular cultured cells, an effect that may be relevant to the development of type II diabetes. This protein also exhibits a bactericidal, antimicrobial activity. [provided by RefSeq, Sep 2014]. Inhibits the growth of Staphylococcus aureus and Escherichia coli [129]	in brains of Alzheimer's disease patients, particularly in those with type-2 diabetes [130].See review for common links between bacteria, diabetes and Alzheimer's disease [131]
IDO1 indoleamine 2,3-dioxygenase 1	Catalyses the production of N-formylkynurenine from tryptophan. Expression is stimulated by interferon gamma and other inflammatory cytokines.	IDO1 expression is increased in the AD hippocampus and is associated with amyloid plaques and neurofibrillary tangles. Quinolinic acid immunoreactivity is localised

	This diverts tryptophan metabolism away from serotonin production, towards kynurenines and can lead to overproduction of the kynurenic acid and quinolinic acid, N-methyl-D-aspartate receptor antagonist and agonist respectively. The subsequent depletion of tryptophan is deleterious to many microbes that depend upon this metabolite [132]. Diversion to the kynurenine pathway also produces metabolites activating the aryl hydrocarbon receptor which also plays a role in antimicrobial defence and immune activation. This pathway is relevant to anti-bacterial and antiviral effects[133]. Involed in C.albicans defence [134] and in the response to B.	in microglial and astrocytic cells around amyloid plaques and in the vicinity of neurofibrillary tangles [145-147].

	Burgdorferi [135].Restricts C.Pneumoniae replication in dendritic cells [136].Induced by HSV-1 [137], Influenza and hepatitis C infection [138,139] . Induced by C.Albicans at sites of infection and in dendritic cells and effector neutrophils [140]. IDO1 activation restricts HCMV replication, but the virus is able to counteract this block [141]. Expression increased by a DPG3 strain of P.Gingivalis [142] . Activated by T.Gondii infection in the mouse spleen [143] . Indiced by the Epstein-Barr virus in human macrophages [144]	
IFNA1 interferon, alpha 1	The protein encoded by this gene is produced by macrophages and has antiviral activity. This gene is intronless and the encoded	The NK cell activity induced by either interferon-alpha (IFN-alpha) or interleukin-2 (IL-2) in DAT was also significantly lower than in

	protein is secreted. [provided by RefSeq, Sep 2011] Orthologs a	the normal controls [148] white matter microglia were intensely labeled for alpha-IFN [149]
IFNB1 Interferon beta 1	The protein encoded by this gene belongs to the type I class of interferons, which are important for defense against viral infections. In addition, type I interferons are involved in cell differentiation and anti-tumor defenses. Following secretion in response to a pathogen, type I interferons bind a homologous receptor complex and induce transcription of genes such as those encoding inflammatory cytokines and chemokines. Overactivation of type I interferon secretion is linked to autoimmune diseases. Mice deficient for this gene display several phenotypes	Increased cytotoxic response by NK cells to IL-2 (mean increase +102%) and IFN-beta (mean increase +132%) in SDAT patients [151].

	including defects in B cell maturation and increased susceptibility to viral infection. [provided by RefSeq, Sep 2015]The Borna virus nucleoprotein inhibits type I IFN expression by interfering with the IRF7 pathway [150] .	
IFNG Interferon Gamma	The active protein is a homodimer that binds to the interferon gamma receptor which triggers a cellular response to viral and microbial infections. Mutations in this gene are associated with an increased susceptibility to viral, bacterial and parasitic infections and to several autoimmune diseases. [provided by RefSeq, Dec 2015]. A P.Gingivalis protease, (gingipain) cleaves interleukin-12, reducing its	Increased spontaneous and IL-2-induced release of IFN-gamma and TNF-alpha from NK cells were found in DAT patients compared to healthy subjects. [154]: IFN-γ and TNF-α levels, in peripheral blood mononuclear cells, assessed in patients with AD in mild and severe stages, respectively, are higher than those observed in patients with moderate stage and MCI [155]. Increased IL2 and IFNG secretion from mononuclear cells observed

	ability to stimulate IFNG production [152] . Upregulated in the brains of Borna virus infected cats [153].	in AD patients in the moderately severe stage of the disease [156] : IFNG levels increased in peripheral blood mononuclear cells [157]. No increase in plasma [158] or CSF levels [159] : higher levels of IL-1beta (interleukin 1beta) (P < .001), IL-1beta to IL-1ra ratio (P < .001), tumor necrosis factor alpha (P = .008), IL-6 (P = .04), and interferon gamma (P = .01) in the non-afflicted offspring of patients with AD [160]. All participants with Apo ε3/ε4 or ε4/ε4 alleles showed a distinct biochemical profile characterized by low C-reactive protein and ApoE levels and by high cortisol, interleukin 13, apolipoprotein B, and gamma interferon

		levels[161] . CSF interferon γ was only detected in cytomegalovirus seropositive subjects and was significantly associated with neurofibrillary tangles [162] . Higher levels of IL-6 and IFN-γ were found more in the cultured T lymphocytes of the AD patients [163]. IFNA5 and IFNG upregulated in the AD hippocampus [29]. Infectious burden and IFNG levels associated with AD (HCMV, HSV-1, B. burgdorferi, C. pneumoniae and H. pylori) [164]
LCN2 lipocalin 2	This gene encodes a protein that belongs to the lipocalin family. Members of this family transport small hydrophobic molecules such as lipids, steroid hormones and retinoids. The protein	Lcn2 levels are decreased in CSF of patients with mild cognitive impairment and AD and increased in brain regions associated with AD pathology in human postmortem brain tissue

	encoded by this gene is a neutrophil gelatinase-associated lipocalin and plays a role in innate immunity by limiting bacterial growth as a result of sequestering iron-containing siderophores. Mice lacking this gene are more susceptible to bacterial infection than wild type mice. [provided by RefSeq, Sep 2015] involved in host defence against C.Pneumoniae possibly by limiting the availability of iron to the pathogen [165]. Upregulated in the gastric mucosa of H.Pylori infected patients [166]	[167] .Plasma levels are increased in mild cognitive impairment [168].
LGALS3 lectin, galactoside binding soluble 3	The protein exhibits antimicrobial activity against bacteria and fungi..[provided by RefSeq, Oct 2014} LGALS3 knockout mice are more susceptible to	Serum levels increased in AD [172]

	C.Albicans infection [169]. Plays an important role in innate immunity to infection and colonization of H. pylori [170]. HSV-1 infection increases the carbohydrate binding activity and the secretion of cellular LGALS3 [171]	
LTF lactotransferrin	Antimicrobial, antiviral, antifungal and antiparasitic activity has been found for this protein and its peptides. Alternatively spliced transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Sep 2014]. Kills T.Gondii and C.Albicans [173]. lactoferricin is generated by gastric pepsin cleavage of lactoferrin and kills albicans, C. tropicalis and C. neoformans[174].Neutralises	expression up-regulated in both neurons and glia in affected AD tissue [181]

	HSV-1 amd prevents replication [175]. Inhibits P.Gingivalis proteases [176]. Effective versus H.Pylori [177]. Inhibits influenza virus hemagglutination [178]. Antiviral versus hepatitis C [179].Inhibits Epstein Barr virus infection [180]	
MAC: Membrane attack complex: A complex composed of complement components C5b to C9 that attaches to bacteria, creating pores that kill by lysis [182].	Activated by C.Albicans but secreted fungal proteases degrade C5 and can inhibit MAC formation [183,184]. Activated by P.Gingivalis which is also able to degrade C5 [185,186].Kills H.Pylori in vitro but the pathogen evades MAC by binding to CD59, and inhibitor of MAC formation [187]. Attacks Borrelia burgdorferi , which retaliates via a protein (CspA) which binds C7 and C9 and blocks MAC assembly and membrane	The complement system is activated in the AD brain and MAC is abundantly present and associated with neurofibrillary tangles, in the neuronal cytoplasm, lipofuscin granules, lysosomes, dystrophic neurites within neuritic plaques, and neuropil threads [190-192]

	insertion [188]. HSV-1 infected neuronal or skin cells activate complement and though initially resistant to MAC deposition the skin cells eventually succumb to MAC deposition. Neuronal Paju cells are more resistant but MAC is deposited on ~10% of these [189].	
MRC1 mannose receptor, C type 1	The protein encoded by this gene is a type I membrane receptor that mediates the endocytosis of glycoproteins by macrophages. The protein has been shown to bind high-mannose structures on the surface of potentially pathogenic viruses, bacteria, and fungi so that they can be neutralized by phagocytic engulfment.[provided by RefSeq, Sep 2015]. Recognises C.Albicans [193]. Higher fungal burdens	mRNAs for TNF, AGI, MRC1 and CHI3L1; CHI3L2 were significantly increased in the AD brain [195]

	for C.Neoformans in MRC1 knockout mice [194]	
NAIP NLR family, apoptosis inhibitory protein	Senses bacterial flagellin [196] and type III secretion system needle proteins from several bacterial pathogens, including Salmonella typhimurium, enterohemorrhagic Escherichia coli, Shigella flexneri, and Burkholderia species [197]. Inhibits Legionella pneumophila infection [198].	Upregulated in the AD hippocampus [29]
NLRP1 NLR family pyrin domain containing 1	Activated by Bacillus anthracis lethal toxin, Toxoplasma gondii, muramyl dipeptide (a constituent of both Gram-positive and Gram-negative bacteria) [199]. NLRP1 and NLRP3 both activated by T.Gondii [200]	Monocyte expression of NLRP1, NLRP3, PYCARD, caspases 1, 5 and 8) and downstream effectors (IL-1β, IL-18) up-regulated in severe and mild AD [201]
NLRP3 NLR family pyrin domain containing 3	Activated by Staphylococcus aureus , Candida albicans and	The NLRP1 and NLRP3 inflammasomes are both

	the influenza virus as well as beta-amyloid [202].Activated by C.Neoformans [203], C.Pneumoniae [204], H.Pylori [205] and by P.Gingivalis LPS [206] but also subject to proteolysis by the bacterium [207]. Activated and subsequently inhibited by HSV-1 [208].Activated by the Hepatitis C virus [209] and by the Influenza a virus in dendritic cells [210]. An Epstein-Barr virus micro RNA can be secreted from infected B cells via exosomes to inhibit the NLRP3 inflammasome [211]	activated in AD monocytes [201]
NOD1 nucleotide binding oligomerization domain containing 1	This protein is an intracellular pattern-recognition receptor (PRR) that initiates inflammation in response to a subset of bacteria through the detection	

	of bacterial diaminopimelic acid. Multiple alternatively spliced transcript variants differring in the 5' UTR have been described, but the full-length nature of these variants has not been determined. [provided by RefSeq, Oct 2009]. P. gingivalis outer membrane vesicles induce strong TLR2 and TLR4-specific responses and moderate responses in TLR7, TLR8, TLR9, NOD1 and NOD2 expressing-HEK-Blue cells [212]. Nod1(-/-) and Nod2(-/-) mice show delayed bacterial clearance of C. pneumoniae [213]. H. pylori activates the intracellular NOD1, NOD2, and NLRP3 [214]	
NOD2 nucleotide binding oligomerization domain containing 2	The protein is primarily expressed in the peripheral blood leukocytes. It plays a	

	role in the immune response to intracellular bacterial lipopolysaccharides (LPS) by recognizing the muramyl dipeptide (MDP) derived from them and activating the NFKB protein. Mutations in this gene have been associated with Crohn disease and Blau syndrome. Alternatively spliced transcript variants encoding distinct isoforms have been found for this gene. [provided by RefSeq, Jun 2014] P. gingivalis outer membrane vesicles induce strong TLR2 and TLR4-specific responses and moderate responses in TLR7, TLR8, TLR9, NOD1 and NOD2 expressing-HEK-Blue cells [212]	
RARRES2 retinoic acid receptor responder 2:	The active protein has several roles, including that as an	Upregulated in the hippocampus [29]

	adipokine and as an antimicrobial protein with activity against bacteria and fungi. [provided by RefSeq, Nov 2014] Antimicrobial effects against E. coli ,S. aureus P. aeruginosa and C. albicans [215].	
RARRES3 retinoic acid receptor responder 3	Viral RNA detector [216-220]	Upregulated in the hippocampus [29]
S100A4 S100 calcium binding protein A4	Dimerises with S100A9 and stimulates AGER and TLR4 [221]	Upregulated in the hippocampus [29]
Calprotectin = S100A8+S100A9	TLR4 agonist that is secreted during the stress response of phagocytes. Involved in promoting the inflammatory response to infections and a potent amplifier of inflammation [222]. Cytoplasmic calprotectin inhibits C.Neoformans growth [223]. Restricts H.Pylori growth [224]. Kills	Faecal levels increased in AD patients [227] . S100B, S100A9 and S100A12, but not S100A8, were consistently associated with the neuropathological hallmarks of AD in post-mortem brains [228]

	Candida Spp Escherichia coli, Klebsiella spp, Staphylococcus aureus, and Staphylococcus epidermidis [225]. Confers resistance to P.Gingivalis [226].	
S100A8 S100 calcium binding protein A8	See Calprotectin	S100B, S100A9 and S100A12, but not S100A8, were consistently associated with the neuropathological hallmarks of AD in post-mortem brains [228]
S100A9 S100 calcium binding protein A9	See Calprotectin S100A9 is also required for the maturation of TLR3 , which recognises viral double standed RNA in the endosomal compartment of macrophages [229].	Low CSF S100A9 and beta-amyloid levels in AD correlate with each other [230]
S100A11 S100 calcium binding protein A11	Expression increased in the blood of infectious myocarditis patients (staphylococcal IE and streptococcal) [2,231]	Upregulated in the hippocampus [29]
S100A12 S100 calcium	S100A12 has antifungal	S100B, S100A9 and

binding protein A12	activity against Candida albicans, C. krusei, C. glabrata and C. tropicalis and Listeria monocytogenes but not Escherichia coli K-12 or Pseudomonas aeruginosa[232]. Induced in response to H. pylori infection and inhibits bacterial growth by binding nutrient zinc [224].	S100A12, but not S100A8, were consistently associated with the neuropathological hallmarks of AD in post-mortem brains [228] Upregulated in the hippocampus [29].
S100B S100 calcium binding protein B	Pathogenic bacteria increase S100B expression in human enteric glial cells where S100B integrates bacteria-induced Toll-like receptor signalling [233]. Forms complexes with TLR2 ligands, particularly fungal RNA and inhibits TLR2 via AGER (advanced glycosylation end product-specific receptor), dampening pathogen-induced inflammation. In addition,	Low serum S100B levels in AD patients [237]. S100B, S100A9 and S100A12, but not S100A8, were consistently associated with the neuropathological hallmarks of AD in post-mortem brains [228]

	upon binding to nucleic acids, S100B activates intracellular toll receptors which feedback to inhibit S100B transcription [234]. Low blood levels of S100B are a marker for invasive aspergillosis [235]. S100B expression is reduced in Borna virus-infected brains and no upregulation of the expression of S100B, or RAGE, was observed in the persistently infected brains even when incited with several inflammatory stimuli, including lipopolysaccharide [236].	
TLR1 toll like receptor 1	Recognises peptidoglycan , a component of bacterial cell walls and acylated lipoproteins as a heterodimer with TLR2[238,239]. cotransfection of TLR2-	Upregulated in the hippocampus [29]

	TLR1 or TLR2-TLR6 required for the activation induced by H. pylori LPS preparations [240]. agonists of TLR1/2, TLR3, TLR4 and TLR9 increase the phagocytosis of encapsulated Cryptococcus neoformans [241].P.Gingivalis fimbriae use TLR1 or TLR6 for cooperative TLR2-dependent activation of transfected cell lines while the bacterial lipopolysaccharide prefers TLR1 [242].TLR1/TLR2 dimers recognise Borrelia burgdorferi [243]. Borna disease virus nucleoproteins and host NFKB1 share a common ankyrin-like motif. When THP1-CD14 cells were pre-treated with the viral nucleoprotein, NFKB1 activation by Toll-like receptor ligands was	

	suppressed (for TLR1/2; TLR4; TLR2/6; TLR2; TLR7/8). [244].	
TLR10 toll like receptor 10	Involved in the response to influenza infection [245]. A TLR2/TLR10 heterodimer functions in H. pylori lipopolysaccharide and Listeria monocytogenes recognition[246,247] .	Upon Aβ stimulation, AD PBMCs generally down-regulated TLR ratios, whereas control PBMCs up-regulated TLR ratios. TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, and TLR10 ratios exhibited the greatest difference between patients and control subjects [248]
TLR2 toll like receptor 2	TLR2 and TLR4, acting via the adapter protein MyD88, signal responses to Cryptococcus neoformans, Aspergillus fumigatus and Candida albicans [249]. TLR2 and TLR4 are activated by H.Pylori [250]. Activated by herpes simplex (HSV-1) and Listeria monocytogenes in microglial cells [251,252] Activated by	TLR2 and TLR4 expression are increased in AD peripheral blood mononuclear cells [266]

	Porphyromonas gingivalis [253]. Stimulated by the hepatitis C core protein [254]. TLR2 is induced by Haemophilus influenza (bacterium) [255] . TLR2 and TLR9 synergistically stimulate innate antiviral activities, thereby protecting against HSV infection in the brain[256]: TLR2 TLR4 and TLR9 ligands promote the microglial uptake of beta-amyloid [257] . Amyloids from bacterial curli fibrils (from E. coli, Salmonella, and some Enterobacteriales)activate TLR2 [258]: TLR2 recognizes many microbial components. including lipoproteins/lipopeptides from various pathogens, peptidoglycan and lipoteichoic acid from Gram-positive bacteria,	

	lipoarabinomannan from mycobacteria, glycosylphosphatidylinositol anchors from Trypanosoma cruzi, modulin from Staphylococcus epidermis, zymosan from fungi and glycolipids from Treponema maltophilum, and lipopolysaccharides preparations from Leptospira interrogans, Porphyromonas gingivalis and Helicobacter pylori [259]. HSV-1 glycoprotein B activates NF-κB activation through TLR2/TLR6 but not with TLR1 although it coimmunoprecipitates with TLR1,2 and 6[260] Activated by C.Pneumoniae which also activates TLR4 but to a lesser extent [261,262]. the production of tumor necrosis factor (TNF) α by	

	macrophages in response to Toxoplasma gondii glycosylphosphatidylinositols require the expression of both Toll-like receptors TLR2 and TLR4 [263]. Recognises HCMV [264]. Epstein-Barr virus activates TLRs, including TLR2, TLR3, and TLR9 [265].	
TLR3 toll like receptor 3	Recognises double stranded viral RNA [267]. Antiviral against HSV-1 and upregulated by the virus in neural stem cells, resulting in beta-interferon induction [268]. TLR3 and TLR4 activate cholesterol-25-hydroxylase producing 25-hydroxycholesterol [269], which along with 27-hydroxycholesterol inhibits the replication of enveloped and non-enveloped viruses [270]. TLR3 and TLR9	TRL3- and TLR8-expressing Monocytes/macrophages are increased in Alzheimer's disease patients and in mild cognitive impairment [272]

	recognise HCMV [271]	
TLR4 toll like receptor 4	Lipopolysaccharide [273] leptospiral LPS Campylobacter jejuni [274] Helicobacter pylori [250] C.Neoformans glucuronoxylomannan [275] TLR2 and TLR4 activation reduce Hepatitis B infection [276] TLR4 896 A>G increased risk for all parasitic infections (ORG 1.59; 95%CI 1.05-2.42), malaria (1.31; 95%CI 1.04-1.66), brucellosis (2.66; 95%CI 1.66-4.27), cutaneous leishmaniasis (7.22; 95%CI 1.91-27.29), neurocysticercosis (4.39; 95%CI 2.53-7.61), Streptococcus pyogenes tonsillar disease (2.93; 95%CI 1.24-6.93) , typhoid	TLR2 and TLR4 expression are increased in AD peripheral blood mononuclear cells [266]. TLR4 expression increased in the Alzheimer's disease brain in regions of beta-amyloid deposition[283]

	fever (2.51; 95%CI 1.18-5.34) and adult urinary tract infections (1.98; 95%CI 1.04-3.98), but was protective for leprosy (0.36; 95%CI 0.22-0.60). TLR4 1196 C>T effects were similar to TLR4 896 A>G for brucellosis, cutaneous leishmaniasis, leprosy, typhoid fever and S. pyogenes tonsillar disease, and was protective for bacterial vaginosis in pregnancy (0.55; 95%CI 0.31-0.98) and Haemophilus influenzae tonsillar disease (0.42; 95%CI 0.17-1.00). The majority of significant associations were among predominantly Asian populations and significant associations were rare among European populations. Hepatitis C viral protein	

	NS5A downmodulates NKG2D on natural killer cells via the TLR4 pathway [254]. TLR2 and TLR4 activated by HSV-1 in astrocytes [277].P. gingivalis GroEL protein may contribute to cardiovascular disorders by increasing TLR4 expression [278]. P. gingivalis outer membrane vesicles induce strong TLR2 and TLR4-specific responses and moderate responses in TLR7, TLR8, TLR9, NOD1 and NOD2 expressing-HEK-Blue cells [212]. Senses the C.Pneumoniae heat shock protein [279] and a bacterial phospholipase D [280]. Phagocytosis of B. burgdorferi by microglia increases expression of TLR1, -2, 4 and 5 [281]. Induced by HCMV [282]	

TLR5 toll like receptor 5	Recognises bacterial flagellin [284]. Microglia and astrocytes respond to B. burgdorferi through TLR1/2 and TLR5. Phagocytosis of B. burgdorferi by microglia increases expression of TLR1, -2, 4 and 5 [281]. Toxoplasma gondii- derived profilin triggers human TLR5-dependent cytokine production [285]. HCMV infection potentiates TLR5 ligand-stimulated cytokine production [286].	Upregulated relative to aged controls in the AD hippocampus and superior frontal gyrus [287]
TLR6 toll like receptor 6	TLR2/TLR6 dimers recognise bacterial lipoproteins (from Refseq) but are also activated in response to viral infection (Dengue virus, hepatitis C, HIV-1, influenza, inter alia) [288-291]. HSV-1 glycoprotein B activates NF-κB activation through	NF

	TLR2/TLR6 but not with TLR1 although it coimmunoprecipitates with TLR1,2 and 6[260]. P.Gingivalis fimbriae use TLR1 or TLR6 for cooperative TLR2-dependent activation of transfected cell lines [242]. Involved in responses to B .Burgdorferi outer surface protein A lipoprotein[292].	
TLR7 toll like receptor 7	Senses single stranded RNA viruses in endosomes [293]. TLR7 and TLR8 act as endosomal recognition receptors for a number of ssRNA viruses including influenza, HIV-1, VSV, Sendai virus, coxsackie B virus, coronaviruses (mouse hepatitis virus and severe acute repiratory syndrome coronavirus), and flaviviruses (HCV, dengue virus and	Upregulated relative to aged controls in the AD superior frontal gyrus [287]

	West Nile virus) [294]. P. gingivalis outer membrane vesicles induce strong TLR2 and TLR4-specific responses and moderate responses in TLR7, TLR8, TLR9, NOD1 and NOD2 expressing-HEK-Blue cells [212]. Borrelia burgdorferi induces the production of type I interferons by human dendritic cells via TLR7 and TLR9. Indoleamine 2,3-dioxygenase (IDO1) induction and kynurenine production were mediated by the same TLR7-dependent recognition process [135]. TLR7 stimulates the expression of Epstein-Barr virus latent membrane protein 1in infected cells [295].Epstein-Barr virus inhibits the stimulatory effect of TLR7/8 and TLR9	

	agonists in human B lymphocytes enabling evasion of the immune system [296]	
TLR8 toll like receptor 8	An endosomal receptor that recognizes single stranded RNA viruses such as Influenza, Sendai, and Coxsackie B viruses. Also recognises bacterial RNA from streptococci [297] and Staphylococcus aureus [298]. P. gingivalis outer membrane vesicles induce strong TLR2 and TLR4-specific responses and moderate responses in TLR7, TLR8, TLR9, NOD1 and NOD2 expressing-HEK-Blue cells [212]. TLR8 is activated by Borrelia burgdorferi RNA in the phagosome of human monocytes[299] .	TRL3- and TLR8-expressing Monocytes/macrophages are increased in Alzheimer's disease patients and in mild cognitive impairment [272]
TLR9 toll like receptor 9	This gene is preferentially expressed in immune cell	The rs187084 variant homozygote GG was

	rich tissues, such as spleen, lymph node, bone marrow and peripheral blood leukocytes. Studies in mice and human indicate that this receptor mediates cellular response to unmethylated CpG dinucleotides in bacterial DNA to mount an innate immune response. [provided by RefSeq, Jul 2008]. TLR3, TLR7, TLR8, and TLR9 also detect distinct forms of viral nucleic acids [294].TLR2 and TLR9 protect against HSV-1 infection in the mouse brain [256] P. gingivalis outer membrane vesicles induce strong TLR2 and TLR4-specific responses and moderate responses in TLR7, TLR8, TLR9, NOD1 and NOD2 expressing-HEK-Blue cells [212]. Unmethylated	significantly associated with a decreased AD risk in a Chinese study. This protective variant related to increased TLR9 expression in peripheral blood monocytes [301] . Transcription of TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, and TLR10 following beta-amyloid stimulation is depressed in mononuclear cells of AD patients [248]

	CpG motifs in Toxoplasma gondii DNA induce TLR9- and IFN-β-dependent expression of DEFA5 in intestinal epithelial cells.[89].Upregulated in dendritic cells by C.Pneumoniae nasal infection [300]	
ZBP1 Z-DNA binding protein 1	This gene encodes a Z-DNA binding protein. The encoded protein plays a role in the innate immune response by binding to foreign DNA and inducing type-I interferon production. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. [provided by RefSeq, Dec 2011]. ZBP1 recognises foreign DNA in the cytosol and inhibits HSV-1 replication[302].HCMV induces the interferon	ZBP1 was identified as an Alzheimer's disease susceptibility gene using hippocampal atrophy as a quantitative Trait [304]

	response via ZBP1[303].	

Reference List

[1] Barichello T, Generoso JS, Goularte JA, Collodel A, Pitcher MR, Simoes LR, Quevedo J, Dal Pizzol F (2015) Does Infection-Induced Immune Activation Contribute to Dementia? *Aging Dis* **6**, 342-348.

[2] Donato R (2007) RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins. *Curr Mol Med* **7**, 711-724.

[3] Wozniak KL, Hole CR, Yano J, Fidel PL, Jr., Wormley FL, Jr. (2014) Characterization of IL-22 and antimicrobial peptide production in mice protected against pulmonary Cryptococcus neoformans infection. *Microbiology* **160**, 1440-1452.

[4] van Zoelen MA, van der Sluijs KF, Achouiti A, Florquin S, Braun-Pater JM, Yang H, Nawroth PP, Tracey KJ, Bierhaus A, van der PT (2009) Receptor for advanced glycation end products is detrimental during influenza A virus pneumonia. *Virology* **391**, 265-273.

[5] Tadie JM, Bae HB, Banerjee S, Zmijewski JW, Abraham E (2012) Differential activation of RAGE by HMGB1 modulates neutrophil-associated NADPH oxidase activity and bacterial killing. *Am J Physiol Cell Physiol* **302**, C249-C256.

[6] Rojas A, Gonzalez I, Rodriguez B, Romero J, Figueroa H, Llanos J, Morales E, Perez-Castro R (2011) Evidence of involvement of the receptor for advanced glycation end-products (RAGE) in the adhesion of Helicobacter pylori to gastric epithelial cells. *Microbes Infect* **13**, 818-823.

[7] Pollreisz A, Hudson BI, Chang JS, Qu W, Cheng B, Papapanou PN, Schmidt AM, Lalla E (2010) Receptor for advanced glycation endproducts mediates pro-atherogenic responses to periodontal infection in vascular endothelial cells. *Atherosclerosis* **212**, 451-456.

[8] Cohen-Or I, Katz C, Ron EZ (2011) AGEs secreted by bacteria are involved in the inflammatory response. *PLoS One* **6**, e17974-

[9] Tsuji A, Wakisaka N, Kondo S, Murono S, Furukawa M, Yoshizaki T (2008) Induction of receptor for advanced glycation end products by EBV latent membrane protein 1 and its correlation with angiogenesis and cervical lymph node metastasis in nasopharyngeal carcinoma. *Clin Cancer Res* **14**, 5368-5375.

[10] Lue LF, Yan SD, Stern DM, Walker DG (2005) Preventing activation of receptor for advanced glycation endproducts in Alzheimer's disease. *Curr Drug Targets CNS Neurol Disord* **4**, 249-266.

[11] Marksteiner J, Imarhiagbe D, Defrancesco M, Deisenhammer EA, Kemmler G, Humpel C (2014) Analysis of 27 vascular-related proteins reveals that NT-proBNP is a potential biomarker for Alzheimer's disease and mild cognitive impairment: a pilot-study. *Exp Gerontol* **50**, 114-121.

[12] Ghidoni R, Benussi L, Glionna M, Franzoni M, Geroldi D, Emanuele E, Binetti G (2008) Decreased plasma levels of soluble receptor for advanced glycation end products in mild cognitive impairment. *J Neural Transm (Vienna)* **115**, 1047-1050.

[13] Emanuele E, D'Angelo A, Tomaino C, Binetti G, Ghidoni R, Politi P, Bernardi L, Maletta R, Bruni AC, Geroldi D (2005) Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. *Arch Neurol* **62**, 1734-1736.

[14] Stahl T, Reimers C, Johne R, Schliebs R, Seeger J (2006) Viral-induced inflammation is accompanied by beta-amyloid plaque reduction in brains of amyloid precursor protein transgenic Tg2576 mice. *Eur J Neurosci* **24**, 1923-1934.

[15] Agrawal A, Singh PP, Bottazzi B, Garlanda C, Mantovani A (2009) Pattern recognition by pentraxins. *Adv Exp Med Biol* **653**, 98-116.

[16] Ezzahiri R, Stassen FR, Kurvers HR, Dolmans V, Kitslaar PJ, Bruggeman CA (2006) Chlamydia pneumoniae infections augment atherosclerotic lesion formation: a role for serum amyloid P. *APMIS* **114**, 117-126.

[17] Gilchrist KB, Garcia MC, Sobonya R, Lipke PN, Klotz SA (2012) New features of invasive candidiasis in humans: amyloid formation by fungi and deposition of serum amyloid P component by the host. *J Infect Dis* **206**, 1473-1478.

[18] Crawford JR, Bjorklund NL, Taglialatela G, Gomer RH (2012) Brain serum amyloid P levels are reduced in individuals that lack dementia while having Alzheimer's disease neuropathology. *Neurochem Res* **37**, 795-801.

[19] Tripathi S, Tecle T, Verma A, Crouch E, White M, Hartshorn KL (2013) The human cathelicidin LL-37 inhibits influenza A viruses through a mechanism distinct from that of surfactant protein D or defensins. *J Gen Virol* **94**, 40-49.

[20] Kim J, Kim S, Lim W, Choi H, Kim O (2015) Effects of the antimicrobial peptide cathelicidin (LL-37) on immortalized gingival fibroblasts infected with Porphyromonas gingivalis and irradiated with 625-nm LED light. *Lasers Med Sci* **30**, 2049-2057.

[21] McCrudden MT, Orr DF, Yu Y, Coulter WA, Manning G, Irwin CR, Lundy FT (2013) LL-37 in periodontal health and disease and its susceptibility to degradation by proteinases present in gingival crevicular fluid. *J Clin Periodontol* **40**, 933-941.

[22] Hase K, Murakami M, Iimura M, Cole SP, Horibe Y, Ohtake T, Obonyo M, Gallo RL, Eckmann L, Kagnoff MF (2003) Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against Helicobacter pylori. *Gastroenterology* **125**, 1613-1625.

[23] Lusitani D, Malawista SE, Montgomery RR (2002) Borrelia burgdorferi are susceptible to killing by a variety of human polymorphonuclear leukocyte components. *J Infect Dis* **185**, 797-804.

[24] Michalkiewicz J, Helmin-Basa A, Grzywa R, Czerwionka-Szaflarska M, Szaflarska-Poplawska A, Mierzwa G, Marszalek A, Bodnar M, Nowak M, Dzierzanowska-Fangrat K (2015) Innate

immunity components and cytokines in gastric mucosa in children with Helicobacter pylori infection. *Mediators Inflamm* **2015**, 176726-

[25] Konermann A, Stabenow D, Knolle PA, Held SA, Deschner J, Jager A (2012) Regulatory role of periodontal ligament fibroblasts for innate immune cell function and differentiation. *Innate Immun* **18**, 745-752.

[26] Dolganiuc A, Norkina O, Kodys K, Catalano D, Bakis G, Marshall C, Mandrekar P, Szabo G (2007) Viral and host factors induce macrophage activation and loss of toll-like receptor tolerance in chronic HCV infection. *Gastroenterology* **133**, 1627-1636.

[27] Avdic S, McSharry BP, Steain M, Poole E, Sinclair J, Abendroth A, Slobedman B (2016) Human Cytomegalovirus-Encoded Human Interleukin-10 (IL-10) Homolog Amplifies Its Immunomodulatory Potential by Upregulating Human IL-10 in Monocytes. *J Virol* **90**, 3819-3827.

[28] Chen YL, Chen FX, Deng CB, Xia B, Wu LP, Wu ZL, Lu HM (2015) Expression of CD163 in children with Epstein-Barr virus infection. *Zhongguo Dang Dai Er Ke Za Zhi* **17**, 492-495.

[29] Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, Landfield PW (2004) Incipient Alzheimer's disease: microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proc Natl Acad Sci U S A* **101**, 2173-2178.

[30] Pey P, Pearce RK, Kalaitzakis ME, Griffin WS, Gentleman SM (2014) Phenotypic profile of alternative activation marker CD163 is different in Alzheimer's and Parkinson's disease. *Acta Neuropathol Commun* **2**, 21-

[31] Gao N , Yu FS (2015) Chitinase 3-Like 1 Promotes Candida albicans Killing and Preserves Corneal Structure and Function by Controlling Host Antifungal Responses. *Infect Immun* **83**, 4154-4164.

[32] Qureshi AM, Hannigan A, Campbell D, Nixon C, Wilson JB (2011) Chitinase-like proteins are autoantigens in a model of inflammation-promoted incipient neoplasia. *Genes Cancer* **2**, 74-87.

[33] Olsson B, Lautner R, Andreasson U, Ohrfelt A, Portelius E, Bjerke M, Holtta M, Rosen C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K, Zetterberg H (2016) CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol*

[34] Teunissen CE, Elias N, Koel-Simmelink MJ, Durieux-Lu S, Malekzadeh A, Pham TV, Piersma SR, Beccari T, Meeter LH, Dopper EG, van Swieten JC, Jimenez CR, Pijnenburg YA (2016) Novel diagnostic cerebrospinal fluid biomarkers for pathologic subtypes of frontotemporal dementia identified by proteomics. *Alzheimers Dement (Amst)* **2**, 86-94.

[35] Wennstrom M, Surova Y, Hall S, Nilsson C, Minthon L, Hansson O, Nielsen HM (2015) The Inflammatory Marker YKL-40 Is Elevated in Cerebrospinal Fluid from Patients with Alzheimer's but Not Parkinson's Disease or Dementia with Lewy Bodies. *PLoS One* **10**, e0135458-

[36] Craig-Schapiro R, Perrin RJ, Roe CM, Xiong C, Carter D, Cairns NJ, Mintun MA, Peskind ER, Li G, Galasko DR, Clark CM, Quinn JF, D'Angelo G, Malone JP, Townsend RR, Morris JC, Fagan AM, Holtzman DM (2010) YKL-40: a novel prognostic fluid biomarker for preclinical Alzheimer's disease. *Biol Psychiatry* **68**, 903-912.

[37] Chaipan C, Soilleux EJ, Simpson P, Hofmann H, Gramberg T, Marzi A, Geier M, Stewart EA, Eisemann J, Steinkasserer A, Suzuki-Inoue K, Fuller GL, Pearce AC, Watson SP, Hoxie JA, Baribaud F, Pohlmann S (2006) DC-SIGN and CLEC-2 mediate human immunodeficiency virus type 1 capture by platelets. *J Virol* **80**, 8951-8960.

[38] Ramasubramanyan S, Osborn K, Al Mohammad R, Naranjo Perez-Fernandez IB, Zuo J, Balan N, Godfrey A, Patel H, Peters G, Rowe M, Jenner RG, Sinclair AJ (2015) Epstein-Barr virus transcription factor Zta acts through distal regulatory elements to directly control cellular gene expression. *Nucleic Acids Res* **43**, 3563-3577.

[39] Satkunanathan S, Kumar N, Bajorek M, Purbhoo MA, Culley FJ (2014) Respiratory syncytial virus infection, TLR3 ligands, and proinflammatory cytokines induce CD161 ligand LLT1 expression on the respiratory epithelium. *J Virol* **88**, 2366-2373.

[40] Germain C, Meier A, Jensen T, Knapnougel P, Poupon G, Lazzari A, Neisig A, Hakansson K, Dong T, Wagtmann N, Galsgaard ED, Spee P, Braud VM (2011) Induction of lectin-like transcript 1 (LLT1) protein cell surface expression by pathogens and interferon-gamma contributes to modulate immune responses. *J Biol Chem* **286**, 37964-37975.

[41] Gillespie L, Roosendahl P, Ng WC, Brooks AG, Reading PC, Londrigan SL (2016) Endocytic function is critical for influenza A virus infection via DC-SIGN and L-SIGN. *Sci Rep* **6**, 19428-

[42] Gardner JP, Durso RJ, Arrigale RR, Donovan GP, Maddon PJ, Dragic T, Olson WC (2003) L-SIGN (CD 209L) is a liver-specific capture receptor for hepatitis C virus. *Proc Natl Acad Sci U S A* **100**, 4498-4503.

[43] Klimstra WB, Nangle EM, Smith MS, Yurochko AD, Ryman KD (2003) DC-SIGN and L-SIGN can act as attachment receptors for alphaviruses and distinguish between mosquito cell- and mammalian cell-derived viruses. *J Virol* **77**, 12022-12032.

[44] Koppel EA, Ludwig IS, Hernandez MS, Lowary TL, Gadikota RR, Tuzikov AB, Vandenbroucke-Grauls CM, van Kooyk Y, Appelmelk BJ, Geijtenbeek TB (2004) Identification of the mycobacterial carbohydrate structure that binds the C-type lectins DC-SIGN, L-SIGN and SIGNR1. *Immunobiology* **209**, 117-127.

[45] Caparros E, Serrano D, Puig-Kroger A, Riol L, Lasala F, Martinez I, Vidal-Vanaclocha F, Delgado R, Rodriguez-Fernandez JL, Rivas L, Corbi AL, Colmenares M (2005) Role of the C-type lectins DC-SIGN and L-SIGN in Leishmania interaction with host phagocytes. *Immunobiology* **210**, 185-193.

[46] van D, I , Cummings RD (2006) Glycans modulate immune responses in helminth infections and allergy. *Chem Immunol Allergy* **90**, 91-112.

[47] Branzk N, Lubojemska A, Hardison SE, Wang Q, Gutierrez MG, Brown GD, Papayannopoulos V (2014) Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. *Nat Immunol* **15**, 1017-1025.

[48] Tiirola T, Sinisalo J, Nieminen MS, Silvennoinen-Kassinen S, Paldanius M, Saikku P, Jauhiainen M, Leinonen M (2007) Chlamydial lipopolysaccharide is present in serum during acute coronary syndrome and correlates with CRP levels. *Atherosclerosis* **194**, 403-407.

[49] de Maat MP , Kluft C (2001) Determinants of C-reactive protein concentration in blood. *Ital Heart J* **2**, 189-195.

[50] Nazmi A, Diez-Roux AV, Jenny NS, Tsai MY, Szklo M, Aiello AE (2010) The influence of persistent pathogens on circulating levels of inflammatory markers: a cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis. *BMC Public Health* **10**, 706-

[51] Ardila CM , Guzman IC (2015) Comparison of serum amyloid A protein and C-reactive protein levels as inflammatory markers in periodontitis. *J Periodontal Implant Sci* **45**, 14-22.

[52] Kostiala I, Kostiala AA, Elonen E (1987) Serial study of C-reactive protein during fungal esophagitis and enterocolitis. *Infection* **15**, 417-421.

[53] Duran A, Gonzalez A, Delgado L, Mosquera J, Valero N (2016) Serum level of C-reactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. *J Med Virol* **88**, 351-355.

[54] O'Bryant SE, Lista S, Rissman RA, Edwards M, Zhang F, Hall J, Zetterberg H, Lovestone S, Gupta V, Graff-Radford N, Martins R, Jeromin A, Waring S, Oh E, King M, Baker L, Hampel H (2016) Comparing biological markers of Alzheimer's disease across blood fraction and platforms: Comparing apples to oranges. *Alzheimers Dement (Amst)* **3**, 27-34.

[55] Gong C, Wei D, Wang Y, Ma J, Yuan C, Zhang W, Yu G, Zhao Y (2016) A Meta-Analysis of C-Reactive Protein in Patients With Alzheimer's Disease. *Am J Alzheimers Dis Other Demen* **31**, 194-200.

[56] Song IU, Chung SW, Kim YD, Maeng LS (2015) Relationship between the hs-CRP as non-specific biomarker and Alzheimer's disease according to aging process. *Int J Med Sci* **12**, 613-617.

[57] Kok EH, Alanne-Kinnunen M, Isotalo K, Luoto T, Haikonen S, Goebeler S, Perola M, Hurme MA, Haapasalo H, Karhunen PJ (2011) CRP gene variation affects early development of Alzheimer's disease-related plaques. *J Neuroinflammation* **8**, 96-

[58] Zhang Z, Kim T, Bao M, Facchinetti V, Jung SY, Ghaffari AA, Qin J, Cheng G, Liu YJ (2011) DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense dsRNA in dendritic cells. *Immunity* **34**, 866-878.

[59] Tingting P, Caiyun F, Zhigang Y, Pengyuan Y, Zhenghong Y (2006) Subproteomic analysis of the cellular proteins associated with the 3' untranslated region of the hepatitis C virus genome in human liver cells. *Biochem Biophys Res Commun* **347**, 683-691.

[60] Chen G, Liu CH, Zhou L, Krug RM (2014) Cellular DDX21 RNA helicase inhibits influenza A virus replication but is counteracted by the viral NS1 protein. *Cell Host Microbe* **15**, 484-493.

[61] Watanabe Y, Ohtaki N, Hayashi Y, Ikuta K, Tomonaga K (2009) Autogenous translational regulation of the Borna disease virus negative control factor X from polycistronic mRNA using host RNA helicases. *PLoS Pathog* **5**, e1000654-

[62] Majerciak V, Deng M, Zheng ZM (2010) Requirement of UAP56, URH49, RBM15, and OTT3 in the expression of Kaposi sarcoma-associated herpesvirus ORF57. *Virology* **407**, 206-212.

[63] Lischka P, Toth Z, Thomas M, Mueller R, Stamminger T (2006) The UL69 transactivator protein of human cytomegalovirus interacts with DEXD/H-Box RNA helicase UAP56 to promote cytoplasmic accumulation of unspliced RNA. *Mol Cell Biol* **26**, 1631-1643.

[64] Wisskirchen C, Ludersdorfer TH, Muller DA, Moritz E, Pavlovic J (2011) Interferon-induced antiviral protein MxA interacts with the cellular RNA helicases UAP56 and URH49. *J Biol Chem* **286**, 34743-34751.

[65] Lin CW, Cheng CW, Yang TC, Li SW, Cheng MH, Wan L, Lin YJ, Lai CH, Lin WY, Kao MC (2008) Interferon antagonist function of Japanese encephalitis virus NS4A and its interaction with DEAD-box RNA helicase DDX42. *Virus Res* **137**, 49-55.

[66] Choi H, Lee H, Kim SR, Gho YS, Lee SK (2013) Epstein-Barr virus-encoded microRNA BART15-3p promotes cell apoptosis partially by targeting BRUCE. *J Virol* **87**, 8135-8144.

[67] Doorbar J, Elston RC, Napthine S, Raj K, Medcalf E, Jackson D, Coleman N, Griffin HM, Masterson P, Stacey S, Mengistu Y, Dunlop J (2000) The E1E4 protein of human papillomavirus type 16 associates with a putative RNA helicase through sequences in its C terminus. *J Virol* **74**, 10081-10095.

[68] Upadya MH, Aweya JJ, Tan YJ (2014) Understanding the interaction of hepatitis C virus with host DEAD-box RNA helicases. *World J Gastroenterol* **20**, 2913-2926.

[69] Chen JY, Chen WN, Poon KM, Zheng BJ, Lin X, Wang YX, Wen YM (2009) Interaction between SARS-CoV helicase and a multifunctional cellular protein (Ddx5) revealed by yeast and mammalian cell two-hybrid systems. *Arch Virol* **154**, 507-512.

[70] Habjan M, Andersson I, Klingstrom J, Schumann M, Martin A, Zimmermann P, Wagner V, Pichlmair A, Schneider U, Muhlberger E, Mirazimi A, Weber F (2008) Processing of genome 5' termini as a strategy of negative-strand RNA viruses to avoid RIG-I-dependent interferon induction. *PLoS One* **3**, e2032-

[71] Rivero Vaccari JP, Brand FJ, III, Sedaghat C, Mash DC, Dietrich WD, Keane RW (2014) RIG-1 receptor expression in the pathology of Alzheimer's disease. *J Neuroinflammation* **11**, 67-

[72] Ostareck DH, Naarmann-de Vries IS, Ostareck-Lederer A (2014) DDX6 and its orthologs as modulators of cellular and viral RNA expression. *Wiley Interdiscip Rev RNA* **5**, 659-678.

[73] Ward AM, Bidet K, Yinglin A, Ler SG, Hogue K, Blackstock W, Gunaratne J, Garcia-Blanco MA (2011) Quantitative mass spectrometry of DENV-2 RNA-interacting proteins reveals that the DEAD-box RNA helicase DDX6 binds the DB1 and DB2 3' UTR structures. *RNA Biol* **8**, 1173-1186.

[74] Ericksen B, Wu Z, Lu W, Lehrer RI (2005) Antibacterial activity and specificity of the six human {alpha}-defensins. *Antimicrob Agents Chemother* **49**, 269-275.

[75] Kim C, Slavinskaya Z, Merrill AR, Kaufmann SH (2006) Human alpha-defensins neutralize toxins of the mono-ADP-ribosyltransferase family. *Biochem J* **399**, 225-229.

[76] Kim C, Gajendran N, Mittrucker HW, Weiwad M, Song YH, Hurwitz R, Wilmanns M, Fischer G, Kaufmann SH (2005) Human alpha-defensins neutralize anthrax lethal toxin and protect against its fatal consequences. *Proc Natl Acad Sci U S A* **102**, 4830-4835.

[77] Giesemann T, Guttenberg G, Aktories K (2008) Human alpha-defensins inhibit Clostridium difficile toxin B. *Gastroenterology* **134**, 2049-2058.

[78] Dugan AS, Maginnis MS, Jordan JA, Gasparovic ML, Manley K, Page R, Williams G, Porter E, O'Hara BA, Atwood WJ (2008) Human alpha-defensins inhibit BK virus infection by aggregating virions and blocking binding to host cells. *J Biol Chem* **283**, 31125-31132.

[79] Smith JG , Nemerow GR (2008) Mechanism of adenovirus neutralization by Human alpha-defensins. *Cell Host Microbe* **3**, 11-19.

[80] Chang TL, Vargas J, Jr., DelPortillo A, Klotman ME (2005) Dual role of alpha-defensin-1 in anti-HIV-1 innate immunity. *J Clin Invest* **115**, 765-773.

[81] Dietrich DE, Xiao X, Dawson DV, Belanger M, Xie H, Progulske-Fox A, Brogden KA (2008) Human alpha- and beta-defensins bind to immobilized adhesins from Porphyromonas gingivalis. *Infect Immun* **76**, 5714-5720.

[82] Salvatore M, Garcia-Sastre A, Ruchala P, Lehrer RI, Chang T, Klotman ME (2007) alpha-Defensin inhibits influenza virus replication by cell-mediated mechanism(s). *J Infect Dis* **196**, 835-843.

[83] Aceti A, Mangoni ML, Pasquazzi C, Fiocco D, Marangi M, Miele R, Zechini B, Borro M, Versace I, Simmaco M (2006) Alpha-defensin increase in peripheral blood mononuclear cells from patients with hepatitis C virus chronic infection. *J Viral Hepat* **13**, 821-827.

[84] Watt AD, Perez KA, Ang CS, O'Donnell P, Rembach A, Pertile KK, Rumble RL, Trounson BO, Fowler CJ, Faux NG, Masters CL, Villemagne VL, Barnham KJ (2015) Peripheral alpha-defensins 1 and 2 are elevated in Alzheimer's disease. *J Alzheimers Dis* **44**, 1131-1143.

[85] Szekeres M, Ivitz E, Datki Z, Kalman J, Pakaski M, Varhelyi ZP, Klivenyi P, Zadori D, Somogyvari F, Szolnoki Z, Vecsei L, Mandi Y (2016) Relevance of defensin beta-2 and alpha defensins (HNP1-3) in Alzheimer's disease. *Psychiatry Res* **239**, 342-345.

[86] Kocsis AK, Ocsovszky I, Tiszlavicz L, Tiszlavicz Z, Mandi Y (2009) Helicobacter pylori induces the release of alpha-defensin by human granulocytes. *Inflamm Res* **58**, 241-247.

[87] Wilde CG, Griffith JE, Marra MN, Snable JL, Scott RW (1989) Purification and characterization of human neutrophil peptide 4, a novel member of the defensin family. *J Biol Chem* **264**, 11200-11203.

[88] Tanabe H, Sato T, Watari J, Maemoto A, Fujiya M, Kono T, Ashida T, Ayabe T, Kohgo Y (2008) Functional role of metaplastic paneth cell defensins in Helicobacter pylori-infected stomach. *Helicobacter* **13**, 370-379.

[89] Santamaria MH, Perez CE, Corral RS (2016) Unmethylated CpG motifs in Toxoplasma gondii DNA induce. *Parasitology* **143**, 60-68.

[90] Tesse R, Santoro N, Giordano P, Cardinale F, De Mattia D, Armenio L (2009) Association between DEFB1 gene haplotype and herpes viruses seroprevalence in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* **26**, 573-582.

[91] Kocsis AK, Kiss ZF, Tiszlavicz L, Tiszlavicz Z, Mandi Y (2009) Potential role of human beta-defensin 1 in Helicobacter pylori-induced gastritis. *Scand J Gastroenterol* **44**, 289-295.

[92] Wiechula B, Cholewa K, Ekiel A, Romanik M, Dolezych H, Martirosian G (2010) HBD-1 and hBD-2 are expressed in cervico-vaginal lavage in female genital tract due to microbial infections. *Ginekol Pol* **81**, 268-271.

[93] Circo R, Skerlavaj B, Gennaro R, Amoroso A, Zanetti M (2002) Structural and functional characterization of hBD-1(Ser35), a peptide deduced from a DEFB1 polymorphism. *Biochem Biophys Res Commun* **293**, 586-592.

[94] Ryan LK, Dai J, Yin Z, Megjugorac N, Uhlhorn V, Yim S, Schwartz KD, Abrahams JM, Diamond G, Fitzgerald-Bocarsly P (2011) Modulation of human beta-defensin-1 (hBD-1) in plasmacytoid

dendritic cells (PDC), monocytes, and epithelial cells by influenza virus, Herpes simplex virus, and Sendai virus and its possible role in innate immunity. *J Leukoc Biol* **90**, 343-356.

[95] Williams WM, Torres S, Siedlak SL, Castellani RJ, Perry G, Smith MA, Zhu X (2013) Antimicrobial peptide beta-defensin-1 expression is upregulated in Alzheimer's brain. *J Neuroinflammation* **10**, 127-

[96] Kawauchi K, Yagihashi A, Tsuji N, Uehara N, Furuya D, Kobayashi D, Watanabe N (2006) Human beta-defensin-3 induction in H. pylori-infected gastric mucosal tissues. *World J Gastroenterol* **12**, 5793-5797.

[97] Hardwick RJ, Machado LR, Zuccherato LW, Antolinos S, Xue Y, Shawa N, Gilman RH, Cabrera L, Berg DE, Tyler-Smith C, Kelly P, Tarazona-Santos E, Hollox EJ (2011) A worldwide analysis of beta-defensin copy number variation suggests recent selection of a high-expressing DEFB103 gene copy in East Asia. *Hum Mutat* **32**, 743-750.

[98] Schroder JM , Harder J (1999) Human beta-defensin-2. *Int J Biochem Cell Biol* **31**, 645-651.

[99] Uehara N, Yagihashi A, Kondoh K, Tsuji N, Fujita T, Hamada H, Watanabe N (2003) Human beta-defensin-2 induction in Helicobacter pylori-infected gastric mucosal tissues: antimicrobial effect of overexpression. *J Med Microbiol* **52**, 41-45.

[100] Crack LR, Jones L, Malavige GN, Patel V, Ogg GS (2012) Human antimicrobial peptides LL-37 and human beta-defensin-2 reduce viral replication in keratinocytes infected with varicella zoster virus. *Clin Exp Dermatol* **37**, 534-543.

[101] Kreuter A, Skrygan M, Gambichler T, Brockmeyer NH, Stucker M, Herzler C, Potthoff A, Altmeyer P, Pfister H, Wieland U (2009) Human papillomavirus-associated induction of human beta-defensins in anal intraepithelial neoplasia. *Br J Dermatol* **160**, 1197-1205.

[102] Kota S, Sabbah A, Chang TH, Harnack R, Xiang Y, Meng X, Bose S (2008) Role of human beta-defensin-2 during tumor necrosis factor-alpha/NF-kappaB-mediated innate antiviral response against human respiratory syncytial virus. *J Biol Chem* **283**, 22417-22429.

[103] Quinones-Mateu ME, Lederman MM, Feng Z, Chakraborty B, Weber J, Rangel HR, Marotta ML, Mirza M, Jiang B, Kiser P, Medvik K, Sieg SF, Weinberg A (2003) Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication. *AIDS* **17**, F39-F48.

[104] Morampudi V, Braun MY, D'Souza S (2011) Modulation of early beta-defensin-2 production as a mechanism developed by type I Toxoplasma gondii to evade human intestinal immunity. *Infect Immun* **79**, 2043-2050.

[105] Wang G, Li X, Wang Z (2016) APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Res* **44**, D1087-D1093.

[106] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, Moir RD (2010) The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* **5**, e9505-

[107] Bruns AM, Leser GP, Lamb RA, Horvath CM (2014) The innate immune sensor LGP2 activates antiviral signaling by regulating MDA5-RNA interaction and filament assembly. *Mol Cell* **55**, 771-781.

[108] Childs KS, Randall RE, Goodbourn S (2013) LGP2 plays a critical role in sensitizing mda-5 to activation by double-stranded RNA. *PLoS One* **8**, e64202-

[109] Twine NA, Janitz K, Wilkins MR, Janitz M (2011) Whole transcriptome sequencing reveals gene expression and splicing differences in brain regions affected by Alzheimer's disease. *PLoS One* **6**, e16266-

[110] Munir M , Berg M (2013) The multiple faces of proteinkinase R in antiviral defense. *Virulence* **4**, 85-89.

[111] Williams BR (1999) PKR; a sentinel kinase for cellular stress. *Oncogene* **18**, 6112-6120.

[112] Lu B, Nakamura T, Inouye K, Li J, Tang Y, Lundback P, Valdes-Ferrer SI, Olofsson PS, Kalb T, Roth J, Zou Y, Erlandsson-Harris H, Yang H, Ting JP, Wang H, Andersson U, Antoine DJ, Chavan SS, Hotamisligil GS, Tracey KJ (2012) Novel role of PKR in inflammasome activation and HMGB1 release. *Nature* **488**, 670-674.

[113] Hull CM , Bevilacqua PC (2015) Mechanistic Analysis of Activation of the Innate Immune Sensor PKR by Bacterial RNA. *J Mol Biol* **427**, 3501-3515.

[114] Vladimer GI, Marty-Roix R, Ghosh S, Weng D, Lien E (2013) Inflammasomes and host defenses against bacterial infections. *Curr Opin Microbiol* **16**, 23-31.

[115] Gray JS, Bae HK, Li JC, Lau AS, Pestka JJ (2008) Double-stranded RNA-activated protein kinase mediates induction of interleukin-8 expression by deoxynivalenol, Shiga toxin 1, and ricin in monocytes. *Toxicol Sci* **105**, 322-330.

[116] Ziehr B, Vincent HA, Moorman NJ (2016) Human Cytomegalovirus pTRS1 and pIRS1 Antagonize Protein Kinase R To Facilitate Virus Replication. *J Virol* **90**, 3839-3848.

[117] Mohr I (2004) Neutralizing innate host defenses to control viral translation in HSV-1 infected cells. *Int Rev Immunol* **23**, 199-220.

[118] Qashqari H, Al Mars A, Chaudhary A, Abuzenadah A, Damanhouri G, Alqahtani M, Mahmoud M, El Sayed ZM, Fatima K, Qadri I (2013) Understanding the molecular mechanism(s) of hepatitis C virus (HCV) induced interferon resistance. *Infect Genet Evol* **19**, 113-119.

[119] Iwakiri D , Takada K (2010) Role of EBERs in the pathogenesis of EBV infection. *Adv Cancer Res* **107**, 119-136.

[120] Yamashita M, Kamitani W, Yanai H, Ohtaki N, Watanabe Y, Lee BJ, Tsuji S, Ikuta K, Tomonaga K (2005) Persistent borna disease virus infection confers instability of HSP70 mRNA in glial cells during heat stress. *J Virol* **79**, 2033-2041.

[121] Dumurgier J, Mouton-Liger F, Lapalus P, Prevot M, Laplanche JL, Hugon J, Paquet C (2013) Cerebrospinal fluid PKR level predicts cognitive decline in Alzheimer's disease. *PLoS One* **8**, e53587-

[122] Paccalin M, Pain-Barc S, Pluchon C, Paul C, Besson MN, Carret-Rebillat AS, Rioux-Bilan A, Gil R, Hugon J (2006) Activated mTOR and PKR kinases in lymphocytes correlate with memory and cognitive decline in Alzheimer's disease. *Dement Geriatr Cogn Disord* **22**, 320-326.

[123] Takemura T, Granger DN, Evans DJ, Jr., Evans DG, Graham DY, Anderson DC, Wolf RE, Cepinskas G, Kvietys PR (1996) Extract of Helicobacter pylori induces neutrophils to injure endothelial cells and contains antielastase activity. *Gastroenterology* **110**, 21-29.

[124] Sun G, Ota C, Kitaoka S, Chiba Y, Takayanagi M, Kitamura T, Yamamoto K, Fujie H, Mikami H, Uematsu M, Hino-Fukuyo N, Munakata M, Kure S, Haginoya K (2015) Elevated serum levels of neutrophil elastase in patients with influenza virus-associated encephalopathy. *J Neurol Sci* **349**, 190-195.

[125] Nelson D, Potempa J, Kordula T, Travis J (1999) Purification and characterization of a novel cysteine proteinase (periodontain) from Porphyromonas gingivalis. Evidence for a role in the inactivation of human alpha1-proteinase inhibitor. *J Biol Chem* **274**, 12245-12251.

[126] Merlini M, Wanner D, Nitsch RM (2016) Tau pathology-dependent remodelling of cerebral arteries precedes Alzheimer's disease-related microvascular cerebral amyloid angiopathy. *Acta Neuropathol* **131**, 737-752.

[127] Smith MA, Richey PL, Kalaria RN, Perry G (1996) Elastase is associated with the neurofibrillary pathology of Alzheimer disease: a putative link between proteolytic imbalance and oxidative stress. *Restor Neurol Neurosci* **9**, 213-217.

[128] Carter CJ (2011) Alzheimer's Disease: APP, Gamma Secretase, APOE, CLU, CR1, PICALM, ABCA7, BIN1, CD2AP, CD33, EPHA1, and MS4A2, and Their Relationships with Herpes Simplex, C. Pneumoniae, Other Suspect Pathogens, and the Immune System. *Int J Alzheimers Dis* **2011**, 501862-

[129] Wang L, Liu Q, Chen JC, Cui YX, Zhou B, Chen YX, Zhao YF, Li YM (2012) Antimicrobial activity of human islet amyloid polypeptides: an insight into amyloid peptides' connection with antimicrobial peptides. *Biol Chem* **393**, 641-646.

[130] Verma N, Ly H, Liu M, Chen J, Zhu H, Chow M, Hersh LB, Despa F (2016) Intraneuronal Amylin Deposition Peroxidative Membrane Injury and Increased IL-1beta Synthesis in Brains of Alzheimer's Disease Patients with Type-2 Diabetes and in Diabetic HIP Rats. *J Alzheimers Dis*

[131] Miklossy J , McGeer PL (2016) Common mechanisms involved in Alzheimer's disease and type 2 diabetes: a key role of chronic bacterial infection and inflammation. *Aging (Albany NY)* **8**, 575-588.

[132] MacKenzie CR, Heseler K, Muller A, Daubener W (2007) Role of indoleamine 2,3-dioxygenase in antimicrobial defence and immuno-regulation: tryptophan depletion versus production of toxic kynurenines. *Curr Drug Metab* **8**, 237-244.

[133] Mehraj V , Routy JP (2015) Tryptophan Catabolism in Chronic Viral Infections: Handling Uninvited Guests. *Int J Tryptophan Res* **8**, 41-48.

[134] De Luca A, Carvalho A, Cunha C, Iannitti RG, Pitzurra L, Giovannini G, Mencacci A, Bartolommei L, Moretti S, Massi-Benedetti C, Fuchs D, De Bernardis F, Puccetti P, Romani L (2013) IL-22 and IDO1 affect immunity and tolerance to murine and human vaginal candidiasis. *PLoS Pathog* **9**, e1003486-

[135] Love AC, Schwartz I, Petzke MM (2015) Induction of indoleamine 2,3-dioxygenase by Borrelia burgdorferi in human immune cells correlates with pathogenic potential. *J Leukoc Biol* **97**, 379-390.

[136] Njau F, Geffers R, Thalmann J, Haller H, Wagner AD (2009) Restriction of Chlamydia pneumoniae replication in human dendritic cell by activation of indoleamine 2,3-dioxygenase. *Microbes Infect* **11**, 1002-1010.

[137] Haruki T, Miyazaki D, Inata K, Sasaki S, Yamamoto Y, Kandori M, Yakura K, Noguchi Y, Touge C, Ishikura R, Touge H, Yamagami S, Inoue Y (2015) Indoleamine 2,3-dioxygenase 1 in corneal endothelial cells limits herpes simplex virus type 1-induced acquired immune response. *Br J Ophthalmol* **99**, 1435-1442.

[138] Schulz S, Landi A, Garg R, Wilson JA, van Drunen Littel-van den Hurk (2015) Indolamine 2,3-dioxygenase expression by monocytes and dendritic cell populations in hepatitis C patients. *Clin Exp Immunol* **180**, 484-498.

[139] Fox JM, Crabtree JM, Sage LK, Tompkins SM, Tripp RA (2015) Interferon Lambda Upregulates IDO1 Expression in Respiratory Epithelial Cells After Influenza Virus Infection. *J Interferon Cytokine Res* **35**, 554-562.

[140] Bozza S, Fallarino F, Pitzurra L, Zelante T, Montagnoli C, Bellocchio S, Mosci P, Vacca C, Puccetti P, Romani L (2005) A crucial role for tryptophan catabolism at the host/Candida albicans interface. *J Immunol* **174**, 2910-2918.

[141] Zimmermann A, Hauka S, Maywald M, Le VT, Schmidt SK, Daubener W, Hengel H (2014) Checks and balances between human cytomegalovirus replication and indoleamine-2,3-dioxygenase. *J Gen Virol* **95**, 659-670.

[142] Arjunan P, El Awady A, Dannebaum RO, Kunde-Ramamoorthy G, Cutler CW (2016) High-throughput sequencing reveals key genes and immune homeostatic pathways activated in myeloid dendritic cells by Porphyromonas gingivalis 381 and its fimbrial mutants. *Mol Oral Microbiol* **31**, 78-93.

[143] He JJ, Ma J, Song HQ, Zhou DH, Wang JL, Huang SY, Zhu XQ (2016) Transcriptomic analysis of global changes in cytokine expression in mouse spleens following acute Toxoplasma gondii infection. *Parasitol Res* **115**, 703-712.

[144] Liu WL, Lin YH, Xiao H, Xing S, Chen H, Chi PD, Zhang G (2014) Epstein-Barr virus infection induces indoleamine 2,3-dioxygenase expression in human monocyte-derived macrophages through p38/mitogen-activated protein kinase and NF-kappaB pathways: impairment in T cell functions. *J Virol* **88**, 6660-6671.

[145] Wu W, Nicolazzo JA, Wen L, Chung R, Stankovic R, Bao SS, Lim CK, Brew BJ, Cullen KM, Guillemin GJ (2013) Expression of tryptophan 2,3-dioxygenase and production of kynurenine pathway metabolites in triple transgenic mice and human Alzheimer's disease brain. *PLoS One* **8**, e59749-

[146] Bonda DJ, Mailankot M, Stone JG, Garrett MR, Staniszewska M, Castellani RJ, Siedlak SL, Zhu X, Lee HG, Perry G, Nagaraj RH, Smith MA (2010) Indoleamine 2,3-dioxygenase and 3-

hydroxykynurenine modifications are found in the neuropathology of Alzheimer's disease. *Redox Rep* **15**, 161-168.

[147] Guillemin GJ, Brew BJ, Noonan CE, Takikawa O, Cullen KM (2005) Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. *Neuropathol Appl Neurobiol* **31**, 395-404.

[148] Araga S, Kagimoto H, Funamoto K, Takahashi K (1991) Reduced natural killer cell activity in patients with dementia of the Alzheimer type. *Acta Neurol Scand* **84**, 259-263.

[149] Yamada T, Horisberger MA, Kawaguchi N, Moroo I, Toyoda T (1994) Immunohistochemistry using antibodies to alpha-interferon and its induced protein, MxA, in Alzheimer's and Parkinson's disease brain tissues. *Neurosci Lett* **181**, 61-64.

[150] Song W, Kao W, Zhai A, Qian J, Li Y, Zhang Q, Zhao H, Hu Y, Li H, Zhang F (2013) Borna disease virus nucleoprotein inhibits type I interferon induction through the interferon regulatory factor 7 pathway. *Biochem Biophys Res Commun* **438**, 619-623.

[151] Solerte SB, Fioravanti M, Pascale A, Ferrari E, Govoni S, Battaini F (1998) Increased natural killer cell cytotoxicity in Alzheimer's disease may involve protein kinase C dysregulation. *Neurobiol Aging* **19**, 191-199.

[152] Yun PL, Decarlo AA, Collyer C, Hunter N (2001) Hydrolysis of interleukin-12 by Porphyromonas gingivalis major cysteine proteinases may affect local gamma interferon accumulation and the Th1 or Th2 T-cell phenotype in periodontitis. *Infect Immun* **69**, 5650-5660.

[153] Wensman JJ, Ilback C, Hjertstrom E, Blomstrom AL, Gustavsson MH, Jaderlund KH, Strom-Holst B, Belak S, Berg AL, Berg M (2011) Expression of interferon gamma in the brain of cats with natural Borna disease virus infection. *Vet Immunol Immunopathol* **141**, 162-167.

[154] Solerte SB, Cravello L, Ferrari E, Fioravanti M (2000) Overproduction of IFN-gamma and TNF-alpha from natural killer (NK) cells is associated with abnormal NK reactivity and cognitive derangement in Alzheimer's disease. *Ann N Y Acad Sci* **917**, 331-340.

[155] Belkhelfa M, Rafa H, Medjeber O, Arroul-Lammali A, Behairi N, Abada-Bendib M, Makrelouf M, Belarbi S, Masmoudi AN, Tazir M, Touil-Boukoffa C (2014) IFN-gamma and TNF-alpha are involved during Alzheimer disease progression and correlate with nitric oxide production: a study in Algerian patients. *J Interferon Cytokine Res* **34**, 839-847.

[156] Huberman M, Shalit F, Roth-Deri I, Gutman B, Brodie C, Kott E, Sredni B (1994) Correlation of cytokine secretion by mononuclear cells of Alzheimer patients and their disease stage. *J Neuroimmunol* **52**, 147-152.

[157] Reale M, Iarlori C, Feliciani C, Gambi D (2008) Peripheral chemokine receptors, their ligands, cytokines and Alzheimer's disease. *J Alzheimers Dis* **14**, 147-159.

[158] Singh VK , Guthikonda P (1997) Circulating cytokines in Alzheimer's disease. *J Psychiatr Res* **31**, 657-660.

[159] Engelborghs S, De Brabander M, De Cree J, D'Hooge R, Geerts H, Verhaegen H, De Deyn PP (1999) Unchanged levels of interleukins, neopterin, interferon-gamma and tumor necrosis factor-alpha in cerebrospinal fluid of patients with dementia of the Alzheimer type. *Neurochem Int* **34**, 523-530.

[160] van Exel E, Eikelenboom P, Comijs H, Frolich M, Smit JH, Stek ML, Scheltens P, Eefsting JE, Westendorp RG (2009) Vascular factors and markers of inflammation in offspring with a parental history of late-onset Alzheimer disease. *Arch Gen Psychiatry* **66**, 1263-1270.

[161] Soares HD, Potter WZ, Pickering E, Kuhn M, Immermann FW, Shera DM, Ferm M, Dean RA, Simon AJ, Swenson F, Siuciak JA, Kaplow J, Thambisetty M, Zagouras P, Koroshetz WJ, Wan HI, Trojanowski JQ, Shaw LM (2012) Plasma biomarkers associated with the apolipoprotein E genotype and Alzheimer disease. *Arch Neurol* **69**, 1310-1317.

[162] Lurain NS, Hanson BA, Martinson J, Leurgans SE, Landay AL, Bennett DA, Schneider JA (2013) Virological and Immunological Characteristics of Human Cytomegalovirus Infection Associated with Alzheimer's Disease. *J Infect Dis*

[163] Jabbari AF, Talaei A, Rafatpanah H, Yousefzadeh H, Jafari R, Talaei A, Farid HR (2014) Association between Cytokine production and disease severity in Alzheimer's disease. *Iran J Allergy Asthma Immunol* **13**, 433-439.

[164] Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, Liang CR, Wang QH, Wang X, Cao HY, Yi X, Deng B, Liu CH, Xu J, Zhang LL, Gao CY, Xu ZQ, Zhang M, Wang L, Tan XL, Xu X, Zhou HD, Wang YJ (2015) A study on the association between infectious burden and Alzheimer's disease. *Eur J Neurol* **22**, 1519-1525.

[165] Bellmann-Weiler R, Schroll A, Engl S, Nairz M, Talasz H, Seifert M, Weiss G (2013) Neutrophil gelatinase-associated lipocalin and interleukin-10 regulate intramacrophage Chlamydia pneumoniae replication by modulating intracellular iron homeostasis. *Immunobiology* **218**, 969-978.

[166] Alpizar-Alpizar W, Laerum OD, Illemann M, Ramirez JA, Arias A, Malespin-Bendana W, Ramirez V, Lund LR, Borregaard N, Nielsen BS (2009) Neutrophil gelatinase-associated lipocalin (NGAL/Lcn2) is upregulated in gastric mucosa infected with Helicobacter pylori. *Virchows Arch* **455**, 225-233.

[167] Naude PJ, Nyakas C, Eiden LE, Ait-Ali D, van der HR, Engelborghs S, Luiten PG, De Deyn PP, den Boer JA, Eisel UL (2012) Lipocalin 2: novel component of proinflammatory signaling in Alzheimer's disease. *FASEB J* **26**, 2811-2823.

[168] Choi J, Lee HW, Suk K (2011) Increased plasma levels of lipocalin 2 in mild cognitive impairment. *J Neurol Sci* **305**, 28-33.

[169] Linden JR, De Paepe ME, Laforce-Nesbitt SS, Bliss JM (2013) Galectin-3 plays an important role in protection against disseminated candidiasis. *Med Mycol* **51**, 641-651.

[170] Park AM, Hagiwara S, Hsu DK, Liu FT, Yoshie O (2016) Galectin-3 Plays an Important Role in Innate Immunity to Gastric Infection by Helicobacter pylori. *Infect Immun* **84**, 1184-1193.

[171] King RD, Lubinski JM, Friedman HM (2009) Herpes simplex virus type 1 infection increases the carbohydrate binding activity and the secretion of cellular galectin-3. *Arch Virol* **154**, 609-618.

[172] Wang X, Zhang S, Lin F, Chu W, Yue S (2015) Elevated Galectin-3 Levels in the Serum of Patients With Alzheimer's Disease. *Am J Alzheimers Dis Other Demen* **30**, 729-732.

[173] Orsi N (2004) The antimicrobial activity of lactoferrin: current status and perspectives. *Biometals* **17**, 189-196.

[174] Vorland LH, Ulvatne H, Andersen J, Haukland H, Rekdal O, Svendsen JS, Gutteberg TJ (1998) Lactoferricin of bovine origin is more active than lactoferricins of human, murine and caprine origin. *Scand J Infect Dis* **30**, 513-517.

[175] Valimaa H, Tenovuo J, Waris M, Hukkanen V (2009) Human lactoferrin but not lysozyme neutralizes HSV-1 and inhibits HSV-1 replication and cell-to-cell spread. *Virol J* **6**, 53-

[176] Dashper SG, Pan Y, Veith PD, Chen YY, Toh EC, Liu SW, Cross KJ, Reynolds EC (2012) Lactoferrin inhibits Porphyromonas gingivalis proteinases and has sustained biofilm inhibitory activity. *Antimicrob Agents Chemother* **56**, 1548-1556.

[177] Yuan Y, Wu Q, Cheng G, Liu X, Liu S, Luo J, Zhang A, Bian L, Chen J, Lv J, Dong X, Yang G, Zhu Y, Ma L (2015) Recombinant human lactoferrin enhances the efficacy of triple therapy in mice infected with Helicobacter pylori. *Int J Mol Med* **36**, 363-368.

[178] Kawasaki Y, Isoda H, Shinmoto H, Tanimoto M, Dosako S, Idota T, Nakajima I (1993) Inhibition by kappa-casein glycomacropeptide and lactoferrin of influenza virus hemagglutination. *Biosci Biotechnol Biochem* **57**, 1214-1215.

[179] Allaire A, Picard-Jean F, Bisaillon M (2015) Immunofluorescence to Monitor the Cellular Uptake of Human Lactoferrin and its Associated Antiviral Activity Against the Hepatitis C Virus. *J Vis Exp*

[180] Zheng Y, Zhang W, Ye Q, Zhou Y, Xiong W, He W, Deng M, Zhou M, Guo X, Chen P, Fan S, Liu X, Wang Z, Li X, Ma J, Li G (2012) Inhibition of Epstein-Barr virus infection by lactoferrin. *J Innate Immun* **4**, 387-398.

[181] Kawamata T, Tooyama I, Yamada T, Walker DG, McGeer PL (1993) Lactotransferrin immunocytochemistry in Alzheimer and normal human brain. *Am J Pathol* **142**, 1574-1585.

[182] Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT (2015) Complement System Part II: Role in Immunity. *Front Immunol* **6**, 257-

[183] Gropp K, Schild L, Schindler S, Hube B, Zipfel PF, Skerka C (2009) The yeast Candida albicans evades human complement attack by secretion of aspartic proteases. *Mol Immunol* **47**, 465-475.

[184] Triebel T, Grillhosl B, Kacani L, Lell CP, Fuchs A, Speth C, Lass-Florl C, Steinmann J, Dierich MP, Wurzner R (2003) Importance of the terminal complement components for immune defence against Candida. *Int J Med Microbiol* **292**, 527-536.

[185] Poole S, Singhrao SK, Chukkapalli S, Rivera M, Velsko I, Kesavalu L, Crean S (2015) Active invasion of Porphyromonas gingivalis and infection-induced complement activation in ApoE-/- mice brains. *J Alzheimers Dis* **43**, 67-80.

[186] Slaney JM , Curtis MA (2008) Mechanisms of evasion of complement by Porphyromonas gingivalis. *Front Biosci* **13**, 188-196.

[187] Rautemaa R, Rautelin H, Puolakkainen P, Kokkola A, Karkkainen P, Meri S (2001) Survival of Helicobacter pylori From complement lysis by binding of GPI-anchored protectin (CD59). *Gastroenterology* **120**, 470-479.

[188] Hallstrom T, Siegel C, Morgelin M, Kraiczy P, Skerka C, Zipfel PF (2013) CspA from Borrelia burgdorferi inhibits the terminal complement pathway. *MBio* **4**

[189] Hook LM, Lubinski JM, Jiang M, Pangburn MK, Friedman HM (2006) Herpes simplex virus type 1 and 2 glycoprotein C prevents complement-mediated neutralization induced by natural immunoglobulin M antibody. *J Virol* **80**, 4038-4046.

[190] Yasojima K, Schwab C, McGeer EG, McGeer PL (1999) Up-regulated production and activation of the complement system in Alzheimer's disease brain. *Am J Pathol* **154**, 927-936.

[191] Itagaki S, Akiyama H, Saito H, McGeer PL (1994) Ultrastructural localization of complement membrane attack complex (MAC)-like immunoreactivity in brains of patients with Alzheimer's disease. *Brain Res* **645**, 78-84.

[192] Webster S, Lue LF, Brachova L, Tenner AJ, McGeer PL, Terai K, Walker DG, Bradt B, Cooper NR, Rogers J (1997) Molecular and cellular characterization of the membrane attack complex, C5b-9, in Alzheimer's disease. *Neurobiol Aging* **18**, 415-421.

[193] Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL (2015) Immune defence against Candida fungal infections. *Nat Rev Immunol* **15**, 630-642.

[194] Dan JM, Kelly RM, Lee CK, Levitz SM (2008) Role of the mannose receptor in a murine model of Cryptococcus neoformans infection. *Infect Immun* **76**, 2362-2367.

[195] Colton CA, Mott RT, Sharpe H, Xu Q, Van Nostrand WE, Vitek MP (2006) Expression profiles for macrophage alternative activation genes in AD and in mouse models of AD. *J Neuroinflammation* **3**, 27-

[196] Halff EF, Diebolder CA, Versteeg M, Schouten A, Brondijk TH, Huizinga EG (2012) Formation and structure of a NAIP5-NLRC4 inflammasome induced by direct interactions with conserved N- and C-terminal regions of flagellin. *J Biol Chem* **287**, 38460-38472.

[197] Yang J, Zhao Y, Shi J, Shao F (2013) Human NAIP and mouse NAIP1 recognize bacterial type III secretion needle protein for inflammasome activation. *Proc Natl Acad Sci U S A* **110**, 14408-14413.

[198] Vinzing M, Eitel J, Lippmann J, Hocke AC, Zahlten J, Slevogt H, N'guessan PD, Gunther S, Schmeck B, Hippenstiel S, Flieger A, Suttorp N, Opitz B (2008) NAIP and Ipaf control Legionella pneumophila replication in human cells. *J Immunol* **180**, 6808-6815.

[199] Chavarria-Smith J , Vance RE (2015) The NLRP1 inflammasomes. *Immunol Rev* **265**, 22-34.

[200] Gorfu G, Cirelli KM, Melo MB, Mayer-Barber K, Crown D, Koller BH, Masters S, Sher A, Leppla SH, Moayeri M, Saeij JP, Grigg ME (2014) Dual role for inflammasome sensors NLRP1 and NLRP3 in murine resistance to Toxoplasma gondii. *MBio* **5**

[201] Saresella M, La Rosa F, Piancone F, Zoppis M, Marventano I, Calabrese E, Rainone V, Nemni R, Mancuso R, Clerici M (2016) The NLRP3 and NLRP1 inflammasomes are activated in Alzheimer's disease. *Mol Neurodegener* **11**, 23-

[202] Lamkanfi M , Kanneganti TD (2010) Nlrp3: an immune sensor of cellular stress and infection. *Int J Biochem Cell Biol* **42**, 792-795.

[203] Guo C, Chen M, Fa Z, Lu A, Fang W, Sun B, Chen C, Liao W, Meng G (2014) Acapsular Cryptococcus neoformans activates the NLRP3 inflammasome. *Microbes Infect* **16**, 845-854.

[204] Eitel J, Meixenberger K, van Laak C, Orlovski C, Hocke A, Schmeck B, Hippenstiel S, N'guessan PD, Suttorp N, Opitz B (2012) Rac1 regulates the NLRP3 inflammasome which mediates IL-1beta production in Chlamydophila pneumoniae infected human mononuclear cells. *PLoS One* **7**, e30379-

[205] Perez-Figueroa E, Torres J, Sanchez-Zauco N, Contreras-Ramos A, Alvarez-Arellano L, Maldonado-Bernal C (2016) Activation of NLRP3 inflammasome in human neutrophils by Helicobacter pylori infection. *Innate Immun* **22**, 103-112.

[206] Guo W, Wang P, Liu Z, Yang P, Ye P (2015) The activation of pyrin domain-containing-3 inflammasome depends on lipopolysaccharide from Porphyromonas gingivalis and extracellular adenosine triphosphate in cultured oral epithelial cells. *BMC Oral Health* **15**, 133-

[207] Huck O, Elkaim R, Davideau JL, Tenenbaum H (2015) Porphyromonas gingivalis-impaired innate immune response via NLRP3 proteolysis in endothelial cells. *Innate Immun* **21**, 65-72.

[208] Johnson KE, Chikoti L, Chandran B (2013) Herpes simplex virus 1 infection induces activation and subsequent inhibition of the IFI16 and NLRP3 inflammasomes. *J Virol* **87**, 5005-5018.

[209] Chen W, Xu Y, Li H, Tao W, Xiang Y, Huang B, Niu J, Zhong J, Meng G (2014) HCV genomic RNA activates the NLRP3 inflammasome in human myeloid cells. *PLoS One* **9**, e84953-

[210] Fernandez MV, Miller E, Krammer F, Gopal R, Greenbaum BD, Bhardwaj N (2016) Ion efflux and influenza infection trigger NLRP3 inflammasome signaling in human dendritic cells. *J Leukoc Biol* **99**, 723-734.

[211] Haneklaus M, Gerlic M, Kurowska-Stolarska M, Rainey AA, Pich D, McInnes IB, Hammerschmidt W, O'Neill LA, Masters SL (2012) Cutting edge: miR-223 and EBV miR-BART15 regulate the NLRP3 inflammasome and IL-1beta production. *J Immunol* **189**, 3795-3799.

[212] Cecil JD, O'Brien-Simpson NM, Lenzo JC, Holden JA, Chen YY, Singleton W, Gause KT, Yan Y, Caruso F, Reynolds EC (2016) Differential Responses of Pattern Recognition Receptors to Outer Membrane Vesicles of Three Periodontal Pathogens. *PLoS One* **11**, e0151967-

[213] Shimada K, Chen S, Dempsey PW, Sorrentino R, Alsabeh R, Slepenkin AV, Peterson E, Doherty TM, Underhill D, Crother TR, Arditi M (2009) The NOD/RIP2 pathway is essential for host defenses against Chlamydophila pneumoniae lung infection. *PLoS Pathog* **5**, e1000379-

[214] Pachathundikandi SK, Tegtmeyer N, Backert S (2013) Signal transduction of Helicobacter pylori during interaction with host cell protein receptors of epithelial and immune cells. *Gut Microbes* **4**, 454-474.

[215] Banas M, Zabieglo K, Kasetty G, Kapinska-Mrowiecka M, Borowczyk J, Drukala J, Murzyn K, Zabel BA, Butcher EC, Schroeder JM, Schmidtchen A, Cichy J (2013) Chemerin is an antimicrobial agent in human epidermis. *PLoS One* **8**, e58709-

[216] Wang MQ, Huang YL, Huang J, Zheng JL, Qian GX (2015) RIG-I detects HIV-1 infection and mediates type I interferon response in human macrophages from patients with HIV-1-associated neurocognitive disorders. *Genet Mol Res* **14**, 13799-13811.

[217] Kowalinski E, Louber J, Gerlier D, Cusack S (2012) [RIG-I: a viral RNA detector molecular switch]. *Med Sci (Paris)* **28**, 136-138.

[218] Spengler JR, Patel JR, Chakrabarti AK, Zivcec M, Garcia-Sastre A, Spiropoulou CF, Bergeron E (2015) RIG-I Mediates an Antiviral Response to Crimean-Congo Hemorrhagic Fever Virus. *J Virol* **89**, 10219-10229.

[219] Gack MU, Kirchhofer A, Shin YC, Inn KS, Liang C, Cui S, Myong S, Ha T, Hopfner KP, Jung JU (2008) Roles of RIG-I N-terminal tandem CARD and splice variant in TRIM25-mediated antiviral signal transduction. *Proc Natl Acad Sci U S A* **105**, 16743-16748.

[220] Karpus ON, Heutinck KM, Wijnker PJ, Tak PP, Hamann J (2012) Triggering of the dsRNA sensors TLR3, MDA5, and RIG-I induces CD55 expression in synovial fibroblasts. *PLoS One* **7**, e35606-

[221] Bjork P, Kallberg E, Wellmar U, Riva M, Olsson A, He Z, Torngren M, Liberg D, Ivars F, Leanderson T (2013) Common interactions between S100A4 and S100A9 defined by a novel chemical probe. *PLoS One* **8**, e63012-

[222] Ehrchen JM, Sunderkotter C, Foell D, Vogl T, Roth J (2009) The endogenous Toll-like receptor 4 agonist S100A8/S100A9 (calprotectin) as innate amplifier of infection, autoimmunity, and cancer. *J Leukoc Biol* **86**, 557-566.

[223] Mambula SS, Simons ER, Hastey R, Selsted ME, Levitz SM (2000) Human neutrophil-mediated nonoxidative antifungal activity against Cryptococcus neoformans. *Infect Immun* **68**, 6257-6264.

[224] Haley KP, Delgado AG, Piazuelo MB, Mortensen BL, Correa P, Damo SM, Chazin WJ, Skaar EP, Gaddy JA (2015) The Human Antimicrobial Protein Calgranulin C Participates in Control of Helicobacter pylori Growth and Regulation of Virulence. *Infect Immun* **83**, 2944-2956.

[225] Steinbakk M, Naess-Andresen CF, Lingaas E, Dale I, Brandtzaeg P, Fagerhol MK (1990) Antimicrobial actions of calcium binding leucocyte L1 protein, calprotectin. *Lancet* **336**, 763-765.

[226] Nisapakultorn K, Ross KF, Herzberg MC (2001) Calprotectin expression in vitro by oral epithelial cells confers resistance to infection by Porphyromonas gingivalis. *Infect Immun* **69**, 4242-4247.

[227] Leblhuber F, Geisler S, Steiner K, Fuchs D, Schutz B (2015) Elevated fecal calprotectin in patients with Alzheimer's dementia indicates leaky gut. *J Neural Transm (Vienna)* **122**, 1319-1322.

[228] Shepherd CE, Goyette J, Utter V, Rahimi F, Yang Z, Geczy CL, Halliday GM (2006) Inflammatory S100A9 and S100A12 proteins in Alzheimer's disease. *Neurobiol Aging* **27**, 1554-1563.

[229] Tsai SY, Segovia JA, Chang TH, Shil NK, Pokharel SM, Kannan TR, Baseman JB, Defrene J, Page N, Cesaro A, Tessier PA, Bose S (2015) Regulation of TLR3 Activation by S100A9. *J Immunol* **195**, 4426-4437.

[230] Horvath I, Jia X, Johansson P, Wang C, Moskalenko R, Steinau A, Forsgren L, Wagberg T, Svensson J, Zetterberg H, Morozova-Roche LA (2016) Pro-inflammatory S100A9 Protein as a Robust Biomarker Differentiating Early Stages of Cognitive Impairment in Alzheimer's Disease. *ACS Chem Neurosci* **7**, 34-39.

[231] Thuny F, Textoris J, Amara AB, Filali AE, Capo C, Habib G, Raoult D, Mege JL (2012) The gene expression analysis of blood reveals S100A11 and AQP9 as potential biomarkers of infective endocarditis. *PLoS One* **7**, e31490-

[232] Cunden LS, Gaillard A, Nolan EM (2016) Calcium Ions Tune the Zinc-Sequestering Properties and Antimicrobial Activity of Human S100A12. *Chem Sci* **7**, 1338-1348.

[233] Turco F, Sarnelli G, Cirillo C, Palumbo I, De Giorgi F, D'Alessandro A, Cammarota M, Giuliano M, Cuomo R (2014) Enteroglial-derived S100B protein integrates bacteria-induced Toll-like receptor signalling in human enteric glial cells. *Gut* **63**, 105-115.

[234] Sorci G, Giovannini G, Riuzzi F, Bonifazi P, Zelante T, Zagarella S, Bistoni F, Donato R, Romani L (2011) The danger signal S100B integrates pathogen- and danger-sensing pathways to restrain inflammation. *PLoS Pathog* **7**, e1001315-

[235] Dix A, Czakai K, Springer J, Fliesser M, Bonin M, Guthke R, Schmitt AL, Einsele H, Linde J, Loffler J (2016) Genome-Wide Expression Profiling Reveals S100B as Biomarker for Invasive Aspergillosis. *Front Microbiol* **7**, 320-

[236] Ohtaki N, Kamitani W, Watanabe Y, Hayashi Y, Yanai H, Ikuta K, Tomonaga K (2007) Downregulation of an astrocyte-derived inflammatory protein, S100B, reduces vascular inflammatory responses in brains persistently infected with Borna disease virus. *J Virol* **81**, 5940-5948.

[237] Chaves ML, Camozzato AL, Ferreira ED, Piazenski I, Kochhann R, Dall'Igna O, Mazzini GS, Souza DO, Portela LV (2010) Serum levels of S100B and NSE proteins in Alzheimer's disease patients. *J Neuroinflammation* **7**, 6-

[238] Farhat K, Riekenberg S, Heine H, Debarry J, Lang R, Mages J, Buwitt-Beckmann U, Roschmann K, Jung G, Wiesmuller KH, Ulmer AJ (2008) Heterodimerization of TLR2 with TLR1 or TLR6 expands the ligand spectrum but does not lead to differential signaling. *J Leukoc Biol* **83**, 692-701.

[239] Jin MS, Kim SE, Heo JY, Lee ME, Kim HM, Paik SG, Lee H, Lee JO (2007) Crystal structure of the TLR1-TLR2 heterodimer induced by binding of a tri-acylated lipopeptide. *Cell* **130**, 1071-1082.

[240] Yokota S, Ohnishi T, Muroi M, Tanamoto K, Fujii N, Amano K (2007) Highly-purified Helicobacter pylori LPS preparations induce weak inflammatory reactions and utilize Toll-like receptor 2 complex but not Toll-like receptor 4 complex. *FEMS Immunol Med Microbiol* **51**, 140-148.

[241] Redlich S, Ribes S, Schutze S, Eiffert H, Nau R (2013) Toll-like receptor stimulation increases phagocytosis of Cryptococcus neoformans by microglial cells. *J Neuroinflammation* **10**, 71-

[242] Hajishengallis G, Tapping RI, Harokopakis E, Nishiyama S, Ratti P, Schifferle RE, Lyle EA, Triantafilou M, Triantafilou K, Yoshimura F (2006) Differential interactions of fimbriae and lipopolysaccharide from Porphyromonas gingivalis with the Toll-like receptor 2-centred pattern recognition apparatus. *Cell Microbiol* **8**, 1557-1570.

[243] Oosting M, Ter Hofstede H, Sturm P, Adema GJ, Kullberg BJ, van der Meer JW, Netea MG, Joosten LA (2011) TLR1/TLR2 heterodimers play an important role in the recognition of Borrelia spirochetes. *PLoS One* **6**, e25998-

[244] Makino A, Fujino K, Parrish NF, Honda T, Tomonaga K (2015) Borna disease virus possesses an NF-kB inhibitory sequence in the nucleoprotein gene. *Sci Rep* **5**, 8696-

[245] Lee SM, Kok KH, Jaume M, Cheung TK, Yip TF, Lai JC, Guan Y, Webster RG, Jin DY, Peiris JS (2014) Toll-like receptor 10 is involved in induction of innate immune responses to influenza virus infection. *Proc Natl Acad Sci U S A* **111**, 3793-3798.

[246] Nagashima H, Iwatani S, Cruz M, Jimenez Abreu JA, Uchida T, Mahachai V, Vilaichone RK, Graham DY, Yamaoka Y (2015) Toll-like Receptor 10 in Helicobacter pylori Infection. *J Infect Dis* **212**, 1666-1676.

[247] Regan T, Nally K, Carmody R, Houston A, Shanahan F, Macsharry J, Brint E (2013) Identification of TLR10 as a key mediator of the inflammatory response to Listeria monocytogenes in intestinal epithelial cells and macrophages. *J Immunol* **191**, 6084-6092.

[248] Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, Sayre J, Zhang L, Zaghi J, Dejbakhsh S, Chiang B, Hui J, Mahanian M, Baghaee A, Hong P, Cashman J (2007) Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. *Proc Natl Acad Sci U S A* **104**, 12849-12854.

[249] Levitz SM (2004) Interactions of Toll-like receptors with fungi. *Microbes Infect* **6**, 1351-1355.

[250] Uno K, Kato K, Shimosegawa T (2014) Novel role of toll-like receptors in Helicobacter pylori - induced gastric malignancy. *World J Gastroenterol* **20**, 5244-5251.

[251] Aravalli RN, Hu S, Rowen TN, Palmquist JM, Lokensgard JR (2005) Cutting edge: TLR2-mediated proinflammatory cytokine and chemokine production by microglial cells in response to herpes simplex virus. *J Immunol* **175**, 4189-4193.

[252] Aravalli RN, Hu S, Lokensgard JR (2008) Inhibition of toll-like receptor signaling in primary murine microglia. *J Neuroimmune Pharmacol* **3**, 5-11.

[253] Hajishengallis G , Harokopakis E (2007) Porphyromonas gingivalis interactions with complement receptor 3 (CR3): innate immunity or immune evasion? *Front Biosci* **12**, 4547-4557.

[254] Imran M, Waheed Y, Manzoor S, Bilal M, Ashraf W, Ali M, Ashraf M (2012) Interaction of Hepatitis C virus proteins with pattern recognition receptors. *Virol J* **9**, 126-

[255] Mikami F, Gu H, Jono H, Andalibi A, Kai H, Li JD (2005) Epidermal growth factor receptor acts as a negative regulator for bacterium nontypeable Haemophilus influenzae-induced Toll-like receptor 2 expression via an Src-dependent p38 mitogen-activated protein kinase signaling pathway. *J Biol Chem* **280**, 36185-36194.

[256] Sorensen LN, Reinert LS, Malmgaard L, Bartholdy C, Thomsen AR, Paludan SR (2008) TLR2 and TLR9 synergistically control herpes simplex virus infection in the brain. *J Immunol* **181**, 8604-8612.

[257] Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K (2006) Role of toll-like receptor signalling in Abeta uptake and clearance. *Brain* **129**, 3006-3019.

[258] Tukel C, Wilson RP, Nishimori JH, Pezeshki M, Chromy BA, Baumler AJ (2009) Responses to amyloids of microbial and host origin are mediated through toll-like receptor 2. *Cell Host Microbe* **6**, 45-53.

[259] Takeda K , Akira S (2005) Toll-like receptors in innate immunity. *Int Immunol* **17**, 1-14.

[260] Cai M, Li M, Wang K, Wang S, Lu Q, Yan J, Mossman KL, Lin R, Zheng C (2013) The herpes simplex virus 1-encoded envelope glycoprotein B activates NF-kappaB through the Toll-like receptor 2 and MyD88/TRAF6-dependent signaling pathway. *PLoS One* **8**, e54586-

[261] Prebeck S, Kirschning C, Durr S, da Costa C, Donath B, Brand K, Redecke V, Wagner H, Miethke T (2001) Predominant role of toll-like receptor 2 versus 4 in Chlamydia pneumoniae-induced activation of dendritic cells. *J Immunol* **167**, 3316-3323.

[262] Costa CP, Kirschning CJ, Busch D, Durr S, Jennen L, Heinzmann U, Prebeck S, Wagner H, Miethke T (2002) Role of chlamydial heat shock protein 60 in the stimulation of innate immune cells by Chlamydia pneumoniae. *Eur J Immunol* **32**, 2460-2470.

[263] Debierre-Grockiego F, Niehus S, Coddeville B, Elass E, Poirier F, Weingart R, Schmidt RR, Mazurier J, Guerardel Y, Schwarz RT (2010) Binding of Toxoplasma gondii glycosylphosphatidylinositols to galectin-3 is required for their recognition by macrophages. *J Biol Chem* **285**, 32744-32750.

[264] Boehme KW, Guerrero M, Compton T (2006) Human cytomegalovirus envelope glycoproteins B and H are necessary for TLR2 activation in permissive cells. *J Immunol* **177**, 7094-7102.

[265] van Gent M, Braem SG, de Jong A, Delagic N, Peeters JG, Boer IG, Moynagh PN, Kremmer E, Wiertz EJ, Ovaa H, Griffin BD, Ressing ME (2014) Epstein-Barr virus large tegument protein BPLF1 contributes to innate immune evasion through interference with toll-like receptor signaling. *PLoS Pathog* **10**, e1003960-

[266] Zhang W, Wang LZ, Yu JT, Chi ZF, Tan L (2012) Increased expressions of TLR2 and TLR4 on peripheral blood mononuclear cells from patients with Alzheimer's disease. *J Neurol Sci* **315**, 67-71.

[267] Alexopoulou L, Holt AC, Medzhitov R, Flavell RA (2001) Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* **413**, 732-738.

[268] Sun X, Shi L, Zhang H, Li R, Liang R, Liu Z (2015) Effects of Toll-like receptor 3 on herpes simplex virus type-1-infected mouse neural stem cells. *Can J Microbiol* **61**, 201-208.

[269] Park K , Scott AL (2010) Cholesterol 25-hydroxylase production by dendritic cells and macrophages is regulated by type I interferons. *J Leukoc Biol* **88**, 1081-1087.

[270] Lembo D, Cagno V, Civra A, Poli G (2016) Oxysterols: An emerging class of broad spectrum antiviral effectors. *Mol Aspects Med*

[271] Yew KH, Carsten B, Harrison C (2010) Scavenger receptor A1 is required for sensing HCMV by endosomal TLR-3/-9 in monocytic THP-1 cells. *Mol Immunol* **47**, 883-893.

[272] Saresella M, Marventano I, Calabrese E, Piancone F, Rainone V, Gatti A, Alberoni M, Nemni R, Clerici M (2014) A complex proinflammatory role for peripheral monocytes in Alzheimer's disease. *J Alzheimers Dis* **38**, 403-413.

[273] Martin MU , Wesche H (2002) Summary and comparison of the signaling mechanisms of the Toll/interleukin-1 receptor family. *Biochim Biophys Acta* **1592**, 265-280.

[274] Stahl M , Vallance BA (2015) Insights into Campylobacter jejuni colonization of the mammalian intestinal tract using a novel mouse model of infection. *Gut Microbes* **6**, 143-148.

[275] Levitz SM (2002) Receptor-mediated recognition of Cryptococcus neoformans. *Nihon Ishinkin Gakkai Zasshi* **43**, 133-136.

[276] Zhang E , Lu M (2015) Toll-like receptor (TLR)-mediated innate immune responses in the control of hepatitis B virus (HBV) infection. *Med Microbiol Immunol* **204**, 11-20.

[277] Villalba M, Hott M, Martin C, Aguila B, Valdivia S, Quezada C, Zambrano A, Concha MI, Otth C (2012) Herpes simplex virus type 1 induces simultaneous activation of Toll-like receptors 2 and 4 and expression of the endogenous ligand serum amyloid A in astrocytes. *Med Microbiol Immunol* **201**, 371-379.

[278] Huang CY, Shih CM, Tsao NW, Lin YW, Shih CC, Chiang KH, Shyue SK, Chang YJ, Hsieh CK, Lin FY (2016) The GroEL protein of Porphyromonas gingivalis regulates atherogenic phenomena in endothelial cells mediated by upregulating toll-like receptor 4 expression. *Am J Transl Res* **8**, 384-404.

[279] Kang Y, Wang F, Lu Z, Ying H, Zhang H, Ding W, Wang C, Shi L (2013) MAPK kinase 3 potentiates Chlamydia HSP60-induced inflammatory response through distinct activation of NF-kappaB. *J Immunol* **191**, 386-394.

[280] Benagiano M, Munari F, Ciervo A, Amedei A, Paccani SR, Mancini F, Ferrari M, Della BC, Ulivi C, D'Elios S, Baldari CT, Prisco D, de Bernard M, D'Elios MM (2012) Chlamydophila pneumoniae phospholipase D (CpPLD) drives Th17 inflammation in human atherosclerosis. *Proc Natl Acad Sci U S A* **109**, 1222-1227.

[281] Bernardino AL, Myers TA, Alvarez X, Hasegawa A, Philipp MT (2008) Toll-like receptors: insights into their possible role in the pathogenesis of lyme neuroborreliosis. *Infect Immun* **76**, 4385-4395.

[282] Yew KH, Carpenter C, Duncan RS, Harrison CJ (2012) Human cytomegalovirus induces TLR4 signaling components in monocytes altering TIRAP, TRAM and downstream interferon-beta and TNF-alpha expression. *PLoS One* **7**, e44500-

[283] Walter S, Letiembre M, Liu Y, Heine H, Penke B, Hao W, Bode B, Manietta N, Walter J, Schulz-Schuffer W, Fassbender K (2007) Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. *Cell Physiol Biochem* **20**, 947-956.

[284] Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR, Eng JK, Akira S, Underhill DM, Aderem A (2001) The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature* **410**, 1099-1103.

[285] Salazar Gonzalez RM, Shehata H, O'Connell MJ, Yang Y, Moreno-Fernandez ME, Chougnet CA, Aliberti J (2014) Toxoplasma gondii- derived profilin triggers human toll-like receptor 5-dependent cytokine production. *J Innate Immun* **6**, 685-694.

[286] Smith PD, Shimamura M, Musgrove LC, Dennis EA, Bimczok D, Novak L, Ballestas M, Fenton A, Dandekar S, Britt WJ, Smythies LE (2014) Cytomegalovirus enhances macrophage TLR expression and MyD88-mediated signal transduction to potentiate inducible inflammatory responses. *J Immunol* **193**, 5604-5612.

[287] Cribbs DH, Berchtold NC, Perreau V, Coleman PD, Rogers J, Tenner AJ, Cotman CW (2012) Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study. *J Neuroinflammation* **9**, 179-

[288] Chen J, Ng MM, Chu JJ (2015) Activation of TLR2 and TLR6 by Dengue NS1 Protein and Its Implications in the Immunopathogenesis of Dengue Virus Infection. *PLoS Pathog* **11**, e1005053-

[289] Henrick BM, Yao XD, Rosenthal KL (2015) HIV-1 Structural Proteins Serve as PAMPs for TLR2 Heterodimers Significantly Increasing Infection and Innate Immune Activation. *Front Immunol* **6**, 426-

[290] Rajalakshmy AR, Malathi J, Madhavan HN (2015) Hepatitis C Virus NS3 Mediated Microglial Inflammation via TLR2/TLR6 MyD88/NF-kappaB Pathway and Toll Like Receptor Ligand Treatment Furnished Immune Tolerance. *PLoS One* **10**, e0125419-

[291] Tuvim MJ, Gilbert BE, Dickey BF, Evans SE (2012) Synergistic TLR2/6 and TLR9 activation protects mice against lethal influenza pneumonia. *PLoS One* **7**, e30596-

[292] Bulut Y, Faure E, Thomas L, Equils O, Arditi M (2001) Cooperation of Toll-like receptor 2 and 6 for cellular activation by soluble tuberculosis factor and Borrelia burgdorferi outer surface protein A lipoprotein: role of Toll-interacting protein and IL-1 receptor signaling molecules in Toll-like receptor 2 signaling. *J Immunol* **167**, 987-994.

[293] Brencicova E , Diebold SS (2013) Nucleic acids and endosomal pattern recognition: how to tell friend from foe? *Front Cell Infect Microbiol* **3**, 37-

[294] Lester SN , Li K (2014) Toll-like receptors in antiviral innate immunity. *J Mol Biol* **426**, 1246-1264.

[295] Valente RM, Ehlers E, Xu D, Ahmad H, Steadman A, Blasnitz L, Zhou Y, Kastanek L, Meng B, Zhang L (2012) Toll-like receptor 7 stimulates the expression of Epstein-Barr virus latent membrane protein 1. *PLoS One* **7**, e43317-

[296] Younesi V, Nikzamir H, Yousefi M, Khoshnoodi J, Arjmand M, Rabbani H, Shokri F (2010) Epstein Barr virus inhibits the stimulatory effect of TLR7/8 and TLR9 agonists but not CD40 ligand in human B lymphocytes. *Microbiol Immunol* **54**, 534-541.

[297] Eigenbrod T, Pelka K, Latz E, Kreikemeyer B, Dalpke AH (2015) TLR8 Senses Bacterial RNA in Human Monocytes and Plays a Nonredundant Role for Recognition of Streptococcus pyogenes. *J Immunol* **195**, 1092-1099.

[298] Bergstrom B, Aune MH, Awuh JA, Kojen JF, Blix KJ, Ryan L, Flo TH, Mollnes TE, Espevik T, Stenvik J (2015) TLR8 Senses Staphylococcus aureus RNA in Human Primary Monocytes and Macrophages and Induces IFN-beta Production via a TAK1-IKKbeta-IRF5 Signaling Pathway. *J Immunol* **195**, 1100-1111.

[299] Cervantes JL, La Vake CJ, Weinerman B, Luu S, O'Connell C, Verardi PH, Salazar JC (2013) Human TLR8 is activated upon recognition of Borrelia burgdorferi RNA in the phagosome of human monocytes. *J Leukoc Biol* **94**, 1231-1241.

[300] Shimada K, Crother TR, Arditi M (2012) Innate immune responses to Chlamydia pneumoniae infection: role of TLRs, NLRs, and the inflammasome. *Microbes Infect* **14**, 1301-1307.

[301] Wang YL, Tan MS, Yu JT, Zhang W, Hu N, Wang HF, Jiang T, Tan L (2013) Toll-like receptor 9 promoter polymorphism is associated with decreased risk of Alzheimer's disease in Han Chinese. *J Neuroinflammation* **10**, 101-

[302] Pham TH, Kwon KM, Kim YE, Kim KK, Ahn JH (2013) DNA sensing-independent inhibition of herpes simplex virus 1 replication by DAI/ZBP1. *J Virol* **87**, 3076-3086.

[303] DeFilippis VR, Alvarado D, Sali T, Rothenburg S, Fruh K (2010) Human cytomegalovirus induces the interferon response via the DNA sensor ZBP1. *J Virol* **84**, 585-598.

[304] Potkin SG, Guffanti G, Lakatos A, Turner JA, Kruggel F, Fallon JH, Saykin AJ, Orro A, Lupoli S, Salvi E, Weiner M, Macciardi F (2009) Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease. *PLoS One* **4**, e6501-