**Supplementary Table 1.** The immune or pathogen-related properties of the 78 GWAS AD genes. Definitions of the Alzheimer’s disease susceptibility genes studied. The properties isolated in this table focus specifically on immune and pathogen-related effects.

|  |  |  |
| --- | --- | --- |
| **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 [1]. |
| 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 [2]. |
| ADAMTS20 | ADAM metallopeptidase with thrombospondin type 1 motif, 20 | Cleaves the chondroitin sulfate proteoglycan, versican, 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 [3]. |
| AP2A2 | adaptor-related protein complex 2, alpha 2 subunit: (subunit of the AP-2 adaptor protein complex, which is involved in linking lipid and protein membrane components with the clathrin lattice) | Induces the renewal and maintenance of hematopoietic stem cells [4]. |
| APOC1 | apolipoprotein C-I | APOC1 binds to 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 [5]. |
| APOE | apolipoprotein E | APOE4 favors cerebral access of HSV-1 in mice [6] and enhances *C. pneumoniae* adherence to host cells [7] and HIV-1 cell entry *in vitro* [8], but is protective against chronic hepatitis C virus infection [9]. |
| 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 [10]. Also plays a role in abnormal red blood cell adhesion in sickle cell disease (c.f., malaria) [11]. Acts as a receptor for *E. coli* cytotoxic necrotizing factor 1, a toxin found in *E. coli* strains causing meningitis [12]. |
| 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 [13]. |
| BIN1 | bridging integrator 1 | BIN1 negatively controls the expression of indoleamine 2,3-dioxygenase IDO1 in cancer cells [14]. IDO1 activation diverts tryptophan metabolism to N-formyl-kynurenine (away from serotonin production) and 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 [15]. A BIN1 isoform is required for macrophage phagocytosis, a key mechanism in the destruction of many pathogens [16]. |
| CASS4 | Cas scaffolding protein family member 4 | One of a member of scaffold proteins regulated by and mediating cell attachment, growth factor, and chemokine signalling [17]. |
| CD2AP | CD2-associated protein | CD2AP and other endocytosis-associated proteins play a role in enteropathogenic Escherichia coli pedestal formation [18]. Also required for late endosomal trafficking of the *H. pylori* VacA toxin [19]. 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 [20]. 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 [21]. |
| CD33 | CD33 molecule  (siglec-3) | CD33-related SIGLEC’s regulate adaptive immune responses and are also important as macrophage pattern recognition receptors for sialylated pathogens, including enveloped viruses [22]. |
| CDON | cell adhesion associated, oncogene regulated | A gene associated with the acquisition of Staphylococcus aureus bacteraemia [23]. |
| CEACAM16 | carcinoembryonic antigen-related cell adhesion molecule 16 | The CEACAM family are docking sites for pathogenic bacteria and *C. albicans* [24,25] but this particular protein has not been characterized in relation to this effect. |
| CELF1 | CUGBP, Elav-like family member 1 | A downstream effector of interferon beta signalling in macrophages [26]. |
| 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 [27,28]. |
| CNTNAP2 | contactin associated protein-like 2 | None found |
| CR1 | complement component (3b/4b) receptor 1 (Knops blood group) | Many pathogens are recognized by the complement system and coated with complement components C1q, C3b and iC3b. This “opsonization” prepares the microbe for phagocytosis via binding of the complement components to complement receptors, including CR1 [29]. |
| CUGBP2 (changed to CELF2) | CUGBP, Elav-like family member 2 | Silences the expression of cyclo-oxygenase 2 (PTGS2), thus regulating inflammatory processes [30]. CELF2 is regulated in response to T-cell signaling and increased CELF2 expression drives a network of activation-induced alternative splicing events in Jurkat cells [31]. |
| DISC1 | disrupted in schizophrenia 1 | The viral recognition toll-like receptor (TLR3) (activated by viral double-stranded RNA or the viral mimic poly(I:C)) downregulates neuronal DISC1 expression [32]. 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 [33]. 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 [34]. Such traffic is also important in the regulation of the immunological synapse and in the building of functional phagosomes [35]. |
| ECHDC3 | enoyl CoA hydratase domain containing 3 | Expressed in whole blood cells and platelets, but no functional data available [36,37]. |
| EPHA1 | EPH receptor A1 | Suppresses T cell activation and Th2 cytokine expression, while preventing activation-induced cell death in the lung [38]. |
| EXOC3L2 | exocyst complex component 3-like 2 | None found |
| FAM113B (now PCED1B) | PC-esterase domain containing 1B | This family may play a role in pathogen defence by removing acyl groups from pathogen glycans to make them more amenable for degradation by glycohydrolases [38,39]. |
| 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 [38,40]. Gab2 knockout mice show reduced inflammatory cytokine levels in, and are relatively protected against Mycobacterium tuberculosis infection [38,41]. |
| GRIN3B | glutamate receptor, ionotropic, N-methyl-D-aspartate 3B | Expressed in human lymphocytes [38,42]. |
| HLA-DRB1 | major histocompatibility complex, class II, DR beta 1 | Bind to pathogen antigens and present them to T-cells [43]. |
| HLA-DRB5 | major histocompatibility complex, class II, DR beta 5 |
| HMHA1 | histocompatibility (minor) HA-1 | 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-sulfotransferase 1 | 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 [RefSeq, Jul 2008]. Heparan sulphates act as attachment sites for many viruses [44]. |
| IGH | immunoglobulin heavy locus | Forms the heavy chain of multiple antibodies [43]. |
| INPP5D | inositol polyphosphate-5-phosphatase, 145kDa | 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. Key regulator of neutrophil migration, by governing the formation of the leading edge and polarization required for chemotaxis. (Definition from Uniprot). Binds to Dectin1 (CLEC7A) a C-type lectin receptor that couples sensing of pathogens such as fungi to induction of innate responses. Involved in reactive oxygen species generation following recognition of *C. albicans* [38,45]. |
| LUZP2 | leucine zipper protein 2 | None found |
| MEF2C | myocyte enhancer factor 2C | MEF2C orchestrates early B-cell development [38,46] and is also involved in the activation induced cell death of macrophages after priming with Salmonella typhimurium, type 5 adenovirus or Interferon-gamma [38,47]. |
| MMP12 | matrix metallopeptidase 12 (macrophage elastase) | Intracellular MMP12 mediates NFKB inhibitor alpha (NFKBIA) transcription, leading to interferon alpha secretion and host protection: Extracellular MMP-12 cleaves the IFN-α receptor 2 (IFNAR2) binding site of systemic interferon alpha, preventing an unchecked immune response. A membrane-impermeable MMP-12 inhibitor elevates systemic interferon-alpha levels and reduces coxsackievirus replication in the pancreas [38,48]. |
| 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 [49]. Bacterial clearance is reduced in MMP3 knockout mice [50]. |
| 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 [51]. |
| MS4A3 | membrane-spanning 4-domains, subfamily A, member 3 (hematopoietic cell-specific) | Modulates cell cycle progression in hematopoietic cells [52]. |
| MS4A4A | membrane-spanning 4-domains, subfamily A, member 4A | Localized in Hematopoietic cells [52]. 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 [53,54]. |
| MS4A4E | membrane-spanning 4-domains, subfamily A, member 4E | None found |
| MS4A6A | membrane-spanning 4-domains, subfamily A, member 6A | Localized in lymphoid tissues, kidney, colon and Wilm’s tumor cells [52]. |
| MSRA | methionine sulfoxide reductase A Catalyses two reactions (from KEGG)  (1) peptide-L-methionine + thioredoxin disulfide + H2O = peptide-L-methionine (S)-S-oxide + thioredoxin;  (2) L-methionine + thioredoxin disulfide + H2O = L-methionine (S)-S-oxide + thioredoxin | The product, thioredoxin is an antioxidant protein: The thioredoxin system is involved in the regulation of redox signaling and plays many roles in growth promotion, neuroprotection, inflammatory modulation, antiapoptosis, immune function, and atherosclerosis [55]. |
| 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 [56] also a known risk factor for Alzheimer’s disease [57]. |
| PAX2 | paired box 2 | PAX2 negatively regulates beta defensin-1, an antimicrobial peptide implicated in the resistance of epithelial surfaces to microbial colonization [58]. |
| PCDH11X | protocadherin 11 X-linked | None found |
| PCNX1 | pecanex homolog (Drosophila) | None found: This gene encodes an evolutionarily conserved transmembrane protein similar to the pecanex protein in Drosophila. The fly protein is a component of the Notch signaling pathway, which functions in several developmental processes. [provided by RefSeq, Jul 2016]. |
| PICALM | phosphatidylinositol binding clathrin assembly protein | Involved in clathrin-mediated endocytosis, a process used by many viruses to gain entry to the cell [59](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 | Plays a role in DNA repair and homologous recombination (Refseq). |
| 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 TLR signaling (TLR2, TLR4) in macrophages [60]. |
| PVR | poliovirus receptor | Mediates entry of the poliovirus and binds to NECTIN1 ( a receptor for HSV-1 and 2) [61] and NECTIN3 ( a receptor for HSV-1) [62,63,64]. |
| PVRL2 | poliovirus receptor-related 2 (herpesvirus entry mediator B) | Entry receptor for HSV-1 [65]. |
| 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 [66]. 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 [67]. |
| 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 [68]. |
| 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 [69]. |
| SASH1 | SAM and SH3 domain containing 1 | Scaffold molecule involved in Toll receptor (TLR4) signaling, a receptor involved in the recognition of bacterial LPS [70]. |
| 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 signaling [71].SCIMP binds to the bacterial lLPS TLR TLR4 and facilitates the TLR4-mediated production of proinflammatory cytokines [72]. |
| 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 | The encoded preproprotein is proteolytically processed to generate the mature receptor, which likely plays roles in endocytosis and sorting. (Refseq). |
| SPPL2A | signal peptide peptidase like 2A | Cleaves CD74, the invariant chain of the MHCII complex, and an important chaperone regulating antigen presentation for the immune response [73]. |
| SQSTM1 | sequestosome 1 | Autophagy can either promote or restrict viral replication. SQSTM1 is an autophagy receptor involved in the life cycles of the Chikungunya virus [74], Coxsackievirus [75], Dengue virus [76], the encephalomyocarditis virus [77], enterovirus 71 [78], hepatitis B [79], HIV-1 [80], Herpes simplex (HSV-1) [81], Kaposi's sarcoma virus [82], measles [83], Varicella zoster [84], and the West Nile virus [85]. |
| 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 [86]. |
| 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 [87]. TOMM40 is involved in the mitochondrial import of the Enteropathogenic Escherichia coli MAP effector protein and the Neisseria gonorrhoeae outer membrane protein PorB to host mitochondria [88,89]. |
| TREM2 | triggering receptor expressed on myeloid cells 2 | A receptor for bacterial LPS that acts as a phagocytic receptor for bacteria. It also inhibits the production of inflammatory cytokines induced by TLRs [90-92]. Binds to *P. mirabilis* *S. pyogenes* and *E. faecalis and to* bacterial LPS, peptidoglycan, or lipoteichoic acid: *E. coli* and *Staphylococcus aureus* bind specifically to TREM2- transfected cells [93]; Also binds to cholera toxin [94]. TREM2 knockout mice are less able to defend against Burkholderia pseudomallei, a bacterium related to sepsis [95]. |
| TREML2 | triggering receptor expressed on myeloid cells-like 2 | Expressed on T cells and regulates interleukin-2 and interferon-gamma production [96]. Also potentiates neutrophil antibacterial activity and chemotaxis [97]. |
| TRIP4 | thyroid hormone receptor interactor 4 | None found: |
| 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 [98]. The IRF family proteins bind to the interferon-stimulated response element and regulate expression of genes stimulated by type I Interferons, 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. [RefSeq]. |

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

|  |  |  |
| --- | --- | --- |
| **Gene and Function** | **Alzheimer’s disease** | |
| **Antimicrobial peptides and related** | | |
| **Amyloid-β**  Antimicrobial peptide with broad spectrum activity against bacterial (Enterococci, E.coli, streptococci, staphylococci, pseudomonas, listeria), fungal (*C. albicans*) [1] and viral species (HSV-1 and Influenza A) [2,3]. | Key component of amyloid plaques | |
| **AZU1 azurocidin 1**  Kills bacteria and *C. albicans*. An AZU1 derived peptide is antiviral (adenovirus, HSV-1) [4] | Increased expression in pyramidal neurons of the parietal cortex in AD [5] and in the cerebral microvasculature in AD (no expression in controls) [6] | |
| **CAMP cathelicidin antimicrobial peptide (LL-37)**  Antiviral versus influenza [7], Hepatitis C [8], and HSV-1 [9]. Kills *C. albicans* [10] and *P. gingivalis* [11]. DEFB1 and CAMP kill *H. pylori* [12]. *B. burgdorferi* is killed by human polymorphonuclear leukocyte granule components (elastase ELANE, CAMP, bactericidal/permeability-increasing protein, and DEFA1/DEFA1B [13]. Neutralizing antibodies directed against alpha-defensins, EDN, and LL-37 significantly reduces the antiviral effect of LTB(4), (cytomegalovirus) [14]. | High immunostaining in microglia and astrocytes of the AD temporal cortex, and not in control brains [15] | |
| **CHGA Chromogranin A**  CHGA derived peptides (catestatin, cateslytin, vasostatin, and chromofungin) have antimicrobial effects against Gram-positive bacteria, filamentous fungi and yeasts [16] including *C. albicans* and *C. neoformans* [17]. | Component of AD plaques able to activate microglia [18] | |
| **DCD Dermcidin**  Antifungal and antibacterial peptide with activity against *E. coli*, *Salmonella typhimurium*, Listeria monocytogenes, *Staphylococcus aureus*, and *C. albicans* [19] | Protein upregulation in AD serum[20] CSF [21]and in the tears of AD patients [22] | |
| **DEFA1 defensin alpha 1**  Binds to *P. gingivalis* [23]. Antiviral versus Influenza A [24]. Alpha-defensin transcription activated by the hepatitis C core protein [25]. Alpha (DEFA1 to 6) and beta defensins DEFB103B active against HSV-1 [26,27]: Kills *C. albicans* [28] | Defensins alpha1 and 2 (now coded only by DEFA1) are upregulated in AD blood cells [29]; DEFA1/DEFA1B, DEFA3 and DEFB4A increased in sera and CSF of AD patients [30] | |
| **DEFA1B defensin alpha 1B**  Binds to *P. gingivalis* [23]. Release induced by *H. pylori* [31]. *B. burgdorferi* is killed by human polymorphonuclear leukocyte granule components (ELANE, CAMP, bactericidal/permeability-increasing protein, and DEFA1/DEFA1B) [13]. Antiviral (HSV-1, human cytomegalovirus, influenza A) [32]. | DEFA1/DEFA1B, DEFA3 and DEFB4A increased in sera and CSF of AD patients [30] | |
| **DEFA3 defensin alpha 3**  Antiviral versus HSV-1 [33]. Active against *C. neoformans* and other fungi [34]. | DEFA1/DEFA3/ DEFB4A elevated in the serum and CSF of AD patients [29] | |
| **DEFA4 defensin alpha 4**  Kills *E. coli*, *S. faecalis*, and *C. albicans* [35]. | Upregulated in the hippocampus [36] | |
| **DEFB1 defensin beta 1**  A gene associated with *H. pylori* or chlamydial infections [37,38], also endowed with antimicrobial activity against *C. neoformans, C. albicans*, and other pathogens [39,40]. DEFB1 and CAMP (cathelicidin/LL-37) kill *H. pylori* [12]. Gene and protein expression increased in dendritic cells and monocytes following infection with influenza, HSV-1, and Sendai virus [41]. | Upregulated in the AD choroid plexus and in granulovacuolar degeneration structures [42] | |
| **DEFB4A defensin beta 4A**  Potent antimicrobial activity against Gram-negative bacteria and Candida, but not Gram-positive *Staphylococcus aureus* [43]. Kills *H. pylori* [44-47]. Binds to *P. gingivalis* [23]. *T. gondii* induces high levels of DEFB4A gene expression in human intestinal epithelial cells [48]. Kills *C. albicans* [49]. Reduces *B. burgdorferi* viability [50]: Upregulated by *C. pneumoniae* in U937 cells, and monocytes [51] | DEFA1/DEFA3/ DEFB4A elevated in the serum and CSF of AD patients [29] | |
| **ELANE elastase, neutrophil expressed**  Kills *B. burgdorferi* [13]. *H. pylori* extract-activated human neutrophils result in endothelial cell detachment from human umbilical vein endothelial cells monolayers which can be blocked by an elastase antibody. The bacterium also inhibits elastase [52]. Elevated serum levels in patients with influenza virus-associated encephalopathy [53]. 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 [54]. | 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 [55]. In the brain parenchyma elastase immunoreactivity is restricted to neurons and is markedly elevated in a proportion of neurofibrillary tangle-bearing neurons [56]*.* | |
| **HAMP hepcidin**  Antimicrobial activity against bacteria and fungi (Refseq) Expression induced by *H. pylori* infection [57] and by *C. pneumoniae* infection [58]. Serum levels increased by Borrelia infection in mice [59]. Induced by bacterial of influenza infection in mice [60]. Kills *C. albicans* and Aspergillus species: antibacterial activity against *E. coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and group B Streptococcus [61]: Gastric HAMP levels increased by *H. pylori* infection [57]: Antiviral versus hepatitis C [62]. | High serum levels in AD: Protein expression reduced in AD brains and restricted to the neuropil, blood vessels, and damaged neurons [63,64]. | |
| **HTN1 histatin 1**  Histatins are found in saliva and exhibit antibacterial, antifungal activities and function in wound healing (Refseq). Kills *C. albicans* [65] | Upregulated in the hippocampus [36] | |
| **IAPP islet amyloid polypeptide (Amylin)**  Bactericidal, antimicrobial activity [Refseq]. Inhibits the growth of *Staphylococcus aureus* and *E. coli* [66] . | Accumulates intraneuronally in brains of AD patients, particularly in those with type-2 diabetes [67] | |
| **LCN2 lipocalin 2**  Limits bacterial growth by sequestering iron-containing siderophores [RefSeq]. Involved in host defense against *C. pneumoniae* [68]. Upregulated in the gastric mucosa of *H. pylori* infected patients [69]. Levels increased in *C. neofornans* infected mice [70]: Sensitivity to Listeria monocytogenes, *C. albicans* and Staphylococcus aureus increased in LCN2 knockout mice [71]. Upregulated by *P. gingivalis* in bone marrow stromal cells [72]. | 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 [73]. Plasma levels are increased in mild cognitive impairment [74] | |
| **Leukotriene B4 (synthesized by 5-lipoxygenase, ALOX5)**  Possesses antibacterial and antiviral effects against HSV-1, influenza A, the cytomegalovirus via upregulation of antimicrobial peptide production [14,75,76] . Increases phagocytosis of *B. burgdorferi* [77]: Also regulates innate defense against *C. albicans* [78] and neutrophil recruitment to *C. neoformans* [79]: Pre-exposure of polymorphonuclear leucocytes to the Epstein-Barr virus leads to increased production of LTB(4) upon stimulation with either the ionophore A23187, the chemotactic peptide fMLP, or phagocytic particles (zymosan) [80]. LTb4 gastric levels increased in *H. pylori* infected children [81]. Ltb4 kills *T. gondii* [82]. | Increased 5-lipoxygenase (ALOX5) activity in AD peripheral blood mononuclear cells together with increased levels of leukotriene B4 [83]: ALOX5 protein expression increased in the AD brain [84] | |
| **LGALS3 lectin, galactoside binding soluble 3**  Antimicrobial activity against bacteria and fungi [RefSeq]. LGALS3 knockout mice are more susceptible to *C. albicans* infection [85]. Plays an important role in innate immunity to infection and colonization of *H. pylori* [86]. HSV-1 infection increases the carbohydrate binding activity and the secretion of cellular LGALS3 [87]. Regulates the inflammatory response to *T. gondii* [88]. Inhibits influenza replication [89]. | Serum levels increased in AD [90] | |
| **LTF lactotransferrin**  Antimicrobial, antiviral, antifungal, and antiparasitic activity has been found for this protein and its peptides [RefSeq]. Kills *T. gondii* and *C. albicans* [91]. Inhibits *P. gingivalis* proteases [92]. Effective versus *H. pylori* [93]. Antiviral versus HSV-1 [94], hepatitis C [95], Influenza A [96], Epstein Barr virus [97]. Lactoferricin, generated by pepsin cleavage of lactoferrin, kills *C. albicans*, *C. tropicalis*, and *C. neoformans* [98]. | Expression upregulated in both neurons and glia in affected AD tissue [99]: Also seen in reactive microglia in the cerebral cortex and monocytes/macrophages infiltrating from the circulation [100] | |
| **LYZ Lysozme**  Natural substrate is the bacterial cell wall peptidoglycan (cleaving the beta[1-4] glycosidic linkages between N-acetylmuramic acid and N-acetylglucosamine) (Refseq): Kills *H. pylori* [101]. Also has antifungal activity against *C. albicans*, *C. neoformans*, and others [102,103]. | Increased levels in the AD CSF and colocalizes with Aβ in plaques [104] | |
| **MAC: Membrane attack complex**  A complex composed of complement components C5b to C9 that attaches to bacteria, creating pores that kill by lysis [105]. Activated by *C. albicans* but secreted fungal proteases degrade C5 and can inhibit MAC formation [106,107]. Deposited on *C. pneumoniae* [108]. Activated by *P. gingivalis* which is also able to degrade C5 [109,110]. Kills *H. pylori in vitro* but the pathogen evades MAC by binding to CD59, and inhibitor of MAC formation [111]. Attacks *B. burgdorferi* [112]. HSV-1 infected neuronal or skin cells activate complement and though initially resistant to MAC deposition the skin cells eventually succumb to MAC deposition. [113]. Hepatitis C impairs C9 synthesis and formation of MAC [114]. | 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 [115-117] | |
| **RARRES2 retinoic acid receptor responder 2: (chemerin)**  Adipokine and antimicrobial protein with activity against bacteria and fungi [Refseq]. Antimicrobial effects against *E. coli*, *S. aureus*, *P. aeruginosa*, and *C. albicans* [118] and against oral pathogens including *P. gingivali*s [119]. | Upregulated in the hippocampus [36] | |
| **REG3A regenerating family member 3 alpha** (antibacterial protein)  Binds peptidoglycan and kills gram positive bacteria *Listeria innocua* and *Enterococcus faecalis* [120]. | Upregulated in the hippocampus [36] | |
| **S100A7 (psoriasin)**  Antimicrobial activities against bacteria (Refseq). *B. burgdorferi* increases expression in keratinocytes [121]: Antifungal versus *Aspergillus fumigatus*, *Malassezia furfur*, *Microsporum canis*, *Rhizopus oryzae*, *Saccharomyces cerevisiae*, and *Trichophyton mentagrophytes* but not *C. albicans* [122]. | Protein increased in the CSF and brain of AD dementia subjects as a function of clinical dementia [123] | |
| **S100A8+S100A9 = Calprotectin**  TLR4 agonist secreted during the stress response of phagocytes. Involved in promoting the inflammatory response to infections and a potent amplifier of inflammation [124]. Cytoplasmic calprotectin inhibits *C. neoformans* and *H. pylori* growth [125,126]. Kills Candida Spp *E. coli*, Klebsiella spp, *Staphylococcus aureus*, and *Staphylococcus epidermidis* [127]. Confers resistance to *P. gingivalis* [128].Inhibits the growth of *B. burgdorferi* [129]: upregulated by poly I:C suggesting a role in viral resistance [130]. S100A9 upregulated by Influenza virus [131] | Fecal levels increased in AD patients [132]. S100B, S100A9 and S100A12, consistently associated with the neuropathological hallmarks of AD in postmortem brains [133] | |
| **S100A12 S100 calcium binding protein A12**  The protein includes an antimicrobial peptide with antibacterial activity [Refseq]. Antifungal activity against *C. albicans*, *C. krusei*, *C. glabrata,* and *C. tropicalis* and Listeria monocytogenes but not *E. coli* K-12 or *Pseudomonas aeruginosa* [134]. Induced in response to *H. pylori* infection and inhibits bacterial growth by binding nutrient zinc [126]. | S100B, S100A9, and S100A12, but not S100A8, were consistently associated with the neuropathological hallmarks of AD in postmortem brains [133]. Upregulated in the hippocampus [36] | |
| **S100B S100 calcium binding protein B**  Pathogenic bacteria increase S100B expression in human enteric glial cells [135]. 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, upon binding to nucleic acids, S100B activates intracellular toll receptors which feedback to inhibit S100B transcription [136]. Low blood levels of S100B are a marker for invasive aspergillosis [137]. S100B relocates around phagosomes during BV-2micriglial phagocytosis of opsonized C. Neoformans [138]. Inhibits hepatitis C replication [139] | Low serum S100B levels in AD patients [140]. S100B, S100A9, and S100A12, but not S100A8, were consistently associated with the neuropathological hallmarks of AD in postmortem brains [133] | |
| **SNCA alpha-synuclein**  Exhibits antibacterial activity against *E. coli* and *Staphylococcus aureus* and antifungal activity against *C. albicans* and other fungi [141]: Human antibodies against the Epstein-Barr virus cross-react with SNCA [142]: Systemic infection with the H5N1 influenza virus produces microglial activation and synuclein aggregation [143]. | alpha- and gamma-synuclein levels are increased in CSF from elderly individuals with AD, Lewy body disease, and vascular dementia, compared to normal controls [144]. Component of plaques and tangles [145,146] | |
| **Pattern recognition receptors and related** | | |
| **CD14 molecule**  Coreceptor for bacterial lipopolysaccharide (Refseq) including *B. burgdorferi*, *C. Pneumoniae*, *H. pylori*, and *P. gingivalis* [147-150] and *C. neoformans* capsular glucuronoxylomann [151]. Cytomegalovirus binding to CD14 increases TNF expression [152]: Required for influenza induced cytokine production [153] | High immunoreactivity on parenchymal microglia spatially correlated to characteristic AD lesion sites in AD brains [154] | |
| **CD36 molecule**  Directly mediates cytoadherence of *Plasmodium falciparum* parasitized erythrocytes (Refseq). Upregulated by *C. pneumoniae* in human umbilical vein endothelial cells [155] or by *P. gingivalis* in macrophages [156] and in stomachs of *H. pylori* infected mice : Human vascular endothelial cell activation in response to *H. pylori* or *P. gingivalis* lipopolysaccharide was requires the formation of heterotypic receptor complexes comprising of TLR2, TLR1, CD36, and CD11b/CD18 [157,158]: Recognizes beta-glucan from *C. albicans* and *C. neoformans* [159]. Upregulated by the cytomegalovirus in monocytes/macrophages [160]: Coreceptor for hepatitis C [161]: Upregulated in the brains of *T. gondii* infected mice [162]. | Expressed on microglia and on vascular endothelial cells in the brains of AD patients [163] | |
| **CD163 CD163 molecule**  May also function as an innate immune sensor for bacteria and inducer of local inflammation [Refseq]. Upregulated in the gastric mucosa of H. pylori infected children [164]. Upregulated by *P. gingivalis* in periodontal ligament cells [165]. Kupffer cell/macrophage activation indicated by increased CD163 is found in the livers of hepatitis C infected patients [166]. The cytomegalovirus encoded IL10 chemokine mimic upregulates CD163 in macrophages [167]. Serum levels of soluble CD163 in Epstein-Barr virus positive children positively correlate with EBV-DNA copies [168]. Serum levels increased in influenza encephalitis patients [169]. | mRNA upregulated in the AD hippocampus [36]. Parenchymal microglia were immunoreactive for CD163 in all of 31 AD cases often associated with amyloid plaques [170] | |
| **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 [171]. Expression induced by Epstein-Barr infection of Akata cells [172]. | mRNA upregulated in the AD hippocampus [36] | |
| **CLEC2D C-type lectin domain family 2 member D**  Expression is induced in B cells and inflamed tonsils following viral infection (Epstein-Barr virus or HIV infection) and in inflamed tonsils [173]. | mRNA upregulated in the AD hippocampus [36] | |
| **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 [RefSeq]. 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, human cytomegalovirus : CLEC4M also a receptor for *Mycobacterium tuberculosis*, Schistosomes, and *Leishmania infanti* [174-180]. | mRNA upregulated in the AD hippocampus [36] | |
| **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 [RefSeq]. Activated by *C. albicans* and *Mycobacterium bovis* [181], but probably not by *C. neoformans* [182]. | mRNA upregulated in the AD hippocampus [36] | |
| **FPR1 formyl peptide receptor 1**  Also FPR2 and FPR3. FPR1, 2, and 3 recognize a variety of bacterial pathogen-associated molecular patterns (bacterial signal peptides) including *B. burgdorferi* triggering multiple innate defense mechanisms [183]. | No data on FPR1 or FPR3 in AD | |
| **FPR2 (aka FPRL1) formyl peptide receptor 2**  FPR2 and FPR3 are activated by a peptide from *H. pylori* [184,185]: Induced by *C. neoformans* infection in mice [186]. Activated by Influenza A [187]: Recognition receptor for listeria monocytogenes [188]. | High levels of FPR2 gene expression by CD11b+ mononuclear phagocytes surrounding and infiltrating Congo-red positive plaques in brain tissues of patients with AD (also activated by Aβ) [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 [RefSeq]. Recognizes *C. albicans* [190]. Higher fungal burdens for *C. neoformans* in MRC1 knockout mice [191]. | mRNAs for TNF, AGI, MRC1 and CHI3L1; CHI3L2 significantly increased in the AD frontal cortex [192] | |
| **TLR1 toll like receptor 1**  Recognizes peptidoglycan, a component of bacterial cell walls and acylated lipoproteins as a heterodimer with TLR2 [193,194]. Cotransfection of TLR2-TLR1 or TLR2-TLR6 required for the activation induced by *H. pylori* LPS [195]. *P. gingivalis* fimbriae use TLR1 or TLR6 for cooperative TLR2-dependent activation of transfected cell lines while the bacterial lipopolysaccharide prefers TLR1 [196]. TLR1/TLR2 dimers recognize *B. burgdorferi* [197]. 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). [198]. TLR1, 2, 4, and 6 recognize *C. albicans* and *C. neoformans* glucuronoxylomannan or glucuronoxylomannan [199]. TLR1, TLR2, and TLR6 recognize HSV-1 glycoprotein B [200]. TLR2/TLR1heterodimer is a functional sensor for HCMV [201]. TLR1, 2, and 6 involved in hepatitis C viral recognition [202]: TLR1/2 dimers recognize *B. burgdorferi* [197]. | Upregulated in the hippocampus [36] | |
| **TLR2 toll like receptor 2**  TLR2 and TLR4, acting via the adapter protein MyD88, signal responses to *Cryptococcus neoformans*, *Aspergillus fumigatus,* and *C.albicans* [203]. TLR2/TLR4 activated by *H. pylori* [204], HSV-1) and Listeria monocytogenes in microglial cells [205,206] Activated by *P. gingivalis* [207]. Stimulated by the hepatitis C core protein [208]. 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 *T. cruzi*, modulin from *Staphylococcus epidermis*, zymosan from fungi, glycolipids from *Treponema maltophilum*, and lipopolysaccharides preparations from *Leptospira interrogans*. Activated by *C. pneumoniae* which also activates TLR4 but to a lesser extent [209,210]. The production of tumor necrosis factor (TNF) α by macrophages in response to *T. gondii* lycosylphosphatidylinositols require the expression of both Toll-like receptors TLR2 and TLR4 [211]. Recognizes HCMV [201]. Epstein-Barr virus activates TLRs, including TLR2, TLR3, and TLR9 [212]. TLR1, 2,4 and 6 recognize *C. albicans* and *C. neoformans* glucuronoxylomannan or glucuronoxylomannan [199]. Induced and activated by influenza A in neutrophils [213]. | TLR2 and TLR4 expression are increased in AD peripheral blood mononuclear cells [214] | |
| **TLR3 toll like receptor 3**  Recognizes double stranded viral RNA [215]. Antiviral against HSV-1 and upregulated by the virus in neural stem cells, resulting in beta-interferon induction [216]. Recognizes Epstein-barr virus RNA [217], influenza A [218], and hepatitis C [219]. TLR3 and TLR4 activate cholesterol-25-hydroxylase (CH25H) producing 25-hydroxycholesterol [220], which along with 27-hydroxycholesterol (synthesized by cytochrome p450 CYP27A) inhibits the replication of enveloped and non-enveloped viruses [221]. TLR3 and TLR9 recognize HCMV [222], Recognizes *B. burgdorferi* [223]: TLR1/2, TLR3, TLR4, and TLR9 ligands stimulate the microglial phagocytosis of *C. neoformans* [224]. Activated by *C. albicans* [225] and *C. pneumoniae* [226]. | TRL3- and TLR8-expressing Monocytes/macrophages are increased in AD patients and in mild cognitive impairment [227]. 27-hydroxycholesterol levels are increased in the AD brain (late-onset AD) [228] and also in early onset AD patients with the Swedish APP 670/671 mutation [229]. CH25H expression upregulated in the AD hippocampus [36] | |
| **TLR4 toll like receptor 4**  Recognizes Lipopolysaccharide from *H. pylori* [204]. TLR1, 2, 4, and 6 recognize *C. albicans* and *C. neoformans* glucuronoxylomannan or glucuronoxylomannan[199]. Hepatitis C viral protein NS5A downmodulates NKG2D on natural killer cells via the TLR4 pathway [208]. TLR2 and TLR4 activated by HSV-1 in astrocytes [230]. *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 [231]. Senses the *C. pneumoniae* heat shock protein [232] and a bacterial phospholipase D [233]. Phagocytosis of *B. burgdorferi* by microglia increases expression of TLR1, 2, 4, and 5 [234]. Induced by HCMV [235]. TLR4, TLR7, TLR8, and RIG1 recognize influenza viruses in human lymphocytes [236]: Activated by *T. gondii* in macrophages [237]. | TLR2 and TLR4 expression are increased in AD peripheral blood mononuclear cells [214]. TLR4 expression increased in the AD brain in regions of Aβ deposition [238] | |
| **TLR5 toll like receptor 5**  Recognizes bacterial flagellin [239]. 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 [234]. *T. gondii*-derived profilin triggers human TLR5-dependent cytokine production [240]. HCMV infection potentiates TLR5 ligand-stimulated cytokine production [241]. *H. pylori* stimulates IL8 production via TLR2 and 5 [242] : increased in monocytes of hepatitis C-infected patients [243]: TLR2 and TLR5 expression increased by fungi in nasal polyp fibroblasts [244]. | Upregulated relative to aged controls in the AD hippocampus and superior frontal gyrus [245] | |
| **TLR7 toll like receptor 7**  Senses single stranded RNA viruses in endosomes [246]. 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 respiratory syndrome coronavirus), and flaviviruses (HCV, dengue virus, and West Nile virus) [247]. *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 [231]. *B. burgdorferi* induces the production of type I interferons by human dendritic cells via TLR7 and TLR9. TLR7 stimulates the expression of Epstein-Barr virus latent membrane protein 1in infected cells [248]. Epstein-Barr virus inhibits the stimulatory effect of TLR7/8 and TLR9 agonists in human B lymphocytes enabling evasion of the immune system [249]. Senses single stranded RNA from *C. albicans* [199]. Activated by *T. gondii* in mice [250]: Activated by the human cytomegalovirus or Epstein–Barr virus to increase B cell proliferation [251,252]. | Upregulated relative to aged controls in the AD superior frontal gyrus [245] | |
| **TLR8 toll like receptor 8**  An endosomal receptor that recognizes single stranded RNA viruses such as Influenza, Sendai, and Coxsackie B viruses. Activated by the Epstein-Barr virus. Also recognizes bacterial RNA from streptococci and Staphylococcus aureus [253-255]: Hepatitis C induces TNF in hepatocytes via TLR7, TLR8 [256] activated in human monocytic cells following *H. pylori* phagocytosis [257]. *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 [231]. Activated by *B. burgdorferi* RNA in the phagosome of human monocytes [258]. Upregulated by *C. pneumoniae* in monocytes [259]. | TRL3- and TLR8-expressing monocytes/macrophages are increased in AD patients and in mild cognitive impairment [227] | |
| **TLR9 toll like receptor 9**  Mediates cellular response to unmethylated CpG dinucleotides in bacterial DNA to mount an innate immune response [RefSeq]. Also responds to *T. gondii* CpG motifs [260]. TLR3, TLR7, TLR8, and TLR9 also detect distinct forms of viral nucleic acids [247]. TLR2, TLR3, and TLR9 activated by the Epstein-Barr virus [212].TLR2 and TLR9 protect against HSV-1 infection in the mouse brain [261]. Activated by human cytomegalovirus in plasmacytoid dendritic cells [262]. Activated by hepatitis C in murine microglial cells [263] . Blood TLR2, TLR3, TLR9 expression increased in the patients with influenza H1N1 2009 infection [264]. *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 [231]. Unmethylated CpG motifs in Toxoplasma gondii DNA induce TLR9- and IFN-β-dependent expression of DEFA5 in intestinal epithelial cells [260]. Upregulated in dendritic cells by *C. pneumoniae* nasal infection [265]. Recognizes fungal DNA from many species including *C. neoformans* and *C. albicans* [199]: *B. burgdorferi* induces the production of type I IFNs by human dendritic cells [266] through TLR7 and TLR9 signaling [266]:Activated by *H. pylori* [267]. | The rs187084 variant homozygote GG was significantly associated with a decreased AD risk in a Chinese study. This protective variant related to increased TLR9 expression in peripheral blood monocytes [268]. Transcription of TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, and TLR10 following Aβ stimulation is depressed in mononuclear cells of AD patients [269] | |
| **TLR10 toll like receptor 10**  Involved in the response to influenza infection [270]. A TLR2/TLR10 heterodimer functions in *H. pylori* lipopolysaccharide and Listeria monocytogenes recognition [271,272] . | Upon Aβ stimulation, AD PBMCs generally downregulated TLR ratios, whereas control PBMCs upregulated TLR ratios. TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, and TLR10 ratios exhibited the greatest difference between patients and control subjects [269] No data on basal expression | |
| **TREM2 triggering receptor expressed on myeloid cells 2**  Binds to *P. mirabilis* *S. pyogenes,* and *E. faecalis* and tobacterial lipopolysaccharide, peptidoglycan, or lipoteichoic acid: *E. coli* and *Staphylococcus aureus* bind specifically to TREM2- transfected cells [273]; also binds to cholera toxin [274]. TREM2 knockout mice are less able to defend against *Burkholderia pseudomallei*, a bacterium related to sepsis [275]. | High expression in laser-captured early-onset AD plaques [276]. mRNA expression increased in the AD hippocampus [277] and in leukocytes [278]. Increased protein expression in the AD temporal cortex [279] | |
| **AGER advanced glycosylation end product-specific receptor (more commonly known as RAGE)**  AGER(-/-) mice were relatively protected from influenza virus induced mortality showing improved viral clearance, enhanced cellular T cell response, and activation of neutrophils [280]. AGER activation enhances the ability of neutrophils to eradicate bacteria (*E. coli*) *in vitro* and *in vivo* via activation of NADPH oxidase [281]. Involved in the adhesion of *H. pylori* to gastric epithelial cells [282]. *P. gingivalis* infection enhances AGER expression in Murine aortic endothelial cells [283]. The Epstein Barr viral protein LMP1 binds to the AGER promoter [284]. | Increases in protein levels and in the percentage of AGER expressing microglia in the AD brain linked with disease severity [285]. Plasma protein levels increased in AD [286] but decreased levels of a soluble isoform [287,288] | |
| **APCS amyloid P component, serum**  Binds to several bacterial lipopolysaccharides (*S. pyrogens* and rough strains of *E. coli*) preventing complement activation [289]. Increased levels of APCS in the atherotic plaques of *C. pneumoniae* infected mice fed an atherogenic diet [290] . Binds avidly to *C. albicans* when amyloid is formed in fungal cell walls [291]. | 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 [292] | |
| **CHI3L1 chitinase 3 like 1 (aka YKL-40)**  CHI3L1 is induced by fungal infection (*C. albicans*) and induces *C. albicans* killing and the antimicrobial peptides beta-defensin 3 and cathelicidin (CAMP) [293,293]. In transgenic mice expressing the Epstein-Barr virus, LMP1 protein CHI3L1 is induced in the epidermis and is secreted and autoantibodies to CHI3L1 are generated [294]. | CSF levels of CHI3L1 are associated with AD [295-297]. Plasma levels are also increased and the protein is found in astrocytes near a subset of amyloid plaques [298] | |
| **CRP C-reactive protein, pentraxin-related**  Involved in several host defense related functions based on its ability to recognize foreign pathogens and damaged cells of the host [RefSeq]. High CRP levels observed in *H. pylori* and *C. pneumoniae* infection [299]. High antibody response to multiple pathogens (cytomegalovirus, herpes simplex virus-1, Hepatitis A virus, *H. pylori,* and *C. pneumoniae*) associated with CRP in atherosclerosis patients [300]. Antibodies to *P. gingivalis* associate with high levels of SAA and high concentrations of CRP in periodontitis patients [301]. Serum CRP elevated in fungal esophagitis or enterocolitis due to *C. albicans* [302]. 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 [303]. | High serum levels associated with AD (dependent on methodology) [304], but levels of CRP in a mild and moderate dementia subgroup were significantly lower than that in the control group [305]. A recently developed high-sensitivity (Hs) test reported high serum levels of Hs-CRP in AD patients[306]. CRP staining of the hippocampal CA1/2 region correlates with Aβ staining in the AD brain [307] | |
| **Viral detectors** |  | |
| **APOBEC1 apolipoprotein B mRNA editing enzyme catalytic subunit 1**  Induced in neurons by HSV-1 and produces antiviral effects via DNA editing of the viral genome [308]. Also inhibits Hepatitis C and HIV replication [309]. | mRNA upregulated in the AD hippocampus [36] | |
| **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 [310]. Binds to hepatitis C biotinylated RNA [311]. | Down regulated in the AD hippocampus [36] | |
| **DDX21 DEAD-box helicase 21**  DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense double stranded viral RNA in dendritic cells [310]. DDX21 inhibits replication of the influenza virus [312]. Interacts with a Borna virus protein [313]. | mRNA upregulated in the AD hippocampus [36] | |
| **DDX39A DEAD-box helicase 39A**  The UL69 gene product of the human cytomegalovirus belongs to a family of regulatory proteins conserved among all herpesviruses and binds to DDX39A [314]. Mx proteins exert their antiviral activity against the influenza virus by interfering with the function of the RNA helicases DDX39B and DDX39A [315] .Upregulated by *P. gingivalis* in smooth muscle cells [316]. | mRNA upregulated in the AD hippocampus [36] | |
| **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 [317]. Also a potential target of an Epstein-Barr viral microRNA [318]. | mRNA upregulated in the AD hippocampus [36] | |
| **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 [RefSeq]. DDX3, 5, and 6 play a role in hepatitis C and Influenza A viral replication [319,320]. | Down regulated in the AD hippocampus [36] | |
| **DDX58 DEXD/H-box helicase 58 (commonly known as RIG-1)**  Involved in viral double-stranded RNA recognition and the regulation of immune response [RefSeq]. Antiviral versus HSV-1, influenza, hepatitis C, and Epstein-Barr viruses [321-324]. mRNA upregulated in bone marrow stromal cells in response to *P. gingivalis* secreted product [72]. Upregulated by the cytomegalovirus, which also degrades DDX58 [325]. | Expression increased in the temporal cortex and plasma of mild cognitive impairment patients with pathologic evidence of senile plaques and neurofibrillary tangles. Primary human astrocytes stimulated with a DDX58 ligand showed increased expression of amyloid AβPP and Aβ id [326] | |
| **DDX6 DEAD-box helicase 6**  Controls gene expression in RNA viruses [327]. DDX3, 5, and 6 play a role in hepatitis C viral replication [319]. Binds to a Dengue virus RNA [328]. | mRNA upregulated in the AD hippocampus [36] | |
| **DHX58 DEXH-box helicase 58 (aka LGP2)**  Detects double stranded viral RNA and activates antiviral responses [329,330]. Recognizes hepatitis C [331] and certain strains of Influenza A [332]. | Upregulated in total brain and frontal lobe of AD patients [333] | |
| **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 inhibition of protein synthesis necessary for viral replication. Activation also results in the production of interferons alpha and beta [334]. Activated by lipopolysaccharide or bacterial RNA or by the mycotoxin deoxynivalenol, shiga toxin, and ricin [335-339]. Activated by HCMV, but the virus possesses proteins able to antagonize EIF2AK2 [340]. Activated by HSV-1 which is also able to evade EIF2AK2 activation [341]and by hepatitis C and influenza viruses [342]. Epstein-Barr virus-encoded small RNAs bind the protein PKR and inhibit its activation [343]. Also mediates anti-microbial activity against *T. gondii* [344]. | mRNA upregulated in the AD hippocampus [36] and CSF [345] and activated in AD lymphocytes [346]. High CSF levels correlate with a greater rate of cognitive decline in AD patients [345] | |
| **IFI16**  Senses nuclear viral DNA and activates the immune response and antiviral cytokine production [347]. Relevant to many viruses including, Epstein-Barr, HSV-1, human cytomegalovirus, Influenza A [348-350]. | mRNA upregulated in the AD hippocampus [36] | |
| **IFNA1 interferon, alpha 1**  The protein encoded by this gene is produced by macrophages and has antiviral activity [RefSeq]. Expression induced by *B. burgdorferi* [351] and HSV-1 [352]. | The NK cell activity induced by either interferon-alpha (IFN-alpha) or interleukin-2 (IL-2) in AD was also significantly lower than in the normal controls [353], white matter microglia were intensely labelled for IFNA1 [354] | |
| **IFNB1 Interferon beta 1**  Belongs to the type I class of interferons, which are important for defense against viral infections [RefSeq]. The Borna virus nucleoprotein inhibits type I IFN expression by interfering with the IRF7 pathway [355]. | Increased cytotoxic response by natural killer cells to IL-2 (mean increase +102%) and IFN-beta (mean increase +132%) in AD patients [356] | |
| **MX1 MX dynamin like GTPase 1**  The encoded protein is induced by type I and type II interferons and antagonizes the replication process of several different RNA and DNA viruses (Refseq), including influenza, hepatitis C [357,358], human cytomegalovirus and HSV-1[359]: Also activated by *B. burgdorferi* DNA or RNA in mice [360] | High protein expression in reactive microglia, including those on senile plaques [354] | |
| **RARRES3 retinoic acid receptor responder 3**  Viral RNA detector (HSV-1, Influenza A, Hepatitis C, and Epstein-Barr) [324,361-367]. | mRNA upregulated in the hippocampus [36] | |
| **Sirtuins: All 7 sirtuins (SIRT1-7) have broad spectrum antiviral activity against DNA and RNA viruses (HSV-1 (sirt 1,2,4,5,6), cytomegalovirus (all sirtuins), adenovirus (all sirtuins) and influenza A (all sirtuins) [368]** | | |
| **SIRT1**  Upregulated by hepatitis C core protein in HepG2 cells [369] and by *P. gingivalis* lipopolysaccharide in in human periodontal ligament cells [370]. | | Decreased protein expression in AD blood and in the AD parietal cortex[371,372] : Decreases protein expression in the hippocampus, entorhinal cortex (localized in neurons) [373]. mRNA upregulated in peripheral blood mononuclear cells of an AD positive identical twin and not in the unaffected twin [374] |
| **SIRT2** | | mRNA upregulated in the hippocampus [36], rs10410544 C/T SIRT2 polymorphism associated with AD (meta-analysis) [375] |
| **SIRT3** | | mRNA expression increased in the AD temporal cortex [376] |
| **SIRT4** | | ? |
| **SIRT5** | | Expression increased in parallel with AD expression (entorhinal cortex and hippocampus), possibly reflecting a microglial location [373] |
| **SIRT6** | | mRNA upregulated in the hippocampus [36], but downregulated in the hippocampus and temporal cortex in another study [377] |
| **SIRT7** | | mRNA upregulated in the hippocampus [36] |
| **Tripartite motif-containing proteins**  tripartite motif-containing proteins play key roles in antiviral immunity - either as viral restriction factors or as regulators of pathways downstream of viral RNA and DNA sensors, and the inflammasome [378]: Lipopolysaccharide or TLR3/4 ligands also stimulate the expressions of TRIM14, 15, 31, 34, 43, 48, 49, 51. and 61 mRNA in macrophages [379]. | | |
| **TRIM14 tripartite motif containing 14**  Mediates the antiviral response via the retinoic acid-inducible gene-I-like pathway [380]: Inhibits hepatitis C infection and replication [381]. Involved in antiviral response to HSV-1 [382]. | Expression increased in the AD hippocampus [36] | |
| **TRIM26**  Regulates innate immune responses against RNA viruses and to bacterial Lipopolysaccharide [383,384]. | Expression increased in the AD hippocampus [36] | |
| **TRIM32**  Senses and counters influenza virus infection by limiting viral replication [385]. | Expression decreased in the AD hippocampus [36] | |
| **TRIM37**  Antiviral against HIV-1 [386]. | Expression decreased in the AD hippocampus [36] | |
| **TRIM38**  Essential for cytosolic RNA or DNA sensor-mediated innate immune responses to both RNA and DNA viruses [387]. | Expression increased in the AD hippocampus [36] | |
| **TRIM44**  Promotes an antiviral response by stabilizing the mitochondrial antiviral signaling protein (MAVS) [388]. | Expression increased in the AD hippocampus [36] | |
| **TRIM68**  Turns off and limits type I IFN production in response to anti-viral detection systems [389]. | Expression increased in the AD hippocampus [36] | |
| **ZBP1 Z-DNA binding protein 1**  Plays a role in the innate immune response by binding to foreign DNA and inducing type-I interferon production. [RefSeq]. Recognizes foreign DNA in the cytosol and inhibits HSV-1 replication[390]. HCMV induces the interferon response via ZBP1[391]. | ZBP1 was identified as an AD susceptibility gene using hippocampal atrophy as a quantitative trait [392] | |
| **ZC3HAV1 zinc finger CCCH-type containing, antiviral 1**  Overexpression of ZC3HAV1 produces a cellular antiviral state against Retroviridae, Togaviridae (e.g.S, indbis virus, Semliki Forest virus, Ross River virus, and Venezuelan equine encephalitis virus, and Filoviridae virus (e.g., Ebolavirus, Marburg virus) family members and the influenza virus, but not against HSV-1, which degrades ZC3HAV1 mRNA.[393-395]. Upregulated by the human cytomegalovirus [396]. Expression increased by C.Pneumoniae in epithelial HeLa cells [397]. | Expression increased in the AD hippocampus [36] | |
| **Oxysterols**  Chlolesterol-25- hydroxylase (CH25H) is an interferon stimulated gene that converts cholesterol to 25-hydroxycholesterol which has antiviral properties against enveloped viruses including HSV-1 and HIV [398] and against non-enveloped viruses including the human papillomavirus-16, 25-hydroxycholesterol inhibits in vitro infection of airway epithelial cells by influenza [399]. 27-hydroxycholesterol (synthesized by CYP27A1), and to a lesser extent 7α-hydroxycholesterol, 7β-hydroxycholesterol, and 7-ketocholesterol also have antiviral activity against these non-enveloped viruses [400]. CH25H expression in macrophages and dendritic cells is rapidly induced by the Toll-like receptor ligands poly I:C and lipopolysaccharide [220]. CYP27A1 is also upregulated by lipolysaccharide in macrophages [401].CH25H is activated by the hepatitis C virus and also inhibits viral replication by binding to the viral NS5A protein [402]. EBI2, a gene induced by the Epstein-Barr virus is an oxysterol receptor that regulates chemotaxis of B cells in lymphoid tissues [403]. | CH25H expression increased in the AD hippocampus [36].In postmortem frontal and occipital AD cortex, the levels of many antiviral oxysterols including 25- and 27–hydroxy cholesterol, 7α-and 7β-hydroxycholesterol and 7-ketocholesterol increase in line with the progression of AD. CYP27A1 expression is also increased in these AD samples [404]. 27-hydroxycholesterol levels are also increased in the frontal cortex, occipital cortex, basal ganglia, and pons in AD [228] | |
| **General Phagocytic and other immune host defense** | | |
| **CR1 Complement receptor 1**  Complement fragments (opsonins; C1q, C3b, and iC3b) interact with complement cell-surface receptors (C1qRp, CR1, CR3 (a dimer of integrins ITGAM/ITGB2) and CR4 (dimer of integrins ITGAX/ITGB2) to promote phagocytosis and a local pro-inflammatory response [405]. CR1, 3, and 4 bind opsonzsed *C. neoformans* [406]. CR1, CR3 phagocytose opsonized *C. albicans* [407]. HSV-1 binds to CR1 [408]. *H. pylori* and *P. gingivalis* LPS-induced vascular cell activation is mediated through TLR1, 2, CD36, and CR3 [157]. | CR1 expression increased in the AD hippocampus [36] and parietal cortex [409]: Microglial in and around amyloid plaques express class II major histocompatibility (MHC) antigens and complement receptors CR3 and CR4 [410] | |
| **Complement receptor 3 (ITGAM/ITGB2)**  Complement receptor CR3 mediates the phagocytosis of complement C3-coated particles. Involved in *B. burgdorferi* or *C. neoformans* phagocytosis [411,412]. Involved in *C. albicans* killing [413]: dendritic cell CR3 presents class I-restricted antigens after lung infection with influenza or HSV-1 [414]. Binding of *P. gingivalis* fimbriae to CXCR4 induces CR3 activation [415]. CR3 and CR4 are in contrast downregulated by the human cytomegalovirus as an avoidance strategy [416]. | Increased levels of microglial CR3 in amyloid plaques in AD and in reactive microglia [417,418] | |
| **Complement receptor 4 (ITGAX/ITGB2)**  CR3 and CR4 mediated migration of monocytes across human umbilical endothelial cells exposed to *B. burgdorferi* [419]. ITGB2 is a receptor for the *H. pylori* VacA toxin [420]: ITGAX limits HSV-1 infection [421]. | Microglial cells in and around amyloid plaques express class II major histocompatibility (MHC) antigens and complement receptors CR3 and CR4 [410] | |
| **Fc receptors**  Bind to antibodies that are attached to infected cells or invading pathogens [422]. | Fc gamma RI, II and III detected by immunoreactivity in control and AD microglia throughout the brain and in AD senile plaques: [423] . FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa expression increased in AD microglia [424] | |
| **IDO1 indoleamine 2,3-dioxygenase 1**  Catalyses the production of N-formylkynurenine from tryptophan. Expression is stimulated by interferon gamma and other inflammatory cytokines. 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 [425]. Diversion to the kynurenine pathway also produces metabolites activating the aryl hydrocarbon receptor which also plays a role in antimicrobial defense and immune activation. This pathway is relevant to anti-bacterial and antiviral effects [426]. Involved in *C. albicans* defense [427] and in the response to *B. burgdorferi* [266]. Restricts *C. pneumoniae* replication in dendritic cells [428]. Induced by HSV-1 [429], Bornavirus, Influenza, and hepatitis C infection [430-432]. IDO1 activation restricts HCMV replication, but the virus is able to counteract this block [433]. Expression increased by a DPG3 strain of *P. gingivalis* [434]. Activated by *T. gondii* infection in the mouse spleen [435]. Induced by the Epstein-Barr virus in human macrophages [436]. | IDO1 expression is increased in the AD hippocampus and is associated with amyloid plaques and neurofibrillary tangles. Quinolinic acid immunoreactivity is localized in microglial and astrocytic cells around amyloid plaques and in the vicinity of neurofibrillary tangles [437-439] | |
| **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 [RefSeq]. A *P. gingivalis* protease (gingipain) cleaves interleukin-12, reducing its ability to stimulate IFNG production [440]. Upregulated in the brains of Borna virus infected cats [441]. | Increased spontaneous and IL-2-induced release of IFN-gamma and TNF-alpha from natural killer cells were found in AD patients compared to healthy subjects [442]. 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 mild cognitive impairment [443]. Increased IL2 and IFNG secretion from mononuclear cells observed in AD patients in the moderately severe stage of the disease [444]. CSF interferon γ was only detected in cytomegalovirus seropositive subjects and was significantly associated with neurofibrillary tangles [445]. Higher levels of IL-6 and IFN-γ were found more in the cultured T lymphocytes of the AD patients [446]. IFNA5 and IFNG mRNA upregulated in the AD hippocampus [36]. Infectious burden and IFNG levels associated with AD (HCMV, HSV-1, *B. burgdorferi*, *C. pneumoniae,* and *H. pylori*) [447] | |
| **NAIP NLR family, apoptosis inhibitory protein**  Senses bacterial flagellin [448] and type III secretion system needle proteins from several bacterial pathogens, including Salmonella typhimurium, Escherichia coli, Shigella flexneri, and Burkholderia species [449]. Inhibits Legionella pneumophila infection [450]. | Decreased mRNA expression in the entorhinal cortex correlating with Braak stage [407,451] | |
| **NLRP1 NLR family pyrin domain containing 1**  Activated by Bacillus anthracis lethal toxin, *T. gondii*, muramyl dipeptide (a constituent of both Gram-positive and Gram-negative bacteria) [452]. NLRP1 and NLRP3 both activated by T.Gondii [453]. NLRP1 expression increased by *B. burgdorferi* in human dermal fibroblasts [454]. | 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 [455] | |
| **NLRP3 NLR family pyrin domain containing 3**  Activated by Staphylococcus aureus, *C. albicans* and the influenza virus as well as Aβ [456]. Activated by *C. neoformans* [457], *C. pneumoniae* [458], *H. pylori* [459] and by *P. gingivalis* LPS [460]. Activated and subsequently inhibited by HSV-1 [461]. Activated by the Hepatitis C virus [462] and by the Influenza a virus in dendritic cells [463]. An Epstein-Barr virus micro RNA can be secreted from infected B cells via exosomes to inhibit the NLRP3 inflammasome [464]. | The NLRP1 and NLRP3 inflammasomes are both activated in AD monocytes [455] | |

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