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The Role of Innate Immunity in Alzheimer's Disease

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Abstract

The amyloid hypothesis has dominated Alzheimer's disease (AD) research for almost 30 years. This hypothesis hinges on the predominant clinical role of the amyloid beta (Aβ) peptide in propagating neurofibrillary tangles (NFTs) and eventual cognitive impairment in AD. Recent research in the AD field has identified the brain resident macrophages, known as microglia, and their receptors as integral regulators of both the initiation and propagation of inflammation, Aβ accumulation, neuronal-loss, and memory decline in AD. Emerging studies have also begun to reveal critical roles for distinct innate immune pathways in AD pathogenesis, which has led to great interest in harnessing the innate immune response as a therapeutic strategy to treat AD. In this review, we will highlight recent advancements in our understanding of innate immunity and inflammation in AD onset and progression. Additionally, there has been mounting evidence suggesting pivotal contributions of environmental factors and lifestyle choices in AD pathogenesis. Therefore, we will also discuss recent findings suggesting that many of these AD risk factors influence AD progression via modulation of microglia and immune responses.

Keywords

amyloid beta; Alzheimer's disease; microglia; neurodegenerative disease; neuroimmunology; TREM2

INTRODUCTION

AD pathology:

Alzheimer's disease (AD) is a neurodegenerative disease characterized by neuronal loss, neuroinflammation, and pronounced memory decline.[1,2] Risk factors for developing this neurodegenerative disease include age, genetics, sex, brain injury, and various environmental

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COMPETING INTERESTS

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factors.[3] Regardless of origin, neuropathologies consistent among AD patients are amyloid beta (Aβ) and neurofibrillary tangle (NFT) deposition.[4] Aβ can deposit in the brain decades prior to clinical symptom onset and stimulate other AD pathologies such as hyperphosphorylated tau (p-Tau) aggregation which triggers subsequent NFTs and neuronal death.[5–9] These NFTs can mediate neuronal damage that propagates mild cognitive impairment (MCI) and dementia.[10] Given that Aβ accumulation precedes NFT formation and memory decline by many years, the focus on Aβ production has dominated AD research.[10] Aβ is a cleavage product of amyloid precursor protein (APP).[11] APP cleavage can follow two pathways: amyloidogenic and nonamyloidogenic. The former has a cleavage event spurred by β-secretase and γ-secretase to produce neurotoxic Aβ, while the latter undergoes APP cleavage by α-secretase and γ-secretase to generate distinct products, some of which have important neuroprotective functions.[11,12]

The Aβ peptide can act as a building block to produce several distinct higher-order forms of Aβ, some of which are more neurotoxic than others.[11] For instance, monomers of Aβ peptide can accumulate to form oligomers that can travel throughout the brain and constitute the soluble fraction of Aβ levels in the AD brain.[11] Aβ oligomers are the most toxic form of Aβ and have been shown to incite synaptic dysfunction and neuronal cell death signaling.[13] Aβ oligomers can seed Aβ fibrils to promote the formation of Aβ aggregates known as “plaques”.[14] Monomers of the Aβ peptide can have varying lengths depending on their cleavage.[11] However, Aβ42 and Aβ40 are the most prevalent in AD pathogenesis, with Aβ42 being more likely to incorporate into Aβ aggregates.[15] AD brains are also marked by dystrophic neurites.[16] Dystrophic neurites exhibit axonal transport defects and are often found surrounding Aβ plaques.[4] Recent evidence suggests that dystrophic neurites can directly contribute to AD pathology propagation by promoting β-secretase-mediated cleavage of APP and subsequent Aβ peptide generation.[17]

Biomarkers:

The identification of biomarkers relating to AD risk and pathology prior to clinical onset has become an important area of focus in hopes of manipulating AD onset and progression. For decades, the diagnosis of AD relied on post-mortem brain histological assessment to identify Aβ and NFT pathologies. However, recent technological advancements in genetic testing, PET imaging, and sampling of the cerebrospinal fluid (CSF) and blood have opened doors to the possibility of earlier AD diagnosis. There is great hope that the identification of reliable AD biomarkers will move the field toward preventative medicine; however, continued progress on this front is needed to make this a reality.

There are two classifications of AD based on disease origin and onset: (1) early-onset AD (EOAD) (also known as familial AD or FAD) and (2) late-onset AD (LOAD). EOAD accounts for 5% of all AD cases and is primarily caused by mutations in APP, presenilin-1 (PSEN1), and presenilin-2 (PSEN2), all of which can lead to elevated levels of total Aβ and increased production of Aβ40 and Aβ42.[18,19] EOAD often occurs in individuals younger than 65 years of age.[20] In contrast, the origin of LOAD is linked to an interplay between genetic mutations, environment, and neuroinflammatory responses.[21] Interestingly, many of the mutations linked to LOAD risk are known to affect innate immune signaling pathways

(Table 1). The most common variant associated with LOAD risk is apolipoprotein E gene (APOE) ε4 allele.[18] APOE has three isoforms which include ε2, ε3, and ε4, with ε4 being the allele exerting the greatest AD risk.[22] In homeostasis, APOE is synthesized for lipid transport.[23] However, during stress, APOE ε4 is markedly more susceptible to proteolytic cleavage to generate products that promote NFT formation and mitochondrial dysfunction, both of which can contribute to AD progression.[23] In addition, APOE has been reported to promote Aβ aggregation and is often found in large quantities within Aβ plaques, further implying its role in AD pathogenesis.[24,25] Patients with the APOE ε4 allele are at 3-times higher risk for developing AD.[22] The combination of APOE ε4 and chronic inflammation further increases risk for these carriers, emphasizing an important link between genetics and inflammation in AD risk.[26] LOAD is also associated with mutations in receptors expressed by microglia, the brain's resident immune cells.[27] Recent research shows that multiple microglial receptors are critically involved in Aβ clearance and that mutations in multiple microglial immune receptors dramatically increases the risk for LOAD.[27]

Diagnosing AD in patients has become amenable with the use of positron emission tomography (PET) imaging of Aβ and tau in the brain.[28] PET imaging is able to detect high levels of Aβ in the brains of patients with cognitive impairment, allowing for highly sensitive diagnosis of AD.[29–31] In addition, the detection of tau using PET has also proven to aid in the tracking of AD progression.[28,32] An early diagnosis of AD is also made possible with PET imaging of the initial inflammation of disease, which is often characterized by microglial activation.[33] Biomarkers in the CSF and blood are also used to diagnose and detect AD progression.[34] CSF markers include levels of Aβ and tau, with AD patients presenting with a decrease in Aβ42 and a significant increase in phosphorylated and total tau.[35,36] Blood is an alternative medium to measure for AD biomarkers, and is especially attractive due to its low invasiveness and medical cost.[37] Blood biomarkers for AD include decreased levels of Aβ42, a lower Aβ42:Aβ40 ratio, and increased tau.[37] In addition, the level of neurofilament light chains (NfLs) is another blood marker for AD.[38] Increased levels of NfLs in the blood is distinct in EOAD patients prior to symptom onset, and changes in NfL levels are often greatest when AD patients transition from the presymptomatic to symptomatic stages of AD.[38] Therefore, NfLs can be used to predict AD onset and track its progression in a non-invasive manner.

Innate immune function of AD pathologies:

While numerous physiological functions have been assigned to Aβ and tau, there is still a general lack of consensus as to what roles these AD-related molecules play in homeostasis. Interestingly, it has recently been proposed that Aβ may help provide protection against pathogens by functioning as an antimicrobial peptide (AMP) (Fig. 1).[39] Such studies demonstrate that Aβ oligomers are critically involved in limiting both fungal and bacterial infections in cell culture, *C. Elegans,* and mice.[40] Additionally, bacterial infections have been shown to incite the seeding of Aβ in the 5xFAD AD mouse model.[40] Aβ's AMP function may explain why the peptide has been conserved across a breadth of species for hundreds of millions of years.[41] Further implicating Aβ in the innate immune response is the finding that certain microorganisms' cell membranes are covered with amyloid-like fibrillous structures.[42] Bacteria with these amyloid structures, also known as curli fibrils,

present a pattern recognized by receptors on immune cells to initiate signaling to remove these invaders.[43,44] A similar response is elicited when Aβ itself is recognized by microglial pattern recognition receptors (PRRs) in the brain.[45] Unfortunately, chronic innate immune activation augmented by sustained Aβ recognition provokes subsequent inflammation that can lead to further propagation of AD pathologies and neurodegeneration.[2,46]

Although the explicit link between Aβ-seeding and tau accumulation has remained elusive, recent research has begun to shed light on this topic.[5] For instance, it has been demonstrated that Aβ-induced dystrophic neurites accumulate endogenous tau that eventually form into neurofibrillary tangles that correlate with cognitive deficits.[5] In homeostasis, endogenous tau participates in the assemblage and stabilization of microtubules in neurons, and, as a result, tau is believed to play functionally important roles in neuronal transport.[47] However, the detachment of tau from microtubules and hyperphosphorylation of tau can incite aberrant microglial activation and proinflammatory cytokine production.[48] This feedback drives further production of pathogenic tau to enter a cycle that perpetuates its overproduction and neurotoxicity.[48] Interestingly, herpes simplex virus (HSV-1), which infects two-thirds of the global population, has been shown to phosphorylate tau.[49,50] In accordance with this finding, antiviral medication has been reported to decrease phosphorylated tau accumulation and Aβ load.[51] A clinical trial is currently investigating the efficacy of the antiviral drug valacyclovir for AD patients with HSV-1 or HSV-2.[52] This further suggests a link between both neuropathologies of AD and the innate immune response that requires further exploration.

The role of microglia in homeostasis and AD: As current AD research acknowledges the role of the innate immune response and neuroinflammation in driving neurodegenerative disease, microglia have taken center stage.[53] Mounting research suggests that LOAD is, at least in part, mediated by the failure of microglia to properly clear Aβ.[54] In fact, frequent variants identified with genome-wide association study (GWAS) in AD patients link mutations in microglia pattern recognition receptors (PRRs) with disease risk.[55] Despite microglia being integral for proper phagocytosis and degradation of Aβ, their chronic activation can also provoke maladaptive neuroinflammatory responses with the potential to propagate Aβ production and neuronal distress.[56] This has sparked controversy over the enigmatic roles of microglia in AD[56–58], which will be discussed in greater detail throughout this review.

During development, microglia arise from progenitor cells originating in the yolk sac before populating the brain.[59] In homeostasis, microglia have been shown to undergo self-renewal to maintain their numbers in the central nervous system (CNS).[59] Microglia act as innate immune sentinels of the brain parenchyma, and perform classical macrophage functions such as coordinating phagocytic disposal of debris and inflammatory cytokine production.[60] However, microglia have additional functions in neurogenesis, blood-brain barrier (BBB) permeability, vasculogenesis, myelination, synapse pruning, and neuronal connectivity.[60] Microglial morphology transforms during activation, going from a highly branched or “ramified” state during homeostasis to an “ameboid” activated state in response to infection, injury, protein aggregate deposition, and other overt activators of innate immune signaling.[61] Microglia express a repertoire of cell surface receptors known as PRRs that enable them to

sense and respond to a diverse array of immunostimulatory triggers in the CNS.[62] Microglia associated with disease are commonly found to be in an activated state and upregulate PRR expression.[63] Accordingly, microglia are capable of sensing endogenous damage/danger-associated molecular patterns (DAMPs) as well as exogenous pathogen-associated molecular patterns (PAMPs).[62] Microglia can also sense neurodegeneration-associated molecular patterns (NAMPs) that are generated in AD and other forms of neurodegenerative disease.[64] In turn, the heterogeneity of microglia populations based on activation state and cell surface receptor expression has piqued interest in their distinct roles in health and disease.

Microglia receptors implicated in AD:

TREM2 -—One of the best-characterized microglia PRRs involved in AD is triggering receptor expressed on myeloid cells 2 (TREM2) (Fig. 2). TREM2 engages with DAP12 as an adaptor protein, and upon TREM2 activation, the phosphorylation of the DAP12 immunoreceptor tyrosine-based activation motif (ITAM) is stimulated, leading to the recruitment of spleen tyrosine kinase (SYK) to these sites.[65] Engagement of the TREM2 receptor is believed to stimulate pathways responsible for cytoskeletal reorganization, myeloid cell survival, phagocytosis, and the production of pro-inflammatory cytokines.[65] The rare Arginine-47-Histidine (R47H) mutation of TREM2 significantly increases LOAD risk.[66,67] This R47H mutation is thought to contribute to AD risk by limiting proper TREM2-mediated sensing of lipids by microglia.[68] TREM2 recognizes Aβ, lipids released from damaged neurons, and the Aβ chaperone APOE in AD.[68–70] Activation of TREM/DAP12 signaling limits Aβ accumulation and other harmful forms of AD pathology, as well as modulates cytokine production.[65] Therefore, disruption of TREM2/DAP12 signaling can markedly contribute to the progression of Aβ pathology in AD.[65] An additional mechanism by which TREM2 limits Aβ pathology is by promoting plaque compaction.[71] Plaque morphology is dynamically regulated by microglia, with less-compacted and fibrillous plaques being more neurotoxic than compact plaques.[72] Microglia function as a physical barrier to protect neurons from the neurotoxicity of Aβ plaques and curtail further Aβ seeding.[72,73] Such studies suggest that the loss of *Trem2* function impairs microglial sensing of Aβ, leading to defective Aβ clearance, increased Aβ plaque toxicity, and neuronal dystrophy in 5xFAD mice.[68,71]

Patients with the *TREM2* R47H mutation and mice with *Trem2* deficient microglia also present with enhanced autophagy stemming from the dysregulation of the mammalian target of rapamycin (mTOR) signaling.[74] This amplification of autophagy impairs microglial response to Aβ and suggests that TREM2 also regulates AD pathology through the maintenance of proper microglial metabolism.[74] Recent studies also show that genetic ablation of TREM2 in APPPS1 AD mice (APPPS1; $Trem2^{-/-}$) and loss-of-function *TREM2* mutations in humans both result in reduced association of APOE with Aβ plaques.[75] As a result, these APPPS1; $Trem2^{-/-}$ mice have increased seeding of Aβ compared with APPPS1 controls.[75] Microglia depletion was also found to significantly reduce APOE levels that were associated with Aβ plaques, which further implicates a TREM2-APOE pathway in microglia.[75] Interestingly, crosstalk between TREM2 and APOE has also been reported to promote a transcriptional shift in microglia during AD, which can further propagate neuronal loss.[76]

Recent studies also suggest the proteolytic cleavage of TREM2 and the subsequent secretion of soluble TREM2 (sTREM2) can ameliorate AD-related disease progression in mouse models. sTREM2 is found at higher levels in the CSF of AD patients, and as such, has been proposed as a potential future biomarker for disease.[77] The supplementation of sTREM2 into the brain of 5xFAD mice influences microglia signaling to improve Aβ clearance preventing further neuritic dystrophy while promoting microglia proliferation and migration.[78] Continuation of sTREM2 supplementation, using an adeno-associated virus (AAV) mediated expression technique, was also found to rescue memory and long-term potentiation (LTP) deficits seen in the 5xFAD mice.[78] Overall, these studies implicate beneficial roles for TREM2 in the context of proper Aβ sensing and clearance.

CD33 & CD22 -—Microglial sialic-acid binding immunoglobulin-like lectin (Siglec) receptors have also been shown to play important roles in AD and aging. For instance, CD33, also known as Siglec-3, is another microglial receptor implicated by GWAS in AD risk.[79] CD33 binds the sialic acids found ubiquitously on cell membranes.[80,81] In addition, sialic acids are also decorated on the glycoproteins and glycolipids found in Aβ plaques, and can, therefore, stimulate CD33 signaling in the AD brain.[80] However, in contrast to TREM2 which signals utilizing ITAMs, CD33 has intracellular immunoreceptor tyrosine-based inhibitory motifs (ITIMs).[80] The phosphorylation of ITIMs promotes the docking of Src homology 2 domain-containing phosphatases (SHPs) to inhibit downstream microglial signaling mediated by ITAMs that would have otherwise led to the removal of Aβ in the brain parenchyma.[80] The CD33 *rs3865444*^{C} AD risk allele leads to increased CD33 receptor expression which results in impaired Aβ42 phagocytosis.[82] Increased expression of *CD33* is significantly associated with a higher clinical score in AD patients and elevated AD pathology.[83,84] Further implicating CD33 in AD risk, 5xFAD mice lacking *Cd33* (5xFAD;*Cd33*$^{-/-}$) have decreased Aβ burden and improved memory compared with *Cd33* sufficient 5xFAD mice.[85]

More recent studies demonstrate that like CD33, CD22 (also known as Siglec-2), can also hinder microglial phagocytosis in aging and models of AD.[86] For instance, *Cd22* is found upregulated in aged microglia, and antibody-mediated blockade was shown to increase Aβ clearance.[86] In addition, microglia in aged mice take on an age-related transcriptional profile that under continued inhibition of *Cd22*, is reverted to a more homeostatic state.[86] The inhibition of *Cd22* also ameliorates age-related cognitive decline.[86] In summary, both CD33 and CD22 are negative regulators of microglial phagocytic functions in AD that have emerged as attractive therapeutic targets.

CLEC7A -—Recent studies have shown that the receptor CLEC7A, also known as Dectin-1, is dynamically upregulated by microglia in AD, particularly in microglia in intimate contact with Aβ plaques.[76] CLEC7A has been best described in fungal infections where it has been shown to coordinate cytokine production and phagocytosis.[87] Similar to TREM2, CLEC7A signals through its intracellular ITAM.[87] Although the exact role of CLEC7A in AD still remains to be determined, emerging evidence indicates that changes in microglial *Clec7a* expression are associated with AD progression.[76] In fact, increased microglial *Clec7a* expression is a hallmark of numerous neurodegenerative disorders and

aging.[63] Interestingly, multiple human studies have begun to link fungal infections with AD. This work has identified that fungi can be detected in the brains of AD patients.[88–90] Levels of chitinase, the enzyme that breaks down chitin found in fungal cell walls, have also been reported to be elevated in the CSF of AD patients.[91] This has led to growing speculation that during CNS fungal infections, neuroinflammatory responses and Aβ production are mounted to protect the brain from the fungal pathogens.[92] However, the downside of this is that it may inadvertently set AD pathology in motion. The essential role that CLEC7A is known to play in numerous fungal infections coupled with the pronounced upregulation of microglial CLEC7A expression observed in AD progression, points toward a potentially important role for CLEC7A in AD. However, additional studies probing the specific involvement of CLEC7a in AD pathogenesis are needed.

RAGE –—The binding of Aβ to the microglial receptor of advanced glycosylation end products (RAGE) stimulates NF-kB activation resulting in increased production of pro-inflammatory cytokines.[93] RAGE is a PRR found on many immune cells that can be upregulated in response to increased ligand production during injury, aging, and neurodegeneration.[94,95] In addition to being a potent inducer of NF-kB signaling and downstream inflammation, RAGE has also been shown to promote microglial survival and proliferation in a MAPK-dependent fashion.[95,96] In the context of neurodegenerative disease, overexpression of RAGE in the mAPP AD mouse model triggers IL-1β and TNF-α production.[97] RAGE has also been reported to instigate Aβ accumulation in the brain by aiding in the transport of Aβ across the BBB and into the brain.[98] Additionally, RAGE signaling in microglia can incite Aβ accumulation and amplify memory deficits.[97] The exaggerated inflammation incited by this Aβ and RAGE interaction can compromise neuronal health and in turn, negatively affect memory in AD mouse models.[93] Despite increased RAGE expression found in the brains of AD patients, clinical trials targeting RAGE have yielded underwhelming results.[99,100]

Complement associated receptors: CR3 and C1qR -—CR3 and C1qR are microglial receptors that can coordinate deleterious synapse pruning in AD.[101] The complement receptors CR3 and C1qR are activated by the complement cascade proteins C3 and C1q, respectively.[101] In homeostatic neurodevelopment, C3 and C1q contribute to proper synapse pruning and are required to sculpt healthy synaptic connections.[102] In contrast, reactivation of C3 and C1q signaling during aging is believed to cause detrimental synapse loss in the hippocampus, the brain structure critical for learning and memory.[103,104] In fact, aged C3-deficient mice exhibit decreased synapse loss, reduced neuronal loss, and improved memory compared with age-matched WT controls.[103] In the context of AD, genetic ablation of C3 in APPPS1 AD mice results in reduced synapse loss, lower numbers of microglia interacting with Aβ plaques, and improved behavior despite increased Aβ load.[105] However, CR3 deficiency in APP AD mice has been shown to limit Aβ levels by a mechanism involving increased expression of proteolytic enzymes that are known to breakdown Aβ in the extracellular compartment.[106] In turn, the presence of C3 or CR3 in WT mice actually enhances Aβ42 fibrillar phagocytosis.[107] These findings suggest enigmatic roles for CR3 in modulating the AD brain environment, which are likely impacted by the kinetics and model of disease.

Recent studies demonstrate that microglial-derived C1q is typically found to be elevated in the hippocampus of aged mouse brains and AD human brains.[104,108,109] C1q tags synapses that are meant to be eliminated by microglia.[110] However, C1q-mediated synaptic tagging and subsequent microglial clearance can result in synapse loss in the hippocampus, specifically to the engram cell synapses, which are known to be involved in memory storage.[110] Interestingly, the deletion of microglia, impairments in microglial phagocytosis, and inhibition of the complement pathway have all been shown to block this synapse loss and preserve memory in mice.[110] Collectively, this illustrates that complement signaling regulated by microglia is needed to ensure proper synapse formation in neurodevelopment. However, unchecked activation of this pathway can propagate aberrant synapse loss and contribute to subsequent aging-induced memory decline and AD-associated phenotypes in mouse models.

Microglial clearance of Aβ and tau:

Clearance of AD pathology by microglia is executed by several discrete processes. These include receptor-mediated phagocytosis and endocytosis, expression of degradative factors, extracellular chaperone-mediated clearance, and induction of autophagy.[111] Each mechanism allows for homeostatic maintenance of the brain parenchyma, and can potentially be targeted to ameliorate Aβ and tau accumulation in disease.

Clearance by phagocytosis and endocytosis ––Microglial phagocytosis and endocytosis is a critical method of Aβ clearance, and as a result, there has been tremendous interest in targeting these processes to treat AD. Receptors that mediate this form of clearance include TREM2, toll-like receptors (TLRs), scavenger receptors, and Fc receptors (FcRs) (Fig. 2).[111] In recent years, TREM2 has emerged as a major mediator of Aβ endocytosis. Details regarding how TREM2 mechanistically coordinates endocytic clearance of Aβ can be found earlier in the review. TLRs are most highly expressed by microglia in the brain. Microglial TLRs have been reported to bind oligomeric and fibrillar forms Aβ and this is thought to initiate a signaling cascade that promotes subsequent phagocytic clearance of Aβ.[112] Consistent with this idea, genetic deletion of TLR2 and TLR4 in transgenic mouse models of AD has been shown to promote increased Aβ deposition and this is generally believed to result from deficits in phagocytosis.[113,114] TLR co-receptors including the TLR4 coreceptor and LPS detector CD14 have also been implicated in AD.[115] In a similar fashion to TLRs, CD14 is thought to orchestrate the phagocytosis of fibrillar Aβ.[116] The endocytosis of Aβ in both fibrillar and oligomeric forms can also be stimulated by class A and class B scavenger receptors. For example, the scavenger receptors CD40 and CD36 have been described to initiate Aβ endocytosis.[111]

Lastly, Aβ plaques that have been bound by either host-derived or engineered anti-Aβ antibodies can be phagocytosed following engagement of FcRs on microglia.[117] Engineered anti-Aβ antibodies and vaccine strategies that elicit robust anti-Aβ antibody production have been shown to promote impressive clearance of Aβ from the brains of Aβ-overexpressing AD mouse models.[118] FcR-mediated phagocytosis of Aβ complexes coated with antibodies is thought to be a major mechanism promoting Aβ reduction following anti-Aβ antibody infusions and anti-Aβ vaccination.[118] Unfortunately, recent clinical trials in AD patients

testing antibody-mediated Aβ reducing strategies have not been promising.[119] Current thinking is that anti-Aβ antibodies were introduced too late in the disease process to protect neurons that were either already lost or well on their way to neuronal demise. Despite this setback, hope still remains that earlier interventions with anti-Aβ antibodies may still hold clinical promise. However, for this to become a reality, improved AD diagnostic biomarkers to identify high-risk patients at earlier stages of disease are required.

Clearance by degradative factors ––—In addition to phagocytic pathways, microglia are able to clear AD pathology through their production of degradative factors. These mechanisms include the use of insulin degrading enzyme (IDE), neprilysin, endothelin degrading enzyme (EDE), and the proteasomal degradation pathway.[111] IDE, neprilysin, and ECE are all metalloendopeptidases known to degrade Aβ.[111] IDE can be produced by microglia and secreted into the extracellular space to degrade monomeric Aβ.[120] Interestingly, there is a link between taking statins, which lower cholesterol, and a decreased risk for AD.[121] One mechanism by which statins are believed to deter AD development is via their promotion of microglial IDE production to degrade Aβ.[121] Neprilysin is another important enzyme in the breakdown of Aβ.[122] In fact, an age-related neprilysin decline in AD brains is thought to contribute to the increased levels of Aβ that occurs with aging.[122] In line with this hypothesis, areas of the brain with high Aβ plaque load, such as the hippocampus, are known to have decreased neprilysin levels.[123] In addition, genetic ablation of neprilysin in APP transgenic AD mice has been reported to cause increased Aβ deposition in the brain and more severe cognitive decline.[124] Similar to IDE and neprilysin, ECE can also promote Aβ degradation and ECE-deficient mice have increased Aβ burden in the brain.[125] Finally, the proteasomal degradation of AD pathology is regulated by the ubiquitin proteasome system (UPS).[126] This system tags mis-folded proteins with ubiquitin to mark them for proteasomal degradation.[36] In AD, this process is believed to be impaired, which in turn leads to increased retention of tau and Aβ aggregates in the brain.[36]

Extracellular chaperone-mediated clearance ––—Extracellular chaperone-mediated clearance is another mechanism by which Aβ can be cleared from the brain. It has been shown that APOE binds to Aβ and acts as a chaperone to promote its clearance via endosomes.[127] The chaperone function of APOE is thought to prompt microglial response to Aβ plaques, driving Aβ compaction and in turn, reducing neuronal damage.[128] Interestingly, an APOE-TREM2 pathway has emerged in which TREM2 function is shown to be critical for the APOE association with Aβ plaques to promote plaque compaction.[75] The binding of APOE and Aβ to microglial lipoprotein receptor-related protein 1(LRP-1) receptor is also thought to initiate signaling through JNK and NF-kB pathways to promote pro-inflammatory cytokine production.[129] The AD risk variant, APOE ε4, is characterized to be less effective at these chaperone-mediated Aβ clearance duties in addition to inciting an increase in neuroinflammation.[127,130]

Autophagic clearance -—Autophagy acts as an additional mechanism for the clearance of Aβ. Autophagy is a lysosome-dependent, homeostatic process, whereby organelles and proteins such as Aβ are broken down and recycled.[131] Interestingly, autophagy is linked with many aspects of the innate immune response, including the regulation of pro-

inflammatory cytokine production.[131] Fibrillar Aβ can be cleared by microglial autophagy, and the impairment of this process has been shown to propagate NLRP3 inflammasome activation.[132] In addition, treatment with trehalose to enhance autophagy markedly decreases tau aggregation in cell culture settings and can reduce neuronal tau inclusions in a tauopathy mouse model.[133,134] Dystrophic neurites are also known to accumulate autophagic vesicles, further supporting a potential role for autophagy in regulating neuronal health.[135] In line with a beneficial role for autophagy in AD, boosting autophagic signaling has been shown to ameliorate memory deficits in AD mice.[136] Therefore, modulating autophagy presents another potential therapeutic avenue for the treatment of AD that will surely be intensely pursued in future studies.

Disease associated microglia:

The dispute surrounding whether microglia exert beneficial or detrimental roles in AD remains a hotly debated topic. Single-cell RNA-seq recently identified a new subset of microglia known as “disease associated microglia” (DAM).[63] In the past, microglia were largely thought of as a homogenous cell population. However, this diversified transcriptional profile of microglia in the AD and aging brain environment has prompted many new questions surrounding their role in disease onset and progression. DAMs are classified by two distinct stages: the initial TREM2-independent Stage 1 and TREM2-dependent Stage 2.[63] Stage 1 and 2 DAMs are identified by their downregulation of characteristic homeostatic microglial genes (i.e. *P2ry12*, *Cx3cr1*, and *Tmem119*). Stage 1 DAMs upregulate phagocytic related genes such as *Apoe* and *Dap12* while Stage 2 DAMs upregulate *Clec7A* and *Trem2*.[63] As previously discussed in this review, APOE variants are a major risk factor for LOAD, while TREM2, DAP12, and CLEC7A are receptors previously described in phagocytic pathways.[23,65,87] Initiation of this shift of microglia from a homeostatic phenotype to the DAM signature is believed to be dependent on sensing of NAMPs, engagement of TREM2 signaling, and extended interactions of microglia with Aβ plaques.[64]

The DAM subtype is accepted to serve in a beneficial capacity through their coordination of Aβ clearance.[63] However, this function remains strictly regulated by the inhibitory signaling of CX3CR1, perhaps acting as a harness on DAM function.[63] Therefore, future research efforts will likely focus on stimulating the DAM phenotype early on in disease to reduce AD progression. However, the possibility also exists that over-excessive and/or chronic activation of the DAM phenotype may trigger neurotoxic consequences and propagate AD pathology. This possibility will likely encourage a new AD-microglia field focused on determining how to revert DAM back to their homeostatic microglial state. The multi-faceted roles of microglia underscore the temporal complexities of their function, and will likely keep them in the AD research spotlight for years to come.

Loss of microglial homeostatic function in AD:

Homeostatic microglia possess a signature defined by the expression of receptors such as CX3 chemokine receptor 1 (CX3CR1) and purinergic receptor P2RY12.[27] CX3CR1, which is activated in response to its ligand fractalkine, performs inhibitory duties to sustain a resting-state microglia population.[137] Although fractalkine is found at higher levels in the

blood of AD patients, *Cx3cr1* is downregulated in DAMs.[63,138] CX3CR1 is thought to have complex roles in AD. For example, deficiency in *Cx3cr1* reduces neuronal loss in the 3xTgAD mouse model, which develop both Aβ plaques and NFTs.[139] In contrast, the loss of *Cx3cr1* in the Aβ-mediated hAPP-J20 AD mouse model spurs microglial toxicity and intensifies cognitive deficits.[140] The presence of Aβ also downregulates fractalkine in the hAPP-J20 AD mouse model.[140] These findings suggest that the role of CX3CR1 is variable depending on the different models of AD being used. Despite these inconsistencies, CX3CR1 appears to be a critical modulator of DAM biology. However, without this CXC3R1 check and balance, excessive microglia activation may contribute to neuronal loss and functional decline, while its overabundance may act to inhibit necessary DAM response to AD pathology. Purinergic receptor P2RY12, on the other hand, is important for microglial migration, and it is highly expressed in homeostatic microglia.[141,142] However, the role of P2RY12 downregulation in plaque-associated DAMs and AD remains unclear and requires further investigation.

Impact of microglial elimination in AD:

The often-contradictory roles of microglia in varying states and stages of neurodegenerative disease have prompted researchers to explore the impact of microglia depletion in AD. In recent years, treatment with the colony stimulating factor 1 receptor (CSF-1R) inhibitor, Plexxikon, has emerged as a popular approach to study the functional role of microglia in vivo. CSF-1R signaling is required for the survival of microglia and other peripheral macrophages, and as a result, Plexxikon treatment results in rapid and robust depletion of microglia from the brain.[143] Results from recent studies using Plexxikon indicate a complex role for microglia in mouse models of AD that is greatly influenced by the timing and efficacy of depletion as well as the AD mouse model studied. For example, when 3xTgAD mice were depleted of 30% of their microglia, and aged to have existing Aβ plaques and tau aggregation, the mice were shown to have improved cognition but this partial deletion of microglia had no effect on Aβ plaque load or tau aggregation.[144] In comparison, a 90% microglial depletion in PS19 AD mice, aged to have tau aggregation, led to significant reductions in tau propagation.[145] Meanwhile, partial depletion of microglia in the APPPS1 mouse model of AD was found to improve memory and ameliorate synaptic degeneration, while having no effect on Aβ load.[146] 5xFAD mice depleted of 80% of their microglia similarly showed improved memory and decreased neuronal damage without modulation of Aβ levels.[147] However, 5xFAD mice depleted of greater than 97% of their microglia prior to Aβ plaque seeding-onset (i.e. Plexxikon treatment beginning at 1.5 months of age) exhibited reductions in Aβ load as well as a rescue of anxiety-related behaviors.[148] However, the almost complete depletion of microglia in these studies was also found to promote increased numbers of dystrophic neurites, as microglia were no longer present to protect surrounding neurons from the neurotoxicity of the few remaining Aβ plaques.[148] Taken together, current data in mice indicates that partial depletion of microglia does not affect Aβ plaque and tau load but can result in improved memory and less neuronal damage compared to controls.[144,146,147] However, near-complete depletion of microglia amid or prior to AD pathology onset attenuates Aβ and tau load.[145,148] While these studies all point to critical roles of microglia in AD, they also highlight that microglia-targeting therapeutics must carefully take

into account the status of disease and desired microglia depletion efficacy to maximize beneficial clinical outcomes and safety.

AD immune cells: microglia or macrophages?

These intriguing findings from Plexxikon depletion studies have prompted speculation over whether microglia or peripheral monocytes repopulate this niche when the depletion drug is removed. As mentioned above, CSF-1R inhibition with Plexxikon treatment can deplete microglia, peripheral macrophages in other tissues, and potentially other cell types reliant on CSF-1R signaling for survival.[143] This has led to speculation over the discrete roles of microglia versus other peripherally derived cell types in AD. Plexxikon microglial depletion treatment by itself does not compromise the BBB, and expansion of the few remaining microglia is thought to repopulate the brain following cessation of Plexxikon treatment.[149,150] However, injury models, such as traumatic brain injury (TBI), can cause BBB breakdown and subsequent infiltration of immune cells into the brain.[151,152] Likewise, AD pathology is also thought to propagate the loss of BBB integrity.[153] Microglial depletion and repopulation after TBI has been reported to replace chronically activated microglia with resting-state myeloid cells, resulting in decreased neuroinflammation and neuronal loss.[151] The neuroprotection conferred by the repopulated myeloid cells post-TBI relies on their induction of IL-6 trans-signaling to enhance learning and memory.[154] Therefore, the replacement of activated microglia with more quiescent myeloid cells may underlie neuroprotection. However, while it is speculated that depleted microglia die and are cleared away following Plexxikon treatment, the identity of the repopulating cells in BBB-compromised settings remains poorly understood.[149] Multiple myeloid cell types have been proposed to fill this niche including peripheral macrophages and microglia from the small Plexxikon-resistant subset. However, future studies are needed to better understand this process and how it affects neurological disease. This further illuminates the complexity and heterogeneity of CNS macrophages, and maintains speculation surrounding their capacity to be manipulated during neurodegenerative disease.

Initial studies exploring the ability of CNS-infiltrating monocytes to influence AD-related disease in the APPPS1 AD mouse model initially showed that chemokine receptor *CCR2* deficiency prevents monocytes from entering the brain and that this results in fewer IBA-1^{+} myeloid cells in the brain and impaired Aβ clearance.[155] These data suggest that peripheral monocytes are important for properly controlling AD pathology. In contrast, *CCR2* deficiency in the same mouse model was later shown by a different lab to increase plaque-associated microglia numbers and have minimal impact on Aβ accumulation.[156] What underlies the discrepancies between these two studies remains to be fully resolved. One possibility explaining the divergent outcomes may be related to the latter study's use of irradiation, which can encourage the recruitment and retention of peripherally-derived monocytes in the brain.[157] Notably, recent research utilizing an irradiation-independent model has established brain engrafting macrophages that maintain a distinct transcriptional profile from microglia and are able to repopulate the brain following partial microglia depletion.[158] Other work also demonstrates that TREM2 can promote peripheral monocytes to enter the brain in APPPS1 mice.[159] In contrast to the belief that peripheral myeloid cells are critical for proper AD control, parabiosis studies with WT and 5xFAD mice show

minimal infiltration of peripheral monocytes from WT mice into 5xFAD brains.[71] Likewise, these parabiosis findings have also been confirmed in the APP/PS1 mouse model.[71] In addition, recent research using tdTomato lineage tracing in 5xFAD mice convincingly shows that $CX3CR1^+$ microglia comprise virtually all of the myeloid cells surrounding the Aβ plaques, with virtually no $CCR2^+$ peripheral monocytes found in the vicinity of Aβ in the brain.[57] In terms of Aβ aggregation mouse models, which include 5xFAD and APPPS1 transgenic mice, microglia appear to be the key myeloid cell type responding to Aβ, with little assistance from infiltrating monocytes. However, this work cannot exclude the potential of peripheral monocyte assistance under all conditions associated with human neurodegenerative disease, especially those that are not fully recapitulated in mouse models. In particular, it will be important for future studies exploring the roles of discrete myeloid cell lineages in AD to assess how combined Aβ and tau pathology can influence outcomes.

Inflammatory mediation of AD: Neuroinflammation centrally contributes to various aspects of AD pathologies and this has led to increasing interest in harnessing inflammatory cytokine signaling to treat AD.[2,160] The role of inflammation in AD remains a hotly debated topic in the field. While on the one hand, chronic inflammation can negatively impact neuronal health, an ever-increasing body of literature also demonstrates that controlled activation of specific inflammatory pathways can help to mobilize beneficial immune functions to promote Aβ clearance and neurotrophic factor production.[161,162] In this section, we will discuss the double-edged nature of inflammation in AD.

Cytokines in AD:

Multiple innate immune cytokines including type I interferon (IFN), TNF-α, IL-18, IL-1β, IL-33, IL-34, IL-12, IL-23, and IL-10 have been described to play important roles in various aspects of AD pathogenesis.[163–170] Resting levels of pro-inflammatory cytokines are found to be higher in the blood and cerebrospinal fluid (CSF) of AD patients, suggesting a role for them in disease pathogenesis.[171] The deposition of Aβ, and resultant neuronal damage, provide ligands to activate microglial phagocytosis of Aβ while also promoting microglia-mediated production of proinflammatory cytokines.[58] Acutely, this process can lead to the proper clearance of Aβ allowing the brain parenchyma to restore homeostasis (Fig. 3).[172] However, these inflammatory mediators can have complex effects in AD. For example, under chronic inflammation, this process can lose its effectiveness in clearing amyloid beta, while continuing its inflammatory response to further propagate neurotoxicity in a feed-forward mechanism (Fig. 3).[173] Catalysts for this continued and detrimental response include factors such as age, genetics, injury, and peripheral inflammation.[2] The production of specific pro-inflammatory cytokines, such as IFN-γ, also has the potential to encourage further production of Aβ as well as to recruit microglia activation to respond to neurotoxic Aβ species.[174] Therefore, cytokine production can promote a cycle that is difficult to resolve.

As was alluded to above, IFN cytokines play significant roles in shaping microglial responses in AD and aging.[163,175] Several AD mouse models show a distinct IFN-stimulated gene (ISG) signature.[176] IFN has been described to be expressed by immune cells sensing nucleic acids.[177] Of note, fibrillar amyloid beta often contains nucleic acids that can elicit an

inflammatory ISG signature in microglia.[176] This neurotoxic type of microgliosis has been shown to promote complement-mediated synapse loss that can be curtailed with IFN-receptor blockage.[176] Researchers have also shown that knocking out IFN-γ receptor type I in transgenic APP Swedish mutant AD mice leads to a reduction in Aβ plaque load and reactive microglia.[174] In addition, *in vitro* studies indicate that IFN-γ promotes microglial release of TNF-α, and both of these cytokines promote β-secretase cleavage of APP to produce more Aβ.[174] These results strongly suggest that IFN is associated with AD propagation.

The role of TNF-α in AD has remained enigmatic, as some research has focused on the therapeutic benefit of its inhibition, while others show beneficial or benign roles for the cytokine. In support of a detrimental role for TNF-α in AD, it has been shown that higher CSF levels of TNF-α correlate with impaired "functional connectivity," a measure of the communication between different brain regions underlying various functions such as learning, memory, inhibition, etc.[178] In line with pathologic functions of TNF-α in AD, APPPS1 mice deficient in TNF receptor 1 (TNFR1) have been described to have decreased levels of Aβ, lower expression of inflammatory factors, improved maintenance of choroid plexus tissue and CSF-blood barrier integrity, and preserved memory compared to TNFR1 sufficient APPPS1 mice.[179] In contrast, an injection of murine TNF-α AAV into the hippocampus of APP transgenic mice has been reported to attenuate Aβ deposition and incite increased microglial responses without increasing APP levels.[180] This suggests that under certain spatial and temporal contexts TNF-α may promote plaque clearance. Finally, the proposed causal relationship between TNF-α and AD has recently come into question, as Mendelian randomization modeling of GWAS studies show no causality between peripheral TNF-α expression levels and the risk of developing AD.[181]

IL-1 family cytokines, such as pro-inflammatory IL-18, IL-1β, and IL-33, have also been implicated in modulating AD pathogenesis.[167,182,183] For example, IL-18 promotes β-secretase mediated cleavage of APP to produce more Aβ40.[184] However, loss of *IL-18* in the APPPS1 AD mouse model was found to incite seizure through a proposed mechanism that involves excessive excitatory synapse activity and impaired dendritic pruning.[185] IL-1β has conflicting roles in AD pathologies. Increased peripheral levels of IL-1β and its propensity to incite neuroinflammation have led scientists to focus on neutralizing its functions in hopes of therapeutic benefit in AD.[171,186] For instance, IL-1 receptor inhibition in 3xTgAD mice was reported to rescue cognitive deficits, decrease tau phosphorylation, and modestly modulate Aβ levels.[186] Interestingly, conditional overexpression of *IL-1β* in 3xTgAD mice was conversely found to markedly decrease Aβ levels while concomitantly leading to increased tau phosphorylation, further highlighting the complex role of neuroinflammation in AD.[187] Increased IL-1 production is also known to promote S100B protein release from astrocytes.[188] The S100B protein is a neurotrophic cytokine that often acts as a pro-inflammatory cytokine in AD.[189] Higher levels of S100B have been documented in AD patients and appears to be associated with increased Aβ plaque load and gliosis.[190–192]

IL-33, an alarmin in the IL-1 cytokine family, has also been implicated in AD. *IL-33* is expressed by oligodendrocytes and its receptor, ST2, is often expressed by microglia.[193] *IL-33* expression is reduced in the brains of AD patients, identifying this cytokine as a

potential modulator of disease.[194] Accordingly, intraperitoneal injection of IL-33 was recently shown to restore LTP deficiency, improve contextual memory, and decrease Aβ levels in APPPS1 AD mice.[167] IL-33 treatment accomplishes this rescue by increasing microglial Aβ phagocytosis and anti-inflammatory gene expression, while also decreasing microglial pro-inflammatory gene expression.[167]

IL-34 and CSF-1 activate the CSF-1 receptor (CSF-1R) to promote microglial population survival and maintenance.[149] Interestingly, AD patients have been shown to have increased expression of *IL-34* in the white matter compared with age-matched controls, highlighting its importance in regulating AD pathogenesis.[195] More recent work, however, shows reduced expression of *IL-34* in the inferior temporal gyrus (ITG) and an increase in expression of CSF-1 in the ITG and middle temporal gyrus (MTG) of AD patients.[196] On one hand, research has found neuroprotective roles for IL-34 in AD. For instance, intracerebroventricular injection of IL-34 into APPPS1 mice promotes improved memory and lower levels of oligomeric Aβ through a mechanism that involves increased expression of insulin degrading enzyme and heme-oxygenase-1.[168] In contrast, using microglial cultures from AD human brains, researchers show that IL-34 stimulation decreases expression of genes associated with phagocytosis such as CD68, which is a lysosomal marker commonly used to evaluate phagocytic potential in AD mouse models.[196] Collectively, these findings highlight the potential temporal and anatomical complexity of IL-34 in the AD brain.

Increasing evidence also supports the role of IL-10, IL-12, and IL-23 in AD pathogenesis. For example, the shared subunit of IL-12 and IL-23 (i.e. p40) and IL-10 are found at elevated levels in the CSF of AD patients.[197,198] A blood biomarker study also found IL-10 and p40 at increased levels in cognitively normal patients that exhibit abnormally high levels of Aβ deposition.[199] In turn, the ablation of p40 can attenuate cognitive deficits and Aβ levels in APPPS1 mice.[197] Peripheral treatment with anti-p40 antibody in APPPS1 mice is also able to decrease Aβ levels.[197] Interestingly, the loss of IL-12 and IL-23 signaling through p40 genetic ablation has sex-specific effects in which only males exhibit a reduction in Aβ plaques.[200] The silencing of p40 in aged senescence-accelerated mouse prone-8 (SAMP8) mice also mitigates cognitive decline, Aβ load, and neuronal death.[169] Lastly, ablation of *IL-10* in the context of AD is also considered beneficial. In fact, APPPS1 mice lacking *IL-10* show improved synaptic health and cognition compared with APPPS1 controls.[170] Therefore, the unchecked functioning of these cytokines during chronic inflammation of AD poses a serious threat to brain health and function.

Role of inflammasomes in AD:

Recent studies suggest a detrimental role for inflammasomes in AD.[201–204] Inflammasomes are multimolecular complexes that form following receptor activation in response to various DAMPs, PAMPs, and NAMPs.[205] The formation of these complexes initiates a signaling cascade in which active caspase-1 promotes the cleavage of inflammatory pro-IL-1β and pro-IL-18 cytokines into their active forms and also incites cell death.[205] Inflammasome-mediated cell death is termed “pyroptosis” and is executed by cleaved gasdermin-D.[206] Gasdermin-D proteins are cleaved by caspase-1,−4,−5, or −11, and this product comes

together to form a pore on the cell membrane to promote cell lysis and the exit of pro-inflammatory cytokines from the cell.[207] The NLRP3 inflammasome, in particular, has been identified as an important contributor to AD pathogenesis.[185,201,202,208–210] NLRP3 is upregulated and activated in AD, with increased mRNA and protein expression in immune cells.[211] The loss of NLRP3 inflammasome in APPPS1 mice attenuates spatial memory and LTP deficits, in addition to decreasing Aβ burden.[201] NLRP3 was also recently shown to promote tau hyperphosphorylation and aggregation.[212,213] Accordingly, inhibitors such as the JC-124 drug or fenamate class NSAIDs have been developed to successfully inhibit the NLRP3 inflammasome to mirror these improvements in a potentially therapeutic format.[202,214] Recent research shows that apoptosis-associated speck-like protein containing CARD (ASC), an adaptor protein critical for the formation of the NLRP3 inflammasome, binds with Aβ.[215] This ASC-Aβ interaction initiates NLRP3 inflammasome activation and prevents proper clearance of Aβ.[216] In turn, the increased Aβ levels promote microglial pyroptosis leading to the extracellular release of more ASC that can bind Aβ to activate the cycle again, generating a chronic neuroinflammatory cascade.[216]

The AIM2 inflammasome, which is activated by double-stranded DNA, has also been implicated in AD.[204] *Aim2* deficient 5xFAD AD mice have decreased Aβ plaque load, however, this is not sufficient to rescue memory deficits. Additionally, 5xFAD;*Aim2*$^{-/-}$ mice have increased inflammation mediated by preserved *IL-1* expression and an increase in the expression of pro-inflammatory cytokines *IL-6* and *IL-18* in the brain.[204] This may suggest parallel inflammatory mechanisms to compensate for the loss of *Aim2* in AD mouse models. Interestingly, our lab and others have shown the loss of *Aim2* impacts neuronal morphology and negatively influences several behaviors such as anxiety and memory.[217,218] Furthermore, our recent studies demonstrate that defects in the AIM2 inflammasome can alter neurodevelopment.[217] Thus, it is feasible that changes in brain development existing before Aβ deposition may influence disease outcomes in AD mouse models. Moving forward, it will be interesting to revisit the role of the AIM2 inflammasome in AD using approaches that conditionally ablate AIM2 signaling following neurodevelopment.

Role of age, environmental factors, and sex in AD:

In recent years, there has been increasing appreciation for the instrumental roles that aging, environmental factors, and lifestyle choices play in AD pathogenesis (Fig. 4).[219] Interestingly, emerging work has shown that many of these environmental and lifestyle factors influence AD progression by modulating aspects of inflammatory signaling.[2] In this section, we will spotlight up-and-coming work describing how changes to inflammatory responses are now believed to underlie the ability of many environmental and lifestyle factors to influence AD.

Age is by far the greatest risk factor for developing AD.[220] Interestingly, recent studies suggest that aging profoundly impacts microglial biology and that this can hinder their ability to properly handle and dispose of Aβ.[86] Along with their propensity to take on the DAM transcriptional profile, aging also alters microglia morphology, enhances their activation status, limits their motility, and curbs their ability to phagocytose Aβ.[63,221–223] Unfortunately, all of these age-related microglial changes have the potential to promote AD

pathology. The ability of microglia to self-sustain their population is also speculated to make them particularly susceptible to telomeric shortening and cellular senescence, and it has been proposed that the acquisition of this senescence phenotype can cause microglial dysfunction.[224] An additional mechanism by which aging contributes to AD is the loss of "youthful" blood-derived factors as one ages. Such studies demonstrate that parabiosis or plasma transfer from young mice to old mice improves learning and memory.[225,226] Two factors shown to be elevated in young blood include thrombospondin-4 and SPARCL1, which support synaptic connectivity.[227] It has also been shown that blood from old mice negatively impacts cognition in young mice.[228] One factor suggested to contribute to this phenomenon is the chemokine CCL1, as it is elevated in aged-mice plasma levels and directly impairs cognition in recipient young mice.[228]

Obesity and exercise have also been implicated in AD prevalence and severity.[166,229–232] Researchers have shown that obese individuals have high levels of the short chain fatty acid known as palmitate in the CSF and that this can lead to impaired neuronal insulin signaling.[166] They further report that increased levels of palmitate in the CSF of aged mice provokes pro-inflammatory TNF-α cytokine production and that this can lead to memory deficits.[166] Indeed, they showed that TNF-α receptor deficient mice treated with palmitate perform better on memory tests compared with palmitate treated wildtype controls.[166] In addition, an intracerebroventricular injection of infliximab, a TNF-α neutralizing antibody, was also found to improve memory and ameliorate microgliosis in mice on a high fat diet.[166]

Routine exercise, on the other hand, has been shown to help limit AD development and progression[233]. One mechanism that may explain this phenomenon is the release of the myokine FNDC5/irisin from the muscle to the brain during exercise.[230] FNDC5/irisin production following exercise increases synaptic plasticity, a critical aspect of memory formation and maintenance[230,234]. A mechanism by which memory formation is promoted by irisin is its ability to activate the memory-associated cAMP–PKA–CREB signaling pathway.[235] Frequent exercise is also linked with decreased risk of viral and bacterial infections.[236] Therefore, an increased susceptibility to infection as a result of insufficient exercise, which is shown to contribute to neurodegenerative pathology, may account for another mechanism by which exercise is linked with AD pathogenesis.[237]

Oral hygiene also appears to play a role in AD risk.[238] More specifically, people with the gum disease known as periodontitis have persistent inflammation that is linked with AD.[238,239] For example, it has been demonstrated that serum antibody levels for periodontitis-associated bacteria are increased in AD patients, suggesting a potential link between AD and this peripheral chronic inflammation.[240] In addition, levels of the pro-inflammatory cytokine TNF-α are increased in the serum of patients with periodontal disease.[241] Accordingly, TNF-α levels are also significantly increased in AD patients, suggesting a potential link between this specific inflammatory cytokine resulting from oral infection and the propagation of AD brain pathology.[241–243]

Exposure to pathogens in the environment has also been shown to influence AD risk. Mounting evidence has produced a consequential list of bacteria, viruses, and fungi found in the AD brain, with some even directly associating with Aβ plaques and influencing tau

phosphorylation.[90,244–247] Moreover, it has been reported that AD patients experiencing acute systemic inflammatory responses characterized by increased levels of TNF-α exhibit a two-fold increase in cognitive deficits.[248] In fact, patients with sepsis present with long-term cognitive deficits, hippocampal atrophy, and are at a higher risk for developing dementia.[249,250]

TBI has emerged as a major non-genetic risk factor for developing AD and other neurodegenerative disorders later in life. TBI not only significantly increases one's risk of developing AD, but has also been linked to earlier onset and more aggressive disease progression.[251–254] More specifically, findings from a number of studies demonstrate that moderate to severe brain injury can increase the risk of developing AD by between 2.3- to 4.5-fold.[255–257] These numbers increase exponentially with repetitive brain injuries and interactions with genetic risk factors.[258] For instance, possessing one allele of APOE ε4 doubles the risk of developing AD, whereas this risk increases by 10 fold for individuals who carry one copy of the APOE ε4 allele and have a history of brain injury.[259] One mechanism thought to underlie the link between TBI and AD is BBB breakdown. TBI-induced vascular shear stress has been shown to appreciably disrupt BBB integrity.[260] Cerebrovascular injury induced by TBI and AD has been postulated to be another pathological loop in which BBB breakdown propagates AD pathology and the presence of AD pathology can also incite the loss of BBB integrity.[260] For instance, 30% of brains from TBI patients have Aβ plaques, and TBI can induce tau phosphorylation and Aβ aggregation.[251,261,262] The accumulation of Aβ and tau can then promote BBB breakdown to initiate the cycle once again.[260] These findings suggest a link between this inflammatory brain injury and AD progression.

An additional mechanism by which brain injury and neurodegenerative disease interact involves the (re)discovery of the meningeal lymphatics in the CNS.[263] In particular, the role of the meningeal lymphatics in neuroinflammation and Aβ accumulation may provide another compelling angle to the relationship between TBI and AD.[264,265] For instance, TBI has recently been shown to compromise meningeal lymphatic function, namely its ability to drain inflammatory byproducts to lymph nodes following injury.[266] Interestingly, meningeal lymphatic drainage defects are known to significantly increase meningeal Aβ load and to provoke memory deficits in 5xFAD AD mice.[265] Therefore, meningeal lymphatic dysfunction may provide another explanation for the association between AD pathogenesis and brain injury, with promising clinical implications that require further investigation.

BBB permeability is also known to be influenced by gut microbiota composition.[267] Indeed, changes in intestinal microbiota landscape have been shown to have prominent effects on the brain either directly via production of microbial products that shape BBB function or indirectly through the modulation of peripheral immune responses.[267,268] Increased gut permeability allows for bacteria, bacterial toxins, and LPS to enter the bloodstream and has been coined "leaky gut."[269,270] This leakiness is instigated by chronic inflammation and gut dysbiosis, which can contribute to systemic inflammation and the decreased BBB integrity associated with aging and AD.[229,269,271] BBB breakdown can ultimately lead to impaired removal of toxic species from the CNS and entry of pathogenic mediators from the periphery.[269,271] Interestingly, compared to WT controls, APPPS1 mice have altered

bacterial species in the gut, including higher levels of the bacteria *B. thetaiotaomicron*.[229] In these studies, it was also shown that modulating the gut microbiota landscape with probiotics and exercise treatment can improve cognitive functions in APPPS1 mice.[229]

In addition to rescuing memory, the modulation of microbiota composition upon fecal transfer from WT mice to ADLP^{APT} AD mice has been shown to attenuate Aβ load, tau pathology, and microgliosis.[272] Antibiotic cocktail treatment to alter microbiota species in the gut of APPPS1–21 AD mice has likewise been reported to reduce Aβ load and microglial activation in males specifically.[273] Accordingly, cognitively impaired patients with high levels of Aβ also have altered gut microbiota populations. Interestingly, this skew in microbiota composition seen in cognitively impaired individuals is commonly characterized by the outgrowth of commensal microbes that have been linked with enhanced pro-inflammatory cytokine production.[274] Dietary changes in patients with MCI also appears to alter the microbiota population and their association with Aβ and p-Tau levels in the CSF.[275] These data convey how peripheral inflammation induced by dysbiosis in the gut can have broad clinical applications for mitigating AD risk and pathology in the future.

Sleep deficits have long been associated with cognitive decline.[276] In fact, many AD patients present with shifts in their circadian rhythm.[277] However, research also shows that problems with sleep can precede neurodegeneration and increase the risk of developing AD.[277,278] Notably, Aβ and tau levels are known to be elevated in the CSF and brains of sleep-deprived individuals.[279–281] In healthy patients, levels of Aβ shift, with an increase during the day and a marked decline during sleep.[282] However, following Aβ aggregation, this alignment with the sleep-wake cycle dissipates.[282] The half-life of Aβ more than doubles with age, likely allowing for improper protein folding and aggregate formation acting as a magnet for extracellular Aβ and preventing its transport into the CSF.[283] Impaired microglial clearance of Aβ likely contributes to this enhancement in Aβ half-life. Deficits in sleep itself shift microglia to an activated state and aged phenotype, characterized by impaired Aβ clearance.[284] Additionally, sleep disturbances increase the risk for inflammatory disease, which also has the potential to prime microglia to contribute to their impaired function with aging.[224,285]

The disparity between female and male prevalence of AD has also sparked research to distinguish the pathways underlying this sexual dimorphism. The increase in incidence of AD in females is thought to involve females' dramatic decrease in estrogen levels during menopause, which is known to impact mitochondrial metabolism.[286–288] In line with this hypothesis, estrogen replacement therapy (ERT) has been shown to significantly reduce the risk of developing AD.[289] The decrease in testosterone in males occurs as a gradual decline, and therefore, it is believed to have a less detrimental effect on mitochondrial function.[287] The decrease in sex hormone levels, characteristic during aging, affect mitochondrial metabolism by decreasing mitochondrial energy production and calcium efflux while increasing oxidative stress and reactive oxygen species (ROS) release.[287,290] The surge of oxidative stress and ROS amplifies inflammatory responses.[291] Accordingly, the release of ROS can trigger NLRP3 inflammasome activation and lead to downstream proinflammatory cytokine production, pyroptosis, and ASC speck seeding of Aβ spread.[201,202,213,216,291,292] Some AD researchers are in favor of a "mitochondrial cascade hypothesis" in which

mitochondrial dysfunction precedes AD pathogenesis by stimulating an increase in Aβ production and leading to the phosphorylation of tau.[293] In a feed-forward mechanism, the AD pathologies themselves also propagate mitochondrial dysfunction and inflammatory ROS production which is consistently found at higher levels in AD patients.[294,295] This has led to great interest in AD therapeutics that promote mitophagy to eliminate impaired mitochondria.[296] In fact, boosting mitophagy has been shown to attenuate cognitive deficits and promote microglial phagocytosis of Aβ while decreasing neuroinflammation in APPPS1 AD mice.[297]

An additional sex-specific factor involved in AD is the sexual dimorphism of microglia. Female microglia display distinct morphology, decreased density, and altered function.[27] It has also been demonstrated that male and female microglia in mice exhibit distinct transcriptional profiles that are retained when transplanted into the opposite sex.[298] This suggests that the sex-specific microglia transcriptome does not rely on maintenance by sex-steroids. However, this does not exclude the possibility that the sex-steroids have a permanent effect on microglia during development. In fact, the development of microglia, as measured by gene expression profiles, occurs at disparate paces between the sexes.[299] In turn, there is also a sex-specific divergence in the functionality of microglia in mice. For example, using a 5xFAD AD mouse model, it has been shown that female APOE ε4/5xFAD mice exhibit decreased microglia-mediated compaction of Aβ-plaques, decreased *Trem2* expression, and increased plaque burden compared with male APOE ε4/5xFAD mice.[300] Such studies suggest that sex-based differences in microglial response might help to explain the higher rates of AD in females.

CONCLUSIONS

The role of innate immunity in the modulation of AD pathology and progression poses exciting new avenues for neurodegenerative research. Mounting evidence suggests that microglia and the maintenance of a healthy neuronal environment appear to be inextricably linked. Decades of research have been dedicated to targeting the processing and production of Aβ, while disappointing clinical results have left researchers to look broader. The new focus on innate immunity, microglia, and neuroinflammation in AD has generated a burgeoning field, and exploring their roles will likely help to identify new and much-needed drug targets to combat this devastating neurodegenerative disease. Recent advancements in AD and neuroimmunology research have begun to uncover critical roles for the innate immune system in AD onset, pathology, and progression. Results from this relatively new area of study suggest that AD treatment is subject to variables such as immune response, environmental factors, and lifestyle choices that are pointing the field to a more individualistic style of therapeutics.

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Abbreviations:

AAV	adeno-associated virus
Aβ	amyloid beta
AD	Alzheimer's disease
AMP	antimicrobial peptide
APOE	apolipoprotein E gene
APP	amyloid precursor protein
ASC	apoptosis-associated speck-like protein containing CARD
BBB	blood-brain barrier
CNS	central nervous system
CSF	cerebrospinal fluid
CSF-1R	colony stimulating factor-1 receptor
CX3CR1	CX3 chemokine receptor
DAM	disease associated microglia
DAMP	damage associated molecular pattern
EDE	endothelin degrading enzyme
EOAD	early onset AD
ERT	estrogen replacement therapy
FAD	familial AD
FcR	Fc receptor
GWAS	genome-wide association study
HSV	herpes simplex virus
IDE	insulin degrading enzyme
IFN	interferon
IL	interleukin
ISG	IFN-stimulated gene
ITAM	immunoreceptor tyrosine-based activation motif
ITG	inferior temporal gyrus
ITIM	immunoreceptor tyrosine-based inhibitory motif

LOAD	late onset AD
LTP	long-term potentiation
MCI	mild cognitive impairment
MTG	middle temporal gyrus
NAMP	neurodegeneration-associated molecular patterns
NfL	neurofilament light chain
NFT	neurofibrillary tangle
NLRP3	NOD-like receptor family pyrin domain containing 3
NOD	Nucleotide-binding oligomerization domain
PAMP	pathogen-associated molecular pattern
PET	positron emission tomography
PRR	pattern recognition receptor
PSEN1	presenilin-1
PSEN2	presenilin-2
p-Tau	hyperphosphorylated tau
R47H	rare Arginine-47-Histidine
RAGE	receptor of advanced glycosylation end products
ROS	reactive oxygen species
SAMP8	senescence-accelerated mouse prone-8
SHP	Src homology 2 domain-containing phosphatase
Siglec	sialic-acid binding immunoglobulin-like lectin
sTREM2	soluble TREM2
SYK	spleen tyrosine kinase
TBI	traumatic brain injury
TLR	toll-like receptor
TNF	tumor necrosis factor
TNFR1	TNF receptor 1
TREM2	triggering receptor expressed on myeloid cells 2
UPS	ubiquitin proteasome system

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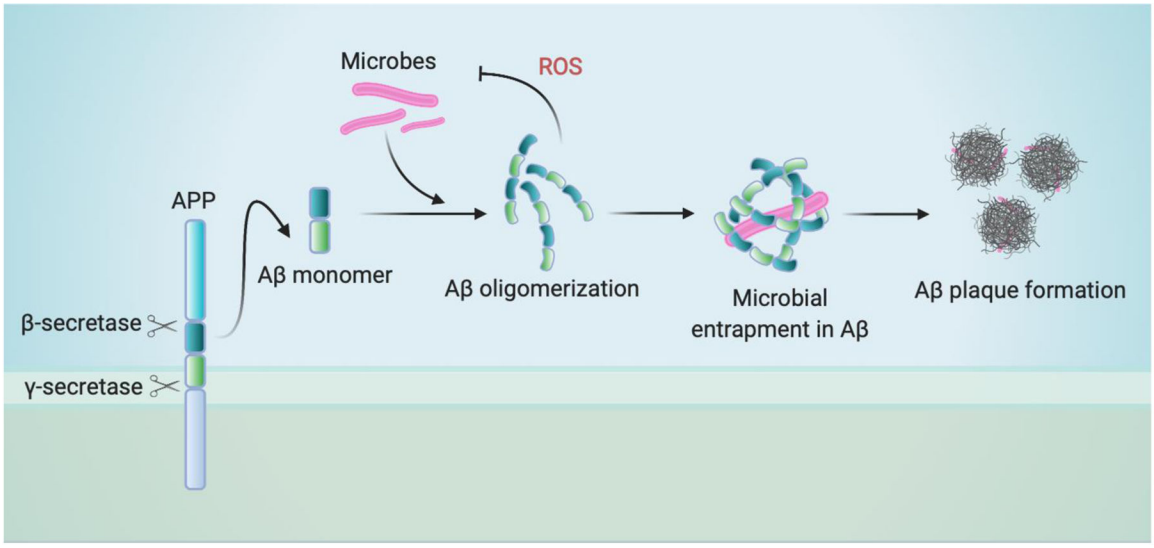

Figure 1. The antimicrobial protection hypothesis of amyloid beta and Alzheimer's disease.

The cleavage of the amyloid precursor protein (APP) can produce amyloid beta (Aβ) in its monomeric form. The oligomerization of Aβ is thought to help protect the brain against CNS-invading microbes. Aβ oligomers are believed to limit pathogen spread in the brain by promoting the production of reactive oxygen species (ROS) and also by physically encapsulating microbes to limit invasion of host cells. In line with this reasoning, many different microbes have been found to associate with Aβ upon examination of post-mortem AD brains. While the antimicrobial functions of Aβ can potentially play beneficial roles, this process must be tightly controlled as the formation of Aβ aggregates in response to infection can incite the spread of pathological Aβ plaques.

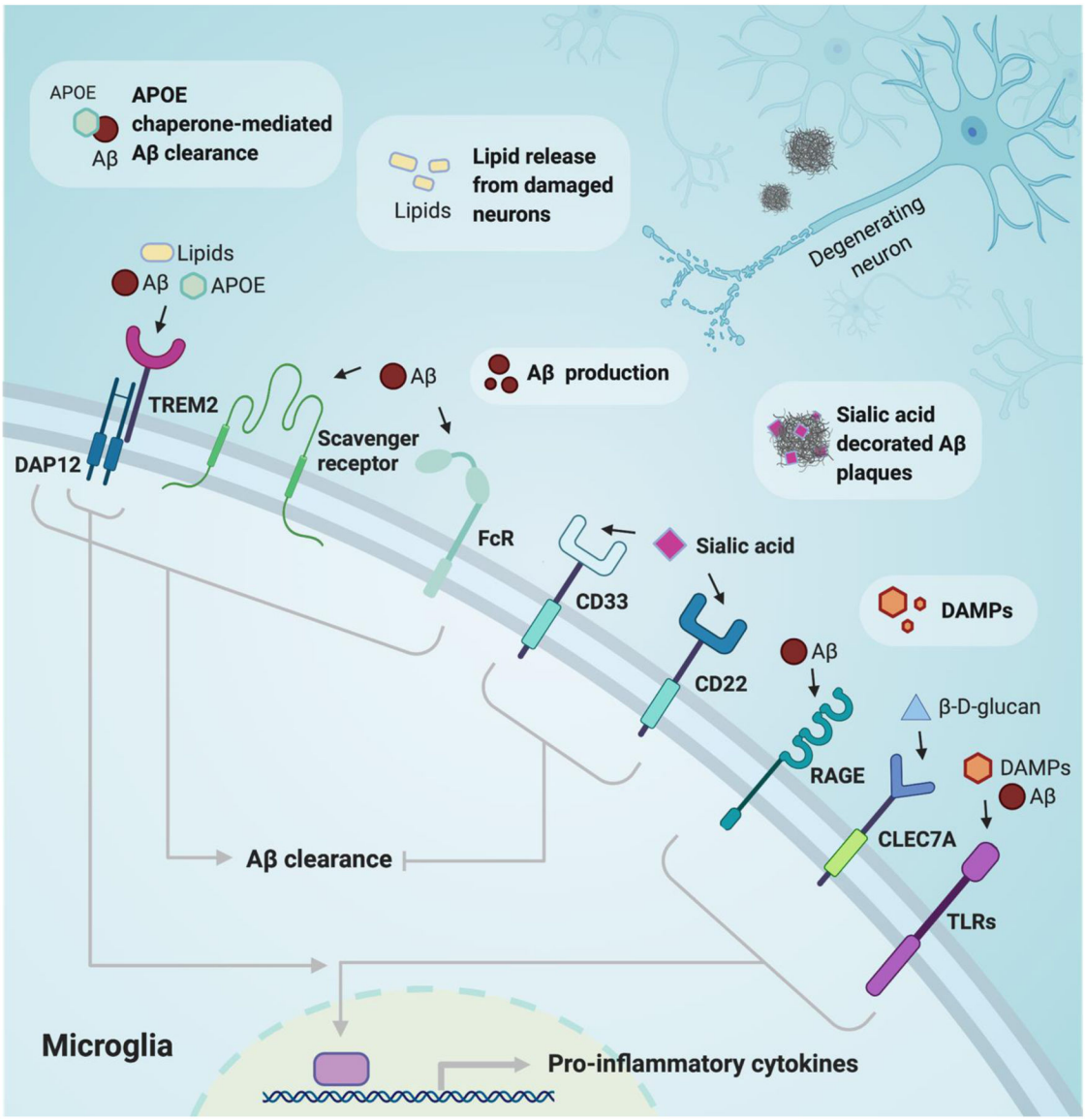

Figure 2. Microglial surface receptors that coordinate innate immune responses in AD.

TREM2 recognizes Aβ, lipids released from damaged neurons, and the Aβ chaperone APOE in AD. TREM2 activation critically contributes to Aβ clearance and also regulates downstream cytokine production. Aβ activation of scavenger and Fc receptors (FcRs) coordinates microglial-mediated Aβ clearance. In contrast, CD33 and CD22 bind sialic acid that decorates Aβ plaques, and inhibit downstream signaling events that are required for beneficial microglial responses and Aβ clearance. RAGE, Clec7a, and TLRs are also known to modulate microglial cytokine production in response to Aβ and DAMPs associated with AD.

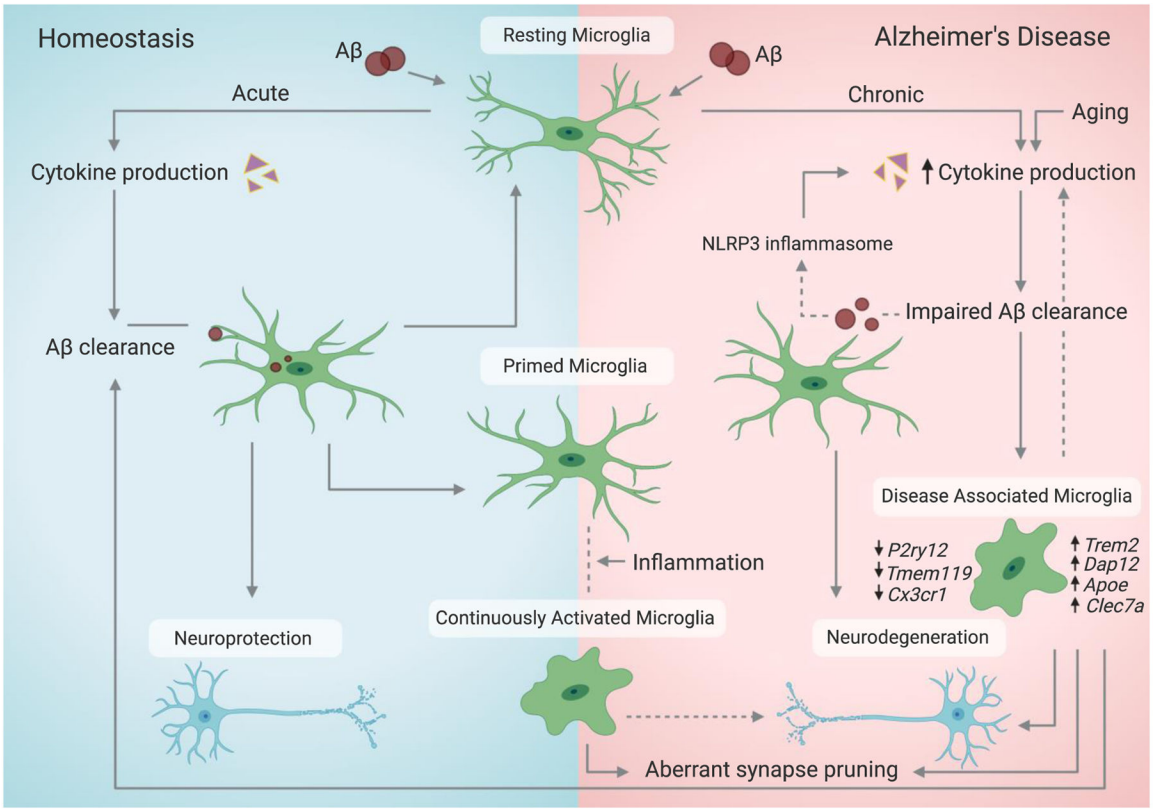

Figure 3. The evolving functions of microglia in homeostasis and disease.

In homeostasis, acute exposure of microglia to Aβ initiates a temporary cytokine response that promotes Aβ clearance. Following proper disposal of Aβ, microglia typically revert back to a homeostatic resting state. However, this exposure can also prime microglia, and upon secondary or chronic exposure to stress, such as inflammation, this can lead the activated microglia to initiate neurotoxic mechanisms that provoke neuronal loss and excessive synaptic pruning. Upon aging or chronic exposure to Aβ, as microglia witness in AD, excessive levels of cytokines are produced which can impair proper microglial clearance of Aβ. Deposition of Aβ can promote NLRP3 inflammasome activation, which further perpetuates inflammatory cytokine production and subsequent deficits in Aβ clearance. In both aging and AD, microglial populations are known to take on a transcriptional signature known as “disease associated microglia” or DAM. This change is distinguished by microglial downregulation of homeostatic genes and an upregulation of genes associated with increased microglial activation and inflammatory responses. The role of DAMs in the AD brain are thought to be enigmatic in nature. For instance, DAMs are neurotoxic and lead to neuronal damage and synapse loss. However, DAMs are also able to promote Aβ clearance.

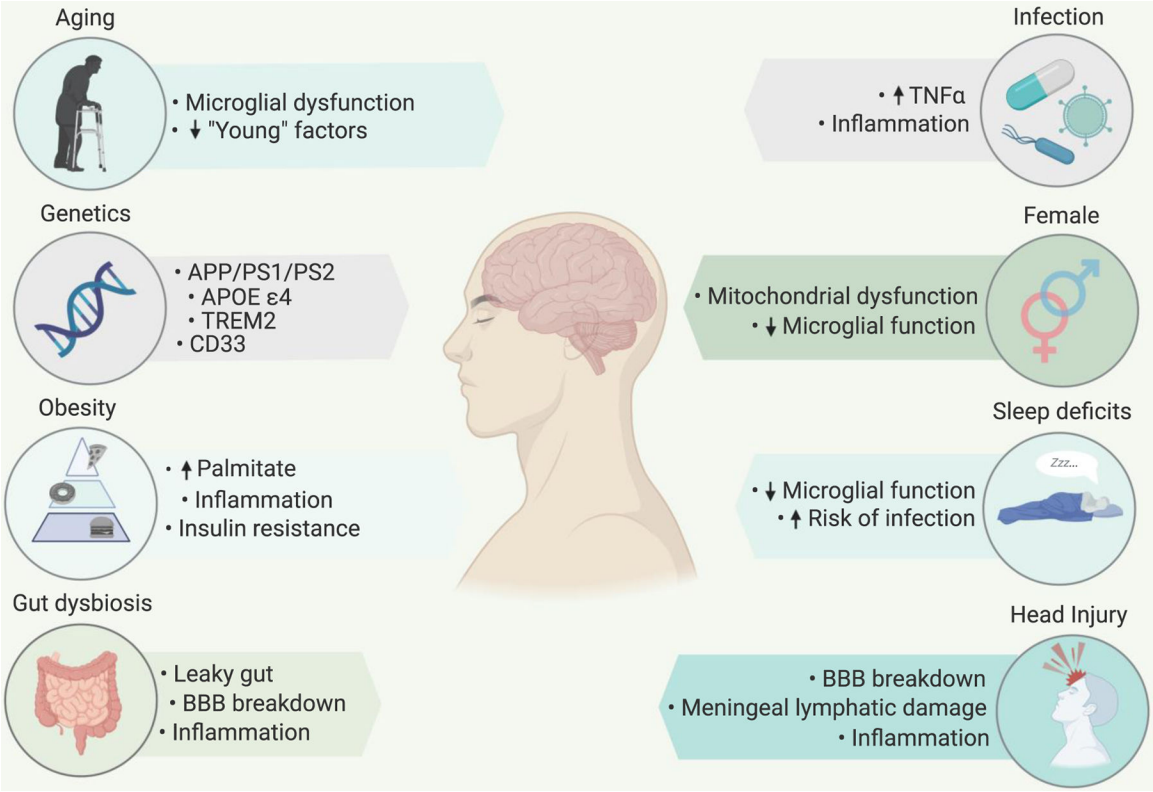

Figure 4. Immune dysfunction underlies the ability of AD risk factors to impact neurodegenerative disease development.

Several genetic and peripheral factors are known to modulate AD risk. Among these factors, increased AD risk can arise from impaired microglial function amidst aging, genetic variation, sleep deficits, and in females. Additionally, obesity, gut dysbiosis, systemic inflammation, and head injury are known to cause disruptions in blood-brain barrier (BBB) integrity. BBB disruptions can contribute to a heightened risk of disease by means of altered microglial function and impaired removal of AD pathology.

Table 1.

AD GWAS variants associated with innate immune signaling

Gene	Function	Variant function in AD	References
APOE	Lipid transport	Aβ aggregation APP transcription Tangle pathology Mitochondrial dysfunction	23,24,301
TREM2	Inflammatory response Phagocytosis Cellular metabolism	Aβ accumulation Impaired microglial response	65,302,303
CD33	Cellular activity inhibition	Aβ accumulation	79,82,304,305
CLU	Extracellular chaperone Lipid transport Immune modulation Complement	Binding of Aβ	306–308
ABCA7	Lipid homeostasis Cell membrane transport	APP processing regulation Aβ secretion Impaired phagocytosis	79,309,310
BIN1	Endocytosis Inflammation Calcium homeostasis	Tau propagation Neuronal degeneration	311,312
CR1	Complement Microglial phagocytosis	Aβ accumulation Inflammation	306,313
SORL1	Endocytosis Lipid metabolism	APP processing Aβ accumulation	314
IL-34	Survival and differentiation of monocytes	Aβ neurotoxicity	168,315,316
MS4A gene cluster	Calcium signaling Immunity	Reduced sTREM2 production	79,304,317,318
CD2AP	Cytoskeletal dynamics Endocytosis Synapse function	Enhanced Aβ generation Tau-induced toxicity	79,304,319
EPHA1	Immunity Endocytosis	Uncharacterized	79,304,320
INPP5D	Immunity Myeloid cell regulation	Inhibition of TREM2 signaling	321,322
SHARPIN	Inflammation NF-κB activation	Attenuated inflammatory response	323
TREML2	Microglial proliferation	Neuronal degeneration	324
SPPL2A	TNF signaling	Immune cell regulation	308,325
HLA-DR	Immunity Antigen presentation	Aβ accumulation Inflammation	308,326