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REVIEW

Advances in the Understanding of the Correlation Between Neuroinflammation and Microglia in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a fatal neurodegenerative disease with a subtle and progressive onset and is the most common type of dementia. However, its etiology and pathogenesis have not yet been fully elucidated. The common pathological manifestations of AD include extraneuronal β-amyloid deposition (Aβ), intraneuronal tau protein phosphorylation leading to the formation of 'neurofibrillary tangles' (NFTs), neuroinflammation, progressive loss of brain neurons/synapses, and glucose metabolism disorders. Current treatment approaches for AD primarily focus on the 'Aβ cascade hypothesis and abnormal aggregation of hyperphosphorylation of tau proteins', but have shown limited efficacy. Therefore, there is an ongoing need to identify more effective treatment targets for AD. The central nervous system (CNS) inflammatory response plays a key role in the occurrence and development of AD. Neuroinflammation is an immune response activated by glial cells in the CNS that usually occurs in response to stimuli such as nerve injury, infection and toxins or in response to autoimmunity. Neuroinflammation ranks as the third most prominent pathological feature in AD, following Aβ and NFTs. In recent years, the focus on the role of neuroinflammation and microglia in AD has increased due to the advancements in genome-wide association studies (GWAS) and sequencing technology. Furthermore, research has validated the pivotal role of microglia-mediated neuroinflammation in the progression of AD. Therefore, this article reviews the latest research progress on the role of neuroinflammation triggered by microglia in AD in recent years, aiming to provide a new theoretical basis for further exploring the role of neuroinflammation in the process of AD occurrence and development.

Keywords: neuroinflammation, microglia, Alzheimer's disease, review, *Trem2*

Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease, is the most common type of dementia in elderly people. Currently, there are approximately 10 million AD patients in China, and by 2050, this number is expected to increase to more than 40 million. AD is characterized by progressive cognitive decline, mental and behavioral abnormalities, and a reduced ability to perform daily activities.[1] The characteristic pathological changes are cortical atrophy and a decrease in the number of memory neurons, accompanied by amyloid-β (Aβ) deposits and neurofibrillary tangles (NFTs).[2,3] The etiology and pathogenesis of AD remain unclear, despite an increase in the number of patients with this disease in recent years. The amyloid cascade hypothesis and tau hypothesis are the main explanations of the pathogenic mechanisms of AD.[4] However, recent failures in therapeutic strategies targeting Aβ have raised doubts about the accuracy of the Aβ cascade hypothesis. Further research has revealed that neuroinflammation, abnormal calcium regulation, mitochondrial dysfunction, and abnormalities in the autophagic lysosomal degradation pathway are also closely linked to the development of AD.[5,6] High levels of neuroinflammatory factors have been observed in the cerebral cortex and cerebrospinal fluid of AD patients, indicating a sustained inflammatory response in their brains. The

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identification of AD risk genes associated with innate immune function and related pathologies suggests that neuroinflammation plays an important role in the pathogenesis of AD.[7,8] High levels of neuroinflammatory factors have been observed in the cerebral cortex and cerebrospinal fluid of AD patients, indicating a sustained inflammatory response in their brains[7]. Moreover, hyperactivation of microglia leads to a persistent inflammatory response that contributes to the progression of AD.[9]

To date, the US Food and Drug Administration has approved a total of seven drugs for treating AD. These include three acetylcholinesterase inhibitors (donepezil, galantamine, and carboplatin), the N-methyl-D-aspartate receptor antagonist memantine hydrochloride, Namzaric, and two anti-Aβ-mab approvals in January 2021 and January 2023—adunizumab and lencanizumab.[10] However, it is important to note that these drugs only improve symptoms and do not reverse the condition. Some drugs or therapies have not been validated in clinical trials and may even have a negative impact on cognitive function in AD patients.[10] The exact cause of AD is still unknown, and a definitive cure or effective symptom relief has not yet been developed. Neuroinflammation, which plays a key role in AD, could be a promising new target for therapy.[11] Microglia are a crucial component of the innate immune system in the central nervous system (CNS), playing a significant role in neuroinflammatory responses. They are involved in various pathological processes related to neurodegenerative diseases and contribute to acute and chronic inflammatory responses, influencing the direction of inflammatory outcomes.[12,13] During brain development, microglia and neurons form simultaneously. Microglia support neuron survival and neural circuit formation by releasing neurotrophic factors like insulin-like growth factor-1.[14] They also participate in non-inflammatory clearance of damaged neurons through TREM2 signaling-mediated phagocytosis, inducing programmed cell death in neurons.[15] Additionally, microglia regulate synaptic density, glutamatergic receptors, and dendritic spines, as well as synaptic plasticity through DAP12 signaling.[16,17] Overall, microglia play a crucial role in maintaining CNS homeostasis. Thus, this article reviews recent research on neuroinflammation, particularly focusing on the role of microglia in the development of AD, to stimulate further consideration among researchers regarding potential directions for diagnosing and treating AD.

Microglia and AD

Microglia

Glial cells in the CNS are primarily composed of Microglia, astrocytes, and oligodendrocytes.[18] Microglia, which constitute approximately 10% of the total cell population in the CNS, are the predominant mononuclear transitional phagocytes within brain tissue.[19,20] The brain is an immune-privileged organ, and microglia are one of the only resident immune cells of the brain, providing the primary immune defense of the CNS[21,22] (Figure 1). Resting state (M0 type) microglia have a branched morphology and play an "immunosurveillance" role. In the activated state, microglia are phagocytic, and when disease or injury occurs, activated microglia can participate in the inflammatory response and immune response as colonized inflammatory cells in the CNS.[23,24] Classically activated (M1 type) microglia release proinflammatory factors and toxic substances to kill pathogens[20] (Figure 2). Clinical studies have shown that overactivated M1 microglia can cause neuronal dysfunction, injury, and degeneration and play an important role in AD.[25] The alternatively activated (M2) microglia engage in phagocytosis to remove harmful substances such as bacteria, dead cells, and aggregated proteins from the CNS and secrete soluble factors (eg, chemoattractants, cytokines, and neurotrophic factors) to participate in the immune response and repair of damaged brain tissues, thus participating in neuroprotection.[19,20]

In recent years, several genome-wide association studies based on clinical AD patient samples have shown that over 50% of confirmed genetic variants in AD-related genes are linked to innate immune function and microglial function. Specifically, genes such as triggering receptor expressed on myeloid cells-2 (TREM2), CD33, apolipoprotein E (APOE) 4, CR1, and HLA-DRB1 have been implicated. Activation of microglial cell surface receptors such as TREM2 and Toll-like receptors in pathological states such as AD has been observed, with these receptors binding to Aβ and APOE and migrating directionally toward sites of injury.[26,27] In October 2020, a novel gene, FAM171A2, was discovered to regulate the production of progranulin (PGRN), a precursor of vascular endothelial cells. PGRN, a secreted glycoprotein, plays various roles in neural development, regeneration, neuroinflammation, and autophagy, among other life processes.[28,29] Dysregulation of PGRN has been associated with the development of neurodegenerative disorders such as AD,

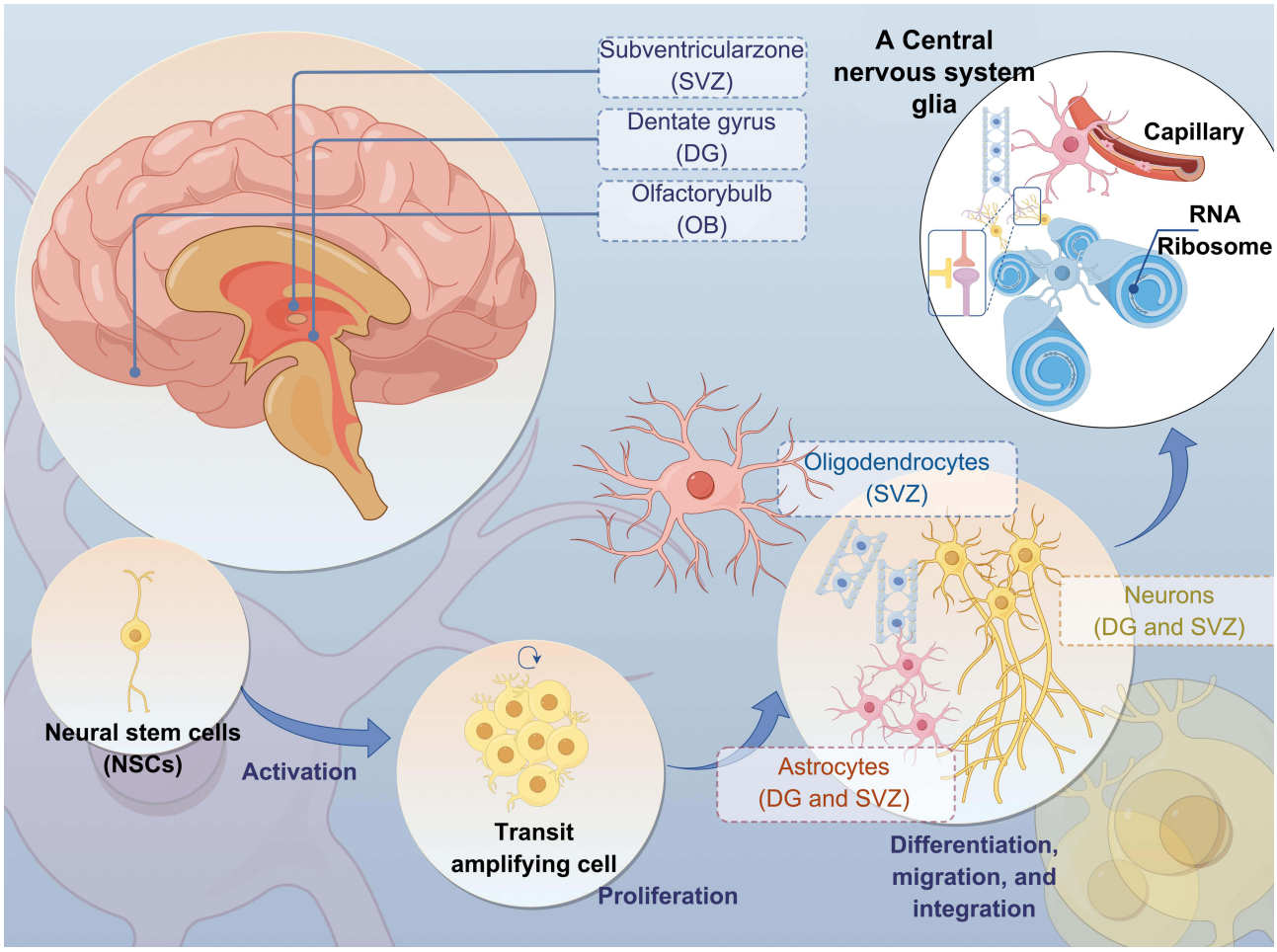

Figure 1 Illustration depicting the associations between neurons and glial cells in the CNS. (The CNS is primarily made up of neurons and glial cells, including astrocytes, oligodendrocytes, and microglia. Glial cells play a crucial role in supporting the survival of neurons by providing them with trophic factors).

Parkinson's disease, and frontotemporal lobe dementia.[30–33] Furthermore, some studies have proposed that microglia can specifically detect amyloid plaques in the early stages of AD pathogenesis by aggregating around these plaques to create a physical barrier that impedes the spread of neurotoxicity.[34] This suggests that microglia-mediated neuroinflammation plays a crucial role in AD pathology and may be linked to the diversity and functional heterogeneity of microglia in the context of AD[30] (Figure 3).

TREM2 and sTREM2

The protein encoded by the TREM2 gene is an intrinsic immune cell receptor expressed on the surface of myeloid cells, and in the brain, it is expressed on microglia;[35] this protein is located mainly in the intracellular Golgi apparatus and plays an important role in the regulation of microglial energy metabolism and polarization. TREM2 has now been identified as a potential therapeutic target for AD. Research has shown that a variant of the TREM2, R47H, is strongly associated with AD, and its impact on disease progression is comparable to that of the apolipoprotein E ε4 gene. In vitro, the common variant (CV) of TREM2 has been shown to interact with anionic lipids, while the R47H mutation hinders this binding ability. In this study, researchers created transgenic mice that expressed human CV or R47H TREM2 but lacked endogenous TREM2 in the 5XFAD AD model.[36] The results showed that only the CV transgene was able to restore Aβ-induced microgliosis and microglial activation, suggesting that R47H hinders TREM2 function in vivo.[36] TREM2 is a single-channel transmembrane receptor belonging to the immunoglobulin superfamily. It consists of an extracellular structural domain with immunoglobulin-containing regions, a transmembrane domain, and a short

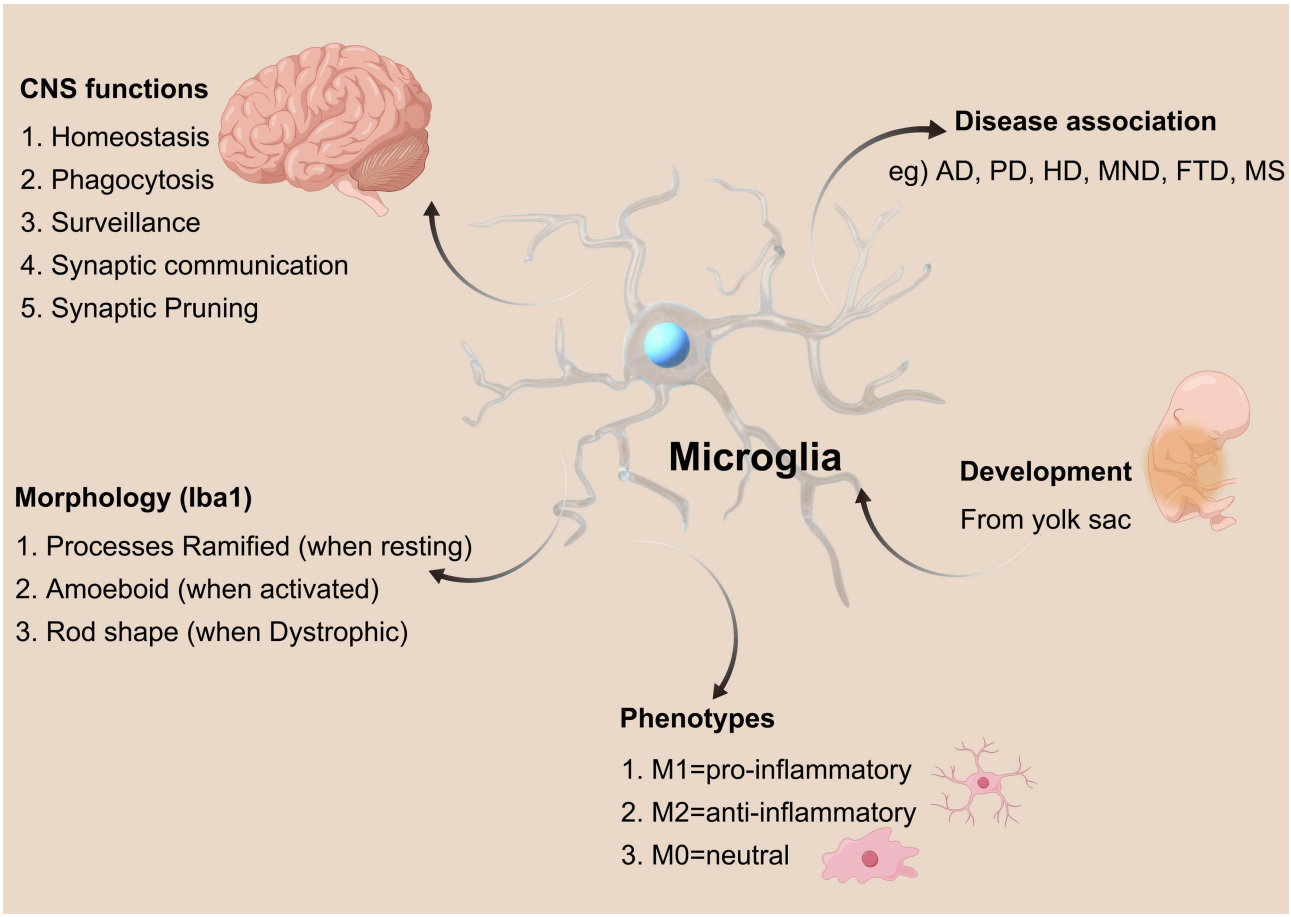

Figure 2 Microglia Function and Communication (Microglia play essential roles in the CNS, such as synaptic pruning, synaptogenesis, axon fasciculation, neurite formation, programmed cell death, astrocyte activation and proliferation, and oligodendrocyte differentiation and myelogenesis).

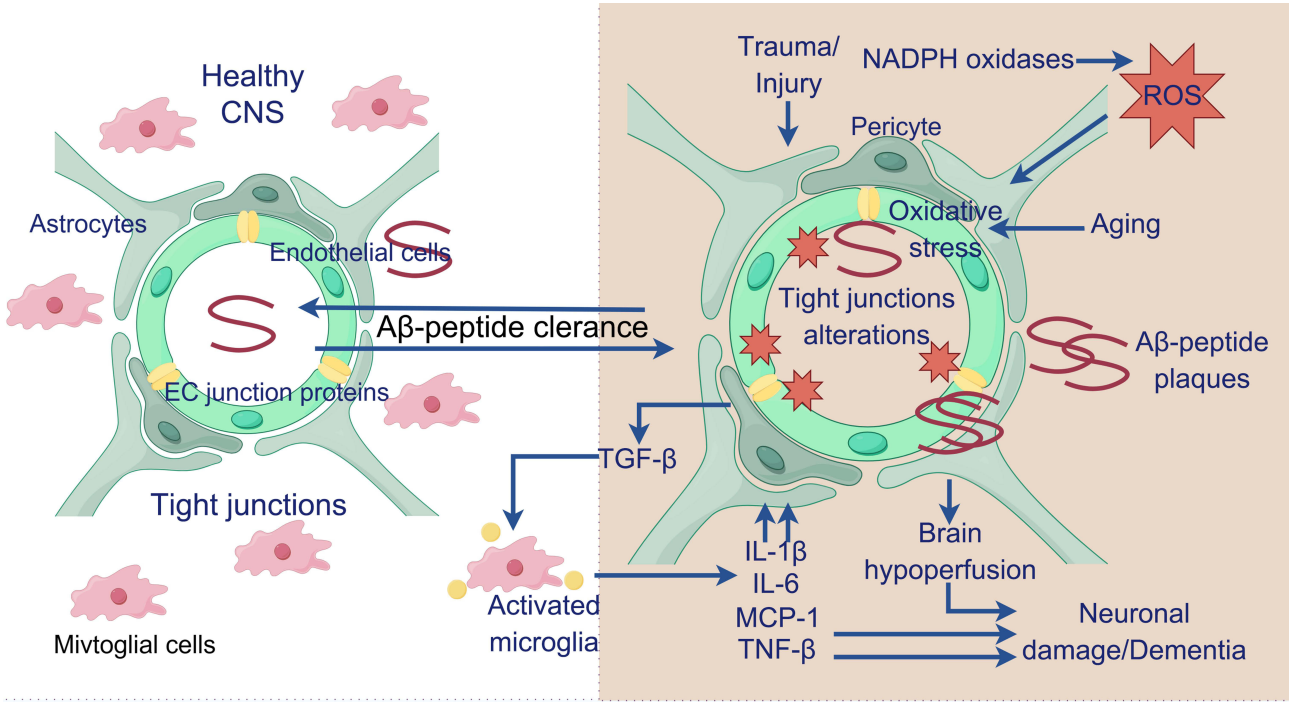

Figure 3 Impact of microglia on AD. (Healthy and young cells, such as microglia, release pro- and anti-inflammatory mediators, growth factors, and bioenergetic pathway mediators. These substances play a role in maintaining brain homeostasis, supporting neuronal survival, and preserving cognitive function).

cytoplasmic tail region.[37] This receptor is capable of binding various molecules, such as pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cellular debris, lipids, and apolipoproteins, through its immunoglobulin domains. Activation through cleavage by ADAM family enzymes such as ADAM10 and ADAM17 results in the release of a secreted form of the extracellular domain known as soluble triggering receptor expressed on myeloid cells-2 (sTREM2), halting the signaling cascade associated with TREM2. This cascade is crucial for microglial survival and proinflammatory signaling.[38,39] On the other hand, the transmembrane domain of TREM2 can transmit intracellular signals by interacting with a ligand called transmembrane immune signaling adaptor (TYROBP or DAP12). DAP12, a signaling bridging protein expressed in cells involved in the innate immune response. DAP12 contains an immunoreceptor tyrosine-based activation motif that is activated by binding to the TREM2 transmembrane domain, leading to a cascade of intracellular signaling events.[40] The association between TREM2 and DAP12 is coordinated by an electrostatic interaction between a lysine in TREM2 and an aspartic acid in DAP12, and once DAP12 binds to TREM2, the tyrosine residue on DAP12 is phosphorylated, causing the recruitment of spleen tyrosine kinase. This triggers a series of tyrosine phosphorylation events that subsequently activate downstream mediators such as phospholipase Cγ2, phosphatidylinositol 3-kinase (PI3K), mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK),[41,42] leading to cellular activation. Functional studies have demonstrated that the absence of TREM2 hinders proper microglial reactions to damage and cues that typically induce cell movement in various ways. In a brain slice assay conducted ex vivo, the lack of TREM2 diminished the migration distance of microglia.[43] In an in vivo experiment, microglia deficient in TREM2 exhibited reduced migration toward injected apoptotic neurons. Additionally, the extension of microglial processes toward areas of laser-induced focal CNS injury in the somatosensory cortex is delayed.[43] These findings suggest that alterations in the gene expression of TREM2 and sTREM2 affect microglial function (Figure 4).

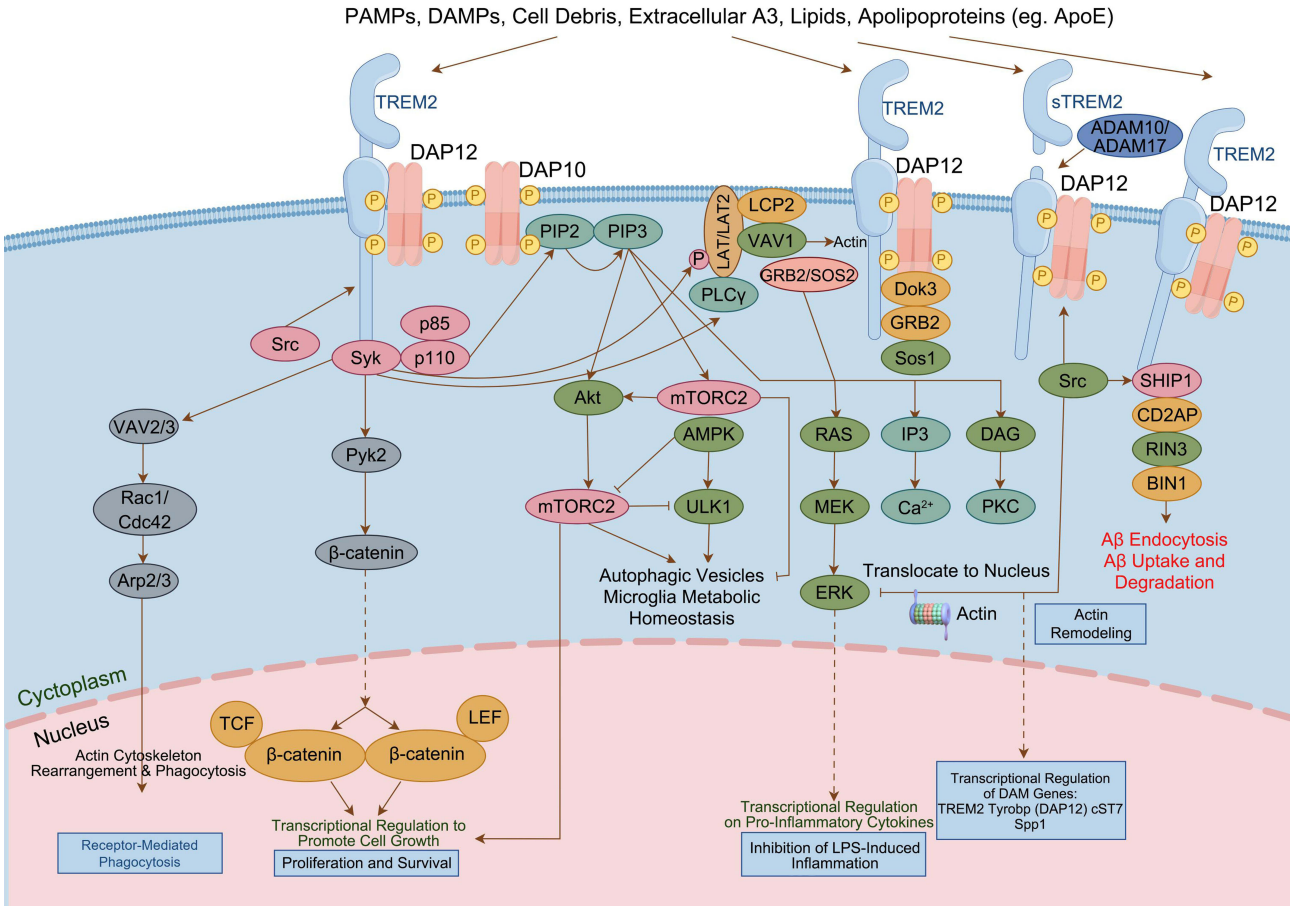

Figure 4 Schematic diagram of TREM2 signaling interactions.

CD33

Research on AD has identified more than 30 genetic loci, many of which are linked to the immune response and microglia.[44] Notably, CD33 and TREM2 have been highlighted in these studies.[45–49] CD33 encodes a sialic acid-binding immunoglobulin-like lectin found on myeloid progenitor cells, monocytes, and macrophages. It plays a role in cell adhesion and endocytosis, as well as inhibiting cytokine release and regulating immune cell growth[50] and TLR4 signaling.[51] CD33 is a type I transmembrane protein that acts as an inhibitory immune receptor. It is part of the Siglec family. The external domains of Siglecs can be used to detect glycans containing sialic acid, influencing immune cell signaling pathways via their internal tail.[52] CD33 belongs to the CD33-related subgroup of Siglecs and displays evolutionary variation among different mammalian species.[53] Its presence in microglia within the brain is particularly intriguing due to its association with AD susceptibility.[54]

NLRP3 Inflammasome

Nucleotide-binding domain-like receptor protein 3 (NLRP3) is widely distributed in the CNS and is highly expressed in microglia. Microglia are among the major regulators of the neuroinflammatory response, and neurodegeneration involves overactivation of microglia and upregulation of proinflammatory factors, which play important roles in neurodegenerative diseases.[55–57] In addition, abnormal Aβ amyloid aggregation, mitochondrial dysfunction, autophagy, and defective dopamine receptor function are strongly associated with microglial NLRP3 inflammasome-mediated neuroinflammation.[58–60]

The NLRP3 inflammasome is a multiprotein complex composed of the pattern recognition receptor NLRP3, the junction protein apoptosis-associated speck-like protein, and the aspartate-specific cysteine protease 1 precursor.[61] The NLRP3 receptor is expressed in glial cells and the CNS and is composed of three distinct structural domains: the leucine-rich repeat (LRR) domain, the nucleoside triphosphatase domain, and the pyrin domain (PYD).[61] The LRR domain recognizes PAMPs or DAMPs, the nucleoside triphosphatase domain plays a crucial role in receptor activation, and the PYD domain mediates downstream signaling. When cells are exposed to DAMP- or PAMP-associated stimuli, which are recognized by the LRR at the carboxyl terminus of NLRP3, NLRP3 oligomerizes and accumulates the splice protein apoptosis-associated speck-like protein through PYD-PYD interactions and then binds to the pro-caspase-1 domain to assemble the inflammasome complex, which induces Caspase-1 autocatalysis.[62,63] Finally, inflammatory factors such as interleukin (IL)-1β and IL-18 are cleaved from inactive precursors to activated forms and released from the cell.[56,57] Additionally, activated Caspase-1 can trigger pyroptosis, a form of inflammatory programmed cell death characterized by plasma membrane rupture, the release of inflammatory mediators, and DNA damage.[64,65] The mechanism of pyroptosis remains unclear.[66] Activated Caspase-1 cleaves the GSDMD protein into two parts (the N-terminal domain and C-terminal domain) by inducing enzymatic activity. The N-terminal domain of GSDMD can form pores in the lipid membrane, destroy the osmotic pressure balance between the inside and outside of the cell, cause water influx and membrane expansion, ultimately leading to membrane dissolution and inducing the apoptosis of microglia and neurons[67,68] (Figure 5).

TREM2 and AD

In the pathogenesis of AD, the accumulation of Aβ in the brain is often accompanied by increased glial cell proliferation and lipid deposition, leading to the progressive development of neuroinflammation.[69] Microglia can recognize amyloid through receptors such as TREM2, Toll-like receptors, and CR1, triggering a signaling cascade that prompts microglia to detect and migrate to the site of injury.[70–72] Subsequently, soluble Aβ and tau proteins are engulfed by microglia through phagocytosis, and upon fusion with lysosomes, vesicles and their contents are released and degraded,[73] ultimately reducing Aβ levels and slowing the formation of senile plaques. This process also helps prevent the formation of NFTs, thereby aiding in the prevention and delay of AD onset and clinical progression.[74] Senile plaques are nerve spots formed by abnormal deposition of Aβ39-42 in the brain. Aβ39-42 is a protein composed of 39~42 amino acid residues formed by amyloid precursor protein (APP) cleaved by β- and γ-secretory enzymes. Aβ exists in monomeric, oligomeric, and fibrillar forms, with oligomeric Aβ being the primary contributor to cognitive impairment and neurodegeneration in AD. Aβ oligomers can bind to the following receptors and influence nerve cell function through distinct signaling pathways.[75] Research has revealed that microglia rich in TREM2 play a crucial role in surrounding and compacting early amyloid

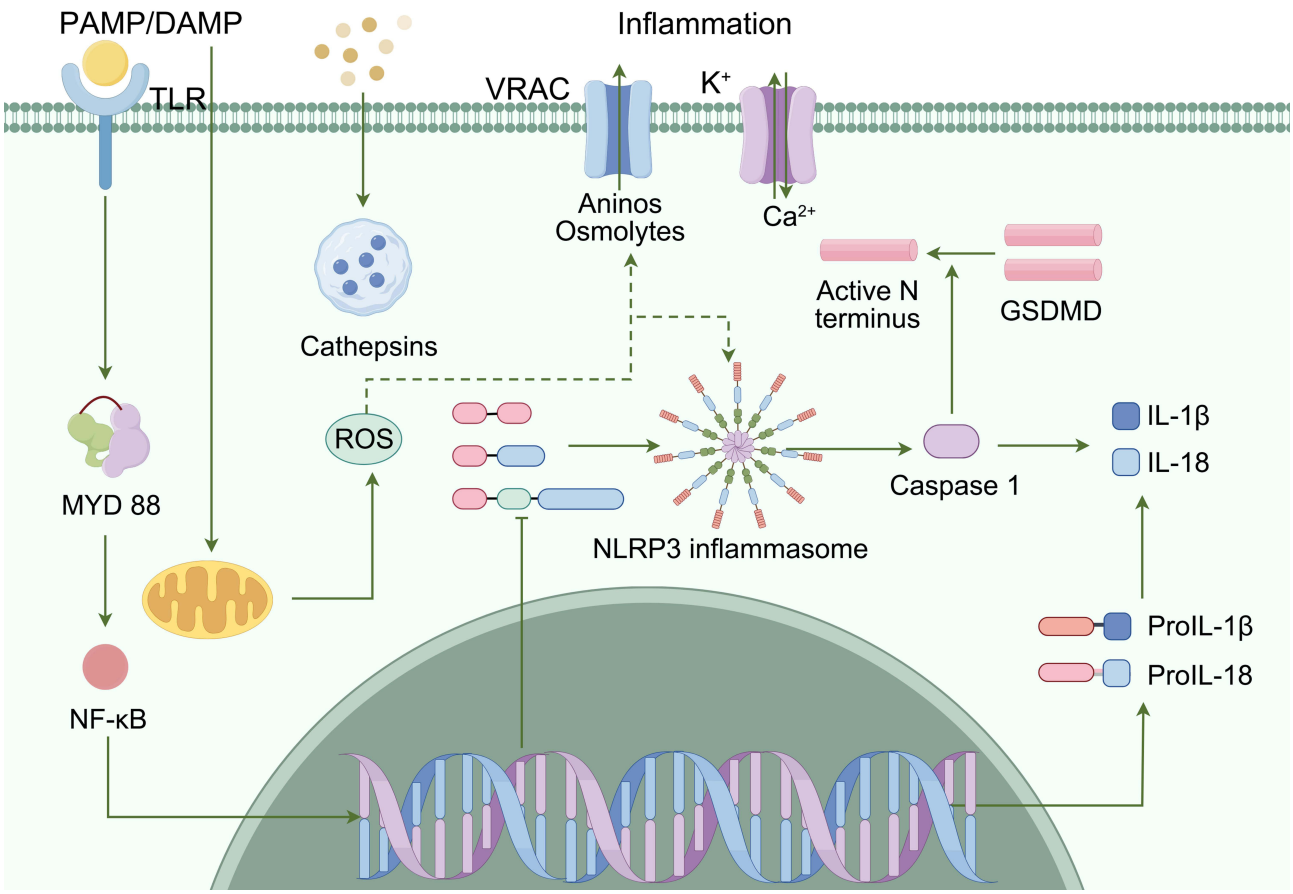

Figure 5 Schematic diagram of NLRP3 inflammasome signaling pathway.

fibrils and plaques. In mice lacking TREM2 or DAP12, as well as in individuals with the R47H mutation in the TREM2 gene, microglia exhibit a significantly diminished capacity to encase amyloid deposits.[76]

Consequently, there was an increase in the formation of more diffuse plaques containing elongated and branched amyloid fibrils, leading to increased exposure of neighboring neurites.[76] This alteration was accompanied by intensified neuritic tau hyperphosphorylation and axonal degeneration surrounding amyloid deposits.[76] The extracellular domain of TREM2 is responsive to the accumulation of Aβ in AD,[77] and TREM2 has the ability to bind to various forms of Aβ, with the strongest affinity for Aβ oligomers.[78] Knocking out TREM2 results in impaired proliferation and activation of microglia near the lesion site, preventing them from carrying out their normal brain-protective functions effectively and ultimately worsening disease progression.[79–81] In mouse models of AD, microglia lacking TREM2 are unable to multiply and form clusters around the Aβ plaques associated with AD.[36] TREM2-deficient N9 microglial cell lines, macrophages, and primary microglia all exhibited significantly decreased uptake of antibody-bound Aβ, leading to reduced clearance of amyloid plaques.[82] This study revealed a decrease in the expression of APOE and APOC1 in TREM2-deficient human microglia. Differentially expressed genes were found to be enriched in pathways related to "calcium signaling pathway regulation", "ERK1 and ERK2 cascade", and "cell migration". Upon activation of the TREM2 pathway, downregulated genes in TREM2-deficient microglia were significantly upregulated, leading to a shift in the enrichment pathway toward "positive regulation of leukocyte chemotaxis", "cellular response to tumor necrosis factor", and "positive regulation of the ERK1 and ERK2 cascade".[83] In terms of metabolism, TREM2 plays a role in maintaining cellular energy and biosynthesis, contributing to the pathological process of AD.[71] Additionally, an increase in the number of autophagic vesicles was detected in the microglia of a TREM2-knockout 5XFAD mouse model, which was reduced upon the addition of cyclocreatine to improve energy storage, indicating energy metabolism disorders in the microglia of TREM2-knockout mice.[71] In terms of cell activity, a study showed that TREM2 enhances

microglial survival through the activation of the Wnt/β-catenin signaling pathway. This finding also suggested that restoring Wnt/β-catenin signaling can be achieved when TREM2 activity is inhibited or decreased.[84] This highlights the potential of targeting the TREM2/β-catenin signaling pathway for AD treatment. Research has identified a group of lipoprotein particles, including LDL, and apolipoproteins, such as CLU/APOJ and APOE, as ligands of TREM2.[82] The binding of these ligands by TREM2 is hindered or decreased by disease-associated mutations such as AD. Aβ attaches to lipoproteins, and this combination is effectively absorbed by microglia in a TREM2-dependent manner.[82] Microglia lacking Trem2 displayed decreased internalization of LDL and CLU. The absorption of Aβ-lipoprotein complexes was diminished in macrophages from individuals with a TREM2 AD variant.[82] These findings establish a connection between three genetic risk factors for AD and shed light on a potential mechanism through which mutant TREM2 increases the risk of AD.

Microglia play a crucial role in controlling synaptic remodeling within the CNS. Activation of the classical complement pathway facilitates microglia-driven synaptic pruning both in developmental stages and during disease progression.[85] Studies using conditional knockout mice revealed that the specific deletion of SIRPα in microglia leads to a reduction in synaptic density.[85] In human tissue, a decrease in microglial SIRPα expression has been noted to be correlated with the progression of AD.[85] CD47, which shields synapses from excessive pruning during development, points to the involvement of microglial SIRPα, a receptor for CD47, in the process of synaptic remodeling.[85,86] Furthermore, the absence of microglial SIRPα results in an increased loss of synapses due to microglial engulfment, ultimately leading to heightened cognitive impairment.[85,87] A separate study revealed that the extracellular domain of TREM2 binds strongly to C1q, which is responsible for initiating the classical complement pathway, effectively inhibiting the activation of this pathway.[88,89] In postmortem brain tissue samples from AD patients, TREM2 was observed to form protein complexes with C1q. The number of these complexes was found to have a negative correlation with the level of complement protein C3 deposition and a positive correlation with synaptic protein levels.[88] Using a mouse model of AD in which the Trem2 gene was absent, researchers noted that in the early stages of the disease, the absence of the Trem2 gene did not impact the level of AD pathologic protein deposition or the morphology or quantity of microglia.[88] However, in a mouse model of AD in which the Trem2 gene was absent, researchers noted that in the early stages of the disease, the absence of the Trem2 gene did not impact the level of AD pathologic protein deposition or the morphology or quantity of microglia[88] (Figure 6).

sTREM2 and AD

sTREM2 can penetrate the cerebrospinal fluid-brain barrier and is found at heightened levels in the cerebrospinal fluid of patients with various neurological disorders, including AD, Parkinson's disease, frontotemporal dementia with granulosomal protein mutations, and individuals with normal cognitive function who are undergoing natural aging.[91–94] This finding suggested that sTREM2 levels can serve as an indicator of microglial activation status and neuronal degeneration.[95] Research has validated sTREM2 as a potential biomarker for detecting AD.[96] Moreover, no vesicular phagocytosis of APOE was detected in TREM2-deficient microglia.[97] Furthermore, studies have revealed that sTREM2 may play a role in reducing microglial apoptosis by activating the Akt-GSK3β-β-catenin signaling pathway and promoting microglial survival through the PI3K/Akt signaling pathway, thereby exerting neuroprotective effects.[39,83] Experiments in which the sTREM2-Fc protein was injected into the hippocampus of normal mice and TREM2-knockout mice revealed increased expression levels of inflammatory factors, altered microglial morphology, and enhanced immune responses, suggesting that enhancing the sTREM2 signaling pathway could be a therapeutic approach for AD.[98] In addition, direct injection of recombinant sTREM2 protein or adenovirus transfection into 5xFAD mice to increase sTREM2 levels can promote the proliferation and phagocytic activity of microglia near amyloid plaques and accelerate the phagocytosis and clearance of Aβ plaques.[98] One study was the first to examine CSF sTREM2 within the amyloid/tau/neurodegeneration classification framework. The findings from the AD Imaging Initiative cohort show that elevated levels of CSF sTREM2 in the early stages correspond with increased tau pathology and neurodegeneration. Conversely, lower levels of CSF sTREM2 are linked to Aβ deposition without tau deposition and neurodegeneration. Studies have shown that microglial phagocytosis may not always be beneficial, and its effects vary depending on the specific clinical stage. In patients with AD who exhibit only pathophysiological changes without significant clinical symptoms, increased microglial phagocytosis can decrease Aβ levels and slow the formation of SPs and NFTs.[74] However, due to the limited number of lysosomes, microglial phagocytosis decreases after the uptake of Aβ and tau proteins.[99] Subsequent to phagocytosis, the inflammatory vesicular cascade triggered by cellular

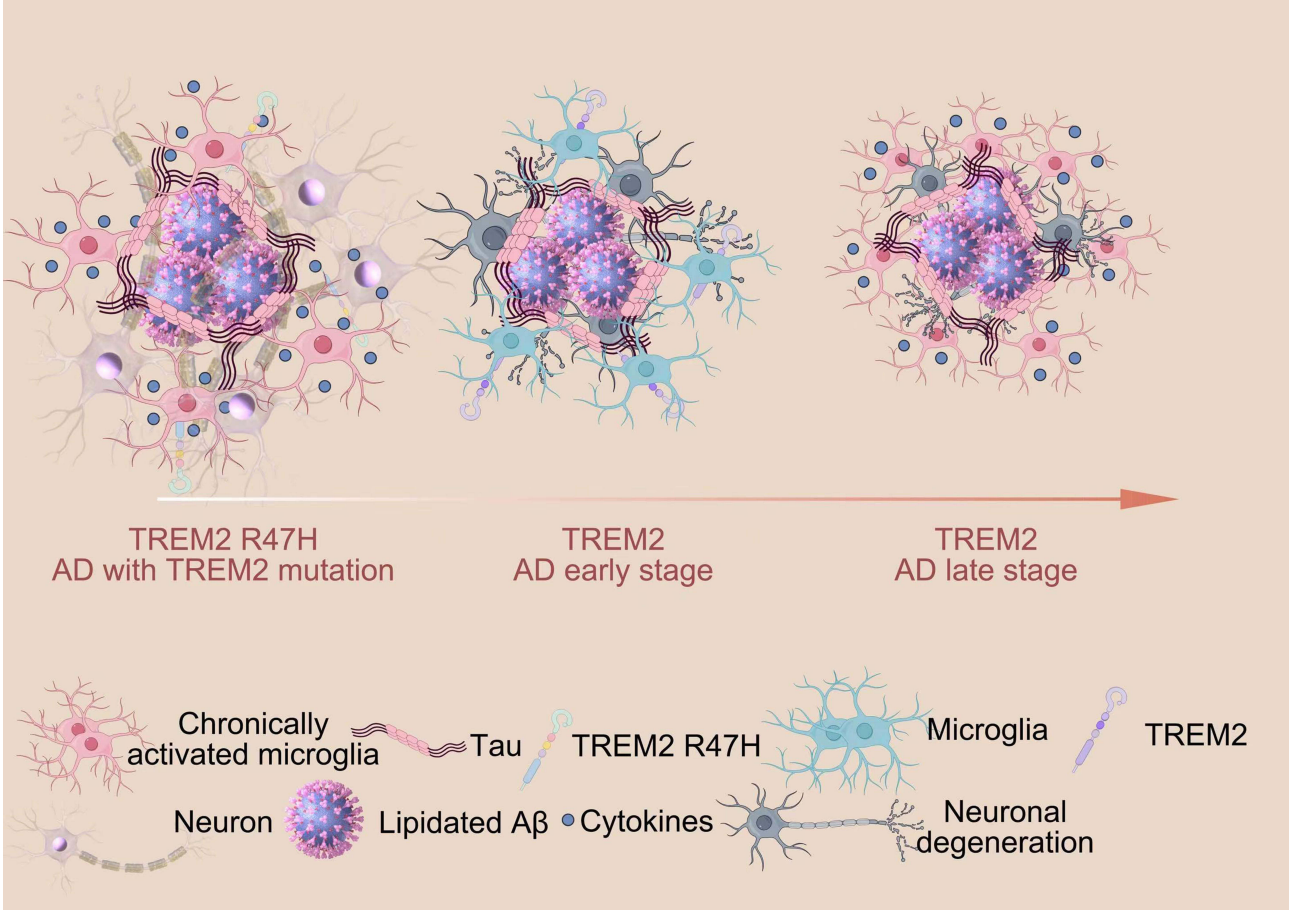

Figure 6 Function of TREM2 in AD.[90] (TREM2 expression plays a crucial role in regulating the proliferation, migration, and phagocytosis ability of microglia. In the early stages of AD, microglia expressing TREM2 effectively surround and interact with lipidated Aβ plaques to clear them, thus preventing the spread of Aβ. However, in the late stages of AD, these TREM2-expressing microglia struggle to clear the aggregates, leading to chronic inflammation, reduced phagocytosis ability, and the induction of tau phosphorylation and aggregation. Individuals with TREM2 mutations experience weakened TREM2 affinity, resulting in impaired microglial proliferation and migration, which hinders the effective clearance of Aβ aggregates. Furthermore, TREM2 mutations lead to increased cytokine secretion from microglia, ultimately exacerbating the spread of Aβ and the phosphorylation and aggregation of tau, thereby worsening AD pathology).

metabolism, including NLRP3 and inflammatory cytokines such as TNF-α and IL-1, leads to microglial polarization toward a proinflammatory state. This, in turn, induces the secretion of proinflammatory cytokines, exacerbates the inflammatory response, hampers Aβ phagocytosis, and promotes the pathological accumulation of the Tau protein.[100,101]

CD33 and AD

The number of CD33-expressing microglia was found to be positively correlated with plaque burden and cognitive decline in AD.[102,103] However, higher CD33 expression in AD may be a response to disease pathology, such as brain inflammation. Research has shown that specific cytokines, such as IL-15, can induce the upregulation of CD33.[104,105] CD33 is predominantly expressed by microglia in the brain, suggesting that the genetic correlation between CD33 and AD susceptibility may be due to the regulation of microglial cell function by CD33.[106,107] Although a contributing role in myeloid cells outside the brain cannot be definitively ruled out, initial findings indicated increased expression of CD33 on microglia in AD brains.

The connection between CD33 and AD was initially revealed through genome-wide association studies, which identified the rs3826656 SNP as a susceptibility factor for late-onset AD.[45] Studies have shown increased CD33 expression in microglia within the AD brain, and the protective allele of the CD33 SNP rs3865444 was found to be correlated with decreased CD33 expression and insoluble Aβ42 levels in the brain.[102] The rs3865444 SNP is located in the CD33 promoter, which is located 372 base pairs upstream of the transcription start site. Initially, thought to affect

CD33 gene expression,[108] further analysis revealed a coinherited SNP, rs12459419, located four nucleotides into exon 2 of CD33, which influences mRNA splicing.[108,109] A recently identified CD33 SNP, rs2455069, has been suggested to be linked to the risk of developing AD in a small group of Italian patients.[110] In silico analysis indicated that a change in the amino acid at position 69 of hCD33 from arginine to glycine in the rare rs2455069 SNP could increase the affinity for Sia-containing ligands.[110] Further investigation is needed to confirm the association of this SNP with AD susceptibility in a larger patient population.

In the context of developing novel and effective approaches for treating AD, immunomodulatory receptors on microglia, including CD33, are considered promising targets for drug discovery.[111] Notably, various anti-CD33 antibody targeting strategies have made progress in the clinical treatment of acute myeloid leukemia.[111,112] CD33 has been found to hinder microglial uptake and clearance of Aβ42, leading to a reduced plaque burden in APP/PS1 CD33-/-mice.[102] Higher levels of CD33 expression in the brain are associated with greater cognitive decline[103] and increased AD pathology,[75] making CD33 a potential therapeutic target for AD. Research has shown that CD33 knockout in 5xFAD mice leads to a decrease in Aβ pathology and an improvement in cognition.[113] However, the effects of TREM2 knockout were reversed.[113] TREM2 knockout resulted in a reduction in the clustering of Iba1+ myeloid cells around plaques, a phenomenon that could not be reversed by CD33 knockout.[113] Furthermore, differential gene expression in 5xFAD; CD33−/− microglia was found to be dependent on the presence of TREM2.[113] These findings suggest that TREM2 functions downstream of CD33 and that the loss of microglial clearance capacity could be reversed through therapeutic inhibition of CD33.[114]

The application of antibodies remains an exciting therapeutic option for the treatment of human diseases. With features such as high target specificity, slow hepatic or renal metabolism, and the need for less frequent administration, antibodies are attractive small molecules.[115] Anti-CD33 antibodies have a long history of use in the clinic for treating leukemia,[116–118] with gemtuzumab ozogamicin being the first approved antibody–drug conjugate for treating acute myeloid leukemia.[119] These antibodies target the V-set domain (encoded by exon 2), exclusively targeting hCD33M, and show promise for preclinical studies in AD patients.[118,120] A phase 1b clinical trial of AL003, a human-specific anti-CD33 monoclonal antibody developed for AD treatment, was successfully completed. Promising assessments of tolerability and pharmacokinetics have been reported, with the antibody being well tolerated and showing target engagement in peripheral and CNS compartments.[111] As a result, AL003 is now being considered for further investigation in a proof-of-concept Phase 2 study.[111]

NLRP3 Inflammatory Complex and AD

Numerous studies have demonstrated the involvement of the NLRP3 inflammasome in regulating the neuroinflammatory response in AD, highlighting its critical role in the pathogenesis and progression of AD.[121,122] Indeed, Aβ activation of the NLRP3 inflammasome in microglia is fundamental for IL-1β maturation and subsequent inflammatory events.[123,124] In 2008, Halle[123] et al reported that the injection of Aβ into the lateral ventricle of mice could activate the NLRP3 inflammasome in microglia, causing the maturation and secretion of IL-1β and IL-18 mediated by Caspase-1, which was the first direct demonstration of the role of the NLRP3 inflammasome in AD. Further studies showed that knocking out the NLRP3 gene in APP/PS1 transgenic mice reduced caspase-1 activity, enhanced Aβ phagocytosis by microglia, and decreased Aβ deposition.[125] Additionally, spatial memory deficits in APP/PS1 mice were mitigated. These findings are supported by other researchers, indicating the important role of the NLRP3 inflammasome in AD.[126–128] Heneka[125] reported that mice with mutations linked to familial AD, specifically Nlrp3−/− or Casp1−/−, exhibited significant protection against spatial memory loss and other symptoms of AD. These mice exhibited decreased activation of brain caspase-1 and IL-1β, along with improved clearance of amyloid-β. Additionally, the absence of the NLRP3 inflammasome led to a shift in microglia toward the M2 phenotype and reduced Aβ deposition in the APP/PS1 model of AD.[125] These findings highlight the importance of the NLRP3/caspase-1 axis in AD pathogenesis and suggest that inhibiting the NLRP3 inflammasome is a promising therapeutic approach for this condition.

The activation products of the NLRP3 inflammasome, IL-1β and IL-18, are crucial for initiating and perpetuating the neuroinflammatory response in AD.[129,130] IL-1β and IL-18 produced after inflammasome activation recruit intracellular junction molecules (MyD88, IRAK and TRAFl5) through their respective receptors, IL-1βr and IL-18R, to activate NF-κB and the c-Jun N-terminal kinase, and the p38 MAPK signaling pathway simultaneously activates a variety of inflammatory cells, such as microglia and astrocytes, inducing them to transform into proinflammatory phenotypes, secrete more

inflammatory factors and proinflammatory mediators, such as IL-1β, IL-6, IL-18 and cyclooxygenase-2, macrophage inflammatory proteins (MIP-1α, MIP-1β and MIP-2) and inducible nitric oxide synthase,[130] induce inflammatory cascade reactions and aggravate AD. A substantial body of evidence indicates that targeting the glia–neuron cycle could be a promising strategy for developing new therapeutic approaches for AD that could alter the progression of the disease.[131–134] Research strongly suggests that IL-1 plays a crucial role in the pathogenesis and progression of AD.[135,136] Analysis of AD brain tissue revealed an overproduction of IL-1, particularly in activated microglia surrounding Aβ plaques and neurons with NFTs, the two main neuropathological features of AD.[137] This overproduction of IL-1 is closely associated with the severity of neuropathology in a specific brain region.[137] Additionally, studies on cells have demonstrated that IL-1 can induce the production of various harmful molecules from microglia, astrocytes, and neurons. For instance, IL-1 can trigger the production of α-1 anti-chymotrypsin, IL-6, S100B, and inducible nitric oxide synthase, which are elevated in the AD brain. These molecules, either independently or by promoting the production of other molecules, contribute to a neuroinflammatory cascade that is believed to lead to cell damage, dysfunction, and death in AD.[138] This theory is reinforced by the observed neuroprotection when the neuroinflammatory cascade is suppressed in AD animal models. Furthermore, several studies on IL-1 genetics have revealed that polymorphisms in the IL-1 and IL-1 receptor genes can increase the risk of AD by up to three times in homozygous carriers.[139] Multiple studies have indicated that IL-1β can have a detrimental effect on hippocampus-dependent learning and may inhibit long-term potentiation, with the extent of impact varying based on concentration.[140] Additionally, other inflammatory cytokines produced by microglia have been shown to similarly decrease long-term potentiation.[141] Chronic administration of an IL-1R blocking antibody to 3xTg-AD mice results in significant changes in brain inflammatory responses, improvements in cognitive deficits, reductions in tau pathology, and partial decreases in certain forms of Aβ.[142] These alterations in inflammatory responses are associated with decreased NF-κB activity.[142] Additionally, blocking IL-1 signaling leads to reduced activity of various tau kinases in the brain, such as cdk5/p25, glycogen synthase kinase 3β, and p38-MAPK, as well as decreased levels of phosphorylated tau.[142] One study also revealed a decrease in the levels of the astrocyte-derived cytokine S100B and neuronal Wnt/β-catenin signaling in 3xTg-AD brains.[142] The proinflammatory factor IL-18 exhibited a similar impact to that of IL-1β in AD. In vitro experiments revealed that IL-18 enhances Aβ deposition in human neuroblastoma SHSY5Y cells, which are commonly used as a neuronal model.[143] Furthermore, IL-18 was shown to upregulate the expression of glycogen synthase kinase 3β and cyclin-dependent kinase 5, both of which are implicated in the hyperphosphorylation of the Tau protein.[144] Studies have indicated that IL-18 may induce the protein expression of APP, β-site APP-Cleenzyme 1, and certain subunits of the γ-secretase complex, potentially accelerating Aβ production.[145] Moreover, meta-analyses have linked gene polymorphisms in the IL-18 promoter region to an increased risk and poorer prognosis of AD.[146] These findings suggest that immune mechanisms mediated by IL-1β and IL-18, which are products of the NLRP3 inflammatory complex, play crucial roles in the pathological progression of AD (Figure 7).

Discussion

The development of drugs for AD has progressed slowly, and the currently approved drugs can only improve cognitive symptoms for a limited time and cannot reverse the disease process. Various interventions targeting Aβ amyloid deposition, tau hyperphosphorylation, neuroinflammation, and neuroprotection are under investigation.[148,149] In recent years, most studies on the role of neuroinflammation in the development of AD have focused on microglia, astrocytes and neurons. Targeted therapy for these cells within the CNS or reducing CNS inflammation by impacting peripheral inflammatory processes could offer a new approach for diagnosing and treating AD. At present, the number of trials focusing on anti-neuroinflammatory drugs in Phase I and Phase II trials has notably increased. Drug experimental studies on microglia are still in the early stages, with a primary focus on regulating the phenotype of microglia. Study has found that promoting a microglial switch from the inflammatory M1 phenotype to the protective M2 phenotype in APP/PS1 mice can have a neuroprotective effect and improve cognitive dysfunction in mice with AD.[150] Another research has indicated that peroxisome proliferator-activated receptor gamma (PPAP-γ) agonists can elevate M2 phenotype microglia markers such as CD206, IL-4, TGF-β, G-CSF levels, while reducing the levels of M1 phenotype microglia markers like CD86, COX-2, iNOS, IL-1β, and IL-6. This demonstrates their ability to shift microglial cells from an M1 phenotype to an M2 phenotype, enhancing their phagocytic function and promoting amyloid clearance in animal models. However, there is no evidence supporting the efficacy of Rosiglitazone Monotherapy(PPAP-γ agonists) in improving cognition or

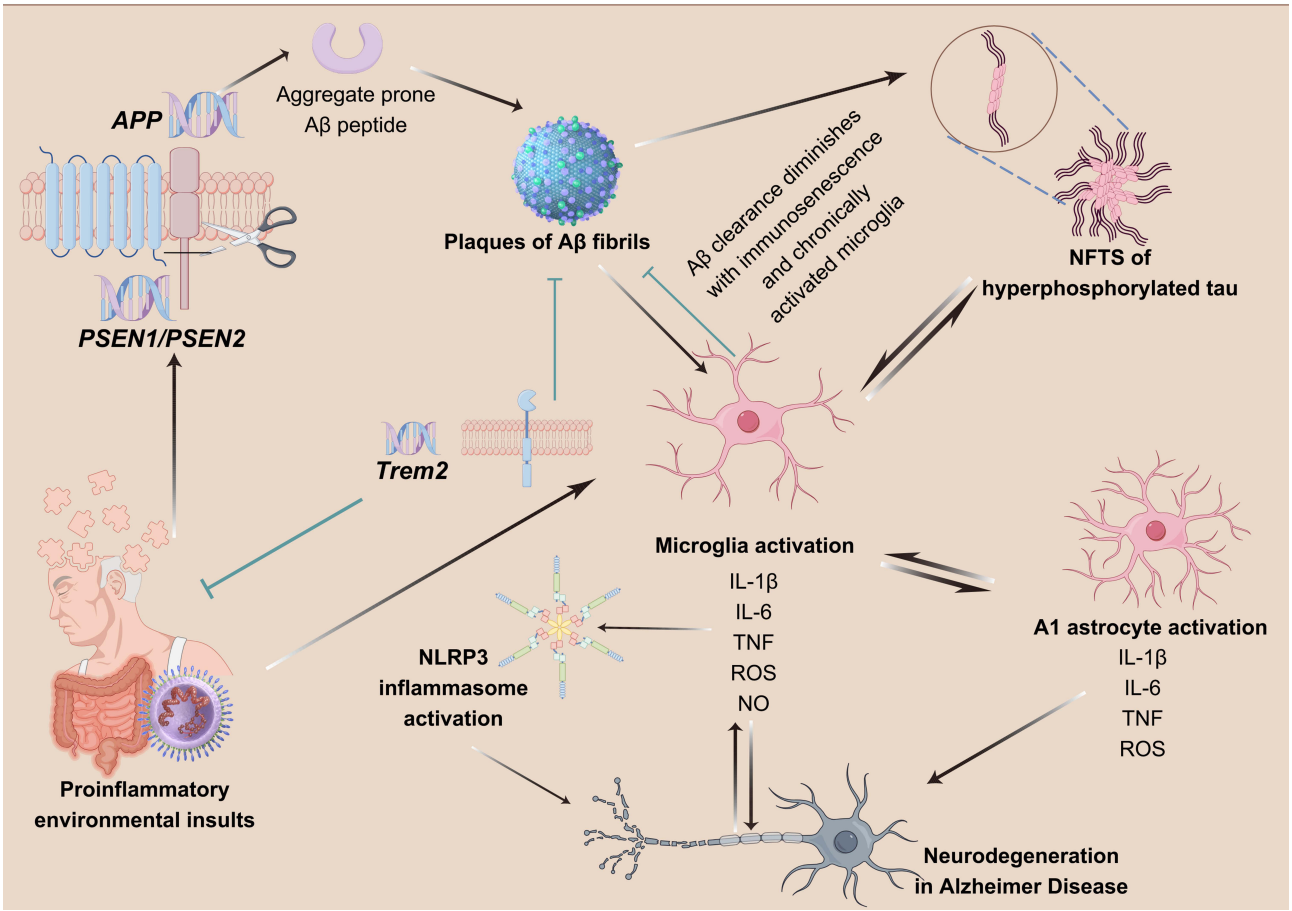

Figure 7 The role of NLRP3 inflammasome in AD.[147] (Microglia are activated in response to DAMPs from Aβ plaques, and are mobilized to eliminate them. However, prolonged activation of microglia and immunosenescence can reduce their effectiveness over time. TREM2 plays a role in regulating the activity and survival of microglia. Mutations in TREM2 can affect the ability of microglia to regulate cytokine production and clear neural debris. Failure to clear Aβ plaques can lead to the formation of NFTs, triggered by both the plaques and the persistently activated microglia. Additionally, hyperphosphorylated tau protein can further stimulate microglia.

global function in APOE-E4-negative individuals or other analysis populations.[151] The findings suggest that there is still significant potential for further exploration in modulating microglia for the treatment of AD. However, further verification in vivo, particularly in human studies, is necessary.

In a meta-analysis of 40 studies on blood and 14 on CSF, individuals with AD exhibited elevated levels of IL-6, TNF-α, IL-1β, TGF-β, IL-12, and IL-18 in blood, as well as increased levels of TGF-β in CSF, when compared to control groups.[151,152] A more recent meta-analysis of 175 blood studies revealed heightened levels of IL-1β, IL-2, IL-6, IL-18, IFN-γ, TNF-α converting enzyme, soluble TNF receptors 1 and 2, and reduced levels of IL-1 receptor antagonist and leptin in AD patients compared to controls.[153] These findings provide further support for the presence of inflammatory responses in individuals with AD. Candidate markers associated with microglia have been extensively investigated. One study found that YKL-40, a protein primarily produced by astrocytes and encoded by the Chi3l1 gene, is a well-researched biomarker in CSF that tends to increase with age and in the early stages of AD[154] and in the late preclinical AD stages compared with early preclinical stages.[155] Using a mouse model of AD (APP/PS1), researchers observed that deleting Chi3l1 led to a reduction in Aβ accumulation and an increase in the expression of the microglial lysosomal marker CD68 around the plaques.[154] This suggests that Chi3l1 may inhibit the activation of glial cells involved in phagocytosis and contribute to the buildup of amyloid. In line with this, lowering Chi3l1 levels was found to enhance the phagocytosis of zymosan particles and Aβ peptide by both astrocytes and microglia in vitro.[154] Activated microglia express translocator protein 18 kDa (TSPO) on the outer membrane of their mitochondria. TSPO contains an isoquinoline site that binds 11C-(R)-PK11195. TSPO PET imaging has revealed varying degrees of microglial activation in groups of patients with clinically probable AD and cases of amnestic mild cognitive impairment (MCI).[156] A study has provided evidence supporting the

role of neuroinflammation in the neurodegenerative pathology of a majority of MCI cases related to AD.[157] Statistical parametric mapping identified clusters of elevated PK11195 binding in 85% of our Aβ-positive amnestic MCI (prodromal AD) subjects.[157] The aforementioned research offers a novel approach to the diagnosis and intervention of AD through microglia.

While microglia and neuritis are recognized as crucial components in the pathological mechanisms of AD, the role of microglia in this process is multifaceted, encompassing both neuroprotective and neurotoxic functions, akin to a double-edged sword. The intricate actions of microglia in AD are predominantly influenced by TREM2 and its regulation of associated genes such as CD33 and NLRP3. Consequently, targeting the inflammasome of TREM2 and NLRP3 holds promise as a therapeutic strategy for treating AD in the future. Nevertheless, it is imperative to acknowledge that the precise mechanisms by which the NLRP3 inflammasome contributes to the onset and progression of AD, as well as the upstream regulatory mechanisms governing NLRP3 inflammasome activation, necessitate further elucidation. Additionally, the TREM2-APOE pathway has emerged as a critical modulator of the functional phenotype of microglia in AD, suggesting that this pathway is a potential novel target for restoring microglial homeostasis.[158] Hence, delving deeper into this research direction is likely to reveal additional therapeutic strategies for AD and present novel interventions for its clinical management, thereby offering fresh perspectives on the treatment of this debilitating condition.

Conclusion

The role of microglia in AD is intricate, demonstrating both neuroprotective and neurotoxic effects, with its actions largely influenced by the regulation of other related genes. Targeting microglia is a promising approach to delaying AD progression; however, challenges such as drug bioavailability, specificity, and safety remain unresolved. Enhancing the targeting specificity of microglia could offer novel intervention strategies for treating AD in humans.

Abbreviations

AD, Alzheimer's disease; CNS, Central nervous system; Aβ, Amyloid-β; NFTs, Neurofibrillary tangles; TREM2, Triggering receptor expressed on myeloid cells-2; APOE, Apolipoprotein E; PGRN, Progranulin; CV, Common variant; PAMPs, Pathogen-associated molecular patterns; DAMPs, Damage-associated molecular patterns; sTREM2, soluble Triggering receptor expressed on myeloid cells-2; PI3K, Phosphatidylinositide 3-kinases; mTOR, mammalian Target of rapamycin; MAPK, Mitogen-activated protein kinase; NLRP3, Nucleotide-binding domain-like receptor protein 3; LRR, Leucine-rich repeat; PYD, Pyrin domain; IL, Interleukin; APP, Amyloid precursor protein; TSPO, Translocator protein of 18KD; MCI, Mild cognitive impairment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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