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## Inflammation as a Central Mechanism in Alzheimer's Disease

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Review Article

# Inflammation as a central mechanism in Alzheimer's disease

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## Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by cognitive decline and the presence of two core pathologies, amyloid  $\beta$  plaques and neurofibrillary tangles. Over the last decade, the presence of a sustained immune response in the brain has emerged as a third core pathology in AD. The sustained activation of the brain's resident macrophages (microglia) and other immune cells has been demonstrated to exacerbate both amyloid and tau pathology and may serve as a link in the pathogenesis of the disorder. In the following review, we provide an overview of inflammation in AD and a detailed coverage of a number of microglia-related signaling mechanisms that have been implicated in AD. Additional information on microglia signaling and a number of cytokines in AD are also reviewed. We also review the potential connection of risk factors for AD and how they may be related to inflammatory mechanisms. © 2018 Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Keywords:

Alzheimer's disease; Inflammation; Microglia; Cytokines; Microglia receptors

## 1. Overview

Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common cause of dementia and is characterized by the decline in cognitive and function and neuronal loss. AD currently affects over 5 million Americans [1] and is expected to become increasingly prevalent with the rise in life expectancy. It is estimated that by 2050, 13.8 million Americans will be living with AD [2]. The financial burden imposed by AD currently exceeds \$230 billion and is expected to reach \$1.1 trillion by 2050 [3]. Given the clinical and financial burden associated with AD, the identification of novel mechanisms responsible for pathogenesis, as well as novel therapeutic targets, is urgently needed.

AD is characterized by two core pathologies, the presence of  $\beta$ -amyloid ( $A\beta$ ) plaques and neurofibrillary tangles

(NFTs).  $A\beta$  pathology arises from the improper cleavage of the amyloid precursor protein (APP) resulting in  $A\beta$  monomers that aggregate forming oligomeric  $A\beta$  and eventually aggregating into  $A\beta$  fibrils and plaques [4]. The function of APP is unknown but is believed to have a role in cell health and growth [5]. Critical aspects of understanding the onset of  $A\beta$  pathology rests on knowing the mechanisms of the generation of  $A\beta$  monomers, their clearance, and their aggregation into oligomeric  $A\beta$ . Normal processing of the APP sequence consists of nonamyloidogenic proteolysis of APP via  $\alpha$ -secretase and  $\lambda$ -secretase, producing soluble fragments [6]. When APP is cleaved by  $\lambda$ -secretase and erroneous  $\beta$ -secretase, it leads to insoluble amyloid  $\beta$  peptides that aggregate in the brain to form  $\beta$ -amyloid plaques [4,7–17]. The precise role of  $A\beta$  in AD pathology remains an open question as  $A\beta$  plaques may accumulate up to 10 years before any observable AD symptoms or diagnosis.

The second core pathology, NFT, arises from the hyperphosphorylation of tau, a microtubule-associated protein that stabilizes microtubules [18–27]. Phosphorylation of tau serves a necessary role in intracellular trafficking to

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remove tau from microtubules, allowing transport, followed by dephosphorylation to return tau to the microtubule [28]. In AD, tau protein is phosphorylated at multiple sites resulting in the removal of tau from the microtubule and causing the collapse of microtubule structures and disruption in a number of cellular processes ranging from protein trafficking to overall cellular morphology [29–31]. In addition, the hyperphosphorylated tau (ptau) aggregates into paired helical fragments that eventually form neurofibrillary tangles [20,24,25,32,33]. The accumulation of ptau tangles and the compromised cellular function leads to loss of neuronal function, and ultimately apoptosis [30].

Despite extensive and productive research investigating the mechanisms responsible for both core pathologies, as well as approaches aimed at the prevention of A $\beta$  plaques and NFT, there remains no treatment that effectively alters either pathology in clinical populations [34]. Furthermore, there exists a considerable gap in the understanding of AD pathogenesis given these two pathological features. As stated previously, patients may exhibit A $\beta$  plaque pathology for up to or greater than a decade before any overt diagnosis of AD [35,36]. For NFT, the overall tangle load is correlated with cognitive decline in AD; however, the appearance of NFT appears to occur before the inauguration of AD pathology in clinical populations and preclinical animal models [37–39]. The combination of the aforementioned gaps in the pathophysiology of AD suggests that other pathological mechanisms may be driving both the onset of the disorder, as well as the progression of the disease.

Over the last 10 years, a third core feature of AD has emerged that may provide insight into AD pathogenesis, as well as provide a link between the other two core pathologies. A number of investigations initially demonstrated that in addition to A $\beta$  plaques and NFT, the brains of patients with AD exhibited evidence of a sustained inflammatory response [40–50]. The inflammatory response has now been observed in multiple studies of postmortem tissues of AD patient samples [51–57] and is routinely observed in preclinical model systems of AD.

Acute inflammation in the brain is a well-established defense against infection, toxins, and injury, but when a disruption in the equilibrium of anti-inflammatory and pro-inflammatory signaling occurs, as seen in AD, it results in chronic inflammation (neuroinflammation) [58–61]. This chronic neuroinflammation is attributed to activated microglia cells and the release of numerous cytokines. The presence of a sustained immune response in the brain is not exclusive to AD. A number of studies have demonstrated elevated markers of inflammation in the brain of patients with Parkinson's disease (PD) [62–66], and traumatic brain injury associated with chronic traumatic encephalopathy (CTE) [67–70], amyotrophic lateral sclerosis (ALS) [70], and Multiple Sclerosis (MS) [71] to name a few key examples. It is increasingly recog-

nized that a sustained immune response is a central feature of neurodegenerative disorders [71–77].

The presence of a sustained inflammatory response in the brain of patients with AD was, at one point, thought to be reactive to the neuronal loss occurring in the disorder. However, substantial body of research has now demonstrated that a persistent immune response in the brain is not only associated with neurodegeneration but it also facilitates and exacerbates both A $\beta$  and NFT pathologies. Furthermore, it has been suggested that the inflammatory response may provide a link between the initial A $\beta$  pathology and the later development of NFT [78–83]. In the succeeding sections, we highlight some of the recent data indicating the role of inflammation in AD, as well as data indicating inflammation may be a central mechanism driving A $\beta$  pathology and progression.

This review highlights the research supported by the National Institutes of General Medical Sciences (NIGMS) through Center for Biomedical Research Excellence (COBRE) awards that develop the national research infrastructure.

## 2. Inflammation in AD

Many studies now point to the involvement of neuroinflammation playing a fundamental role in the progression of the neuropathological changes that are observed in AD. Since the 1980s, there have been reports of immune-related proteins and cells located within close proximity to  $\beta$ -amyloid plaques [43,84]. Beginning in the 1990s, several large epidemiological and observational studies were published indicating that anti-inflammatory treatments used in diseases, such as rheumatoid arthritis, showed protective qualities against developing AD, demonstrating as much as a 50% reduction in the risk for developing AD in patients who are long-term nonsteroidal anti-inflammatory drug (NSAID) users [77,85–87]. These studies lead to studies utilizing animal transgenic AD models demonstrating that NSAIDs can reduce AD pathology [88]. Human trials of NSAIDs showed variable outcomes with no convincing evidence of benefit using the trial methods of the time [89].

These various epidemiological studies and observational studies serve as the bedrock of support for neuroinflammation playing a major role in developing sAD. Unlike other risk factors and genetic causes of AD, neuroinflammation is not typically thought to be causal on its own but rather a result of one or more of the other AD pathologies or risk factors associated with AD and serves to increase the severity of the disease by exacerbating  $\beta$ -amyloid and tau pathologies [90,91].

Brain inflammation appears to have a dual function, playing a neuroprotective role during an acute-phase response, but becomes detrimental when a chronic response is mounted [92]. Chronically activated microglia release a variety of proinflammatory and toxic products, including

reactive oxygen species, nitric oxide, and cytokines. In deceased patients suffering from recent head trauma, there is an increase in cerebral A $\beta$  deposits 1–3 weeks postinjury, and it has been shown that elevated levels of interleukin 1 (IL-1) are responsible for the increased APP production and A $\beta$  load [93,94]. In addition, elevated levels of IL-1 $\beta$  has been shown to increase the production of other cytokines, including IL-6, which in turn has been shown to stimulate the activation of CDK5, a kinase known to hyperphosphorylate tau [95]. The neuroinflammation observed in AD appears to serve a primary role in exacerbating A $\beta$  burden and tau hyperphosphorylation, suggesting that this dual role could be a leading link between these seemingly disparate core AD pathologies. The mounted immune response via the brain's resident macrophage (microglia) is now a central tenant in the investigation of AD.

### 2.1. Microglia

Microglia are the resident immune cells within the central nervous system (CNS) [96]. In a healthy brain, microglia are in an inactive, "resting" state and are described morphologically as ramified cells with small somas [97,98]. In this state, the cell somas are stationary, while the cell processes extend and retract, surveying their environment and communicating with neurons and other glia cells [99–101]. Overall surveillance of the surrounding neuronal environment is accomplished via a large number of signaling mechanisms [99,102]. This includes surveillance of the local neuronal milieu via numerous receptors for classical neurotransmitters [103], receptors for numerous cytokines and chemokines [104–106], and a number of receptors, such as fractalkine (CX3CR1), that bind ligands constitutively released in healthy neuronal environments [107]. When microglia recognize a threat to the CNS, such as invasion, injury, or disease, it leads to microglial activation, causing a morphological change resulting in retraction of processes, enlargement of the cell, and migration [99,108–111]. Transitioning into an activated state may be triggered by alterations in any number of the aforementioned mechanisms involved in surveillance.

In AD, it is hypothesized that the primary driver of activation of microglia is the presence of A $\beta$ . Activated microglia respond to A $\beta$  resulting in migration to the plaques and phagocytosis of A $\beta$  [108,112,113]. A number of investigations have demonstrated that activated microglia phagocytose A $\beta$  [114–117]; however, these microglia become enlarged and after prolonged periods are no longer able to process A $\beta$  [114,118]. Early in AD pathogenesis, the mounted immune response results in clearance of A $\beta$  and has been demonstrated to exert positive effects on AD-related pathologies in animal models' systems [77,119,120]. However, prolonged activation of the immune response has been demonstrated to result in an

exacerbation of AD pathology, likely as a result of sustained activation of microglia in a feed forward loop, referred to as reactive microgliosis. This results in an accumulation of A $\beta$  and sustained pro-inflammatory cytokine signaling beginning to damage neurons [118,121,122]. The sustained activation also results in a decrease in microglia efficiency for binding and phagocytosing A $\beta$  and decreases in A $\beta$  degrading enzyme activity of microglia leading, in turn, to a reduced ability to break down the A $\beta$  plaques [123,124]. However, data indicate that the microglial capacity for producing pro-inflammatory cytokines is unaffected [118]. These data demonstrate a unique feature of pathogenesis in that overall clearance of A $\beta$  becomes compromised while immune activation continues simultaneously. The continued release of pro-inflammatory cytokines and associated neurotoxins from microglia serves to exacerbate the neuroinflammation and contribute to neurodegeneration, leading to the activation of yet more microglia.

As the microglia are involved in clearance of A $\beta$ , they release a number of proinflammatory cytokines that recruit additional microglia to plaques [125–127], resulting in a characteristic halo of activated microglia surrounding plaques [112,128]. More recent data indicate that as microglia become less able to clear A $\beta$ , peripheral macrophages may be recruited to A $\beta$  plaque deposition in an effort to clear A $\beta$  [129]. The recruitment of peripheral macrophages into the brain likely exacerbates the effects of sustained inflammation and thus AD pathology. Some of the most compelling data for the importance of inflammation in AD pathogenesis and the regulation of the immune response comes from the recent demonstration that a mutation in the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) confers a greater likelihood of developing AD [129–132]. A rare missense mutation in TREM2 results in a substantial elevated risk of AD [133–136].

### 3. The role of TREM2 in Alzheimer's disease pathology

Recent identification of a number of genetic variants of *TREM2* has ignited a flurry of research into the mechanistic contributions of this critical innate immune-regulating receptor to the pathogenesis of AD and numerous other neurodegenerative diseases. Original interest in the role of TREM2 and neurodegeneration was generated in the early 2000s, when associations were identified between *TREM2* loss of function mutations and polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS), or Nasu-Hakola disease [137–139]. This rare but aggressive neurodegenerative disorder is characterized by abnormal bone cysts and early-onset dementia with profound frontal lobe degeneration and is also associated with mutations in *TYROBP*, the intracellular signaling coreceptor for TREM2 [140–142]. In 2012, two independent studies reported strong associations between



the R47H variant of *TREM2* and late-onset AD [133,136]. The conferral of 2–4.5 fold increased risk of developing late onset AD (LOAD) in carriers of the R47H allele positions *TREM2* as the strongest associated risk gene behind only apolipoprotein E- $\epsilon$ 4 (*ApoE4*), and further implicates innate immunity as a key component to the pathogenesis of AD [143,144]. In addition to the R47H variant, the R62H *TREM2* mutation has been associated increased risk of LOAD. Using a variety of approaches with cell and rodent models along with human patient tissue and data, great strides have been made to elucidate the mechanistic contributions of *TREM2* in the context of AD.

Early studies addressing the contributions of *TREM2* to AD pathology utilized the APP/PS1 and 5XFAD mouse models of A $\beta$  pathology along with human AD brain tissues. Initial characterization of *TREM2* in AD revealed strongly upregulated protein and transcripts on neuritic plaque-associated macrophages in the brain, but not within microglia or myeloid cells distal to A $\beta$  deposits in amyloid mice and human AD brain tissues [129,145]. Further characterization of these plaque-associated cells using flow cytometry revealed cell surface signatures consistent with peripheral macrophages, including high expression of CD45, Ly6c, and CD11 b, although subsequent studies utilizing parabiosis failed to detect these infiltrates [129,132,146]. Several studies have identified increased *TREM2* expression in human AD blood, further suggesting roles for peripheral *TREM2* in modifying disease outcomes [147–149].

Next, the mechanistic roles of *TREM2* were explored in the context of amyloid pathology using APP/PS1 and 5XFAD mice, along with various cellular models. Both haploinsufficiency and complete deletion of *Trem2* dramatically reduces the number of plaque-associated macrophages throughout all time points of disease in A $\beta$ -bearing mice [129,150]. Interestingly, this decrease in plaque-associated macrophages reduces hippocampal plaque load at 4-months of age but ultimately exacerbates pathological outcomes by the 8-month time point [146]. This phenomenon was accompanied by decreases in inflammatory cytokines including IL1 $\beta$ , IL6, and TNF $\alpha$  as well as decreased astrocytosis as measured by GFAP and S100 $\beta$  later in mid-late stages of pathology. This suggests that *TREM2* alters the inflammatory milieu not only through macrophage-mediated responses but also through alterations in astrocyte activation.

Given the profound loss of plaque-associated macrophages in *TREM2*-deficient amyloid mice, myeloid cell survival and proliferation were of interest in these models. It has been shown that *TREM2*-deficient mice have dramatically decreased numbers of proliferating plaque-associated macrophages as measured by proliferation markers Ki67, and BrdU in aging APP/PS1 and 5XFAD mice [146,151]. In addition, it was shown by the Colonna lab that *TREM2* deficiency results in

increased cleaved caspase-3 activation, resulting in enhanced myeloid cell death [151]. Utilizing super resolution microscopy, Yuan et al. further demonstrated that haploinsufficiency of *TREM2* in mice or humans harboring the R47H mutation results in altered plaque compaction with much more diffuse and fibrillar plaques present, and fewer thioflavin S<sup>+</sup> dense core plaques [152]. In this situation, more neurotoxic oligomeric and fibrillar A $\beta$  may be present leading to increased neuronal dystrophy and death. Along with plaque compaction issues, microglia and macrophages lacking *TREM2* have been shown to have decreased capacity to phagocytose and clear A $\beta$ , apoptotic cells, as well as other proteins and complexes [131,153,154]. *TREM2*-deficient myeloid cells also exhibit increased numbers of autophagy-associated phagolysosomes reflective of aberrant mTOR activation resulting in dysregulated metabolic homeostasis within the context of A $\beta$  pathology [155].

More recently, the contributions of *TREM2* to tau pathology have been addressed by the Lamb and Holtzman groups. Utilizing hTau mice harboring the entire human tau gene on a complete murine tau knockout background, Bemiller et al. demonstrated that *TREM2* deficiency worsens cortical soluble and insoluble tau pathology at 6-months of age [156]. This worsening was accompanied by the presence of morphologically dystrophic microglia and widespread neuronal stress kinase hyperactivation, including within ERK-, JNK-, and GSK3 $\beta$ -associated pathways. The Holtzman group recently reported mitigated neuroinflammation, astrocytosis, and reduced neurodegeneration at advanced ages in the PS19 mouse model of tauopathy, an aggressive model of tauopathy harboring the FTD-associated P301S 4R familial tau mutation [157]. Similar to *TREM2* signaling in the context of amyloid pathology, there appear to be disease stage-specific contributions of *TREM2*, which normally are protective in early stages of disease by facilitating clearance of intracellular and extracellular pathological tau species and damaged neuronal debris, but transformation to becoming pathogenic during neurodegenerative phases of disease where inflammation, astrocytosis, and aberrant synaptic and neuronal engulfment dominate.

The nuanced roles of *TREM2* in promoting neurodegeneration can be attributed to three key aspects as currently understood within the context of AD: (1) regulation of phagocytic and autophagic processes; (2) myeloid cell survival and proliferation; and (3) regulation of inflammation. Recent studies by the Amit, Colonna, and Schwartz groups highlighted distinct activation patterns for what have been termed “damage-associated microglia” [158]. In these studies, the authors demonstrate distinct myeloid activation patterns, which initially are independent of *TREM2* activation, but later rely on *TREM2*-dependent pathways to convert to a neurodegenerative transcriptional program altering phagocytosis and lipid metabolism. These studies have further highlighted the disease stage-specific

responses to pathology along with the incredible heterogeneity of cells involved in neurodegenerative processes.

#### 4. Additional microglial receptors

In addition to the TREM2 receptor, a number of other microglia-specific receptors have been explored in the investigation of the exaggerated immune response in AD.

##### 4.1. CX3CR1 and AD

To limit the activated role of microglia under resting, basal conditions in the brain, neurons release a variety of inhibitory factors, including CX3CL1, a chemokine frequently referred to as fractalkine [107]. CX3CL1 consists of a chemokine domain attached to a mucin-rich stalk on the extracellular domain and is synthesized as a membrane-anchored protein that may be cleaved into a soluble form [159,160]. CX3CL1 binds to its obligate receptor, CX3CR1, on the surface of microglia [161]. Originally identified on lymphocytes, CX3CR1 is involved with immune regulation on other tissues, including bone, kidney, and in the cardiovascular system [162–164]. Despite the widespread distribution of CX3CL1/CX3CR1 signaling throughout the body, CX3CR1 has been most extensively studied in microglia [165–167], which have an expression of CX3CR1 nearly >1000-fold higher when compared with both peripheral myeloid cells and other CNS cell types, including both neurons and astrocytes [168,169]. Unlike other promiscuous chemokines, CX3CL1 is the exclusive ligand for CX3CR1, binding rapidly and with a high affinity [170]. CX3CL1 is a pleiotropic protein involved in the abatement of microglia under basal conditions but also regulates microglial activity by influencing migration and proliferation in injury conditions [171].

Numerous studies demonstrate that CX3CL1 can dose-dependently reduce the expression of nitric oxide, IL-6, and TNF $\alpha$  following stimulation by lipopolysaccharide and suppress neuronal death induced by microglial activation [172,173]. CX3CR1-mediated neuronal signaling to microglia can be disrupted by replacing CX3CR1 with a green fluorescent protein (GFP) reporter gene that leads to systemic inflammation and exacerbated microglial neurotoxicity in a variety of animal models, including PD ALS [165,174].

However, the role of fractalkine signaling in AD pathogenesis appears to be complex and is not well understood. One of the pathogenic hallmarks of AD is aberrant microglial activation, making the CX3CL1-CX3CR1 pathway an ideal candidate for investigations of AD pathophysiology. The effect of CX3CR1 deficiency in mouse models of AD has been discordant, depending on the type of models and methods used. For example, CX3CR1 deletion in a tau transgenic mouse led to increased tau phosphorylation and aggregation, increased microglial activation, and exacerbated deficits in

hippocampal-dependent learning [175]. Conversely in amyloidogenic AD models, deleting CX3CR1-attenuated neuronal loss and microglial activation with no impact on amyloidogenesis in 3XTg mice [166] but reduced  $\beta$ -amyloid deposition in both the APP/PS1 and R1.40 mouse models [167].

Studies investigating alterations in CX3CL1-CX3CR1 signaling in humans are rare compared with *in-vitro* and animal studies; however, the emerging human literature suggests that the fractalkine pathway may play an important role in AD pathogenesis. Cortical levels of fractalkine are reduced in the brains of healthy elderly adults with no history of dementia or other neurodegenerative disorders when compared with the brains of healthy, middle-aged adults, suggesting a potential age effect that may be associated with altered surveillance by fractalkine receptors and inflammation [176]. Plasma levels of soluble fractalkine are elevated in patients with both mild cognitive impairment (MCI) and AD [177]. In addition, these same researchers found higher levels of plasma in individuals with mild-moderate AD than in patients with severe AD and the highest levels in MCI patients, which is considered a key turning point from normal aging into AD pathogenesis. Since inflammation often precedes AD pathology, plasma levels of CX3CL1 could potentially be a useful systemic biomarker. Postmortem analyses show modest reductions of CX3CR1 and markedly lower levels of CX3CL1 in the hippocampus of AD brains compared with age-matched nondemented controls [178].

##### 4.2. Alternative receptors on microglia

###### 4.2.1. GABA and GABA<sub>B</sub>

In the central nervous system, gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter released by neurons. Neurons produce GABA by conversion of glutamate to GABA via glutamate decarboxylases (GADs), which is released in response to neuronal activity. The released GABA binds to a fast-acting chloride channel (GABAA) resulting in rapid hyperpolarization or binding to a receptor coupled to a metabotropic G-protein coupled receptor (GABA<sub>B</sub>) that results in a slow inhibitory postsynaptic current (IPSC) [179]. As alterations in GABAergic signaling have been reported in AD [180–184], and GABA plays a central role in learning and memory [185,186], there has been interest in its role in AD. GABA also plays a role in regulation of immune signaling [186]. Microglia express GABA<sub>B</sub> receptors [187] that are in G<sub>i/o</sub> subclass of GPCR receptors. Activated microglia exhibit an upregulation of GABA<sub>B</sub> receptors compared with resting microglia [187]. GABA and GABA<sub>B</sub> also have anti-inflammatory properties. Studies have demonstrated that when GABA is released by astrocytes into the extracellular fluid, it inhibits inflammatory responses of activated microglia and astrocytes

[186,188,189]. GABA has also been demonstrated to decrease the release of pro-inflammatory cytokines, TNF $\alpha$  and IL-6, by activated astrocytes and microglia via GABA<sub>B</sub> [186]. In an LPS-induced inflammatory response, activation of the GABA<sub>B</sub> receptor reduces the release of IL-12 from microglia [187]. By utilizing baclofen, a GABA<sub>B</sub> receptor agonist, intracellular inflammatory pathways were reduced by 40–60% [186]. These data clearly indicate GABA<sub>B</sub> on microglia serve an anti-inflammatory role [187] suppressing proinflammatory signaling. In addition, astrocytes synthesize GABA via monoamine oxidase B (MAOB) [190], and it has been demonstrated that reactive astrocytes release large quantities of GABA [186,191] in what is hypothesized to help regulate microglia function. The aforementioned data indicate a pathway that is likely involved in the regulation of microglia function. The expressed GABA<sub>B</sub> receptors on microglia likely serve a role in surveillance of neuronal function as GABA released from local synapses bind to GABA<sub>B</sub> on microglia to suppress pro-inflammatory signaling in a similar fashion to the fractalkine ligand and receptor. Furthermore, when microglia and astrocytes move into a more active state, GABA release from astrocytes appears to be a mechanism to regulate and suppress pro-inflammatory signaling in microglia. If GABAergic tone is compromised in AD, this suggests the loss of a mechanism to regulate microglia function. This mechanism is currently the focus of research in our Center of Biomedical Research Excellence (COBRE) award, in particular, the investigation of changes in GABAergic signaling in AD, as well as the role of GABA<sub>B</sub> on microglia.

The impact of the TREM2 mutation and other alterations in microglia receptors that alter microglia activation lead to the upregulation of a number of pro- and anti-inflammatory cytokines that regulate the immune response. The evaluation of these cytokines has become a central part of AD inflammation investigations.

#### 4.3. Specific cytokine signaling in AD

##### 4.3.1. Pro-inflammatory signaling: TNF- $\alpha$

TNF- $\alpha$  is one of the more important proinflammatory cytokines in AD, playing a central role in both initiation and regulation of the cytokine cascade during a response to an inflammatory challenge [41,192]. TNF- $\alpha$  increases vascular endothelial adhesion molecules, allowing leukocytes and immune cells to migrate into areas under duress [193].

TNF- $\alpha$  exerts its biological functions by binding to two main receptors, TNFR1 and TNFR2 [194]. The overexpression of TNFR1 in mouse hippocampal tissue was necessary for the activation of NF $\kappa$ B- and A $\beta$ -induced neuronal apoptosis [195]. Conversely, mice lacking TNFR1 crossed with the APP23 transgenic AD model exhibit reduced plaque deposition, mitigated hippocampal

microglial activation, and improved performance in cognitive tasks [196]. High levels of soluble TNFR1 and TNFR2 can be detected in cerebrospinal fluid (CSF) of patients diagnosed with MCI who progress to AD on a 6-year follow-up [197].

Increased levels of TNF- $\alpha$  have been reported in both the brains and plasma of patients with AD [198]. A $\beta$  can directly stimulate microglia production of TNF- $\alpha$  through activation of the transcription factor NF $\kappa$ B [199]. In addition, TNF- $\alpha$  can increase A $\beta$  burden through the upregulation of  $\beta$ -secretase production and increased  $\gamma$ -secretase activity [11,200].

##### 4.3.2. Pro-inflammatory signaling: IL-1 $\beta$

IL-1 $\beta$  has been described as a “master regulator” within the brain inflammatory cascade due to its integral role in regulating the expression of other proinflammatory cytokines, including TNF- $\alpha$  and IL-6, and that disruptions to IL-1 $\beta$  can delay the onset of neuroinflammation and neurodegeneration [201].

IL-1 is a proinflammatory cytokine that is upregulated early in AD development and is considered crucial for  $\beta$ -amyloid plaque deposition [41]. IL-1 $\beta$  is similarly elevated in both MCI and AD patients compared with controls, suggesting that increased IL-1 $\beta$  production begins early and remains elevated as the disease progresses [202]. Specific IL-1 $\beta$  polymorphisms resulting in higher IL-1 $\beta$  production are linked to increased AD risk [203]. Increased levels of IL-1 $\beta$  have been detected in the prefrontal cortex and hippocampus in brain tissue of patients with AD [204]. IL-1 $\beta$ -mediated actions are through binding to the IL-1 receptor, which is expressed throughout the brain but can be found in greatest concentration in the dentate gyrus and pyramidal cells in the hippocampus, which are key areas in the early development of AD pathology [205].

IL-1 $\beta$  regulates the synthesis of APP, increased APP secretion from glial cells, and amyloidogenic processing of APP through the activation of protein kinase C and increased  $\gamma$ -secretase activity [11,206]. The ability of IL-1 $\beta$  to increase A $\beta$  burden and plaque deposition creates a self-sustaining cycle wherein the increase of A $\beta$  load results in further microglia activation and IL-1 $\beta$  production [207,208].

##### 4.3.3. Pro-inflammatory signaling: IL-6

IL-6 is an important, multifunctional cytokine that can be considered proinflammatory or anti-inflammatory depending on the amount and condition in which it was released [209]. IL-6 is crucial for normal homeostasis of neuronal tissue, and removal of this signaling pathway leads to reduced microglial activation, yet overproduction of IL-6 leads to chronic neuroinflammation and neurodegeneration [210].

Elevated levels of peripheral IL-6 during late midlife have been reported to effectively predict cognitive decline in a 10-year longitudinal study [211]. IL-6 is elevated in



the CSF and serum of AD patients and is considered a significant contributor to neuroinflammation observed in LOAD [212,213].

Studies have demonstrated that IL-6 staining in the hippocampus and cortex is strongly associated with A $\beta$  plaques, which is absent in age-matched controls [214,215]. A $\beta$  has been shown to stimulate the synthesis and release of IL-6 by glial cells [207]. Activation of IL-6 receptors, which show a regional distribution strongest in the hippocampus and cortex, has been shown to enhance APP transcription and expression, as does the IL-6/soluble IL-6 receptor complex, which can be readily found in serum and CSF [216]. IL-6 has also been demonstrated to result in the hyperphosphorylation of several tau epitopes by increasing CDK5 activity via the CDK5 activator p35, potentially serving as an important bridge between the core AD pathologies [95].

#### 4.3.4. Pro-inflammatory signaling: NF $\kappa$ B

The transcription factor NF $\kappa$ B is considered a primary regulator of inflammatory responses by responding to proinflammatory stimuli, such as TNF- $\alpha$  or IL-1 [217]. Activated NF $\kappa$ B is predominately found in neurons and glial cells that are surrounding A $\beta$  plaques and is central to reactive gliosis observed in AD brains [218].

NF $\kappa$ B has been shown to play an important role in regulating  $\beta$ -site APP cleaving enzyme 1 (BACE1) transcription, as numerous NF $\kappa$ B binding sites have been identified near the BACE1 promoter [219]. In addition, A $\beta$  has been shown to stimulate cytokine production through the NF $\kappa$ B-dependent pathway, resulting in a cyclical loop of exacerbating pathology [199].

Both *in vitro* and *in vivo* studies demonstrate that utilizing an NF $\kappa$ B inhibitor, such as 6-amino-4-(4-phenoxyphenylethylamino) quinazoline, can reduce TNF- $\alpha$ -induced BACE1 transcription, resulting in lower A $\beta$  burden [196,220]. Certain NSAIDs, such as flurbiprofen and indomethacin, have been shown to reduce NF $\kappa$ B activity, which subsequently results in lower levels of A $\beta$ <sub>1-40</sub> and A $\beta$ <sub>1-42</sub> [221,222].

#### 4.3.5. Anti-inflammatory signaling: IL-10

Interleukin 10 (IL-10) is an anti-inflammatory cytokine that is found in healthy brain tissue but is upregulated in patients with AD [223]. There is a correlation between IL-10 levels and the progression of AD, suggesting that IL-10 could serve as a biomarker for AD diagnosis and/or progression. IL-10 is released by both microglia and astrocytes in response to the increase in pro-inflammatory cytokines to attempt to maintain homeostasis in the immune system [224]. IL-10 has been shown to inhibit pro-inflammatory cytokines, including IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and the chemokine MCP-1 [223]. These findings suggest that increases in IL-10 may also be a possible therapeutic target to manage chronic inflammation, though clinical trials involving anti-inflammatory agents

have been unsuccessful, and in some studies even exacerbated the disease [225]. Alternative studies have supported this claim, by demonstrating that IL-10 can promote neuroinflammation and cause dysfunction of microglia. In early AD, microglia perform their role of activation, migration, and phagocytosis to alleviate the disease, but as the disease progresses, these functions are inhibited. A study by Guillot-Sestier et al. (2015) suggests that this microglia inhibition is related to IL-10. IL10-deficient APP/PS1 mice (APP/PS1+IL-10 $-/-$ ) showed a reduction of A $\beta$  in the cerebrum and an increase in the amount of activated microglia surrounding the remaining A $\beta$ , suggesting an increase in microglia migration and phagocytosis [226]. This study also demonstrated that APP/PS1+IL-10 $-/-$  mice have reduced synaptic loss and behavioral impairments in comparison with APP/PS1+IL-10 $+/+$  mice. Research also shows that a polymorphism of IL-10 increases the risk of developing AD in some populations [227,228].

#### 4.3.6. Anti-inflammatory signaling: TGF- $\beta$ 1

Transforming growth factor- $\beta$  (TGF- $\beta$ ) is involved in the regulation of cell growth, cell differentiation, and immunosuppression. Studies have shown that TGF- $\beta$  is elevated in CSF, serum, and brain microvascular endothelial cells of patients with AD [229,230]. Grammas et al. demonstrates that this increase of TGF- $\beta$  in endothelial cells also provokes the release of pro-inflammatory cytokines, IL-1 $\beta$  and TGF- $\alpha$ , promoting an inflammatory response [230]. Within this family of cytokines, the most abundant isoform is TGF- $\beta$ 1, which is secreted by astrocytes and is a ligand for receptors found on neurons, astrocytes, and microglia [231]. TGF- $\beta$ 1 is neuroprotective against A $\beta$  production, deposition, and damage, regulates neuroinflammation, and inhibits the pathway for the tau-phosphorylating enzyme, GSK-3 $\beta$  [232]. It is also responsible for causing an increase in the expression of Bcl-2 and Bcl-xl, anti-apoptotic proteins. The quantity of TGF- $\beta$ 1 in plasma has been shown to be decreased in patients with AD [233,234]. When A $\beta$  oligomers are injected into the hippocampus of mice, decrease in synaptic protein levels and atrophy of astrocytic processes occur. However, intracerebroventricular infusion of 10 ng TGF- $\beta$ 1 30 minutes before an injection of 10 pmol A $\beta$  oligomers resulted in reduced levels of the proteins, drebrin, PSD-95, and synaptophysin, and strengthening of astrocytic processes [235]. Also, mice that were intracerebroventricularly injected with A $\beta$  failed to spend more time with a novel object in a novel object recognition test, whereas the mice previously injected with TGF- $\beta$ 1 did not show memory impairments [235]. TGF- $\beta$ 1 deficiency also causes impairment in the TGF- $\beta$ 1/Smad signaling pathway. The disruption of this pathway contributes to the ectopic phosphorylation of Smad2/3, which has been found in the hippocampal cytoplasm of neurons attached to NFT and within A $\beta$  plaques. There is a negative correlation

between TGF- $\beta$ 1 mRNA levels and NFT, suggesting that TGF- $\beta$ 1 deficiency advances tau pathology, causing further impairment of the TGF- $\beta$ 1/Smad pathway [232]. These studies demonstrate how disruption of TGF- $\beta$ 1 signaling contributes to the AD pathogenesis.

The aforementioned studies demonstrate a number of specific roles for inflammatory mechanisms altered in AD, as well as a number of mechanisms that are likely related to AD pathogenesis. Given the very strong relationship between the missense mutation in TREM2 and the risk for developing AD, a number of other known risk factors for AD for which the mechanism underlying the risk is not known have now been hypothesized to be linked to inflammation.

#### 4.4. Relevance of inflammation and risk factors for AD

A number of risk factors have been identified that confer greater risk for developing AD. These include age [236], cardiovascular changes [237], traumatic brain injury [94,238–240], and metabolic disorders such as diabetes. Interestingly, each of the aforementioned risk factors also is associated with an immune response, including in the brain. This has led to hypotheses that elevated inflammation and/or inflammatory signaling may be increasing the risk [241]. As mechanisms are numerous, we have explained one example below in more detail.

##### 4.4.1. Diabetes mellitus (DM), AD, and inflammation

In addition to the aforementioned pathological hallmarks, AD is also characterized by abnormal metabolic changes. Decreased cerebral glucose metabolism is now considered a distinct characteristic of the AD brain [242–244]. The association between T2DM and AD is well established, along with other neurodegenerative diseases, including vascular dementia and PD [245–247]. One of the first key studies, the 1999 Rotterdam Study, found that type-2 diabetes mellitus (T2DM) could double the risk for the development of AD [248]. Since that seminal Rotterdam Study, numerous studies have since substantiated this finding that T2DM nearly doubles the risk for AD [249,250], including that T2DM serves as a useful predictor for the development of AD in a 12-year longitudinal study [251,252].

The defining characteristics of T2DM are impairments in insulin signaling and hyperglycemia [253,254], which appear to be the main contributing factors increasing the risk for AD. Impairments in brain insulin signaling as seen in T2DM has been found to get progressively worse as the pathology advances in patients with AD, corresponding to increased levels of amyloid peptides and, in particular, neuroinflammation [255,256].

A considerable literature has demonstrated that alterations in insulin levels and insulin receptor resistance (in particular in T2DM) within the brain impact survival and function of both neurons and glial cells that are dependent on intact insulin signaling [257,258]. Insulin is even neuroprotective by preventing  $\beta$ -amyloid oligomers

from binding within the hippocampus to protect against AD-related synaptic deterioration [259], and the alterations in insulin signaling (including insulin receptor resistance) results in cerebrospinal fluid levels of A $\beta$  being higher in patients with T2DM than nondiabetic controls [260].

Insulin resistance that arises from DM is proposed to manifest from a prolonged, mild state of inflammation occurring within peripheral tissue. Adipose tissue has been shown to recruit macrophage and stimulate the secretion of numerous proinflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, which are then easily distributed throughout the rest of the body causing systemic inflammation [261–263]. TNF- $\alpha$  is, in turn, a potent inducer of insulin resistance occurring within adipose tissue [261,264].

Numerous studies have demonstrated the correlation between peripheral inflammation and cognitive deficits, particularly with MCI and AD [265,266]. A meta-analysis of 40 studies revealed that peripheral cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, and TGF- $\beta$  are higher in patients with AD [267]. Whether the peripheral inflammation is arising from adiposity or another source, proinflammatory cytokines can cross the blood-brain barrier, which triggers brain-specific inflammatory responses [268,269]. Systemic inflammation is also a primary cause of damage to the blood-brain barrier, allowing entry of peripheral immune cells into the brain. Decreased blood-brain barrier integrity can be observed in rodents that feed on high-fat, high-energy diets, leading to increased blood-brain barrier permeability, excessive microglial activation, and hippocampal-dependent learning deficits [270–272]. Compromised blood-brain barrier integrity can also allow chronic, low-grade systemic inflammation, as observed in obesity and T2DM, to induce central inflammation.

Microglia are primed in AD brains to be more susceptible to secondary inflammatory insults, resulting in an exacerbated inflammatory response [273]. High-fat chow can be used in the APP/PS1 mouse model to induce systemic inflammation that results in profound neuroinflammation and accelerated AD-pathology, including A $\beta$  and tau hyperphosphorylation, and central insulin resistance [274].

The mechanism of neuronal insulin resistance appears to be similar with A $\beta$  oligomers inducing microglial activation, which in turn release numerous pro-inflammatory cytokines, including TNF- $\alpha$  [275]. Although activation of microglia by A $\beta$  is an adaptive physiological response to reducing A $\beta$  burden through phagocytosis, chronic inflammation leads to exacerbated AD pathology and metabolic abnormalities, which in turn further exacerbate pathogenesis. These data are providing evidence for links between molecular pathways and biochemical abnormalities associated with inflammatory mechanisms shared between AD and DM.

##### 4.4.2. APOE and inflammation

Apolipoprotein (ApoE) is produced primarily peripherally within the liver and by astrocytes within the CNS. While the main roles of ApoE involve cholesterol transport,

regulation of lipid transport, and aid of injury repair within the brain, ApoE plays a role in glucose metabolism [276,277]. Owing to the ApoE- $\epsilon$ 4 allele representing the strongest genetic risk factor for late-onset AD (LOAD), present in nearly  $\sim$ 40% of all patients with AD [278], and the increasing risk that metabolic disturbances play in dementia progression, the links between ApoE- $\epsilon$ 4, glucose metabolism, and recently inflammation are important to understanding the shared underlying mechanisms between these risk factors.

A recent investigation has highlighted a particularly important aspect of ApoE risk in AD as it is related to inflammation. Krasemann et. al., (2017) identified a role for ApoE signaling in the regulation of microglia phenotype in response to amyloid  $\beta$ , as well as in other neurodegenerative disorders [279]. Even more compelling is that TREM2 signaling appears to mediate a return to nonpathogenic and reduced phagocytosis of neurons by microglia. This suggests a completely novel interaction between one of the major risk factors for developing AD and microglia function. Additional studies are required to determine the relationship between ApoE and inflammation, but this may serve as another example of the central role of inflammation driving AD pathology. ApoE- $\epsilon$ 4 appears to synergistically combine with other AD risk factors, including cardiovascular disease, atherosclerosis, and type-2 diabetes [280]. As each of these other risk factors includes an evoked immune response in the brain the possibility exists that inflammation may be the common thread for increased risk.

## 5. Summary

The aforementioned sections highlight the central role that investigations of inflammation in AD has taken in the last decade and highlight a number of interrelated mechanisms that may contribute to AD pathogenesis. As the literature demonstrating the role of inflammation in accelerating core AD pathologies increases, so should the investigations of therapeutic approaches targeting the sustained inflammatory response. In addition, extensive investigations in AD patient populations as well as pre-clinical model systems needs to further evaluate microglia signaling cascades and numerous receptors that have not yet been well characterized. Given recent hypothesis that extend beyond the findings of inflammation exacerbating AD pathologies to suggestions that the inflammatory response evoked by Ab may serve to seed the onset of tau pathology, the identification of how the microglia response is regulated and how to modify the response has become an important topic in potential treatments of AD.

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## RESEARCH IN CONTEXT

1. Systematic review: Inflammation in Alzheimer's disease (AD) has emerged as a central pathology that likely plays a role in onset and progression of the disease. Numerous investigations have highlighted that the sustained inflammation in the brain accelerates other core pathologies, making inflammatory mechanisms viable targets for therapeutic development as well. In the below review, we highlight a number of the inflammatory mechanisms that have been implicated in AD pathogenesis. We also highlight links between risk factors for AD and potential interactions with inflammatory mechanisms.
2. Interpretation: In the present review we provide coverage of the interactions of inflammatory signaling and the progression of AD. We also discuss a number of possible mechanisms that may account for connections between altered inflammatory signaling and the changes observed in AD.
3. Future directions: This review highlights several emerging mechanisms that may provide a better understanding of AD pathogenesis as well as may serve as novel therapeutic targets for treatment and/or onset of AD.

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