Targeting neuroinflammation in Alzheimer’s disease: from mechanisms to clinical applications

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Abstract
Alzheimer’s disease is characterized by sustained neuroinflammation leading to memory loss and cognitive decline. The past decade has witnessed tremendous efforts in Alzheimer’s disease research; however, no effective treatment is available to prevent disease progression. An increasing body of evidence suggests that neuroinflammation plays an important role in Alzheimer’s disease pathogenesis, alongside the classical pathological hallmarks such as misfolded and aggregated proteins (e.g., amyloid-beta and tau). Firstly, this review summarized the clinical and pathological characteristics of Alzheimer’s disease. Secondly, we outlined key aspects of glial cell-associated inflammation in Alzheimer’s disease pathogenesis and provided the latest evidence on the roles of microglia and astrocytes in Alzheimer’s disease pathology. Then, we revealed the double-edged nature of inflammatory cytokines and inflammasomes in Alzheimer’s disease. In addition, the potential therapeutic roles of innate immunity and neuroinflammation for Alzheimer’s disease were also discussed through these mechanisms. In the final section, the remaining key problems according to the current research status were discussed.

Key Words: Alzheimer’s disease; astrocytes; immune signaling; inflammatory cytokines; microglia; neuroinflammation; neurotoxicity; therapeutic strategies

Introduction
Along with the aging of the global population and recent improvements in medical care, Alzheimer’s disease (AD) has become a burden on the public health system worldwide. However, the limited efficacy of currently available treatments has led to an unmet need for more effective therapies. The amyloid cascade hypothesis put forward in the 1990s proposes that misfolded and aggregated amyloid-beta (Aβ) protein triggers the pathological hallmarks of AD, such as neuronal cell death and dementia (Hardy and all, 1991; Hardy and Higgins, 1992). The tau hypothesis put forward in 2013 postulates that tau is a primary factor that promotes the onset of AD (Giaccia and Gold, 2013). Clinical progress based on these two hypotheses has remained slow over the past decades. Ample evidence suggests that neuroinflammation could be a significant driver of AD progression alongside AD’s two classical pathological hallmarks of tau and Aβ aggregation. Investigating the crucial role of neuroinflammation in AD development could help identify novel markers of AD progression and therapeutic targets (Fan et al., 2017; Wang et al., 2017; Zolezzi et al., 2017). There is overwhelming evidence substantiating that in the central nervous system (CNS), microglia and astrocytes are the predominant mediators of inflammation and prime candidates for investigations of neuroinflammatory processes in AD (Hamelin et al., 2016; Schwartz and Deczkowska, 2016; Alves et al., 2017; Daria et al., 2017). The quantification of inflammation levels and inflammatory ligands has revealed that neuroinflammation is one of the earliest detectable indicators of AD (Gispert et al., 2016; Hall et al., 2017). Targeting the physiological processing and inflammation involved in glia, cytokine release, and inflammasome formation is the best approach for cognitive disorders, including AD (Calsolaro and Edison, 2016; Ryan and Kelly, 2016; Torigi et al., 2019). Growing evidence suggests that glia, cytokines, and inflammasomes are involved in numerous inflammatory diseases, providing the foothold to develop novel treatment strategies (Arancio, 2020; Raffi and Anzen, 2020; Shi et al., 2020; Zhu et al., 2022). Herein, we provide an overview of the roles of the glia-associated inflammation in AD pathogenesis and updated information on the role of microglia and astrocytes in AD pathology. Then, we discuss the dual nature of inflammatory cytokines and inflammasomes that may contribute to AD pathology. In the final section, we provide a brief overview of the therapeutic potential of innate immunity and neuroinflammation for AD, highlighting the beneficial and detrimental roles of inflammation and the feasibility of inflammation as a therapeutic strategy.

Clinical and Pathological Characteristics of Alzheimer’s Disease
AD is a common neurodegenerative disease characterized by memory loss, pronounced cognitive decline, and extensive synaptic and neuronal loss (Sierksma et al., 2020). The neuropathological features for AD patients include intracellular neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein (p-tau), as well as extracellular amyloid plaques formed by Aβ (Condello et al., 2020; Wen et al., 2022). The production of neurotoxic Aβ depends on the amyloidogenic pathway of amyloid precursor protein (APP) cleavage, driven by β-secretase and γ-secretase (Figure 1). Current evidence suggests that pathological manifestations of Aβ deposition arise earlier than clinical symptom onset. The formation of NFTs leads to the onset of neuronal damage and AD (Arancio, 2020; Fratamico et al., 2020; Figure 2). However, the pathological progression for Aβ and Tau in different brain regions is heterogeneous.

References
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The Role of Immune Cells in Alzheimer’s Disease

Microglia

Microglia arise from the yolk sac during development and constitute 0.5–16% of all glia in human brains and 5–12% in rodent brains (Hamelin et al., 2018). Historically, microglia have been classified into different subtypes such as quiescent (also called resting or ramified), activated, and phagocytotic (also called amoeboid) cells according to their morphology, electrophysiological properties, density, and the surface expression of immune molecules (Stratoulias et al., 2019). The implementation of single-cell RNA sequencing and cytometry by time-of-flight mass spectrometry has demonstrated distinct gene expression profiles of microglia under different conditions, providing a high-resolution view of the developmental and spatial heterogeneity of microglia across multiple brain regions (Masuda et al., 2020). Microglia are widely acknowledged to be critical for the development of the CNS and contribute to the regulation and connection of neurons and support neural development. For example, microglia are responsible for synaptic pruning to eliminate inappropriate synapses and ensure normal neuronal activity. Microglia also regulate learning, memory, and cognitive functions in the adult brain (Udeochu et al., 2018).

As the resident immune cells in the CNS, microglia in the brain mediate the acute immune response to harmful stimuli, such as misfolded Aβ peptides. However, the benefits and physiological functions of acute microglial activation may be abrogated if the acute response associated with harmful stimuli is not resolved (Johansson et al., 2018; Figure 3). This means that the ‘activation’ of microglia has both beneficial and detrimental roles in the pathogenesis of AD (Venegas et al., 2017; Zhao et al., 2018). Acute microglial activation contributes to decreased accumulation of Aβ via increased clearance or phagocytosis (Ziegler-Waldkirch et al., 2018), whereas chronic microglial activation may provoke dysregulated neuroinflammatory responses and lead to neuronal distress, synapse loss, Aβ production, and neurotoxicity via multiple pro-inflammatory cascades (Shi et al., 2019; Ng et al., 2020; Zhang et al., 2020).

Homeostasis

Microglia are the resident innate immune cells in the brain, derived from primitive hematopoietic progenitors. By adopting different states in AD, microglia migrate to damage sites, secrete various inflammatory molecules, and phagocytose debris and aggregated proteins (Prinz et al., 2019). It is becoming increasingly clear that microglia do not just play a secondary role in AD processes but virtually contribute to neuron loss, synaptic dysfunction, and the buildup of neurotoxic proteins in the very early stages of AD (Leng and Edison, 2021).

Astrocytes

Astrocytes (also astroglia) are glia that play a critical role in supplying nutrition to neurons; regulating neurotransmission; the modulation of synapse formation, maturation, and elimination; and calcium homeostasis (Habib et al., 2020). Astrocytes exhibit altered morphology in different CNS disorders, which may reflect different functions and accelerate disease pathogenesis (Harris et al., 2020). Induced pluripotent stem cell-derived astrocytes from patients with familial and sporadic AD reportedly exhibit a less complex
Cytokines and Immune Signaling in Alzheimer’s Disease

Over the years, many natural immune cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-10, IL-12, IL-18, IL-23, IL-33, IL-34, IL-1β, and IL-18, have been mentioned in the context of AD processes (Mizuno et al., 2011; Bhaskar et al., 2014; Tan et al., 2014; Guillot-Sestier et al., 2015; Fu et al., 2016; Taylor et al., 2018; Thawker and Kaur, 2019; Melo et al., 2020; Si and Wang, 2020). Elevations in pro-inflammatory cytokines and cerebrospinal fluid (CSF) Aβ deposition with AD indicate their important roles in AD development. Moreover, Aβ deposition and its resultant neurotoxicity provide ligands to activate microglial Aβ phagocytosis and promote the production of microglial pro-inflammatory cytokines (Lai et al., 2017). This process can significantly promote the clearance of Aβ and help the brain parenchyma rebuild homeostasis (Polazzi and Monti, 2010; Clayton et al., 2017). Under chronic inflammation, these inflammatory mediators lose effectiveness in clearing Aβ and sustain the inflammatory response in a self-perpetuating manner to propagate neurotoxicity (Yamamoto et al., 2007). Catalytic factors for this detrimental and sustained response include injury, genetics, age, and peripheral inflammation (Gorle and Van Eldik, 2019). Moreover, specific pro-inflammatory cytokines (e.g., interferon-γ) have been shown to cause additional Aβ secretion while activating microglia in response to the neurotoxic Aβ (Roy et al., 2020).

Table 1 | Astrocyte reactivity modulating signaling pathways

| Inflammation category | Signaling pathway | Significance on astrocytes | References |
|------------------------|-------------------|---------------------------|------------|
| DAMPs-ATP | P2X7/PYR-Ca2+ | Proinflammatory | Frank et al., 2012 |
| DAMPs-Ros | NF-κB, PI3K, MAPK | Proinflammatory | Nahrijm et al., 2013 |
| DAMPS-NO | Soluble guanylyl cyclase | Proinflammatory | Brahmacari et al., 2006 |
| | (molecular imaging, neuronal injury, and death) | | |
| PAMPs-LPS | TRL4/NF-κB | Proinflammatory | Gorina et al., 2011 |
| PAMPs-dsRNA(poly-A/C) | TRL3 | Antiviral and proinflammatory | De Miranda et al., 2009 |
| PAMPs-ssRNA/CpG DNA | TRP-Med88/NF-κB | Antiviral and proinflammatory | Butchi et al., 2010 |
| PAMPs-Cytosolic DNA | cGAS-STING/IFN | Antiviral and proinflammatory | Jeffries and Marriott, 2017 |
| NAMPS-Ab | RAGE/NF-κB | Proinflammatory (inflammatory, cytotoxicity and Norris) | Akama et al., 1998 |
| NAMPS-Glutatione | CN-NFAT | Context dependent (triggers or inhibits astrocyte reactivity) | Giraud et al., 2010 |
| Cytokines-IFN-γ | IFNGR-JAK/STAT1 | Potentiates astrocytes reactivity | John et al., 2003 |
| Cytokines-IFN-β | JAK/STAT1 | Antiviral | Hwang et al., 2018 |
| Cytokines-TNF | JAK/STAT1, NF-κB and/or CN-NFAT | Activates expression of target genes | Ben Haim et al., 2015a |
| Cytokines-IL-12/IL-15 | GP130-JAK/STAT3 | Regulates expressions of IL-12, IFN-γ, GATA-3, and STAT3, and other genes with STAT responses | Ben Haim et al., 2015b |
| Cytokines-TGF-β | IFNGR-JAK/STAT1 | Increases vimentin, actin, and GAP43 expression; contributes to scar formation | Schachtrup et al., 2010 |
| Cytokines-IL-1β | NF-κB | Proinflammatory | Ben Haim et al., 2015a |

However, no consensus has been reached on the effects of TNF-α on AD. Certain studies have shown that inhibiting TNF-α signaling has a therapeutic effect (Conti-Corazza et al., 2020). For example, TNF receptor 1-deficient APP mice exhibited enhanced cholinergic plexus tissue preservation, decreased levels of AD-related factors, CSF blood-brain barrier integrity, lower expression of inflammatory markers, and preserved memory compared with TNF receptor 1-deficient APP mice (Steeland et al., 2018). Injection of a TNF-α adeno-associated virus resulted in enhanced microglial reactions and attenuated Aβ deposition, suggesting that TNF-α may promote plaque clearance under specific spatial and temporal contexts (Chakraborty et al., 2011). Studies have also found that anti-TNF therapy for arthritis was associated with a lower risk of AD, suggesting its potential for AD treatment (Camargo et al., 2015; Chou et al., 2016). These inconsistencies in TNF-α in AD may be attributed to the fact that these studies investigated different stages of AD. However, the proposed causal relationship between TNF-α and AD remains subject to debate. The risk of developing AD and peripheral inflammation causality is still unclear in the pathophysiological modeling of genome-wide association studies (Yarwood et al., 2016). Thus, the precise role of TNF-α in AD warrants further studies.

Interleukin family members

The pro-inflammatory cytokines IL-1β, IL-18, IL-33, and all members of the IL-1 family have been shown to modulate AD pathogenesis (Su et al., 2016; White et al., 2017). In this regard, it has been shown that inhibition of the IL-1β decreases tau phosphorylation in Alzheimer’s pathological cultures and modestly modulates Aβ levels in 3×TgAD mice (Sutinen et al., 2012). In contrast, Aβ levels were markedly decreased in 3×Tg AD mice overexpressing IL-1β, highlighting that neuro-inflammatory cytokines affect AD (Herrmann et al., 2015). Moreover, IL-18 can promote the production of Aβ40 through β-secretoase-mediated cleavage of APP, while lack of IL-18 in APP/Ps1 mice incites seizures via impaired dendritic pruning and excessive synaptic activity (Tzeng et al., 2018). IL-33 is downregulated in AD brains, indicating that IL-33 functions as a potential modulator for AD (Liew et al., 2016). Moreover, intraperitoneal injection of IL-33 into APP/Ps1 AD mice could decrease Aβ levels, improve contextual memory, and restore long-term potentiation deficiency (Chapuis et al., 2009). IL-34 has been upregulated in AD brains and is involved in the regulation of cytokines and immune signaling in Alzheimer’s disease. However, the pro-inflammatory cytokines IL-1β and IL-12 were increased in serum and CSF even before signs of increased Aβ or tau were present (Schuitemaker et al., 2009).

ATP: Adenosine 5′-triphosphate; Aβ: amyloid-beta; CGS: cyclic GMP-AMP synthase; DAMPs: damage-associated molecular patterns; GAL: glial fibrillary acidic protein; GSDMD: Gasdermin-D; IFN: interferon; IFNGR: interferon gamma receptor; JAK/STAT: JAK-STAT1 signaling pathway; LPS: lipopolysaccharides; MAPKs: mitogen-activated protein kinases; MyD88: myeloid differentiation factor 88; NAMPS: neurodegeneration-associated molecular patterns; NF-κB: nuclear factor kappa B; NFAT: nuclear factor of activated T-cells; NO: nitric oxide; P2Rs: P2 purinoreceptors; PAMPs: pathogen-associated molecular patterns; PI3K: phosphoinositide-3 kinase; poly I:C: polyinosinic-polycytidylic acid; RAGE: receptor for advanced glycation; ROS: reactive oxygen species; SAMD: mothers against DAPD homolog 1; STAT: signal transducers and activators of transcription; STING: interferon genes; TGF-β: transforming growth factor-beta; TRL: toll-like receptor.

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Inflammation-targeting therapeutic strategies for Alzheimer’s disease.

The hypothesis that microglia activation promotes AD progression has prompted researchers to develop microglia depletion strategies using pharmacology or genetics. Microglia depletion in AD mouse models has been shown to have beneficial effects. CSF1R inhibitors can suppress neuroinflammation, decrease amyloid plaque burden, and improve cognition in different AD mouse models (Dagher et al., 2015; Sosna et al., 2018). Furthermore, improving certain aspects of microglial function represent novel therapeutic strategies for AD treatment, targeting innate immune signaling and immunomodulation in microglia. TLR4-activating antibodies, including antibody 1 and antibody 2 identified by Amgen and AL002 and AL002a/c identified by Alelecor, can reportedly boost myeloid cell function, abrogate survival defects, and can potentially be therapeutic in AD (Cheng et al., 2018; Price et al., 2020; Wang et al., 2020). In an AD mouse model, only AL002a increased amyloid-β aggregation around amyloid plaques, thus improving cognition in SxFAD mice. Another antibody clone, 49D, has been reported to be a very potent binder to the extracellular domain of TREM2 (Schlepckow et al., 2020), causing selective reduction of soluble oligomers in an APP knock-in mouse model.

Chemical inhibition of the inflammasome pathway is also potentially effective. Pterostilbene is a natural compound that attenuates the neuroinflammatory response induced by Aβ by inhibiting the NLRP3/caspase-1 inflammasome pathway in microglia (Lu et al., 2018). Sulforaphane is an active isothiocyanate component obtained from broccoli seeds and sprouts and exerts an anti-inflammatory effect on human microglia by inhibiting NLRP3 inflammasome activation and IL-1β production (An et al., 2016). Moreover, synthesized docosahexaenoic-acid-acylated astaxanthin diesters alleviate cognitive decline by reducing inflammatory cytokines in APP/PS1 mice (Gu et al., 2018). Artemisinin also exhibits inhibitory effects on neuroinflammation and amyloidogenesis by inhibiting NLRP3 inflammasome activation as well as NF-κB production (Shi et al., 2013). Interestingly, β-hydroxybutyrate, one of the main components of ketone bodies, can reportedly reduce reactive oxygen species secretions among patients with AD through activation of Nrf2 signaling, along with the deactivation of the NLRP3 inflammasome and NF-κB to decrease neuroinflammation and thus improves memory decline (Pinto et al., 2018).

The P2X7 receptor (P2X7R) is another regulator for amyloid-mediated NLRP3 inflammasome activation. P2X7R is critical for the Aβ peptide-mediated function protein can reduce Aβ deposition in the brains of SxFAD mice (Wu et al., 2017) but is not able to sufficiently restore memory capability, as the loss of AIM2 promotes IL-6 and IL-18 expression and preserves IL-1 levels in the brain and, thus, constitutes a compensatory effect to induction of Aβ deposition.

Neuroinflammation-targeting therapeutic strategies for Alzheimer’s disease.

Although the United States Food and Drug Administration has recently approved aducanumab for the treatment of AD, we cannot ignore the fact that many multinational pharmaceutical companies and research institutes spend billions of dollars on anti-Aβ or anti-tau strategies that fail to obtain results, emphasizing the need for novel approaches.

The hypothesis that microglia activation promotes AD progression has prompted researchers to develop microglia depletion strategies using pharmacology or genetics. Microglia depletion in AD mouse models has been shown to have beneficial effects. CSF1R inhibitors are well-established as a critical surface receptor for microglia (Elmore et al., 2014). CSF1R inhibitors can suppress neuroinflammation, decrease amyloid plaque burden, and improve cognition in different AD mouse models (Dagher et al., 2015; Sosna et al., 2018). Furthermore, improving certain aspects of microglial function represent novel therapeutic strategies for AD treatment, targeting innate immune signaling and immunomodulation in microglia. TLR4-activating antibodies, including antibody 1 and antibody 2 identified by Amgen and AL002 and AL002a/c identified by Alelecor, can reportedly boost myeloid cell function, abrogate survival defects, and can potentially be therapeutic in AD (Cheng et al., 2018; Price et al., 2020; Wang et al., 2020). In an AD mouse model, only AL002a increased amyloid-β aggregation around amyloid plaques, thus improving cognition in SxFAD mice. Another antibody clone, 49D, has been reported to be a very potent binder to the extracellular domain of TREM2 (Schlepckow et al., 2020), causing selective reduction of soluble oligomers in an APP knock-in mouse model.

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The P2X7 receptor (P2X7R) is another regulator for amyloid-mediated NLRP3 inflammasome activation. P2X7R is critical for the Aβ peptide-mediated...
The critical roles of innate immunity and neuroinflammation in regulating the progression and pathology of AD opens up exciting new avenues for research into the therapeutic strategies for neurodegenerative disorders (Ennifer and Lukens, 2020). Increasing evidence suggests that glia, inflammatory cytokines, and inflammasomes are intricately linked to a healthy neuronal environment. The activation of microglia and astrocytes, including the secreted cytokines and immune signaling pathways, contribute to pathological neuroinflammation responses, leading to neurotoxicity in AD. Targeting neuroinflammation has strong prospects for clinical applications for AD treatment. Numerous studies have focused on Aβ generation and inflammation. The activation of Nrf2/HO-1 cascade in human THP-1 macrophages. Neurobiol Aging 38:1-20.

The release of the chemokine ligand CCL3, associated with pathogenic CD8+ T cell recruitment in AD animal models (Martin et al., 2019). Moreover, Aβ can induce accumulation of IL-1β in microglia from wild-type but not from P2X7R−/− mice (Sanz et al., 2009). The activation of P2X7R can also boost the release of IL-6, CCL2, and TNF-α in microglia (Shieh et al., 2014). Therefore, antagonizing P2X7 signaling is a promising approach for inhibiting neuroinflammation in AD patients. Interestingly, it has been shown that blocking the selective and high blood-brain-barrier-permeable P2X7R antagonist, blocks Aβ42-induced inflammatory responses and diminishes spatial memory impairment and cognitive deficits in a mouse model (Chen et al., 2014). Another selective P2X7R antagonist, A740003, can block Aβ-dependent IL-1β release (Facchi et al., 2018). Many chemicals have been developed to antagonize P2X7 signaling in the brain in recent years. However, only a few chemicals can cross the blood-brain barrier. Thus, pharmacokinetic properties need to be improved to ensure these chemicals are excellent candidates for clinical trials for AD treatments. Certain nutrients or foods (e.g., vitamin D, vegetables, and fruits) can improve cognitive function. The Multicultural Healthy Diet (NCT03240406) should help formulate specific guidelines based on foods with anti-inflammatory properties for the prevention of cognitive impairment (Scarneas et al., 2018).

**Limitations**

This review is subject to several limitations. The primary limitation to the generalization of the review is that the PubMed database was used to search the literature, and incomplete retrieval of identified research was inevitable. Secondly, the researchers behind the cited works come from diverse cultural backgrounds with naturally varying personal opinions regarding specific phenomena, which may affect the rationality of the research.

**Conclusion**

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