Review Article

Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the brain, which is characterized by the formation of extracellular amyloid plaques (or senile plaques) and intracellular neurofibrillary tangles. However, increasing evidences demonstrated that neuroinflammatory changes, including chronic microgliosis are key pathological components of AD. Microglia, the resident immune cells of the brain, is constantly survey the microenvironment under physiological conditions. In AD, deposition of β-amyliod (Aβ) peptide initiates a spectrum of cerebral neuroinflammation mediated by activating microglia. Activated microglia may play a potentially detrimental role by eliciting the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) influencing the surrounding brain tissue. Emerging studies have demonstrated that up-regulation of pro-inflammatory cytokines play multiple roles in both neurodegeneration and neuroprotection. Understanding the pro-inflammatory cytokines signaling pathways involved in the regulation of AD is crucial to the development of strategies for therapy. This review will discuss the mechanisms and important role of pro-inflammatory cytokines in the pathogenesis of AD, and the ongoing drug targeting pro-inflammatory cytokine for therapeutic modulation.

Keywords: Alzheimer's disease (AD); microglia; pro-inflammatory cytokines; neurodegeneration; amyloid-β; therapy

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Introduction

Alzheimer's disease (AD) is a chronic, multifactorial neurodegenerative disorder in people over the age of 65 (1), which creates a huge burden to affected individuals, their families, and society (2). Pathological Characters of AD including: extracellular deposition of β-amyliod (Aβ) and intracellular neurofibrillary tangles (3,4), which is believed to play an important role in the pathogenesis of this disease. Aβ deposition and tau protein cause loss of synaptic function, mitochondrial damage, activation of microglia, and the final neuronal death (5). However, it is becoming increasingly evident that neuroinflammation cascades mediated by primed microglia cells also contribute to AD pathogenesis (6). Recently, a wealth of information linking the pro-inflammatory cytokines [such as IL-1, IL-6, and tumor necrosis factor-α (TNF-α)] released from microglia has received considerable attention for its role in AD.

As the most common immune cells in the central nervous system (CNS), microglia has long been a hotspot in AD due to their dramatic responses to the pathophysiology of the disease. Microglia activation have dual effects on AD progression: one side, activation of microglia leads to reducing Aβ accumulation by increasing its phagocytosis, clearance and degradation, which prevents the formation of amyloid plaques in the brain. On the other side, prolonged microglia activation leads to the release of pro-inflammatory cytokines, which initiates a pro-inflammatory cascade and

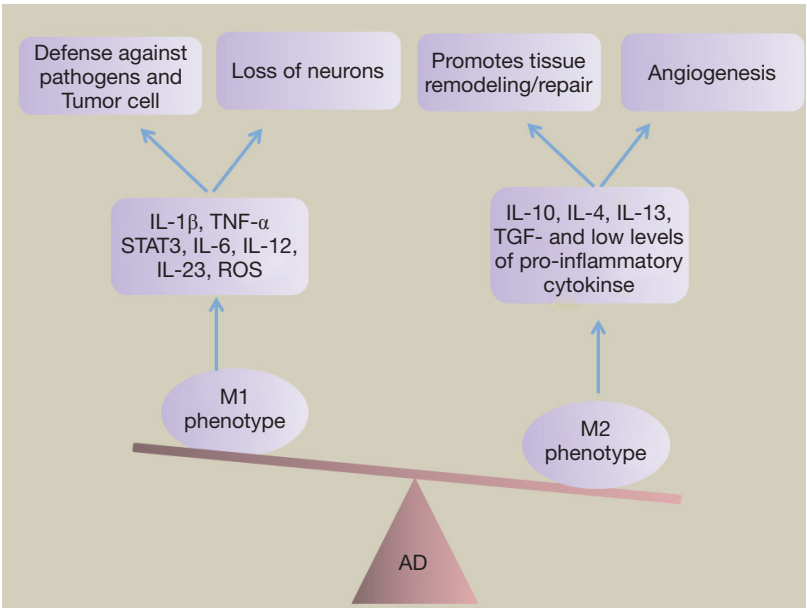

Figure 1 The role of different inflammatory cytokines released from different subtypes of microglia in AD. AD, Alzheimer's disease.

subsequently contributes to neuronal damage and losses (7-9). In this article, we review the recent findings of pro-inflammatory cytokines released from microglia, speculate its possible role in AD progression, and present the recent advances and challenges in targeting pro-inflammatory cytokines for AD therapy.

The effects of microglia, detrimental or beneficial?

As the resident immune cell of the CNS, microglia plays a nuanced and complex role in the progression of AD (10). Recently, microglia became more important than ever before in demonstrating strong genetic implications for microglia molecules and the immune system, especially when genome-wide association study (GWAS) have identified variants of several immune genes are risk factors for late onset Alzheimer's disease (LOAD) (11,12). These genes include CD33 (11-13), TREM2 (14,15) and the HLA-DRB4-DRB1 region (16), etc. Under physiological conditions, microglia are active to maintenance of homoeostasis, neuroprotection and neuro repair by release growth factors such as brain-derived neurotrophic factor (BDNF) and transforming growth factor (TGF) β with ramified morphology. Under pathological conditions, such as altered neuronal function, infection, injury, ischemia, and inflammation, microglia become activated, proliferate and change from a ramified to an amoeboid, macrophage-like morphology.

Depending on their activation status and the encountered pathologic events, microglia are able to exert a variety of effecter functions, which may be either neurotoxic or neuroprotective (17). Microglia activated by lipopolysaccharide (LPS), IFN-γ or TNF-α is considered to be "M1" ("classically activated") form of microglial (18,19). M1-skewed microglial activation plays a vital role in the defense against pathogens and tumor cell by production of proinflammatory cytokines, such as IL-1β, TNF-α, STAT3, IL-6, IL-12, IL-23 and free radicals such as reactive oxygen species (ROS). Besides, it also associated with the loss of neurons. Conversely, the alternative M2 anti-inflammatory phenotype promotes tissue remodeling/repair and angiogenesis through release high levels of anti-inflammatory cytokines such as IL-10, IL-4, IL-13, and TGF-β, and low levels of pro-inflammatory cytokines (20) (*Figure 1*). For AD mouse models, there have been reported increase in both M1 (such as IL-1β, TNF-a, iNOS, and IL-6) and M2 (notably YM1, Arg-1, Mrc and IL-10) markers compared to age-matched wild-type controls. During the course of disease, microglia undergoes a switch from a neuroprotective to a more classically activated phenotype. In consistent with this finding, it has been proved that the later stages of AD microglia undergo a switch from a neuroprotective M2 to a more classically activated phenotype (*Figure 2*). NALP3 inflammasome, which mediates IL-1β production, is one of the important

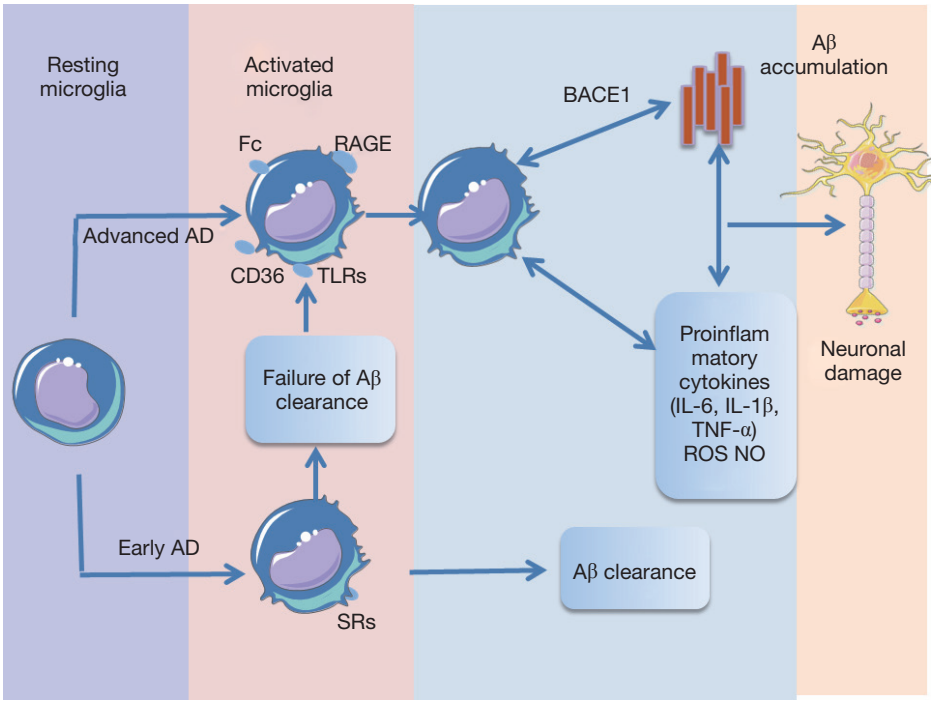

Figure 2 Possible mechanisms underlying microglial activation Aβ deposition and subsequent pro-inflammatory cytokine release contribute to AD. In the early stages of AD microglial activation can promote Aβ clearance via microglia's SRs. The persistent microglial activation stimulated by Aβ via the receptor for CD36, Fc receptors, TLRs and RAGE, creating a vicious circle between microglia activation, neuroinflammation, and Aβ accumulation. A crucial role on pathogenesis of AD is an absolute culprit for both amyloid plaque and other pathologic change such as the neuronal damage. Aβ, amyloid-β; AD, Alzheimer's disease; SRs, scavenger receptors; TLRs, toll-like receptors; RAGE, complement receptors advanced glycation end products; NO, nitric oxide; ROS, reactive oxygen species.

players driving the innate immune response towards Aβ and determining the cytokine milieu in the brain. Recently, Heneka *et al*. revealed that inhibition of NLRP3 can induce microglial phagocytosis and to an M2 phenotype (21). These findings are often viewed as evidence that microglia activation adapt to different stimulatory contexts and pass through a sequence of reactive profiles. The delicate balance between the pro-inflammatory and anti-inflammatory or neurotoxic and neuroprotective determines the role of microglia in a disease or condition.

In AD, the microglia has the capacity to respond to various stimuli, including amyloid peptides, their precursor protein (APP), and neurofibrillary tangles (22). In the early stages of AD, microglial activation can promote Aβ clearance via microglia's scavenger receptors (SRs) (23), and hinder the AD progression. The persistent microglial activation stimulated by Aβ via the receptor for CD36 (24), Fc receptors, toll-like receptors (TLRs) (25), and complement receptors advanced glycation end products (RAGE) (26), can increase Aβ production and decrease Aβ clearance, ultimately cause neuronal damage. Inhibiting Aβ-induced microglial activation can relieve the inflammatory cytokines production (27), lower Aβ deposition (28) and also ameliorate behavioral damage *in vivo* (29). These evidences suggest that Aβ indirectly contribute to activation of inflammatory systems, then lead to progression of AD. In 2008, Sastre *et al*. found that inflammation increase Aβ generation via β-secretase (BACE1), the main enzyme responsible for Aβ generation (30), therefore creating a feed-forward loop (*Figure 2*). What's more, these molecular mediators of neuroinflammation have also been linked with tau-mediated neurodegeneration (31).

In parallel with their negative effects, microglia also play a beneficial role in reducing Aβ accumulation by increasing its phagocytosis, clearance and degradation in early stages of AD (32). Recently, Parkhurst *et al*. also found that microglia promote learning-related synapse formation through BDNF signaling in learning and memory with CX_3CR1^{CreER}

mice (33). However, environmental stimulus, signal specificity, and intercellular influence decide whether the activated microglia plays a detrimental or beneficial role on the adult brain. Future studies have the task to investigate this double-edged sword.

Dysregulation of pro-inflammatory cytokine in AD

Dysregulation of pro-inflammatory cytokines in the brain

Experimental and clinical evidence have demonstrated the increased synthesis of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-6, IL-18, and the upregulation of their cognate receptors in the AD brain (34-37). However, the interactions between pro-inflammatory cytokines and senile plaques—a cardinal feature of AD have been reported. Chronic deposition of Aβ in brain drives cerebral neuroinflammation by activating microglia, which is reported to be a major source of pro-inflammatory cytokines in AD (38). Aβ binding to the microglial cell surface induces pro-inflammatory gene expression and results in the elevation of pro-inflammatory cytokine such as TNF-α, IL-1β, IL-6, IL-18, which lead to tau hyperphosphorylation and neuronal loss (39). Additionally, studies showed that the levels of transcripts for a number of pro-inflammatory markers such as TNF and IL-1β were elevated in AD, specifically in response to tau (40,41). As indicated above, chronic inflammation could be the consequence of AD pathology that further exacerbates the deleterious effects exerted by Aβ and tau. However, this interpretation have been questioned and new data assumed that neuroinflammation can also be a cause of AD for increase in Aβ and tau phosphorylation in the brain (42). In support of this, previous study has revealed that transgenic mice inducing neuroinflammation by injecting LPS triggered intracellular Aβ deposition (43,44) and tau phosphorylation (45) in the brain. Yet, intriguingly, previous studies reported that synergistic effects may also occur between pro-inflammatory cytokines and Aβ, such as, IFN-γ synergize with Aβ causing the release of TNF-α and reactive nitrogen species which is toxic to neurons.

Early expression of pro-inflammatory cytokines in the AD brain by non-neuronal cells, including endothelial cells, likely plays an important role in the development of disease. AD brain microvessels release significantly higher levels of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6 than microvessels in age-matched controls (46). The cerebral microvasculature participates in a destructive cycle of events where inflammation precedes Aβ deposition and Aβ in turn promotes release of inflammatory mediators. In this aspect, exposure of brain endothelial cells to Aβ arises a series of proinflammatory responses. This is supported by the finding that exposure of cultured human brain endothelial cells to Aβ1-40 up-regulate expression of inflammatory genes IL-1β and IL-6, which is confirmed by quantitative RT-PCR analysis (47). These results suggest that the cerebral microcirculation contributes proinflammatory cytokines to the milieu of the AD brain and may be involved in the pathogenesis of neuronal injury and death in this disorder.

In addition, several studies (48,49) suggest that sustained inflammation from the periphery can cause pro-inflammatory cytokines in the CNS by crossing the blood-brain barrier (BBB) and can contribute to cognitive decline in AD patients. Indeed, Capuron and Miller (50) recently reviewed the pathways for the transport of pro-inflammatory cytokines to brain from systemic circulation. In addition, Aβ could also across the BBB from the periphery into brain, which is mediated by RAGE (51). And the Aβ binding to RAGE on microglia permitted the microglia to undergo the sustained activation and inflammatory response, resulting in increased proinflammatory cytokines (*Figure 3*). In America, studies have shown that Aβ associated BBB leakage could be present in patients with cerebral amyloid angiopathy, which affects most patient with AD (52). Based on these findings, one can envisage that brain pro-inflammatory cytokines may be considered as a biomarker of AD. This is supported by data in triple-transgenic mice models of AD where targeting the increased circulating levels of proinflammatory cytokine IL-1β with a neutralizing antibody dramatically reduce the activity of several tau kinases and levels of phosphorylated tau (p-tau), and also reduce the load of oligomeric and fibrillar Aβ (fAβ). Thus, it seems that any significant inflammatory response within the brain tissue will be associated with pro-inflammatory cytokines dysfunction, raising the potential use of pro-inflammatory cytokines measure as a surrogate marker for a local inflammatory response in AD.

Dysregulation of pro-inflammatory cytokines in cerebral spinal fluid (CSF)

Altered levels of biomarkers in CSF are supported to be active long before the symptoms appear; moreover the CSF near to the brain parenchyma and the extracellular fluid of the brain. Thus, CSF analysis has been considered an ideal

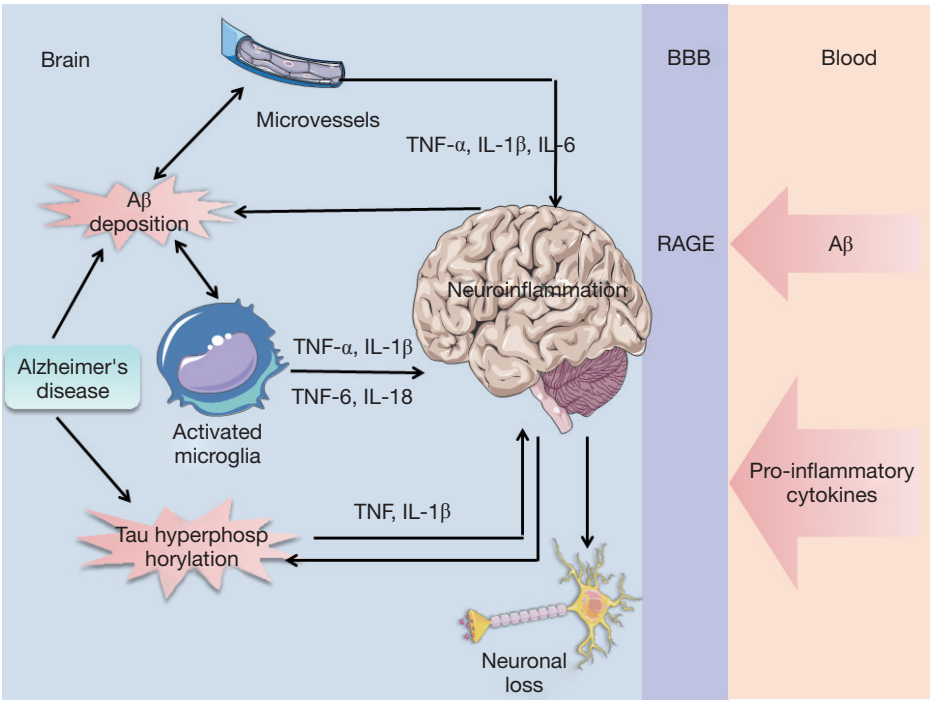

Figure 3 Speculative model of dysregulation of pro-inflammatory cytokines in the AD brain. (I) A vicious circle between microglia activation, pro-inflammatory cytokines production, and Aβ, tau accumulation in AD brain; (II) AD cerebral microvessels participates in a destructive cycle of events where inflammation precedes Aβ deposition and Aβ in turn promotes release of proinflammatory cytokines; (III) pro-inflammatory cytokines and Aβ could across the BBB from the periphery into brain, the latter is mediated by RAGE. AD, Alzheimer's disease; Aβ, amyloid-β; RAGE, complement receptors advanced glycation end products; BBB, blood-brain barrier.

Table 1 Dysregulation of pro-inflammatory cytokines in cerebrospinal fluid

Pro-inflammatory cytokines	Increased	Decrease	Unchanged
Interleukin-6	(54-59)	(60,61)	(59,62)
Interleukin-1β	(63)	(61)	(55,56,62,64,65)
Interleukin-18	–	–	(66)
Tumor-necrosis factor-α	(58,63,67-70)	(61,71)	(62)

Note that sometimes the same biomarkers has been found to be increased or decreased or unchanged reflecting the heterogeneity of the disease. AD, Alzheimer's disease; –, unfound.

source for viable biomarkers in AD. Currently, the only possible biomarker to aid a diagnosis of AD is the CSF total tau (t-tau) to $A\beta_{42}$ and phosphorylated tau181 (p-tau181) (53). However, the utility of CSF Aβ and tau as marker may be limited because of its fluctuations over time in CSF or it can be seen in other dementias. Recently, the occurrence of a plaque-dependent inflammation in AD has been extensively documented. There is intense interest in the use of proinflammatory cytokines as biomarkers of AD because they are upregulated during the earliest, oligomeric-induced inflammatory process in AD brains.

Different cytokines have been measured in CSF such as IL-1α, IL-1β, IL-6, IL-18 and TNF-α, as shown in *Table 1*, the measurements are very divergent between the different groups. There's evidence suggesting that IL-1α is as a promising candidate in AD for its important role in disease staging. Pathological altered of IL-1α levels is associated with plaque evolution and the rate of cognitive decline among clinically diagnosed MCI subjects. Advanced studies demonstrated that upregulation of brain levels of IL-1α activity in AD brain is an early event, as IL-1α levels are already significantly increased in MCI CSF, which might represent a novel biomarker of early detection of AD (72,73). Therefore, proinflammatory cytokines levels in CSF

Table 2 The source and the association of pro-inflammatory cytokine with AD pathogenesis

Pro-inflammatory cytokine	CNS origin	Effects on neurons	Synaptic effects	Effects on Aβ	Effects on tau	References
TNF-α	Microglia, astrocytes neurons	Pro-apoptotic; prevent apoptosis	Synaptic excitotoxicity; LTP ↓	↑ Aβ synthesis; ↓ Aβ clearance	↑ tau hyperphosphorylation	(74,75)
IL-1β	Microglial, astrocytes	Neuronal death and damage↑	LTP ↓ synaptic plasticity↓	↑ Aβ synthesis ↓ Aβ-related pathology	↑ tau phosphorylation ↓ tau pathology	(76-79)
IL-6	Microglial astrocytes endothelial cells	Rescue neurons	LTP ↓ prevents synaptic loss	↓ Aβ deposition	↑ tau phosphorylation	(80-82)
IL-18	Activated microglia, astrocytes and ependymal cells	Pro-apoptotic	↓ the induction of LTP	↑ production of APP ↑Aβ	↑ hyperphosphorylation of tau	(83-85)

CNS, central nervous system; TNF-α, tumour necrosis factor alpha; IL, interleukin; LTP, long term potentiation; Aβ, amyloid beta; ↑↓, increase or decrease.

are potential biomarkers of disease diagnosis, but remain unrealized.

Pro-inflammatory cytokine signaling in AD

The deregulation of several pro-inflammatory cytokines has been demonstrated implicated in the pathogenesis of AD. Here we will focus the attention on TNF-α, IL-1, IL-6, IL-12 and IL-18, and speculate their possible roles in AD progression (*Table 2*).

Tumor necrosis factor alpha (TNF-α)

TNF-α, a pleiotropic pro-inflammatory cytokine, is elevated in both the brains and plasma of AD patients and is proximal to amyloid plaques on autopsy, which appear to be reflective of disease severity and contribute to the inflammatory milieu. As early as 2001, a GWAS found single-nucleotide polymorphisms in TNF-α and/or its receptor is associated with sporadic AD. McAlpine *et al*. (86) recently reported that when neuron-specific TNF-α is chronically overexpressed in triple-transgenic AD mice (3xTg-AD) using adeno associated virus (AAV) vectors, there is increased intracellular Aβ in the short-term, enhanced inflammation and Tau pathology, and in the long-term that leads to neuronal cell death. The study portends that overexpression TNF-α signaling enhances AD-associated pathology and is detrimental to neuronal viability (87). However, TNF-α is also related to a deleterious role induced by Aβ on promote learning and memory deficits and synaptic memory mechanisms in AD. Inhibition of TNF-α reduced impairment induced by Aβ on recognition memory via long-term potentiation (LTP), electophysiological experiments correlate with learning and memory (88). Meanwhile, the cognitive deficit is reduced by the pharmacological inhibition of TNF-α in mice (89). The results suggest that selectively preventing neuronal TNF-α signaling through targeted blocking of receptor expression, may preserve neurons during the course of AD.

There are two cognate transmembrane receptors for TNF-α, termed TNF receptor 1 (TNFR1) (also known as Tnfrsf1a/p55, CD120a) and TNFR2 (Tnfrsf1b/p75, CD120b). Their biological effects are differentially expressed and regulated. Signaling via the cognate TNF-R receptors elicits distinct cellular responses, including cell proliferation, cell migration, and apoptosis mediated through the activation of several downstream signal transduction cascades involving NF-κB, c-Jun N-terminal kinase (JNK), p38, and ceramide-sphingomyelinase pathways (90). In the context of AD, deletion of the TNFR1 gene in APP transgenic mice reduced plaque deposition and improves the cognitive deficits by down-regulating BACE1 promoter activity. Moreover, McAlpine *et al*. reported that knock-out TNF-RI in the brains of 3xTg-AD mice can suppress AD-related amyloid pathology. In the same study, short-term inhibiting soluble TNF signaling can

prevent AD-associated amyloid pathology using the 3xTg-AD mouse model (86). However, long-term global deleted TNF receptors I and II signaling in the 3xTg mouse model exacerbates hallmark amyloid and neurofibrillary tangle pathology without cell type or stage specificity (91), which suggested that long-term anti-TNF-α should be taken caution. What's more, the study also suggested that a more selective of TNF signaling and stage of disease should be investigated. Recently, Montgomery *et al*. found that knockdown of TNF-RII in the long-term in hippocampal neurons via rAAV2 vectore mediated siRNA delivery enhances Aβ plaque deposition and paired helical filament (PHF) formation (90), which have shown TNF-RII may exert protective responses that may be required to counteract TNF-RI driven signal transduction.

However, neuroprotective effects have also been reported for TNF-α. For example, As early as 1995, Barger *et al*. has found that in the presence of Aβ peptide, dissociated neuronal cultures pretreated with TNF-α were spares cells from Aβ-induced neuronal death by suppressing accumulation of ROS and Ca^{2+} via NF-κB-dependent signaling (92). Subsequently, TNF-α has also been reported to be trophic to rat hippocampal neurons and to protect against glutamate, free radical, and Aβ toxicity in enriched cultures of primary neurons (93). Moreover, Tarkowski *et al*. proved intrathecal levels of TNF-α were significantly inversely correlated to the intracerebral apoptosis and neuronal degradation (67). Furthermore, incubation of human neuronal cells with TNF-α led to production of bcl-2, a molecule known to down-regulate neuronal apoptosis. These data indicate the complexity of the TNF signaling pathway, more investigation is deserved to better understand the cell-specific roles of TNF-α in the context of AD.

Interleukin-1β

IL-1β, a member of the IL-1 cytokine family, is considered to be a major proinflammatory cytokine in the brain and play a key role in the progress of AD. IL-1β is synthesized and released by both activated microglia and astrocytes in pro-forms, pro-IL-1β, in the cytoplasm in response to variety of stimuli. In order to generate mature and bioactive form, pro-IL-1β must be cleaved by the protease caspase-1, which is activated by cytosolic multiprotein complexes called inflammasomes (94,95). Recently, Parajuli *et al*. described that soluble oligomeric amyloidβ (oAβ) increased the processing of pro-IL-1β into mature IL-1β in microglia via ROS-dependent activation of NLRP3 inflammation (96).

Previous studies have identified that over-expression of the immune modifying cytokine IL-1β released by microglia and astrocytes surrounding Aβ plaques occur in AD brain and in animal models of AD in relative to age-matched controls (97,98). The production of IL-1β depends on the activation of MAP kinases and NF-κB signaling pathways. Recently, studies clearly demonstrated IL-1β contributing to APP processing *in vitro*. Subsequently, many researchers confirmed that overexpression of IL-1β exacerbates tau phosphorylation and tangle formation through aberrant activation of p38-MAPK and glycogen synthase kinase 3 (GSK3) (76,99), which affect synaptic plasticity, inhibiting LTP and subsequently learn and memory (100). Blocking or neutralizing IL-1β in an AD mouse model could largely protect from cognitive deficits, decrease tau pathology, synthesis of S100, and fAβ (76). In addition, fAβ has been reported to activate microglia, leading to increased synthesis and release of neurotoxic secretory products, pro-inflammatory cytokines such as IL-1β and ROS (101). Based on these findings, it would be interestingly supposed that Aβ deposits can be both a cause and a consequence of IL-1β expression in AD patients. Some studies have suggested that these two factors participate in a vicious cytokine cycle that once induced and derived AD pathology (*Figure 4*). In addition, the increased expression of IL-1β, was found to impair microglial Aβ clearance functions (102) and increase BBB permeability, which can promote the accumulation of Aβ in the brain (103). In contrast, evidence points that IL-1β may play a beneficial role in limiting AD pathology. It has been shown that sustained overexpression of IL-1β reduces Aβ-related pathology by modulating microglia-dependent plaque degradation or promoting non-amyloidogenic APP cleavage in a mouse model of AD and in a cell culture model (77,104,105). Thus, IL-1β may play a complex role in AD pathogenesis.

Interleukin-6

IL-6 is a pleiotropic inflammatory cytokine mainly produced by activated microglia, astrocytes in different brain regions. In addition, IL-6 could stimulate microglia and astrocytes to release a cascade of proinflammatory cytokines and acute-phase proteins, such as C-reactive protein (CRP) (106). The levels of IL-6 have been found significantly elevating in the brains, cerebrospinal fluid, and plasma, especially locally around amyloid plaques in AD patients and animal models. Therefore, it has been proposed IL-6 is involved in the etiopathology of AD with acute or chronic inflammatory

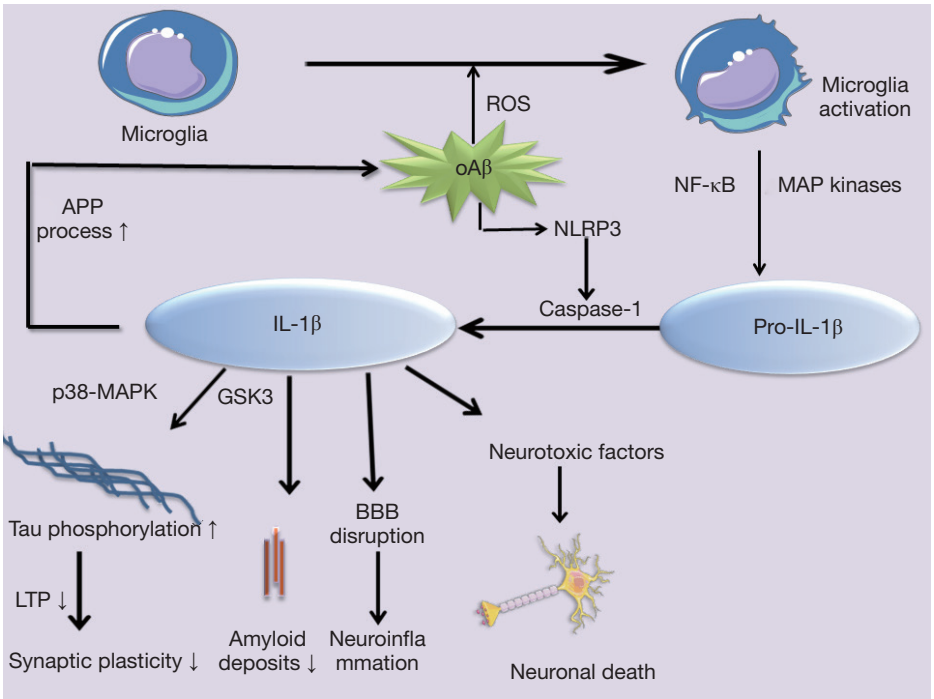

Figure 4 A hypothetical model linking the IL-1β activation to AD pathogenesis. AD, Alzheimer's disease; oAβ, oligomeric amyloidβ; GSK3, glycogen synthase kinase 3; LTP, inhibiting long-term potentiation; BBB, blood-brain barrier; pro-IL-1β, pro forms IL-1β; ROS, reactive oxygen species; ↑↓, increase or decrease.

components.

A number of studies have investigated the molecular mechanism underlying the association of IL-6 with AD including tau and Aβ. Production of IL-6 by human neurons is reportedly stimulated by glycation end product-modified tau and Aβ. Firstly, studies clearly demonstrated the role of IL-6 that contribute to APP processing and production in primary rat cortical neurons (80). In turn, fAβ has been reported can activate microglia, which lead to increase synthesis and release of IL-6 (47). Production of IL-6 depends on the activation of Toll-like receptor 2 (TLR2)-MyD88 signaling pathways in microglia and the JNK-AP1 pathway in human brain endothelial cells (47,107). Secondly, hippocampal cells treated with IL-6 could contribute to NFT formation by inducing Tau phosphorylation through cd k5/p 35 or pathway deregulation. In addition, IL-6 can also activate the JAK/STATs, NMDA receptor and the MAPK-p38 protein kinases, both involved in hyperphosphorylation of tau (80). However, *in vivo* studies, overexpression of IL-6 in APP transgenic mice and nontransgenic littermates induced by AAV1 leads to marked suppression of Aβ deposition, which does not significantly alter APP levels, APP processing, or steady-state Aβ generation. The date suggest that IL-6-induced neuroinflammation attenuation in Aβ levels instead of exacerbation Aβ plaque pathology, is most likely due to activation of microglia to a predominantly beneficial (M2) phenotype enhanced Aβ phagocytosis (108).

IL-6 in neuroinflammation and neurodegeneration also plays a complex role in regulating cognitive function (109). As early as 2002, Weaver *et al*. has found that elevated IL-6 correlated with age-related cognitive decline in humans (110). Subsequently, many researchers confirmed that under inflammatory conditions, excessive IL-6 through activation of neuronal NADPH-oxidase induced by aging or inflammation may impair cognitive processes, such as spatial learning and memory (81). By contrast, a recently study reported in cases where inflammation is not prominently elevating IL-6 and/or its downstream JAK/STAT signaling pathway may improve executive function in the mice orbito frontal cortex (111).

Interleukin-18

IL-18 (interferon-γ-inducing factor, IL-1γ), a pro-inflammatory

cytokines belonging to the IL-1 cytokine family, is synthesized as an inactive 24-kDa precursor protein (pro-IL-18) and cleaved by the intracellular cystein protease caspase-1 and proteinase-3 to generate a 18 kDa mature and biologically active form. Activated microglia, astrocytes and ependymal cells and neurons in the CNS are all the source of IL-18. Up-regulated IL-18 expression can lead to a harmful vicious cycle of inflammation: IL-18 drives the local production of IL-1β and IFN-γ, the latter cleaves inactive precursor protein of IL-1β and IL-18 to their mature and biologically active form via caspase-1, and it also increases IL-18 gene expression which may play an important role in the pathogenesis of AD (83).

Recently, accumulating date demonstrated that IL-18 may involve in the different aspects of neurodegeneration in AD. Evidences showed that IL-18 possibly has a direct influence on neuronal survival, synaptic plasticity. IL-18 binding to its receptor complex can lead to activation of JNK and MAPK p38, which can activate pro-apoptotic signaling pathways both in intrinsic and extrinsic. The effect seems to be mediated through induction of expression of p53 and Fas ligand (83), which suggests that IL-18 may be one of the apoptosis-inducing factors contributing to AD progression. In addition, studies have shown that IL-18 is cytotoxic to cardiomyocytes, which leads to increased intracellular Ca^{2+} levels, and calcium dysregulation plays an important role in the pathogenesis of AD (112). More specifically, IL-18 inhibits the induction of LTP in the dentate gyrus, a paradigm for the cellular mechanisms underlying learning and memory (84). However, lower levels of IL-18 related to polymorphisms in the cytokine gene may be associated with improved physical functioning in aged healthy men, which suggested that it may have neuroprotective effects (113). Therefore, a precise involvement of IL-18 in the pathogenesis of AD remains elusive and needs additional investigations.

A number of studies have investigated the molecular mechanism underlying the association of IL-18 with AD pathogenesis, although the exact role of IL-18 in AD still needs to be clarified. In 2012, Sutinen *et al*. proved IL-18 can increase production of APP and its Thr668 phosphorylation in neuron-like differentiated human SH-SY5Y cells. It can also increase amyloidogenic processing to Aβ by inducing expression of BACE-1 and N-terminal fragment (NTF) of PS-1, part of the functional γ-secretase complex (83), Which suggest heightened or prolonged levels of IL-18 may contribute to the process of AD via increased Aβ. Study conducted by Ojala *et al*. found that IL-18 may have an impact on the hyperphosphorylation of tau mediated by Cdk5/p35 and GSK-3β kinases (85). Further, increased expression of IL-18 in the brain and peripheral blood associated to cognitive impairment, have been also reported (114). However, a precise involvement of IL-18 in the pathogenesis of AD remains elusive and needs additional investigations.

Pro-inflammatory cytokine modulation as a therapeutic target for AD

Promoted by the substantial science and clinical evidence, pro-inflammatory cytokines is centrally involved in the pathogenesis of AD. Therefore, raises the logical postulation that intervention with drugs targeting modulation microglia proinflammatory cytokine production might be a viable strategy for subverting the disease course. Despite a large body of literature indicating detrimental roles for pro-inflammatory cytokines, neuroprotective effects have also been reported. Thus, strategies to modulate pro-inflammatory cytokines in the disease setting may require selective tuning and specificity to ensure that protective signaling outcomes are not compromised.

Recent studies are focusing on some other pro-inflammatory cytokines modulators such as melatonin, mainly secreted by the pineal gland in mammals, which has been shown to be produced by nonpineal cells and possess anti-inflammatory actions. It reduced the proinflammatory response, decreasing nearly 50% of the Aβ-induced levels of proinflammatory cytokines IL-1β, IL-6, and TNF-α (115). Subsequently experiment reported that melatonin improves the cognitive deficits of rats by inhibiting the local proinflammatory response, mediated by IL-1β induced glial activation *in vivo* (116). There is also overwhelming studies indicating the potential role of melatonin as an effective adjuvant in AD management (117,118). Unfortunately, a clinical observation indicated essentially negative results after using melatonin in patients with AD (119). Minocycline, a semisynthetic derivative of tetracycline with anti-inflammatory properties, significantly decreased pro-inflammatory cytokines IL-6 and TNF-α released by astrocytes in response to minocycline treatment (120,121). It is previously shown that minocycline treatment reduced the amount of aggregated tau in the cortex of young htau mice and amyloid pathology (122), and improved behavioural symptoms in transgenic mouse models of AD (121,123,124), which may be a potential target to treat AD. In addition, the antirheumatic drug

in China xanthoceraside has recently been demonstrated the protective effects on AD pathology by inhibited the Aβ 25-35/IFN-γ–induced pro-inflammatory cytokine NO, IL-1β, and TNF-α in microglia via TLR2/MyD88 pathway to down-regulation of MAPK and NF-kB activities. This study suggesting that xanthoceraside may be a potential therapeutic target for AD treatment (125). More importantly, montelukast a cysteinyl leukotriene receptor 1 (CysLT1R) antagonist, has been used for treatment of inflammatory diseases such as asthma, and currently been proved may ameliorate Aβ-induced memory impairment via inhibiting TNF-α and IL-1β and apoptosis mediated by CysLT1R signaling. Taken together, these results indicated that pro-inflammatory cytokines modulators may be a treatment strategy for AD.

However, some studies are focusing on individual cytokines for therapeutics of AD. Among numerous pro-inflammatory cytokines associated with AD, IL-1β has received particular attention for the role implicated in pathogenic. Blocking IL-1 signaling is able to alter brain inflammatory responses through the reduction of NF-kB activity, markedly reduce tau pathology and partly reduces certain fibrillar and oligomeric forms of amyloid-b in 3xTg-AD mice. Thereby Kitazawa *et al.* raised the possibility that abrogating IL-1β signaling may offer therapeutic benefit to AD patients (76). In addition, some studies have revealed the relationship between excessive TNF in the brain and the pathological features of AD. By blocking TNF signaling transiently (4 weeks) with soluble TNF-selective dominant negative TNF inhibitor XENP345, amyloid plaques were drastically reduced in the brains of 3xTg-AD mice exposed to chronic systemic inflammation (86). A recent study demonstrated that administration of TNF-α monoclonal antibody (Infliximab) on the AD pathological features in aged APP/PS1 double transgenic mice reduced amyloid plaques and tau phosphorylation (126). Subsequently, many researchers confirmed that administration of TNF-α inhibitor thalidomide in APP23 and 3xTg-AD mice resulted in a significant decrease in the activation of microglia, BACE1 level and activity, Aβ load, plaque formation and tau phosphorylation (127,128). On the contrary, Montgomery *et al*. reported that long-term knock-down of TNF-RII in hippocampal neurons via rAAV2 vector mediated siRNA delivery enhanced amyloid- and tau-related pathologic features (90). The present work builds on existing data suggested that caution must be taken on selectively modulate TNF signaling in specific cell types and at different stages of disease. Further work is necessary to confirm findings from earlier studies pro-inflammatory cytokine modulation as a therapeutic target for AD.

Conclusions

Increasing evidence has firmly certified that the inflammation induced by Aβ plays a key role in AD pathogenesis. The inflammatory process itself is driven by microglial activation through the induction of pro-inflammatory molecules and related signaling pathways, thus leading to Aβ aggregation, tau formation, synaptic damage, neuronal loss, and the activation of other inflammatory participants. These pro-inflammatory cytokines may have multiple roles in both neurodegeneration and neuroprotection, the use of the beneficial pro-inflammatory cytokine and the control of the detrimental pro-inflammatory cytokine released from microglia depends on our knowledge of their role in AD. However, our knowledge of the intricate role of pro-inflammatory cytokine in AD is far from completion and may lead to variable outcomes. It is critical to get the precise role of pro-inflammatory cytokine in AD, which helps to evaluate the therapeutic value of pro-inflammatory cytokine modulation for AD. Nonetheless, both science and clinical evidences suggest inhibiting pro-inflammatory cytokines therapeutics may be a viable strategy for subverting the disease course. However, strategies to modulate pro-inflammatory cytokines in the disease setting may require selective tuning and specificity to ensure that protective signaling outcomes are not compromised. There are many important questions still need to be answered, such as how different factors and agents modulate pro-inflammatory cytokines signaling in homeostasis and how pro-inflammatory cytokines signaling is intertwined with other innate and adaptive immune pathways. Future studies should focus on in-depth understanding of how they contribute to AD pathology, and it might provide more cues for the development of therapeutic strategies in AD.

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