

Neuroinflammation in Alzheimer's disease

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Abstract: Amyloid- β plaques and neurofibrillary tangles are the main neuropathological hallmarks in Alzheimer's disease (AD), the most common cause of dementia in the elderly. However, it has become increasingly apparent that neuroinflammation plays a significant role in the pathophysiology of AD. This review summarizes the current status of neuroinflammation research related to AD, focusing on the connections between neuroinflammation and some inflammation factors in AD. Among these connections, we discuss the dysfunctional blood-brain barrier and alterations in the functional responses of microglia and astrocytes in this process. In addition, we summarize and discuss the role of intracellular signaling pathways involved in inflammatory responses in astrocytes and microglia, including the mitogen-activated protein kinase pathways, nuclear factor-kappa B cascade, and peroxisome proliferator-activated receptor-gamma transcription factors. Finally, the dysregulation of the control and release of pro- and anti-inflammatory cytokines and classic AD pathology (amyloid plaques and neurofibrillary tangles) in AD is also reviewed.

Keywords: inflammation, blood-brain barrier, glial cells, intracellular signaling pathways, inflammatory factors

Introduction

Neuroinflammation is defined as the brain's activation of the innate immune system, and its main function is to protect the central nervous system (CNS) against infectious insults, injury, or disease.¹ It has been well established that neuroinflammation is actively involved in neurological diseases and disorders such as Alzheimer's disease (AD).² It is a complex response involving a host of cellular and molecular changes, recruitment of peripheral immune cells, induction of some intracellular signaling pathways, and release of inflammatory mediators in the brain. All these factors can contribute to the occurrence of neuronal dysfunction and death in AD, either alone or in combination.^{3,4} These observations and other researches indicate that neuroinflammation is an early and continuous feature of AD. In the following contents, we will emphasize the role of the blood-brain barrier (BBB) and glial cells during neuroinflammation in the CNS and provide an outline of the involvement of intracellular signaling pathways and inflammatory mediators produced by glial cells and the main neuropathological hallmarks in the pathological cascade of events leading to AD.

BBB and neuroinflammation

BBB is a specialized barrier between blood and brain mainly consisting of specific endothelial cells, tight liner sheets formed by astrocytic end-feet and pericytes, and tight junctions (TJs) that are brought together.⁵ Because of the importance of the CNS, a physical and transport barrier for blood-borne cells and toxic solubles to invade the CNS parenchyma is indispensable.⁶ The BBB and blood-nerve barrier restrict exchanges of soluble factors and cells between the neural tissue and blood, thus playing

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a crucial role in the maintenance of the peripheral nervous system and CNS homeostasis.⁷

Increasing evidence indicates that amyloid- β (A β) and BBB disruption may mutually promote their effects on AD. P-glycoprotein, a transporter on the luminal surface of the BBB transports A β from the brain to the blood efficiently.⁸ The dysfunction of BBB can result in A β accumulation by inducing BBB leakage or insufficient clearance. A β 42 is able to modify the expression of TJs and alter barrier properties functionally *in vitro*.⁹ A β accumulation can lead to BBB dysfunction by endothelial toxicity and increased monocyte adhesion.¹⁰ One cause of the BBB dysfunction is inflammatory cytokines. For example, it has been reported that tumor necrosis factor- α (TNF- α), interleukin-(IL)1 β , and IL-17A could loosen the TJs and breach the BBB.¹¹ Neuroinflammatory response is involved in the altered expression of TJs and loss of BBB integrity in capillary cerebral amyloid angiopathy,¹² and BBB transcriptome changed in systemic inflammation.¹³ In an animal model of AD using an Alzheimer amyloid precursor protein (APP)-transgenic mouse (APP-Tg), the increase in brain inflammatory cytokine (IL-6) level is significantly higher in APP-Tg than in wild-type mice after peripheral lipopolysaccharide injection, and the BBB becomes more permeable during peripherally evoked inflammation. The results indicate the increased vulnerability of the BBB to inflammation in this animal model of AD.¹⁴ Research has usually focused on structural integrity rather than functionality, and BBB alteration has traditionally been explained as a consequence rather than a cause. But current knowledge suggests that BBB integrity plays a more important role than previously thought, and pharmacological modulation of the BBB may offer a new therapeutic target for AD treatment. For example, there is a patent showing that ultrasound neuromodulation can control the permeability of the BBB for the selective penetration of drugs or other substances into the target.¹⁵

Cell mediators of neuroinflammation

Astrocytes and microglia are the major types of glial cells in the CNS, and their activation involves various types of neurodegenerative processes. Reactive glial cells are closely associated with plaques and parallel tangles in AD.¹⁶ Once activated, their processes become hypertrophied; both astrocytes and microglia produce multiple inflammatory factors, including cytokines, prostanoids, chemokines, reactive oxygen species, and cyclooxygenase-(COX)2.¹⁷ Similarly, as indications of neuroinflammation, elevated levels of

inflammatory cytokines are discovered in AD (see the section Cytokines and neuroinflammation).

Microglia

Due to the presence of the BBB, the lack of lymphatic drainage, and the reduced capability of leukocytes to invade the CNS, the need arises for a different approach to remove and eliminate injured tissue. Therefore, the CNS is equipped with high specificity of innate immune cells named microglia. They are the resident macrophages, accounting for approximately 5%–10% of the adult brain cell population in the CNS.¹⁸ These cells actually arise early from progenitors in the embryonic yolk sac and appear to persist into adulthood. Furthermore, microglia exist in all stages of brain development.¹⁹ Their main functions are to facilitate host defense by destroying invading pathogens, eliminating deleterious debris, and promoting tissue repair and homeostasis, partly by affecting the surrounding astrocytes and neurons.²⁰ And inflammatory conditions have been shown to increase the supplement of circulating myeloid progenitors and differentiation into microglia.²¹ As the primary regulators of inflammation in the CNS, the activation of microglia can quickly lead to the release of inflammatory cytokines.²² In culture, it has been shown that microglia can release several potentially cytotoxic substances, such as cytokines, nitric oxide, arachidonic acid derivatives, proteases, reactive oxygen intermediates, excitatory amino acids, and various neurotrophic factors.²³

Now, there is no doubt that activated microglia are involved in neuronal death and cognitive deficits in AD. Morales et al showed that Tau polymers induce activation of microglia and change their cellular morphology and the release of the inflammatory cytokine IL-6; furthermore, conditioned media of activated microglia induced neurofibrillary degeneration of hippocampal neurons in culture.²⁴ In a triple-transgenic model of AD, activated microglia increased significantly compared with nontransgenic controls, and the activation of microglia was closely associated with A β plaque formation, smaller A β deposits, and A β plaques.²⁵ Griciuc et al investigated the AD risk gene, CD33. AD brains have increased CD33 and CD33-positive microglia. Mice lacking the gene of CD33 have less AD pathology, revealing a role for microglia in A β clearance.²⁶ Early in the emergence of senile plaques, microglia are strongly activated; they serve to limit the growth of senile plaques and then minimize local inflammatory damage to the brain components.²⁷ Microglia express scavenger receptors of class A or B and receptors for advanced-glycosylation end products that promote A β

phagocytosis.^{28,29} In addition, microglia also secrete proteolytic enzymes that degrade A β , such as insulin-degrading enzyme, matrix metalloproteinase, and plasminogen-plasmin complex.^{30,31} Moreover, microglia can secrete a number of soluble factors at the same time, such as the glia-derived neurotrophic factor, which plays a part in promoting the survival of neurons.³² It has been shown that bone marrow-derived microglia could delay or stop the progress of AD, and preventing their recruitment contributes to the pathology.³³ Although there is a growing body of evidence to support a role for microglia in neuroprotection and A β clearance, why A β continues to accumulate and why AD pathology progresses despite continued microglia activation and recruitment remain to be answered. Possible explanations for the failure of microglia to slow AD pathology progresses would be that microglia become overloaded by the large amount of A β produced, cannot keep pace with the generation of A β , become more proinflammatory,³⁴ and their activation is gradually diminished in the later stages of plaque formation (>150 days).²⁷ The ability of the microglia to interact with A β fibrils undergoes an age-dependent decrease and their ability to phagocytize them is lost;³⁵ thus, the uptake and degradation of A β are reduced. Major microglial functions progressively decline with the appearance of A β plaques in AD, and lowering A β burden could reverse this functional impairment.³⁶ Microglia interact with A β , overproduction of inflammatory cytokines (IL-1 β , TNF- α , IL-6) and substances released by dying neurons, activated β -secretase-1 (BACE1) and γ -secretases to reduce A β clearance, thereby promoting A β production,³⁴ further proliferation and activation of microglia and neuronal damage, resulting in a vicious cycle in AD.³⁷ Above all, the role of microglia in neuroinflammation of AD could be seen as a double-edged sword. Therefore, it is important to understand the activation of microglia in different stages of AD to be able to estimate the effect of potential therapies. A seminal study conducted by Heneka et al revealed that microglia-specific inflammasome is a promising type of cell-specific molecular target for therapeutic intervention of AD in the CNS.³⁸ It could be proposed that pharmacological agents targeting microglia represent a novel angle for the therapeutic intervention of AD.

Astrocytes

Astrocytes are specialized glial cells accounting for approximately 35% of the total CNS cell population and are found in all the CNS regions.³⁹ Like neurons and oligodendrocytes, they are derived from the neuroectoderm, which is in contrast to microglia.⁴⁰ Astrocytes are morphologically

heterogeneous. Fibrous astrocytes are shown in the white matter, and protoplasmic astrocytes are shown in the gray matter.⁴¹ The reaction of fibrous astrocytes and protoplasmic astrocytes is very different. Following mechanical injury, both of them undergo the process of hypertrophy of the cell bodies and processes. Fibrous astrocytes simplify and retract their branching structure, but not protoplasmic astrocytes.⁴² Astrocytes assume a variety of roles in maintaining an optimally suited milieu for neuronal function. Select astrocytic functions include the removal of debris and toxins from the cerebrospinal fluid, the regulation of neurotransmitter, the production of trophic factors and ion concentrations, and the maintenance of redox potential. These functional impairments associated with the injury of astrocytes during physiological reactions could trigger or exacerbate neuronal dysfunction.⁴³

Glial cells are abundant in the CNS and play multiple roles in brain structure and function. In response to A β oligomers, reactive astrocytes are closely associated with the activation of the transcriptional factor nuclear factor-kappa B (NF- κ B) and upregulation of TNF- α , IL-1 β , and COX-2 in the rat cortex *in vivo*.⁴⁴ Some scientists think that astrocytes are conductors of the AD neuroinflammatory symphony⁴⁵ and astrocyte senescence as a component of AD.⁴⁶ On the one hand, it has been demonstrated that primary human astrocytes or astrocytoma cells could be induced by interferon- γ in combination with IL-1 β or TNF- α to produce A β .⁴⁷ The astrocyte-secreted proinflammatory factors could contribute to the expression level of secretases, thereby enhancing the conversion of APP into neurotoxic, insoluble, fibrillary A β on the membrane of neurons.^{48,49} Reactive astrocytes express BACE, the enzyme responsible for the generation of A β , suggesting that they may promote A β accumulation in aged transgenic AD mice model.^{50,51} Reactive astrocytes from sporadic AD patients also have increased levels of presenilin-1, the catalytic component of the γ -secretase complex that is involved in the formation of A β .⁵² As the largest number of brain cells, activated astrocytes may represent a very important source of A β during neuroinflammation in AD.⁵³ On the other hand, by providing trophic support to neurons and forming a protective barrier between neurons and A β deposits, astrocytes are known to promote the A β clearance and degradation.⁵¹ Reactive astrocytes could express A β -degrading enzymes, mainly matrix metalloproteinases-2, -3, and -9 and neprilysin.^{54,55} A β increases apoE protein levels, which is associated with neuroinflammatory responses and A β clearance in astrocytes. It may be a neuroprotective response to A β -induced cytotoxicity, in accordance with

apoE's role in cytoprotection.⁵⁶ Thus, astrocytes undergoing modifications and chronic inflammation might suffer a deleterious transformation: acquire the capacity to generate A β and lose the ability to remove and degrade them.⁵⁷

Astrocytes are closely involved in inflammatory and immunological events occurring in the CNS due to their ability to secrete and respond to a very large number of inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, IL-8, IL-10, transforming growth factor (TGF)- β , interferon- γ , and interferon- β .⁵⁸ The mechanisms of astrocyte activation in response to A β may include NF- κ B-mediated pro- and/or inflammatory gene expression.⁴⁴ A β induces astrocytic glutamate release, synaptic loss, and extrasynaptic N-methyl-D-aspartic acid receptor activation.⁵⁹ In vitro, A β 42 triggered senescence, driving the expression of positive senescent astrocytes. Senescent astrocytes produce a number of inflammatory cytokines including IL-6, and an accumulation of senescent astrocytes may be associated with increased risk of sporadic AD with advancing age.⁶⁰ Astrocytes exposure to increased amounts of A β for a long time, these cells must to clear large amounts of A β , hence, neglect their other functions, at last impairs the transmitter recycling and metabolic support of astrocytes in AD patients.⁶¹ Recently, the potential of astrocyte-targeted therapeutics in an intact animal model of AD was tested. When adeno-associated virus vectors containing the promoter of astrocyte-specific Gfa2 was used to target hippocampal astrocytes in APP/PS1 mice, APP/PS1 mice exhibited improved synaptic function, cognitive, lower amyloid levels, and reduced glial activation.⁶² The results lay the foundation to explore other novel astrocyte-based therapies.

Intracellular signaling pathway and neuroinflammation

The regulation of inflammatory cytokine production in activated microglia and astrocytes is under the control of intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK) signaling pathway, the NF- κ B signaling cascade, and peroxisome proliferator-activated receptor- γ (PPAR- γ).

Role of MAPK

MAPK signaling pathways are widespread and highly evolutionarily conserved regulation mechanisms of the eukaryotic cell. MAPKs include extracellular signal-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK1/2/3), and p38 kinase (p38 α β δ).^{63,64} They orchestrate the regulation of gene transcription, protein biosynthesis, cell cycle control, differentiation, and apoptosis.⁶⁵ Loss of MAPK signaling

regulation is implicated in diseases and cancer affecting the brain and the immune system.^{66,67}

The ERKs were the first identified mammalian MAPKs. In many cases, the ERKs can be triggered by inflammatory cytokines including the TNF family. These mechanisms of ERK activation play important roles in inflammation and innate immunity.⁶⁵

The JNKs are multifunctional signaling molecules that are activated in response to a wide range of inflammatory mediators and cellular stresses. JNKs regulate various processes, such as neuroinflammation, neuronal death, memory formation, brain development, and repair. These findings suggest that the JNKs play a role in Tau pathology and cognitive deficits⁶⁸ and regulate soluble A β oligomers in AD mouse model.⁶⁹ Activation of JNK in the brain triggered by intracellular A β accumulation leads to neuronal death in AD animal models and patients.⁷⁰ The generation of proinflammatory cytokine induced by A β 42 might be related to the toll-like receptor 2-dependent JNK/NF- κ B signal pathway, at least in part. Blockade of this pathway could be beneficial in the AD pathogenesis.⁷¹

The first p38 MAPK isoform, α isoform, isolated from extracts of endotoxin-treated cells, could play multiple roles in AD pathophysiology. Microglial p38 MAPK leads to the inflammation of the AD brains, and astrocytes p38 MAPK modulates the excitotoxicity and expands the inflammatory response, while the neuronal p38 MAPK contributes to depression of synaptic plasticity, Tau phosphorylation, and neurofibrillary tangle (NFT) formation.⁷² Some effects on neuroinflammatory processes are summarized in Table 1.

Among the effects, the MAPK signaling pathways play a pivotal role in lipopolysaccharide-, cytokine-, or A β -induced neuroinflammation and highlight the evidence of the potential inhibition of neuroinflammation through MAPK signaling pathways. Targeting this single kinase might have the potential to change the disease process. However, there are two unsolved problems: first, a single kinase inhibitor might not provide therapeutic efficacy, and whether three kinase common inhibitors possess the ability to have better effects is still unknown; second, the same potential drug targets the different MAPK signaling pathways in vivo and in vitro. For example, potential drug epigallocatechin gallate has different targets, mediated inflammation via ERK and NF- κ B in vivo,^{1,85} but via NF- κ B, p38, and JNK inhibition in vitro (U373MG).⁸⁶ The same potential drug targets the different MAPK signaling pathways in vivo and in vitro. The pharmacodynamics of potential drugs is still missing, and clinical application of drugs targeting the MAPK in the brain still has a long way to go.

Table 1 Summary of some effects on neuroinflammatory processes

Drugs or effects	Immune effects	Model	References
Lipopolysaccharide induced	Mediate generation of NO and TNF- α through p38	In vitro (primary rat and human microglia)	73,74
A β -induced	Mediate neuroinflammation through microglial p38	In vivo (rat brain)	75
A β -induced	Mediate glutamate excitotoxicity through p38	In vitro (primary rat astrocytes)	76
TNF- α /IL-1 β -induced	Modulate iNOS induction through JNK I	In vitro (astrocytes)	77
	Modulate iNOS induction through ERK		78
JNK inhibitory peptide (JIP)	Reduce NADPH oxidase-mediated H ₂ O ₂ productivity through JNK	In vitro (BV-2 microglia)	79
JNK inhibitor, D-JNKI-1	The involvement of the JNK pathway on Tau pathology and cognitive deficits	In vivo (6-month-old SAMP8 mice)	68
Inhibition of phosphorylation of JNK	Suppresses A β -induced ER stress and upregulates prosurvival of mitochondrial proteins	In vitro (rat hippocampus)	80
HO-1 activator, CopplX	Reverse iNOS/NO upregulation and HO-1 downregulation through JAK I/JNK/STAT1 signaling pathway	In vitro (BV-2 microglia)	81
p38 β knockout	Mediate proinflammatory cytokines and neuron death through p38 α but p38 β MAPK is dispensable	In vitro (WT microglia co-culture with WT neurons)	82
Overexpression of JNK	Induce neurite extension	In vitro (primary neurons or PC12 cells)	83
Hyperphosphorylated Tau	Mediate amounts of aggregated Tau through p38	In vivo (transgenic mice)	84

Abbreviations: A β , amyloid β ; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; HO-1, heme oxygenase-1; IL-1 β , interleukin 1 β ; iNOS, inducible nitric oxide synthase; JAK, Janus Kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; SAMP8, senescence-accelerated prone mouse 8; TNF- α , tumor necrosis factor- α ; WT, wild type.

Besides the MAPK pathways, various transcription factors, including NF- κ B⁸⁷⁻⁹⁰ and PPAR- γ ^{91,92} have been shown to be involved in inflammatory responses in astrocytes and microglia.

Role of NF- κ B

The NF- κ B pathway was discovered in 1986 as a modulator of transcription in the light chain of B lymphocyte immunoglobulins.⁹³ NF- κ B is a redox transcription factor located within the cytoplasm and responsible for regulation in cytokine production. It is a dimer composed of members of the Rel family transcription factors: RelA (p65), RelB, c-Rel, p52, and p50. Normally, NF- κ B is kept inactive by interaction with its inhibitors, which are family members of the inhibitor κ B (I κ B) protein (I κ B α , I κ B β , I κ B γ , I κ B ϵ , I κ B δ , and Bcl-3) in the cytoplasm. I κ B kinases (IKKs), components of a serine–threonine kinase complex, catalyze I κ B phosphorylation. It is composed of three elements: a regulatory subunit, NEMO (also called IKK- γ), and two catalytic subunits, IKK- α and IKK- β .^{94,95} When the pathway is activated, phosphorylated NF- κ B dimers are released and translocated to the nucleus, bind to the DNA sequences κ B, and induce transcription of target genes. The effects caused by NF- κ B activity are usually based on the control of neurite outgrowth, synaptic plasticity, and neuronal apoptosis in the CNS.⁹⁵ In terms of neuroinflammation, NF- κ B activation has been shown to mediate cytokine expression^{87,88} and inducible nitric oxide synthase (iNOS) induction and nitric oxide production⁸⁹

in microglia. Furthermore, its activation is also involved in COX-2 expression in activated astrocytes,⁹⁰ a molecule that mediates the formation of prostaglandin and seems to play a significant role in the processes of neuroinflammation. It has also been suggested that NF- κ B plays an important role in sustaining the vicious cycle of inflammatory response and in neuroglial interactions in neurons and astrocytes.⁹⁶

Several molecules have the ability to activate NF- κ B, including TNF- α ,⁹⁷ IL-1 β ,⁹⁸ A β , and secreted APP.^{99,100} In turn, the NF- κ B is involved in A β 42 oligomer production.^{101,102} NF- κ B signaling upregulates BACE1 gene expression and facilitates APP processing, and the levels of NF- κ B/p65 and BACE1 in the brains of AD patients were significantly increased.¹⁰³ In mice models of AD (Tg2576), the increase of NF- κ B activity has been associated with neuronal apoptosis and the process of the disease.¹⁰⁴ Using different NF- κ B kinase modulators in pharmacological approach, the results indicate that NF- κ B pathways are involved in A β production.¹⁰⁵ In the promoter region of human BACE1, two functional NF- κ B-binding elements were identified, and disruption of NF- κ B/p65 decreased the expression of BACE1 gene in RelA(p65) knockout cells and expression of NF- κ B/p65 upregulated BACE cleavage and A β production.¹⁰³ Paris et al have also shown that different kinds of NF- κ B inhibitors reduce A β generation in 7W CHO cells overexpressing A β PP.¹⁰⁶ Moreover, nonsteroidal anti-inflammatory drugs such as indomethacin effectively decreased A β production through the inactivation of NF- κ B activity.¹⁰⁷

Now a new study suggests that the expression level of the NF- κ B1 (p105/50) gene in peripheral mononuclear cells of patients with AD was significantly higher than adult age-matched controls; furthermore, various NF- κ B target genes expression and NF- κ B/p65 and NF- κ B/p50 DNA-binding activity were also increased.¹⁰⁸ So it may be a promising pathogenic research tool for early diagnosis of AD at the peripheral levels. Taking all these reports into consideration, NF- κ B can be viewed as a potential therapeutic target for AD treatment by directly inhibiting A β production.

Role of PPAR- γ

The PPARs belong to the superfamily of nuclear hormone receptors, a ligand-inducible transcription factor. Its activities are regulated by lipid and steroids metabolites.¹⁰⁹ At present, three different PPAR subtypes (PPAR- α , PPAR- β [PPAR- δ], and PPAR- γ) have been identified.¹¹⁰ PPARs bind to PPAR response elements in target DNA sequences as heterodimers with the retinoid X receptor, leading to the transcription of target genes. It has been reported that they control the expression of genes related to inflammatory responses and glucose and lipid homeostasis.¹¹¹

Under physiological conditions, PPAR- γ is expressed at low levels in the CNS.¹¹² However, in some pathological conditions, PPAR- γ expression and mRNA levels, rather than other subtypes, were shown to be elevated in AD patients.¹¹³ These findings suggested that PPAR- γ may play a regulatory role in pathophysiological features of AD. In addition, PPAR- γ activation in microglia decreased the expression of inflammatory cytokines, iNOS, and nitric oxide (NO) production.⁹¹ These latter effects resulting from the PPAR- γ activation suppress the expression of proinflammatory genes by inhibiting NF- κ B-mediated inflammatory signaling at multiple sites.¹¹⁴ Besides microglia, emerging data indicate neurons and astrocytes as basic cell type targets for the beneficial effects of PPAR- γ ligands.⁹² PPAR- γ activation has been reported to promote neurogenesis, and agonists regulate the proliferation and differentiation of neuronal stem cell.¹¹⁵

PPAR- γ target drugs have been largely described to have neuroprotective effects in neuropathological conditions, including A β -induced neurodegeneration and neuroinflammation.¹¹⁶ For example, cannabidiol reduces neuroinflammation induced by A β and promotes hippocampal neurogenesis through PPAR- γ .¹¹⁷ PPAR- γ agonists could suppress A β -mediated microglia activation, inhibit inflammatory gene expression, alter A β homeostasis, exhibit neuroprotective effects,^{91,118–120} and protect neurons through

modulation of the mitochondrial fusion–fission events,¹²¹ thereby ameliorating the pathogenesis and progression of AD. Pioglitazone treatment decreased BACE1 and lowered the plaque burden in an animal model of AD.¹²² It protects cortical neurons against inflammatory mediators by improving peroxisomal function¹²³ and reduces the levels of brain A β 42 in Tg2576 mice.¹²² Furthermore, PPAR- γ agonists could reduce Tau protein phosphorylation, thereby inhibiting the accumulation of NFT in AD.¹²⁴

At present, the main evidence suggests that PPAR- γ play a critical role in regulating pathophysiological features of AD. But there is evidence revealing that PPAR- α/δ have been involved in the pathogenesis of neuroinflammation.^{125,126} PPAR- δ deficiency leads to cognitive impairment associated with enhanced astrogliosis, inflammation, and Tau hyperphosphorylation in the cortex.¹²⁷ These two isoforms are attracting more and more attention.

Cytokines and neuroinflammation

Cytokines are small, nonstructural proteins secreted from various cell types with molecular weights ranging from 8,000 Da to 40,000 Da that play varied biological activities. Chronic neuroinflammation induced by cytokines released from activated microglia and astrocytes has been recognized as one of the major mechanisms of AD neuropathology. Key to this review, we introduce both anti- and pro-inflammatory responses mediated by cytokines. Among these factors, we shall focus on cytokines and their interaction with A β and AD pathologies.

Tumor necrosis factor- α

TNF- α is a pleiotropic cytokine regulating numerous physiological and pathological processes, including differentiation, inflammation, and cell death. TNF- α expression levels in the healthy brain are low under physiological conditions. TNF is thought to play a central role in inflammatory or disease states. More and more studies present TNF as a neuromodulator in the process of AD pathologies.¹²⁸ The dysregulation of TNF- α production has been linked to AD.¹²⁹ Compared to the age-matched healthy controls, serum TNF- α levels significantly increased in the early-onset AD patients (age of onset <65) and late-onset AD patients (age of onset >65) groups.¹³⁰ It has been shown that TNF- α regulate A β PP in mouse model of AD¹³¹ and induce A β production by increasing the expression of BACE1¹³² and the activity of γ -secretase.¹³³ TNF- α synthesis inhibitor (3,6'-dithiothalidomide) suppresses A β -induced microglial activation, neuronal degeneration, and memory dysfunction and attenuates inflammation markers

and AD pathology in the setting of neuroinflammation and AD.¹³⁴ However, there are some opposing results. In their study, Uslu et al observed a correlation of A β 42 levels with mini-mental state examination scores and body mass indexes in AD patients, but not with IL-6 and TNF- α levels in serum.¹³⁵ The relationship between TNF- α and AD needs urgent solution and further research.

Interleukin-1

IL-1 is a kind of inflammatory cytokine that is usually produced by microglia in the brain and seems to play a significant role in the AD pathogenesis.¹³⁶ A 10-year follow-up study of 133 institutionalized elderly patients in a nursing home indicates that systemic inflammatory IL-1 during agitation stage are risk factors in the development of AD.¹³⁷ A recent study suggests that the polymorphism of IL-1 gene clusters may play a relevant role in AD pathogenesis in Brazilians.¹³⁸ IL-1 β can promote A β production by modulating γ -secretase activity in neurons.¹³³ Enhanced message translation of IL-1 β promotes the increase of A β PP synthesis in astrocytes.¹³⁹ Likewise, IL-1 β increased the levels of soluble amyloid precursor protein (sAPP) in a dose-dependent manner in the culture medium of primary neurons.¹⁴⁰ Some studies have also demonstrated that IL-1 β induces Tau protein phosphorylation and triggers the formation of paired-helical filaments, thus aggregating into NFTs.^{141,142} Sustained IL-1 β overexpression increases in Tau phosphorylation and exacerbates Tau pathology in an IL-1 β overexpression (IL-1 β XAT) AD mouse model.¹⁴³ In response to A β deposition, IL-1 β released from astrocytes may be an important trigger of Tau pathology in the AD brain.⁴⁵ Chronic hippocampal IL-1 β overexpression and peripheral and intracerebral injection of IL-1 β directly also impair long-term memory.^{144,145} However, one study indicates that IL-1 β may play a beneficial role in limiting AD pathology. In the study by Matousek et al, regardless of the duration of cytokine expression or age, IL-1 β overexpression leads to plaque clearance, and sustained IL-1 β did not cause overt apoptosis in the hippocampus of an APP^{sw}/PS1^{dE9} AD mouse model.¹⁴⁶

Above all, there is no doubt that IL-1 β causes AD pathologies in neuroinflammation, but its mechanism remains unclear and some key points have to be solved.

Interleukin-6

IL-6 is a major cytokine in the CNS. It plays an important role in the brain.¹⁴⁷ IL-6 gene maps to chromosome 7p21 and has been assumed to be a good candidate for AD genetic risk factor.¹⁴⁸ Recent studies showed that IL-6 polymorphisms

are associated with risk of AD.^{149,150} Through a 10-year follow-up study on 133 elderly patients, they also found that systemic inflammatory IL-6 during the agitation stage are risk factors in AD development.¹³⁷ In AD brain, IL-6 stimulates and promotes the recruitment of microglia and astrocytes to release proinflammatory cytokines,¹⁵¹ and it also promotes the Tau phosphorylation in neurons.¹⁵² But a meta-analysis suggested that IL-6-174G/C polymorphism would be a protective factor for AD in Asians but not in Caucasians. It may contribute to a decreased risk of AD.¹⁵³ Taking into account the multifactorial etiology of AD, more complete case-control studies of stratified analysis of different environmental exposure, ethnic background, or other risk factors should be carried out to evaluate possible roles of IL-6 in the AD pathogenesis in the future.

Interleukin-10

IL-10 is one of the main anti-inflammatory cytokines and plays an important role in cell survival and neuronal homeostasis. Preexposure of glial cells to IL-10 inhibits the production of proinflammatory cytokines induced by A β or lipopolysaccharide.¹⁵⁴ However, the stimulation of IL-10 did not suppress A β deposition in the mouse brain.¹⁵⁵ It is inefficient in A β 42 degradation and could potentially increase the ratio of A β 42/A β 40 (A β 42 promotes amyloid deposition but A β 40 inhibits it) in Tg2576 mice.¹⁵⁶ A recent study shows that IL-10 in the periphery obviously associated with brain atrophy in AD.¹⁵⁷ The relationship between IL-10 and AD needs more compelling evidence.

Transforming growth factor- β

TGF- β s are pleiotropic cytokines produced by various cell types throughout the body. They play an important role in some biological effects, such as brain development, neuroendocrine roles, synaptogenesis, synaptic functions, adult neurogenesis, and neuroprotection.¹⁵⁸ In the brains of AD patients, increased levels of TGF- β 1 in plasma and cerebrospinal fluid were demonstrated.^{159,160} Furthermore, increased levels of TGF- β 1 mRNA expression was found before the manifestation of obvious dementia in AD patients, suggesting that it is mobilized in the process of AD pathology.¹⁶¹ The levels of TGF- β 1 expression correlate with the degree of cerebrovascular amyloid deposition in AD.¹⁶² In contrast, some scientists found decreased levels of TGF- β 1 in AD patients compared with the control group in serum¹⁶³ and plasma.¹⁶⁴

Peripheral mononuclear phagocyte TGF- β signaling in deficient AD mice increased the accumulation of microglia

around A β plaques and reduced AD-like pathology.¹⁶⁵ Reduced TGF- β 1 signaling contributes to microglial activation and ectopic cell-cycle reactivation in neurons; both lead to neurodegeneration in the AD brain.¹⁶⁶ TGF- β secreted by IL-34-treated microglia enhances the neuroprotective property of microglia and suppresses their proliferation.¹⁶⁷ TGF- β 1 modulates the activation of microglia partially through the Smad pathway, leading to reduced cytotoxicity and increased A β clearance.¹⁶⁸ However in a transgenic AD model mice, it was observed that TGF- β 1 promotes amyloidogenesis and A β deposition.¹⁶⁹ Chronic overexpression of TGF- β 1 negatively impacts hippocampal structure and impairs hippocampus-dependent learning.¹⁷⁰ Due to methodological problems of individual studies and several underpowered studies, the effects of TGF- β s in AD pathology remain controversial.

A β plaques and NFTs as causes and consequences of neuroinflammation

It is critical to note in this review that both A β plaques and NFTs may represent causes and consequences of neuroinflammation in AD.

A β peptides, the main constituents of amyloid plaques, are derived from the proteolytic cleavage of APP.^{171,172} Diverse lines of evidence suggest that A β and APP contribute to the pathogenesis of AD causally. The conversion from preclinical AD to clinical AD is not only associated with widespread A β plaque deposition and NFT pathology but also with the appearance of various soluble/dispersible A β aggregates in the neuropil.¹⁷³ A β regulates synaptic and neuronal activities, and A β accumulation in the brain leads to an interesting combination of synaptic depression and aberrant network activity.¹⁷⁴ For the neuroinflammation, A β plaques are frequently associated with the activation of microglia and astrocytes (see the section “Cell mediators”). A β induces the expression of inflammatory cytokines and inflammatory enzymes such as COX-2 and iNOS. Inflammatory cytokines (such as TNF- α and IL-1 β), in turn, enhance APP production and the process of APP proteolytic cleavage to increase the production of A β 42 peptide. A β is able to stimulate NF- κ B and MAPK signaling pathways. Both these signaling pathways are associated with the transcription of inflammatory mediators (see the section “Intracellular signaling pathway”). Also NF- κ B participates in A β production through regulation of APP and BACE and γ -secretases; NF- κ B/p65 is closely related to BACE1 expression, cleavage and A β production.^{103,105} A β can disrupt gliotransmitter release and astrocytic calcium signaling, and alter synaptic plasticity, which are vital processes for astrocyte–neuron

communication.¹⁷⁵ So, A β can be viewed both as a cause and consequence of neuroinflammation in AD. However, A β has also shown some antioxidant and neuroprotective effects under certain experimental conditions.¹⁷⁶ A recent work suggests that A β immunotherapy leads to downregulation of microglial activation and reduction of A β and Tau pathology.¹⁷⁷ Joseph-Mathurin et al used old lemurs to study A β immunotherapy. Worsening of iron accumulation is the side effect of A β immunization treatment at prodromal stages of AD.¹⁷⁸ Now there are a growing number of studies on A β immunotherapy, such as the active anti-A β vaccine (AN1792), bapineuzumab and solanezumab, but the side effects were obvious and the clinical trials were disappointing. Second-generation anti-A β immunotherapies (crenezumab and gantenerumab) and A β vaccines (CAD106, ACC-001, and Affitope AD02) are being tested in AD patients.¹⁷⁹

NFTs are the major neuropathological hallmarks in the brains of AD patients. They form intracellularly, aggregated and reorganized through hyperphosphorylation and acetylation of Tau proteins.^{180–182} The microtubule-associated protein, Tau, plays an important role in the stabilization and assembly of microtubules, which are crucial for normal cellular morphology and trafficking. Its aggregation in AD leads to deficits through a loss-of-function mechanism.¹⁸³ Synapse degeneration closely correlates with cognitive decline in AD, while soluble, oligomeric Tau, as a synaptotoxic species, may contribute to synapse degeneration.¹⁸⁴ During the process of the AD, the mechanisms and the triggers of Tau proteins aggregating into NFTs are unclear, but neuroinflammation could play a role.¹⁸⁵ The number of NFTs and the progression of neurodegeneration as well as dementia showed a significant positive correlation in AD,¹⁸⁶ leading to a common assumption that NFTs are neurotoxic. The repeated immunization with phosphorylated-Tau peptides causes neuroinflammation in NFT and wild-type mice.¹⁸⁷ Similar to A β , NFTs can also be viewed both as causes and consequences in the neuroinflammation of AD.

Thus, in line with the study by Anand et al the amyloid- and Tau-based therapeutics may be the main direction of AD research and therapy in the near future.¹⁸⁸

Conclusion

In this review, we described the potential role of inflammation factors in the process of neuroinflammation associated with AD. Neuroinflammation is currently recognized as an important pathophysiological feature of this neurodegenerative disorder. At the same time, it seems that every factor that associates with neuroinflammation could be a target for

AD treatment and every single factor represents an attractive therapeutic target. But which one is the main cause of the process? There is usually no simple solution to complex problems and AD is sadly a complex neurodegenerative disorder. To date, preventative and therapeutic researches on AD focus on a single target, and few drugs are available to effectively treat this disease. Combination therapies with drugs targeting different causal or modifying factors may be the most successful treatment strategies, such as interruption of deleterious inflammatory pathways and improved plaque clearance by activated microglia.

Epidemiological evidences suggest that long-term use of non-steroidal anti-inflammatory drugs has a sparing effect on AD, but it failed to slow the progression of disease or improve the symptoms in patients with early or moderate AD in randomized clinical trials. Possible reasons for the failure of anti-inflammatory drugs in clinical trials may be associated with the advanced state of the disease in patients and the dosing regimens of the trials. Currently, most of the available anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs, are not really “anti-inflammatory”. They prevent the pro-inflammatory response, but do not trigger the anti-inflammatory response. Given that neuroinflammation is now being recognized as a complex process that has both beneficial and detrimental aspects, rather than suppressing inflammation, orchestrating specific elements of the neuroinflammation may be a more appropriate therapeutic objective.

Finally, it is essential to define early biomarkers that correctly indicate inflammation of the CNS for potential AD subtypes. Disappointments of anti-inflammation drugs in AD suggest that attention should be taken in the intervention strategy, which is likely a better way to prevent the incidence of AD. It is crucial to develop better diagnostics relying upon peripheral inflammatory biomarkers. For example, serum or plasma inflammatory cytokines closely related to the AD pathological process can be used as indicators of AD. Efforts to discover more sensitive and selective biomarkers should be continued and integrated with more innovative approaches to clinical trial design. Certainly, neuroinflammation remains a young discipline, and our basic understanding of the neuroinflammatory network into therapeutic interventions still has a long way to go.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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