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Targeting Neuroinflammation as a Therapeutic Strategy for Alzheimer's Disease: Mechanisms, Drug Candidates, and New Opportunities

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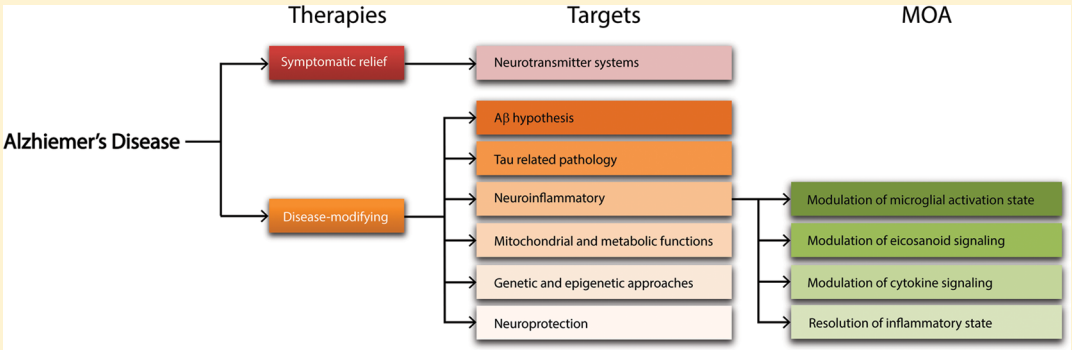
Supporting Information



ABSTRACT: Alzheimer's disease is a progressive neurodegenerative disease, and its incidence is expected to increase owing to the aging population worldwide. Current therapies merely provide symptomatic relief. Therefore, interventions for AD that delay the disease onset or progression are urgently required. Recent genomics and functional studies suggest that immune/inflammatory pathways are involved in the pathogenesis of AD. Although many anti-inflammatory drug candidates have undergone clinical trials, most have failed. This might be because of our limited understanding of the pathological mechanisms of neuroinflammation in AD. However, recent advances in the understanding of immune/inflammatory pathways in AD and their regulatory mechanisms could open up new avenues for drug development targeting neuroinflammation. In this Review, we discuss the mechanisms and status of different anti-inflammatory drug candidates for AD that have undergone or are undergoing clinical trials and explore new opportunities for targeting neuroinflammation in AD drug development.

KEYWORDS: *Neurodegenerative diseases, microglia, inflammation, cytokines, interleukins*

INTRODUCTION

Alzheimer's disease (AD), a major type of dementia whose prevalence is increasing, affects an estimated 47 million people worldwide. AD patients exhibit diminished cognitive functions as well as changes in personality, behavior, and emotions. Thus, AD is a global public health challenge that is incurring severe socioeconomic burdens. In AD brains, neuropathological changes include amyloid plaques (the extracellular deposits of amyloid-beta [$A\beta$] aggregates), neurofibrillary tangles (intracellular accumulation of hyperphosphorylated tau protein), neuropil threads, dystrophic neurites around amyloid plaques, early synaptic loss followed by neuronal loss, which contributes to the progressive cortical and hippocampal atrophy, and also morphological changes of glial cells accompanied by neuroinflammation in AD pathogenesis.[1] The amyloid hypothesis posits that the accumulation of toxic $A\beta$ plays a central role in triggering neuroinflammation and impairment of synaptic functions in the brain, which contribute to the deterioration of cognitive functions.[2] The five drugs currently available for AD—donepezil, rivastigmine, galantamine, memantine, and Namzaric (a combination of donepezil and memantine)—modulate neurotransmitter systems but only provide symptomatic relief.[3,4] Significant efforts have been made to develop disease-modifying therapeutic interventions that control disease progression. Approximately 200 AD drug candidates have been tested in clinical trials, but more than 100 have failed. In the past 15 years, no new disease-modifying drugs have been released into the market. Most of the mechanisms of disease-modifying drug candidates in

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clinical trials are based on the amyloid hypothesis and thus aim to inhibit the generation and aggregation of Aβ or enhance its removal.[4] Other strategies involve tau-related pathology, neuroprotection, modulation of mitochondrial or metabolic function, genetic or epigenetic approaches, or reducing inflammation.[4]

The latest genomics, bioinformatics, functional, and epidemiological studies provide increasing evidence that the inflammatory and immunity responses in the brain are critical contributors to AD pathogenesis and progression.[2,5] Various inflammatory and immune-related genes such as cluster of differentiation 33 (CD33), triggering receptor expressed on myeloid cell 2 (TREM2), complement receptor 1 (CR1), and bridging integrator 1 (BIN1) are associated with AD risk.[6] In the brains of AD patients, ^{18}F-DPA-714 positron emission tomography (PET) shows microglial activation during the prodromal stage.[7] Moreover, AD patients exhibit elevated levels of proinflammatory cytokines such as interleukin (IL)-1β in the cerebrospinal fluid.[8] In the past several decades, more than 30 drugs that modulate inflammatory status, half of which are repurposed drugs, have been used to treat various inflammatory disorders and inflammatory-related diseases (Supporting Information Table 1). However, most failed to delay or ameliorate the pathological symptoms of patients with mild cognitive impairment (MCI) or AD. In the first half of 2018, large-scale phase III clinical trials showed that azeliragon, pioglitazone, and verubecestat failed to delay or ameliorate AD symptoms, although azeliragon and pioglitazone were associated with inflammation modulation. The high failure rate of inflammatory drug development in clinical trials for AD is in part due to our limited understanding of the roles of neuroinflammation in the progression of AD as well as a lack of appropriate diagnostic markers to evaluate stages of the disease.

Herein, we review the literature investigating the mechanisms of drugs that exhibit anti-inflammatory effects, including drugs that failed or are in ongoing clinical trials (Supporting Information Table 1). We also discuss potential interventions aiming to modulate neuroinflammation for AD treatment.

MICROGLIA AND ASTROCYTES MEDIATE NEUROINFLAMMATION IN AD PROGRESSION

Asymptomatic AD patients exhibit neuroinflammation, which negatively impacts neural cell functions during AD pathogenesis and progression.[9] Microglia and astrocytes are the two major neural cell types responsible for mediating neuroinflammation.

Microglia, the resident immune cells in the central nervous system, are considered critical regulators that mediate the inflammatory responses in the brain.[10] They exhibit multiple activation phenotypes to accommodate pleiotropic functions in response to environmental changes. The physiological functions of microglia, which include phagocytosis of cell debris and misfolded proteins, neurotrophic factor and cytokine secretion, and synaptic pruning, are crucial for maintaining homeostasis of the brain microenvironment (Figure 1).[11] Microglia express a plethora of cell-surface molecules related to innate immunity that constantly survey the surrounding extracellular space. Once they detect endogenous proteins released from damaged cells, termed damage-associated molecular patterns (DAMPs), or exogenous pathogen-derived molecules, termed pathogen-associated molecular patterns (PAMPs), they initiate inflammatory

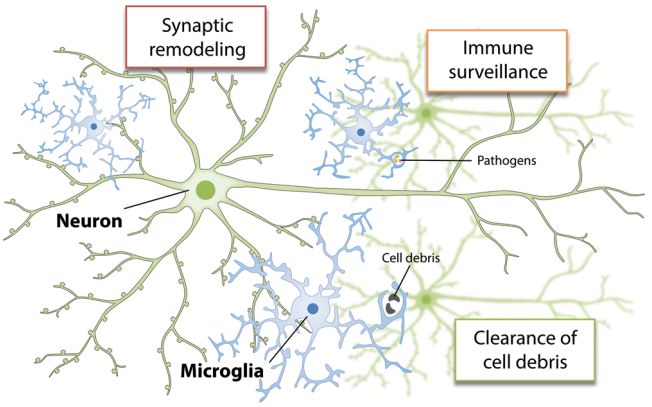

Figure 1. Physiological roles of microglia. In the resting stage, microglia play critical roles in synaptic remodeling, immune surveillance, and clearance of pathogen and cell debris.

responses such as enhancing phagocytosis, or generating or secreting proinflammatory cytokines. Cytokine generation is hypothesized to play a neuroprotective role by clearing pathogens and aiding tissue repair.[12] During chronic inflammation, owing to inefficient pathogen clearance, deregulated cytokines can damage brain cells and exacerbate AD progression.[12]

Aβ is a well-known inflammatory agent in AD pathogenesis.[2] Various surface receptors including CD36, scavenger receptor type 1 (SRA1), and receptor for advanced glycosylation end-products (RAGE) expressed in microglia are Aβ receptors.[13] In the early stages of AD, microglia can effectively clear Aβ through phagocytosis and secrete Aβ-degrading enzymes.[14] However, when AD becomes severe, microglia become inefficient to clear Aβ, and the resultant accumulation of Aβ stimulates microglia to increase production of proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6.[14] In turn, this leads to microglial dysfunction, which ultimately deregulates and damages neurons and other neural cells, which is associated with cognitive decline in AD[14,15] (Figure 2).

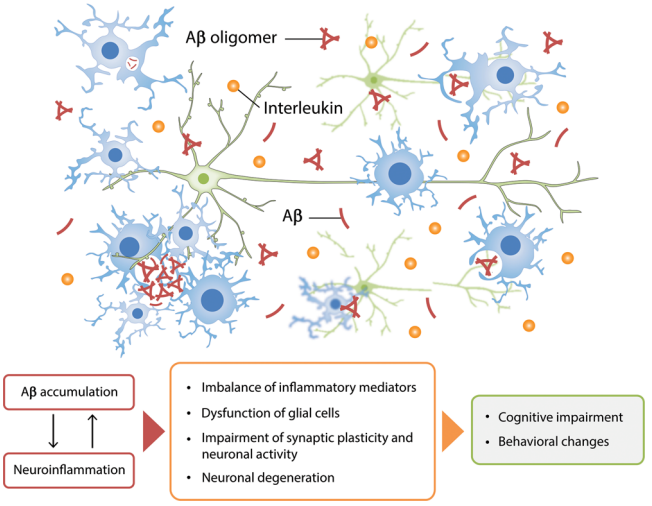

Figure 2. Neuroinflammation in AD. During AD progression, Aβ-mediated chronic inflammation leads to microglial dysfunction, which subsequently affects neuronal function and survival, and ultimately leads to cognitive deterioration.

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Astrocytes act as housekeeping cells in the brain and are critical for maintaining the homeostatic environment in the brain. Astrocytes provide trophic support for neuron metabolism and survival. They have modulatory roles by regulating synaptic functions including synaptic formation and elimination, which shape the neuronal network.[16] The close proximity of astrocytic end-feet with endothelial cells is important for maintaining the integrity of the blood−brain barrier and regulating blood flow in the brain.[16] Similar to microglia, astrocytes undergo morphological, phenotypic, and functional changes in response to environmental changes or under pathological conditions such as AD. Astrocytes also phagocytose Aβ and are the major source of proinflammatory cytokines in AD.[16,17]

CLINICAL TRIALS OF DRUGS WITH ANTI-INFLAMMATORY EFFECTS

Modulation of Glial Cell Activation State. Given that microglia are powerful regulators of inflammatory responses, a group of drug candidates that aim to modulate the activation and functional states of microglia have been developed for AD treatment. Granulocyte−macrophage colony-stimulating factor (GM-CSF) is a hematopoietic growth factor and cytokine that mediates the proliferation and differentiation of myeloid progenitor cells into granulocytes or macrophages.[18] Compared to age-matched controls, AD patients exhibit reduced expression of the α-subunit of GM-CSF receptor, suggesting that GM-CSF signaling is impaired in AD.[19] In an AD mouse model, GM-CSF exhibited a neuroprotective effect by promoting the recruitment of microglia to amyloid plaques and altering the activation state of microglia.[20] Sargramostim is a synthetic GM-CSF[21] that is indicated for leukemia. Sargramostim was developed into an AD treatment because it might enhance the microglial phagocytosis of Aβ and suppress the generation of proinflammatory cytokines. Accordingly, sargramostim is now in phase II clinical trials, which are expected to finish in November 2018 (NCT01409915).

Meanwhile, the renin−angiotensin system, which is crucial for the regulation of cardiovascular function, is another potential intervention target for AD treatment. Aged people with hypertension have an elevated risk of AD.[22] Angiotensin II, a major hormone peptide that binds to angiotensin II type 1 and type 2 receptors (AT1R and AT2R, respectively) expressed in neurons, microglia, and astrocytes, has pleiotropic roles in the brain, including mediation of inflammation and neuronal cell injury.[23] Activation of AT1R signaling mediates the generation of proinflammatory cytokines and oxidative stress. In contrast, AT2R signaling has a neuroprotective role by restraining the overactivation of AT1R signaling. The angiotensin II-dependent regulation of signaling is impaired upon aging or neurodegeneration.[23] In an AD transgenic mouse model, blockade of AT1R signaling directed the microglia toward a less proinflammatory stage, suppressed the expression of inflammatory genes, and reduced the amyloid plaque load.[24,25] Two antagonists of AT1R used to treat hypertension, candesartan (NCT02646982) and telmisartan (NCT02085265), are now in phase II clinical trials for AD.

With their plethora of surface receptors, microglia facilitate immune surveillance functions. Certain receptors mediate microglial Aβ phagocytosis, thereby enhancing Aβ clearance and ameliorating AD.[5,14] $P2Y_6$ is a purinergic receptor expressed on microglia that mediates inflammation and regulates microglial activation and phagocytosis.[26] The uracil nucleotide uridine 5′-diphosphate (UDP) is a specific ligand for $P2Y_6$ receptor that can be released from damaged neurons to recruit microglia to phagocytose cell debris. Meanwhile, GC021109, a small molecule reported to bind to $P2Y_6$ receptor to stimulate microglial phagocytosis and suppress proinflammatory cytokine release from microglia. Although Phase Ia trials (NCT02386306) yielded positive results, no further action was taken by the clinical trial sponsor. Nonetheless, activation of some receptors on microglia can result in a neurotoxic phenotype and the release of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6.[5,14] While RAGE is a pattern-recognition receptor expressed on microglia and astrocytes that induces proinflammatory or cytotoxic responses, it is also expressed on brain endothelial cells and mediates transcytotic delivery.[27] Specifically, RAGE binds to Aβ[28] and mediates the neurotoxic effects of Aβ oligomers.[29] Moreover, in AD patients, RAGE expression is elevated in astrocytes and microglia in the hippocampus.[30] Accordingly, azeliragon, a small antagonist of RAGE, has been evaluated in clinical trials.[31] Blockade of Aβ−RAGE interaction suppressed the inflammatory responses of microglia and attenuated the transcytotic influx of circulating Aβ into the brain in a transgenic AD mouse model.[32] However, the small molecule failed in phase III clinical trials (NCT02080364 and NCT02916056) in early 2018 owing to a lack of efficacy.

Modulation of Eicosanoid Signaling. Epidemiological studies show that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the incidence of AD development in the normal aging population.[33,34] Therefore, NSAIDs were one of the early classes of anti-inflammatory drugs subjected to AD drug development. The main actions of NSAIDs are thought to be mediated through the inhibition of cyclooxygenase (COX) activity.[35] Cyclooxygenases (COX-1 and COX-2) mediate the oxidation of arachidonic acid into eicosanoid lipid mediators including prostaglandins, thromboxanes, and leukotriene B4; these are critical mediators of inflammatory and immune responses, and play central roles in various neurological disorders and neurodegenerative diseases including AD.[35] In various AD transgenic mouse models, levels of arachidonic acid, COX-2, and prostaglandins are elevated in the hippocampus.[36,37] Some NSAIDs (e.g., ibuprofen and indomethacin) exert their effects by acting as agonists of peroxisome proliferator-activated receptor-γ (PPARγ),[38] while they (e.g., ibuprofen, tarenflurbil and CHF5074) can reduce $A\beta_{42}$ peptide generation in a COX-independent manner through modulating γ-secretase activity. Unfortunately, most tested NSAIDs failed in AD clinical trials owing to a lack of efficacy in ameliorating AD symptoms; some even exacerbated symptoms in the late stages of AD.[39] Recent reviews point out that neuroinflammation occurs in the early stages of AD before the severe symptoms of cognitive deterioration appear. Thus, administration of NSAIDs during the asymptomatic or prodromal stages of AD might achieve a better outcome. Given the multifaceted pathological characteristics of AD, combination therapy of ibuprofen together with cromolyn (ALZT-OP1) targets the early stages of AD by combining approaches that intervene in plaque formation and ameliorate neuroinflammatory responses; phase III clinical trials were started in 2015 (NCT02547818).

Modulation of Cytokine Signaling. Some classes of anti-inflammatory drugs developed for AD aim to regulate cytokine expression or activity. More specifically, TNF-α is a pleiotropic

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proinflammatory cytokine that is associated with many human diseases such as diabetes, rheumatoid arthritis, and neuroinflammation in AD.[40,41] It is toxic to various neural cells under pathological conditions.[42] TNF-α mediates inflammation through binding with TNF receptor-1 (TNF-R1), which triggers the activation of nuclear factor κB (NF-κB), c-Jun NH2-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38 MAPK) signaling.[43] TNF-α is suggested to control synaptic transmission and plasticity[44] and be involved Aβ-induced synaptic dysfunction.[45,46] Moreover, TNF-α is associated with Aβ generation by regulating β-secretase 1 activity.[47] In AD patients, serum level of TNF-α is associated with the severity of AD symptoms.[48,49] Etanercept is a recombinant protein consisting of two copies of the extracellular ligand-binding domain of the human TNF-α receptor and the Fc end of human immunoglobulin G (IgG); as such, it functions as a decoy receptor for binding to TNF-α[50] to inhibit TNF signaling. However, phase II clinical trials of etanercept for AD did not significantly improve cognition or behavior.[51]

Some drugs exhibit an anti-inflammatory effect because of their ability to inhibit the expression or secretion of proinflammatory cytokines in immune cells. Thalidomide is one such drug and inhibits the release of TNF-α in monocytes.[52] One study reports that thalidomide not only inhibits TNF-α production by microglia and astrocytes, but also exhibits a neuroprotective effect in the hippocampus in an inflamed AD mouse model.[53] However, the AD patients exhibit poor tolerability to thalidomide in the clinical trials.[54] Meanwhile, neflamapimod inhibits p38, which is a downstream signaling kinase critical in mediating glial cells to generate inflammatory cytokines such as IL-1β and TNF-α.[55] Neflamapimod is reported to significantly decrease Aβ load in AD transgenic mice.[56] In addition, it is reported to exert beneficial effects on synaptic functions by enhancing the expression of synaptic proteins such as postsynaptic density protein-95 (PSD-95) and improving the performance of aged rats in memory behavior tests such as the Morris water maze.[56] In early 2018, neflamapimod finished phase IIa clinical trials with excellent results including significant improvements in episodic memory;[57] therefore, phase IIb clinical trials are moving forward (NCT03402659).

Both AD and type 2 diabetes involve chronic inflammation and share similar pathological features including insulin resistance, hyperglycemia, and increased advanced glycation end-products.[58] Patients with type 2 diabetes have an increased risk of developing AD.[59] This is likely because impaired insulin signaling attenuates the production and function of insulin-degrading enzyme in the brain, which might lead to inefficient Aβ clearance. Moreover, insulin resistance is strongly associated with increased levels of proinflammatory cytokines including TNF-α, IL-6, and IL-1. Therefore, antidiabetic drugs have been suggested for AD treatment.[60] For example, pioglitazone and rosiglitazone are agonists of PPARγ that have been used for diabetes, specifically to ameliorate the pathogenesis of insulin resistance and hyperglycemia.[60] PPARγ is a nuclear hormone receptor that acts as a transcription factor in the regulation of inflammatory gene expression. Agonists targeting PPARγ suppress the expression of proinflammatory genes by cooperating with other transcriptional factors such as NF-κB, AP-1, and STAT1.[61,62] In AD transgenic mouse models, PPARγ reduced the inflammatory response of microglia, enhanced Aβ phagocytosis by regulating the phagocytic receptors Axl and MerTK, and improved cognitive functions.[63,64] In addition, in a diabetes mouse model, pioglitazone inhibited the NLRP3 (NLR Family Pyrin Domain Containing 3) inflammasome, a critical microglial sensor for mediating Aβ-induced IL-1β secretion.[65] These findings suggest that PPARγ agonist might decrease inflammatory responses in AD, which made it a promising therapeutic paradigm for AD. However, both pioglitazone (NCT00982202) and rosiglitazone[66] failed in phase III clinical trials owing to a lack of efficacy.

RESOLUTION OF INFLAMMATORY STATE IN THE AD BRAIN

The resolution of inflammatory response by anti-inflammatory agents is another approach for AD treatment. Minocycline, an antibiotic that can permeate the blood-brain barrier, exhibits anti-inflammatory and neuroprotective effects.[67] Minocycline inhibits IL-1β, TNF, and IL-6 production by microglia in vitro; suppresses microglial activation; reduces neuronal loss; and improves cognitive decline in AD transgenic mice.[68,69] Minocycline is currently undergoing clinical trials investigating its efficacy for treating the early stages of AD (NCT01463384). Human plasma-derived products such as intravenous immune globulin (IVIg), which is a mixture of polyclonal IgG antibodies prepared from thousands of healthy human donors, have been investigated in AD clinical trials.[70] IVIgs such as Gammagard, Flebogamma, and Octagam have been used to treat various autoimmune and infectious diseases for several decades.[71] Besides exhibiting anti-inflammatory effects, antibodies against pathological proteins such as Aβ and tau have been detected in these IVIg preparations. While clinical trials of Gammagard for AD were discontinued,[72] phase II clinical trials Flebogamma (NCT01561053) and Octagam (NCT00812565) are ongoing. In addition, in a parabiosis study, plasma from young mice stimulated the remodeling of the cerebral vasculature and promoted adult neurogenesis, which enhanced cognitive function in aged mice.[73] In early 2018, GRF6019, a proprietary plasma protein fraction derived from young humans entered phase II clinical trials for AD (NCT03520998).

Recent findings suggest that one of the physiological roles of Aβ is to protect the brain against infection.[74] Aβ can bind to fungi, bacteria, and viruses, forming aggregates to trap and eliminate these pathogens. Epidemiological studies show that viral infection is one of the etiological causes of AD. Herpesviruses such as herpes simplex virus type 1 (HSV-1), human herpesvirus 6A (HHV-6A), and human herpesvirus 7 (HHV-7) have been detected in the brains of AD patients and are associated with the promotion of amyloid plaque deposition in AD progression.[75,76] Moreover, human herpesviruses can remain latent in the trigeminal ganglion for several decades and reactivate under certain conditions (e.g., in the presence of genetic risk factors, stress, or aging).[77] The reactivated viruses infiltrate other brain regions, especially the limbic system, and induce neuronal damage and inflammation.[77] In a recent study, HSV-1 infection accelerated amyloid pathology in an AD transgenic mouse model, although these mice exhibited better antiviral activity than control mice.[77] These results raise the intriguing possibility that the long-term presence of latent herpesvirus in the brain might accelerate amyloid pathology in AD. Accordingly, valaciclovir, an antiviral drug, is undergoing two phase II clinical trials for early AD treatment (NCT02997982 and NCT03282916).

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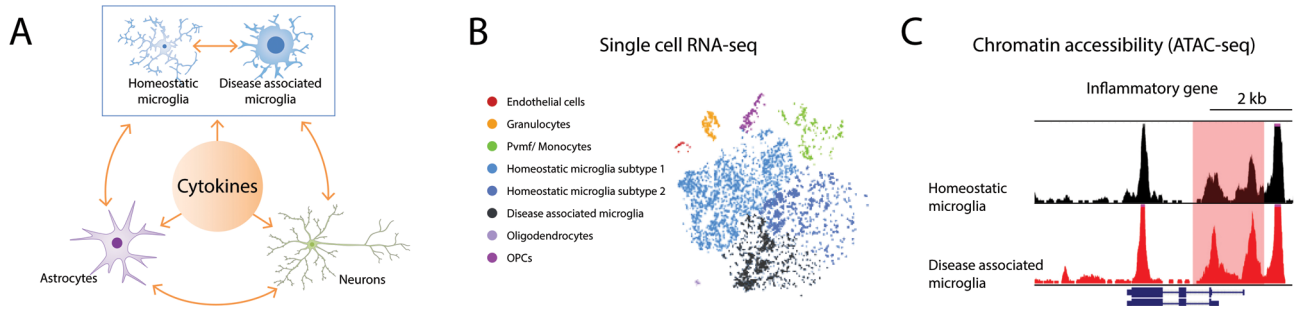

Figure 3. Future directions for elucidating how the mechanisms of neuroinflammation contribute to AD pathogenesis. (A) Understanding how the actions of inflammatory networks (e.g., interleukins) affect the functions of different neural cells during AD progression. (B) Investigating the phenotypic and functional changes of different immune cell types, (e.g., examining the differential transcriptome by single-cell RNA sequencing analysis) in AD progression. (C) Understanding the molecular regulation (i.e., epigenetic landscape that regulates the transcriptome profiling) of the transition of the activation state of different immune cells in AD progression (e.g., transition of microglial subsets from a homeostatic state to a disease-associated state).

FUTURE PERSPECTIVES OF NEUROINFLAMMATION AS A THERAPEUTIC INTERVENTION TARGET FOR AD

Most of drug candidates discussed above aim or aimed to ameliorate neuroinflammation. While microglia and astrocytes are the major cell types that contribute to neuroinflammation, emerging evidence suggests that these cells are heterogeneous with specific unique subpopulations in different regions of the brain under both physiological and pathological conditions. However, the lack of understanding of the identity of these subpopulations of cells or the molecular controls underlying the cell transition during pathological development hinders the design and development of strategies targeting these specific glial subpopulations. Meanwhile, the "unfocused" strategy aiming to attenuate the global inflammatory state in the brain further complicates the effectiveness of drug candidates by possibly attenuating the functions of glial cell subpopulations.

The pathological roles of various immune molecules such as cytokines and complement factors in AD progression have been studied extensively in recent years.[15] However, it remains elusive how these immune molecules contribute to AD pathogenesis. While the causal relationship between neuroinflammation and AD progression is unclear, modulating various cytokines and neuroinflammation status have shown promising results in AD transgenic mouse models. For example, IL-33 administration, blockade of IL-10 or IL-12/IL-23 signaling, and attenuation the activation of NLRP3 inflammasome (a signaling complex that mediates the maturation and secretion of IL-1β and IL-18) have been reported to ameliorate inflammatory responses and amyloid pathology as well as improve cognitive performance in different AD transgenic mouse models.[78−83] These findings suggest that targeting cytokines might be a feasible therapeutic intervention approach for AD. However, it is important to understand how these cytokines interact and regulate the phenotypes of different neural cells including microglia and astrocytes (two types of glial cells that exhibit phenotypic changes in AD conditions) (Figure 3A) as well as infiltrating immune cells including macrophages, monocytes, and adaptive immune cells types in different stages of AD. It is also important to understand how phenotypic transitions can result in beneficial outcomes in AD, including states of neuroinflammation, synaptic functions, neural network activity, and neuronal cell survival.

Microglia are the predominant immune cells in the brain as well as the primary immune effectors and target of various cytokines including IL-33 and IL-10.[78,80,81,84] The functional plasticity and dynamically changing activation of microglia are essential for their functional adaptation in response to the constantly changing brain microenvironment.[85,86] However, the identities of different microglial subtypes have yet to be clearly defined. Recent studies involving single-cell RNA sequencing (scRNA-seq) of glial cells (Figure 3B) in various mouse models of neurodegenerative diseases such as AD and amyotrophic lateral sclerosis (ALS) have identified various distinct subpopulations of microglia under pathological conditions. These subpopulations include populations of homeostatic microglia and a unique population of disease-associated microglia (DAM), which have a distinct transcriptome and functional signature during disease progression.[87] This DAM subpopulation adopts a disease-associated state characterized by increased expression of AD risk genes (e.g., *ApoE* and *Trem2*) and loses its "homeostatic" signature (e.g., *P2ry12*, *Cx3Cr1*, and *Tmem119*).[88,89] The genes expressed by microglia isolated from elderly humans and AD patients exhibit transcriptomic signatures similar to those of DAM.[90] Furthermore, DAM are found in close proximity to amyloid plaques in AD transgenic mouse models.[91] Therefore, the initiation of the DAM phenotype in the early phases of AD is suggested to protect brain cells, whereas DAM become dysfunctional and exacerbate the pathology of AD in the late stages of AD.[92] However, the exact characteristics and mechanisms by which the DAM subpopulation contribute to AD pathogenesis remain unclear. Two different types of reactive astrocytes, A1 and A2, were recently identified under pathological conditions. A1 astrocytes are neurotoxic and contribute to the death of neurons and oligodendrocytes under chronic inflammation, whereas A2 astrocytes are neuroprotective.[93] The induction of A1 reactive astrocytes is associated with activated microglia under neuroinflammation and can be found in AD patients.[94] Thus, understanding the interrelation between the regulatory and mechanistic roles of different microglial and astrocytic subtypes as well as their exact roles in different phases of disease progression will provide insights for the development of effective treatments for AD.

Remodeling of the epigenetic landscape, which regulates the transcriptome profile during the phenotypic transition of different immune cells,[10,85,86] can be controlled at multiple

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levels including the modification of chromatin accessibility, nucleosome occupancy, and the transcription factor-binding landscape as well as the post-translational modification of histone residues.[95] These modifications are coordinated with transcription machinery and regulate the rate of transcription. Given that modulating the activation states of microglia and astrocytes by cytokines has emerged as a promising intervention strategy for AD, it is important to understand how remodeling of the epigenetic landscape regulates the transition between cell activation states in AD and after cytokine manipulation (Figure 3C). A recent trend in drug research is exploring the use of epigenetic drugs for AD treatment.[96] As such, two epigenetic drugs are currently undergoing clinical trials: ORY-2001 and vorinostat. ORY-2001, which is undergoing a phase II clinical trial in Europe, is an epigenetic drug that selectively inhibits the activity of the lysine (K)-specific demethylase 1A (LSD1) and monoamine oxidase B (MAOB). LSD1 exhibits demethylase activity at Lys4 of histone H3 in regulating gene repression. In preclinical studies, ORY-2001 exhibited anti-inflammatory and neuroprotective activities in a transgenic mouse model of ALS. Meanwhile, vorinostat, a histone deacetylase 2 (HDAC2) inhibitor,[97] is undergoing phase I clinical trials. HDAC2 has been shown to decrease the expression of genes related to synaptic function. Moreover, depletion of HDAC2 expression in the brain is reported to improve cognitive function in a mouse model of neurodegeneration.[98] Diminished HDAC activity in microglia is reported to reduce amyloid plaque burden by enhancing microglial phagocytic activity in an AD mouse model.[99]

AD is a progressive neurodegenerative disease with a multifaceted pathogenesis. Neuroinflammation occurs in the AD brain at the early stages before histopathological and pathological features can be detected. Therapeutic intervention at the asymptomatic and prodromal stages of AD is currently favored for drug development. While basic, translational, and clinical studies have started to explore the mechanistic roles of neuroinflammation and how it contributes to the AD pathogenesis, many questions remain to be tackled in order for AD drug development to proceed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acschemneuro.8b00402.

Clinical trials of AD drug candidates that target neuroinflammation (PDF)

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W.Y.F. and N.Y.I. conceived the idea. W.Y.F., X.W., and N.Y.I. wrote the manuscript.

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Notes

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