Review

Targeting the chemokine-microglia nexus: A novel strategy for modulating neuroinflammation in Alzheimer's disease

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Abstract

An increasing body of evidence suggests neuroinflammation has a prominent role in the pathogenesis of Alzheimer's disease (AD). The amyloid-β-tau-neurodegeneration (ATN) classification system is now being expanded toward an amyloid-β-tau neurodegeneration-neuroinflammation (ATN(I)) system. Activated microglia and reactive astrocytes are the key hubs for neuroinflammation in AD, and chemokines are recognized as pivotal modulators of microglial innate immune functions. In this review, based on the chemokine-microglia regulatory axis, we elucidate the mechanisms through which chemokines influence microglial function, potentially modulating neurotoxicity or neuroprotection in AD. The key chemokines that significantly affect microglial polarization, such as CCL2, CCL3, and CXCL1, are summarized, and their role in disease progression are elaborated. Additionally, we explore prospective therapeutic interventions centered on the chemokine-microglia regulatory axis, offering valuable perspectives on pathobiology of AD and avenues for pharmacological advancements.

Keywords

Alzheimer's disease, chemokines, cytokine, M1 phenotype, M2 phenotype, microglia, microglia polarization, neurodegeneration, neuroinflammation

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Introduction

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by the accumulation of amyloid-β (Aβ) and neurofibrillary tangles resulting from hyperphosphorylated tau protein.[1] These anomalies initiate an inflammatory cascade, gradually impairing neuronal integrity in brain regions vulnerable to AD, thereby conceptualizing it as a chronic neuroinflammatory condition.[2–4] Initially, the brain's immune cells exhibit neuroprotective functions; however, as the disease progresses, activated glial cells enhance the production of pro-inflammatory cytokines, leading to oxidative stress and exacerbating neuroinflammation and neurotoxicity.[5–8] Microglia (MG), which are closely associated with neuronal inflammation, particularly following injury, actively participate in all stages of AD.[9–15]

Chemokines, small cytokines or proteins (8–12 kDa) secreted by various cells, have been categorized into 50 chemokines and 20 chemokine receptors, which are further divided into four subfamilies (XC, CC, CXC, CX3C) based on the position of the n-terminal cysteine residues.[16–22] Chemokine receptors are classified into four groups (XCR, CCR, CXCR, CX3CR) (as illustrated in Figure 1 and Table 1). They are further subclassified into pro-inflammatory, homeostatic, and dual-functional chemokines.[23–27] The relationship between

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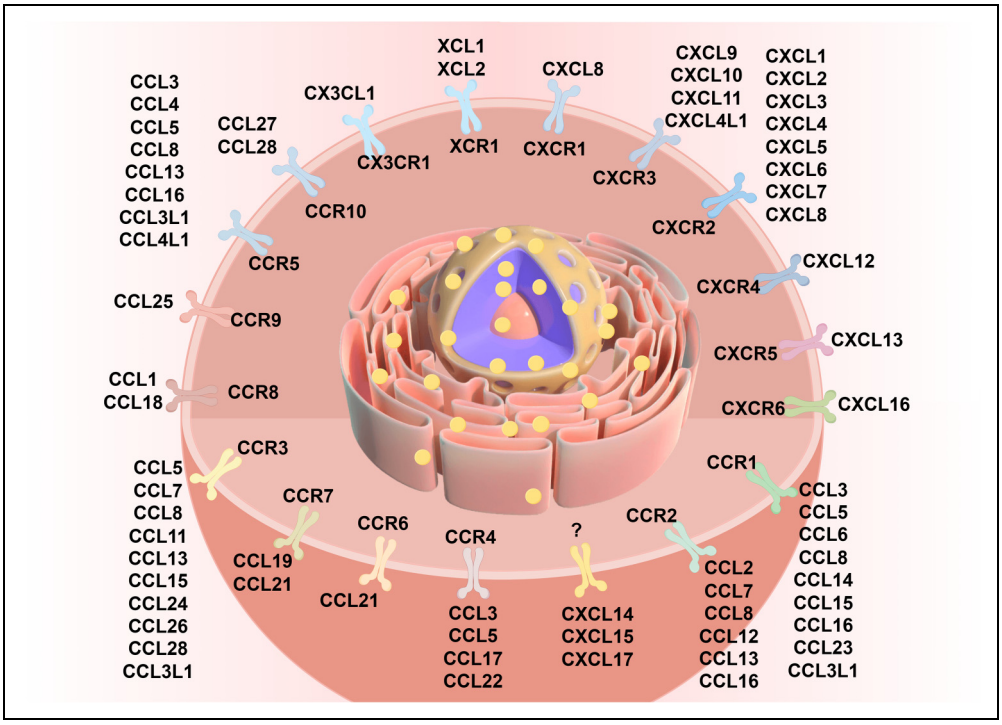

Figure 1. CC family, CXC family, CX3CL family, and XC family chemokines and their receptors.

chemokines and neuroinflammation in AD, particularly in the context of MG, is a key area of ongoing research.

Therefore, this article aims to elucidate the impact of chemokines on MG function and its subsequent influence on the onset and progression of AD, thereby providing novel insights for the therapeutic management of AD.

Microglia in Alzheimer's disease

Microglia play a pivotal role in neuronal injury and regeneration by detecting neural signals and participating in neural network remodeling.[28–30] Following brain injury, MG differentiate into M1 and M2 phenotypes. The M1 phenotype exerts neurotoxic effects through the secretion of pro-inflammatory cytokines,[31–33] whereas the M2 phenotype offers neuroprotection through phagocytic activity[34] (as depicted in Figure 2). Consequently, MG effectively regulate neuronal injury and regeneration through distinct phenotypic transformations. In AD, MG perform multifaceted roles in both immune response and CNS maintenance.[35–37] As AD progresses, MG respond to Aβ aggregation and abnormal tau phosphorylation by becoming activated and polarized, attempting to eliminate these pathological entities.[38–44] MG activation can be categorized into pro-inflammatory M1 and anti-inflammatory M2 subsets, which may vary across different stages and anatomical locations of the disease.[45,46] Throughout AD, MG undergo various alterations, including morphological transitions, molecular marker modulation, and functional adjustments.[41,47–50] These alterations exemplify the macrophage response to the disease, such as Aβ engulfment, production of inflammatory mediators, and interactions with other cell types, which can either exacerbate neuroinflammation or contribute to neural tissue repair.

Chemokine in Alzheimer's disease

Chemokines, such as CCL1, play a crucial role in the neuroinflammation observed in AD. The interaction between CCL1 and CCR8 intensifies inflammatory responses.[51] Elevated CCL1 levels in patients with mild cognitive impairment suggest underlying brain injury.[52] Mendelian randomization studies have shown a positive correlation between increased CCL27 levels and the risk of AD. Compelling evidence indicates a significant causal relationship between CCL5 dysfunction and the progression of AD.[53,54] In AD patients, increased expression of monocyte CXCL1 facilitates the transendothelial migration induced by Aβ.[55] CXCL1 interacts with CXCR2 expressed on human brain microvascular endothelial cells (HBMECs), thereby influencing the migration of monocytes to the brain. A meta-analysis has revealed elevated concentrations of chemokines in both the plasma and cerebrospinal fluid of AD patients, highlighting the strong connection between these factors and neuroinflammation.[56] Notably, CCL11 levels are elevated in chronic traumatic encephalopathy but remain unchanged in AD.[57] These data suggest that chemokines are involved in modulating inflammatory processes in AD.

Table 1. Classification information of chemokines.

Family	Name	Other Name	Receptors
CC	CCL1	I-309, TCA3	CCR8
	CCL2	MCP-1	CCR2, CCR4, ACKR1, ACKR2
	CCL3	MIP-1α	CCR1, CCR5, ACKR2
	CCL3L1	LD78β	CCR1, CCR3, CCR5, ACKR2
	CCL4	MIP-1β	CCR5, ACKR2
	CCL4L1	LAG-1	CCR5
	CCL5	RANTES	CCR1, CCR3, CCR4, CCR5, ACKR2
	CCL6	C-10, MRP-1	Unknown
	CCL7	MARC, MCP-3	CCR2, CCR3, ACKR1, ACKR2
	CCL8	MCP-2	CCR1, CCR2, CCR3, CCR5, ACKR1, ACKR2
	CCL9/10	MIP-1γ, MRP-2, CCF18	Unknown
	CCL11	Eotaxin-1	CCR3, ACKR2
	CCL12	MCP-5	CCR2
	CCL13	MCP-4, NCC-1, Ckβ10	CCR2, CCR3, CCR5, ACKR1, ACKR2
	CCL14	HCC-1, MCIF, Ckβ1, NCC-2, CCL	CCR1, ACKR1, ACKR2
	CCL15	Leukotactun-1, HCC-2, MIP-5, NCC-3	CCR1, CCR3
	CCL16	HCC-4, NCC-4, LEC (human only)	CCR1, CCR2, CCR5, ACKR1
	CCL17	TARC, dendrokine, ABCD-2	CCR4, ACKR1, ACKR2
	CCL18	PARC, DC-CK1, AMAC-1, Ckβ7, MIP-4	CCR8, ACKR6
	CCL19	MIP-3β, ELC, Exodus-3, Ckβ11	CCR7, ACKR4
	CCL20	MIP-3α, LARC, Exodus-1, Ckβ4	CCR6
	CCL21	SLC, 6Ckine, Exodus-2, Ckβ9, TCA-4	CCR6, CCR7, ACKR4
	CCL22	MDC, DC/β-CK	CCR4, ACKR1, ACKR2
	CCL23	MPIF-1, Ckβ8, MIP-3, MPIF-1	Unknown
	CCL24	Eotaxin-2, MPIF-2, Ckβ6	CCR3
	CCL25	TECK, Ckβ15	CCR9, ACKR4
	CCL26	Eotaxin-3, MIP-4α, IMAC, TSC-1	CCR3, CX3CR1
	CCL27	CTACK, ILC, Eskine, PESKY, skinkine	CCR10
	CCL28	MEC	CCR3, CCR10
CXC	CXCL1	Gro-α, GRO1, NAP-3	CXCR2, ACKR1
	CXCL2	Gro-β, GRO2, MIP-2α	CXCR2, ACKR1
	CXCL3	Gro-γ, GRO3, MIP-2β	CXCR2, ACKR1
	CXCL4	PF-4	Unknown
	CXCL4L1	PF4V1	Unknown
	CXCL5	ENA-78	CXCR2, ACKR1
	CXCL6	GCP-2	CXCR1, CXCR2, ACKR1
	CXCL7	NAP-2, CTAPIII, β-Ta, PEP	CXCR2, ACKR1
	CXCL8	IL-8, NAP-1, MDNCF, GCP-1	CXCR1, CXCR2, ACKR1
	CXCL9	MIG, CRG-10	CXCR3
	CXCL10	IP-10, CRG-2	CXCR3
	CXCL11	I-TAC, β-R1, IP-9	CXCR3, ACKR1, ACKR4
	CXCL12	SDF-1, PBSF	CXCR4, ACKR3
	CXCL13	BCA-1, BLC	CXCR5, ACKR1, ACKR4
	CXCL14	BRAK, bolekine	Unknown
	CXCL15	Lungkine, WECHE	Unknown
	CXCL16	SRPSOX	CXCR6
	CXCL17	DMC, VCC-1	Unknown
CX3CL	CX3CL1	Fractalkine, Neurotactin, ABCD-3	CX3CR1
XC	XCL1	Lymphotactin α, SCM-1α, ATAC	XCR1
	XCL2	Lymphotactin β, SCM-1β	XCR1

Chemokines regulate microglia in Alzheimer's disease

Effect of chemokines on microglia

The generation of MG is dependent on chemokines. Neural progenitor cells, which are pluripotent stem cells, have the ability to differentiate into neurons, MG cells, and various other neural tissue cells. These cells are crucial for migrating to the site of brain injury, where they transform into different cell types to fulfill their functions. Chemokines play a central role in this migratory and differentiation process (refer to Figure 3).[24,58–62] In AD, chemokines can

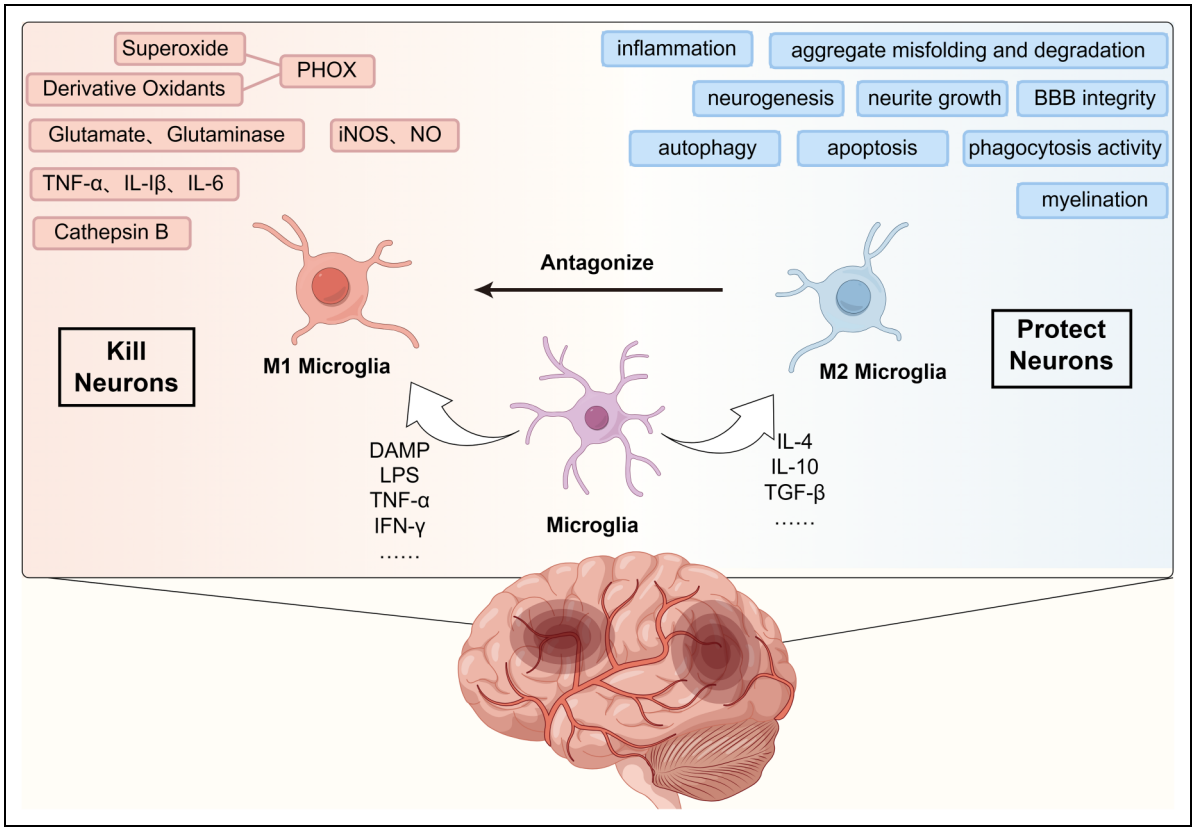

Figure 2. Numerous mechanisms have been discovered through which M1 MG exerts neurotoxic effects. (I) stimulating phagocytic cell NADPH oxidase (PHOX) to generate superoxide and related oxidants, (II) expressing inducible nitric oxide synthase (iNOS) to produce NO and associated oxidants, (III) releasing glutamate and glutaminase, (IV) releasing TNF-α, (V) releasing matrix metalloproteinase B, (VI) phagocytosis of stressed neurons, and (VII) reducing the release of neurotrophic factors BDNF and IGF-1. On the other hand, M2 MG perform neuroprotection through the following mechanisms: (I) inhibiting inflammation to safeguard neurons, (II) fostering the misfolding and degradation of aggregates for neuronal protection, (III) stimulating neurite growth as a means of neuronal protection, (IV) promoting neurogenesis, (V) curbing autophagy, (VI) preventing apoptosis, (VII) facilitating myelination, (VIII) preserving the integrity of the blood-brain barrier, and (IX) augmenting phagocytosis activity.

significantly enhance MG phagocytic function, induce M2-type polarization, and increase proliferation and secretion. Conversely, they can exert opposite effects, such as reducing MG density, promoting M1 phenotype polarization, and inhibiting MG activation (illustrated in Figure 4). These findings support the notion that chemokines exert regulatory effects on MG in AD, thereby influencing the incidence and progression of the disease.

Mechanisms of important chemokines regulating microglia impact on Alzheimer's disease

Pro-inflammatory chemokines

CCL2. Elevated levels of CCL2 are associated with a rapid decline in cognitive function and an increased risk of AD. Individuals with the CCL2 rs4586-CC genotype show slower Aβ deposition but faster tau accumulation compared to those with TT/TC genotypes.[63] High CCL2 expression and production are well-documented to increase MG proliferation, elevate the APP/CCL2 ratio, and enhance Aβ plaque aggregation.[64] Protein-protein interaction (PPI) network analysis reveals upregulation of CCL2 and CXCR4 in AD, with immune infiltration indicating elevated levels of M0 macrophage infiltration and a positive correlation between M2 macrophages and VCAM1 as well as CXCR4 at peak levels.[65] CCL2, linked to diminished cognitive function and elevated AD risk, activates M1 MGs by promoting MG proliferation and Aβ plaque aggregation, thereby exacerbating inflammation in AD.

CCL3. CCL3 has been implicated in the development of memory dysfunction and neuroinflammation.[66] A study observed upregulated expression of CCL3, CCL4, and CCL6 in the cortex and hippocampus of conditional double knockout (cDKO) mice at 3 and 4 months old, with CCL3 facilitating microglial recruitment.[67] CCL3, CCL4, and CCL5, along with their receptor CCR5, act as novel mediators of detrimental crosstalk between MG and neurons. By inhibiting neuronal autophagy and exacerbating

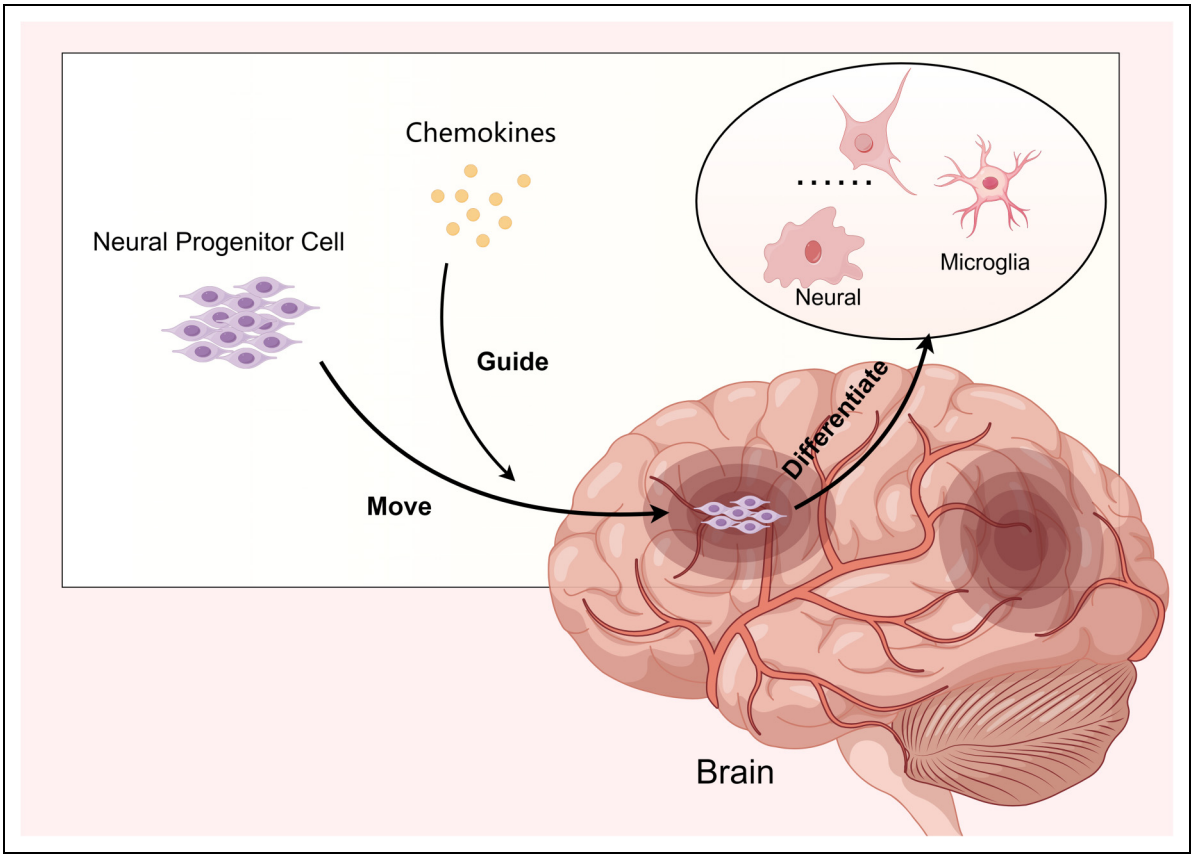

Figure 3. Chemokines guide neural progenitor cells to migrate to brain injury sites.

the accumulation of aggregating proteins through the activation of mTORC1, they contribute to neuroinflammation and worsen AD conditions.[68] CCL3, which is involved in the progression of memory dysfunction and neuroinflammation, promotes detrimental cell-to-cell communication in neurodegeneration by binding to its receptor CCR5.

CCL4. The expression of CCL4 is significantly upregulated in various chronic inflammatory diseases, including AD, suggesting its pivotal role in the inflammatory processes associated with AD. A study has shown that Orosomucoid2 (ORM2) effectively inhibits microglial migration and activation induced by CCL4 by blocking the interaction between CCL4 and CCL5.[69] ORM2 is elevated in various chronic inflammatory conditions, including AD, and it may play a crucial role in the inflammatory process by influencing microglial migration and activation.

CCL7. A study demonstrated significantly elevated CCL7 levels in APP/PS1 mice compared to wild-type controls, suggesting a potential link to AD.[70] Jiao Wang et al. reported that the absence of Dcf1 (Dendritic cell-derived factor 1) modulates the expression of CXCL1 and CCL7, which in turn promotes neuroinflammation and impairs the functionality of activated MG, thereby impeding their migration and phagocytic capabilities.[71] These results suggest that CCL7 could regulate AD progression by suppressing microglial activity.

CCL11. It is shown that the induction of CCL11 by MG enhances the production of reactive oxygen species through the upregulation of nicotinamide adenine dinucleotide phosphate oxidase 1 (NOX1), exacerbating neurotoxic effects and exacerbating the severity of AD.[72]

CCL20. Although direct evidence linking CCL20's regulatory effects on MG in AD is lacking, it has been suggested as a potential plasma biomarker for the condition.[73] Current studies have determined that IL-1β, TNF-α, and IL-6 production induced by CCL20 plays a crucial role in driving microglial activation in vitro.[74] Further investigation is required to determine whether CCL20 indeed regulates MG to affect AD.

CXCL1. Monocytes from AD patients demonstrate an overexpression of CXCL1, which, along with CXCR2 expressed on HBMEC, plays a role in facilitating monocyte migration from the bloodstream to the brain in AD patients.[55] In CNS fungal infections, MG utilize the transcription factor CARD9 to regulate IL-1β expression,

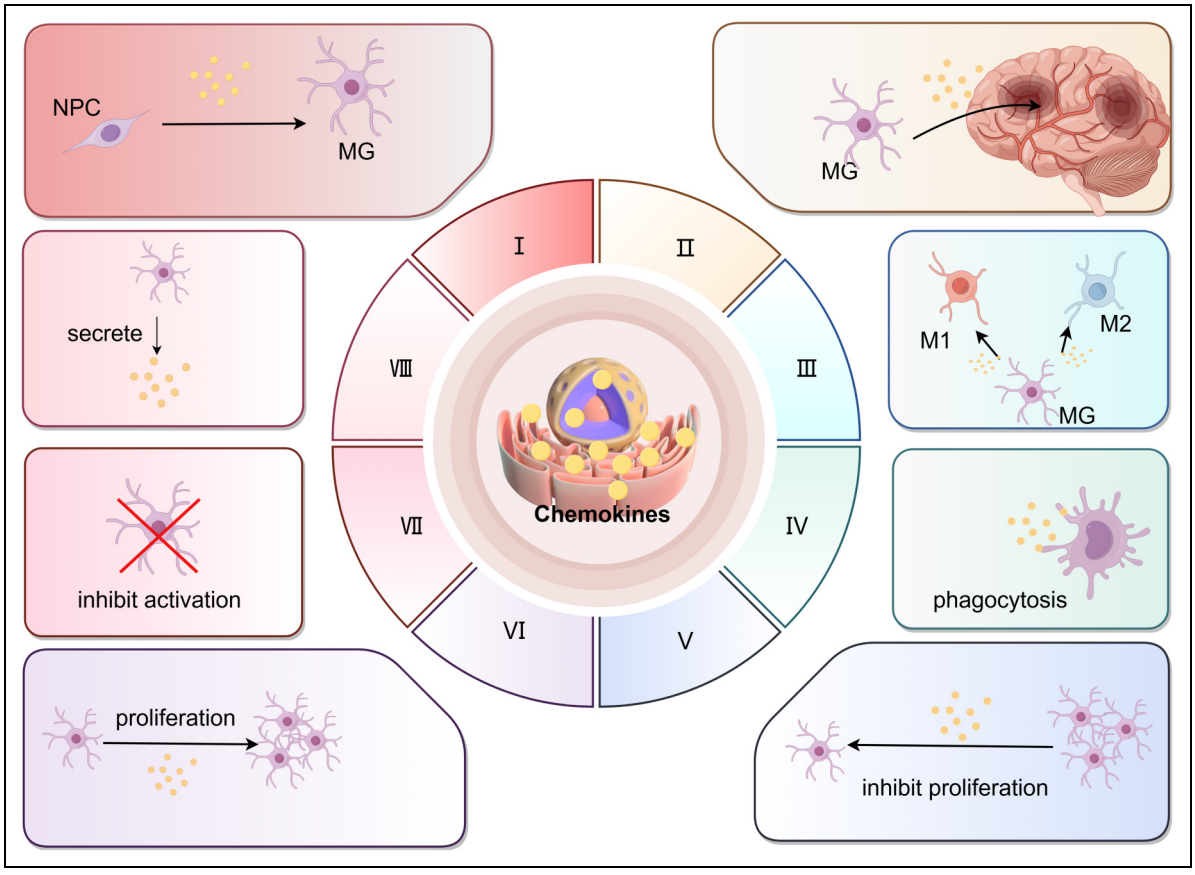

Figure 4. Chemokines control the influence of microglia on AD through regulating different pathways. (I) promoting MG production; (II) stimulating MG migration; (III) affecting MG differentiation; (IV) enhancing MG phagocytosis; (V) inhibiting MG proliferation; (VI) preventing MG activation; and (VII) stimulating MG secretion.

activate the inflammasome, and bind chemokine CXCL1, thereby generating IL-1β. CXCL1 also influences AD by promoting IL-1β production through MG.[75] Collectively, these findings suggest that CXCL1 may influence the progression of AD by modulating microglial migration.

CXCL5. In animal models of AD, early alterations in white matter are observed before the formation of Aβ plaques but subsequent to intracellular Aβ accumulation. The chemokine CXCL5, associated with AD, not only promotes neutrophil chemotaxis but also significantly inhibits the phagocytic activity of MG towards myelin debris.[76,77] The link between the CXCR2-CXCL signaling pathway and white matter damage could contribute to cognitive impairment and AD pathology, making it a promising target for early intervention and therapeutic strategies.[78] In summary, CXCL5 may affect cognitive function in AD by enhancing neutrophil chemotaxis and inducing microglial phagocytosis of myelin debris, leading to white matter damage.

CXCL10. The study by Gaetani et al. suggests that immune mediators may play a role in maintaining the stability of the blood-brain barrier (BBB) in AD. Notably, chemotactic factors such as MCP-2, CXCL11, and CXCL10 activate immune cells that participate in inflammatory responses.[79] CSF from patients with mild AD showed elevated levels of CXCL10 compared to healthy controls, indicating that this molecule may be involved in the early stages of the disease when inflammation is significant.[80] Krauthausen et al. demonstrated that in the APP/PS1 mouse model, the activation of CXCR3 impairs microglial phagocytosis of fibrillar $A\beta_{1-42}$ (fAβ), leading to plaque formation and behavioral changes.[81] This implies that CXCL10 could influence disease progression in AD by modulating microglial function.

CXCL12. Gavriel et al. found that CXCL12 activates CXCR4 signaling in microglia and astrocytes, leading to the release of pro-inflammatory cytokines such as TNF-α.[82] This pathway represents an innovative approach for AD intervention, with the novel treatment showing promise for managing AD. By attracting microglia and initiating the inflammatory cascade, this signaling pathway could significantly influence the progression of AD.

Homeostatic chemokines

CCL6. The role of CCL6 in MG remains unclear. However, recent research suggests that exposure to 6M RF-EMFs results in decreased levels of Aβ in an AD mouse model. This decrease is attributed to the inhibition of microglial proliferation, accompanied by a significant increase in CCL6 expression. This finding implies a potential association between CCL6 and MG function,[83] suggesting its involvement in the regulation of AD. Additionally, the activation of neuronal CCR1 and the PI3K/Akt pathway inhibits glutamate neurotoxicity, which is mediated by CCL6 through the neuronal chemokine receptor CCR1. This mechanism exerts neuroprotective effects, aiding in the suppression of AD and the promotion of MG migration.[84]

CCL8. Ying Lu and her colleagues have demonstrated that CCR5 serves as the primary receptor for CCL8 on monocytes, activated T cells, MG, and transfected cell lines. This interaction activates T cells and enhances the phagocytic capabilities of MG, ultimately affecting AD.[85]

CCL21. Some analyses indicate that CCL21 exhibits a neuroprotective effect by mitigating neuroinflammation.[86] Studies have demonstrated a decrease in chemotaxis dependent on CCL19, but not CCL21, in patients with mild AD. This observation is consistent with the anti-inflammatory properties attributed to CCL21. However, current research solely demonstrates the regulation of tumor-associated MG activation by CCL21.[86] The impact of CCL21 regulation on microglial activation specifically in AD remains to be explored.

CXCL3. MG express CXCR2, which is linked to AD along with its ligands.[87,88] Furthermore, targeting CXCR2 has been suggested as a potential therapeutic approach for inflammatory diseases.[89] Under steady-state conditions, CXCR2 expression is absent in MG. However, during CNS pathology, MG activation leads to a significant induction of CXCR2 mRNA and protein expression by CXCL3 in BV-2 MG.[90] These observations hint that CX3CL3 may influence the progression of AD by modulating MG activity.

CX3CL1. In vitro and in vivo research results have shown that the interaction between CX3CL1 and CX3CR1 and the subsequent signal-transduction processes are crucial for maintaining the resting phenotype of MG.[91,92] Moreover, they can effectively regulate the recruitment and proliferation of MG inhibit the excessive release of pro-inflammatory cytokines, and significantly enhance the phagocytic function of presynaptic elements.[93] In the early stage of AD, the CX3CL1-CX3CR1 signaling pathway promotes the clearance of Aβ by enhancing the phagocytic ability of MG, thus exerting an important neuroprotective effect. However, as neurons gradually die, the secretion of CX3CL1 decreases, which may lead to further activation of MG and consequently exacerbate the progression of AD.[94]

The current study exclusively focuses on CX3CL1 (fractalkine). Prior research has demonstrated that patients with mild-to-moderate AD exhibit higher plasma levels of CX3CL1 compared to those with severe AD.[95] In AD, hippocampal neurons expressing the human tau P301L mutant protein enhance CX3CL1 production. Elevated CX3CL1 expression is noted in neurons damaged by tau in AD patients, where MG function as a rescue signal.[96,97] In summary, neurons produce CX3CL1, which regulates MG activation and function through interaction with its receptor, CX3CR1, on MG. This interaction influences Aβ clearance and neuroprotection.

Dual-functional chemokines

CCL5. The CCL5/CCR5 axis consists of CCL5 and its primary receptor, CCR5. A Mendelian randomization analysis has demonstrated a causal link between CCL5 and AD, implying that the chemokine gene may play a role in various mechanisms underlying AD.[54] CCR5 is crucial for the activation and accumulation of glial cells in the hippocampus. In CCR5-knockout mice, overexpression of $A\beta_{1-40}$ in the hippocampus results in reduced astrocyte and MG aggregation, while alleviating cognitive impairment and synaptic dysfunction.[98] However, previous studies have shown upregulated expression of CCR5 receptor ligands (CCL3 and CCL4) in MG from APP/PS1 mice, as well as in postmortem AD brains.[99,100] Further evidence suggests that downregulation of CCR5 expression in the dorsal CA1 region prevents $A\beta_{1-42}$-induced microglial activation and rescues memory deficits during the object place recognition (OPR) test. These findings indicate that deficiency or antagonism of CCR5 may potentially serve as a therapeutic approach for cognitive deficits associated with AD.[101]

CXCL8. In the CNS, monocytes, MG, astrocytes, and neurons all contribute to the elevation of CXCL8 levels in response to Aβ and proinflammatory cytokines, such as IL-1β and TNF-α. This, in turn, facilitates the recruitment of activated MG to damaged brain regions.[102]

It has been established that IL-8 can influence GSK3β phosphorylation and regulate protein phosphatase activity in vitro, thereby enhancing tau phosphorylation.[103] Notably, the levels of CXCL8 in AD brain lysates exhibit a significant increase. When stimulated by Aβ and/or proinflammatory cytokines, microglia, astrocytes, and neurons are all capable of producing CXCL8 in vitro.[104] Consequently, CXCL8 potentially plays a detrimental role in the pathogenesis of AD.[105]

However, Ashutosh et al. present an alternative perspective, suggesting that, while CXCL8 alone does not affect neuronal survival, it does inhibit neuronal apoptosis

induced by Aβ and enhances the production of brain-derived neurotrophic factor (BDNF) in neurons. The combined findings from Ashutosh et al.'s research indicate that CXCL8 can exert neuroprotective effects by regulating neuronal function.[105]

Potential therapeutic strategies

Therapeutic strategies based on regulating microglia

Gene therapy. MG constitute the predominant immune cell population within the CNS and are indispensable for preserving neural health.[35] The *APOE* genotype serves as a pivotal genetic determinant of susceptibility to AD.[106,107] There exist three primary polymorphic variants of *APOE* in the human population: *APOE2*, *APOE3*, and *APOE4*. *APOE2* is associated with a decreased risk of AD, conversely, *APOE4* is robustly linked to an elevated risk for AD.[108–111] Alterations in the *APOE* gene can influence the transcriptional profile of MG, consequently impacting the pathological and immunomodulatory mechanisms underpinning AD.[112] Consequently, the modulation of APOE and MG has emerged as a promising therapeutic avenue for AD treatment.[113]

Research has indicated that interventions aimed at the *APOE4* gene have demonstrated encouraging outcomes in experimental models, encompassing strategies such as elevating apolipoprotein apoprotein E levels, employing apolipoprotein e mimetics, inhibiting the APOE-Aβ interactions, silencing APOE expression, and utilizing gene-editing techniques to convert *APOE4* to *APOE2* or *APOE3*.[114,115] Nonetheless, bexarotene exhibits limited CNS penetration in humans, resulting in only a nominal increase in apolipoprotein E levels within the cerebrospinal fluid.[116–118]

CD33, a transmembrane protein expressed on the surface of MG, is implicated in the pathogenesis of AD.[119,120] Elevated CD33 levels impede the uptake and clearance of Aβ, and CD33 ablation has been shown to alleviate Aβ plaque accumulation in murine AD models.[121,122] Gene therapeutic approaches, which involve the administration of artificial microRNAs targeting CD33 via adeno-associated virus (AAV) vectors, have demonstrated potential in reducing AD pathology by reducing the expression of CD33.[123,124]

TREM2 is a receptor protein that regulates the activity of MG and facilitates the clearance of Aβ aggregates.[125] Therapeutic strategies, such as activating antibodies and gene therapy, have demonstrated potential in treating AD. For instance, antibodies like AL002c and AL002a activate TREM2, thereby enhancing MG phagocytosis and eliciting an anti-inflammatory response.[126–128] Additionally, gene therapy techniques, involving viral vector-mediated gene delivery, may be utilized to augment TREM2 expression in brain MG, thereby potentially restoring cognitive function in AD patients.[129,130]

CD200 is a factor that can inhibit MG activation and M1 polarization, enhance its phagocytosis of Aβ, and suppress neuroinflammation. Its receptor, CD200R, is expressed on MG. Clinical studies have found that the expression level of CD200 in the peripheral blood of patients with AD is significantly decreased. This decline in the expression level impairs the function of MG in phagocytosing Aβ and inhibits the activation of MG in AD patients by regulating the translocator protein (TSPO) level.[131,132] In vitro experiments have shown that dexmedetomidine can attenuate the inhibitory effect of lipopolysaccharide (LPS) on CD200R in microglial cells, which is related to its anti - inflammatory effect.[133] These findings indicate that CD200 is expected to become a target for AD treatment based on microglial cells.

In conclusion, this research yields a novel concept for the therapeutic management of AD through the modulation of microglial function, via the lens of gene therapy.

Other therapy. Studies have demonstrated that we can employ blood-brain barrier-penetrating nanocarriers to exclusively target MG autophagy for AD therapy. The utilization of hybrid nanoparticles enables the inhibition of oxidative damage capacity in BV-2 MG cells activated by $A\beta_{42}$, facilitating the permeation of the BBB and mitigating cognitive impairment in APP/PS1 mice. PPA nanoparticles exhibit potential as therapeutic candidates for reducing the damage induced by mitochondrial oxidative stress in AD.[134]

The angiotensin II type 2 receptor agonist C21 has been confirmed by preclinical studies to facilitate M2 polarization in MG, thereby ameliorating neuroinflammation.[135] The recent research[136] indicates the development of a novel neuroregulatory technology, capable of precisely regulating MG function. This innovative approach is anticipated to facilitate the "targeted clearance" of toxic proteins associated with AD, opening a new avenue for the development of targeted drugs to combat this condition. Furthermore, a research group has created a naturally derived HDL-inspired nanoscavenger.[137] This nanoscavenger consists of phosphatidic acid-functionalized HDL, curcumin, and β-site APP cleavage enzyme 1 targeting siRNA, which can be utilized to regulate microglial dysfunction. The study revealed that the nanoscavenger exhibits a tripartite regulatory effect, including the promotion of Aβ clearance, the restoration of MG function to normal levels, and the reduction of Aβ production. The synergistic effect of MG-induced inflammation on the progression of AD pathology has spurred researchers to investigate various, and even conflicting, strategies for treating AD.

In essence, these methodologies, when simplified, the employment of mixed nanoparticles has been demonstrated to inhibit oxidative damage in BV-2 MG cells activated by $A\beta_{42}$ and to mitigate cognitive impairment. The angiotensin type II receptor agonist C21 can promote the M2 polarization of MG cells, thereby ameliorating neuroinflammation.

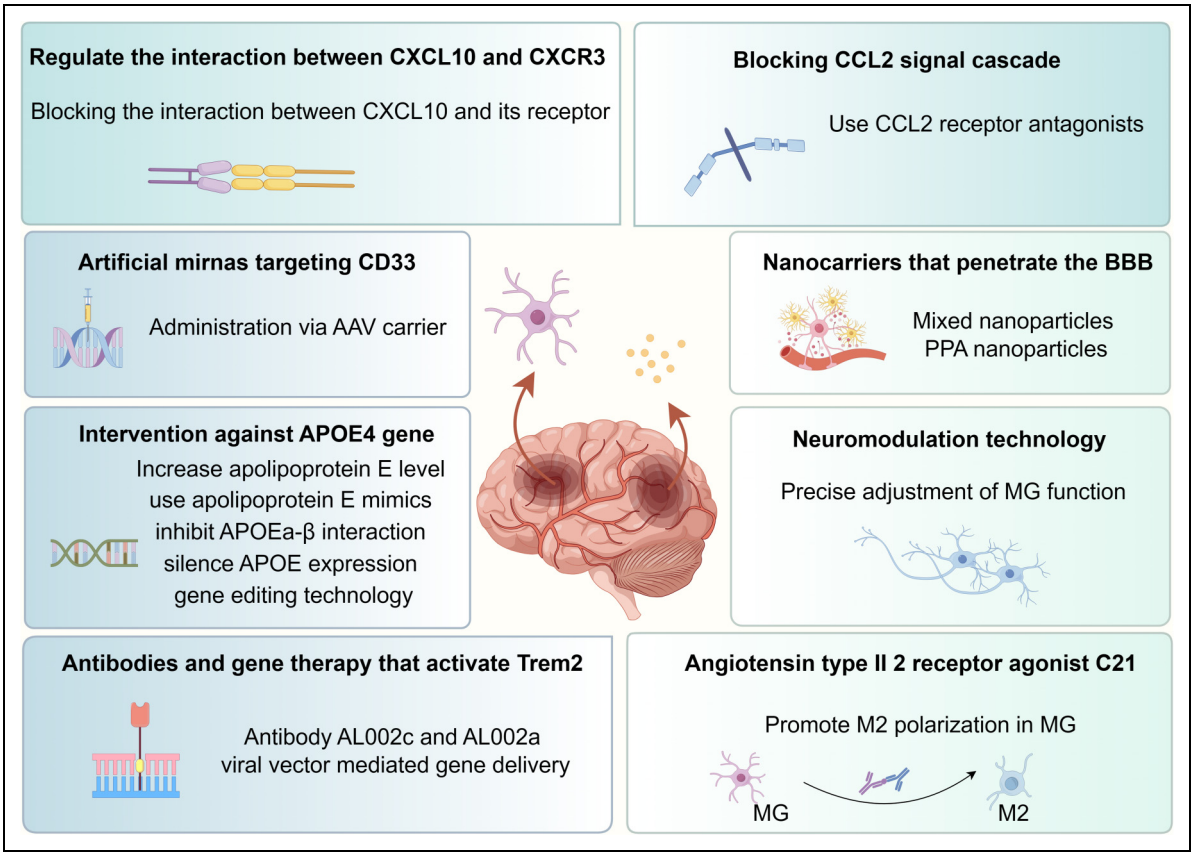

Figure 5. Potential therapeutic strategies based on microglia and chemokines.

The development of cutting-edge neuroregulatory technologies that can precisely modulate the function of MG and enhance the "targeted clearance" of toxic proteins linked to AD is also noteworthy.

Therapeutic approaches based on chemokines

A variety of chemokines (including CXCL1, CCL2, and CCL5) serve as crucial regulators of neuroinflammatory responses,[138] Extant research has substantiated the curative effects of targeting chemokines in animal models. For instance, the chemokine CCL2 has been demonstrated to exert a pivotal influence in AD.[139,140] It has been observed that elevated CCL2 expression in AD patients is correlative with the aggregation of Aβ plaques. By hindering the CCL2 signaling cascade, the accrual of these plaques can be curtailed, thereby enhancing cognitive function.[141] In experimental animal models, the administration of CCL2 receptor antagonists has been shown to markedly diminish the assembly of Aβ plaques, concomitantly resulting in a substantial amelioration of cognitive function post-treatment,[63] indicating that CCL2 may represent a viable therapeutic target.

Additionally, another chemokine, CXCL10, and its receptor CXCR3, also significantly participate in the pathological progression of AD.[142,143] Primarily secreted by immune cells in response to inflammatory stimuli, CXCL10 serves to recruit additional inflammatory cells to the site of injury. The modulation of the interaction between CXCL10 and its receptor has been evidenced to alleviate symptoms in certain mouse models of AD.[144,145] Specifically, by impeding the interaction between CXCL10 and its receptor, it is possible to reduce neuroinflammation and alleviate neuronal injury.[146] Animal studies have demonstrated that interventions focusing on CXCL10 substantially mitigate inflammatory reactions and enhance behavior in AD model mice, providing further corroboration of the efficacy of this therapeutic approach.

In summary, we emphasize the crucial function of chemokines in governing the activation state and functionality of MG, which possess significant implications for the progression of AD. This notion suggests that modulating MG behavior through the regulation of chemokines could potentially serve as a viable strategy for the management of AD (refer to Figure 5).

Conclusion

MG and chemokines play crucial roles in AD. As immune cells in the central nervous system, MG can regulate

inflammation and protect neurons via their M1 and M2 phenotypes. In the early stages of AD, MG contribute to the clearance of Aβ and the activation of inflammation. However, as AD progresses, persistent inflammation leads to the polarization of MG towards the M1 phenotype, resulting in an increase in harmful cytokines, neuronal damage, and the exacerbation of AD.

Chemokines play a dual role in AD. Pro-inflammatory chemokines can exacerbate the effects of M1 MG, whereas others can facilitate MG polarization towards the M2 phenotype, enhancing Aβ clearance and neuroprotection, thereby reducing the risk of AD. Strategies aimed at regulating MG polarization and chemokine function may represent novel therapeutic approaches for AD.

Current research on the utilization of MG and chemokines in the treatment of AD remains unclear, necessitating further investigation into how chemokines influence microglia. Future research should concentrate on elucidating the modulation of microglia's M1 and M2 states and the mechanisms underlying chemokine effects. This could potentially result in the identification of novel drug targets for AD. A comprehensive understanding of the roles of microglia and chemokines in AD is crucial for the development of new therapeutic strategies.

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Statements and declarations

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Author contributions

Bingyang Xu (Data curation; Resources; Validation; Writing – original draft); Chao Tang (Conceptualization; Methodology; Project administration); Rongshou Han (Investigation; Methodology; Writing – original draft); Chaomin Zhu (Formal analysis; Visualization); Yuxuan Yang (Project administration; Software); Heyi Li (Investigation; Validation); Ning Wu (Funding acquisition; Resources); Dian He (Funding acquisition; Supervision; Validation; Writing – review & editing).

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