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The Potential Role of Chemokines in Alzheimer's Disease Pathogenesis

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and leading cause of dementia, which begins with impaired memory. The neuropathological hallmarks of AD include destructive alterations of neurons by neurofibrillary tangles, neuritic amyloid plaques, and neuroinflammatory process in the brain. Chemokines have a major role in inflammatory cell attraction and glial cell activation and/or modulation in the central nervous system. Moreover, the clinical and immunopathological evidence could show dual key role of chemokines in their pro- and anti-inflammatory properties in AD. However, their effects in neurodegeneration and/or neuroprotection remain an area of investigation. This review article provides an overview of characteristic, cellular source and activity of chemokines, and their roles in neuronal glial cell interaction in AD.

Keywords

Alzheimer's disease, chemokine, inflammation, neurodegeneration, CCL2, CCL3, CCL5, CXCL8, CXCL12, CX3CL1, MIF

Introduction

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder characterized by destructive alterations of neurons and cognitive impairment. The pathological hallmarks of AD include intracellular neurofibrillary tangles (NFTs) and deposition of Abeta (Aβ) in a compact structure of neuronal outside. The Aβ is processed from a larger protein named amyloid precursor protein (APP) by processing enzymes (α, β, and γ secretases) and then deposits in extracellular plaques known as senile plaques.[1-3] The Aβ deposits lead to the accumulation of activated glial cells surrounding senile plaques, and these activated glial cells seem to be responsible for the ongoing neuroinflammatory process in the AD caused by the release of cytokines, chemokines, and neurotoxins including reactive oxygen species (ROS), nitric oxide (NO), and excitatory amino acids, which may in turn contribute to the neuronal degeneration observed in AD.[4] Therefore, AD pathology is characterized by inflammation that could contribute to the course of disease. Inflammation is the part of initial innate immune response to recruit the immune cells to the site of stress especially through chemotactic activity of involved chemokines.[5,6]

Chemokines are the largest family of cytokines in human immunophysiology. Their name is derived from their ability to induce directed chemotaxis in responsive cells.[7] Proteins are classified as chemokines according to shared structural characteristics such as small size (they are approximately 8-10 kDa in size and usually of 60-90 amino acids in length) and the presence of 4 cysteine residues in conserved locations that are key for forming their 3-dimensional shape. Traditionally, the names given to chemokines were based primarily on their cellular sources or functional properties, creating a great deal of ambiguity and confusion. However, recently chemokines have been classified into 4 main subfamilies based on the motif displayed by the first 2 cysteine residues located near their N-terminal end: α (CXC), β (CC), δ (CX3C), and γ (XC).[8]

All of these chemokines exert their biological effects by interacting with specific G-protein-coupled receptors (GPCRs) called chemokine receptors that are selectively found on the surface of their target cells.[9,10] Chemokine receptors are divided into 4 families relevant to the type of chemokine that binds them; CXCR that binds to the CXC chemokines, CCR that binds to the CC chemokines, CX3CR1 that is only connected to the CX3CL1 chemokine, and XCR1 that binds both XCL1 and XCL2 chemokines.[11]

The biological functions of the chemokines superfamily using the specific receptors are relevant to immune responses, such as cell recruitment, cell activation, microbicidal activity, polarization

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Table 1. Chemokines Source, Receptor, and Function in AD Pathogenesis.

Chemokine Name	Cell source in Brain	Receptor	Function in AD Brain
CCL2 (MCP-1)	Astrocyte, microglia, neuron, and infiltrated monocyte	CCR2	Mononuclear phagocyte infiltration and neuroinflammation
CCL3 (MIP-1α)	Astrocyte, microglia, neuron, infiltrated monocyte, and T cell	CCR1 CCR5	Accumulation of activated glial cells, and T cells' transendothelial migration from blood to brain
CCL5 (RANTE)	Endothelial, glial, and neuron throughout the brain	CCR1, CCR3, CCR5	Data are repugnant: Leukocyte recruitment and activation that coincide with increased neuronal death in a brain injury. Increase in cell survival, modulatory effect on activated microglia, and increased NO secretion
CXCL8 (IL-8)	Monocyte, microglia, astrocyte, and neuron	CXCR2 and likely CXCR1	Potent chemoattractant for activated microglia; proinflammatory cytokine stimulation; neuronal survival and neuroprotection by upregulated BDNF production
CXCL12(SDF-1)	Neuron and astrocyte	CXCR4	Anti-inflammatory properties and neurogenesis. Recruitment of brain resident and nonresident circulating cells
CX3CL1(Fractalkin)	Neuron	CX3CR1	Neuroprotective role; suppresses the activation of microglia
MIF	Neuron and microglia	CD74	Promotes the production of several inflammatory mediators such as TNF-α, IL-6 and IFN-γ; role in plaque formation and inflammatory process surrounding the plaques

Abbreviations: AD, Alzheimer's Disease; BDNF, brain-derived neurotrophic factor; IFN, interferon; IL, interleukin; NO, nitric oxide; TNF, tumor necrosis factor; MIF, migration inhibitory factor; SDF-1, stromal cell–derived factor 1; RANTE, regulated upon activation, normal T cell expressed and secreted; MIP-1α, human macrophage inflammatory protein 1α; MCP-1, monocyte chemoattractant protein 1.

of $CD4^+$ T cells, and effects on structural cells.[12] In the central nervous system (CNS), chemokines regulate leukocyte migration through the brain endothelium as well as the activation and movement of cells within the brain parenchyma.[13]

Immune cells including monocytes, T cells, and B cells, which can secrete some chemokines are present in the AD brain because they migrate from the periphery through the blood–brain barrier (BBB), which differs in AD compared to healthy individuals.[14-16] Moreover, studies by Xia et al showed that the Aβ has the ability to stimulate the production of some chemokines including CXCL8, CCL2, CCL3, and CCL4 from human monocytes.[17] These chemokines play a notable role in leukocyte migration to the inflammatory sites or to second lymphoid organs. In CNS, the resident cells play a key role in attraction of immune cells by producing chemokines.[18]

Recent investigations have demonstrated that chemokines and their receptors are also involved in development, by regulating hematopoiesis, cardiogenesis, vascular and cerebellar development, and in the maintenance of normal brain homeostasis. Chemokines are constitutively expressed in the brain in both glial cells and neurons. Several recent studies suggest that chemokines can have a neurotransmitter/neuromodulatory role in brain functions similar to several neuropeptides reported so far.[9] Moreover, these proteins have an important role in the development of the CNS and are involved in normal brain functions such as synaptic transmission. Microglia, the main representative of the immune system in the CNS, originates in the bone marrow, migrates into the blood, and enters the brain in a chemokine-dependent manner. Chemotactic migration of leukocytes largely depends on adhesive interaction with the substratum and recognition of a chemoattractant gradient. Both factors, cell adhesion and chemotaxis, are regulated by chemokines.[12,14,16,18,19]

Recent findings point to enhanced lymphocytes transmigration as part of an amplified immune response of the aging brain to acute inflammatory insults.[20] In the brain, infiltrated T lymphocytes can interact directly with microglia through cell–cell contact mechanisms to upregulate the release of numerous proinflammatory and anti-inflammatory cytokines.[21,22] Giuliani et al has reported that the interaction of activated T cells with microglia led to the substantial increase in tumor necrosis factor (TNF)-α level.[23] Interestingly, Bromley et al showed that certain chemokine gradients have the potential to suppress T-cell activation by preventing the formation of the immunological synapse (a specialized cell–cell contact before a T cell could be fully activated). Their findings indicated that the immunosuppressive effect of chemokines engaging with CXCR3 and CCR7 receptors but not CCR2, CCR4, CCR5, or CXCR4 receptors.[24]

The Role of Chemokines in AD Pathogenesis

There is a growing evidence that chemokines and their receptors are upregulated in resident CNS cells, which may play important roles in neuroinflammation and neuronal death in neurodegenerative disorders, including AD, Parkinson's disease (PD), multiple sclerosis (MS), human immunodeficiency virus–associated dementia (HAD), and stroke.[16,25] In AD, prolonged and sustained inflammation may have cytotoxic effects, aggravating the incidence and the severity of the disease, and acceleration of disease progression.[15,26] In AD and in its prodromal stage, mild cognitive impairment (MCI), several chemokines including inducible protein 10 (IP-10), CCL2, and CXCL8 are increased both in brain tissue and in cerebrospinal fluid (CSF).[27,28] The IP-10 is specifically increased in MCI and decreased with AD progression, whereas CCL2 and CXCL8 are also upregulated in late stages of the disease, suggesting

a role in phases where neurodegeneration is prevalent.[29] Other data suggest that these modifications occur very early during the development of the disease, possibly explaining the failure of trials with anti-inflammatory drug in patients with severe AD. Although a variety of chemokines have been detected in and around the brain plaques and tangles, identification of these mediators in blood and CSF is easier to access than those in the brain and may contribute to early diagnosis and monitoring of disease progression.[27,28,30] Since access to the brain is essentially possible only postmortem, the CSF and blood samples allow follow-up studies on the same patients to evaluate disease progression and eventual treatment efficacy.[31] Olson and Humpel, proposed the utility of growth factors, cytokines, and chemokines as putative surrogate biomarkers in CSF and blood for diagnosing AD and MCI. It should be noted that, the expression levels of growth factors, cytokines, and chemokines are very heterogenous, indicating the pathological diversity of these diseases.[32]

Regarding the chemokine induction and their upregulation during CNS pathology, some members of the chemokine family can be applied as biological markers. Due to the correlation between CXCR4 and CXCL12 expression and the progression of glioblastoma tumor, they could be recommended as marker for grading this type of CNS tumor. Also CCR1, by its specific expression in Aβ plaques, may be a marker for AD pathology.[14] In addition, Galimberti et al suggested that evaluation of chemokine levels combined with other known CSF markers, including Aβ, total tau (T-tau), and hyperphosphorylated tau (P-tau) levels as well as other possible neuropsychological and neuroimaging tools, may be useful as early markers in MCI to predict conversion to AD.[29] Since the onset of pathologic processes in AD started several years before the initial symptoms, these biomarkers may provide tools for early diagnosis of the disease. Apart from diagnostic role, these biomarkers may also be used for prognosis, assessing disease progression, monitoring treatment effects, developing new treatments, and studying disease mechanisms.[33]

Hence, the search for new biomarkers is necessary. At present, several biomarkers have been introduced in CSF.[33] Corrêa et al suggest that the levels of CCL2 in CSF are involved in the pathogenesis of AD,[27] and CSF levels of CCL2 are inversely correlated with serum levels. Moreover, they suggested that CCL2 may be an additional useful biomarker for monitoring disease progression.[27,34,35]

Recently, Alsadany et al suggest CXCL8 plasma levels as noninvasive peripheral biomarkers with a high degree of sensitivity and specificity could be a useful biomarker in following AD progression.[36] There are several other interesting candidate biomarkers, such as visinin-like protein-1,[37] neurogranin,[38] YKL-40,[39] and F2-isoprostane, in CSF.[40]

The reasons for choosing the following cited cytokines in this review include their importance, abundance, and also their strong association with AD mechanism.

CCL2 (Monocyte Chemoattractant Protein 1)

Among molecules produced during inflammation associated with neuronal death, monocyte chemoattractant proteins (MCPs) seem to be particularly important.[15] Monocyte chemoattractant protein 1 is one of the MCPs, a major monocyte chemokine also known as CCL2, which plays a significant role in inflammatory processes including neurodegenerative disorders.[17] Interestingly, the CSF levels of CCL2 were found to be influenced by age, since a significant correlation has been observed between the age of Japanese population and the elevated CCL2 levels.[41]

CCL2 is upregulated in the AD brain, and increased brain levels of CCL2 leads to the recruitment of activated monocytes into the brain, where they are differentiated into macrophages producing neurotoxic and inflammatory molecules.[42] In recent research, Zhang et al demonstrated that in patients' blood with early stages of AD, expression of monocyte CCL2 receptor (CCR2) was decreased; however, plasma CCL2 levels were significantly increased and were related to the degree of monocyte/macrophage activation in AD.[43] Moreover, microglial cells were shown to display an increased migratory response to CCL2, suggesting that this molecule may play an important role in trafficking of mononuclear phagocytes in the brain.[44]

Porcellini et al in 2013 suggested that activated microglia express a large number of chemokines including CCL2. The potential role of CCL2 in AD pathogenesis is supported by the overexpression of CCL2 associated with an increase in amyloid deposition in transgenic mice.[45]

To confirm the above-mentioned fact, reactive microglia and inflammatory factors were reported to be present in Aβ deposits (senile plaques) in AD, suggesting the presence of CCL2 in senile plaques. Accordingly, in a study by Ishizuka et al, CCL2 was found immunohistochemically in mature senile plaques and reactive microglia but not in immature senile plaques of the brain tissues from patients with AD.[46]

Interaction of CCL2 with its receptor CCR2 regulates mononuclear phagocyte accumulation; thus, CCR2 deficiency leads to lower mononuclear phagocyte infiltration and is associated with higher brain Aβ levels, specifically around blood vessels, suggesting that monocytes can be accumulated at sites of Aβ deposition. Indeed, enhancing mononuclear phagocyte accumulation delays AD progression.[19,42] Also in a recent research on Aβ precursor protein/presenilin 1 (APP/PS-1) in double-transgenic mice, it was reported that CCL2 deficiency influences behavioral abnormalities and disease progression in mice. Here, augmented cortical and hippocampal Aβ deposition is coincident with the formulation of Aβ oligomers. Deficits in peripheral Aβ uptake and its scavenger as well as neuroprogenitor and microglial cell functions are linked to deficient Aβ clearance, which all serve to accelerate memory dysfunction. In conclusion, decreased CCR2 expression in bone marrow–derived microglia may therefore play a major role in the etiology of AD.[47,48]

In contrast with microglia, in astrocytes, the increased expression of CCR2 leads to the activation of this cell causing Aβ deposit and production of proinflammatory cytokines and chemokines that lead to neuronal cell death in the pathogenesis of AD.[49] Another study provided in vivo and in vitro evidence that CCL2 stimulates astrocytes via CCR2 to induce astrocytosis in amyotrophic lateral sclerosis (ALS) with superoxide

dismutase 1 (*SOD1*) gene mutation. Accordingly, it is likely that CCL2-/CCR2-mediated signaling is involved in disease progression.[50]

Lawrence et al reported that the transcription factor nuclear factor κB (NF-κB), and possibly NF-I, contributes to the upregulation of CCL2 chemokine production during the differentiation of human progenitor cells toward an astrocyte phenotype.[42,51] Immunohistochemistry for CCL2 confirmed this increase and determined localization of these factors in astrocytes, neurons, and plaque pathology. Liao et al in 2011 reported that the levels of CCL2 and CCL3 in the temporal and frontal cortices, and also in the hippocampus of patients with AD, were significantly higher than those of the controls. Moreover, they observed an increased number of glial cells stained with glial fibrillary acidic protein around the senile plaques in AD brains. There were significant correlations between NF-κBp65 and CCL-2 chemotactic factors in AD brains.[52]

In a study by Corrêa et al in 2011, the expression of CCL2 was increased in the CSF of patients with AD. Also, a positive correlation was observed between Aβ levels and CCL2, CXCL8, and CXCL10 and between CCL2 and p-tau levels. These results suggest that the levels of CCL2 in CSF must be considered in the pathogenesis of AD, and it may be an additional useful biomarker for monitoring disease progression.[27]

Westin et al suggest that CCL2 in CSF could be a useful biomarker for prediction of disease progression rate in prodromal AD. Moreover, CCR2-related signaling pathways might be new therapeutic targets for therapies aiming at slowing down the disease progression rate of AD.[53] Also, Ho et al found elevated CCL2 expression in the frontal cortex of patients with MCI who are at high risk of developing AD. Their findings suggest that additional application of the CCL2 to current diagnostic criteria may lead to improved traumatic brain injury (TBI) detection and more sensitive outcome measures for clinical trials. Induction of CCL2 in response to TBI might be a potential predisposing factor that may increase the risk of AD development.[54] Finally, logistic linear regression modeling determines that CCL2 is the most reliable predictor of AD.[35]

Collectively, these data indicate that CCL2, by producing neurotoxic and inflammatory molecules, may play a dominant role in chronic inflammation in AD.[35] However, in an initial attempt by recruitment of phagocytic cells, it was found that CCL2 has a beneficial effect on Aβ clearance.

CCL3 (Human Macrophage Inflammatory Protein 1α)

CCL3 or human macrophage inflammatory protein 1α (MIP-1α) is a member of the β-chemokine subfamily, which plays a considerable role in AD pathogenesis, mainly via its expression by neurons and microglia.[55] These molecules exert their effects through activation of its receptor CCR5. The CCL3-/CCR5-signaling pathway is critical for the accumulation of activated glial cells in the hippocampus and, therefore, for the inflammation and cognitive failure induced by Aβ in the CNS.[56]

Moreover, higher CCL3 expression in peripheral T lymphocytes of patients with AD leads to the expression of CCR5 on human brain microvascular endothelial cells (HBMECs) that resulted in increased lymphocyte transendothelial migration from blood to brain.[57,58] Recent investigation on phenotypes of circulating immune cells in patients with AD by Goldeck et al showed that the proportion of cells expressing CCR4 (Th2 cells) and CCR5 (Th1 cells and dendritic cells) was greater in patients with AD than in age-matched controls and was more pronounced on CD4+ than on CD8+ T cells. Moreover, it is shown that the percentage of CCR6+ cells was higher in patients with AD than in controls. This chemokine receptor is primarily expressed on proinflammatory memory cells and Th17 cells.[31] There is some evidence that suggest the involvement of natural killer (NK) cells in AD immunopathogenesis. The NK cells express some chemokine receptors such as CCR5 and thus they can respond to its ligand CCL3 and migrate to distinct inflammatory sites in AD brain. However, it has been demonstrated that in the brain, CCR5 is expressed by neurons, microglia, and astrocytes, but immunohistochemical analyses have shown the expression of CCR5, on the microglia of both normal and AD brains, accompanied by increased expression on some reactive microglia in AD.[55,59]

In AD mouse model, it was revealed that activation of the CCL3-/CCR5-signaling pathway is one of the earliest events after injection of $A\beta_{1-40}$, representing an important signal for the accumulation of activated glial cells as well as inflammatory response, synaptic dysfunction, and cognitive failure.[56]

CCL5 (Regulated Upon Activation, Normal T cell Expressed and Secreted)

CCL5 is also known as regulated upon activation, normal T cell expressed and secreted (RANTES). The expression of the β-chemokine CCL5 and their G-protein-coupled receptors is found on endothelial cells, glia, and neurons throughout the brain. CCL5 has been indicated in neurodegenerative diseases including AD, and elevated expression of CCL5 in the cerebral microcirculation of patients with AD is shown. In astrocytes, CCL5 is upregulated in response to a cytokine-mediated increase in ROS. Likewise in animal model, oxidative stress upregulates CCL5 expression in brain endothelial cells and increases CCL5 contributed to the recruitment of immune cells that coincide with increased neuronal death in a brain injury model.[60-63] It has also been shown in cell culture model that CCL5 can stimulate chemotaxis, increase NO secretion, and attenuate IL-10 as well as IGF-1 production in activated microglia.[64]

Based on the existing data and the related literature, it has been suggested that CCL5 in addition to its chemoattractant function also has modulatory effect on microglia activation.[64] Lee et al in 2012 reported that alternative activation of microglia in AD mice is associated with elevated CCL5 expression following transplantation of intracerebral BM-derived mesenchymal stem cells (MSCs). Therefore, the beneficial effects of alternative microglia recruitment into the brain are driven

by CCL5 secretion from the transplanted BM-MSCs, which itself is induced by Aβ deposition in the AD brain.[65] In other study, Kester et al in 2011 suggested that relative messenger RNA (mRNA) expression levels of CCL5 was lower in patients with AD than in controls. On the other hand, in vitro study showed that treatment of neurons with CCL5 results in an increase in cell survival and a neuroprotective effect against the toxicity of thrombin and sodium nitroprusside. Also, Avdoshina et al examined the potential effect of morphine in neuroprotection and showed that morphine elicited a time-dependent release of CCL5 from astrocytes that may exhibit a neuroprotective activity.[63,66,67]

CXCL8 (Interleukin 8)

CXCL8, also known as interleukin (IL) 8, is an inflammatory chemokine produced in response to proinflammatory signals. Several functions were introduced for CXCL8 in various cell types in different tissues. CXCL8 function included cell adhesion, recruitment and homing of neutrophils and lymphocytes, neuronal protection, and brain development. However, the principal function of CXCL8 is the recruitment of neutrophils to inflammatory sites in response to injury or infection. In the periphery, neutrophils, monocytes, macrophages, and endothelial cells secrete CXCL8. In the CNS, monocytes, microglia, astrocytes, and neurons, all contribute to the enhanced CXCL8 levels upon Aβ and proinflammatory cytokine stimulation, such as IL-1β and TNF-α, to contribute for recruiting activated microglia into the areas of the brain damaged.[68,69]

Increasing evidence suggests that CXCL8 and its receptors (CXCR1/CXCR2) may play a role in MCI and AD pathogenesis, which are consistently upregulated in neurons, plaque, and CSF of these patients.[29,35] In a recent study, Alsadany et al in 2013 demonstrated that plasma levels of histone deacetylases and copper may be used as peripheral biomarkers in the diagnosis of AD, while CXCL8 level could be a useful biomarker in following AD progression.[36] Conversely, Bonotis et al in 2008 suggested that no significant differences were observed in CXCL8 levels between patients and controls in mild to moderate and severe stages.[70]

However, little is known about biological effects of CXCL8 on neuronal survival, but these data are controversial; on one hand, Thirumangalakudi et al showed that CXCL8 was able to increase apoptosis in primary rat neurons; and on the other hand, a protective effect of CXCL8 was shown by Watson and Fan in murine neonatal hippocampal neurons.[71,72] Also, Ashutosh et al demonstrated that neurons contribute to elevated CXCL8 levels during AD and may affect neuronal survival and function. CXCL8 inhibits Aβ-induced neuronal apoptosis and upregulates the production of neuronal brain-derived neurotrophic factor (BDNF). Altogether, CXCL8 production in glial and neuronal cells as a paracrine or autocrine neuroprotective mechanisms could regulate neuronal functions in the pathological process of AD.[73]

CXCR2 or CXCL8 receptor B is a strongly expressed chemokine receptor that has immunoreactivity on neuron subsets in various regions of the brain and spinal cord. Immunohistochemical analysis of the involved brain tissues from patients with AD revealed high expression of CXCR2 in the neuritic portion of plaques surrounding deposits of amyloid as well as in microglia and astrocytes.[74,75] In addition, Liu et al suggested that CXCR2 contributes to regulating T-cell migration, and peripheral T cells derived from patients with AD overexpress CXCR2 to enhance its transendothelial migration. In this study, T-cell migration through in vitro blood–brain barrier model was effectively blocked by anti-CXCR2 antibody or CXCL8 RNAi (RNA interference) in HBMECs.[76]

However, many studies have shown that CXCR2 is strongly expressed in the CNS, whereas published data on the expression of another CXCL8 receptor CXCR1 in the healthy or pathologic human brain is very limited. First, in 2003 Flynn et al reported that microglia and astrocytes expressed CXCR1 at highest and moderate levels, respectively, then in 2008 Goczalik et al. suggested that CXCR1 can be expressed not only in glial cells but also in neuronal cells.[68,77]

CXCL12 (Stromal Cell–Derived Factor 1)

The chemokine CXCL12, also known as stromal cell–derived factor 1(SDF-1), controls many functions of bone marrow–derived stem cell. In the human brain, CXCL12 is constitutively expressed in neurons and astrocytes of the deep and cortical gray matter of the brain to promote neuroprotective effects and support neurogenesis in the CNS, showing a significant role in the recruitment of brain resident and nonresident circulating cells toward the sites of lesion.[78-80] In neuronal and glial cells, CXCR4 is a receptor for CXCL12. In neuronal precursors, CXCR4 is localized in both neuronal precursors and the cell body; whereas in mature neurons, it is primarily expressed on axons and dendrites to encourage neuroprotective effects.[81]

In addition, CXCL12 activates the expression of CXCR4 in a variety of neural cells, and CXCR4–CXCL12 interaction and signaling results in diverse biological effects and anti-inflammatory properties. It enhances migration and proliferation of cerebellar granule cells, chemoattracts microglia, and stimulates cytokine secretion and glutamate release by astrocytes.[82]

In human study, data indicated that CXCL12 plasma levels in patients with early AD are low and also CXCL12 plasma level has a significant inverse correlation with dementia severity. Moreover, in CSF of patients with AD, the CXCL12 levels are significantly lower in comparison with age- and gender-matched patients having other noninflammatory neurological disease.[80] In animal experiment with Tg2576 mouse model of AD, it has been shown that chemokine's (CXCL12) mRNA, protein, and receptor are downregulated, coinciding with cognitive deficits.[14,79,83] Moreover, another study in APP/PS1 transgenic mice showed that CXCL12 treatment decreased the area and the number of Aβ deposits, increased the level of Iba-1 a marker of microglia, and increased the number of plaque-associated microglia in the parenchyma.[84]

In vitro study showed that pretreatment with MIP-2 or CXCL12 significantly protected neurons from Aβ-induced

dendritic regression and apoptosis through activation of Akt, ERK1/2, and maintenance of metalloproteinase ADAM17, especially with CXCL12.[85]

CX3CL1 (Fractalkine)

It appears that the CX3CL1 (Fractalkine) and its receptor CX3CR1 play a direct role in neuroprotection depending on the CNS insult, therefore, following the chronic inflammation in the CNS, and prolonged activation of microglia triggers the release of several neurotoxic products and proinflammatory cytokines including IL-1β, IL-6, and TNF-α.[86,87] These inflammatory responses in the brain could be tightly regulated at multiple levels so that many are produced by neurons; here one form of immune regulation occurs via CX3CL1 and its receptor CX3CR1 that is expressed by microglia. CX3CL1 is produced and expressed constitutively by neurons and suppresses microglial activity under inflammatory conditions.[14,88]

In this connection, in vitro and in vivo studies provided evidence that showed that the CX3CL1–CX3CR1 interaction and signaling contribute to the microglial's ability to maintain a resting phenotype that resulted in the uptake of Aβ fibrils. Moreover, CX3CL1, through interactions with microglia, serves as an endogenous neuronal modulator for controlling the overproduction of inflammatory mediators (iNOS, IL-1β, TNF-α, and IL-6). However, when neurons are injured, CX3CL1 levels are decreased, neuron–microglial CX3CL1-signaling failure, which results in recruitment and activation of microglia, leading to reduced Aβ deposition in mouse models of AD that is potentially mediated by altered activation and phagocytic capability of CX3CR1-deficient microglia.[86,89,90]

On the other hand, the regulatory role of NK cells in Th1 responses on inflammatory diseases not only in CNS but also in periphery is demonstrated, and it has been shown that the accumulation of NK cells in the CNS is a CX3CL1-mediated process, and CX_3CL1 produced by neurons is necessary and sufficient to conduct CX_3CR1-bearing NK cells to inflamed brain.[91]

In recent studies, it was demonstrated that the level of plasma-soluble CX3CL1 was significantly greater in the patients with mild to moderate AD than in the patients with severe AD. In addition, there was a positive correlation between MMSE score and plasma-soluble CX3CL1 level in the patients with AD.[92] Some findings demonstrated that CX3CL1 plays a neuroprotective role in 6-hydroxydopamine–induced dopaminergic lesion, and it might be an effective therapeutic target for many neurodegenerative diseases, including AD and PD, where inflammation plays an important role.[88] However, the role of soluble exogenous CX3CL1 in AD has not yet been investigated, and it is unknown whether addition of exogenous CX3CL1 beyond otherwise physiologically normal levels could decrease microglia activation and thereby minimize the secondary neurodegeration following a neurotoxic insult.[88,92]

Collectivity, all the above-mentioned studies focused on the role of CX3CL1/CX3CR1 signaling in pathological conditions, whereas ignored the relevance of CX3CL1/CX3CR1 signaling under physiological conditions. Only in a new study, Rogers et al revealed that under physiological status, disruption in CX3CL1 signaling will lead to impairment in cognitive function and synaptic plasticity via increased action of IL-1β, which may led to NF-κB-dependent transcription of proinflammatory cytokines including TNF-α, IL-6, and interferon-γ (IFN-γ).[86,93]

Migration Inhibitory Factor The macrophage migration inhibitory factor (MIF) is a pleiotropic proinflammatory cytokine, which promotes the production of several inflammatory mediators such as TNF-α, IL-6, and IFN-γ and plays a central role in the immune response and pathogenesis of several inflammatory and autoimmune diseases.[26,94] In the brain, MIF is found in both microglia and neurons of the hypothalamus, hippocampus, and cortex.[95] Likewise, in response to proinflammatory stimuli, a significant upregulation of MIF mRNA and protein is expressed in the neurons of the hippocampus and other regions of the brain.[96]

Migration inhibitory factor is a pituitary factor with endocrine properties that can mediate phosphorylation of the extracellular signal–regulated kinase 1/2 MAP kinases.[95] In a clinical study by Popp et al in 2009, increased MIF concentrations were significantly found in the CSF of AD and of patients with MCI compared to controls, with respect to the fact that there was no significant difference between the MIF levels in MCI and in AD.[26]

Moreover, other studies showed a strong role for MIF in the pathogenesis of AD so that it suggests that inhibition of MIF may provide a valuable avenue of investigation for the prevention of disease. The functional studies in murine and human neuronal cell lines revealed that Aβ-induced toxicity could be reversed significantly by ISO-1((S, R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester), a small-molecule inhibitor of MIF. The ISO-1 significantly improves survival and reduces disease progression and/or severity in multiple murine models where MIF is implicated.[94,97]

In addition to neuron, another cellular source for the MIF is the activated microglia in Aβ, so that clustering of this cell at sites of amyloid deposition suggests that microglia migrates to these sites and attempts to remove the amyloid protein. In 2000, Oyama et al explained that MIF is able to bind Aβ in the AD brain, and then toxicity of Aβ can directly be attributed to the increased expression of MIF, however, due to the insoluble nature of amyloid and the fact that it is presented in substantial quantities, it seems that microglia are unable to clear it. Thus, amyloid deposits remain and continue to attract microglial cells over prolonged periods of time.[26,97]

The possible role of MIF in plaque formation and inflammatory process surrounding the AD plaques has been provided by a recent report presenting a significant upregulation of CD74. The CD74 is an integral membrane protein that acts as both a chaperone for MHC class II molecules and a receptor-binding site for MIF.[95] Yoshiyama et al determined that CD74 is increased in microglia of patients with AD compared to age-matched controls. Until in latter immunohistochemistry analysis, Bryan at al revealed a significant increase in CD74 primarily in NFTs, Aβ plaques, and microglia. This was the first finding that CD74 is increased in neurons of patients with AD compared to age-matched controls.[95,98]

In addition, the immunoreactivity for another chemokines including CCL4 (MIP-1β), CCL7 (MCP-3), CCL27, CXCL9 (Mig), CXCL10 (IP-10), and chemokine receptors including CCR1, CCR2, CCR3, CCR5, CXCR1, CXCR2, CXCR3, CXCR4, and Duffy antigen have been demonstrated in resident cells of the CNS, and the upregulation of some of them are associated with pathological changes in many neurodegenerative diseases such as AD.[17,29,64,99]

Conclusions

There are numerous hypotheses about the etiology of AD, and investigations in this field show the fact that the essential causes for AD onset appear to be multifactorial including APP pathogenic cleavage, protein misfolding, neurotransmitter and ion dyshomeostasis, cytoskeletal destabilization, metal ion accumulation, oxidative stress and inflammation as well as neuronal death and gene mutations.[100]

One of these factors is inflammation, and research about the potential role of inflammation show the complexity of the involved mechanisms and even an immune system dysfunction in AD.[101] Newest data demonstrated that chemokines as mediators of immune system in CNS have dichotomous effects in AD pathogenesis so that some of them have neuroprotective and neurogenesis efficacy compared to others that have neurodegenerative effects, and therefore upregulation of them is associated with the pathological changes in AD. In recent studies, upregulation of some chemokines is evaluated in CSF and blood of patients with AD compared with age-matched controls, and hence the association between chemokine expression and AD risk and its progression has been considered. Therefore, the evaluation of chemokine production in patients with AD could be useful in searching of AD biomarkers. For instance, there is evidence indicating that CCL2 plasma level could act as a biomarker to monitor the inflammatory process in AD.[102] The identification of AD biomarkers using blood or blood-derived cells may allow an early, less invasive, and more accurate diagnosis for monitoring disease progression and therapeutic efficacy.[27]

In addition, study of chemokine profile in CSF and blood of patients with AD may lead to a better understanding of its pathological mechanisms and therefore introducing new therapeutic strategy and drug discovery. Up to now, several successful strategies have been established to develop chemokines targeting their receptors, but it has not yet resulted in much new therapies. This is due to a complexity in the chemokine system that has been characterized by pleiotropy, redundancy, and differences among their species.[103]

One of the new therapeutic targets is CCR2. CCR2 is found on the surface of monocytes, microglia, and of a small percentage of T cells. In early stages of AD, the expression of CCR2 is decreased. Moreover, this revealed that decreased CCR2 expression in bone marrow-derived microglia may play a major role in the etiology of AD, with aggravating cognitive impairment and amyloid pathology in transgenic mouse model of AD.[48,104] Accordingly, El Khoury et al reported that CCR2 deficiency accelerates the AD progression hallmarks in APP Tg2576 and APPSwe/PS1 transgenic mice models of AD, because CCR2-deficient microglia do not phagocytize soluble Aβ since disruption of Aβ clearance by microglia is the most principal mechanism accounting for the accumulation of Aβ in a context of CCR2 deficiency.[105-107]

Magga et al demonstrated that hematopoietic stem cell (HSC)-derived monocytic cells share in regular characteristics with peripheral monocytes and microglia and they can even reduce Aβ faster than microglia.[108] Consequently, Naert and Rivest suggested that gene therapy using a lentivirus-expressing CCR2 transgene in HSCs prevents the cognitive decline in the APP(Swe)/PS1 mice model of AD (transgenic mice expressing a chimeric APP [APPSwe] and PS-1). Furthermore, the injection of CCR2 lentiviruses can restore CCR2 expression and function in monocytes. Therefore, upregulating *CCR2* gene expression in HSCs could be a novel therapeutic approach with great potential in the near future.[48]

As mentioned, during the AD course, CCL2 in an initial attempt by recruitment of phagocytic cells has a beneficial effect on Aβ clearance, especially in early stages of AD. However, in late stages of AD by inducing inflammatory states, CCL2 may play a dominant role in chronic inflammation.[35] Additional findings by Westin et al revealed that CCL2 was associated with a faster rate of cognitive decline in AD. Therefore, CCL2-/CCR2-related signaling pathways might be new therapeutic targets for slowing the AD progression rate.[53] Phillips et al showed that IFN-γ plus M-CSF or PMA plus ionomycin downregulate CCR2 expression in monocytes and this could be replicated with a −1220/+115 hCCR2 promoter-pGL3 luciferase reporter.[109] In another study, Chen et al revealed that PPAR-γ ligands including rosiglitazone downregulate CCR2 in circulating monocytes, whereas cholesterol slightly upregulates CCR2.[110]

CCL2 can also function as a regulator for gene transcription. The binding of CCL2 to CCR2 induces expression of novel transcription factor MCP-1–induced protein (MCPIP). The MCPIP was originally discovered as a zinc finger protein induced by CCL2, which is also induced by other inflammatory agents.[111] The MCPIP initiates a sequence of signaling event that causes oxidative and endoplasmic reticulum stress, leading to autophagy that can result in differentiation or cell death, depending on the cellular context.[112] Niu et al suggested that MCPIP has a therapeutic value perhaps through inhibition of IκB kinase complex, resulting in the blockade of NF-κB (a prominent component of the proinflammatory cytokine-signaling pathway) and subsequently attenuation of the proinflammatory state.[113]

Epidemiological findings suggest that anti-inflammatory therapies may slow the onset of AD. Recently, chemokine receptor antagonists have been proposed for inhibiting the chemokine-signaling pathways. In this connection, several studies provided exciting findings for treatment of neurological disease. Chemokine receptor antagonists including CCR2 antagonists (RS 504393, BMS CCR2 22, and INCB 3284 dimesylate), CXCR2 antagonists (SB 265610 and SB 225002), and CCR5 antagonists (DAPTA and Maraviroc) have shown their efficacy in reducing disease severity in animal models of neurological disorder.[14,114] For instance, Rosi

et al suggested that D-Ala-peptide T-amide (DAPTA) and other CCR5 antagonists may reduce microglia and astrocyte activation within the hippocampus in a neuroinflammatory rat model of AD. In addition, DAPTA treatment reduced the number of immunoreactive cells expressing NF-κB.[115] Therefore, in the future, chemokine receptor antagonists could be a potential therapeutic strategy in human AD.

It should be noted that inhibition of chemokine receptor signaling is not the only therapeutic aim; as mentioned, CXCL12/CXCR4 has anti-inflammatory properties and also CX3CL1/CX3CR1 reduces neurotoxicity and controls microglial activation.[13] It is suggested that the CXCL12 levels are decreased in patients with AD as compared to controls. To confirm this, Parachikova and Cotman showed that CXCL12 mRNA, protein, and its receptor are downregulated in the Tg2576 mouse model of AD coinciding with cognitive deficits. In this experiment, young nontransgenic mice treated with an antagonist to the CXCR4 also showed selectively impaired learning and memory, suggesting a potential role for CXCR4/CXCL12 in cognitive functioning.[83] Accordingly, Pabon et al demonstrated that recombinant CX3CL1 could suppress microglia activation in the rat model of PD. The reduced microglia activation was observed to be neuroprotective, thus the CX3CL1-treated rats had a smaller lesion volume in the striatum, and significantly fewer neurons were lost in the CX3CL1-treated rats.[88] These findings demonstrated that CX3CL1 and CXCL12 with their neuroprotective efficacy might be an effective therapeutic target for many neurodegenerative diseases, including AD and PD.

On the other hand, MIF is a proinflammatory cytokine that has been implicated as a causative factor in many diseases. Inhibition of MIF by its small-molecule inhibitor ISO-1 may provide a valuable avenue of investigation for the prevention of AD. The binding of ISO-1 to the tautomerase active site of MIF inhibits its proinflammatory activity. Al-Abed and VanPatten revealed that like neutralizing anti-MIF antibodies, ISO-1 substantially improved survival and alleviates disease progression in murine models where MIF is implicated. In addition, functional studies in human and murine neuronal cell lines showed that Aβ-induced toxicity could be reversed significantly by ISO-1.[94,97,116]

Finally, chemokines and their receptors could be therapeutic targets in the AD animal model. However, the fact that chemokines and their receptors can be a therapeutic strategy in human AD therapy needs more examination in both humans and its animal experimental models.

Declaration of Conflicting Interests

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