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The role of chemokines and chemokine receptors in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease that is characterized by leukocyte infiltration and subsequent axonal damage, demyelinating inflammation, and formation of sclerosing plaques in brain tissue. The results of various studies in patients indicate that autoimmunity and inflammation make an important impact on the pathogenesis of MS. Chemokines are key mediators of inflammation development and cell migration, mediating various immune cell responses, including chemotaxis and immune activation, and are important in immunity and inflammation, therefore we focus on chemokines and their receptors in multiple sclerosis. In this article, we summarize the study of the role of prominent chemokines and their receptors in MS patients and MS animal modelsand discuss their potential significance in inflammatory injury and repair of MS. We have also summarized the progress in the treatment of multiple sclerosis antagonists in recent years with chemokine receptors as targets.

1. Introduction

Multiple sclerosis is an immune-mediated, chronic, demyelinating disorder, which is commonly considered to result from the interaction of environmental and genetic factors that still unclear [26,100]. It's the most common neurological disease among young adults and meanwhile a major cause of physical disability among young adults [26,85]. Current MS phenotypic classifications contain RRMS, CIS, PPMS and SPMS, which means relapsing-remitting multiple sclerosis, clinically isolated syndrome, primary-progressive multiple sclerosis, and secondary-progressive multiple sclerosis respectively [71]. Among them, RRMS accounts for the majority of patients (about 80%) [87]. The hallmark of MS is leukocyte infiltration of brain tissue and subsequent axonal injury, demyelination inflammation and the formation of sclerosing plaques [54].

Abnormal inflammatory response initiated by CD4 + T cells promotes tissue damage of the CNS in EAE and MS. Among the CD4 + T cells, Th1 cells and Th17 cells are dominant, the former producing IFN-γ (interferon-γ), the latter secreting IL-17A, IL-17F, IL-21, IL-22, and GM- CSF (granulocyte–macrophage colony-stimulating factor) [60,123]. After the secreted substances enter the central nervous system, they activate astrocytes and microglia, produce a large number of chemokines and cytokines, and recruit peripheral immune cells to sites of inflammation [123]. The use of CXCR3 and CCR6 as markers of identification of Th17 cells not only reflects their pro-inflammatory status but also reflects their ability to migrate to localized sites of inflammation [118]. The initiation of T cell entry into the CNS is governed by integrin-dependent vascular adhesion and chemokine-driven *trans*-blood–brain barrier [1]. The pathophysiology of MS is not fully understood. It appears that the autoimmune activity of Th17 cell-mediated aggressive attacks is one of the key mechanisms. Th1 cells secrete cytokines (IL-4, IL-10) leading to activation of macrophages and cytotoxicity while cytokines (IFN-γ) produced by Th2 cells lead to activation of B cells and induction of antibody production. Th1 cytokines inhibit Th2 development, and Th2-related cytokines inhibit Th1 responses. The results of some studies indicate that a specific Th1-mediated immune response contributes to the pathogenesis of MS disease and that inhibition of Th1 response is protective against the development of MS, and it is reported that the transition from Th1 to Th2 cytokine has a beneficial effect on the clinical course of MS [46].

Although most research on the pathogenesis of MS has focused on the role of CD4 T cells, in fact, compared to most animal models, the main T cells found in the central nervous system of MS patients are CD8 T cells, suggesting that CD8 T Cells may play an important role in human disease [52]. There is growing evidence indicates that successful treatments are often related to changes in many other lymphocyte subpopulations, including B cells, NK cells, Lti cells, other ILC cells, γδT cells, NKT cells, MAIT cells and innate B cells. These findings not only indicate that multiple lymphocyte subpopulations are involved in the pathogenesis of the disease, but also identify the cells as potential

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targets for immunotherapy [117].

Classically studied animal models of MS are (1) allergic encephalomyelitis/experimental autoimmune (EAE); (2) virus-induced models and (3) toxin-induced demyelination models [90].Experimental autoimmune encephalomyelitis (abbreviated as EAE), an experimental animal model of human MS, is obtained by using myelin oligodendrocyte protein(MOG), proteolipid protein(PLP) or myelin basic protein (MBP) immuning and inducing in certain susceptible experimental animals such as mice and other rodents [44]. Besides, EAE can be triggered by the adoptive transfer of myelin antigen-specific T cells, CD8 + T lymphocytes and Th1 and Th17 type CD4 + cells [66,87]. The pathogenesis of EAE consists of two phases. First, the EAE priming phase: DC migrates to peripheral lymph nodes for self-antigen presentation, induces encephalitogenic Th cells. The second point is encephalitis Th cells are accumulated in the CNS to re-occur cognate antigen on local and CNS-invasive APC(antigen-presenting cells, homologous antigen) [102]. The pathological characteristics of experimental autoimmune encephalomyelitis are not uniform because they vary widely depending on the type of animal used and the type of epitope. The EAE model is relevant for RRMS mostly. MOG induces chronic progressive disease which is closer to SPMS in C57BL/6 mice whereas chronic relapsing-remitting disease in NOD/Lt and SJL mice and Lewis rats [87], non-classical chronic relapsing EAE in PL/J mice. MOG_{35-55}-immunized NOD mice will first develop an acute episode of EAE and then undergo a secondary progressive EAE course. This model can be used to simulate the secondary progressive disease of some MS patients [39]. In DA (Dark Agouti) rats, recombinant rat MOG can be used to induce EAE, which is characterized by demyelinating and spinal cord injury with subcutaneous and perivascular inflammatory infiltration [25]. In SJL/J mice, $PLP_{139-151}$ induced disease mimicking relapsing-remitting EAE [21,25]. MBP can induce acute self-limiting or chronic recurrent disease / progressive disease in guinea pigs. T cell clones reactive with MBP peptides induce EAE in SJL/J mice, which is characterized by acute paralysis attacks, and mice can be partially or fully recovered [39]. Furthermore, spinal cord homogenate can be used to induce EAE in Biozzi ABH mice, recapitulating the clinical characteristics of MS, including secondary progressive disability and relapsing-remitting episodes, which can address the role of an adaptive immune response in neurodegeneration [55].

Mouse Hepatitis (corona) Virus (MHV) and Theiler's virus (TMEV) are the two most widely used viral in inducing chronic encephalomyelitis as MS animal models. Systemic exposure of animals to cuprizone(CPZ) is most commonly used for toxic demyelination models, other demyelination models caused by focal toxins, including focal injections of lysolecithin or ethidium bromide in specific white matter tracts and focal injections of some other toxins not widely in use, such as ionomycin, diphtheria toxin or 6-aminonicotinamide in the spinal cord [13,63]. Among them, the CPZ model simulates the acute and chronic courses of MS and may be a useful tool for the development of new therapies that protect oligodendrocytes and stimulate myelin regeneration. The TMEV infection model is an animal model that specializes in studying the mechanisms of virus-mediated acute and primary progressive MS [87].Chemokines regulate lymphoid tissue development, lymphocyte transport, and homing, and leukocyte maturation as we all know [10]. In autoimmune diseases such as MS, characterized by uncontrolled inflammatory states and increased immune cell infiltration into tissue parenchyma, upregulated expression of chemokines is associated with elevated infiltration of macrophages, monocytes, and lymphocytes in lesions and plaques [62]. The levels of specific chemokine ligands such as CCL2, CCL5, CXCL12, and CX3CL1 continue to rise, resulting in sustained infiltration of immune cells [22,97]. Many chemokines that are produced locally in the tissue, attract different kinds of leukocytes to the sites of infection and inflammation via selective receptors [10]. Chemokines could induce and activate leukocyte adhesion molecules, establishing a chemotactic concentration gradient that causes transendothelial monolayer recruitment [64,110]. The induction of proteolytic enzymes promotes the opening of the BBB and mediates the retention of leukocytes in the central nervous system. Chemokines can also increase adhesion and migration of target cells through the BBB via interacting with leukocyte integrins [12,106]. For example, autoreactive T cells targeting myelin components are triggers for MS disease and that's a vital step for the transport of inflammatory T cells to the CNS in MS. A lot of reports have analyzed the role of chemokines and chemokine receptors in the intrathecal accumulation of T cells in MS [111].

2. Chemokines and chemokine receptors

Chemokines are small proteins that own conserved sequence and structural features, which usually have 70–80 amino acid residues, typically 8–10 kDa in MW(molecular weight) [113]. Human and other mammalian genomes encode approximately 50 chemokines respectively. Most Chemokines contain four cysteine residues, naturally, they are divided into four classes according to structure character that the spacing between the first two of cysteine residue: CC(β), CXC(α), CX3C(γ) and C(δ) [113,121]. In the first three subfamilies, the two cysteine residues are spaced out by 0, 1, and 3 residues separately, while in the XC subfamily the second cysteine residues do not exist [113]. The systematic names of chemokines consist of a prefix like CCL, CXCL, CX3CL or CL followed by an identifying number. Chemokine receptors are named according to which group of chemokines they bind [68], therefore their systematic names consist of a prefix like CCR, CXCR, CX3CR or CR followed by an identification number. In the system nomenclature, the "L" signifies a ligand while the "R" denotes a receptor. For example, CCL2 and CCR2, are named based on the above rules [113].

Besides the above criteria, chemokines may be categorized according to their biological roles [113]. Inflammatory chemokines are those activated and upregulated under inflammatory conditions and have roles in response to tissue damage, infection, and other physiological abnormalities in both adaptive and innate immunity, including CXCL1-3 and CXCL5-8 [86]. Their expression is temporary, until the resolution of the situation [3,127]. Homeostatic chemokines expressed in lymphoid or other organs constitutively, including CXCL12和CXCL13 [86]. They mediate the homeostatic migration and homing of different cells containing lymphocytes, which is needed for the proper function of the immune system. In addition, developmental processes that related to the patterning of cells and complex movements often involve homeostatic chemokines [3,127]. There is also a third class of bifunctional chemokines that are elevated in case of inflammatory conditions and are participated in normal immune defense. This group includes CXCL9, 10, 11,16, CCL1, CCL20, CCL25, etc [86,99].

Chemokines are critical mediators of inflammation, development and cell migration during routine immune surveillance [3], which can be secreted by activated T lymphocytes and regulate the accumulated and migration of monocytes/macrophages and lymphocytes to damaged CNS districts and promote the differentiation, therefore maintain the immune response process [126]. Chemokine receptors are γ subfamily rhodopsin GPCRs (G protein-coupled receptors). This family includes members such as angiotensin, somatostatin, fMLP, bradykinin and adrenomedullin receptors (ADMRs) [27]. A great majority of chemokines bind and activate multiple receptors and in turn, a great majority of chemokine receptors respond to more than one chemokines [113]. Chemokines bind to GPCRs(chemokine receptors more precisely) cause conformational changes that touch off intracellular signaling pathways involved in cell activation and movement [27], thus mediates various leukocyte responses, including chemotaxis and immune activation [123].

Different chemokine/chemokine receptors represent different immune responses types:

CCR1, CCR5, and CXCR3 are a feature of Th-1 immune response, and CCR3, CCR4, and CCR10 are the feature of Th-2 immune response

[1]. In addition, CCR4 and CCR6 are highly expressed in Th17 cells while CCR6 and CXCR3 are highly expressed in Th17.1 cells [1,67]. In humans and mice, chemokine receptors have different expression levels in memory T cells and effector cell subsets, providing specificity for cell trafficking in both homeostasis and inflammation. CCR6 directs Th17 cells into the CNS and CXCR7 inhibits T cell migration. CCR7 migrates naive T cells and central memory T cells to peripheral lymph nodes [66]. Small molecule-mediated upregulation of CCR7 can ameliorate EAE through this role at the initial stage of the disease, providing a promising strategy for the more effective disease therapies development of MS [66]. CNS white matter trauma in MS and acute EAE shows high levels of CCL2, 3, 4, 5, and CCL7, which are involved in the aggregation and activation of leukocytes expressing CCR2, CCR4, 5 and CCR6 receptors [123].

3. CC family and their receptors in MS

The CC class chemokine is the largest of the four chemokines [95], consisting of at least CCL1-28, 28 chemokine members which signal through CCR1-10. CC chemokines have chemotactic effects on monocytes and lymphocyte subsets, but also stimulate eosinophils, basophils and natural killer cells [86]. Chemokine receptors that bind to CC class chemokines are mainly expressed by monocyte-macrophages and T cells, the cell types are related to chronic inflammation such as multiple sclerosis that with persistent leukocyte infiltration into the site of inflammation [122].

3.1. CCL2/Ccr2

CCL2, also known as MCP-1, is a potent chemokine for the recruitment process of macrophages, monocytes, activated T cells and NK cells to the CNS [47]. MCP is an important member of the CC subfamily. To date, five MCPs are identified and classified: from MCP-1to MCP-5, which means CCL2, CCL8, CCL7, CCL13, and CCL12. Among MCPs, MCP-1was the first one to be discovered and is the most characteristic CC subclass chemokine in humans [15]. CCL2 can be produced by cells such as endothelial cells, astrocytes, macrophages and microglia [47]. One study showed that the efflux of CCL2 may be mediated by the astrocyte ABC transporters (MRP-1 and P-glycoprotein), thereby promoting the migration of immune cells across the brain endothelial cells, involved in the process of neuroinflammation [57].

CCR2 is crucial for the induction of acute EAE. It has been determined that all five MCPs play their roles through interaction with the CCR2 receptor [15]. Due to the highest affinity of CCL2 for CCR2, most studies have focused on it [128]. There are two alternative splicing types of CCR2 in humans, CCR2A and CCR2B, which are 360 and 374 amino acids, respectively [15]. CCR2 is expressed on T cell subsets, immature dendritic cells, and monocytes, mediating their migration to endogenous CC chemokines such as CCL2 [124]. The endogenous ligands for CCR2 in humans are CCL2, CCL7, CCL8, CCL11, CCL13, CCL16, CCL24, and CCL26. It is worth noting that the first six are agonists while the last two are antagonists [113]. The endogenous ligands in mice for CCR2 are CCL2, CCL7, CCL8, CCL11 and in rats are CCL2, CCL7, CCL11. (http://guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId = 59 (accessed 19 September 2019))

CCL2 levels in CNS are reduced during increased disease activity in MS [82]. According to the discovery of Franciotta D et al., CCL2 can be constitutively produced in the brain and CCL2 CSF levels in acute MS are lower than those in stable MS [34]. As demonstrated by Gd-enhanced lesions on MRI, RRMS patients with acute exacerbations had significantly lower CCL2 levels in CSF and serum than those without enhanced lesions [107]. However, in another study, the results were determined to have higher levels of CCL2 in CSF in patients with RRMS compared to controls. This difference between studies may be due to differences between populations, differentiation in CCL2 production at unequal stages of the disease, rarely using healthy controls or the different components of the control group in the study [83]. MS relapses have been shown to be induced by the depression of Th2 cytokines and predominance of Th1, while CCL2 can affect T cell differentiation and adjust the Th1/Th2 cytokine profiles. Thus, the decreased CCL2 levels in CSF might reflect an increase in Th1 activity during an acute episode [107]. CCL2 mRNA expression levels are dramatically increased in both the spinal cord and brain and CCL2 protein expression levels are significantly upregulated in the brain during the relapsing phase of MS. The CCL2 expression has a biologically relevant function in the relapsing EAE disease process due to the ability to improve relapsing clinical disease with anti- CCL2 treatment. The inhibition of relapsing EAE is relevant to a decreased influx of macrophages [51].

Data demonstrate that the level of CNS CCL2 protein production is low in preclinical B6129PF2/J or C57BL/6J mice, but as the disease rises (MOG induced) sharply through the initial clinical symptoms to the development of acute disease peaks [32]. Hulkower et al. not only demonstrated that CCL2 (MCP-1) mRNA was expressed with close temporal relation to symptom onset in the CNS of rats, but also noted that CCL2 mRNA could no longer be detected when the animals entered remission. It's a reasonable hypothesis that the encephalitogenic T cells secrete certain proinflammatory cytokines contains IFN-g and TNF-a, which is able to induce astrocytes to express CCL2(MCP-1) and RANTES etc. leads to the recruitment of additional mononuclear cells [51]. Upregulation of CCL2 in activated oligodendrocyte progenitors near the demyelinating region,it's possible that CCL2 differentiates into mature myelin to form oligodendrocytes by enhancing the activity of oligodendrocyte progenitor cells, thereby allowing remyelination [31]. CCL2 and CCL3 play a role in a region-specific manner in cuprizone-induced demyelination(in C57BL/6J mice) and astrocyte activation, with special effects on gray matter [47]. In addition, current MS therapies (6-methylprednisolone or IFN-β1a treatment) do not modify the circulating levels of CCL2 [34]. It is known that the proportion of $CCR2^{+}$ $Ly6C^{high}$ cells in the CNS is positively correlated with the EAE clinical score. The recruitment of the proinflammatory $CCR2^{+}Ly6C^{high}$ monocyte subpopulation involves chemokine CCL2 [49]. In addition, $CCR2^{-/-}$ mice did not illustrate CNS histopathology or clinical EAE(MOG induced in B6129PF2/J or C57BL/6J mice) and decreased obviously in T cell infiltrating when compared with control mice [32]. Recent evidence suggests that the highly phagocytic and inflammatory macrophages produced by blood-derived $CCR2^{rfp/+}$ monocytes elicit demyelination in EAE. According to Nielsen et.al., assessment of the demyelinating effect of $CCR2^{+}$ monocytes on cortical shows: $Th/^{+}$ $CCR2^{-/-}$ mice developed EAE later than $Th/^{+}$ $CCR2^{+/+}$ mice, but their severity is comparable. More importantly, both perivascular cortical and subpial demyelination(MOG induced in C57BL/6J mice) of $Th/^{+}$ $CCR2^{-/-}$ mice were significantly reduced compared with $Th/^{+}$ $CCR2^{+/+}$ mice [61]. The CCR2 + 190 G/A(rs1799864) polymorphism might elevate susceptibility to multiple sclerosis, but the effect appears to be limited to the individuals with no primary risk allele HLA-DRB1 * 15:01 [48].

3.2. CCL3/ Ccr1

MIP-1 includes MIP-1alpha (CCL3), MIP-1β(CCL4), MIP-1delta (CCL9/10) and MIP-1 gamma (CCL15), which are produced by various cells, especially macrophages, lymphocytes, and dendritic cells. MIP-1 proteins act through CCR1, CCR3-5 on B cells, T cells, DCs, and eosinophils, are best known for chemotaxis and pro-inflammatory effects, but also promote homeostasis [73,101].In detail, the functions of CCL3 and CCL4 are chemotaxis, phagocytic, synthesis of inflammatory mediators and degranulation in target cells during the acute phase of inflammation, and the activation and recycling of leukocytes [109]. CCL3 is an effective chemokine of lymphocytes and monocytes, one of the most unique features is its ability to coordinate the compartmentalization and mobilization of MPC (myeloid precursor cells). Preclinical studies further demonstrate that CCL3 is released after the

induction of the Th1 response [101].

CCR1 is expressed on a great amount leukocytes including dendritic cells, monocytes, NK cells, T cells, basophils, and eosinophils. CCR1 is considered a target for MS due to the observation of perivascular staining of CCL3 and CCR1 in immunohistochemical studies of biopsy of the deceased [2]. The chemokines CCL3, CCL5 and CCL7 and their receptor CCR1 are strongly expressed in the brain inflammatory foci of patients [30].

In a study by Mohammad Soleimani et al., they found an obvious increase in CSF levels of CCL3 in RMSS patients compared with the control group [109]. Eltayeb, S et al found that the use of a DNA vaccination protocol to generate an immunologically neutralizing antibody against CCL3 effectively inhibits disease induction in DA rat EAE(MOG induced). The deletion of the CCR1 gene results in partial disease protection in the MS mouse model. The above data provide a strong argument that CCR1-expressing macrophages activated through CCL3-mediated is critical for neuroinflammatory processes in EAE [30].

3.3. CCL5/Ccr5

CCL5 also has the name of RANTES, which is a marker for M1 macrophages. Infiltrating T cells are able to express and secrete chemokine CCL5 [38], but CCL5 is mainly expressed in perivascular cells, vascular endothelial cells and astrocytes [31]. CCL5 is possible to adjust glutamate release and plasticity in the MS brain with associated effects for the disease clinical manifestations [79] and was detected in active demyelinated MS lesions. CCL5 and its receptor CCR5 have strong monocyte chemotaxis [92]. CCR5 is mainly expressed on immature dendritic cells, T cells, and a small number of monocytes [2] and is expressed on most monocytes, macrophages and CD8 + T cells in inflammatory MS lesions [31]. There are two ways for CCR5 to be involved in the pathogenesis of MS. One is the increase in the number of CCR5-positive INF-γ-secreting T cells in the circulation of MS patients, and the other is that the monocytes having phagocytosis function greatly enriched CCR5 expression in CSF and peripheral blood [72].

In the research of E. Sindern et al., CCL5 was not detected in the CSF of RR-MS, but CCL5 release in serum was increased [107]. However, in the 2015 study by Mori F et al., including RRMS patients, CCL5 level was higher in CSF in patients than in the control group, and CCL5 increased during MS disease activity [79]. Other than that, one research by Sørensen et al. confirmed the presence of elevated CCL5 in cerebrospinal fluid in patients with acute MS and the fact that lymphocytes expressing CCR5 in the active MS lesions of autopsied brain tissue. The above pieces of evidence suggesting the role of CCL5 in the development of MS [107].

C57BL/6J mice infected with mouse hepatitis virus (MHV) in the brain can reproducibly result in acute encephalomyelitis and develop into chronic demyelinating disease. In the chronic disease stage, neuropathology is primarily immune-mediated, similar to human demyelinating disease MS (multiple sclerosis). Using this animal model, CCL5 is significantly expressed in the CNS during acute disease, and anti-CCL5 mAb-mediated neutralization results in delayed viral clearance with concomitant reduction of CCL5-induced migration of virus-specific T cells and activated macrophages, T cell and macrophage infiltration decreased and demyelination decreased. Experiments show that CCL5 contributes to macrophage entry and demyelination [38]. However, in another animal model, EAE model of MS, the immunological neutralization of CCL5 has no modulating effect. The use of DNA vaccination protocols to generate immunoneutralization antibodies against CCL5 also failed to inhibit disease induction in rat EAE(MOG induced in DA rats). CCR5 genomics deletion also did not protect EAE mice [30,96].

The impact of CCL5 genetic polymorphism (high producer allele) is relevant to the worse progression of MS disability, and low producer alleles are associated with a decreased risk of severe axonal loss [126]. The expression of CCL5 may be disrupted by gene mutations and downregulation of its receptor CCR5. For example, a genetic polymorphism, ie, a single nucleotide substitution (A to G) at 403 position of the CCL5 gene promoter results in lower expression of CCL5, or in the 303 position of its receptor CCR5 promoter sequence, X32 (32 base pair deletion) of CCR5 gene coding region is associated with a lower MS severity index [79]. Although a significant increase in CCR5 expression has been found in MS patients, it appears that besides the CCR5Δ32 mutation, other haplotypes or polymorphisms, as well as other possible epigenetic and genetic factors, are vital for CCR5 expression in multiple sclerosis patients [37]. In addition, based on a summary of one review, there appears to be no consensus on the association of CCR5Δ32 mutations with MS, and the differences in the reports may reflect the genetic background of the study population and their exposure to environmental factors [37].

3.4. Ccl18

CCL18 also called alternative macrophage activation associated CC chemokine, AMAC-1; or Pulmonary and Activation-Regulated Chemokine, PARC [104]. CCL18 is one specific marker of M2 macrophages and is the highest chemokines expression level in several human chronic inflammatory diseases and are synthesized by dendritic cells and monocytes during infection or inflammation [116]. It has the function of attracting T cells, inducing a CD4 + CD25 + FoxP3 + regulatory T cell phenotype, which may be an important factor in inhibiting the local pro-inflammatory immune response in the CNS [74].

CCL18 levels correlate with neurodegenerative and inflammatory brain MRI results: CCL18 levels were higher in progressive multiple sclerosis compared to healthy individuals and RR-MS, and various correlations with MRI measurements were discovered. Higher CCL18 levels were related to decreased DGM(deep grey matter), NCV(normalized cortical volume) and thalamic volume, and increased T2-LV (lesion volume) and LVV(lateral ventricular volume). These shreds of evidence support the function of CCL18 in the progression of MS, but no correlation between CCL18 levels and EDSS(expanded disability status scale) as well as disease duration was found [126]. However, another study suggests that CCL18 can inhibit CCR1, CCR2, CCR4 and CCR5-mediated chemotaxis [58].

CCL18 was identified as one of the top 3 up-regulated genes on the verge of chronic active MS lesions, where there is a large amount of foam and microglia/macrophages that accumulate myelin. This is consistent with previous research by Boven LA et al [41,112]. CCL18 recruits a subset of human regulatory T cells and inhibits the proliferation of effector T cells through the IL-10 production in vitro. CCL18 expressed by macrophages also ingests myelin, producing an immunosuppressive phenotype [41]. Incubation of microglia with dexamethasone resulted in a significant upregulation of CCL18 [74]. CCL18 is considered to be an anti-inflammatory factor [18].

3.5. CCL20/Ccr6

CCL20 is produced by many kinds of cells, including endothelial cells and macrophages that respond to stimuli such as IL-6, IFN-γ, TNF-α, IL-1β and so on [65]. CCL20 attracts lymphocytes but does not attract monocytes [1]. CCL20 is expressed in a site called the choroid plexus where T cells enter the CNS. CCR6, the receptor of CCL20, is selectively expressed by CD4 + T cells that produce the cytokine IL-17. Thus, the CCL20-CCR6 interaction is involved in the BBB disruption and follow-up migration of pathogenic T cells into the CNS [29]. Moreover, IL-17 secreted by circulating Th17 cells expands the pro-inflammatory response via NF-κB signaling to enhance CCL20 transcription [29].

In one study by El Sharkawi FZ et al., serum CCL20 levels in patients with SPMS and RRMS are obviously higher than healthy subjects. This trend is identical with the results of the 2017 research of CCL20 serum levels in RRMS patients and controls by Li R et al, as well as the results that higher CCL20 serum levels in patients with SPMS, RRMS and PPMS

in a 2014 study by Jafarzadeh A et al. [46,65]. The study also shows that serum levels of CCL20 were associated with a progression index and showed a higher than remission period during relapse, while treatment type did not influence chemokine levels. This is also consistent with previous research results. However, serum CCL20 levels were higher during remission than in relapse significantly according to Kalinowska-Lyszczarz et al. [29]. One study showed a negative correlation between SIRT1 activity levels and serum CCL20 levels in patients. It is speculated that SIRT1 may down-regulate the transcriptional activity of NF-κB by deacetylating p65 in the promoter region of the CCL20 gene, thereby decreasing the expression of CCL20. This speculation requires further research to prove [65]. Serum CCL20 levels are not affected by disease patterns, gender and treatment options [46]. The researchers found that anti-CCL20 levels were inversely associated with clinical severity of EAE, and MS patients had lower antibodies levels which against CCL20 than healthy controls. Moreover, high levels of anti-CCL20 antibodies in human serum have biological activities that inhibit the TH17 CCR6 positive T cells migration. Based on experimental results, Abraham M et al. hypothesized that natural vaccination against CCL20, which can protect humans from autoimmunity MS development. It is further supposed that exposure to pathogens early in life might result in the production of CCL20 by autoantibodies and trigger a protective effect against MS development [1]. In the research of Jafarzadeh A et al., the CCL20 and CCR6 expression levels in the spinal cord of EAE mice (MOG induced in C57BL/6J mice) administered with PBS were evidently elevated compared to the control group [43,44].

The results of the study of the concomitant effects of single nucleotide polymorphism (SNP) (-786 T > C(rs6749704))on MS susceptibility showed that the CT genotype frequency of rs6749704 in CCL20 gene and the C allele frequency of multiple sclerosis patients were obviously higher than the control group. The accompanying polymorphism of the gene in MS patients in Egypt shows an increased risk of MS rather than an individual locus [29]. Another study from Iran showed that the rs6749704 polymorphism is associated with the SPMS model [45].

3.6. CCL22/Ccr4

CCL22 is a chemokine for the accumulation and movement of CCR4-expressing cells (contains Th2/Treg cells) into the site of inflammation [44] and can be produced by microglia and astrocytes [81]. Macrophage-derived chemokines (CCL22) are produced by monocyte-derived dendritic cells and macrophages upon stimulation with anti-CD40 antibodies or microbial products and are downregulated by Th1 type cytokines, but upregulated by Th2 type cytokines [46].

CCR4 has been identified as one of the risk genes for MS and found on Treg, Th2 and Th17 cells. In particular, CCR4 is a marker for Th2 cells [2]. Since Th2 cells produce anti-inflammatory cytokines, CCL22 participated in the accumulation of a subset of cells with anti-inflammatory functions in the brain. Regulatory T cells suggest that CCL22 may involve in counteracting pro-inflammatory Th1 responses and ultimately lead to a reduced degree of myelin damage [36].

Decreased serum CCL22 levels have been reported in multiple sclerosis patients [46]. In a 2008 research, CCL22 levels of CSF in women were higher than in men. CCL22 may only have an effect on the MS development in women, affecting the brain recruitment of Th2 cells, which can produce anti-inflammatory cytokines [35]. In a 2014 study, women MS patients showed lower serum CCL22 levels, representing that a decrease in chemokine levels might have a great impact on the MS pathogenesis of women [46]. Compared with OND patients (non-inflammatory neurological diseases), the CSF level of CCL22 was evidently increased in MS patients at baseline [75]. The trend of the decrease in the A allele of CCL22 C/A SNP was put forward in MS patients compared with the control group [36]. CCL22 may primarily attract Treg cells, shutting down the adaptive immune response effectively [20]. The expression levels of CCR4 and CCL22 in the spinal cord of EAE mice(MOG induced in C57BL/6J mice) were significantly increased [43,44]. CCL22 expression is related to increased severity of EAE, and anti-CCL22 treatment may improve EAE development, possibly by regulating inflammatory macrophage accumulation [28].

4. CXC family and their receptors in MS

In the CXCL subfamily, chemokines can be divided into ELR + ve (ELR positive) group and ELR-ve (ELR negative) group. The former has a characteristic three-sequence ELR (Glu-Leu-Arg), but the latter does not have. ELR + ve chemokines (eg., CXCL1-3, CXCL7-8) combine with CXCR2 and typically attract neutrophil and activate neutrophil degranulation, which causing a release of myeloperoxidase and some other enzymes [86,120]. ELR negative CXC chemokines (including CXCL4, 10 and CXCL12-13) combine with CXCR3-5, control the chemotaxis of lymphocytes together with XCL chemokines [120].

4.1. CXCL1/ CXCL5/ Cxcr2

Rumble JM et al. demonstrated for the first time that the peak level of plasma CXCL5, the ELR $^{+}$ CXC chemokine, is consistent with the development of new inflammatory lesions in relapsing MS patients. It was also demonstrated that the expression of CXCL1 and CXCL5 is associated with radiological and clinical measurements of CNS lesions in MS [98].

The expression of inflammation-inducible receptor CXCR2 in the endothelium was increased in MS plaques, and Haarmann A et al. demonstrated that CXCL5 and CXCL8 interfere with endothelial cell membrane barrier morphology and function via CXCR2. Inhibition of CXCR2 in brain endothelial cells prevents the decomposition of BBB in EAE but does not directly affect vascular permeability [40]. The oligodendrocyte lineage cells and neutrophils in the CNS express CXCR2, and CXCR2-positive neutrophils promote inflammatory demyelination, which is the first chemokine receptor to show contributes to the control of remyelination and the inflammatory process that cause demyelination [69].

4.2. CXCL12/Cxcr4

CXCL12 is an effective chemoattractant for immune cells, interacts with the CXCR4 receptor, and also binds to atypical chemokine receptor 3. Migration of B cells, CD4 and CD8 cells can be blocked by using CXCR4 neutralizing antibodies in vitro. CXCL12 is elevated in both inactive and active MS lesions, as well as in astrocytes of MS patients. Some reports found that MS patients had higher CSF levels of CXCL12 than healthy subjects.

CXCR4 is the only chemokine receptor that has been proved to be vital to life, which is constitutively expressed in various tissues [56]. CXCR4 has been found in many kinds of cells such as microglia, astrocytes, neurons, naive T cells, effector T cells and vascular endothelial cells in the human brain [7,56].

CXCL12 $_{(P2G2)}$ is a CXCL12 mutant that has been shown to be an antagonist of CXCL12, which is identical to human CXCL12$_{(1-67)}$ except that the proline is replaced by glycine 7 in position two [56]. The data of Kohler RE et al. showed that CXCL12 $_{(P2G2)}$ can effectively inhibit the migration of activated mouse T cells by CXCL12. Interference with the action of CXCR4 and a synthetic receptor antagonist inhibits EAE(PLP induced in SJL/J mice) and reduces the accumulation of encephalitogenic CD4(+) T cells in the CNS, thus inhibiting the sensitization phase of EAE. CXCL11 is involved in the localization T cells in the CNS, CXCL11 inhibits the effector phase of the immune response, thus targeting CXCR4 and CXCR3 might be beneficial for the CNS autoimmune diseases treatment [56].

4.3. CXCL13/Cxcr5

CXCL13 is a B cell chemokine, also known as B lymphocyte chemoattractant (BLC) or B cell attracting chemokine(BCA-1). Infiltrating macrophages/DC myeloid cells and microglia may be one of the sources of CXCL13 in the central nervous system during inflammation. In addition, CXCL13-expressing cells were found only in the brainstem meninges with strong infiltrating leukocyte proliferation [70]. F. Sellebjerg et al. found that the CSF concentration of CXCL13 correlated with the CSF leukocyte count significantly in patients with RRMS, PPMS,

CIS, and SPMS and even stronger with the CSF B-cell count in patients with CIS and RRMS [105]. In addition to B cells, there is a direct correlation in the cerebrospinal fluid of MS patients between CXCL13 levels and the number of plasmablasts and T cells [59]. Khademi M et al. determined the concentration of CXCL13 in CSF in healthy control populations and patients with MS and other neurological diseases (bacterial and viral infections), and the results showed a lesser extent rise by MS patients. Taken together, we believe that early detection of CXCL13 predicts disease prognosis [53]. CXCR5 is expressed in most B cells in the CSF compartment and all B cells in the blood, and in 20% to 30% of CD4 + T cells in both CSF and blood [89]. The deficiency of CXCL13 attenuated the glial hyperplasia and inflammation of white matter in the acute and chronic phases of EAE, indicating an improvement in the condition [9]. The results reflect that CXCL13 may bind CXCR3. Thus, CXCL13 may be involved in recruiting mononuclear cells expressing CXCR5 or CXCR3 to the intrathecal compartment in MS [105]. CXCL13 levels are reduced by natalizumab treatment in MS [53,82]. According to Quinn JL et al., the antibody against CXCL13 could block Tfh transport and significantly reduce disease expression in Th17 EAE (EAE that induced by the myelin-specific Th17 cells transfer in C57BL / 6 J mice) [91].

5. CX3C family and their receptors in MS

CX3C family has only one member, CX3CL1, an atypical chemokine in membrane-bound type and soluble form, which is able to act as an effective adhesion molecule and chemoattractant through a non-integrin-dependent mechanism [5].

5.1. CX3CL1/Cx3cr1

CX3CL1, also known as fractalkine, has 373 amino acids. CX3CL1 is the only neuronal chemokine in the body with pro-inflammatory, anti-inflammatory and neuroprotective effects [6]. In the brain, CX3CL1 is expressed in neuronal cells, and when stimulated with TNF-α and IFN-γ, microglia and astrocytes also produce CX3CL1. It can also be expressed by activated endothelial cells(ECs), which are located on the surface of the cavity, indicating that it arrests circulating cells in the EC membrane [14]. CX3CL1 promotes glial activation, ICAM-1 expression, pro-inflammatory cytokine secretion, and recruitment of CD4 + T cells into the CNS during neuroinflammatory processes [114]. CX3CL1 exists in two forms: shed glycoprotein and membrane anchoring. The former soluble form has chemotactic activity against monocytes, T cells and NK cells [78].

CX3CL1 only combines with CX3CR1, which is a GPCR (G-protein coupled receptor) that expressed by microglia, astrocytes, dendritic cells (DCs), NK cells, monocytes, B cells, and T cell subsets [14].

CX3CL1 levels are elevated in CSF from CIS patients, cerebrospinal fluid and serum samples from RRMS patients. In the early inflammatory response of multiple sclerosis, CX3CL1 induced accumulation of CX3CR1(+) ICAM-1(+)CD4(+) T cells in the CNS [14]. The results of Broux B et al. showed that CD4(+)CD28(-)T cells migrated to the inflammation sites that responsd to the chemotactic gradient of CX3CL1, which contributes to the inflammatory process in MS patients [17].

Choroid plexus, the barrier between the cerebrospinal fluid and blood in the brain, is the main entry site for immune cells to enter the central nervous system. CX3CL1 was induced on the choroid plexus during EAE. And the results showed that blocking CX3CL1 prevented the development of EAE and inhibited lymphocytes across into the CNS [77]. Blocking CX3CL1 can protect mice from EAE invasion. The data by Wenjun Zhu et al. showed that CX3CL1 signaling in dorsal horn SC neurons can activate the up-regulation pathway involved in nociceptive transmission during the early inflammatory phase of pre-myelinating MS [125]. MOG-induced EAE(in DA rats) is associated with cells that express CX3CR1 mRNA are clearly accumulated in inflammatory brain injury. The vast majority of these cells are microglia-macrophage lineage cells, and the accumulation of cells other than microglia indicates that CX3CL1 may participate in controlling the invasion of peripheral leukocytes into the brain [115].

NK cells were obviously reduced in the inflamed CNS of CX3CR1-deficient EAE mice(MOG or PLP induced in C57BL/6J mice), while monocytes/macrophages, T cells, and NKT cells are recruited to the CNS during EAE do not require CX3CR1, CX3CL1-mediated chemical attraction of NK cells is relatively specific for the CNS [42].

Arli B et al. believe that VI of the V249I CX3CL1 receptor haplotype may have a protective effect on conversion to SPMS, but V249I CX3CL1 receptor haplotype genotype II patients have a higher risk of disability [6].

6. Chemokine receptors as therapeutic targets

Studies of chemokine receptor antagonists offer potential lead compounds for the treatment of MS as well as a deep understanding of the pathogenesis of EAE. Their anti-inflammatory effects may be due to inhibition of chemotaxis, thereby preventing leukocytes from flowing into the affected tissues [11]. There are the following methods to modulate chemokine receptors: peptide antagonists, neutralizing antibodies and small non-peptidyl antagonists [72]. Immunoneutralization of specific chemokines (such as CCL3) does not provide information as to which receptors are important because they commonly interact with diverse chemokine receptors. In the case of CCL3, both CCR5 and CCR1 can combine with it. Both from the perspective of therapeutic and mechanistic, it is meaningful to administer a selective low molecular drug to inhibit the effective effect of chemokine receptors on acute EAE and MS in the induction phase of an autoimmune response [30]. Take the redundancy of chemokines expression in pathology in the account, it is preferred to select a compound that blocks multiple inflammatory chemokine receptors simultaneously.

6.1. CCR1 antagonists

CCR1 is one chemokine receptor that mediates monocytes trafficking to the site of inflammation when stimulated, particularly by CCL3 and CCL5 [76]. CCR1 is important for controlling the earliest pro-inflammatory events in the border zones of inflammatory brain injury in active MS and advanced EAE [30]. Interfering with CCL3-mediated CCR1 activation in vivo with a specific antibody or by genomic deletion of CCR1 gene results in a significant reduction in paralytic disease [30].

The first selective CCR1 antagonist, BX-471, was entered into clinical trials by Berlex Biosciences. There are no considerable effects of an orally administered CCR1 antagonist (BX-471) on ICAM-3 expression in RRMS patients [93]. It failed in the phase II trial because of the efficacy lack. But it lays the foundation for the clinical development of other chemokine receptor antagonists [103]. High-throughput screening of Merritt JR et al's combinatorial series identified a new, moderately effective CCR1 antagonist 3. Library Hit 3 was optimized in order to synthesis advanced lead compound, therefore compound 4 was obtained. The IC50 of Compound 4 that inhibits CCR1-mediated monocyte chemotaxis was 20 nM [76]. The results of the study showed that although the antagonist did not stop the peripheral anti-MOG response(in DA rats), it prevented T cell infiltration effectively, macrophage infiltration and activation, thereby preventing subsequent CNS

inflammation in the model. A single CCR1 selective antagonist, 5-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-2,2-diphenylpentanenitrile, can suppress MOG-induced EAE, indicating that CCR1 plays a non-redundant role at this stage [30].

6.2. CCR2 antagonists

Many therapies currently target leukocyte trafficking and inflammation in the CNS. Some CCR2 targeted drugs have entered MS in the past, which generally shown a favorable safety profile in clinical trials but failed in efficacy and are not involved in clinical research currently [31].

BMS22 is a classic competitive antagonist CCR2 [8]. A great quantity of multi-QSAR modeling techniques (eg, pharmacodynamic mapping, 3D-QSAR CoMFA, etc.) were performed on a data set consisting of eighty-three CCR2 antagonists to design higher active molecules. Sk. Abdul Amin et al. designed seven new molecules that are expected to be more active than the best active antagonists in this series (cpd 34) [4].Extracellular loop 1 in verso (ECL1i), a native 7-d-amino acid peptide CCR2 inhibitor that selectively and potently inhibits CCL2 triggering chemotaxis and it has allosteric antagonism against human and mouse CCR2 [8].MLN-1202, a kind of humanized anti-CCR2 antibody did not show efficacy in patients with multiple sclerosis, although the administration of MLN-1202 reduced the circulating monocytes numbers in peripheral blood [119]. INCB3344 is a small molecule antagonist and the therapeutic dose significantly reduces the clinical symptoms of the disease in EAE mice(MOG induced in C57BL/6 mice) (disease incidence and severity) [16]. Buntinx M et al. identified JNJ-27141491 as a non-competitive, potent hCCR2 antagonist that exerts anti-inflammatory activity in mice expressing transgenic hCCR2. JNJ-27141491 (20 mg/kg q.d.) treatment delayed the onset and reduced signs of the nervous system in EAE temporarily but significantly. However, there are no pieces of evidence that the disease can be improved over the long term. Therefore the authors say that the use of JNJ-27141491 may not be successful in MS patients [19].

Merck Corporation has disclosed a number of CCR2 antagonists, containing compound MK-0812. The IC 50 of MK-0812 is 5.0 nM, indicating a potent CCR2 antagonistic activity, and has undergone clinical trials for MS. The primary endpoint of the trails was a new GD-enhanced lesion by MRI. MK-0812 entered phase II clinical trials of MS but did not improve significantly compared to placebo [31,88] Incyte also exploited a variety of CCR2 antagonists, of which INCB3284 is one of the compounds in phase II clinical research of MS, but there are no subsequent reports of the trial results [88]. Lagumersindez-Denis, N et al. hypothesized that targeting CCR2 may be an effective treatment strategy against cortical demyelination. They developed a kind of novel mouse anti-human CCR2 monoclonal antibody aiming to deplete $CCR2^{+}$ monocytes. Compared to isotype-treated controls, monocyte-depleted animals revealed less perivascular type 2 cortical demyelination and less subpial type 3 cortical demyelination significantly, which is in line with the ameliorated clinical disease course [61].

6.3. CCR4 & CCR6 antagonists

CCR4 is mainly expressed on Th2 / Treg lymphocytes [44].CCR4 antagonists are classified into two categories of aryl sulphonamides lipophilic and heteroarenes [108]. Small molecule antagonists, like endogenous ligands, have also shown different ability to induce receptor internalization, which may be relevant to different biological effects. Some CCR4 antagonists combine with the allosteric site of CCR4, not the binding site of CCR4 to the ligand [102]. It may be for this reason that CCR4 antagonist compound 22 inhibits the Th1 and Th17 cell polarization as well as ameliorate EAE, but the CCR4 antagonist AF399 / 420/18025 had no significant impact on the clinical score of EAE [80,84]. It is not optimistic that most of the CCR4 antagonists tested have not been approved for MS treatment. For example, in Phase I clinical trials, there was only one kind of CCR4 antagonists, GSK 2239633, as a possible treatment for asthma but still had no further development due to low bioavailability. This condition might be caused by complex pharmacology that has not been resolved, such as the CCR4 regulation on surface expression and transport aspects [102]. CCR4-deficient mice(MOG induced in C57BL/6 mice) have been reported to exhibit low-grade EAE symptoms [33].

CCR6 is expressed on Th17 cells, immature dendritic cells, and Langerhans cells. CCR6 is a unique chemokine receptor because it combines with chemokine CCL20 exclusively [44]. CCR6 deficient mice have high resistance to EAE(MOG induced in C57BL/6 mice) that induced by MOG immunization [43]. In addition, double knockout $CCR4^{-/-}$ and $CCR6^{-/-}$ mice showed a low degree of EAE severity(MOG induced in C57BL/6 mice). The number of CNS infiltrating cells in knockout mice was obviously decreased compared with wild type mice [81]. Th17 cells highly express CCR6. In addition, dendritic cells, B cells, and other T cells subpopulations also express CCR6 [1].

6.4. CCR5 antagonists

CCL3, CCL4, and CCL5 are major chemokines that induce immune cells recruited to the CNS by interacting with their corresponding receptors CCR5 [37]. Initial studies have shown that gene targeting to disrupt CCR5 does not affect the severity of EAE [1].

Maraviroc (Celsentri^{TM}) is the first CCR5 antagonist that approved for the treatment of HIV-1 infection by EMA (European Medicines Agency) [24]. Together with the approved use of AMD3100 (CXCR4 antagonist) and a large number of clinical trials of small molecules and biologics currently underway, reflecting the belief that chemokine systems serve as therapeutic targets for treatment [103]. During the development of EAE disease following influenza infection, CCL5 / CCR5 may mediate the type I T cells infiltration into the CNS. Administration of the CCR5 antagonist, TAK-779, significantly ameliorated the exacerbated EAE [24].

6.5. CX3CR1 antagonists

Ridderstad Wollberg A et al. demonstrated the expression of CX3CR1 mRNA on inflammatory cells in the active plaque region of MS brain autopsies. AZD8797, a CX3CR1 inhibitor, is effective outside the CNS. In order to verify the function of CX3CR1 in the pathogenesis of MS, AZD8797 was treated in Dark Agouti rats with MOG-induced EAE. Then it led to reduced CNS pathology, paralysis and recurrence and is effective after the acute phase [94]. Karlström S et al. exploited two parallel series, series A and series B of CX3CR1 antagonists for the MS treatment. By modifying the 7-Amino-5-thio-thiazolo[4,5-d]pyrimidines, they developed the first selective and potent oral antagonist of CX3CR1, 18a [50]. Blocking CX3CR1 on the leukocytes that outside the CNS could be another alternative approach to treat multiple sclerosis [94].

7. Conclusions

The onset of MS is closely related to immune dysfunction, which is demonstrated by inflammation, oligodendrocyte death, loss of myelin and various degrees of axonal damage. The formation of MS plaques begins with antigen-presenting cells activating myelin-reactive T lymphocytes, resulting in multifocal immune cells infiltrating into the CNS (see Fig. 1) [126]. In inflammatory infiltrating cells with active demyelinating lesions, 10% are CD8 + and CD4 + T cells and 90% are macrophages from resident microglia and infiltrating monocytes [23]. Activated immune cells activate the proinflammatory cytokine cascade in the CNS, ultimately leading to demyelination, glial scars, and axonal lesions. Regulating the immune response and cell infiltration in the CNS is a therapeutic strategy that will improve treatment efficacy [123]. The role of chemokines and their receptors in autoimmunity and

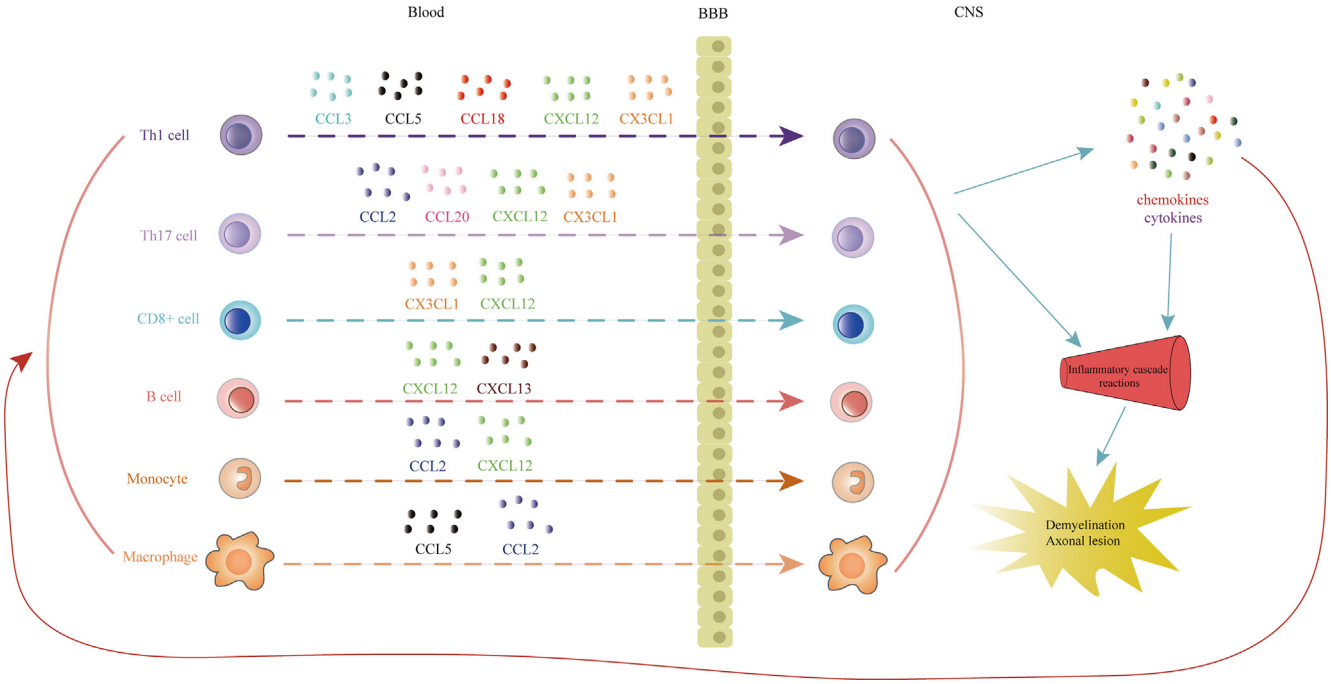

Fig. 1. Chemokines attract different immune cells infiltrating into the CNS during MS disease.

inflammation is recognized, and they also have important impacts on normal homeostasis, including lymphoid tissue development and cell transport. The chemokine system is rich in ligands and receptors, and studies have shown that a lot of chemokines and their receptors can be effective therapeutic targets for MS disease. By specifically interfering with chemokine and chemokine receptor function, it can prevent the infiltration of inflammatory cells, control the cascade of inflammation, and may also prevent demyelinating damage and promote remyelination, bringing a new treatment to MS. hope. However, the development of a single chemokine receptor antagonist has not achieved imaginary success, overcoming the redundancy of chemokine action, the development of multi-target antagonists or the combination of multiple antagonists may be the future The direction of MS drug development.

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