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*Review*

# Chemokines and central nervous system disorders

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**Chemokines and their receptors are large families of inflammatory molecules responsible for a number of biologic functions including the accumulation of leukocytes at tissue sites. Over the past 8 years, a number of studies have indicated a role for chemokines in the pathogenesis of CNS inflammatory diseases. This minireview provides a brief summary of our current knowledge of chemokines and CNS inflammatory diseases including experimental autoimmune encephalomyelitis, multiple sclerosis, virus-induced demyelinating diseases, Alzheimer's disease, and central nervous system bacterial-induced diseases.** *Journal of NeuroVirology* (2001) **7,** 493–500.

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## Chemokines and chemokine receptors

Chemokines are small molecular weight chemotactic cytokines that can be classified into four subfamilies based on the position of the amino-terminal cysteines as shown in Figure 1. The known CXC, CC, C, and $CX_3C$ chemokines and the new systematic nomenclature are shown in Table 1 (Murphy *et al*, 2000; Zlotnik and Yoshie, 2000). The CxC chemokines can be further categorized based on the presence or absence of a glutamate-leucine-arginine (ELR) motif in the amino terminus. Those chemokines that possess the ELR motif are chemotactic for neutrophils and are angiogenic, whereas the non-ELR CxC chemokines are chemotactic for activated T cells and are angiostatic (Strieter *et al*, 1995). The CC family of chemokines are chemoattractant for a wide variety of cells types including monocytes/macrophages, T lymphocytes, basophils, eosinophils, and dendritic cells (Davatelis *et al*, 1988; Schall, 1991; Taub *et al*, 1993). The C family, lymphotactin, is chemotactic for T cells and NK cells (Hedrick *et al*, 1997) and the $Cx_3C$ chemokine contains a chemokine domain attached to a membrane-bound mucin chain that produces a soluble chemoattractant after proteolysis or mRNA processing (Bazan *et al*, 1997). This chemokine is a chemoattractant for T cells, NK cells, and neutrophils (Murphy *et al*, 2000).

Chemokines induce a variety of downstream cellular signals through specific seven-transmembrane spanning, G protein-coupled receptors (Ward and Westwick, 1998). The most characterized biologic response is cellular chemotaxis, although other cellular outcomes such as cytokine expression, cellular differentiation, and cellular survival have been described (Ward and Westwick, 1998). As shown in Table 2, chemokine receptors can also be subdivided into four families based on the chemokine family members that are specific ligands for those particular receptors. The working hypothesis in the field of neuroimmunology has been that chemokines induce leukocyte accumulation in the central nervous system (CNS) through interaction with specific receptors on the cell surface of T cells, monocytes, and neutrophils. The induction of chemokine expression in the CNS is a complex set of events that include stimuli from infiltrating inflammatory cells as well as endogenous expression. The exact tissue-specific chemokine regulatory events are not well understood.

## Experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is a $CD4^+$ T cell-mediated, CNS demyelinating disease that serves as a model for multiple sclerosis (MS). Several reports have demonstrated an association between chemokine mRNA or protein expression and appearance of clinical disease. Hulkower

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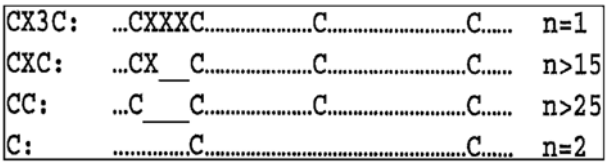


**Figure 1** Alignment of chemokine sequences between family members.

*et al* (1993) were the first to demonstrate the correlation between chemokine expression and EAE in the Lewis rat model. Ransohoff *et al* (1993) described expression of chemokine mRNA in the CNS of SJL/J mice with relapsing EAE. Using semi-quantitative RT-PCR and *in situ* hybridization they demonstrated that CXCL10 and CCL2 were expressed in the spinal cord. Additional studies of relapsing EAE demonstrated up-regulation of mRNA chemokine expression for CCL5, CCL4, CCL3, CCL1, CXCL10, CCL2, CXCL1, and CCL7 just prior to the first appearance of clinical symptoms in a mouse model of EAE and that the chemokine levels remained elevated throughout the course of the disease (Godiska *et al*, 1995). In addition to these chemokines, CCL6 expression has also been associated with EAE (Asensio *et al*, 1999).

CNS chemokine mRNA correlates with histological signs of inflammation as expression is not detected in the absence of leukocyte infiltration (Glabinski *et al*, 1995, 1998). Colocalization experiments have shown that CCL3 and CCL5 were expressed by

**Table 1** Chemokine family members and systematic nomenclature

| *CXC chemokines*[a] | | *CC chemokines* | | *C chemokines* | | *CX3C chemokines* | |
|---|---|---|---|---|---|---|---|
| CXCL1[b] | Gro$\alpha$; KC; MIP-2 | CCL1 | I-309; TCA-3 | XCL1 | Lymphotactin-$\alpha$; SCM-1$\alpha$ | CX3CL1 | Fractalkine; neurotactin |
| CXCL2 | Gro$\beta$; MIP-2$\beta$ | CCL2 | MCP-1; JE | XCL2 | Lymphotactin-$\beta$; SCM-1$\beta$ | | |
| CXCL3 | Gro$\gamma$ | CCL3 | MIP-1$\alpha$; LD78 | | | | |
| CXCL4 | PF-4 | CCL4 | MIP-1$\beta$ | | | | |
| CXCL5 | ENA-78 | CCL5 | RANTES | | | | |
| CXCL6 | GCP-2 | CCL6 | C10; MRP-1 | | | | |
| CXCL7 | PBP; CTAP-III; $\beta$-TG; NAP-2 | CCL7 | MCP-3 | | | | |
| CXCL8 | NAP-1; GCP-1; IL-8 | CCL8 | MCP-2 | | | | |
| CXCL9 | Mig | CCL9 | MRP-2; MIP-1$\gamma$ | | | | |
| CXCL10 | IP-10; CRG-2 | CCL10 | | | | | |
| CXCL11 | I-TAC; $\beta$-R1; IP9; H174 | CCL11 | Eotaxin | | | | |
| CXCL12 | SDF-1$\alpha$; SDF-1$\beta$; PBSF | CCL12 | MCP-5 | | | | |
| CXCL13 | BCA-1; BLC | CCL13 | MCP-4 | | | | |
| CXCL14 | BRAK; bolekine; BMAC | CCL14 | CC-1; Hcc-1; NCC-2; CCCK-1; CK$\beta$1 | | | | |
| CXCL15 | lungkine | CCL15 | HCC-2; leukotactin; MIP-5; CC-2; NCC-3; MIP-1$\delta$ | | | | |
| CXCL16 | | CCL16 | HCC-4; LEC; NCC-4; LMC; monotactin-1; LCC-1; ILINCK | | | | |
| | | CCL17 | TARC | | | | |
| | | CCL18 | DC-CK-1; PARC; MIP-4; AMAC-1; CK-$\beta$7 | | | | |
| | | CCL19 | MIP-3$\beta$; ELC; exodus-3; CK$\beta$11 | | | | |
| | | CCL20 | MIP-3$\alpha$; LARC; exodus-1; ST38 | | | | |
| | | CCL21 | 6Ckine; SLC; exodus-2; TCS4; ck$\beta$9 | | | | |
| | | CCL22 | MDC; cd/$\beta$ck; abcd-1 | | | | |
| | | CCL23 | MPIF-1; MIP-3; ck$\beta$8-1 | | | | |
| | | CCL24 | MPIF-2; eotaxin-2; ck$\beta$6 | | | | |
| | | CCL25 | TECK; ck$\beta$15 | | | | |
| | | CCL26 | Eotaxin-3; MIP-4$\alpha$ | | | | |
| | | CCL27 | Eskine; CTACK; ILC; ALP; skinkine | | | | |
| | | CCL28 | | | | | |

[a]For the CXC, CC, C, and CX3C chemokines the systematic name is listed in the first column and some common synonyms are listed in the second column.
[b]ELR-containing chemokines include CXCL1, CXLC2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8.

**Table 2** Chemokine receptors

| *Protein* | *Cellular distribution*[a] | *Ligands* |
|---|---|---|
| CXCR1 | N, M, T, NK, Bs, Ms, En | CXCL8; CXCL6 |
| CXCR2 | N, M, T, NK, As, Nn, Ms, En | CXCL1; CXCL2; CXCL3; CXCL7; CXCL5; CXCL6 |
| CXCR3 | T, As | CXCL10; CXCL9; CXCL11 |
| CXCR4 | My, T, B, Ep, En, DC, Nn | CXCL12 |
| CXCR5 | B, T | CXCL13 |
| CXCR6 | T | CXCL16 |
| CCR1 | N, M, T, NK, B, Ms, As, Nn | CCL5; CCL3; CCL14; CCL8; CCL7; CCL15 |
| CCR2 | M, T, B, Bs | CCL2; CCL8; CCL7; CCL13; CCL12 |
| CCR3 | Eo, Bs, T | CCL11; CCL24; CCL26; CCL5; CCL8; CCL7; CCL13; CCL15 |
| CCR4 | T | CCL17; CCL22 |
| CCR5 | T, M, DC | CCL5; CCL3; CCL4; CCL8 |
| CCR6 | T, B, DC | CCL20 |
| CCR7 | T, B, DC | CCL19; CCL21 |
| CCR8 | M, Thymus | CCL1 |
| CCR9 | T, Thymus | CCL25 |
| CCR10 | T | CCL27 |
| CCR11 | Heart, small intestine, lung | CCL2; CCL8; CCL13; CCL19; CCL21; CCL25 |
| XCR1 | T, B, NK | XCL1; XCL2 |
| CX3CR1 | N, NK, M, T | CX3CL1 |

[a]Abbreviations: As, astrocytes; B, B cells; Bs, basophils; DC, dendritic cells; En, endothelial cells; Eo, eosinophils; Ep, epithelial cells; M, monocytes/macrophages; Ms, mast cells; My, myeloid cells; NK, natural killer cells; Nn, neurons; T, T cells.

infiltrating leukocytes, whereas CXCL10 and CCL2 were expressed only by astrocytes (Glabinski *et al*, 1997). In addition to the association between CNS mRNA levels and tissue-specific inflammation, CNS chemokine protein levels have been associated with differential phases of relapsing disease. CCL3 and CXCL10 protein levels have been shown to be elevated in the CNS following adoptive transfer of activated neuroantigen specific T cells (Karpus *et al*, 1995; Fife *et al*, 2001) and correlate with acute disease development, whereas CCL2 levels increase with the development of the relapsing phase of disease (Kennedy *et al*, 1998). It should be emphasized that the emerging data suggests different chemokine expression patterns in different EAE models and also in different mouse strains (Karpus and Ransohoff, 1998).

The biological importance of CNS chemokine expression in EAE as been demonstrated by two approaches: *in vivo* anti-chemokine antibody treatments or chemokine knockout mice. Anti-CCL3 (Karpus *et al*, 1995) and anti-CXCL10 (Fife *et al*, 2001) treatment prevented acute clinical EAE whereas anti-CCL2 treatment was shown to prevent relapsing disease (Kennedy *et al*, 1998). In addition to the role for CCL2 in relapsing EAE, through the use of knockout mice, this chemokine has also been shown to be important for CNS monocyte accumulation during acute clinical disease (Huang *et al*, 2001). A significant finding from the *in vivo* neutralization studies is that while a wide variety of chemokines may be expressed during inflammatory autoimmune disease, only a subset of chemokines actually plays a significant biological role in disease pathogenesis.

Using a variety of EAE models, chemokine receptor mRNA analysis has been performed to demonstrate expression in the CNS (Jiang *et al*, 1998; Charles *et al*, 1999; Matejuk *et al*, 2000; Rajan *et al*, 2000) with the general conclusion that as inflammation ensues, there is an accumulation of inflammatory cells bearing chemokine receptors. Correspondingly, a reduction in CNS inflammation results is less chemokine receptor mRNA expression. A number of recent studies using genetically deficient mice have shown that CCR1 (Rottman *et al*, 2000) and CCR2 (Fife *et al*, 2000) expression are biologically important for the development of acute EAE. In the CCR1 knockout mice, there was approximately a 50% decrease in clinical disease severity; however, the mechanism behind disease attenuation is not known. Because both T cells and monocytes have been shown to express CCR1 (Gao *et al*, 1997), it is possible that CCR1 expression by either lymphocytes or monocytes or perhaps both is required for EAE development. In the CCR2 knockout mice, there was almost a total absence of disease due to a failure of monocytes to traffic to the CNS (Fife *et al*, 2000). These two examples are in contrast to EAE induction in CCR5 knockout mice where the same level of disease severity was seen compared to wild-type control animals (Tran *et al*, 2000). An advance that has come from both the chemokine and chemokine receptor studies in EAE is development of small molecular weight antagonists to chemokine receptors. Indeed, a small molecular

weight antagonist of CCR1 has shown efficacy in the inhibition of clinical EAE (Hesselgesser *et al*, 1998; Liang *et al*, 2000).

## Virus-induced demyelinating disease models

A number of virus-induced CNS demyelinating disease models for MS exist and two of these, murine hepatitis virus (MHV) and Theiler's murine encephalomyelitis virus (TMEV), are well studied with respect to pathogenetic mechanisms of disease induction and progression. CXCL10, CXCL9, CCL5, CCL2, CCL7, CCL4, CXCL1 mRNA expression has been shown to correlate with viral encephalitis in the brains of MHV-infected mice (Lane *et al*, 1998; Liu *et al*, 2001). Furthermore, CXCL10, CCL5, and CCL4 mRNA expression was related to the demyelinating phase of this disease. *In vivo* neutralization experiments using the anti-chemokine treatment approach revealed that CXCL9 (Liu *et al*, 2001) and CXCL10 (Liu *et al*, 2000) were functionally important for early CNS viral clearance, and CCL5 was shown to be a pivotal chemokine in the recruitment of inflammatory cells during the demyelinating phase of disease (Lane *et al*, 2000).

Chemokine expression has also been shown to be associated with clinical disease development in TMEV-induced demyelinating disease. CXCL10, CCL5, and CCL2 mRNA expression was found in the CNS of both susceptible and resistant mouse strains following viral infection (Murray *et al*, 2000). This same study demonstrated re-expression of CXCL10, CCL5, and CCL2 in the CNS of susceptible, but not resistant, mouse strains following viral clearance and coinciding with development of demyelination. CCL2 and CCL3 protein expression in the spinal cords of the susceptible SJL mouse strain also correlated with development of clinical disease symptoms (Hoffman *et al*, 1999) with CCL2 being biological important for clinical disease development (our unpublished observations). These examples demonstrate the correlation of chemokine presence with development of histological and clinical CNS demyelinating disease.

## Multiple sclerosis

The role of chemokines in the pathogenesis of MS has not been well established. An early study demonstrated elevated CCL3 expression in the CSF of MS patients compared to control patients with other neurological diseases and the increased levels correlated with increased CSF leukocyte counts (Miyagishi *et al*, 1995). Bennetts *et al* (1997) analyzed a population of MS and control patients for a correlation between the absence of one of the CCL3 receptors, CCR5, and clinical disease presentation. Although they found that the absence of functional CCR5 had a significant protective effect against HIV infection, it did not have a protective effect against development of MS. However, the CCR5Δ32 mutation has been reported to confer a lower risk of recurrent disease activity (Sellebjerg *et al*, 2000). A number of investigators have demonstrated the expression of chemokines in CNS tissue of MS patients (Hvas *et al*, 1997; McManus *et al*, 1998; Simpson *et al*, 1998; Balashov *et al*, 1999; Van *et al*, 1999; Simpson *et al*, 2000a, 2000b). Recently, the expression of chemokines in the CSF of MS patients undergoing clinical episodes of disease has been examined, and the data showed that CXCL10 and CCL5 production were elevated in MS patients compared to controls and the levels of CXCL10 correlated with increased CSF leukocyte counts (Sorensen *et al*, 1999). Because both CXCL10 and CCL5 are potent T-cell chemoattractants, it is reasonable to postulate that the elevated levels of these chemokines during active episodes of MS induced migration of T cells into the CNS. Furthermore, an increase in $CXCR3^+$ and $CCR5^+$ T cells in the peripheral blood of MS patients has been recently reported (Balashov *et al*, 1999). IFN-$\beta$ is currently a common treatment modality for MS. A recent study has shown that *in vitro* exposure of T cells to IFN-$\beta$1a selectively inhibited mRNA expression for CCL5 and CCL3 (Zang *et al*, 2001). Furthermore, T-cell surface expression of CCR5 was significantly reduced in MS patients treated with IFN-$\beta$, correlating with decreased T-cell transmigration toward CCL5 and CCL3 (Zang *et al*, 2001). Collectively, these results demonstrate the emerging significance of chemokine expression in the CNS during human demyelinating disease as well as the increase in chemokine receptor-bearing cells and suggest a critical role for these molecules in the pathogenesis of disease development and progression.

## Alzheimer's disease

It is becoming increasingly evident that Alzheimer's disease (AD) has an inflammatory component and that chemokine expression may contribute to the development and/or the progression of disease (Xia and Hyman, 1999). Immunohistochemical analysis of human brain for CCL4, CCL3, CCL5, CCL11, and CCL7 indicated that CCL4 was predominantly expressed in a subpopulation of reactive astrocytes that were more widespread in AD than control brains, yet CCL3 was predominantly expressed in neurons and weakly in some microglia in both AD and controls (Xia *et al*, 1998). In this same study, the investigators noted that many of the $CCR3^+$- or $CCR5^+$-reactive microglia and $CCL4^+$-reactive astrocytes were found associated with amyloid deposits. Additional evidence for chemokines in AD suggests that A$\beta$ can activate both

astrocytes and oligodendrocytes to express CCL2 and CCL5 (Johnstone *et al*, 1999). Moreover, A$\beta$1-42 has been shown to induce the *in vitro* CCL2-, CCL3-, CCL4-, and CXCL8-dependent migration of monocytes (Fiala *et al*, 1998). A$\beta$ 25–35 was also shown to induce CCL3 and CXCL10 expression by cultured human monocytes and mouse microglial cells (Meda *et al*, 1999). Although these studies do not explicitly demonstrate a causal role for chemokines and pathogenesis, they are the first steps toward understanding the role of chemokines and inflammation in AD.

## CNS bacterial infections

The role of chemokines in control of CNS bacterial infections is also not well understood. However, there has been significant progress toward understanding the functions of these molecules in both experimental models and in patients. In experimental bacterial meningitis induced by *Listeria monocytogenes*, both CXC and CC chemokines namely CCL3, CCL4, and CXCL1 are produced intrathecally by meningeal macrophages and leukocytes that infiltrate into the CNS. In comparison, patients with bacterial meningitis demonstrate CXCL8, CXCL1, CCL2, CCL3, and CCL4 expression in the CSF (Lahrtz *et al*, 1998). In experimental CNS infections using *Haemophilus influenzae* type b, mRNA for CXCL1, CCL3, CCL2, and CCL5 was detected in the brain of neonatal rats (Diab *et al*, 1999). *In vivo* neutralization of CXCL1 or CCL3 resulted in a reduction of neutrophil accumulation, whereas anti-CCL2 treatment resulted in reduction of monocyte accumulation in the CNS (Diab *et al*, 1999). The study of a bacterial-induced brain abcess model has increased the understanding of chemokine function in CNS infections. When mouse brains were infected with *Staphylococcus aureus*, a number of chemokines were expressed locally. These included CCL3, CCL4, CXCL1, CCL2, and CCL1 (Kielian *et al*, 2001). Control of bacterial clearance and disease development appeared to be a function of CXCL1 expression as mice without CXCR2 expression failed to clear the infection because of reduced neutrophil accumulation (Kielian *et al*, 2001). These examples point to the requirement of CXC chemokines for the control of CNS bacterial infections and the subsequent development of bystander tissue destruction that results in CNS inflammatory disease.

## HIV-associated dementia

CNS dysfunction has been described in HIV-infected individuals and most likely results from viral infection of cells through the use of chemokine receptors as coreceptors (reviewed in (Kaul *et al*, 2001). Chemokine receptors, most notably CCR5, CXCR4, and Cx3CR1 have been described as coreceptors for HIV and a number of studies have shown chemokine receptor expression on neurons (Horuk *et al*, 1997), astrocytes (Tanabe *et al*, 1997; Cota *et al*, 2000), endothelia (Molino *et al*, 2000), and microglia (He *et al*, 1997; Ghorpade *et al*, 1998). Neuronal damage following HIV infection could result from either an infiltration of inflammatory leukocytes (Persidsky *et al*, 1999) resulting in cellular death, direct neuronal apoptosis (Zheng *et al*, 1999), or indirect stimulation of glia-derived neurotoxic factors (Kaul and Lipton, 1999). The role of chemokines in HIV-associated dementia (HAD) is not well understood. For instance, in patients with HAD, the levels of CCL3, CCL4, and CCL5 in the CSF positively correlate with dementia although low levels of CCL3 may be neuroprotective (Letendre *et al*, 1999). Moreover, CCL3, CCL4, and CCL5 have been shown to protect neurons from gp120-induced cell death (Meucci *et al*, 1998; Kaul and Lipton, 1999). It is clear that chemokines and chemokine receptors are involved in the pathogenesis of HAD although the mechanisms are not clearly understood.

## Summary

Chemokines and their receptors are a growing family of inflammatory molecules that are associated with many tissue-specific inflammatory events and the CNS is no exception. One current view of chemokines is to regulate the migration and/or accumulation of leukocytes at a particular tissue site for the general function of infection clearance and tissue repair. However, aberrant accumulation of leukocytes, including antigen-specific T cells and monocytes, can induce pathology and result in tissue-specific autoimmune and/or inflammatory disease. Our greatest understanding of the role of chemokines in CNS disorders comes from the EAE model where the temporal and spatial chemokine expression patterns appear to regulate mononuclear cell accumulation and subsequent disease development (Karpus and Ransohoff, 1998). In the case of autoimmune disease or bystander inflammatory disease, it would be beneficial to limit the biological effect of chemokine expression to limit the extent of self-tissue damage.

To this end, small molecular weight chemokine receptor antagonists have been developed and are being evaluated for efficacy in disease models as well as human disease (Ransohoff and Bacon, 2000). However, in the case of CNS bacterial infections it would be deleterious to generally inhibit the function of chemokines; as a subset, these molecules are required for the accumulation of neutrophils and the resulting clearance of infection. In this particular instance, it might be beneficial to use selective antagonists for monocytes and T cells to inhibit self tissue destruction while allowing accumulation of neutrophils. Nevertheless, understanding the role

of this superfamily of inflammatory molecules in diseases of the CNS will shed light on specific pathogenetic mechanisms as well as provide targets for therapeutic intervention.

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