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PROSPECT

Regulation of Neuroinflammation: The Role of CXCL10 in Lymphocyte Infiltration During Autoimmune Encephalomyelitis

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Abstract The movement of lymphocytes from the microvasculature into the central nervous system (CNS) parenchyma is an essential step in the pathogenesis of a variety of infectious and autoimmune neuroinflammatory diseases. The lymphocyte chemoattractant CXCL10 and its receptor, CXCR3, are expressed by the CNS and by CNS infiltrating lymphocytes, respectively, only in patients with ongoing CNS inflammation, suggesting an important role for these molecules in the pathogenic process. Numerous studies utilizing animal models and transgenic approaches have indeed supported a role for CXCL10 in the intraparenchymal trafficking of lymphocytes during acute CNS inflammation; however, other studies suggest that its expression is not required for the development of autoimmune forms of CNS inflammation and, in fact, that interference with CXCL10 signaling could lead to increased neuroinflammation. This review will consider the data from these studies and attempt to reconcile them through comparisons of both the neuroinflammatory models and the effects of CXCL10 in the CNS versus lymphoid tissues. Finally, it will define directions for future analyses of CXCL10 and CXCR3 in CNS inflammation so that their potential therapeutic utility can be more completely determined. J. Cell. Biochem. 92: 213–222, 2004. © 2004 Wiley-Liss, Inc.

Key words: chemokine; lymphocyte; trafficking; central nervous system; autoimmunity

Inflammation in the central nervous system (CNS) is unique; the brain lacks its own lymphoid tissue and resident dendritic cells and allows limited lymphocyte trafficking, even for the purpose of immune surveillance, through its blood-brain barrier (BBB) [Hickey, 2001]. Thus, when this barrier is breached by an invading pathogen or becomes dysfunctional during autoimmune attack, the CNS must direct its own immune responses through the transformation of many of its resident cells into the required cellular components of immunity. Activated microglia present antigen while virally infected astrocytes express cytokines [Minagar et al., 2002]. These activities firmly establish and amplify the inflammatory response, leading to disruption of the BBB through the upregulation of molecules that influence the movement of leukocytes across it [Ransohoff et al., 2003]. In most tissues, leukocyte recruitment is orchestrated by a series of coordinated leukocyte-endothelial interactions involving several families of molecular regulators including adhesion molecules, such as selectins and integrins, and chemokines, which are distinguished by their ability to act a distance to direct leukocyte activities [Luster, 1998].

The chemokine superfamily contains 48 structurally homologous chemotactic cytokines that induce leukocyte migration and activation by binding to seven transmembrane-spanning receptors shown to be coupled to pertussis toxin (PTX) sensitive $G\alpha_i$ proteins. Chemokines have

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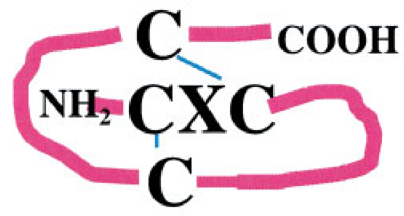
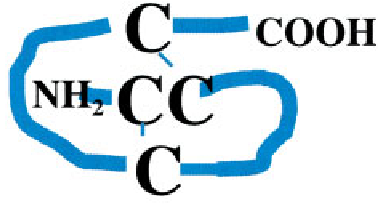
been subdivided according to the placement of amino acids between the first two cysteine residues [Rossi and Zlotnik, 2000]. These structural motifs bear functional differences in terms of chemoattraction for various leukocyte cell types. Thus, CC chemokines may attract monocytes, lymphocytes, basophils, eosinophils, dendritic, and NK cells, while CXC chemokines may attract neutrophils or lymphocytes. This latter subfamily is further divided into neutrophil-specific chemokines, which contain a glutamic acid-leucine-arginine (ELR) motif near the N-terminus, and lymphocyte-specific chemokines, which do not. Because numerous chemokines are expressed during the course of neuroinflammatory diseases, a fundamental question is how do the patterns of CNS chemokine expression determine which leukocyte subsets traffic into the CNS and whether this is the basis for the wide range of pathology observed as a result of CNS inflammation.

Given the role of Th1 lymphocytes in viral clearance and in the development of autoimmunity, knowledge of the chemokines responsible for their recruitment during CNS inflammation is considered crucial for the development of therapies to treat various forms of encephalitis. The list of lymphocyte chemoattractants and their receptors has expanded considerably (see Table I). Although the expression patterns of many of these chemokines during CNS inflammatory diseases have not yet been thoroughly investigated, several non-ELR CXC chemokines have become the focus of numerous studies examining this process in both patients and animal models. CXCL9, CXCL10, and CXCL11 are related, interferon (IFN)-γ-inducible chemokines that have been shown to play essential roles in Th1 inflammatory diseases [Campbell and Hayglass, 2000]. These chemokines all bind CXCR3 on activated T-cells, natural killer cells, and monocytes/macrophages [Rossi and Zlotnik, 2000]. While all three of these chemokines are expressed by monocytes and activated astrocytes, endothelial cells and fibroblasts also express CXCL9 and CXCL10, indicating some distinct roles for these molecules during tissue inflammatory responses. In addition to its role in chemoattraction, CXCL10 has been observed to enhance IFN-γ release both in vitro and in vivo and is involved in the development of antigen-driven T-cell responses, suggesting that this chemokine plays an important role in the overall evolution of Th1 peripheral immune responses [Gangur et al., 1998; Hancock et al., 2001; Dufour et al., 2002]. Other Th1 chemokines include the β-chemokines CCL3, CCL4, and CCL5, which are secreted by CNS infiltrating macrophages, activated NK cells and T-cells, thus serving to further amplify the initial inflammatory response [Miyagishi et al., 1997].

Altered patterns of chemokine expression are observed in many CNS inflammatory diseases, including viral encephalitis and multiple sclerosis (MS), where the infiltration of leukocytes into the CNS is a central mechanism in disease pathogenesis [Hvas et al., 1997; Rosler et al., 1998; Balashov et al., 1999]. Elevated cerebrospinal fluid levels (CSF) levels of CCL3, CCL5, CXCL9, and CXCL10 have been observed in patients with HSV and HIV encephalitides and MS [Letendre et al., 1999; Sorensen et al., 1999] and activated T-cells expressing CCR5 and CXCR3 are increased in the peripheral blood and CSF and in CNS lesions of MS patients [Misu et al., 2001]. These findings suggest that these receptors and their ligands are important for lymphocyte trafficking into the CNS during Th1 neuroinflammatory diseases. A variety of chemokines expressed in CNS tissues of animals with neuroinflammatory diseases have been observed to correlate with the appearance of pathogenic T-cells bearing chemokine receptors that bind these ligands (see Table II). Efforts to determine the roles of each of these molecules in the lymphocytic contribution to the pathogenic process, using neutralizing antibodies and targeted gene deletion in animal models of CNS inflammation, have produced varying results depending on the model used (see Table III). Thus, while inactivation of CCR5 was shown to decrease lymphocyte trafficking during acute viral encephalitis [Glass et al., 2001], loss of CCR5 activity in mouse models of MS were without effect [Tran et al., 2000]. Similarly, loss of CCR5 in humans fails to protect against MS [Bennetts et al., 1997], but may slow disease progression [Kantor et al., 2003]. Thus, CCR5 may play a role in lymphocyte trafficking during established CNS autoimmune inflammation rather than in disease induction.

Examination of CXCR3 and its ligands also demonstrated an important role for these molecules in acute encephalitis [Liu et al., 2001b]. However, use of similar approaches in the study of CXCL10 in rodent models of MS have yielded conflicting results that suggest

TABLE I. Chemokines and Their Receptors: Chemoattractants for Activated T-Cells

	Systematic (Common) Names	Receptor(s)
	CXCL9 (Mig)	CXCR3
	CXCL10 (IP-10)	CXCR3
	CXCL11 (I-TAC)	CXCR3
	CXCL16	CXCR6
	CCL1 (I-309/TCA-3)	CCR8
	CCL2 (MCP-1/MCAF/JE)	CCR2
	CCL3 (MIP-1α/LD78α)	CCR1, -5
	CCL4 (MIP-1β)	CCR5
	CCL5 (RANTES)	CCR1, -3, -5
	CCL7 (MCP-3/MARC)	CCR1, -2, -3
	CCL8 (MCP-2)	CCR2, -3, -5
	CCL9/10 (MIP-1γ/MRP-2)	CCR1
	CCL11 (Eotaxin-1)	CCR3
	CCL12 (MCP-5)	CCR2
	CCL13 (MCP-4)	CCR1, -2, -3
	CCL16 (HCC-4/LEC)	CCR1
	CCL17 (TARC/ABCD-2)	CCR4
	CCL19 (MIP-3β/ELC/Exodus-3)	CCR7
	CCL21 (6Ckine/SLC/Exodus-2)	CCR7
	CCL22 (MDC/STCP-1/ABCD-1)	CCR4
	CCL24 (MPIF-1/Eotaxin-2)	CCR3
	CCL25 (TECK)	CCR9
	CCL26 (Eotaxin-3)	CCR3
	CCL27 (ILC/ESKine/CTACK)	CCR3, -2, -10
	CCL28 (MEC)	CCR10
	CX3CL1 (Fractalkine)	CX3CR1

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

multiple roles for this molecule in the development of CNS autoimmunity, both in the CNS and at the lymph node, and, interestingly, indicate that its role in lymphocyte infiltration into the CNS is intimately linked to BBB integrity. This review will analyze these data, focusing on the differing CXCL10 expression patterns within these animal models, in an attempt to understand the basis for the seemingly disparate observations obtained. In addition, it will evaluate the evidence supporting the use of CXCR3 and its ligands as targets for the treatment of autoimmune neuroinflammatory diseases.

TABLE II. Chemokine Expression and Neuroinflammatory Disease Models

Animal model	Chemokine	Recruited cell (receptor)	References
Viral encephalitis			
MHV	CXCL9, -10	act. T-cell (CXCR3)	[Lane et al., 1998, 2000; Chen et al., 2001; Glass et al., 2001; Liu et al., 2001a,b,c; Glass and Lane, 2003]
LCMV	CXCL10 CCL2, -4, -5, -7	CD8+ T-cell Macrophages (CCR1, -2, -5)	[Asensio et al., 1999a]
SIV	CXCL10 CCL3,-4, -5, -7	Mononuclear cells (CXCR3, -4, CCR3, -5)	[Sasseville et al., 1996; Westmoreland et al., 1998]
HSV-1	CXCL10 CCL2, -5	Unknown	[Carr, 1998; Poliani et al., 2001]
Sindbis virus	CXCL10 CCL2, -7	Unknown	[Johnston et al., 2001]
Borna virus	CXCL10 CCL4, -5	Unknown (CXCR3) Microglia	[Morimoto et al., 1996; Sauder et al., 2000; Rauer et al., 2002]
Measles	CXCL10 CCL5	Unknown	[Manchester et al., 1999]
Experimental autoimmune encephalitis			
Adoptive transfer	CXCL10, -12 CCL1-5, -8, -19, -21	act. T-cells (CCR1-5, CCR7)	[Godiska et al., 1995; Fife et al., 2001; Alt et al., 2002]
Active immunization	CXCL9, -10, -11 CXCL1, -2 CCL1-7, -22	act. T-cell (CCR1-8, CXCR2, -3)	[Ransohoff et al., 1993; Godiska et al., 1995; Asensio et al., 1999b; Fischer et al., 2000; Columba-Cabezas et al., 2002; Glabinski et al., 2002; Hamilton et al., 2002]

STUDIES OF CXCL10-MEDIATED LYMPHOCYTE TRAFFICKING DURING CNS AUTOIMMUNITY

The role of CXCL10 in lymphocyte trafficking into the CNS has been examined in detail utilizing the rodent animal model of MS, experimental autoimmune encephalomyelitis (EAE). EAE is a T-cell mediated Th1 inflammatory demyelinating disease of the CNS that can be induced in rats or mice by immunization with myelin peptides or via adoptive transfer of myelin-specific CD4+ T-cells [Martin and McFarland, 1995; Swanborg, 1995]. As in MS, mice with EAE develop an ascending paralysis with CNS demyelinating lesions containing Ag-

TABLE III. Inactivation of Lymphocyte Chemoattractants and Their Receptors in Neuroinflammatory Diseases

Animal model	Chemokine/receptor target	Result	References
Viral encephalitis			
MHV	CCL5	↓Macrophages ↓Demyelination	[Lane et al., 2000]
	CXCL9 CXCL10	↓Macrophages, T-cells ↓Demyelination	[Liu et al., 2001c]
	CCR5	↓Macrophages CD4+ T-cells ↓Demyelination	[Glass et al., 2001] [Glass and Lane, 2003]
Experimental autoimmune encephalitis			
Adoptive Transfer	CXCL10	↓EAE	[Fife et al., 2001] [Wildbaum et al., 2002] [Huang et al., 2001]
	CCL3	↓EAE	[Karpus et al., 1995] [Youssef et al., 1998]
	CCL4	↑EAE	[Youssef et al., 1998]
	CCL5	No effect	[Youssef et al., 1998]
Active Immunization	CXCL10	↑EAE	[Narumi et al., 2002] [Klein et al., 2004]
	CCL3	No effect	[Tran et al., 2000]
	CCR1	↓EAE	[Rottman et al., 2000]
	CCR5	No effect	[Tran et al., 2000]
	CCR1/5	No effect	[Matsui et al., 2002]

specific T-cells and macrophages. As effective T-cell activation and extravasation into the CNS is required for the development of EAE, the development of EAE appears to involve MHC-restricted activation of CNS infiltrating autoreactive T-cells [Martin and McFarland, 1995]. Studies examining the recruitment of lymphocytes during acute viral encephalitis had determined that both CXCL9 and CXCL10 were essential for the migration of virus-specific effector lymphocytes into the CNS [Liu et al., 2001b]. Neutralization of either chemokine was associated with decreased numbers of CNS infiltrating T-cells, lower levels of IFN-γ within CNS tissues, and inhibition of viral clearance. In addition, loss of one CXCR3 ligand was associated with lower levels of the others, suggesting that their expression during viral infection relies on the infiltration of Th1 cytokine-expressing mononuclear cells. It was thus surmised that lymphocyte trafficking during autoimmune inflammation in the CNS would also be regulated by CXCR3 and its ligands. Initially, several groups utilizing neutralizing antibodies to CXCL10 reported results consistent with this, suggesting that CXCL10 is essential for the recruitment of T-lymphocytes into the CNS during adoptive transfer EAE.

In the first study, Fife et al. [2001] examined the effect of CXCL10 neutralizing antibodies in adoptive transfer EAE. Two doses of anti-CXCL10 antisera administered at the time of adoptive transfer of encephalitogenic T-cells inhibited the development of mononuclear infiltrates and led to decreased clinical EAE, suggesting that CXCL10 is required for the movement of transferred encephalitogenic CD4+ T-cells into the CNS. In addition, blockade of CXCL10 during adoptive transfer EAE resulted in increased numbers of mononuclear cells in peripheral lymphoid organs by an unknown mechanism. Loss of CXCL10 signaling in this model did not, however, affect peripheral immune responses; examination of Th1 cytokine and proliferative responses of lymph node cells and splenocytes from animals with EAE were not affected by antibody administration. These results support the notion that CXCL10 neutralization decreases clinical EAE via alterations in T-cell trafficking.

An alternative effect of anti-CXCL10 antibody-mediated suppression of EAE was demonstrated by Youssef et al. [1998] using the active immunization model of EAE. In this study which vaccination with a plasmid encoding self CXCL10 was observed to inhibit both the induction of and ongoing disease. Administration of the vaccine was shown to specifically augment the expression of neutralizing anti-CXCL10 antibodies observed in both serum and CSF, which was associated with decreases in peripheral expression of Th1 cytokines TNF-α and IFN-γ and an increase in the expression of the Th2 cytokine IL-4. The authors also demonstrated that CXCL10 alone could induce Th1 polarization of CD4+ T-cells. These data suggest that CXCL10 plays an important role in T-cell polarization suggesting that the basis for the anti-CXCL10 antibody suppression of EAE in this model may involve a redirection of T-cell polarization toward a Th2 phenotype, which is associated with recovery from EAE, rather than solely an effect on T-cell trafficking.

While these studies identified CXCL10 as a potential therapeutic target for the treatment of lymphocyte recruitment into the CNS during inflammation, they also suggested that alternative CXCR3 ligands did not play a role in lymphocyte trafficking into the CNS during CNS autoimmunity and that manipulation of CXCL10 signaling during autoimmunity was likely to affect the evolution of peripheral immune responses during Th1 inflammatory diseases. Several recent studies have addressed these questions and have demonstrated that loss of CXCL10 function could potentially exacerbate autoimmune disease because of compensatory effects of alternative CXCR3 ligands and because of its role in the development of peripheral immune responses. These studies also demonstrated a lack of requirement of CXCL10 expression in the recruitment of lymphocytes into CNS parenchyma.

In a recent report that similarly utilized CXCL10 neutralizing antibodies in active immunization EAE in rats, Narumi et al. [2002] reported that loss of CXCL10 signaling exacerbated EAE regardless of the immunization schedule. Animals with worsened disease were observed to have smaller draining lymph nodes with increased numbers of lymphocytes in the blood and increased CNS infiltrating CD4+ T-cells. Examination of all CXCR3 ligands in CNS and peripheral lymphoid disease revealed that animals expressed CXCL9 and CXCL10 in their draining lymph nodes and CXCL10 and CXCL11 in their CNS prior to the onset of

clinical EAE. These data suggested not only that CXCL10 activity may not be required for the trafficking of encephalitogenic CD4+ T-cells, but that its blockade could intensify CNS autoimmune disease. Since CXCL10 has been shown to be crucial for the retention of Th1 lymphocytes within dendritic cell clusters in lymph nodes [Yoneyama et al., 2002], the authors speculated that, in contrast to previous conclusions, anti-CXCL10 antibody treated rats released encephalitogenic CD4+ T-cells into the periphery and that CXCL11 induced their trafficking into the CNS. An explanation for the differing results in these studies may lie in the pattern of CXCL10 expression in the two models. As observed with viral invasion of the CNS [Liu et al., 2001a], adoptive transfer EAE is associated with astrocyte expression of CXCL10 that precedes the onset of acute EAE [Fife et al., 2001] whereas in active immunization EAE, CXCL10 expression is not detectable until there is histological evidence of leukocyte infiltration [Ransohoff et al., 1993; Fife et al., 2001; Liu et al., 2001a]. As adoptively transferred encephalitogenic T-cells enter the CNS within several days of transfer, breach of the BBB occurs very soon in the course of the disease in this model. Indeed, damage of BBB in adoptive transfer EAE has been observed via magnetic resonance imaging at 3 days post-transfer [Seeldrayers et al., 1993]. In active immunization EAE, however, BBB damage is believed to occur during the acute clinical phase of the disease. Thus, expression of CXCL10 appears to coincide with Th1 proinflammatory effects on BBB permeability. This may partly explain the difference between the results obtained with the two models where the temporal associations between T-cell entry and CXCL10 neutralization differ significantly.

We explored the differential effects of CXCL10 in the CNS versus primary lymphoid tissue further in a study that examined the induction of EAE in mice with targeted deletion of CXCL10. In this study, CXCL10-deficient mice not only did not show unaltered expression of EAE, but also demonstrated an enhanced susceptibility to EAE, developing marked disease after immunization with lowered doses of myelin peptide that produced significantly less disease in wild-type littermates [Klein et al., 2004]. Interestingly, induction of EAE in IP-10-deficient mice was associated with upregulation of CXCL11 in the CNS and decreased expression of CXCL9 in draining lymph nodes, suggesting that de novo loss of CXCL10 may alter the natural expression of other CXCR3 ligands. Loss of CXCL10 in the lymph node was associated with decreased lymph node levels of the regulatory cytokine transforming growth factor (TGF)-β1, suggesting that CXCL10 plays a role in the delivery or expression of T-cell regulatory activity at the lymph node.

While these results consistently define a role for CXCL10 in shaping the extent of Th1 inflammatory responses at the lymph node, they question the absolute requirement for CXCL10 in the trafficking of activated T-cells into the CNS. To further address this question, the impact of CXCL10 production in the CNS on lymphocyte recruitment was evaluated using transgenic and viral expression approaches [Boztug et al., 2002; Trifilo and Lane, 2003]. While transgenic mice with astrocyte-directed production of CXCL10 were noted to have increased leukocyte infiltrates in multiple brain regions, these infiltrates were limited to the meninges and perivascular compartments with no leukocyte movement noted in parenchymal regions and no associated neuropathology or clinical manifestations of CNS inflammatory disease. In addition, while these meningeal infiltrates could be enhanced by peripheral immune activation, their movement into CNS parenchyma was not affected. Similar results were obtained using a replication-deficient adenovirus that expresses murine CXCL10 [Trifilo and Lane, 2003]. Thus, while CNS CXCL10 expression could direct lymphocytes towards the BBB, this expression alone was not sufficient to direct these cells to cross it and induce pathology. These data all indicate that CXCL10 expression is not sufficient for the recruitment of lymphocytes across an intact BBB and that additional signals are need to induce autoimmune neurologic disease.

RESOLVING THE QUESTION OF T-CELL CHEMOATTRACTANTS IN THE CNS

The biological relevance of inhibiting leukocyte migration in the treatment of MS has already been well established. In a recent placebo-controlled trial, treatment with an antagonist of alpha4 integrin, an adhesion molecule involved in the migration of all mononuclear cells into parenchymal tissues, led to fewer inflammatory brain lesions and fewer relapses over a 6-month

period in patients with relapsing forms of MS [Miller et al., 2003]. Because lymphocytes in particular are involved in a variety of actions upon entering the CNS, from viral clearance to initiating autoimmunity, understanding the mechanisms responsible for lymphocyte recruitment into the CNS is important for developing therapies that can either enhance their anti-viral abilities or limit their inflammatory activities, depending on the disease in question. Thus, while the studies described here have uncovered important and interesting roles for CXCL10 in the evolution of Th1 inflammatory responses, the question of signals responsible for the recruitment of activated lymphocytes into the CNS remains to be fully resolved and further studies are required to determine how CXCR3 and its ligands may be used as therapeutic targets.

CXCR3 Ligands and Their CNS Patterns of Expression

The cellular patterns of CXCL9, CXCL10, and CXCL11 expression in various neuroinflammatory diseases may underlie their observed differences in CNS pathology and ultimately lead to the utilization of each of these chemokines as distinct therapeutic targets. CXCL9 expression occurs primarily by BBB constituents, including CNS endothelial cells and astrocytes whereas CXCL10 and CXCL11 are expressed by reactive astrocytes within the CNS parenchyma [Sorensen et al., 1999; Salmaggi et al., 2002]. In addition, although IFN-γ has been shown to induce the expression of all of these chemokines, they can exhibit individual expression patterns in response to different combinations of cytokine stimuli. For instance, in astrocytes, IFN-γ is required to induce expression of CXCL9, TNF-α induces high expression of CXCL11 while CXCL10 expression can be induced by exposure to either cytokine [Salmaggi et al., 2002]. Thus, the temporal pattern of expression of these three chemokines may be due to their individual responses to the cytokines expressed when lymphocytes encounter antigen at the BBB. In addition, the further expression of CXCL9 and CXCL11, whose IFN-γ-induced expression has been shown to be further unregulated by IL-4 in certain cell types [Albanesi et al., 2000], may be regulated indirectly by the level of expression of CXCL10 through its effect on the balance of Th1/Th2 cytokines during autoimmune EAE. This may partially explain why loss of CXCL10 signaling was observed to lead to changes in the expression of the other CXCR3 ligands. Use of transgenic approaches with overexpression of all CXCR3 ligands by various neural cell types may shed insight into the individual and overlapping functions of these chemokines in T-cell trafficking and activation in the CNS. These mice could be used to examine the role of these chemokines in the trafficking of lymphocytes directed at CNS-derived antigens into the CNS. Use of inactivated versus activated myelin-specific T-cells could also address whether expression of specific CXCR3 ligands in the CNS is sufficient for the generation of effector T-cell functions at this site.

CXCR3 as a Therapeutic Target for CNS Th1 Inflammatory Diseases

The discovery that all of the CXCR3 chemokine ligands are expressed within the CNS during numerous Th1 inflammatory diseases raises the question of CXCR3 as a general target for the treatment of all neuroinflammatory states. Further studies, utilizing neutralizing antibodies, targeted deletion or small molecule inhibitors to block CXCR3 signaling in activated T-cells will be needed to determine the affect of CXCR3 activity on the development of CNS inflammatory infiltrates in both viral and autoimmune encephalitis models. Recently, a non-peptide synthetic CCR5 antagonist, TAK-779 (N, N-dimethyl-N-[4-[[[2-(4-methylphenyl)-6, 7-dihydro-5H-benzocyclohepten-8-yl]carbon-yl] amino]benzyl]-tetrahydro-2H-pyran4-aminium chloride), was observed to block ligand binding to CCR5 and CXCR3 as well as CCR5 or CXCR3-mediated cell adhesion and chemotaxis and inhibit the development of experimentally induced arthritis by modulating the migration of CCR5(+)/CXCR3(+) T-cells to joints [Gao et al., 2003]. Given that both of these receptors have been implicated in T-cell trafficking in neuroinflammatory disorders, use of TAK-779 and/or other inhibitors of CXCR3 in infectious and autoimmune CNS inflammatory models are of particular interest.

CONCLUSIONS

The search for therapeutic targets for the prevention of T-cell infiltration in neuroinflammation has yielded important information regarding the chemokine and cytokine networks involved and has determined a crucial role for

CXCL10 in the accumulation of lymphocytes at the BBB. Future studies examining the temporal expression of CXCR3 ligands by constituent cell types along the path of lymphocyte migration into the CNS are needed to produce biologically based therapies that specifically target the molecule(s) responsible for this recruitment.

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