

MICROGLIA AND CHEMOKINES IN INFECTIOUS DISEASES OF THE NERVOUS SYSTEM: VIEWS AND REVIEWS

Tammy Kielian

Department of Anatomy and Neurobiology, University of Arkansas for Medical Sciences, Little Rock, AR

TABLE OF CONTENTS

1. Abstract
2. Immune Functions of Microglia
3. Chemokines and chemokine receptors- a brief review
 - 3.1. Chemokines
 - 3.2. Chemokine receptors
4. Microglial chemokines and chemokine receptors
 - 4.1. Chemokines produced by microglia
 - 4.2. Chemokine receptors expressed by microglia
5. Microglia and chemokines in CNS infectious diseases
 - 5.1. HIV encephalitis (HIVE)
 - 5.2. Viral encephalitis
 - 5.2.1. Cytomegalovirus (CMV) encephalitis
 - 5.2.2. Herpes simplex virus (HSV) encephalitis
 - 5.2.3. Mouse hepatitis virus (MHV)
 - 5.2.4. Measles virus (MV)
 - 5.2.5. Chemokine-chemokine receptor mimicry by viruses
 - 5.3. Experimental brain abscess
 - 5.4. Bacterial meningitis
 - 5.4.1. *Listeria monocytogenes* (LM) and *Haemophilus influenzae* meningitis
 - 5.4.2. *Streptococcus pneumoniae* meningitis
 - 5.5. Other CNS infectious diseases
 - 5.5.1. *Toxoplasma gondii*
 - 5.5.2. Mouse adenovirus-type 1 (MAV-1)
 - 5.5.3. *Cryptococcus neoformans*
 - 5.5.4. Prion model of neurodegeneration
6. Conclusions and Perspectives
7. Acknowledgements
8. References

1. ABSTRACT

Microglia are one of the resident mononuclear phagocyte populations within the central nervous system (CNS). These cells share many phenotypical and functional characteristics with macrophages, suggesting that microglia participate in innate immune responses in the brain. As such, microglia are uniquely poised to provide an initial line of defense against invading pathogens into the CNS prior to peripheral leukocyte infiltration. Numerous studies have shown that microglia are capable of producing a wide array of chemokines that act to initiate or promote inflammatory processes in the CNS through facilitating the recruitment of peripheral immune cells into the CNS parenchyma. In addition, microglia also express numerous chemokine receptors that are involved in cell migration and serve as co-receptors for human immunodeficiency virus-1 (HIV-1) infection. The findings obtained from studies of chemokine expression in animal models of CNS infectious diseases as well as from patient populations highlight a marked promiscuity in cerebral chemokine expression patterns with simultaneous expression of multiple chemokines being the general rule. A detailed discussion regarding the profiles and implications of chemokine and

chemokine receptor expression in the context of various CNS infectious diseases including HIV-1 encephalitis, other viral encephalitides, bacterial meningitis, and brain abscess is presented. Future studies dissecting the potential roles of individual chemokines and their receptors in the context of CNS infectious diseases may provide insights into the complex regulatory network dictating neuroinflammatory responses.

2. IMMUNE FUNCTIONS OF MICROGLIA

Microglia are one of the resident mononuclear phagocyte populations within the central nervous system (CNS), constituting approximately 10 to 15% of the total cell population in the parenchyma. These cells share many phenotypical and functional characteristics with macrophages, suggesting that microglia participate in innate immune responses in the brain. As such, microglia are uniquely poised to provide an initial line of defense against invading pathogens into the CNS prior to peripheral leukocyte infiltration. Based upon morphological and functional criteria in the normal and inflamed CNS,

microglia have been categorized into various activation states. Resting microglia are highly ramified cells present in the normal adult CNS parenchyma that display a immunologically quiescent phenotype characterized by the lack of phagocytic activity and expression of membrane receptors that are essential for normal macrophage functions. Subsequent to infection or trauma, ramified microglia transform into activated microglia that exhibit a rounded morphology and are highly phagocytic. At this stage, activated microglia acquire the expression of numerous receptors including major histocompatibility antigens (MHC Class I and II), Fc receptors, complement receptors, and co-stimulatory molecules (1). Activated microglia have been shown to have numerous functions in the CNS innate immune response, including the induction of neuroinflammation, phagocytosis, cytotoxicity, and regulation of T lymphocyte responses through antigen presentation (1). To achieve these effector functions, numerous studies have demonstrated that microglia are capable of producing a wide array of proinflammatory mediators that act to initiate or promote inflammatory processes in the CNS (1, 2). However, in addition to the beneficial effects microglia have in initiating protective immune responses against CNS pathogens, when chronically and/or pathologically activated, microglia have been implicated in contributing to tissue damage. For example, many reports demonstrate that microglia may exacerbate Alzheimer's disease and multiple sclerosis through secreting a battery of inflammatory cytokines and cytotoxic agents, including TNF- α , IL-1 β , and nitric oxide (3-7). Therefore, the implications of microglial activation in the context of CNS infectious diseases must be evaluated by recognizing the relative contributions of beneficial versus detrimental effector functions, which may have important implications in therapeutic approaches to disease.

3. CHEMOKINES AND CHEMOKINE RECEPTORS- A BRIEF REVIEW

3.1. Chemokines

Chemokines are small molecular weight (8-14 kDa) chemotactic cytokines that are produced locally at sites of inflammation and establish a concentration gradient resulting in the active recruitment of target cell populations. Chemokines are a structurally and functionally related family of proteins subdivided into four groups based on the relative position of conserved N-terminal cysteine residues (8-10). In general, the chemokine subfamilies show similar, often overlapping specificity with regards to the movements of target cell populations they orchestrate. Recently in an attempt to clarify the confusing and complex nomenclature associated with the naming of individual chemokines, a systematic nomenclature has been established to parallel that of the straightforward receptor nomenclature system (11, 12). Therefore, for the purposes of this review when introducing a chemokine for the first time, the traditional name will be provided along with the systematic name. Subsequently, all chemokines will be referred to according to their systematic name. The CXC and CC chemokines represent the largest groups and contain four conserved cysteines. In the CXC family, the first two N-terminal cysteines are separated by one

intervening amino acid denoted as "X", whereas in the CC family they are adjacent. Chemokines belonging to the CXC family are further subdivided into those that contain a conserved N-terminal glutamic acid-leucine-arginine (ELR) motif prior to the CXC domain and those that lack this domain. Examples of ELR-containing CXC chemokines include CXCL8/IL-8 in the human and its functional rodent homologues macrophage-inflammatory protein-2 (CXCL2/MIP-2) and CXCL2/KC that are neutrophil-specific chemoattractants and have also been demonstrated to possess angiogenic activity (13-15). The non-ELR CXC chemokines including interferon gamma-inducible protein of 10 kDa (CXCL10/IP-10) and monokine-induced by interferon gamma (CXCL9/MIG) are inert towards neutrophils but are potent lymphocyte and monocyte chemoattractants. Chemokines belonging to the CC family, including monocyte chemoattractant protein-1 (CCL2/MCP-1) and macrophage inflammatory protein-1alpha (CCL3/MIP-1alpha), attract a wider array of leukocytes including monocytes, T lymphocytes, basophils, and eosinophils. The CX3C subfamily only contains one member at present, CX3CL1/fractalkine, where the first two cysteines are separated by three intervening amino acids. CX3CL1 is unique compared to other members of the chemokine family in that it exists in both membrane-bound and soluble forms that serve as chemoattractants for microglia, macrophages, NK cells, and CD8-positive T cells (16-20). Finally, C chemokines serve as lymphocyte chemoattractants and are represented by two members, XCL1/lymphotactin-alpha and XCL2/lymphotactin-beta, which contain only two of the four conserved N-terminal cysteine residues.

3.2. Chemokine receptors

Chemokines exert their biological activities by binding to cell surface receptors belonging to the superfamily of seven transmembrane spanning G-protein coupled receptors. Although within a subfamily, chemokines can exhibit promiscuous binding to multiple chemokine receptors, chemokine-chemokine receptor interactions are normally restricted within a single subclass. Therefore, the classification of chemokine receptor nomenclature is based upon the chemokine subfamily group to which their ligand(s) belong. To date, six CXC chemokine receptors (CXCR1-6) and 10 CC chemokine receptors (CCR1-10) have been identified based upon their interactions with defined chemokine ligands (9, 10). The C and CX3C chemokine subfamilies only have one identified receptor (XCR1 and CX3CR1, respectively).

The binding of a particular chemokine to its receptor induces the subsequent release of intracellular calcium and other second messengers in target cells. This in turn, induces the expression of integrins required for cell extravasation, reorganization of the actin cytoskeleton, formation of focal adhesions, and pseudopod extension that ultimately lead to cell migration. Indeed, a recent study has revealed that CCL2, CCL3, regulated upon activation T cell expressed and secreted (CCL5/RANTES), CXCL8, and CXCL10 induce changes in the distribution of f-actin and migration in adult rat microglia and the human microglial cell line CHME3 *in vitro* (21). In addition to orchestrating

Chemokines in CNS infectious diseases

Table 1. Chemokines produced by microglia in response to infectious stimuli

Chemokine family	Common name ¹	Systematic name
• CXC		
▪ ELR-containing	IL-8 (human)	CXCL8
	MIP-2 (mouse)	CXCL2
	KC (mouse)	CXCL2
▪ Non-ELR containing	IP-10	CXCL10
• CC	TCA-3	CCL1
	MCP-1	CCL2
	MIP-1alpha	CCL3
	MIP-1beta	CCL4
	RANTES	CCL5

¹ IL, interleukin; MIP, macrophage inflammatory protein; IP-10, interferon gamma-inducible protein of 10 kDa; MCP, monocyte chemoattractant protein; RANTES, regulated upon activation T cell expressed and secreted.

cell movement, chemokine receptor engagement has also been shown to induce the production of reactive oxygen intermediates and matrix metalloproteinases in microglia (22), the latter of which may have an important role in the breakdown of the blood-brain barrier during the course of neuroinflammation.

4. MICROGLIAL CHEMOKINES AND CHEMOKINE RECEPTORS

4.1. Chemokines Produced by Microglia

The recruitment of peripheral leukocytes into the CNS is a critical step in the development of host defense responses to neurotrophic pathogens. To achieve this, chemokines produced locally within the CNS parenchyma play an essential role. Microglia are the resident macrophage population in the CNS parenchyma and are uniquely poised to serve as an initial line of defense against invading pathogens and responses to injury and trauma. Numerous studies have documented the ability of microglia to produce chemokines following exposure to various inflammatory stimuli including lipopolysaccharide from gram-negative bacteria, gram-positive bacteria and their cell wall products, and viral pathogens (see below; Table 1). Therefore, by virtue of their ability to secrete chemokines upon exposure to infectious insults, microglia play a pivotal role in the initiation and amplification of pathogen-specific immune responses the recruitment of peripheral immune cell populations into the CNS parenchyma.

Gram-negative bacteria such as *Niesseria meningitidis*, *Escherichia coli*, and *Haemophilus influenzae* type b (Hib) are major meningeal pathogens in bacterial meningitis, although other organisms are capable of causing disease, which appears to be age-related (23, 24). The incidence of Hib meningitis has greatly declined in the infant population in developed countries due to the widespread use of the Hib vaccine; however, this pathogen remains a leading cause of meningitis in non-developed countries (23, 24). Lipopolysaccharide (LPS) is a major product of the outer cell wall of gram-negative bacteria and has been well documented as a potent immunostimulatory agent for proinflammatory mediator release by numerous cell types. With regards to CNS neuroinflammation, many studies have demonstrated that LPS is capable of inducing the expression of a wide array of chemokines in primary rodent microglia, including CXCL2, CXCL10, CCL2,

CCL3, CCL4, and CCL5 (25-34)(Table 1). Similarly, primary human fetal microglia have been shown to produce CXCL10, CCL2, CCL3, CCL4, and CCL5 in addition to CXCL8, a potent neutrophil chemoattractant (30, 31, 33, 35-39). Interestingly, exposure of primary human fetal microglia to the anti-inflammatory cytokines IL-10 and TGF- β led to the down-regulation of CCL5 and CXCL8 production, providing a mechanism by which microglial chemokine release may be attenuated during the chronic stages of CNS neuroinflammation (36, 38).

In addition to studies characterizing the profile of chemokines released from LPS-stimulated microglia, recent reports have revealed that products from gram-positive bacteria, neurotrophic viruses, and bacterial DNA are also capable of inducing robust chemokine synthesis by microglia. Our laboratory has recently characterized chemokine expression in primary mouse microglia following exposure to heat-inactivated *S. aureus* or its cell wall component peptidoglycan (PGN), one of the main pathogenic agents of brain abscess in humans. Stimulation with either *S. aureus* or PGN led to the expression of numerous chemokines in microglia including CCL1, CCL2, CCL3, CCL4, CCL5, and CXCL2 (40, 41), suggesting that parenchymal microglia may play a role in the initial recruitment of peripheral immune cells into brain abscesses. Similarly, exposure of primary mouse microglia to pneumococcal cell walls was found to induce the release of CXCL2, CCL2, CCL3, and CCL5 that may be reflective of responses observed during the course of acute bacterial meningitis (34). Human cytomegalovirus (CMV), an opportunistic pathogen prevalent during fetal development and in patients with advanced AIDS, has been shown to induce the expression of CCL4, CCL5, and CXCL10 (42). Another CNS viral pathogen, Theiler's virus, leads to the production of CXCL2, CXCL10, CCL2, CCL3, CCL4, and CCL5 in primary mouse microglia which may play a role in the recruitment of macrophages/microglia and lymphocytes that mediate CNS tissue destruction and demyelination (43). Finally, exposure of primary mouse microglia to synthetic oligodeoxynucleotides (ODN) containing CpG motifs that mimic the effects of bacterial DNA have been reported to lead to the rapid induction of CCL3 and CCL4 expression (44). Overall, regardless of the nature of the infectious insult, microglia serve as a major source of both CC and CXC chemokines, although they produce a wider array of the former. Collectively, these studies indicate that subsequent to CNS infection, resident microglia have the

Table 2. Chemokine receptors expressed by microglia in CNS infectious diseases

Chemokine receptor	Ligands [†]
• CC family	
▪ CCR2	CCL2/MCP-1, CCL7/MCP-3, CCL13/MCP-4
▪ CCR3	CCL5/RANTES, CCL7/MCP-3, CCL8/MCP-2, CCL11/eotaxin, CCL13/MCP-4
▪ CCR5	CCL3/MIP-1alpha, CCL4/MIP-1beta, CCL5/ RANTES, CCL8/MCP-2
• CXC family	
▪ CXCR4	CXCL12/SDF-1
• CX3CR1 family	
• CX3CR1	CX3CL1/fractalkine

[†] MCP, monocyte chemoattractant protein; RANTES, regulated upon activation T cell expressed and secreted; MIP, macrophage inflammatory protein; SDF, stromal cell-derived factor.

potential to dictate the nature of the ensuing inflammatory response by regulating the types of infiltrating peripheral immune cells, which may influence disease outcome and pathological tissue damage.

4.2. Chemokine receptors expressed by microglia

Increasing evidence suggests that chemokines can also stimulate the migration of microglia to sites of inflammation and injury. Microglia in the normal and inflamed CNS have been reported to express numerous chemokine receptors including, CCR2, the receptor for the monocyte/lymphocyte chemoattractants CCL2, CCL7, and CCL13 (45-47); CCR3, the receptor for CCL5, CCL7, and CCL13 (48-51); CCR5, the receptor for CCL3, CCL4, and CCL5 (48, 49, 52); CXCR4, the receptor for CXCL12 (48, 50, 53); and CX3CR1, the receptor for CX3CL1 (54-58) (Table 2). Unlike the majority of other chemokines, CX3CL1 is not produced by peripheral leukocytes but is constitutively expressed in the brain, kidney, heart, and lung (16, 17). In the normal brain, the majority of studies have identified neurons as the primary CNS cell type responsible for CX3CL1 production (57, 59, 60). CX3CL1 has been shown to serve as a potent chemoattractant for microglia (18, 19) and can also attract natural killer cells and CD8-positive T cells (20). In microglia, ligation of CX3CR1 induces an intracellular calcium flux, kinase activation, and actin rearrangement (19). Due to the fact that neurons constitutively express CX3CL1 and microglia constitutively express CX3CR1, this suggests that this ligand-receptor pair may influence neuronal-glia interactions *in vivo*, although this remains speculative (61). Therefore, in addition to the ability to produce various chemokines, microglia are poised to respond to various chemokine products by virtue of their expression of numerous chemokine receptors, which likely play a role in their accumulation at sites of neuroinflammation as well as serving as targets for infection by HIV as detailed in the following section.

5. MICROGLIA AND CHEMOKINES IN CNS INFECTIOUS DISEASES

5.1. Human immunodeficiency virus (HIV) encephalitis (HIVE)

CNS disease is usually a late complication of HIV-1 infection, although viral entry into the CNS is a relatively early phenomenon (62-64), revealing a considerable lag between the initial establishment of CNS infection and the onset of clinically overt disease. Nearly 25% of HIV-1 infected persons develop cognitive, behavioral, and/or motor abnormalities commonly referred

to as HIV-1-associated dementia (HAD). HIV encephalitis (HIVE) is a common manifestation of HAD and is characterized histologically by monocyte/macrophage infiltration into the brain, microglial nodules, formation of macrophage-derived multinucleated giant cells, and myelin pallor (65). The major pathway for HIV entry into the CNS is via infected monocytes/macrophages. Subsequent to their penetration through the blood-brain barrier, the principle targets of HIV-1 infection in the CNS are cells of the mononuclear phagocyte lineage where viral RNA and antigens have been demonstrated in association with macrophages, ramified microglia and multinucleated giant cells (66-69). Despite this infection pattern, the number of HIV infected cells and the amount of viral antigen in the CNS do not correlate well with measures of cognitive deficits in HAD (70, 71). This phenomenon coupled with the finding that the topographic distribution of apoptotic neurons in the CNS of HIV infected individuals is closely associated with markers of macrophage/microglial activation, suggests that factors released from activated macrophages/microglia are the source of neurotoxic compounds leading to neuronal dysfunction (72-74). Indeed, several reports have revealed that HIV-infected macrophages/microglia express elevated levels of numerous factors implicated in neurotoxicity including but not limited to, proinflammatory cytokines (TNF-alpha, IL-1beta, IL-6), chemokines (CCL4, CCL5), nitric oxide (NO), and excitatory amino acids (glutamate, L-cysteine) (73, 74). Therefore, these findings suggest that HIV infection in the CNS promotes neuronal injury and/or neurotoxicity through the release of soluble factors produced by infected macrophages/microglia.

In addition to HIV-1 infection triggering inflammatory mediator release from macrophages/microglia, there is evidence to suggest that viral proteins either directly shed from the virus or released from infected cells are capable of inducing macrophage/microglial activation. For example, recombinant HIV-1 proteins including Tat, Nef, and gp120 have been shown to induce neuropathology when directly injected into the brain, providing further support for the role of immune activation in the neurological dysfunction of HAD (75-79). Recent studies have demonstrated that the HIV-1 viral proteins Tat (46) and Vpr and Nef (80, 81) are capable of inducing CC chemokine expression in primary human fetal microglia and/or macrophages. In addition, HIV-1 Tat protein was found to co-localize with CCL3 and CCR5 expression in microglial nodules in tissues from HIVE patients (82). Collectively, these studies suggest that in addition to direct viral infection, HIV-1

Chemokines in CNS infectious diseases

Table 3. Chemokines associated with infectious diseases of the CNS in human and animal models

Disease ¹	Chemokine expression profiles	References
• HIVE, HAD	CCL2, CCL3, CCL4, CCL5	50, 98-102
Other viral encephalitides		
▪ CMV	CXCL10, CCL2, CCL4, CCL5, CCL7	110, 115, 117
▪ HSV	CXCL8, CXCL10, CCL2, CCL3, CCL5	113, 121
▪ MHV	CXCL9, CXCL10, CCL2, CCL4, CCL5, CCL7	127-129, 131, 132
• Brain Abscess	CXCL2, CCL1, CCL2, CCL3, CCL4, CCL5	40, 138, 140
• Bacterial meningitis		
▪ CSF of patients	CXCL8, CCL2, CCL3, CCL4	146-151
▪ <i>Listeria</i>	CXCL2, CCL3, CCL4	149, 152
▪ <i>Haemophilus</i>	CXCL2, CCL2, CCL3, CCL5	153
▪ <i>Strep. pneumoniae</i>	CXCL2, CXCL8	155, 156
▪ Other CNS infectious diseases		
▪ Toxoplasmosis	CXCL2, CXCL9, CXCL10, CCL2, CCL3, CCL4, CCL5, CCL7	160-162

¹ HIVE, human immunodeficiency virus-1 (HIV-1) encephalitis; HAD, HIV-1-associated dementia; CMV, cytomegalovirus; HSV, herpes simplex virus; MHV, mouse hepatitis virus, CSF, cerebrospinal fluid

proteins are capable of augmenting macrophage/microglial activation and subsequent chemokine production providing a potential mechanism for amplifying the CNS inflammatory response following HIV-1 infection.

Both chemokines and their receptors have been implicated as playing key roles in HIV infection and progression. The cellular tropism of HIV-1 is determined by the interactions of the viral envelope glycoprotein gp120 with CD4 in conjunction with a particular chemokine co-receptor(s). In general, macrophage-tropic (M-tropic) strains of HIV-1 utilize CCR5 as a co-receptor, whereas T cell-tropic viruses use CXCR4. Generally speaking, HIV-1 viruses that infect the CNS are M-tropic. In addition, there are other subsets of HIV-1 and HIV-2 that can utilize one or more alternative chemokine receptors, making the relationship between infection and co-receptor usage quite complex. The expression of several chemokine receptors has been found to be increased in patients with HAD compared to non-demented HIV-positive or uninfected controls including CCR1, CCR3, and CCR5, suggesting that chemokine receptors are intimately linked to the pathogenesis of HAD (50, 83). Indeed, macrophage-tropic strains of HIV-1 utilize CD4 along with the chemokine receptors CCR5 and CCR3 for productive infection (84-87). The first evidence that chemokine receptors serve as co-receptors for HIV-1 entry in microglia originated from studies demonstrating that the CC chemokines CCL4 and CCL11, ligands for CCR5 and CCR3, respectively, were capable of inhibiting HIV infection in primary human glia (48). Subsequent reports have confirmed the involvement of CCR5 in mediating HIV entry in microglia (88-90), however, another independent study found no evidence for either CCR5 or CCR3 as co-receptors for HIV-1 infection in primary human fetal microglia, suggesting the involvement of additional chemokine receptors whose usage is likely dependent on the viral variant (49, 91). The reasons responsible for the disparity in chemokine co-receptor usage reported in these studies is not clear but may be a result of differences in the purity and source of primary microglia as well as variations in the strains of HIV-1 evaluated. Although the chemokine receptors that serve as potential co-receptors for the entry of neurotropic HIV-1 strains have been characterized, the functional

importance of these molecules *in vivo* remains elusive. However, natural deletions/mutations in chemokine receptor genes in the human population have provided unique insights into the relative importance of various receptors in HIV-1 infection. For example, individuals homozygous for a 32-bp deletion in CCR5 are highly resistant to HIV-1 infection and peripheral blood mononuclear cells isolated from these individuals fail to support viral infection with M-tropic HIV-1 strains (92-96). In addition, individuals heterozygous for the CCR5 allele show slower progression to AIDS. Nonetheless, the evidence to date supports a role for chemokine receptors in the entry of HIV into macrophages/microglia.

Chemokine expression has also been postulated to play an important role in HIV infection. In particular, the production of CC chemokines in the infected CNS has been implicated in the recruitment of new pools of peripheral blood mononuclear cells that can serve as additional targets for HIV-1 infection (97). Indeed, several reports have revealed elevated levels of the CC chemokines CCL2, CCL3, CCL4, and CCL5 in the CSF or brain tissue of HIVE patients (50, 98-102; Table 3). However, the relative contribution of microglia to chemokine levels in HIVE remains unknown due to the difficulties in definitively differentiating resident activated microglia from infiltrating macrophages on the basis of immunohistochemical criteria. Interestingly, HIV-1-infected microglia have been shown to increase monocyte transmigration through an artificial blood-brain barrier model compared to uninfected cells, providing functional evidence that microglia serve as a potent source of CC chemokines following HIV-1 infection (103).

Interestingly, in addition to its tropism for macrophages/microglia, HIV-1 has been shown to non-productively infect astrocytes within the CNS (104-108). A recent study revealed that although viral replication was not sustained in HIV-1-infected primary human fetal astrocytes, treatment with IL-1beta or co-culture with macrophages led to the recovery of infectious virus from latently infected astrocytes (108). These findings suggest that astrocytes may serve as reservoirs of latent HIV-1 and upon reactivation serve as a source to propagate the infection to neighboring macrophages/microglia.

The consequences of chemokine expression in the pathogenesis of HIV are currently not defined but can be postulated to either favor or hinder infection, realizing that the two possibilities may not necessarily be mutually exclusive. As previously mentioned, numerous CC chemokines are produced subsequent to HIV-1 infection of primary macrophages/microglia and many of these same chemokines are detected at significant levels in HIV patients (50, 98-102). The CC chemokines CCL3, CCL4, and CCL5 have been reported to prevent the entry of HIV-1 into macrophages/microglia to variable extents (48, 84, 86, 89, 90), suggesting that chemokine release could be a protective host response following infection to compete with HIV-1 for co-receptor binding in an attempt to contain the spread of virus within the CNS. Conversely, enhanced CC chemokine production during the course of HIV may have deleterious consequences through the recruitment of additional peripheral blood mononuclear cells into the CNS that could serve as targets for new rounds of HIV-1 infection and replication (97). In addition, it is important to acknowledge the potential contribution of the relatively high mutation rate associated with the reverse transcriptase activity of HIV-1 to influence chemokine co-receptor usage. For example, over time the profile(s) of chemokine co-receptor usage may be substantially different from that utilized by the original parental virus due to the emergence of viral variants produced during the virus swarm stage of acute infection. Therefore, the release of CC chemokines by activated macrophages/microglia in the CNS may not have any effect on the infectivity of target cells by new viral variants. The overall consequences of CC chemokine expression in the context of HIV and progression to HAD remain to be completely defined but may be dictated by changes in viral phenotype and co-receptor usage throughout the evolution of disease.

5.2. Viral encephalitis

CNS infection with a number of different classes of viruses can provoke vigorous inflammatory responses with subsequent recruitment of large numbers of leukocytes. In viral encephalitis, the inflammatory response primarily involves activated T cells and monocytes that are recruited into the subarachnoid space. Chemokines produced locally within the CNS parenchyma play an important role in initiating the extravasation of responding leukocytes in viral encephalitis (Table 3). Indeed, CCL2 and CXCL10 have been identified as the main chemokines whose expression is elevated in the CSF of patients suffering from viral meningitis (109). Overall, the findings obtained from studies of animal models of viral encephalitis as well as from patient populations highlight a marked promiscuity in cerebral chemokine expression patterns with simultaneous expression of multiple chemokines being the general rule (110).

5.2.1. Cytomegalovirus (CMV) encephalitis

CMV encephalitis occurs primarily during fetal development and is a common opportunistic infection of patients in the advanced stages of AIDS. There is a wide range of complications associated with CMV encephalitis, ranging from long-term cognitive deficits to death. The pathologic manifestations of human CMV encephalitis

include two main forms: micronodular encephalitis and ventriculoencephalitis (111). Micronodular encephalitis is typified by diffuse microglial syncytia and astrocyte aggregates. In contrast, ventriculoencephalitis is a necrotizing infection of the ependyma and subependymal layers although occasionally the necrosis can extend deep into the brain parenchyma. *In vitro*, CMV has been shown to productively infect astrocytes but not mature neurons or microglia (112, 113). Due to strict viral host specificity, *in vivo* studies with CMV have obvious limitations. However, as is seen in human CMV disease, infection of mice with lymphocyte choriomeningitis virus (LCMV) develop an acute monophasic disease in the meninges, choroid plexus, and ependymal membranes leading to the development of seizures and death within 6 to 8 days following infection (114). The cellular infiltrates associated with CMV infection consist of predominantly macrophages and T cells which correlated with the production of numerous chemokines including CXCL10, CCL2, CCL4, CCL5, and CCL7 (110, 115). Although they are not permissive for CMV infection, microglia have been implicated in orchestrating peripheral immune cell infiltration following CMV stimulation as revealed by studies demonstrating that primary human microglia express numerous chemokines following exposure to CMV *in vitro* including CXCL8, CXCL10, CCL2, CCL3, and CCL5 (42, 110, 113, 116). In addition, enhanced levels of CCL2 have been detected in the CSF of HIV-infected patients with CMV encephalitis implicating CCL2 in macrophage/microglia recruitment and providing a potential mechanism to augment HIV-1 replication in the CNS (117).

5.2.2. Herpes simplex virus (HSV) encephalitis

HSV causes a devastating CNS infection that results in an acute focal necrotizing encephalitis with severe neuroinflammation and edema (118, 119). The mechanism(s) responsible for tissue damage following infection appear to involve both direct virus-mediated damage and indirect immune-mediated destruction of brain parenchyma. Indeed, studies have demonstrated that long-term neuroimmune activation and cytokine/chemokine production persist following HSV infection (120). Primary human astrocytes and neurons are permissive for CMV infection but do not serve as a source of proinflammatory cytokines or chemokines (121). In contrast, microglia do not support extensive viral replication but non-permissive CMV infection leads to the induction of a wide array of chemokine mediators including CXCL8, CXCL10, CCL3, and CCL5 (113, 121). The exact brain-specific chemokine events that regulate the course of HSV infection remain to be elucidated; however, there is evidence to suggest an important role for CCL2. CCL2 has been shown to play a pivotal role during the chronic phase of HSV-2-induced encephalomyelitis where its neutralization was found to improve disease severity (122). In addition, elevated levels of numerous chemokines including CCL2, CCL3, and CCL5 have been detected in the CSF of patients presenting with HSV-1 encephalitis and appear to correlate with disease severity (123), suggesting they influence the course of disease progression. Interestingly, recent evidence suggests that chemokines such as CXCL10 are capable of inhibiting HSV replication in primary neurons, providing

Chemokines in CNS infectious diseases

an alternative mechanism for these mediators in addition to their chemotactic properties (113, 121).

5.2.3. Mouse hepatitis virus (MHV)

MHV is a positive-strand RNA virus that infects the CNS and results in an acute encephalomyelitis followed by a chronic demyelinating disease that is similar in pathology to multiple sclerosis. A robust CNS immune response is elicited following MHV infection typified by the infiltration of macrophages/monocytes and CD4 and CD8 T cells (124), the latter of which are important for the clearance of infectious virus from the brain during acute disease (125-127). MHV infection of the CNS results in an orchestrated expression of the chemokines CXCL9, CXCL10, CCL2, CCL4, CCL5, and CCL7 suggesting an important role for these molecules in leukocyte recruitment (128). Functional evidence to support the importance of CC chemokines in the pathogenesis of MHV encephalitis is provided by recent studies using chemokine and chemokine receptor knockout mice. Infection of CCR5 KO mice with MHV, where CCR5 serves as the receptor for the CC chemokines CCL3, CCL4, and CCL5, resulted in defective T cell recruitment into the CNS along with a concomitant increase in viral burdens during the acute phase of disease (129). However, at the later stages of infection, the degree of lymphocytic infiltration and viral titers were similar between CCR5 KO and WT mice, suggesting that CCR5 expression is not essential for host defense and revealing the redundancy of chemokine receptors in leukocyte recruitment. In addition, MHV-infected CCR5 KO mice exhibited reduced macrophage/microglia infiltration that was associated with a significant reduction in the severity of demyelination during the chronic stage of MHV infection which has also been reproduced following neutralization of CCL5 in this model (127, 129). Studies with CCR2 knockout mice revealed that this receptor also plays a critical role in the host immune response to MHV in the CNS. An intracerebral inoculation of MHV in CCR2 KO mice resulted in increased mortality and viral burdens that correlated with impaired T cell and macrophage/microglial infiltration into the brain parenchyma (130).

Interestingly, although many of the chemokines induced following MHV infection in the CNS exhibit promiscuous receptor binding (i.e. CCL3, CCL4, and CCL5 binding to CCR5), studies using specific chemokine knockout mice reveal an important role for individual chemokines in the pathogenesis of MHV encephalitis. For example, CCL3 knockout mice exhibited reduced numbers of CD8-positive T cells in the CNS following MHV infection that correlated with delayed viral clearance (131). Furthermore, the absence of CCL3 led to a subsequent impairment in cytokine production along with a significant attenuation in macrophage influx into the infected CNS. Neutralization of CCL5 activity was also found to inhibit macrophage infiltration into the brain following MHV infection, suggesting it also influences the profile of infiltrating leukocytes (127). Finally, a recent study has revealed that CXCL10 is critical for the trafficking and generation of effector T cells following MHV infection (132). Collectively, these studies suggest that although the

chemokine-chemokine receptor families exhibit overlapping interactions, certain mediators appear more critical than others in dictating the course of MHV disease progression, revealing that our understanding of the complex interactions between chemokines-chemokine receptors in the pathogenesis of CNS infectious diseases remains to be completely defined.

5.2.4. Measles virus (MV)

Recent studies using a transgenic mouse model of neuron-restricted MV infection have revealed the expression of numerous chemokines within the CNS including CCL5 and CXCL10 (133, 134). Both CCL5 and CXCL10 were found to co-localize with MV-infected neurons *in vivo* with both chemokines also produced by primary hippocampal neurons from transgenic mice following infection with MV *in vitro* (134). Therefore, CCL5 and CXCL10 in the context of MV infection may play a role in the resultant anti-viral immune response in the CNS.

5.2.5. Chemokine-chemokine receptor mimicry by viruses

Many viruses, particularly those of the herpesvirus and poxvirus families, encode chemokine and chemokine receptor homologues that have been proposed to interfere with the action of endogenous chemokines and/or allow viruses to evade host defenses (135). For example, the M3 gene of gamma herpesvirus 68 encodes for a secreted protein that acts as a sink for endogenous CC chemokines by preventing their ligation to host CC receptors (136). This strategy may allow virus-infected cells to evade the host immune response by effectively reducing the number of effector leukocytes recruited into infected tissues due to low levels of functional chemokine expression. Studies with a M3 gamma herpesvirus mutant identified M3 as an essential virulence factor in that animals infected with mutant virus displayed lower viral burdens in the brain (136). Interestingly, the presence or absence of the viral M3 gene dictated the profile of the ensuing leukocyte infiltrate into the infected brain. Mice infected with the wild type M3 virus exhibited a predominant neutrophil infiltrate likely due to the blockade of endogenous CC chemokine gene expression by the M3 protein (136). In contrast, immune infiltrates in animals receiving the M3 mutant virus were typified by the influx of lymphocytes and macrophages due to the lack of antagonism of endogenous CC chemokine activity. In summary, it is clear from the experimental evidence that different viral infections of the CNS result in the simultaneous expression of multiple chemokine genes, the patterns of which are qualitatively similar.

5.3. Experimental brain abscess

Brain abscesses represent a significant medical problem, accounting for 1 in every 10,000 hospital admissions in the United States, and remain a serious situation despite recent advances made in detection and therapy (137). In addition, the emergence of multi-drug resistant strains of bacteria has become a confounding factor that is magnified the inability of many antibiotics to reach high therapeutic levels in brain tissue. In addition to

infection containment, the immune response that is an essential part of abscess formation also destroys surrounding normal brain tissue, which can have detrimental consequences. Indeed, some long-term effects following brain abscess resolution include seizures, loss of mental acuity, and focal neurological defects. Our laboratory has developed an experimental brain abscess model in the mouse using *S. aureus*, one of the main etiologic agents of brain abscess in humans (40, 138). The mouse brain abscess model closely mimics human disease, in that the abscess progresses through a series of well-defined stages (40, 139). The early stage, or early cerebritis, occurs from days 1 to 3 post-infection and is typified by neutrophil accumulation, tissue necrosis, and edema. Microglial and astrocyte activation are also hallmarks at this stage of disease and persist throughout the evolution of the lesion. The intermediate, or late cerebritis stage, occurs from days 4 to 9 and is associated with a predominant macrophage and lymphocyte infiltrate. The final, or capsule stage occurs from days 10 onward and is associated with the formation of a well-vascularized abscess wall, in effect sequestering the lesion and protecting the surrounding normal brain parenchyma. We have established that *S. aureus* leads to the immediate induction of proinflammatory cytokine and chemokine expression within the CNS parenchyma within 1 to 6 h following infection (40, 138, 140). Among the chemokines produced upon *S. aureus* infection include CXCL2, CCL1, CCL2, CCL3, CCL4, and CCL5 (40; Table 3). The rapid kinetics of chemokine induction following *S. aureus* infection implicated resident CNS cells as the initial source since peripheral immune cells do not begin to accumulate at significant levels until approximately 24 h following *S. aureus* exposure (40). In support of this hypothesis, we have recently demonstrated that both primary microglia and astrocytes are capable of recognizing both *S. aureus* and its cell wall product peptidoglycan (PGN), and respond by elaborating a similar array of chemokines detected in brain abscesses *in vivo* including CXCL2, CXCL10, CCL1, CCL2, CCL3, CCL4, and CCL5, implicating these cells in the initial inflammatory response to bacteria in the brain parenchyma (40, 41, 138). In addition to the direct damage induced by pathogens, the host anti-bacterial response elicited can be detrimental to neurons and other glia in the CNS due to the toxic effects of cytokines, chemokines, proteolytic enzymes, and oxidants produced locally at the site of infection. Indeed, we have recently demonstrated that the expression of CXCL2, a potent neutrophil chemokine, persists throughout the chronic stages of experimental brain abscess development in the context of relatively low bacterial burdens and correlated with the continued influx of neutrophils into the infected CNS (Baldwin and Kielian, manuscript submitted). Since neutrophils have been implicated in pathological tissue destruction, the continued influx and activation of these leukocytes may contribute to the extensive damage characteristic of brain abscesses although this remains to be determined.

Although we have characterized the profile of chemokine gene expression during the course of experimental brain abscess development, relatively little is

currently known regarding the functional importance of these mediators in disease pathogenesis. Recently, our laboratory has demonstrated the importance of CXCR2 ligands in the pathogenesis of experimental brain abscess using CXCR2 knockout mice (40). Neutrophil infiltration into brain abscesses was compromised in CXCR2 KO animals, with a concomitant increase in bacterial burdens observed during the later stages of infection. Strikingly, the majority of neutrophils in CXCR2 KO mice were sequestered within small blood vessels surrounding the lesion, most likely due to their inability to respond to the CXCR2 ligands MIP-2 and KC (40). This finding indicated that there is either a defect in tight adhesion or extravasation but not in the localization of neutrophils to vascular endothelium in CXCR2 KO mice. Interestingly, the levels of CXCL2 expression in brain abscesses from CXCR2 KO mice were found to be elevated compared to WT animals, suggesting that the loss of CXCR2 may interfere with an autocrine negative feedback loop(s) designed to regulate chemokine expression in the infected CNS. The relative paucity of neutrophils in the brains of CXCR2 KO mice indicates that CXCR2 ligands are the major chemotactic signals required for neutrophil influx into brain abscesses and that their activity cannot be substituted for by alternative chemotactic factors such as complement split products (i.e. C3a, C5a), prostaglandins, leukotrienes, or other chemokines. We are currently extending these studies to investigate the potential functional importance of additional chemokine mediators expressed during the course of experimental brain abscess development.

5.4. Bacterial meningitis

Bacterial meningitis is one of the top ten infectious causes of death worldwide, and approximately one-half of patients surviving the infection have neurological deficits and other sequelae of the disease (24, 141). To establish infection, the pathogen must gain access to the bloodstream, penetrate the blood-brain barrier (BBB), and replicate in the subarachnoid space. The major meningeal bacterial pathogens are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Hemophilus influenzae*, although other organisms are capable of causing disease which appears to be age-related (24, 137). The pathological changes that occur during meningitis include intense brain edema, impairments in cerebrospinal fluid (CSF) flow, increased intracranial pressure, seizures, and alterations in cerebral blood flow that may lead to focal areas of ischemia and necrosis. Peripheral immune cells are attracted into the infected subarachnoid space by inflammatory mediators that are initially produced by meningeal macrophages, ependymal cells, and choroid plexus epithelium, and later also by recently emigrated leukocytes and local microglia (142-144). In addition to the direct damage induced by pathogens during bacterial meningitis, the host anti-bacterial response elicited can be detrimental to neurons and other glia in the CNS due to the toxic effects of cytokines, chemokines, proteolytic enzymes, and oxidants produced locally at the site of infection (23, 24, 145).

Neutrophils represent the main leukocyte infiltrate associated with bacterial meningitis. Accordingly, CXCL8 is one of the predominant chemokines detected in

Chemokines in CNS infectious diseases

the CSF of patients with bacterial meningitis (146-150). However, in addition to CXCL8, the CSF of patients with bacterial meningitis have been shown to contain high levels of numerous CC chemokines including CCL2, CCL3, and CCL4 (147-151; Table 3). This finding is intriguing since mononuclear cells are not the predominant cell type observed in the CSF during the acute phase of bacterial meningitis.

5.4.1. *Listeria monocytogenes* (LM) and *Haemophilus influenzae* meningitis

LM is another causative agent of bacterial meningitis in humans. Within 24 h following intracerebral LM infection in an experimental mouse model, more than 80% of the invading cells were neutrophils whereas monocytes consisted of approximately 50% of the cellular infiltrate after 72 h. These infiltrates were associated with the production of the CXC and CC chemokines CXCL2, and CCL3 and CCL4, respectively (149, 152). Similar findings were obtained with a neonatal rat model of *Haemophilus influenzae* meningitis where infection led to an increase in CXCL2, CCL2, CCL3, and CCL5 expression within 24 to 48 h that correlated with the influx of neutrophils and macrophages into the meninges (153). The cellular localization of CCL5 expression in the *Haemophilus* meningitis model was identified as resident microglia and astrocytes whereas CCL2 was detected in astrocytes and infiltrating neutrophils and macrophages. The functional importance of CXCL2, CCL2, and CCL3 in inflammatory cell recruitment in the *Haemophilus* meningitis model has been demonstrated using neutralizing antibody studies. As expected, neutralization of CCL2 significantly decreased macrophage infiltration into the meninges; however, unexpectedly, treatment of infected neonatal rats with either antibodies against CXCL2 or CCL3 led to a diminution in neutrophil infiltrates (153). The latter is particularly intriguing since CCL3, a known CC chemokine, is not capable of inducing neutrophil chemotaxis *in vitro*. A separate study examining the effects of systemic LPS on immune cell influx into the lung has also implicated CCL3 in neutrophil recruitment *in vivo* (154). It is not clear whether these findings represent a direct action of CCL3 on neutrophils *in vivo*, or if CCL3 induces the subsequent expression of alternative CXC chemokines leading to neutrophil infiltration.

5.4.2. *Streptococcus pneumoniae* meningitis

To date, the majority of experimental meningitis models have utilized a direct intracerebral route of pathogen inoculation to evaluate the course of disease progression. A recent report has established an intranasal model of experimental pneumococcal meningitis in the mouse using *Streptococcus pneumoniae* to more accurately mimic the route of natural infection in humans (155). As has been observed in other meningitis models, intranasal delivery of *Streptococcus pneumoniae* led to the expression of the neutrophil chemokine CXCL2, the murine functional homologue of human CXCL8. Other studies using experimental meningitis models have sought to determine the functional contribution of CXCL8 in the pathogenesis of disease and have revealed an intriguing relationship between the route of chemokine neutralization and the resultant effect on neutrophil influx into the CNS. In a

rabbit model of *Streptococcus pneumoniae*-induced meningitis, intravenous treatment with CXCL8 neutralizing antibodies significantly attenuated leukocyte influx into the CSF whereas intracisternal delivery had no effect on cellular infiltration (156). Similar findings were obtained in a rabbit model of experimental LPS-induced meningitis (157), collectively arguing that the functional activity of CXCL8 in mediating leukocyte entry into the CSF appears to be located on the bloodstream side of the microvascular endothelium of the blood-brain barrier. In summary, a much broader array of chemokines are expressed in bacterial meningitis compared to viral meningitis and the former is typified by quantitatively higher levels of chemokine expression in the CSF (149). This may be the result of higher levels of immunostimulatory products associated with bacterial infections such as cell wall products and/or secreted virulence factors inducing maximal chemokine expression in the CNS. However, additional studies are needed to ascertain the relative importance and redundancy of individual chemokine mediators in the context of bacterial meningitis and whether effective therapeutic approaches can stem from manipulation of the chemokine milieu following infection.

5.5. Other CNS infectious diseases

Several studies have examined the profile of chemokine expression following exposure to numerous other CNS pathogens including *Toxoplasma gondii*, mouse adenovirus-type 1, *Cryptococcus neoformans*, and prions, each revealing the importance of chemokine induction in peripheral immune cell recruitment into the CNS (Table 3).

5.5.1. *Toxoplasma gondii*

Toxoplasmosis caused by the intracellular protozoan *Toxoplasma gondii* is a widespread parasitic infection affecting both humans and animals. Natural infection with *T. gondii* results from the ingestion of cysts or oocysts found in infected animal meat or feline feces. Once ingested, the parasite matures into a tachyzoite, invades the intestines and disseminates to most organs including the CNS (158, 159). *T. gondii* infection induces a strong cell-mediated immune response that leads to the transformation of tachyzoites into dormant cysts, resulting in a chronic, asymptomatic infection. In the brain, *T. gondii* infection has been shown to induce the widespread expression of numerous chemokines including CXCL2, CXCL9, CXCL10, CCL2, CCL3, CCL4, CCL5, and CCL7 that correlated with the coordinate recruitment of leukocytes into the CNS (160-162). Microglia were found to be the source of CCL5 and CXCL9 expression following *T. gondii* infection in the CNS, whereas astrocytes were the major producers of CXCL10 and CCL2 (161, 162). The functional importance of CXCL10 in *T. gondii* infection has been demonstrated by antibody neutralization studies in mice. Administration of anti-CXCL10 led to increases in mortality and enhanced parasite burdens in the brain tissue of *T. gondii* infected animals, suggesting that CXCL10 plays a critical role in the anti-parasitic immune response in the CNS (160). Likewise, CCR1 and CXCR2 have been reported to influence the pathogenesis of *Toxoplasma* infection as evident by enhanced parasite burdens in the brains of both CCR1 and CXCR2 knockout mice compared to wild type littermates (163, 164).

Chemokines in CNS infectious diseases

5.5.2. Mouse adenovirus-type 1 (MAV-1)

MAV-1 infection leads to a fatal hemorrhagic encephalopathy in susceptible strains of mice, where pathology is induced by the productive infection of cerebral vascular endothelial cells resulting in necrosis of the vasculature and subsequent infarction and hemorrhage (165, 166). MAV-1 infection leads to the induction of numerous chemokines and chemokine receptors in the CNS including CXCL10, CCL2, CCL3, CCL4, CCL5, and CCR1-5, suggesting an important role for these chemokines-chemokine receptors in disease progression (167).

5.5.3. *Cryptococcus neoformans*

Cryptococcus neoformans is a common opportunistic infection of AIDS patients with infection being acquired via the respiratory tract and disseminating to the CNS (168, 169). Immunity against disseminated *C. neoformans* is mediated primarily by macrophages and T cells, suggesting the importance of CNS-derived chemokines in the effective recruitment of these effector cell types to contain infection. An important role for CCR5 in controlling the dissemination and growth of *C. neoformans* in the brain was recently established using CCR5 knockout mice. Interestingly, although CCR5 KO animals had no observable defects in leukocyte extravasation into the lungs, mononuclear cell infiltrates were significantly reduced in the brains of KO mice that correlated with the development of clinical signs of cryptococcal meningitis, a finding that was not manifested in wild type animals (170). In addition, CCL3 has been shown to be another critical chemokine in CNS cryptococcal infection, where CCL3 KO mice were found to exhibit decreased leukocyte recruitment and cryptococcal clearance from the brain compared to wild type animals (171).

5.5.4. Prion model of neurodegeneration

Finally, in a prion model of chronic neurodegeneration, the expression of CX3CL1 was found to be increased in astrocytes while its receptor CX3CR1 was augmented in microglia suggesting that interactions between this chemokine-chemokine receptor pair may influence the nature of the local cytokine milieu during chronic inflammation in the CNS (57).

6. CONCLUSIONS AND PERSPECTIVES

Several divergent CNS pathogens lead to the systematic induction of numerous chemokines and regulate chemokine receptor expression. The use of chemokine and chemokine receptor knockout mice has begun to allow for the identification of key mediators involved in various CNS infectious diseases; however, much remains to be learned regarding the complex interactions between chemokines and chemokine receptors *in vivo*. Remarkably, although many CNS infections are typified by the simultaneous induction of numerous chemokine mediators, many with redundant activities, studies using knockout mice have revealed important roles for individual chemokines. This finding raises the possibility of alternative functions for chemokines in the context of CNS infectious diseases that have not yet been appreciated.

Microglia are a major source of both CC and CXC chemokines in the inflamed CNS. Indeed, activated microglia are thought not only to participate in the generation of protective pathogen-specific immune responses, but under certain circumstances can contribute to excessive CNS tissue damage through the dysregulated release of proinflammatory cytokines and chemokines. For example, the production of CC chemokines by activated macrophages/microglia during HIV-1 encephalitis may inadvertently facilitate ongoing CNS infection through the recruitment of mononuclear cells that can serve as targets for new rounds of virus replication.

A relatively new approach available to discriminate between the actions of various chemokines and chemokine receptors in the context of CNS infectious diseases will be through the use of newly designed small molecule inhibitors or agonists of chemokine receptors. Alternatively, inhibition of microglial activation by classes of structurally distinct anti-inflammatory compounds known to attenuate glial cytokine and chemokine expression, such as minocycline and peroxisome proliferator-activated receptor agonists (PPARs) may be capable of modulating peripheral immune cell infiltrates into the CNS and infectious disease progression (172-176). However, issues related to the timing and dose of drug administration will be important to consider since quelling the CNS immune response prior to effective pathogen neutralization in the brain will likely have undesirable consequences. Importantly, in addition to their effects on resident microglia, minocycline and PPAR-gamma agonists may also influence the responses of peripheral immune cells recruited into the infected CNS. Finally, another intriguing issue to consider regarding the role of microglia in infectious diseases of the CNS relates to the functional heterogeneity of microglia in various CNS compartments. Although regional variation in microglial responses has been proposed for quite some time, evidence in the past few years has provided functional proof that microglial activation may be dictated, in part, by the CNS microenvironment (177-179). Therefore, it will be important to investigate whether the production of chemokines by activated microglia differs in various brain regions in the context of CNS infectious diseases and whether functional differences can be linked to pathology.

In summary, the findings obtained from studies of animal models of CNS infectious diseases as well as from patient populations highlight a marked promiscuity in cerebral chemokine expression patterns with simultaneous expression of multiple chemokines being the general rule. Microglia serve as a major source of many of these chemokines suggesting they play an important role in orchestrating the ensuing immune response to CNS pathogens. In addition, microglia express several chemokine receptors that are likely involved in their recruitment and activation during the acute stages of infection, effectively allowing for the amplification of pathogen-specific immune responses. Future studies dissecting the potential roles of individual chemokines and their receptors in the context of CNS infectious diseases

may provide insights into the complex regulatory network dictating neuroinflammatory responses.

7. ACKNOWLEDGEMENTS

I would like to thank my colleague Dr. Paul Drew for critical review of the manuscript. This work was supported in part, by NIH RO1 NS40730 and MH65297 (both to T.K.).

8. REFERENCES

1. Aloisi, F: Immune function of microglia. *Glia* 36, 165-179 (2001)
2. Hanisch, U. K: Microglia as a source and target of cytokines. *Glia* 40, 140-155 (2002)
3. Benveniste, E. N: Role of macrophages/microglia in multiple sclerosis and experimental allergic encephalomyelitis. *J Mol Med* 75, 165-173 (1997)
4. Combs, C. K. Karlo, J. C. Kao, S. C. & G. E. Landreth: beta-Amyloid stimulation of microglia and monocytes results in TNFalpha-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. *J Neurosci* 21, 1179-1188 (2001)
5. Meda, L. Cassatella, M. A. Szendrei, G. I. Otvos, L., Jr. Baron, P. Villalba, M. Ferrari, D. & F. Rossi: Activation of microglial cells by beta-amyloid protein and interferon-gamma. *Nature* 374, 647-650 (1995)
6. Renno, T. Krakowski, M. Piccirillo, C. Lin, J. Y. & T. Owens: TNF-alpha expression by resident microglia and infiltrating leukocytes in the central nervous system of mice with experimental allergic encephalomyelitis. Regulation by Th1 cytokines. *J Immunol* 154, 944-953 (1995)
7. Tran, E. H. Hardin-Pouzet, H. Verge, G. & T. Owens: Astrocytes and microglia express inducible nitric oxide synthase in mice with experimental allergic encephalomyelitis. *J Neuroimmunol* 74, 121-129 (1997)
8. Rollins, B. J: Chemokines. *Blood* 90, 909-928 (1997)
9. Luster, A. D: Chemokines--chemotactic cytokines that mediate inflammation. *N Engl J Med* 338, 436-445 (1998)
10. Ransohoff, R. M: The chemokine system in neuroinflammation: an update. *J Infect Dis* 186 Suppl 2, S152-156 (2002)
11. Zlotnik, A. & O. Yoshie: Chemokines: a new classification system and their role in immunity. *Immunity* 12, 121-127 (2000)
12. Bacon, K. Baggiolini, M. Broxmeyer, H. Horuk, R. Lindley, I. Mantovani, A. Maysushima, K. Murphy, P. Nomiya, H. Oppenheim, J. Rot, A. Schall, T. Tsang, M. Thorpe, R. Van Damme, J. Wadhwa, M. Yoshie, O. Zlotnik, A. & K. Zoon: Chemokine/chemokine receptor

nomenclature. *J Interferon Cytokine Res* 22, 1067-1068 (2002)

13. Koch, A. E. Polverini, P. J. Kunkel, S. L. Harlow, L. A. DiPietro, L. A. Elner, V. M. Elner, S. G. & R. M. Strieter: Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science* 258, 1798-1801 (1992)
14. Strieter, R. M. Polverini, P. J. Arenberg, D. A. Walz, A. Opdenakker, G. Van Damme, J. & S. L. Kunkel: Role of C-X-C chemokines as regulators of angiogenesis in lung cancer. *J Leukoc Biol* 57, 752-762 (1995)
15. Koch, A. E. Volin, M. V. Woods, J. M. Kunkel, S. L. Connors, M. A. Harlow, L. A. Woodruff, D. C. Burdick, M. D. & R. M. Strieter: Regulation of angiogenesis by the C-X-C chemokines interleukin-8 and epithelial neutrophil activating peptide 78 in the rheumatoid joint. *Arthritis Rheum* 44, 31-40 (2001)
16. Bazan, J. F. Bacon, K. B. Hardiman, G. Wang, W. Soo, K. Rossi, D. Greaves, D. R. Zlotnik, A. & T. J. Schall: A new class of membrane-bound chemokine with a CX3C motif. *Nature* 385, 640-644 (1997)
17. Pan, Y. Lloyd, C. Zhou, H. Dolich, S. Deeds, J. Gonzalo, J. A. Vath, J. Gosselin, M. Ma, J. Dussault, B. Woolf, E. Alperin, G. Culpepper, J. Gutierrez-Ramos, J. C. & D. Gearing: Neurotactin, a membrane-anchored chemokine upregulated in brain inflammation. *Nature* 387, 611-617 (1997)
18. Tong, N. Perry, S. W. Zhang, Q. James, H. J. Guo, H. Brooks, A. Bal, H. Kinnear, S. A. Fine, S. Epstein, L. G. Dairaghi, D. Schall, T. J. Gendelman, H. E. Dewhurst, S. Sharer, L. R. & H. A. Gelbard: Neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system. *J Immunol* 164, 1333-1339 (2000)
19. Maciejewski-Lenoir, D. Chen, S. Feng, L. Maki, R. & K. B. Bacon: Characterization of fractalkine in rat brain cells: migratory and activation signals for CX3CR1-expressing microglia. *J Immunol* 163, 1628-1635 (1999)
20. Imai, T. Hieshima, K. Haskell, C. Baba, M. Nagira, M. Nishimura, M. Kakizaki, M. Takagi, S. Nomiya, H. Schall, T. J. & O. Yoshie: Identification and molecular characterization of fractalkine receptor CX3CR1, which mediates both leukocyte migration and adhesion. *Cell* 91, 521-530 (1997)
21. Cross, A. K. & M. N. Woodroffe: Chemokines induce migration and changes in actin polymerization in adult rat brain microglia and a human fetal microglial cell line in vitro. *J Neurosci Res* 55, 17-23 (1999)
22. Cross, A. K. & M. N. Woodroffe: Chemokine modulation of matrix metalloproteinase and TIMP production in adult rat brain microglia and a human microglial cell line in vitro. *Glia* 28, 183-189 (1999)

Chemokines in CNS infectious diseases

23. Koedel, U. Scheld, W. M. & H. W. Pfister: Pathogenesis and pathophysiology of pneumococcal meningitis. *Lancet Infect Dis* 2, 721-736 (2002)
24. Scheld, W. M. Koedel, U. Nathan, B. & H. W. Pfister: Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. *J Infect Dis* 186 Suppl 2, S225-233 (2002)
25. Hayashi, M. Luo, Y. Laning, J. Strieter, R. M. & M. E. Dorf: Production and function of monocyte chemoattractant protein-1 and other beta-chemokines in murine glial cells. *J Neuroimmunol* 60, 143-150 (1995)
26. Calvo, C. F. Yoshimura, T. Gelman, M. & M. Mallat: Production of monocyte chemotactic protein-1 by rat brain macrophages. *Eur J Neurosci* 8, 1725-1734 (1996)
27. Ren, L. Q. Gourmala, N. Boddeke, H. W. & P. J. Gebicke-Haerter: Lipopolysaccharide-induced expression of IP-10 mRNA in rat brain and in cultured rat astrocytes and microglia. *Brain Res Mol Brain Res* 59, 256-263 (1998)
28. Spleiss, O. Gourmala, N. Boddeke, H. W. Sauter, A. Fiebich, B. L. Berger, M. & P. J. Gebicke-Haerter: Cloning of rat HIV-1-chemokine coreceptor CKR5 from microglia and upregulation of its mRNA in ischemic and endotoxemic rat brain. *J Neurosci Res* 53, 16-28 (1998)
29. Gourmala, N. G. Limonta, S. Bochelen, D. Sauter, A. & H. W. Boddeke: Localization of macrophage inflammatory protein: macrophage inflammatory protein-1 expression in rat brain after peripheral administration of lipopolysaccharide and focal cerebral ischemia. *Neuroscience* 88, 1255-1266 (1999)
30. De Groot, C. J. & M. N. Woodroffe: The role of chemokines and chemokine receptors in CNS inflammation. *Prog Brain Res* 132, 533-544 (2001)
31. Gebicke-Haerter, P. J. Spleiss, O. Ren, L. Q. Li, H. Dichmann, S. Norgauer, J. & H. W. Boddeke: Microglial chemokines and chemokine receptors. *Prog Brain Res* 132, 525-532 (2001)
32. Thibeault, I. Laflamme, N. & S. Rivest: Regulation of the gene encoding the monocyte chemoattractant protein 1 (MCP-1) in the mouse and rat brain in response to circulating LPS and proinflammatory cytokines. *J Comp Neurol* 434, 461-477 (2001)
33. Lee, Y. B. Nagai, A. & S. U. Kim: Cytokines, chemokines, and cytokine receptors in human microglia. *J Neurosci Res* 69, 94-103 (2002)
34. Hausler, K. G. Prinz, M. Nolte, C. Weber, J. R. Schumann, R. R. Kettenmann, H. & U. K. Hanisch: Interferon-gamma differentially modulates the release of cytokines and chemokines in lipopolysaccharide- and pneumococcal cell wall-stimulated mouse microglia and macrophages. *Eur J Neurosci* 16, 2113-2122 (2002)
35. Peterson, P. K. Hu, S. Salak-Johnson, J. Molitor, T. W. & C. C. Chao: Differential production of and migratory response to beta chemokines by human microglia and astrocytes. *J Infect Dis* 175, 478-481 (1997)
36. Ehrlich, L. C. Hu, S. Sheng, W. S. Sutton, R. L. Rockswold, G. L. Peterson, P. K. & C. C. Chao: Cytokine regulation of human microglial cell IL-8 production. *J Immunol* 160, 1944-1948 (1998)
37. McManus, C. M. Brosnan, C. F. & J. W. Berman: Cytokine induction of MIP-1 alpha and MIP-1 beta in human fetal microglia. *J Immunol* 160, 1449-1455 (1998)
38. Hu, S. Chao, C. C. Ehrlich, L. C. Sheng, W. S. Sutton, R. L. Rockswold, G. L. & P. K. Peterson: Inhibition of microglial cell RANTES production by IL-10 and TGF-beta. *J Leukoc Biol* 65, 815-821 (1999)
39. Hua, L. L. & S. C. Lee: Distinct patterns of stimulus-inducible chemokine mRNA accumulation in human fetal astrocytes and microglia. *Glia* 30, 74-81 (2000)
40. Kielian, T. Barry, B. & W. F. Hickey: CXC chemokine receptor-2 ligands are required for neutrophil-mediated host defense in experimental brain abscesses. *J Immunol* 166, 4634-4643 (2001)
41. Kielian, T., Mayes, P., & M. Kielian: Characterization of microglial responses to *Staphylococcus aureus*: effects on cytokine, costimulatory molecule, and Toll-like receptor expression. *J Neuroimmunol* 130(1-2), 86-99. (2002)
42. Cheeran, M. C. Hu, S. Sheng, W. S. Peterson, P. K. & J. R. Lokensgard: CXCL10 production from cytomegalovirus-stimulated microglia is regulated by both human and viral interleukin-10. *J Virol* 77, 4502-4515 (2003)
43. Palma, J. P. & B. S. Kim: Induction of selected chemokines in glial cells infected with Theiler's virus. *J Neuroimmunol* 117, 166-170 (2001)
44. Takeshita, S. Takeshita, F. Haddad, D. E. Janabi, N. & D. M. Klinman: Activation of microglia and astrocytes by CpG oligodeoxynucleotides. *Neuroreport* 12, 3029-3032 (2001)
45. Boddeke, E. W. Meigel, I. Frenz, S. Gourmala, N. G. Harrison, J. K. Buttini, M. Spleiss, O. & P. Gebicke-Haerter: Cultured rat microglia express functional beta-chemokine receptors. *J Neuroimmunol* 98, 176-184 (1999)
46. McManus, C. M. Weidenheim, K. Woodman, S. E. Nunez, J. Hesselgesser, J. Nath, A. & J. W. Berman: Chemokine and chemokine-receptor expression in human glial elements: induction by the HIV protein, Tat, and chemokine autoregulation. *Am J Pathol* 156, 1441-1453 (2000)
47. Rezaie, P. Trillo-Pazos, G. Everall, I. P. & D. K. Male: Expression of beta-chemokines and chemokine receptors in human fetal astrocyte and microglial co-cultures: potential role of chemokines in the developing CNS. *Glia* 37, 64-75 (2002)

48. He, J. Chen, Y. Farzan, M. Choe, H. Ohagen, A. Gartner, S. Busciglio, J. Yang, X. Hofmann, W. Newman, W. Mackay, C. R. Sodroski, J. & D. Gabuzda: CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. *Nature* 385, 645-649 (1997)
49. Ghorpade, A. Xia, M. Q. Hyman, B. T. Persidsky, Y. Nukuna, A. Bock, P. Che, M. Limoges, J. Gendelman, H. E. & C. R. Mackay: Role of the beta-chemokine receptors CCR3 and CCR5 in human immunodeficiency virus type 1 infection of monocytes and microglia. *J Virol* 72, 3351-3361 (1998)
50. Sanders, V. J. Pittman, C. A. White, M. G. Wang, G. Wiley, C. A. & C. L. Achim: Chemokines and receptors in HIV encephalitis. *Aids* 12, 1021-1026 (1998)
51. Flynn, G. Maru, S. Loughlin, J. Romero, I. A. & D. Male: Regulation of chemokine receptor expression in human microglia and astrocytes. *J Neuroimmunol* 136, 84-93 (2003)
52. Rottman, J. B. Ganley, K. P. Williams, K. Wu, L. Mackay, C. R. & D. J. Ringler: Cellular localization of the chemokine receptor CCR5. Correlation to cellular targets of HIV-1 infection. *Am J Pathol* 151, 1341-1351 (1997)
53. Lavi, E. Strizki, J. M. Ulrich, A. M. Zhang, W. Fu, L. Wang, Q. O'Connor, M. Hoxie, J. A. & F. Gonzalez-Scarano: CXCR-4 (Fusin), a co-receptor for the type 1 human immunodeficiency virus (HIV-1), is expressed in the human brain in a variety of cell types, including microglia and neurons. *Am J Pathol* 151, 1035-1042 (1997)
54. Jiang, Y. Salafranca, M. N. Adhikari, S. Xia, Y. Feng, L. Sonntag, M. K. deFiebre, C. M. Pennell, N. A. Streit, W. J. & J. K. Harrison: Chemokine receptor expression in cultured glia and rat experimental allergic encephalomyelitis. *J Neuroimmunol* 86, 1-12 (1998)
55. Boddeke, E. W. Meigel, I. Frentzel, S. Biber, K. Renn, L. Q. & P. Gebicke-Harter: Functional expression of the fractalkine (CX3C) receptor and its regulation by lipopolysaccharide in rat microglia. *Eur J Pharmacol* 374, 309-313 (1999)
56. Jung, S. Aliberti, J. Graemmel, P. Sunshine, M. J. Kreuzberg, G. W. Sher, A. & D. R. Littman: Analysis of fractalkine receptor CX(3)CR1 function by targeted deletion and green fluorescent protein reporter gene insertion. *Mol Cell Biol* 20, 4106-4114 (2000)
57. Hughes, P. M. Botham, M. S. Frentzel, S. Mir, A. & V. H. Perry: Expression of fractalkine (CX3CL1) and its receptor, CX3CR1, during acute and chronic inflammation in the rodent CNS. *Glia* 37, 314-327 (2002)
58. Mizuno, T. Kawanokuchi, J. Numata, K. & A. Suzumura: Production and neuroprotective functions of fractalkine in the central nervous system. *Brain Res* 979, 65-70 (2003)
59. Harrison, J. K. Jiang, Y. Chen, S. Xia, Y. Maciejewski, D. McNamara, R. K. Streit, W. J. Salafranca, M. N. Adhikari, S. Thompson, D. A. Botti, P. Bacon, K. B. & L. Feng: Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. *Proc Natl Acad Sci U S A* 95, 10896-10901 (1998)
60. Schwaeble, W. J. Stover, C. M. Schall, T. J. Dairaghi, D. J. Trinder, P. K. Linington, C. Iglesias, A. Schubart, A. Lynch, N. J. Weihe, E. & M. K. Schafer: Neuronal expression of fractalkine in the presence and absence of inflammation. *FEBS Lett* 439, 203-207 (1998)
61. Bacon, K. B. & J. K. Harrison: Chemokines and their receptors in neurobiology: perspectives in physiology and homeostasis. *J Neuroimmunol* 104, 92-97 (2000)
62. Goudsmit, J. de Wolf, F. Paul, D. A. Epstein, L. G. Lange, J. M. Krone, W. J. Speelman, H. Wolters, E. C. Van der Noordaa, J. Oleske, J. M. & et al.: Expression of human immunodeficiency virus antigen (HIV-Ag) in serum and cerebrospinal fluid during acute and chronic infection. *Lancet* 2, 177-180 (1986)
63. Resnick, L. Berger, J. R. Shapshak, P. & W. W. Tourtellotte: Early penetration of the blood-brain-barrier by HIV. *Neurology* 38, 9-14 (1988)
64. Achim, C. L. & C. A. Wiley: Inflammation in AIDS and the role of the macrophage in brain pathology. *Curr Opin Neurol* 9, 221-225 (1996)
65. Lipton, S. A. & H. E. Gendelman: Seminars in medicine of the Beth Israel Hospital, Boston. Dementia associated with the acquired immunodeficiency syndrome. *N Engl J Med* 332, 934-940 (1995)
66. Koenig, S. Gendelman, H. E. Orenstein, J. M. Dal Canto, M. C. Pezeshkpour, G. H. Yungbluth, M. Janotta, F. Aksamit, A. Martin, M. A. & A. S. Fauci: Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. *Science* 233, 1089-1093 (1986)
67. Michaels, J. Price, R. W. & M. K. Rosenblum: Microglia in the giant cell encephalitis of acquired immune deficiency syndrome: proliferation, infection and fusion. *Acta Neuropathol (Berl)* 76, 373-379 (1988)
68. Kure, K. Lyman, W. D. Weidenheim, K. M. & D. W. Dickson: Cellular localization of an HIV-1 antigen in subacute AIDS encephalitis using an improved double-labeling immunohistochemical method. *Am J Pathol* 136, 1085-1092 (1990)
69. Kure, K. Weidenheim, K. M. Lyman, W. D. & D. W. Dickson: Morphology and distribution of HIV-1 gp41-positive microglia in subacute AIDS encephalitis. Pattern of involvement resembling a multisystem degeneration. *Acta Neuropathol (Berl)* 80, 393-400 (1990)

Chemokines in CNS infectious diseases

70. Glass, J. D. Fedor, H. Wesselingh, S. L. & J. C. McArthur: Immunocytochemical quantitation of human immunodeficiency virus in the brain: correlations with dementia. *Ann Neurol* 38, 755-762 (1995)
71. Masliah, E. Heaton, R. K. Marcotte, T. D. Ellis, R. J. Wiley, C. A. Mallory, M. Achim, C. L. McCutchan, J. A. Nelson, J. A. Atkinson, J. H. & I. Grant: Dendritic injury is a pathological substrate for human immunodeficiency virus-related cognitive disorders. HNRC Group. The HIV Neurobehavioral Research Center. *Ann Neurol* 42, 963-972 (1997)
72. Adle-Biassette, H. Chretien, F. Wingertsmann, L. Hery, C. Ereau, T. Scaravilli, F. Tardieu, M. & F. Gray: Neuronal apoptosis does not correlate with dementia in HIV infection but is related to microglial activation and axonal damage. *Neuropathol Appl Neurobiol* 25, 123-133 (1999)
73. Garden, G. A.: Microglia in human immunodeficiency virus-associated neurodegeneration. *Glia* 40, 240-251 (2002)
74. Kaul, M. Garden, G. A. & S. A. Lipton: Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature* 410, 988-994 (2001)
75. Wang, P. Barks, J. D. & F. S. Silverstein: Tat, a human immunodeficiency virus-1-derived protein, augments excitotoxic hippocampal injury in neonatal rats. *Neuroscience* 88, 585-597 (1999)
76. Bansal, A. K. Mactutus, C. F. Nath, A. Maragos, W. Hauser, K. F. & R. M. Booze: Neurotoxicity of HIV-1 proteins gp120 and Tat in the rat striatum. *Brain Res* 879, 42-49 (2000)
77. Sporer, B. Koedel, U. Paul, R. Kohleisen, B. Erfle, V. Fontana, A. & H. W. Pfister: Human immunodeficiency virus type-1 Nef protein induces blood-brain barrier disruption in the rat: role of matrix metalloproteinase-9. *J Neuroimmunol* 102, 125-130 (2000)
78. Corasaniti, M. T. Piccirilli, S. Paoletti, A. Nistico, R. Stringaro, A. Malorni, W. Finazzi-Agro, A. & G. Bagetta: Evidence that the HIV-1 coat protein gp120 causes neuronal apoptosis in the neocortex of rat via a mechanism involving CXCR4 chemokine receptor. *Neurosci Lett* 312, 67-70 (2001)
79. Corasaniti, M. T. Maccarrone, M. Nistico, R. Malorni, W. Rotiroti, D. & G. Bagetta: Exploitation of the HIV-1 coat glycoprotein, gp120, in neurodegenerative studies in vivo. *J Neurochem* 79, 1-8 (2001)
80. Swingler, S. Mann, A. Jacque, J. Brichacek, B. Sasseville, V. G. Williams, K. Lackner, A. A. Janoff, E. N. Wang, R. Fisher, D. & M. Stevenson: HIV-1 Nef mediates lymphocyte chemotaxis and activation by infected macrophages. *Nat Med* 5, 997-103 (1999)
81. Si, Q. Kim, M. O. Zhao, M. L. Landau, N. R. Goldstein, H. & S. Lee: Vpr- and Nef-dependent induction of RANTES/CCL5 in microglial cells. *Virology* 301, 342-353 (2002)
82. Bonwetsch, R. Croul, S. Richardson, M. W. Lorenzana, C. Valle, L. D. Sverstiuk, A. E. Amini, S. Morgello, S. Khalili, K. & J. Rappaport: Role of HIV-1 Tat and CC chemokine MIP-1alpha in the pathogenesis of HIV associated central nervous system disorders. *J Neurovirol* 5, 685-694 (1999)
83. Vallat, A. V. De Girolami, U. He, J. Mhashilkar, A. Marasco, W. Shi, B. Gray, F. Bell, J. Keohane, C. Smith, T. W. & D. Gabuzda: Localization of HIV-1 co-receptors CCR5 and CXCR4 in the brain of children with AIDS. *Am J Pathol* 152, 167-178 (1998)
84. Alkhatib, G. Combadiere, C. Broder, C. C. Feng, Y. Kennedy, P. E. Murphy, P. M. & E. A. Berger: CC CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* 272, 1955-1958 (1996)
85. Choe, H. Farzan, M. Sun, Y. Sullivan, N. Rollins, B. Ponath, P. D. Wu, L. Mackay, C. R. LaRosa, G. Newman, W. Gerard, N. Gerard, C. & J. Sodroski: The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* 85, 1135-1148 (1996)
86. Deng, H. Liu, R. Ellmeier, W. Choe, S. Unutmaz, D. Burkhart, M. Di Marzio, P. Marmon, S. Sutton, R. E. Hill, C. M. Davis, C. B. Peiper, S. C. Schall, T. J. Littman, D. R. & N. R. Landau: Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 381, 661-666 (1996)
87. Doranz, B. J. Rucker, J. Yi, Y. Smyth, R. J. Samson, M. Peiper, S. C. Parmentier, M. Collman, R. G. & R. W. Doms: A dual-tropic primary HIV-1 isolate that uses fusin and the beta-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell* 85, 1149-1158 (1996)
88. Shieh, J. T. Albright, A. V. Sharron, M. Gartner, S. Strizki, J. Doms, R. W. & F. Gonzalez-Scarano: Chemokine receptor utilization by human immunodeficiency virus type 1 isolates that replicate in microglia. *J Virol* 72, 4243-4249 (1998)
89. Albright, A. V. Shieh, J. T. Itoh, T. Lee, B. Pleasure, D. O'Connor, M. J. Doms, R. W. & F. Gonzalez-Scarano: Microglia express CCR5, CXCR4, and CCR3, but of these, CCR5 is the principal coreceptor for human immunodeficiency virus type 1 dementia isolates. *J Virol* 73, 205-213 (1999)
90. Kitai, R. Zhao, M. L. Zhang, N. Hua, L. L. & S. C. Lee: Role of MIP-1beta and RANTES in HIV-1 infection of microglia: inhibition of infection and induction by IFNbeta. *J Neuroimmunol* 110, 230-239 (2000)

Chemokines in CNS infectious diseases

91. Gabuzda, D. & J. Wang: Chemokine receptors and mechanisms of cell death in HIV neuropathogenesis. *J Neurovirol* 6 Suppl 1, S24-32 (2000)
92. Dean, M. Carrington, M. Winkler, C. Huttley, G. A. Smith, M. W. Allikmets, R. Goedert, J. J. Buchbinder, S. P. Vittinghoff, E. Gomperts, E. Donfield, S. Vlahov, D. Kaslow, R. Saah, A. Rinaldo, C. Detels, R. & S. J. O'Brien: Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the *CCR5* structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* 273, 1856-1862 (1996)
93. Samson, M. Libert, F. Doranz, B. J. Rucker, J. Liesnard, C. Farber, C. M. Saragosti, S. Lapoumeroulie, C. Cognaux, J. Forceille, C. Muyldermans, G. Verhofstede, C. Burtonboy, G. Georges, M. Imai, T. Rana, S. Yi, Y. Smyth, R. J. Collman, R. G. Doms, R. W. Vassart, G. & M. Parmentier: Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the *CCR-5* chemokine receptor gene. *Nature* 382, 722-725 (1996)
94. Huang, Y. Paxton, W. A. Wolinsky, S. M. Neumann, A. U. Zhang, L. He, T. Kang, S. Ceradini, D. Jin, Z. Yazdanbakhsh, K. Kunstman, K. Erickson, D. Dragon, E. Landau, N. R. Phair, J. Ho, D. D. & R. A. Koup: The role of a mutant *CCR5* allele in HIV-1 transmission and disease progression. *Nat Med* 2, 1240-1243 (1996)
95. Paxton, W. A. Martin, S. R. Tse, D. O'Brien, T. R. Skurnick, J. VanDevanter, N. L. Padian, N. Braun, J. F. Kotler, D. P. Wolinsky, S. M. & R. A. Koup: Relative resistance to HIV-1 infection of CD4 lymphocytes from persons who remain uninfected despite multiple high-risk sexual exposure. *Nat Med* 2, 412-417 (1996)
96. Rana, S. Besson, G. Cook, D. G. Rucker, J. Smyth, R. J. Yi, Y. Turner, J. D. Guo, H. H. Du, J. G. Peiper, S. C. Lavi, E. Samson, M. Libert, F. Liesnard, C. Vassart, G. Doms, R. W. Parmentier, M. & R. G. Collman: Role of *CCR5* in infection of primary macrophages and lymphocytes by macrophage-tropic strains of human immunodeficiency virus: resistance to patient-derived and prototype isolates resulting from the delta *ccr5* mutation. *J Virol* 71, 3219-3227 (1997)
97. Reinhart, T. A.: Chemokine induction by HIV-1: recruitment to the cause. *Trends Immunol* 24, 351-353 (2003)
98. Conant, K. Garzino-Demo, A. Nath, A. McArthur, J. C. Halliday, W. Power, C. Gallo, R. C. & E. O. Major: Induction of monocyte chemoattractant protein-1 in HIV-1 Tat-stimulated astrocytes and elevation in AIDS dementia. *Proc Natl Acad Sci U S A* 95, 3117-3121 (1998)
99. Schmidt-mayerova, H. Nottet, H. S. Nuovo, G. Raabe, T. Flanagan, C. R. Dubrovsky, L. Gendelman, H. E. Cerami, A. Bukrinsky, M. & B. Sherry: Human immunodeficiency virus type 1 infection alters chemokine beta peptide expression in human monocytes: implications for recruitment of leukocytes into brain and lymph nodes. *Proc Natl Acad Sci U S A* 93, 700-704 (1996)
100. Cinque, P. Vago, L. Mengozzi, M. Torri, V. Ceresa, D. Vicenzi, E. Transidico, P. Vagani, A. Sozzani, S. Mantovani, A. Lazzarin, A. & G. Poli: Elevated cerebrospinal fluid levels of monocyte chemoattractant protein-1 correlate with HIV-1 encephalitis and local viral replication. *Aids* 12, 1327-1332 (1998)
101. Kelder, W. McArthur, J. C. Nance-Sproson, T. McClernon, D. & D. E. Griffin: Beta-chemokines MCP-1 and RANTES are selectively increased in cerebrospinal fluid of patients with human immunodeficiency virus-associated dementia. *Ann Neurol* 44, 831-835 (1998)
102. Letendre, S. L. Lanier, E. R. & J. A. McCutchan: Cerebrospinal fluid beta chemokine concentrations in neurocognitively impaired individuals infected with human immunodeficiency virus type 1. *J Infect Dis* 180, 310-319 (1999)
103. Persidsky, Y. Ghorpade, A. Rasmussen, J. Limoges, J. Liu, X. J. Stins, M. Fiala, M. Way, D. Kim, K. S. Witte, M. H. Weinand, M. Carhart, L. & H. E. Gendelman: Microglial and astrocyte chemokines regulate monocyte migration through the blood-brain barrier in human immunodeficiency virus-1 encephalitis. *Am J Pathol* 155, 1599-1611 (1999)
104. Nuovo, G. J. Gallery, F. MacConnell, P. & A. Braun: In situ detection of polymerase chain reaction-amplified HIV-1 nucleic acids and tumor necrosis factor-alpha RNA in the central nervous system. *Am J Pathol* 144, 659-666 (1994)
105. Ranki, A. Nyberg, M. Ovod, V. Haltia, M. Elovaara, I. Raininko, R. Haapasalo, H. & K. Krohn: Abundant expression of HIV Nef and Rev proteins in brain astrocytes in vivo is associated with dementia. *Aids* 9, 1001-1008 (1995)
106. Bagasra, O. Lavi, E. Bobroski, L. Khalili, K. Pestaner, J. P. Tawadros, R. & R. J. Pomerantz: Cellular reservoirs of HIV-1 in the central nervous system of infected individuals: identification by the combination of in situ polymerase chain reaction and immunohistochemistry. *Aids* 10, 573-585 (1996)
107. Takahashi, K. Wesselingh, S. L. Griffin, D. E. McArthur, J. C. Johnson, R. T. & J. D. Glass: Localization of HIV-1 in human brain using polymerase chain reaction/in situ hybridization and immunocytochemistry. *Ann Neurol* 39, 705-711 (1996)
108. Sabri, F. Tresoldi, E. Di Stefano, M. Polo, S. Monaco, M. C. Verani, A. Fiore, J. R. Lusso, P. Major, E. Chiodi, F. & G. Scarlatti: Nonproductive human immunodeficiency virus type 1 infection of human fetal astrocytes: independence from CD4 and major chemokine receptors. *Virology* 264, 370-384 (1999)

109. Lahrtz, F. Piali, L. Nadal, D. Pfister, H. W. Spanaus, K. S. Baggiolini, M. & A. Fontana: Chemotactic activity on mononuclear cells in the cerebrospinal fluid of patients with viral meningitis is mediated by interferon-gamma inducible protein-10 and monocyte chemotactic protein-1. *Eur J Immunol* 27, 2484-2489 (1997)
110. Asensio, V. C. Kincaid, C. & I. L. Campbell: Chemokines and the inflammatory response to viral infection in the central nervous system with a focus on lymphocytic choriomeningitis virus. *J Neurovirol* 5, 65-75 (1999)
111. Arribas, J. R. Storch, G. A. Clifford, D. B. & A. C. Tselis: Cytomegalovirus encephalitis. *Ann Intern Med* 125, 577-587 (1996)
112. Lokensgard, J. R. Cheeran, M. C. Gekker, G. Hu, S. Chao, C. C. & P. K. Peterson: Human cytomegalovirus replication and modulation of apoptosis in astrocytes. *J Hum Virol* 2, 91-101 (1999)
113. Lokensgard, J. R. Cheeran, M. C. Hu, S. Gekker, G. & P. K. Peterson: Glial cell responses to herpesvirus infections: role in defense and immunopathogenesis. *J Infect Dis* 186 Suppl 2, S171-179 (2002)
114. Buchmeier, M. J. Welsh, R. M. Dutko, F. J. & M. B. Oldstone: The virology and immunobiology of lymphocytic choriomeningitis virus infection. *Adv Immunol* 30, 275-331 (1980)
115. Asensio, V. C. & I. L. Campbell: Chemokine gene expression in the brains of mice with lymphocytic choriomeningitis. *J Virol* 71, 7832-7840 (1997)
116. Cheeran, M. C. Hu, S. Yager, S. L. Gekker, G. Peterson, P. K. & J. R. Lokensgard: Cytomegalovirus induces cytokine and chemokine production differentially in microglia and astrocytes: antiviral implications. *J Neurovirol* 7, 135-147 (2001)
117. Bernasconi, S. Cinque, P. Peri, G. Sozzani, S. Crociati, A. Torri, W. Vicenzi, E. Vago, L. Lazzarin, A. Poli, G. & A. Mantovani: Selective elevation of monocyte chemotactic protein-1 in the cerebrospinal fluid of AIDS patients with cytomegalovirus encephalitis. *J Infect Dis* 174, 1098-1101 (1996)
118. Kimberlin, D. W: Herpes simplex virus infections of the central nervous system. *Semin Pediatr Infect Dis* 14, 83-89 (2003)
119. Hu, Z. Yang, Q. Bo, X. & J. Li: Herpes simplex encephalitis. *Lancet* 362, 280 (2003)
120. Halford, W. P. Gebhardt, B. M. & D. J. Carr: Persistent cytokine expression in trigeminal ganglion latently infected with herpes simplex virus type 1. *J Immunol* 157, 3542-3549 (1996)
121. Lokensgard, J. R. Hu, S. Sheng, W. vanOijen, M. Cox, D. Cheeran, M. C. & P. K. Peterson: Robust expression of TNF-alpha, IL-1beta, RANTES, and IP-10 by human microglial cells during nonproductive infection with herpes simplex virus. *J Neurovirol* 7, 208-219 (2001)
122. Nakajima, H. Kobayashi, M. Pollard, R. B. & F. Suzuki: Monocyte chemoattractant protein-1 enhances HSV-induced encephalomyelitis by stimulating Th2 responses. *J Leukoc Biol* 70, 374-380 (2001)
123. Rosler, A. Pohl, M. Braune, H. J. Oertel, W. H. Gemsa, D. & H. Sprenger: Time course of chemokines in the cerebrospinal fluid and serum during herpes simplex type 1 encephalitis. *J Neurol Sci* 157, 82-89 (1998)
124. Lane, T. E. & M. J. Buchmeier: Murine coronavirus infection: a paradigm for virus-induced demyelinating disease. *Trends Microbiol* 5, 9-14 (1997)
125. Williamson, J. S. & S. A. Stohman: Effective clearance of mouse hepatitis virus from the central nervous system requires both CD4+ and CD8+ T cells. *J Virol* 64, 4589-4592 (1990)
126. Yamaguchi, K. Goto, N. Kyuwa, S. Hayami, M. & Y. Toyoda: Protection of mice from a lethal coronavirus infection in the central nervous system by adoptive transfer of virus-specific T cell clones. *J Neuroimmunol* 32, 1-9 (1991)
127. Lane, T. E. Liu, M. T. Chen, B. P. Asensio, V. C. Samawi, R. M. Paoletti, A. D. Campbell, I. L. Kunkel, S. L. Fox, H. S. & M. J. Buchmeier: A central role for CD4(+) T cells and RANTES in virus-induced central nervous system inflammation and demyelination. *J Virol* 74, 1415-1424 (2000)
128. Lane, T. E. Asensio, V. C. Yu, N. Paoletti, A. D. Campbell, I. L. & M. J. Buchmeier: Dynamic regulation of alpha- and beta-chemokine expression in the central nervous system during mouse hepatitis virus-induced demyelinating disease. *J Immunol* 160, 970-978 (1998)
129. Glass, W. G. Liu, M. T. Kuziel, W. A. & T. E. Lane: Reduced macrophage infiltration and demyelination in mice lacking the chemokine receptor CCR5 following infection with a neurotropic coronavirus. *Virology* 288, 8-17 (2001)
130. Chen, B. P. Kuziel, W. A. & T. E. Lane: Lack of CCR2 results in increased mortality and impaired leukocyte activation and trafficking following infection of the central nervous system with a neurotropic coronavirus. *J Immunol* 167, 4585-4592 (2001)
131. Trifilo, M. J. Bergmann, C. C. Kuziel, W. A. & T. E. Lane: CC chemokine ligand 3 (CCL3) regulates CD8(+)-T-cell effector function and migration following viral infection. *J Virol* 77, 4004-4014 (2003)

Chemokines in CNS infectious diseases

132. Dufour, J. H. Dziejman, M. Liu, M. T. Leung, J. H. Lane, T. E. & A. D. Luster: IFN-gamma-inducible protein 10 (IP-10; CXCL10)-deficient mice reveal a role for IP-10 in effector T cell generation and trafficking. *J Immunol* 168, 3195-3204 (2002)
133. Manchester, M. Eto, D. S. & M. B. Oldstone: Characterization of the inflammatory response during acute measles encephalitis in NSE-CD46 transgenic mice. *J Neuroimmunol* 96, 207-217 (1999)
134. Patterson, C. E. Daley, J. K. Echols, L. A. Lane, T. E. & G. F. Rall: Measles virus infection induces chemokine synthesis by neurons. *J Immunol* 171, 3102-3109 (2003)
135. Murphy, P. M: Viral exploitation and subversion of the immune system through chemokine mimicry. *Nat Immunol* 2, 116-122 (2001)
136. van Berkel, V. Levine, B. Kapadia, S. B. Goldman, J. E. Speck, S. H. & H. W. Virgin: Critical role for a high-affinity chemokine-binding protein in gamma-herpesvirus-induced lethal meningitis. *J Clin Invest* 109, 905-914 (2002)
137. Townsend, G. C. & W. M. Scheld: Infections of the central nervous system. *Adv Intern Med* 43, 403-447 (1998)
138. Kielian, T. Cheung, A. & W. F. Hickey: Diminished virulence of an alpha-toxin mutant of *Staphylococcus aureus* in experimental brain abscesses. *Infect Immun* 69, 6902-6911 (2001)
139. Flaris, N. A. & W. F. Hickey: Development and characterization of an experimental model of brain abscess in the rat. *Am J Pathol* 141, 1299-1307 (1992)
140. Kielian, T. & W. F. Hickey: Proinflammatory cytokine, chemokine, and cellular adhesion molecule expression during the acute phase of experimental brain abscess development. *Am J Pathol* 157, 647-658 (2000)
141. Nau, R. & W. Bruck: Neuronal injury in bacterial meningitis: mechanisms and implications for therapy. *Trends Neurosci* 25, 38-45 (2002)
142. Zysk, G. Bruck, W. Huitinga, I. Fischer, F. R. Flachsbarth, F. van Rooijen, N. & R. Nau: Elimination of blood-derived macrophages inhibits the release of interleukin-1 and the entry of leukocytes into the cerebrospinal fluid in experimental pneumococcal meningitis. *J Neuroimmunol* 73, 77-80 (1997)
143. Tauber, M. G. & B. Moser: Cytokines and chemokines in meningeal inflammation: biology and clinical implications. *Clin Infect Dis* 28, 1-11; quiz 12 (1999)
144. Trostorf, F. Bruck, W. Schmitz-Salue, M. Stuert, K. Hopkins, S. J. van Rooijen, N. Huitinga, I. & R. Nau: Reduction of meningeal macrophages does not decrease migration of granulocytes into the CSF and brain parenchyma in experimental pneumococcal meningitis. *J Neuroimmunol* 99, 205-210 (1999)
145. Pfister, H. W. & W. M. Scheld: Brain injury in bacterial meningitis: therapeutic implications. *Curr Opin Neurol* 10, 254-259 (1997)
146. Halstensen, A. Ceska, M. Brandtzaeg, P. Redl, H. Naess, A. & A. Waage: Interleukin-8 in serum and cerebrospinal fluid from patients with meningococcal disease. *J Infect Dis* 167, 471-475 (1993)
147. Sprenger, H. Rosler, A. Tonn, P. Braune, H. J. Huffmann, G. & D. Gemsa: Chemokines in the cerebrospinal fluid of patients with meningitis. *Clin Immunol Immunopathol* 80, 155-161 (1996)
148. Spanaus, K. S. Nadal, D. Pfister, H. W. Seebach, J. Widmer, U. Frei, K. Gloor, S. & A. Fontana: C-X-C and C-C chemokines are expressed in the cerebrospinal fluid in bacterial meningitis and mediate chemotactic activity on peripheral blood-derived polymorphonuclear and mononuclear cells in vitro. *J Immunol* 158, 1956-1964 (1997)
149. Lahrtz, F. Piali, L. Spanaus, K. S. Seebach, J. & A. Fontana: Chemokines and chemotaxis of leukocytes in infectious meningitis. *J Neuroimmunol* 85, 33-43 (1998)
150. Mastroianni, C. M. Lancella, L. Mengoni, F. Lichtner, M. Santopadre, P. D'Agostino, C. Ticca, F. & V. Vullo: Chemokine profiles in the cerebrospinal fluid (CSF) during the course of pyogenic and tuberculous meningitis. *Clin Exp Immunol* 114, 210-214 (1998)
151. Inaba, Y. Ishiguro, A. & T. Shimbo: The production of macrophage inflammatory protein-1alpha in the cerebrospinal fluid at the initial stage of meningitis in children. *Pediatr Res* 42, 788-793 (1997)
152. Seebach, J. Bartholdi, D. Frei, K. Spanaus, K. S. Ferrero, E. Widmer, U. Isenmann, S. Strieter, R. M. Schwab, M. Pfister, H. & et al.: Experimental *Listeria* meningoencephalitis. Macrophage inflammatory protein-1 alpha and -2 are produced intrathecally and mediate chemotactic activity in cerebrospinal fluid of infected mice. *J Immunol* 155, 4367-4375 (1995)
153. Diab, A. Abdalla, H. Li, H. L. Shi, F. D. Zhu, J. Hojberg, B. Lindquist, L. Wretling, B. Bakhiet, M. & H. Link: Neutralization of macrophage inflammatory protein 2 (MIP-2) and MIP-1alpha attenuates neutrophil recruitment in the central nervous system during experimental bacterial meningitis. *Infect Immun* 67, 2590-2601 (1999)
154. Standiford, T. J. Kunkel, S. L. Lukacs, N. W. Greenberger, M. J. Danforth, J. M. Kunkel, R. G. & R. M. Strieter: Macrophage inflammatory protein-1 alpha mediates lung leukocyte recruitment, lung capillary leak, and early mortality in murine endotoxemia. *J Immunol* 155, 1515-1524 (1995)

155. Zwijnenburg, P. J. van der Poll, T. Florquin, S. van Deventer, S. J. Roord, J. J. & A. M. van Furth: Experimental pneumococcal meningitis in mice: a model of intranasal infection. *J Infect Dis* 183, 1143-1146 (2001)
156. Ostergaard, C. Yieng-Kow, R. V. Larsen, C. G. Mukaida, N. Matsushima, K. Benfield, T. Frimodt-Moller, N. Espersen, F. Kharazmi, A. & J. D. Lundgren: Treatment with a monoclonal antibody to IL-8 attenuates the pleocytosis in experimental pneumococcal meningitis in rabbits when given intravenously, but not intracisternally. *Clin Exp Immunol* 122, 207-211 (2000)
157. Dumont, R. A. Car, B. D. Voitenok, N. N. Junker, U. Moser, B. Zak, O. & T. O'Reilly: Systemic neutralization of interleukin-8 markedly reduces neutrophilic pleocytosis during experimental lipopolysaccharide-induced meningitis in rabbits. *Infect Immun* 68, 5756-5763 (2000)
158. Hill, D. & J. P. Dubey: *Toxoplasma gondii*: transmission, diagnosis and prevention. *Clin Microbiol Infect* 8, 634-640 (2002)
159. Bhopale, G. M: Pathogenesis of toxoplasmosis. *Comp Immunol Microbiol Infect Dis* 26, 213-222 (2003)
160. Khan, I. A. MacLean, J. A. Lee, F. S. Casciotti, L. DeHaan, E. Schwartzman, J. D. & A. D. Luster: IP-10 is critical for effector T cell trafficking and host survival in *Toxoplasma gondii* infection. *Immunity* 12, 483-494 (2000)
161. Strack, A. Schluter, D. Asensio, V. C. Campbell, I. L. & M. Deckert: Regulation of the kinetics of intracerebral chemokine gene expression in murine *Toxoplasma* encephalitis: impact of host genetic factors. *Glia* 40, 372-377 (2002)
162. Strack, A. Asensio, V. C. Campbell, I. L. Schluter, D. & M. Deckert: Chemokines are differentially expressed by astrocytes, microglia and inflammatory leukocytes in *Toxoplasma* encephalitis and critically regulated by interferon-gamma. *Acta Neuropathol (Berl)* 103, 458-468 (2002)
163. Khan, I. A. Murphy, P. M. Casciotti, L. Schwartzman, J. D. Collins, J. Gao, J. L. & G. R. Yeaman: Mice lacking the chemokine receptor CCR1 show increased susceptibility to *Toxoplasma gondii* infection. *J Immunol* 166, 1930-1937 (2001)
164. Del Rio, L. Bennouna, S. Salinas, J. & E. Y. Denkers: CXCR2 deficiency confers impaired neutrophil recruitment and increased susceptibility during *Toxoplasma gondii* infection. *J Immunol* 167, 6503-6509 (2001)
165. Guida, J. D. Fejer, G. Pirofski, L. A. Brosnan, C. F. & M. S. Horwitz: Mouse adenovirus type 1 causes a fatal hemorrhagic encephalomyelitis in adult C57BL/6 but not BALB/c mice. *J Virol* 69, 7674-7681 (1995)
166. Charles, P. C. Guida, J. D. Brosnan, C. F. & M. S. Horwitz: Mouse adenovirus type-1 replication is restricted to vascular endothelium in the CNS of susceptible strains of mice. *Virology* 245, 216-228 (1998)
167. Charles, P. C. Chen, X. Horwitz, M. S. & C. F. Brosnan: Differential chemokine induction by the mouse adenovirus type-1 in the central nervous system of susceptible and resistant strains of mice. *J Neurovirol* 5, 55-64 (1999)
168. Rodrigues, M. L. Alviano, C. S. & L. R. Travassos: Pathogenicity of *Cryptococcus neoformans*: virulence factors and immunological mechanisms. *Microbes Infect* 1, 293-301 (1999)
169. Mamidi, A. DeSimone, J. A. & R. J. Pomerantz: Central nervous system infections in individuals with HIV-1 infection. *J Neurovirol* 8, 158-167 (2002)
170. Huffnagle, G. B. McNeil, L. K. McDonald, R. A. Murphy, J. W. Toews, G. B. Maeda, N. & W. A. Kuziel: Cutting edge: Role of C-C chemokine receptor 5 in organ-specific and innate immunity to *Cryptococcus neoformans*. *J Immunol* 163, 4642-4646 (1999)
171. Huffnagle, G. B. & L. K. McNeil: Dissemination of *C. neoformans* to the central nervous system: role of chemokines, Th1 immunity and leukocyte recruitment. *J Neurovirol* 5, 76-81 (1999)
172. Petrova, T. V. Akama, K. T. & L. J. Van Eldik: Cyclopentenone prostaglandins suppress activation of microglia: down-regulation of inducible nitric-oxide synthase by 15-deoxy-Delta12,14-prostaglandin J2. *Proc Natl Acad Sci U S A* 96, 4668-4673 (1999)
173. Bernardo, A. Levi, G. & L. Minghetti: Role of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) and its natural ligand 15-deoxy-Delta12, 14-prostaglandin J2 in the regulation of microglial functions. *Eur J Neurosci* 12, 2215-2223 (2000)
174. Drew, P. D. & J. A. Chavis: The cyclopentenone prostaglandin 15-deoxy-Delta(12,14) prostaglandin J2 represses nitric oxide, TNF-alpha, and IL-12 production by microglial cells. *J Neuroimmunol* 115, 28-35 (2001)
175. Tikka, T. M. & J. E. Koistinaho: Minocycline provides neuroprotection against N-methyl-D-aspartate neurotoxicity by inhibiting microglia. *J Immunol* 166, 7527-7533 (2001)
176. Tikka, T. Fiebich, B. L. Goldsteins, G. Keinanen, R. & J. Koistinaho: Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. *J Neurosci* 21, 2580-2588 (2001)
177. Schroeter, M. Jander, S. Witte, O. W. & G. Stoll: Heterogeneity of the microglial response in photochemically induced focal ischemia of the rat cerebral cortex. *Neuroscience* 89, 1367-1377 (1999)

Chemokines in CNS infectious diseases

178. Ren, L. Lubrich, B. Biber, K. & P. J. Gebicke-Haerter: Differential expression of inflammatory mediators in rat microglia cultured from different brain regions. *Brain Res Mol Brain Res* 65, 198-205 (1999)

179. Schmid, C. D. Sautkulis, L. N. Danielson, P. E. Cooper, J. Hasel, K. W. Hilbush, B. S. Sutcliffe, J. G. & M. J. Carson: Heterogeneous expression of the triggering receptor expressed on myeloid cells-2 on adult murine microglia. *J Neurochem* 83, 1309-1320 (2002)

Key Words: Microglia, Chemokines, Chemokine Receptors, HIV-1, Encephalitis, Brain Abscess, Bacterial Meningitis, Viral Meningitis, Review

Send correspondence to: Tammy Kielian, Ph.D., Department of Anatomy and Neurobiology, University of Arkansas for Medical Sciences, Room 110B Biomedical Research Center, 4301 W. Markham, Little Rock, AR 72205, Tel: 501-526-6348, Fax: 501-526-6756, E-mail: KielianTammyL@uams.edu