Immunologic Research 2001;24/2:111–119

Chemokine Expression and Viral Infection of the Central Nervous System: Regulation of Host Defense and Neuropathology

Michael T. Liu
*Thomas E. Lane**

Department of Molecular Biology and Biochemistry
University of California, Irvine, CA

Abstract

An effective host response against viral infection of the central nervous system (CNS) is the principal factor dictating the outcome of infection. It is the responsibility of the immune response to contain and control viral replication. Paradoxically, it is the immune response that may also contribute to the development of neuropathology. We have used mouse hepatitis virus (MHV), a positive-strand RNA virus, infection of the CNS to understand the dynamic interaction between viral replication, protection, and pathology with an emphasis on understanding how chemokines participate in these interrelated processes. Herein, we demonstrate the complexity of the chemokine response to MHV infection of the CNS and the delicate balance that exists between host defense and development of disease.

Key Words

Chemokines
Virus
T Lymphocytes
Macrophages
Demyelination

Introduction

Viral infection of the central nervous system (CNS) presents unique problems in how the host is able to encounter, recognize, and eliminate foreign antigen. Contributing factors include anatomic difficulties imposed by the blood-brain-barrier as well as the absence of evident lymphatic drainage. Furthermore, the relative absence of MHC class I and II expression combined with limited numbers of antigen presenting cells suggest that mounting an effective immune response against a viral antigen is difficult. However, in spite of these apparent obstacles, activated cells of the immune system are able to enter the CNS and participate in elimination of viral antigen. Moreover, the presence of activated immune cells e.g., T lymphocytes and macrophages contribute to the development of pathology in various viral model systems.

The molecular mechanisms governing the development of inflammatory events and an adaptive immune response to viral infection of the CNS are just now being understood *(1–3)*. Increasing evidence has demonstrated the importance of chemokines in orchestrating events surrounding inflammation follow-

Thomas E. Lane, Ph.D.
Department of Molecular Biology and Biochemistry
University of California, Irvine
3205 Biological Sciences II
Irvine, CA 92697-3900
E-mail: tlane@uci.edu

0257–277X/01/
24/2:111–119/$12.25

ing viral infection or injury. Chemokines represent an ever-growing family of secreted proteins that function as potent mediators of inflammation *(4)*. The chemokine superfamily is divided into four subfamilies based on both structural and functional criteria. The two major subfamilies are the CXC and CC chemokines. The CXC subfamily is structurally characterized by conserved cysteine residues that are separated by an amino-acid whereas the CC subfamily has the conserved cysteine residues adjacent to one another. Lymphotactin, the sole member of the C family, is chemotactic for T lymphocytes. The CX3C chemokine, fractalkine, is unique in that it is expressed on the surface of cells as well as being secreted into the surrounding environment. Chemokines target distinct leukocyte populations during periods of inflammation through interaction with specific receptors. The CXC chemokines function primarily in attracting neutrophils, yet have a limited effect on T lymphocytes and monocytes. However, there are exceptions to this rule in that CXC chemokines that lack the glutamic acid-leucine-arginine (ELR) motif on the amino terminus are chemotactic for T cells by binding to the shared receptor CXCR3. The CC chemokines attract T lymphocytes, monocytes, and macrophages but not neutrophils. To date, all chemokine receptors identified are members of the seven-transmembrane G protein-coupled receptor superfamily *(5)*. Following chemokine binding to its cognate receptor, signaling events are initiated that result in various cellular processes such as increases in intracellular calcium, production of cytokines and chemokines, adhesion to the endothelial matrix, and chemotaxis *(6)*. In addition, there is growing evidence that chemokine receptors influence the polarization of T cell immune response (i.e., Th1 vs. Th2) in tissue *(7)*.

Viral infection of the CNS results in a temporal expression of chemokines by resident cells of the CNS e.g., astrocytes and microglia as well as by inflammatory cells. Recent studies have demonstrated a relationship between chemokine expression and leukocyte entry into the CNS following viral infection *(8–11)*. There is an increasing amount of evidence indicating that chemokine expression is beneficial by attracting lymphocytes that participate in an antiviral response. Conversely, chronic chemokine expression in response to persistent viral infection of the CNS may contribute to neuropathology by attracting activated T lymphocytes and macrophages into the CNS which then release cytotoxic factors. This brief review will focus on recent studies evaluating the functional significance of chemokine expression as it relates to both host defense and disease development following mouse hepatitis virus (MHV) infection of the CNS.

MHV Infection and Neurologic Disease

MHV is a positive-strand RNA virus that is a member of the *Coronaviridae* family *(12)*. Intracranial infection of susceptible strains of mice with MHV results in an acute encephalomyelitis characterized by viral replication in glia and neurons accompanied by leukocyte infiltration into the CNS. A robust cell-mediated immune response is essential in control of viral replication. Increased mortality and enhanced recovery of virus from the CNS has been reported in mice lacking functional $CD4^+$ or $CD8^+$ lymphocytes *(1,13–15)*. Adoptive transfer of MHV-specific T cell clones mediates protection from disease and clearance of MHV from the CNS *(16,17)*. Moreover, MHV infection of IFN-$\gamma^{-/-}$ mice results in increased disease severity accompanied by a diminished ability to control viral replication within the brain *(18,19)*. Collectively, these data indicate

that a Th1 response characterized by the accumulation of both $CD4^+$ and $CD8^+$ T lymphocytes and expression of IFN-γ is required for protection from neurologic disease and clearance of MHV.

MHV infection of the CNS results in a complex, well-orchestrated expression of chemokine genes which appears to be dictated, in part, by viral burden *(8)*. IP-10 mRNA transcripts are detected early (day 1 postinfection p.i.) and colocalize with areas of MHV replication. By day 6 p.i., virus has spread throughout the parenchyma and chemokine transcripts detected at this time include IP-10, RANTES, Mig, MCP-1, MCP-3, MIP-1α, MIP-1β, and RANTES. Analysis of chemokine receptor mRNA expression indicates CXCR3, CCR1, CCR2, and CCR5 are predominantly expressed during acute disease (M.T.L. and T.E.L., unpublished observations). Double-labeling revealed that astrocytes and microglia expressed mRNA transcripts for IP-10 and Mig during the acute stage of disease *(3,8)*. Macrophage/microglial cells (determined by F4/80 antigen expression) were determined to express the chemokine receptor CCR5 whereas both $CD4^+$ and $CD8^+$ T lymphocytes expressed CXCR3 (M.T.L. and T.E.L., unpublished observations; *2*).

By day 12 p.i., mice clear virus below levels of detection (as determined by plaque assay), however, viral RNA and antigen persists within white matter tracts. Persistent infection of mice with MHV results in demyelination in the majority of mice characterized clinically by partial-to-complete hind-limb paralysis and histologically by T lymphocyte and macrophage accumulation at sites of myelin destruction *(1,14,15,20–23)*. Due to the similarities in both clinical and histologic disease between MHV-induced demyelination and the human demyelinating disease multiple sclerosis (MS), the MHV system is considered to be an excellent model in which to study the underlying immunopathological mechanisms contributing to demyelination in MS patients *(14,19)*. Similar to MS, components of the immune system e.g., T lymphocytes and macrophages are considered important in contributing to the development of demyelination *(1,15,22,23)*. *In situ* hybridization analysis revealed that IP-10 and RANTES are predominantly expressed surrounding demyelinating lesions present in the spinal cords of mice persistently infected with MHV *(1,8)*. In addition, astrocytes were determined to be the cellular source of IP-10 at this stage of disease whereas inflammatory cells expressed RANTES *(1,8)*.

The focus of our research is aimed at characterizing the role of chemokines in CNS host defense as well as immune-mediated demyelination utilizing the MHV model of viral-induced CNS disease. As stated earlier, $CD4^+$ and $CD8^+$ T lymphocytes contribute to an antiviral response during the acute stage of disease. The majority of T lymphocytes which infiltrate into the CNS expressed the chemokine receptor CXCR3 *(2,3)*. This suggests that the ligands for CXCR3, IP-10 and Mig, may perform prominent roles in host defense through attraction of T lymphocytes into the CNS following viral infection. However, although T lymphocytes are essential in host defense, $CD4^+$ T lymphocytes have also been shown to participate in MHV induced demyelination during the chronic stage of infection *(1)*. As mentioned earlier, IP-10 and RANTES are prominently expressed surrounding demyelinating lesions suggesting that chronic expression of these molecules may participate in MHV induced demyelination through attraction of inflammatory $CD4^+$ T lymphocytes and macrophages into the CNS *(1,8)*. Herein, we present data focused on defining the functional significance of IP-10, Mig, and RANTES expression as it relates to both

host defense and neuropathology following MHV infection of the CNS.

Chemokines and CNS Host Defense

IP-10 and Mig are non-ELR (glutamic acid-leucine-arginine) CXC chemokines that exert a chemotactic effect on T lymphocytes through interaction with the receptor CXCR3 *(24–27)*. IP-10 expression is inducible by both IFN-α/β and IFN-γ while Mig expression is strictly dependent upon IFN-γ *(26)*. Analysis of the kinetics of IP-10 and Mig mRNA expression within the CNS of MHV-infected mice revealed that IP-10 is clearly detectable by day 2 p.i. and is prominently expressed at days 7, 12 and 35 p.i. *(8)*. In contrast, Mig expression is limited to days 7 through 12 p.i. which coincides with the presence of IFN-γ mRNA transcripts *(3)*. Based upon these data, it is interesting to speculate that early expression of IP-10 may reflect local production of IFN-α/β in response to MHV infection which in turn activates both infected and uninfected cells to produce IP-10. On the other hand, Mig expression is delayed until activated T lymphocytes enter the CNS and produce IFN-γ.

In order to characterize the functional significance of IP-10 and Mig expression following MHV infection of the CNS, rabbit antisera specific for either IP-10 or Mig was administered to infected mice. Neutralization of either IP-10 or Mig activity resulted in a dramatic increase in mortality when compared to control mice treated with normal rabbit serum (NRS) *(2,3)* (Fig. 1). Surviving mice treated with either anti-IP-10 or anti-Mig displayed significantly higher titers of virus as compared to titers present in NRS-treated mice indicating that neutralization of either IP-10 or Mig activity during acute disease results in increased mortality that correlated with an increase in viral burden within the CNS *(2,3)* (Table 1).

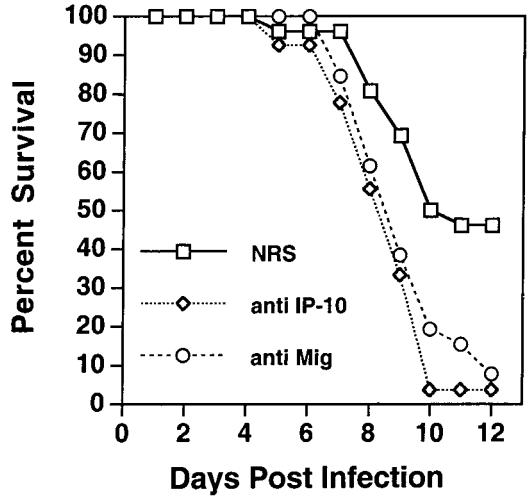

Fig. 1. Increased mortality in MHV-infected mice treated with either anti-IP-10 or anti-Mig. Mice were intracranially infected with 10 pfu of MHV and treated intraperitoneally with either anti-IP-10, anti-Mig or NRS at days 0, 2, 5, 7 and 9 p.i. By 12 d p.i., approx 50% of NRS treated mice survived the infection whereas less than 10% of anti-IP-10 and anti-Mig treated mice survived.

Table 1. CNS viral titer following antisera treatment

Treatment days	Post infection	*n*	Log_{10} PFU/g
anti-IP-10	7	4	5.9 ± 0.1[a]
	10	4	5.7 ± 0.3[b]
anti-Mig	7	4	5.9 ± 0.04
	10	4	5.4 ± 0.3[b]
NRS	7	4	5.0 ± 0.07
	10	4	2.1 ± 0.2

[a]Data presented as mean ± SEM

[b]$p<0.001$ when compared to NRS treated mice

As previously mentioned, $CD4^+$ and $CD8^+$ T lymphocytes present within the CNS of MHV infected mice express CXCR3, the shared receptor for Mig and IP-10 *(2)*. This

Table 2. CNS T lymphocyte infiltration flow cytometric analysis

Treatment	Days post infection	*n*	CD4	CD8
Sham	7	2	0.32 ± 0.13[a]	0.45 ± 0.07
anti-IP-10	7	5	3.1 ± 2.3[b]	6.3 ± 2.1[b]
anti-Mig	7	5	9.1 ± 1.8[b]	8.2 ± 2.6[b]
NRS	7	5	16.4 ± 3.9	19.8 ± 3.7

[a]data presented as mean ± SEM

[b]$p<0.005$ when compared to mice treated with NRS.

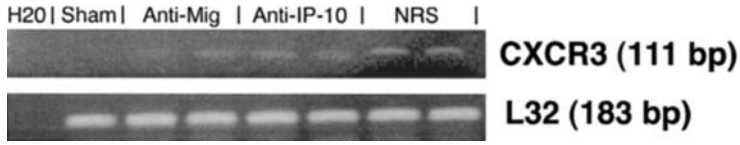

Fig. 2. Decreased levels of CXCR3 mRNA transcripts in brains of mice treated with either anti-IP-10 or anti-Mig. Total RNA was extracted from the brains of MHV infected mice treated with either anti-IP-10, anti-Mig or NRS at 7 d p.i. and subjected to RT-PCR analysis. Mice treated with either anti-IP-10 or anti-Mig show a marked decrease in the levels of CXCR3 in the CNS when compared to NRS treated mice. **Top panel:** CXCR3; **bottom panel:** L32 control (Sham, $n = 1$; anti-IP-10, $n = 2$; anti-Mig, $n = 2$; NRS, $n = 2$).

suggested that both IP-10 and Mig are able to attract T lymphocytes into the CNS in response to viral infection. Indeed, treatment of MHV infected mice with either anti-IP-10 or anti-Mig resulted in a significant decrease in the numbers of $CD4^+$ and $CD8^+$ T lymphocytes infiltrating into the CNS when compared to control mice *(2,3)* (Table 2). Correlating with the decrease in T lymphocyte infiltration was a marked decrease in the transcript levels of CXCR3 present within the CNS of MHV infected mice treated with either anti-IP-10 or anti-Mig *(2,3)* (Figure 2).

One mechanism by which T cells participate in viral clearance is through the release of the T_H1 cytokine IFN-γ *(18,19)*. Examination of IFN-γ transcript levels within the CNS of MHV infected mice revealed that anti-IP-10 and anti-Mig treated mice displayed a significant decrease in IFN-γ mRNA levels as compared to levels present in NRS treated control mice *(2,3)*. Corresponding with the decrease in IFN-γ transcript levels was a significant decrease in IFN-γ protein levels in anti-IP-10 and anti-Mig treated mice *(2,3)* (Fig. 3).

Neutralization of IP-10 and Mig activity results in increased mortality, delayed viral clearance and inhibition of a protective T_H1 response characterized by infiltrating T lymphocytes and IFN-γ expression *(2,3)*. Collectively, these data indicate that both IP-10 and Mig are important sentinel molecules that help promote a protective immune response characterized by T lymphocyte infiltration and IFN-γ expression following MHV infection of the CNS.

Table 3. Inflammation and demyelination

Mouse type	Days post infection	*n*	Inflammation[c]	Demyelination[d]
C57BL/6 (WT)	12	3	2.8 ± 0.4	2.6 ± 0.3
$CD8^{-/-}$	12	3	2.5 ± 0.5	2.6 ± 0.7
$CD4^{-/-}$	12	3	1.4 ± 0.3[a]	1.2 ± 0.2[b]
anti-RANTES	12	3	1.4 ± 0.6[a]	1.1 ± 0.3[b]

[a]$p<0.05$ when compared to both wild-type and $CD8^{-/-}$ mice.

[b]$p<0.001$ when compared to both wild-type and $CD8^{-/-}$ mice.

[c,d]Data presented on a previously described scale of 0–4, with 4 being most severe ***(1)***.

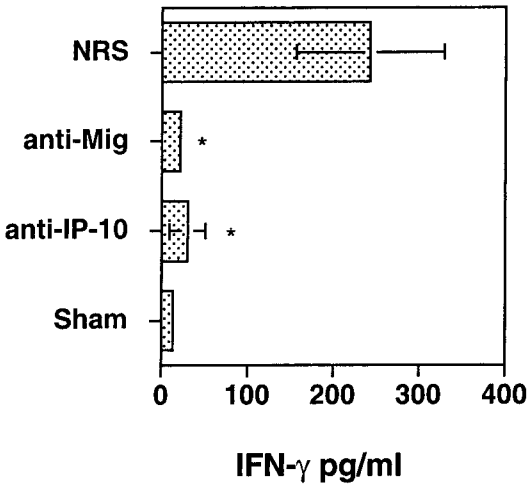

Fig. 3. Decreased expression of IFN-γ in anti-IP-10 and anti-Mig treated mice. IFN-γ protein levels present within the brains of mice at 7 d p.i. were determined by ELISA. Data are presented as mean ± SEM. (* $p<0.05$ when compared to NRS treated mice.)

Chemokines and MHV-Induced Demyelination

We have recently assessed the contributions of $CD4^+$ and $CD8^+$ T lymphocytes to demyelination by infecting either $CD4^{-/-}$ or $CD8^{-/-}$ mice with MHV and evaluating the severity of neurologic disease *(1)*. MHV infection of $CD4^{-/-}$ and $CD8^{-/-}$ mice resulted in increased mortality and delayed clearance of virus from the CNS which is consistent with previous studies demonstrating an important role for T lymphocytes in CNS host defense *(1,13, 14,28,29)*. Interestingly, infected $CD4^{-/-}$ mice displayed a significant decrease in the level of CNS inflammation as well as demyelination when compared to both $CD8^{-/-}$ and wild-type mice (Table 3). Immunophenotyping of the CNS cellular infiltrate in $CD4^{-/-}$ mice revealed a significant decrease in the numbers of activated macrophage/microglia *(1)*. Furthermore, analysis of chemokines expressed within the brains of $CD4^{-/-}$, $CD8^{-/-}$, and wild-type mice revealed significantly lower levels of RANTES mRNA and protein within the CNS of infected $CD4^{-/-}$ mice as compared to wild-type and $CD8^{-/-}$ mice. These data suggested that $CD4^+$ T lymphocytes either produced and/or influenced the production of RANTES by other cellular sources e.g., glial cells and/or lymphocytes. Furthermore, RANTES is known to exert a potent chemotactic effect on macrophages suggesting that the decreased demyelination and inflammation within $CD4^{-/-}$ mice is, in part, due to diminshed RANTES expression that results in decreased macrophage infiltration into the CNS *(30)*.

To directly characterize the role of RANTES in contributing to MHV-induced CNS inflammation and demyelination, MHV-infected mice were treated with goat antisera specific for RANTES. Consistent with the disease phe-

notype observed in $CD4^{-/-}$ mice, treatment of mice with anti-RANTES resulted in delayed viral clearance from the CNS, decreased cellular infiltration, and a significant reduction in the severity of demyelination (Table 3) *(1)*. The impaired capacity to clear virus from the brain correlates with the limited infiltration of $CD4^+$ and $CD8^+$ T lymphocytes into the brain following anti-RANTES treatment *(1)*.

Summary and Conclusions

Our studies on the functional activity of chemokines during MHV-induced CNS disease illustrate the complexity of chemokine expression as it relates to both host defense and disease development. Early expression of the T lymphocyte chemoattractant chemokines IP-10 and Mig represents a dominant response to MHV infection of the brain and is important in attracting IFN-γ producing T lymphocytes (both $CD4^+$ and $CD8^+$ subsets) into the CNS which then participate in viral clearance. Further, RANTES expression also contributes to host defense by exerting a chemotactic effect upon T lymphocytes and macrophages. However, MHV RNA and antigen persists within white matter tracts of the CNS and animals develop a demyelinating disease in which T lymphocytes and macrophages are important contributors. Chronic expression of the chemokines IP-10 and RANTES are detected within areas of MHV persistence undergoing demyelination suggesting that these molecules participate in the disease process by maintaining a chronic inflammatory response. Indeed, anti-RANTES treatment of persistently infected mice resulted in diminished macrophage infiltration into white matter tracts accompanied by a decrease in the severity of demyelination. In addition, we have recently determined that anti-IP-10 (but not anti-Mig) treatment of MHV infected mice with established demyelinaton resulted in decreased T lymphocyte infiltration into the CNS, decreased demyelination, and increased remyelination to damaged axons (M.T.L. and T.E.L., unpublished observations). With regards to chronic expression of chemokines and immune-mediated demyelination, a similar situation exists in MS patients. Recent studies have clearly demonstrated increased expression of chemokines and chemokine receptors within the cerebral spinal fluid of MS patients undergoing acute clinical attack as well as within demyelinating lesions suggesting a pathogenic role for these molecules by attracting leukocytes into the CNS *(31–33)*. IP-10, Mig, and RANTES are among the chemokines expressed in MS patients and are associated with demyelinating lesions *(31–33)*. Therefore, it is interesting to speculate that these chemokines function to attract T lymphocytes and macrophages into the CNS which ultimately results in white matter destruction. Finally, it is important to note that our studies on antibody-mediated neutralization of chemokine activity as a means to modulate the severity of neuroinflammation and neurologic disease supports and extends earlier studies that have suggested that targeting chemokines may offer novel methods for interventional therapies aimed at treating human neuroinflammatory diseases such as MS *(34,35)*.

Acknowledgments

The authors gratefully acknowledge support from the following sources: T.E.L. is supported by grants NS37336 from the National Institutes of Health and RG30393A1/T from the National Multiple Sclerosis Society. M.T.L. is supported by National Institutes of Health Training Grant T32NS07444.

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