8

Chemokines and Viral Infections of the CNS

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1. Introduction

A critical factor in the host immune response to invading pathogens, such as viral infections, is the recruitment and infiltration of immune cells to infected tissues. Although the goal of the recruited leukocytes is to eliminate the invading pathogens, collateral tissue damage may be induced in the process, and, in certain circumstances, may pose a serious threat to the survival of the host. The central nervous system (CNS) is a unique site with limited regenerative potential and therefore a low threshold for inflammation-induced tissue damage. However, as the CNS may become the target of life-threatening viral infections, it is imperative that immunological surveillance and efficient effector responses occur in this organ to aid in pathogen clearance. Although traditionally characterized as a site of "immune privilege," evidence suggests that immune surveillance and antiviral immunity does occur in the CNS (Carson *et al.*, 2006). Understanding how the local inflammatory response within the CNS is regulated is a key to understanding the pathogenesis of viral infections in the CNS and developing therapies that promote protective and limit pathogenic responses.

Leukocyte recruitment to any organ site is generally a complex, multistep process. Under normal conditions, leukocyte migration into the CNS is maintained at low levels (Hickey, 2001). During virus-induced inflammation, however, the extravasation of leukocytes is increased and targeted to specific compartments of the CNS depending on the inflammatory stimulus and the infected region. Chemokines and chemokine receptors have been identified as pivotal players in regulating immune cell trafficking into the CNS. Chemokines consist of a large family of small, structurally related, chemotactic cytokines that are involved in regulating the normal lymphocytic traffic to both the lymphoid and nonlymphoid organs and leukocyte emigration into sites of injury and infection (Rossi & Zlotnik, 2000). Chemokines select leukocytes for tissue entry based on their expression of chemokine receptors, G-protein-coupled cell surface receptors, which have a characteristic seven transmembrane structure (Premack & Schall, 1996). In addition to targeting distinct leukocyte populations during inflammation, chemokines and their receptors have emerged as crucial mediators of a variety of biological processes including development and tissue homeostasis. With regard to virus-induced inflammation in the CNS, chemokines and chemokine receptors are in a strategic position to coordinate immune responses through both the regulation of leukocyte extravasation and also in the final positioning and activation of infiltrating cells.

Immune surveillance of the CNS and the effector function of infiltrating leukocytes into the CNS dictate the host-pathogen relationship during viral pathogenesis of the CNS. The

challenge of viral pathogenesis research in the CNS has been to define how immune cells traffic in and out of the CNS to recognize foreign antigen and their effect on the biology of the CNS. In this chapter, clinically relevant viral infections of the CNS that cause meningitis or encephalitis in humans and the murine models used to study these infections will be discussed as well as the current understanding of the role of chemokines and chemokine receptors in host protection and/or in neuropathology. Because many viral infections of the CNS are rare and without animal models, we have chosen to discuss those for which chemokine studies exist and have shed light on important aspects of antiviral and immunopathologic responses. A clearer understanding of how chemokines and chemokine receptors impact the inflammatory response to viral infections within the CNS will lead to the identity of targets that can potentially be manipulated for either host defense or recovery.

2. Flaviviruses

2.1 WNV

Viruses of the family *Flaviviridae* consist of approximately 70 members, of which four, West Nile virus (WNV), St. Louis encephalitis virus (SLE), Japanese encephalitis virus (JEV) and Murray Valley encephalitis virus (MVE) comprise the neurotropic Japanese encephalitis (JE) serogroup (Mukhopadhyay *et al.*, 2005). These viruses are primarily spread through arthropod vectors. For instance, West Nile Virus (WNV) is a neurotropic virus that exists in nature as a zoonosis and is transmitted by the *Culex* mosquito to humans and other vertebrates (Hayes & Gubler, 2006). Most humans infected with WNV are asymptomatic, yet approximately 20% may develop a minor flu-like illness, known as West Nile Fever (Mostashari *et al.*, 2001). Less than 1% of these patients develop severe neurological complications, such as encephalitis, that may potentially be lethal (Petersen & Roehrig, 2001). Increased age and defects in cell-mediated immunity are risk factors for developing WNV neuroinvasive disease (Campbell *et al.*, 2002; Murray *et al.*, 2008), which provides clues to mechanisms of viral clearance within the CNS.

A mouse model of WNV has contributed to the understanding of the pathogenesis of WNV encephalitis. Typically, mice are infected intra-dermally with WNV where it is taken up by Langerhans dendritic cells and brought to draining lymph nodes where replication results in primary viremia (Johnston *et al.*, 2000). The virus continues to replicate in the spleen, kidney, and epithelial tissues before it enters the CNS (Chung *et al.*, 2007). After entering the CNS, through both retrograde axonal transport and hematogenous dissemination (Samuel & Diamond, 2005; Hunsperger & Roehrig, 2006), WNV typically infects the brain stem, hippocampal, and spinal cord neurons (Eldadah & Nathanson, 1967; Omalu *et al.*, 2003; Shrestha *et al.*, 2003; Fratkin *et al.*, 2004). Following infection of the CNS, $CD4^+$ and $CD8^+$ T cells, as well as NK cells and infiltrating monocytes/macrophages accumulate in the CNS and localize primarily in the vicinity of WNV-infected neurons. To clear virus from infected brain tissues, T cells, particularly virus-specific $CD8^+$ T cells, monocytes, macrophages and γδ T cells as well as key cytokines, IFN-γ and TNF-α, are necessary and aid in the immune response during WNV infection of the brain. The murine model of WNV encephalitis exploits age-related differences in virologic control. While eight week-old mice exhibit 50-70% survival due to both peripheral and CNS control of viral replication, five week-old animals exhibit only a 10-20% survival rate due to inadequate virologic control within the CNS (Diamond *et al.*, 2003).

2.2 Role of chemokines in WNV-induced encephalitis

The recruitment of effector cells into the infected regions of the CNS is crucial for host defense against WNV and successful viral clearance within this compartment. Increased expression of inflammatory chemokines and their receptors (including CCR1, CCR2, CCR5, CXCR3 and CX3CR1) have been detected in the WNV-infected brain of 8 week-old mice (Glass *et al.*, 2005). One of the first chemokine receptors identified to have a clear functional role in the mouse model of WNV is CCR5. WNV infection of mice with targeted deletion of CCR5 results in a fatal outcome due to the loss of virologic control in the CNS. In addition, loss of CCR5 was associated with reduced infiltration of $CD4^+$ and $CD8^+$ T cells, NK cells and macrophages in the CNS of WNV-infected mice (Glass *et al.*, 2005). Thus, CCR5-depedent influx of leukocytes into the virally infected CNS is fundamental to viral clearance and recovery from WNV encephalitis.

One of the most highly expressed chemokines in the CNS in response to WNV infection is CXCL10, which is known to recruit NK and activated T cells (Muller *et al.*, 2010). CXCL10 is expressed relatively early in the course of neuroinvasion of WNV, primarily because WNV-infected neurons are the source of this chemokine (Klein *et al.*, 2005). In the mouse, CXCL10 expression exhibits a caudal-to-rostral pattern of expression, first found within Purkinje and granule cell neurons of the cerebellum and then detected within neurons of the hippocampus, frontal cortex and olfactory bulb. In mice with targeted deletion of CXCL10, the ability to control viral replication within the CNS is lost and mortality is enhanced (Klein *et al.*, 2005). The receptor for CXCL10, CXCR3, is also strongly upregulated by WNV in the mouse model and CXCR3 knockout mice demonstrate a similar increased susceptibility to the virus (Zhang *et al.*, 2008). The loss of the ability of neurons to express CXCL10 or the loss of CXCR3 resulted in decreased leukocyte trafficking, specifically $CD4^+$ and $CD8^+$ T cells, particularly within the cerebellum. Thus, WNV differentially induces CXCL10 within the brain, which results in the recruitment of effector T cells via the chemokine receptor CXCR3. These studies demonstrate the ability of resident cells of the CNS to generate antiviral immune responses in a region-specific manner.

Of interest, CXCL10 has also been shown to induce apoptosis of CXCR3-expressing neurons (Sui *et al.*, 2006). During WNV, elevated levels of CXCL10, however, promote lymphocyte entry and do not appear to simultaneously enhance neuronal death (Zhang *et al.*, 2010). Using in vivo and in vitro systems, it was determined that WNV-infected neurons also express TNF-α, which leads to down-regulation of CXCR3 mRNA levels and loss of surface expression of CXCR3 on neurons. Neuronal loss of CXCR3 in the context of WNV-infection promoted bystander survival of uninfected neurons, suggesting an adaptive mechanism to prevent CXCL10-mediated neuronal damage in the face of viral infections that require the entry of antiviral lymphocytes.

Monocytes also play an important role during CNS injury and infection as precursors to macrophages and microglial cells (Getts *et al.*, 2008). The accumulation of monocytes in the CNS occurred following a lethal intranasal inoculation with a non-neurotropic strain of WNV. Following treatment with an anti-CCL2 antibody, infiltration of these cells was delayed and survival was prolonged, suggesting a CCR2-dependent, pathogenic role for monocytes in the brain in this model (Getts *et al.*, 2008). In contrast, monocyte depletion in mice challenged intraperitoneally with a neurotropic strain of WNV resulted in increased mortality (Ben-Nathan *et al.*, 1996), suggesting a protective role for these cells. The ligands for CCR2, CCL2 and CCL7, are induced following WNV infection in the CNS (Glass *et al.*, 2005; Lim *et al.*, 2010) and in mice with targeted deletion of CCR2, increased mortality and

increased viral burden occurs (Lim *et al.*, 2010). Monocytosis occurs following WNV infection in WT mice and peaks just before monocytes begin to traffic into the brain (Lim & Murphy, 2011). This appears to be dependent on CCR2 since the numbers of recruited $CD4^+$ and $CD8^+$ T cells and NK cells in the brain of CCR2 knockout mice following WNV infection are similar to wild-type mice, whereas, the accumulation of inflammatory monocytes in the CNS is severely deficient. Thus, monocytes may be beneficial or harmful depending on the infection model.

Studies of WNV infection in five week-old WT mice, which exhibit a 10-20% survival rate, indicated that impaired viral clearance and survival may be partially due to lack of migration of antiviral $CD8^+$ T cells into the CNS parenchyma. Normally, infiltrating T cells are retained in perivascular spaces through the interaction of CXCR4 with its ligand CXCL12, which is found along abluminal surfaces of the entire CNS vasculature (McCandless *et al.*, 2006; McCandless *et al.*, 2008). Following WNV infection in eight week-old mice, CXCL12 levels decline by day two post-infection, allowing egress of antiviral T cells (Durrant, unpublished data). In contrast, five week-old mice do not exhibit down-regulation of CXCL12 until eight days post-infection, which is associated with perivascular accumulation of CXCR4-expressing T cells and increasing numbers of WNV-infected neurons. These data suggest that developmental changes in regulation of CXCL12 expression at the blood-brain barrier may contribute to antiviral immune responses. In support of a critical role for CXCL12 in limiting egress of virus-specific $CD8^+$ T cells, administration of the specific CXCR4 antagonist, AMD3100, was associated with increased migration of effector T cells into the CNS and enhanced viral clearance (McCandless *et al.*, 2008). CXCR4 antagonism was also associated with a rapid decrease in immune cell trafficking as virologic control ensued, suggesting that an early increase in virus-specific immune cell trafficking that controls viral infection ultimately leads to a rapid dampening of inflammation that would otherwise have pathologic consequences.

Taken altogether, these studies support a role for chemokines in the final positioning of effector cells that dictates outcome of immune responses in response to viral invasion within the CNS. Since resolution of CNS infection is often a balance between immune-mediated pathogen clearance and the deleterious effects of inflammation, studies utilizing the murine WNV encephalitis model suggest that if the appropriate cells reach critical regions at the appropriate time, virologic control may be accomplished and less severe disease occur.

2.3 CCR5 in human WNV disease

Studies of patients that carry a 32 base-pair deletion within the coding sequence of CCR5 (*CCR5Δ32*) indicate that human CCR5 is important in WNV pathogenesis. A genotype-phenotype association study of patients carrying *CCR5Δ32*, who lack functional CCR5, suggested that WNV-infected *CCR5Δ32* homozygous individuals exhibit higher incidences of symptomatic infection. Ultimately, CCR5 deficiency resulted in 100% susceptibility to severe symptomatic disease (Glass *et al.*, 2006). This genetic deficiency supports the observations in the WNV mouse model that functional CCR5 is critical for viral control and disease progression.

2.4 JEV

Japanese encephalitis virus (JEV) is a mosquito borne pathogen that occurs throughout most of Asia. JEV causes infection of the CNS with a high mortality rate (Parida *et al.*, 2006).

Clinical manifestation of JEV include fever, headache, vomiting, altered consciousness, and severe meningo-encephalitis (Kumar *et al.*, 1990). Children appear to be at greatest risk of infection in endemic areas for unknown reasons. Following entry into the host, JEV generates a rapid inflammatory response, which results in infiltration of neutrophils into the CNS. JEV is highly neurotropic, infecting neuronal rather than non-neuronal tissues in humans (Vaughn & Hoke, 1992) with neuronal precursors as the major target cells for infection (Kimura-Kuroda *et al.*, 1993). The course of disease for JEV in humans is faithfully replicated in murine models. Following extraneural inoculation with JEV, young mice are highly susceptible to neuroinvasion and rapidly die soon after virus is detected within the CNS (Johnson *et al.*, 1985; Hase *et al.*, 1990). Thus, viral titers of JEV in the brain generally peak at five days post-infection with death occurring between five and six days post-infection.

2.5 Chemokines and JEV-associated encephalitis

Expression of the chemokines CXCL10 and CXCL1 is upregulated in neuroblastoma cells infected with JEV (Gupta *et al.*, 2010). In a JEV-infected mouse model, similar chemokines were significantly upregulated including CXCL9, CXCL10 and CXCL12 (Gupta *et al.*, 2010). In addition to the robust expression of proinflammatory chemokines there was also increased numbers of infiltrating inflammatory cells into the brain at day five post-infection. Similar to WNV, JEV-infected neurons were found to be the source of CXCL10. CCL5 was also detected in JEV-infected neuroblastoma cells, indicating a possible role for this chemokine in the early stages of infection. Interestingly, neuronal death and mortality rate increases in patients with elevated levels of proinflammatory cytokines and chemokines, including CCL5, in the serum and cerebrospinal fluid (Winter *et al.*, 2004). Whether this is simply correlative data or whether these chemokines actually contribute to pathogenesis is currently unknown. An improved understanding of the proinflammatory effects responsible for immune-mediated control of viral infection and neuronal injury during JEV infections is essential to determine the viral pathogenesis of JEV in the CNS.

2.6 TBEV

Tickborne encephalitis virus (TBEV) is an additional member of the *Flaviviridae* family that causes Tickborne encephalitis (TBE), a severe infection of the CNS. TBEV is usually transmitted to patients by infected *Ixodes ricinus* ticks (Gunther & Haglund, 2005). Infection with TBEV is characterized by a biphasic clinical course with early nonspecific influenza-like symptoms and subsequent development of neurological symptoms or meningoencephalitis (Haglund & Gunther, 2003; Holzmann, 2003). In most fatal cases, TBEV can be found in the brain tissue (Gelpi *et al.*, 2005). An animal model for TBEV has not been established to date.
The pro-inflammatory cytokines CCL2, CCL5, CXCL10 and CXCL11 have been detected in the CSF of TBE patients (Grygorczuk *et al.*, 2006; Lepej *et al.*, 2006; Michalowska-Wender *et al.*, 2006). Although these chemokines exhibit known anti-viral roles in WNV encephalitis, their specific role in TBE is yet to be fully determined. One significant study, however, demonstrated an association between carriage of the *CCR5Δ32* allele and TBE (Kindberg *et al.*, 2008). Similar to WNV, an association between severe TBE and *CCR5Δ32* homozygosity was observed. Therefore, loss of CCR5 function in humans is a risk factor for TBE in patients exposed to TBEV. Increased expression of CCL5 in the CSF of patients with TBE suggests it may indeed play a role in leukocyte trafficking within TBEV-infected patients. Thus, CCR5

may be essential for limiting viral replication within the CNS through effective antiviral immune responses that shorten the course and limit the lethality of encephalitis.

3. HSV

Herpes simplex virus (HSV) types 1 and 2 establish latent infection in dorsal root ganglia for the entire life of the host. From this reservoir they can reactivate to cause human morbidity and mortality. HSV-1 is the causative agent of encephalitis and several disorders of the peripheral nervous system. HSV-2 is responsible for meningitis in neonates and in adults (Steiner *et al.*, 2007). HSV encephalitis is considered the most frequent cause of sporadic encephalitis in North America (Whitley, 1981). In a murine model of HSV-1 infection, the intracranial inoculation of a neurotropic HSV-1 strain causes encephalitis and death by day six after infection (Vilela *et al.*, 2008). In a murine model of HSV-2 infection, intraperitoneal inoculation with a neurovirulent HSV-2 strain causes meningoencephalitis (Kristensson *et al.*, 1978) and death occurs 10-14 days after infection. Pathology of HSV-2 infection has been shown to be T-cell mediated, due specifically to the actions of Th2 cells (Ikemoto *et al.*, 1995).

3.1 Chemokines and HSV

Following intracranial inoculation of HSV-1, early chemokine expression is dominated by CCL2, CCL3, CCL5, CXCL9 and CXCL10 (Wickham *et al.*, 2005; Carr *et al.*, 2006). CCL2, in particular, exhibits an important role in the early immune response to CNS infection with HSV-1 as monocyte recruitment to the CNS is significantly diminished in mice with targeted deletion of CCL2, thus hindering viral clearance (Kodukula *et al.*, 1999). CXCR3-deficient mice similarly exhibit elevated CNS viral titers of HSV-1, but only on day seven post-infection. Interestingly, survival was enhanced in CXCR3-deficient mice compared with wild-type mice following HSV-1 infection (Wickham *et al.*, 2005), suggesting a more complex role for CXCR3. Coinciding with increased viral titer, protein levels of CCL5, CXCL9, CXCL10 and IFN-γ were increased in the CNS as well as $CD8^+$ lymphocytes, suggesting a role for this receptor in antiviral adaptive immunity. In the absence of CXCR3, a transient increase in viral burden facilitates an elevated protective immune response.

In HSV-1-infected, CCR5-deficient mice, viral load was decreased in the CNS but associated with greater neuropathology and increased lethality (Teixeira *et al.*, 2010). Following infection, CCR5-deficient mice exhibited increased chemokine levels, including CCL5 and CCL2; enhanced expression of cytokines, such as TNF-α; and a significant increase in leukocyte migration into the brain (Teixeira *et al.*, 2010). Thus, in the absence of CCR5, greater control of viral replication was achieved, but at the cost of enhanced neuropathology and ultimately death. Generally, CCR5 deficiency would lead to decreased leukocyte infiltration; therefore, these results are surprising and may be unique to HSV-1 encephalitis. Treatment with anti-CCL5 antibodies or with small molecule antagonists of CCR1 and CCR5, both CCL5 receptors, had no effect on viral titers but led to significant reduction of the number of leukocytes infiltrating into the brain (Vilela *et al.*, 2009). Therefore, blocking CCR1 and CCR5 did not affect HSV-1 replication, suggesting that other immune mechanisms are involved in the process of viral control.

CCL2 has been identified as an initiator of Th2 responses and has a pathogenic role in the development of disease in HSV-2-infected mice (Karpus *et al.*, 1997; Hogaboam *et al.*, 1998). In the absence of CCL2 the severity of disease decreased dramatically, and the amount of Th2 cytokine production also decreased (Nakajima *et al.*, 2001). It appears that a population

of macrophages in mouse CSF is the primary producers of CCL2, which are postulated to increase severity of disease through induction of Th2 responses. Of note, CCL2 has been detected in the CSF from patients with herpes simplex encephalitis and has been correlated with clinical severity of herpes simplex encephalitis (Rosler *et al.*, 1998).

4. LCMV

Lymphocytic choriomeningitis virus (LCMV) is spread by the common house mouse and can cause aseptic meningitis in children and adults, neurological dysfunction in newborns and may induce spontaneous abortion in pregnant women (Enders *et al.*, 1999). Infection with LCMV can present with two separate clinical phases. Symptoms of the first phase include fever, malaise, headache and nausea, which resolve after several days and are then followed by the second phase of illness, which is characterized by symptoms of meningitis (Bonthius, 2009) with an abundant number of lymphocytes within the CSF (Chesney *et al.*, 1979). Although recovery from CNS disease is common, severe neurological disease as well as death, although rare, may occur. Congenital infection with LCMV is often fatal for the fetus or newborn (Biggar *et al.*, 1975). Survivors of congenital LCMV infection usually experience severe visual and cognitive impairment (Barton *et al.*, 1995). LCMV infection of the brain parenchyma may extend specifically to neuronal precursor cells, especially in prenatal or neonatal infections (Bonthius *et al.*, 2007).

LCMV is essentially a noncytolytic virus (Hotchin & Weigand, 1961) and in murine models of LCMV-induced meningoencephalitis (LCM), intracranial infection of LCMV into healthy adult mice results in fatal meningitis between seven and ten days after viral infection (Cole *et al.*, 1972; Allan *et al.*, 1987). Symptoms of disease are accompanied by a massive infiltration of mononuclear cells into the meninges, choroid plexus, CSF, and ependymal membranes (Doherty & Zinkernagel, 1974; Buchmeier *et al.*, 1980; Ceredig *et al.*, 1987; Doherty *et al.*, 1990). $CD8^+$ T cells and macrophages dominate the cellular infiltrate (Allan *et al.*, 1987; Ceredig *et al.*, 1987), whereas $CD4^+$ T cells and polymorphonuclear leukocytes are present in limited numbers (Ceredig *et al.*, 1987; Dixon *et al.*, 1987; Christensen *et al.*, 1995). It appears that the T cell response is a critical component for LCM because lethal meningitis does not occur in immunodeficient (irradiated or T-cell-depleted) mice following intracranial infection (Doherty *et al.*, 1974; Christoffersen *et al.*, 1976). Moreover, in the absence of $CD8^+$ T cells, mice will invariably survive intracranial LCMV infection (Christoffersen *et al.*, 1976; Leist *et al.*, 1987), suggesting that virus-specific $CD8^+$ cytotoxic T lymphocytes mediate fatal tissue damage (Buchmeier *et al.*, 1980; Doherty *et al.*, 1990). The role of virus-specific $CD8^+$ T cells during lethal LCM appears to be dependent on the strain of virus. Mice infected with the Armstrong strain of LCMV leads to killing of virus-infected cells in the meninges via a perforin-dependent mechanism (Kagi *et al.*, 1994), which leads to increased immunopathology. Whereas, mice infected with the Traub strain of LCMV exhibit lymphocytic infiltration of the neuroparenchyma rather than meningeal inflammation, which leads to a more fatal outcome (Christensen *et al.*, 2004). Overall, pathogenesis and death may be directly related to the influx of virus-specific T cells into critical regions of the CNS.

4.1 Chemokines and Lymphocytic choriomeningitis

During the mouse model of LCMV infection, expression of the T cell chemoattractants CCL2, CCL4, CCL5 and CCL7 as well as CXCL9, CXCL10 and CXCL11 is detected in the virus-infected tissues, as well as in the meninges, as early as day three post-infection

(Asensio & Campbell, 1997; Nansen *et al.*, 2000; Nansen *et al.*, 2002; Lindow *et al.*, 2003). On days six to seven post-infection, expression of these chemokines is significantly increased and accompanied by increased expression of granulocyte chemoattractants including XCL1 and CXCL2, CXCL6, CXCL16, and CCL3 (Asensio & Campbell, 1997; Nansen *et al.*, 2000). The main chemokine-producing cell types are resident cells of the CNS, particularly the meninges and choroid plexus together with astrocytes (Loetscher *et al.*, 2001). This surge of chemokine activity coincides with immune cell infiltration into the infected tissue. An analysis of chemokine receptor expression revealed local expression of receptors for these chemokines including CCR1, CCR2 and CCR5 as well as CXCR3 around day six to seven post-infection. (Nansen *et al.*, 2000; Lindow *et al.*, 2003). The analyses of cells from the inflammatory exudate of LCMV-infected mice indicate that T cells express CCR2, CCR5, and CXCR3, whereas macrophages are the predominant cell type expressing CCR1 (Nansen *et al.*, 2000; Lindow *et al.*, 2003; Christensen *et al.*, 2004). Thus, the elevated expression of these chemokines and chemokine receptors is likely to result in T lymphocytic and macrophage infiltration to the inflammatory site.

The chemokines CXCL9, CXCL10 and CXCL11 are the three known ligands for the receptor CXCR3 (Loetscher *et al.*, 2001). CXCL10 is rapidly upregulated in the virus-infected CNS (Asensio *et al.*, 1999; Nansen *et al.*, 2000), which results in the recruitment of $CXCR3^+$ cells into critical regions of the CNS. CXCL9 and CXCL11 are also expressed, but their role appears to be redundant (Christensen *et al.*, 2006). The majority of cells found to be expressing CXCR3 were activated IFN-γ-producing $CD8^+$ T cells (Homann *et al.*, 2001; Christensen *et al.*, 2004). A strong positive feedback loop is established through the local production of IFN-γ, which brings about further, marked upregulation of CXCL10 expression and therefore continued recruitment of $CXCR3^+$ effector cells. This robust recruitment positions CXCL10 as a key mediator of severe LCMV-induced CNS disease. In the absence of CXCL10, approximately half of LCMV (Traub) intracranially infected mice are protected from a lethal viral dose (Christensen *et al.*, 2006). CXCL10-deficient mice show no impairment of effector T cell generation or of immune cell infiltration, except for reduced $CD8^+$ T cell accumulation in parenchymal regions such as the corpus callosum (Christensen *et al.*, 2006). On the other hand, CXCL10 appears to be dispensable for the development of fatal neuroinflammation following infection with LCMV (Armstrong) (Hofer *et al.*, 2008). This highlights that there are underlying differences in viral strains and chemokine utilization with regards to disease outcome.

The chemokine receptor CXCR3 is upregulated in LCMV-infected CNS (Lindow *et al.*, 2003), and is predominately expressed on activated $CD8^+$ T cells (Christensen *et al.*, 2004). During intracranial infection with LCMV (Traub), CXCR3 deficiency leads to partial protection from immunopathology and death (Christensen *et al.*, 2004). In immunocompetent mice infected with LCMV (Traub), $CD8^+$ T cells preferentially traffic to the leptomeninges and choroid plexus and are also found in some parenchymal regions, such as the corpus callosum (Christensen *et al.*, 2004). However, in the absence of CXCR3, trafficking of these cells to specific regions was significantly delayed (Christensen *et al.*, 2004). This suggests that during LCMV infection, the expression of certain chemokines is necessary to target effector cells into infected CNS regions. However, this targeting, while important for viral control, may cause neuropathology. In addition, it is apparent that not only the recruitment of effector cells but the over-accumulation of the cells in infected regions of the CNS through the establishment of a CXCL10-mediated positive feedback loop may lead to immunopathology in these critical regions.

In addition to CXCR3, other chemokine receptors may also contribute to effector T cell recruitment, since in the absence of CXCR3 only partial protection is achieved. The expression of CCR1, CCR2, and CCR5, has also been associated with meningeal inflammation (Nansen *et al.*, 2000). A subpopulation of activated $CD8^+$ T cells expresses high levels of CCR2 and CCR5 (Andersson *et al.*, 1995). Yet, when CCR5 expression is absent there is no impairment of the LCMV-induced inflammation (Nansen *et al.*, 2002), supporting the notion that other chemokine receptors contribute to T cell recruitment. Overall, in addition to CXCR3, virus-activated $CD8^+$ T cells were found to express CCR2 and CCR5, whereas activated macrophages expressed CCR1 (Nansen *et al.*, 2000).
LCM is essentially the result of anti-viral effector T cells unable to control rapid replication of LCMV in the brain. Following viral infection, a highly potent T cell response is induced. There is a rapid and robust infiltration of effector T cells into the meninges of the CNS, which leads to increased local expression of IFN-γ, which leads to increased chemokine production and amplification of effector T cell infiltration. Lack of effective viral clearance contributes to persistent chemokine expression, which promotes excessive inflammation within the meninges and eventually the brain parenchyma, leading to a fatal outcome.

4.2 CXCL10/CXCR3 in human LCMV infection

One characteristic of LCMV infection in immunocompetent adults and children is the abundance of lymphocytes in the CSF (Bonthius, 2009). $CD8^+$ T cells are thought to infiltrate into the CSF to primarily clear the virus, which subsequently leads to the symptoms of aseptic meningitis during LCMV infection (Buchmeier & Lane, 1999). A predominant chemokine found in the CSF of patients with viral meningoencephalitis is CXCL10 (Lahrtz *et al.*, 1997). CXCL10 and its receptor CXCR3 have integral roles in the development of neuropathology in the mouse model of LCMV infection and may also have similar roles in the LCMV-infected CNS of certain patients. The infiltration of effector T cells into the CSF, CXCL10 expression and the resulting neuropathy are reminiscent of the mouse model, however the host factors that contribute to disease severity and, in some cases, lethality are not currently understood. Overall, chemokines appear to be important in viral control but, as seen with murine models of LCMV, also contribute to neuropathology.

5. HIV

Human immunodeficiency virus-1 (HIV) targets $CD4^+$ cells and macrophages. Infection of the CNS by HIV-1 occurs in about 80% of infected individuals. HIV-1 arrives in the CNS via infected macrophages that cross the blood-brain barrier. Neurological symptoms include meningitis, encephalitis, neuropathies, and HIV-1-associated dementia (HAD), with cognitive, motor, and behavioral dysfunctions (Marcotte *et al.*, 2003). Chemokine involvement in HIV-1 neuropathogenesis is well recognized because of their roles in the recruitment of HIV-1 infected immune cells, inflammatory responses, and as ligands for the HIV-1 coreceptors, CXCR4 and CCR5, which are expressed by neurons and directly mediate neurotoxicity and cell death (Hesselgesser *et al.*, 1998; Klein *et al.*, 1999; Hosking & Lane, 2010).
Chemokines that recruit monocytes/macrophages and lymphocytes into the brain, such as CCL2, have been detected in the CSF of individuals with HIV-1 infection (Kolb *et al.*, 1999). CCL2 levels are significantly increased during HIV-1-induced encephalitis (HIVE) and the chemokine accumulates in the CSF and brains of patients with HAD and HIVE, as well as in

macaques with Simian immunodeficiency virus (SIV)-induced encephalitis (SIVE) (Mankowski *et al.*, 2004; Monteiro de Almeida *et al.*, 2005; Monteiro de Almeida *et al.*, 2006). The expression of CCL2 in the CNS is associated with enhanced progression of HIV encephalitis, due to its ability to recruit monocytes and lymphocytes (Dhillon *et al.*, 2008). In addition to CCL2, CXCL10 also can attract inflammatory cells and has been detected in the CSF of HIV-1-infected patients (Kolb *et al.*, 1999). CXCL10 is chronically expressed within the brains of patients suffering from HIV-associated neurological disorders (Christo *et al.*, 2009). In addition, HIV-1 envelope glycoprotein gp120 can induce CXCL10 gene expression in astrocytes independent of IFN-γ (Asensio *et al.*, 2001). The encephalitic brain from SIV-infected animals exhibits elevated immunohistochemical expression of CCL3, CCL4, CCL5, CCL7 and CXCL10 (Sasseville *et al.*, 1996), suggesting a role for one or multiple chemokines in the pathogenesis of acquired immune deficiency syndrome encephalitis. Elevated levels of CCL7, another ligand for CCR2, are also detected within activated astrocytes in the brains of SIV-infected macaques, and are increased further in response to TNF-α, which thus initiates neuroinvasion by SIV/HIV-infected monocytes (Renner *et al.*, 2011). The prevention of monocyte infiltration into the brains of HIV-infected patients is therefore a critical step in limiting the ability of the CNS to act as a viral reservoir.

Chemokines may also act as neuromodulators within the HIV-infected CNS. The HIV glycoprotein gp120 may induce neuronal death via excitotoxicity during activation of CXCR4 receptors (Ohagen *et al.*, 1999; Chen *et al.*, 2002) and the CXCR4 ligand, CXCL12 may be converted into a neurotoxic agent via proteolytic cleavage with the resulting peptide capable of inducing neurotoxicity and apoptosis through engagement of the chemokine receptor CXCR3 (Vergote *et al.*, 2006). Thus, in addition to attracting inflammatory cells that contribute to neuropathology, CXCL10 can also synergize with CXCL12 cleavage products to induce neuronal cell death (van Marle *et al.*, 2004).

6. Concluding remarks

An effective anti-viral immune response is vital to maintain a balance between pathogen control and immunopathology during viral infection resolution within the CNS. While chemokines may contribute to viral clearance through focused amplification of inflammatory responses, they may also contribute to immune-mediated damage that depends on the type of virus and affected CNS compartment or region. However, targeting chemokines to abrogate all CNS infiltration may lead to untoward effects on immunosurveillance, as evidenced by the recent increase in opportunistic CNS viral infection with JC virus in patients treated with the anti-α4-integrin monoclonal antibody, natalizumab. Natalizumab treats multiple sclerosis, a chronic, inflammatory demyelinating disease, by preventing leukocyte entry at CNS endothelial barriers (Kleinschmidt-DeMasters & Tyler, 2005). A side effect of this treatment is the occurrence of progressive multifocal leukoencephalopathy (PML), a fatal opportunistic viral infection of the CNS caused by the reactivation of latent JC virus infection (Havrdova *et al.*, 2009). Thus, blockade of immune cell trafficking into the CNS interferes with essential components of immune surveillance that prevent opportunistic infections. PML underscores how vital immune cell trafficking in the CNS is for monitoring and regulating immune responses.

In summary, chemokines are integrally involved in recruiting targeted leukocyte populations to critical regions of the CNS that contribute both to host defense and the pathogenesis of disease. It is clear that these proinflammatory molecules exert

nonredundant roles in contributing to neuroinflammation following viral infection of the CNS thus meriting further studies on chemokines with regards to viral-induced disease. Finally, it is clear that chemokines and their receptors may represent viable targets in modulating the severity of human neuroinflammatory diseases.

7. References

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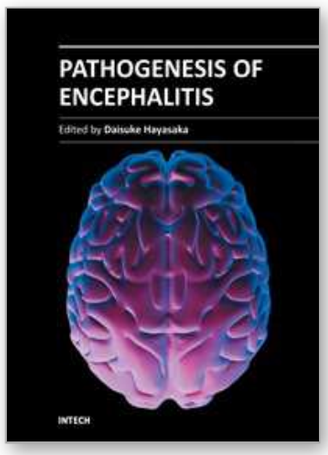

Pathogenesis of Encephalitis
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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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