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Review

Neuropathogenesis of Simian Immunodeficiency Virus infection in macaque monkeys

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Patients infected with human immunodeficiency virus (HIV) develop immunologic dysfunction and multiorgan inflammatory diseases directly associated with HIV-1 infection. Of these inflammatory diseases, the most devastating to the HIV-infected patient is involvement of the central nervous system (CNS). The pathogenesis of the clinical syndrome observed in these patients, termed HIV-associated dementia, remains poorly understood. However, as most of the detectable virus in the CNS is in cells of monocyte/macrophage lineage, it is clear that penetration of the blood-brain barrier by HIV-1 and the subsequent influx of monocytes into the brain are crucial components in the neuropathogenesis of HIV-associated dementia. Using the SIV-infected macaque model of acquired immunodeficiency disease, much has been learned about viral neuroinvasion occurring soon after experimental infection. The aim of this review is to discuss these recent advances and provide insight into plausible mechanisms for monocyte entry into the CNS.

Keywords: human immunodeficiency virus; simian immunodeficiency virus; acquired immune deficiency syndrome; HIV-associated dementia; rhesus macaques

Introduction

Approximately 25% of human immunodeficiency virus type 1 (HIV-1)-infected individuals develop neurologic disease (Janssen *et al*, 1991; McArthur, 1996). The clinical syndrome observed in these patients, termed HIV-associated dementia, is characterized by a range of cognitive, motor and behavioral changes (Michaels *et al*, 1988; Persidsky *et al*, 1995; Price *et al*, 1987, 1988). A correlation between HIV-associated dementia and the presence of HIV-1 in the central nervous system (CNS) (Wiley and Achim, 1994), dendritic pathology (Masliah *et al*, 1992), neuronal loss (Everall *et al*, 1991; Ketzer *et al*, 1990), the spatial pattern of neurons (Asare *et al*, 1996) and increased numbers of macrophages in the brain (Glass *et al*, 1995) has been shown. Despite these advances, the pathogenesis of HIV-associated dementia remains an enigma.

Many individuals with HIV-associated dementia also have HIV encephalitis (HIVE). HIVE is defined by the presence of characteristic histopathologic changes and/or detectable HIV-1 nucleic acid or antigen in the CNS (Budka *et al*, 1991b). The typical lesions of HIVE are astrocytosis, glial nodules and parenchymal and perivascular infiltrates of macrophages and multinucleate giant cells (Kure *et al*, 1990; Nielsen *et al*, 1984; Price *et al*, 1988; Wiley *et al*, 1986). HIV antigens, nucleic acid and viral particles have been consistently localized to macrophages/microglia in these lesions (Epstein *et al*, 1985; Gyorkey *et al*, 1987; Koenig *et al*, 1986). Evidence for infection of astrocytes, oligodendrocytes, endothelial cells and neurons is less convincing (Koenig *et al*, 1986; Moses *et al*, 1993; Saito *et al*, 1994; Tornatore *et al*, 1994; Wiley *et al*, 1986). Thus, as productive HIV-1 infection in HIVE is primarily confined to macrophage/microglial infiltrates in the CNS, the mechanisms of neuronal dysfunction are unclear. For these reasons research on the pathogenesis of this disorder has focused on indirect mechanisms of neuronal dysfunction and death (Bernton *et al*, 1992; Brenneman *et al*, 1988; Genis *et al*, 1992; Giulian *et al*, 1990; Lipton, 1991; Pulliam *et al*, 1991). These studies suggest that the keystone of HIV-associated dementia is the HIV-1-

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infected brain macrophage/microglial cell that either produces or induces other CNS resident cells to release factors that ultimately result in neuronal injury. Thus, while a direct relationship between HIV-infected macrophages/microglia and neuropathology is evident, the association between neuropathology and the clinical disorder remains controversial (Wiley and Achim, 1995). Nor do we understand the inciting mechanisms responsible for initial monocyte/macrophage recruitment to the brain during HIV-1 infection.

SIV-infected macaque monkey model

Similar to HIV-1-infected patients, many simian immunodeficiency virus (SIV)-infected macaque monkeys develop lentivirus-induced encephalitis (SIV encephalitis, SIVE) (Table 1). SIVs are immunosuppressive nonhuman primate lentiviruses that have extensive sequence homology, morphology, and biologic properties similar to HIV-1 and HIV-2 (Desrosiers *et al*, 1990). As with HIV-1, the target for SIV infection *in vivo* and *in vitro* (Desrosiers *et al*, 1991; Lackner *et al*, 1991; Ringler *et al*, 1989; Wyand *et al*, 1988) is the CD4 molecule expressed on lymphocytes and monocyte/macrophages. Moreover, as with HIV-1, SIV isolated from encephalitic brains has been shown to be macrophage-tropic (Desrosiers *et al*, 1991; Simon *et al*, 1992, 1994; Watkins *et al*, 1990; Wiley and Budka, 1991). Even when animals are infected with molecularly cloned lymphotropic virus (eg SIVmac239), approximately 30% of infected animals develop highly macrophage-competent variants (Desrosiers *et al*, 1991). Macrophage tropism of SIVmac239 variants and high levels of virus replication in the CNS have been associated with specific sequence changes in the *env* gene (Kodama *et al*, 1993; Mori *et al*, 1992). Thus, as neuronal dysfunction in many patients with HIV-associated dementia is most likely a result of macrophage/microglial infection (Budka, 1991), the SIV-infected macaque monkey is an excellent model for examining how monocytes/macrophages infiltrate the CNS.

Table 1 Comparison of human and simian immunodeficiancy virus infection of the nervous system

	HIV	*SIV*
Encephalitis		
multinucleate giant cells	+	+
vascular orientation	+	+
mineralization	pediatric cases	juvenile/adults
atrophy	+	+
white matter pallor	+	−
Myelitis		
multinucleate giant cells	+	+
vacuolar myelopathy	+	rare
Behavioural alterations	+	+
Peripheral neuropathy	+	−
Opportunistic infections	common in adults	rare

Early events in lentivirus invasion of the CNS

A major unanswered question is why only a portion of HIV-infected patients and SIV-infected monkeys develop HIVE and SIVE. There is a strong association between macrophage-tropism and HIVE/SIVE. There is also evidence that the host immune system plays a major role in controlling viral infection in the CNS (Bell *et al*, 1993; Nathanson *et al*, 1994). To answer this question, one has to look at how virus and host interact early in infection. Soon after infection, during peak viremia which occurs just prior to or at the time of seroconversion (Gaines *et al*, 1987), HIV-1 is frequently isolated from the cerebrospinal fluid (CSF) in both symptomatic (Albert *et al*, 1987; Gaines *et al*, 1987; Gouldsmit *et al*, 1986; Ho *et al*, 1985) and asymptomatic (Chiodi *et al*, 1986, 1988; Sinclair *et al*, 1992) patients. A subpopulation of patients will develop an acute meningoencephalitis (Carne *et al*, 1985; Cooper *et al*, 1985). Generally, following this acute phase of primary lentivirus infection, the onset of an immune response is associated with a decrease of HIV antigen and virus in the CNS (Gaines *et al*, 1987; Gouldsmit *et al*, 1986). During this asymptomatic phase of infection, neurologic signs may be absent, but patients may have chronic or subacute meningoencephalitis. Patients who progress to advanced HIVE usually have decreased immune function with a transition to symptomatic AIDS (Bell *et al*, 1993; Chiodi and Fenyö, 1991; Michaels *et al*, 1988; Price *et al*, 1987; Rhodes, 1993; Sharer *et al*, 1991). Similarly, in macaque monkeys infected with SIV there is a very early burst in viral replication in both lymphoid organs and the CNS. We have shown that even molecularly cloned lymphotropic virus (SIVmac239) induces an acute meningoencephalitis indistinguishable from that induced by other pathogenic isolates of SIV by 2 weeks postinoculation (Lackner *et al*, 1994). These initial rounds of viral replication decrease as the host immune system responds (Lackner *et al*, 1994; Reimann *et al*, 1994). In the CNS, as in the lymphoid tissues, both SIV-specific cytotoxic lymphocytes and antibody are involved (Smith *et al*, 1995; Von Herrath *et al*, 1995). Similar to HIV-infected patients, as the disease progresses and the immune system fails, a portion of the animals develop SIVE. Thus, sometime early in infection or during the asymptomatic period unique viral and host factors in conjunction with viral entry into the CNS are likely responsible for progression to SIVE. In order to elucidate the pathogenesis of this complex disease, factors involved in viral entry into the brain have to be closely examined at the level of initial leukocyte interaction with CNS endothelium.

Leukocyte and endothelial interactions

It is widely assumed that HIV-1 enters the brain within monocytes (Trojan horse theory) (Peluso *et*

al, 1985). Whether these monocytes migrate into the brain as part of the normal replacement of resident perivascular macrophages or in response to activation and subsequent chemotactic stimuli is unknown. In addition, the role of the endothelial cell may be crucial. To address these questions, one has to consider the unique interplay of circulating leukocytes and CNS endothelium. The brain is one of the 'privileged' sites in the body: the circulatory system and the CNS parenchyma are physically separated. This separation, called the blood-brain barrier (BBB), is maintained by tight junctions between brain endothelial cells, intact basement membranes, and the perivascular glia limitans composed of astroglial and perivascular macrophage cell foot processes (Lassmann *et al*, 1991). Of these components, macrophages/microglia are the primary cells infected with HIV/SIV and thus the focus of attention for pathogenesis studies.

There are five separate populations of brain macrophages: the parenchymal (resident microglia), choroid plexus, meningeal, gitter cell, and perivascular. Of these, the meningeal and perivascular macrophages may play a significant role in antigen presentation and activation of immune responses (Altman, 1994; Hickey *et al*, 1991; Hickey and Kimura, 1988; Lassmann *et al*, 1991). Although phenotypically and functionally similar to non-CNS tissue macrophages and parenchymal microglia, these perivascular macrophages may differ in origin and turnover rate in both normal and inflamed CNS (Lassman *et al*, 1993). In normal adult rodent and human brain, it has been shown that perivascular macrophages are replaced continuously via recruitment from the circulating monocyte pool through the intact BBB (Hickey and Kimura, 1988; Lawson *et al*, 1992; Unger *et al*, 1993). Thus, HIV/SIV-infected monocytes may enter the CNS parenchyma in the absence of concurrent inflammation (Figure 1). Furthermore, studies in Lewis rats have demonstrated that recruitment of perivascular macrophages is accelerated during CNS inflammation, while the resident parenchymal microglia are seldom replaced by hematogenous cells (Lassman *et al*, 1993). Moreover, activated macrophages can in turn activate other cell types, notably, astrocytes and endothelium, via secretion of IL-1β, TGF-β, and TNF-α (Giulian *et al*, 1986; Selmaj *et al*, 1990). IL-1β and TNF-α are potent inducers of endothelial adhesion molecules *in vitro* and *in vivo* (Bevilacqua and Nelson, 1993; Bevilacqua *et al*, 1985; Briscoe *et al*, 1992; Dustin *et al*, 1986) and probably are crucial in recruitment of leukocytes to the CNS in HIVE. Thus, HIV/SIV-infected circulating monocytes may be a source of CNS infection via the natural or accelerated replacement of perivascular macrophages (Figure 1). In our studies using the acutely SIV-infected macaque monkey model, neuroinvasion by SIV has been associated with intrathecal immune activation (Sasseville *et al*, 1995; Smith *et al*, 1992). Significant increases in the density of perivascular macrophages/microglia coincide with viral neuroinvasion and marked elevation of CSF quinolinic acid (Lane *et al*, 1996). Moreover, in support of the Trojan horse theory, combined *in situ* hybridization and immunohistochemistry demonstrate that these infected perivascular cells are macrophages/microglia (Lane *et al*, 1996).

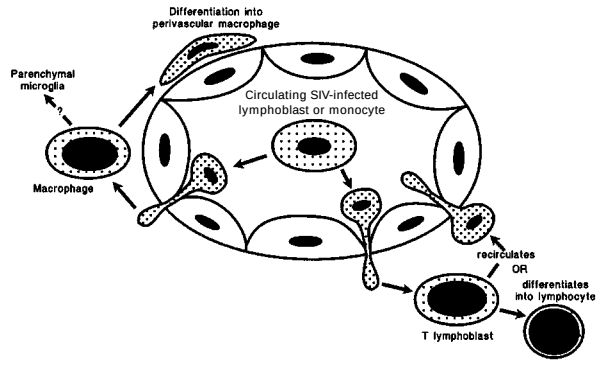

Figure 1 Theorectical model of cell-associated SIV invasion of the CNS utilizing normal leukocyte trafficking mechanisms

Studies in rats have also demonstrated that T-lymphoblasts, but not mature T-cells, randomly enter the CNS (Figure 1). However, in the absence of specific antigen recognition they exit within 1 to 2 days (Hickey *et al*, 1991) (Figure 1). Thus, HIV/SIV-infected T-lymphoblasts may also be a potential source of initial HIV-1 infection of the CNS. What effect normal or augmented cell trafficking to the CNS has on the development of HIV-induced CNS disease is unknown and needs to be examined.

Role of adhesion molecules and chemokines in neuroinvasion

Although the mechanisms governing recruitment of leukocytes to the CNS from the systemic circulation are not fully characterized, upregulation of leukocyte and endothelial adhesion molecules and chemoattractants (eg chemokines) are likely critical components (Miller and Krangel, 1992; Springer, 1994). It is well established that the sequential interactions of selectins, integrins and members of the immunoglobulin gene superfamily and their corresponding ligands are crucial for leukocyte rolling, firm adhesion, and transendothelial migration at sites of tissue injury (Springer, 1994). In fact, numerous *in vivo* studies have demonstrated that monoclonal antibody blockade of these pathways significantly reduces the influx of cellular infiltrates into inflamed tissues. For instance, in rodent experimental allergic encephalomyelitis (EAE), a model of multiple sclerosis, mononuclear cell infiltrates were abrogated by blockade of the VCAM-1/α4β1 pathway (Baron *et al*, 1993; Yednock *et al*, 1992). Likewise, we have demonstrated upregulated VCAM-1 in macaque monkeys with SIVE and documented that VCAM-1/α4β1 interac-

tions are involved in monocyte adherence to endothelium in encephalitic brain (Sasseville *et al*, 1992, 1994). In addition, human brain microvascular endothelial cells cocultured with activated HIV-infected monocytes express elevated levels of VCAM-1 and E-selectin (Nottet *et al*, 1996). Elevated levels of these two adhesion molecules paralleled the levels of HIV-1 gene products and proinflammatory cytokines in encephalitic brain from HIV-1-infected patients (Nottet *et al*, 1996). Studies utilizing the SCID mouse model of HIVE demonstrate the direct relationship between macrophage/microglia activation, which occurs in response to neuroinvasion of HIV-1-infected monocytes, and subsequent VCAM-1 expression by CNS endothelial cells and monocyte infiltration into the CNS (Persidsky *et al*, 1996). Taken together, these studies strongly support a role for cytokine-induced endothelial adhesion molecules in leukocyte recruitment to the CNS in HIVE/SIVE.

In addition to the interactions of leukocyte and endothelial adhesion molecules, monocytes are also activated and migrate in response to chemotactic gradients elicited from inflammatory sites (Furie and Randolf, 1995; Springer, 1994). Pivotal components of this process are a group of chemotactic cytokines, termed chemokines. Chemokines are structurally related, low-molecular-weight, proinflammatory proteins that are induced in various cell types (including endothelial cells and leukocytes) and are distinct from classical chemoattractants in that they affect the migration of specific subsets of leukocytes (Schall *et al*, 1990, 1993; Taub *et al*, 1993). Based on the presence or absence of an amino acid separating the first pair of cysteines, they are divided into two subfamilies (α or C-X-C and β or C-C chemokines). For the most part, the C-X-C chemokines stimulate and attract neutrophils, whereas the C-C chemokines activate and attract monocytes, lymphocytes and eosinophils (Furie and Randolf, 1995; Loetscher *et al*, 1994b; Rot *et al*, 1992; Schall *et al*, 1993). Although these chemokines are potent mediators of inflammation, recent studies have focused on their antiviral properties.

The C-C chemokines, RANTES (regulated on activation normal T cell expressed and secreted) and macrophage inflammatory protein-1α and -β (MIP-1α and β) have been shown to be major HIV-suppressive factors released by $CD8^+$ cells (Cocchi *et al*, 1995). Another group of investigators showed elevated levels of these three chemokines in purified populations of $CD4^+$ lymphocytes from HIV-negative individuals who were repeatedly exposed to HIV (Paxton *et al*, 1996). Moreover, they showed that these $CD4^+$ lymphocytes were more resistant to *in vitro* infection with multiple primary isolates to HIV-1 than were $CD4^+$ lymphocytes isolated from nonexposed individuals (Paxton *et al*, 1996). Exactly how these chemokines exerted their effect was not resolved in these studies. For years investigators have been searching for a coreceptor that acts in conjunction with CD4, which dictates T cell- and/or macrophage-tropism of HIV/SIV isolates. Recently, Feng *et al*. reported that a fusion receptor ('fusin' or LESTR) along with CD4 enables T cell line-tropic HIV isolates to infect lymphocytes (Feng *et al*, 1996). Moreover, antibodies against LESTR/fusin blocked envelope-mediated fusion and viral entry into susceptible cells (Feng *et al*, 1996). This cofactor, a putative seven-transmembrane, G protein-coupled receptor is similar (37% amino acid identity) to the receptor for the C-X-C chemokine interleukin-8 (Feng *et al*, 1996; Loetscher *et al*, 1994a). More recently, the lymphocyte chemoattractant stromal cell-derived factor-1 (SDF-1) has been shown to be the natural ligand for LESTR/fusin (Bleul *et al*, 1996; Oberlin *et al*, 1996). In cells expressing CD4 and LESTR/fusin, SDF-1 inhibits infection by T-cell tropic strains of HIV (Bleul *et al*, 1996; Oberlin *et al*, 1996). Therefore, some chemokine receptors may function as fusin cofactors, but MIP-1α, MIP-1β and RANTES do not bind to LESTR/fusin. Which receptors are responsible for the antiviral activity of MIP-1α, MIP-1β and RANTES? Many independent groups have identified the C-C chemokine receptor 5 (CC-CKR5) as the major coreceptor for macrophage-tropic strains of HIV-1 (Choe *et al*, 1996; Deng *et al*, 1996; Doranz *et al*, 1996; Dragic *et al*, 1996). However, additional chemokine receptors, CC-CKR2b and CC-CKR3, are utilized by other HIV-1 isolates (Choe *et al*, 1996; Doranz *et al*, 1996). In agreement with earlier observations that macrophage-tropism of HIV/SIV isolates is determined by sequence variations in the V3 loop of HIV-1 gp120 (Korber *et al*, 1994; Power *et al*, 1994). Choe *et al* demonstrated that the utilization of specific chemokine receptors by T cell- or macrophage-tropic isolates was dictated by the sequence of the V3 region (Choe *et al*, 1996). Thus, these findings demonstrate that some monocyte-tropic strains of HIV-1 utilize C-C chemokine receptors (eg CC-CKR5) as coreceptors for infection, whereas T cell-tropic HIV-1 strains use C-X-C receptors (eg LESTR/fusin).

Despite strong *in vitro* data demonstrating the antiviral properties of certain chemokines, *in vivo* data from our laboratory and others reveal that elevated chemokines do not appear to prevent virus infection in the CNS. Brain from patients with HIV-associated dementia showed more MIP-1α and MIP-1β mRNA than brain from HIV-infected patients without dementia (Schmidtmayerova *et al*, 1996). Recently, we have demonstrated that encephalitic brain from SIV-infected animals has elevated immunohistochemical expression of MIP-1α, MIP-1β, RANTES, monocyte chemotactic protein-3 (MCP-3), and interferon-inducible protein-10 (IP-

10) (Sasseville *et al*, 1996). These results in SIV-infected macaque monkeys and HIV-infected patients demonstrating elevated immunohistochemical expression of chemokines on endothelium and perivascular infiltrates in encephalitic brain containing abundant virus suggest that at least in the brain these chemokines play no role in containing viral replication, and probably function as mediators of inflammation. MIP-1α and MIP-1β are potent chemoattractants for monocytes and lymphocytes (Koch *et al*, 1994; Taub *et al*, 1993) and in conjunction with cytokine-induced adhesion molecule expression provide a likely mechanism for monocyte recruitment to the CNS in HIV-infected patients. However, the *in vivo* role of chemokines in HIV infection remains to be determined.

Summary

From our time-course studies of SIV-infected macaque monkeys early after experimental infection, we have begun to unravel some of the complex interactions in initial viral neuroinvasion. In agreement with the Trojan horse theory of neuroinvasion, we have demonstrated that, independent of cellular tropism of the initial virus (macrophage- or T cell-tropic), SIV enters the CNS within 2 weeks of infection. Coincident with viral neuroinvasion, there is a significant increase in the density of perivascular macrophages/microglia and evidence of macrophage activation (i.e. increased quinolinic acid levels). We hypothesize that virus within infected circulating monocytes enters the CNS by natural or increased trafficking mechanisms (Figure 1). Once extravasated, these virus-infected activated monocytes differentiate and become further activated and release cytokines and chemokines that stimulate surrounding resident cells (eg, macrophage/microglia, astrocytes, endothelium) (Figure 2). In particular, the CNS endothelium produces and binds chemokines, increasing the chemotactic gradient, and increases expression of cytokine-inducible adhesion molecules that bind circulating leukocytes, augmenting leukocyte recruitment (Figure 2).

With the onset of an immune response to SIV, virus recovery from the CSF, the density of perivascular macrophages and quinolinic acid levels decrease sharply. However, the few animals, termed rapid progressors, that fail to mount a significant immune response to SIV generally have the highest density of perivascular macrophages and VCAM-1 expression. Some of these animals will develop fulminant SIVE. Thus, early after infection there is a strong association between lack of an immune response to SIV and the development of SIVE.

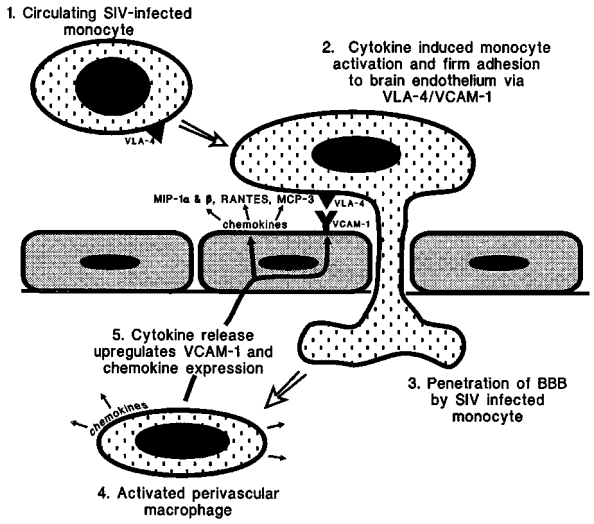

Figure 2 Theorectical model of recruitment of SIV-infected leukocytes via activated CNS endothelium. SIV-infected leukocytes enter the CNS through normal or enhanced trafficking mechanisms causing localized endothelial activation (chemokine release and upregulation of adhesion molecules). Additional circulating activated SIV-infected leukocytes (particularly monocytes) with upregulated surface integrin receptors (1) selectivity bind to activated endothelium (2); penetrate the blood-brain barrier (3); differentiate into perivascular macrophages and become further activated (4), and release additional cytokines and chemokines augmenting the chemoattraction and adhesion molecule expression on surrounding leukocytes and endothelium (5). This results in increased recruitment of leukocytes into the CNS further amplifying the process

The pathogenesis is less clear in the animals that are able to mount an initial immune response to SIV and to clear virus from the CNS but subsequently develop terminal SIVE. We know that adhesion molecule and chemokine expression is elevated in all animals with SIVE, whether they are classified as rapid progressors or not. Thus, in terminal AIDS is it the enhanced localized expression of adhesion molecules and chemokines and increased cellular trafficking to the CNS that allows SIV to reenter the CNS, or is the virus crossing the BBB first and the subsequent induction of these factors that set the stage for SIVE to develop?

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