Neurotoxicity Research, 2005, VOL. 8(1-2). pp. 107-116

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The Role of Monocytes and Perivascular Macrophages in HIV and SIV Neuropathogenesis: Information from non-Human Primate Models

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(Received 25 March 2005; Revised 28 June 2005; In final form 05 July 2005)

Perivascular macrophages are located in the perivascular space of cerebral microvessels and thus uniquely situated at the intersection between the brain parenchyma and blood. Connections between the nervous and immune systems are mediated in part through these cells that are ideally located to sense perturbations in the periphery and turnover by cells entering the central nervous system (CNS) from the circulation. It has become clear that unique subsets of brain macrophages exist in normal and SIV- or HIV-infected brains, and perivascular macrophages and similar cells in the meninges and choroid plexus play a central role in lentiviral neuropathogenesis. Common to all these cell populations is their likely replacement within the CNS by monocytes. Studies of SIV-infected non-human primates and HIV-infected humans underscore the importance of virus-infected and activated monocytes, which traffic to the CNS from blood to become perivascular macrophages, potentially drive blood-brain barrier damage and cause neuronal injury. This review summarizes what we know about SIV- and HIV-induced neuropathogenesis focusing on brain perivascular macrophages and their precursors in blood that may mediate HIV infection and injury in the CNS.

Keywords: Perivascular macrophages; Monocytes; HIV; SIV; Blood-brain barrier; CNS

INTRODUCTION

Brain macrophages have received considerable attention due to their central role in HIV-induced neuropathogenesis. Brain macrophages are heterogeneous in their location, phenotype, turnover, and possibly function. Perivascular macrophages, located in the perivascular (Virchow-Robin) space of cerebral vessels, are immunophenotypically distinct from the resident brain macrophages, parenchymal microglia (Ford *et al*., 1995; Becher and Antel, 1996; Dick *et al*., 1997; Walker, 1999; Fischer-Smith *et al*., 2001; Williams *et al*., 2001). We and others have addressed the relative contribution of perivascular macrophages and parenchymal microglia in AIDS neuropathogenesis (Fischer-Smith *et al*., 2001; Williams *et al*., 2001). These studies found that perivascular macrophages, in addition to parenchymal microglia, play a central role in neuropathogenesis. It has been repeatedly shown that perivascular macrophages are a major cell type productively infected with HIV and its close relative simian immunodeficiency virus (SIV) in the brain (Gabuzda *et al*., 1986; Smith TW *et al*., 1990; Schindelmeiser and Gullotta, 1991; Hurtrel *et al*., 1993; Lane *et al*., 1996; Rostasy *et al*., 1999; Jones *et al*., 2000; Fischer-Smith *et al*., 2001; Williams *et al*., 2001). As such, perivascular macrophages with parenchymal microglia produce soluble mediators, many of which are potentially deleterious to endothelial cells of the blood-brain barrier (BBB) and neurons. Very recent studies in HIV and SIV infection underscore the importance of understanding monocyte activation and traffic to the CNS as it defines the role of the brain as a viral reservoir and the biology of perivascular macrophages and their precursors in the neuropathogenesis of AIDS (Salemi *et al*., 2005b; Williams *et al*., 2005).

In this review, we first address the biology of perivascular macrophages in the context of HIV and SIV neuropathogenesis. We then discuss possible roles of monocyte infection, activation and traffic to the CNS in relation to brain infection and neuronal injury. We sug-

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ISSN 1029 8428 print/ ISSN 1476-3524 online.

gest that understanding the linkage between dysregulated macrophage immunity and neuronal dysfunction may provide the basis of therapeutic interventions of HIV neuropathogenesis and other neurodegenerative disorders.

BIOLOGY AND TURNOVER OF PERIVASCULAR MACROPHAGES

What makes perivascular macrophages a unique brain macrophage population? It is likely their location and source. Perivascular macrophages are located in the perivascular space of Virchow-Robin. The Virchow-Robin spaces surrounding cerebral vessels are invaginations of subpial space and are a distinct compartment that connects blood, cerebrospinal fluid, and brain parenchyma (Hutchings and Weller, 1986; Esiri and Gay, 1990; Ichimura *et al*., 1991). The perivascular spaces also provide a major site of infiltration of blood-derived cells in both normal and inflammatory conditions in the CNS (Ransohoff *et al*., 2003). Indeed, perivascular accumulation of monocyte/macrophages and multinucleated giant cells (MNGC) is a prominent feature of HIV and SIV encephalitis (HIVE/SIVE) (Budka, 1986; Pumarola-Sune *et al*., 1987; Ward *et al*., 1987; Lackner *et al*., 1991).

As cells situated at the intersection of the CNS and blood, they are likely the first to sense activating stimuli from the circulation and to encounter infiltrating monocytes and T lymphocytes with CNS inflammation. Intravenous injection of lipopolysaccharide or interleukin-1 induces cyclooxygenase-2 (COX-2) expression on perivascular macrophages in the rat that are all ED2+, but not on ED2- parenchymal microglia, within a few hours, exhibiting the great sensitivity of perivascular macrophages to peripheral challenges (Elmquist *et al*., 1997; Schiltz and Sawchenko, 2002). The early detection of CNS inflammation has been demonstrated by increased expression of ED2 on perivascular macrophages that precedes the onset of EAE (Polfliet *et al*., 2002).

Perivascular macrophages, in contrast to parenchymal microglia, are distinctively equipped for phagocytosis and antigen presentation demonstrated by selective label with fluorescent dextran dyes following intracerebral injection (Streit and Graeber, 1993) and expression of MHC class II and costimulatory molecules including B7-1 and CD40 (Laman *et al*., 1998; Hofmann *et al*., 2002; Fabriek *et al*., 2005). In HIVE and SIVE, perivascular macrophages are considered to be a significant source of metabolic markers and immune mediators such as inducible nitric oxide synthase (iNOS), matrix metalloproteinase-2 (MMP-2), COX-2, indolamine 2,3-dioxygenase (IDO), and amyloid precursor protein (Rostasy *et al*., 1999; Ghorpade *et al*., 2001; Fiala *et al*., 2002; Depboylu *et al*., 2004; Vehmas *et al*., 2004). Given such a distinct nature, perivascular macrophages may play distinct functions, as opposed to parenchymal microglia, in normal CNS physiology and in CNS inflammatory diseases. Recent studies show that perivascular macrophages indeed play distinct roles in CNS inflammation including bacterial meningitis, EAE, and cryptococcal infection (Polfliet *et al*., 2001; 2002; Aguirre and Miller, 2002).

As a part of normal physiology, bone marrow-derived blood monocytes continuously traffic to CNS and become perivascular macrophages (Hickey and Kimura, 1988). The traffic can be accelerated in response to inflammation and infection that often leads to immune activation of monocytes/macrophages (Lassmann *et al*., 1993; Reuter *et al*., 2004). Studies in adult rodents show that perivascular macrophages are repopulated regularly by bone marrow-derived blood monocytes while the turnover of their parenchymal counterpart, resident microglia, is limited at least under non-inflammatory conditions (Kennedy and Abkowitz, 1997; Vallieres and Sawchenko, 2003; Hess *et al*., 2004; Galimi *et al*., 2005). In light of their turnover, it is not hard to envision that virus-infected monocytes, destined to become perivascular macrophages, do so while carrying virus to the CNS. Since proposed for visna virus by Peluso *et al*. (1985), monocyte-associated virus traffic rather than cell-free virus traffic has been the prevailing view for entry mode of HIV and SIV into the brain (Schindelmeiser and Gullotta, 1991; Lane *et al*., 1996; Mesquita *et al*., 1998; Barrow *et al*., 2003). In the case of HIV, monocytes appear less able to replicate virus while transiting in the blood, but are more able to do so once they enter tissues and become macrophages (Gendelman *et al*., 1986). Traffic of non viral pathogens to the CNS by monocytes has also been demonstrated (Williams and Blakemore, 1990).

Evidence supporting monocyte-associated HIV entry comes from experiments where SIV directly injected into the brain does not result in CNS infection (Hurtrel *et al*., 1993; Boche *et al*., 1995; Smith MS *et al*., 2002), and from studies demonstrating a requirement of macrophage tropism for development of encephalitis (Desrosiers *et al*., 1991; Simon *et al*., 1992). More recently, using an *in vitro* BBB model, it was shown that cell-associated SIV is required for the activation of the BBB that occurs during neuroinvasion (MacLean *et al*., 2004b). It is, therefore, very likely that the precursors to perivascular macrophages are infected outside the CNS and their traffic result in HIV CNS disease.

In line with this idea, we and others have found that virus-infected perivascular macrophages are immunophenotypically similar to a subset of blood monocytes (Fischer-Smith *et al*., 2001; Williams *et al*., 2001; Kim *et al*., 2003a). This discrete subset of blood monocytes expands during HIV and SIV infection and preferentially harbor virus, suggesting a strong likelihood of this subset being a vehicle for HIV and SIV.

PERIVASCULAR MACROPHAGES AND HIV INFECTION IN CNS

HIV and SIV invade the brain early, within days to weeks of infection (Chakrabarti *et al*., 1991; Davis *et al*., 1992). Most neurological manifestations of virus infection of the brain occur long after initial infection in the periphery, with the development of AIDS. It is likely that productive CNS infection by HIV and SIV occurs with AIDS. Using SIV-infected monkeys, we found that productive CNS infection occurs transiently early after infection and consistently later with the development of AIDS and encephalitis (Williams *et al*., 2001). Serial sacrifice studies in monkeys demonstrate that productively infected perivascular macrophages are detected in the brain between 7-21 days post infection, occurring with peak viremia and then are detected later in disease with development of AIDS. The kinetics of monocyte traffic to CNS early after infection may in part account for the observed kinetics of virus entry and productive infection in the CNS. If so, these findings suggest the productive infection of the CNS may occur primarily via infected monocytes that become perivascular macrophages and this process requires an active seeding of virus from the periphery. There is an alternative view that reactivation of virus that is latent in the CNS might also be operative.

Evidence supporting the need for continued virus seeding from the blood and bone marrow can be found from HIV and SIV sequence data. Phylogenetic analysis of HIV gp160 sequences in a patient with HIV-associated dementia (HAD) demonstrates most close relatedness of the sequences found in deep white matter, blood monocytes, and bone marrow among the tissues examined (Liu *et al*., 2000). A similar study has shown that sequences found in brain macrophages are similar to those in macrophages of the lung and gut, organs where macrophages are significant targets of infection (Wang *et al*., 2001). A sequencing study of brain isolates, which approximates the "age" of virus, suggests that variants associated with HIVE, the histopathological correlate of HAD, have appeared only a year before AIDS developed in the patients that had been infected for 9-10 years (Hughes *et al*., 1997). Analysis of SIV sequences in macaques with AIDS also shows that the presence of similar macrophage-tropic virus in the CNS and gut closely correlates with histopathology in the CNS and gut (Kodama *et al*., 1993). Very recently, a "phylodynamic" analysis based on HIV gp120 DNA sequences isolated from different brain compartments of an AIDS patient with HAD demonstrated that HIV isolates, all macrophage-tropic, evolve much faster in the meninges and temporal lobe than in other compartments possibly due to recurrent infection or expansion of infected macrophages (Salemi *et al*., 2005a,b). Taken together, these data support the notion that CNS disease develops with the development of AIDS where we and others have documented activated and infected monocytes that have the potential to traffic to the CNS and the presence of productively infected monocytes in perivascular cuffs.

ROLE OF BLOOD MONOCYTES IN HIV NEUROPATHOGENESIS

Given that perivascular macrophages are of recent monocytic origin, it is plausible that blood monocytes are infected and differentiated into perivascular macrophages carrying HIV. Although it was known that HIV could infect monocyte-derived macrophages *in vitro* (Ho *et al*., 1986), *in vivo* infection of CD14+ monocytes by HIV was less commonly demonstrated until recently (McElrath *et al*., 1991; Innocenti *et al*., 1992). Recently, Sonza *et al*. (2001) have shown that HIV-1 can be isolated from macrophages derived from monocytes isolated from seropositive patients. Zhu *et al*. (2002) have isolated HIV-1 DNA from freshly isolated CD14+ monocytes. Evidence of circular DNA forms of recently replicated HIV-1 recovered from blood monocytes in seropositive patients and from macrophages infected in the brains of demented patients with AIDS supports the notion that ongoing virus replication and/or recent infection in monocytes are likely critical for CNS disease (Teo *et al*., 1997; Sonza *et al*., 2001).

Similar to macrophage populations in the brain and elsewhere, blood monocytes are not a homogeneous population. There are numerous reports regarding their subpopulations, and it is now widely accepted that monocytes can be differentiated into select populations using relative levels of CD14 and CD16 (Ziegler-Heitbrock *et al*., 1991; Ziegler-Heitbrock and Ulevitch, 1993; Ziegler-Heitbrock, 2000; Geissmann *et al*., 2003) and more recently CX3CR1 (Geissmann *et al*., 2003). Whether there is a restriction of productive HIV and SIV infection to a specific subset of blood

monocytes is undefined. It has been suggested that a population of CD14+ monocytes expressing high levels of CD16 monocytes is a primary target of HIV in blood (Ellery *et al*., 2003). More recently, Shiramizu *et al*. (2005) demonstrated that HIV proviral DNA is preferentially harbored in a minor population expressing CD14/CD16 . Similarly, we found that SIV DNA is consistently localized in a CD14lowCD16high subset (Kim *et al*., 2003b; Williams *et al*., 2005).

Interestingly, expansion of CD14/CD16 monocytes in response to HIV infection has been repeatedly reported (Locher *et al*., 1994; Nockher *et al*., 1994; Thieblemont *et al*., 1995; Dunne *et al*., 1996; Pulliam *et al*., 1997). Treatment of cultured monocytes with HIV envelop protein gp120 mimics the expansion of the monocyte subset expressing high levels of CD16 *in vivo* following HIV infection (Durrbaum-Landmann *et al*., 1994; Zembala *et al*., 1997). It should be noted that highly active antiretroviral therapy (HAART) reverses such expansion (Amirayan-Chevillard *et al*., 2000). Using SIV-infected, CD8-depleted rhesus macaques, we have demonstrated the expansion of CD14/CD16 population, particularly CD14lowCD16high subset following SIV infection (Kim *et al*., 2003a; Williams *et al*., 2005). Since there is no direct evidence that this specific subset of monocytes traffic to the CNS, the expansion of this subset does not necessarily mean that their traffic to the CNS is increased. It has been recently shown that CD16+ monocytes express high levels of CX3CR1 and they undergo transendothelial migration in response to endothelial fractalkine (Ancuta *et al*., 2003; 2004). Thus, this migratory property possibly makes these cells ideal candidates destined to traffic to the CNS. It should be noted that in humans and non-human primates, no specific marker for perivascular macrophages has been available until recently (Fabriek *et al*., 2005). In our recent studies of CD163, thought to be a homologue of ED2 in rats, we have found that CD163 identifies perivascular macrophages in the normal and SIV-infected monkeys and that these cells in the CNS are also SIV RNA positive. In addition, we found a population of CD163, CD14, and CD16 positive blood monocytes that are similar immunophenotypically to CNS perivascular macrophages. Thus, CD163 with CD14, CD16, and CX3CR1 serve as markers to study precursors to SIV-infected perivascular macrophages in blood (Kim *et al*., 2005; Williams *et al*., 2005).

By examining monocyte infection/activation longitudinally during SIV infection and monitoring CNS neuronal injury *in vivo*, we found that the timing of monocyte infection and activation coincides with neuronal injury (Kim *et al*., 2003b; Williams *et al*., 2005). Combination antiretroviral treatment, which slightly lowered plasma virus, efficiently inhibited monocyte infection/activation and quickly and completely reversed neuronal injury. When compared to SIV-infected rhesus macaques with encephalitis, SIV-infected animals that had received antiretroviral treatment showed minimal inflammatory macrophages expressing CD16 and no evidence of productive viral replication. These findings indicate not only a temporal correlation between monocyte infection/activation, CNS productive infection, and neuronal injury, but also underscore a relationship between the presence of SIV-infected CD16+ monocytes in the brain and neuronal injury. These studies strongly suggest that infection/activation of a subset of monocytes leads to the traffic of such cells to the CNS, which results in CNS productive infection and contributes CNS neuronal injury.

PERIVASCULAR MACROPHAGES, BBB DISRUPTION AND HIV NEURODEGENERATION

It is estimated that about 60% of HIV-infected patients develop neurologic dysfunction ranging from minor cognitive impairment to severe dementia. Neurologic dysfunctions are related to decreased synaptic density, dendritic injury, and neuronal injury; however, the underlying mechanisms are poorly understood. Because neurons are not directly infected by virus, indirect or immunopathogenic mechanisms are likely to be operative. Neuronal injury could be caused by viral proteins secreted from virus-infected cells or mediated through microglia and astrocytes activated by immune effector molecules in response to infection. The fact that virus injected directly into the CNS does not result in CNS disease in monkeys favors the latter (Hurtrel *et al*., 1993; Boche *et al*., 1995; Smith MS *et al*., 2002). Since CNS inflammation, probably initiated in the perivascular spaces, is the most common component in neurodegeneration, it is likely that perivascular macrophages play a central role. In SIV-infected monkeys, productive infection of brain macrophages is associated with inflammation, iNOS expression, dendritic injury, and motor and cognitive dysfunction (Li *et al*., 1999).

Early studies of HIV CNS infection showed that HAD is highly associated with vascular changes and that such vascular changes are hallmarks of HIVE (Mizusawa *et al*., 1988; Scaravilli *et al*., 1989; Weis *et al*., 1996). Vascular changes include BBB disruption, endothelial cell injury, perivascular space enlargement, hyalinization, and amyloid beta deposition (Petito and

Cash, 1992; Izycka-Swieszewska *et al*., 2000; Green *et al*., 2005). The CNS is highly vascularized and CNS microvessels are spread throughout the parenchyma. Given the high vascularity of the brain, pathogenic events in the perivascular spaces would explain widespread neuronal dysfunctions. In fact, diffusible factors secreted by activated and productively infected macrophages accumulated in this compartment clearly correlate with disease.

Monocyte-derived macrophages *in vitro* infected with HIV or perivascular macrophage infected with HIV or SIV produce a number of potentially neurotoxic effectors including viral proteins, cytokines, chemokines, nitric oxide (NO), and quinolinic acid (QUIN) and express enzymes to synthesize such factors. Kusdra *et al*. (2002) showed that the percentage of activated blood monocytes, which are potential precursors to perivascular macrophages, were significantly greater in HAD patients than in non-HAD patients and controls, and that macrophages derived from HAD patients cause more neurotoxicity.

Although several substances including viral proteins, and some chemokines and cytokines have all been shown to be neurotoxic *in vitro*, to date whether they cause neuronal injury *in vivo* in physiologic doses is less clear. Besides, little study has been done comparing the respective contribution of these potentially neurotoxic factors at their physiological concentrations *in vivo*. Although these neurotoxic factors may directly drive CNS neuronal injury and dysfunction, instead of discussing an exhaustive list of neurotoxic factors we will focus on injury resulting secondary to inflammation. Perivascular macrophages increase production of select effector molecules thought to mediate monocyte infiltration and vascular changes. Such molecules have been found in the CNS with HIV and SIV infection. Perivascular macrophages and MNGC are the main source of IDO and QUIN (Burudi *et al*., 2002), and antiretroviral treatment that lowers virus burden also decreases SIV-infected perivascular macrophage infiltration and IDO expression (Depboylu *et al*., 2004). Interestingly, QUIN is expressed by human monocytes and its expression has been shown to increase in response to HTLV-1 (Venkateshan *et al*., 1996). Perivascular macrophages in HIV encephalitic brain express MMP-2, COX-2 and iNOS, all of which have been shown to compromise the BBB (Rostasy *et al*., 1999; Ghorpade *et al*., 2001). Not surprisingly, these same molecules are also found in blood monocytes (Kalebic *et al*., 1994; Bukrinsky *et al*., 1995). Perivascular macrophages also produce chemokines including MCP-1 that is important for monocyte traffic (Buch *et al*., 2004). Interestingly, injection of the HIV protein Tat or nef-transduced macrophages into rats cause a cascade of events initiated with inflammation although the resultant neuropathogenesis including inflammatory cell types found is different (Jones *et al*., 1998; Pu *et al*., 2003; Mordelet *et al*., 2004). Tat has been shown *in vitro* to alter tight junction and apoptosis of endothelial cells. These results suggest that HIV-induced CNS inflammation may underlie the vascular changes observed in HIV CNS disease and may contribute to the development of HIV dementia by inducing further invasion of monocytes into the perivascular spaces.

As discussed above, HIV-induced neuropathogenesis can be at least in part driven by elements of the vascular system in the CNS. A cohort study showed that ischemic cerebrovascular events are more prevalent in HIV-infected patients than in the control group (Evers *et al*., 2003). The BBB is found disrupted in HIVE and the compromised BBB is tightly associated with monocyte invasion into the perivascular space (Smith TW *et al*., 1990; Rhodes, 1991; Petito and Cash, 1992; Power *et al*., 1993; Hurwitz *et al*., 1994; Dallasta *et al*., 1999; Boven *et al*., 2000; Persidsky *et al*., 2000; Fiala *et al*., 2002; Avison *et al*., 2004a). BBB compromise associated with perivascular macrophage accumulation has been shown in monkeys that developed SIVE (Luabeya *et al*., 2000). In addition, studies of BBB changes during the primary infection showed that BBB is transiently disrupted or activated early in infection without gross morphological alterations (Smith MO *et al*., 1995; Mankowski *et al*., 1999; Stephens *et al*., 2003; MacLean *et al*., 2004a). The temporal correlation between BBB disruption and perivascular infiltration of monocytes/macrophages suggests that a part of neuronal injury caused by HIV infection might be initiated at the vasculature. Support for this can be found in the reduction of BBB compromise in patients on HAART that is accompanied by an amelioration of neurocognitive impairment (Tracey *et al*., 1998; Avison *et al*., 2004b). Diffuse myelin pallor is a prominent feature of HIV-induced neuropathogenesis observed both at early stage of HIV infection and also in HIVE (Gray *et al*., 1992). It has been shown that white matter changes are caused by alteration of the BBB (Smith TW *et al*., 1990; Power *et al*., 1993). As in vascular dementia, white matter damage may be associated with MMP-2 expressing perivascular macrophages (Rosenberg *et al*., 2001).

CONCLUDING REMARK

Immune activation or dysfunction during the course

of HIV infection leads to increased monocyte activation/infection, monocyte traffic to the CNS, which in turn can lead to BBB compromise and neuronal injury. Understanding the biology and traffic of perivascular macrophages and their precursors in blood is fundamental to elucidate the role of monocyte/macrophages in HIV disease including HIV dementia.

Acknowledgment

This work was supported by National Institute of Health grants NS37654 (K.W.), NS40237 (K.W.), RR13213 (K.W.), and RR00164 (X.A.).

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