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CNS Inflammation and Macrophage / Microglial Biology Associated with HIV-1 Infection

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Abstract

HIV-1 infection of the central nervous system (CNS) can result in neurological dysfunction with devastating consequences in a significant proportion of individuals with AIDS. HIV-1 does not infect neurons directly, but induces damage indirectly through the accumulation of activated macrophage/microglia (M/M) cells, some of which are infected, that release neurotoxic mediators including both cellular activation products and viral proteins. One mechanism for the accumulation of activated M/M involves the development in infected individuals of an activated peripheral blood monocyte population that traffics through the blood brain barrier (BBB), a process that also serves to carry virus into CNS and establish local infection. A second mechanism involves the release by infected and activated M/M in the CNS of chemotactic mediators that recruit additional monocytes from the periphery. These activated M/M, some of which are infected, release a number of cytokines and small molecule mediators as well as viral proteins that act on bystander cells and in turn activate them, thus amplifying the cascade. These viral proteins and cellular products have neurotoxic properties as well, both directly and through induction of astrocyte dysfunction, which ultimately lead to neuronal injury and death. In patients effectively treated with antiretroviral therapy, frank dementia is now uncommon and has been replaced by milder forms of neurocognitive impairment, with less frequent and more focal neuropathology. This review summarizes key findings that support the critical role and mechanisms of monocyte/macrophage activation and inflammation as a major component for HIV-1 encephalitis or HIV-1 associated dementia.

1. INTRODUCTION

An early event in HIV-1 infection is the entry of the virus into the central nervous system (CNS), which may result ultimately in the development of several types of neurological defects. Neurological disorders associated with HIV-1 affect between 40% and 70% of infected individuals, involving the central nervous system (CNS) and the peripheral nervous system (McArthur et al., 2005). Although neurological disorders may become evident at any point during the course of infection, most develop in association with advanced disease. In the era of highly active antiretroviral therapy (HAART), the neuropathology of primary HIV-1 associated CNS disorders (as distinguished from secondary processes such as

opportunistic infections or malignancies) has evolved and is now characterized as HIV-1 associated neurocognitive disorders (HAND), comprised of three categories based on standardized measures of dysfunction (Antinori et al., 2007): HIV-1 associated dementia (HAD; also called AIDS dementia complex, ADC), characterized by severe cognitive impairment causing marked interference in day-to-day functioning; mild neurocognitive disorder (MND; also called minor cognitive motor disorder, MCMD), in which milder cognitive impairment causes some interference in daily functioning; and asymptomatic neurocognitive impairment (ANI), where mild cognitive impairment is present but does not interfere with activities of daily living (Antinori et al., 2007).

The development of HIV-associated dementia (HAD) is one of the most devastating consequences of HIV-1 infection. HAD is characterized by neurocognitive impairment (forgetfulness and poor concentration), emotional disturbance (apathy and social withdrawal), and motor abnormalities (weakness, ataxia, clumsy gait, tremor) (Boisse et al., 2008). HAD was frequently seen in untreated individuals with advanced infection, but has become less common following the introduction of HAART whereas less severe forms of neurocognitive impairment have become more prevalent. Before effective treatment, the annual incidence of dementia was 7% or greater in patients with AIDS (McArthur et al., 1993). With the introduction of HAART, the incidence of dementia has fallen dramatically. Newly diagnosed moderate to severe dementia decreased from 6.6% in 1989 to 1% in the year 2000 (McArthur et al., 2003; Saksena and Smit, 2005). The Multicenter AIDS Cohort study showed a decline in incidence from 21.3 per 1000 person-years in 1990–92 to 10 per 1000 person-years in 1996–98 (Sacktor et al., 2001), and other studies have reported decreases of ~50% in the incidence of dementia (Robertson et al., 2004; Sacktor et al., 2006). Despite this improvement, cognitive loss continues to be a frequent feature of HIV-1 infection. The Northeastern AIDS Dementia Consortium cohort study reported a 37% prevalence of HAD or MCMD in advanced AIDS, even with HAART (Sacktor et al., 2002). The AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) study of individuals on HAART showed a baseline prevalence of mild-to-moderate impairment of 26%, and a cumulative incidence of 21% in individuals who were neurologically normal at baseline (Robertson et al., 2007). The sub-group ANI was recently introduced under HAND but, although quite common, the impact and outcome of ANI remains to be defined. One study of HIV-1 infected women compared the standard American Association of Neurology (AAN) criteria with AAN criteria modified to include asymptomatic neurocognitive impairment. By standard AAN criteria, 54% of subjects were considered neurocognitively normal, 19% had a diagnosis of MCMD, and 23% had HAD. By the modified criteria however, only 31% of subjects were cognitively normal while 20% had ANI. Thus, a substantial subgroup of HIV-infected patients show asymptomatic neurocognitive impairment, and may include more than one-third of those initially considered normal (Wojna et al., 2006).

The histopathological hallmarks of HIV-1-associated neuropathology include: infiltration and accumulation of macrophages; the formation of microglial nodules and multinucleated giant cells in central white matter and deep gray matter, suggestive of virus-induced fusion of microglia and/or macrophages; widespread reactive astrogliosis, indicative of astrocyte activation and damage; the loss of specific neuron subpopulations, particularly those in

hippocampus and basal ganglia involved in cognition and motor function; the loss of synaptic connections; and myelin pallor, or the loss of myelin surrounding neuronal axons, indicating damage to oligodendrocytes (Gendelman et al., 1994; Lawrence and Major, 2002). These neuropathological abnormalities are collectively called HIV-1 encephalitis (HIVE).

Although severe HAD is typically observed during the late stages of infection, it is evident that moderate neuropsychological, neurophysiological and neuroimaging abnormalities can occur well before the end stages of AIDS (Heaton et al., 1995). These observations suggest that HIV-1-induced neurological injury is a gradual process that, in many patients, may begin early in the course of infection.

As with clinical disease, antiretroviral therapy has led to a shift in the neuropathology of HIV-1 infection. Macrophage/microglial activation continues to be seen but the extent and sites appear to have changed. While pre-HAART cases show strong involvement of basal ganglia, it is reported that post-HAART cases show inflammation in the hippocampus and adjacent parts of entorhinal and temporal cortex (Anthony et al., 2005; Anthony and Bell, 2008). In addition, neuropathology in HAART treated individuals include variant patterns involving perivascular lymphocytic infiltration, and what is described as ‘burnt-out’ form of HIVE (Gray et al., 2003; Everall et al., 2005). Also, increased presence of Alzheimer’s disease-like amyloid- β plaques has been reported in the brains of HAART treated individuals (Esiri et al., 1998; Green et al., 2005). Therefore, HAART has a significant effect on the incidence of HAD but fails to fully prevent the development of neurocognitive impairment. Some of the key changes in HIV-1 associated neurological disorders in the post-HAART era are summarized in Table I.

While HIV-1 enters the CNS early in infection (Davis et al., 1992) (and is often associated with an aseptic meningitis syndrome in acute infection), HAND is typically seen later in disease. Yet viral RNA can be found in the CSF throughout the course of disease. Recent evidence suggests that in subjects without neurocognitive disease most of the CSF virus originates from the systemic compartment, but subjects with HAD have a genetically compartmentalized population of virus indicative of replication within the brain (Ritola et al., 2005; Schnell et al., 2009). Thus, HIV-1 replication within the brain appears to be an important element in the pathogenesis of HAD.

Unlike most viral encephalities, HIV-1 does not productively infect neurons. Instead, productive replication within the brain occurs only in perivascular macrophages and microglia (Koenig et al., 1986; Wiley et al., 1986; Williams et al., 2001). But viral infection within the CNS does not itself seem to be the principal determinant for the induction of disease. Instead, a better correlate for the severity of clinical disease appears to be the number of brain mononuclear phagocytes and their degree of activation, including perivascular macrophages and microglia, rather than the amount of virus or the number of infected cells (Glass et al., 1995; Adle-Biassette et al., 1999). Although macrophages and microglia may have neuroprotective properties in the context of HIV-1 infection, especially early in the infection (Gras et al., 2003; Vallat-Decouvelaere et al., 2003), their predominant role in the pathogenesis of HAND seems to be neuroinflammatory and neurotoxic. In this

review we will highlight the role of macrophages/microglia in the pathogenesis of HIV-1 associated neurocognitive impairment.

2. MICROGLIA AND BRAIN MACROPHAGES IN HIV-1 PATHOGENESIS

HIV-1 is believed to enter the CNS via trafficking of infected monocytes and lymphocytes across the blood-brain barrier (Dunfee et al., 2006). The main target cells for infection in the CNS are macrophages and microglia (Cosenza et al., 2002). Parenchymal microglia consist of long-lived, fixed cells of the central nervous system, while perivascular microglia cells are believed to be in a slow turnover mode with blood monocytes (Kennedy and Abkowitz, 1997). In contrast to primate model of SIV infection, where infection is restricted largely to perivascular macrophages (Williams et al., 2001), in HIV-1 infection immunopositivity maybe restricted to the perivascular compartment or show widespread staining of parenchymal microglia (Morris et al., 1999). Of note, infection of long-lived macrophages and microglia in the CNS is believed to contribute not only to neurological dysfunction but also serve as a long-term reservoir resulting in persistence of HIV-1 within a sanctuary site, an important issue for treatment and potential eradication of infection, but which is outside the scope of this review.

Whether the accumulation of HIV-1 immunopositive cells in the brain represents ongoing rounds of infection and viral amplification within long-term CNS resident cells, or a continuing influx of infected cells from the blood stream is still unclear. While monocyte-derived macrophages are most frequently used to model infection of these cells, replication of HIV-1 in cultured primary microglia isolated from adult, infant and fetal brains is also well described (Ioannidis et al., 1995; McCarthy et al., 1998; Albright et al., 2000). The presence of HIV-1 DNA has also been described in astrocytes and neurons isolated from HIVE brain tissue by laser capture microdissection (Trillo-Pazos et al., 2003), although it remains unclear whether this reflects true latent infection and, if so, what role it may play in pathogenesis. Thus, neurological dysfunction in HAND appears to be an indirect consequence of microglial infection and activation, with multiple overlapping pathways involved.

3. ACCUMULATION OF MONOCYTES/MACROPHAGES IN THE CNS IN HIVE

Replenishment of the perivascular macrophage population by circulating monocytes that migrate into the brain has the consequence of enabling HIV-1 entry though trafficking of infected monocytes from the circulation. After the monocytes enter the CNS they differentiate into macrophages, as they do in other tissues, which increases their ability to support virus replication. This process has been described as the “Trojan horse” mechanism of neuroinvasion (Meltzer et al., 1990). Once HIV-1 replication is established in the CNS it leads to production of chemotactic and inflammatory mediators that further recruit and activate monocytes/macrophages (M/M). We refer to this mechanism of M/M recruitment into the CNS as the “pull” mechanism. In addition, another set of factors appears to contribute to M/M accumulation and activation in the CNS, in which an expanded population of activated blood monocytes develops in some subjects and is believed to reflect an invasive phenotype that accumulates in the brain. These activated invasive monocytes,

which we refer to as the “push” mechanism, may also preferentially carry HIV-1, augmenting the cascade. These two mechanisms, an expanded peripheral blood neuroinvasive monocyte population (“Push”) and recruitment to the CNS by chemotactic mediators (“Pull”) are non-mutually exclusive and both appear to contribute to CNS M/M accumulation and activation, and are further detailed below.

An activated population of blood monocytes in patients with HAD (“push”)

More than a decade ago it was recognized that individuals with HIV-1 associated neurological defects exhibited an expanded population of CD14+ peripheral blood monocytes that co-express the marker CD16 (Pulliam et al., 1997). CD16 is an Fc receptor (FcγRIII), but these monocytes also express higher levels of other markers of activation including HLA-DR, CD86 and CD40 and greater TNFα and IL-1β production (Thieblemont et al., 1995). These cells are believed to have invasive properties that enable them to enter tissues, in particular may cross the blood-brain barrier (BBB) and enter the CNS in HAD in response to chemokines such as MCP-1, fractalkine (CX3CL1) and others (Ancuta et al., 2004). Brain specimens from patients with HIV-1 encephalopathy (HIVE) have shown that the majority of accumulated perivascular macrophages and cells in microglial nodules are CD14+/CD16+. These CD16+ monocytes also appear to be preferentially susceptible to infection and can serve as a reservoir harboring proviral DNA (even in individuals on antiretroviral therapy) (Shiramizu et al., 2005; Ellery et al., 2007; Jaworowski et al., 2007), and macrophages derived from CD16+ monocytes are particularly efficient at forming conjugates with T cells that promote T-cell activation, virus transfer and HIV-1 replication (Ancuta et al., 2006b; Ancuta et al., 2006c). Within the CNS, viral p24 antigen colocalizes with both CD14 and CD16 suggesting that the CD14+/CD16+ macrophage is the major reservoir for virus in CNS (Fischer-Smith et al., 2001).

Another surface marker expressed both by circulating monocytes in HIV-infected subjects and on CD16+ HIV-infected perivascular macrophages in HIVE brain is CD163, a scavenger receptor for the haptoglobin-haemoglobin complex (Fischer-Smith et al., 2008b; Fischer-Smith et al., 2008a). Like CD16, CD163 expression is absent in parenchymal microglia and points towards the increased influx of inflammatory monocytes across the BBB (Sulahian et al., 2000). CD163 may be a monocyte/macrophage bacterial sensor that participates in macrophage activation in response to bacterial translocation from the gut into the systemic circulation (discussed below) (Fabriek et al., 2009). Alternatively, as a hemoglobin/haptoglobin scavenger molecule, CD163 may play a role in perivascular macrophage protection from BBB breakdown and leakage (Borda et al., 2008).

Recent studies have provided important insight into mechanisms that may be responsible for this expanded population of invasive, activated monocytes. Accumulating evidence suggests that an early event in HIV-1 infection is damage to the gastrointestinal mucosa, including preferential loss of mucosal lymphocytes, leading to translocation of bacterial endotoxin (LPS) as a principal cause of generalized systemic immune activation associated with HIV-1 infection (Brenchley et al., 2006). LPS and other translocation products trigger monocyte activation via CD14 and TLR signaling, resulting in release of soluble CD14 and pro-inflammatory cytokines that contribute to chronic systemic immune activation, believed to

be a central driver of immunopathogenesis in AIDS (Brenchley et al., 2006; Douek, 2007). Recently, microbial translocation has also been linked specifically to increased monocyte activation in the development of dementia (Ancuta et al., 2008), thus suggesting a mechanism driving expansion of this population. Furthermore, integrity of the BBB can be compromised in vivo by exposure to elevated levels of LPS in the circulation (Zhou et al., 2006). In fact, LPS compromise of BBB integrity and HIV-1 infection of monocytes may act synergistically to enhance BBB disruption and monocyte transmigration across the barrier (Wang et al., 2008).

Recruitment of monocytes in response to chemokines (“pull”)

In addition to the invasive activated monocyte phenotype, the accumulation of M/M in the CNS clearly results also from recruitment of cells along a chemotactic gradient. Of particular importance is the chemokine MCP-1, which is elevated in the CSF and brain tissue in HAD (Kelder et al., 1998; Asensio et al., 2001). MCP-1 levels correlate with CSF viral load, severity of neurocognitive impairment, and increase over time in patients who develop dementia (Kelder et al., 1998; Letendre et al., 1999). Brain macrophages are a major source of MCP-1 and other proinflammatory mediators that recruit T cells and additional monocytes into the CNS (Boven et al., 2000; Fantuzzi et al., 2003; Persidsky and Gendelman, 2003) (and promote neuronal cell death, discussed further, below). MCP-1 is also produced by astrocytes in response to quinolinic acid (QA), which is elevated in AIDS dementia (Guillemin et al., 2003). In addition, MCP-1 dependent disruption of the BBB, as evidenced by enhanced permeability, reduction of tight junction proteins, and expression of matrix metalloproteinases (MMP)-2 and MMP-9 has also been demonstrated (Eugenin et al., 2006). MCP-1 is also produced by astrocytes in response to the viral protein Nef (Lehmann et al., 2006). MCP-1 therefore acts as a principal chemoattractant in the recruitment of monocytes across the BBB.

Another chemokine that is up-regulated in brain tissue and CSF of HAD patients is fractalkine (CX3CL1) (Pereira et al., 2001; Cotter et al., 2002; Sporer et al., 2003). Fractalkine exists in both membrane-bound and soluble forms (Fong et al., 2000; Harrison et al., 2001). In the CNS it is constitutively expressed by neurons and up-regulated by inflammatory stimuli. The receptor for fractalkine, CX3CR1, is expressed on monocytes and brain microglia, T cells, NK cells, dendritic cells, neurons and astrocytes. A potential role for fractalkine in the recruitment of the CD16⁺ monocyte subset to inflamed tissues has been suggested (Ancuta et al., 2003). Endothelial cell-expressed fractalkine triggers CD16⁺ monocytes to produce IL-6, MCP-1, and MMP-9, likely by engagement of CX3CR1 (Ancuta et al., 2006a). This finding supports a model in which accumulation of CD16⁺ monocytes onto inflamed endothelial beds expressing fractalkine contributes to tissue injury during HIV-1 infection in which this monocyte subset is expanded. Engagement of CX3CR1 on CD16⁺ monocytes may lead to a second wave of monocyte recruitment into the brain in response to MCP-1, followed by IL-6-triggered activation and differentiation of monocytes into macrophages.

SDF-1 α (CXCL12) is also overexpressed in HIVE and may contribute to recruitment of inflammatory cells (Rostasy et al., 2003; Peng et al., 2006). Recent studies have identified a

novel molecular mechanism whereby SDF-1 α activation of its receptor CXCR4 in primary human monocytes enables transmigration across an endothelial BBB model. This work showed that the Src family kinase Lyn is a critical mediator that relays signals from CXCR4 in response to SDF-1 α leading to two events necessary for transmigration. First, SDF-1 α /CXCR4 signaling through Lyn downregulates the active epitope of monocyte β 2 integrins (“inside out signaling”) enabling detachment from inflamed brain microvascular endothelial cells (BMVEC) mediated by β 2 integrin (LFA-1)/ICAM-1 adhesion. Second, this signal pathway is then responsible for chemotaxis. The net result of SDF-1 α /CXCR4/Lyn signaling is a decrease in monocyte attachment to BMVECs and migration toward SDF-1 α gradient (Malik et al., 2008). It remains to be determined whether this pathway reflects a generalized signaling mechanism regulating monocyte migration across endothelial barriers in response to other chemokines.

4. ACTIVATION OF BRAIN MACROPHAGES AND MICROGLIA BY HIV-1

Clinical disease in HAD correlates best with microglial activation and macrophage infiltration, rather than viral load (Glass et al., 1995; Adle-Biassette et al., 1999). Furthermore, both infected and uninfected M/M are involved, as the extent of M/M activation is often greater than the extent of direct infection (Tyor et al., 1992; Nuovo and Alfieri, 1996). M/M activation within the CNS appears to be a consequence of both direct infection and indirect mechanisms. Several viral proteins have been identified by which HIV-1 activates M/M both directly and *in trans*, with inflammatory mediators produced as a result that are responsible for amplifying and perpetuating the cascade (Xu et al., 2004).

Activation of M/M by gp120

The HIV-1 envelope glycoprotein is composed of a transmembrane domain gp41 and a non-covalently associated surface subunit gp120, which mediates infection of target cells through interaction with cellular CD4 plus one of two chemokine receptors, CCR5 or CXCR4 (with CCR5 used by most HIV-1 primary isolates and most of those that enter the CNS). In addition to mediating infection, gp120 is also released by infected cells, shed from virions, or available to interact with its receptors in the context of noninfectious virion particles (Dreyer et al., 1990; Kaul and Lipton, 1999). gp120 has been detected in the brain of HIV-1 infected individuals, localized to microglia and multinucleated giant cells (Jones et al., 2000). Exposure of M/M to natural and recombinant gp120 triggers a range of activation responses, including the release of TNF- α , IL-1 β , IL-6, and GM-CSF and ROS (Clouse et al., 1991; Corasaniti et al., 1998; Viviani et al., 2001; Lee et al., 2005; Cheung et al., 2008). gp120 also stimulates the production of MCP-1, MIP-1 α , MIP-1 β and RANTES in monocytes / macrophages (Choe et al., 2001; Del Corno et al., 2001; Fantuzzi et al., 2001). In addition, monocytes treated with gp120 have an increased proportion of CD14+CD16+ cells that are elevated in the blood of AIDS patients and as discussed earlier, are associated with HAD (Zembala et al., 1997). Thus, in addition to mediating target cell infection, gp120 appears to act as an important ligand that activates M/M.

The mechanism by which gp120 activates M/M appears to be linked to the chemokine receptors that serve as the HIV-1 entry receptors. Besides their role in HIV-1 entry, CCR5

and CXCR4 are G-protein coupled receptors that can activate multiple intracellular signaling pathways, and multiple signaling events have been identified in primary human macrophages in response to gp120/chemokine receptor interactions. These include intracellular Ca^{2+} increases, several ionic currents, and activation of protein kinases including the focal adhesion-related kinase Pyk2, members of the MAPK family, phosphoinositol-3 (PI-3) kinase, and Lyn kinase (Liu et al., 2000b; Del Corno et al., 2001). Together these mechanisms appear to be responsible for cytokine and chemokine release following gp120/CCR5 interactions, particularly TNF- α production independently and IL-1 β (Lee et al., 2005; Tomkiewicz et al., 2006; Cheung et al., 2008). Recent data from our laboratory also sheds light on the interactions among these signaling events involved in gp120 induced cytokine release. Binding of HIV-1 gp120 to macrophage CCR5 triggers PI-3K and Pyk2 re-localization to the membrane and formation of a signaling complex with Lyn. Activation of this complex leads to IL-1 β production, likely through the action of downstream MAPKs and nuclear transcription factors (Cheung et al., 2008). These gp120-triggered signaling pathways may be responsible for the aberrant production of pro-inflammatory cytokines by macrophages, which then contribute to the immunopathogenesis of HAD.

M/M activation by Tat

Another HIV-1 protein implicated is Tat, the virally encoded transactivator of transcription that can be released by HIV-1-infected cells in tissue culture and is found in the extracellular space and sera of infected individuals (Chang et al., 1997), as well as in CSF and the brains of people with HIVE (Wiley et al., 1996; Hudson et al., 2000). Although it is unclear whether the majority of Tat protein in the CNS is released by infected cells locally or is transported across the BBB from sera (Banks et al., 2005), it appears to contribute to neuropathogenesis through several mechanisms. Tat has the ability to stimulate pro-inflammatory responses in mononuclear phagocytes, resulting in production of several cytokines including IL-1 β , TNF- α , IL-6 and TGF- β (Zauli et al., 1992; Zauli et al., 1993; Lafrenie et al., 1997). Treatment of human microglia with Tat triggers secretion of the chemokines MCP-1, IL-8, IP-10, MIP-1 α , MIP-1 β and RANTES, which are chemotactic factors for monocytes and/or lymphocytes (149). MCP-1 is a potent chemoattractant for monocytes and as mentioned elsewhere in this review, is elevated in the CSF and brains of HAD patients.

Tat induced TNF- α production in monocytes involves the simultaneous activation of different G proteins, Ca^{2+} mobilization and activation of the protein kinase C pathway followed by the downstream activation of NFkappaB (Contreras et al., 2003; Contreras et al., 2005). In addition, Tat synergizes with host soluble factors like IFN- γ resulting in the induction of chemokines like IP-10 by macrophages. IP-10 production is dependent on the activation of the p38 MAPK and the JAK/STAT pathways (Dhillon et al., 2008). Other studies have reported the involvement of ERK 1/2 and PI-3K in the production of IP-10 in response to Tat (D'Aversa et al., 2004). Together, these effects of gp120 and Tat on macrophage/microglia suggest that the presence of viral proteins are important contributors to the sequence of M/M activation events leading to neuropathogenesis.

5. NEUROTOXIC PRODUCTS RELEASED BY INFECTED MACROPHAGES

HIV-1 does not infect neurons directly, and the end result of neurotoxicity is mediated by factors released by activated and infected M/M. The two components responsible appear to be HIV-1 encoded proteins derived from infected M/M that themselves injure neurons directly, and cellular products released by the activated M/M (both of which also serve to amplify the cascade of M/M activation, discussed above).

Neurotoxic viral proteins

Among the HIV-1 proteins, gp120, Tat and Vpr have each been demonstrated to directly induce neuronal cell death.

gp120 from CXCR4-using (X4) strains of HIV-1 can be directly neurotoxic by inducing neuronal apoptosis, mainly through interactions with the chemokine receptor CXCR4, as inhibition of CXCR4 activity blocks gp120 mediated toxicity in rat neurons (Hesselgesser et al., 1997; Hesselgesser et al., 1998; Catani et al., 2000; Bachis and Mocchetti, 2004; Bachis et al., 2009). Recombinant gp120 from the CCR5-using (R5) HIV-1 strains also induces apoptosis in a human neuronal cell line, suggesting a role for CCR5 which is also expressed on neurons (Xu et al., 2004). Neuronal apoptosis induced by gp120 involves disrupted calcium homeostasis that triggers mitochondria membrane disruption and activation of caspases and endonucleases via the intrinsic pathway (Dreyer et al., 1990; Lannuzel et al., 1995; Mattson et al., 2005). Recent data indicates that gp120-induced neuronal apoptosis may also involve the extrinsic pathway by upregulation of the death receptor Fas as well (Thomas et al., 2009). HIV-1 gp120 also induces apoptosis in primary human fetal neurons through a pathway that involves the production of ceramide (Jana and Pahan, 2004).

Tat has been extensively studied for toxic effects on CNS cells, often resulting in apoptosis, especially of the neurons (Kruman et al., 1998; Bonavia et al., 2001; Bruce-Keller et al., 2003; Eugenin et al., 2003; Miagkov et al., 2004; Singh et al., 2004; Pocernich et al., 2005; Aksenova et al., 2006; Eugenin et al., 2007). The toxic effect of Tat on neurons is, in part, a result of the cytokines, chemokines and nitric oxide released by microglia (Polazzi et al., 1999; Turchan-Cholewo et al., 2009). In addition, Tat appears to activate the neuronal excitatory NMDA receptor, leading to excitotoxicity and consequent apoptosis (Haughey et al., 2001; Song et al., 2003; Eugenin et al., 2007; Li et al., 2008). Intracerebral injection of

Tat into rat striatum results in neuronal degeneration and infiltration of macrophages/microglia (Bansal et al., 2000; Aksenov et al., 2003). Astrocytes and endothelial cells are also susceptible to Tat-induced inflammatory responses further augmenting infiltration of monocytes into the brain (Pu et al., 2003). Finally, Tat may also contribute to the disruption of the BBB by altering the distribution of endothelial cell tight junction proteins such as claudin-1, claudin-5, ZO-1 and ZO-2 which may lead to enhanced transmigration of monocytes and lymphocytes (Andras et al., 2003; Toborek et al., 2003).

Vpr is a 96 amino acid HIV-1-encoded virion-incorporated protein that is essential for HIV-1 replication in macrophages (Emerman, 1996; Subbramanian et al., 1998). Vpr is present in detectable amounts in both the basal ganglia and frontal cortex, mainly in the macrophages

and neurons of HIVE patients (Wheeler et al., 2006). Soluble HIV-1 Vpr protein is also detected in the CSF and serum of infected patients with neurological disorders (Levy et al., 1994). Vpr treatment of glial cells induces the secretion of cellular neurotoxins. Furthermore, expression of HIV-1 Vpr in mouse brain monocytoïd cells results in abnormalities in motor tasks and neuronal injury (Jones et al., 2007). Treatment of neurons with soluble Vpr leads to changes in neuronal membrane potentials, with the induction of apoptosis (Patel et al., 2000; Jones et al., 2007). These observations suggest that Vpr in the CNS may play a role in neuronal injury, including both direct cytotoxic actions on neurons but also activate glia resulting in the release of neurotoxic molecules.

Cytokines

As noted above, multiple pro-inflammatory cytokines such as IL-1 β , TNF- α , IL-6, GM-CSF and M-CSF are elevated in the CNS and /or CSF of HAD patients (Oster et al., 1987; Perrella et al., 1992; Achim et al., 1993; Foli et al., 1997; Zhao et al., 2001). Increased expression of these pro-inflammatory cytokines can be a result of direct viral infection or an effect of shed viral proteins which stimulate uninfected mononuclear phagocytes to express elevated levels of cytokines (Sundar et al., 1991; Ehrenreich et al., 1993; Rappaport et al., 1999). Once initiated, many of these cytokines can act in an autocrine or paracrine manner and augment the expression leading to a pro-inflammatory environment in the CNS. In addition, several of these have direct or indirect neurotoxic properties and appear to also contribute to neuronal injury. We will specifically discuss the role of TNF- α , IL-1 β and M-CSF in macrophages/microglia mediated neurotoxicity in HAD.

TNF- α is elevated both in the brain and CSF in HAD patients (Grimaldi et al., 1991; Wilt et al., 1995; Nuovo and Alfieri, 1996; Wesselingh et al., 1997). M/M exposure to gp120 or Tat results in elevated TNF- α expression (Yeung et al., 1995; Nicolini et al., 2001). TNF- α damages the BBB and also induces the expression of the adhesion molecules ICAM-1, VCAM-1 and E-selectin on astrocytes and endothelial cells, resulting in HIV-1-infected M/M transmigration into the CNS (Collins et al., 1995; Fiala et al., 1996; Lee et al., 1998). In addition, TNF- α up-regulates the expression and release of various chemokines in the CNS such as MCP-1, a chemoattractant for monocytes and macrophages (Strieter et al., 1989; Hurwitz et al., 1995). By increasing the BBB permeability and inducing adhesion molecule and chemokine expression TNF- α plays an important role in facilitating the entry of HIV-infected cells into the brain. TNF- α also has toxic effects on human neurons (Gelbard et al., 1993). It causes the over-stimulation of the glutamate receptors such as the *N*-methyl-D-aspartate (NMDA) receptors which are expressed on neurons. Along with SDF-1 α , TNF- α also increases release of the excitotoxic neurotransmitter glutamate from astrocytes and microglia (Bezzi et al., 2001). HIV-1 infected macrophages are a source of extracellular glutamate and glutamate concentrations in the CSF of HIV-1 infected patients are higher as compared to uninfected controls (Jiang et al., 2001; Zhao et al., 2004; Erdmann et al., 2007). Production of excess glutamate by HIV-infected macrophages in HAD may contribute to neuronal cell death.. TNF- α also inhibits glutamate uptake by astrocytes, resulting in increased extracellular levels (Casado et al., 1993; Fine et al., 1996; Wang et al., 2003b). These multiple effects of TNF- α causes over-stimulation of the NMDA receptor, resulting in Ca²⁺ mobilization (Lipton, 1994), formation of nitric oxide (NO) and superoxide

toxicity (Bonfoco et al., 1995). TNF- α can also upregulate the expression of fractalkine by neurons and astrocytes, which induces adhesion, chemoattraction and activation of other inflammatory cells, including M/M, upon binding to its receptor CX3CR1 (Tong et al., 2000; Erichsen et al., 2003). These findings suggest that TNF- α is proinflammatory and can lead to further M/M activation and recruitment, is a direct neurotoxin and can lead to both astrocyte activation and to decreased astrocyte uptake of excitotoxic neurotransmitter glutamate and potentiates glutamate neurotoxicity.

Another cytokine that appears to have a central role in both the inflammation and neurotoxicity associated with HAD is IL-1 β . In the CSF and brains of HIV-1 infected patients with HAD, IL-1 β is significantly increased compared to non-demented HIV-infected patients (Gallo et al., 1989; Tyor et al., 1992; Zhao et al., 2001; Brabers and Nottet, 2006). IL-1 β shares many neurotoxic properties with TNF- α . Like TNF- α , IL-1 β induces the expression of ICAM-1, VCAM-1 and E-selectin on endothelial cells and astrocytes, facilitating monocyte infiltration into the CNS (Collins et al., 1995; Lee et al., 1998; Winkler and Beveniste, 1998). IL-1 β induces the release of L-cysteine from macrophages and microglia (Yeh et al., 2000). Furthermore, IL-1 β is able to induce ceramide expression via the activation of membrane-bound sphingomyelinase, which is thought to be involved in ROS formation and apoptosis in neurons (Haughey et al., 2004).

M-CSF is a hematopoietic growth factor controlling survival, proliferation, differentiation and other functions of monocyte/macrophage lineage cells. Infection of human monocyte-derived macrophages (MDMs) with HIV-1 results in increased M-CSF production and secretion (Gruber et al., 1995). Increased M-CSF production in HIV-1-infected MDMs parallels the kinetics of HIV-1 replication (Gruber et al., 1995) which may reflect the effect of M-CSF on HIV-1 replication (Kalter et al., 1991; Kutza et al., 2000). In HIV-1-infected individuals M-CSF levels are elevated in the CSF (Oster et al., 1987; Gallo et al., 1994). M-CSF may contribute to the expansion of mature and/or activated monocytes in circulation and their trafficking into the CNS. Interestingly, as mentioned earlier, an increase in the number of circulating CD14⁺ monocytes that co-express CD16 has been seen in patients with HIV-1 dementia (Pulliam et al., 1997; Fischer-Smith et al., 2001), and *in vitro* studies show CD16 upregulation by monocytes when treated with M-CSF (Ji et al., 2000; Saionji and Ohsaka, 2001). In combination with IL-10 and IL-4, M-CSF also contributes to the development of CD14⁺CD16⁺ monocytes that produce high levels of TNF- α and IL-1 β (Li et al., 2004). CD163 is also up-regulated by M-CSF treatment of human monocytes (Buechler et al., 2000). M-CSF enhances the production of β -chemokines MIP-1 β , MIP-1 α and RANTES, which can block HIV-1 entry through the CCR5 coreceptor but, at low concentrations, may be involved in target cell recruitment to sites of infection (Haine et al., 2006). At the same time, M-CSF also up-regulates expression of the CD4/CCR5 viral entry receptor complex on monocytes and macrophages (Bergamini et al., 1994; Wang et al., 1998). Though controversial, several reports suggest that microglial activation may be mediated by a M-CSF autocrine loop that results in release of inflammatory cytokines (IL-1 β , MIP-1 α , IL-6 and CSF-1) and nitric oxide (Hao et al., 2002; Vincent et al., 2002; Mitrasinovic et al., 2005). Thus, several lines of evidence suggest a central role for M-CSF in multiple facets in the development of HAD.

Small molecule soluble factors

Among the neurotoxic products of activated macrophages is quinolinic acid (QA), which is implicated in several inflammatory and neurodegenerative brain diseases including HAD, Huntington's disease and others (Heyes et al., 1991; Sei et al., 1995; Heyes et al., 2001; Guillemin et al., 2005). Macrophages produce QA when infected by HIV-1, with multiple mechanisms identified. The HIV-1 proteins Tat and Nef induce macrophages to produce QA (Brew et al., 1995; Nottet et al., 1996; Kerr et al., 1997; Heyes et al., 2001; Smith et al., 2001). Infection appears to be synergistic with other activation stimuli, as treatment of HIV-1 infected monocytes by LPS induces several fold higher levels of QA (Brew et al., 1995; Nottet et al., 1996). QA is also produced by macrophages in response to stimulation by TNF- α , IFN- γ and IFN- α at concentrations that are neurotoxic (Pemberton et al., 1997). QA induces astrocytes to release MCP-1, and lesser amounts of RANTES and IL-8, and increases SDF-1 α and fractalkine expression (Guillemin et al., 2003). Moreover, QA leads to up-regulation of the chemokine receptors CXCR4, CCR5, and CCR3 in human fetal astrocytes. Most of these effects are comparable to those induced by TNF- α / IFN- γ , suggesting that QA may be critical in the amplification of brain inflammation in HIV-1 dementia and reflects the effect on M/M of both direct infection and activation (Croitoru-Lamoury et al., 2003). QA mediates its neurotoxic effect mainly by stimulation of neuronal excitotoxic receptors, and is synergistic with other excitotoxins (Schurr and Rigor, 1993; Bazzett et al., 1996; Giulian et al., 1996; Jhamandas et al., 2000; Puntel et al., 2005; Stone and Behan, 2007).

Platelet activating factor (PAF) is an arachidonic acid metabolite that is another significant mediator of neurotoxicity in HAD, and is detected at high levels in the CSF of patients with HAD (Genis et al., 1992; Gelbard et al., 1994). HIV-1 Tat induces PAF by activation of vascular endothelial growth factor receptor (Del Sorbo et al., 1999; Arese et al., 2001). Tat-induced PAF synthesis plays a critical role in triggering the events involved in the migratory response of monocytes (Del Sorbo et al., 1999). TNF- α also induces production of PAF. The mechanisms by which it causes neurotoxicity are not clear but may include direct excitotoxicity, or elicitation of QA or TNF- α -induced neurotoxicity (Bito et al., 1992; Lipton, 1994; Smith et al., 2001; Bellizzi et al., 2005).

Nitric oxide (NO) is a free radical enzymatically formed from L-arginine by the enzyme nitric oxide synthase (NOS), and its release from activated astrocytes and microglia is believed to contribute to neuronal cell death in HIV-1 dementia (Nuovo and Alfieri, 1996; Rostasy et al., 1999; Vincent et al., 1999; Zhao et al., 2001; Liu et al., 2002). The levels of iNOS in severe HAD coincide with increased expression of the HIV-1 gp41, and gp41 induces iNOS in primary cultures of mixed rat neuronal and glial cells and kills neurons through a NO-dependent mechanism (Adamson et al., 1996). HIV-1 gp120 and Tat, which may be released by infected M/M, induces iNOS in human astrocytes and astrocytic cell lines (Liu et al., 2002; Walsh et al., 2004). A similar effect of Tat has also been seen in microglial cells (Polazzi et al., 1999). In addition to viral protein-induced iNOS production, cytokine and chemokine signaling in activated microglia also contribute to the pool of iNOS in the brains of HAD patients (Bhat et al., 1998).

The final mediator of note is the excitotoxic neurotransmitter glutamate (Ferrarese et al., 2001). While some studies have shown glutamate release by activated and/or infected M/M directly (Jiang et al., 2001; Erdmann et al., 2007), its principal role appears to involve indirect mechanisms initiated by HIV-1 in the CNS. In particular, the ability of astrocytes to re-uptake glutamate, a critical mechanism of glutamate homeostasis, is impaired through multiple pathways including HIV-1 proteins Tat and gp120, and M/M activation products such as TNF- α (Benos et al., 1994; Fine et al., 1996; Patton et al., 2000). Acting on the neuronal NMDA-type receptor to trigger excitotoxic injury, glutamate may be a final common pathway and/or act synergistically with other triggers, in the ultimate result of neuronal injury and death (Haughey et al., 2001).

6. IMPLICATIONS FOR ADJUNCTIVE THERAPY OF HAND

The identification of specific M/M activation mechanisms as key components of neurological injury in HIV-1 infection has led to efforts to develop adjunctive therapies that focus on blocking these pathways or their target effects. Minocycline is a tetracycline antimicrobial agent that mitigates microglial activation in vitro and in animal models, and reduces glutamate toxicity and caspase independent and dependent mitochondrial mediated cell death (Wang et al., 2003a). In an experimental SIV model of HIV CNS disease, minocycline decreased the expression of CNS inflammatory markers and reduced the severity of encephalitis. In vitro, minocycline also inhibits SIV and HIV replication (Si et al., 2004; Zink et al., 2005). These findings have led to phase I clinical trials of minocycline in HIV-1 associated neurocognitive impairment (ACTG 5235 & ClinicalTrials.gov identifier: NCT00855062).

Memantine is an uncompetitive NMDA receptor antagonist that was recently approved for the treatment of Alzheimer's disease, and may also have therapeutic potential in HAND. Memantine inhibits the HIV gp120-dependent calcium changes in neurons and astrocytes and protects neurons from gp120-induced cell death (Nath et al., 2000). Memantine is beneficial in various murine models of HIVE (Toggas et al., 1996; Anderson et al., 2004), and preserves dopamine levels and upregulates brain-derived neurotrophic factor (BDNF) in the brains of SIV-infected macaques (Guillin et al., 2003; Meisner et al., 2008). Although a short term study in HIV-1 infected subjects with cognitive impairment did not find statistically significant improvement in neurocognitive function, magnetic resonance spectroscopy imaging showed improved neuronal metabolism, suggesting a beneficial effect that justifies further investigation (Schifitto et al., 2007b).

Sodium valproate (VPA) is an anticonvulsant known to promote neurite outgrowth and increase β -catenin through inhibiting glycogen synthase kinase 3 β activity and tau phosphorylation (Dou et al., 2003). A pilot study of VPA in HIV-1 infected neurocognitively impaired subjects showed a trend toward improved neuropsychological performance and imaging evidence of brain metabolism (Schifitto et al., 2006). In contrast, selegiline is a MAO inhibitor with antioxidant and neurotrophic properties that did not show benefit in HIV-1 infected neurocognitively impaired individuals (Schifitto et al., 2007a).

Several other agents targeting these mechanisms have been studied in in vitro and animal models. PMS-601 is a PAF receptor antagonist proposed as a candidate for adjunctive therapy in HAND (Eggert et al., 2009), based on in vitro effects on neuroinflammatory responses (Gelbard et al., 1994; Martin et al., 2000; Persidsky et al., 2001; Tong et al., 2001). In a SCID mouse model of HIVE, PMS-601 reduced macrophage inflammatory mediator secretion, neuronal loss and microgliosis (Eggert et al., 2009). Lithium protects neurons from neurotoxicity induced by HIV-1-infected macrophage secretory products in vitro, which is mediated through the PI3K/Akt and GSK-3 β pathways (Dou et al., 2005). Lithium also protects neurons from gp120-mediated toxicity in vitro and in murine models (Everall et al., 2002).

Whether these agents will show benefit in HIV-1 infected individuals with neurocognitive impairment remains to be determined, but the identification of specific M/M dependent mechanisms of neuronal injury in HIV-1 highlight the potential targets of adjunctive therapies for HIV-1 dementia and other neuroinflammatory disorders

7. CONCLUSION

This review has focused on the central role of macrophage/microglia cells in the CNS inflammation associated with HIV-1 infection. As shown in Fig 1, although HIV-1 infection within the CNS is necessary for the development of HAD, pathogenesis requires the development of M/M activation and CNS inflammation. In the periphery, the inflammatory environment leads to an activated monocyte population that is invasive and enters the CNS, carrying with it virus that is upregulated following differentiation into monocytes. These invasive, activated and in part infected M/M release both viral proteins and cellular activation products, neurotoxic as well as inflammatory. At the same time these factors serve to recruit additional M/M, thereby reinforcing the cycle. Accumulation of the inflammatory M/M subset in the CNS is a strong correlate of neurological dysfunction. Viral products, chemokines and cytokines, all contribute to the macrophage accumulation and dysregulation, and to the end result of neuronal injury. A critical next challenge in research on this topic is to determine how these pathogenic mechanisms identified in the more severe example of HAD relate to the pathogenesis of milder forms of neurocognitive impairment including patients on therapy.

Finally, in addition to elucidating the mechanisms of HIV-1 associated neurocognitive impairment, these findings will provide insight into a range of other neurodegenerative and neuroinflammatory diseases where M/M activation is believed to play a role. Neurotoxic mediators released from M/M are thought to be involved in the pathogenesis of multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and others. For example, in MS inflammatory mediators released from activated microglia contribute to damage of the glial cells contributing to demyelination (Jack et al., 2005). Alzheimer's disease is characterized by presence of amyloid- β plaques, which, in addition to being directly neurotoxic, also stimulate the release of inflammatory factors from activated microglia that then perpetuate injury (Rogers and Lue, 2001). Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, and M/M are believed to be a principal source of inflammatory and oxidative stress products that are

involved in pathogenesis of Parkinson's Disease (Hirsch et al., 1998; Wu et al., 2002; Gao et al., 2003). Interestingly, similar to the circulating levels of plasma LPS in HAD, there is a correlation between LPS levels and the degree of M/M activation in patients with ALS (Zhang et al., 2009) and LPS-mediated macrophage activation has been implicated in murine models of ALS (Nguyen et al., 2004). In addition, LPS has been extensively used as a microglial activator for the induction of inflammatory dopaminergic neurodegeneration in animal models of Parkinson's disease (Castano et al., 1998; Liu et al., 2000a; Arai et al., 2004; Ling et al., 2004; Zhang et al., 2005; Dutta et al., 2008). These data suggest M/M activation contributes to inflammation and neuronal injury in a number of neurological disorders, and that mechanisms may be shared with pathways identified in HIV-associated neurocognitive disorders. In this regard, insights gleaned from studies of M/M activation in HAND will likely be used for understanding the mechanisms of neurodegeneration in other CNS diseases.

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Fig. 1. Model of monocyte / macrophage involvement in CNS inflammation in HIV-1 neuropathogenesis

In the periphery, chronic immune activation develops as a result of anti-HIV-1 immune responses, elevated levels of LPS due to microbial translocation from the gut, and viral proteins such as gp120 and Tat. Immune activation is believed to drive systemic immunopathogenesis but also leads to an expanded subset of activated monocytes (characterized by CD16 and CD163 expression), some of which are also infected. These monocytes have enhanced migratory capacity and traffic through the blood brain barrier (BBB), whose integrity is comprised by viral proteins, pro-inflammatory mediators and LPS (“push” mechanism). In the CNS these cells differentiate into macrophages and release infectious virus that infects other cells through the CD4/CCR5 receptor complex. They also release viral proteins (such as gp120, which can activate bystander cells through CD4/CCR5, and Tat), cytokines and chemokines that activate bystander macrophages and microglia to perpetuate the M/M inflammation as well as activating astrocytes. Chemokines such as MCP-1 and SDF-1 α are released, which further recruit monocytes into the CNS (“pull” mechanism). Some of these factors also upregulate adhesion molecules (ICAM-1, VCAM-1) on various cell types including brain microvascular endothelial cells (BMVEC), which further enhances inflammatory cell recruitment. Together these processes lead to accumulation of activated M/M in the brain that correlates with neurological injury. Neuronal injury results from the combined effects of viral proteins with neurotoxic effects released from infected M/M, cytokines that injure neurons released from both infected and noninfected activated cells, and other soluble M/M activation products like quinolinic acid (QA) and platelet activating factor (PAF) that lead to neuronal cell death. Astrocyte

dysfunction contributes as well, including dysregulated homeostasis of the excitotoxic neurotransmitter glutamate.

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TABLE I

Changes in disease status of HAND as a result of HAART

•	Decreased incidence of HAD; increase in MND
•	Lower levels of CNS viral replication
•	Persistent microglial activation and inflammation; less frequent in some studies and more focal
•	More frequent involvement of hippocampus, temporal cortex; less frequent basal ganglia involvement
•	Increased presence of amyloid plaques (similar to AD)