Review

Insights into the role of immune activation in HIV neuropathogenesis

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How does HIV infection lead to the development of central nervous system disease? Central to this question is identification of the relative contributions of (1) the virus, (2) its host cells, and (3) secondary or downstream events to the pathological process. These are re-examined in this brief review. Also, a greater appreciation for the role of systemic events in neuroinflammation is emerging, with likely relevance to HIV-associated dementia. We propose here a model for HIV neuropathogenesis that highlights the role of systemic monocyte activation and subsequent neuroinvasion in initiating the disease. *Journal of NeuroVirology* (2002) **8,** 69–75.

Introduction

Early descriptions of the clinical spectrum of HIV infection included neurological symptoms, particularly those reflecting disease within the central nervous system (CNS) (Snider *et al*, 1983; Britton and Miller, 1984). Subsequently, the term AIDS dementia complex (ADC) was put forth as a descriptor for the collection of symptoms—cognitive, motor and behavioral—characteristic of adult AIDS patients with dementia (Navia *et al*, 1986) [The terms HIV dementia and HIV-associated dementia or HAD are more commonly used today]. HIV-associated progressive encephalopathy (PE) refers to a similar pattern of deficits in children, with the addition of compromised brain growth (Epstein *et al*, 1985; Exhenry and Nadal, 1996). In some adults, a less-pronounced impairment is present, termed HIV-associated minor cognitive/motor disorder (Janssen *et al*, 1991). This disorder appears to represent a distinct clinical entity, because it does not always progress to frank dementia and, hence, may reflect an independent etiology.

How does HIV infection lead to the development of neurological disease, in particular, dementia? Central

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to this question is identification of the relative roles of (1) the virus, (2) its host cells, and (3) secondary or downstream events in the pathological process. Considerable controversy still exists regarding such basic questions as which cell types within the brain are susceptible to HIV infection, although most agree that neurons cannot serve as hosts. Also, assumptions have been made for which the evidence is lacking. In this brief review, we re-examine some of these issues.

HIV entry and persistence within the CNS
Although HIV appears to enter the brain during acute infection or shortly thereafter (Ho *et al*, 1985; Resnick *et al*, 1988; Davis *et al*, 1992), it is not clear whether this entry leads to significant viral persistence. The brain is susceptible to immune-mediated clearance of many viruses (Griffin *et al*, 1997; Hooper *et al*, 1998; Liu and Chambers, 2001; reviewed in Dietzschold, 1993; Dorries, 2001), and the detection of intrathecal synthesis of HIV-specific antibody (Resnick *et al*, 1985; Chiodi *et al*, 1988b; Resnick *et al*, 1988; Van Wielink *et al*, 1990) and cytotoxic T-cells in cerebrospinal fluid (CSF) (Jassoy *et al*, 1992) suggests that clearance is a possibility in the case of HIV infection. Infectious HIV can be recovered from CSF during all stages of infection (Chiodi *et al*, 1988a; Resnick *et al*, 1988; Chiodi *et al*, 1992), but infection of the brain parenchyma is separate from infection of the leptomeninges (Sharer, 1992) and, hence, it should not be assumed that the presence or level of HIV in CSF accurately reflects infection within the parenchyma. For obvious reasons, most studies of

patient brain tissues have not included examination of specimens collected during the asymptomatic stage of infection. From those that have, however, comes evidence suggesting little or no infection during this time (Bell *et al*, 1993; Donaldson *et al*, 1994). Even in those cases where DNA was present, HIV expression was usually absent (Gray *et al*, 1992; Gosztonyi *et al*, 1994; Sinclair *et al*, 1994).

This lack of expression could reflect viral latency or the presence of replication-incompetent genomes. In considering viral latency, it is important to recall that most of the HIV DNA in the brain is present as unintegrated molecules (Shaw *et al*, 1985; Pang *et al*, 1990), whose longevity and ability to support transcription remains in question. In any event, it is difficult to imagine how HIV infection could persist for years in the absence of viral expression and, certainly, intracranial spread of the infection would be curtailed. Persistence might also be compromised by the fact that the only productively infected hosts appear to be cells of the mononuclear phagocyte lineage. These are typically located at some distance from one another and, under normal circumstances, their numbers are limited, features that would hinder infection of new targets. Macrophages are long-lived cells, yet, some transfer of the infection to new hosts would undoubtedly be required to maintain the infection for many years. Moreover, although it has been assumed that the resident microglia are major targets for productive infection, this may not be the case. Recent *in vivo* evidence from the simian immunodeficiency virus (SIV) system indicates that, among the macrophage subpopulations within brain, the perivascular macrophage (PVM) is the primary host for SIV replication (Williams *et al*, 2001). We have observed a similar situation in brains from AIDS patients (manuscript in preparation). Also of relevance, intravenous, but not direct, intracranial inoculation of SIV leads to brain pathology (Hurtrel *et al*, 1991; Baskin *et al*, 1992).

If the initial entry does not establish a permanent HIV infection within the parenchyma, then how do we account for the presence of the virus at end-stage disease where levels, in some cases of HIV encephalitis, can be high? One possibility, as we have previously proposed (Gartner, 2000), is that during end-stage infection, as a consequence of immune activation or other systemic events, there is an increase in the trafficking of blood-borne monocytes, both HIV-infected and uninfected, into the brain. [This event appears to be part of a more generalized phenomenon that extends to other nonlymphoid tissues (Hirsch *et al*, 1991; Donaldson *et al*, 1994).] Based on several reported observations (Persidsky *et al*, 1997; Pulliam *et al*, 1997; Boven *et al*, 2000), we suggest that a state of cellular activation enhances this transendothelial migration. Upon entry into the brain, these monocytes become PVM, which explains why HIV expression and multinucleated giant cells are often perivascular in location (Sharer *et al*, 1985; Budka *et al*, 1987;

Vazeux, 1991) . Small numbers of blood monocytes enter the brain regularly (Hickey and Kimura, 1988; Hickey *et al*, 1992), so it is likely that during the asymptomatic phase, an occasional infected monocyte does enter. Enhanced entry of monocytes could also help to account for HIV encephalitis.

Host cells for HIV infection
It is now generally accepted that macrophages are the only host cells for productive HIV infection within the brain. As noted earlier, whether or not all subsets of brain macrophages are susceptible and permissive is now in question. Numerous studies have shown that macrophages recovered from normal brain tissue, and exposed to HIV *in vitro*, can become productively infected (He *et al*, 1997; Shieh *et al*, 1998; Watkins *et al*, 1990) It is unlikely, however, that this cultured population is derived exclusively from PVM, given their low numbers in normal brain. Several questions arise: When cultured, do resting microglia adopt the phenotype characteristic of CD14+ cells? Is this phenotype required for HIV infection and/or expression? Do resting microglia become CD14+ when activated *in vivo*?

Considerable evidence suggests that astrocytes, particularly neoplastic cell lines, are susceptible to infection *in vitro* with some HIV strains (Cheng-Mayer *et al*, 1987; Chiodi *et al*, 1987; Dewhurst *et al*, 1987; reviewed in Brack-Werner, 1999). The consensus of opinion is that this infection is inefficient and that expression is limited primarily to accessory gene products. In a limited number of studies, this restricted expression has also been observed *in vivo* (Saito *et al*, 1994; Tornatore *et al*, 1994; Ranki *et al*, 1995). This phenomenon may be a consequence of a block in Rev function (Neumann *et al*, 1995; Ludwig *et al*, 1999), inefficient translation of the structural proteins (Gorry *et al*, 1999), or defects in envelope processing (Shahabuddin *et al*, 1996). Other reports, however, indicate a block at the level of virus entry (Canki *et al*, 2001). Few studies have attempted to rigorously quantitate HIV DNA in primary astrocytes following virus exposure. One such recent study concluded that neither R5 nor X4 HIV isolates can penetrate purified embryonic astrocytes, although the cells express CCR5, CCR3, CXCR4, and CD4 transcripts (Boutet *et al*, 2001).

Attempts have been made to quantitate astrocyte infection *in vivo* using *in situ* PCR and immunohistochemistry, with varying results suggesting that up to 20% of these cells may harbor the viral genome (Gosztonyi *et al*, 1994; Nuovo *et al*, 1994; Saito *et al*, 1994; Tornatore *et al*, 1994; Brew *et al*, 1995; Ranki *et al*, 1995; Bagasra *et al*, 1996; Takahashi *et al*, 1996). Some of these results are difficult to reconcile with tube-based DNA PCR studies of brain tissue in which much lower levels of HIV DNA have been detected (Johnson *et al*, 1996; Lazarini *et al*, 1997). Perhaps these conflicting findings can be accounted for by differences in case selection (e.g., random selection

versus selection of only those with HIV encephalitis) or methodological issues. In addition, few if any studies of astrocyte infection have taken into consideration the fact that most of the HIV DNA in brain appears to be unintegrated. Important, relevant questions include (1) is integration required for accessory gene expression and (2) what percentage of genome-positive astrocytes might, under conditions of astrocytosis, enter cell cycle, thus providing for the possibility of integration?

HAD and microglial activation
A number of pathological changes within the brain have been described in association with HIV infection. These include encephalitis, leukoencephalopathy, axonal damage and dendritic simplification, and diffuse glial poliodystrophy (Kleihues *et al*, 1985; Budka *et al*, 1987; Gray *et al*, 1988; Sharer, 1992; Wiley and Achim, 1994; Masliah *et al*, 1997). Neuronal loss may be mild or severe, and appears to occur, at least in some cases, via an apoptotic pathway (Gelbard *et al*, 1995; Petito and Roberts, 1995; Shi *et al*, 1996; Adle-Biassette *et al*, 1999). Opportunistic infections and neoplasms may also be present. Although it would seem plausible that clinical dementia arises as a consequence of one or more of these pathologies, definitive evidence for causal links remains lacking. Rather, it has been shown that HAD does not correlate with the presence or severity of (1) HIV infection within the brain (Glass *et al*, 1995; Johnson *et al*, 1996; Lazarini *et al*, 1997), (2) leukoencephalopathy (Glass *et al*, 1993; Gray *et al*, 1996; Adle-Biassette *et al*, 1999), (3) axonal damage (Giometto *et al*, 1997; Adle-Biassette *et al*, 1999), or (4) the number of apoptotic neurons or neuronal loss within the cerebral cortex (Weis *et al*, 1993; Everall *et al*, 1994; Adle-Biassette *et al*, 1999). [Extensive neuronal loss, however, may account for dementia in a small number of cases (Gray *et al*, 1991).] Furthermore, there appears to be no correlation between the presence of productive HIV infection within the brain and the degree of neuronal apoptosis (Adle-Biassette *et al*, 1999). Although abundant *in vitro* evidence would suggest otherwise, these findings raise questions regarding the role of HIV proteins and neuronal loss in the etiology of HAD. To address these apparent disparities, multifactorial models have been proposed that suggest that dementia arises as a consequence of neuronal injury mediated by a combination of viral, macrophage, and astrocyte-derived toxins, and also loss of neuronal support functions such as those astrocytes provide (reviewed in Kaul *et al*, 2001).

One feature characteristic of most of the aforementioned pathological changes is microglial activation. Although nonspecific in nature, this phenomenon may play a pivotal role in the development of HAD. HAD has been shown to correlate with macrophage abundance within the brain (Glass *et al*, 1995) and with increased levels of macrophage products in CSF and brain tissue (reviews in Kolson *et al*, 1998; Krebs

et al, 2000). Also, microglial activation is a better correlate of neuronal damage or loss than the presence of productive HIV infection within the CNS (Adle-Biassette *et al*, 1999; Wiley *et al*, 2000). The increased levels of macrophage products could result from either up-regulation of these molecules as a consequence of cellular activation, and/or an increase in macrophage number arising via increased entry of blood monocytes or local monocyte/macrophage proliferation.

If macrophage/microglial activation does plays a primary role in the development of HAD, what initiates and maintains this state of activation? [See Figure 1.] Once initiated, chronic activation could be self-perpetuating, maintained in an autocrine or paracrine fashion by the continued presence of macrophage-derived molecules, HIV proteins, or downstream products from astrocytes or other cells expressed as a consequence of microglial activation. Regarding the initial trigger, certainly, introduction of HIV into the brain could serve as the stimulus. However, microglial activation has been observed in AIDS brains where no HIV expression could be detected (Adle-Biassette *et al*, 1999). Alternatively, the entry of significant numbers of blood-borne monocytes into the brain might initiate microglial activation. This enhanced entry might occur as a consequence of systemic monocyte activation, the cells being primed for transendothelial migration. In support of this possibility is the observed correlation between HAD and levels of circulating activated monocytes (Pulliam *et al*, 1997), as well as the strong association between microglial activation and HIV encephalitis, a feature of which is the accumulation of large numbers of PVM.

Using brain MR-spectroscopy, elevated levels of molecules associated with glial activation, such as myoinositol, have been observed in HIV infection (Laubenberger *et al*, 1996; Chang *et al*, 1999a; von Giesen *et al*, 2001), and reversal of these abnormalities following the introduction of highly active antiretroviral therapy (HAART) has been reported (Chang *et al*, 1999b). Although puzzling when considered in light of the poor brain penetrance of protease inhibitors (PIs), this reversal may be linked to a decline in the level of macrophage/microglial activation and monocyte trafficking into the brain. Treatment with PIs leads to decreased numbers of circulating activated (CD16+) monocytes (Amirayan-Chevillard *et al*, 2000). Similarly, reversal of Sjögren's syndrome-related dementia and radiologic brain abnormalities has been seen following glucocorticoid treatment (Caselli *et al*, 1991; Kawashima *et al*, 1993), which also reduces CD16+ monocyte levels (Fingerle-Rowson *et al*, 1998). Thus, if increased monocyte entry plays a primary role in initiating a more generalized state of microglial activation, limiting this entry could lead first to a normalization of PVM levels, followed by a return of resident microglia to a resting state. This scenario is in keeping with
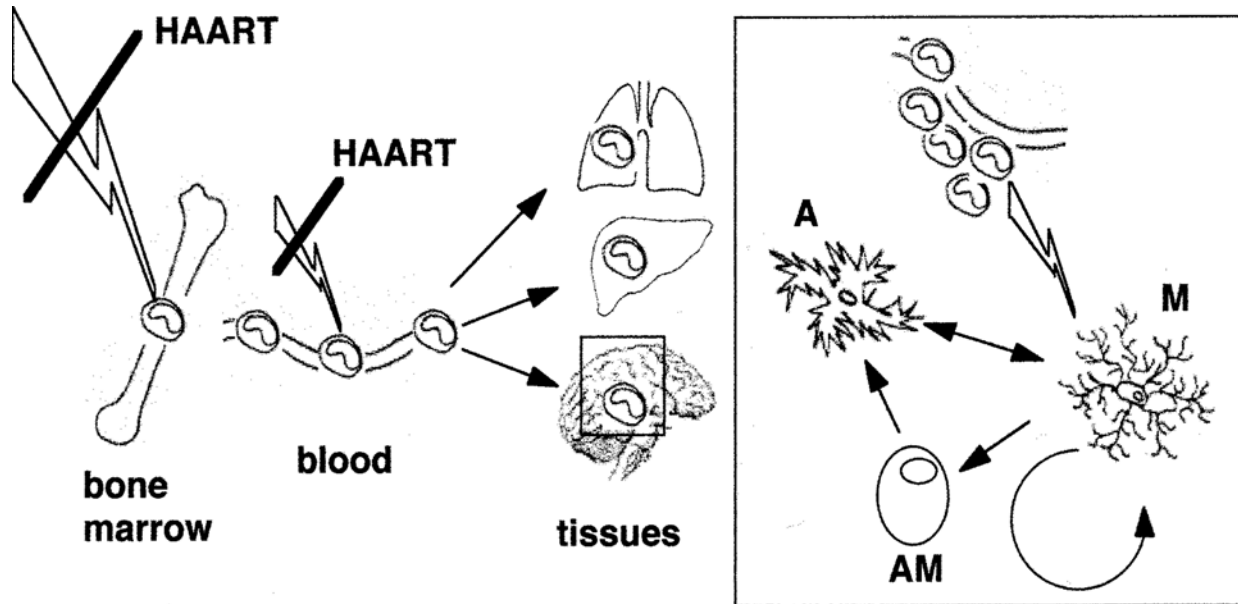
Figure 1 A model for the role of monocyte activation in initiating the development of HAD. During late-stage HIV infection, monocytes become activated prior to departing the bone marrow (indicated by the thunderbolt). This could be instigated by events relating to a generalized immune activation, immune suppression, or local HIV replication. Activation of monocytes might also take place in blood, but probably to a lesser extent. Upon activation, these monocytes become primed for transendothelial migration, and consequently enter the tissues in increased numbers. The brain is a site of this increased entry. Other factors such as perturbation of the endothelium or enhanced circulating cytokine levels may also facilitate monocyte ingress. Both HIV-infected and uninfected monocytes may be activated and enter the brain, but in most cases, the uninfected population predominates. The entering monocytes accumulate within the perivascular space and initiate activation of the resident microglia (M) (see insert). The microglia can, in turn, activate astrocytes (A) and also transform into ameboid macrophages (AM). The astrocytes and microglia affect each other via the production of cytokines and other molecules. Microglial activation may also be self-perpetuating. As a consequence of these events, neuronal damage will develop and if not curtailed, will lead to dementia. Host genetic factors are likely to impact the rapidity of the pathological process. HAART can limit the activation of monocytes, thereby reducing their trafficking into the brain. If introduced prior to significant neuronal damage, HAART can reverse HAD.

the observed 6-to-9-month interval between the introduction of HAART and reversal of imaging-detected abnormalities (Chang *et al*, 1999b), and the turnover rate for PVM (Hickey *et al*, 1992; Bechmann *et al*, 2001). Does long-term microglial activation, then, require a periodic initiating stimulus?

We have focused here on the early events involved in the development of HAD, and have proposed a pivotal role for macrophage/microglial activation. There are a number of ways in which this activation could lead to neuronal injury. These are reviewed in detail elsewhere (Zheng and Gendelman, 1997; Kolson *et al*, 1998; Krebs *et al*, 2000; Kaul *et al*, 2001).

Conclusions

Although considerable progress has been made towards delineating the etiology of HAD, many important questions remain. Some of these may have relevance to other dementing illnesses. For example, why is the subcortical region of the brain the primary anatomical target for HIV pathology? Interestingly, subcortical or white matter dementia is seen in subsets of patients with multiple sclerosis and other autoimmune diseases that, like HIV infection, are characterized by a state of immune activation, including activation of monocytes. Also, do host genetic factors play a role in the development of HAD? An increased incidence of HAD has been seen among carriers of the tumor necrosis factor-α-308 A allele (Quasney *et al*, 2001), and the apolipoprotein E4 allele (Corder *et al*, 1998), the latter of which predisposes to Alzheimer's disease. A definitive understanding of HIV neuropathogenesis may lie with pursuit of immunological and genetic characteristics shared among the white matter dementias.

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