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Review

Virus-host interaction in the simian immunodeficiency virus–infected brain

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With the increased survival of human immunodeficiency virus (HIV)-infected individuals resulting from therapy, disorders in other target organs of the virus, such as the brain, are becoming more prevalent. Here the author reviews his laboratory's work on the simian immunodeficiency virus (SIV)/nonhuman model of acquired immunodeficiency syndrome (AIDS), which has revealed unique characteristics of both the virus that infects the brain, and the innate and adaptive immune response within the central nervous system (CNS) to infection. Similar to findings in humans, neurocognitive/neurobehavioral disorders during the chronic phase of infection can be detected in monkeys, and recent findings reveal potential mechanisms of CNS damage due to the virus-host interaction. *Journal of NeuroVirology* (2008) **14,** 286–291.

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Happy is he who gets to know the reasons for things.
Virgil

Introduction

With the onset of the acquired immunodeficiency syndrome (AIDS) pandemic, research on the pathobiology of lentivirus infections became paramount. The parallels found in human immunodeficiency virus (HIV) infection to lessons learned from studies on other lentiviruses, such as Bill Narayan's work in visna virus, revealed HIV's persistent infection of the brain (Narayan *et al*, 1974) and development of viral variants (Narayan *et al*, 1977). Narayan's past research enabled other researchers not only to stand on the shoulders of this giant, but also as he then set his great skills to work on HIV and its monkey counterpart, simian immunodeficiency virus (SIV), to gain needed insight from his studies on these viruses.

Bill Narayan's accomplishments have had a profound influence on the studies performed by my laboratory and others on the effects of SIV on the brain of monkeys, modeling neuroAIDS in humans. One of the concepts we have focused on is best stated in his review on lentiviral diseases of ungulates: "Consistent low-grade viral replication sets the pace for disease by providing continuous antigenic stimulation for the inflammatory cellular immune response . . . " (Narayan and Cork, 1985). Indeed Bill's work had nicely shown in rodents that the host response can a major effector in central nervous system (CNS) dysfunction following viral infection (Narayan *et al*, 1983). Another concerns the nature of CNS infection itself, with the particular characteristics of both the virus and the target cell. Again, to directly quote from his writings, his laboratory found that "different macrophage populations in the body may select specific phenotypes of lentivirus from the quasispecies of virus . . . " (Sharma *et al*, 1992).

There are many good reviews of the SIV model for HIV neuropathogenesis (Buch *et al*, 2004; Burudi and Fox, 2001; Kim *et al*, 2005; Sopper *et al*, 2002; Zink and Clements, 2002). Here I will review how my laboratory has applied the lessons learned from the studies of Bill Narayan and others to uncover unique

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This article is dedicated to the work, spirit, and life of Opendra "Bill" Narayan.

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aspects of the virus-host interaction resulting from SIV infection of the nonhuman primate brain.

CNS virus

The majority of viral strains and molecular clones utilized in monkey neuropathogenesis studies originate from the SIVmac251 virus stock, the first described pathogenic nonhuman primate model for AIDS (Letvin *et al*, 1985). This stock infects both CD4+ T cells and macrophages, and in a subset of animals results in a distinctive pathology, SIV encephalitis, resembling HIV encephalitis. A molecular clone (SIVmac239) derived from this stock was found not to infect macrophages, but replacement of parts of the genome with sequences from other SIVs as well as HIV, followed in some cases by serial passage through bone marrow or brain, could restore macrophage infectivity and CNS infection (Anderson *et al,* 1993; Mankowski *et al*, 1997; Raghavan *et al*, 1997; Westmoreland *et al*, 1998; Zink *et al*, 1999).

Although some controversy exists over additional targets, myeloid-derived cells—macrophages and microglia—are the primary and predominant infected cells in the brains of HIV-infected people and SIV-infected monkeys. In order to enrich for a viral stock capable of infecting these cells in the brain, we isolated microglia from a chronically, SIVmac251-infected animal, and inoculated a naïve animal with these cells intravenously. This serial passage was repeated, and resulted in a high rate of encephalitis in the recipients (Watry *et al*, 1995).

Initial characterization of the viral genome changes induced by the microglia passage focused on the *Env* gene. Distinct changes were found, either through selection of subspecies present in the original SIVmac251 stock or through mutation, which were then maintained in subsequent passage (Lane *et al*, 1995). Further analysis from an additional passage, including the *Nef* gene and the 3′ long terminal repeat (LTR) in addition to *Env*, revealed the convergent evolution and uniqueness of the resulting virus when compared to other macrophage-tropic and/or neurovirulent SIVs (Gaskill *et al*, 2005). In this study, molecular clones from the microglia-passaged virus were also characterized for *in vitro* infectious phenotype. Differences were found when compared to the parental stock, in that the microglia-passaged virus showed a robust early virus production on macrophages and microglia, compared to a much lower level of infection for the parental SIVmac251 stock (Gaskill *et al*, 2005). Such an infectious phenotype may aid in both the establishment and spreading of infection in the brain.

Although many study the viral genome for the basis of changes in viral properties, changes in the virion, such as host modification of viral proteins or virion incorporation of host proteins, can also affect the phenotype of infection. Because HIV/SIV in the brain is largely derived from macrophages, we examined whether the infectious phenotype of virions produced in macrophages might differ from those produced in T cells. Such virions showed no difference in genomic RNA/Gag or Env/Gag ratios, and sequence analysis revealed no mutations resulting from production in the different cell types. Infectivity assays, using a number of *in vitro* and *in vivo* derived targets, revealed a significantly higher infectivity of macrophage-derived virions (Gaskill *et al*, 2008). Because both Env and host proteins incorporated into virions can be glycosylated, and virion glycosylation can affect infectivity, we then assessed the effect of treating virions with glycosidases. Mannosidase, but not neuraminidase, increased the infectivity of T-cell, but not macrophage, virions (Gaskill *et al*, 2008). Thus the greater infectivity of macrophage-derived virions may be linked a lower number of mannose residues on proteins in the virions themselves. The 3- to 10-fold higher level in infectivity of macrophage-derived virions, amplified over even a few rounds of viral replication, can result in a greatly increased spread of infection in the brain, where macrophages are the drive and are the targets for infection.

In addition to enriching for a neuroinvasive, neurovirulent virus, we have also used a serial passage technique to address another problem in the field, the shortage of rhesus monkeys available for AIDS research. Investigators typically have used India-derived rhesus monkeys, as some data indicated that the course of SIV-induced disease might differ in monkeys from other provenances, such as China. However, such Indian monkeys are in extremely short supply. Recognizing that, in fact, the SIVmac251 virus itself was derived from a serial passage through Indian-derived monkeys (Mansfield *et al*, 1995), we performed a serial passage of our microglia-derived stock through Chinese-origin monkeys (using plasma). Indeed, a virulent stock was derived, capable of inducing simian AIDS with CNS disease in China-derived monkeys (Burdo *et al*, 2005).

CNS host response

The innate and adaptive responses to HIV and SIV infection in the CNS play a large role in the course of CNS disease, but is less well characterized than the response found in the blood and lymphoid organs. Virus enters the brain early, and if an effective systemic immune response occurs, remains relatively quiescent until end-stage disease, when in a fraction of people and animals pronounced neurological symptoms can occur, accompanied by encephalitis. In monkeys, one can shorten the time scale to obtain a rapid CNS disease through the use of combinations of viruses, which lead to pronounced CD4+ T-cell depletion, high viral loads, and CNS disease

(Mankowski *et al*, 2002), or by depletion of CD8 cells, which inhibits the immune response, resulting in high viral loads and CNS disease (Madden *et al*, 2004; Roberts *et al*, 2003; Williams *et al*, 2005).

We have performed a molecular examination of the different stages of SIV infection of the brain by gene array transcriptional profiling. During the acute infection (2 weeks after inoculation), a large number of genes in the interferon and interleukin-6 responsive pathways were up-regulated (Roberts *et al*, 2004a), likely representing the innate CNS response to viral invasion and infection. Indeed others have identified interferon-β as a causative agent in the induction of viral transcriptional latency in the brain (Barber *et al*, 2006). During chronic infection in otherwise healthy, asymptomatic animals (9 months after inoculation), expression of only a few host genes was found to differ significantly in the brains of SIV-infected animals. These up-regulated genes represent discrete aspects of immune responsiveness (Roberts *et al*, 2006). Examination of the expression of these genes in the brain over the varied stages of disease revealed that CCL5 (formerly known as RANTES) was up-regulated throughout infection, and was produced by brain-infiltrating CD8 lymphocytes (Roberts *et al*, 2006). CCL5 can exert both protective and damaging effects in the infected brain, and exemplifies the duality of controlling HIV/SIV in the brain—activating processes that eliminate or restrain the virus and virally infected cells, while needing to minimize damage to the brain. Finally, during SIV encephalitis, a wide range of genes are up-regulated, again with a substantial proportion representing immune-related processes (Roberts *et al*, 2003). Interestingly, the expression of these molecules localized to endogenous brain cells in addition to infiltrating immune cells (Roberts *et al*, 2003).

In addition to presenting a comprehensive assessment of CNS gene expression, these studies have provided clues to mechanistic insights. For example, we have recently focused on osteopontin, which was identified in our gene array studies as being up-regulated in the brain in SIVE (Roberts *et al*, 2003). Although characterized in part for its chemotactic properties, we found that it did not exert chemotaxis on monocytes. Instead, in an *in vitro* model system where monocytes cross an endothelial layer, osteopontin inhibits monocytes from reverse transmigrating back across the endothelial cells, the equivalent of leaving a tissue such as the brain (Burdo *et al*, 2007). In addition, we found that osteopontin is also an antiapoptotic factor for monocytes (Burdo *et al*, 2007). Thus osteopontin expression in the brain can lead to accumulation of macrophages, which was found to be the best pathological correlate of HIV-induced CNS dysfunction (Glass *et al*, 1995). Interestingly, our recent work in monkeys reveals that both plasma osteopontin and one of its receptors on monocytes, CD44v6, are increased in animals developing SIV encephalitis (Marcondes *et al*, 2008), and that in HIV-infected people, osteopontin levels increase with increasing severity of CNS dysfunction (Burdo *et al*, 2008).

A second molecular clue to HIV/SIV neuropathogenesis was provided by our finding of increased expression of CD163, the monocyte/macrophage receptor for the haptoglobin-hemoglobin complex, in SIV encephalitis, which localized not only to CNS macrophages but to microglia cells (Roberts *et al*, 2003). We also examined brains with HIV encephalitis, Alzheimer's disease, and variant Creutzfeldt-Jakob disease, and found CD163-expressing ramified microglia only in SIV and HIV encephalitis (Roberts *et al*, 2004b). Recent work by others has revealed that expression of CD163 could be induced on microglia by the haptoglobin-hemoglobin complex, and such complex could be found in the brain in SIV encephalitis, suggesting that such expression marks breakdown of the blood-brain barrier in this condition (Borda *et al*, 2008).

The adaptive immune response to the chronic infection of the brain has been a long-standing interest of my laboratory. During the chronic, asymptomatic phase of infection, through behavioral and neurophysiological testing, we find functional abnormalities of the CNS in the absence of observable CNS histopathology. However, in keeping with the above results of up-regulated immune molecules in the chronically infected brain, we find infiltrating lymphocytes in the infected CNS, specifically CD8+ T cells (Marcondes *et al*, 2001, 2003, 2007; Roberts *et al*, 2006; von Herrath *et al*, 1995). These represent, in large part, SIV-specific cytotoxic T lymphocytes (CTLs), demonstrated through SIV protein specific *in vitro* killing assays (von Herrath *et al*, 1995) and by the use of SIV epitope–specific tetramer reagents (Marcondes *et al*, 2007).

These CTLs have enabled us to identify unique aspects of adaptive immunity in the CNS. An enrichment of SIV-specific CTLs is found in the brain, compared to the blood, lymphoid, and other organs (Marcondes *et al*, 2007). In addition, certain CTL specificities, both in terms of antigen recognition and T-cell receptor clonal repertoire, could be found in the brain but not in the rest of the body (Marcondes *et al*, 2003, 2007). This accumulation and persistence is due to the specialized nature of immune interactions in the brain, in particular the cytokine environment. Following SIV infection, interleukin (IL)-15 is increased in the brain, expressed by astrocytes. This increase in IL-15, in the absence of IL-2, creates an environment conducive to CTL persistence, confirmed by *in vitro* studies (Marcondes *et al*, 2007). As with the molecules we find increased in infected brains, these CTLs represent double-edged swords—necessary to control the virus, but with a high capacity to injure the brain.

CNS function

Neurological abnormalities are often apparent in animals that rapidly progress to end-stage simian AIDS with the development of SIV encephalitis, and can be documented with behavioral and neurophysiological testing (Gray *et al*, 2006; Marcario *et al*, 1999; Raymond *et al*, 1998, 2000; Weed *et al*, 2003). However, an early study in SIV-infected monkeys documented behavioral/cognitive abnormalities during the asymptomatic phase of infection showing a normal time course (Murray *et al*, 1992). We have utilized a number of testing modalities, including brainstem and cortical sensory-evoked potentials, motor and cognitive skill tasks, and body movement assessment. These indeed revealed that CNS abnormalities are common in otherwise asymptomatic SIV-infected rhesus monkeys (Gold *et al*, 1998; Horn *et al*, 1998; Marcondes *et al*, 2001, 2007; Prospero-Garcia *et al*, 1996; Roberts *et al*, 2006; Weed *et al*, 2004). Although often the specific functional deficits can differ between the animals, we have found two of these tests—a bimanual motor task, used to measure manual dexterity, procedural learning, and motivation to work for a preferred food reinforcer (raisins); and electrophysiological measurement of brainstem auditory-evoked potentials—are quite sensitive and reproducible to assess the CNS deficits induced by SIV infection in the chronic, asymptomatic, as well as he later symptomatic stages of disease.

CNS functional abnormalities are more profound in animals with SIV encephalitis. Interestingly, analysis of the circadian rhythms of body temperature and movement in monkeys that developed SIV encephalitis revealed impairments in circadian rhythms that preceded clinical symptoms, and which became more severe with the progression of disease (Huitron-Resendiz *et al*, 2007). Interestingly, circadian abnormalities have also been documented in HIV infection (Bourin *et al*, 1993; Rondanelli *et al*, 1997; Swoyer *et al*, 1990; White *et al*, 1995), and circadian alterations can lead to a number of cognitive and behavioral abnormalities. Examination of the hypothalamus in animals with SIV encephalitis and circadian abnormalities reveals increased macrophage accumulation, microglia activation, and the presence of viral gene expression (Huitron-Resendiz *et al*, 2007). Because our previous studies revealed the dominance of interferon-induced genes in the brains of animals with SIV encephalitis (Roberts *et al*, 2003), and interferon treatment of mice induced altered circadian rhythms and interferon-induced genes in the hypothalamus (Ohdo *et al*, 2001), interferon or other immune mediator effectors are prime candidates in causing circadian dysfunction.

The link between the CNS immune findings and the CNS functional abnormalities is not clear, the presence of both increased immune response–related gene expression and accumulation of SIV-specific CTLs are certainly correlated with the functional abnormalities in the chronic, asymptomatic stage, and greatly increased inflammatory gene expression and macrophage accumulation in encephalitis at end-stage CNS disease. Yet other contributing mechanisms, such as the actions of viral proteins, remain potential mechanisms leading to functional deficits.

Summary

HIV, and its nonhuman primate counterpart, SIV, provides a unique opportunity to study the effect of a chronic viral infection of the CNS. Aspects of both the virus and the host response are noteworthy in the brain. Viruses in the brain have specific genotypic and phenotypic properties that enable efficient infection of macrophage/microglia, enabling the maintenance of a chronic infection. The host response within the brain to infection is also distinctive. Following the acute phase, where the brain's innate responses occur, a chronic virus-host interaction occurs, in which the adaptive immune response is active in the brain. With the development of immunodeficiency, unchecked viral replication, accompanied again by an innate-response picture, can occur in the CNS of a proportion of subjects. Although this end-stage disorder can lead to severe CNS symptoms, the finding of CNS disorders during the chronic stage, both in the SIV model as well as in HIV-infected humans (Antinori *et al*, 2007), point to the need to better understand this aspect of the pathogen-host relation in the brain, which, over the now prolonged course of HIV infection, is resulting in increased morbidity in infected individuals.

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