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Review

Paving the path to HIV neurotherapy: Predicting SIV CNS disease

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ABSTRACT

HIV-induced damage to the CNS remains a major challenge for over 30 million people in the world despite the successes of combined antiretroviral therapy in limiting viral replication. Predicting development and progression of HIV-associated CNS disease is crucial because prevention and early intervention could be more effective than attempts to promote repair. The SIV/macaque model is the premier platform to study HIV neuropathogenesis, including discovery of predictive factors such as neuroprotective host genes and both blood and CSF biomarkers that precede and predict development of SIV CNS disease. This report details the role of macaque MHC class I genes, longitudinal alterations in biomarkers in the circulation, and expression of inflammatory and neuronal damage markers in CSF using samples from SIV-inoculated pigtailed macaques collected during acute, asymptomatic, and terminal stages of infection.

Contents

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1. Introduction

In addition to causing acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) also damage multiple organs including the central nervous system, peripheral nervous system, lung, and heart. In the central nervous system (CNS), macrophages and microglia are the primary targets for infection and, in turn, produce infectious virus (Chakrabarti et al., 1991; Gabuzda et al., 1986; Zink et al., 1997). Combined antiretroviral treatment (cART) has significantly reduced the incidence of severe HIV dementia, but the cumulative prevalence of HIV-induced neurocognitive impairment (NCI) has nonetheless increased in the cART era (McArthur et al., 2003). The broad spectrum of neurologic disease associated with HIV-1 infection is known collectively as HIV-associated neurocognitive disorders (HAND), a term that encompasses clinical presentations ranging from the mildest form (asymptomatic neurocognitive impairment) to the most severe (HIV-associated dementia [HAD]) (Antinori et al., 2007). Before the advent of effective cART, HAD was recognized as a relatively common condition in HIV-infected individuals, especially those with low CD4+ T-cell counts and high viral load. After introduction of effective cART, the incidence of HAD drastically decreased along with the incidence of AIDS (Antinori et al., 2007; Heaton et al., 2010). Unfortunately, mild to moderate forms of HAND persist despite viral suppressive cART, and amongst the mildest forms of HAND, the overall incidence of NCI has actually increased in the post-cART era (Heaton et al., 2010). For instance, the 2010 CHARTER study reported that, overall, 52% of HIV-1 infected individuals had some level of NCI; of these, only 7% were diagnosed with HAD, 12% had mild NCI, and 33% had evidence of asymptomatic NCI (Heaton et al., 2010).

Despite the recognition of persistent neurologic disease as an important manifestation of HIV infection, the pathogenesis of HAND in successfully cART-treated individuals continues to be elusive. There are numerous possible explanations, including the legacy effect (viral or inflammatory-mediated damage that develops prior to initiation of therapy), ongoing CNS inflammation, immune restoration disorder, host genetic factors, potential cART neurotoxicity, and poor CNS penetrance of cART (Levine et al., 2012; Mothobi and Brew, 2012). Most likely, HAND is the end result of multiple pathophysiologic factors that contribute to a complex neurobehavioral outcome. The continued high prevalence of HAND in the post-cART era is especially concerning because affected individuals have poorer clinical outcomes, with higher mortality, lower quality of life, and worse adherence to treatment (Mothobi and Brew, 2012).

2. Non-human primate models of neuroAIDS

SIV infection of macaques produces an excellent model of systemic and CNS disease induced by HIV (Letvin and King, 1990; Murray et al., 1992). The neuropathological changes induced by SIV closely resemble those present in HIV-infected individuals, with characteristic postmortem histopathologic findings consisting of multifocal perivascular cuffs of macrophages and multinucleated giant cells harboring replicating virus (Sharer et al., 1988). Collectively, these lesions, along with glial responses, typify SIV encephalitis. Animal models are particularly useful in studying the neuropathogenesis of HIV because CNS samples can be obtained from multiple time points throughout infection, ranging from acute through asymptomatic to terminal disease. Biological fluids may be collected from the same animal at various post-infection time points and compared with a pre-infection baseline. Additionally, adherence to treatment may be a challenge in HIV patient cohort studies, while animal models of cART-treated HIV infection allow consistent and verifiable adherence to treatment protocols. Most primate models of AIDS use rhesus macaques (*Macaca mulatta*), and most primate models of neuroAIDS use either $SIV_{mac}239$ or $SIV_{mac}251$, both R5-tropic viruses that cause acute viremia (Williams et al., 2008). Only $SIV_{mac}251$ causes encephalitis and glial activation in the neuropil at a high frequency and both viruses are capable of inducing meningitis (Williams et al., 2008). Although $SIV_{mac}251$ provides an excellent model for HIV neuropathogenesis, there are several limitations: only approximately one quarter of infected rhesus macaques will actually progress to develop encephalitis, and the delay until the development of AIDS is long and inconsistent, taking two years or more (Williams et al., 2008). For this reason, several accelerated models of SIV CNS disease have been established.

In one model, classic lentiviral encephalitis can be induced in up to 90% of SIV-infected rhesus macaques by administering monoclonal antibodies that deplete CD8+ cells (Ratai et al., 2011; Schmitz et al., 1999; Williams and Burdo, 2012). Although this model highlights the importance of cytotoxic T lymphocyte (CTL) immunologic control in the development of HIV encephalitis, it is limited because two important subsets of CD8+ immune cells, CD8+ T cells and NK cells, are both eliminated. Another method that researchers have used to reliably induce SIV encephalitis is to develop neurotropic (able to infect cells in the CNS) and neurovirulent (able to induce neuropathology) strains of SIV. Macrophage tropism has long been known to play an important part in the development of HIV encephalitis (Brinkmann et al., 1992; Koyanagi et al., 1987); however, studies have shown that macrophage tropism alone is necessary but not sufficient to induce the development of neurologic disease (Mankowski et al., 1997). Studies with recombinant SIV indicate that portions of the *env* gene impart macrophage tropism, but that complete *env*, *nef*, and 3'LTR sequences are necessary for neurovirulence (Mankowski et al., 1997; Thompson et al., 2003).

Building on this understanding of the SIV determinants of neurovirulence, the Retrovirus Laboratory at Johns Hopkins University developed a non-human primate model of neuroAIDS by inoculating pigtailed macaques simultaneously with the neurovirulent molecular clone SIVmac/17E-Fr and the immunosuppressive swarm SIV/DeltaB670. With this combination, approximately 60% of pigtailed macaques develop SIV encephalitis while all animals develop AIDS-defining criteria within three months (Mankowski et al., 2002a; Zink et al., 1999). Although most studies of SIV pathogenesis work with rhesus macaques, pigtailed macaques have thus proven to develop CNS disease more consistently when compared with rhesus macaques given the same SIV inoculum (Beck et al., 2015).

This SIV/pigtailed macaque model offers many parallels to HIV infection, including the development of characteristic CNS inflammation that correlates with high viral load in the brain, cognitive and motor deficits typical of HIV-associated dementia, and the typical lesions of HIV/SIV encephalitis, including neurodegeneration

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