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Non-human primate models of SIV infection and CNS neuropathology

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Non-human primate models of AIDS and neuroAIDS are the premiere model of HIV infection of the CNS and neuropathogenesis. This review discusses current SIV infection models of neuroAIDS emphasizing findings in the last two years. Consistent in these findings is the interplay between host factors that regulate immune responses to virus and viral replication. Several rapid models of AIDS with consistent CNS pathogenesis exist, each of which modulates by antibody treatment or viruses that cause rapid immune suppression and replicate well in macrophages. Consistent in all of these models are data underscoring the importance of monocyte and macrophage activation, infection and accumulation in the CNS.

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Introduction

A significant proportion of untreated individuals with human immune deficiency virus type 1 (HIV-1) develop HIV-associated dementia (HAD) or HIV encephalopathy (HIVE). The development and effective use of combination anti-retroviral therapy (cART) has decreased the incidence of HAD/HIVE, but neurocognitive disorders, including HIV-1 associated neurocognitive disorders (HAND) persist [1••]. Several questions exist regarding the mechanisms for such disorders, which are difficult to study in humans.

Non-human primate (NHP) models of HIV central nervous system (CNS) disease are the premier models of — neuroAIDS. Benefits of NHP models include the ability to know the exact time of infection, and the ability to use defined viral swarms or viral clones with defined cellular tropism. Additionally, it is possible using such models to sample plasma, cerebrospinal fluid (CSF) and tissues longitudinally, to have timed well controlled sacrifices, and to use experimental therapies and imaging techniques focusing on the CNS. This brief review will examine recent findings using NHP models of neuroAIDS with regard to novel findings of neurotropic viral sequences, viral evolution and macrophage tropism outside and within the CNS, neuropathogenesis, immunity and genetic restriction, and proposed mechanisms of neuropathogenesis. In this review, we restrict our discussion to historically important background references and papers published in the last few years.

When discussing the utility of animal models of HIV infection of the CNS and pathogenesis it is first necessary to point out that NHP models are just that, models with inherent advantages and disadvantages. Caveats of these models include the relatively rapid progression to AIDS and severity of CNS inflammation which can be ideal in terms of duration and cost of studies, but have amplified pathology and perhaps augmented immune responses. Additionally, some models use immune modulation or depletion of lymphocyte subsets or viruses that rapidly deplete lymphocyte subsets, both of which have similar outcomes to compress the time window of infection and AIDS. As such, these models might not fully recapitulate HIV infection in humans on cART, but they are amenable to ART therapy. Despite the caveats of the NHP model, it has consistently provided and will continue to provide unique insight into HIV infection in individuals on cART and those who are not. Seminal observations made using NHP models of AIDS and neuroAIDS include the observation that following viral inoculation in the periphery, virus is detected in the CNS early, within 3 days p.i. [2•]. Additionally, studies using NHPs demonstrated the importance of monocyte and macrophage activation and infection early and subsequent activation that drives CNS disease [2•,3••,4,5]. Non human primate studies have defined the necessity of macrophage viral tropism and immune suppression (CD4 and CD8 T cells) for CNS infection and neuropathogenesis [3••,6••,7]. Lastly, putative therapies targeting monocyte trafficking or macrophage activation in the CNS and other organs including the heart, underscore the importance of developing adjunctive therapies in humans on ART targeting macrophages. In this brief review we discuss NHP models of neuroAIDS. Specifically we review the role of SIV genetic sequences regulating CNS infection and pathogenesis; the formation of macrophage and neurotropic SIV; the role of the CNS as a viral reservoir; plasma, CSF and CNS

biomarkers of neuroAIDS; and the role of monocyte activation and macrophage accumulation in the neuropathogenesis of AIDS. Lastly, we briefly discuss the necessity of therapies targeting activation and/or infected monocytes and macrophages as adjunctive therapies targeting HIV associated co morbidities including CNS and cardiac disease.

Non-human primate models of neuroAIDS

Several models of neuroAIDS in NHPs exist. Historically early models used rhesus macaques (RM) or pigtail macaques (PM) and different viral clones or swarms that resulted in immune suppression (AIDS) macrophage tropism for CNS infection, and SIV encephalitis (SIVE) in approximately 30 percent of the animals in RM and higher percentages of PM [8] (Table 1). More recently, immune modulation (depletion) of CD4 and CD8 T lymphocytes, and/or serial passage of virus through monkeys for enhanced macrophage replication and neurotropism have been used [6••,9–11] (Table 1). One model uses mAb depletion of CD8 lymphocytes and infection with the viral swarm SIVmac251. This model results in persistent, high viremia, rapid AIDS (3–4 months versus 2–3 years in non lymphocyte depleted animals) and a high incidence of SIVE (greater than 80% versus approximately 30% in non depleted animals) [3••]. Using this model important observations regarding the correlation with monocyte turnover from bone marrow [12••], accelerated accumulation of macrophages in the CNS [13], the recruitment of inflammatory macrophages to the CNS [14], elevated levels of soluble CD163 in plasma that correlate with CNS [5] and cardiac macrophage accumulation [15], and the role of macrophage traffic in neuropathogenesis [5] have been demonstrated. A second model uses mAb depletion of CD4+ T lymphocytes before SIV infection that also results in increased viral replication and progression to AIDS [6••] (Table 1). Of particular interest with this early CD4 T cell depletion is associated with a shift to a high percentage and incidence of infected macrophages in the periphery and the CNS without CD4+ T cells in blood, LN and tissues. Additionally, using this model the authors found a high level of SIV infection of parenchymal microglia [6••]. These data underscore a role for macrophages in AIDS pathogenesis. It should be noted, that earlier work using a simian-human immune deficiency virus (SHIV) that rapidly depleted CD4 T cells in rhesus macaques also resulted in rapid AIDS and CNS pathology [16,17] (Table 1). These two models demonstrate the association of rapid AIDS and severe CNS infection. These models also underscore the importance of CD8 T lymphocytes (that control viral load) and CD4 T lymphocytes (that are a primary target of HIV and SIV early after infection and a critical arm of acquired immunity) in AIDS and the pathogenesis with neuroAIDS.

A third model of rapid AIDS with a high incidence of SIVE uses pigtail macaques infected with a combination of a neurovirulent molecular clone that replicates efficiently in macrophages, SIVmac/17E-Fr, and a immune suppressive viral swarm SIVsm/Delta B670 that rapidly depletes CD4 T lymphocytes within 2–4 weeks post i.v. inoculation [18,19] (Table 1). This model has been used to study mechanisms of CNS and peripheral nerve pathogenesis, cardiac pathogenesis, innate immunity in the CNS and putative CNS therapies for use in humans [20–22]. Two other models deserve note. Hirsch and colleagues used a serially passaged SIVSmE543 and obtained SIVsm804E that established infection of the CNS early and resulted in a high incidence of SIVE. Gabuzda and collaborators similarly identified a macrophage tropic SIV env glycoprotein variant also found in the blood early in infection found in early infection of SIV251 infected animals, and made a molecular clones that enters the CNS early after inoculation and results in a high degree of

Table 1

Nonhuman primate models of neuroAIDS discussed in review

Viral clones	Rapid AIDS[a]	Immune modulation	Disease
SIVmac239, SIVmac251, SIVmac316	No	None	SIVE[b], cardiovascular
CD4-depletion, SIVmac251 [6••]	Yes	Decreased CD4 T cells Increased macrophage infection	CNS[c], SIVE
CD8-depletion, SIVmac251 [12••,13–15,25,33,34]	Yes	Decreased CD8 T cells and NK cells Increased macrophage infection	CNS, SIVE, cardiovascular, gut
Molecular clone of SIVmac251 variant [11]	No	Increased macrophage infection Early infection of brain	CNS
Passaged SIVsm804E [10]	No	Increased macrophage infection Early infection of brain	CNS, SIVE
SIVDeltaB670, SIV/17EFr [18,19,32]	Yes	Decreased CD4 T cells Increased macrophage infection	CNS, SIVE
Simian-Human Immunodeficiency Virus (SHIV) [16,17]	No	Decreased CD4 T cells Increased macrophage activation	CNS, SIVE

[a] Progression to AIDS occurs within 6 months of SIV infection.
[b] Model focuses on development of SIV associated encephalitis (SIVE), often with higher incidence.
[c] Model focuses on increased CNS infiltration of macrophages and virus or macrophage infection.