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Non-human primate models of SIV infection and CNS neuropathology

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Abstract

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 regulated 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.

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

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mechanisms of neuropathogenesis. In this short 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 [2–5]. 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 prior to 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 SIVE [10,11] (Table 1). The viral sequence data from these two models are discussed below. Overall, all of the models discussed above with and without cART have provided fundamental data underscoring the role of viral evolution and macrophage tropism that facilitates rapid and consistent AIDS with neuropathogenesis that underscore the role acquired and innate immunity in CNS disease.

Viral sequence, sequence evolution and neuroAIDS

Studies of viral infection and sequence data in the context of neuroAIDS consistently point to early seeding of the CNS and other viral reservoirs within days of infection[4]. Whitney et al. recently studied early viral seeding outside the CNS in early acute infection prior to viremia after mucosal infection[23]. The authors found that using cART on day 3 p.i. blocked viral RNA and DNA detection in blood and reduced or abrogated the development of SIV specific humoral and cellular immune responses[23]. Earlier reports in humans and NHP have demonstrated SIV DNA and RNA in the CNS by 3 days p.i., but active and consistent productive infection of CNS macrophages is not found until immune suppression

with AIDS in SIV infected naturally progressing animals or models of rapid AIDS with SIVE. In both cases, it is clear that host genetic factors including TRIM5 and MHC Class I genes play a role as do SIV-gag CTL epitopes [10,24] and macrophage tropism [18]. It is also clear that the emergence of macrophage and neurotropic SIV sequences in the periphery correlate with and perhaps predict the rate and incidence of SIVE development [25,26] as do innate immune responses and levels of monocyte activation and turnover [5,12].

Monocyte or macrophage tropic sequences are usually found late in disease in animals that are not rapid progressor. Gabuzda et al., identified macrophage tropic env from animals two weeks p.i. that was closely related to CNS sequences from animals with SIVE that are highly fusogenic and replicate in macrophages and T cells [11](Table 1). Strickland et al., characterized in depth the relationship between intra-host viral evolution and pathogenesis, and viral population dynamics and gene flow between peripheral and CNS tissues and saw a steady increase in viral effective population sizes that peaked 50–80 days p.i just prior to animals developing AIDS[25]. Using sequence analysis these authors found evidence of continual viral seeding in the CNS from the periphery where the last migration occurred before terminal AIDS from bone marrow. Another study by the same group using SIVmac251 in naturally progressing monkeys found that *nef* sequences diverge from the founder virus faster than gp120[26]. At necropsy similar brain *nef* sequences were found in different macaques indicating convergent evolution but gp120 sequences remained host specific. These data indicate that early adaptation of *nef* in the host was essential for successful infection while the convergent evolution of CNS *nef* sequences underscore a role of *nef* establishing neurotropic strains [26]. Matsuda et al., characterizing SIV that induces rapid encephalitis with high frequency found a viral strain that is established early after infection that replicated to high levels in PBMC's and monocyte derived macrophages in vitro[10]. Additionally, using SIVsm804E the authors demonstrated both MHC-I and TRIM5alpha as restrictive host genotypes, underscoring both the role of viral sequences as well as host viral restriction factors in SIVE development[10]. Similar restrictive host genetic MHC I alleles, were reported by Beck et al., in pig tail macaques [8]. These factors underscore the importance of innate anti-viral factors within macrophages, as well as CTL responses most likely against SIV-gag proteins. Another viral factor that deserves note is SIV-*vpx*. Westmoreland and co authors demonstrated using a strain of SIVmac239 lacking *vpx*, termed SIVmac239-*vpx* (hereafter *vpx*), animals developed AIDS but not SIVE [27]. In this study the number of macrophages and SIV+ cells in lymphoid and GI tissues was comparable between *vpx* and the parental SIVmac239 infected animals, without macrophage infection. However, animals infected with *vpx* had delayed progression to AIDS and did not develop SIVE despite high percentages of SIV infected T cells[27].

Biomarkers of neuroAIDS

In recent years the search for dependable markers that predict development of CNS AIDS has emerged. Interestingly, and perhaps not surprisingly, the markers consistently are linked to immune activation and often tied specifically to innate immune responses and monocyte/macrophage activation and or expansion. Predictive hematologic markers include elevated hemoglobin levels and platelet counts[28] both of which are related to bone marrow dysregulation and acute phase protein responses. Elevation of absolute numbers of

monocytes, and/or the percentage of activated CD14+CD16+ monocytes also are predictive of CNS disease in humans and monkeys [3,12]. Interestingly, the percentage of monocytes in blood that are labeled in the bone marrow with bromodeoxyuridine (BrdU), a marker of monocyte turnover, correlates with the development of AIDS and the severity of CNS histopathology [12]. In these animals, it is possible to distinguish between animals that develop rapid AIDS and the severity of CNS pathogenesis as early as day 8 pi, and consistently by day 21[12]. A correlate of the number of BrdU+ monocytes in these animals was sCD163 in plasma. This is significant because sCD163 is only made and shed by myeloid cells, specifically activated monocytes, macrophages and dendritic cells, and sCD163 in plasma correlated with the numbers of BrdU monocytes, and the severity of CNS neuropathogenesis [12]. Soluble CD163 in plasma of humans also correlates with HIV RNA in plasma of acute and chronically infected humans pre and post ART [29]. Additionally, sCD163 correlates with the presence and volume of non-calcified vulnerable cardiac plaque in patients on durable ART [30,31]. The sCD163 data, initially found using the SIV infected CD8 lymphocyte depletion monkey model, underscores the importance of monocyte turnover, and essentially the innate immune responses that might differ between infected individuals, in macrophage infection and CNS and cardiac disease. They also underscore the utility of NHP models, in this case CD8 lymphocyte depletion as a valuable tool to understand CNS pathogenesis with HIV. In addition to plasma and hematologic markers of SIV associated disease, chemokines and cytokines including CCL2 and IL-6, and neopterin are found in the CSF that correlate with monocyte and macrophage inflammation [28]. Human cartilage glycoprotein 39 (YKL-40) and neurofilament light chain (NF-L) are markers of neuronal damage that are also found in the CSF [28].

The role of monocyte/macrophages in CNS disease and therapies targeting these cells

Recent studies using NHP models of neuroAIDS have underscored the role of monocyte traffic in and out of the CNS in establishing and maintaining a CNS reservoir of productive SIV infection. Early studies using cART demonstrated a biphasic activation and expansion of CD14+CD16+ monocytes first at the time of infection and later with the emergence of AIDS, regardless of whether animals were rapid or normal progressors [4,5]. Using cART after infection decreased or eliminated the second wave of activated monocytes that correlated with a lack of development of SIVE and decreased neuronal injury (Figure 1). Studies using the antibiotic minocycline also blocked or decreased the incidence of SIVE[32,33]. The decrease in the incidence of SIVE correlated with a down regulation of monocyte activation and macrophage accumulation in the CNS (Figure 1). In proof of concept studies we used Tysabri®, an anti-VLA-4 antibody that blocks traffic of leukocytes into the CNS as well as the gut. In this study, using CD8 lymphocyte depleted SIV Infected macaques; we found treatment at the time of infection blocked the traffic of SIV and productive infection of the CNS and the gut[34]. Treatment later in infection, when CNS neuronal injury and infected macrophages in the CNS had already occurred, resulted in blocking SIVE and either a reversal or stabilization of neuronal injury[34] (Figure 1). More recently, using dextran dyes injected into the third ventricle of monkeys, labeling all of the perivascular macrophages, we studied the role of monocytes that become perivascular

macrophages early in infection, in mid infection, and terminally before sacrifice. In these studies we found that that rate of macrophage recruitment and accumulation in the CNS increased in animals with AIDS and SIVE [13]. Additionally we found that perivascular macrophages that were in the CNS prior to the development of SIVE lesion formation, comprised the majority of the cells in the SIVE lesions, suggesting they migrated to the site of the lesion, or alternatively proliferated at the lesion site. Lastly, we found that macrophages accumulated at the lesion site late, as opposed to the cells that were there early. These cells also, had significantly higher levels of SIV RNA, suggesting that there is a continuous influx of virus into the CNS, more so with the loss of immune control[13]. We have recently found that increased monocyte expansion in blood, as early as 8 days p.i., based on CD14+CD16+ phenotype, correlates with the development of SIVE as we have previously found, but, also in these animals, the presence of SIVE correlates with cardiovascular disease that includes cardiomyocyte damage, cardiac fibrosis, and aortic or coronary artery inflammation (unpublished data). Overall, these observations support the notion of a link between monocyte/macrophage activation, CNS pathogenesis, and cardiac pathogenesis.

Summary

Non-human primate models of AIDS and neuroAIDS have provided important models in which to understand CNS neuropathogenesis and HIV prior to the use of anti-retrovirals and with anti-retroviral therapy. These models underscore the importance of monocyte/macrophage activation, infection, traffic and accumulation in the CNS. The development of viral sequences that infect monocytes and macrophages are important and predictive of the development of neuroAIDS. Such viral sequences when found early in the CNS and the periphery increase the probability of the development of SIVE. Biomarkers in plasma, CNS tissues and sometimes the CSF that predict or correlate with CNS pathogenesis are often linked to monocyte and macrophage activation, expansion in blood, and traffic to the CNS. Importantly, many of the findings using models of neuroAIDS in monkeys, have been informative with regard to HIV infection in humans and CNS disease.

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Highlights

Non human primate models (NHP) of AIDS and neuroAIDS are the premier models.

NHP models of AIDS and neuroAIDS have provided many insights regarding CNS neuropathogenesis with HIV

All NHP models of neuroAIDS have virus or immune modulation that results in immune suppression of CD4 T cells and high viral replication in macrophages

Activation of monocytes in the periphery and macrophage accumulation in the CNS is required for CNS neuroAIDS in NHP models

Figure 1. Targeting Monocyte/macrophage (MΦ) Activation and Infection

A. A biphasic increase in the number of CD14+CD16+ pro-inflammatory monocytes occurs early and late after SIV infection in untreated animals. Red dotted box and arrows point to a schematic of what is seen in blood and CNS during peak CD14+CD16+ monocyte activation early (left) and late (right) in infection. With early increases in CD14+CD16+ monocytes, monocyte/macrophage migration and accumulation in the CNS. At this time, SIV– DNA, RNA and protein (SIVp28) are detected in the CNS, with increased numbers of monocyte/macrophages and CD163+ MΦ (left). After this initial monocyte traffic, during the asymptomatic phase, only SIV– DNA is detected in the CNS, not viral RNA or SIV-p28. With the second increase in CD14+CD16+ monocytes in blood, increased monocyte/macrophage traffic occurs in the CNS and SIV-DNA, RNA and p28 are readily detected. SIVE lesions are present that are comprised of SIV-infected and uninfected

monocyte/macrophages, CD163+ M Φ , microglia and multinucleated giant cells (MNGCs) (right). **B. The effects of ART and minocycline treatment with SIV infection.** Treatment with cART (red line) or minocycline (blue line) 28 days p.i. diminishes or prevents a second peak of monocyte activation and monocyte/macrophage trafficking and accumulation in CNS late in infection. This reduction of activated monocytes correlates with reduced percentage of SIV infected macrophages and the number of accumulated monocyte/macrophages. **C. The effects of initiating anti-VLA-4 mAb treatment on the day of infection (0 dpi).** Anti-VLA-4 treatment does not reduce the number of activated CD14+CD16+ monocytes, but prevents their migration to the CNS. When treatment is initiated on the day of infection, SIV– DNA, RNA and p28 are not detected in the CNS and M Φ accumulation does not occur. **D. Treatment with anti-VLA-4 mAb starting 28 dpi, after an initial increase in monocyte traffic.** An initial increase in CD14+CD16+ monocytes in early infection results in monocyte migration across CNS barriers. At this time, SIV– DNA, RNA and p28 are detected in the CNS and there are increased numbers of monocyte/macrophages and CD163+ M Φ in the CNS (left). Following anti-VLA-4 mAb at 28 dpi, after the initial increase in CD14+CD16+ monocytes, SIV– DNA, RNA and p28 and M Φ accumulation in the CNS is significantly reduced and SIVE lesions are not detected (right).

Table 1

Nonhuman primate models of neuroAIDS discussed in review

Viral Clones	Rapid AIDS¹	Immune Modulation	Disease
SIVmac239, SIVmac251, SIVmac316	No	None	SIVE ² , Cardiovascular
CD4-depletion, SIVmac251 [6]	Yes	Decreased CD4 T cells Increased macrophage infection	CNS ³ , SIVE
CD8-depletion, SIVmac251 [12–15, 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

¹Progression to AIDS occurs within 6 months of SIV infection.

²Model focuses on development of SIV associated encephalitis (SIVE), often with higher incidence.

³Model focuses on increased CNS infiltration of macrophages and virus or macrophage infection.