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Role of T lymphocytes in HIV neuropathogenesis

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Abstract

Purpose of the review: The purpose of this review is to summarize the current knowledge on the role of $CD4^+$ T lymphocytes leading to HIV assault and persistence in the central nervous system (CNS) and the elimination of HIV-infected CNS resident cells by $CD8^+$ T lymphocytes.

Recent findings: HIV targets the CNS early in infection, and HIV-infected individuals suffer from mild forms of neurological impairments even under antiretroviral therapy (ART). $CD4^+$ T cells and monocytes mediate HIV entry into the brain and constitute a source for HIV persistence and neuronal damage. HIV-specific $CD8^+$ T cells are also massively recruited in the CNS in acute infection to control viral replication but cannot eliminate HIV-infected cells within the CNS.

Summary: This review summarizes the involvement of $CD4^+$ T cells in seeding and maintaining HIV infection in the brain and describes the involvement of $CD8^+$ T cells in HIV neuropathogenesis, playing a role still to be deciphered, either beneficial in eliminating HIV-infected cells or deleterious releasing inflammatory cytokines.

Keywords

HIV neuropathogenesis; T lymphocytes; CNS HIV invasion; HIV-infected cell killing; CNS inflammation

Introduction

The advent of potent antiretroviral therapies has considerably reduced severe forms of dementia subsequent to HIV infection (HIV-associated dementia) and prolonged the life expectancy of HIV-infected individuals. However, individuals with long-term HIV are now

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facing complications, including mild forms of HIV-associated neurocognitive disorder (HAND) [1,2]. Magnetic resonance spectroscopy, neuropsychological testing, and neuroimaging are used to diagnose neurologic dysfunction, including impairment in attention, learning, and executive function that persists despite ART [3, 4, 5•, 6]. Impaired neurological performance is in part due to sustained immune activation and inflammation in successfully treated individuals [7]. Biomarkers such as neopterin (microglia activation) and neurofilament light chain (neuronal breakdown) are increased in the cerebrospinal fluid (CSF) of HIV-infected individuals on suppressive therapy and indicate underlying neuroinflammation and neuronal damage [3, 8•, 9, 10]. The lowest frequencies of neurological impairment have been described when ART is initiated before the $CD4^+$ T cell count drops to low levels, and, conversely, a low CD4 nadir count has been linked to higher risks of developing impairment [11]. A loss of neurons has been described in the majority of asymptomatic individuals even within 100 days post infection [12]. Initiation of ART in acute infection (Fiebig I to II) [13] in HIV^+individuals prevents severe neuronal damage after 6 months of treatment [14], avoids elevation and shedding of inflammation markers such as sCD163 [15], and confirms the benefit of initiating antiretroviral treatment early in the course of infection to prevent neuronal injury [16]. However, in some participants having high HIV RNA in the CSF prior to ART in acute infection, reduced neuropsychological performance is still observed [14].

The CSF provides an opportunity to study the events occurring in the central nervous system (CNS). Meningeal lymphatic vessels in the CNS drain CSF and participate in immune surveillance in the brain [17–20, 21•]. T cells are the major cellular component of the CSF, and only one percent of the T cells in the periphery have been estimated to be found in the CSF in physiological conditions [22]. Low-level T cell migration in the brain occurs in healthy individuals [23] as the CNS is an immune privileged site where cell trafficking is controlled by the blood brain barrier (BBB) and blood-CSF barrier. $CD4^+$ T cell trafficking is more frequent than $CD8^+$ T cells leading to a higher CD4/CD8 T cell ratio in CSF compared to blood [22, 24].

Following HIV-1 exposure, systemic inflammation and the virus itself are thought to trigger BBB disruption. HIV may enter the CNS freely [4], but the main source of infection of the CNS is believed to occur through infiltration of infected monocytes and T lymphocytes after alteration of the BBB [25, 26]. This review addresses the role of $CD4^+$ T lymphocytes compared to monocytes in mediating HIV infection in the brain and their contribution to the establishment of a viral reservoir and the persistence of inflammation. In HIV-infected individuals, $CD8^+$ T cells are predominantly present in the CSF pre- and post-ART with a lower CD4/CD8 T cell ratio [24, 27]. The massive $CD8^+$ T cell infiltration correlates with CSF HIV RNA in HIV-infected individuals off ART [24]. This review addresses the role of $CD8^+$ T cells in the elimination of HIV-infected cells in the brain and their potential implication as a contributor to neuronal damage.

Source of infection and persistence

HIV RNA in the CSF can be detected as early as 8 days after the estimated day of infection [26, 25, 28]. A recent study sampling CSF in HIV-infected participants in acute infection

evaluated HIV RNA in the CSF in 51% of participants at Fiebig I-II and 92% at Fiebig III-V. The detection of HIV RNA in plasma peaked at Fiebig III, whereas the peak of HIV RNA in the CSF was detected later at Fiebig IV [29•]. Low level HIV RNA can be detected in the CSF in about 40% of HIV-infected participants showing impaired neurocognitive performance during ART [8•].

Role of $CD4^+$T lymphocytes in HIV entry into the CNS

Accumulating evidence supports the theory that $CD4^+$ T cells may be critical for HIV entry in the meninges and in the choroid plexus during early infection [30]. Viral RNA loads in the CNS during the course of primary infection can be associated with CSF pleocytosis implying that the increase of HIV RNA may result from an increased number of infected $CD4^+$ T cells trafficking from the periphery into the CNS [31]. Transmitted/founder viruses have been found to be R5 T cell tropic strains requiring a high level of CD4 to enter the cells and are consequently poorly adapted to infect macrophages [22, 24]. Activated memory $CCR5^+CD4^+$ T cells are the main targets of HIV in the blood. The $CD4^+$ T cells in the CSF represent about 300,000 cells for 150 ml of CSF in healthy individuals. In HIV-uninfected individuals, CD4+ T cells are the main population found in the CSF, suggesting a preferential trafficking into the brain compared to the $CD8^+$ T cells, with a phenotype of activated central memory, and are thus highly susceptible to HIV [22, 24] infection. Initiation of ART triggers a rapid decay of viral load in the CSF in most individuals, implying that the main viral replication is sustained in short lived cells such as $CD4^+$ T cells [22].

In rhesus macaques infected with SIVmac251, administration of natalizumab -- a monoclonal antibody against α4β1α4β7 integrins -- during early infection prevented T lymphocyte and monocyte infiltration across the endothelial cells in the brain, and was associated with no detectable SIV RNA or SIV DNA in tissue brain sections in five out of six treated animals [32]. A late treatment 28 days after infection with natalizumab, however, only prevented monocyte/macrophage accumulation in the brain and stabilized the extent of neuronal damage. These observations underline the involvement of $CD4^+$ T lymphocytes in seeding the infection, while suggesting that monocytes may play a role in triggering and maintaining neuronal injury [32]. In line with these observations, a non-accelerated SHIV model in rhesus macaques developed to reflect the early clinical course of HIV infection in humans recently demonstrated no accumulation of monocytes/macrophages in the CNS, while $CD4^+$ T lymphocytes were seen to infiltrate into the meningeal space in some animals at week 12 after infection [33•]. SHIV RNA could also be detected in brain parenchyma and meninges in some animals without any evidence of BBB disruption. Additionally, SHIV RNA positive cells in brain parenchyma and meninges could be detected, including in animals without CSF viremia. The inflammation mediated by the T cells concomitant to SHIV infection in the brain and meninges was proposed to be the source of early neurologic inflammation [33•]. Corroborating these findings, the trafficking and the establishment of HIV infection in the brain by $CD4^+$ T cells has been demonstrated using BLT and T cell only humanized mice ToM, in which human macrophages are absent [21•]. After CNS entry, $CD4^+$ T cells may rapidly transmit the viruses that may integrate into perivascular

macrophages and microglial cells, which are the major cells harboring HIV replication in the brain [28].

Role of myeloid cells in HIV entry into the CNS

An alternative hypothesis for HIV entry into the CNS pictures a Trojan horse model in which circulating HIV-infected monocytes mediate neuroinvasion and accumulate in the brain to then differentiate into perivascular macrophages. They harbor replication competent viruses that lead to infection of resident cells and subsequent neuro-inflammation and neuronal damage [28, 34]. Activated non-classical $CD14^+CD16^+$ monocytes present in blood increase from 6 to 40% in chronic HIV-infected individuals with low CD4 count and in a setting of AIDS dementia [35]. HIV DNA in $CD14^+CD16^+$ monocytes has been found to be associated with neuropsychological performance in patients with HAND while on therapy [36]. These $CD14^+CD16^+$ monocytes are thought to transmigrate through the BBB thanks to their high surface expression of CXCR5, CX3CR1, and integrin CD11b [4], junctional proteins, and chemokine receptors CCR2 [37] and CXCR7 [38]. The non-classical monocyte subset with low CD14 expression and high CD16 and CCR2 expression was found reduced in the periphery, and was associated with worse neurocognitive performance in ART-naïve individuals [39]. Virally suppressed HIV-1 infected participants performed better after 24 weeks of treatment intensification with a dual CCR2/CCR5 antagonist [40]. Moreover, activated monocytes are able to secrete proinflammatory nano-sized vesicles that might transfer their content to endothelial cells and promote monocyte chemotaxis to the brain by increasing surface adhesion molecules expression [41].

Role of $CD4^+$ T cells and myeloid cells in viral reservoir persistence

HIV can persist in CNS tissues despite successful control of systemic viral replication as suggested by the detection of CSF HIV RNA in neurologically stable individuals or asymptomatic individuals [28]. In successfully treated SIV-infected rhesus macaques, SIV RNA positive cells were detected before but also after ART initiation in the brain [42••]. Because $CD4^+$ T cells are not frequent in the brain parenchyma, an alternate T cell reservoir may exist in the CNS compartment: choroid plexus or lymphoid follicles in the meninges could participate in maintaining the infection [26]. Additionally, in an inflammatory environment, lipid mediators such as leukotrienes can be elevated in the CNS [43]. In vitro studies have revealed that exposure of astrocytes to leukotriene C4 elicits CX3CL1/Fractalkine production that acts as chemoattractant for activated $CD4^+$ T cells and enhances their migration across a BBB model. Hence, the sustained neuroinvasion of activated $CD4^+$ T cells could contribute to renew HIV target cells and to maintain HIV replication. When $CD4^+$ T cells are HIV-infected, their transmigration gives rise to productive infection of primary monocytes-derived macrophage sustaining replication in a stable reservoir [44]. Similarly, interferon-gamma inducible protein 10 (IP10), a potent chemoattractant for activated $CD4^+$ T cells, is elevated in CSF samples of HIV^+ individuals [45].

Over the course of infection, the virus evolves to become macrophage tropic [22, 46], and infection of macrophages, long lived cells, leads to a productive infection that is not cytopathic [47]. Thus, myeloid cells may play an important role in the HIV reservoir, contributing to driving persistent neuroinflammation and development of CNS lesions even

after ART [48]. In virally suppressed SIV-infected pig-tailed macaques, a model for AIDS and HIV encephalitis with no detectable viral RNA in the brain, brain macrophages are found to be latently infected, able to be reactivated with latency reversal agents, and can produce competent viruses [49]. Consequently, both an influx of peripheral $CD4^+$ T cells and monocyte/macrophages could contribute to supporting a low level of infection in the CNS. HIV replication in the brain may also be supported at low level by tissue perivascular and meningeal macrophages, as well as microglial cells. This replicating HIV could reseed the periphery and potentially lead to virological failure [3, 28]. It has recently been demonstrated that astrocytes can replicate viruses when in contact with lymphocytes or after stimulation by cytokines, and consequently they could also contribute to maintaining a reservoir [50]. Neurons and oligodendrocytes are not productively infected by HIV but can also harbor some virions and may participate in CNS pathogenesis [26, 47]. Resident cells release inflammatory cytokines, neurotoxic products and viral proteins, thus sustaining neuronal damage [3, 26, 47].

II/ Role of the $CD8^+$ T lymphocytes in HIV neuropathogenes

In HIV infection, $CD8^+$ T cells are known to massively infiltrate the CNS, a phenomenon only partially reversed by ART [24, 51•, 52], $CD8^+$ T cells may contribute to CNS immune surveillance by mediating the clearance of infected $CD4^+$ T cells, monocytes/macrophages, and resident cells. However, through the release of proinflammatory cytokines and chemokines, they may also contribute to sustaining the inflammatory environment and neuronal damage. In individuals on stable suppressive ART, a massive infiltration of $CD8^+$ T cells in the brain can even lead to $CD8^+$ T cell associated encephalitis and trigger severe neurocognitive impairment and cerebral inflammation [27].

Role of $CD8^+$ T lymphocytes in eliminating HIV-infected cells

The contribution of $CD8^+$ T lymphocytes in eliminating HIV-infected cells in the brain has been demonstrated in chronically SIV-infected rhesus monkeys after injection of a depleting anti-$CD8^+$ antibody into the CSF caused an increase in CSF viral load and an overall activation of microglia cells indicating viral replication [26, 53]. In another study, a unique subset of $CD8^+$ T cells expressing a low level of surface CD4 ($CD4^{dim}cD8^{bright}$ T cells) displaying a terminally differentiated phenotype and potent anti-HIV activity has been found in the brain of mice reconstituted with human PBMCs [54]. These cells appear to originate from the single CD8 expressing T cells, and their presence is associated with lower HIV content, implying that they may participate in the control of HIV infection. In SIV-infected macaques ART-treated at 4 days post-infection and successfully suppressed, a high number of $CD8^+$ T cells were identified in the basal ganglia [55], suggesting an enhanced trafficking of T lymphocytes into the brain after treatment in order to control HIV infection.

HIV-specific $CD8^+$ T cells with memory phenotype have been detected in the CSF in ART-naïve viremic controllers and non-controllers [52]. Our group has also detected the presence of HIV-specific $CD8^+$ T cell in the CSF of HIV-infected participants in the acute phase of infection at peak viremia [51•]. These cells are derived from expansion of specific clonotypes compared to the periphery, suggesting compartmentalization of HIV-specific

responses in the brain as early as acute infection [51•]. The presence of these activated cells containing HIV-specific $CD8^+$ T cells is associated with CSF viral load in acute infection but not with markers of neuronal damage, in contrast to chronic infection. These cells may eliminate HIV-infected cells in acute infection, as we showed in the periphery that HIV-specific $CD8^+$ T cells were associated with higher reduction of viral replication and lower reservoir seeding [56••]. The presence of HIV-specific $CD8^+$ T cells in CSF after successful ART has not been reported yet; therefore, their role in ART-suppressed individuals is unknown.

Role of $CD8^+$ T lymphocytes in CNS inflammation and damage

Though $CD8^+$ T cells are massively recruited in the brain, their capacity to eliminate CNS resident infected cells still remains to be demonstrated. In the periphery, *ex vivo* experiments demonstrated that the killing capacities of circulating $CD8^+$ T cells toward HIV-infected macrophages appear to differ from the killing mechanism involved to eliminate HIV-infected $CD4^+$ T cells. Macrophage killing by $CD8^+$ T cells is impaired and triggers higher IFN-γ secretion by $CD8^+$ T cells [57••]. $CD8^+$ T cells would therefore be less efficient in eliminating infected macrophages in the brain and would rather contribute to maintaining an inflammatory environment by activating macrophages through IFN-γ secretion. Corroborating these latter observations, it has been recently shown that in *ex vivo* peripheral $CD8^+$ T cells from HIV-infected participants pre- and post-ART, a granzyme B response from HIV-specific $CD8^+$ T cells is linked to a reduction in HIV reservoir instead of IFN-γ production from HIV-specific $CD8^+$ T cells [58•]. Supporting this notion, IFN-γ–producing $CD8^+$ T cells recruited in the brain of individuals having detectable HIV RNA in the CSF is strongly correlated with severity of neurocognitive impairment. Their presence in CSF also positively correlates with the presence of HAND in successfully treated individuals [59]. A high frequency of constitutive IFN-γ^+ expression in $CD8^+$ T cells endowed with low lytic capacities has also been found in a variety of neuroinflammatory diseases such as multiple sclerosis [59]. We have also shown that activated $CD8^+$ T cells in the CSF of chronically HIV-infected individuals exhibit gene expression profiles suggesting impaired effector functions and associate with soluble markers of neuronal damage [51•].

Several studies have highlighted an increase in activation markers on $CD8^+$ T cells during chronic HIV infection that associate with severity of neurocognitive impairment and persist under ART [60, 61]. $CD8^+$ T cells with reduced cytolytic capacity are also associated with HAND in ART naïve individuals, arguing for a deleterious role of $CD8^+$ T cells in neurocognitive impairment [61]. Of note, our group previously demonstrated a high level of activation and proliferation of circulating blood HIV-specific $CD8^+$ T cells in late acute HIV infection associated with mitochondrial dysfunction and a high oxidative profile leading to higher susceptibility to apoptosis [62] that could trigger cellular toxicity, immune activation, and underlie neuronal damage and loss [63].

A massive T cell infiltration into the CNS, which is particularly important when ART is initiated in severely immunocompromised HIV-infected patients, can lead to encephalitis described as the central nervous system immune reconstitution inflammatory syndrome (CNS IRIS). CNS IRIS arises in virally suppressed ART treated individuals who experience

a deregulated immune response against a preexisting infection in the setting of $CD4^+$ T cell recovery, often highly detrimental for the host since it leads to neuronal damage, encephalopathy, demyelination, breakdown of the BBB, and progressive cerebral atrophy. This syndrome is estimated to develop in the CNS in 1% of ART-treated individuals [64]. CNS IRIS is characterized by a massive infiltration of activated $CD4^+$ T and $CD8^+$ T lymphocytes. In HIV and in the absence of opportunistic infection, CNS IRIS is mainly mediated by infiltration of $CD8^+$ T cell directed against HIV reservoirs or self-antigens [64]. Early intervention with ART appears to prevent the development of CNS IRIS.

Conclusion

Early ART initiation has proven to considerably suppress viral replication and reduce neurocognitive impairment. Although it reduces the establishment of the HIV reservoir and limits immune damage, it does not completely eradicate the virus or fully restore the immune system. HIV targets the brain very early in the course of infection via HIV-infected $CD4^+$ T cells and monocytes, and establishes latency in resident long-lived cells. The relative contribution of $CD4^+$ T cells and monocytes in mediating HIV entry in the CNS at different stages of HIV infection still remains to be determined. The CNS thus represents a potential tissue sanctuary for HIV replication and leads to HIV compartmentalization. In addition, poor penetrance of certain antiviral drugs in the brain and development of drug resistance can lead to CNS HIV viral escape.

The increased trafficking of $CD8^+$ T cells into the CNS is subsequent to HIV invasion and may target local infected cells to contain the infection. Whether the HIV-specific $CD8^+$ T cells are able to reach, detect, and efficiently eliminate the infected cells in the CNS compartment is still questionable. $CD8^+$ T cells with high levels of activation but low cytolytic capacity have been identified and may contribute to damaging the CNS. Moreover, given the high inflammatory environment in the CNS during HIV infection, cytokine-driven proliferation of nonspecific bystander cells may amplify a pathogenic role of $CD8^+$ T cells. Overall, the recruitment of activated and HIV-specific $CD8^+$ T cells in the brain may control viral replication in the early stages of HIV infection. However, their presence in later stages of infection and on ART, if functionally impaired or apoptotic, may be associated with detrimental effects to the CNS.

Determining the mechanisms leading to HIV infection in the brain and defining the beneficial or detrimental role of $CD8^+$ T cells in HIV neuropathogenesis are critical issues to address to develop new strategies to prevent HIV dissemination in the brain and CNS inflammation. To achieve improved control of infected cells while preventing CNS damage, a protective anti-viral immunity might involve inducing HIV-specific functional T cells via immune therapeutic interventions. However, the impact on the brain of using immune modulators or immune intervention aiming at modifying cell trafficking, restoring HIV-specific $CD8^+$ T cell functions, or using latency reversing agents to reactivate latent virus in ART treated participants need to be carefully assessed.

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