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Reservoir of human immunodeficiency virus in the brain: New insights into the role of T cells

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Abstract: Human immunodeficiency virus (HIV) infection of the central nervous system (CNS) has attracted significant attention because it contributes to severe complications of acquired immunodeficiency syndrome (AIDS) and seriously impairs the life quality of infected patients. In this review, we briefly describe the latent infection of HIV in CNS and focus on the role of the important immune cells, such as T cells, in the formation and maintenance of the HIV reservoir in CNS. This review explores the mechanisms by which T cells enter CNS and establish latent infection of HIV in the CNS. In conclusion, we summarize the role of these cells in the interaction between HIV and CNS. With our better understanding of the underlying mechanisms, we propose future directions for the development of novel strategies to eliminate HIV reservoirs in the CNS based on cellular components.

Introduction

In 2021, approximately 37.7 million people in the world had human immunodeficiency virus (HIV) infection, including 5.8 million in the Asia-Pacific region. In 2020, 1.5 million adults and children were newly infected with HIV globally, including 240,000 in the Asia-Pacific region (WHO, 2022). Due to the wide application of combined antiretroviral therapy (cART), new HIV infections and AIDS-related deaths have decreased in the past 10 years. However, it remains a challenge for the eradication of HIV infection and cure of HIV-induced acquired immunodeficiency syndrome (AIDS).

With the prolongation of the lifespan of people infected by HIV and AIDS patients, some complications related to chronic HIV infection have been paid more attention. One of the most important complications is HIV-associated neurocognitive disorders (HAND), closely related to HIV latency in the central nervous system (CNS). Similar to the latent infection reservoir in the peripheral environment, the HIV reservoir in CNS is based on the immune cells such as T cells and macrophages, and HIV in CNS interreacts closely with the components of CNS, leading to HAND and other HIV-related brain diseases. Understanding the mechanism of the interaction between HIV and CNS is important to develop novel strategies to eliminate latent infection of HIV in CNS and achieve the final goal of curing AIDS.

In this review, we briefly describe the latent infection of HIV in CNS and focus on the role of the important immune cells, such as T cells, in the formation and maintenance of HIV reservoir in CNS. In particular, we explore the mechanisms by which T cells enter the CNS and establish latent infection of HIV in CNS.

Human Immunodeficiency Virus in Latency and Its Reservoir

The viral reservoir formed by latent HIV has become the primary obstacle to curing AIDS. The latent HIV has been defined as replicant competent HIV DNA integrated into cell populations of patients under ART. The integration and latency of HIV involve multiple mechanisms, including the stability of the latent infection and the replication of the cells with HIV DNA integrated. HIV DNA in the integrated host usually has only one copy and keeps silent in the infected cells (Josefsson *et al.*, 2011; Josefsson et al., 2013a). The infected cells make a stable and replicant-competent HIV reservoir (Josefsson et al., 2013b).

HIV reservoirs are established in peripheral blood and special anatomical sites with resident immune cells.

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Peripheral blood and lymph node reservoir of HIV mainly include $CD4^+$ T cells (García *et al.*, 2018; Barton *et al.*, 2016). In addition to the viral reservoir in the peripheral tissues, one of the most important reservoirs is a viral reservoir in the CNS because the replicant-competent HIV spreads the virus in CNS and around the body and causes nervous disorders such as HAND and HIV encephalitis.

Latent Infection of Human Immunodeficiency Virus in the Central Nervous System

Central nervous system and human immunodeficiency

According to recent studies in Africa, among HIV hosts, up to 33% will finally develop HAND, and this ratio is up to 50% for older adults living with HIV/AIDS (PLWHA) (Belete *et al.*, 2017; Flatt *et al.*, 2021). HAND is a common neurological complication associated with HIV replication in the CNS. HAND is caused mainly by inflammatory responses mediated by infected non-neuron cells such as macrophages and microglial cells (Honeycutt *et al.*, 2016; Letendre, 2011; NIH 2022). On the other hand, the T cells are even more important in this process. Upon infection by HIV, these cells could establish a reservoir of latent infection of HIV in the brain.

Normally, the brain is free from foreign pathogens. The blood-brain barrier (BBB) protects the CNS from harmful foreign substances and controls the entry of immune cells into the brain. However, in PLWH, the tight junction of BBB is disrupted by HIV protein Tat (András *et al.*, 2003; Xu *et al.*, 2012; Woollard *et al.*, 2014; Killingsworth and Spudich, 2022). Consequently, the infected cells, including macrophages and T cells, as well as viral particles, enter the brain tissue to establish a latent reservoir in the CNS (Sturdevant *et al.*, 2015). Moreover, although T cells entering CNS protect the CNS against HIV infection, T cells could activate inflammation responses that further disturb the tight junction of BBB and contribute to the deterioration of HAND (Killingsworth and Spudich, 2022; Subra and Trautmann, 2019). As a result of the early responses, HIV succeeds in keeping its latency in the CNS. Samples from six donors showed reactivation of the HIV reservoir in CNS 53 days after ART had been interrupted, and contributed to the virus spreading around the whole body (Chaillon *et al.*, 2020).

In the following sections, we will focus on the role of T cells, which are one of the most important cell-sets in the response of the body to HIV infection and in the establishment and maintenance of the latent HIV reservoir in CNS. In addition, we will discuss the interaction between ART and other treatments and HIV reservoir in CNS.

T cells and human immunodeficiency virus reservoir in the central nervous system

$CD4^+$ T cells are regarded as the largest reservoir in the circulation of PLWH, and these cells are intricately connected to inflammation in the brain (Subra and Trautmann, 2019). HIV-infected T cells also suffer from high transcript level of HIV RNA, and they can establish reservoirs in other sites, such as brain tissue and lymph nodes (García *et al.*, 2018; Barton *et al.*, 2016; Suzuki *et al.*, 2022). Since it is almost impossible to figure out the real cell population and infection state of HIV in living people through repetitive biopsy or imaging, cerebrospinal fluid (CSF) has become the only available approach to examine HIV status in CNS. A recent study showed that CSF may reflect various resources, including both CNS and blood, so the time of sampling is quite important (Chan and Spudich, 2022).

Although macrophages were considered the primary cellular reservoir of HIV-1 in CNS (Saro *et al.*, 2021; Farhadian *et al.*, 2022) found that a considerable number of central memory $CD4^+$ T cells in CNS released HIV-1 RNA based on single-cell RNA sequencing of freshly drawn CSF from PLWH. In acute HIV infection, more than 90% of cells in the CSF of PLWH are T cells, and the primary activated T cells in CSF are $CD8^+$ T cells that cannot be found in the CSF of HIV-negative populations, showing the efforts of the body of PLWH to clear infected $CD4^+$ T cells in CNS (Sadagopal *et al.*, 2008a, 2008b). However, the $CD8^+$ T cell is the predominant cell type contributing to lymphocytic pleocytosis in symptomatic HIV escape (Chan and Spudich, 2022). These findings show that $CD8^+$ T cells also play a significant role in supporting or establishing HIV reservoirs in the CNS.

In fact, $CD8^+$ T cell is the primary cell type in CSF that participates in the acute inflammatory response in PLWH (Killingsworth and Spudich, 2022). Autopsy of patients with HIV-CD8-associated encephalitis showed diffuse cerebral infiltration by $CD8^+$ T cells in the white matter (Lucas *et al.*, 2021). $CD8^+$ T cells also express a unique TCR V-beta repertoire, suggesting a local expansion and delayed differentiation of T cells in CNS (Takata *et al.*, 2017). However, upregulated $CD8^+$ T cells can also activate neuropathogenic and persistent inflammatory responses, such as HIV $CD8^+$ encephalitis reported in a Thailand cohort (Subra and Trautmann, 2019; Sailasuta *et al.*, 2012). Therefore, $CD8^+$ T cells could promote the damage of BBB and facilitate the entry of HIV into CNS.

Interestingly, a special type of $CD8^+$ T cell, which has low CD4 expression on the cell surface ($CD4^{dim}$ $CD8^{bright}$ T cell), is upregulated after HIV infection. This double-positive expression is activated by astrocytes (Fig. 1A). Different from the premature cells, which also express both CD4 and CD8, this group of $CD8^+$ T cells are highly activated mature $CD8^+$ T cells that upregulate CD4 expression *de novo* on the surface and also highly express CD32 (Sullivan *et al.*, 2001; Virdi *et al.*, 2020). Due to the CD8 expression on the cell surface, $CD4^{dim}$ $CD8^{bright}$ T cell may help prevent HAND (Richards *et al.*, 2016). A study suggested that this kind of T cell contributes to the adaptive immune reaction in the defense against viral infections (Marrero *et al.*, 2021). Suni *et al.* demonstrated that these hybrid cells upregulated the cytolytic response in HIV infection, and the reaction probably favored the existence of these cells in the brain (Clénet *et al.*, 2017). However, the CD4 receptors on the double-positive T cells have a critical impact on the susceptibility of these cells to HIV, making these cells a potential vehicle for the virus to enter other tissues like CNS (Choi *et al.*, 2018). Swanstorm *et al.* (2014) reported a special HIV subtype that prefers cells with relatively low level of CD4 expression on their surface, like macrophages

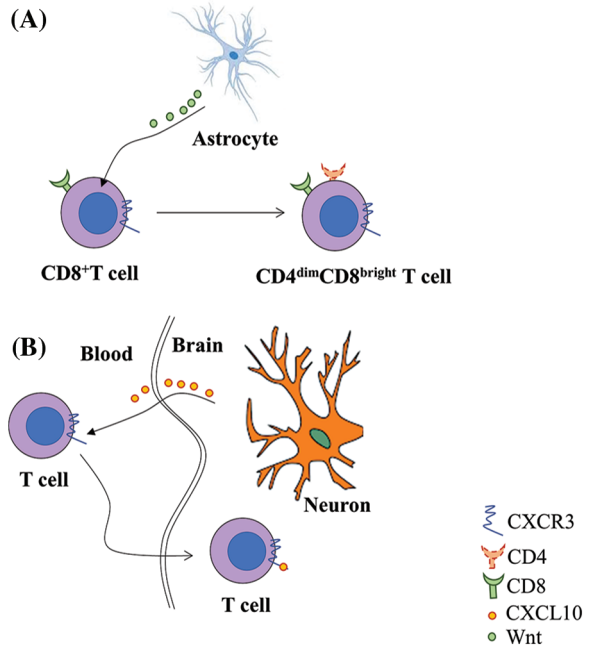

FIGURE 1. $CD4^{dim}$ $CD8^{bright}$ T cell serves as a reservoir for Human immunodeficiency virus (HIV) in the central nervous system. A. Single positive $CD8^+$ T cells differentiate into CD4 cells through Wnt/β-catenin pathway with Wnt from astrocytes in the brain after HIV infection. B. The increase in chemokine receptor 3 (CXCR3) on the cell surface induces the cells to cross the blood-brain barrier by binding with C-X-C motif chemokine ligand 10 (CXCL10) from neurons.

('M tropic') (Joseph *et al.*, 2014). Since the double-positive T cell has low CD4 expression on their surface, these cells should be susceptible to the M tropic HIV subtype. This subtype can also replicate in infected cells like their high-CD4 tropic kind, making their hosts serve as a 'Trojan horse' for HIV into deep tissues like the brain to establish a viral reservoir that can hardly be eliminated (Zhu *et al.*, 2002). Since the CD8 T cell is the major lymph cell in CSF circulation and brain inflammation, and the double-positive T cell is still a special subtype of CD8 T cell, it is likely to become an aggressive virus reservoir that breaks down the defense barrier of the brain.

Discussion

As the life span of people infected with HIV extends, the HIV reservoir in CNS has become important because of the viral escape and related symptoms like HAND. The CNS latent reservoir remains the most primary barrier between the existing functional cure and HIV eradication. Myeloid cells and lymphocytes play important roles in establishing and maintaining this reservoir. During the establishment of HIV latent reservoir in CNS, one the most important cells is the T cell, which consists of the most favorable target of HIV and the major viral reservoir in AIDs patients.

Although T cell is a less important HIV latent reservoir than macrophages in CNS, it is essential for the interaction between HIV and CNS. T cells contribute to the invasion of HIV into the CNS, especially $CD4^+$ T cells, which function as a 'bridge' for HIV between peripheral circulation and potential cells for the central reservoir; while $CD8^+$ T cells have double effects. On one hand, $CD8^+$ T cells clear the infected $CD4^+$ T cells. On the other hand, $CD8^+$ T cells secrete proinflammatory cytokines, which may lead to a fatal inflammatory response in the brain. Interestingly, a special type of $CD8^+$ T cell ($CD4^{dim}$ $CD8^{bright}$ T cell), is both important in the immune reaction in HIV infection and susceptible to HIV. A study on animal models showed that in humanized mice, these double-positive cells would home to the brain through CXCL10/Wnt pathway with HIV loaded (Fig. 1B) (Albalawi *et al.*, 2022).

However, because of the ethical constraints and poor accessibility of human brain tissue with active virus from autopsy, only a few studies directly based on human samples or human patients. Moreover, novel methods for the treatment of AIDS mainly focus on ART and major viral reservoirs such as macrophages and CD4 T cells, while few studies aim to develop therapies that directly target CD8 T cells and double-positive T cell, which may be the key to eradicating HIV from patients.

In conclusion, CD8 T cells and the double-positive mature T cells derived from them probably play a more important role in the progression of AIDS than inflammatory and defense response. The potential ability to deliver latent HIV into deep tissues like the brain leads to HIV escape in AIDs patients and neural complications of AIDs like HANDs. We should pay more attention to these special T cells and explore the mechanism by which these cells interact with HIV to develop novel strategies to eliminate HIV reservoir in CNS based on cellular components.

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