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Review Article

HIV-1 Persistence in Macrophage Reservoirs during Antiretroviral Therapy

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Abstract

For almost 30 years, plasma viral load and CD4+ T-cell counts have been the primary indicators of human immunodeficiency virus type-1 (HIV-1) disease; however, with access to combined antiretroviral therapy (cART), HIV-infected individuals often maintain low plasma viral loads and adequate CD4+ T-cell counts and still yield to a variety of inflammatory diseases and cancers. HIV-1 immune-cell cycle data show that in the absence of cART, when the T-cell population begins to fail, a persistently infected macrophage reservoir is important for disease progression. In patients on cART, a much slower process of macrophage infection and activation sustains HIV-1 disease and contributes to life-threatening pathologies. This has encouraged the development of drugs that target the replication of macrophage-tropic viruses and macrophages activated by HIV-1.

Keywords: Macrophages; HIV-1; HIV-related cancers; Vascular disease; Antiretroviral therapy

Abbreviations

HIV-1: Human Immunodeficiency Virus; cART: Combined Antiretroviral Therapy; AIDS: Acquired Immune Deficiency Syndrome; ARL: AIDS-Related Lymphoma; KS: Kaposi's Sarcoma; EBV: Epstein Barr Virus; HHV8: Human Herpes Virus 8; HAD: HIV-Associated Dementia; HAND: HIV-Associated Neurological Disease

Introduction

Acquired Immune Deficiency Syndrome (AIDS) occurs due to infection with HIV-1. Once an individual is infected, HIV-1 invades their immune system, infecting multiple cell types, including T-cells, monocytes, macrophages, Langerhans and dendritic cells [1]. The virus evolves and adapts in multiple tissues, eventually crippling immune defenses and enabling the development of a number of debilitating and fatal diseases [2]. The host's cells are damaged either directly by the virus or by immune responses to the virus. The antiviral immune response depends on the amount of virus present, the tissues infected, and the length of the infection [3,4]. Early in the HIV-1 epidemic, measurements of viral load and T-cell counts showed there were three well-defined stages of HIV-1 infection. The acute stage lasts 2-10 weeks at which time there is a decrease in circulating $CD4^+$ T-cells and an increase in viral load. During the asymptomatic stage, which may last up to10 years, $CD4^+$ T-cell populations return to near normal levels and viral load drops; however, viruses continue to multiply and infect new cells. Even though the virus may appear to be resting in this phase, there is a rapid turnover of infected cells and it is the cellular and humoral immune response that keeps viral loads to a constant level [5]. Furthermore, during this chronic phase, the within-host viral diversity increases [6]. Also, because $CD4^+$ T-cells are a primary target of the virus, their number slowly decreases. During the last stage, AIDS, there is a final increase in viral load, complete collapse of the $CD4^+$ T-cell reservoir and opportunistic infections are common [7,8].

The ability to monitor $CD4^+$ T-cell levels and viral loads contributed immensely to the successful development of cART. However, because a patient's viral load and T-cell count are easily measured with simple laboratory tests; the perception that HIV-1disease is primarily T-cell driven has been exaggerated. While cART has increased the HIV-infected patient's lifespan, cART does not cure disease or clear the virus permanently from the body. HIV-1-infected patients on so-called "effective cART", wherein viral loads and T-cell levels are controlled, can still succumb to a variety of diseases including cancers, neurological disease, and vascular diseases.

Resting T-cells and their contribution to HIV-1 pathogenesis

Much research has focused on HIV-1 latency, defined as a state of reversibly nonproductive infection of individual resting T-cells [9]. The presence of the latent T-cell reservoir is said to be responsible for low-level viremia, lifelong persistence of HIV-1, and the "most worrisome" reservoir because of the inability of cART to clear HIV-1 from these cells [10]. While latent T-cells indeed present a significant problem when designing drugs to control infection, other HIV-1 infected cell types are also present in compartments and reservoirs with unknown cART penetration.

Anatomical HIV-1 reservoirs and compartments

Many HIV-1 anatomical reservoirs exist and their role in HIV-1 persistence varies according to the microenvironment where the virus replicates [11]. HIV has been isolated from genital foreskin [12], lung [13], liver [14], meninges [15], lymph nodes [14], spleen [14], thymus [16], stomach [14], brain [17], and many other tissue sites. Of these tissues, the brain is the most well known compartment. Due to the blood-brain barrier, the brain is not directly targeted by cART. HIV-1 that has entered the brain prior to therapy has the potential to expand and evolve independently from lymphoid tissues. While all tissues share several HIV-1 target immune cells, the brain is unique

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because it is void of T-cells and the primary immune target cell for HIV-1 is the macrophage.

The HIV-1 infected macrophage reservoir

Macrophages are long-lived reservoirs of HIV-1 in most tissues types [12,18,19]. Un-integrated viral HIV-1 DNA is unusually stable in macrophages and maintains biological activity along with persistent viral gene transcription [20]. Studies show that HIV-1 can be found in macrophages from patients on extended cART therapy [21,22]. During late-stage disease, when $CD4^+$ T cell counts drop to undetectable levels, HIV-1-infected macrophages continue to proliferate and are found at high levels in different tissue types [23]. Circulating monocytes (macrophage precursors) also harbor HIV-1 and are permissive to viral replication after they differentiate into tissue macrophages [24,25]. Macrophages can disturb immune function and metabolism by altering cytokine immune-system signaling responses [26], increasing cholesterol efflux [27,28], blocking normal immune responses [29] and inducing tumor-promoting factors [30].

Abnormal macrophage function is associated with diseases that still concern the HIV-1 cART treated community. For example, a variety of cancers including B-cell lymphoma, Hodgkin's lymphoma, anal, head/neck/oral, liver, lung, testicular cancer and Kaposi's sarcoma (KS) are frequently diagnosed in patients on cART. Some of these cancers are associated with other viral infections, for example AIDS-related lymphoma (ARL) is associated with Epstein Barr Virus (EBV) infection and KS is associated with Human Herpes Virus 8 (HHV8) infection, but there are clearly inflammatory-mediated factors encouraging these cancers beyond EBV and HHV8 infection as nearly half of HIV-1 ARLs do not contain detectable EBV [30] and the development of KS usually depends upon HIV-induced immune dysfunction [31]. One study found that during ARL, HIV-1 migrates to metastatic sites within the lymphatic system where it becomes compartmentalized in tumors [14]. Another study found that macrophages form specialize conduits that specifically transfer the HIV-1 nef protein into B-cells [32], which may underscore the macrophage-cancer association [33]. The HIV-1 Nef protein is an accessory protein that is not required for HIV-1 replication in some cultures systems [34], but is necessary for HIV-1 replication in vivo and has been associated with a wide range of cellular interactions [35,36].

Compared to the uninfected populations, the HIV-1-infected population has up to twice the risk of developing cardiovascular disease, atherosclerosis, dyslipidemia or insulin resistance [37-39]. Along with cART side effects, chronic immune activation and inflammation drive these diseases. In particular, macrophages are the primary cell-type associated with atherosclerotic plaque formation. Fitch et al. found that increased monocyte activation was associated with noncalcified coronary plaque in a young, asymptomatic HIV-1 infected female cohort [40]. Burdo et al. identified that sCD163, a marker for macrophage activation, is increased and associated with noncalcified coronary plaque in men with chronic HIV-1 infection and low or undetectable viremia [41].

Prior to cART, severe HIV-associated dementia (HAD) was frequently identified in HIV-1 infected individuals. At autopsy, the most strongly associated post-mortem finding associated with HAD was the number of activated macrophages present within affected areas of the brain [42]. Since the introduction of cART, less severe HIV-associated neurological disease, termed HAND, is more prevalent. HAND is associated with a higher risk of developing other AIDS-associated illnesses [43]. The best correlates of central nervous system disease are high viral loads, elevated $CD16^+$ monocytes [44,45] and sCD14, a marker for macrophage activation [46]. Increased numbers of $CD16^+$ monocytes escalates their capacity to migrate across the blood-brain-barrier, infect brain macrophages, and establish a persistent infection [47]. HIV-1 infection in the brain can begin early [48] and while cART likely reduces the viral burden outside and within the brain compartment, long-lived HIV-infected or activated macrophages in the brain likely cause damage over time through the production of neurotoxic inflammatory mediators [49,50], cytokines [51-53] and the alteration of normal signaling pathways [35].

Discussion

The HIV-1 infected macrophage reservoir is emerging as the next major challenge in controlling HIV-1-related pathologies [54,55]. Macrophages possess three different macrophage activation states: 1) M1 is the IFN-γ classically activated macrophage that displays a pro-inflammatory response, 2) M2 is the macrophage activated by IL-4 and IL-13 that displays an anti-inflammatory response and, 3) dM represents a macrophage deactivated by IL-10 which leads to immune suppression [26]. Some advances have been made to modulate macrophages that are alternatively activated due to a chronically pathogenic environment. C-reactive protein may inhibit macrophage transformation to the M2 phenotype [56]. Thioredoxin-1 and adiponectin also promote anti-inflammatory macrophages of the M2 phenotype [57,58]. Macrophage activation inhibitors could include drugs that alter macrophage-signaling pathways and directly treat diseases where infiltrating macrophages contribute to their progression [59,60]. Peroxisome proliferator-activated receptors(PPAR) are ligand-activated factors that that play a role in oxidative stress [61], control lipid and glucose metabolism [62], as well as the inflammatory response [63,64]. Targeted inhibition of the enzyme MLK3 has been presented as a strategy to reverse HAND and rebuild synaptic architecture [65]. A novel candidate drug called PA300 was recently described that decreases the number of activated macrophages in the hearts of macaques with cardiac disease [66]. These approaches are being considered because it is clear that even when T-cell levels and viral loads are controlled, many people infected with HIV-1 may develop potentially deadly pathologies that are less common in those uninfected with HIV-1. The ability to modify macrophage activation states has great potential to alter the course of HIV-1 disease in those on cART.

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