Main Consequences of Human Immunodeficiency Virus Infection

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Human immunodeficiency virus (HIV) types 1 and 2 (HIV-1 and HIV-2, respectively) are the causative agents of acquired immunodeficiency syndrome (AIDS). At the end of 2021, an estimated 38.4 million people were infected with HIV (mainly HIV-1), which has claimed 40.1 million lives since the beginning of the AIDS pandemic. Even in the presence of highly active and multi-target antiretroviral drugs, HIV resists eradication. More importantly, through the direct induction of CD4+ lymphocyte depletion and the establishment of a chronic inflammatory environment, HIV infection is the primary driver of premature immune senescence and exhaustion, creating a series of deleterious conditions that enable the proliferation and decontrol of multiple pathogens, the development of tumors, and the onset of other non-AIDS comorbidities such as neurocognitive disorders and cardiovascular disease.

HIV immunodeficiency inflammation co-morbidities

1. Introduction

HIV is mainly transmitted through unprotected vaginal, anal, and oral sex. HIV can also be transmitted by blood transfusion, the sharing of contaminated needles, and vertical transmission from an infected and untreated mother to her child during pregnancy, childbirth, and breastfeeding. Following HIV transmission through the sexual mucosa, viral spread occurs through draining lymph nodes and the bloodstream, allowing viral infection to spread to multiple compartments of the body, namely the brain, lungs, and gut-associated lymphoid tissue (GALT) [1].

The pathogenesis of HIV infection is based on three interrelated events: (i) the ability to infect T- CD4+ lymphocytes and macrophages, which is determined by the expression of the HIV cell receptor CD4 [2][3], and a member of the chemokine receptor family acting as a co-receptor, namely, CCR5, CXCR4, or other alternative receptors [4][5]; (ii) the establishment of latently infected cells harbouring the HIV genome integrated into the chromosomal DNA of the cell [6]; and (iii) the induction of immune hyperactivation throughout infection, leading to accelerated immune senescence [7]. These three features have both local and systemic consequences, leading to lifelong infection, irreversible CD4+ T lymphocyte depletion and dysfunction, and immune senescence and exhaustion.

2. HIV as a Cytopathic Retrovirus

T-CD4+ lymphocytes and macrophages are the major target cells for HIV infection and replication *in vivo*. Although infection of the latter is characteristically non-cytopathic, allowing for the survival of infected macrophages with low levels of virus production throughout the cell's life [8], infection of T-CD4+ lymphocytes invariably leads to their destruction and to an irreversible depletion of this crucial immune cell population [9]. This depletion is observed in the peripheral blood, as reflected by a decrease in circulating T-CD4+ lymphocytes [10], but it has also been documented in mucosa-associated lymphoid tissues, such as GALT [11][12].

One of the key questions in HIV pathogenesis concerns how CD4+ T lymphocytes die during HIV infection. One of the processes involved is the apoptosis of infected and bystander non-infected cells [13][14]. The death of non-infected bystander cells involves multiple mechanisms and players and includes the activation of host cell pathways (e.g., FAS ligand, TNF-α, TRAIL) that induce apoptotic events [13][15][16], and the effect of viral proteins released from infected cells that induce bystander cell death, such as Nef, Tat, Vpr, or Vpu [17][18][19][20][21].

In addition to apoptotic mechanisms, HIV contributes to CD4+ T lymphocyte depletion by the induction of pyroptosis in non-permissive CD4+ T lymphocytes [22] (discussed in more detail bellow), and by direct cytopathic effects through the formation of syncytia, particularly in lymphoid tissues [23][24][25].

3. Establishment of Latently Infected Cells

One of the most important features of the HIV life cycle in an infected human host is resistance to eradication, even in the presence of highly active and multi-target antiretroviral drugs. In addition, when antiretroviral therapy (ART) is stopped, HIV viremia that was suppressed and undetectable during ART rebounds and returns to pre-ART levels.

This inability to cure HIV infection has been the subject of intense research and is based on HIV's ability to infect cells that act as cellular reservoirs in multiple body compartments. These cells are latently infected, as defined by the absence of viral production, and consist mainly of memory CD4+ T lymphocytes, monocytes, and macrophages.

The establishment of latency is one of the strategies used by HIV to persist in infected hosts; it results from the HIV replication cycle, in which viral double-stranded DNA is retrotranscribed from genomic RNA. Under certain circumstances, this proviral DNA can be maintained in a non- transcriptional state so that HIV antigens are not expressed, and infected cells cannot be detected and targeted for a cytolytic lymphocyte response.

There are two types of latency: pre-integration latency and post-integration latency. Pre- integration latency is defined by the presence of complete or incomplete forms of viral double- stranded DNA that are not integrated into the cellular chromosomes. It appears to be quite common and occurs in resting CD4+ T lymphocytes [26][27][28][29]. However, the pre-integrated form of viral DNA in resting CD4+ T lymphocytes appears to be labile and short-lived, with a half- life of approximately one day [28], although other reports have found a longer lifespan of one week [30].

Post-integration latency in memory CD4+ T lymphocytes is considered the true latency state responsible for the lifelong persistence of HIV in an infected host. It is established after the integration step of the retroviral replication cycle and relies on the complete silencing of proviral transcription. The mechanisms underlying this non-transcriptional state include the epigenetic regulation of proviral transcription and post-transcriptional regulation (reviewed in [31]). Furthermore, it has been noted that the survival of latently infected CD4+ T lymphocytes in patients on long-term ART regimens depends not only on HIV gene silencing, but also on high expression levels of immune checkpoint molecules that negatively regulate T lymphocyte immune function [32][33][34][35][36].

In addition to CD4+ T lymphocytes, cells of the monocyte/macrophage lineage are also susceptible to HIV infection soon after transmission through genital and anorectal mucosa [37]. This susceptibility includes both those viruses that enter the cells through engagement of the CD4 and CCR5 chemokine receptors (R5 viruses) and those that use the CD4 and CXCR4 chemokine receptors (X4 viruses) [38][39][40]. This cell group includes peripheral blood monocytes, tissue macrophages, dendritic cells, and Langerhans cells.

Due to their functions as antigen-presenting cells and their ability to be recruited to sites of infection and inflammation, HIV-infected macrophages have been detected in several tissues and mucosa. In addition, HIV infection in macrophages is non-cytopathic, allowing for the survival of infected macrophages with low levels of virus production throughout the cell's life [8]. Taken together, these features contribute to the establishment of a latently infected, low-level virus- producing cell population that is responsible for the creation of body sanctuaries where HIV persistence can be maintained for extended periods of time, ensuring long-term virus production even in patients on ART [41]. These HIV sanctuaries have been identified in several body compartments, including the brain, lungs, semen, urethra, liver, and several lymphoid tissues such as GALT [41].

4. Induction of Chronic Inflammation

Persistent systemic inflammation is considered one of the signatures of HIV infection and is observed even in patients on ART and with sustained suppressed viremia. Defined as the continuous (even low-level) production of pro-inflammatory cytokines and other soluble factors over long periods of time (e.g., IL-6, IL-8, which is also known as CXCL8, CCL2, which is also known as MCP-1, CCL3, CXCL10, which is also known as IP-10, IFNγ, and sCD14), chronic inflammation is responsible for severe tissue damage and an increased risk of non-AIDS comorbidities (cardiovascular disease, cancer, renal disease, neurocognitive disorders, and liver disease) and mortality [42]. These abnormally persistent and pathological levels of inflammation are multifactorial and mainly result from the direct effects of HIV-induced immune activation and from GALT-associated CD4+ lymphocyte depletion, leading to microbial translocation.

Several factors contribute to the chronic inflammation that is directly associated with HIV infection. Some originate from HIV proteins such as Nef and Vpr, which trigger immune activation [43][44]. In the case of the Nef protein, its effects may be systemic, as Nef-containing exosomes have been detected in plasma even in patients with suppressed viremia, exerting distinct effects on cells that ultimately lead to inflammation [43]. Other factors arise from the detection of viral nucleic acid by pattern recognition receptors (PRRs) during the HIV replication cycle.

Both RNA and dsDNA, as well as viral proteins, are detected by PRRs [45]. HIV RNA molecules are mainly detected by retinoic acid-inducible gene I (RIG-I), while dsDNA is detected by cyclic GMP-AMP synthase (cGAS) and interferon-gamma-inducible protein 16 (IFI16), the latter playing an important role in the detection of incompletely retrotranscribed viral DNA, leading to caspase-1 activation and pyroptosis [22]. The accumulation of these incomplete viral DNA molecules is the result of an abortive replication cycle that occurs in non-activated T-CD4+ lymphocytes. Considering that 95% of the total population of T-CD4+ lymphocytes do not allow for a productive replication cycle, and are thus prone to accumulate incomplete DNA retrotranscripts, pyroptosis is not only the main pathway of cell death but also has additional consequences in the induction of potent pro-inflammatory signals [46].

Extensive damage to the intestinal mucosa is another key driver of the pathogenic chronic inflammatory response observed during HIV infection. Soon after transmission, HIV spreads to the GALT and irreversibly destroys a large proportion of mucosal-associated CD4+ T lymphocytes [11], particularly the T helper 17 (Th17) subset, which plays a critical role in promoting mucosal defence against microorganisms and barrier integrity [47]. This injury occurs during the acute phase of HIV infection, and, in contrast to the observed partial recovery of peripheral blood CD4+ T lymphocyte counts, the depletion of GALT resident cells is not reversed; this leads to mucosal dysfunction, which in turn leads to microbial translocation [48]. In fact, intestinal mucosal dysfunction allows microbes and microbial by-products from the intestinal lumen to invade the surrounding tissues and the bloodstream and also contributes to mucosal dysbiosis, which is defined as the unbalanced composition of the gut microbiota. In turn, this microbial translocation and associated dysbiosis promotes mucosal injury, further expanding and self-perpetuating HIV-induced inflammation both locally and systemically, clearly distinguishing HIV infection of human hosts from SIV infection in African non-human primates [49].

In addition, microbial translocation from the intestinal lumen into the bloodstream, as evidenced by elevated plasma levels of lipopolysaccharide (LPS), provides an additional layer of inflammatory induction [50]. LPS is a major component of the outer membrane of a significant number of Gram-negative bacteria and of some Gram-positive bacteria. LPS is sensed by Toll-like receptor 4 (TLR4), one of the PRRs present in the cell membrane, and its activation leads to intracellular signalling through NF-κB, which culminates with the production of inflammatory cytokines [51].

In conclusion, HIV infection is responsible for several direct and indirect mechanisms that lead to immune dysfunction and chronic inflammation, both local and systemic. This in turn leads to accelerated immune senescence and ageing, referred to as “inflammmageing” [52]. This scenario creates a series of deleterious factors that allow for the amplification and decontrol of several pathogens, particularly those that latently infect HIV-infected individuals, the most notable of which is *Mycobacterium tuberculosis*.

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