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Review Article

Parameters Determining the Final Aids Phase are Dictated by the Dynamics of Early Evolution and Establishment of Specifically Latent Hiv-1 Infection

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Abstract

Dynamics of final resolution of an HIV-1 infection within the individual patient and within whole susceptible populations to such infection render unattainable the eradication of persistent multiple foci of latent infection by the HIV-1 within such organs as draining lymph nodes and the gut-associated lymphoid tissues. The further participation of multiple strains of HIV-1 that tend to emerge indicates the modulated mutations of the infecting HIV-1 that adapts itself to evasion from immune effector cells. The evolving depletion of the CD4+ T lymphocytes and of other CD4 receptor bearing cells dominates the stereotyped formulations of the disease course in a manner specifically characterizing the profile-depleted state of the AIDS phase. Paramount dynamics for further persistence of latently infected tissues and organs come to operatively dictate the clinical and pathogenic attributes of the early transmission and establishment of HIV-1 infection; these operate not only in the individual patient, but also within whole populations of susceptible individuals ranging from intravenous drug addicts, homosexuals, heterosexuals and regional groups of endemic infection by the HIV-1 organism.

Key words: Human immunodeficiency virus; Acquired Immune deficiency syndrome; viral latency; Tuberculosis.

Introduction

There has been a progressive increase in the world-wide incidence of the HIV-1 pandemic and attempts at developing an effective vaccine have so far proved disappointing. Some 40 million individuals are estimated to be infected by HIV-1. Devastating infection with the human immuno-deficiency virus-1 (HIV-1) depends especially on the creation of latency of the infection in many pools of cells, including, in particular, CD4+ receptor-bearing cells of the monocyte-macrophage lineage. Blood transcriptional signatures are promising for tuberculosis detection clinically [1]. In such manner, reactivation of latent viral forms in dentritic cells of the lymphoid germinal centers, microglia, circulating monocytes and fixed tissue macrophages presents a powerful and progressive source for persistent depletion of CD4+ T lymphocytes throughout the body, including within blood and secretions.

Antiretroviral therapy is ineffective against integrated proviruses [2]. "Shock and kill" strategy is intended to eradicate latent HIV by reactivating provirus in the context of combined anti-retroviral drug administration [3,4]. Residual inflammation during Anti-Retroviral Therapy (ART) is probably critically involved in HIV persistence [5]. The HIV testing rate in the absence of previous positive test is an important parameter of public health [6].

The mechanisms governing viral latency are highly complex [7]. The gut-associated lymphoid tissue is a particularly important source of persistent exposure of the body to infectious HIV-1 viral particles. The whole series of progressive disease-associated changes are embedded within the gut-related lymphoid tissue in a manner that renders the alimentary tract a prominent source and specific contributor towards both reactivation and proliferation of new HIV-1 particles throughout much of the course of the infection leading directly to AIDS. Infection with HIV is an important risk factor for tuberculosis [8]. Also, substance-abusing sexual minorities require attention as they are at elevated risk for HIV, but are a heterogeneous risk group [9]. Community sexual bridging probably affects socio-geographic distribution of heterosexually transmitted HIV [10].

Bone Marrow Suppression

The concurrent suppression of lymphopoiesis and bone marrow stem cells prevents the replacement of the CD4+ T lymphocytes that eventually become severely depleted. In addition, there is also destruction of other elements of the lymph node architecture affecting stromal cells and other nodal tissue components. The decreased T-lymphocyte cell count per micro liter of peripheral blood correlates directly with progression of the HIV-1 infection.

Latency phenomena of HIV-1 infection further constitute the incorporation of a broad range of antigenic-specific proviral forms within the host cell genome, not only within a particular regional population of infected patients, but also within the single infected individual. The efficacy of currently used agents in a "shock and kill" strategy to actively integrated provirus has remained disappointing [11]. Individuals who present with more recent HIV

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infection have significantly lower virus reservoirs, and combined ART tends to decrease their reservoirs to a greater extent [12]. Infected macrophages in the central nervous system harbor viral subpopulations that play a key role in the emergence of escape HIV variants and in viral rebound following discontinuation of antiretroviral therapy [13].

The biology of multiple antigenically specific forms of the virus appears to arise as the infection within a given individual progresses, in spite of the initially often limited antigenic variants of HIV-1 in the early stages of acquisition of the infection.

Latency

Latent infectious particles within multiple cell pools throughout the body implicate the presence of immunologically invisible but infected cell pools. It is thus with reference to such latent infection that HIV-1 that progression to the AIDS phase is almost universal in untreated patients. In fact, therapy with combined anti-retroviral drug regimens fails to eradicate latent virally infected cell pools that subsequently usually may be re-activated. There has been rapid development of multi-drug-resistant HIV strains, poor bioavailability, and cumulative toxicities, with a need for alternative strategies for antiretroviral drug discovery and drugs with novel action models or targets [14].

Parameters of CD8+ T cells are central to a potential attack on virally infected cells, including also the recruitment of natural killer cells and stem cells from the bone marrow. Indices of activation of CD8+ T cells correlate closely with activity of HIV-1 infection. Particularly significant is the early diagnosis of HIV-1 infection in the potential control of the proliferating viral particles that becomes prominent in 2-3 weeks after exposure to the HIV-1 organisms. There is evidence that early anti-retroviral therapy may more effectively control the disease course.

Co-Infections

Significant is co-infection with the Mycobacterium tuberculosis and with Mycobacterium Avium-Intracellularae complex. Latent tuberculous infection and HIV-coinfection are challenges in the control of tuberculosis transmission [15]. Practically all episodes of tuberculosis disease are preceded by a period of asymptomatic Mycobacterium tuberculosis infection [16]. The whole gamut of opportunistic infections that develops concurrently with the severe depletion of CD4+ T lymphocytes indicates the pathogenetically relevant roles played by a depletion of a broad range of macrophage-related and of antigen-presenting cells throughout the tissues and organs of the body. It is in such manner that the persistence of HIV-1 infection is superimposed on reactivation phases throughout the disease course, with progressive depletion of immune-competent cell components. Transcriptional gene silencing by short interfering RNA may mimic epigenetic changes associated with HIV-1 latency [17].

Biology in pathogenesis of HIV-1 infection, therefore, centers on the integration of the proviral forms within the genome of the host cells. The whole plethora of events that follow attachment of the viral particle to the CD4+ receptor and viral entry within the cell are related to such integration of the provirus that, in turn, promotes reverse transcription of the viral RNA genome to complementary DNA.

Latent HIV-1 might be activated by Tumor-Necrosis Factor-alpha released by cells, upon ingestion of exosomes released by infected cells; this may be relevant for designing new therapeutic interventions focusing on HIV eradication [18]. The interactions between virus and host cells, as seen also with viral-protease and host-cell protease activities, are primarily responsible to the creation of persistently latent forms of infection in a manner that allows the subsequent propagation of the infected host cells.

Proliferation and Spread

Dimensions of proliferation of the HIV-1 particles are coupled with spread throughout the body and are reflected especially within the circulating blood. Activating HIV-1 proviruses in latent reservoirs combined with inhibition of viral spread might be an effective therapeutic strategy. However, specific delivery of drugs into cells latently infected with HIV and without the use of viral vectors is critically required [19]. The terms of reference include the persistent activation of the immune system and the surveillance activities of lymphocytes and macrophages that promote, paradoxically the institution of immuno-senescence and depletion.

Further dynamics are especially integral to the subsequent emergence of AIDS with also of opportunistic infections and related malignancies such as Kaposi sarcoma and non-Hodgkins' lymphoma. Host protein biomarkers may help identify active tuberculosis in HIV-infected and non-infected patients [20].

Viral Load

The size of the HIV-1 viral load increases the likelihood of transmission of the infection and also increases the progressiveness of the proliferation of the viral particles. The severity of the inflammatory reaction, as evident especially with relation to the genital portal of exposure, increases the number of cells that become infected with the HIV-1 virus. The pivotal roles of the CD4+T cells in centrally modulating the immune response to the infection render susceptible the whole immune system, with progressive depletion of this cell subset. Latent reservoirs of reactivation-competent HIV virus are a major barrier to cure and may not be susceptible to either viral cytopathic or CD8 (+) T-cell-mediated mechanisms [21]. HIV infects multipotent hematopoietic progenitor cells with the creation of latent reservoirs, and the disturbance of bone marrow microenvironment and immune dysregulation [22].

The release of soluble gp120 envelope protein leads to binding to the CD4+ receptor even in the absence of host-cell infection by the intact virus; such binding renders this receptor incapable of immune modulation of the defence response. The broad range of depletive phenomena in immune-competent components leads to a progressiveness of the infection in its own right. It is to be emphasized that cellular microRNAs play an important role in regulating HIV-1 latency [23]. ncRNAs, specifically short

interfering (si)RNA and short hairpin (sh)RNA, target molecular mechanisms of HIV-1 transcription [24].

Co-infections by other organisms such as herpes simplex virus, hepatitis B and C, cytomegalovirus, HTLV-1 and HTLV-2, cooperatively operate to further affect the immune system as a whole, and do not appear to significantly mitigate against infection by the HIV-1. The AIDS phase of the HIV-1 infection is hence a uniformly occurring late phase in the infected host that is not eradicated with combined anti-retroviral therapy.

Limiting dilution assays are often employed to measure infection extent, and in HIV-infected patients, represent an essential mode of studying latency and, potentially, of curative strategies [25].

Significant to such parameters of progressive infection is the systemic encroachment and infection of tissues by micro-organisms from the gut. These further promoted effects are constitutive source for the emergence of multi-organism infection in terms of a large variety of infectious agents that compound both the proliferative and latent components of the HIV-1 infection. Epigenetic mechanisms including histone post-translational acetylation and methylation and DNA methylation of the proviral DNA and microRNAs are implicated in HIV-1 latency [26].

Aids Pandemic

The AIDS-related neoplasms such as Kaposi sarcoma and non-Hodgkins' lymphomas are disease-defining lesions in a manner that are suggestive of near-uniform evolutionary susceptibility to progression of the immune impairment in the host. With reference also to such lesions as hepatic- and nephro-toxicity, it is evident that template rigidity in outcome dynamics of the HIV-infected host leads to an AIDS phase that has resulted in the permanent depletion of multiple components of the immune system besides CD4+ T lymphocytes. Eradication of HIV infection necessitates identification of all cellular reservoirs that harbor latent virus infection [27].

The JAK-STAT pathway is central to HIV-1 transcription, together with NF-kB, JNK and ERK1/2 that may have complementary roles in reversal of HIV-1 latency [28]. Permanent immuno-senescence indicates the severe depletion of lymphoid progenitor cells and of stem cells in hematopoietic tissues such as the bone marrow. Hence, no reconstitution of the immune system, short of stem cell transplantation, is possible in AIDS patients.

Concluding Remarks

It is evident that the latency potentialities of HIV-1 infection are centrally- operative effector mechanisms in the subsequent multi-step re-activation of the HIV-1 infection in a manner that specifically dictates the dynamics of emergence and establishment of the AIDS phase in these patients. The central nervous system, in particular, proves a site for HIV persistence capable of reseeding the periphery [29]. Long-standing activation, on the other hand, of the immune surveillance of the host generally fails to eradicate the HIV-1 infection and leads directly to immune exhaustion. It is in terms of immuno-senescence that the AIDS phase proves usually an inevitable outcome of persistent HIV-1 infection. Quantifying latently infected cells is essential for determination of efficacy of therapeutic strategies [30].

Parameters for further homeostatic mechanisms in establishment and spread of the HIV-1 infection are therefore modulators for dynamics of progression in terms of such cooperatively inducing exhaustion of the immune system. In particular, the dual infection with both HIV-1 and Mycobacterium tuberculosis is devastating with interactive progression of both forms of infection within the individual patient.

Most deaths in untreated patients with HIV-1 infection are due to opportunistic infections, the commonest being Pneumocystis pneumonia. Other parameters of combined highly active anti-retroviral therapy also fail to eradicate completely the HIV-1 infection, although there is controlled decrease in the occurrence of opportunistic infections in these patients.

The interactions between HIV-1 and the host cells have proved to be extremely complex. The use of cytopathic mechanisms to control the viral infection has targeted in particular the tropism of HIV-1 for CD4+ cells, particularly in view of the currently ineffective methods of induction of a specific or broad antibody response by vaccination.

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