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HIV-1 Primarily Targets the Innate Immune System and Only Secondarily Modulates Adaptive Immune Cell Depletion

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ABSTRACT

Persistence of HIV-1 infection allows for permissive microenvironmental conditioning in terms of contextual innate immune participation. The progression of host cell injury constitutes an additional parametric formulation in self-amplifying modulation of the adaptive immune response in a manner that inclusively promotes the emergence of a final stage of AIDS that is both depletive and permissive for opportunistic infections and various forms of neoplasia. It is within contextual indices of promotion of depleted T-helper lymphocytes and of augmented viremic loads that manifesttations of classic lesions emerge as the AIDS phenomenon. It is further to be realized that an apoptotic response of multiple cell subtypes including T-lymphocytes includes host-cell participation within formulated settings of further persistence of the retroviral infection. An all-inclusive phenomenon of dendritic cell-lymphocyte synapse formulation corresponds to the establishment of HIV-1 infection that specifically conditions all subsequent stages in depletion of the injured host cells regardless of the dynamics or kinetics of the retroviral replicative infectious process itself.

Keywords: HIV-1; Infection; Aids; Immune; Persistence

1. Introduction

HIV-1 infection is inherently a progressive disorder that is especially productive of a chronic participation of injury to CD4+ T-lymphocytes within additional contextual conditioning of the AIDS phenomenon. This inherently progressive infection is suggestive in itself of a profound involvement of the innate immune system in particular. Interferon lamba 3 activates the innate immune system through the JAK-STAT pathway in macrophages. It inhibits HIV-1 replication in these cells and induces many antiviral cellular factors and interferon regulatory mediators [1]. Plasmacytoid dendritic cells serve as an essential link between innate and adaptive immune systems; the fate of these cells in HIV-1 infection is unclear [2]. The realization of monocyte/macrophage participation in the accumulation of the HIV-1 virions indicates the essential character of an infection that arises primarily from innate immune defects. Macrophages and their monocyte precursors show marked heterogeneity and may be either proinflammatory or alternatively activated [3].

The ongoing development of infection to multiple hematopoietic cell lineages is a highly prominent feature of injury that is ultimately the criterion for the ensuing infection that is manifested primarily as acquired immune deficiency. CNS opportunistic infections vary according to HIV induced defects of innate immunity versus abnormal adaptive immunity [4].

The emergence of cellular injury therefore constitutes the establishment of multi-lineage cellular injury that is productive of the progressive nature to the AIDS pandemic. B lymphocyte abnormalities precede CD4(+) T cell decline [5].

2. Cascade Events

The closely parallel involvement of systems of cascade signalling in HIV-1 infected cell lines correlates especially with the recombinant HIV-1 virion variants that establish themselves in the circulating blood of persistently infected individuals. The further emergence of highly characteristic opportunistic infections and also especially of different forms of neoplasia are further promotional events in the establishment of progression as the main pathogenic mechanisms leading to the AIDS process. Chronic immune activation appears to result from untimely innate immune responses and is believed to be implicated in dynamics of emergence of AIDS in HIV-1 infected individuals [6].

Indications of non-resolution of the HIV-1 infection arise as perpetuating involvement by a virion that is relatively slowly replicative but that is capable of exquisite evasion of the immune system. HIV-1 Nef appears important in HIV-1 transmission by dendritic cells to activated CD4(+) T cells [7]. Vpu promotes suppression of innate immunity and counteracts natural killer cells by interfering with CD1d expression and antigen presentation; it also suppresses expression of NK-T and B cell antigen [8].

Recombinant variants of this retrovirus indicate the enormous capability for adaptability to a changing microenvironment in terms of the further participation of injury to multiple cell types. In this regard, the essential representation of the infectious process is closely allied to a formulated recombination of multiple sero-strains as further evidenced by subtypes of the HIV-1 virion M, O and N, and by the subtypes of the M variant itself.

3. HIV-1 Progression

Indications of realization of HIV-1 progression appear to arise primarily as a consequence of chemokine and cytokine pathobiology as relative especially to coreceptors to the CD4+ receptor. IL-7 effectively protects the CD4(+) T cell pool during acute SIV infection in macaques [9]. The attributes of complicating neoplastic lesions in these patients are closely formulated consequences of the prolonged persistence of a dual coinfection by both HIV-1 and accompanying oncogenic viruses such as human herpes virus-8, Ebstein-Barr virus and human papilloma virus subtypes.

In such manner, proportional accumulation of HIV-1 virions within persistently infected host cells correlates with the emergence of depletion of the CD4+ T lymphocytes and of the increasing circulating viremic load.

Macrophages are essentially implicated in HIV-1 infection, viral rebound and clinical emergence of AIDS [10]. Glutathione-enhanced natural killer cells tend to suppress mycobacterial tuberculosis infection within human monocytes [11].

Establishment of the HIV-1 infection arises as a main consequence of an activation phenomenon that affects both T and B lymphocytes. In such manner, the conesquential attributes of recombinant subtypes of coinfecting HIV-1 virions indicate a prominent derived character for persistence towards the development of a profound immune deficiency.

The latter phenomenon is itself a source for sequential transformation of cells towards malignant neoplastic emergence. Vpu (viral protein U) may have evolved as a promoter of human-to-human HIV-1 transmission due to an interplay between viral factors versus host restriction factors [12].

4. Disease Setting

The whole setting of attributes of HIV-1 infection is conclusive parameter for the induction of further cellular injury that primarily includes depletion of lymphocyte subsets without in fact direct overwhelming infection of such lymphocytes. In such manner, profound immune cell depletion is a complex evolution involving bystander effect and also the induction of apoptosis of multiple cell-subtypes. Premature immunosenescence of the innate immune system may be mediated by chronic endotoxemia, residual viremia, telomere attrition and altered cellular signalling [13].

Inflammation is an exquisite setting for the production of cellular injury in AIDS infections in a further contextual setting of persistent HIV-1 infection. Leukotrienes influence microglial infection and may partly control viral load in the central nervous system [14]. It is with regard to a multiplicity of steps in the production of new retroviral virions that a whole panorama of adaptive change involves an inflammatory response to the viral infection and to the persistent process of immune deficiency state leading generally to the AIDS process.

Activation of lymphocytes characterizes the early stages of HIV-1 infection with the profound incorporation of replicative viral activity especially within monocytes/macrophages. Type I interferon response by the innate immune system is produced by plasmacytoid dendritic cells and appears to control HIV-1 productive infection and disease progression [15].

Formulated patterns include the emergence of systematic processes of integration of the cDNA of the HIV-1 genome in manners that implicate insertional mutagenesis. The further confounding chemokine and cytokine accompaniments by such factors as activation of the viral reverse transcriptase indicate an overall close homology of virion capability towards host-cell components as further evidenced by the persistent articulation of cellular injury to CD4+ T helper lymphocytes.

5. Viremia

High levels of viremia in the establishment of the infectious process reflect an adherence of patterned formulation within pathways and cascades that include a prominent paracrine microenvironmental effect. The innate immune response appears a critical factor in initial HIV transmission and dissemination, implicating type I interferon, defensins and whey acidic proteins [16]. Enhanced IL-2 production and improved proliferation of CD4 T helper cells are restricted to viremic individuals. When regulatory T cells are depleted from circulating monocytes in viremic patients, IL-10 production decreases and proinflammatory cytokines increase [17]. In this regard the participation of multiple cellular lineages collaborates

with the involvement of multiple cell-signaling pathways that promote adaptive potentiality towards the host cell that is infected. Homology of genomic components of the virion correlates with the adoption of multiple parameters that belie a single main pathogenic mechanism in reaching establishing persistence of the HIV-1 infection.

6. Activation

It is in terms of adherence of host-cell response as activtion mechanisms that promote a realization of cellular injury that there is included widespread apoptosis of T helper lymphocytes.

Correlates of a promotional nature that are mainly characterized by a marked activation of lymphocyte subsets include the formulation for further persistence of cell injury within contextual reproduction of multiple prominent lineage participations. Plasmacytoid dendritic cells possibly enable HIV-1 elite controllers to control HIV-1 viremia [18]. Activated nervous system mononuclear phagocytes and astrocytes expressing HIV-1 gene products in specific patterns may promote neurodegeneration [19]. It is in a microenvironmentally conditioned inflammatory response that parameters of spread of the HIV-1 virus include the evolution of viral resistance to various drug treatment protocols that is commonly seen in patients treated with anti-retroviral therapy.

Included participation of multiple cell-type infection in HIV-1 phases of evolution allow for the development of specific regulatory disorders that incorporate the persistent infection. Intrinsic antiviral immunity tends to restrict infection by blocking viral replication directly in an immediate manner [20]. Replicative activity of the retrovirus is accompanied by a very high mutability that self-promotes the ensuing infection as productive of the AIDS stage of infection.

7. Aids Phase

In terms of such ongoing participation of cellular injury in the creation of a conducive setting for persistence of the HIV-1 infection, it is a dual involvement of inflammatory reactivity with the emergence of subsequent severe immune deficiency that permits evolution of patterns of modulated participation of such cellular injury to lymphocyte depletion and AIDS phase establishment. Toll-like receptors as innate immune components induce activation of NF-kappaB that in turn promotes HIV-1 replication [21]. Humanized mice are optimal for studying HIV-1 immunopathogenesis and for the development of novel immune-based therapies [22].

Indicative inclusion of mutability would allow for the acquisition of a capability for pronounced depletion of immune cells as these relate particularly to impaired expression of human histocompatibility antigens. The dendritic cells in particular appear a primal form of patterned involvement in patients infected with HIV-1. It is in terms of augmented activation of immune cells on the one hand and of impaired resolution of the cellular injury that inflammatory microenvironmental paracrine effect further promotes the emergence of injury to lymph nodes and gastrointestinal associated lymphoid tissue. Fibrosis accompanies a severely progressive lymphocytic depletion in modes of further involvement of the innate immune system in particular. Dendritic cells are participants in the production of spread of the HIV-1 infection as evidenced by monocytes/macrophages that accumulate highly replicative sites for the retrovirus.

Polymorphisms of innate immune genes affecting Toll-like receptors and defensins modulate progression of HIV-1 infection in children [23]. Inclusion dynamics of the virion particles promote establishment of integrated viral genomes within host-cell genomes as indicated by the elaborate phases of entry and attachment to the cell membrane, the reverse transcription of the viral RNA genome and the formulation of transport of viral components from the nucleus to the cytoplasm and plasmalemma. CD4 binding site directed inhibitors (monoclonal antibodies) act preferentially by blocking free virus transmission while still allowing HIV-1 to spread through cell-cell contacts [24].

The failure to recognize a single essential pathogenic step in HIV-1 infection is symptomatic of a variety of inducing environments that promote the production of further attributes of the overall persistence of the viral replication and release. The neutralizing antibody constant domain functionally links innate and adaptive immune systems to harness innate immune response [25]. In primary HIV-1 infection there develops dysfunction of dendritic cells and this is independent of interaction with gp120 [26].

8. Micro-Environment

Inclusive formulations of multiple component pathways are irreducible parameters in the development of such micro-environmental conditioning.

In such terms, inclusive forces such as pressure-induced mutability of the HIV-1 genome, including such factors as anti-retroviral drug therapy, affect the pathobiologic attributes of the AIDS syndrome phase. Within a range phenomenon of inclusive parameters, the HIV-1 infection arises largely as an integral component of the micro-environmental milieu of inflammation and of evolving immune deficiency. Autophagy is increasingly being implicated in pattern recognition paradigms affecting innate immunity [27].

TRIM5 as a restriction factor may indicate how the innate immune system detects distinct molecular features of HIV-1 [28].

Promotional attributes of cohesive participating roles in such micro-environmental conditioning indicates that HIV-1 is a privileged infectious agent that creates and modulates multiple facets of inclusive formulation that are directed primarily in the creation of recombinant forms of the virion in the individual patient with AIDS. It is further to be noted that the innate immune system involvement accounts for the establishment of multiple facets of involvement as coreceptivity as promoted by disordered chemokine and cytokine biology. Host invasion and viral replication appear orchestrated by Nef actions in macrophages including receptor expression, intracellular signalling and production of mediators of inflammation [29].

Of particular relevance is the dendritic cell-lymphocyte/macrophage synapse in infectious modes of modulated effect leading to a process of accumulation relevant towards the ongoing persistence of the infection by HIV-1 virus. Virological synapses between infected dendritic/T lymphocytes and uninfected T cells may very well prove the dominant mode of HIV-1 spread [30]. The attributes of activation of lymphocytes are clearly also a modulation step in the evolution of the retroviral infection as an established persistence of further induction in microenvironmental conditioning. The emergence of multiple forms of neoplasia in the AIDS patient is suggestive also of endothelial cell participation, particularly within a setting of augmenting viremic levels that circulate in the peripheral blood.

9. Redistribution

An inclusively overall parameteric redistribution of the HIV-1 virions accounts for the promotional persistence as evidenced by a clinical setting of multiple forms of opportunistic infection and of neoplastic lesions including Kaposi sarcoma, non-Hodgkin lymphoma, and cervical carcinoma. In such terms, implication of further evolving pathogenesis allows a permissive environment that conditions also the profound immune deficiency. In effective terms, the whole integrative phenomenon of persistent HIV-1 infection is a parent process of subsequent derivative pathways of essential amplifying proportions.

Inflammasome genes are implicated in susceptibility to HIV-1 infection [31]. The processes of derivative parameters are all-inclusive formulations that essentially modulate the innate immune pathways as primary constitutive targets of HIV-1 rather than as a primary infection of T lymphocytes per se. It is with reference to multiple inducible pathways of reproduction that macrophages, natural killer cells and dendritic cells promote a setting of modulated permissiveness that contributes directly to the establishment of the persistent nature of the HIV-1 infection. Strong antibody mediated activation of Natural Killer cells to HIV-1 Env occurs in persistent HIV-1 infection [32].

Apoptosis may be viewed as an essential reflection of such amplifying microenvironmental conditioning with regard to secondary acquisition of the T helper lymphocyte depletion.

Activation of both T and B lymphocytes appears a correlative phenomenon in itself that demarcates potentiality for persistence of the retroviral infection. A promotional accumulative viral load empowers the emergence of persistent viral infection, regardless of the degree of viral particle replication within specific cellular or immune cellular subsets. HIV-1 is able to productively infect nondividing cells as well as dividing cells at interphase by actively delivering its DNA into the nucleus by means of host nuclear import machinery [33].

Replicative activity of host cells correlates with viral replication formulas and promotes the microenvironmental conditioning that harbors further potential nonresolution of cell injury of virally infected host cells.

Redistribution of lymphocytes and also of other cell-types such as dendritic cells promotes a systemically promotional effect to HIV-1 infection as also noted with regard to the AIDS phase of infection.

10. Concluding Remarks

Parameters of induction and non-resolution of HIV-1 infection indicate an exquisite acquisition of a self-amplifying range of potentialities that specifically indicate a primary all-embracing involvement of the innate immune system; this responds by implicating in secondary fashion a pathobiologic activation of the adaptive immune response.

Further evolution of the retroviral infection imposes pressure effects on multiple cell subtypes in a manner that implicates cytokine and chemokine modulation within a microenvironmental inflammatory milieu. The apoptosis of host cells is sharply distinct from a dynamoics that solely targets such cells as replicative reservoirs of the HIV-1; this phenomenon is suggestive of a modulation that is specifically both an activating and depletive inclusive formulation of viremic and host-cell co-infectivities.

A systemic redistribution of host cell injury evolves within a contextual representation of multiple cell subtypes ranging from macrophages, dendritic cells, natural killer cells to endothelial cells in inducing persistence of the infection as the one paramount dynamics of HIV-1 involvement of the individual patient progressing to AIDS as a distinct disease phase.

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