

Immune Mediated Containment And The Consequences Of The Human Immunodeficiency Virus Infection

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ABSTRACT

The Human immunodeficiency virus infection is essentially an infection of the immune system, with progressive and profound defects in the cell mediated immune response. The pathogenesis of the Human immunodeficiency virus infection is a multifactorial process, consisting of aberrant cellular activation and the dysregulation of nearly every aspect of the immune system.

The lentivirus subverts the immune system by infecting the CD4+Tcells that normally orchestrate immune responses and by activating the immune system and inducing a cytokine milieu that the virus uses to its own replication advantage. The disease outcome depends on the innate immune response, the adaptive immune response, the host genetic factors and the differences in viral pathogenicity.

Key Words : Human immunodeficiency (HIV) virus, Chemokines, Innate immunity, Adaptive immunity.

MAIN ARTICLE

Acquired immune deficiency syndrome (AIDS), [1] is a condition in which the human immune system begins to fail, leading to life-threatening opportunistic infections. [1] On exposure to the Human immunodeficiency virus (HIV), most individuals develop an early immune response that limits, but does not stop the virus from spreading throughout the body and destroying the host immune defenses. [1] Many recent studies have shed light on some of the potentially important factors of protective immune responses and have provided further insight into the viral kinetics, which determine the immune control, the viral adaptation and the immune escape. [1],[2]

Human immunodeficiency virus type 1 (HIV-1) sequences that pre-date the recognition of AIDS are critical in defining the time of origin and the timescale of the virus evolution. [2] The global HIV epidemic is due to a cross-species infection of humans by a chimpanzee lentivirus, called the simian immunodeficiency virus (SIVcpz), which occurred in West Central Africa.[3] Chimpanzees, are supposed to have acquired the SIVcpz sometime after their divergence into multiple sub-species viz. Pan troglodytes and Pt.schweinfurthii which are naturally infected.[4] SIVcpz is mostly an asymptomatic infection in chimpanzees and the experimental transmission of these viruses to susceptible non-natural hosts results however, in progressive and profound immunodeficiency and Acquired Immune Deficiency Syndrome (AIDS).

Acquired Immune Deficiency Syndrome is defined by the development of serious opportunistic infections, neoplasms, or life threatening manifestations resulting from progressive HIV-induced immunosuppression. AIDS was first recognized in mid-1981, when unusual clusters of Pneumocystis jirovecii pneumonia and Kaposi's sarcoma were reported in young, previously healthy, homosexual men in North America. [5] In 1983, two years after the first reports of AIDS, a cytopathic retrovirus was isolated from persons who were suffering with AIDS and associated conditions such as chronic lymphadenopathy.[6], [7]

MECHANISMS OF HIV TRANSMISSION

Most cases of HIV infections worldwide are the result of sexual transmission across a mucosal surface, but the important modes also include parenteral transmission or transmission from mother to infant. For sexual transmission, the risk of male to male transmission is greater than the risk of heterosexual transmission, and it is highest in persons practicing receptive anal intercourse.[7][8] Other factors that are hypothesized to possibly amplify transmission, include other co-infections (eg, malaria and tuberculosis, sexually transmitted diseases(STD), or in particular, the co-transmission of STD and HIV.[9]

THE IMMUNOLOGY OF HIV INFECTION[10]

HIV induces the dysfunction of nearly all elements of the immune system and the pathogenesis of HIV disease is multifactorial. [10] The immune response against HIV-1 is modulated by multiple host genetic determinants, many of which are directly or indirectly implicated in recognition of the virus [includes chemokine receptors, human leukocyte antigen (HLA), T-cell receptor (TCR), antibodies, Toll-like receptors (TLRs)], immune cell trafficking (includes chemokines and receptors, adhesion molecules), and immune response amplification (includes the molecules which are involved in signaling pathways and in the cytokine genes) [10]. The immune response which is generated by the host and the selection pressure which is exerted on the virus, particularly at the time of early infection, direct the emergence of adaptive escape mutants. Accordingly, some mutations reduce the viral fitness and make it either revert to the wild-type or gradually wane out, whereas others might rescue the virus from host surveillance. [11] Thus, viruses have the ability to adapt and evolve differentially at varying rates in different individuals, depending on their host genetic architecture and their concordance in the immunome. In general, greater the immune concordance between the virus donor and the recipient, the easier it is for the virus to transcend and re-establish itself in the new host.[11-12]

HIV ENTRY AND DISSEMINATION: The first step in HIV and SIV infections involves the interaction between the gp120 and the

CD4+T cells. [11] The two major chemokine co-receptors for HIV/SIV infections are the C-X-C chemokine receptor types 4 and 5 (CXCR4 & CCR5).[12], [13] A number of other chemokine receptors and related proteins can serve as co-receptors for the HIV/SIV fusion and the infection in cultured cells. These include CCR2b, CCR3, CCR8, APJ, Bonzo (STRL33), BOB (GPR15), and US28.[14] The primary function of the viral Env glycoproteins is to promote a fusion reaction between the viral and the target cell membranes. This membrane fusion enables the viral core to gain entry into the host cell cytoplasm.

IMMUNE MEDIATED CONTAINEMENT: Retroviruses possess the ability to convert their single-stranded RNA (ssRNA) genomes into dsDNA during the early stages of the infection process.[15],[16] This reaction is catalysed by the enzyme, reverse transcriptase, in conjunction with its associated ribonuclease (RNAase H) activity. The retroviral genome is packaged into the virion as two copies of ssRNA. [15],[16] A distinguishing feature of the retrovirus replication is the insertion of a DNA copy of the viral genome into the host cell chromosome after reverse transcription. The integrated viral DNA (the provirus) serves as a template for the synthesis of viral RNA and is maintained as a part of the host cell genome for the lifetime of the infected cell. [17] The recovery from many human viral infections is not associated with the eradication of infection, but rather with immune mediated containment. Although HIV infection is associated with progressive and ultimately profound immunosuppression, a highly variable course of disease has been seen among the infected persons. The disease outcome depends on the innate immune response, the adaptive immune response, the host genetic factors and the differences in viral pathogenicity.

INNATE IMMUNE RESPONSES

The initial immune response to HIV involves innate immune mechanisms.

A) DENDRITIC CELLS (DC's): Plasmacytoid dendritic cells (pDCs) are important mediators of innate immunity that act mainly through the secretion of interferon - (IFN-) . [18]DCs are among the first cells to encounter HIV after mucosal exposure and are probably responsible for transporting the virus to the lymphoid organs, thus facilitating the infection of the CD4+T cells and viral dissemination. DCs express several different chemokine receptors that can be used as HIV co-receptors for entry.[18],[19] Beignon et al showed that toll like receptors(TLR) on plasmacytoid dendritic cells(pDCs) are activated by HIV-1 RNA via TLR-7, resulting in high levels of interferon alpha (IFN-) ,interleukin-12, tumour necrosis factor alpha(TNF-), and IL-6(Interleukin-6), which together result in a profound activation of the immune system. [20],[21] These plasmacytoid dendritic cells are also infectable with HIV, and may contribute to impaired dendritic cell functions in infected persons.[22] ; additionally, pDCs have been shown to be severely reduced in number in the peripheral blood of HIV-infected individuals. [18]-[21]

B) NATURAL KILLER CELLS: Natural killer cells (NK) are also a part of the innate immune response to HIV. The presumed role of the Natural killer cells is to provide immunosurveillance against the virus-infected cells, certain tumour cells, and the allogeneic cells. Abnormalities of NK cells are observed throughout the course of the HIV disease and these abnormalities increase with disease progression. NK cells from HIV- infected individuals are defective in their ability to kill typical NK target cells, as well as the gp160-expressing cells. HIV viraemia is inversely correlated with the ability of the Natural killer cells and the NK- derived cell supernatants to suppress virus replication.[23] The abnormality in NK cell lysis

is thought to occur after the binding of the NK cell to its target. [24] Natural killer cells from HIV-infected individuals are able to mediate ADCC (Antibody-Dependent Cell-mediated Cytotoxicity) [25] and are an important source of HIV inhibitory chemokines in HIV- infected individuals. NK cells which are isolated from HIV-infected individuals produce high constitutive levels of Macrophage Inflammatory Protein -1 (MIP -1), Macrophage Inflammatory Protein 1 (MIP -1), and RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted).[26],[27] Thus, NK cells, like CD8+T cells, may inhibit HIV replication by cell- mediated killing, as well as by the secretion of soluble HIV inhibitory factors.

C) NEUTROPHILS: Dysregulation of neutrophil function occurs at all stages of the HIV infection. The oxidative capacity of neutrophils, after priming with the granulocyte-macrophage colony stimulating factor, is also increased in HIV-infected individuals. [27] The opsonising activity of neutrophils is significantly impaired. Neutrophils from AIDS patients undergo apoptosis at an increased rate, as compared with those from the normal controls.[28] The dysfunction of neutrophils in HIV-infected individuals, especially in women, is characterized by an increased incidence and the severity of candida infection, due to a defective non-oxidative killing.[29]

D) MONOCYTES-MACROPHAGES: Cells of the monocyte-macrophage lineage play key roles in the immunopathogenesis of the HIV disease. These cells serve as reservoirs of viral infection. The dysfunction of these cells contributes to CD4+T cell dysfunction and to the impaired host defense against intracellular pathogens.[30] Monocytes express CD4 and numerous HIV co-receptors on their surface, including CCR5,CXCR4, and CCR3, and serve as targets for HIV infection. [31],[32] HIV is relatively non-cytopathic for cells of the monocyte-macrophage lineage than the CD4+Tcells, and HIV can replicate extensively in these cells. [33] Cells of the monocyte-macrophage lineage are central, even to the pathogenesis of the HIV-induced central nervous system disease. The HIV infection of the brain microglial cells, derived from the monocyte lineage, may lead to encephalopathy, neuropathy, astrocytosis, and cerebral vasculitis.[34] The levels of monocyte chemotactic protein type 1(MCP-1) are markedly elevated in the cerebrospinal fluid of AIDS patients. HIV infected macrophages are likely to be a major source of these high levels of MCP-1. MCP-1 in turn, recruits and activates monocytes, which elaborate pro-inflammatory cytokines and thereby enhance HIV replication and induce neuropathological diseases.[35]

Impaired accessory cell function may result from decreased MHC (Major Histocompatibility complex) class II expression, decreased interleukin-12 secretion, and from increased IL-10 secretion. HIV- induced dysregulation of antigen presentation can in turn cause the hypo-responsiveness of the CD4+T cells. HIV-associated abnormalities in antigen uptake, oxidative burst, and chemotaxis have been described in monocyte-macrophages [36] as a consequence of the poor intracellular killing of the *Candida* species yeast forms, [37] *Toxoplasma gondii*, [38] and *Histoplasma capsulatum*[39].

ADAPTIVE IMMUNE RESPONSES

A) HUMORAL IMMUNE RESPONSES: Human immunodeficiency virus infection is associated with the development of antibodies that appear within one week of the initial infection. A subset of these can neutralize the virus, either by binding directly to the envelope glycoprotein trimer on the surface of the free virions, or following CD4-gp120 binding after virus attachment, thus preventing the fusion of the viral and the cell membranes, which is essential for viral entry.[40] The viral envelope is highly glycosylated, and

these sugars prevent antibody binding to the underlying peptidic structure. These neutralizing antibody responses are sufficiently strong to influence viral evolution, thus leading to mutant viruses that escape recognition. New antibodies develop to neutralize the mutant virus that escapes again. [41]

B) CELLULAR IMMUNE RESPONSES

1) CD8+T CELL RESPONSES: Adaptive immunity generally involves the rapid expansion of the CD8+T cells which recognize foreign proteins on the infected cell surface, which are presented by the HLA antigen class I molecules. Direct cytotoxicity by the CD8+T cells occurs, which recognizes the viral oligo-peptides at the cell surface, thereby eliminating the production of the virus from that cell. In the early weeks following HIV infection, the viral load was found to decrease from an average of 1×10^6 copies/ml to an average of 30,000 copies/ml.[42] The CD8+T cells of HIV-infected patients secrete soluble factors that are able to inhibit viral replication in the absence of cell killing. Suppressiveness is mediated by chemokines, MIP-1, MIP-1, and RANTES. These chemokines are natural ligands for CCR5, a co-receptor for the R5 strain of HIV-1 and inhibit viral replication primarily by blocking virus entry. In addition, after the entry of the virus, the chemokines suppress HIV transcription in the infected cells.[43]

2) CD4+T CELL RESPONSES: The optimal function of the CD8+T cells depends on the presence of virus-specific CD4+T cells which help to co-ordinate an effective cytotoxic T-lymphocyte(CTL) response that mediates the restriction of virus replication by the production of Interferon- γ . [44]

HOST GENETICS AND VIRAL CONTROL

One of the strongest predictors of disease progression is the HLA type of the host. The HLA class I alleles, B*27 and B*57 are associated with a low viral load and prolonged asymptomatic infection.[45] Other HLA alleles which are associated with a more rapid disease progression, include the subtype HLA B35 allele, which is referred to as HLA B35px.[46]

CONCLUSIONS

HIV has the capability to subvert the activation of the human immune system to its own replication advantage. The immune control of HIV often fails due to viral escape from the cellular and the humoral host immune responses. [47] Many viral factors and host genetic characteristics play a crucial role in the control of the HIV disease by delaying the progression to AIDS or even by preventing infection. [48] Further, the HIV disease progression is intimately related to virus replication, and the net amount of virus replication reflects a balance among the factors that either induce or downregulate the virus expression [49],[50]. Chemokine receptors function as the necessary cofactors for HIV entry into the target cells and represent new potential targets of therapeutic intervention. [51],[52] Elements of both humoral and cell mediated immune responses against HIV have been implicated in the partial control of virus replication. A near complete understanding about the virus-host interactions that lead to the dysfunction and the depletion of the immune system, can only aid in the development of prevention and effective therapeutic strategies.

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DECLARATION ON COMPETING INTERESTS: No competing Interests.

Date of Submission: **10/1/2010**
Peer Review Completion: **10/21/2010**
Date of Acceptance: **12/28/2010**
Date of Publication: **02/06/2011**