Indian Journal of Basic & Applied Medical Research; December 2011: Issue-1, Vol.-1, P. 47-55

"HIV INFECTION: REASONS FOR IMMUNE FAILURE."

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Abstract:

Human immunodeficiency virus (HIV) infection results in a highly variable disease course ranging from rapid progression to long-term non progression. Presumably because of the selective pressure exerted by the immune system, viruses like HIV have evolved proteins that interfere with antigen presentation by major histocompatibility complex. HIV viral persistence is not thwarted by the presence of vigorous, virus-specific immune responses. Several factors are thought to contribute to persistent viral replication, like the destruction of virus-specific T helper cells, the emergence of antigenic escape variants, and the expression of an envelope complex that minimizes antibody access to conserved epitopes.

Key words: Immune failure, Human immunodeficiency virus (HIV) infection, persistent viral replication.

Introduction:

Human immunodeficiency virus (HIV) infection results in a highly variable disease course ranging from rapid progression to long-term nonprogression[1] Presumably because of the selective pressure exerted by the immune system, many viruses have evolved proteins that interfere with antigen presentation by major histocompatibility complex (MHC) class I molecules. These viruses utilize a whole variety of ingenious strategies to inhibit the MHC class I pathway. Viral proteins have been characterized that exploit bottlenecks in the MHC class I pathway, such as peptide translocation by the transporter associated with antigen processing. Alternatively, viral proteins can cause the degradation or mislocalization of MHC class I molecules. This is often achieved by the subversion of the host cell's own protein degradation and trafficking pathways. MHC class I molecules are expressed on the cell surface of all nucleated cells and present peptide fragments derived from intracellular proteins. These peptides are normally derived from the cell's own 'house-keeping' proteins but in a virally infected cell, peptides derived from viral proteins may also be presented. Virus specific Cytotoxic T lymphocytes (CTL)

monitor cell surface MHC class I molecules for peptides derived from viral proteins and eliminate infected cells. Some proteins that interfere with the MHC class I pathway are encoded by adenoviruses and retroviruses.[1,2,3] These include the adenovirus E3/19K and the human immunodeficiency virus-1 (HIV-1) Nef gene products.

I) FUNCTIONAL DEFECTS:

Wide arrays of immune defects are associated with HIV infection. Immunodeficiency may become sufficiently profound in the late stages of disease that HIV- specific antibody and CTL responses diminish in the face of high levels of ongoing viral replication.

A)LYMPHOID TISSUE: Advanced stages of HIV infection are marked by striking disruption of lymphoid tissue architecture. Follicular involution, hypervascularity, and fibrosis are some of the histopathologic changes evident in lymph nodes from patients with advanced HIV disease.

The ability to mount immune response against new antigens and the ability to maintain memory responses are severely impaired in the absence of an intact follicular dendritic cell (FDC) network.[2] Direct toxicity to cells by viral gene products may contribute to loss of FDC network integrity. Tat and/gp120 has been shown to be capable of disrupting normal intracellular signaling [3] as well as inducing apoptosis.[4]

B) CD4+T CELLS: CD4+T cell dysfunction, both quantitative and qualitative, is the hallmark of HIV disease. The opportunistic infections observed in advanced HIV disease are primarily due to defects in T-cell number and function that result directly or indirectly from HIV infection. Direct effects on CD4+T cell function include direct infection of these cells and resultant cytotoxicity with loss of absolute cell numbers. Indirect effects of HIV infection result in decreased CD4+T cell proliferation and differentiation, dysregulation and decreased production of IL-2 & other cytokines, decreased IL-2 receptor expression, and defective T- cell colony formation.[5] The percentage of CD4+Tcells expressing CD28(i.e., the major co-stimulatory receptor necessary for normal activation of T cells) is decreased during HIV infection in comparison to cells from uninfected individuals.[6] CD28- cells do not respond to activation signals, including anti-CD3 monoclonal antibodies or mitogens, and express markers of terminal activation, including HLA-DR, -CD38, and -CD45RO.[7] Interference with CD4 expression of HIV gp120,[8] Nef,[9] and Vpu,[10] may impair the ability of an infected CD4+T cell to interact with appropriate MHC class II molecules. HIV preferentially infect CD4+CD45RO+ memory cells, the increased susceptibility of these cells to the cytopathic of HIV infection or both may in part increase in the risk of infection with opportunistic organism.[11,12]

The three main potential factors for increased CD4+T cell depletion are:

i) Increased destruction, **ii**) Decreased production & **iii**) Redistribution.; and are described below-

i) Increased destruction of CD4+ T cells

a) **Direct Infection**:- CD4+T cells are the principal targets of HIV infection in vivo[13, ,14]& that HIV infection of CD4+T cells in vitro causes cytopathicity [15,16] led to a reasonable assumption that direct infection of CD4+T cells in vivo results in their depletion. The proportion of HIV – infected peripheral blood CD4+T cells in individuals in the early asymptomatic stage of HIV infection is typically in the range of 1:1000 to 1:1,00,000.[17,18] This frequency increases with disease progression and becomes 1:100 in AIDS patients.[19]

b) **Apoptosis**: - Aberrant intracellular signals transduced by HIV might prime CD4+T cells for apoptosis & thereby result in depletion of these cells during the course of HIV infection.[20] Cross linking of CD4 followed by ligaton to the T- cell receptor is sufficient to induce apoptosis, which suggests that uninfected CD4+T cells could be depleted inappropriately upon encountering antigen if CD4 had been cross-linked by gp120. The viral Tat protein can also lead to apoptotic cell death, possibly by up regulating CD95 ligand, by enhancing activation of cyclin-dependant kinases, or both.[21]

c) **Autoimmune Phenomena**:-Autoimmunity may occur as a result of molecular mimicry by viral components, by abnormal release of nuclear antigens from cells dying of apoptosis. Highly homologous region exist in the carboxyl terminus of the HIV-1 envelope glycoprotein and the aminoterminal domain of different HLA-DR & -DQ alleles.[22] Similar instances of molecular mimicry between HIV-1 envelope and host proteins that may result in pathogenic autoimmune responses include the collagen-like region of complement component C1q-A[23] MHC class I heavy chains; HLA-DR4& -DR2 alleles;[24]

d) **Bystander Phenomena**: - Immune responses that target HIV determinants on infected cells may also contribute to elimination of uninfected cells bearing HIV proteins, (eg. gp120) on their surface. Targeting of such “innocent bystander” cells by antibody and cellular immune responses has been described.[25]

ii) Decreased production: Decreased production of CD4+T cells could occur by disruption of the thymic microenvironment & by HIV- induced depletion of thymocytes. [26] Thymic epithelial cells normally secrete IL-6 which in turn increase HIV replication in infected cells.[27]Uninfected thymocytes from HIV infected patients are primed for apoptotic death, suggesting indirect mechanisms of defective thymopoiesis. Disruption of normal hematopoiesis may contribute to the depletion of CD4+T cells during HIV infection. Viral proteins and HIV induced cytokines can impair the survival & clonogenic potential of CD34+ progenitor cells. The HIV envelope gp120 and the Tat proteins have been implicated in these effects on CD34+ progenitor cells, possibly due to gp120- and Tat mediated up

regulation of TGF-β or gp120-mediated up regulation of TNF-α .[28]

iii) Redistribution: McCune suggests that there is significant trafficking of CD4+T cells from the peripheral blood to lymphoid tissue in acute and chronic HIV infection. This trafficking in part is mediated, through the expression of receptors, such as CD62L, on CD+T cells. These markers cross-link circulating T cells onto ligands on endothelial venule cells, & the T cells extravasate from the peripheral blood to lymph nodes. Because CD62L expression on CD+T cells is up regulated following HIV infection, it is possible that redistribution contributes to depletion of circulating CD4+T cells that have trafficked to lymphoid tissues are destroyed by apoptosis or other mechanisms. [29]

C) CD8+ T cells: Dysregulation of CD8+T cell numbers and function is evident throughout the course of HIV disease. During HIV disease progression, CD8 + T cells assume an abnormal phenotype characterized by the expression of certain activation markers and the absence of expression of the CD25 molecule (IL-2 receptor). Individuals whose CD8+T cells express HLA-DR but not –CD38 after seroconversion experience a stabilization of their CD+T cell counts and a less fulminant course, whereas individuals whose CD8+T cells express both HLA-DR and –CD38 experience a more aggressive course with rapid CD4+T cell depletion and a poorer prognosis.[30,31]

The loss of CTL activity is not restricted to HIV specific CTLs: a loss of cytotoxic activity to other common antigens including Epstein-Barr virus(EBV) and Mycobacterium tuberculosis has also been observed.[32,33] Other CD8+T cell function ,such as non-cytolytic non-MHC restricted CD8+T cell-derived HIV suppression is impaired.[34]Chronic antigenic stimulation by persistent viruses can lead to exhaustion of CD8+T cells by preventing them from the normal progression to renewable memory cells.[35,36]

D) B-LYMPHOCYTES: Dysregulation of B-cell activation and the decreased ability of the cells to respond to antigen lead to increase in certain bacterial infections leading to increased morbidity and mortality associated with bacterial infections. The number of B cells may be decreased in primary HIV infection, this is usually transient. Soon after the resolution of acute HIV infection, hypergammaglobulinemia and B cell hyper-activation are noted. HIV viremia induces the appearance of a subset of B cells whose function is impaired and that may be responsible for hypergammaglobulinemia. B cells from HIV infected individuals secrete increased amounts of TNF & IL-6, cytokines known to increase HIV replication and express surface- bound TNF that can induce the production of HIV from infected CD4+T cells.[37,38] HIV gp120binds to an immunoglobulin variable chain (VH3) and activate these B cells in much the same way as superantigen.[39,40.]This leads in part to hypergammaglobulinemia and B lymphocytes

hyperactivation of HIV infection. Gp 41 directly activate B cells in a non-superantigen-mediated manner.[41]

II) VIRAL FACTORS

A) *Broad genetic diversity resulting in CTL"escape" mutations:*Mutations produced during the reverse transcription process combined with high levels of replication over a prolonged period result in a highly diverse population of viruses that circulate in a given patient. These mutants accumulate in the peripheral blood and are associated with decreased response to the non mutated sequence. Examples of escape mutants that alter HLA binding and dominant viral sequence have been observed for HLA-B8,-A3, and –B4. [42, 43] **B)***MHC down regulation* causing diminished recognition of HIV-infected cells.HIV nef, tat, and vpu are each capable of down-modulating surface expression of MHC class I molecules necessary for recognition of infected cells.[44, 45, 46]

III) GENETIC FACTORS: 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 low viral load and prolonged asymptomatic infection.[45] Other HLA alleles associated with more rapid disease progression, in particular subtype of HLA B35 allele referred to as HLA B35px.[46]

Infection with the human immunodeficiency virus results in prolonged, continuous viral replication in the infected host. Remarkably, viral persistence is not thwarted by the presence of apparently vigorous, virus-specific immune responses.[46] Several factors are thought to contribute to persistent viral replication, most notably the destruction of virus-specific T helper cells, the emergence of antigenic escape variants, and the expression of an envelope complex that structurally minimizes antibody access to conserved epitopes.[46,47]

Conclusion: The pathogenesis of HIV infection is multifactorial process consisting of aberrant cellular activation and dysregulation of nearly every aspect of the immune system. Disease progression is intimately related to virus replication, and the net amount of virus replication reflects a balance among factors that either induce or down regulate virus expression and thereby lead to quantitative and qualitative abnormalities of the immune system by direct and/ indirect mechanisms.[47]

Chemokine receptors function as necessary cofactors for HIV entry into target cells. These represent new potential targets of therapeutic intervention. Elements of both humoral and cell mediated immune responses against HIV have been implicated in the partial control of virus replication. HIV is the quintessential opportunist, as illustrated by its

ability to subvert activation of the immune system to its own replication advantage. The virus is able to disarm multiple components of the host immune system via both direct and indirect mechanisms. [47]

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Conflict of Interest: Nil, Source of support: Nil
Date of Initial Acceptance: 3 November 2011
Date of Peer Review Approval: 24 November 2011
Date of Final Approval: 26 November 2011
Date of Gallery proof confirmation: 28 November 2011
Date of Publication: 2 December 2011