Journal of Antivirals & Antiretrovirals
ISSN: 1948-5964

Bharaj and Chahar, J Antivir Antiretrovir 2015, 7:1
DOI: 10.4172/jaa.1000115

Review Article Open Access

Immune Activation and HIV Pathogenesis: Implications for Therapy

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Abstract

HIV infection is associated with continued activation of immune system and this is known to be the driving force behind CD4+ T cell depletion and progression to AIDS. Nonpathogenic Simian Immunodeficiency Virus (SIV) infections of natural hosts are characterized by low levels of immune activation even in the chronic phase of infection. Effective Antiretroviral Therapy (ART) does not fully resolve immune activation and HIV infected patients continue to experience non-AIDS related events leading to premature immune senescence. In this review, we summarize the possible mechanisms driving HIV associated immune activation, and novel therapeutic interventions that show promise in treating the disease.

Keywords: HIV; AIDS; immune; Therapy; Virus

Introduction

Nearly 35 million people all over the world are infected with Human Immunodeficiency Virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS). Around 2 million people get infected with the virus each year and the pandemic continues to devastate despite three decades of our understanding of the pathogenesis [1]. The mechanisms by which HIV causes AIDS are multifaceted and still not completely understood and this is the main reason why HIV has not been eradicated from the world. While therapeutic interventions are ongoing, there is a pressing need for in-depth understanding of correlates of protection and the development of an effective HIV vaccine. The early hypothesis that AIDS is a result of uncontrolled replication and that with the administration of Antiretroviral Therapy (ART), the diseases is 'latent'; is no longer supported by the available scientific evidence. The observation that Simian Immunodeficiency Virus (SIV) infection of natural hosts is nonpathogenic despite high viremia and short life span of infected cells demonstrates that AIDS is not the necessary consequence of any primate lentiviral infection [2,3]. Multiple studies have shown that several immunological features play a crucial role in causing progression to AIDS. The most prominent reason is the establishment of chronic state leading to generalized immune activation strikingly absent in nonpathogenic model of SIV infection [4,5]. Chronic HIV infection is mainly characterized by increased expression of pro-inflammatory cytokines and increased expression of T cell activation or exhaustion markers. Among pro-inflammatory cytokines, interferons, IL-6, IL-8, IL-1β and certain serum markers of inflammation including soluble CD14 (sCD14), C-Reactive Protein (CRP), D dimers have been implicated in HIV associated immune activation [6-9]. T cell activation markers like CD38 and HLA-DR, Programmed Death-1 (PD-1), Tim-3, CTLA-4 and PD-1 Homologue (PD-1H) may also interfere with ongoing HIV specific cell responses [6-9]. It is now believed that levels of chronic immune activation predict the progression to AIDS independently from viral loads or CD4+ T lymphocyte counts. Both HIV and SIV infections of natural hosts are associated with loss of integrity of the mucosal barrier in the intestine leading to translocation of microbial products like Lipopolysaccharide (LPS) and flagellins into the circulation [10]. Serum levels of LPS, flagellin, peptidoglycan and CpG rich DNA correlated strongly with T cell activation levels leading to conclusion that translocation of immune stimulatory products contribute to systemic immune activation [11]. Pathogenic HIV and SIV infections lead to irreversible loss of memory CD4+ T cells leading to decline in CD4+ T cell pool and establishing a "latent pool" of HIV infected cells. In recent years, multiple studies have shown that HIV infected individuals have elevated levels of immune activation markers and these do not normalize with long term ART [12-14]. In addition, immune activation is most likely to be a significant contributor in initial establishment and maintenance of viral reservoir, which is the key obstacle to any HIV eradication strategy [15,16]. In this review, we discuss our understanding of HIV associated immune activation and several therapeutic approaches with the goal to decrease persistent immune activation.

Why is understanding immune activation important?

Immune activation, a natural host response during an infection is tightly regulated by a complex cascade of biochemical signals directed at clearing the pathogen. Immune activation clears in majority of the infections and eventually gets resolved itself to prevent immune-mediated pathology and exhaustion. However, in case of HIV or Hepatitis C infection, the virus persists indefinitely and in response the body maintains its state of immune activation [17]. Once the viral loads are brought under control, immune activation decreases dramatically but residual virus provides a constant trigger to the immune system and low-level activation persists [18].

Highly active ART was assumed to have an asymptomatic phase of infection with undetectable viral loads and improved lifestyle. It came as a surprise when in patients with undetectable viral load; continual CD4+ T cell depletion was observed and could not be linked to actively replicating virions. Preliminary hypothesis included direct toxicity of antiretroviral drugs, [19,20], metabolic changes, and additional risk factors such as smoking, alcohol and other substance abuse [21]. However, none of these factors fully explained all the risk of non-AIDS

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Received January 22, 2015; **Accepted** February 11, 2015; **Published** February 18, 2015

Citation: Bharaj P, Chahar HS (2015) Immune Activation and HIV Pathogenesis: Implications for Therapy. J Antivir Antiretrovir 7: 015-021. doi:10.4172/jaa.1000115

related mortality. The concept of chronic immune activation was first proposed by Ascher and Sheppard [22] and further recognized by other groups. Dr. Giorgi pioneered in advocating her theory of immune activation in by suggesting that although it starts out as a protective mechanism towards enhancing survival, immune activation ultimately proves to be more pathogenic than being protective [23]. Thus while HIV infection leads to AIDS, the hallmark of which is immune deficiency, the larger part of the chronic pathology of HIV infection is founded on persistent immune activation [24].

Causes of persistent immune activation

Breach of gastro-intestinal mucosa and microbial translocation: A potential mechanism contributing to chronic immune activation is the mucosal immune dysfunction demonstrated by severe and rapid depletion of $CD4^+$ T cells from the gut [25]. This is associated with loss of intestinal epithelial cells, disruption of tight junctions, and compromised integrity of the mucosal intestinal barrier that results in a significant increase in bacterial components, including LPS and 16s DNA in the blood [10,26-28]. Gut associated lymphoid tissue constitutes nearly 95% of the body's $CD4^+$ T cells and this compartment is essentially lost and never restored even with rigorous ART [29]. LPS concentrations in the circulation of HIV-infected individuals correlate strongly with T-cell activation levels [26,30]. Other bacterial products, such as flagellin, peptidoglycan, and bacterial CpG-rich DNA domains that are recognized by Toll Like Receptor (TLR) 2, 5, and 9 respectively, may also contribute to immune activation [31]. Through the stimulation of TLRs, these bacterial products may also induce pro-inflammatory cytokine production such as TNF-α, IL-6, IL-8, IL-1β and type I interferons [32,33]. Although it is widely accepted that insults to mucosa result in immune activation, the relative contribution of this phenomenon is incompletely understood. Follow up studies in macaques have shown that in spite of survival of mucosal $CD4^+$ T cells, activation was observed suggesting that immune activation due to gut damage may not be required to develop AIDS [34-36].

To maintain the balance of immune system there is a sync between the numbers of a specialized T cell category called the regulatory T cells (Tregs) and Th17 cells that produce IL-17, IL-21 and IL-22 [37,38]. Disruption of gut integrity in pathogenic SIV and HIV infection is associated with depletion of Th17 cells that has been held responsible for chronic immune activation in pathogenic HIV infection [39,40]. In SIV infected Rhesus Macaques (RM), treatment with IL-21 resulted in the maintenance of intestinal Th17 cells, and a reduction of microbial translocation and systemic inflammation [41]. Currently, the Th17/Treg balance and the role of Th17 cells and Th17-derived cytokines in HIV infection is a subject of intensive study.

HIV replication and immune response to the virus: HIV infection itself is the prime cause of immune activation. HIV RNA directly activates TLR7 and 8 further inducing the release of type I interferons [42,43]. Both HIV antigens and its components can activate T, B and NK cells and lead to release of pro-inflammatory cytokines like IFN-α, IL-6, IL-8, Macrophage Inflammatory Protein (MIP)-1a, adhesion molecules like ICAM and VCAM [44-47]. In spite of the proven contribution of HIV replication to immune activation and inflammation, several hitches exist. Firstly, the frequency of activated T cells exceed the number of cells infected that does not include other cells types that get activated like B, NK cells and monocytes [26,28,48]. Secondly, immune activation is a better predictor of declining $CD4^+$ T cells counts as compared to viral loads [23,49]. Thirdly, despite successful ART administration and viral replication control to undetectable levels, the main markers of immune activation remain high [12,50]. Fourthly, in natural hosts of SIV infection, high viral loads fail to induce sufficient T cell proliferation or activation and progression to AIDS [51,52]. Lastly, in a rare subset of HIV infected population called Virologic Non Progressors (VNPs), $CD4^+$ T cell counts are maintained remarkably well and despite high viral loads, immune activation markers are comparable to uninfected individuals [53]. Together, these studies have shown that HIV viral loads play a critical role in immune activation but are neither exclusively responsible nor necessary to induce pathological levels of immune activation. Thus, in the last couple of years, attention has been focused on the causes of immune activation and modulation strategies that help regulate immune activation.

Loss of specific $CD4^+$ T-cell subsets: $CD4^+$ T cells can be classified based on phenotype, function, and anatomic distribution in broad subsets of naïve, central memory, and transitional memory and effector memory cells. Based on their function, cytokine, and transcriptional profile, they are classified as Th1, Th2, Th17, Tfh, and regulatory T-cells. Being the prime targets for HIV/SIV infection, restoring CDt^+ T cell counts is an attractive strategy to combat infection related abnormalities. Moreover, some subsets were affected differently in HIV and SIV infection suggesting their variable roles in the course of disease progression. Thus, characterization of these different subsets in cases of HIV/SIV infection may lead to determining the role of these cells in establishing immune activation.

Th17 cells: Th17 cells are recognized by their ability to produce IL-17 and IFN-γ. The levels of these cytokines in HIV infected patients are increased and have been shown to directly contribute to maintenance of gut surface integrity [54,55]. Th17 cell numbers are relatively well preserved in SIV infected macaques that show no microbial translocation and lack chronic immune activation [37,39]. In HIV infected individuals classified as long term non progressors, there is a preferential preservation of intestinal Th17 cells [56,57]. The severity of Th17 cell depletion correlates with microbial translocation, chronic immune activation, and disease progression in HIV/SIV-infected subjects [56,58].

Central memory $CD4^+$ T cells: $CD4^+$ T Central Memory (TCM) cells are long lived self-renewing cells that reside in the lymphoid tissues and represent the largest reservoir of infected $CD4^+$ T cells in HIV-1 infection [15,59]. In SIV-infected primates, progressive depletion of $CD4^+$ TCM defines progression to AIDS, [60,61]. It has been hypothesized that memory $CD4^+$ T cells are the reservoir that carry HIV-1 provirus. The process includes infection of a $CD4^+$ T cell being infected in an activated state and surviving long enough to move to resting state [62]. However, some evidence indicates that a $CD4^+$ T cell may be permissive to HIV-1 infection without being activated [63]. It has been proposed that naïve CCR5-$CD4^+$ T cells may in fact have a very low level expression of CCR5 that may be sufficient to support infection by HIV-1 [64].

Infection and depletion of $CD4^+$ TCM cells is hypothesized to contribute to the establishment of chronic immune activation by either affecting T cell proliferation or activation concentrated in local anatomic sites [52]. Low levels of TCM infection have been described in (i) long-term non-progressors, (ii) early treated patients that show a prolonged control of viremia and preserve $CD4^+$ T cells after ART interruption, and (iii) VNPs that preserve $CD4^+$ T-cell counts despite high levels of viral load [65].

Regulatory T cells: Tregs are identified by the expression of CD25 and FOXP3. These cells are important for maintaining immune system homeostasis by preventing autoimmunity and by suppressing activation and effector functions mainly through expression of IL-10

and TGF-β [66,67]. The role of Tregs in HIV infection and associated chronic immune activation is still intensively debated. On one end Tregs suppress general immune activation that may be beneficial to host by delaying progression to AIDS [68,69]. On the other hand, Tregs may suppress HIV related effector T cell immune responses contributing to HIV pathogenesis [70,71].

T-follicular (Tfh) helper cells: Tfh are found in the lymphoid germinal centers expressing high levels of ICOS, CD40 ligand, PD-1, BTLA, as well as high levels of the cytokine IL-21. These cells play a critical role in the activation, differentiation, and survival of B cells. The role of Tfh cells in HIV immune activation is unclear. In SIV infection, TfH cells have been shown to suffer decreased survival, cycling, and trafficking suggesting a loss of function, while another study showed that Tfh cells remain capable of stimulating B cells' Ig production [72,73].

CD8⁺ T cells and HIV infection; Control of plasma viral loads in acute infection of HIV directly coincides with CD8⁺ T cell functions [74]. In both acute and chronic models of primates with SIV infection, CD8⁺ T cell numbers tightly regulate viral replication. The primary function of CD8⁺ T cells is to recognize and kill infected cells via perforin/granzymes or via Fas ligand [75]; they are quite competent in producing a broad array of cytokines like IL-2, IFN-γ, TGF-β and TNF-α, RANTES, MIP-1α, MIP-1β [76]. T-bet, a transcription factor and regulator of cytolytic effector cells has been shown to play a pivotal role as a determinant of Th1 lineage commitment and is essential for the development of autoimmune diseases in transgenic mice [77-79]. During HIV infection, CD8⁺ T cells lose the ability to express T-bet and this correlates to cytolytic dysfunction [77]. In elite controllers, T-bet expression levels are maintained as compared to chronic progressors [80]. Of note, the number of CD8⁺ T cells secreting cytokines did not differ between chronic progressors and elite controllers but they were able to produce more cytokines especially IL-2 per cell suggesting that the quality of CD8⁺ T cells responses is directly related to immune protection [81-84]. It is becoming increasingly clear that polyfunctionality of these cells and transcription factors like T-bet should also be used to define correlates of immune activation. In conclusion, the mechanism of HIV pathogenesis and its contribution to immune activation significantly relies on the balance of the different CD4⁺ T-cell subsets.

Immune exhaustion: In addition to immune activation, another feature of chronic HIV-1 infection is 'immune exhaustion'. Immune exhaustion is characterized by the loss of T cell effector functions [85], upregulation of negative regulatory markers on both CD4 and CD8⁺ T cells [6,7,8,86] and deficiency of positive costimulatory molecules such as CD28 and BB-1 [87,88]. Blocking of negative regulatory molecules like PD-1 has received considerable attention due to partial restoration of immune functions upon modulation of these receptors [6,7,89,90]. Recently a new member of the same family, PD-1H was implicated to play an important role in pro inflammatory cytokine secretion and enhancing immune responses to HIV antigens [9]. The authors demonstrated that PD-1H in primary human monocytes led to secretion of pro-inflammatory cytokines like IL-6, TNF-α and IL-1β. In patients with chronic HIV infection on ART, PD-1H levels on monocytes were significantly higher as compared to elite controllers and uninfected donors. Surprisingly, in patients with acute HIV infection, PD-1H levels were lower than those in chronic phase, emphasizing that PD-1H maybe the molecule or a part of the mechanism responsible in triggering immune activation especially in the chronic stage of the disease. In addition, PD-1H expression on monocytes in chronic HIV patients correlated with T cell immune activation (CD38 and HLA-DR) and exhaustion (PD-1) markers suggesting that this molecule should be pursued to target immune activation and exhaustion both in HIV infected patients.

Pathogenic effects of immune activation and inflammation: The role of chronic immune activation is well established in the setting of HIV infection even though it is still not fully comprehended how it makes host immune system dwindle under its pressure. One of the proposed mechanisms is the preferential depletion of CD4⁺ T helper cells that are the key components to host immune response [85]. Reduction in numbers of these cells may eventually lead to inability

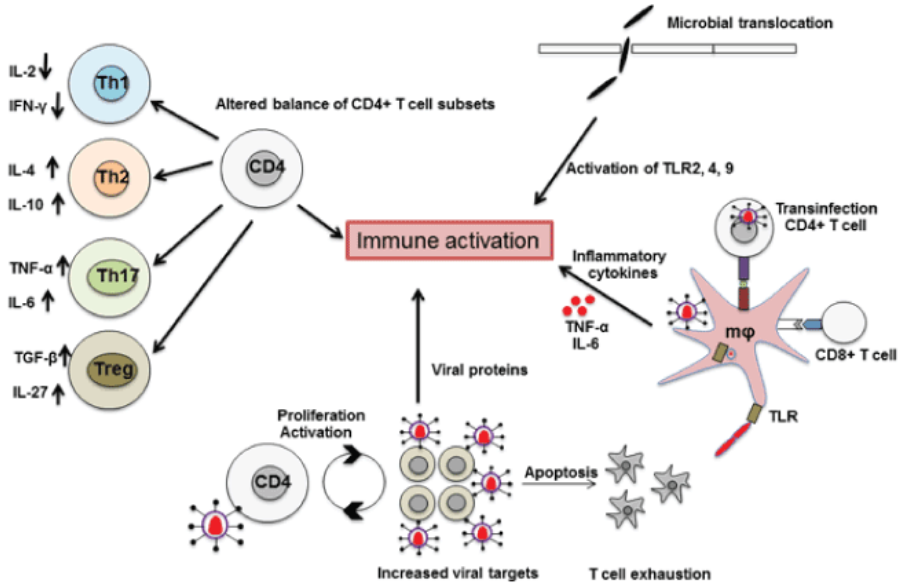

Figure 1: Factors involved in HIV associated immune activation. Various factors are associated with HIV associated immune activation. Acute/chronic immune activation maybe a result of activation induced by binding of viral proteins to TLRs, altered CD4⁺ T cell subsets, CD4⁺ T cell proliferation and apoptosis, pro-inflammatory milieu generated by infected antigen presenting cells or activation of cytolytic T cells and leaky gut allowing microbial translocation. In addition, each mechanism may inadvertently synergize with other mechanisms and alter the relative contribution of each factor [10,25,31,32,37,43,57,61,69,71,73,77].

of the body to deal with range of potential pathogens. The other mechanism is by providing targets for HIV replication (Figure 1). Depletion of $CD4^+$ T cells may trigger activation, proliferation and differentiation of naïve and memory T cells to maintain homeostasis. However, they may also get infected by HIV and sustain a vicious cycle in which infection leads to cell death and further proliferation [86]. An additional key mechanism may be inhibition of normal functions by B, NK and other antigen presenting cells leading to less efficient viral control, increased virus replication and thus immune activation [87,88]. Further immune activation of these cells may lead to secretion of pro-inflammatory cytokines that can induce cardiovascular damage and cancer [89]. Immune activation studies in HIV/SIV infection have shown structural damage to lymphoid tissues that are crucial for T cell regeneration and function [90,91]. Loss of lymphoid network may lead to loss of cytokines that maybe essential to the survival and decreased availability of T cells [90]. In a nutshell, chronic immune activation wreaks havoc in the setting of an established pathogenic HIV/SIV infection in humans and macaques via multiple ways. The best way to determine interventions would be blocking them and optimizing treatment in humans.

Interventions to control chronic immune activation

Targeting chronic immune activation is of prime importance in optimizing HIV infection in humans. Over the last couple of years it has become clear that non-AIDS related events such as increased aging, cardiovascular disorders, neurodegenerative disorders and cancers correlate with increased mortality in HIV patients. Vaccine based approaches are not eliciting the required response to prevent or cure HIV infection; thus new strategies need to be explored to improve overall immune function.

Antiretroviral therapy

Introduction of potent ART has made it possible to achieve control of viral replication and improved immune function in majority of the treated patients [92,93]. As ART significantly reduces morbidity and mortality associated with HIV replication, interruption in the regimen fails to achieve functional eradication of the infection [94,95]. Although ART has achieved reduction in immune activation to significantly lower levels with successful control of viremia, the immune activation never returns to the baseline like uninfected controls [96]. The mechanisms underlying immune activation are multifactorial and do not solely depend on virus replication, hence ART can achieve only so much. The size of stable reservoir compartments needs to be closely monitored as it appears to be the determinant of the level of residual virus replication [15].

Alternative drug therapies

Cyclosporine A is a cyclic peptide commonly used as an immune suppressive agent, inhibits T cell activation, proliferation and effector functions [97]. Studies conducted in HIV patients show that administration of cyclosporine A as supplemental therapy may help stabilize mean $CD4^+$ T cell counts and even lower the risk of progression to AIDS [98,99]. However, there have been contradictory studies stating no beneficial effects in terms of viral replication or any immunologic benefits [100,101]. Thus, cyclosporine A has been concluded to not have any advantage during ART treatment. Among other classes of tested agents include chloroquine that showed significant promise in reducing HIV viral loads in ART naïve patients without the patients developing drug resistance [102,103]. HIV infection is associated with excessive production of TNF-α, thus blocking TNF-α secretion appears to be an appropriate choice to reduce HIV related immune activation. Etanercept protein binds to TNF receptor acting as a competitive inhibitor for TNF-α and encouragingly appears to improve HIV related symptoms [104,105]. Certain cytokines when administered exogenously may help regulate the proliferation and survival of $CD4^+$ T cells. Naïve and memory $CD4^+$ T cells progressively deplete during HIV infection and IL-7 administration has been shown to be important in restoring their function [106]. IL-7 treatment may also activate latent virus replication thereby helping in targeting viral reservoirs [15]. Another cytokine IL-21 has been shown to prevent Th17 cell loss during SIV infection [58]. Certain other compounds like rapamycin and mycophenolic acid may help as additive therapy in conjunction with ART in HIV infected patients by reducing T cell proliferation and activation, thus reducing available targets for HIV replication and viral loads as well [107,108].

Conclusions

Immune activation associated with HIV infection in recent years has been given undivided attention. The factors responsible and the mechanisms behind immune activation are being aggressively pursued. As recent studies have shown immune activation is linked to the perturbations in the human body and predictor of progression to AIDS in case of HIV infection, active research on both viral and host factors contributing to this phenomenon are underway. This review highlights the benefits associated with targeting immune activation to reduce disease progression and non-AIDS related pathological side effects on HIV induced chronic immune activation.

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