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Immunopathogenesis of Asymptomatic Chronic HIV Infection: The Calm before the Storm

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Abstract

Purpose of review—HIV and pathogenic SIV infection are characterized by chronic immune activation. This review addresses the factors that influence immune activation and may thus determine the rate of disease progression during the asymptomatic period of HIV.

Recent findings—Immune activation stems from foreign antigen stimulation including HIV, microbial products and co-infections, and compensatory homeostatic mechanisms. Continuous immune stimulation creates a permissive environment for further viral replication, while temporarily allowing successful replenishment of the T cell pool. Type I IFN, microbial translocation, activated (but ineffective) effector T cells, unruly regulatory T cells and inadequate Th17 cells all play important roles in the cycle of activation, functional exhaustion and T cell death that leads to immunodeficiency.

Summary—The asymptomatic chronic phase of HIV infection is a dynamic balance between host and virus, the outcome of which determines an individual's course of disease. Evaluation of the factors that determine the immunologic threshold of disease progression could assist in designing therapeutic strategies including individualized timing of ART.

Keywords

Immune activation; Th17; type I interferons; homeostasis; T cells

Introduction

HIV infection is characterized by an initial, occasionally symptomatic acute phase followed by an asymptomatic period of variable length culminating in clinically evident immunodeficiency. Recent findings tying immune activation to disease pathogenesis have focused attention on earlier stages of HIV. A better understanding of factors that influence the precarious immunologic balance during early disease will assist development of targeted interventions, possibly including earlier or individualized timing of antiretroviral therapy (ART).

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Immune Activation as the Protagonist in HIV Immunopathogenesis

Persistent immune activation is manifested by increased turnover of T cells, monocytes and NK cells, high levels of CD4 and CD8 T cell apoptosis and polyclonal B cell activation with hypergammaglobulinemia [1-8]. Immune activation is strongly predictive of HIV disease progression, even when measured prior to seroconversion [9,10]. Recent studies showing that IL-6, D-dimer and changes in C-Reactive Protein (CRP), all biomarkers associated with inflammation, predict mortality in HIV+ patients further revitalized interest in immune activation [11]. The specifics of how HIV hijacks the immune system into a perpetual cycle of activation and failure of viral control remain unclear.

The central role of immune activation in HIV pathogenesis has been demonstrated in studies of sooty mangabeys (SM) and African green monkeys (AGM), the natural hosts of simian immunodeficiency virus (SIV) infection. Sooty mangabeys develop high levels of SIV viremia without CD4 T cell losses or clinical disease. In contrast, rhesus macaques (RM) have lower or similar levels of SIV viremia but develop progressive CD4 T cell loss, leading to clinical manifestations similar to AIDS. The most evident difference between pathogenic (RM) and non-pathogenic (SM and AGM) SIV infection is the lack of immune activation in the latter [12].

Markers of immune activation in HIV include CD38 [13], HLA-DR [14], CD71 [9], intracellular Ki67 expression [3,7,15], total CD8 T cell counts and serum immunoglobulins [16,17], serum β 2-microglobulin, soluble IL-2 receptor and neopterin [1,18,19]. Although many studies have found associations between immune activation and levels of HIV viremia [4,20], immune activation can be a stronger predictor of disease progression [1,13,18,21-23]. In one recent study, elite controllers (patients with plasma HIV RNA levels below the limit of detection in the absence of ART) with evidence of CD4 T cell depletion had elevated levels of predominantly CD8 T cell activation compared to controls or HIV+ patients on ART [24]. In contrast, patients with idiopathic CD4 lymphopenia (ICL) who have low CD4 T cells counts in the absence of HIV show evidence of immune activation in CD4 but not CD8 T cells [25]. These studies suggest that CD4 T cell activation may be at least partly related to lymphopenia-driven T cell proliferation [15,25,26]. Regardless of the stimulus, the presence of activated CD4 T cells appears to be essential for viral replication [27].

Continuous CD4 T cell loss and replenishment eventually leads to immunodeficiency as the regenerative capacity of weary naïve and central memory cells gradually dwindles despite apparent excess of homeostatic cytokines in the peripheral blood and lymphoid tissue [28-31]. This exhaustion of the T cell “supply” may be due to direct killing by the virus, virus-induced apoptosis, immunologic senescence and/or the architectural destruction of lymphoid organs from fibrosis induced by TGF- β and other cytokines [32,33] that may interfere with dendritic-T cell interactions and access to homeostatic cytokines.

This review addresses the different factors that determine the immunologic juncture at which the battle with HIV is lost and immunodeficiency ensues. We propose that some of these factors may become useful in assessing the “immune profile” or “immune score” of patients with asymptomatic HIV infection. Assessment of the immune score combined with age, genetic profiling [34-37] and co-morbidities such as cardiovascular disease or diabetes, could guide individualized therapeutic strategies prior to clinical manifestations of HIV immunodeficiency.

Gut: the veiled site of HIV pathogenesis

The gut is a key site of HIV infection and pathogenesis. Epithelial injury and CD4 T cell loss in the gut during acute infection may lead to dissemination of microbial products that fuel immune activation. Acute HIV infection results in enterocyte apoptosis and dysfunction,

defects in mucosal repair, and earlier and more massive depletion of mucosal CD4 T cells [38,39] than in peripheral blood or lymphoid tissue [40-43]. This CD4 T cell depletion is likely due to a combination of direct viral infection, activation-induced cell death, and host-derived cytotoxic responses. Due to constant exposure to foreign antigens, a large proportion of gut CD4 T cells are activated and express CCR5, a co-receptor that enables HIV entry, providing fertile ground for HIV replication. In addition, as shown by Arthos et al [44], HIV may be actively recruiting T cells to the gut via $\alpha 4\beta 7$, an integrin that mediates migration of lymphocytes to the gut. Engagement of $\alpha 4\beta 7$ on CD4 T cells by gp120 leads to activation of lymphocyte function-associated molecule 1 (LFA-1) or $\alpha L\beta 2$, facilitating formation of virologic synapses and increasing the efficiency of HIV infection [44].

The gut houses a large percentage of the total body CD4 T cells, consequently, losses in chronic asymptomatic HIV infection are probably not accurately reflected in peripheral blood. While the degree of CD4 T cell depletion in the gut has not been linked to disease prognosis per se, it may be indirectly enhancing immune activation in chronic HIV infection. An earlier study showed increased circulating lipopolysaccharide (LPS) and soluble CD14 (produced by macrophages in response to LPS) in HIV infected patients and SIV infected RM but not SM [45]. Interestingly, significant CD4 T cell depletion in the gut mucosa during acute SIV infection is seen in both SM and AGM [46,47]. Persistently elevated circulating LPS may lead to unabated stimulation of the innate immune system, with production of type I interferons and pro-inflammatory cytokines further augmenting immune activation and generating targets for HIV replication. A convincing experiment involving administration of LPS to AGM led to increases in both CD4 T cell activation and SIV viral load [48]. On the other hand, increased plasma LPS levels were also observed in ICL patients at levels similar to HIV+ patients with comparable CD4 T cell counts, suggesting that the HIV-induced apoptosis of enterocytes is not the main pathogenic mechanism [49]. Furthermore, CD8 T cell activation is not characteristic of ICL, indicating that elevated LPS levels are not always associated with CD8 T cell activation [24,49].

Why do SIV natural hosts have evidence of CD4 T cell depletion in the gut without enteropathy or circulating LPS? One piece of the puzzle may be Th17 cells, a subset of memory CD4 T cells that produce IL-17 and IL-22 in response to bacterial and fungal antigens [50]. The loss of Th17 cells in the gut may contribute to epithelial injury and enhance local inflammation and immune activation. Indeed, HIV+ patients and SIV-infected RM have significant depletion of gut Th17 CD4 T cells with an increase in Th1 CD4 T cells [50,51]. This may be due to preferential targeting of Th17 CD4 T cells, a shift toward Th1 differentiation, or infiltration of the gut by Th1 cells [51]. Notably, SM and AGM maintain Th17 cells in the gut despite mucosal CD4 T cell losses [50]. More importantly, in the SIV model, lack of Th17 response promoted *S. typhimurium* dissemination from the gut, tying together immunologic observations and known clinical consequences (recurrent Salmonella bacteremia) of HIV infection [52].

Several factors limit the execution and/or interpretation of studies involving the gut mucosa: the invasive nature of biopsies, differences in selection of biopsy sites, differences in methodology (flow cytometry or immunohistochemistry) and limited sampling material. A harmonized approach to studying the gut mucosa and measuring or estimating total body and total gut CD4 T cells would greatly advance this field.

The Elusive Role of Regulatory T cells in HIV Infection

The role of regulatory T cells (Tregs) in HIV disease progression is still unclear. As Tregs are capable of suppressing T cell activation, they could be of either benefit (suppressing over-activation, diminishing “bystander apoptosis” and T cell loss) or harm (suppressing HIV-specific T cell responses and hindering viral clearance) [53]. In support of the former, long-

term non-progressors (LTNP) show greater maintenance of functional Tregs in chronic infection, with associated reduction in T cell activation [54,55]. Previous reports [56,57] have supported a strong correlation between Treg loss and increased CD4 T cell activation. Other studies found no association with disease progression or increased proportion of Tregs in advanced disease [58]. There is also disagreement over whether Tregs are spared [59] or targeted [57,60] by HIV.

Accumulation of Tregs has been reported in the lymph nodes [61] and gut of viremic patients [62]. After ART, gut Tregs appear to return to normal, suggesting that accumulation in tissues is related to HIV replication [62]. In AGM, an immediate emergence of Tregs is seen during acute SIV (non-pathogenic) infection, with concomitant TGF- β production dampening T cell activation [63]. In pigtail macaques, Tregs are depleted in the lamina propria shortly after pathogenic SIV infection, but are maintained or expand in peripheral blood and lymph tissue [64,65] possibly suppressing anti-viral responses. Interventional studies in non-pathogenic (AGM) and pathogenic (RM) animal models attempting to deplete (administration of Ontak) or block the function of (administration of anti-CTLA) Tregs in SIV infection have led to worsening immune activation and increasing viremia [48,51].

Three factors limit current investigations of Tregs in HIV: (i) phenotype does not equal function, as activated T cells can upregulate FoxP3, and TGF- β can induce FoxP3 and CD25 in naïve T cells without conferring suppressive function [66]; (ii) functional studies are difficult to perform due to cell number limitations; (iii) sampling of peripheral blood, which contains <5% of the lymphocyte population, may be suboptimal due to sequestration in lymphoid tissue. Considering the technical difficulties of studying small subsets of CD4 T cells in patients with significant CD4 lymphopenia, further Treg studies will depend on identification of markers that reliably predict function. Nevertheless, current evidence supports a potentially beneficial role of Treg in containing immune activation in HIV/SIV infection.

The Decisive Role of Type I Interferons in Chronic HIV Infection

In viral infections, type I interferons contribute to direct anti-viral activity and maturation of effector T cells [67,68]. Type I interferons also promote apoptosis of infected cells and suppress T and B cell development of mice in the thymus and bone marrow predominantly by interfering with IL-7 signaling [69-71]. IFN α is involved in the activation of T, NK, and B cell subsets and appears to be a significant link between innate and adaptive immunity in HIV disease pathogenesis [72]. Despite evidence for anti-HIV activity of type I interferons [73,74], the innate immune response during HIV infection may be the main driver of immune activation and disease progression [75]. Plasmacytoid dendritic cells (pDCs), in response to HIV virus or particles, produce type I interferons that lead to CD4 T cell apoptosis via TNF-related apoptosis inducing ligand (TRAIL) and expression of the tryptophan-catabolizing enzyme indoleamine-2,3-dioxygenase (IDO). IDO inhibits TCR-triggered T cell proliferation [76] and can induce differentiation of naïve CD4 T cells into Tregs [77]. Boasso et al [76] showed that T cell activation occurs within 24h of in vitro infection of peripheral blood mononuclear cells (PBMC) – before any HIV-specific response can be generated, is associated with diminished proliferation to TCR signaling and can be reduced by more than 50% when IFN α was blocked. Despite increased circulating IFN α in patients with progressive disease, pDCs from HIV+ patients demonstrate a blunted IFN response upon stimulation in vitro [78]. This functional exhaustion of pDCs is the consequence of continuous in vivo stimulation as shown in HIV/HCV co-infected patients who have diminished in vitro pDC responses following treatment with exogenous IFN [79]. Supporting evidence comes also from microarray comparisons of activated CD4 T cells from HIV+ individuals with those from HIV- controls confirming markedly greater expression of IFN target genes in HIV [80].

In early pathogenic SIV infection of macaques, Mallaret et al [81] demonstrated an initial increase in peripheral pDCs, followed by recruitment to lymph tissue and concomitant depletion in peripheral blood. Depletion mirrored increases in plasma SIV-RNA and IFN-I, IDO, IFN γ , and IL-18 levels. Control of viremia with ART reduced the observed pDC tissue sequestration and dampened cytokine elevation. Consistent with HIV infection, in which IFN- α levels correspond to disease progression, SIV-infected RMs produce significantly higher IFN- α levels than SMs in response to SIV [82] (figure 1). SIV leads to pDC activation via TLR7 and TLR9 stimulation with subsequent IFN α production in human and RM PBMC that is markedly attenuated in SMs. This selective lack of innate response to acute SIV infection in SMs with muted NK cell activation, DC maturation and homing and abrogated INF α but not TNF α response warrants further investigation. These studies have clearly highlighted the role of pDCs and type I IFN in immune activation and their potential as therapeutic targets.

Effective CD8 T cells in HIV infection: A case for strength and youth

The role of CD8 T cells in controlling HIV and SIV viremia has been extensively studied. We selectively review publications of the past year that highlighted distinct features of CD8 T cells from LTNP, the potential role of inhibitory receptors and the presence of auto-reactive CD8 T cells in HIV+ patients.

The degree or polyfunctionality of anti-HIV specific CD8 T cell response, as measured by cytokine production, does not predict disease progression [83]. Nonetheless, the CD8 T cells of LTNPs appear to be different than those of progressors. Progressors initially mount a strong polyfunctional anti-HIV CD8 T cell response, but unlike LTNPs are unable to sustain it [83]. Previous studies have shown that HIV-specific CD8 T cells from LTNPs were more proliferative in response to HIV peptides or autologous CD4 T targets than those from progressors [84]. Most recently, CD8 T cells from LTNPs were shown to be more effective killers of HIV-infected CD4 T cells by release of perforin and granzyme B [85].

Another study highlighted a different aspect of the CD8 T cell advantage in elite controllers: telomeres in their HIV-specific CD8 T cells were significantly longer (and telomerase more active) compared to progressors [86]. CD8 T cells that have lost expression of CD27 and CD28 due to repeated stimulation and activation were incapable of reviving telomerase levels but were still capable of producing IFN γ and perforin upon stimulation. Thus, loss of telomerase may represent a state of end-stage differentiation and not functional exhaustion [86]. Enhanced T cell survival after TCR stimulation and $\gamma\epsilon$ cytokine signaling was also shown in the memory CD4 T cells of elite controllers compared to both progressors and HIV-uninfected controls and was found to be related to higher levels of phosphorylated FOX3a, a transcription factor that has anti-proliferative and pro-apoptotic effects in its unphosphorylated, transcriptionally active form [87,88]. Blocking FOXO3a by siRNA in this study improved T-cell survival after TCR stimulation [87].

Programmed death receptor (PD)-1 was first identified as a marker of T cell “exhaustion” correlating with HIV disease progression [89]. PD-1 was found to be over-expressed and associated with activation, impaired proliferation and reduced anti-viral activity in memory CD8 T cells of progressors as compared to LTNP [90]. Although blockade of PD-1 was shown to increase T cell survival [90], PD-1 is also expressed by activated, functional T cells, and may simply be an indicator of over-activation as opposed to the cause of T cell exhaustion [89,91]. However, treatment of SIV-infected RM in vivo with anti-PD-1 antibody improved CD8 T cell proliferation, increased SIV-specific CD8 T cell responses, decreased measurable viral load and improved survival [92]. These changes were seen primarily in TCR-triggered CD8 T cells, mitigating concerns about frank autoimmunity but evoking the possibility of selection of resistant viral mutants. Another inhibitory molecule, the T cell immunoglobulin

and mucin domain-containing protein-3 (Tim-3), is up-regulated independently of PD-1 and is also associated with T cell dysfunction that can be partially reversed with blockade of its pathway [93]. The description of other inhibitory receptors on CD8 T cells that appear to co-regulate T cell exhaustion in chronic viral infections [94] as well as the presence of similar receptors on B lymphocytes in HIV infection [95] highlight the complexity of this field and the potential for multiple therapeutic targets.

Finally, self-reactive CD8 T cells may contribute to systemic immune activation in HIV. In mice, lymphopenia-induced proliferation can lead to loss of tolerance and auto-immunity [96]. In an intriguing study, Rawson et al [97] found that HIV infected patients have evidence of auto-reactive effector CD8 T cells specific for caspase-cleaved peptides from apoptotic T-cells. The number of effector CD8 T cells correlated with apoptotic CD4 T cells in HIV infected patients and decreased with ART.

The Role of Co-infections

Progression and transmission of HIV disease can be altered by bacterial and viral co-infections, which may actively participate in immune activation. Genital co-infections are associated with increased susceptibility to HIV, possibly due to local activation of Langerhan's cells enhancing transfer of HIV virions to CD4 T cells over viral degradation [98]. Genital HSV-2 infection also increases the local population of immature DC, leading to an influx of activated, CCR5+ CD4 T cell targets for HIV [99]. Infection with other viruses, especially adenovirus, has received attention following the STEP vaccine trial [100]. Perreau et al [101] found that adenovirus immune complexes (Ad5-IC) induce DC maturation and activation in vitro, resulting in increased production of TNF α and type I interferons. Ad5-IC significantly increased in vitro HIV infection, suggesting that adenovirus may create a "permissive environment" for HIV infection.

Mycobacterium tuberculosis (MTB) increases HIV-1 viral replication and immune activation at sites of infection. Interestingly, this increase in HIV replication is most pronounced in patients with normal CD4 T cell counts, suggesting that the synergy of the two infections may be dependent on the magnitude of immune response and activation [102]. Parasitic coinfections have also been shown to influence the natural history of HIV [103]. Rhesus macaques with schistosomiasis and SIV experience higher levels of SIV RNA than those infected with SIV alone [104]. In addition, treatment of lymphatic filariasis in HIV-infected patients led to decreases in plasma viremia, while treatment of *A. lumbricoides* led to CD4 T cell count increases [105,106].

Hepatitis C (HCV) co-infection appears to increase the percentage of activated, less mature CD8 but not CD4 T cells [107] and antiretroviral therapy interruption in hepatitis B or C co-infection is associated with non-opportunistic disease related death [108]. Further studies characterizing the interactions of HIV and chronic viral hepatitis and other latent chronic viral infections such as CMV and EBV will be critical in understanding their effects on HIV pathogenesis and disease prognosis.

Conclusion

Immune activation is at the crux of the complex interplay of innate and adaptive immunity throughout the asymptomatic stage of HIV infection (figure 2). Based on current evidence, the most effective preventive or therapeutic interventions may be those that maintain low levels of immune activation with either low (the elite controllers paradigm) or variable levels of HIV viremia (the sooty mangabey paradigm). Further elucidation of factors that influence the immunologic threshold to HIV disease progression may lead to therapeutic strategies that target immune activation and could include individualized timing of ART.

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	Sooty Mangabey No Immune Activation	Rhesus Macaque Immune Activation
Viremia	✓	✓
Disease Progression		✓
Peripheral CD4 depletion		✓
Gut CD4 depletion	✓	✓
Regulatory T cell preservation	✓	
IFN α pDC response		✓
Th17 cell loss in blood and gut		✓
↑ LPS in peripheral blood		✓

Figure 1.
Summary of differences between nonpathogenic (sooty mangabeys) and pathogenic (rhesus macaques) SIV infection.

Figure 2. Immune activation in HIV infection results from dysregulated innate and adaptive immune responses to HIV, microbial products, co-infections and homeostatic signals.