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Role of Immune Activation in Progression to AIDS

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Abstract

Purpose of the review—To review recent insights into the impact of HIV-associated immune activation on AIDS and non-AIDS morbidity and mortality.

Recent findings—Immune activation has long been recognized as an important consequence of untreated HIV infection and predictor of AIDS progression, which declines but fails to normalize during suppressive antiretroviral therapy (ART), and continues to predict disease in this setting. Thus, a major research agenda is to develop novel therapies to reduce persistent immune activation in treated HIV infection. Yet, the optimal targets for interventions remain unclear. Both the specific root causes of immune activation and the many interconnected pathways of immune activation that are most likely to drive disease risk in HIV-infected individuals remain incompletely characterized, but recent studies have shed new light on these topics.

Summary—In the context of this review, we will summarize recent evidence helping to elucidate the immunologic pathways that appear most strongly predictive of infectious and non-infectious morbidity. We will also highlight the likelihood that not all root drivers of immune activation - and the discrete immunologic pathways to which they give rise - are likely to produce the same disease manifestations and/or be equally attenuated by early ART initiation.

Keywords

Immune activation; monocyte activation; HIV infection; non-AIDS events; AIDS

Introduction

The first clue that immune activation was a central feature of HIV pathogenesis came in the first case reports of AIDS in 1981, long before HIV-1 was even recognized as the cause of AIDS [1]. In this initial report, Gottlieb et al noted that the young gay men dying of pneumocystis pneumonia in Los Angeles had not just very low CD4+ T cell counts, but also extraordinarily high levels of the surface marker “T10” on their lymphocytes. This marker T10 was later renamed CD38 and became one of the most commonly used markers to assess T cell activation in the pre-antiretroviral therapy (ART) era. Giorgi and colleagues

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subsequently demonstrated that greater CD38 expression on CD8+ T cells predicted more rapid disease progression independently of CD4+ T cell count and the extent of viral replication (and in later work, more strongly than the degree of viral replication) [2, 3]. It is also noteworthy that during this same period, neopterin and β2-microglobulin - markers of innate immune (and more specifically monocyte/macrophage) activation – were also found to be abnormally high in untreated HIV infection and to predict more rapid progression to AIDS, though not quite as strongly as T cell activation [2, 4]. This was an important initial clue that while HIV caused generalized activation of the innate and adaptive immune systems, it was the adaptive immune defects that seemed to be playing a more important role in driving AIDS and other infectious complications. While this may seem intuitive, it is an important insight, suggesting that several distinct pathways of immune activation differentially drive end organ disease manifestations.

Persistent Immune Activation during ART

While ART-mediated viral suppression causes significant reductions, many immune activation pathways remain abnormal during suppressive ART, particularly among those who initiated ART at late disease stages [5–11]. Indeed, early initiation of ART (within the first 6 months of infection) appears to achieve a lower immune activation set-point than when ART is delayed even a few years [12, 13]. Nevertheless, even very early ART – initiated in the first few weeks of HIV infection – fails to completely normalize several pathways of innate immune activation [14], suggesting that while many pathways of immune activation clearly get worse with progressive untreated infection, some irreversible drivers of immune activation are established very early. Conversely, hypercoagulability (i.e. D-dimer elevations) and some adaptive immune defects are nearly completely reversed by very early ART [14, 15], suggesting that some pathways of HIV-associated immune dysfunction (and presumably their drivers) require at least several months of untreated infection before defects become irreversible. This is an important point as the two largest clinical trials of early ART (START and Temprano) primarily demonstrated benefit of this strategy in reducing infectious complications and malignancies (mostly infection-associated), with less evidence for a robust decline in cardiovascular events [16, 17].

While the specific drivers of persistent immune activation during suppressive ART are incompletely characterized, HIV persistence (particularly in lymphoid tissues), microbial translocation, and chronic viral co-infections (particularly cytomegalovirus [CMV]) likely contribute [18]. A critical issue that remains largely unaddressed is whether these putative drivers of persistent immune activation, each of which may get worse (and potentially less reversible) with progressive untreated HIV disease, are equally ameliorated by the very early initiation of ART and/or drive the same end-organ disease manifestations. Indeed, just as discrete immune activation pathways had differential prognostic capacity in the pre-ART era, not all immune activation pathways –and their root drivers – are likely to predict specific morbidities equally with suppressive ART. For example, among ART-suppressed HIV-infected individuals in North America, innate immune activation and inflammatory markers were much more strongly predictive of mortality than T cell activation (the opposite inference from the pre-ART era) [19, 20], presumably because most of the causes of death were non-infectious in etiology (e.g., cardiovascular, non-AIDS cancer, etc). Conversely,

among ART-suppressed individuals in resource-limited settings, where infectious complications remain much more important causes of death [16, 17], T cell activation and pathways conferring adaptive immune defects are much stronger predictors of mortality [21–23]. Thus, it would not be surprising if the final common immunologic pathways driving disease vary by end-organ complication. For example, adaptive immune defects may be more important for infectious complications and infection-related malignancies whereas monocyte/macrophage activation may be more important for cardiovascular, metabolic, and neurocognitive complications [24–26]. Much less discussed, however, is whether the root drivers of immune activation may vary in their contributions to these pathways. For example, since HIV is preferentially expressed in inductive lymphoid tissues, it would not be surprising if HIV reservoirs were a primary mediator of adaptive immune defects that persist during ART. Conversely, other co-infections like CMV may be preferentially expressed in endothelial tissues, potentially playing a more important role in cardiovascular complications [27–29]. These hypotheses will be important to address to identify the most important interventional targets to prioritize for clinical trials, the specific morbidities (or their surrogates) to include as primary outcome measures, and the specific patient populations at highest risk (i.e., those who began ART during early vs. advanced HIV infection).

Specific Immunologic Pathways that Predict Disease in HIV Infection

T cell activation and dysfunction

T cell activation –characterized as either the co-expression of CD38 and HLA-DR or the intensity of CD38 expression on CD8+ T cells - has long been established as an important predictor of the rate of disease progression in untreated HIV infection, independent of plasma HIV RNA levels, and more strongly than soluble markers of innate immune activation [2, 3, 30, 31]. After more than two decades of research, it remains unclear whether CD38 and HLA-DR expression on CD4+ and CD8+ T cells are in and of themselves causally associated with disease or instead markers of exhaustion and/or dysfunction [32] in response to HIV, co-infection, or homeostasis- or activation-induced proliferation [33]. These markers continue to predict disease during ART-mediated viral suppression, but not as strongly as in the pre-ART era (when AIDS complications dominated) [19, 20, 22], and primarily in resource-limited settings [23].

Interestingly, phenotypic markers of CD8+ T cell differentiation and/or proliferative history appear to be more important predictors of mortality in treated HIV infection than CD38 and HLA-DR expression (or PD-1 expression, for that matter [19, 20]). For example, effector CD28−CD8+ T cells – while expanded – express the terminal differentiation and proliferative history marker CD57 at abnormally low frequencies in both untreated and treated HIV infection [34]. This is the exact opposite effect of aging and CMV infection on effector CD8+ T cells, and appears to predict subsequent mortality during ART-mediated viral suppression to a much greater degree than T cell activation [15]. The determinants of these maturational and and/or proliferative effector CD8+ T cell defects in HIV infection remain unclear, but may provide insights into novel interventions to reverse adaptive immune defects that persist even in individuals who start ART during very early HIV

infection. Indeed, approximately 1% of the immediate ART arm in START experienced an AIDS complication within 5 years of treatment initiation, despite maintaining normal CD4+ T cell counts. Similarly, while early ART diminished the risk of TB in TEMPRANO subjects with high CD4+ T cell counts, there was a clear additive benefit of INH prophylaxis and a substantial ongoing risk of TB even in this subgroup.

Indoleamine 2,3-dioxygenase-1 (IDO) Activity

The IDO pathway is a potentially important link between innate and adaptive immune defects in HIV infection. In both untreated and treated HIV, type I and II interferons and other inflammatory stimuli induce IDO expression in activated myeloid cells, which results in the catabolism of tryptophan into several downstream catabolites that have important immunologic and neurologic effects. For example, the tryptophan catabolites kynurenine and picolinic acid suppress T and NK cell proliferation in vitro [35, 36], potentially directly impairing both innate and adaptive immune function. The tryptophan catabolite 3-hydroxyanthralinic acid (3-HAA) also promotes regulatory T cell expansion (further impairing T cell function) while suppressing Th17 and Th22 cells, resulting in impaired gut epithelial barrier integrity and potentially contributing to microbial translocation and further innate immune activation [37]. Recently, three cohort studies have now linked systemic IDO activity (typically assessed as the plasma kynurenine/tryptophan ratio) to increased mortality during suppressive ART, suggesting that this pathway may well be clinically relevant [19–21]. This pathway might also contribute to neurologic morbidity. IDO activity may deplete tryptophan stores in the brain, which are essential for serotonin synthesis, thereby promoting depression as suggested in a recent observational study [38]. The tryptophan catabolite quinolinic acid is also an established neurotoxin and had been linked to AIDS dementia complex in the pre-ART era [39]. Given its multiple potential deleterious effects on immune and neurologic function, and that it may promote a positive feedback loop of microbial translocation and immune activation via 3-HAA, the IDO pathway remains an important interventional target. Fortunately, several IDO inhibitors are in various stages of development for cancer (one of many immune checkpoint inhibitor strategies being pursued), so new tools may be available to attenuate this pathway in the near future.

Monocyte activation

Monocyte and tissue macrophage activation has become increasingly recognized as a potential mediator of non-AIDS morbidity and mortality in the modern treatment era. HIV results in a shift from “classical” CD14++CD16− to “non-classical” CD14+CD16+ and “intermediate” CD14++CD16+ monocytes, which are associated with an inflammatory phenotype [40–42] and greater viremia and/or CD4+ T cell depletion [42, 43]. High expression of the PD1 homologue (PD-1H), which is associated with increased production of TNF, IL-1β, and IL-6, may also contribute to the pro-inflammatory state of these monocytes [44]. CD16+ non-classical and intermediate monocytes have a high migratory capacity, which has been attributed to expression of the chemokine receptors CCR2, CCR5, [45, 46] and CX3CR1 [47]. Indeed, higher expression of the monocyte adhesion molecule CXCL8 was associated with death in SMART [48]. These migratory monocytes have been postulated to facilitate HIV dissemination into tissues such as the intestine and liver and contribute to reservoir establishment [49]. While ART reduces these pro-inflammatory

monocytes [40, 41], it is less clear whether ART suppresses inflammatory tissue macrophages that were established prior to ART. Persistence of the HIV reservoir, microbial translocation, and co-infections despite ART may continue to stimulate inflammation in tissue macrophages..

Monocyte recovery, viability, and protein expression can be compromised during cell processing, cryopreservation, and thawing. Thus, circulating biomarkers released by activated monocytes such as soluble CD14 (sCD14), soluble CD163 (sCD163), IL-6, neopterin, and interferon gamma-induced protein 10 (IP-10) are often used to identify monocyte activation. CD14 is the LPS receptor, and sCD14 is shed or secreted by monocytes in response to LPS stimulation, but also potentially by neutrophils and hepatocytes. Whether sCD14 is specific or quantitative for microbial translocation remains controversial [50, 51], but the rapid decrease in sCD14 levels without changes in LPS after initiating ART suggests other inflammatory cytokines may contribute to its shedding [52]. CD163, the haptoglobin receptor, is expressed exclusively by macrophages and monocytes and its shedding is at least in part mediated by TNF [53]. Tissue macrophages express higher levels of CD163 than circulating monocytes, suggesting high sCD163 may reflect underlying tissue inflammation. Other markers of inflammation, including IL-6, IP-10 and neopterin [54] [55] [56], are less specific for monocyte activation Given the differing sources and drivers of these biomarkers, it is not surprising that they do not consistently correlate with each other [13, 40, 57]. Nonetheless, high IP-10, neopterin, and sCD163 levels - but not sCD14 - were associated with an increased frequency of increased intermediate CD14++CD16+ monocytes in HIV-infected individuals [40], whereas only high IP-10 levels have been associated with decreased frequencies of classical CD14+ +CD16−.monocytes [40]. Notably, sCD163 correlated with tissue factor (TF) on both classical and intermediate monocytes, consistent with its association with some (though not all [24]) surrogate markers of cardiovascular disease [40, 58, 59].

High levels of biomarkers of monocyte activation may reflect or even predict HIV disease progression. High plasma IP-10, IL-6 and sCD14 all consistently predict increased subsequent morbidity and mortality during ART [42, 43, 60], and high sCD163 levels have been associated with surrogate markers of neurologic and cardiovascular disease (though perhaps not cardiovascular events [61]), as well as all-cause mortality in a recent report [26, 57–59, 62, 63]. As many of these biomarkers of monocyte activation may be increased by smoking and/or alcohol use, many of these associations with morbidity and mortality may be at least in part driven by behavioral risk factors and not HIV itself, though a recent report suggests that these associations persist despite adjustment for behavioral risk factors [64]. However, similar to T cell activation, whether the association of monocyte activation with morbidity and mortality is causative or correlative remains unclear.

Type I interferons

Type I IFNs may contribute to monocyte activation and thereby facilitate HIV dissemination and disease progression. Data from the CAPRISA 004 study suggest that IFN signaling may render women more susceptible to infection. Women with detectable MIP-1a and MIP-1b and higher levels of IP-10, all of which are upregulated by interferons, in cervicovaginal

lavage were at increased risk of HIV acquisition [65]. The increased risk is likely attributed to increased HIV target cell recruitment to the vaginal mucosa by these three chemokines [65]. However, IFNα administration prior to high-dose SIV rectal challenge delayed acquisition of systemic infection [66]. Thus, increased IFN signaling may facilitate HIV acquisition in target-limited tissues and protect against acquisition in target-rich tissues.

However, blocking type I IFNs during acute SIV infection accelerates progression to AIDS and death [66], indicating their role in inducing antiviral responses supercedes the detrimental consequences of activating monocytes and creating and recruiting target cells. Indeed, in cervical explants, poly IC initiates an IFN signaling cascade through the master IFN signaling regulator, IRF7, and decreases HIV replication. IFN signaling may even be synergistic with antiretroviral drugs such as tenofovir to suppress HIV replication [67]. Moreover, genetic polymorphisms that interfere with IFN signaling are associated with rapid disease progression [68]. However, the balance of the benefits of HIV control with the potentially detrimental pro-inflammatory effects of type I IFNs warrant consideration. IFNα upregulates Siglec-1 on monocytes and dendritic cells (DCs) [69] and therefore facilitates myeloid cell capture of HIV. These myeloid cells can then transfer HIV to CD4+ T cells via cell-to-cell contact. As Siglec-1+ cells have been identified in the perifollicular CD4+ T cell-rich region of the lymph node, it is not surprising that high Siglec-1 expression correlates with high plasma viral load and low CD4+ T cell counts [69]. In addition to upregulating Siglec-1, in vitro data suggest IFNα interferes with IL-7- and IL-2-mediated CD4+ T cell proliferation and thereby further increases CD4+ T cell death [70]. Several studies are queued to evaluate the effects of IFNα administration or blockade using an experimental drug in the setting of suppressive ART [71]. These interventions will likely have opposite effects on immune activation and possibly on CD4+ T cell counts and further illuminate causal factors in CD4+ T cell depletion. However, these studies are not designed to assess long-term clinical consequences including non-infectious complications and mortality.

Lymphoid tissue fibrosis

Lymphoid tissue fibrosis begins in acute retroviral infection [72]. Studies of pathogenic non-human primate models demonstrated that collagen deposition in lymphoid tissue [72] begins as early as 7 days post-infection and in response to stimuli such as LPS and HIV itself. These stimuli induce an inflammatory response reflected by increased expression of the interferon-stimulated gene Mx1 and of the cell proliferation marker Ki67. Regulatory T cells are then activated to express TGFβ, the canonical driver of fibrosis. Resident fibroblasts deposit collagen I, III, fibronectin, and other components of the extracellular matrix [72], destroying the lymph node structure. This destruction of the discrete pathway of fibroblast reticular cells that guides T cells, especially naive T cells, to the paracortical T-cell zone, prevents their interaction with antigen-presenting cells and survival and proliferation signals such as IL-7. Similarly, the pathway guiding B cells to the primary follicles where they encounter follicular dendritic cells and their cognate antigens is destroyed. In contrast to pathogenic hosts, natural hosts of SIV infection do not upregulate TGFβ in lymphoid tissue or develop lymphoid tissue fibrosis [73]. SIVcpz confers an intermediate phenotype in the

chimpanzee, with substantial variability noted among animals and fibrosis primarily occurring in non-captive animals [74, 75].

Thus, fibrosis compromises clonal expansion of T cells and germinal center formation [73]. This fibrosis also involves the gut-associated lymphoid tissue (GALT), which may further perpetuate microbial translocation and fibrosis. As the vast majority of T cells are found in lymphatic tissue, greater lymphoid tissue fibrosis and duodenal TGFβ expression correlate with lower CD4+ T cell counts. In the GALT, this TGFβ appears to be produced by intestinal myofibroblasts in response to LPS stimulation [76]. Captive chimpanzees virtually normalize their T cell and monocyte activation, perhaps due to the lack of additional pro-inflammatory environment stimuli. However, increased collagen deposition in the T cell zone of lymphoid tissue was maintained and CD4+ T cell counts remained decreased compared to healthy animals [75]. Thus, the transient inflammation that resulted in collagen deposition in the lymphoid tissue is sufficient to suppress CD4+ T cell counts. In contrast, non-pathogenic SIV models without lymphoid fibrosis or microbial translocation do not progress to AIDS [73]. Ultimately, interventions to improve or prevent impaired gut integrity and increased intestinal LPS levels may reduce lymphoid fibrosis. As fibrosis limits CD4+ T cell recovery on ART and may impair antigen-specific responses [77], interventions that attenuate lymphoid tissue may have pleiotropic benefits.

Conclusion

HIV activates several arms of the immune system, which likely gives rise to several different infectious and non-infectious disease manifestations, even during ART-mediated viral suppression. These discreet immunologic pathways, while overlapping, likely have distinct roles in mediating different disease manifestations and may even have distinct root causes. A better understanding of which pathways drive specific disease manifestations, the root causes of those pathways, and the degree to which they can be reversed by early ART initiation will help prioritize interventional targets to study and identify the populations at highest risk. This systematic approach is likely to help accelerate the development of novel interventions to further improve the health of HIV-infected individuals in the modern treatment era.

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Key Bullet points

- Early ART appears to be most effective at decreasing infectious complications.
- The degree to which early ART reverses discreet pathways of immune activation and their drivers may differ.
- The extent to which discreet pathways of immune activation drive morbidity and mortality may differ according to the end-organ disease of interest and environment.
- Understanding the immune activation pathways and their root drivers that are most strongly predictive of disease may help prioritize targets for interventions to pursue in clinical trials and identify individuals at highest risk.