The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

Cytokines and T-Cell Homeostasis in HIV Infection

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Untreated human immunodeficiency virus (HIV) infection is characterized by progressive $CD4^+$ T-cell depletion and $CD8^+$ T-cell expansion, and $CD4^+$ T-cell depletion is linked directly to the risk for opportunistic infections and infection-associated mortality. With suppression of HIV replication by antiretroviral therapy, circulating $CD4^+$ Tcell numbers typically improve while $CD8^+$ T-cell expansion persists, and both $CD4^+$ T-cell cytopenia and $CD8^+$ T-cell expansion are associated with morbidity and mortality. In this brief review, we report on the role that selected homeostatic and inflammatory cytokines may play both in the failure of $CD4^+$ T-cell restoration and the $CD8^+$ T-cell expansion that characterize HIV infection.

Keywords. HIV; T cells; cytokines.

Cells communicate directly through contact, indirectly through elaboration of soluble mediators, or by both mechanisms. In fact, the multiple interactions among immune cells carefully orchestrated in space and time by contact and by soluble factors are key determinants of effective innate and adaptive immune responses. Politically, a cell can have great influence on the immune environment by elaborating soluble mediators that can persuade cells to do its bidding at a distance without requiring cell-to-cell contact. The importance of this signaling at a distance is likely diluted by distance from the source, and thus cytokines (or cell movers) are thought to exert most of their activities locally. Cytokines are typically proteins or glycoproteins, but lipid-containing cellular products are also important mediators of intercellular interactions, as are membrane-enclosed extracellular vesicles containing mediators within. In typical clinical settings, cytokine levels are measured in plasma, but their role in circulation is uncertain. It is likely that cytokines in plasma are reflective mostly of what is leaked into circulation from tissues where they are most active.

CYTOKINES IN ACUTE HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Acute HIV infection sometimes manifests clinically as a nonspecific viral infection syndrome with fever, sore throat, lymphadenopathy, or localizing symptoms, such as aseptic meningitis. The systemic symptoms of this acute seroconversion syndrome are thought to be due to a systemic cytokine storm, as plasma levels of inflammatory cytokines are characteristically elevated [1]. As illness symptoms resolve, the cytokines that drive the febrile response typically diminish, but many do not normalize. Acute HIV infection is accompanied by a reduction of $CD4^+$ T-cell numbers in blood, mucosa, and tissues and by an increase in overall $CD8^+$ T-cell numbers, but how cytokines are involved in these changes is not well defined [2].

CYTOKINES IN CHRONIC UNTREATED INFECTION

In untreated HIV infection, plasma levels of inflammatory mediators such as interferons (IFNs), interleukin 6 (IL-6), and tumor necrosis factor (TNF) are typically elevated [3]. The sources of these cytokines are not clear, and it is likely that local elaboration of these mediators, perhaps at multiple sites, contributes to their sustained elevated levels.

CYTOKINES IN TREATED INFECTION

With antiretroviral therapy (ART), $CD4^+$ T-cell numbers often recover, while $CD8^+$ T-cell numbers remain elevated. Plasma levels of inflammatory cytokines typically diminish, but the degree to which they diminish and the pace at which they fall appear to vary among studies and also may vary among different combination antiretroviral regimens [3–5]. In treated HIV infection, residual levels of inflammatory mediators predict morbid outcomes [6], and, importantly, even pre-ART levels of cytokines have a similar prediction for morbid events, suggesting that there is an inflammatory set point in untreated infection that persists after ART-mediated virologic suppression. It is therefore important to better understand the ways in which these mediators may drive immune homeostasis or be a response to it.

In this review, we will identify and examine several inflammatory (IL-6, interleukin 1β [IL-1β], TNF, and type I IFNs [IFN-I]) and homeostatic (interleukin 2 [IL-2], interleukin 7 [IL-7], interleukin 15 [IL-15], and interleukin 21 [IL-21]) cytokines thought to be important during acute, chronic untreated, and antiretroviral-treated HIV infection.

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The Journal of Infectious Diseases® 2016;214(S2):S51–7

DOI: 10.1093/infdis/jiw287

INFLAMMATORY CYTOKINES

IL-6

IL-6 is produced by many cell types, including dendritic cells (DCs), activated monocytes, macrophages, B cells, T cells, epithelial cells, keratinocytes, fibroblasts, astrocytes, and muscle cells (including cardiomyocytes) [7–9]. While IL-6 is critical for early clearance of pathogens, persistent expression during chronic inflammation is linked to increased morbidity in several settings [10, 11]. IL-6 can be induced in monocytes by lipopolysaccharide (LPS), IL-1β, TNF, and platelet-derived growth factor [12]. IL-6 signals through a heterodimer of the IL-6 receptor (IL-6R), whose expression is limited to certain cell types, and a ubiquitously expressed coreceptor glycoprotein 130 (gp130) [7, 13, 14]. IL-6R exists in both membrane-bound and soluble forms. IL-6 can signal in *trans* by complexing with soluble IL-6R and then together binding gp130 on the cell surface [7, 14, 15]. IL-6 *trans* signals can be inhibited by binding of soluble gp130 to the soluble IL-6R/IL-6 complex [14].

IL-6, like IL-1β and TNF, mediates a systemic acute-phase response to infection or tissue damage by which tissue macrophages and blood monocytes initiate a cascade of events that eventually leads to attraction of innate immune cells, fever, and hepatic acute phase protein expression [11]. Specifically, IL-6 induces expression of C-reactive protein and serum amyloid A that bind microbial cell walls and act as opsonins to aid complement-mediated microbial clearance [11].

IL-6 is important in wound healing [16], in fibrosis resulting from unresolved inflammation [17], and in cardiac fibrosis [18], in part by upregulating transforming growth factor β receptor expression [19, 20]. Fibrosis in lymphoid tissues can hinder T-cell access to IL-7 and increase apoptotic cell death [21–23]. On the other hand, IL-6 has been shown to promote survival of immune cells in some mouse studies [24, 25] and in certain human inflammatory diseases [26, 27]. IL-6 may block T-cell apoptosis by maintaining levels of the survival factor Bcl2 [24, 26], but whether IL-6 directly promotes T-cell proliferation remains unclear [12, 25, 28, 29]. Our in vitro studies stimulating human peripheral blood mononuclear cells (PBMCs) with recombinant IL-6 suggest that IL-6 induces $CD4^+$ but not $CD8^+$ T-cell cycling without concomitant induction of the survival factor Bcl2 [30]. Thus, in environments with high levels of IL-6, $CD4^+$ T cells may be driven to cycle and turnover without replenishing the $CD4^+$ T-cell pool.

In HIV infection, elevated plasma levels of IL-6 during ART has been consistently associated with increased morbidity and mortality [6, 31, 32]. Antiretroviral-treated HIV-infected patients unable to reconstitute circulating $CD4^+$ T cells (immune failures) have elevated plasma levels of IL-6, increased cycling of $CD4^+$ memory T cells [33], and decreased $CD4^+$ T-cell expression of Bcl2 [34, 35]. In addition, by driving memory $CD4^+$ T cells to cycle, it is plausible that IL-6 could then drive HIV out of latency [36]. Exposure of T cells to IL-6 downregulates expression of CD127, the α chain of the IL-7 receptor [30], and preincubation of PBMCs with IL-6 reduced several IL-7–mediated effects on T cells, including maintenance of STAT5 phosphorylation, induction of integrin α4β7, and Bcl2 upregulation [30]. Consistent with these in vitro findings, reduced CD127 expression and decreased responsiveness to IL-7 have been identified in treated HIV infection [37] and in immune failure [38]. IL-6 has also been accused of promoting thymic involution [39] that results in decreased numbers of circulating naive T cells [39]. In HIV disease, IL-6 may hinder the recovery of $CD4^+$ T cells by promoting premature thymic atrophy, contributing to lymph node fibrosis, decreasing responsiveness to the homeostatic cytokine IL-7, and increasing $CD4^+$ T-cell turnover.

Paradoxically, IL-6 can also promote antiinflammatory responses. IL-6 signaling through STAT3 can induce suppressor of cytokine signaling 3, which in turn inhibits IL-6–mediated proinflammatory functions [40]. IL-6 can also control the inflammation induced by IL-1β and TNF by inducing the production of IL-1β receptor antagonist and soluble TNF receptor p55 by macrophages [41].

IL-1β

IL-1β is initially generated as inactive pro–IL-1β after a primary signal, such as inflammasome-activating Toll-like receptor (TLR) ligation. Upon a second signal, inactive pro–IL-1β is cleaved by caspase 1 to become mature, active IL-1β [41–43]. Neutrophils, monocytes, macrophages, DCs, mast cells, natural killer (NK) cells, B and T cells, and endothelial cells are all sources of IL-1β [41, 43, 44]. IL-1β signals through a heterodimeric receptor consisting of the IL-1 receptor I (IL-1RI) protein and IL-1 receptor accessory protein (IL-1RAcP) [41]. IL-1β signaling is very similar to pathogen-associated molecular pattern or damage-associated molecular pattern signaling through TLRs, as both IL-1RI and TLRs have a cytoplasmic Toll/IL-1 receptor (TIR) domain [41]. Like soluble gp130 for IL-6/IL-6R complexes, IL-1RII is a decoy receptor with a shortened cytoplasmic domain that captures IL-1β without signaling. IL-1 activity can also be blocked by the soluble IL-1R antagonist (IL-1Ra) that binds IL-1RI [41].

IL-1β is one of the earliest cytokines generated during the acute-phase response to infection or injury [11, 43], and sustained expression in chronic inflammatory disorders is linked to morbidity [45]. Although IL-1β has been difficult to detect in plasma of patients with chronic HIV infection, one report found elevated levels in antiretroviral-treated patients and increased levels of IL-1β have been observed in the lymph nodes of antiretroviral-treated HIV-infected subjects [30, 46–48].

IL-1β can have an adjuvant-like effect, enhancing antigen-specific $CD4^+$ T-cell expansion, possibly by increasing IL-2 production or IL-2 receptor expression [49, 50, 51, 52], but it is not clear whether this is a direct effect on T cells [53, 54]. PBMCs cultured with IL-1β in vitro downregulate expression of CD127, and as is the case for IL-6 (above), IL-1β pretreatment can

abrogate the effects of IL-7 on T cells [30]. IL-1β exposure can induce cycling and proliferation of memory $CD4^+$ but not $CD8^+$ T cells in vitro without upregulating Bcl2 [30], and this effect appears to be an indirect effect mediated via a monocyte product (Shive, unpublished data). It is unknown whether IL-1β–induced cycling and proliferation of memory $CD4^+$ T cells contributes to HIV persistence.

In lymphoid tissues, abortive HIV infection of memory $CD4^+$ T cells activates caspase 1 and induces pyroptosis, an inflammatory programmed cell death mechanism associated with inflammasome activation [55, 56]. Pyroptotic death promotes release of IL-1β that can accelerate the cycle of chronic inflammation [43]. We have found that IL-1β–induced memory $CD4^+$ T-cell cycling induced the expression of the exhaustion and senescence markers PD-1 and CD57 [34]. Thus, abortive HIV infection in lymphoid tissue could lead to proinflammatory $CD4^+$ T-cell death by pyroptosis, releasing IL-1β, which in turn drives cycling, exhaustion, and senescence of memory $CD4^+$ T cells, decreasing $CD4^+$ T-cell numbers and function.

TNF

TNF is potent antiviral molecule that is mainly produced by hematopoietic cells—macrophages and T cells [57]. This transmembrane protein is solubilized by metalloprotease cleavage. TNF is a major driver of inflammatory diseases, such as rheumatoid arthritis and psoriasis. Plasma levels of TNF are increased in all phases of HIV infection, and circulating levels of TNF receptors are often used as indicators of TNF activity in vivo [58, 59]. In antiretroviral-treated HIV infection, soluble TNF receptor II (TNF-RII) levels are further increased in cytomegalovirus-seropositive individuals, suggesting coinfection with cytomegalovirus drives additional inflammation [60].

Binding of TNF to its receptor triggers several signaling cascades: NF-κB, MAPK, ERK, and JNK pathways [57, 58]. TNF may inhibit HIV replication, as TNF signaling downregulates CD4 and CCR5 by direct [61] and indirect [62] mechanisms and also induces other HIV restriction factors [58]. The effects of TNF on $CD8^+$ T-cell homeostasis are less clear, but TNF promotes lymphocyte apoptosis and may limit the effector phase of the HIV-specific $CD8^+$ T-cell response [63].

TNF may enhance histone deacetylase–induced HIV reactivation [64, 65], but HIV is suboptimally induced to reactivate from latently infected cells by TNF alone [64]. The effects of anti-TNF therapy in HIV-infected individuals have not been well characterized, but initial studies suggest that anti-TNF therapy may improve HIV-associated symptoms and does not appear to increase HIV-associated mortality [58]. Given the key role of TNF in effective immunity and the profound immune suppression present in HIV-infected persons, anti-TNF therapy during HIV infection must be approached with caution to guard against opportunistic infections and other unwanted side effects.

IL-10

Although primarily considered an antiinflammatory cytokine, IL-10 is also an important driver of T-cell function that could contribute to control of HIV infection. The receptor for IL-10 is a heterodimer of an α subunit (IL-10RA) specific for IL-10 and a β-subunit (IL-10R2) shared with a number of related family members, including the receptors for interleukin 22, interleukin 26, interleukin 28, and interleukin 29 [66]. IL-10 receptors are broadly expressed on hematopoietic cells, allowing many different immune cell types to respond to IL-10 signals. In mouse models of chronic infection, inhibiting IL-10 signals improves T-cell control of chronic infection [67, 68], but $CD8^+$ T-cell–derived IL-10 is critical in the proper control of primary influenza virus infection [69].

In HIV infection, plasma IL-10 levels positively correlate with viral load, and monocytes are thought to be a major source of IL-10 [70, 71]. IL-10 signals in $CD4^+$ T cells can upregulate CCR5 expression (and blocking IL-10 reduces CCR5 expression), but IL-10 seems to have little or no effect on CXCR4 [66, 72]. Thus, IL-10 might promote HIV infection by making target cells more susceptible to R5 HIV infection. Alternatively, IL-10 may enhance $CD4^+$ T-cell apoptosis, thus contributing to control of HIV infection but potentially at the expense of efficient immune responses to future pathogen exposure. Notably, in a genetic study of HIV-negative South African women, individuals with genotypes associated with high IL-10 levels showed a reduction in HIV susceptibility, but if they did become infected, they had increased viral loads during the acute phase of infection [73]. Early and high expression of IL-10 may also contribute to control of HIV disease in African green monkeys, which do not develop simian AIDS [74].

IFN-I

IFN-I cytokines have potent antiviral and immunoregulatory activities [75, 76]. In humans, there are 16 IFN-I cytokine family members, all of which bind to the heterodimeric IFN-I receptor (IFN-αR). Among the IFN-I cytokines, IFN-α and IFN-β are the most widely expressed and therefore best characterized [77]. IFN-I can be expressed by almost all cell types in response to direct viral and bacterial infections but are expressed at a higher level by plasmacytoid DCs than by other cell types [78]. IFN-I production occurs after detection of microbial products by pattern-recognition receptors on the cell surface, in endosomal compartments, and in the cytosol [76]. IFN-I expression and receptor engagement induce an antiviral state that is mediated by the products of >300 IFN-stimulated genes (ISGs) [79]. In addition to its antiviral activity, IFN-I regulates the activity of immune cells by activation of NK cell cytotoxicity, enhancement of antigen processing in DCs, and inhibition of cellular proliferation [76, 79]. The IFN-I cytokines are proapoptotic, as they can increase cell death by Bak- and TRAIL-mediated mechanisms in uninfected cells, inhibit T-cell proliferation, and be drivers of $CD8^+$ T-cell activation [80, 81]. Both antiviral and immunoregulatory

activities are important for the control of acute stage viral infections [82]. IFN-I expression may have deleterious effects during chronic infections: blocking IFN-αR promoted clearance of persistent lymphocytic choriomeningitis virus (LCMV) infection in mice by increasing the effector function of LCMV-specific T cells [83].

IFN-I is produced in both the acute and chronic stages of HIV infection. In chronic infection, ISG expression correlates with markers of disease progression, such as plasma viremia level and lower $CD4^+$ T-cell count [81]. In acute simian immunodeficiency virus (SIV) infection, IFN-I receptor blockade increased the risk of death while systemic or topical IFN-I administration was protective against SIV and simian-human immunodeficiency virus (SHIV) challenge [84, 85]. Sustained IFN-I administration in chronic SIV infection promoted $CD4^+$ T-cell depletion and increased the size of the viral reservoir [84]. Thus, it appears that it is all in the timing and that IFN-I is an important host antiviral defense, but sustained expression during chronic uncontrolled infection can be detrimental for the host. Plasma IFN-α levels are increased in untreated infection, are related directly to levels of HIV replication and inversely with circulating $CD4^+$ T-cell counts, and decrease with ART [81]. Sustained IFN-I exposure in chronic infection appears to result in desensitization, as IFN-αR expression is diminished in proportion to increased HIV RNA levels and is decreased with lower $CD4^+$ T-cell counts [86].

Despite undetectable plasma IFN-I levels in antiretroviral-treated HIV infection, IFN-I gene expression signatures remain increased in T cells from patients with immune failure [87], and plasma levels of the IFN-inducible protein IP-10 are increased [88]. $CD4^+$ T cells from patients with immune failure have a diminished signaling response to IL-7 [89] that may result in a failure of homeostatic T-cell expansion [34]. Exposure of T cells to IFN-α inhibits IL-7–induced signaling and proliferation that may be linked to induction of cell death and inhibition of thymopoiesis [90–92].

HOMEOSTATIC CYTOKINES

IL-2

IL-2 is a monomeric glycoprotein with 4 α helices folded in the typical configuration of the common γ chain type-1 cytokine family [93] that includes IL-2, interleukin 4, IL-7, interleukin 9, IL-15, and IL-21. The high-affinity IL-2 receptor (IL-2R) is expressed on the cell surface [94] and is a complex of α (IL-2Rα, CD25) and beta (IL-2Rβ, CD122) chains and the common γ chain (γc; CD132) [95]. IL-2Rβ and γc are expressed by a number of hematopoietic cell types, including NK cells, resting T cells, monocytes, and neutrophils [96].

IL-2 triggers T cells to switch from quiescence into the proliferative phases of the cell cycle. Binding of IL-2 to the high-affinity IL-2R leads to rapid internalization of the complex, leaving only a short window for intracellular signaling. Upon activation, IL-2R is rapidly upregulated on conventional T cells and NK cells. Following IL-2 binding and activation, IL-2Rβ and γc induce phosphorylation of JAK1 and JAK3, respectively; IL-2Rα does not participate in signaling but increases affinity of the receptor for the cytokine ligand. IL-2 also activates the MAP kinase and PI3K-Akt signaling pathways, promoting cell growth and survival [97].

In untreated HIV infection, spontaneous expression of IL-2 is increased in lymph node explants [98]. On the other hand, one of the first functional defects detected in asymptomatic HIV-infected individuals was low inducible T-cell expression of IL-2, which was predictive for loss of $CD4^+$ T cells, clinical progression to AIDS, and death [99], and IL-2 administration could increase circulating $CD4^+$ T-cell counts in HIV-infected persons [100, 101]. It was therefore postulated that therapeutic administration of IL-2 could potentiate systemic immune responses and improve $CD4^+$ T-cell counts in HIV-infected persons receiving ART. IL-2 administration induced $CD4^+$ and $CD8^+$ T-cell activation, proliferation, and apoptosis, but the net outcome of therapy has been a significant expansion of circulating $CD4^+$ T cells [101, 102]. In persons without uncontrolled viremia levels, cycles of IL-2 administration were associated with transient but reproducible increases in plasma levels of HIV [100].

The clinical effect of IL-2 in combination with ART was explored in 2 large multicenter trials (ESPRIT and SILCAAT). These studies failed to demonstrate any clinical benefit of IL-2 administration in preventing opportunistic diseases or death despite $CD4^+$ T-cell expansion [103]. IL-2–expanded $CD4^+$ T cells have characteristics similar to those of regulatory T cells (Tregs), expressing both CD25 and FoxP3 [104]. Thus, IL-2–expanded $CD4^+$ T cells may not provide the kind of help that is deficient in chronic HIV infection and that may be needed to prevent the morbid complications of HIV-related immune deficiency.

IL-7

IL-7 is primarily produced by stromal and epithelial cells, particularly in the thymus, lymph nodes, and intestinal epithelium [105, 106]. IL-7 can also be expressed by keratinocytes [107], in fetal and adult liver tissue [108, 109], in hair follicles [110], and by tonsil follicular and bone marrow–derived DCs [111, 112]. IL-7 signaling results in the phosphorylation of STAT5 and downstream activation of the PI3K, Akt, and MAP kinase pathways [113–115].

IL-7 is a key regulator of thymocyte development and mature T-cell homeostasis. It supports T-cell survival by modulating expression of Bcl2 and its family members [116]. In early thymocytes, IL-7 supports the survival of triple-negative ($CD3^-CD4^-CD8^-$)–stage cells [117] and promotes expansion of T-cell precursors. IL-7 is also important in the extrathymic development and homeostatic expansion of T cells [118] and is critical for γδ T-cell and innate lymphoid cell (ILC) development [119, 120].

Naive T cells express the α chain of the IL-7 receptor (IL-7Rα, CD127) and are exquisitely dependent on IL-7 signals for maintenance of the peripheral naive T-cell pool [118, 121]. In a lymphopenic environment, such as after bone marrow transplantation, IL-7 promotes the proliferation and survival of T cells, with effects on both thymopoiesis and on peripheral T cells [122, 123]. IL-7 signals are crucial for T-cell proliferation in response to peptide/HLA complexes with low affinity for the T-cell receptor [116, 124]. Thus, it is thought that these interactions are important for the homeostatic maintenance of naive T-cell numbers, and, in this regard, IL-7 has been shown to induce naive T-cell cycling [30] and is thought to be a major factor in the maintenance of T-cell receptor diversity [118]. In addition, IL-7 levels increase during periods of lymphopenia, largely, it is thought, as a consequence of diminished clearance as receptor levels fall [34, 123, 125].

IL-7 can act as a co–stimulatory factor, coupling with other T-cell activation signals to enhance T-cell proliferation and cytokine production; this is accomplished at least in part by the induction of IL-2Rα [126, 127].

IL-7 also has an underappreciated role in T-cell trafficking. IL-7 signals result in the upregulation of the gut-homing integrin α4β7 [30]. Given its production by intestinal epithelium, its role in γδ T-cell and ILC generation, and its ability to induce gut-homing molecules, IL-7 is therefore very important in intestinal immunity. IL-7 also stimulates expression of the chemokine receptor CXCR4 [128], a coreceptor for HIV that may be important in more-advanced stages of disease.

IL-7 also may play a role in HIV persistence via driving homeostatic proliferation of infected cells [129, 130]. IL-7 can augment T-cell susceptibility to HIV in vitro [128], and this may be mediated in part via inhibition of the activity of the HIV restriction factor SAMHD1 [131]. In vivo administration of IL-7 has been associated both with blips in plasma levels of HIV [132] and with increases in total numbers of peripheral blood T cells containing proviral HIV DNA [133]. Studies in the SIV animal model of HIV infection have provided conflicting results, as IL-7 was shown to increase T-cell numbers without inducing virus [125, 134].

Given its roles in T-cell proliferation and survival, the role of IL-7 has been examined closely in the setting of prolonged immunodeficiency, particularly among antiretroviral-treated persons with incomplete $CD4^+$ T-cell recovery (ie, immune failure) [30, 135]. In these patients, $CD4^+$ T cells appear relatively refractory to IL-7 signals, even though IL-7 levels are increased in plasma [34]. Although the mechanisms for this impairment in IL-7 responsiveness are not fully understood, persistent IFN-I signals may override the cell's ability to respond to IL-7 [90], and, as noted above, both IL-1β and IL-6 can decrease expression of IL-7Rα, diminishing T-cell responsiveness to IL-7 in vitro [30]. Alternatively, IL-7 signals might be inhibited as a result of fibrosis in the lymph nodes and thymus during chronic HIV infection [21, 136] that may interfere with intercellular communications. Diminished T-cell expression of IL-7α, impaired access to IL-7, and reduced responsiveness to IL-7 may all contribute to impaired T-cell homeostasis and $CD4^+$ T-cell cytopenia in HIV infection [21, 34, 136, 137].

IL-7 has been given systemically to HIV-infected persons with immunologic failure, and the pharmacologic levels of IL-7 achieved have reliably enhanced recovery of circulating $CD4^+$ T-cell numbers [133, 138–140]. These expanded $CD4^+$ T cells after IL-7 therapy do not have the Treg-like characteristics observed after systemic IL-2 administration [133]. Nonetheless, it is not yet clear whether the $CD4^+$ T-cell expansion seen after IL-7 administration enhances immune function or confers clinical benefit.

IL-15

Expression of IL-15 is detected in many cell types, including antigen-presenting cells, monocytes and macrophages [141], and lymph node stromal cells [98]. Although IL-15 messenger RNA (mRNA) is widely expressed in different cell types, it has been difficult to demonstrate IL-15 in supernatants of many cell cultures. This discordance between IL-15 mRNA expression and IL-15 protein production led to the observation that IL-15 expression is posttranscriptionally regulated by multiple elements [142]. As a consequence, demonstration of IL-15 RNA species in clinical samples may not always reflect expression of bioactive protein.

The main mechanism by which IL-15 interacts with its receptor in vivo is by *trans* presentation [143]. In contrast to IL-2 or IL-7, which interact directly with their cellular receptor complexes, IL-15 is assembled with the IL-15 receptor α chain (IL-15Rα) to form a complex in the endoplasmic reticulum, and then the IL-15/IL-15Rα heterodimer and CD122 are jointly expressed on the IL-15–producing cell surface, where this complex ultimately binds the γc receptor (CD132) on responding T cells and NK cells [143, 144]. IFN-Is serve as potent inducers of IL-15 during the antiviral immune response [145], and DCs stimulated with TLR ligands such as polyinosinic:polycytidylic acid and bacterial LPS are induced to express IL-15 [146]. This process potentiates immunity, as IL-15 stimulation of DCs leads to increases in surface levels of key accessory molecules CD11b, CD11c, CD40, CD80, CD86, and major histocompatibility complex, as well as increases in intracellular interleukin 12 levels [147].

Another important effect of IL-15 is on the maintenance and survival on memory $CD8^+$ T cells and NK cells [148]. Mice genetically deficient in IL-15 lack memory $CD8^+$ T cells [149]. In vivo administration of IL-15 has been shown to drive the proliferation of effector/transitional memory $CD8^+$ T cells in nonhuman primates [150–152]. Furthermore, IL-15 has been shown to play a role in the maintenance of tissue-resident memory $CD8^+$ T cells [144, 153].

Increased levels of IL-15 mRNA have been detected in monocytes and macrophages in HIV-1–infected patients [141, 154],

and we have found increased expression of IL-15 protein in the lymph nodes of untreated HIV-1–infected persons [98] that normalizes with ART [155]. Moreover, the cytolytic phenotype induced by IL-15 exposure in vitro bears many similarities to the cytolytic phenotype seen in circulating $CD8^+$ T cells in HIV infection.

IL-15 has been characterized as a danger molecule that alerts the immune system that tissue is under attack; exposure to IL-15 expands and arms cytolytic cells to mediate tissue destruction [144]. We suspect that high levels of IL-15 in lymphoid tissue promote $CD8^+$ T-cell expansion and help drive tissue damage and fibrosis that characterize chronic HIV infection [21, 156]. Furthermore, we hypothesize that IL-15 maintains an activated cytolytic effector $CD8^+$ T-cell phenotype in HIV infection, which has been linked to cardiovascular disease in HIV-uninfected persons [157].

IL-21

$CD4^+$ T cells are the major producers of IL-21, particularly T follicular helper (Tfh) cells and T-helper type 17 (Th17) cells [158–160]. IL-21 signals through a heterodimeric receptor composed of IL-21R and γc, initiating JAK1 and JAK3 activation that ultimately results in STAT1 and STAT3 phosphorylation [160]. IL-21R is abundantly expressed by many cell types and has a wide array of targets and responsive genes [160, 161].

In addition to its well-defined roles in the regulation of B-cell immunity [160], IL-21 has many effects on NK and T-cell responses [160–162]. IL-21 contributes to the differentiation of $CD4^+$ T cells into Tfh or Th17 lineages and may inhibit naive cell differentiation into Tregs [159]. Thus, IL-21 participates in a positive feedback loop in which IL-21–producing Tfh and Th17 populations contribute to their own development and differentiation [159].

In $CD8^+$ T cells, IL-21 signals have a synergistic effect on proliferation and cytotoxic function in combination with IL-7, IL-15, or T-cell receptor activation [163, 164]. Importantly, IL-21 signals were shown to be essential for proper control of chronic viral infection in mice, in part by IL-21–mediated effects on $CD8^+$ T-cell regulation of virus replication [165–167]. Direct IL-21 signals also seem to be essential for the generation of effector and memory $CD8^+$ T-cell populations in lymphopenic conditions [168].

The above findings suggest that IL-21 might have an important role in the immune response to HIV infection and highlight IL-21 as a possible therapeutic intervention. Although plasma levels of IL-21 are initially increased during acute SHIV infection of rhesus macaques [169], IL-21 levels in the serum are decreased during primary HIV infection of humans [170]; serum IL-21 levels are positively correlated with $CD4^+$ T-cell counts, and IL-21 levels recover partially during ART [170, 171]. IL-21 levels are not as diminished in the sera of elite controllers [170], and this observation may be linked to improved numbers of IL-21–producing Th17 cells in the gut mucosa and/or the finding that HIV-specific $CD8^+$ T cells from elite controllers are capable of secreting IL-21 [172]. In nonprogressive SIV infection of sooty mangabeys, Th17 cell numbers are sustained, whereas they are depleted in both the blood and rectal mucosa in progressive infection of rhesus macaques [173].

Therapeutic administration of IL-21 has shown promise in cancer and autoimmunity [160, 174]. IL-21 administration increased Th17 cell numbers, reduced microbial translocation, and enhanced SIV-specific $CD8^+$ T-cell effector cytokine and lytic granule expression in SIV-infected macaques [173, 175, 176]. Additionally, IL-21 administration decreased inflammation and reduced the viral reservoir when coupled with ART in SIV-infected macaques [177]. The antiviral activity of IL-21 in $CD4^+$ T cells may be mediated via STAT3-mediated upregulation of the antiviral microRNA-29 [178]. Thus, in addition to its positive effects on $CD8^+$ T-cell effector responses, exogenous IL-21 administration in vivo might protect IL-21R–expressing $CD4^+$ T cells from direct HIV infection and replication.

CONCLUSIONS

HIV infection, both untreated or controlled (but not cured) by ART, is characterized by profound immunologic abnormalities that include dysregulated expression of a number of bioactive cytokines. Elevated plasma levels of these intercellular communicators are linked to the inflammatory morbidities of HIV infection, but their roles in the perturbed T-cell homeostasis of HIV infection ($CD4^+$ T-cell depletion and $CD8^+$ T-cell expansion) are less clear. A far too simple summary links overexpression of inflammatory mediators (eg, IL-1β, IL-6, and IFN-I) to an inhibition of IL-7–induced homeostatic $CD4^+$ T-cell expansion despite the increased levels of IL-7 that are likely a consequence of lower level expression of the receptor and lower cytokine clearance as a result. Overexpression of IL-15 may contribute to $CD8^+$ T-cell expansion that is typically seen only in cytomegalovirus-infected patients and is linked to morbidity. How (or if) these and other cytokines that were not included in this review work in combination to affect immune homeostasis is poorly understood. Likewise, the tissue sources of these cytokines that are often found to be elevated in plasma of persons with HIV infection are also poorly understood. Sorting out these relationships will be difficult. Carefully designed clinical studies of agents that selectively decrease (or for some, such as IL-7, increase) their activity may help clarify their role in the dysregulated immune homeostasis and morbidities of chronic HIV infection.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Supplement sponsorship. This article appears as part of the supplement "Persistent Inflammation in Treated HIV Disease," sponsored by Case Western Reserve University and supported by funds from the James B. Pendleton Charitable Trust.

Financial support. This work was supported by the Case Western Reserve University Center for AIDS Research (grant AI036219; developmental award to M. L. F.), the Case Western Reserve University AIDS Clinical Trials Unit (grant AI069501), and the Richard J. Fasenmyer Foundation.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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51–178. These references are available in the Supplementary Appendix.