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Aging of the Human Innate Immune System in HIV Infection

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Abstract

HIV infection is associated with a chronic inflammatory state arising from multiple factors, including innate immune recognition of HIV, increased microbial translocation, and release of endogenous ligands from damaged cells (such as CD4 T cells). In many respects, this heightened pro-inflammatory environment resembles that associated with aging in the absence of HIV infection, and evidence of dysregulated innate immune responses can be found in not only older HIV-negative adults, but also adults with HIV infection. While the study of innate immune aging in HIV infection is still in its early stages, it seems likely that at least additive, or potentially synergistic effects of aging and HIV infection will be found.

The life expectancy of a 20-year-old HIV-positive adult on antiretroviral therapy (ART) is expected to be approximately 70 years [1,2], and it is estimated that by 2015, half of HIV-infected individuals in the United States will be over 50 [3]; aging of the HIV-infected population will occur in the developing world with increased availability of ART, and will profoundly affect HIV care. Consequently, understanding the nexus of immune activation from chronic viral infection with age-associated alterations in immune system responsiveness takes on particular urgency [4,5]. Here, we focus on the human innate immune system and the contribution of dysregulated inflammation to the clinical course of older adults with HIV disease.

HIV-Associated Innate Immune Activation: Inflamm-Aging Redux?

The association of HIV infection with a heightened pro-inflammatory environment was described early in the pandemic, with increased plasma levels of neopterin (a byproduct of GTP catabolism associated with macrophage activation), IL-6, TNF- α , TGF- β and others [6]. Elevations in IL-6, D-dimer (a fibrin degradation product that reflects activation of the coagulation cascade), and soluble CD14 (a marker of monocyte activation) were associated with CD4 counts <200 in a cohort of HIV-infected US veterans [7], and several studies have

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shown that HIV infection is associated with immune activation and elevated coagulation factors [8,9]. Enhanced inflammation is also apparent in elite controllers, a subset of HIV-infected patients who maintain low viral loads in the absence of ART, suggesting that high levels of HIV replication are not required for this heightened pro-inflammatory state [10]. Similar increases in neopterin [11], cytokines, coagulation factors, and acute phase reactants [12] have been reported in older, compared to younger, HIV-negative adults; the term “inflamm-ageing” [13,14] was coined to describe this age-associated pro-inflammatory environment. The intersection of HIV disease and immunosenescence is likely to result in potentiation of age-associated immune dysregulation.

Several studies evaluated effects of age on innate immune activation in HIV-negative versus HIV-positive adults (with the caveat that very few HIV-infected older adults were actually studied). For example, CD14⁺ CD16⁺ inflammatory monocytes appear increased in HIV-positive, compared to HIV-negative young adults [15], a finding that has also been reported for older versus young HIV-negative adults [16–18]. Monocytes from older adults have increased expression of CD11b (a marker of monocyte activation), and decreased expression of CD38, CD62L, and CD115. Plasma levels of soluble CD163 (sCD163) and CXCL10, both markers of innate immune activation, also increase with age [16]. Notably, these findings were also found in HIV-infected young men [15]; in a cohort of women age 20–63 yrs levels of plasma sCD163 levels in HIV-infected subjects matched levels seen in uninfected women 14.5 years older [19].

Monocyte TLR Function in Aging

TLR function also shows dysregulation in monocytes from older adults and HIV-infected individuals. In older adults, an age-related decrease in TLR1/TLR2-mediated cytokine production was associated with decreased TLR-1 surface expression [18,20]; in addition, generalized age-associated defects in TLR-induced expression of CD80 and CD86 are associated with influenza vaccine response [21]. At the same time, TLR4-induced cytokine production in CD14⁺ CD16⁺ inflammatory monocytes was increased with age [16], and TLR5-induced IL-6 and IL-8 production were increased in monocytes isolated by adherence to plastic from older, compared to young adults [22]. Taken together, these findings suggest that activation state could influence age-associated monocyte TLR responses.

Monocyte TLR Function in HIV Infection

Monocyte TLR function in the context of HIV infection generally show evidence of enhanced responsiveness. For example, using cryopreserved PBMC samples, TLR7/8- and TLR2-dependent intracellular TNF- α production were increased in monocytes from subjects with primary HIV infection, compared to HIV⁺ subjects on ART, elite controllers, or HIV-negative individuals [23]. Analysis of freshly isolated monocytes from chronically infected subjects showed increased expression of TLR2, which was upregulated upon exposure to gp120 [24]. It should be noted that these studies enrolled HIV-infected subjects of a range of ages, but the specific effects of age remain incompletely understood.

Dendritic Cell TLR Function in Aging

Primary dendritic cell function in aging generally shows decreased TLR-dependent cytokine production in both myeloid (mDC) [25,26] and plasmacytoid (pDC) populations (and decreased IFN α production in pDCs) [26–30]. Notably, basal cytokine production was markedly elevated in mDCs and pDCs from older, but not young subjects, reflecting the heightened pro-inflammatory environment of aging and suggesting that impaired TLR responses to newly encountered agonists reflect inability to further upregulate cytokine production [26]. However, monocyte-derived DCs, obtained via IL-4 and GM-CSF stimulation, show both increased cytokine production in response to TLR4 and TLR8 engagement and treatment with self-DNA [31,32] and decreased type I interferon production in response to West Nile virus [33]. Thus, as with monocytes, activation state may also play a role in age-associated alterations in TLR function.

Dendritic Cell TLR Function in HIV Infection

TLR function in DCs from HIV-infected subjects may be influenced by stage of infection. For example, TLR8-induced TNF- α production was diminished in mDCs from cryopreserved PBMC samples at the earliest stages of primary infection [34]. However, in later stages of primary disease (when HIV-specific antibodies become detectable—Fiebig stage V–VI), increased TLR-induced cytokine production is found [23,35], although there is also evidence of impaired TLR-induced IL-12 production [36]. By contrast, in chronic HIV infection, decreased TLR-dependent IL-12 production is reported in monocyte-derived DCs [37–39]. The mechanisms underlying these alterations are likely to be multifactorial, but HIV-1-induced inhibition of autophagy [40] and release of apoptotic microparticles from dying cells during primary infection may contribute [34].

Diminished numbers of pDC have been reported in the peripheral blood of HIV patients [41,42] and in non-infected older adults [27,43]. Studies of TLR-dependent pDC function in primary and established HIV infection have generally demonstrated decreases in both IFN- α production and induction of NK cell cytotoxicity [44–46]. The HIV-1 envelope protein gp120 inhibits TLR9-mediated IFN- α production in pDCs, and so may facilitate this inhibition [47].

Despite lower numbers of pDC, higher plasma levels of IFN- α are found in acute and late stages of HIV infection that are associated with extent of disease progression [48]. Basal transcription of interferon-stimulated genes is increased in pDCs from HIV- and HCV-infected subjects, which could contribute to a heightened baseline level of IFN- α production [45]. In addition, pDCs from HIV-1-infected subjects show persistent IFN- α production in response to repeated in vitro stimulation with HIV-1, associated with increased mRNA expression of IRF7 and incomplete activation as manifested by costimulatory protein expression levels [49]. This HIV-induced dysregulation mirrors the basal elevation in IFN- α production in pDCs from HIV-negative older adults [26].

Sources of Innate Immune Activation in HIV-infected and Uninfected Older Adults

Engagement of Innate Immune Pattern Recognition Receptors by HIV

HIV single-stranded RNA activates TLR7 and TLR8 [50–52] on antigen presenting cells; persistent active viral replication (or at least the production of viral RNA) may occur despite treatment with ART, albeit at very low levels [53,54]. In vitro pre-treatment of PBMCs with TLR7 or TLR8 agonists was associated with augmented LPS-induced cytokine production [55,56], suggesting that HIV-dependent TLR responses could contribute to further inflammatory dysregulation. TLR-mediated recognition of HIV may also influence infection acquisition; using TLR neutralizing antibodies, the HIV envelope protein gp120 was found to be recognized by TLR 2 and 4 on cultured human primary genital epithelial cells, and associated with mucosal barrier disruption [57]. How age-associated alterations in TLR function influence HIV-associated TLR activation remains to be determined.

Microbial Translocation in HIV Infection

CCR5+ CD4 T cells in lymphoid tissues in the gastrointestinal tract are depleted in HIV disease, and intestinal mucosa compromise is also observed [58,59]. These factors likely contribute to translocation of gastrointestinal bacteria into the bloodstream, which is associated with innate immune activation and elevated levels of plasma LPS, soluble CD14, LPS binding protein, and IFN- α [60]. Numerous studies indicate that these parameters remain persistently elevated in HIV patients despite ART and correlate with severity of disease [59,61]. The involvement of IFN- α , typically associated with antiviral responses, was highlighted by a recent study indicating that pDCs—which are particularly adept at producing IFN- α —upregulate the gut homing receptor CD103, and accumulate in gut-associated lymphoid tissue in ART-naïve subjects [41]. Additional studies showed higher plasma levels of bacterial DNA in HIV-infected subjects that correlated with plasma LPS levels [62,63]. A few studies have shown differences in the intestinal microbiome of HIV-infected versus uninfected individuals that are associated with immune activation [64,65]. Notably, a study of older HIV-negative adults (mean age of 69) showed higher levels of LPS binding protein (a surrogate marker of microbial translocation) correlated with worsened physical function, raising the intriguing possibility that microbial translocation could also be a feature of advancing age [66].

CMV and Chronic Viral Infections

Following primary infection, the immunologic impact of CMV arises from cycles of asymptomatic latent virus reactivation that may accompany episodes of acute non-viral illness [67]. Increased frequency and heightened reactivation of CMV are also noted in older adults [68]. While CMV seropositive status is associated with innate immune activation [69], it should be noted that there is an absence of longitudinal data supporting CMV-associated innate immune activation. In fact, in a longitudinal study of 249 subjects, individuals who seroconverted to CMV during the 10-year study period did not show a difference in serum CRP, TNF- α , IL-6, and IL-10 compared to those remaining seropositive [70]. It is possible that multiple cycles of reactivation may be required to induce a state of

immune activation; additional longitudinal data will be needed to further address this question. In HIV infection, CMV is an important cause of opportunistic infection; in addition, there is evidence implicating a detectable CMV viral load as a risk factor for HIV disease progression independent of CD4 count or viral load [71]. Other chronic, persistent viruses including herpesviruses (e.g. Epstein-Barr, Varicella-Zoster) and Hepatitis C virus likely also contribute to a pro-inflammatory state in HIV infection, but the influence of aging on this interface remains incompletely understood.

Damage-Associated Molecular Patterns

Endogenous DNA damage may also contribute to a pro-inflammatory milieu in the context of aging and HIV infection. In this context, the Senescence-Associated Secretory Phenotype (SASP), representing a secretome of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8), growth factors, extracellular matrix proteins, and proteases, is induced by DNA damage from genotoxic stress (e.g. from ionizing radiation or replicative exhaustion) [72,73], though it is worth noting that there is a paucity of data demonstrating an *in vivo* role for the SASP. However, increased levels of endogenous non-cell-associated DNA were present in a cohort of nonagenarians compared to younger subjects, and correlated with higher expression of inflammatory pathways, frailty, and mortality [74,75]; in addition, increased levels of mitochondrial DNA were associated with monocyte activation and elevated plasma cytokines [76]. This age-associated increase in non-cell-associated DNA could be engaged by innate immune pattern recognition receptors or reflect DNA damage associated with the pro-inflammatory SASP. Endogenous extracellular DNA is likely released from necrotic or senescent cells, and it is notable that necrotic cells activate the NLRP3 inflammasome [77–79]. Recent findings propose that bystander CD4⁺ T cells (which are non-productively infected with HIV) die via the related process of pyroptosis due to the presence of cytosolic reverse transcription products, which is dependent on caspase-1 (a crucial component of the inflammasome mediating the processing of pro-IL-1 β and IL-18) [80]. Thus, it seems likely that age-associated increases in cell-free DNA, combined with HIV-1-dependent pyroptosis will augment inflammatory responses in older adults with HIV disease.

Hormonal and Metabolic factors

Estrogen and testosterone treatment result in decreased IL-6 production, and decreases in sex hormone production in menopause or andropause are associated with elevated pro-inflammatory cytokine levels in HIV-negative adults [81–86]. Notably, hypogonadism and low testosterone are common among HIV-infected men [87]. Thus, the pro-inflammatory environment in older HIV-positive adults will also be influenced by age-associated changes in sex hormones, and by hormone replacement therapies in older adults.

Adipose tissue represents another potential source for innate immune dysregulation in the context of aging. In the absence of HIV infection, age-associated loss of subcutaneous adipose tissue and increases in intra-abdominal visceral fat coincide with increases in insulin resistance and metabolic syndrome [88]. Adipose tissue is also a source of pro-inflammatory cytokines; increased pro-inflammatory cytokine production has been observed in aged murine adipocytes [89–91]. In humans, elevated systemic pro-inflammatory cytokines have been correlated with increased levels of visceral adipose tissue in older adults [92–94].

Abnormalities in adipose tissue, or lipodystrophy, associated with HIV have features resembling age-associated fat redistribution, and may consist of a combination of lipotrophy in the face, extremities and buttocks with hypertrophy of visceral fat depots and cervical fat; lipodystrophy is also associated with increased pro-inflammatory cytokine production in adipocytes [95]. Adverse effects of ART are significant contributors to lipodystrophy via inhibition of mitochondrial DNA polymerase γ (Pol γ), leading to loss of mitochondrial DNA (mtDNA) and increased mtDNA mutations [96–99]. Pol γ toxicity was most strongly associated with nucleotide reverse transcriptase inhibitors (NRTIs) no longer in wide use in the developed world, particularly azidothymidine (AZT), stavudine (D4T), and didanosine (DDI) [95,100]. The resultant mtDNA mutations are maintained and may undergo clonal expansion—as reported in muscle biopsies from NRTI-treated compared to treatment naïve subjects [101]. Thus, ART-associated mtDNA mutations may resemble those accumulating in the context of aging [102], and exposure to NRTIs could have long-term consequences beyond the period of actual treatment.

mtDNA content in adipose tissue was also decreased, relative to pre-treatment levels, with ART including widely used agents such as Abacavir/lamivudine (ABC/3TC) or Tenofovir/Emtricitabine (TDF/FTC); TDF/FTC was also associated with decreased enzymatic activity of components of the mitochondrial electron transport chain [103]. Whether such alterations result in global effects on mitochondrial function remains unclear [104], but the potential effects of past and present ART should be considered as older adults with HIV infection are maintained on lifelong therapy. These and other parallels in aging and HIV infection are summarized in Table 1 and Figure 1.

Conclusion

With effective ART, HIV infection is now manageable as a chronic illness. For patients surviving into old age, geriatric issues of multiple co-morbidities and polypharmacy become crucial issues in management, and important covariates in immunologic analyses of such individuals. Moreover, factors such as the duration of HIV infection, and duration, efficacy, and adverse effects of ART will influence inflammatory pathways and age-associated pathways such as telomerase. In this regard, a reasonable hypothetical question would compare innate immune activation in a 30-year-old infected with HIV since birth to a newly infected 60-year-old—and whether merely classifying these subjects on the basis of chronologic age without considering duration of infection and treatment would be appropriate. Future studies of aging adults with HIV infection will need to embrace this complexity.

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Text Box**Effects of ART on Telomerase**

The Telomerase Reverse Transcriptase (TERT) shares homology to retroviral reverse transcriptases [105], including that of HIV-1. NRTIs inhibit telomerase activity in vitro, and are associated with telomere shortening [106,107]. Telomerase inhibition was observed not only for older generation NRTIs, but also for widely used drugs, including Tenofovir (the most potent telomerase inhibitor in one study [106] and Abacavir. In addition, a recent report suggests that the Vpr protein of HIV-1 may also decrease telomerase activity by enhancing ubiquitination of TERT [108]. The juxtaposition of age-associated telomere shortening, in part reflecting replicative senescence [109], and potential long-term effects of ART may further enhance aging phenotypes in the immune system of older adults with HIV infection.

Highlights

- A dysregulated pro-inflammatory state is present in both aging and HIV infection.
- Age- and HIV-related changes in TLR function may contribute to this dysregulation.
- DNA DAMPs, other viruses, fat and hormonal changes also result in dysregulation.
- Effects of microbial translocation and antiretroviral drugs may accumulate with age.
- HIV disease and therapy duration and comorbid illnesses complicate studies of aging.

Figure 1.

Comparison of effects of HIV and aging on innate immune responses. Both HIV and Aging are accompanied by pro-inflammatory environments that are likely to be triggered by elevated levels of pattern recognition ligands (Pathogen-Associated Molecular patterns (PAMPS) and Damage-Associated Molecular Patterns (DAMPS)). Toll-like receptors (TLR) and IFN- α receptor (IFNAR) are depicted. Increases or decreases in TLR-induced cytokine responses are shown by arrows (blue arrow: DC, Orange arrow: Monocytes, Green arrow; Monocyte-derived DC). Abbreviations: IFN, Interferon; mtDNA, mitochondrial DNA; TERT, Telomerase reverse transcriptase; NRTIs, nucleoside reverse transcriptase inhibitors; LPS, Lipopolysaccharide.

TLR8 induced TNF- α is decreased in mDC at the earliest stages of infection

Table 1

Comparison of the alterations in innate immunity and signs of immunosenescence seen in HIV infection and Aging.

HIV Infection	Aging	Immune Category
Heightened pro-inflammatory environment; <ul style="list-style-type: none"> Increased IL-6, TNF-α, Neopterin, sCD14 [6–9]. Increased coagulation factors and acute phase reactants [6–9]. 	Inflamm-Aging; <ul style="list-style-type: none"> Increased cytokines, neopterin [11–12]. Increased coagulation factors, acute phase reactants [11–12]. 	Pro-inflammatory environment; signs of immune activation
<ul style="list-style-type: none"> Inflammatory CD14+, CD16+ monocytes are increased [15]. Monocytes of young HIV infected subjects show increased expression of CD11b, and decreased expression of CD62L and CD115 [15]. Plasma levels of soluble CD163 and CXCL10 resemble those seen in older adults [15,19]. Exhibit impaired phagocytic function, and telomere shortening [15]. 	<ul style="list-style-type: none"> Inflammatory CD14+, CD16+ monocytes are increased [16–18]. Increased expression of CD11b [16]. Decreased expression of CD62L and CD115 [16]. Plasma levels of soluble CD163 and CXCL10 increase with age [16]. Exhibit impaired phagocytosis and shortening of telomeres [16]. 	Monocytes
<ul style="list-style-type: none"> TLR7/8 and TLR2 cytokine production is increased in HIV infection [23]. Increased expression of TLR2, which is upregulated with exposure to gp120 [24]. 	<ul style="list-style-type: none"> Decrease in TLR1/2 mediated cytokine production, and TLR1 surface expression [18,20]. Increased TLR4 induced cytokine production in CD14+ CD16+ monocytes [16]. Increased TLR5 induced cytokine production (adherent monocytes) [22]. 	Monocytes/TLRs
<ul style="list-style-type: none"> TLR-8 induced TNF-α is decreased in mDC at the earliest stages of primary infection [34], increased in later stages of primary infection [23,35]. TLR9 induced cytokine production is decreased at all stages of infection in pDC [23]. Increased plasma levels of IFN-α [48]. Diminished numbers of pDCs in peripheral blood [41,42]. Overall decreased IFN-α production in pDC [44–46]. In chronic HIV infection, decreased TLR-dependent IL-12 production is reported in monocyte-derived DCs [37–39] 	<ul style="list-style-type: none"> Overall decreased TLR-dependent cytokine production in both mDC and pDC [25–30]. Increased basal cytokine production [26]. Diminished numbers of pDCs noted in the peripheral blood [27,43]. Decreased IFN-α production by pDC [26, 27, 29, 30, 43]. Monocyte-derived DCs show increased cytokine production in response to TLR4 and 8 induction and treatment with self-DNA [31,32] Monocyte-derived DCs have decreased type I interferon production in response to West Nile virus [33] 	Dendritic cells and TLRs
<ul style="list-style-type: none"> HIV viremia; HIV RNA stimulates TLR 7/8 [50–52] gp120 stimulates TLR 2 and 4 in genital epithelial cells [57]. Co-infection with herpesviruses; CMV [71]. 	<ul style="list-style-type: none"> CMV reactivation is increased in older adults [68]. Increased plasma LPS binding protein (surrogate for Microbial translocation) [66]. 	PAMPs

HIV Infection	Aging	Immune Category
<ul style="list-style-type: none"> Intestinal mucosa compromise and subsequent microbial translocation [58,59]. 		
<ul style="list-style-type: none"> Increased cell death and pyroptosis of CD4 cells [80]. 	<ul style="list-style-type: none"> Increased plasma cell free DNA [74–76]. 	DAMPs
<ul style="list-style-type: none"> Hypogonadism and low testosterone are common among HIV infected men [87]. Fat redistribution occurs with lipodystrophy, a side effect of ART, and is associated with increased pro-inflammatory cytokines [95]. ART causes inhibition of mitochondrial DNA polymerase γ and leads to increased mtDNA mutations and loss of mtDNA [96–99]. 	<ul style="list-style-type: none"> Decreases in sex hormone production are associated with elevated pro-inflammatory cytokine levels [81–86]. Redistribution of adipose tissue [88]. Adipose tissue is a source of pro-inflammatory cytokines, and increases with age [89–94]. mtDNA mutations accumulate with age [102]. 	Hormones/Metabolic Factors
<ul style="list-style-type: none"> NRTIs inhibit telomerase activity in vitro, and are associated with shortening of telomeres [106, 107]. 	<ul style="list-style-type: none"> Replicative senescence in aging is accompanied by telomere shortening [109]. 	Senescence