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Future Directions -- Lung Aging, Inflammation, and HIV

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SYNOPSIS

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) are unusually prevalent among persons infected with HIV. In many cases these disease states are identified at younger ages than would be expected in the general population. Recent epidemiologic, basic science, and cross-sectional clinical data have implicated immune dysfunction and cellular senescence as potential drivers of advanced presentations of age-related diseases in HIV-infected persons. This article describes how HIV-associated COPD and PH may fit into a paradigm of immunosenescence and outlines the hypothesized associations among chronic HIV infection, immune dysfunction and senescence, and cardiopulmonary outcomes.

Keywords

HIV; chronic obstructive pulmonary disease; pulmonary hypertension; immune activation; immune senescence; inflammation

Background/Introduction

Due to the success of combination antiretroviral therapy (ART) in restoring immune function, there have been marked declines in mortality from HIV infection in individuals with access to treatment[1]. As a result, over 30% of the HIV-infected population in the United States is currently over the age of 50, with 50% expected to be over the age of 50 by the year 2020[2]. Unfortunately, these gains in longevity have been accompanied by a growing burden of age-related diseases, attributable both to natural aging and to a recently described potential for HIV to cause accelerated cellular senescence[3,4].

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Diseases traditionally associated with aging have been identified in several organ systems (including renal, neurologic, and cardiac) at unexpected prevalence in cohorts of midlife HIV-infected individuals[4–8], and similar findings are being investigated in the pulmonary system. Because of its unique exposure to airborne pathogens and toxins, the damage from which may be enhanced by HIV infection, the lung and its circulation may be particularly sensitive to early presentation of chronic disease. Two lung diseases in particular, chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH), are accelerated in HIV and may be linked to senescence[9–21].

The prevalence of COPD increases with age and is associated with senescence in both the HIV-uninfected and HIV-infected populations[11,22–27]. The hypothesis that HIV-associated COPD occurs as a consequence of accelerated cellular aging is particularly compelling because inflammatory dysfunction, a hallmark of HIV-associated senescence, plays a central role in the pathogenesis of COPD[28].

PH is also a possible senescence-related complication of HIV. Although PH is not typically considered an age-dependent phenomenon in the general population, subsets of PH, including those secondary to left ventricular dysfunction[29] or COPD, are associated with increasing age; furthermore, a recent study suggests that COPD-associated PH is related to leukocyte and smooth muscle cellular senescence[30]. While the pathogenesis of HIV-associated PH is poorly understood, current studies are evaluating the possible relationships among immune activation, aging, and the development of HIV-associated PH.

This article reviews the features of cellular senescence and its relationship to HIV and immune activation and examines the foundation of the hypothesis that senescence is associated with COPD and PH in persons with HIV. We address recent advances in the understanding of the complex interplay between antigenic exposures, host immune response, and inflammation in both chronic HIV infection and chronic cardiopulmonary dysfunction. Ongoing studies continue to investigate links between these disease states; these relationships may be instrumental in developing effective prevention and treatment of pulmonary complications associated with chronic HIV infection.

HIV, Immune Activation, and Aging: The Immunosenescence Hypothesis

Cellular senescence is one of the central features of aging organ systems and is defined by the inability of a cell to undergo further division. Senescence can be induced either by direct insult to cells (*e.g.* oxidative stress) or via replicative senescence, a phenomenon by which repeated cell division results in proliferative arrest. The cells of the immune system, which are subject to frequent rounds of division via clonal expansion following antigenic exposures[31], are particularly susceptible to replicative senescence. In the case of HIV infection, either HIV itself or the co-infections commonly associated with HIV (including cytomegalovirus (CMV)[32] and hepatitis C[33,34]) drive repeated cycles of immune activation and T-cell proliferation. Due to repeated triggering and expansion, the immune cells reach a replicative limit, characterized by loss of the costimulatory surface receptor CD28 (*i.e.* $CD28^{null}$)[35]. These senescent $CD28^{null}$ T-cells are dysfunctional; they are less able to clear infections, but contribute to a persistent upregulation of the inflammatory response with increases in peripheral inflammatory cytokines[36–38]. This smoldering inflammation resulting from persistent immune activation and immune senescence characterizes the systemic milieu of chronic HIV infection.

During acute and chronic HIV infection, T-cells demonstrate elements of immune cell aging, with features of both chronic senescence and activation[39–41]. An early study of T-cell response to HIV found that during acute infection, both HIV-specific $CD8^+$ cells and the overall $CD8^+$ cell population are highly activated (expressing the cellular activation marker

CD38 and the proliferative marker Ki67). Although the percentage of these activated populations dropped during chronic infection, paralleling the fall in the viral load, the terminally differentiated "senescent" T-cell population ($CD28^{null}$) is markedly enriched in chronic infection, a phenomenon that is even more pronounced in the overall $CD8^+$ population than in HIV-specific $CD8^+$ cells[41]. Further studies of $CD4^+$ and $CD8^+$ cell phenotypes in persons with chronic HIV infection have demonstrated that abnormal immune activation persists even in individuals with sustained viral suppression on ART[42,43].

This state of immune activation and senescence, provoked by chronic HIV and by the chronic viral and recurrent bacterial infections that frequently accompany it, has been linked to features of aging and disease in the cardiovascular system[44] and is suspected to be at play in other disease states. It has been hypothesized that non-immune organs sustain collateral damage due to the systemic inflammatory milieu, either via circulating inflammatory cytokines or from more direct insults, when activation and senescent T-cells are recruited to these organs at sites of injury or infection. Because of its vulnerability to repeated exposures to tobacco smoke, other environmental toxins and microbes (via infection or colonization), the lung and its circulation may be at heightened risk to sustain damage from senescent and activated circulating immune cells. COPD and PH, which are seen at higher than expected prevalence in mid-life HIV-infected persons, have been associated with systemic immune activation and inflammation in the non-HIV population, and are therefore of particular interest.

COPD: Relationships to Immune Activation and Senescence

COPD is common in the HIV-uninfected population and is the fourth leading cause of mortality in the US[45]. This disease typically presents in the sixth decade of life or later, but in the HIV population, it is often diagnosed at a younger age. Investigators have reported severe emphysema in HIV-infected persons in their thirties[13], and studies of COPD in HIV-infected cohorts have found a mean age of those with COPD to range from 40 to 50 years[46]. Studies have found a prevalence of 20–60% of physiologic measures of COPD in HIV-infected persons[12,14,17,46] versus 7% reported in the general population[47]. In general, most ART-era studies of HIV-infected persons show a high overall prevalence of airflow obstruction, ranging from 8–21%[12,14,15,17], despite the relatively young age of the HIV-infected participants. While HIV-infected persons do have particularly high exposure to pulmonary risk factors (most notably cigarette smoking[12,48]) that likely interact with other factors to contribute to chronic respiratory illness, these data provide epidemiologic support for the hypothesis that the lung may be another end-organ affected by senescence in HIV.

Molecular data examining immune-mediated inflammatory pulmonary cell damage and resultant accelerated alveolar epithelial cell senescence also support the role of aging in HIV COPD (Figure 1). Recent advances in COPD have shown that the disease is not driven by one mechanism, but is a syndrome that is precipitated by multiple insults, which may act individually or in concert to cause irreversible damage to the airways or alveoli[49,50]. Immune-mediated inflammatory pulmonary cell damage and resultant accelerated alveolar epithelial cell senescence may contribute to HIV COPD. Immune activation and senescence have not been directly investigated in HIV-associated COPD, but indirect links from studies of aging and inflammation in COPD in the HIV-uninfected population support a role for aging in HIV-associated COPD as well. The presence and severity of obstruction in COPD in the general population has been associated with increased systemic inflammatory cytokines including high sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and fibrinogen. Persistence of this systemic inflammatory phenotype predicts both COPD exacerbation rate and all-cause mortality[51]. A study specifically examining intracellular cytokine levels in circulating leukocytes and bronchoalveolar lavage cells found elevated

interferon (IFN)-γ and tumor necrosis factor (TNF)-α within circulating $CD8^+$ cells and bronchoalveolar lavage $CD8^+$ and $CD4^+$ cells in persons with COPD[52].

While human studies of inflammation and COPD have been largely associative, animal and *in vitro* studies are able to investigate the directionality of the relationship. For example, researchers have determined that chronic systemic inflammation in a murine model results in pulmonary inflammation and senescent lung changes[53]. A recent murine study that induced chronic systemic inflammation via subcutaneous lipopolysaccharide (LPS) implant found that LPS-exposed mice developed pulmonary inflammatory changes (increased alveolar macrophages) and evidence for pulmonary cell DNA double-strand breaks, which are precursors of cellular apoptosis and senescence[53]. In turn, senescence of pulmonary epithelial cells may also lead to regional lung inflammation, creating a vicious cycle of local damage. Induction of an *in vitro* senescent phenotype in lung epithelial cells in culture leads to higher levels of pro-inflammatory NF-kB activation and also results in higher pulmonary epithelial production of the inflammatory cytokines IL-6, IL-8, and TNF-α. *Ex vivo* studies of lung tissue explants established that type II epithelial cells from COPD patients demonstrated higher expression of the cellular senescence marker p16, and that senescent cells more frequently demonstrated a pro-inflammatory phenotype as measured by presence of phosphorylated NF-kB[54]. These findings further bolster the supposition that chronic systemic inflammation may lead to the inflammatory and senescent changes of COPD.

In addition to data supporting inflammation and pulmonary cell senescence as possible drivers of COPD, several investigations have specifically addressed the contributions of immune senescence. A cross-sectional study examining the T-cell repertoire and inflammatory response in association with COPD found that higher senescent ($CD28^{null}$) circulating $CD4^+$ cell percentage correlated with lower forced expiratory volume in one second (FEV_1) percent-predicted and greater midflow obstruction[25]. Although some circulating inflammatory markers (IFN-γ, TNF-α, and IL-1β) were associated with better FEV_1 percent-predicted, when T-cells in culture were activated, the cells from early-stage COPD secreted increased levels of IFN-γ and TNF-α, suggesting that local stimulation (*e.g.*, at the alveolar-capillary interface) of primed senescent cells may lead to enhanced release of these pro-inflammatory cytokines[25]. A cross-sectional assessment of the relationship between immune cell telomere length (where shorter telomeres may identify a more senescent cell phenotype) and lung function found that participants with COPD have shorter telomeres in circulating leukocytes telomeres than do healthy controls. Additionally, telomere shortening was correlated with reduced activity of superoxide dismutase (a free radical scavenger that may provide protection from COPD)[55]. A similar study found that circulating leukocyte telomere shortening was associated with COPD and that higher circulating levels of the inflammatory cytokine IL-6 were associated both with telomere attrition and with the presence of COPD[56]. Given the immune dysfunction described in the previous section, any or all of these mechanisms are likely to play a role in the pathogenesis of HIV-associated COPD.

Pulmonary Hypertension: Relationships to Immune Activation and Senescence

Pulmonary hypertension, like COPD, is described at increased frequency among persons with HIV. Both before and after the availability of combination antiretroviral therapy, PH has been found at a prevalence of 0.5%[20,57] among HIV-infected persons. Further directed investigations assessing pulmonary artery pressures in current-era HIV-infected cohorts have found prevalence of echocardiographic markers of pulmonary hypertension ranging from 15.5–35%[18,21,58], with potential risk factors including male sex[20], injection drug use[20], and $CD4^+$ count < 200 cells/uL[18,20]. Animal models have supported the direct pathogenic

role of HIV in the development of PH. For example, in a recently published study, simian immunodeficiency virus (SIV) and simian-human immunodeficiency virus (SHIV)-infected macaques developed echocardiographic and right heart catheterization findings of PH that were significantly worse when compared to uninfected controls[59]. Mechanisms underlying HIV-associated PH are a subject of ongoing investigation – potential contributors have been covered in another article in this issue and in several previous review articles[16,60,61]. These potential contributors include enhanced production of growth factors also implicated in non-HIV PH (including platelet-derived growth factor and vascular endothelial growth factor) and virus-specific factors, namely *nef* and the viral envelope glycoprotein-120.

As with COPD, immune dysfunction, immune senescence, and constitutive cell (in this case, endothelial and pulmonary artery smooth muscle cell) senescence may play a role in development of HIV-associated PH. Studies of non-HIV PH have demonstrated mixed associations with inflammatory markers, but the data generally suggest that inflammation of some variety contributes to disease pathogenesis. Inflammatory infiltrates of mononuclear cells have been identified in the characteristic plexiform lesions of PH, and a recent study has demonstrated organized lymphoid structures in idiopathic PH[62]. Multiple markers of inflammation and immune dysfunction have been described in association with non-HIV PH, and are summarized in depth in recent review articles[60,63]. Additionally, there is potential evidence for inflammation-mediated senescence in non-HIV PH – a study investigating markers of cell senescence in patients with COPD found that higher circulating IL-6 and shorter telomeres in circulating leukocytes correlate with increasing pulmonary artery pressures[30].

The possible inflammatory and immunosenescent features of HIV-associated PH have only recently been investigated, but early data are promising. One study identified that circulating IL-8, IFN-γ, and activated T-cells ($CD8^+CD69^+$) were associated with elevated pulmonary artery systolic pressure (PASP) and tricuspid regurgitant jet velocity (TRV), as was sputum IL-8[18]. Interestingly, increasing PASP and TRV were independently associated with pulmonary function abnormalities, including worse spirometry and lower diffusing capacity for carbon monoxide. Of note, none of the participants required oxygen, and none had severe COPD, arguing against pre-existing hypoxemic lung disease as the etiology of the elevated pulmonary artery (PA) pressures. Additionally, elevated TRV was associated with serologic markers of poorly-controlled HIV (CD4 < 200 cells/μL or elevated HIV RNA levels), irrespective of ART use[18]. These findings suggest that systemic and/or pulmonary immune activation and resultant inflammation, which is worse in the setting of more advanced HIV, may underlie both pulmonary dysfunction and elevated PA pressures in HIV-infected persons.

The Complex Interplay among HIV, Immune Activation, and Pulmonary Dysfunction: Future Directions

While the accelerated pulmonary disease seen in HIV is in part related to traditional risk factors, the early and unusually prevalent presentations of disorders such as COPD and PH suggest a distinctive contribution of HIV that may involve unique mechanistic pathways (Figure 1). Senescent and activated T-cells, which are commonly elevated even among virally-suppressed persons, may contribute to lung and pulmonary circulatory damage either indirectly (via inflammatory cytokines expressed in the circulation) or directly, when they are recruited to the lung or its circulation in response to stimuli (including cigarette smoke, other inhaled toxins, or pulmonary microbes). There is also potential for cellular aging in the resident immune cells or constitutive cells of the lung and pulmonary artery, either as a direct effect of HIV or as a result of inflammation due to trafficking of dysregulated systemic immune cells. While these relationships are speculative, current research directed

at describing the associations between indicators of HIV-associated immune activation, immune senescence, epithelial and endothelial cell aging, and outcomes of pulmonary dysfunction are currently underway. Determining the roles of accelerated immune aging and chronic inflammation in HIV may eventually allow for effective directed interventions in this population[64].

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KEY POINTS

- HIV is now a chronic disease among persons treated with highly active combination antiretroviral therapy, and it is frequently complicated by comorbid age-related conditions. Pulmonary comorbidities of chronic HIV are increasingly recognized.
- Chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) are both present at increased frequency among persons infected with HIV.
- Sustained HIV-associated systemic inflammation may result in accelerated cellular senescence with cardiopulmonary end-organ injury, thus contributing to COPD and pulmonary vascular disease.

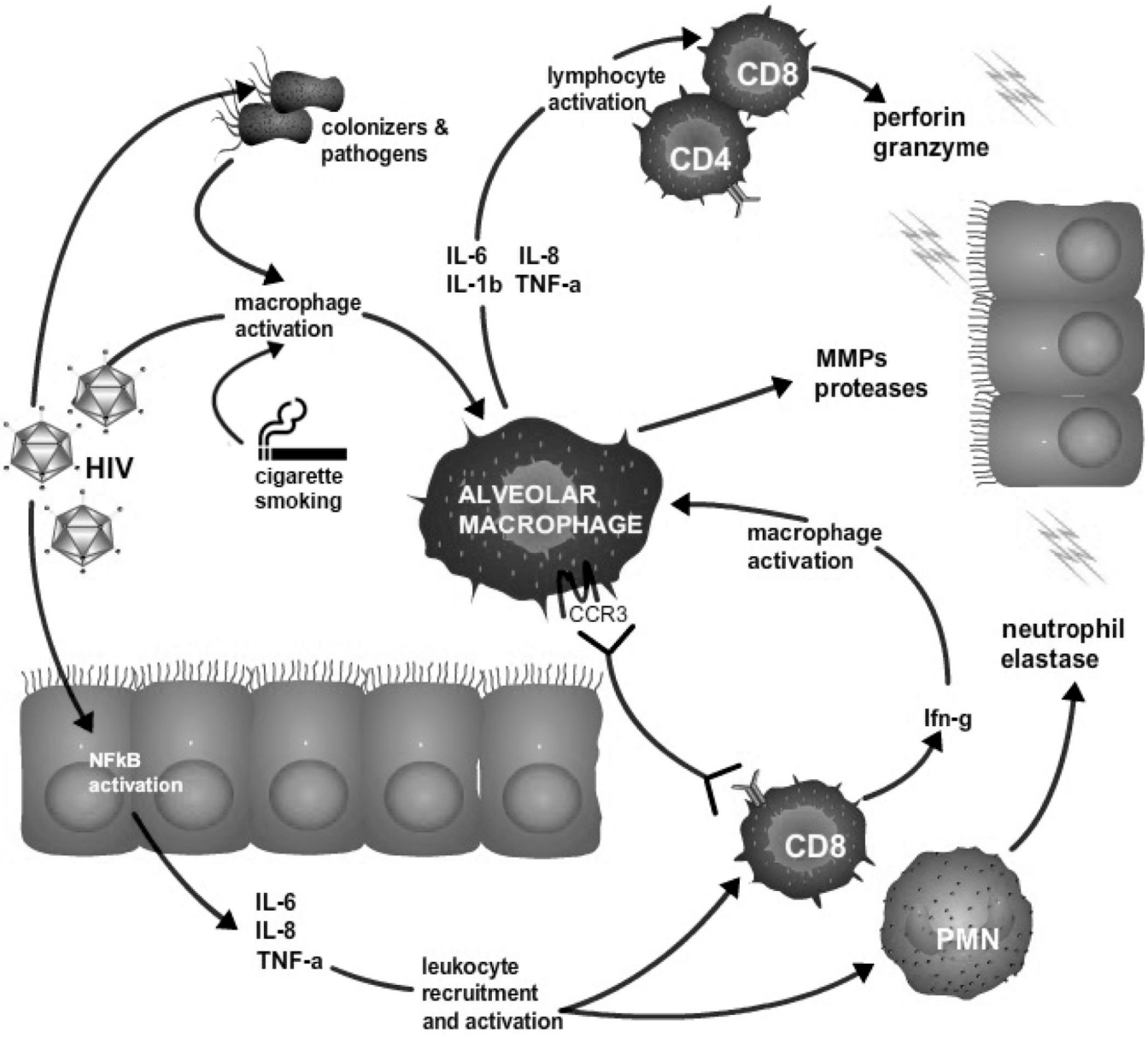

Figure 1. Theoretical framework of development of HIV-associated COPD

HIV-associated immune deficiency allows for high burden of microbial infection and colonization – both HIV virions and other microbes lead to macrophage activation. In addition to releasing matrix metalloproteases, activated alveolar macrophages express inflammatory cytokines that activate local $CD4^+$ and $CD8^+$ lymphocytes. Additionally, activated macrophages express the cytokine receptor CCR3, encouraging trafficking of $CD8^+$ T-cells from the circulation. Activated $CD8^+$ cells (which are likely to be senescent in the setting of chronic HIV infections) elaborate interferon-gamma, which leads to amplification of macrophage activation. Additionally, HIV directly activates NFκB in alveolar epithelial cells, leading to expression of inflammatory cytokines, further driving leukocyte recruitment and activation. Recruited and activated immune cells may cause local pulmonary damage (*i.e.* COPD) and epithelial cell senescence via the expression of proteases, perforin, granzyme, and neutrophil elastase. Abbreviations: CCR, chemokine

receptor; IFN, interferon; IL, interleukin; MMP, matrix metoalloprotease; NF, nuclear factor; PMN, polymorphonuclear cells; TNF, tumor necrosis factor.