Pulmonary Innate Immune Dysfunction in Human Immunodeficiency Virus

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Abstract

The advent of antiretroviral therapy has transformed infection by the type 1 human immunodeficiency virus (HIV) from a rapidly fatal disease to a chronic illness with excellent long-term survival rates. Although HIV primarily targets the adaptive arm of host immunity, it simultaneously impacts the innate immune system, and has profound implications for lung health, even when viral suppression is achieved with antiretroviral therapy. The lung has evolved a unique array of innate immune defenses, and the pathophysiological interactions between HIV and the pulmonary innate immune system deserve particular attention. In this review, we discuss work that elucidates how the components of innate immunity both respond to and are perturbed by infection with HIV.

Keywords: innate immunity; human immunodeficiency virus; macrophage; surfactant; polymorphonuclear cells

Clinical Relevance

This paper reviews the literature on innate immune dysfunction in human immunodeficiency virus in an effort to promote integrated studies that evaluate the effects of the virus on the innate immune system, in parallel with the effects that the different components of the immune system have on each other.

Despite the advent of antiretroviral therapy (ART), rates of lung-specific morbidity and mortality in people living with human immunodeficiency virus/acquired immune deficiency syndrome (PLWHAs) remain substantially increased. Because it primarily targets CD4⁺ T cells, HIV is typically considered a disease of adaptive immunity. Although its effects on adaptive immunity are clearly significant, a growing body of research has identified its deleterious impact on innate immune function as well, impact that has become even more relevant in the context of the increased lifespan conferred by ART. In this review, we briefly summarize the basic science literature in the field, and place these studies into a clinical framework that focuses on the effects of human immunodeficiency virus (HIV) on pulmonary innate immunity.

Innate Immunity in the Lung

Host immunity is typically divided into innate and adaptive components. The latter is distinguished by its presence in higher animals, its antigenic specificity, and its ability to generate immunologic memory. In contrast, innate immunity is a much older evolutionary development. It relies on recognition of a series of pathogen-associated molecular patterns by pattern recognition receptors to activate phagocytic cells and inflammatory cascades. Although the two arms of immunity are often thought of as distinct, they are, in fact, quite interconnected, particularly with regard to the activation of the adaptive immune arm by innate immune effectors.

The lung has evolved many specific mechanisms of innate immunity that reflect its status as an organ constantly challenged by direct contact with the external environment. Innate immunity in the lung is typically divided into two key components: immune recognition of pathogen-associated molecular patterns and danger-associated molecular patterns (including secreted components, such as the collectins, surfactant protein [SP]-A, and SP-D, and cellular components, such as the Toll-like receptor (TLR) family and scavenger receptors), and effector mechanisms responsible for maintaining sterility (including the alveolar epithelium, macrophages and dendritic cells (DCs), and polymorphonuclear cells).

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Noncellular Defenses

Surfactant

Many diseases have been associated with surfactant dysfunction, including infant respiratory distress syndrome, idiopathic pulmonary fibrosis, and lung cancer. In the case of HIV/acquired immune deficiency syndrome (AIDS) research on surfactant has thus far revealed several key points. A mouse model of AIDS and immune-reconstitution syndrome given *Pneumocystis jiroveci* pneumonia demonstrated impaired surfactant function and significant decreases in SP-B (which is, along with SP-C, a major hydrophobic SP) balanced by an increase in SP-D (which is, along with SP-A, a major hydrophilic SP) that appeared to mediate the recruitment of effector cells to the area (1). These findings are similar to those of a clinical study that found increases in SP-A and SP-D (but not SP-B or SP-C) in PLWHAs who presented with *Pneumocystis jiroveci* pneumonia (2). Surfactant dysfunction was significantly more pronounced in PLWHAs undergoing mechanical ventilation as well. SP-A also modulates inflammation in patients coinfecting with tuberculosis, and seems to exert an antiinflammatory effect on uninfected macrophages, while simultaneously increasing inflammation in infected areas of the lung (3). In addition, SP-A binds to HIV and prevents direct infection of CD4⁺ T cells, but also enhances the transfer of virus from DCs to CD4⁺ cells (4). Similar effects have been seen with SP-D, which has direct antiviral effects via binding of HIV envelope glycoprotein 120 and inhibition of viral replication (5). It prevents viral entry into target cells (6), but also facilitates transfer of virus from DCs to T cells (7). A recent pilot study showed evidence of reduced serum SP-D levels with ART (8), pointing to a need for further investigation on the effects of ART on pulmonary homeostasis. Of note, the myriad properties of SPs in HIV have led to work studying the role of SP-D in future vaccines (9). The effects of HIV on pulmonary surfactant and the key role surfactant plays in the modulation of innate immune function will make it an important focus for future therapeutic studies.

Other Noncellular Defenses

The many soluble components of the innate immune system have not been studied in the

setting of HIV in as much detail, but viral interaction was found to compromise the functions of both C1q and mannan-binding lectin (10). In addition, plasma LL-37, a molecule important in pulmonary innate immune defense, was reduced in untreated PLWHAs (11), although the pulmonary-specific implications of that finding have not yet been elucidated. HIV infection also affects the complement pathway via down-regulation of CD46 and CD59 on CD4⁺ cells, an effect that may contribute to T cell depletion in the pulmonary compartment (12).

Effector Cells

Macrophages

Macrophages, the resident innate immune effectors in the alveolar space, are affected by HIV infection, even in individuals with normal CD4 counts and no respiratory disease (13). Importantly, the virus can primarily infect macrophages, which, in turn, act as a reservoir for the virus (14). Although many mechanisms of macrophage infection have been described, in the alveolar macrophage in particular, HIV infection up-regulates expression of FcγRI and complement receptor 1, and these two surface molecules then act as facilitators of HIV entry into cells (15). Other studies have implicated the viral protein, Vpr, in the infection of human macrophages and enhancement of viral replication (16). HIV has also been shown to increase expression of the inflammatory protein, substance P, which, in turn, leads to an increase in CD163 and enhances HIV infection of the alveolar macrophage (17). HIV can remain latent in alveolar macrophages without active replication, but stimulation of these cells *in vitro* can awaken the dormant virus and lead to replication (18).

HIV also appears to alter the interaction between macrophages and the T cells to which they present antigens. Early work on the interactions between the two cells showed that infected macrophages fuse with uninfected CD4⁺ T cells via the HIV-associated glycoprotein, gp-120, *in vitro* (19). Later work found that the interaction between the two can result in active infection of the T cell (via HIV-1-associated group-specific antigen and envelope glycoproteins) (20).

The mechanisms by which HIV infection alters other macrophage functions are not fully understood, but multiple abnormalities in protein expression and cell functions have been observed. Efferocytosis, for example, the process by which macrophages phagocytose apoptotic neutrophils, is impaired in human subjects living with HIV infection (21), a defect that likely contributes to high levels of chronic inflammation in these patients. HIV infection also results in abnormalities in nonimmune functions, such as matrix metalloproteinase expression, possibly contributing to increased rates of emphysema seen in this population (22).

Studies suggest that HIV impairs the innate immune response of alveolar macrophages by dampening of the TLR 4/TNF-α response to LPS (23), decreasing surface expression of TLR 1 and 4 (24), and impairing phagocytosis (25). Studies by our group in an HIV transgenic rat model, in which there is no viral replication, but the entire array of HIV-related proteins are expressed, identified decreased bioavailability of zinc within the alveolar space that impaired alveolar macrophage phagocytosis (26). Given the noninfectious nature of that model, the findings suggest a prominent role for HIV-related viral proteins in the pathogenesis of alveolar macrophage dysfunction. However, despite the clear abnormalities in macrophage function seen in HIV infection, the alveolar microenvironment of PLWHAs did not adversely affect macrophage responses to *Streptococcus pneumoniae* (27). Other investigators have found normal phagocytic function in the alveolar macrophages of PLWHAs, unless the patient abused tobacco as well (28). Although that study was a relatively small cohort, further investigation of alveolar macrophage responses in different settings is clearly warranted.

Alveolar macrophages from PLWHAs have also been found to have lower levels of mannose receptor (a key component in the innate immune response), and demonstrate impaired phagocytosis commensurate with the CD4⁺ T cell counts (29). Similarly, the oxidative burst is an important component of the macrophage's immune function, and is in part mediated by the mannose receptor. Although the exact mechanism by which HIV alters the expression and function of the mannose receptor is unknown, studies have

suggested that the HIV-related protein, negative regulatory factor, is involved in its post-translational down-regulation (30). Interestingly, the oxidative burst is reduced in the alveolar macrophages from otherwise healthy individuals infected with HIV whose $CD4^+$ T cell counts were lower than $200/mm^3$, but not in otherwise comparable individuals with $CD4$ counts greater than $200/mm^3$ (31).

HIV infection alters the response of macrophages to a variety of pathogens as well. For example, exposure to the viral protein, transactivator of transcription, promotes expression of the scavenger receptor, CD91/low density lipoprotein receptor-related protein 1, a molecule important for the internalization of *Leishmania*, thereby resulting in higher intracellular replication of the parasite (32). HIV infection also impairs alveolar macrophage innate immune responses to fungal infections. In one study, alveolar macrophages were infected with a macrophage-tropic HIV strain and cultured with *Cryptococcus neoformans*. Infected cells displayed a significant reduction in fungicidal activity. Interestingly, macrophage viability, as well as binding and internalization of *C. neoformans*, was not affected (33).

Coinfection with HIV and *Mycobacterium tuberculosis* (MTB) has been associated with a decrease in the antiinflammatory cytokine, IL-10, via inhibition of p38/mitogen-activated protein

kinase pathway. This proinflammatory state creates an environment favorable for viral replication (34). However, alveolar macrophages from individuals infected with both HIV and MTB appear to retain the ability to produce and release inflammatory cytokines, as well as their ability to respond to LPS (35). Other data show that the apoptotic response to MTB is impaired in human alveolar macrophages from PLWHAs, likely via a B-cell lymphoma 3-encoded protein-dependent IL-10 effect (36). TNF- α release appears to be lower in these coinfecting individuals as well (37). These impairments may help explain the increased susceptibility to MTB infection in those individuals. Further details on the complex interactions between HIV and MTB can be found in recent reviews dedicated to the subject (38).

DCs

DCs, another key of innate immunity and antigen presentation, are affected by HIV in a variety of ways. As in the case of macrophages, the virus is able to primarily infect DCs, and the infected cells are then able to spread the virus to $CD4^+$ T cells (39). The transmission of virus from the DC to T cell appears to be mediated by the dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (40). In addition, DC function is significantly altered by HIV infection, and the aberrant

responses induced by the virus may be partly responsible for the chronic immune activation and eventual exhaustion often seen in PLWHAs (41). Interestingly, recent data show that viremic controllers (i.e., PLWHAs who demonstrate HIV RNA levels 75–2000 copies/ml for at least 1 yr) demonstrate improved DC antibody responses to HIV antigens. That fact, along with the antigen-presenting properties of the DC, makes it an attractive object of study in vaccine investigations (42).

Alveolar Epithelium

The alveolar epithelium has been relatively understudied in HIV. Evidence from our group and others suggests that the alveolar space is significantly more oxidized in HIV infection (43). We have shown that the expression and function nuclear factor (erythroid-derived 2)-like 2, the master transcription factor that regulates antioxidant defenses, is compromised in the lung of HIV transgenic rats (44), likely due to the effects of viral proteins in the alveolar space. Of note, impairment in nuclear factor (erythroid-derived 2)-like 2 function has been connected with accelerated immunosenescence in a variety of diseases, including HIV (45, 46).

Polymorphonuclear Neutrophils

Polymorphonuclear neutrophils (PMNs) are the effector arm of the innate immune

Figure 1. Summary schema of the alveolar space in human immunodeficiency virus (HIV) infection. Multiple components of innate immunity are affected by HIV infection, including macrophages, dendritic cells, surfactant, and the alveolar epithelium. See main text for further details.

system. Once recruited to a site of infection, PMNs act by releasing a variety of granules that contain elastase, myeloperoxidase, matrix metalloproteinases, and many other defense proteins. They are also critical to pathogen killing via respiratory burst-dependent mechanisms. After completing their tasks, PMNs undergo apoptosis and are ingested by a population of macrophages charged with clearing the airspace of the debris resulting from neutrophil activation.

Studies of PMNs by flow cytometry suggest that they are significantly compromised by HIV infection (47). Specifically, they are activated at baseline, demonstrate defective migration (48), respond inappropriately to endogenous signaling, and undergo accelerated apoptosis (49). They also demonstrate impaired bactericidal activity (50) and depressed superoxide production (51). Recent work suggests that HIV infection modulates the response of neutrophils to TLR signaling and promotes the production of inflammatory cytokines and reactive oxygen species (52). These effects and others appear to help HIV evade host defense mechanisms,

while simultaneously rendering the host more susceptible to opportunistic pathogens. In addition, there is evidence that PMN dysregulation in HIV could contribute to inhibition of T cell function (53). Interestingly, HIV-exposed individuals who fail to seroconvert demonstrate a reduction in neutrophil responses and alterations in pattern recognition receptors that may contribute to the decreased susceptibility to HIV infection in this population (54).

Conclusions and Future Directions

The effects of chronic HIV infection on the lung go far beyond its disruption of adaptive immunity. The robust innate immune system that has evolved in the lung to maintain sterility plays a vital role in protecting the ecosystem from the effects of the virus, but is in turn affected by the virus at multiple levels (Figure 1). As the role of innate immunity in both combating and inadvertently maintaining HIV infection

becomes more clear, new pathways of investigation that allow us to take advantage of the cross-talk between the many levels of the system should crystalize. Already, investigators are making use of antigen-presenting functions of innate immune effectors to propagate vaccines. Thus far, however, the individual components that comprise the innate immune system have primarily been studied in relation to adaptive immunity. Less attention has been paid to how these components interact with one another to produce the demonstrable defects in innate immune function seen in PLWHAs. The urgent need for new therapies to enhance lung health and decrease the persistent morbidity and mortality from lung disease in this vulnerable population calls for an approach that integrates existing knowledge of how the virus interacts with the immune system, as well as how the innate and adaptive immune systems interact with each other. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Atochina-Vasserman EN, Gow AJ, Abramova H, Guo CJ, Tomer Y, Preston AM, Beck JM, Beers MF. Immune reconstitution during *Pneumocystis* lung infection: disruption of surfactant component expression and function by S-nitrosylation. *J Immunol* 2009;182:2277–2287.
- Schmidt R, Markart P, Ruppert C, Temmesfeld B, Nass R, Lohmeyer J, Seeger W, Günther A. Pulmonary surfactant in patients with *Pneumocystis* pneumonia and acquired immunodeficiency syndrome. *Crit Care Med* 2006;34:2370–2376.
- Gold JA, Hoshino Y, Tanaka N, Rom WN, Raju B, Condos R, Weiden MD. Surfactant protein A modulates the inflammatory response in macrophages during tuberculosis. *Infect Immun* 2004;72:645–650.
- Gaiha GD, Dong T, Palaniyar N, Mitchell DA, Reid KB, Clark HW. Surfactant protein A binds to HIV and inhibits direct infection of CD4⁺ cells, but enhances dendritic cell-mediated viral transfer. *J Immunol* 2008;181:601–609.
- Meschi J, Crouch EC, Skolnik P, Yahya K, Holmskov U, Leth-Larsen R, Tornøe I, Tecle T, White MR, Hartshorn KL. Surfactant protein D binds to human immunodeficiency virus (HIV) envelope protein gp120 and inhibits HIV replication. *J Gen Virol* 2005;86:3097–3107.
- Pandit H, Gopal S, Sonawani A, Yadav AK, Qaseem AS, Warke H, Patil A, Gajbiye R, Kulkarni V, Al-Mozaini MA, et al. Surfactant protein D inhibits HIV-1 infection of target cells via interference with gp120–CD4 interaction and modulates pro-inflammatory cytokine production. *PLoS One* 2014;9:e102395.
- Madsen J, Gaiha GD, Palaniyar N, Dong T, Mitchell DA, Clark HW. Surfactant protein D modulates HIV infection of both T-cells and dendritic cells. *PLoS One* 2013;8:e59047.
- Kunisaki KM, Quick H, Baker JV. HIV antiretroviral therapy reduces circulating surfactant protein-D levels. *HIV Med* 2011;12:580–581.
- Gupta S, Clark ES, Termini JM, Boucher J, Kanagavelu S, LeBranche CC, Abraham S, Montefiori DC, Khan WN, Stone GW. DNA vaccine molecular adjuvants SP-D–BAFF and SP-D–APRIL enhance anti-gp120 immune response and increase HIV-1 neutralizing antibody titers. *J Virol* 2015;89:4158–4169.
- Thielens NM, Tacnet-Delorme P, Arlaud GJ. Interaction of C1q and mannan-binding lectin with viruses. *Immunobiology* 2002;205:563–574.
- Honda JR, Connick E, MaWhinney S, Chan ED, Flores SC. Plasma LL-37 correlates with vitamin D and is reduced in human immunodeficiency virus-1 infected individuals not receiving antiretroviral therapy. *J Med Microbiol* 2014;63:997–1003.
- Aries SP, Schaaf B, Hansen F, Weyrich K, Kurowski V, Dennin R, Dalhoff K. Expression of complement receptors and regulatory proteins on alveolar CD4⁺ lymphocytes from human immunodeficiency virus-1 infected individuals. *Eur Respir J* 1997;10:1736–1741.
- Lipman MC, Johnson MA, Poulter LW. Functionally relevant changes occur in HIV-infected individuals' alveolar macrophages prior to the onset of respiratory disease. *AIDS* 1997;11:765–772.
- Cassol E, Alfano M, Biswas P, Poli G. Monocyte-derived macrophages and myeloid cell lines as targets of HIV-1 replication and persistence. *J Leukoc Biol* 2006;80:1018–1030.
- Gilbody J, Lipman MC, Johnson MA, Atkins M, Poulter LW. Progression of HIV disease is associated with increased expression of FcγRI and CR1 on alveolar macrophages. *Clin Exp Immunol* 1997;107:31–36.
- Jacquot G, Le Rouzic E, David A, Mazzolini J, Bouchet J, Bouaziz S, Niedergang F, Pancino G, Benichou S. Localization of HIV-1 Vpr to the nuclear envelope: impact on Vpr functions and virus replication in macrophages. *Retrovirology* 2007;4:84.
- Tuluc F, Meshki J, Spitsin S, Douglas SD. HIV infection of macrophages is enhanced in the presence of increased expression of CD163 induced by substance P. *J Leukoc Biol* 2014;96:143–150.
- Lebargy F, Branellec A, Deforges L, Bignon J, Bernaudin JF. HIV-1 in human alveolar macrophages from infected patients is latent *in vivo* but replicates after *in vitro* stimulation. *Am J Respir Cell Mol Biol* 1994;10:72–78.

19. Crowe SM, Mills J, Kirihaara J, Boothman J, Marshall JA, McGrath MS. Full-length recombinant CD4 and recombinant gp120 inhibit fusion between HIV infected macrophages and uninfected CD4-expressing T-lymphoblastoid cells. *AIDS Res Hum Retroviruses* 1990;6:1031–1037.
20. Groot F, Welsch S, Sattentau QJ. Efficient HIV-1 transmission from macrophages to T cells across transient virological synapses. *Blood* 2008;111:4660–4663.
21. Torre D, Gennero L, Baccino FM, Speranza F, Biondi G, Pugliese A. Impaired macrophage phagocytosis of apoptotic neutrophils in patients with human immunodeficiency virus type 1 infection. *Clin Diagn Lab Immunol* 2002;9:983–986.
22. Kaner RJ, Santiago F, Crystal RG. Up-regulation of alveolar macrophage matrix metalloproteinases in HIV1⁺ smokers with early emphysema. *J Leukoc Biol* 2009;86:913–922.
23. Tachado SD, Zhang J, Zhu J, Patel N, Koziel H. HIV impairs TNF- α release in response to Toll-like receptor 4 stimulation in human macrophages *in vitro*. *Am J Respir Cell Mol Biol* 2005;33:610–621.
24. Nicol MQ, Mathys JM, Pereira A, Ollington K, leong MH, Skolnik PR. Human immunodeficiency virus infection alters tumor necrosis factor alpha production via Toll-like receptor-dependent pathways in alveolar macrophages and U1 cells. *J Virol* 2008;82:7790–7798.
25. Kedzierska K, Azzam R, Ellery P, Mak J, Jaworowski A, Crowe SM. Defective phagocytosis by human monocyte/macrophages following HIV-1 infection: underlying mechanisms and modulation by adjunctive cytokine therapy. *J Clin Virol* 2003;26:247–263.
26. Joshi PC, Raynor R, Fan X, Guidot DM. HIV-1-transgene expression in rats decreases alveolar macrophage zinc levels and phagocytosis. *Am J Respir Cell Mol Biol* 2008;39:218–226.
27. Gordon SB, Jagoe RT, Jarman ER, North JC, Pridmore A, Musaya J, French N, Zijlstra EE, Molyneux ME, Read RC. The alveolar microenvironment of patients infected with human immunodeficiency virus does not modify alveolar macrophage interactions with *Streptococcus pneumoniae*. *Clin Vaccine Immunol* 2013;20:882–891.
28. Elssner A, Carter JE, Yunger TM, Wewers MD. HIV-1 infection does not impair human alveolar macrophage phagocytic function unless combined with cigarette smoking. *Chest* 2004;125:1071–1076.
29. Koziel H, Eichbaum Q, Kruskal BA, Pinkston P, Rogers RA, Armstrong MY, Richards FF, Rose RM, Ezekowitz RA. Reduced binding and phagocytosis of *Pneumocystis carinii* by alveolar macrophages from persons infected with HIV-1 correlates with mannose receptor downregulation. *J Clin Invest* 1998;102:1332–1344.
30. Vigerust DJ, Egan BS, Shepherd VL. HIV-1 Nef mediates post-translational down-regulation and redistribution of the mannose receptor. *J Leukoc Biol* 2005;77:522–534.
31. Koziel H, Li X, Armstrong MY, Richards FF, Rose RM. Alveolar macrophages from human immunodeficiency virus-infected persons demonstrate impaired oxidative burst response to *Pneumocystis carinii* *in vitro*. *Am J Respir Cell Mol Biol* 2000;23:452–459.
32. Lodge R, Ouellet M, Barat C, Andreani G, Kumar P, Tremblay MJ. HIV-1 promotes intake of *Leishmania* parasites by enhancing phosphatidylserine-mediated, CD91/LRP-1-dependent phagocytosis in human macrophages. *PLoS One* 2012;7:e32761.
33. leong MH, Reardon CC, Levitz SM, Kornfeld H. Human immunodeficiency virus type 1 infection of alveolar macrophages impairs their innate fungicidal activity. *Am J Respir Crit Care Med* 2000;162:966–970.
34. Tomlinson GS, Bell LC, Walker NF, Tsang J, Brown JS, Breen R, Lipman M, Katz DR, Miller RF, Chain BM, et al. HIV-1 infection of macrophages dysregulates innate immune responses to *Mycobacterium tuberculosis* by inhibition of interleukin-10. *J Infect Dis* 2014;209:1055–1065.
35. Mwandumba HC, Squire SB, White SA, Nyirenda MH, Zijlstra EE, Molyneux ME, Russell DG, Rhoades ER. Alveolar macrophages from HIV-infected patients with pulmonary tuberculosis retain the capacity to respond to stimulation by lipopolysaccharide. *Microbes Infect* 2007;9:1053–1060.
36. Patel NR, Swan K, Li X, Tachado SD, Koziel H. Impaired *M. tuberculosis*-mediated apoptosis in alveolar macrophages from HIV⁺ persons: potential role of IL-10 and BCL-3. *J Leukoc Biol* 2009;86:53–60.
37. Patel NR, Zhu J, Tachado SD, Zhang J, Wan Z, Saukkonen J, Koziel H. HIV impairs TNF- α mediated macrophage apoptotic response to *Mycobacterium tuberculosis*. *J Immunol* 2007;179:6973–6980.
38. Diedrich CR, Flynn JL. HIV-1/*Mycobacterium tuberculosis* coinfection immunology: how does HIV-1 exacerbate tuberculosis? *Infect Immun* 2011;79:1407–1417.
39. Gringhuis SI, van der Vliet M, van den Berg LM, den Dunnen J, Litjens M, Geijtenbeek TB. HIV-1 exploits innate signaling by TLR8 and DC-SIGN for productive infection of dendritic cells. *Nat Immunol* 2010;11:419–426.
40. Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GC, Middel J, Cornelissen IL, Nottet HS, KewalRamani VN, Littman DR, et al. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. *Cell* 2000;100:587–597.
41. Sabado RL, O'Brien M, Subedi A, Qin L, Hu N, Taylor E, Dibben O, Stacey A, Fellay J, Shianna KV, et al. Evidence of dysregulation of dendritic cells in primary HIV infection. *Blood* 2010;116:3839–3852.
42. Trivedi S, Jackson RJ, Ranasinghe C. Different HIV pox viral vector-based vaccines and adjuvants can induce unique antigen presenting cells that modulate CD8 T cell avidity. *Virology* 2014;468:470–479–489.
43. Cribbs SK, Guidot DM, Martin GS, Lennox J, Brown LA. Anti-retroviral therapy is associated with decreased alveolar glutathione levels even in healthy HIV-infected individuals. *PLoS One* 2014;9:e88630.
44. Fan X, Staitieh BS, Jensen JS, Mould KJ, Greenberg JA, Joshi PC, Koval M, Guidot DM. Activating the Nrf2-mediated antioxidant response element restores barrier function in the alveolar epithelium of HIV-1 transgenic rats. *Am J Physiol Lung Cell Mol Physiol* 2013;305:L267–L277.
45. Swamy SM, Rajasekaran NS, Thannickal VJ. Nuclear factor-erythroid-2-related factor 2 in aging and lung fibrosis. *Am J Pathol* 2016;186:1712–1723.
46. Fitzpatrick M, Crothers K, Morris A. Future directions: lung aging, inflammation, and human immunodeficiency virus. *Clin Chest Med* 2013;34:325–331.
47. Elbim C, Prevot MH, Bouscarat F, Franzini E, Chollet-Martin S, Hakim J, Gougerot-Pocidal MA. Impairment of polymorphonuclear neutrophil function in HIV-infected patients. *J Cardiovasc Pharmacol* 1995;25:S66–S70.
48. Ellis M, Gupta S, Galant S, Hakim S, VandeVen C, Toy C, Cairo MS. Impaired neutrophil function in patients with AIDS or AIDS-related complex: a comprehensive evaluation. *J Infect Dis* 1988;158:1268–1276.
49. Pitrak DL, Tsai HC, Mullane KM, Sutton SH, Stevens P. Accelerated neutrophil apoptosis in the acquired immunodeficiency syndrome. *J Clin Invest* 1996;98:2714–2719.
50. Murphy PM, Lane HC, Fauci AS, Gallin JI. Impairment of neutrophil bactericidal capacity in patients with AIDS. *J Infect Dis* 1988;158:627–630.
51. Pitrak DL, Bak PM, DeMarais P, Novak RM, Andersen BR. Depressed neutrophil superoxide production in human immunodeficiency virus infection. *J Infect Dis* 1993;167:1406–1410.
52. Giraldo DM, Hernandez JC, Velilla P, Urcuqui-Inchima S. HIV-1–neutrophil interactions trigger neutrophil activation and Toll-like receptor expression. *Immunol Res* 2016;64:93–103.
53. Bowers NL, Helton ES, Huijbregts RP, Goepfert PA, Heath SL, Hel Z. Immune suppression by neutrophils in HIV-1 infection: role of PD-L1/PD-1 pathway. *PLoS Pathog* 2014;10:e1003993.
54. Hernandez JC, Giraldo DM, Paul S, Urcuqui-Inchima S. Involvement of neutrophil hyporesponse and the role of Toll-like receptors in human immunodeficiency virus 1 protection. *PLoS One* 2015;10:e0119844.