

The Immunocompromised Host

HIV Infection

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The variety of pulmonary infections encountered in HIV-infected individuals indicates that many components of the host defense network are impaired. In addition to depletion of CD4+ T cell numbers, HIV infection results in functional deficits in CD4+ T cells, CD8+ T cells, and natural killer cells. Although some components of macrophage defense are preserved, lack of activation signals from CD4+ T cells contributes to impaired defense by macrophages. There are few data examining the functional capabilities of neutrophils in the lung, but evidence from peripheral blood neutrophils indicates that defense by these cells is also impaired. An improved understanding of these events in the lung during HIV infection could lead to specific interventions aimed at restoration of deficient function.

Keywords: HIV infections; macrophages, alveolar; neutrophils; opportunistic infections; T-lymphocytes

The variety of pulmonary infections encountered in HIV-infected individuals demonstrates that HIV impairs lung host defenses significantly (1). Although most investigations focus on HIV's effects on systemic immunity, a significant body of literature examines pulmonary immune mechanisms during HIV infection. In some instances, immune defects documented in the periphery are reflected in the lungs. In other instances, effects of HIV on lung cells differ from those in the periphery. This article focuses on the effects of HIV infection on pulmonary host defenses to explain why serious pulmonary infections remain common in this immunocompromised patient population.

The accessibility of lung cells for study by bronchoalveolar lavage (BAL) provides an opportunity to study the effects of HIV and opportunistic pathogens on lung host defenses. Once impairments in pulmonary host defense are understood, novel strategies to correct these defects may be developed for treatment and prophylaxis of pulmonary infections (1).

There are several general mechanisms by which HIV infection can impair pulmonary host defense; the literature documents alterations in cell numbers and in cell function. First, HIV directly infects and kills cells directed against pathogens, leaving decreased numbers of cells available to participate in host defense. Second, HIV infection induces qualitative defects in the metabolic and secretory functions of effector cells. Third, HIV-infected cells may shift their repertoires from elaboration of immunostimulating to immunosuppressive products. Fourth, HIV infection could interfere with the capacity of circulating lymphocytes, monocytes, or neutrophils to migrate into the lungs and to clear pathogens from the alveolar spaces. Finally, coinfection

by a second pathogen can contribute to a breakdown in the host defense cascade.

HIV INFECTION OF LUNG CELLS

One important mechanism by which HIV alters lung host defense is by direct infection of pulmonary cells. Various HIV strains demonstrate tropism for lymphocytes or for monocytes/macrophages. The CD4 molecule, present on lymphocytes and monocytes/macrophages, serves as the primary cellular receptor for HIV-1. In the lung, CD4 is the primary receptor for HIV on alveolar macrophages. Coreceptors are also needed for HIV entry into cells, and cellular coreceptors determine the tropism of HIV strains (Figure 1). Lymphocyte-tropic (T-tropic) strains interact with the chemokine receptor CXCR4 (fusin) to control entry into target cells. Infection with T-tropic strains can be blocked by the CXC chemokine SDF-1, which is a CXCR4 ligand.

In contrast, monocyte-tropic (M-tropic) strains interact with the chemokine receptor CCR5 to control entry into target cells. HIV infection of human alveolar macrophages is preferentially mediated by the CCR5 receptor, although alveolar macrophages also express CXCR4. Infection with M-tropic strains can be blocked with the CC chemokines RANTES, macrophage inflammatory protein-1 α , and macrophage inflammatory protein-1 β , which are CCR5 ligands. As HIV infection progresses, T-tropic virus replaces M-tropic virus, and this change is accompanied by more rapid immunologic decline.

Alveolar macrophages are a primary reservoir of HIV in the lung. HIV reverse transcriptase can be detected in alveolar macrophages obtained by lavage from patients with AIDS, and alveolar macrophages can be infected with HIV *in vitro* (2). Reports comparing the HIV burden of alveolar macrophages and peripheral blood monocytes are discrepant. The relative importance of *in situ* HIV replication in the lung, compared with the influx of previously infected cells from bone marrow and blood, is unclear. The percentages of alveolar macrophages expressing HIV antigens have varied considerably in reports from different laboratories (3). Detection of HIV by polymerase chain reaction suggests that HIV infection of alveolar macrophages is common (4). Alveolar macrophages become infected with increasing frequency as HIV infection progresses (5). When direct comparisons of alveolar macrophages and peripheral blood monocytes have been made, the data suggest that viral burdens in these two cell populations are equivalent (6).

How highly active antiretroviral therapy (HAART) modulates HIV replication in the lung and pulmonary host defense is unknown. Isolation of HIV from BAL in asymptomatic individuals decreases when CD4+ T cell counts are greater than 200/ μ l, and when patients receive HAART (7), suggesting a beneficial effect. However, HIV strains may evolve independently in the lung and blood, as phylogenetic analysis of BAL strains may differ from blood strains in HIV-infected individuals (8). Zidovudine resistance may differ in peripheral blood mononuclear cells and alveolar macrophages of single individuals, suggesting that HAART may have different effects on HIV in

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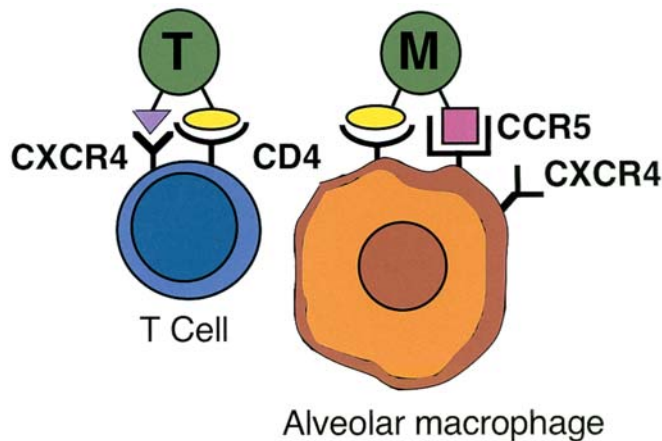


Figure 1. Tropism of HIV strains for lung cells. T-tropic strains infect T cells, using CD4 as the main receptor and CXCR4 as the coreceptor. M-tropic strains infect alveolar macrophages, using CCR5 as the coreceptor, although alveolar macrophages also express CXCR4.

lung cells (9). Recent work comparing resistance patterns of peripheral blood and BAL cells demonstrates that resistant HIV genotypes in the lung may be most widely divergent in individuals exposed to combination antiretroviral therapy (10). Further studies are needed to examine the viral load in the lung during HAART and to determine how HAART modulates pulmonary host defenses (11).

ALTERATIONS IN LUNG CELL NUMBERS AND PHENOTYPES DURING HIV INFECTION

Most of the data describing alterations in lung cell numbers and phenotypes were obtained during bronchoscopies to diagnose pulmonary infections, making the effects of HIV and of opportunistic pathogens difficult to distinguish. Additionally, these studies were conducted before the availability of HAART. These studies revealed that lymphocyte percentages or concentrations are increased in BAL from HIV-infected individuals compared with uninfected individuals. Examination of BAL lymphocyte subsets from patients with AIDS shows decreases in CD4⁺ T cells and increases in CD8⁺ T cells. Therefore, CD4/CD8 ratios in BAL specimens may be lower than the ratios in peripheral blood. Some HIV-infected individuals may manifest pulmonary symptoms as a result of CD8⁺ T-cell influx into the lung, clinically diagnosed as lymphoid interstitial pneumonitis. Late in the course of HIV infection, numbers of CD8⁺ T cells decline. Depletion of CD8⁺ T cells may be associated with the development of disseminated cytomegalovirus and *Mycobacterium avium* infections (12). As in peripheral blood, most T cells in the lung bear $\alpha\beta$ T-cell receptors on their surfaces, but a minority of T cells expresses $\gamma\delta$ T-cell receptors. Numbers of $\gamma\delta$ T cells are reported to be decreased or increased in HIV-infected patients with opportunistic infections.

Macrophage numbers in BAL from patients with AIDS are probably normal, but percentages are decreased by influx of other cells. Several BAL series have reported increases in the concentrations or in the percentages of neutrophils obtained from patients with AIDS compared with uninfected control subjects. Presumably, HAART results in the repopulation of pulmonary host defense cells as in blood, but BAL studies are not available to compare individuals receiving and not receiving HAART.

ALTERATIONS IN LYMPHOCYTE FUNCTION

CD4⁺ T Cells

Recent evidence demonstrates that, in addition to accelerated destruction of CD4⁺ T cells by HIV infection, production of T cells is also impaired. Underproduction can occur from infection-mediated death of progenitor cells and destruction of the hematopoietic stroma. In peripheral blood, T cells from patients with AIDS do not proliferate normally in response to mitogens. Even in patients with AIDS who show serologic evidence of prior infection with cytomegalovirus or herpes simplex virus, T cells fail to proliferate normally in response to these viral antigens. Failure to proliferate may be caused in part by impaired elaboration of IL-2. Peripheral blood T cells from patients with AIDS have impaired IL-2 secretion in response to a variety of stimuli. *In vitro*, recombinant IL-2 can restore some mitogenic responses of blood T cells in patients with AIDS (13). Clinical trials of IL-2 for HIV infection demonstrate that IL-2 increases CD4⁺ T cell counts in recipients without increasing HIV replication, particularly when given intermittently (14). IL-16 may prime mature CD4⁺ memory cells to respond to IL-2, and decreased IL-16 levels correlate with HIV progression. Therefore, IL-16 therapy may be useful in addition to IL-2 to restore CD4⁺ T-cell responses (15).

T cells from HIV-infected individuals do not produce IFN- γ normally in response to mitogens or antigens. The relative ability of peripheral lymphocytes to elaborate IFN- γ correlates with clinical status and CD4⁺ T cell count and predicts progression to AIDS (16). Experimental work suggests that progression from asymptomatic HIV infection to AIDS is accompanied by a switch from Th1-like responses to Th2-like responses. In theory, prevention of this switch in T-cell responses could prevent progression to AIDS. IL-12, a cytokine that favors Th1 development and inhibits Th2 development, has been shown to restore cell-mediated immunity in T cells obtained from HIV-infected individuals (17). Few data exist on the functional capabilities of lung CD4⁺ cells.

CD8⁺ T Cells

As with CD4⁺ T cells, CD8⁺ T cells in blood and lung can be infected with HIV. HIV infection also impairs the functional capacities of CD8⁺ T cells. CD8⁺ T cells obtained from the lungs of HIV-infected individuals do not lyse appropriate targets *in vitro* (18). For example, CD8⁺ T cell-mediated cytotoxicity for influenza virus is decreased in HIV-infected individuals (19). Phenotypically, CD8⁺ T cells from patients with AIDS show increased expression of activation markers, compared with uninfected individuals, and increased percentages of activated cells predict progression of HIV-related disease. Peripheral CD8⁺ T cells in HIV-infected individuals may be poor effectors because they lack required maturation signals (20). An analogous situation likely exists in the lung.

CD8⁺ T-cell alveolitis occurs during HIV infection, but the functional capabilities of these cells and their intended targets require further investigation. Subpopulations of CD8⁺ T cells, obtained from HIV-infected individuals, are cytotoxic for macrophages or B-cell lines expressing HIV antigens (21). The intensity of CD8⁺ alveolitis correlates with HIV load, and the poor prognosis associated with alveolitis may be a result of the elevated viral burden (22). Unlike the periphery, local concentrations of IL-2 and IFN- γ may be increased in the lung during HIV infection due to activation of CD8⁺ T cells (23). The alveolitis may be driven by overproduction of IL-15, a cytokine with IL-2-like effects, by alveolar macrophages. Alveolar macrophages from HIV-infected individuals produce large quantities of IL-15,

which enhances antigen presentation by alveolar macrophages and causes proliferation of lung CD8+ T cells (24).

NK Cells

Increased numbers of NK cells in BAL have been observed in HIV-infected individuals, but with progressive HIV disease, they lose functional capabilities. NK cells may be nonfunctional in HIV infection because they are dependent on signals from CD4+ T cells for optimal function (25). Biologic response modifiers such as recombinant IL-2 restore lytic ability *in vitro* (26), and IFN- γ may augment NK cell activity in early stages of HIV infection (27).

B Cells

Analysis of peripheral B cells from HIV-infected individuals shows elevated numbers of cells that spontaneously secrete immunoglobulins, and patients with AIDS have increases in serum IgA, IgG, and IgM. The IgG increase is predominantly due to IgG subtypes IgG1 and IgG3, with decreases in IgG2 and IgG4. Antibody to polysaccharides in bacterial cell walls is composed of IgG2, and patients with AIDS who have pyogenic infections have lower serum IgG2 than patients without bacterial disease. Concentrations of immunoglobulins in the lung may depend on the stage of HIV infection or the presence of pulmonary pathogens. Compared with uninfected individuals, measurement of immunoglobulins in BAL from patients with AIDS who have pulmonary symptoms shows increases in total amounts of IgG, IgM, and IgA. Local immunoglobulin synthesis may occur in the lung, as shown by increased numbers of IgG-, IgM-, and IgA-secreting cells (28). However, BAL from asymptomatic HIV-infected individuals contains decreased concentrations of IgG compared with uninfected control subjects (29). During HAART, IgG levels in asymptomatic, HIV-infected individuals are increased compared with uninfected volunteers (30).

Antibody responses to specific antigens are impaired in HIV-infected individuals. B-cell abnormalities begin early in HIV infection, with failure to produce antibody in response to mitogen at the time of HIV seroconversion, before T-cell function is affected. B cells from patients with AIDS show impaired proliferation in response to mitogens and do not initiate normal antibody synthesis in response to newly encountered antigens. Decreased IgG concentrations in the lung may be a result of impaired ability of alveolar macrophages to induce IgG secretion from B cells, likely as a result of transforming growth factor- β secretion (29).

ALTERATIONS IN MACROPHAGE FUNCTION

Phagocytosis, Respiratory Burst, and Killing of Organisms

Peripheral blood monocytes from patients with AIDS are reported by some investigators to be defective in chemotaxis to several chemoattractants, but other investigators find unimpaired chemotaxis. Alveolar macrophages from asymptomatic, HIV-infected subjects demonstrate enhanced phagocytosis for *Staphylococcus aureus* (31). BAL cells from HIV-infected individuals demonstrate increased fungistatic activity against *Cryptococcus neoformans* compared with cells from uninfected control subjects (32). The magnitude of the respiratory burst of alveolar macrophages from patients with AIDS *in vitro* is not different from uninfected control subjects, and IFN- γ enhances the response in cells from both groups equivalently (33). Alveolar macrophages and monocyte-derived macrophages do not kill *Toxoplasma gondii* or *Chlamydia psittaci*, whether obtained from patients with AIDS or from uninfected individuals (33). When exposed *in vitro* to IFN- γ , alveolar macrophages obtained from patients with AIDS increase their killing of these organisms in a manner equivalent

to uninfected individuals' cells (33). In contrast, HIV infection may impair phagocytosis of organisms that commonly cause pulmonary infections in susceptible individuals. For example, alveolar macrophages from HIV-infected individuals demonstrate decreased binding and phagocytosis of *Pneumocystis in vitro*, and this defect correlates with decreased expression of alveolar macrophage mannose receptors (34).

Antigen Presentation

During HIV infection, blood monocytes do not present antigens to T cells normally (35). In comparison to blood monocytes, alveolar macrophages are considered to be relatively poor antigen-presenting cells. However, alveolar macrophages from HIV-infected patients have enhanced ability to present antigen compared with alveolar macrophages from uninfected control subjects (36). Dendritic cells are also important antigen-presenting cells in the lung. HIV infection of dendritic cells is cytopathic for these cells, and the numbers of dendritic cells are decreased in asymptomatic HIV-infected individuals and in patients with AIDS (37). Dendritic cells from HIV-infected individuals exhibit defective antigen presentation and may facilitate HIV infection of T cells (38).

Tumor Necrosis Factor Elaboration

Some patients with AIDS are reported to have elevated serum levels of tumor necrosis factor (TNF). When peripheral blood monocytes are examined, they are reported to have high spontaneous release of TNF (39) or suboptimal release after appropriate stimulation (40). Other investigators have found that HIV infection of monocytes or monocyte-derived macrophages *in vitro* does not induce TNF release (41). Alveolar macrophages from asymptomatic, HIV-seropositive individuals have increased spontaneous TNF release, which correlates with extent of HIV expression (42). BAL cells from smokers release less TNF than BAL cells from nonsmokers, suggesting that smoking and HIV interact to suppress macrophage function (43). In the lung, TNF decreases HIV replication in alveolar macrophages by inducing production of RANTES and by decreasing CCR5 expression (44).

ALTERATIONS IN NEUTROPHIL FUNCTION

Although patients with AIDS may have increased numbers of neutrophils at the time of BAL, little is known about the host defense capabilities of these cells. In several studies, peripheral neutrophils from some patients with AIDS who had frequent localized infections showed decreased chemotaxis *in vitro*. Neutrophils from HIV-infected individuals have decreased expression of CD88, the ligand for C5a, which could contribute to increased susceptibility to bacterial infections (45). Recently, pulmonary neutrophils from HIV-infected individuals have been shown to express decreased immunoglobulin G Fc- γ receptor 1 expression compared with neutrophils from uninfected volunteers (46).

The phagocytic capacity of neutrophils during HIV infection is controversial and may depend on the stage and severity of HIV infection. For example, neutrophils from individuals with early HIV infection demonstrate enhanced phagocytosis (47). Phagocytosis of opsonized *S. aureus* is decreased in the peripheral blood neutrophils of some, but not all, patients with AIDS (48). The defect in phagocytosis can be corrected by *in vivo* administration of granulocyte colony-stimulating factor (49). Other investigators find decreased phagocytosis and intracellular killing of *Candida albicans* by neutrophils obtained from intravenous drug-using patients with AIDS, whereas cells from homosexual AIDS patients function normally (50). The authors postulate that these defects are associated with intravenous drug use

rather than HIV infection because cells from seronegative intravenous drug users were also abnormal.

The neutrophil possesses potent oxygen-dependent mechanisms to kill intracellular organisms. Peripheral neutrophils from patients with AIDS are reported to produce subnormal, normal, or supernormal amounts of superoxide when stimulated with phorbol myristate acetate. The ability of pulmonary neutrophils from HIV-infected individuals to produce superoxide is unknown.

CONCLUSION

HIV infection impairs many aspects of host defense in the lung and in the periphery. In addition to depletion of CD4⁺ T cell numbers, HIV results in functional deficits in CD4⁺ T cells, CD8⁺ T cells, and NK cells. Although some components of macrophage defense are preserved, lack of activation signals from CD4⁺ T cells contributes to impaired defense by macrophages. There are few data examining the functional capabilities of neutrophils in the lung, but evidence from peripheral blood neutrophils indicates that defense by these cells is also impaired. An improved understanding of these events in the lung during HIV infection can lead to specific interventions aimed at restoration of deficient function.

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