HIV Infection of the Lung*  
Role of Virus-Infected Macrophages in the Pathophysiology of Pulmonary Disease  
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Tissue Distribution of Virus During HIV Infection  

H uman immunodeficiency virus (HIV) infection is symptomatic as an acute viral syndrome (fever, adenopathy, pharyngitis, and rash) 2 to 4 weeks after exposure in up to 30% to 60% of newly infected individuals. Reports document high titer viremia in both plasma (>1 x 10^6 TCID/ml plasma) and cells (>1 x 10^6 TCID/10^6 cells) during this acute infection. But 3 months after onset of symptoms, HIV load (plasma p24 antigen and infectious virus) decreases to base levels; the number of DNA copies in PBMC falls from the peak by more than 90% to <1,000 copies/10^6 cells. During the long interval of subclinical infection (7 to 10 years), there is little or no free virus in plasma (30 TCID/ml plasma). The principal reservoir for HIV in blood throughout infection is the CD4+ T cell. The fraction of CD4+ T cells that contains HIV DNA is less than 1/1,000: virtually all of these infected T cells carry a single copy of transcriptionally inactive provirus. The frequency of productively infected cells in blood, cells that express HIV mRNA or protein, is <1/10,000. Control of HIV infection in CD4+ T cells is directed at those factors which regulate HIV gene expression in a large pool of latently infected cells.  

The distribution of virus in the various body tissues of HIV-infected individuals is not uniform and very different from that in blood. Analysis of DNA from tissues of infected patients by Southern blot hybridization shows relatively large quantities of HIV DNA in the brain and lymph nodes. Little or no HIV DNA is detected in lungs of lung, liver, or spleen from these same patients. The frequency of productively infected cells in affected areas of brain and lymph nodes from HIV-infected patients can exceed 10%, a frequency 10,000-fold higher than that in blood. In both brain and lymph nodes, the predominant HIV-infected cell is not the CD4+ T cell, but rather the tissue macrophage. Parenchymal and perivascular macrophages, microglia, and the macrophage-derived multinucleated giant cells of brain are each infected at high frequency. In lymph nodes, the principal HIV-infected macrophage is the follicular dendritic cell. In contrast to CD4+ T cells, most HIV-infected macrophages are productively infected, contain scores of HIV DNA copies per cell, and represent active sites of virus replication. Host control of HIV infection in tissue macrophages is directed at those factors which directly regulate virus replication.  

Reports on the amount of HIV in lung tissue are inconsistent. Initial analysis of cells recovered from the lower respiratory tract by bronchoalveolar lavage showed a frequency for productively infected cells that matched that of brain and lymph nodes: 10% to 50% of alveolar macrophages expressed viral proteins. Several recent studies confirm infection of alveolar macrophages during HIV infection in most patients late in disease but report low numbers of HIV DNA copies in these cells and a frequency of infection at <0.01%. Further, most HIV-infected alveolar macrophages recovered by bronchoalveolar lavage are transcriptionally inactive even in the face of active lung inflammation and opportunistic infection.  

Susceptibility of Macrophages to HIV Infection  

HIV can be isolated from blood leukocytes of infected patients after co-cultivation with uninfected monocyte and T cell targets. In early stage disease, monocytes are more efficient for virus isolation than T cells. As the disease progresses, HIV isolates that will infect T cells become more prevalent. Viral isolates initially derived from monocyte targets can be serially passed in both monocytes and T cells. In contrast, HIV isolates derived from T cell targets efficiently infect only T cells. Similarly, HIV laboratory strains serially passed at high titer in T cells or T cell lines replicate poorly or not at all in monocytes. The molecular basis for macrophage tropism resides in a 20 amino acid sequence in the V3 loop of gp120. Interestingly, the V3 loop is far upstream from the CD4 binding region of gp120 and is the site against which most neutralizing antibodies are directed. In a survey of 245 clinical isolates from HIV-infected patients, the consensus V3 loop sequence was that for macrophage tropism. Thus, most of the viral load in HIV disease is macrophage tropic. T cell tropic clinical isolates are statistically rare but become more prevalent in late stage disease. Such T cell tropic viruses are highly...
cytopathic in culture and are recovered from patients during intervals of rapid CD4+ T cell loss and progression to AIDS.\textsuperscript{31}

The role of cell tropism in lentivirus disease pathogenesis is vividly illustrated with simian immunodeficiency virus (SIV) infection in macaques. Progeny virus from cells transfected with a proviral SIV DNA clone replicates in T cells but not macrophages. Animals infected with this virus develop CD4+ T cell depletion and opportunistic infection but not the SIV-induced pneumonia or encephalopathy characteristic of natural infection. Serial passage of bone marrow cells infected with the lymphotropic SIV clone through uninfected macaques produced a viral isolate able to infect macrophages in culture. Animals infected with this macrophage tropic isolate now develop SIV pneumonia and encephalitis. Macrophages of the lung and brain are heavily infected.\textsuperscript{36}

In addition to factors intrinsic to the HIV virion, susceptibility of tissue macrophages to infection is also dependent upon cell differentiation. All macrophages ultimately derive from blood monocyte precursors. There is increasing evidence that the resident population of certain tissues is also renewed through low-level proliferation of indigenous precursor cells. In any case, macrophage differentiation is controlled by local tissue factors in the steady-state. Such factors are responsible for the striking variation in frequency of HIV-infection between the resident macrophages of different tissues.\textsuperscript{35} Freshly isolated blood monocytes are relatively resistant to HIV infection. These same cells placed in culture for 3 to 5 days develop marked susceptibility to infection such that 20% to 40% of total cells express HIV mRNA and protein.\textsuperscript{34} Increased susceptibility to HIV infection with time in culture is unrelated to the number of cells that express CD4 or to the relative density of CD4 per monocyte.\textsuperscript{35} It is not clear which differentiative changes in macrophages are prerequisite for permissive infection, but these changes must affect early events in the HIV life cycle. The number of HIV DNA copies/culture 24 h after infection in monocytes cultured for 7 days is at least 50-fold higher than that in an equal number of freshly isolated cells.\textsuperscript{34}

Several reports show that susceptibility of alveolar macrophages to HIV infection is much greater than that of freshly isolated monocytes and more closely mimics that of differentiated cultured macrophages.\textsuperscript{34} Differences between susceptibility of alveolar macrophages and blood monocytes to HIV infection may directly influence disease pathogenesis. Newly immigrated blood monocytes that traffic to the respiratory tract in response to infection or inflammation are significantly less susceptible to HIV infection than the resident alveolar macrophages. Alternatively, HIV brought to the lung by the rare infected blood monocyte might spread easily and rapidly into the more susceptible alveolar macrophage population.

Not only is macrophage differentiation controlled by local tissue factors, but the steady-state phenotype can be markedly changed by cytokines and other soluble mediators released during inflammation. Macrophage susceptibility to HIV infection and the extent of virus replication in HIV-infected cells are profoundly affected by IL1, IL3, IL4, IL6, IL8, IFNa, IFN\textgamma, IFN\textdelta, M-CSF, GM-CSF, TNFa, and TGF\textbeta.\textsuperscript{37}

Finally, macrophage susceptibility to HIV infection is also dependent upon the route of virus transmission. In the archetypic infection, fluid-phase virus binds to target cell CD4 through a high affinity interaction with gp120. Virus enters the cell through a pH-dependent mechanism or endocytosis. Various other cell membrane determinants (class II MHC, receptors for FcIgG or complement split products, lectins, integrins) may facilitate HIV entry. The outer lipid envelope is removed during gp41-dependent fusion with cytoplasmic vacuoles, and the intracytoplasmic core particle then becomes the site for reverse transcription. Viral DNA translocates into the nucleus and integrates into cell DNA. Large concentrations of fluid-phase virus are found in the interstitial spaces of lymph node germinal centers even in early disease where levels of plasma viremia are exceptionally low.\textsuperscript{36} But infection from the fluid-phase is not an efficient process. Most HIV virions (>90\%) enter macrophage phagosomes through CD4-independent pathways.\textsuperscript{35} Yet permissive infection occurs predominantly through the CD4 receptor: infection of macrophages is completely inhibited by antibodies against CD4 or soluble CD4.\textsuperscript{36} The CD4-independent infection of various cell lines is described but this pathway is exceedingly inefficient and may be physiologically irrelevant.\textsuperscript{36} Superimposed upon this rather complicated route of virus transmission are the intrinsic genetic defects of the HIV virion itself. It is estimated that less than 1/1,000 virions are replication-competent from the fluid phase.

Recent studies suggest at least 2 other more efficient routes of virus transmission. Cell-cell transmission of HIV occurs rapidly (10 to 30 min) in culture systems in the absence of fluid-phase virus. Such transmission requires cell-cell fusion through interactions between the gp120/gp41 expressed on the surface of HIV-infected cells and the CD4 molecules on uninfected cells. No formed viral particles are evident in areas of fusion, yet this event is followed by initiation of unIntegrated viral DNA synthesis in uninfected cells within 2 h. Presumably some as yet undefined viral ribonucleoprotein complex independent of core particles initiates the obligatory reverse transcription into viral DNA which then progresses through the remainder of the HIV life cycle.\textsuperscript{37} Cell-cell transmission of HIV persists with concentrations of neutralizing antibodies effective against fluid-phase virus.\textsuperscript{37} The gp120-CD4 cell fusion event prerequisite for cell-cell transmission is also dependent upon interactions between the leukocyte integrins, LFA-1, and ICAM.\textsuperscript{24} Viral DNA in the apoptotic debris of HIV-infected cells also infects macrophages. The HIV infection of T cells is associated with extensive fragmentation of host cell DNA, but viral DNA remains intact. Macrophages ingest this apoptotic debris and develop productive virus infection even with T cell tropic HIV isolates that can not infect these cells from the fluid-phase (R. Kornbluth, M.D., unpublished data, 1992).

**Changes in Monocyte or Tissue Macrophage Number, Phenotype, and Function During HIV Infection**

Clinical studies document little or no change in blood monocyte number, phenotype, or function during any stage of HIV disease. These observations are not surprising in

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view of the exceedingly low frequency of infected monocytes in circulation (<0.01% of total monocytes) and the inability to detect HIV infection of the CD34-positive myelomonocytic progenitor cells in bone marrow. Current evidence suggests HIV infection of tissue macrophages occurs in the tissue and not from infected blood monocyte precursors.

There have been relatively few studies on tissue macrophages in HIV disease. Follicular dendritic cells in lymph nodes show major degenerative changes early in HIV infection. Such degenerative changes increase in extent with disease progression so that in late stage disease, there is near complete loss of the follicular dendritic network important for antigen presentation in lymph nodes. In the lung, the numbers of macrophages recovered by broncho-alveolar lavage are relatively unchanged throughout disease. The alveolar macrophage remains the predominant cell type (>90% total cells) in these fluids, even in late stage disease. Indeed, the only consistent change reported in this cell population is a CD8+ lymphocytic alveolitis.

Several groups report high level TNFα production by alveolar macrophages of HIV-infected patients. Similarly high levels of TNFα are observed with alveolar macrophages of patients with pulmonary sarcoidosis and coal workers' pneumoconiosis. It is not clear whether the high TNFα levels produced by alveolar macrophages of HIV-infected patients represent a response to low level infection with intrapulmonary pathogens or to an intrinsic dysregulation of cytokine production induced directly by HIV.

Infection of macrophages by HIV in culture is associated with characteristic cytopathic effects. With certain HIV isolates, multinucleated giant cells with literally scores of nuclei per cell become evident in about 10% to 30% of cells in culture. Cell lysis is often coincident with giant cell formation. With other HIV isolates, virus-associated cytopathic effects and cell death are minimal. There is no direct correlation between HIV replication and these cytopathic effects. Interestingly, HIV-associated cytopathic changes identical to those of macrophages in culture are evident in the multinucleated giant cells found in brain tissue of patients with AIDS encephalopathy. Such morphologic changes are not found in alveolar macrophages recovered by lavage.

Little or no change in, macrophage cytokine mRNA or activity levels occurs with HIV-infected cells through weeks of infection even though those cultures with extensive virus-associated cytopathic effects. Levels of IL1β, TNFα, IL6, IFNα, or IFNβ mRNA and activity in HIV-infected macrophages are at base levels and indistinguishable from those of control cells.

The interaction of HIV-infected monocytes with components of the extracellular matrix is markedly different from that of uninfected control cells. The number of HIV-infected cells that attach to and spread on basement membrane proteins (fibronectin, laminin, type IV collagen) is threefold greater than that of control cells. This change in cell morphology is evident within hours of virus infection. By 10 to 12 days, cell processes of HIV-infected macrophages form a dense fferentiated network and enter to a basement membrane gel. Invasion of the basement membrane matrix by HIV-infected monocytes is a direct sequela of proteases able to digest the gel. Levels of neutral protease activity in culture fluids from HIV-infected monocytes are significantly higher than those from uninfected control cells. The predominant protease activity is a 92 kd neutral metalloproteinase/type IV collagenase not present in cultures of control cells. The identical metalloproteinase is induced in alveolar macrophages by bacterial lipopolysaccharides and is implicated in the tissue damage associated with infection and inflammation. It is tempting to speculate a causative role for this HIV-induced macrophage protease in the diffuse alveolar damage of AIDS.

**Central Role of Interferon-Alpha in the Control of Virus Replication in HIV-Infected T Cells and Macrophages**

The high titer viremia of the acute viral syndrome of HIV infection is coincident with high plasma levels of IFNα. Indeed, many of the symptoms of this syndrome mimic those of IFNα administration. But plasma viremia and the high titers of IFN are transient, and both return to baseline levels within weeks of HIV infection. With disease progression (years after onset of infection), IFN reappears in plasma at levels directly related to those for HIV p24 antigen. Indeed, patients with late stage disease very often have high levels of IFN and surrogate markers for IFN activity (β2-microglobulin, neopterin) in plasma.

The major cellular sources for IFNα in man during any viral infection are blood monocytes and tissue macrophages. The HIV virion is a poor inducer of IFN species in both T cells and monocytes. In a survey of 15 different clinical HIV isolates in cultures of T cells and monocytes, no IFN activity (IFNα, IFNβ, or IFNγ) was detected through 2 weeks of infection. Similarly, levels of mRNA for IFNα, IFNβ, and IFNα remained at baseline in lysates of HIV-infected monocytes.

Clinical studies document a profound and disease stage-specific disease in the capacity of blood monocytes from HIV-infected patients to produce IFNα. Monocytes from HIV-infected patients exposed in culture to herpes simplex virus-infected fibroblasts or to vesicular stomatitis virus release markedly depressed levels of IFNα. This HIV-associated defect is specific to IFNα (levels of TNFα production by monocytes in response to the same induction stimuli are normal) and is mediated at the level of IFNα gene transcription. A similar defect in IFNα production by monocytes infected with HIV in vitro is also cytokine specific (production of IFNβ, IL1β, TNFα, and IL6 remain unaffected) and effected through a transcriptional block in IFNα gene expression.

Paradoxically, HIV-infected T cells and monocytes induce high levels of IFNα in monocyte-rich fractions of blood leukocytes from uninfected control subjects. The IFNα induction by the HIV-infected cells is directly related to the extent of virus replication, is relatively specific (IL1β, TNFα, IL6, and IFNβ mRNA and activity are not detected in these cultures), and persists after fixation in 4% paraformaldehyde. Preliminary studies suggest that the major viral determinant for IFNα induction is the gp120 envelope glycoprotein.

The assumption that an IFN response to virus infection is propitious for host resistance to disease may not be valid. There is evidence in animal lentivirus disease that IFN production at the site of virus infection actually promotes
virus replication and tissue damage. The IFN production by pulmonary lymph node lymphocytes is enhanced in the presence of ovine lentivirus-infected alveolar macrophages. Such IFN production during virus-associated lymphoid interstitial pneumonia is coincident with increased virus replication, increased numbers of virus-infected cells, and extensive lung injury.\textsuperscript{46,47}

Clinical trials of IFN in patients with AIDS-associated Kaposi's sarcoma show a significant reduction (\textgtr 75\%) in plasma HIV p24 antigen in treated subjects.\textsuperscript{48} Such preliminary evidence of antiviral efficacy for IFN in HIV-infected patients is matched by other reports that document potent antiviral activity for recombinant IFNα, IFNβ, and IFNγ in HIV-infected T cell and monocyte cultures.\textsuperscript{49} The rate and extent of HIV replication in T cells are only minimally affected by exposure to rIFNα. Concentrations of rIFNα as high as 10,000 IU/ml will not prevent infection. The frequency of infected cells in cultures of IFN-treated and control HIV-infected T cells are virtually identical. Indeed, levels of HIV DNA and RNA in T cells treated with rIFNα at the time of infection and throughout 2 weeks of culture are no different from those of untreated control cells. Similarly, levels of p24 antigen and reverse transcriptase activity in the same cultures are also comparable (<2-fold difference).

But these analyses underestimate the potent effects of IFN on HIV morphogenesis. The major antiviral effects of IFN in HIV-infected T cells are operative in the terminal stages of virus assembly and release.\textsuperscript{50} Viral proteins accumulate within treated HIV-infected T cells in a direct relationship to IFN concentration from 0 to 500 IU/ml rIFNα. Immunofluorescence studies for gpl20 in HIV-infected T cells normally show a characteristic ring pattern: virtually all of envelope glycoprotein is at or on the plasma membrane. In contrast, the identical cells treated continuously with IFN show a bright and diffuse pattern that discloses accumulation of gpl20 in aberrant cell compartments. Such accumulation suggests that this envelope component may not be freely available for virus assembly. Indeed, virions from IFN-treated cells are 100 to 1,000-fold less infectious than equal numbers of virions from control cells. Transmission electron microscopy with immunogold labeled anti-gpl20 provides a molecular basis for this loss of infectivity. The HIV virions are numerous at the plasma membrane of infected T cells 2 weeks after virus infection. The anti-gpl20 immunogold label shows obvious virion-associated gpl20 on most viral particles: the average number of gold particles/virion was 5.5 ± 0.4 (mean ± SEM for 225 virions). There was no appreciable change in number or distribution of virions at the plasma membrane of IFN-treated T cells, but the number of gold particles/virion was 0.5 ± 0.1 (mean ± SEM for 122 virions), a reduction of 91%.\textsuperscript{51} Thus rIFNα induces a profound and selective depletion of HIV envelope gpl20 on the virions released from infected T cells. It is gpl20 depletion that provides the proximate cause for loss of virus infectivity.

The effects of IFN and HIV replication in monocytes are quite different from those in T cells. Monocytes treated with IFN at the time of virus challenge show no evidence of HIV infection. No viral proteins, HIV mRNA, or proviral DNA is detected in these cultures at any time through 4 weeks after infection. The IFN interrupts early events in the virus replication cycle before formation of proviral DNA: attachment, uptake, uncoating, or reverse transcription. Addition of IFN to monocytes chronically infected with HIV 1 or 2 weeks previously induces a seemingly effective series of antiviral reactions: (a) By 48 h, most virions released from IFN-treated monocytes are defective; infectivity of HIV released from treated cells is reduced at least 1,000-fold from that of an equal number of virions from control monocytes; (b) Levels of p24 antigen or reverse transcriptase activity in monocyte culture fluids decrease to baseline within 10 days after IFN treatment; (c) HIV-associated cytopathic effects (multinucleated giant cells and cell death) normally present in 30\% to 50\% of monocytes 2 weeks after HIV infection are not detected in these IFN-treated cultures; and (d) the frequency of cells that express HIV mRNA by in situ hybridization is at background (<2\% of total cells) within 7 days of IFN treatment. About 20\% to 30\% of monocytes in culture controls express HIV mRNA at this time point. Further, no genomic, structural, or regulatory HIV RNA is detected by Northern blot analysis of lysates of infected monocytes within 5 days after IFN treatment.

But these IFN-treated cells are not free of their HIV burden. Levels of HIV DNA in monocytes treated with high concentrations of rIFNα (\textless 1,000 IU/ml) are no different from those of untreated control cells even 2 weeks after treatment (3 or 4 weeks after infection) when no HIV RNA is detected.\textsuperscript{52} The presence of large quantities of HIV DNA in cells with little or no evidence of active transcription suggests true microbiliocic latency. Indeed, direct analysis of HIV gene transcription in nuclear run-on experiments shows a 2- to 3-fold reduction in nuclear transcripts within 24 h of IFN treatment. Such transcriptional restriction of virus replication in the IFN-treated HIV-infected monocytes has no precedent in previously described retroviral systems.

\textbf{Critical Issues in the Pathophysiology of Lung Disease in HIV Infection}

The lung is a major target organ in HIV disease. While macrophages are the principal cell infected with HIV in this tissue, it is not yet known how this infection contributes to the high prevalence of opportunistic infections and the diffuse alveolitis of AIDS. Lung macrophages are only rarely infected with HIV. Indeed, the levels of HIV DNA in lung tissue are no different from that of liver or spleen.\textsuperscript{53} But alveolar macrophages are readily infected by HIV in vitro. What factors account for the apparent inability of HIV to infect the lung? Discrete lobular collections of alveoli that do not directly communicate may form an anatomic barrier to virus dissemination. Infected cells or virus would be rapidly excreted through bronchociliary elimination. Factors in lung lining fluid may inhibit HIV infection in a manner similar to that of the insoluble mucin in saliva.\textsuperscript{54} Intraantioxidant defense mechanisms may also protect cells from HIV infection. Reactive oxygen intermediates activate cellular NF-κB, a nuclear binding factor required for HIV transcription.\textsuperscript{55} In the steady-state, reactive oxygen intermediates are scavenged by antioxidant factors such as glutathione. Indeed, glutathione inhibits HIV replication in vitro.\textsuperscript{56} But glutathione is depleted from HIV-infected patients early in disease.\textsuperscript{57} Air itself may damage HIV: ozone
inactivates HIV at noncytotoxic concentrations.\textsuperscript{39} Hypoxia enhances HIV transcription.\textsuperscript{29} Finally, it is tempting to speculate that the CDS\textsuperscript{+} lymphocytic alveolitis may suppress HIV infection through direct cytotoxicity against HIV-infected cells or through the release of cytokines that inhibit virus replication.\textsuperscript{36} Whatever the mechanisms for HIV resistance, lung disease ultimately remains a cardinal feature of HIV infection: this in the face of exceedingly low numbers of infected cells and the apparent functional integrity of alveolar macrophages. Given the increasingly long life expectancy of HIV-infected individuals, understanding the mechanisms that regulate HIV replication in lung cells and the consequences of HIV infection for tissue integrity and pulmonary function will become major and urgent goals of future investigation.

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Alveolar Macrophages in HIV-1 Infection: Express Accessory Molecules, Activation Markers, and Release Increased Biological Response Modifiers

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Cells of the mononuclear phagocyte system represent the predominant cell population harboring human immuno- deficiency virus type 1 (HIV-1) in the lower respiratory tract. A number of experimental findings substantiate this hypothesis. By employing in situ hybridization techniques and immunoenzymatic assays, it has been demonstrated that alveolar macrophages (AMs) express HIV-1 RNA and stain with monoclonal antibodies (Mabs) specific for the p18 and gp120 HIV-1 proteins. Direct isolation of infectious HIV-1 from AMs and bronchoalveolar (BAL) fluid has also been described, and band p24 HIV-1 antigen can be detected in the supernatants obtained from the cultured AMs.

We recently demonstrated that a discrete proportion of HIV-1-infected patients with (31.5%) and without (33.3%) opportunistic infections show a macrophage alveolitis. Nevertheless, little information is currently available on the phenotypic characteristics and functional properties of AMs during HIV-1 infection. Inasmuch as AMs from HIV-1-infected patients are committed to release a series of biological mediators of the immune response, it has been hypothesized that Pneumocystis carinii pneumonia and/or...