Is the lung important as a privileged site for the human immunodeficiency virus?

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Opportunistic lung infection, particularly *Pneumocystis pneumonia*, is frequently the AIDS defining illness in HIV-1 infected individuals. Even with the widespread use of prophylaxis, pulmonary disease remains a major cause of morbidity and mortality in patients with AIDS. Why the lung is so important for disease in AIDS remains poorly understood. There is now evidence that HIV-1 itself may be involved in local immunosuppression within the lung, facilitating opportunistic pneumonias. However, the importance of infection of alveolar leucocytes by HIV-1 remains controversial.

Molecular techniques have shown that HIV-1 is present in the lung of some individuals early in HIV disease. It is known that, in patients with AIDS, most have HIV-1 detectable in leucocytes from bronchoalveolar lavage (BAL). HIV isolated from BAL fluid can usually be grown in cell cultures and is not defective. This means that the virus is in the lung in a form allowing replication under appropriate conditions. Analysis of the cells in BAL fluid shows that CD4+ alveolar lymphocytes are the predominant HIV-1 infected cells in patients with AIDS. Alveolar macrophages have also been shown to be an important reservoir for HIV. As HIV-1 is found predominantly in alveolar lymphocytes, it has been suggested that virus is transported to the lung within infected lymphocytes as part of the inflammatory response to opportunistic infections such as *Pneumocystis carinii* pneumonia. It has been shown that most HIV-1 infected individuals have a subclinical T lymphocytic alveolitis. Of note, the predominant cell is the CD8+ T lymphocyte or cytotoxic T cell, previously thought to be responding to HIV-1 proteins expressed on the surface of alveolar macrophages. However, it is now known that in some individuals CD8+ cytotoxic T cells may themselves be infected with HIV-1. It has been suggested that these T cells become infected as a result of contact with HIV-1 budding from the surface of alveolar macrophages, providing a third cell population as a potential reservoir for HIV within the lung.

If HIV-1 is indeed introduced to the lung within infected lymphocytes from the blood, and this is the central mechanism whereby HIV-1 reaches the lung, several important issues need consideration. Firstly, HIV-1 strains isolated from the lung should be genetically identical to those in peripheral blood lymphocytes obtained synchronously during inflammatory episodes. Secondly, antiretroviral drug resistant strains of HIV-1 should not be detectable in the lung before detection in the blood as a result of selective pressure from antiretroviral agents, although they might be detectable as a result of random mutations. However, if other mechanisms operated whereby HIV-1 was transported to the lung – for example, free virus in plasma – then the virus could evolve separately and the development of antiretroviral drug resistant strains could be established independent of events at other sites. Elimination of HIV-1 from infected individuals will depend on the ability of individual drugs to penetrate alveolar spaces and destroy HIV harboured within alveolar macrophages. This paper focuses on studies into the uptake of drugs into alveolar macrophages. So far the only study to investigate the presence of HIV-1 antiretroviral drug resistant mutants in peripheral blood and lung found differences in the composition of specific point mutations in the HIV genome known to confer resistance to AZT between viruses in alveolar lymphocytes, alveolar macrophages, and peripheral blood leucocytes. In this respect it is tempting to extrapolate from lymph node studies what may happen to HIV-1 in the lung following the initiation of triple combination antiretroviral therapy. The initiation of triple combination antiretroviral therapy resulted in a marked reduction in detectable HIV-1 in the lymph nodes with 99.9% of virus being cleared within six months. Importantly, not all the virus was cleared and low levels of virus growth could still be detected within macrophages.

Of note, the few molecular studies that have compared HIV-1 genotypes in peripheral blood and lung have concentrated on comparisons between viruses in blood monocytes and alveolar macrophages. One study reported genetic differences in HIV-1 virus detected in blood leucocytes compared with lung cells. This finding underlines the potential importance of the lung in HIV-1 induced disease in view of the strong evidence that the virus is evolving separately and in isolation in the lung compared with the other body compartments. Mathematical modelling has estimated that it may take completely inhibitory treatment with potent antiretroviral therapy for over three years to eliminate HIV from bodily compartments such as the lung.

Several factors control the rate at which virus is thought to evolve including the speed at which the virus grows within cells which differs between alveolar lymphocytes and alveolar macrophages. The effectiveness of the immune response is also important when considering HIV-1 infection of the lung in terms of viral load and evolution. The local immune response may be crucial in respect of the effectiveness of cytotoxic T cells in limiting the growth of HIV. Factors controlling the growth of HIV in organs such as the lung have to be understood before eradication strategies can be contemplated.

Quantitative studies using the polymerase chain reaction (PCR) have shown that the number of HIV-1 infected lymphocytes in peripheral blood is quite small. Recently it has been shown that HIV proliferates mainly in lymph nodes and this process is inexorable throughout the asymptomatic stages. Image analysis and in situ hybridisation studies have shown that the amount of HIV-1 on the surface of follicular dendritic cells in the lymph nodes exceeds the levels of virus detected in peripheral blood. Estimates of the half life of the virus range from six hours to 2.5 days. From dynamic studies it has been shown that viral turnover is extremely rapid. The relative fidelity of the HIV-1 replicative enzymes, particularly the viruses reverse transcriptase, can lead to a rapid evolution of the virus in vivo with the generation of thousands of distinct genetic variants in a short space of time. This results in HIV escaping immune destruction whilst gradually destroying the CD4 cell population, thus exhausting the cellular immune system with eventual progression to AIDS.

HIV-1 infects relatively few alveolar lymphocytes and alveolar macrophages with a frequency of 1% and 0.1%, respectively. Most of the virus in the lung appears to be in a latent state in vivo as HIV-1 RNA could only be detected in a maximum of 0.002% of cells, although in situ hybridisation probably underestimated this frequency.
However, the incorporation of the HIV genome into the host cell chromosome could still result in the dysfunction of these infected cells and contribute to the immune suppression caused by HIV. Some workers have questioned whether growth of the virus in the lung is important as viral RNA could only be detected in alveolar macrophages from 10% of patients tested.36 However, others have recently detected HIV-1 RNA in alveolar macrophages from 67% of patients.37 Interestingly, HIV-1 proteins can be detected in cell free BAL fluid from 23% of patients with AIDS,38 and levels of HIV-1 RNA are particularly high in these fluids during episodes of Pneumocystis carinii pneumonia.39 Whether this is due to increased virus growth in the lung or to serum seepage needs to be determined by the molecular characterisation of the virus from the two fluids. When considering replication of HIV in the lung the low level of growth of the virus in patients without respiratory episodes is of significance. It could be that the virus is contained within the lymph nodes and within the lung macrophages early in the disease with the viral load increasing in the lung as the disease progresses with subsequent spillover into alveolar spaces.

In conclusion, genetic differences are observed between HIV-1 in peripheral blood and the lung. As far as AZT is concerned, different patterns of point mutations associated with resistance to this drug can be distinguished between peripheral blood leukocytes, alveolar lymphocytes, and alveolar macrophages which strongly indicate that the lung is an important site of virus growth with differential resistance patterns emerging. However, strong constraints on the growth of the virus in the lung occur early in the course of the disease which may limit the overall importance of the lung as a reservoir for drug resistant HIV at this stage. However, there are large increases in HIV replication in the lung of AIDS patients during respiratory episodes40 and this may allow the amplification of drug resistant virus unless elimination strategies for HIV using multiple drug combinations are employed. If alveolar macrophages are a privileged site for HIV-1, even small amounts of drug resistant or sensitive virus may be crucial in allowing reseeding of the host to occur.

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