Interactions between opportunist micro-organisms and HIV in the lung

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The lung is a major focus of disease in patients with acquired immunodeficiency syndrome (AIDS) and particular emphasis has always been placed upon the diagnosis and treatment of the opportunistic micro-organisms responsible for the severe and life threatening pneumonias.1 2 Numerous prophylactic approaches for preventing and controlling these opportunistic pathogens have been published. Despite the implementation of these procedures the prognosis for patients with AIDS is poor with an average survival time from diagnosis to death of 17 months.3 As a result of the profound immunosuppression induced by HIV, pneumonias are common during the course of the disease, due to three major types of pathogens: Pneumocystis carinii, Mycobacterium tuberculosis, and pyogenic bacteria. Indeed, even with widespread prophylaxis Pneumocystis carinii remains the commonest opportunistic micro-organism of the lung among patients with AIDS in the industrialised world.2 In sub-Saharan Africa and Asia the most common pulmonary complication in HIV infected individuals is tuberculosis.4 Coupled with the spread of multiple drug-resistant strains of tuberculosis amongst subjects with AIDS in the USA, tuberculosis threatens to spread into the general community. Furthermore, pyogenic bacterial infections are common in patients with AIDS and are an important cause of death in Africa.5 6 The role of viral infections of the lung in HIV infected individuals, particularly those due to cytomegalovirus, remains controversial.

Various mechanisms exist in which immune responses mounted by the host during pneumonia may modify the growth of HIV. These interactions between HIV and infectious agents in the lung may be harmful for the lung itself, and quite probably enhance the progression of the HIV disease in general.7 As HIV replicates best in activated or differentiated cells of the immune system, co-infections of these cells with opportunistic micro-organisms and HIV could enhance viral replication. Alternatively, cells releasing cytokines in response to a pathogen could trigger HIV replication in adjacent cells through a paracrine process. The high frequency of detection of HIV proviral DNA in alveolar lymphocytes and alveolar macrophages from patients with AIDS8 indicates that there is ample opportunity for interaction between opportunistic micro-organisms and HIV in the lung.

Depletion of CD4+ T lymphocytes and subsequent abrogation of the immune system by HIV greatly facilitates the development of Pneumocystis carinii pneumonia and onset of AIDS. However, P carinii pneumonia does not predominate alveolar lymphocytes or macrophages to infection in vivo and, conversely, although P carinii pneumonia is a marker for AIDS, HIV-1 infection of alveolar lymphocytes and macrophages is not a prerequisite for P carinii pneumonia.9 However, P carinii does significantly increase the recovery of HIV-1 from these cells10 11 and there is a fourfold increase in the number of HIV virions detectable in the cell free fluid obtained by bronchoalveolar lavage from individuals with P carinii pneumonia.12 The cellular mechanisms underlying this phenomenon remain unclear, although increased levels of tumour necrosis factor α (TNFα) are secreted by the immunocompetent host in response to P carinii pneumonia.13 Likewise, high levels of TNFα are released by alveolar macrophages in the lung of HIV-1 infected individuals,14 particularly during P carinii pneumonia.15 Interestingly, increased production of TNFα by alveolar macrophages does not correlate with an increase in the number of cells infected with HIV.16 Furthermore, TNFα has been shown to be a potent stimulator of HIV-1 replication17 and thus could offer a mechanism by which significant replication of HIV may occur in the lung. Conversely, in vitro experiments on HIV infected macrophages exposed to P carinii show that they release less TNFα than uninfected cells.18

An early effect of infection with HIV-1 is the reactivation of previously dormant tubercle bacilli. One consequence of interaction between Mycobacterium tuberculosis and HIV is a decreased control of both infections by host cells. An important action of HIV is inhibition of T lymphocyte mediated immune functions that maintain mycobacterial dormancy.19 Both CD4 and CD8 T lymphocyte functions are essential for protection against M tuberculosis. Even a moderate reduction in the number of CD4 T lymphocytes is sufficient to enable reactivation of tuberculosis.20 Furthermore, peripheral blood mononuclear cells from HIV infected subjects with tuberculosis have decreased proliferative and type 1 responses on stimulation with M tuberculosis.21 Consequently, blood monocytes from patients with tuberculosis are more susceptible to the growth of HIV.22 The phagocytosis of M tuberculosis by monocyte cell lines enhances the replication of HIV-1 and HIV-2 in these cell lines23 24 but, surprisingly, whilst virus transcription is increased, release of infectious virus from the cells is reduced. This scenario may facilitate the spread of HIV by
It has been reported that co-infection of cells in vitro with cytomegalovirus (CMV) stimulates HIV replication. Again, the viral proteins produced by CMV and required for the initiation of replication by this virus can also directly stimulate HIV transcription, and it is possible that co-infection with CMV could amplify the effects of HIV infection in the lung. Furthermore, CMV infection of human fibroblasts in vitro has been shown to upregulate cellular nuclear factors within these cells with resultant stimulation of HIV-1 replication. However, the isolation of CMV from respiratory secretions of patients with AIDS and pneumonia did not appear to affect the prognosis adversely, although the isolation or cytological detection of CMV in bronchoalveolar fluid from HIV infected individuals was associated with a significant increase in mortality at three and six months after bronchoscopy in the absence of other complicating factors such as CD4 count. Our own studies indicated that, in patients with AIDS who had detectable HIV and CMV in their alveolar cells, there was no additional reduction in pulmonary function.

Recently, reciprocal enhancement of HIV-1 and HSV-1 replication associated with co-infection of keratinocytes and macrophages in vivo has been reported. Interestingly, the virions were found to be morphologically atypical hybrids and, if verified, this observation could have profound implications for the pathogenesis of AIDS, as it would increase the spread of both viruses in cells and tissues that would not ordinarily be infected due to the lack of appropriate receptors for virus entry.

In summary, a number of pathogens can be found in the lung of HIV seropositive subjects. Whilst some such as P carinii, M tuberculosis, and pyogenic bacteria undoubtedly cause pneumonia, others such as CMV may be innocent passengers at the time of respiratory episodes. However, from in vitro studies it is clear that these micro-organisms can enhance HIV replication. Furthermore, some clinical observations now support the belief that interactions between micro-organisms and HIV occur in vivo and hasten the onset of AIDS. To date the exact mechanisms involved are poorly understood. A better understanding could be beneficial in designing future treatment strategies which limit the deleterious effects of opportunistic infections on disease progression in HIV infected subjects.

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