Potential Role of Viruses in the Pathogenesis of Pulmonary Fibrosis*

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Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease of unknown etiology. The hallmark of the disease is progressive dyspnea and inflammation and fibrosis of the pulmonary interstitium. The disease is relatively insensitive to therapeutic manipulation. Some patients do respond to therapy with corticosteroids or cytoxan, but it is not entirely clear if this can be anticipated on the basis of the pathologic state of their disease. The disease is associated with premature death, with only 50% survival 5 years after the diagnosis is established. There does not appear to be a race or sex predilection for the disease. A primary focus of research related to IPF is the pathogenesis of the disease. One of the first indications that this was an immunologically related disease was the finding that patients with IPF have increased circulating immune complexes. Immune complexes likely are important in the pathogenesis of IPF because they activate macrophages to release factors that attract neutrophils to the lung and factors that increase the proliferation of fibroblasts. Activated macrophages and increased numbers of neutrophils and fibroblasts are important features of the disease process in patients with IPF.

There are also increased numbers of eosinophils and mast cells in the lungs in many patients with IPF. In addition, some patients also have increased numbers of lymphocytes. In many respects, this component of the inflammation present in the lower respiratory tract in IPF resembles the inflammation present in the airways of patients with asthma. In fact, there are usually more mast cells in the lavage fluid of patients with IPF compared to patients with asthma. In addition, increased amounts of histamine and eosinophils in lavage fluid have been related to severity of disease in these patients. Whether there are any true pathogenetic similarities between these 2 diseases remains to be determined. Certainly, these 2 diseases affect different anatomic regions of the lung.

The most important question regarding the pathogenesis of IPF is the etiology of the disorder. An interesting feature of the history obtained from many of these patients is that their disease was preceded by a viral-like illness. This has long been an interest in the study of IPF, however, no one has been able to culture viruses from bronchoalveolar lavage fluid or lung tissue. However, it is known that viruses can persist in a latent state, after an initial infection. It is very unlikely that viruses would be cultured from tissue during latency. The mechanisms of latency are not entirely clear; however, it is clear that the viral genome is intact, as is obvious during reactivation secondary to immunosuppression. In addition, the virus may not be inactive but may express a small portion of its genome. The viral gene products produced during latency could induce disease by several mechanisms: the products of the viral genes could be expressed on the cell surface and function as persistent antigens to drive an "autoimmune" response; they could mimic other immune response genes through sequence homology; or they could act as transacting factors to control the expression of cellular immune response genes. Transacting factors are proteins which either bind directly to DNA by specific consensus sequences or which interact with other DNA binding proteins to modify activity of specific genes. These factors may effect autologous or heterologous promoters, they may act in a positive or negative fashion, and they may modulate an appropriate cellular immune response or trigger an inappropriate cellular immune response.

To investigate the potential role of latent virus in the production of an appropriate immune response, such as that seen in IPF, the effects of human cytomegalovirus (CMV) on the immune response genes of the T cell and the macrophage have been evaluated. These are important cellular systems to study in light of the fact that there may be persistent activation of macrophages and lymphocytes in patients with IPF. In addition, these cells are the natural reservoir for many latent viruses, especially the CMV virus.

Studies from this laboratory have shown that the immediate early (IE) gene products of CMV, which are the products of latent viral genes, can upregulate a variety of cellular genes involved in the immune response. The IE1 gene product markedly upregulates the promoter of the interleukin-1β (IL1β) gene, as well as the levels of steady state IL1β RNA. The effect appears to be specific for the region of the IL1β promoter which is 3' to -131, as progressive truncation of the promoter down to -131 does not effect the ability of IE1 to upregulate the promoter. The IE1 specifically interacts with a cell-derived transacting factor, called NFIL-1BA, which binds to the IL1β promoter 3' to -131 to upregulate expression of the gene.

The IE gene products also upregulate expression of the T cell derived interleukin-2 (IL2) and interleukin-2 receptor (IL2R) genes. Of interest, in these studies it was observed that it was the IE2 gene products, as compared to the IE1 gene product, which upregulated IL2 and its receptor. Studies using deletions in the IL2R promoter have demonstrated an area between -317 and -281 which appears important for this interaction (unpublished data, L. J. Geist, M.D., 1990). This area has internal sequence homology with a 9 base pair region of the CMV IE promoter which mediates IE2 regulation of its own promoter. These studies have not demonstrated binding of the CMV IE2 gene product to the promoter directly, suggesting that IE2, as well as IE1, may act as coactivators, binding to other cellular transcription factors.

It has also been demonstrated that the IE gene products upregulate tumor necrosis factor (TNF) promoter activity in both T cell and monocyte cell lines, and TNF steady state RNA and protein production in monocyte cell lines. The IE2 upregulated promoter activity in the T cell line, while IE1 and IE2 were equally effective in the monocyte cell line. These studies, taken together, imply some degree of cellular specificity to the action of the CMV IE gene products with regard to their interaction with cellular promoters and cellular transcription factors.

Other viruses have been shown to have similar effects on cellular genes. Herpes simplex virus gene products have

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Altered Patterns of Lung Lymphocyte Accumulation in Silicosis in Cytokine-Sufficient (C3H/HeN) and Cytokine-Deficient (C3H/HeJ-LPS\textsuperscript{*}) Mice*

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Lymphocytes accumulate within the evolving lesions of silicosis: in the interstitium, in focal lymphoid aggregates, and in silicotic nodules. An influx of both CD4+ and CD8+ T lymphocytes appear in BAL fluid from rats exposed to silica. A complex network of cytokines, many derived from pulmonary macrophages, appears to promote silicosis through localized effects which perpetuate macrophage activation, stimulate T lymphocyte proliferation and activation, promote silicotic lesion formation, and cause fibroblasts to replicate. Interleukin 1 (IL-1) and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) are prominent in this network. Our goal was to determine whether a genetic deficiency in cytokine responsiveness would alter the expression of chronic silicosis in the mouse.

Mice of the inbred strain C3H/HeJ-LPS\textsuperscript{*} (Hej) are relatively deficient in the production of TNF-\(\alpha\), and probably other cytokines, in response to selected stimuli. We exposed mice of the C3H/HeN (HeN) cytokine-sufficient and the Hej cytokine-deficient strains to an aerosol of \(\alpha\)-quartz silica (Min-U-Sil, 33 mg/m\(^3\), 8 days) and compared the development of silicosis up to 75 days following the exposure.

Mice of the Hej strain demonstrated less histopathologic lung tissue inflammation and fibrosis, less inflammatory cell recruitment in BAL specimens (10% vs 26% neutrophils at 14 days; \(p<0.05\)), and less accumulation of total lung collagen (3.2 vs 4.6 \(\mu\)g OH-proline-mg lung at 75 days; \(p<0.03\)).

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