Pathogenesis of Pulmonary Fibrosis; Implications for the Connective Tissue Diseases

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Connective tissue diseases can affect all of the major structures of the lung: the airways, the alveoli and the pulmonary vasculature. These can lead to bronchiolitis obliterans, pulmonary fibrosis, and pulmonary hypertension. Because the lung is relatively accessible, through fiberoptic bronchoscopy and bronchoalveolar lavage, investigations of the patho-physiologic mechanisms of human lung disease have been possible, particularly in the fibrotic diseases.

Pulmonary fibrosis, a replacement of the normal alveolar structures of the lung with an increased population of fibroblasts and the collagenous connective tissue matrix produced by these cells, frequently results from chronic alveolar inflammation, or alveolitis. Many injurious stimuli seem to activate an inflammatory response and lead to similar sequelae. In the face of lung injury and inflammation, alveolar macrophages are activated to release a host of mediators. It is thought that these mediators may play a role in restoring lung function. Thus, these can be considered to be "mediators of repair." If injury is too severe, however, or if the "mediators of repair" are not released in the proper sequence or amount, tissue fibrosis can result. Thus, for example, macrophages can release mediators responsible for fibroblast recruitment, for fibroblast orientation within tissues and for fibroblast proliferation. The fibrous connective tissue which is deposited following an injury to the lung can thus be directed by alveolar macrophages. Finally, alveolar macrophages can modulate fibroblast production of collagen.

Lung fibroblasts are capable of directed migration in response to chemotactic stimuli. At least three products of activated alveolar macrophages, fibronectin, platelet-derived growth factor and transforming growth factor-beta are capable of inducing fibroblast recruitment. Once recruited to sites of inflammation, fibroblasts must attach to the extracellular matrix.
Under normal conditions, the ability of fibronectin to bind to the collagenous extracellular matrix is a major means for fibroblast adhesion. The ability of fibronectin to bind to sites on fibrin and on the C1q component of complement can provide a nidus for fibroblast attachment at abnormal sites within tissues. Thus, the deposition of immune complexes or polymerized fibrin can lead to subsequent fibroblast attachment. Such a process may account for intra-alveolar fibrosis which is a frequent consequence of inflammatory alveolitis. Once recruited and oriented within tissues, fibroblasts proliferate in response to specific growth stimulators. In general, at least two different classes of growth factors, progression factors and competence factors must be present. Macrophages can also produce growth factors in both of these classes. Fibronectin and the platelet-derived growth factor have both been reported to function as competence factors. Macrophages also produce an insulin-like growth factor which can function as a progression factor. Together these factors can lead to fibroblast proliferation. In addition, macrophage-derived factors such as interleukin 1, tumor necrosis factor, transforming growth factor-beta and gamma interferon may have complex effects, either stimulating or inhibiting fibroblast proliferation, depending on the presence of other factors. Inhibition of fibroblast proliferation may be an important mechanism which limits the development of fibrosis in “normal” conditions. In fibrotic states, macrophages may reduce the release of such inhibitory mediators. This may be a “permissive” requirement for the development of fibrosis. Lastly, once fibroblasts accumulate and proliferate at a site of fibrosis, collagen molecules are synthesized and secreted. The fibers which result likely depend on the ratio of the various collagen types produced, on the amount of collagen produced and on the relative amounts of other connective tissue components such as fibronectin and proteoglycan. It is likely that mediators present in the inflammatory milieu such as prostaglandin E which can decrease Type I collagen production and TGF-beta which can increase collagen and fibronectin production can have a marked effect on the fibers which form in an inflammatory lesion. Of these mediators, simultaneous macrophage production of fibronectin and the insulin-like growth factor AMDGF is associated with clinical progression. The ability to quantify these mediators using bronchoscopy and bronchoalveolar lavage suggests that therapies designed to alter mediator release can be developed.

While it has been classically stated that fibrosis is “irreversible,” recent studies suggest
that remodeling with resorption of fibrosis can, in some circumstances, take place. The processes which underlie this tissue remodeling, are incompletely understood, but likely involve the coordinated activity of connective tissue specific proteases.

In the connective tissue diseases, it is likely that macrophages will play a central role as they are thought to in such primary lung diseases as idiopathic pulmonary fibrosis. In addition, a role for cells other than macrophages is likely. Lymphocytes, for example, can release chemotactic factors for fibroblasts and platelets are a potent source of fibroblast growth factors. The overall pathophysiologic process, that is: (1) inflammation leading to activation of inflammatory cells to (2) produce “mediators of repair” which in turn (3) recruit mesenchymal cells and lead to the development of a fibrous connective tissue scar which (4) replaces normal parenchymal structures is likely to have a close analogy in numerous other fibrotic lesions including cirrhosis of the liver, atherosclerosis and fibrosis of the skin. An interesting concept is that these processes in the lung will be similar to those responsible for disease elsewhere in the body in systemic disorders such as the connective tissue diseases.