Commentary

A new direction in the pathogenesis of idiopathic pulmonary fibrosis?

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Abstract

A recent review article suggested that idiopathic pulmonary fibrosis (IPF) is a disease that is associated more with abnormal wound healing than with inflammation. Data derived from transgenic and gene transfer rodent models suggest that lung inflammation may be a necessary but insufficient component of IPF, and that at some point in the natural history of the disease IPF becomes no longer dependent on the inflammatory response for propagation. Altered microenvironment and involvement of epithelial cell/mesenchymal cell interaction are the most likely contributors to the pathogenesis of this chronic progressive disorder.

Keywords: fibrosis, inflammation, myofibroblast, tissue repair, transforming growth factor (TGF)-β

Introduction

An excellent recent review of IPF by Selman *et al*. [1] outlines current concepts regarding pathogenesis and suggests a new hypothesis for the aetiology of this progressive and usually fatal disease. IPF has recently been classified in diagnostic pathology terms as usual interstitial pneumonia (UIP) in order to differentiate it from other forms of pneumonitis that are associated with different pathogeneses and a more favourable prognosis [2].

A great number of IPF/UIP patients show no evidence of ongoing inflammation, raising questions as to whether IPF is truly associated with chronic inflammation. Through an extensive study of the literature, Selman *et al*. arrived at the conclusion that there is a lack of definitive evidence that IPF is a chronic inflammatory disease and suggested an alternate hypothesis that is consistent with clinical and morphological features. They proposed that IPF is a disorder that involves abnormal wound healing and that ongoing epithelial damage and/or epithelial cell activation results in abnormal mesenchymal cell activation, with derivation of myofibroblasts and excess matrix deposition. These latter aspects of alteration of mesenchymal cell phenotype and chronic interaction with epithelium, through communication by cytokines and matrix, drive the chronic and progressive nature of IPF, rather than any inflammatory component. These concepts are interesting and fit more with clinical findings than the concept of chronic inflammatory cell involvement. Moreover, the lack of reliance on inflammation is in accord with the lack of resolution of the progressive process on treatment with potent anti-inflammatory drugs.

Current concepts of inflammation and fibrosis

After lung injury, acute inflammation and tissue repair mechanisms are engaged to halt the injurious stimulus, remove infectious organisms if present, and initiate immedi-

IL = interleukin; IPF = idiopathic pulmonary fibrosis; TGF = transforming growth factor; UIP = usual interstitial pneumonia.

Table 1

Transfer of cytokines by adenovirus vector to the rodent lung

Cytokine	Degree of inflammation	TGF-β	Myofibroblasts	Fibrosis
IL-1β	Acute +++; alveolar destruction	400 pg/ml	+++	++++
TNF-α	Acute +++	150 pg/ml	+	+
GM-CSF	Acute ++	600 pg/ml	++	++
TGF-β_1	Minimal to absent	>50 ng/ml	++++	++++

Degree of inflammation ranges from 0 to ++++, with 0 representing no detectable inflammation by morphologic examination to ++++ where there is extensive inflammatory cell accumulation throughout the parenchyma and lumen of the lung. Similar ranges are used for myofibroblast presence and extent of fibrosis. GM-CSF = granulocyte/macrophage colony-stimulating factor; IL = interleukin; TGF = transforming growth factor; TNF = tumour necrosis factor.

ate repair to crucial membranes that function to provide gas exchange for survival. This usually results in the eventual return of the organ to normal function. However, in chronic tissue injury, with repeat episodes of inflammation, many of the control mechanisms involved in this otherwise well orchestrated process are bypassed. Continued repair results in disorder of the tissue, distorted matrix deposition, mesenchymal cell proliferation and alteration to normal lung structure, with compromised gas exchange function; this overall process is known as fibrosis. In cases in which the initiating event is known, such as with postradiation fibrosis or with asbestos- or silica-induced injury, the pathogenesis appears to follow the inflammatory response. In the majority of cases of pulmonary fibrosis, however, no known initiating event is recognized and IPF is diagnosed [3].

During the past decade a number of investigators conducted mechanistic studies aimed at defining the pathogenic mechanisms that are involved in IPF. It has long been believed that IPF is a process of chronic repair that results from persistent inflammation with attendant activation of inflammatory cells and local presence of mediators (cytokines and growth factors) that are capable of activating mesenchymal cells, with enhanced matrix production and deposition. Inflammation is usually identified on the basis of morphology and demonstration of accumulation of inflammatory cells, such as neutrophils and/or eosinophils and mast cells in biopsy material. The morphology is mostly descriptive, and there are few specific protein measurements in either lumen washes or in lung tissue regarding the mediators that are involved in the process. Moreover, single snapshots of chronic processes cannot reveal much about a disease that has such a lengthy period (years) and for which there is no known natural history. Thus, we are limited to information gleaned from experimental animal models to help us determine the temporal, cellular and molecular mechanisms of pathogenesis, and develop therapeutic interventions.

Selman *et al*. [1] suggested that the natural history of the disease has more to do with intrinsic aberrant wound healing than with inflammation, and described pathways of interaction between injured alveolar epithelium and parenchymal fibroblasts that result in altered mesenchymal cell phenotype and fibrogenesis (fibroblast proliferation, myofibroblast differentiation and matrix synthesis). In the first instance their argument is compelling and makes sense, given the data obtained in human samples along with those recently obtained in experimental models. Moreover, there are many examples in embryonic development of tissue remodelling through release of cytokines and growth factors, without attendant or preceding inflammation. It is thus reasonable to assume that such activities may be recapitulated in at least some aspects of chronic tissue repair. Communication between the epithelium and mesenchymal cells is crucial for development of the normal lung, and central to organ development is tissue remodelling [4,5].

Is inflammation required for fibrogenesis?

Crucial to the suggested interaction of epithelium and mesenchyme is transforming growth factor (TGF)-β. This factor is involved in normal alveolar development and in regulation of repair processes, in addition to its broad activities in regulating the immune response [6]. Most important is the demonstration that TGF-β is an integral component of fibrotic tissue in IPF [7,8], with a known role in causing the differentiation of myofibroblasts (a critical element in tissue repair and fibrosis) [9].

Importantly, Munger *et al*. [10] recently showed that activation of latent TGF-β through expression of the integrin $\alpha_v\beta_6$ can generate fibrogenic conditions. This could occur either in the presence or absence of ongoing inflammation, and thus could progress to fibrosis in an independent manner.

We conducted studies with adenovirus vectors that express individual cytokine and growth factor genes administered to the lung epithelium. Those studies demonstrate, at least in the animal model, that remodelling can occur subsequent to acute inflammation (as is seen with over-expression with IL-1β) [11] or independent of inflam-

mation (as seen with over-expression of active TGF-β_1) [12]. Over-expression of other factors that have been identified as being profibrogenic exhibit acute inflammation with minimal remodelling, as with tumour necrosis factor-α [13], or both acute and chronic inflammation with moderate remodelling, as with granulocyte/macrophage colony-stimulating factor [14]. The common theme is the generation of active TGF-β, and the extent of fibrosis and myofibroblast induction appears related to the level of TGF-β present (Table 1).

Sheppard [15] commented that the inflammation induced by transient expression of IL-1β and associated with fibrosis is temporal, with fibrogenesis occurring after the transient expression of IL-1β had subsided and the induced levels of TGF-β were prolonged. This suggests that inflammation may precede the onset of fibrosis by setting in motion a series of cell activations and/or matrix alterations that result in prolonged mesenchymal and epithelial interaction, probably through TGF-β. Thus, the chronic process of fibrosis may be separated from the acute process of inflammation, and inflammation appears necessary but not sufficient to explain the pathophysiology of fibrosis. This would appear more consistent with the suspected natural history of IPF.

A further issue, which supports both the need for and absence of inflammation in fibrosis, needs to be considered. This is the recently described expression of CD40 (the receptor for CD40 ligand) by fibroblasts and other mesenchymal cells [16]; the CD40 system is normally associated with induction of the immune response. Phipps [16] summarized the data reported when fibroblast CD40 ligation occurs, resulting in upregulation of cyclo-oxygenase-2 and various cytokines that are characteristic of a T-helper-2-like environment [16], which is known to be preferential to a fibrogenic response [17,18]. In addition to T cells, the platelet is a very rich source of CD40 ligand, and as such mesenchymal cell activation and stimulation may occur through platelet degranulation or immune activation, processes that can occur in the absence of acute inflammation [19].

Conclusion

In summary, the concept of inflammation-independent fibrosis, put forth by Selman *et al*. [1], is supported by clinical, developmental biology and immune regulation data, and gene transfer studies in animals. Similar studies also support the concept of fibrogenesis resulting from acute and chronic inflammation, however. In the absence of knowledge regarding the natural history of IPF, our best guess is that IPF is more likely to be a syndrome rather than one specific disease, and that the end stage of fibrosis, which may be independent from inflammation, can develop through multiple aetiologies. Studies with drugs that block pulmonary fibrosis in humans may clarify the multiple pathways to pathogenesis, and demonstrate the validity of several hypotheses for the mechanism of fibrogenesis.

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