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Review

Fibrosis of two: Epithelial cell-fibroblast interactions in pulmonary fibrosis ☆

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is characterized by the progressive and ultimately fatal accumulation of fibroblasts and extracellular matrix in the lung that distorts its architecture and compromises its function. IPF is now thought to result from wound-healing processes that, although initiated to protect the host from injurious environmental stimuli, lead to pathological fibrosis due to these processes becoming aberrant or over-exuberant. Although the environmental stimuli that trigger IPF remain to be identified, recent evidence suggests that they initially injure the alveolar epithelium. Repetitive cycles of epithelial injury and resultant alveolar epithelial cell death provoke the migration, proliferation, activation and myofibroblast differentiation of fibroblasts, causing the accumulation of these cells and the extracellular matrix that they synthesize. In turn, these activated fibroblasts induce further alveolar epithelial cell injury and death, thereby creating a vicious cycle of pro-fibrotic epithelial cell-fibroblast interactions. Though other cell types certainly make important contributions, we focus here on the "*pas de deux*" (steps of two), or perhaps more appropriate to IPF pathogenesis, the "*folie à deux*" (madness of two) of epithelial cells and fibroblasts that drives the progression of pulmonary fibrosis. We describe the signaling molecules that mediate the interactions of these cell types in their "fibrosis of two", including transforming growth factor-β, connective tissue growth factor, sonic hedgehog, prostaglandin E_2, angiotensin II and reactive oxygen species. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

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1. Introduction

Fibrosis characterizes many chronic diseases that result in end-stage organ failure, and consequently is a major cause of morbidity and mortality. The pathogenesis of fibrosis in many of these diseases is thought to involve aberrant or over-exuberant wound-healing processes initiated to protect the host from injurious stimuli [1]. In response to noxious stimuli of many different types, aberrant repair processes can produce the common result of excessive deposition of extracellular matrix that disrupts normal tissue homeostasis. Repair processes involve multiple cell types, including epithelial cells, fibroblasts, endothelial cells, pericytes and leukocytes, all of which potentially interact with each other. Interactions between two cell types in particular, alveolar epithelial cells and fibroblasts, appear to be central to the pathogenesis of idiopathic pulmonary fibrosis (IPF) [2].

IPF is characterized by progressive fibrosis, with excessive matrix deposition leading to destruction of lung architecture and ultimately fatal impairment of lung function. IPF has a heterogenous clinical course, but the median survival after diagnosis is only 2.5–3.5 years [2]. Although much of the pathogenesis of IPF remains to be elucidated, fibroblasts and epithelial cells have emerged as principal players in this disease, in particular myofibroblasts and type II alveolar epithelial cells. Fibroblasts and myofibroblasts accumulate in IPF lungs in "fibroblastic foci" that, as the predominant sites of excess matrix production, can be thought of as the leading edge of active fibrosis [3]. Fibroblast activation and accumulation in IPF, however, appears to be fundamentally driven by recurrent and/or non-resolving injury to the alveolar epithelium, and therefore in another sense, the injured alveolar epithelium can be thought of as the leading edge of active fibrosis. With fibroblasts and alveolar epithelial cells being in close apposition in the lung, it is not surprising that the *interactions* between these two key cellular players contribute to the development of pulmonary fibrosis. Though other cell types certainly make important contributions, we will focus on

Abbreviations: IPF, idiopathic pulmonary fibrosis; AEC, alveolar epithelial cell; TGF-β, transforming growth factor; CTGF, connective tissue growth factor; Shh, sonic hedgehog; PGE_2, prostaglandin E_2; ROS, reactive oxygen species; H_2O_2, hydrogen peroxide

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the "*pas de deux*" (steps of two), or perhaps more appropriate to IPF pathogenesis, the "*folie à deux*" (madness of two) of epithelial cell-fibroblast interactions as critical drivers of pulmonary fibrosis. Whereas the source of the fibroblasts and myofibroblasts that accumulate in the lung as fibrosis develops – whether these cells arise from resident fibroblasts, resident epithelial cells or circulating precursors – has been an area of controversy, the pro-fibrotic effects of the interactions of fibroblasts and myofibroblasts with resident lung epithelial cells has become increasingly clear. We describe the role of several important mediators in orchestrating the pro-fibrotic interactions of epithelial cells and fibroblasts in their "fibrosis of two", including transforming growth factor-β, connective tissue growth factor, sonic hedgehog, prostaglandin E_2, angiotensin II and reactive oxygen species (Fig. 1).

2. Epithelial cells: targeted cells in IPF

Accumulating evidence points toward recurrent and/or non-resolving injury to the lung epithelium as the "prime mover" of pulmonary fibrosis. Although the cause of this injury in IPF remains enigmatic, the footprints of lung epithelial injury are manifest, both in the form of (1) increased epithelial cell death, and (2) phenotypic alterations of the surviving epithelial cells. Increased numbers of apoptotic and necrotic cells have been observed in both the alveolar and bronchial epithelia of IPF patients [4–6]. Surviving epithelial cells in IPF lungs demonstrate several altered phenotypes [7]. Cuboidal epithelial cells representing type II alveolar epithelial cell (AEC) hyperplasia and/or bronchiolar basal cell proliferation line thickened fibrotic alveolar septa; single layers of flattened epithelial cells suggestive of squamous metaplasia frequently are present overlying fibroblastic foci; and single-layered columnar or pseudostratified columnar epithelial cells often line the abnormally enlarged, restructured air spaces of honeycomb lung. These morphological changes are associated with modifications of epithelial cell expression of specific cytokeratins, suggesting that in addition to their morphology, the differentiation states and functions of epithelial cells are likely profoundly altered in IPF. Of note, although IPF has been traditionally viewed as affecting the parenchymal lung rather than the airways, a potentially central role for the bronchial epithelium in addition to the alveolar epithelium in IPF pathogenesis has been suggested by the recent association of a genetic variant in mucin 5B (*MUC5B*) with both familial and sporadic IPF [8].

The potential of epithelial injury in general to cause pulmonary fibrosis has been demonstrated in several mouse models. Induction of pulmonary epithelial cell death in mice, either by pulmonary delivery of anti-Fas antibody [9,10] or transgenic overexpression of transforming growth factor-β (TGF-β) [11], results in the development of fibrosis, as does genetically targeting diptheria toxin-induced injury to alveolar epithelial cells [12]. Additionally, inhibition of apoptosis attenuates the fibrosis induced by bleomycin challenge, the most commonly used mouse model of pulmonary fibrosis [13].

Finally, in addition to noxious stimuli in the external environment, alterations in the internal environment of epithelial cells can also lead to their death and promote pulmonary fibrosis. For example, the mutations in the gene encoding surfactant protein C (SFTPC) that have been associated with familial pulmonary fibrosis (familial interstitial pneumonia) cause SFTPC misfolding, leading to protein accumulation and endoplasmic reticulum (ER) stress [14–17]. Unresolved or prolonged ER stress activates cellular apoptotic pathways, and the resulting epithelial cell death may cause the pulmonary fibrosis that affects these SFTPC mutation kindreds [18]. Thus epithelial cell injury and death, albeit due to a variety of causes and through a variety of mechanisms, appears to be a common initiating pathway to fibrosis in the lung.

3. Epithelial cell-to-fibroblast interactions: how injured epithelial cells activate fibroblasts

Areas of AEC apoptosis and foci of α-smooth muscle actin (αSMA)-positive myofibroblasts co-localize in the lungs of IPF patients [6], making it plausible for these two cell types to directly influence each other as fibrosis develops. The ability of injured epithelial cells to affect local fibroblast behavior in a paracrine fashion has been demonstrated by *in vitro* co-culture experiments. In these experiments, mechanical injury to epithelial cells induced the expression of α-SMA and type I and III collagen in co-cultured fibroblasts by stimulating the activation of TGF-β in the extracellular matrix [19]. In addition to TGF-β, a growing list of mediators has been found to contribute to the ability of injured epithelial cells activate

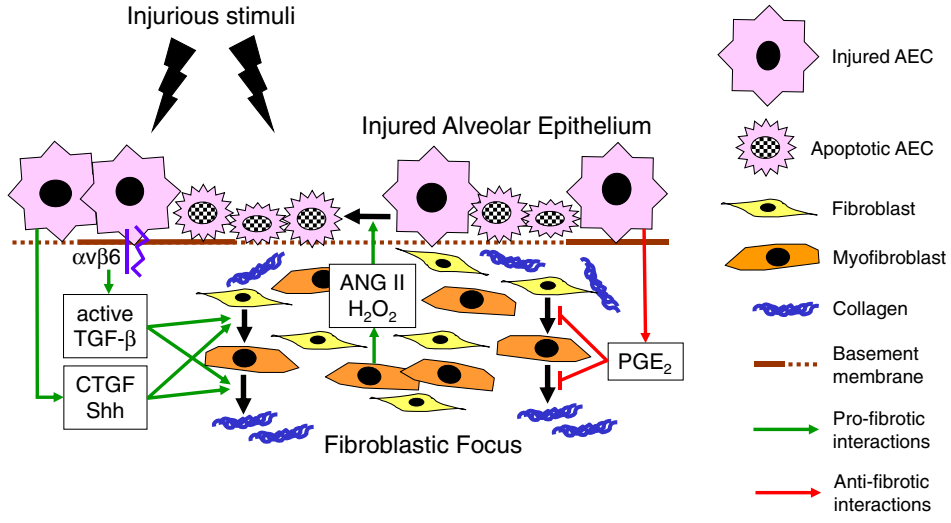

Fig. 1. Epithelial-fibroblast interactions drive the progression of idiopathic pulmonary fibrosis. Environmental stimuli initially injure alveolar epithelial cells (AECs), inducing their apoptosis and their production and/or activation of pro-fibrotic mediators, including TGF-β, CTGF and Shh. These AEC-derived mediators direct fibroblast migration, proliferation, activation and myofibroblast differentiation, resulting in the accumulation myofibroblasts and extracellular matrix in the lung. Myofibroblasts in turn secrete mediators that amplify AEC injury and apoptosis, including ANGII and reactive oxygen species such as H_2O_2, creating a vicious cycle of pro-fibrotic epithelial cell-fibroblast interactions that drives the progression of IPF. PGE_2 normally mediates anti-fibrotic interactions between epithelial cells and fibroblasts, but its production by AECs is reduced in IPF, as is fibroblast PGE_2-responsiveness. Green arrows indicate pro-fibrotic epithelial cell-fibroblast interactions; red arrows indicate anti-fibrotic interactions. TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor; Shh, sonic hedgehog; ANG II, angiotensin II; H_2O_2, hydrogen peroxide; PGE_2, prostaglandin E_2.

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