

The Pathogenesis of Idiopathic Pulmonary Fibrosis Focusing on Epithelial Cells

Jibing Yang*

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan, USA

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease characterized by extracellular matrix deposition and scar tissue formation in the interstitial lungs over time. The epidemiology of IPF is 13 to 20 cases per 100,000 people [1]. Typically the disease is found in people between the ages of 50 and 70 and affects men more frequently than women. There are no proven risk factors for IPF, but a minority of patients has a family history of lung scarring. The clinical presentation includes exertional dyspnea, cough, functional and exercise limitation, impaired quality of life and risk for acute respiratory failure and death. The median survival time is 3-5 years. Unfortunately, there is no FDA approved treatment or cure for IPF and it is ultimately fatal. The accumulation of activated myofibroblasts thought to be the source of interstitial collagens, but the cellular origin of activated fibroblasts and their particular contribution to the deposition of extracellular matrix remains unknown. There are three proposed cellular origins of myofibroblasts including expansion of lung residential fibroblasts, recruitment of bone marrow-derived fibrocytes, and epithelial-mesenchymal transition (EMT) [2]. EMT is defined as Alveolar Epithelial Cells (AECs) that undergo transition into migratory and/or invasive mesenchymal cells. Recent studies show that regulation of EMT involves many transcription factors like Twist, Snail, and Foxm1 to activate mesenchymal protein expression [3-5]. Previous studies suggest that up to a third of fibroblasts in the lung following bleomycin injury are derived from EMT; however the extent to which these EMT-derived fibroblasts contribute to the deposition of fibrillar collagen is unclear [6,7]. This discussion will focus on the contribution of AECs to the pathophysiology of pulmonary fibrosis. Understanding this critical step will facilitate future drug discovery to block or reverse fibrosis development. A complete review of IPF can be found in other places [8,9].

Why Focus on Epithelial Cells

AECs are regularly exposed to externally inhaled air and they become the first defense line during early events in the development of any lung injury. The repair process is critical for reestablishment of normal lung function. Dysfunctional AECs may cause scar tissue formation, fibrogenesis, and aberrant architecture. This initial step emphasizes the role of AECs in the development of pulmonary diseases. AECs contain two different types, I and II, and less is known about the relationship between the two major types. A general belief is that Type II can differentiate into Type I under certain circumstances [10]. AEC type II is more important in alveolar repair and regeneration based on animal studies in bleomycin-induced lung injury. In addition, AECs may activate a progenitor population for epithelial repair and regeneration during alveolar injury [11].

Epithelial-Mesenchymal Transition (EMT) and Regulation of Epithelial-Mesenchymal Crosstalk Signaling

Although EMT has been widely studied in organ development and tumorigenesis, it is still in debate of whether EMT occurs or not

during pulmonary fibrosis. Certainly, there are more published articles using cell lineage fate-mapping techniques or fluorescent markers to support EMT versus against it [12]. The main reason to see the contrary evidences may result from the time point to trace the cell lineage. Expression of the fluorescent marker at a later time point will cause loss of some subpopulation of epithelial cells which may undergo EMT. In order to avoid the argument on the occurrence of EMT and focus more on answering the question of what degree EMT contributes directly to collagen I deposition, Kim's lab has generated mice with conditional deletion of type I collagen (*col1a1^{f/f}*). These mice have been crossed with SPC-rtTA/tetO-Cre mice to specifically and permanently delete *col1a1* in lung epithelial cells and EMT-derived fibroblasts. Intra-tracheal bleomycin was administered to these mice and to littermate control mice lacking one of the transgenes. Mice with lung epithelial-specific deletion of *col1a1* demonstrate significantly reduced accumulation of total collagen (Yang et al., unpublished data). This is strong evidence to support EMT-derived contribution of collagen I in the extracellular matrix. Another principal role for EMT in repair is promotion of fibrosis through epithelial-mesenchymal crosstalk signaling pathways. The crosstalk may be presented not only in secretion of pro-fibrotic factors, but also in production of cytokines to recruit fibrocytes into the lung. Dysfunctional signaling pathways (WNT and β -catenin pathway, PGE2 etc.) in AECs may either activate residential fibroblast into myofibroblasts or inhibit their apoptosis to contribute to matrix deposition.

Endoplasmic Reticulum (ER) Stress

Evidence of ER stress was first found in lung tissues from IPF patients [13]. Expression of a mutant surfactant protein C (L188Q) induced ER stress in mice which showed exaggerated lung fibrosis and increased apoptosis of AECs, implying that a dysfunctional AEC phenotype will promote fibrotic remodeling [14]. The mutant pro-SPC protein causes the accumulation of protein in the ER which may activate UPR pathway to degrade the protein and attenuate ER stress. Alternatively, ER stress may directly induce the apoptosis of epithelial cells by activation of caspase 12/4 pathway [15].

Conclusions and Challenge

IPF is a highly heterogeneous and lethal progressive disease due to the excessive deposition of extracellular matrix within the lung interstitial area. Although what exactly can trigger IPF is still

*Corresponding author: Jibing Yang, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA, Tel: (734) 763-2537; Fax: (734) 615-2331; E-mail: jibing@med.umich.edu

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unknown, a common acceptable concept is the initial dysfunctional repair and remodeling following AECs injury. The initial injury may activate the latent TGF- β which is stored in the matrix, or secreted from inflammatory cells. Although TGF- β signal is necessary to initiate the fibrogenesis, it is not sufficient to maintain or exacerbate the fibrosis process. During epithelial cell dysfunction, EMT contributes significantly to collagen I secretion which may act to recruit or activate local lung fibroblasts. Other EMT derived secreted proteins like CTGF may also play an influential role in fibroblasts recruitment and activation. Other mechanism includes epigenetic regulation of AECs or fibroblasts injury which has not been discussed here. Future challenge mainly comes from further understanding of the signaling pathways that control several key checkpoints during the fibrogenesis including initial epithelial injury, EMT, myofibroblast activation, matrix metalloproteinase secretion, etc. This is crucial to develop novel treatments for the improvement of current IPF patient care.

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