

Review Article

Current Concept for the Pathogenesis of Idiopathic Pulmonary Fibrosis (IPF)

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Fibrosis in interstitial lung disease is caused by the accumulation of extracellular matrix proteins within the interstitium and alveolar space of the lung. The majority of severe cases comprise a classification known as idiopathic pulmonary fibrosis (IPF) for which the origin is unknown [1]. IPF is the most severe chronic form of pulmonary fibrosis and results in gradual exchange of normal lung parenchyma with fibrotic tissue and in the irreversible impairment of gas exchange in the lung. IPF is a deadly fibrotic lung disease with a 5 year mortality of 50-70%, comparable to many cancers. The estimated incidence of IPF is 10 per 100,000 individuals with a prevalence of 30 per 100,000 [2]. The current concept for the development of pulmonary fibrosis including IPF is that at least three physiologically balanced processes implicated in the maintenance of lung fibroblasts populations - proliferation, apoptosis of (myo) fibroblasts and production of ECM - are disturbed [3]. Risk factors for IPF include age, male gender and a history of cigarette smoking [4]. A number of genetic mutations such as the surfactant protein C (SFTPC), surfactant protein A2 (SFTPA2) and telomerase (TERT and TERTC) have also been associated with the development of lung fibrosis [5-7]. IPF is characterized by the accumulation of fibroblasts and collagen within the alveolar wall resulting in obliteration of the gas-exchange surface. Morphological studies have demonstrated that subepithelial accumulation of fibroblasts in a lesion termed the "fibroblastic focus" is the sentinel morphological lesion of IPF [8]. Ultrastructural analysis of the fibroblastic focus has revealed that it is composed of alpha-smooth muscle actin-expressing myofibroblasts enmeshed in a matrix rich in polymerized type I collagen [9]. The key role of the myofibroblast in IPF is established by the observation that progressive expansion of the fibroblastic focus by proliferating myofibroblasts depositing type I collagen leads to permanently scarred alveoli [10-13]. Although this study suggests that myofibroblasts are closely linked to the development of lung fibrosis, the origin of myofibroblasts is still unclear. However, it is speculated that circulating fibrocytes derived from bone marrow, epithelial to mesenchymal transition (EMT) and resident fibroblasts are responsible for the appearance of myofibroblasts [14]. Prior to the activation of myofibroblasts, it is generally believed that an initial or repetitive injury occurs to type I alveolar epithelial cells (AEC-I) which constitute the majority of the alveolar surface

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[15]. When AEC-I is injured, type II alveolar epithelial cells (AEC-II) are thought to undergo hyperplastic proliferation and release growth factors, cytokines and other substance that subsequently promote the activation of myofibroblasts, which secrete collagen and ECMs. The accumulation of ECM and the hyper-proliferation of myofibroblasts ultimately destroy lung parenchyma. In an effort to elucidate the pathogenesis of this deadly disease, several underlying mechanisms have recently been proposed. One of the critical mechanisms in IPF progression is the physical interaction between ECM and cells. Several cell surface receptors including integrins, discoidin domain receptors (DDR), syndecans and CD44 have been identified as components of a complex system responsible for cell immobilization on normal ECM. Among them, integrins have been extensively studied in IPF fibroblasts. ECM is composed of collagens, elastin, proteoglycans (including hyaluronan) and non-collagenous glycoproteins and forms a complex, three-dimensional network among cells of different tissues in an organ-specific manner and reciprocally influences cellular function to modulate diverse fundamental aspects of cell biology [16,17].

Collagens are the most abundant matrix protein in animal tissues and type I collagen is the major component of ECM in skin, bone, ligaments, etc. Type I collagen is composed of glycine- and proline rich two- α 1 (I) and one- α 2 (I) chains [18]. It has been well established that the alteration of integrin function is associated with a pathological IPF fibroblast phenotype. An ECM alteration results from abnormal synthesis or degradation of one or more ECM components and contributes to the progression of IPF [19]. Interestingly, there is a sharp difference in proliferation profiles of human lung fibroblasts when they are cultured on 2D and 3D type I collagen matrices. Studies showed that tissue culture plates coated with 2D monomeric collagen provide a proliferation-permissive environment for normal and IPF lung fibroblasts [20]. Unlike 2D collagen, 3D matrix, which closely imitates the physiological forms of ECM, is composed of polymerized collagen (fibrillar collagen). Immunohistochemical analysis also revealed that α -smooth muscle actin-expressing myofibroblasts are enmeshed in a type I collagen-rich 3D matrix. Unlike 2D matrix,

when normal lung fibroblasts attach to 3D polymerized collagen matrix, cell proliferation is suppressed and apoptosis increases. However, IPF fibroblasts elude the proliferation suppressing and apoptosis inducing effects of polymerized collagen matrix [21,22]. Interestingly, mounting evidence points to similarities between IPF and cancer in some aspects of the IPF phenotype and the underlying disease mechanisms. It is well established that PTEN/PI3K/Akt axis is deregulated in IPF and cancer cells [23-27]. This concept is also supported by other research group's findings that oncogenic proteins such as Ras and tumor suppressor proteins p53 become abnormally altered, implicating the development of lung carcinoma in IPF patients [28-30]. Thus, these studies strongly suggest that the intrinsic changes of IPF fibroblasts enable them to have a highly proliferative and an apoptosis-resistance phenotype in response to 3D polymerized collagen matrix.

Prior research strongly suggest that the understanding the role of cell-ECM interaction is crucial in IPF pathogenesis. This physiological process that accompanies normal wound repair is aberrant in IPF fibroblasts and is mediated by pathological integrin signaling [20]. The α and β chains of integrins cooperate in a specific mode in which the extracellular portion of the α chain is responsible for the ligand-binding specificity of the complex whereas the intracellular domain of the β chain is associated with the induction of intracellular signaling cascades. Recent studies further revealed that $\beta 1$ integrin regulates the crucial PTEN/PI3K/Akt axis, thereby altering IPF fibroblast cell phenotype in response to type I collagen matrix [20,21] and this signaling pathway is closely linked to cell proliferation, migration and apoptosis. Thus the precise understanding of the altered PTEN/PI3K/Akt dependent pathway is thought to be vital for the elucidation of IPF pathogenesis. Various profibrotic factors such as TGF- $\beta 1$, PDGF, ET-1, TNF- α , heat shock protein 47 (HSP47), connective tissue growth factor (CTGF), IL-4, insulin-like growth factor (IGF) and its binding proteins are also known to be associated with the regulation of fibrosis [31]. Furthermore, recent studies suggest epigenetic alterations such as DNA methylation, histone modification and microRNAs also contribute the development of IPF. From this concept, the pathological role of DNA methyl transferases (Dnmts), histone acetyltransferases (HATS) and deacetylases (HDACs) have been highlighted in the development of lung fibrosis [32-34]. Several miRNAs are known to play a major role of conductors in the pathogenesis of fibrosis [35]. It has been found that about 40 miRNAs have also been linked to fibrosis in various organs and disease settings [36]. Among them, miR155, miR-15b, miR-16, miR21, miR23a, miR26a/b, miR-30c and miR338 are thought to be associated with lung fibrosis [36]. However current knowledge about the role of these factors are limited and there should be more future research work needed to establish the pathological function of these regulators in lung fibrosis. Although there has been some progress in understanding the pathogenesis of IPF, the etiology and genesis of IPF remains unknown, and there is still no proven effective therapy available due to the lack of understanding for crucial pathological mechanisms in IPF. Therefore, the precise elucidation of IPF pathogenesis is vital to develop IPF therapy and to further prevent the progression of this deadly disease. In summary, the complexity and heterogeneity exist in IPF studies

and the understanding of genetic and epigenetic alterations in the development of lung fibrosis is required for future investigation, and these efforts will ultimately lead to find effective therapeutic targets for the treatment of IPF.

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