Molecular pathways in idiopathic pulmonary fibrosis pathogenesis: Transcending barriers to optimally targeted pharmacotherapies

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Although the survival of patients with idiopathic pulmonary fibrosis (IPF) still hovers around a median of two to five years, [1] the therapeutic landscape of this devastating interstitial lung disease is encumbered by a paucity of effective pharmacotherapies. Widely used anti-fibrotic medications slow the rate of functional decline [2,3] but are often associated with adverse effects and persistently high symptom burden. As the pathophysiologic mechanisms underlying fibrosis are yet to be fully elucidated, our understanding of disease progression in IPF remains stifled, posing substantial limitations to the potential value that could be gained from more novel therapies targeting these mechanisms. Prior genome-wide associated studies evaluating the genetic profiles of affected patients have identified several notable variants and risk polymorphisms associated with IPF pathogenesis. [4] Likewise, recent epigenomic, transcriptomic, and proteomic data have helped to generate a single-cell atlas of IPF pathogenesis. [4] From a macroscopic perspective, recent investigations have found a significant loss of terminal bronchioles in lung tissue obtained from patients with IPF. [6] From a microscopic perspective, recent investigations have found a significant loss of terminal bronchioles in lung tissue obtained from patients with IPF, implicating genetic pathways well-recognized to be involved in the development and progression of IPF. [6] Other histopathologic analyses and investigations focused on immunophenotyping have identified phenotypically distinct CD4+ T cell infiltrates within the lung tissue in patients with IPF. [6] From a macroscopic perspective, recent investigations have found a significant loss of terminal bronchioles in lung tissue obtained from patients with IPF, implicating the small airways in this disease. [7] Taken together, these underscore numerous efforts that further illuminate the pathophysiology of this complex disease, with the overall goal of identifying optimal therapeutic targets and improving currently existing ones.

In this issue of EBioMedicine, Xu and colleagues [8] examine an array of mechanisms involved in the pathophysiologic progression of previously normal lung tissue to fibrosis in IPF. [8] Their novel and exciting findings link the molecular and cellular events associated with IPF to the concomitant structural and histological events. Specifically, utilizing a total of 78 lung tissue specimens from nine subjects with IPF and four control individuals, they performed a unique combination of multidetector computerized tomography (CT), micro-CT imaging, immunohistochemistry staining, and quantitative histological analyses of selected cores. The authors then leveraged data from these multi-modal volumetric analyses by performing gene expression profiling to explore this relationship further.

In their results, Xu and colleagues demonstrate a striking decrease in the number of terminal bronchioles within fibrotic regions of IPF lungs compared to controls. Their quantitative histological findings of greater infiltration with CD4+ and CD8+ T cells, and B cells, macrophages, and tertiary lymphoid follicles in fibrotic lungs were a refreshing confirmation of immunophenotyping data from other studies that support the role of an active adaptive immune response in IPF. [6,9] Similarly, their gene expression analyses revealed hundreds of differentially expressed genes in areas of pulmonary fibrosis, implicating genetic pathways well-recognized to be involved in the development and progression of IPF. Key among these were the up-regulation of TGFBI, MMP7, TNF, ADAM12, activation of immune costimulatory markers, toll-like receptors, and increased expression of the IPF-related gene MUC5B in both minimal and established fibrotic regions of the lungs. [4] As expected, many of these pathways were linked to coagulation, epithelial–mesenchymal transition, cellular immune responses, bacterial and viral defence, and surfactant and mucous regulation. This study by Xu et al. was distinctive in its ability to depict the occurrence of these genetic pathways on a background of increased infiltration of tissues by immune cells concomitant with the structural loss of terminal airways. Importantly, the authors distinguished this process from the normal lung development occurring in healthy individuals by utilizing a graduated spectrum of fibrotic tissue that ranged from normal to established fibrosis within human lung tissue obtained from the same individual with IPF.

While these findings undoubtedly advance our knowledge of IPF pathophysiology, Xu and colleagues faced certain limitations in their study. Notable among these were the small sample size of the enrolled cohort and significant differences in smoking status between both groups. As tobacco smoking is known to be more prevalent in IPF compared to controls, the authors obtained biopsies from spatially divergent lung regions with differing degrees of fibrosis to mitigate this confounder. However, the differences in direct lung exposure to smoking could still conceivably have affected the nature of inflammatory cells and gene expression patterns between both...
while highly insightful, the perspective provided from these results represents data acquired from different disease stages in the lungs at the same timepoint in each individual assessed. This should not be construed as a longitudinal time-series evaluating changes in an individual assessed at different stages of the disease over time. Indeed, while this study sheds light on the pathogenesis of IPF and identifies pathways that could potentially be therapeutic targets, further research is needed to more thoroughly understand the interplay between these molecular pathways, and the identified mediators must be rigorously explored in future studies.

Building on findings from this study, future work targeting these molecular pathways that occur in the development of fibrosis would bring us closer to effective pharmacotherapies that blunt disease progression, improve quality of life, and increase life expectancy in IPF. Overall, while there are still unknowns in the transition from normal lung parenchyma to pulmonary fibrosis, this study makes great strides in opening doors and providing additional opportunities for the discovery of novel therapeutic targets in IPF.

Declaration of Competing Interest

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