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Ready and Waiting: Where Early-Stage Idiopathic Pulmonary Fibrosis Fibroblasts Are Primed to Be Activated

Idiopathic pulmonary fibrosis (IPF) is a devasting and ultimately lethal lung disease characterized by progressive scarring in lung parenchymal tissues. Diagnosis of IPF is by identification of patterns of usual interstitial pneumonia (UIP) in high-resolution computed tomography and histopathology followed by a multidisciplinary diagnosis panel (1). Examining these UIP regions to determine disease pathogenesis has been the main focus of many studies in IPF, but as the pathological changes required to develop UIP patterns are extensive and, therefore, correspond to regions of advanced disease, studies relating to early disease, such as development of fibroblastic foci or interstitial lung abnormalities (2), have remained somewhat limited. This is compounded by the late-stage presentation of patients with IPF and the rapid progression of the disease, making samples from earlier stages difficult to procure.

One of the key features of IPF pathology is its heterogeneous distribution, with UIP regions localized to the basal and peripheral areas of the lung. As IPF is a progressive disease, it has been hypothesized that areas distal to these basal–peripheral regions may represent earlier and more active stages of disease, such that sampling of lung tissue from multiple regions may provide a timeline of disease progression. This idea of sampling tissue from multiple regions has been applied by a few studies in an attempt to overcome the challenges of obtaining early-stage samples and have shown that in these distal lung regions, despite a normal appearance on histology, gene signatures related to inflammation and fibrosis were expressed (3, 4).

In this issue of the *Journal*, Hanmandlu and colleagues (pp. 53–63) describe the application of a similar concept in their study of IPF, where they uniquely focused on changes in fibroblasts isolated and cultured from the apical regions of the upper lobes from patients who underwent transplant surgery for IPF (5). This is a region where the most "normal" tissue in the IPF lung is likely to be found. Moreover, they examined the epigenetic changes in these fibroblasts by using Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) to identify open chromatin regions and combined these data with gene expression from RNA sequencing and histology. Similar to what was found in other studies that examined these regions in IPF, their data show that, despite having minimal structural changes, these areas were not "normal" at an epigenetic or gene expression level, with many changes present that were related to disease.

In cross-validating their data, the authors found three genes that exhibited consistent changes in IPF fibroblasts: TWIST1, FOXA1, and GATA6. TWIST1 has been extensively associated with differentiation toward a mesenchymal phenotype, including epithelial–mesenchymal transition processes in cancer and fibrotic diseases (6). The authors found TWIST1 to have increased chromatin accessibility and associated gene expression in these "normal region" fibroblasts, indicating that these cells are potentially developing more mesenchymal features. Similarly, FOXA1 was also increased, but this gene has been shown to be antagonistic to TWIST1 and transition processes, promoting a more epithelial phenotype (7). Activation of both of these genes suggest that fibroblasts in these early regions may be involved in a balancing act between factors that promote versus antagonize mesenchymal development. They could also reflect mixed populations of fibroblasts, with some developing more mesenchymal features and others less. The last gene, GATA6, promotes differentiation of fibroblasts to myofibroblasts in IPF and has been found by others to be increased in IPF tissue (8). However, Hammandlu and colleagues found that chromatin accessibility and expression were decreased in these cells, indicating that these fibroblasts likely remain in an inactivated state.

Overall, these results are limited in scope but do open up the possibility that initiation of fibrosis in IPF may be the result of differentiation of fibroblasts to a more mesenchymal phenotype while they remain inactivated, which may explain why these areas remain structurally normal. Like a coiled spring, having a pool of fibroblasts primed for activation in the tissue may also explain the rapid progression of disease in patients with IPF. However, there are also a number of limitations to this study. One limitation is the small sample size, with only three IPF samples examined using assay for transposase-accessible chromatin using sequencing. Another limitation is lack of resolution, as we cannot deconvolute these signals to individual fibroblasts or to specific pathological changes on histology. Confirmation of these results would be interesting but will require extensive further study. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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