From the Gut to the Lung: Evidence of Antifibrotic Activity of Endocrine Fibroblast Growth Factor 19

Idiopathic pulmonary fibrosis (IPF) is the most common and most severe form of pulmonary fibrosis, a scarring disease of the lungs resulting in progressive lung stiffness and hypoxemia with a poor prognosis (1). Pulmonary fibrosis remains the most common indication for lung transplantation despite the emergence of antifibrotic medications. Both of the available antifibrotic medications used in IPF, pirfenidone and nintedanib, have been shown to include fibroblast growth factor (FGF) signaling pathways as their targets. FGFs comprise a family of 22 known growth factor ligands that act in an autocrine, paracrine, or endocrine manner to signal through four known FGF receptors (2). There is evidence that pirfenidone alters FGF2 expression in mouse lungs in response to bleomycin (3), a commonly used agent to induce pulmonary fibrosis in rodents. Nintedanib is a receptor tyrosine kinase inhibitor that primarily inhibits platelet-derived growth factor, vascular endothelial growth factor, and FGF receptors (4). While FGFs and their activated signaling pathways have been implicated in the pathogenesis of pulmonary fibrosis, their specific roles, as well as whether they act as pro or antifibrotic growth factors, remain topics of active investigation.

Early preclinical data suggest that FGFs are integral to the development of pulmonary fibrosis, as inhibition of FGF receptors reduced fibrosis in preclinical models of pulmonary fibrosis (5). There has been mounting evidence, however, that FGFs may play a protective role in pulmonary fibrosis. Overexpression or direct administration of the autocrine and paracrine FGFs, including FGF1, 2, 7, 9, 10, and 18, reduce fibrotic changes in both the bleomycin and Ad-TGFβ1 models of pulmonary fibrosis (6–10). The endocrine FGFs (FGF21 and FGF23) are also capable of reducing experimental pulmonary fibrosis (11, 12).

In this issue of the *Journal*, Justet and colleagues (pp. 173–187) provide an important contribution to this topic by demonstrating that the endocrine FGF ligand, FGF19, acts as an antifibrotic growth factor in pulmonary fibrosis (13). FGF19 has recently been shown to reduce liver fibrosis (14), suggesting that it may have antifibrotic activity in the lung as well. In this report, the authors show that FGF19 expression is reduced in patients with pulmonary fibrosis and then demonstrate that adenoviral-mediated overexpression of FGF19 in mice reduces pulmonary fibrosis induced by bleomycin. Using cultured alveolar epithelial cells and lung fibroblasts, the authors show that FGF19 exerts an antiapoptotic effect in the alveolar epithelium by decreasing Bcl-2-like protein 11 expression, and it reduces myofibroblast differentiation in part by decreasing TGFβ-induced c-Jun N-terminal Kinase phosphorylation.

Importantly, the finding that an endocrine growth factor produced by the kidneys, intestinal tract, and liver may have an effect on pulmonary fibrosis is intriguing and warrants further investigation. Endocrine growth factors such as FGF19 may provide an important link by which the gastrointestinal tract and kidneys regulate fibrotic diseases of several organs, including the lung. Furthermore, this study supports the need for future investigations into whether FGF19 or other endocrine growth factors provide an interorgan link between the gut microbiome, metabolic syndrome, acute and chronic kidney disease, liver disease, and IPF.

There are several strengths to the approach taken by Justet and colleagues. Their experimental design was timed such that adeno-associated virus-induced overexpression of FGF19 peaked after the onset of experimental lung injury induced by bleomycin and TGFβ1 overexpression. As treatment of IPF and pulmonary fibrosis in humans involves treating patients with fibrosis that is already present, the experimental approach from the authors mimics a possible treatment strategy in humans. In addition, expression of FGF19 induced by their adenoviral vector primarily occurred in the liver, mimicking the endocrine effects of FGF19. This approach simulates a potential therapeutic use of systemic FGF19, which would be a more likely therapeutic approach for a small protein like FGF19 than direct administration to the lungs. Finally, the authors employed two *in vivo* models of pulmonary fibrosis in mice (bleomycin and Ad-TGFβ), supporting the idea that the effect of FGF19 is applicable to fibrotic lung disease rather than being limited to a pathway unique to a single experimental model.

The small number of human samples is a limitation of this study. Because of a potential cofounding effect of meal boluses, liver disease, and kidney disease on FGF19 expression, the authors were limited to using samples from patients without cholestasis, chronic hemodialysis, diabetes mellitus, and nonalcoholic fatty liver disease. Human samples also had to be collected after fasting because FGF19 is prone to degradation. This also limits applicability to a broader population of patients with IPF or pulmonary fibrosis, as kidney and liver disease are common comorbidities for patients with pulmonary fibrosis (15, 16).

Although FGF19 signaling via the FGF receptor 4 is well established (17), the precise mechanisms by which FGF receptor signaling and the potential involvement of coreceptors such as β-klotho alters fibroblast activation and myofibroblast differentiation remain an important area of future study, as the therapeutic potential of delivering FGF ligands in a clinical setting may be limited. Small molecule activators of downstream FGF signaling that halt or reverse epithelial apoptosis and/or myofibroblast activation in pulmonary fibrosis may also have significant therapeutic potential.

In summary, the article by Justet and colleagues identifies an intriguing novel mechanism by which the endocrine growth factor FGF19 may constitute a link through which the gastrointestinal tract

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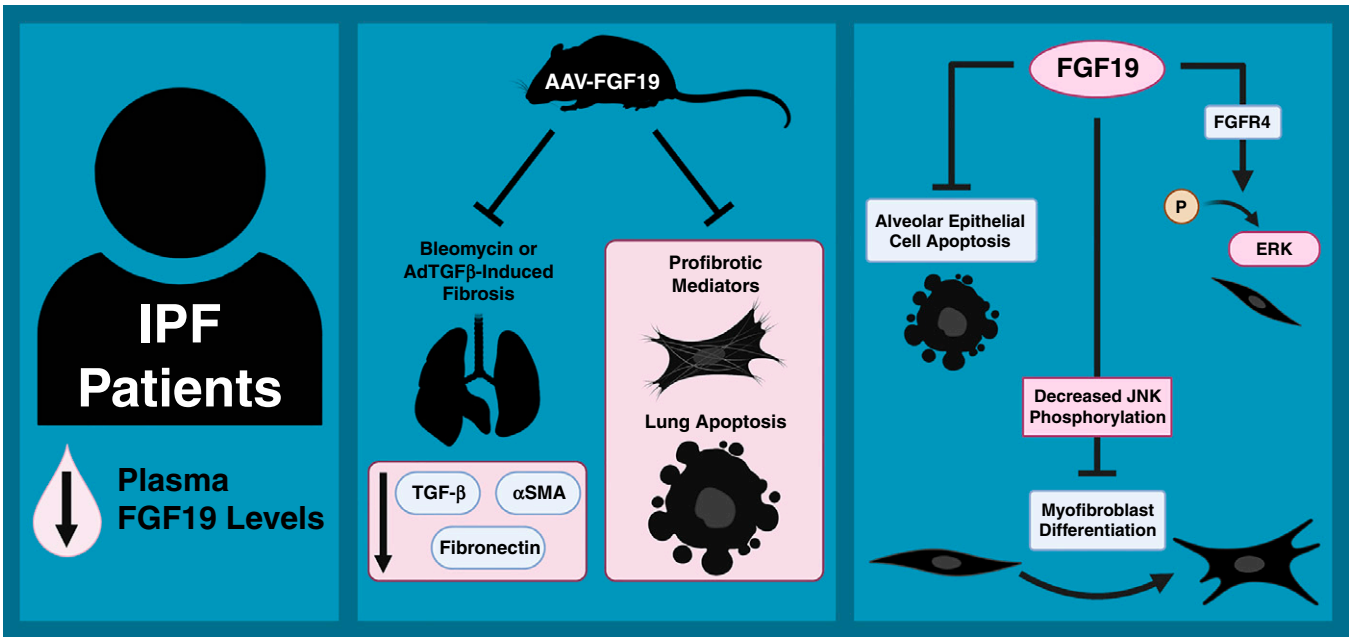

Figure 1. Schematic diagram illustrating the translational results of Justet and colleagues. Findings include decreased plasma fibroblast growth factor 19 (FGF19) concentrations in patients with IPF, and overexpression of FGF19 in mice results in decreased bleomycin-induced fibrosis with downregulation of profibrotic markers in lung fibroblasts accompanied by decreased alveolar epithelial cell apoptosis. On the molecular level, FGF19 is signaled via FGFR4 activating ERK signaling and decreased JNK phosphorylation in lung fibroblasts. AAV = adeno-associated virus; ERK = cextracellular signal-regulated kinase; IPF = idiopathic pulmonary fibrosis; JNK = cc-Jun N-terminal kinase.

could influence pulmonary fibrosis (Figure 1). In addition, their report adds to the growing literature supporting an antifibrotic role of FGFs in the lung and other organs. ■

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