Fibroblast Growth Factor Inhibitors in Lung Fibrosis: Friends or Foes?

Pulmonary fibrosis (PF) is characterized by excessive deposition of extracellular matrix, architectural distortion, and abnormal fibroblast activation. Although some patients with PF have an identified cause, such as autoimmune disease or environmental exposures, one of the most common forms of PF, idiopathic PF (IPF), does not have an identified cause (1). Although the antifibrotic medications pirfenidone and nintedanib slow progression and decrease mortality (2, 3), the prognosis for patients remains poor and IPF remains one of the leading indications for lung transplantation.

Fibroblast growth factors (FGFs), consisting of 18 signaling ligands that bind with variable affinity to four FGF receptors (FGFRs) (4), are implicated in PF. Multiple FGF ligands, including FGF2, FGF9, and FGF18, are upregulated in IPF lungs (5–7), and FGFR expression is increased in fibroblastic foci in IPF (8). Some studies have shown that FGF2 is critical for myofibroblast differentiation in response to TGF-β1 (9), and inhibition of FGF receptors decreases experimental PF induced by bleomycin (10, 11). In addition, nintedanib exerts its antifibrotic effect through inhibition of PDGF, VEGF, and FGF receptor tyrosine kinases (2). Taken together, these findings suggest that inhibition of FGF signaling is important in the treatment of PF. It is still not known whether pharmacologic inhibition of FGFRs alone is sufficient to treat PF.

In a study presented in this issue of the *Journal*, Morizumi and colleagues (pp. 317–326) addressed this question by testing whether a pan-FGFR receptor tyrosine kinase inhibitor, BGJ398, could be used as an antifibrotic agent (12). They found that BGJ398 was effective in blocking FGF2-induced proliferation and migration of cultured MRC-5 fibroblasts, and proliferation of cultured LA4 epithelial cells. Using the murine bleomycin PF model, they then found that daily oral administration of BGJ398 to bleomycin-treated mice, starting either at the time of bleomycin treatment or 10 days after bleomycin treatment, decreased histologic fibrosis and collagen accumulation. Importantly, BGJ398 also caused increased weight loss and mortality in bleomycin-treated animals, as well as increased cleaved caspase-3, increased vascular leak, reduced Ki-67 expression, and increased γ-H2AX (apoptotic marker) in pro-SPC$^+$ alveolar epithelial cells *in vivo*. The authors concluded that the early mortality in the bleomycin+BGJ398 group was due to enhanced lung injury as a result of decreased proliferation and increased apoptosis in pro-SPC$^+$ type 2 alveolar epithelial cells. To address a possible survivorship bias, the authors also used a lower dose of bleomycin to avoid excessive mortality, and still found that BGJ398 decreased PF.

The authors point out that BGJ398 has weak activity against several other signaling pathways, including VEGFR2, acknowledging that the antifibrotic effect and/or increase in epithelial injury and mortality may be due to inhibition of additional pathways besides FGF signaling. It is possible that the harmful effects of BGJ398 on lung epithelium are also indirect, and it is highly likely that other cell types in the lung are affected by FGFR inhibition in addition to epithelium and fibroblasts, including endothelial cells, smooth muscle cells, and macrophages. Furthermore, systemic administration of BGJ398 after intratracheal bleomycin treatment may have harmful effects on other organ systems, such as the kidney, gastrointestinal tract, and cardiovascular system.

These observations raise questions about the relative contribution of FGFR inhibition to the overall effect of nintedanib. Morizumi and colleagues argue that effective FGFR inhibition with nintedanib is weak relative to the effect on PDGFR and VEGFR, and that inhibition of PDGF and VEGF signaling may be the primary mechanism behind its antifibrotic effect. For example, selective inhibition of PDGFR alone decreases experimental PF (13), as does inhibition of VEGFR (14). The authors show an antifibrotic effect of pan-FGFR inhibition, but importantly, they argue that harm induced by pan-FGFR inhibition, specifically inhibition of epithelial FGFRs, outweighs the antifibrotic benefit.

The deleterious effect of nonspecific FGFR inhibition in experimental lung injury and PF is supported by the literature as well. Inhibition of FGFR2 has been shown to increase lung injury and mortality in several models of lung injury, including influenza (15), hyperoxia (16), and bleomycin (17). Depletion of the FGFR2 ligands FGF7 and FGF10 was shown to decrease epithelial recovery from naphthalene (18) and hyperoxia (19). Epithelial-specific FGFR2 is essential for both the maintenance and recovery of type 2 alveolar epithelium in response to bleomycin injury, as mice with deletion of FGFR2 in type 2 alveolar epithelial cells have significantly increased mortality and lung injury after bleomycin administration (17, 20).

There is an increasing recognition of the antifibrotic effects of FGF ligands in experimental PF. Treatment with the FGF ligands FGF1 (21), FGF2 (22), FGF7 (23), FGF9 and FGF18 (7), and FGF10 (24) decreases experimental lung injury, stimulates epithelial proliferation and recovery from injury, and decreases fibrosis in the bleomycin model of murine PF. FGF1, FGF2, and FGF9 have each been shown to antagonize TGF-β1–induced myofibroblast differentiation and collagen production in cultured lung fibroblasts. Novel therapies that involve delivery of FGF ligands or augmentation of FGF signaling may therefore provide an alternative to pan-FGFR inhibition.

The article by Morizumi and colleagues raises the important question of whether it is time to consider a reevaluation of the approach to FGFR inhibition in the treatment of PF. The authors argue that inhibition of epithelial FGFRs should be avoided in

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lung injury and PF. Either targeted inhibition of FGFRs in select cell types (such as fibroblasts) or sparing of epithelial FGFR inhibition should therefore be investigated. Novel FGFR inhibitors could potentially be designed to selectively avoid the unique FGFR2 splice variant expressed only in epithelial cells (FGFR2-IIIb) (25). This approach, in combination with therapies targeting other profibrotic pathways, may allow for improved antifibrotic treatments with fewer side effects. ■

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Robert Guzy, M.D., Ph.D.
Department of Medicine, Section of Pulmonary and Critical Care Medicine
The University of Chicago
Chicago, Illinois

ORCID ID: 0000-0001-8420-6177 (R.G.).

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