A Glowing Opportunity to Target YAP in Lung Fibrosis

Idiopathic pulmonary fibrosis (IPF) remains a devastating disease. Current therapies can slow progression but fail to fully address the medical need. The underlying cause of IPF is unknown, but a wide array of mechanisms driving the development and progression of fibrosis have been elucidated. Activation of fibroblasts into myofibroblasts is a key component, and transforming growth factor (TGF)-β is a central mediator this process. Multiple G protein–coupled receptors have also been implicated in fibrosis, including lysophosphatidic acid, endothelin, sphingosine-1-phosphate, serotonin, and angiotensin II receptor (AT1 R). Importantly, tissue stiffness itself produces a positive feedback signal in fibrotic conditions, with integrin activation potentiating TGF-β signaling and driving intracellular signaling itself (1). A central feature in these mechanisms is activation of the RhoA/ROCK (Rho-associated protein kinase) signaling cascade. Downstream of RhoA/ROCK are actin cytoskeletal rearrangements and activation and nuclear translocation of key transcription coactivators YAP (*yes*-associated protein) and MRTF (myocardin-related transcription factor). The transcription factor partners TEAD (transcriptional enhanced associate domain) and serum response factor both drive expression of important profibrotic genes, including CTGF (connective tissue growth factor), ACTA2, and collagen itself (2, 3).

Transcription factors are challenging drug targets, and indirect modulation of their function is often the most promising approach. Indeed, tool compounds that purport to directly inhibit YAP (such as verteporfin) are highly insoluble and have nonspecific effects that complicate their use both experimentally and as therapeutics. In this issue of the *Journal*, Yang and colleagues (pp. 36–49) used a phenotypic chemical screen based on inhibition of YAP nuclear localization in primary human lung fibroblasts to identify Aurora kinase A as a key activator of YAP-mediated signaling (4). Two of the top hits in the screen were pan–Aurora kinase inhibitors. When they assessed subtype specificity, MK-5108, an Aurora kinase A inhibitor (AURKAi), showed full activity, but an Aurora kinase B inhibitor was inactive. In addition to disrupting YAP nuclear localization, MK-5108 was able to block TGF-β–induced expression of CTGF, ACTA2, and collagen (with some reduction in basal expression as well). YAP nuclear localization was also reduced in primary fibroblasts from patients with IPF and healthy individuals, but no assessment of gene expression was reported.

The effects of MLN-5108 were found to be independent of the Hippo pathway regulators LATS (large tumor suppressor) and MST1 (mammalian STE20-like protein kinase 1) and were not dependent on cell cycle regulation, a well-known effect of Aurora kinase inhibitors. MLN-5108 did, however, reduce TGF-β–induced cytoskeleton rearrangements, as detected by phalloidin staining of actin stress fibers. This could readily explain the effect on YAP nuclear localization. Nuclear localization of the other Rho/actin-regulated transcription factor MRTF-A was also inhibited by MLN-5108.

Finally, the AURKAi MLN-5108 was shown to be effective in the bleomycin lung fibrosis model. It improved lung histology and reduced the increase in hydroxyproline levels by approximately 50%, a typical amount seen in this preclinical model with other agents. The mice did not show any worsened weight loss on MLN-5108, and there may have been a small improvement toward the end of the study.

Aurora kinases are an active target for development as anticancer agents, so the data presented here suggest that there may be a potential for AURKAi as a new therapeutic in IPF. Indeed, the kinase inhibitor nintedanib is one of the two approved drugs with good efficacy in IPF. A key question, however, relates to the adverse effects. Nintedanib significantly slows the progression of lung disease in IPF and may prolong survival, but a major limitation of nintedanib is its adverse effects, primarily gastrointestinal. AURKAi also produced significant adverse effects in phase I clinical trials (5). Depending on the agent and dose, mucositis, diarrhea, and hematologic abnormalities were seen in 25–50% of patients, so that may be a challenge for the clinical application of the findings in this study.

In light of the adverse effect profile of AURKAi, it is intriguing to consider the possibility of combined use with statins. These authors recently showed (6) that statins could reduce YAP nuclear localization (using the same screening methodology), and statins may improve outcomes in IPF (7). If the effects of AURKAi and statins are additive or synergistic, lower doses of each may be used with a corresponding reduction in adverse effects.

There are some limitations to the study. First, the actual mechanism of how Aurora kinase inhibition suppresses YAP nuclear localization and YAP-mediated gene transcription is not clear. The effect on the actin cytoskeleton is the likely mediator of that effect, but how AURKAi suppresses actin polymerization is not known. Also, nuclear localization of MRTF was suppressed by AURKAi. It regulates many of the same genes that YAP does (CTGF, ACTA2, and COL1A1 [collagen, type I, α1]), and MRTF is known to play a role in fibrosis (2). So, it is not clear to what extent YAP and MRTF each plays a role in the effects seen. Indeed, there are reciprocal regulatory mechanisms connecting YAP and MRTF (8), so both may be involved.

With this report, the authors have added a potential new approach to IPF therapeutics. The fact that AURKAis are in active clinical development in cancer opens the door to quick translation. Although they may exhibit similar adverse effect liabilities to nintedanib, new options are always welcome in this challenging disease. ■

Originally Published in Press as DOI: 10.1165/rcmb.2022-0082ED on May 3, 2022

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

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