Inhibiting Jak2 Ameliorates Pulmonary Hypertension: Fulfilling the Promise of Precision Medicine

Recent advances in our understanding of the complex pathobiology of pulmonary arterial hypertension (PAH) have facilitated the adoption of a precision medicine approach to the disease with an aim toward identifying new therapeutics. This directional shift addresses several limitations in the current state of PAH pharmacotherapy. To date, the mainstay of contemporary PAH treatment has focused on three biochemical pathways known to be dysregulated in the disease: prostacyclin, nitric oxide, and endothelin signaling (1). These approved agents primarily target vasoconstriction, which is the predominant disease feature in only ~5–10% of patients, and may affect specific biological processes that are germane to pulmonary vascular remodeling, including cellular proliferation, inflammation, immune cell infiltration, thrombosis, and fibrosis (2, 3). Despite these putative effects, none of the approved agents are curative nor do they significantly reverse established pulmonary vascular or right ventricular (RV) remodeling. The therapeutic efficacy of approved drugs also differs between patients, suggesting the existence of drug-responsive, partially responsive, and unresponsive patient subgroups (4). These differences in drug responsiveness coupled with the recognition that discovery of a "magic bullet" to treat and cure PAH is highly unlikely have fueled the search for rationale-based effective pharmacotherapies, which continues unabated (5).

Precision medicine strategies to identify and advance novel disease interventions have concentrated, in part, on detailed phenotyping on a per-patient and population basis as well as the application of innovative analytics (5). The use of deep clinical and molecular phenotyping to match patients to drugs allows for movement beyond standard regimens to increase the likelihood of a therapeutic response. As part of this approach, the concept of drug repurposing (or repositioning) has been embraced to overcome the slow pace and high cost of *de novo* drug development. Drug repurposing offers the advantage of diminished risk as premarket safety testing has already been accomplished (6). With respect to PAH, drug repurposing studies have been performed: drugs targeting neurohormonal signaling, inflammation, proliferation, or metabolism, among others, have been studied in preclinical models, with some advancing to clinical trial (reviewed in [7]).

Accordingly, viewing PAH vis-à-vis precision medicine, using molecular phenotyping to identify dysregulated factors that can be targeted by repurposing approved drugs gains merit. In this issue of the *Journal*, Yerabolu and colleagues (pp. 100–114) demonstrate the effectiveness of this approach by using an unbiased screen to detect disease-relevant kinase activity, which, in turn, informed a drug repurposing strategy (8). The kinase assay detected increased activity of Janus kinase (Jak) 2 in human PAH pulmonary artery smooth muscle cells compared with controls. This was corroborated by a computational analysis of phosphorylated substrates that predicted Jak2 along with Jak1 and Jak3 as key mediators of kinase activity in PAH cells. Based on these results, the investigators selected ruxolitinib, an orally bioavailable Jak2 inhibitor that is Food and Drug Administration approved for myeloproliferative disease, polycythemia vera, or acute graft-versus-host disease, to test as an intervention in preclinical models of PAH. Ruxolitinib attenuated proliferation of PAH pulmonary artery smooth muscle cells *in vitro* and improved cardiopulmonary hemodynamics and pulmonary vascular and RV remodeling and function in two preclinical models of pulmonary hypertension.

The finding that Jak2 activity is increased in PAH has implications for disease pathogenesis and therapy. It is also intriguing to note that the JAK2 V617F gain-of-function variant, which is associated with myeloproliferative neoplasms, is also found in some individuals without the disease and is linked to clonal hematopoiesis of indeterminate potential or age-related clonal hematopoiesis. Whether or not the 0.1–9.6% of individuals who harbor this JAK2 variant in the absence of myeloproliferative disease are at increased risk of PAH is undetermined (9, 10). In the current study, it is also unknown if the human pulmonary artery smooth muscle cells used in the kinase activity assay expressed the variant. The association between JAK2 V617F and PAH, however, is plausible as preclinical studies in Jak2 V617F transgenic mice reveal that they develop exaggerated pulmonary vascular and RV remodeling when exposed to hypoxia (11).

The idea that Jak2 inhibition should benefit pulmonary vascular remodeling is also supported by preclinical and clinical studies. In smooth muscle cell–specific Jak2 conditional knockout mice subjected to hypoxia, genetic Jak2 deficiency attenuated pulmonary vascular remodeling and improved RV systolic pressures, although neither returned to baseline normoxic levels (12). An observational study of patients with myelofibrosis treated with ruxolitinib who had concomitant pulmonary hypertension also reported improved indices of RV function and heart failure with the drug (13). Taken together, these converging lines of evidence suggest that whereas increased Jak2 activity is permissive for, or associated with, PAH-associated pulmonary vascular remodeling and RV dysfunction, Jak2 inhibition is therapeutic.

Supported by National Heart, Lung, and Blood Institute grant U01 HL125215 and American Heart Association grant 19AIML34980000.

Originally Published in Press as DOI: 10.1165/rcmb.2020-0384ED on October 23, 2020

Although the effect of ruxolitinib on pulmonary artery smooth muscle cell proliferation is undisputed, the mechanism by which ruxolitinib improves RV function is less clear. In the current study, Jak2 was not expressed in the RV in the monocrotaline model whereas its expression and activation state in the mouse hypoxia model was similar to what was seen in normoxic control mice. These results, however, may not have import for the human RV in PAH. For instance, in human failing hearts, kinome profiling (limited to left ventricular tissue) demonstrated upregulation of Jak2, but not Jak1. If this is recapitulated in the failing RV in PAH, then Jak2 inhibition could have a direct benefit on ventricular remodeling (14). This could also extend to disease attributable to the JAK2 V617F variant. In a mouse model with Jak2 V617F restricted to myeloid cells, hypertrophic left ventricular remodeling, increased inflammatory cell infiltration of the myocardium, and increased expression of IL-6, b-type natriuretic peptide, and collagen transcripts occurred in response to pressure overload (15). Although the aforementioned studies support Jak2 inhibition as beneficial for myocardial remodeling, other studies have found the opposite: cardiac-specific deletion of Jak2 in mice promoted hypertrophic ventricular remodeling with a decrease in ejection fraction and expression of sarcoplasmic reticulum calcium regulatory proteins in male mice (16). Although upregulation of Jak2 activity in the left ventricle appears to be pathologic, it also appears necessary for appropriate cardiac development. Thus, unraveling the direct effects of Jak2 inhibition with ruxolitinib on the RV in PAH requires further investigation.

Altogether, the work of Yerabolu and colleagues advances the PAH field by leveraging a new class of drugs, Jak2 inhibitors, as potential therapeutics in PAH and repositions ruxolitinib as a candidate drug (8). The study also suggests that a precision medicine approach of screening patients with a kinase activity assay could determine patient suitability for ruxolitinib akin to a vasodilator test in the cardiac catheterization laboratory. Whether or not the efficacy of ruxolitinib will be broadly applicable to all patients with PAH or only those with pulmonary hypertension attributable to myeloproliferative disease (Group 5 pulmonary hypertension) remains to be determined. Furthermore, if efficacious in patients with PAH, it is envisioned that ruxolitinib would likely be integrated as part of a combination therapy regimen as the drug alone only improved, but did not restore to health, pulmonary vascular and cardiac structure and function. Nonetheless, precision phenotyping leading to target-specific drug repositioning is a highly promising pathway forward to augment the PAH pharmacotherapy armamentarium. ■

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

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