Two Birds with One Stone: Helping the Pulmonary Arteries and the Right Ventricle by Targeting BMPR2 Signaling

Pulmonary arterial hypertension (PAH) is characterized by progressive pulmonary vascular remodeling, resulting in an elevated right ventricle (RV) afterload, heart failure, and death. Importantly, RV function is predictive of survival in PAH (1). Currently available treatment options for PAH consist mostly of pulmonary vasodilators; they do not clearly reverse established disease, nor do they directly assist the RV itself.

BMPR2 (bone morphogenetic protein receptor type 2) germline loss-of-function mutations and the resulting decrease in the downstream signaling pathway have been associated with hereditary PAH (2). Interestingly, it has also been reported that patients with idiopathic PAH without a BMPR2 mutation exhibit reduced expression of BMPR2 in pulmonary arteries. Estrogen can also reduce BMPR2 expression, which may contribute to the higher observed prevalence of PAH in females (3). Augmenting BMPR2 signaling is therefore a clear therapeutic approach for both heritable and nonheritable PAH.

In this issue of the *Journal*, Boehm and colleagues (pp. 272–287) extend a strong body of previous work on the compound FK506 (tacrolimus) in augmenting BMPR2 signaling (4). FK506 was initially identified using a screening approach for drugs that increase BMP signaling mediated by BMPR2, even in the absence of the exogenous ligand (5). This mechanistic, basic translational work led to a phase IIa clinical trial of FK506 in patients with PAH, which demonstrated increases in BMPR2 expression and established the safety and tolerability of the compound (6). In line with these data on using a small molecule, it was found that the administration of BMP9 (a prototypical BMPR2 protein ligand) reverses established experimental pulmonary hypertension (PH) in a humanized mouse model of spontaneous disease after BMPR2 deficiency (*Bmpr2*$^{+/R899X}$) (7). The aggregate body of evidence suggests that increasing BMPR2 pathway signaling will ultimately be identified as a successful approach for treating PAH, and indeed, clinical studies are currently ongoing, including studies of compounds such as sotatercept (8), which is sought as a means of increasing BMPR2 signaling via modulation of TGF-β family ligands.

The study by Boehm and colleagues explores the possibility that augmenting BMPR2 signaling may directly improve RV dysfunction in PH. Although deficient BMPR2 signaling has been linked to RV cardiomyocyte dysfunction, its effects on the RV have not been studied in isolation (9). The primary technique used by the authors involved the pulmonary artery banding mouse model, which results in increased RV afterload, with the advantage of avoiding confounding effects on the pulmonary vasculature. In this model, FK506 administration markedly improved RV function, as evidenced by attenuated left ventricle compression, septal flattening, and RV dilatation. Structural mechanisms underlying this functional improvement include reductions in collagen production and proliferation of cardiac fibroblasts, leading to reduced RV fibrosis with concurrent preservation of RV capillary density.

These findings both confirm and extend what is known about BMPR2 in PH. Adding to the known pathogenetic roles of endothelial-cell (7) and smooth-muscle-cell (10) BMP deficiency in experimental PH, their study identifies a fibroblast-mediated, BMP signaling–induced attenuation of RV remodeling. These findings are concordant with prior reports of decreased BMP signaling in pulmonary and liver fibrosis (11, 12). They are also in agreement with the clinical use of tacrolimus for the management of fibrosis in systemic rheumatic diseases. Although its precise mechanism of action in this context remains unknown, it is conceivable that one of the mechanisms by which tacrolimus may dampen fibrosis in rheumatologic conditions is by promoting BMP signaling (13).

The beneficial effects of BMP pathway reconstitution using the pulmonary artery banding model, specifically in cardiac fibroblasts, are of particular clinical relevance, given that RV function closely tracks with the clinical prognosis in PAH. The significance of an FK506-derived reduction in RV fibrosis in mice, however, must be confirmed in humans. Although BMPR2 deficiency was associated with impaired RV function in both humans with PAH (14) and laboratory animals (9), reduced RV function did not correlate with BMP signaling (14) or the degree of RV fibrosis (15). These conflicting observations underscore the importance of verifying the overall impact of BMP modulation by quantifying key clinical endpoints, such as 6-minute-walk distance and cardiac output. The present study by Boehm and colleagues, as well as their previous clinical trial (6), did not show FK506-induced improvements in cardiac output. Such clinical measurements are important in interpreting the role of FK506, given that some degree of RV fibrosis is likely to be beneficial in allowing RV adaptation to an increased afterload, whereas pathologic, excessive fibrosis is likely detrimental because it increases stiffness.

As clinical applications targeting the TGF-β superfamily continue to evolve, non–fibrosis-related, off-target effects of FK506 and other BMP-enhancing interventions must be taken into careful consideration. One potential example is the effect of BMPR2 on cell metabolism (16). BMP signaling has been implicated in dysregulated RV fatty acid metabolism; precisely how FK506 affects the RV and pulmonary vasculature via modulation of triglyceride and other metabolic substrates remains an interesting but unexplored topic. Whether FK506 inhibits collagen synthesis or augments its degradation and whether inflammatory cells such as macrophages contribute to tissue fibrosis also merit further investigation.

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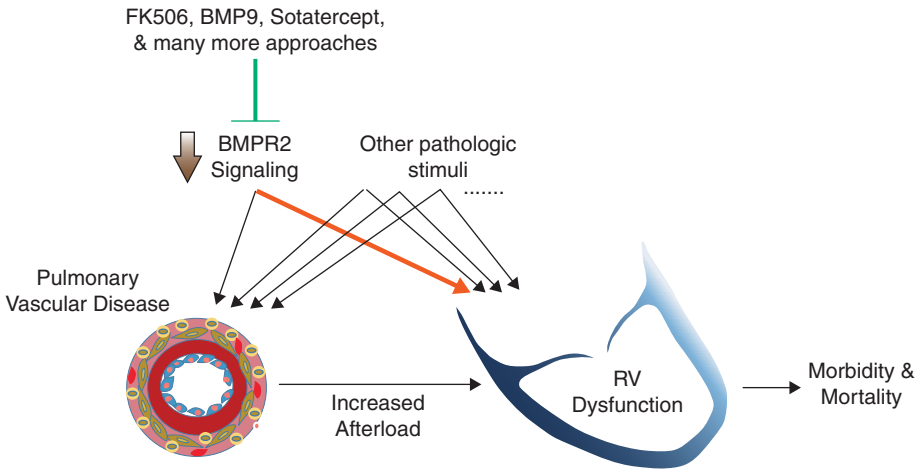

Figure 1. Increasing BMPR2 (bone morphogenetic protein receptor type 2) signaling may benefit both the lungs and the right ventricle (RV) in pulmonary arterial hypertension. Decreased BMPR2 signaling can contribute to both pulmonary vascular and RV disease, along with other potential pathologic stimuli, and targeting this pathway may therefore have dual beneficial effects in pulmonary arterial hypertension. The highlighted arrow is the focus of the present work by Boehm and colleagues (4).

The novel discoveries by Boehm and colleagues introduce new, exciting questions that will help define the role of future therapies directed at improving RV fibrosis in PAH. For example, the optimal timing of antifibrotic therapy initiation remains undefined and will likely depend on the degree of existing RV fibrosis. The potential need for dose adjustment in response to a changing RV afterload—which is reduced through vasodilator treatments or increased owing to progression of the underlying pulmonary vascular disease—will require elucidation. The impact of promoting BMP signaling in PAH with concurrent left ventricle fibrosis, as seen in systemic sclerosis, will also require additional studies.

Augmenting BMP signaling may allow simultaneous targeting of both the lung parenchyma and RV fibrosis in patients (Figure 1), particularly in those with pulmonary fibrosis–induced PH. Furthermore, there may be an opportunity to combine compounds such as BMP9 and FK506 to more precisely modulate BMPR2 pathway signaling, or to develop a personalized approach for patients with genetic mutations in BMPR2, with upstream ligands or downstream intracellular signaling mediators. Overall, the discovery of the FK506-mediated reduction in collagen deposition in the overloaded mouse RV represents an important step toward uncovering the therapeutic potential of BMP-signaling augmentation in PAH. ■

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