Is p38 MAPK a Dark Force in Right Ventricular Hypertrophy and Failure in Pulmonary Arterial Hypertension?

Right ventricular (RV) failure is the main cause of mortality in pulmonary arterial hypertension (PAH), and the response of the right ventricle to increased afterload is an important determinant of outcomes in patients (1). PAH is a severe disorder of the pulmonary circulation that is characterized by increased pulmonary vascular resistance creating strain on the right ventricle. Traditional therapeutic strategies for PAH seek to dilate the pulmonary vasculature and reduce afterload on the right ventricle. However, little is known about the exact pathogenic mechanisms underlying the RV failure. To advance care for patients with PAH, we need to improve our understanding of the basic mechanisms of RV failure and develop novel therapeutic interventions that specifically improve RV function.

Recent studies suggest that inflammation plays an important role in the proliferation of pulmonary vascular cells. In the systemic vasculature, p38 mitogen-activated protein kinase (MAPK) is part of an important inflammatory pathway. In the pulmonary vasculature, p38 MAPK is a new area of investigation and has been found to contribute to the development of endothelial dysfunction and increased fibroblast proliferation in response to acute and chronic hypoxia. Inhibition of p38 MAPK by PH797804 has been shown to prevent and reverse pulmonary vascular remodeling in animal models of pulmonary hypertension (2). However, the role of p38 MAPK in the development of RV dysfunction and failure is unknown.

Clinical studies have found increased activation of p38 MAPK in left-sided cardiovascular diseases, including idiopathic dilated cardiomyopathies and ischemic heart disease (3, 4). In a recent randomized phase 2 trial (SOLSTICE), inhibition of p38 MAPK by losmapimod reduced biomarkers of inflammation and improved left ventricular function in patients with non-ST-segment elevation myocardial infarction (5). Preclinical studies have found that inhibition of p38 MAPK prevents the transforming growth factor β 1 (TGF- β 1) transdifferentiation of fibroblasts into myofibroblasts. TGF- β 1 induces TRPC6 expression through the p38 MAPK and serum response factor (SRF) pathways (6). The role of the TGF- β 1/p38 MAPK/TRPC6 signaling pathway in RV hypertrophy and failure is unknown. The canonical mechanism for cardiac fibrosis involves the TGF- β 1/SMAD pathway, but given p38 MAPK's role in the transdifferentiation of myofibroblasts and its positive effect on pulmonary vascular remodeling, it is also important to investigate the effect of p38 MAPK inhibition on RV function (7).

In this issue of the *Journal*, Kojonazarov and colleagues (pp. 603–614) report two important findings (8): (1) expression and activation of phosphorylated p38 MAPK is upregulated in animal models of hypertrophy and failure of the right ventricle, and in cardiac myocytes from failed human right ventricles; and (2) inhibition of p38 MAPK attenuates RV dysfunction and markers of cardiac fibrosis *in vivo*, as well as TGF- β 1-induced myofibroblast differentiation and collagen production *in vitro*,

through suppression of transcriptional pathways, including SRF and myocardin-related transcription factor A (MRTF-A) (Figure 1).

Kojonazarov and colleagues confirm previous findings that p38 MAPK inhibition reduces pulmonary vascular pressure and remodeling (2, 8). Despite having no effect on systolic RV pressure in the pulmonary artery banding model, p38 MAPK inhibition improved RV function as measured by an increase in cardiac output, increased tricuspid annular plane systolic excursion, and increased myocardial performance index. The improvements in RV function correlate with reduced RV fibrosis, suggesting an RV-specific effect that is independent of changes in the pulmonary circulation. Other groups have effectively used PA banding to show that sildenafil, a PDE5 inhibitor, decreases RV fibrosis and diminishes p38 MAPK activity in the monocrotaline model of pulmonary hypertension (9).

In the current study, Kojonazarov and colleagues propose that crosstalk between the canonical TGF- β 1/SMAD pathway and the noncanonical TGF- β 1/p38 MAPK pathway plays a role in the pathogenesis of cardiac fibrosis. In the TGF- β 1/p38 MAPK pathway, p38 MAPK acts through SRF to increase TRPC6 activity and facilitate the transition of fibroblasts into myofibroblasts. Upregulated TRPC6 expression in pulmonary artery smooth muscle cells also contributes to the transition of pulmonary artery smooth muscle cells from a contractile to a proliferative phenotype (10). SRF can also enhance the transcription of collagen- and smooth-muscle-specific genes after binding with a cofactor such as MRTF-A (11). In this study, the authors show that inhibition of p38 MAPK prevents the translocation of MRTF-A from the cytosol to the nucleus and thus reduces collagen expression. The TGF- β 1/SMAD pathway is the canonical pathway for cardiac fibrosis, but a new finding is that inhibition of p38 MAPK by PH797804 significantly inhibited phospho-SMAD3 nuclear translocation, similarly to direct inhibition of SMAD3 by the inhibitor SIS3. Inhibition of SMAD3 had no effect on MRTF-A translocation and the noncanonical pathway involved in cardiac fibrosis. Although the authors outline new mechanisms of crosstalk between signaling pathways in the pathogenesis of cardiac fibrosis, there are still mechanistic questions about how inhibition of p38 MAPK interacts with SMAD2/3. Two other major MAPK pathways, Jun N-terminal kinase and extracellular signal-regulated kinases, play roles in cell proliferation, differentiation, and migration, but were not investigated here. The structural similarities among the four p38 isoforms (p38 α , p38 β , p38 γ , and p38 δ) will present a challenge for attempts to design a drug that can selectively inhibit one isoform without losing the activity of other isoforms that may play a protective role in cardiac hypertrophy. The MAPK pathway will continue to be a focus of research aimed at determining the precise role of components in the signaling pathway in RV fibrosis and failure.

Role of p38 MAPK on the pathophysiology of pressure overload-induced RV failure.

Figure 1. Inhibition of p38 improved right ventricular (RV) function independently of afterload and reduced cardiac fibrosis through the canonical TGF-β1/SMAD and noncanonical TGF-β1/p38 MAPK/MRTF-A signaling pathways. Key findings of the study by Kojonazarov and colleagues (8), and suggestions for potential strategies to target fibrosis in RV failure, are presented. Kojonazarov and colleagues explored the effects of p38 MAPK inhibition on RV function in a pressure-overload model of pulmonary hypertension to isolate RV-specific effects. Further investigation into signaling pathways of cardiac fibrosis identified potentially important crosstalk between the canonical TGF-β1/SMAD and noncanonical TGF-β1/p38 MAPK/MRTF-A signaling pathways. These pathways may represent potential therapeutic targets for regulating fibrosis in RV failure. α-SMC, α-smooth muscle cell; MKK, mitogen-activated protein kinase kinase; MRTF-A, myocardin-related transcription factor A; p38 MAPK, p38 mitogen-activated protein kinases; PA, pulmonary artery; PH797804, a p38 MAPK inhibitor; siRNA, small interfering RNA; SIS3, a SMAD3 inhibitor; SMAD, proteins that transduce extracellular signals from TGF-β ligands to the nucleus (contraction of Sma and Mad [Mothers against decapentaplegic]); SRF, serum response factor; TAPSE, tricuspid annular plane systolic excursion; TGF-β1, transforming growth factor-β1; TRPC6, transient receptor potential cation channel subfamily C member 6.

Collectively, these findings indicate that p38 MAPK activation may play an important role in RV fibrosis and failure in PAH independently of afterload, and therefore may represent a novel therapeutic target. ■

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

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