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Targeting the Hippo Pathway in Pulmonary Arterial Hypertension

Ryan Quigley:

Welcome to *AudioAbstracts* on ReachMD. I'm Ryan Quigley, and today, I'll be discussing a review article on emerging strategies that target the Hippo signaling pathway in pulmonary arterial hypertension.

For some context, pulmonary arterial hypertension remains a progressive and life-threatening disease despite major advances in vasodilator therapy. Current treatments can improve symptoms and hemodynamics, but they don't directly reverse the vascular remodeling that drives disease progression. As a result, there remains a significant need for therapies that address the underlying cellular mechanisms responsible for pulmonary vascular dysfunction.

A narrative review published in the *Journal of Hypertension* explores one pathway that has attracted growing attention in recent years: the Hippo signaling pathway. The authors summarize emerging evidence linking Hippo signaling to the abnormal cellular behaviors that characterize pulmonary arterial hypertension, including excessive vascular cell proliferation, resistance to apoptosis, inflammation, and endothelial-to-mesenchymal transition.

To understand why this pathway matters, it's helpful to consider its central role in regulating cell growth and tissue repair. Under normal conditions, Hippo signaling keeps cellular proliferation in check through a series of kinase-mediated events. When the pathway is active, it suppresses two key downstream effectors known as Yes-associated protein, or YAP1, and transcriptional coactivator with PDZ-binding motif, commonly called TAZ. When Hippo signaling is suppressed, YAP1 and TAZ move into the nucleus and activate genes that promote cell growth, survival, and vascular remodeling.

The review highlights how this dysregulation may contribute to several hallmark features of pulmonary arterial hypertension. For instance, in pulmonary artery smooth muscle cells, YAP1 activation promotes a shift toward a proliferative and migratory phenotype. This process contributes to vessel wall thickening and increased vascular resistance. Multiple upstream signals, including hypoxia and extracellular matrix stiffness, appear to converge on the Hippo pathway and reinforce this remodeling response.

The pathway also appears to influence endothelial-to-mesenchymal transition. During this process, endothelial cells lose their normal characteristics and acquire features that resemble mesenchymal cells. This transition has been increasingly recognized as a contributor to pulmonary vascular remodeling. The review describes important interactions between YAP1, transforming growth factor beta signaling, and microRNAs that may promote this pathological change.

Beyond endothelial and smooth muscle cells, Hippo signaling may also regulate adventitial fibroblast activation and inflammatory responses. Experimental evidence suggests that components of the pathway interact with inflammatory mediators such as interleukin-6 and the NLRP3 inflammasome. These findings point to a broader role for Hippo signaling in coordinating the cellular and immune processes that sustain disease progression.

So what does this mean therapeutically?

The authors summarize several potential therapeutic approaches for the treatment of pulmonary hypertension that target the Hippo pathway. Among the most notable is verteporfin, a small-molecule inhibitor that disrupts YAP1 activity and has shown the ability to reduce pulmonary artery smooth muscle cell proliferation in preclinical models. Other approaches include integrin-linked kinase inhibitors, as well as naturally derived compounds such as luteolin and resveratrol, although the authors note that resveratrol's Hippo-specific effects haven't yet been demonstrated in pulmonary hypertension models.

At the same time, the authors emphasize some important limitations. Most available evidence remains preclinical, and the Hippo

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pathway regulates many physiological processes throughout the body. That broad biological role raises questions about the specificity of Hippo-targeted therapies, as well as their potential off-target effects and long-term safety. In addition, pathway activity appears to vary across different vascular cell types and disease contexts, making therapeutic modulation complex.

Nevertheless, these findings support continued research into Hippo-directed therapies as a potential complement to current vasodilator-based treatment strategies. Future studies will need to identify reliable biomarkers of pathway activation, clarify safety considerations, and determine whether Hippo-targeted therapies can meaningfully alter disease progression in patients.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:

Zheng D, Guo Y. Targeting the Hippo pathway in pulmonary arterial hypertension: emerging pharmacological strategies. J Hypertens. 2026;44(5):741-751. doi:10.1097/HJH.0000000000004257

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