Regulation is the name of the game in pulmonary arterial hypertension

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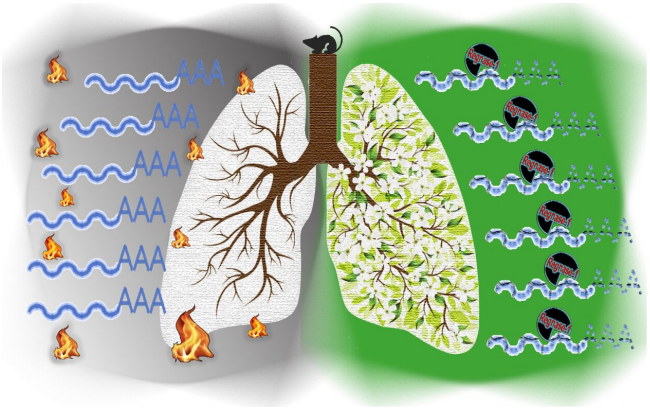

Decay of mRNA by Regnase-1 leads to PAH inhibition in mice. Credit: KyotoU Global Comms/Ai Yaku

Matters of the heart can sometimes be resolved from within. Pulmonary arterial hypertension, or PAH, caused by a thickening of the arterial walls and narrowing of the lumen can be fatal if left untreated. The use of vasodilators has been shown to improve the prognosis in only some cases.

Now, the anti-inflammatory protein Regnase-1 may become the new sheriff in town with the possibility of preventing heart failure and premature death due to PAH. A new study by Kyoto University has found that Regnase-1 gene expression in peripheral blood mononuclear cells from patients was low relative to healthy volunteers.

"In our animal study, mice lacking Regnase-1 in myeloid cells spontaneously developed severe PAH, mirroring the pathology of PAH in humans," says lead author Ai Yaku.

The team discovered that the decay of mRNA by Regnase-1 leads to PAH inhibition. The evidence comes from a comprehensive analysis of combined gene expression of alveolar macrophages and pulmonary arteries from Regnase-1-deficient mice.

Although current PAH treatments target vasodilation, they cannot effectively regulate the abnormal spread of vascular wall cells. Additionally, other studies have not been able to specify the cells producing the cytokines, responsible for chronic inflammation.

"The mice in this study are very unique in that they develop PAH spontaneously," says the author, explaining that PAH model mice are usually prepared by hypoxia or drug exposure.

"It is significant that our mice exhibited the pathology seen in patients with severe PAH that otherwise could not be reproduced by current models."

Using clinical samples, the team found that Regnase-1 demonstrates efficacy in inhibiting the pathogenesis of pulmonary hypertension, particularly connective tissue disease-related PAH, or CTD-PAH.

"We will continue focusing on using our Regnase-1-deficient mouse model to help elucidate the pathogenesis of cardiac fibrosis and other diseases related to CTD-PAH," Yaku says.

The paper "Regnase-1 Prevents Pulmonary Arterial Hypertension Through mRNA Degradation of Interleukin-6 and Platelet-Derived Growth Factor in Alveolar Macrophages" appeared on August 23, 2022 in *Circulation*.

More information: Regnase-1 Prevents Pulmonary Arterial Hypertension Through mRNA Degradation of Interleukin-6 and Platelet-Derived Growth Factor in Alveolar Macrophages, *Circulation* (2022). DOI: 10.1161/CIRCULATIONAHA.122.059435

Provided by Kyoto University

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