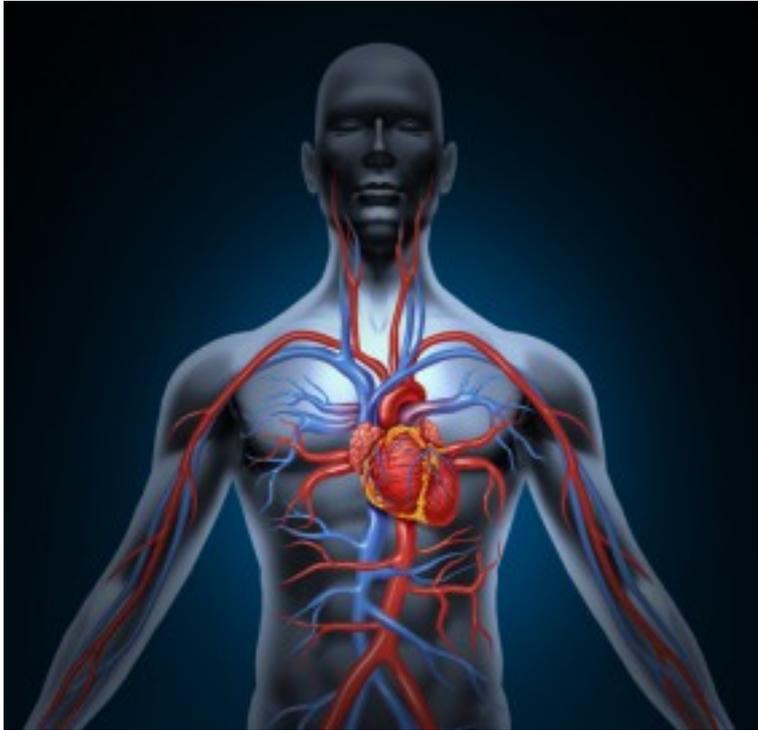


## **Disruption of cellular signaling identified in pulmonary arterial hypertension**

Yale UniversityYale University



Impairment of a key signaling cascade in the pulmonary blood vessels plays an important role in pulmonary arterial hypertension, a Yale study has found. The study appears in the advance online publication of Nature Medicine.

Pulmonary arterial hypertension (PAH) is a disease caused by an increase of blood pressure in the blood vessels of the lungs. If untreated, the majority of patients with the disease will succumb to heart failure and death.

PAH is characterized by the formation of lesions in the lungs composed of abnormally proliferating cells of the endothelium (cell tissue that lines blood vessels and the heart) and vascular smooth-muscle cells. Recent studies have described the role of the gene apelin in the signaling process that maintains normal pulmonary vascular function. Apelin levels have been found to be significantly reduced in patients with PAH.

The Yale team set out to discover the mechanism by which impaired apelin signaling triggers the abnormal proliferation of cells that characterize PAH. They focused on the connection between reduced apelin expression and increased fibroblast growth factor (FGF) signaling. FGF helps to form and maintain blood vessels when functioning normally, but if produced in excess, as it is in diseases such as PAH, it can cause abnormal proliferation of cells, leading to pathologic remodeling of blood vessels.

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In studies of rodent and human tissue samples, the scientists found that increased expression of two key components of FGF signaling, FGF2 and its receptor FGFR1, resulted from decreased levels of two microRNAs that are regulated by apelin. Decreased expression of these microRNAs disrupted the pulmonary vascular system's ability to maintain cellular balance, resulting in abnormal induction of cellular growth in PAH. The scientists found that restoring these microRNAs in rat models of PAH led to dramatic reversal of the disease.

"Our findings could lead to development of new therapies aimed at restoring the signaling balance in the pulmonary vessels in order to treat patients with pulmonary arterial hypertension," said senior author Dr. Hyung Chun, assistant professor of medicine (cardiology) at Yale School of Medicine. "New treatments are critical, as close to half of the patients diagnosed with PAH die within three years despite currently available therapies."

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