Pulmonary arterial hypertension is incurable but animal model study suggests an experimental drug may be effective

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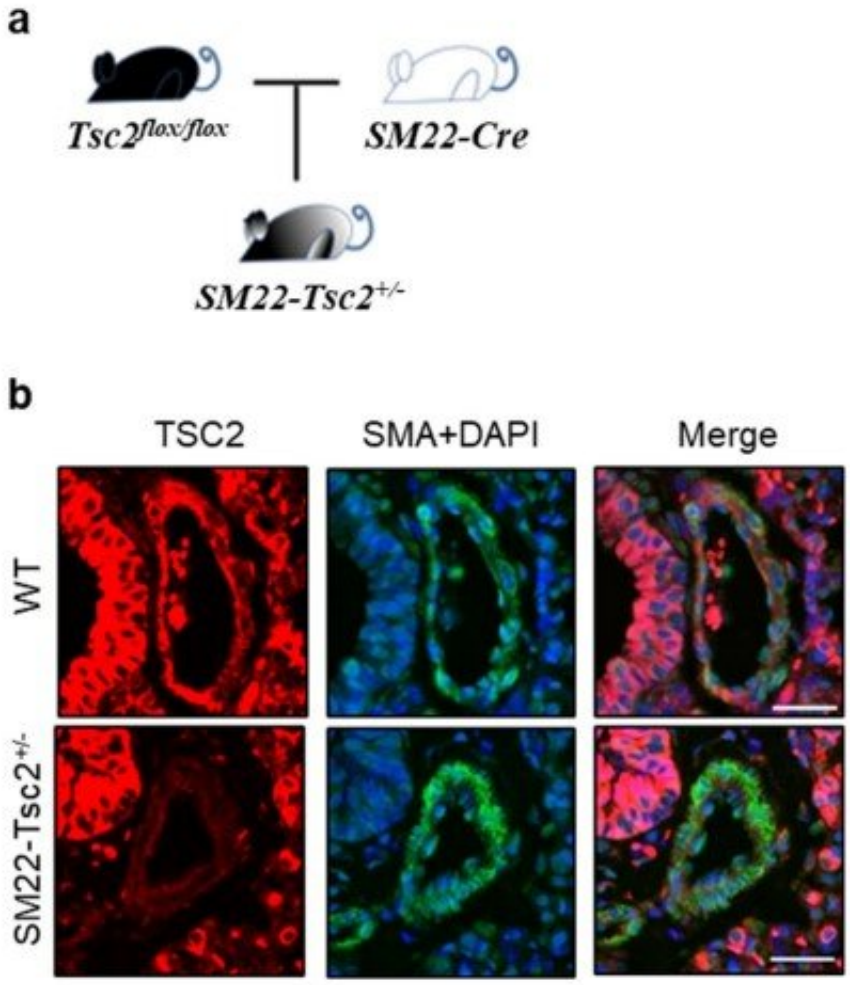

TCS2 protein reduction in SMA-positive areas in small PAs from SM22-Tsc$^{+/-}$ mice. a: SM22-Cre mice were bred with Tsc2$^{flox/flox}$ mice to generate SM22-Tsc$^{+/-}$ mice. b: Immunohistochemical analysis of lung tissue sections of

SM22-Tsc2$^{+/-}$ mice to detect TSC2 (red), smooth muscle α-actin (SMA) (green), and DAPI (blue). Representative images from n=5 WT and 7 SM22-Tsc2$^{+/-}$ mice and 5 PAs/mouse. Scale bar, 30μm. Credit: *Science Signaling* (2022). DOI: 10.1126/scisignal.abn2743

An experimental drug that is already in clinical trials for other diseases could disrupt a positive feedback loop that exacerbates pulmonary arterial hypertension, a dangerous and rapidly fatal condition for which there is no cure.

Pulmonary arterial hypertension develops when small arteries inside the lungs become unusually stiff, leading to dangerously high blood pressure and eventual heart failure. The stiffening and remodeling of pulmonary arteries also causes excessive cell growth and proliferation of pulmonary arterial vascular smooth muscle cells. This manifestation irrevocably damages the lungs and impairs breathing.

Patients experience shortness of breath, dizziness, and chest pressure. Despite a combination of medications and oxygen therapy, which ameliorate symptoms, the condition inevitably worsens and quality of life declines.

"Pulmonary arterial hypertension is partially driven by the proliferation of pulmonary arterial vascular smooth muscle cells induced by stiffening of pulmonary arteries," reports Dr. Yuanjun Shen, lead author of a new study in the journal *Science Signaling*.

Shen, of the Lung Center in the division of pulmonary, critical care and sleep medicine at the University of California, Davis, has been exploring the potential benefits of an experimental drug called SRT2104, which appears to reverse the cause of the disease. The investigational

medication has been studied as a potential treatment for a diverse range of other medical conditions, such as type 2 diabetes, psoriasis, and dyslipidemia.

SRT2104 was developed as a selective small molecule involved in the regulation of energy homeostasis and the modulation of various metabolic pathways. The UC Davis team turned to animal models to determine whether SRT2104 might offer treatment benefits by reversing the invariable downhill course of the disease.

The researchers were well aware that a protein called tuberous sclerosis complex 2 (TSC2) naturally in the lungs can suppress aberrant cell growth in pulmonary arterial hypertension, which prompted Shen and collaborators to ask whether TSC2 possesses a protective role. The question was how to increase TSC2 proteins safely, effectively and abundantly.

The team noted an unusually low abundance of TSC2 proteins in the disease itself, especially in pulmonary arterial vascular smooth muscle cells, which proliferate wildly in the disease. In the examination of lung tissue from 16 patients with pulmonary arterial hypertension, Shen and colleagues noted the hallmarks of the disease: low TSC2 proteins and high levels of pulmonary arterial vascular smooth muscle cells. They further found activated cell growth pathways, which boosted the proliferation of pulmonary arterial vascular smooth muscle cells.

This proliferation, in turn, led to further stiffening, feeding into a vicious cycle—a feedback loop—that worsened harmful vessel remodeling. By comparison, samples from healthy controls showed an abundance of TSC2 proteins and no proliferation of pulmonary arterial vascular smooth muscle cells.

Examining the animal models, Shen and colleagues found that mice

whose smooth muscle was even partially deficient in TSC2 proteins developed stiffer pulmonary arteries and pulmonary hypertension. Yet, when the experimental drug was administered to each of two groups of animal models, SRT2104 restored TSC2 protein abundance, reversed pulmonary arterial remodeling and mitigated pulmonary hypertension in both rodent models. The team concluded that apparent cross-talk between TSC2 and the extracellular matrix controls pulmonary vascular proliferation because the vicious cycle and low TSC2 protein levels do not exist in treated mice—or healthy people.

Pulmonary arterial hypertension is considered a rare disease in the United States because fewer than 200,000 people are diagnosed with it annually. Despite the rare disease designation the disorder is marked by escalating medical costs and is responsible for disproportionately high losses of productivity and personal income.

The U.S. Centers for Disease Control and Prevention notes that the condition can be caused by any one of several possible causes: high blood pressure in the lungs' arteries resulting from certain types of congenital heart disease; connective tissue disease; coronary artery disease; high blood pressure; blood clots to the lungs, and chronic lung diseases, such as emphysema.

The research, which examined the investigational drug SRT2104, involved a far-flung team of collaborators. In addition to investigators at UC Davis, many team members were in Pennsylvania at the University of Pittsburgh's Heart, Lung, Blood and Vascular Medicine Institute as well as the University of Pennsylvania's Perelman School of Medicine. Other investigators were at Brigham and Women's Hospital in Boston and Ohio State University in Columbus.

The researchers posit that their findings may present a new treatment target. "Our preclinical evidence shows that SRT2104, which is already

in clinical trials for other diseases, and has a favorable safety profile, has beneficial effects in human pulmonary arterial hypertension and two rodent models of pulmonary hypertension warranting further assessment," Shen concluded.

More information: Yuanjun Shen et al, Cross-talk between TSC2 and the extracellular matrix controls pulmonary vascular proliferation and pulmonary hypertension, *Science Signaling* (2022). DOI: 10.1126/scisignal.abn2743