Gene essential to making DNA appears to be a good target in minimizing pulmonary hypertension

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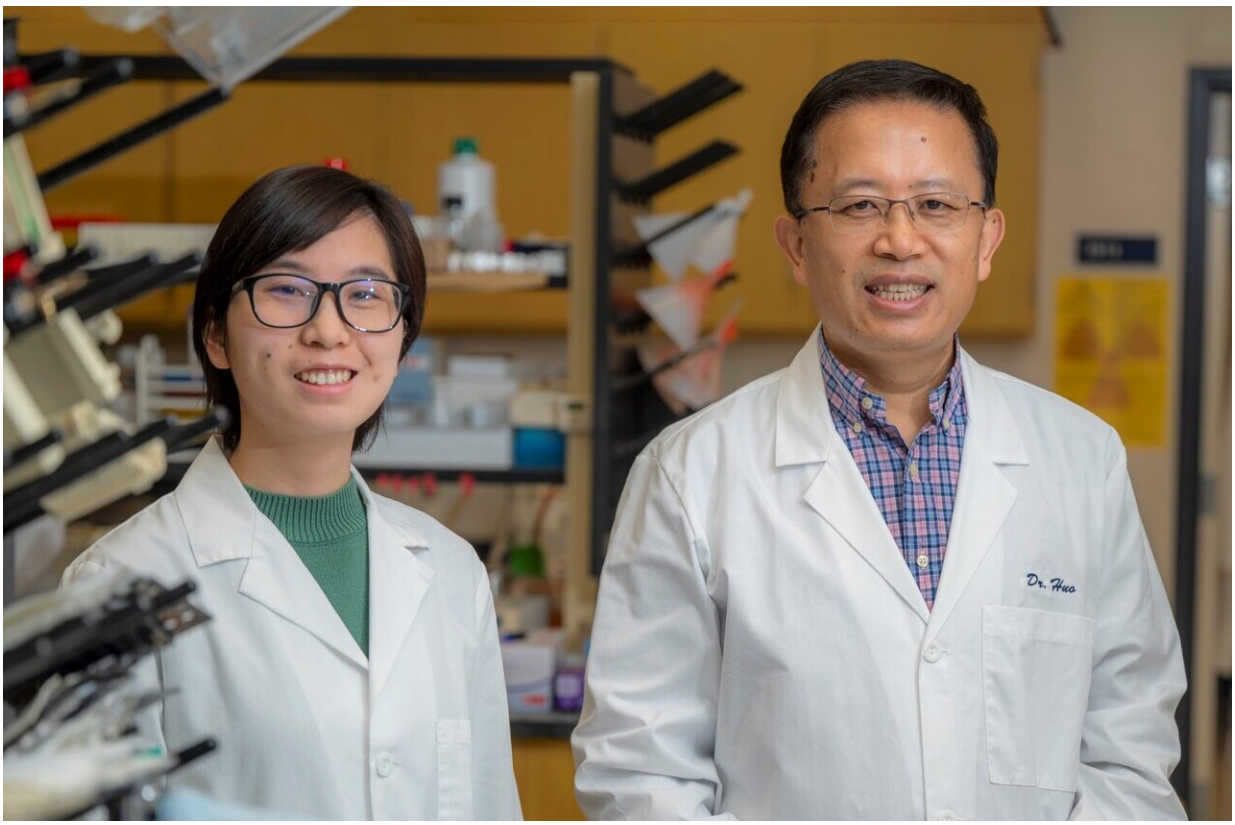

Yuqing Huo, MD, PhD, (left) and Qian Ma, PhD. Credit: Michael Holahan, Augusta University

The vascular smooth muscle cells that normally give blood vessel walls

strength and flexibility proliferate and become destructive in pulmonary hypertension, a typically rapidly progressing condition that makes it hard to get blood inside our lungs and oxygen to our bodies.

Now scientists have found that inhibiting a gene essential to making DNA so the cells can take on this uncharacteristic growth, can significantly reduce the destructive cell proliferation and disease progression, they report in the *European Heart Journal.*

The findings point toward a treatment target for a condition that can inexplicably affect females ages 30 to 60 and that currently does not have great treatment options, says Yuqing Huo, MD, Ph.D., director of the Vascular Inflammation Program in the Vascular Biology Center at the Medical College of Georgia.

Pulmonary hypertension is basically high blood pressure in the lungs that can make breathing difficult and damage or destroy the right side of a heart which has to pump against the abnormally high pressures. It's characterized by remodeling of the pulmonary arteries that feed oxygen-depleted blood to the lungs where it can take up oxygen and lose carbon dioxide, a byproduct of oxygen use. But there is much to be learned about why and how the cells manage the unusual growth and where therapy might best intervene.

The Vascular Biology Center team led by Huo reported late in 2022 in the journal *Circulation* that the vascular smooth muscle cells that encase blood vessels of the heart have the same adverse reaction when fat and cholesterol start getting deposited on their lining. The resulting abnormal proliferation and growth of vascular smooth muscle cells in this scenario worsens heart disease by prompting a thickening of the muscular wall of the blood vessels further narrowing the passageway for blood out to the body, where fat and cholesterol have already taken a stand.

Essential to cell growth, including this unhealthy proliferation, is more DNA, RNA and the proteins they produce. Key to that is purine, one of two chemical compounds in the body used to make the building blocks DNA and RNA. Key to purine production, is the gene ATIC, and in this case, more of it.

The new studies found that, as with the unhealthy proliferation in coronary arteries, when the scientists deleted ATIC from either the vascular smooth muscle cells or body wide, it reduced the development and progression of pulmonary hypertension in their mouse model of the breath-taking condition. It even mitigated a very severe form of the condition.

"If we block this process, the blood vessel wall will stay relatively normal and the blood will still pass through," Hou says.

When the scientists looked in mouse models as well as human pulmonary arteries and lung tissue, they found a similar scenario: Genes essential to production of purine are increased and so is actual purine production, and expression of the ATIC gene.

When they first looked at human genetic data, they had clues that is what they might find: They saw proliferation as well as increased expression of genes that indicated the cells were making purine from scratch, so called de novo purine synthesis, rather than from recycling, which is the body's other option. That's the same high energy purine producing process they found vascular smooth muscle cells on coronary arteries were using.

Huo and his colleagues note that when vascular smooth muscle cells begin to proliferate and become resistant to death, they start resembling cancer cells. What the scientists have now found underlines the similarities between metabolic shifts that occur in both the early

development of pulmonary hypertension and cancer, Huo and his colleagues write. In fact, making purine from scratch also is increased in many cancer cells, which may make ATIC a logical treatment target there as well, Huo and his colleagues write. For example, one way the drug methotrexate, used to slow the growth of cancer cells, is thought to work is by inhibiting ATIC. Also, newer ATIC inhibitors for cancer are under study.

Huo also notes that more specific inhibitors are needed to treat pulmonary hypertension and that the same inhibitors likely would also work in the coronary arteries.

The lungs are extremely vascular and pulmonary arteries branch like a tree in the lungs until they eventually become smaller vessels called arterioles and eventually even smaller, single-layer blood vessels called capillaries, which surround the millions of air sacs in the lungs. The capillaries are where carbon dioxide escapes from the blood and where oxygen from the air we breathe moves in. Huo notes capillaries don't have the typical layer of smooth muscle cells only the endothelial cells that normally just line blood vessels.

Right heart failure is a leading cause of death in people with pulmonary hypertension and is even tougher to treat than left heart failure, which can result from more common problems like coronary artery disease, heart attack and high blood pressure, Huo says.

Postdoctoral Fellow Qian Ma, Ph.D., is first author on the new paper.

More information: Qian Ma et al, Purine synthesis suppression reduces the development and progression of pulmonary hypertension in rodent models, *European Heart Journal* (2023). DOI: 10.1093/eurheartj/ehad044