The molecular mechanism behind abdominal aneurysms

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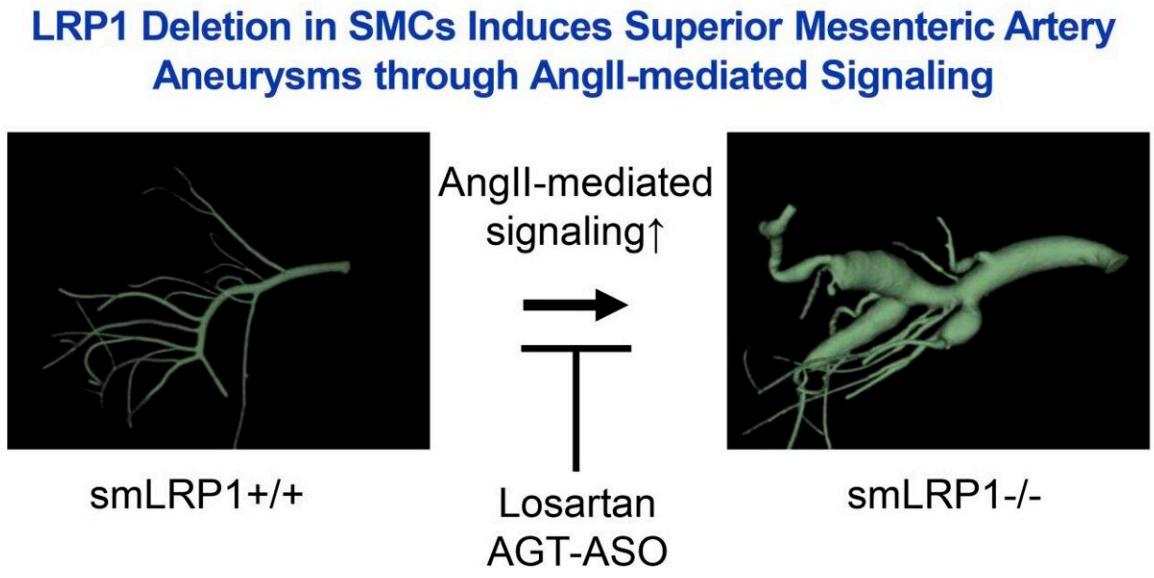

Graphical abstract. Credit: *JCI Insight* (2022). DOI: 10.1172/jci.insight.164751

When the artery that supplies the stomach and the liver forms a bulge that ruptures, this medical emergency results in the deaths of 50 percent of patients before they reach the hospital. This "silent killer" condition, known as abdominal aortic aneurysm, led to the death of Albert Einstein—and is responsible for nearly 5,000 deaths in the U.S. each year. Now researchers have found new clues that eventually could lead to

earlier detection methods to save lives in the future.

Surgery can prevent abdominal aneurysms by inserting a tube inside the damaged artery, but physicians do not have a way to predict who is most at risk and should be screened for this condition. Unlike the more common thoracic aortic aneurysms which occur in the chest, abdominal aneurysms do not have any known genetic risk factors.

In a new study using mice, University of Maryland School of Medicine (UMSOM) researchers were able to tease apart the molecular components involved in abdominal aneurysms to better understand how and why they form.

The findings were published on January 24, 2023, in *JCI Insight*.

"Our next step is to conduct human genetic studies on these newly identified mice components to see if we can find a genetic correlation in abdominal aneurysm patients. My gut feeling says that we will identify previously unknown genetic mutations associated with an increased risk of this condition," said study leader Dudley Strickland, Ph.D., Professor of Surgery and Physiology, Director of the Center for Vascular & Inflammatory Diseases at UMSOM.

"From there, we could screen people to identify those with an increased risk of developing abdominal aneurysms, have their physicians monitor them, and intervene when necessary to save lives."

Having high cholesterol or high blood pressure, and being older, a smoker, or a man can increase one's odds of developing an abdominal aneurysm. Abdominal aneurysms usually are caused by plaque buildup in the arteries, but infection or injury can also cause this condition, according to the Centers for Disease Control and Prevention.

"Certain genetic mutations may make someone more likely to have their repair process end up going haywire causing the portion of the artery to swell like a balloon and instead of healing a section of damaged artery," said study co-author Jackie Zhang, MD, Surgery Resident at UMSOM and researcher in Dr. Strickland's laboratory.

To conduct the study, the research team decided to focus on the protein LRP1, since it is involved in thoracic aortic aneurysms. To test this, they genetically engineered mice that did not have LRP1 in the cells that line blood vessels known as smooth muscle cells. Using CT scans to look at these blood vessels without LRP1, the researchers noticed that the abdominal arteries were abnormally enlarged as compared to vessels in normal mice.

Next, using a highly sophisticated comparative protein analysis of normal and diseased tissue, they found that the enlarged blood vessels in the genetically engineered mice had higher levels of proteins involved in the hormonal angiotensin-renin system that regulates blood pressure and blood vessel growth and development.

For the final part of the study, the researchers were able to prevent the abdominal arteries from enlarging in the engineered mice when they blocked an angiotensin receptor using the blood pressure drug losartan. They also prevented the enlarged arteries by removing a precursor of the angiotensin hormone in the liver of mice, further demonstrating the connection between LRP1 and the angiotensin-renin system in aneurysm development.

"Now that the researchers identified some of the components involved in these aneurysms, they will next need to explore how they interact together," said UMSOM Dean Mark T. Gladwin, MD, Vice President for Medical Affairs, University of Maryland, Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor.

"For example, it's known that LRP1 is involved in transporting proteins from outside the cell to the inside in the region of the cell that digests and recycles those materials, but we do not know how that plays a role in forming or preventing aneurysms."

More information: Jackie M. Zhang et al, LRP1 protects against excessive superior mesenteric artery remodeling by modulating angiotensin II–mediated signaling, *JCI Insight* (2022). DOI: 10.1172/jci.insight.164751

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