Researchers track new path to therapeutic prevention of abdominal aortic aneurysm

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Satoru Eguchi, MD, PhD, FAHA, Professor of Physiology and Professor in the Cardiovascular Research Center, Sol Sherry Thrombosis Research Center, and Center for Metabolic Disease Research at the Lewis Katz School of Medicine at Temple University. Credit: Temple University Health System

The main thoroughfare that carries oxygen-rich blood from the heart to the abdomen is known as the abdominal aorta. Strong and thick-walled, this main highway is built to withstand a lifetime of use. But just like expressways traveled by cars and trucks, too much force on its surfaces and exposure to certain environmental factors can cause the vessel to wear and weaken over time—weakening that can lead to abdominal aortic aneurysm (AAA), a bulge in the aorta wall that has a high risk of rupturing.

Risk of AAA is high in smokers, particularly men over age 50, and there is no cure. Long-term survival is poor, especially for patients with large aneurysms and for those who are not able to undergo surgery to prevent eventual rupture.

But now, new research by scientists at the Lewis Katz School of Medicine at Temple University (LKSOM) suggests that AAA can be prevented therapeutically. In work published online May 28 in the journal *Cardiovascular Research*, they show for the first time in animals that blocking a molecule known as dynamin-related protein 1 (Drp1) can stop AAA from developing.

"While the molecular mechanism of AAA has been unknown, we suspected a connection with mitochondria, which supply cells with energy," explained Satoru Eguchi, MD, Ph.D., FAHA, Professor of Physiology and Professor in the Cardiovascular Research Center, Sol Sherry Thrombosis Research Center, and Center for Metabolic Disease Research at LKSOM. "We were interested especially in how processes called mitochondrial fission and fusion impact AAA."

Fission and fusion are normal processes by which mitochondria divide and recombine to maintain their function. But blood vessel inflammation, which can be caused by smoking, aging, and other factors, causes mitochondria to shift toward fission. This harmful fragmentation process, which is regulated by Drp1, severely compromises the integrity of the aortic thoroughfare—like the subsurface of an expressway crumbling.

Dr. Eguchi and colleagues, including Hannah A.

Cooper, an MD, Ph.D. student in Dr. Eguchi's laboratory at the Cardiovascular Research Center and lead author on the new paper, and collaborators at Okayama University in Japan, observed elevated Drp1 levels in the abdominal aortas of human patients with AAA. They also observed similar Drp1 increases in AAA tissues from mice engineered to develop the condition.

To investigate the significance of elevated Drp1, the researchers treated AAA mice with a compound called mdivi1, which acts as a Drp1 inhibitor. Mdivi1 turned out to attenuate AAA development, based on measurement of the diameter of the abdominal aorta and on molecular study of vascular smooth muscle cells. While treated mice still had high blood pressure associated with their condition, mdivi1 completely protected them against aortic rupture.

Drp1 inhibition was further associated with reduced stress responses in vascular cells. These responses included reduced infiltration of inflammatory cells and decreased senescence, which is characterized by aging-related cellular deterioration.

Dr. Eguchi thinks senescence may be a driving factor behind AAA. Mitochondrial fragmentation accompanied by decreased mitochondrial function and accelerated vascular aging set the stage for increased premature senescence and senescence-associated secretory phenotype (SASP), an aging-related chronic inflammatory condition.

"Human patients and animals with AAA appear young on the outside, but their vascular systems typically show significant aging," Dr. Eguchi said. "Maintaining the mitochondrial fission-fusion balance appears to be fundamental to attenuating senescence and having healthy cardiovascular function. A Drp1 inhibitor may be the therapeutic answer to achieving this goal for persons at risk of AAA."

In future work, Dr. Eguchi and colleagues plan to more deeply explore the mechanisms involved in Drp1-mediated mitochondrial fission and fusion and how they tie into AAA and other cardiovascular diseases.

More information: Hannah A Cooper et al, Targeting Mitochondrial Fission as a Potential Therapeutic for Abdominal Aortic Aneurysm, *Cardiovascular Research* (2020). DOI: 10.1093/cvr/cvaa133

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