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Genetic factor shown to regulate both heart failure and aneurysm disease

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Case Western Reserve University School of Medicine researchers have identified a major indicator of two deadly diseases of the heart and blood vessels: heart failure and aortic aneurysm. The absence of the Kruppel-like Factor 15 (KLF15), when combined with stress, leads to both heart failure and aortic aneurysms. The genetic factor, KLF15, protects the heart and aorta's ability to maintain structural and functional integrity. Patients with these diseases were found to have reduced levels of the protective gene, and in an animal study, the researchers proved that deficiency of this single gene predisposes one to these cardiovascular diseases.

Furthermore, they show that KLF15 exerts its protective effects in the heart and aorta through a common molecular mechanism. Lastly, the researchers show that drugs targeting this molecular pathway can be used to treat heart failure and aortic aneurysms. The unprecedented findings are published in the April 7th online edition of *Science Translational Medicine*, an American Association for the Advancement of Science publication.

All the blood circulating through the human body must be pumped out by the heart and flow though the aorta. These two vital organs must maintain structural integrity in the face of mechanical and biochemical stress, otherwise lethal consequences such as heart failure, aortic aneurysms, and aortic dissection can develop. While it has been known that diseases of the heart and aorta can co-exist, for example in Marfan's syndrome, pregnancy, aging, and growth hormone excess, the

cardiovascular diseases are typically treated independently. The identification of shared molecular mechanism offers new promise for current and future treatment options.

"This is very rare to find a singular genetic factor that governs the response of the entire cardiovascular system. Our research proves KLF15 governs the shared diseases of the heart and blood vessels," says Mukesh K. Jain, M.D., F.A.H.A., senior author of the study and Director of the Case Cardiovascular Research Institute at Case Western Reserve University and the Chief Research Officer for the Harrington-McLaughlin Heart and Vascular Institute at University Hospitals Case Medical Center. In 2002, while at Brigham and Women's Hospital/Harvard Medical School, Dr. Jain and his team of researchers discovered KLF15.

Dr. Jain, along with his fellow researchers from the University of Pennsylvania, University of Medicine and Dentistry of New Jersey, Geisinger Health System, and Harvard Medical School, first observed reduced KLF15 levels in human patients with heart failure or aortic aneurysms. Subsequently, they bred genetically-modified mice deficient in only KLF15; this was where the link between diseases was identified. A major mechanism by which KLF15 exerts its protective effects is through the inhibition of a protein called p53. In some human body tissues, p53 can protect against cancer with its ability to shut down cell growth and new blood vessel formation. However, the researchers found that excess activation of p53 in both the heart and aorta is harmful, particularly when there is KLF15 deficiency. In fact, the mice showed dramatic improvement when the p53 gene was inactivated. The study also showed that KLF15 can block p53's harmful effects on the cardiovascular system by interfering with a process called protein acetylation. Lastly, the research team used the newly discovered molecular pathway to show that blocking the acetylation of p53 with a compound called curcumin can also protect against heart and aortic

disease. Curcumin is the active compound in turmeric, a spice commonly used in Asian cuisine. They hope to harness the function of KLF15 as a drug target which might allow them to selectively block only the harmful effects of p53 in the cardiovascular system, while maintaining its anti-cancer effects in other organs.

Cardiovascular diseases are the leading cause of death and disability in developed countries. Despite the widespread use of medication, many people still suffer complications from these devastating diseases. "The discovery of new molecular pathways that are amenable to therapeutic manipulation is of immense clinical value. Our current study demonstrates proof-of-principle that KLF15 deficiency causes heart failure and aortic aneurysm formation. Thus, we believe that boosting the protective effects of KLF15 in the heart and aorta can prevent the initiation or progression of these diseases," say Saptarsi M. Haldar, M.D. and Yuan Lu, Ph.D., co-first authors on the paper. Dr. Haldar is an Assistant Professor of Medicine and Dr. Lu is a Research Associate in the Case Cardiovascular Research Institute at Case Western Reserve University School of Medicine.

As they look to the future, the researcher team will enhance KLF15's health-giving effects using a variety of approaches. They hope to discover compounds that can increase KLF15 levels or augment its function in the cardiovascular system, which includes screening a library of compounds for their ability to increase levels of the genetic factor. The research also has exciting implications for Marfan's syndrome, a multisystem disease involving the aorta and heart. The current work suggests that the KLF15-p53 axis might be a disease-modifying factor in the syndrome and serve as a potential therapeutic target.

"We hope that such therapies would help maintain the normal pumping-function of the heart and the integrity of aortic structure and thereby prevent patients from developing life-threatening complications such as

sudden cardiac death, aortic rupture and aortic dissection," concludes Dr. Jain.

Provided by Case Western Reserve University

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