Researchers find inflammation critical in aortic dissection

November 16 2009

The aorta, the body's largest artery, stretches from the chest to below the kidneys, expanding and contracting with the pressure of blood driven directly into it by the heart. Although its walls are extraordinarily strong, like other blood vessels the aorta can sometimes develop bulges, called aneurysms. Like other aneurysms, those in the aorta sometimes give way, and the result is what doctors refer to as an "aortic dissection" — a clinical way of saying that the largest artery in your body has just started leaking, and you may well be on your way to becoming one of the nearly 16,000 Americans killed by the phenomenon annually.

Aortic dissection has traditionally been viewed as a simple structural failure, albeit one with poorly understood causes. Certain genetic diseases, such as Marfan syndrome, have been directly linked to the condition; the actor John Ritter inherited a different genetic defect that contributed to his sudden death from aortic dissection in 2003. But the mechanisms that turn a worrisome aortic aneurysm into a catastrophic aortic dissection have remained mysterious.

Now, though, University of Texas Medical Branch at Galveston researchers have uncovered what seem to be the key biochemical processes that chip away at the aorta from within until it finally tears. In a paper to be published online Nov. 16 in the Journal of Clinical Investigation, the UTMB investigators present evidence that implicates inflammatory processes centered on the signaling molecule interleukin-6 in producing the disastrous aortic weakening.

"We found that inflammation is critical in aortic dissection, and IL-6 — which has been recognized for years as a marker of inflammation and also an important cardiovascular risk factor — plays the central role in the process," said UTMB professor Allan Brasier, senior author of the study. "Without it, you don't have dissection."

The UTMB team — graduate students Brian C. Tieu and Xiaoxi Ju, research associates Chang Lee, Hong Sun and Wanda LeJeune, assistant professors Adrian Recinos and Heidi Spratt and professor Ronald Tilton — arrived at its conclusions through experiments with mice and work with human samples provided by their collaborators and co-authors at the University of Texas Health Science Center at Houston, assistant professor Dong-Chuan Guo and professor Dianna Milewicz.

To profile the inflammatory attack that produces aortic dissection, Brasier's group injected the hormone angiotensin into both ordinary lab mice and those genetically modified to "knock out" IL-6 or a cellular receptor for another molecule also involved, known as MCP-1. The human samples, used to substantiate a link between the mouse findings and human disease, came from volunteers undergoing surgical aortic dissection repair without a family history of the disease.

"Angiotensin is a blood-pressure regulating hormone — people who have what we call essential high blood pressure have increased production of angiotensin, and it's the target for anti-hypertension therapies," Brasier said. "What we've found in earlier studies is that it has an inflammatory role as well, causing cells in blood vessel walls to produce IL-6 as well as MCP-1. And this study showed us that MCP-1 helps recruit monocytes [a type of white blood cell] to the vessel where IL-6 activates them."

Playing host to a large number of cells meant for immune defense is bad news for an aorta already strained by an aneurysm, since activated white

blood cells produce proteins that destabilize the structure of the vessel. At the same time, signals produced by the activated white blood cells encourage the blood vessel to generate more IL-6.

"Our data suggest that interleukin-6 and MCP-1 secretion are codependent — without interleukin-6 you get less MCP-1," Brasier said. "But with interleukin-6 it's like throwing more gasoline on the fire, you keep bringing in still more monocytes and activating them, amplifying the effect."

A similar feedback loop kicked into action when human monocytes and cells grown from the human aortic dissection samples were brought together, generating both IL-6 and MCP-1. Once again, though, removing IL-6 damped the response. And microscopic studies of human aortic dissection samples showed substantial levels of IL-6 in the same layer of the aortic wall where the inflammatory molecules were most densely concentrated in mice.

"Our collaboration with the UT-Houston group allowed us to make an important translational linkage between using a mouse model and validating our model by seeing interleukin-6 in human sporadic aortic dissections," Brasier said. "I think this kind of team-oriented collaboration is a model to make significant clinically relevant discoveries in the future."

Source: University of Texas Medical Branch at Galveston

Citation: Researchers find inflammation critical in aortic dissection (2009, November 16) retrieved 30 April 2024 from https://medicalxpress.com/news/2009-11-inflammation-critical-aortic.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.