Study in Circulation provides detail on how low blood flow promotes vascular disease

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Better understanding of signaling pathway to lead to new therapies
Researchers have found the first direct proof that a key protein drives the clogging of arteries in two ways, and that lowering levels of it opens them up, according to study results published in the June edition of the journal *Circulation*. The work establishes cyclophilin A as an exciting target in the design of drugs against atherosclerosis, the number one cause of heart attacks and strokes, which occur when vessels become completely blocked. While the study was in mice, higher levels of the study protein have also been found in the blood of human patients with diseased blood vessels.

The current results build on three major discoveries in cardiovascular science in the last 20 years. The first is that fast blood flow, as it moves along the straight portions of blood vessel walls, creates frictional force that protects those areas against atherosclerosis. At the points where one vessel branches into two, however, blood flow is slowed, frictional force lessened and atherosclerotic plaques more likely to form. Among the consequences of low flow is the creation of highly reactive molecules called reactive oxygen species, which oxidize molecules they encounter and impair vascular function.

The second discovery was that the reaction of the body's immune system to fatty build-up in arteries is as great a contributor to heart attack risk as the fatty build-up itself. Vessel walls mistake fatty deposits for intruders, akin to bacteria, and call in white blood cells to prevent infection. The same cells, unfortunately, also cause inflammation that contributes to

clogs and generate more reactive oxygen species.

In the third discovery, researchers realized that blood vessels to do not just stand by as fatty deposits build up, but instead fight to stay open by aggressively growing (remodeling). Once they reach their growth limit however, the same growth that kept vessels open for so long begins contributing to the clogs by thickening vessel walls. The current study unites the three discoveries by providing strong evidence that cyclophilin A, a protein involved in the immune response, has dual roles in vascular disease. It recruits immune cells that cause inflammation, and it drives pathogenic growth and remodeling, when triggered by reactive oxygen species in diseased blood vessels.

"For years researchers worldwide have sought to determine exactly how low blood flow and the immune reaction to cholesterol deposits, along with the reactive oxygen species created by both, drive the progression of atherosclerosis," said Bradford C. Berk, M.D., Ph.D., professor of Medicine in the Aab Cardiovascular Research Institute within the University of Rochester Medical Center, and senior author of the study. "We are tremendously excited by these results because they provide solid evidence that cyclophilin A is at the center of it all."

Study Details

The study results reflect blood vessel anatomy. Blood flows through the innermost part of a vessel called the lumen. The inside of that inner tube is lined with a layer of endothelial cells, which is surrounded by the fibrous cells of the intima, which is surrounded by a layer of smooth muscle cells in the media. Many blood vessels are muscular because the flexing of such muscle helps to control blood flow (blood pressure).

To examine the reaction of CyPA signaling to the overproduction of reactive oxygen species, Berk's team genetically engineered one group of

mice to produce less CyPA, another group to make more, and compared both groups to "normal" mice as all three groups experienced reduced blood flow in the carotid artery. Reduced blood flow increased CyPA expression in the vascular wall, and promoted the migration of smooth muscle cells into the intima, where they began to grow (proliferate) and contribute to the formation of atherosclerotic lesions. Reduced flow, and the related increase in CyPA signaling, also caused the accumulation of inflammatory cells, an important component in the disease-related thickening of vessel walls. The effects were pronounced in the mice with extra capacity for CyPA production, and lessened in those with less CyPA.

Specifically, the current study demonstrated for the first time in a live animal that cyclophilin A (CyPA) is secreted specifically by smooth muscle cells in response to the production of reactive oxygen species with several consequences. First, CyPA signals for the production of pro-inflammatory molecules like E-selectin and vascular cell adhesion molecule 1 (VCAM-1), both of which call in immune cells circulating in the blood to the site of a cholesterol deposit in blood vessel wall and enable them to stick to it. This represents a first step in the inflammatory component of plaque formation.

The team also showed CyPA stimulates important pathways (e.g. the ERK1/2 and JAK/STAT) that drive smooth muscle cells to divide and grow. Furthermore, CyPA may activate matrix metalloproteinases, enzymes that break down the barrier that usually keeps smooth muscle cells out of the intima, the site of their disease-related proliferation.

Source: University of Rochester Medical Center

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