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Friend or foe? How the body's clot-busting system speeds up atherosclerosis

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Sometimes it's hard to tell friends from foes, biologically speaking. Naturally produced in the body, urokinase plasminogen activator and plasminogen interact to break up blood clots and recruit clean-up cells to clear away debris related to inflammation. In fact, urokinase manufactured as a drug effectively clears clogged arteries by generating clot-busting plasmin from blood-derived plasminogen.

However, despite the efficacy of urokinase and plasmin in clearing blood clots, evidence has shown that humans with a high baseline level of blood plasmin are at increased risk for heart attacks and for fast-developing forms of atherosclerosis. In addition, human arteries affected by atherosclerosis have an abundance of urokinase. These associations between plasmin, urokinase and increased atherosclerosis counter the notion that urokinase and plasmin protect against heart attacks by removing dangerous blood clots.

At first vascular biologists didn't know how to interpret these findings. Specifically, they wondered whether the high level of urokinase in atherosclerotic artery walls was contributing to atherosclerosis or was evidence of the body's efforts to fight it.

To try to resolve this puzzle, Dr. David A. Dichek, the John Locke Jr. Family Endowed Professor of Cardiology and associate director for research in the Division of Cardiology at the University of Washington (UW), and his team generated mice that were genetically engineered to produce more urokinase in their artery walls. These mice developed

arteries with worse atherosclerosis, including thicker walls, narrower interiors, and limited blood flow. The mice died suddenly with clogged arteries and evidence of heart attacks.

Dichek noted other reasons why his team expected that increased activity of the urokinase/plasminogen system would promote atherosclerosis, including the roles of urokinase and plasminogen in inflammation and cell migration.

"However, despite much work," he said, citing other studies that seemed to predict a different outcome, "a coherent picture of the role of the urokinase/plasminogen system in the development of atherosclerosis has not yet emerged. We need to understand the molecular mechanisms that underlie clinically established relationships between urokinase production, activation of plasminogen, and the progression of atherosclerosis."

Discovering such molecular mechanisms might point to new ideas for treating or preventing atherosclerosis, which remains a leading cause of premature death from heart attacks, strokes, and aneurysms. In addition to his laboratory research on the molecular biology of atherosclerosis, Dichek is a general cardiologist at the UW Heart Center, where his clinical interests include heart disease prevention and chronic coronary artery disease treatment.

In recently published research, Dichek and his team bred transgenic mice that were deficient in Apolipoprotein E (and therefore had high cholesterol and triglyceride readings) and whose macrophages—the blood cells that engulf and digest germs and other cellular debris—overproduced urokinase. They also bred mice that didn't produce plasminogen because their genes for plasminogen were "knocked out."

"The transgenic and gene-knock out mice provided a useful experimental setting for investigating the mechanisms that explain the clinical correlations between urokinase-type plasminogen activator, plasminogen activation, and human vascular disease," the researchers wrote.

Their findings appear in the Oct. 29 Early Edition of the Proceedings of the National Academy of Sciences. The researchers found that the urokinase-type plasminogen activator produced by macrophages speeds up the growth of atherosclerotic plaques and promotes dilation of the root of the aorta, one of the heart's major blood vessels. The presence and activation of plasminogen were required for the biochemical pathways that converged to make already diseased blood vessels worse.

"These pathways appeared to affect [atherosclerotic] lesion progression rather than initiation," the authors noted, "and included actions that disproportionately increased lipid accumulation in the artery wall." The researchers found that, because these disease pathways depend on plasminogen, loss of plasminogen protected against atherosclerosis both with normal levels of urokinase and in the genetically engineered mice with increased urokinase.

Source: University of Washington