Inhibiting fatty acids in immune cells decreases atherosclerosis risk

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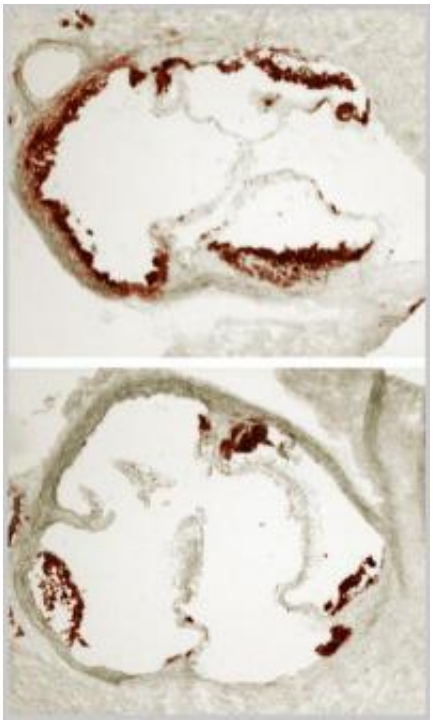

Early areas of atherosclerosis (seen using a red stain that identifies fat) line the artery walls of a mouse fed a high-fat diet (top image), while much less disease is seen in a mouse fed a high-fat diet but unable to make fatty acid synthase in macrophages (bottom image). Credit: Washington University School of Medicine

Scientists at Washington University School of Medicine in St. Louis have found a way to significantly reduce atherosclerosis in mice that does not involve lowering cholesterol levels or eliminating other obesity-

related problems.

They report their findings in the July 23 issue of the Journal of Biological Chemistry.

Atherosclerosis is the process through which fatty substances, such as cholesterol and cellular waste products accumulate in the lining of arteries. Those buildups, called plaques, reduce blood flow through the artery and can contribute to heart attack, stroke and even gangrene. It is common in individuals with obesity-related problems such as high blood pressure, high cholesterol and diabetes.

In this study, the research team inhibited atherosclerosis in mice by interfering with production of a substance called fatty acid synthase. This enzyme converts dietary sugars into fatty acids in the liver, where it plays an important role in energy metabolism. But fatty acids also are involved in atherosclerosis.

"The plaques that clog arteries contain large amounts of fatty acids," says senior investigator Clay F. Semenkovich, MD. "We engineered mice that are unable to make fatty acid synthase in one of the major cell types that contribute to plaque formation. On a standard Western diet high in fat, the mice had less atherosclerosis than their normal littermates."

Animals can't survive without fatty acid synthase, so mice in this study were able to make the substance in most of their tissues. They couldn't manufacture it, however, in macrophages, a type of white blood cell that surrounds and kills invading microorganisms, removes dead cells from the body and stimulates the action of other immune cells. Macrophages are dispatched in response to injury, infection and inflammation.

Atherosclerosis is the most common cause of heart disease, which is the leading cause of death in the United States. Semenkovich, the Herbert S.

Gasser Professor and chief of the Division of Endocrinology, Metabolism and Lipid Research, says doctors tend to concentrate on treating the surrounding risk factors related to atherosclerosis, such as diabetes and high blood pressure, but he says the blockages themselves cause the most serious, life-threatening problems.

"With the current epidemic of obesity and diabetes, people sometimes forget that it's the blockages in the arteries that really kill people," he says. "We've made progress using statin drugs, for example, that lower cholesterol and fight plaque buildup, but a lot of people who take statins still die from cardiovascular disease. We need better therapies."

These mouse experiments suggest targeting fatty acid synthase in macrophages may provide a potential treatment strategy for humans. The researchers identified factors in the fatty acid pathway that seem to be capable of preventing plaques from blocking arteries in mice. He says those substances - LXR-alpha and ABCA1 - eventually may become drug targets.

"It may be possible, for example, to take macrophages out of humans, inhibit fatty acid synthase in those cells, and then infuse the macrophages back into the same person," he says. "From what we've observed in mice, we would hypothesize that approach might prevent or interfere with plaque buildup in people."

Inhibiting fatty acid synthase in macrophages may not keep blood vessels clean forever, according to Semenkovich, but he says it could lower the risk of heart attacks and strokes while people are making lifestyle changes in order to lose weight, gain control of blood sugar levels or lower triglycerides and cholesterol.

"This discovery allows us to separate atherosclerosis from associated conditions such as diabetes and high cholesterol," he says. "In fact, in the

mice without fatty acid synthase in their macrophage cells, there were no effects on diabetes. Cholesterol in the blood remained the same. But there were fewer blockages in arteries. If a similar approach worked for humans, it could help prevent heart attacks and strokes and give people a chance to get healthier by losing weight and lowering cholesterol."

More information: Schneider JG, Yang Z, Chakravarthy MV, Lodhi IJ, Wei X, Turk J, Semekovich CF. Macrophage fatty acid synthase deficiency decreases diet-induced atherosclerosis. Journal of Biological Chemistry, July 23, 2010. Online at www.jbc.org/cgi/doi/10.1074/jbc.M110.100321

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