Source of protection against saturated fat found

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A new report in the December *Cell Metabolism* identifies a protein without which diets high in saturated fat lead to a massive inflammatory response that can prove fatal. The studies in mice suggest that deficiencies in this protective pathway could promote inflammation in those who regularly consume high levels of saturated fat.

"In mice without this protein that ate a lot of saturated fat, the lymph nodes blew up to extreme levels," said Sander Kersten of the Nutrigenomics Consortium and Wageningen University in the Netherlands. "I'd never seen anything like it before."

Kersten said that a connection between saturated fat, inflammation, and chronic diseases, including cardiovascular disease and diabetes, has long been recognized. But it really hadn't been clear why saturated fats can cause harm.

Normally, dietary fats are broken down into fatty acids. Those fatty acids are incorporated in small particles called chylomicrons and released into the circulation after passing through the lymphatic system of the intestine. Those circulating fats are later broken down by an enzyme (called lipoprotein lipase or LPL) to feed tissues such as the heart and skeletal muscle that depend on fatty acids for fuel. But LPL is also found at high levels in immune cells called macrophages, whose job it is to gobble up invaders or foreign particles.

Earlier studies had shown that LPL activity depends on a protein called

Angiopoietin-like protein 4 (Angptl4). In the new study, the researchers wanted to find out what happens in mice lacking Angptl4 when they are fed a diet high in fat.

Mice deficient for the protein showed a severe immune reaction and ultimately died. Those abnormalities occurred only when the animals were fed saturated fats, not unsaturated or medium-chain fats, the researchers report. Lymph nodes associated with the intestine expanded dramatically as the macrophages within them filled up with lipids.

"Normally, this should not be the case," Kersten said, as those immune cells are designed to protect the body against bacteria or other foreign invaders.

When macrophages were incubated in the lab with a milky fluid containing lymph and fatty acids, Angptl4 showed reduced formation of lipid-laden foam cells, lower expression of inflammatory genes, and of a form of cellular stress.

The data show that Angptl4 is a key player in the protection against the severe proinflammatory effects of dietary saturated fat, the researchers conclude.

The findings may have implications for the approximately three percent of the human population who carry a mutation in the Angptl4 gene. "Based on our data in mice, it can be hypothesized that human subjects homozygous for the E40K mutation in Angptl4, which has reduced ability to inhibit LPL and is associated with lower plasma triglycerides, may be particularly sensitive to the proinflammatory effects of dietary saturated fat," the researchers wrote.

Kersten also speculates that Western diets loaded in saturated fats could perhaps overwhelm the system, particularly if it is "not working

perfectly." The findings point more generally to an underappreciated role for the intestinal lymphatic system in managing the response to high concentrations of dietary fats.

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