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Scientists identify target that may reduce complications of obesity

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Although obesity is a risk factor for diabetes and coronary heart disease worldwide, only some obese individuals go on to develop these metabolic complications, while others are relatively protected. Defining these protective factors could help scientists prevent disease in the wider population.

To this end, a research team at the Gladstone Institute of Cardiovascular Disease, led by Suneil Koliwad, MD, PhD, recently added new details that link obesity to diabetes and heart disease.

When individuals become obese from overeating, cells called adipocytes located in the fat tissue fill up with dietary fats and begin to die. Immune cells called macrophages move out of the blood stream and into this tissue, where they accumulate around dying adipocytes. As the macrophages work to clear away the dead cells, they are exposed to large amounts of dietary fat that can result in unwanted consequences. Exposure to saturated fats, in particular, causes the macrophages to enter an inflammatory state. In this state, the macrophages secrete cytokines, such as tumor necrosis factor (TNF) alpha, that encourage the development of insulin resistance, diabetes, and heart disease.

The Gladstone team hypothesized that enhancing the capacity of macrophages to store dietary fats might alter this process. To do this, they focused on an enzyme called DGAT1, which makes triglycerides from dietary fats for storage as cellular energy reserves.

They examined a transgenic strain of mice (aP2-Dgat1) that make large amounts of DGAT1 in both adipocytes and macrophages. On a high-fat diet, these mice became obese, but the macrophages in their fat tissue did not undergo inflammatory activation, and the mice were protected from developing systemic inflammation, insulin resistance, and fatty livers, all problems that were profound in the control mice.

Even more interesting was the team's finding that the protection against diet-induced inflammation and insulin resistance could be conferred on normal mice simply by replacing their macrophages with those from aP2-Dgat1 mice by bone marrow transplantation.

"We found in experimental mice that a single enzyme, DGAT1, in macrophages is involved in many of the problems associated with obesity," said Dr. Koliwad. "This is exciting because humans have this enzyme as well, providing the potential for a therapeutic target to examine."

Using cultured cells, the team also showed that increasing the amount of DGAT1 expressed by macrophages increased their capacity to store triglycerides and protected them against inflammatory activation by saturated fats. Moreover, DGAT1 expression was increased by treatment of macrophages with PPARgamma agonists, which are widely used agents to treat diabetes, and DGAT1 was required for these agents to protect macrophages against inflammatory activation induced by saturated fats.

"Our results are very exciting," said Dr. Robert Farese, senior author on the study. "We have used DGAT1 as a tool to uncover a mechanism by which macrophages might protect individuals from developing serious consequences of obesity."

More information: Koliwad SK, Streeper RS, Monetti M, Cornelissen

I, Chan L, Terayama K, Naylot S, Rao M, Hubbard B, Farese RV, Jr. Increased capacity for triacylglycerol synthesis in macrophages protects mice from deleterious consequences of diet-induced obesity. J. Clin. Invest., In press.

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