Protective gene in fat cells may lead to therapeutic for Type 2 diabetes

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In a finding that may challenge popular notions of body fat and health, researchers at Beth Israel Deaconess Medical Center (BIDMC) have shown how fat cells can protect the body against diabetes. The results may lead to a new therapeutic strategy for preventing and treating type 2 diabetes and obesity-related metabolic diseases, the authors say.

In the last decade, several research groups have shown that fat cells in people play a major role in controlling healthy blood sugar and insulin levels throughout the body. To do this crucial job, fat cells need a small portion of the sugars derived from food. Obesity often reduces the dedicated sugar transport molecules on fat cells, blocking the glucose from entering fat cells. As a result, the whole body becomes insulin resistant, and blood sugar rises, leading to diabetes.

The new study shows why glucose is so important to fat cells. The team discovered a new version of a gene inside fat cells that responds to sugar with a powerful systemic effect.

"If we change that one gene, that makes the animal more prone to or more protected from diabetes," said senior author Barbara Kahn MD, the George R. Minot Professor of Medicine at Harvard Medical School and Vice Chair of the Department of Medicine at BIDMC. "Many foods get converted into sugar, so there is no need to eat more sugar."

The paper is published online April 1 in the journal *Nature*. In the study, the BIDMC researchers pinpointed the fat gene and its effect in mouse

models of human obesity and insulin resistance and reported supporting evidence from fat tissue samples from both lean and obese people.

"Two things were surprising – first, that a lone gene could shift the metabolism of the fat cell so dramatically and then, that turning on this master switch selectively in adipose tissue is beneficial to the whole body," Kahn said. Twelve years ago, Kahn first demonstrated that fat cells are a master regulator of healthy levels of glucose and insulin in mice and require sugar to do the job.

"The general concept of fat as all bad is not true," said first author Mark Herman MD, an investigator in the Division of Endocrinology, Diabetes and Metabolism at BIDMC and Instructor of Medicine at Harvard Medical School (HMS). "Obesity is commonly associated with metabolic dysfunction that puts people at higher risk for diabetes, stroke and heart disease, but there is a large percentage of obese people who are metabolically healthy. We started with a mouse model that disassociates obesity from its adverse effects."

In the latest study, evidence suggests the newfound gene also may account for the protective effect of glucose uptake in human fat. German collaborators found more gene activity in people with greater insulin sensitivity, based on 123 adipose tissue samples from non-diabetic, glucose tolerant people. The fat gene activity also correlated highly with insulin sensitivity in obese, non-diabetic people, as measured in 38 fat samples by another pair of co-authors based in St. Louis.

"It's a really exciting finding," said Ulf Smith MD PhD, a professor at University of Gothenburg, Sweden, and president of the European Association for the Study of Diabetes. He was not involved in this study. "We've been looking for the mechanism to try to understand why glucose metabolism in adipose tissue is so important for whole-body sensitivity to insulin." Eight years ago, Smith extended Kahn's original

findings to people and also showed that fat cells that begin to have trouble taking in sugar can be an early indicator of diabetes. In healthy people, fat cells normally need about 10 percent of the sugars derived from food, he said.

In fat cells, the newfound gene acts as a glucose sensor that converts the sugars into fatty acids, which may play a role in the powerful systemic effect. In response to rising glucose levels, the gene makes a more active version of itself. The active version turns on the cellular machinery that disassembles the sugar molecules and remakes them into fatty acids. The novel version of this gene is called carbohydrate-responsive-element-binding protein-beta, or ChREBP-beta for short.

In the liver, where the original gene was discovered by other scientists, the same fatty acid synthesis process is harmful. There, the transformation of glucose into fatty acids raises triglycerides in the blood and leads to nonalcoholic fatty liver disease.

The mice in the latest study were first developed in Kahn's lab two decades ago to model a surprising feature of human obesity. The number of glucose transporters (GLUT4) drops with obesity – but only on fat cells – and it happens early in the development of diabetes. (GLUT4 is also found on muscle and heart cells.) Kahn generated mice with genetic alterations in the amount of GLUT4 in fat cells, seeking clues to the link between obesity and diabetes.

One set of mice features 5 to 10 times the usual number of glucose transporters in its fat cells. These mice are obese but exhibit none of the diseases usually associated with obesity. Another set of mice is missing the glucose transporters on their fat cells, which causes diabetes symptoms despite the fact that these mice have normal body weight.

"There's something very special about GLUT4," Kahn said. "When you

wake up and haven't eaten all night, the GLUT4 transporters are inside the cell. Within minutes of eating and glucose reaching the blood and stimulating insulin secretion, the GLUT4 transporters move to the cell surface. It's reliable, fast, dynamic and critical to maintaining normal blood sugar after we eat."

Now, the Kahn team has identified how fat cells with GLUT4 can sense the change in glucose transport into the cell and respond by regulating insulin sensitivity in the entire body. The new study reveals a new, potent version of a gene that transforms glucose into fatty acids. "We definitely do not want to imply that people should eat more sugar," Kahn said.

In future research, the team will investigate whether the gene activity could be working directly through fatty acids or altering fat cells and the molecules they secrete in other ways. The BIDMC team is pursuing the fatty acid angle, in part because it seems to fly in the face of conventional wisdom.

The concept that some fatty acids might be beneficial is not new, but "until recently, it was thought that human adipose tissue was not capable of synthesizing many fatty acids," Herman said. In fact, beneficial fatty acids such as omega-3s from fish, and other fatty acids found in olive oil, are usually recommended as part of a healthy diet.

And the fatty acids humans do generate were not thought to be beneficial. "There is a mythology that elevated fatty acids in the blood are detrimental metabolically and generally signal insulin resistance in people," Kahn said. "Our study demonstrates that doesn't have to be the case. It raises the question of whether there are some special fatty acids being made as a result of upregulation of ChREBP."

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