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UCSD Team Discovers Diabetes Trigger in Fatty Diet

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A new study, published in the December 29 issue of the journal *Cell,* reports the discovery of a molecular link between a high-fat, or Western-style, diet, and the disruption of insulin production, explaining how a high-fat diet causes type 2 diabetes.

Researchers at the University of California, San Diego (UCSD) School of Medicine have found that a single gene encoding the enzyme GnT-4a glycosyltransferase (GnT-4a) is key to enabling the pancreatic beta cells to sense blood glucose levels and appropriately produce insulin. They have further demonstrated in mice that this enzyme is suppressed by a high-fat diet. Without enough GnT-4a enzyme, pancreatic beta cell failure occurs, resulting in type 2 diabetes.

While it is widely recognized that type 2 diabetes is directly linked to a high-fat diet and obesity, until now, researchers had not been able to pinpoint how and why.

"We have discovered a mechanistic explanation for beta cell failure in response to a high-fat diet and obesity, a molecular trigger which begins the chain of events leading from hyperglycemia to insulin resistance and type 2 diabetes," said Jamey Marth, Ph.D., UCSD Professor of Cellular and Molecular Medicine and Investigator with the Howard Hughes Medical Institute. "This finding suggests new approaches to the prevention and treatment of diabetes."

Marth, first author Kazuaki Ohtsubo, Ph.D., of the Howard Hughes Medical Institute and UCSD's Department of Cellular and Molecular Medicine, and their colleagues made the discovery by studying glycosylation. This is the process that controls the formation on proteins of sugar linkages called glycans, which are linked to proteins by a large family of related enzymes such as GnT-4a. The key role of the GnT-4a enzyme is to maintain glucose transporters in place on the surface of the beta cell. Pancreatic glucose transporters are necessary at the beta cell surface to sense glucose levels in the blood. When glucose is elevated after a meal, the transport of glucose by these transporters triggers the beta cell to secrete insulin. Proper insulin secretion is essential to enable the rest of the body to metabolize glucose and convert it to cellular energy.

Analyzing mice lacking the GnT-4a gene, the researchers found that these mice had elevated blood glucose concentrations. In mice, as in humans, a high level of sugar in the blood is the first measure and diagnosis of diabetes. The symptoms progressed as a result of beta cell failure to normally secrete insulin, and full blown type 2 diabetes developed.

The UCSD team then fed normal mice a high-fat diet, and found that GnT-4a gene expression was reduced. Insufficient GnT-4a expression caused the glucose transporter to leave the cell surface and become internalized. The resulting failure of the cell to sense and respond to blood glucose levels led to the development of type 2 diabetes in the mice.

"Our findings suggest that the current human epidemic in type 2 diabetes may be a result of GnT-4a enzyme deficiency," said Marth. "The GnT-4a enzyme is required to synthesize a glycan structure that holds the glucose

transporter in place at the beta cell surface. The loss of this key transporter is directly linked to reduced GnT-4a protein glycosylation, a high fat diet, and type 2 diabetes."

When scientists monitor the development of type 2 diabetes - whether in mice or in humans - the initiating trigger has increasingly been suspected to be the failure of pancreatic beta cell to appropriately secrete insulin. After a meal, the rise in blood glucose normally stimulates the pancreatic beta cells to secrete insulin; in minutes this results in increased glucose transport, metabolism and storage.

But in patients with diabetes, insufficient insulin levels occur early in the disease, resulting in hyperglycemia, or elevated blood glucose. Overcompensating, the beta cell produces too much insulin, and eventually the patient develops insulin resistance and full-blown type 2 diabetes.

More than 200 million people worldwide, close to 20 million of them Americans, have been diagnosed with type 2 diabetes. Especially alarming has been the upward spiral of this disease in children, and the link to childhood obesity.

"In fact, the likelihood that obesity will lead to diabetes is so common that this epidemic is sometimes referred to as 'diabesity'," said Marth.

Over the past few years, researchers observed that many genes were changing in response to a high-fat diet and that, in patients with type 2 diabetes, changes were occurring in the beta cell. Using a process called microarray analysis, they surveyed gene expression in the pancreatic cells of humans and mice in order to discover the reason for beta cell failure and the consequent dramatic rise in type 2 diabetes. With such a large number of potential gene candidates to sift through, it might have taken years to find the insulin trigger.

"We weren't expecting that beta cell failure would be solved by analyzing gene expression changes, nor were we focused on addressing this specific problem" said Marth, explaining that his laboratory developed the line of mice lacking the GnT-4a gene because of their interests in learning more about the function of protein glycosylation in the pancreas.

Marth and his colleagues believe that GnT-4a gene expression is regulated by certain transcription factors that may be altered by diet and silenced in type 2 diabetes. Ohtsubo and Marth have observed that some of these transcription factors are also the cause of another form of type 2 diabetes in humans, Mature Onset Diabetes of the Young (MODY). "It is possible that human MODY is due to the loss of GnT-4a expression." says Marth. 'In some forms of MODY including the most common (MODY-3), these transcription factors may not bind to the GnT-4a gene and thereby reduce GnT-4a enzyme levels."

Reduced GnT-4a expression may be caused by a high-fat diet, inheritance of a faulty GnT-4a gene, or as a result of transcriptional factor defects - all leading to type 2 diabetes due to beta cell failure. Approaches to elevating GnT-4a levels may bolster glucose transporter expression enough to preclude the development of type 2 diabetes, a possibility that UCSD researchers Marth and Ohtsubo are now testing.

High levels of insulin have also been implicated in contributing to other diseases such cancer, cardiovascular disease, and stroke. Inhibition of GnT-4a expression may be therapeutic in such cases by reducing the amount of insulin produced by the pancreatic beta cell.

Additional contributors to the paper are Shinji Takamatsu, Biomedical Imaging Research Center, University of Fukui, Japan; and Mari T. Minowa, Aruto Yoshida and Makoto Takeuchi, Central Laboratories for Key Technology, Kirin Brewery Co. Ltd, Japan.

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