Researchers Discover Mechanistic Link Between High-Fat Diet and Type 2 Diabetes

Howard Hughes Medical Institute researchers have discovered a molecular link between a high-fat, Western-style diet, and the onset of type 2 diabetes. In studies in mice, the scientists showed that a high-fat diet interferes with a genetic mechanism they discovered that promotes insulin production, resulting in the classic signs of type 2 diabetes.

In an article published in the December 29, 2005, issue of the journal *Cell*, the researchers report that knocking out a single gene encoding the enzyme GnT-4α glycosyltransferase (GnT-4α) disrupts insulin production. Importantly, the scientists showed that a high-fat diet suppresses the activity of GnT-4α and leads to type 2 diabetes due to failure of the pancreatic beta cells.

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-- Jamey D. Marth

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, a Howard Hughes Medical Institute investigator at the University of California, San Diego (UCSD). Marth and first author Kazuaki Ohtsubo at UCSD collaborated on the studies with researchers from the Kirin Brewery Co. Ltd., and the University of Fukui, both in Japan.

The discovery of the link between diet and insulin production offers new information that may aid in the development of treatments that target the early stages of type 2 diabetes. In its earliest phases, the disease causes failure...
of insulin-secreting beta cells in the pancreas, which leads to elevated blood glucose levels. As the disease progresses, the insulin-secreting beta cells overcompensate for the elevated blood glucose, and eventually pump out too much insulin. This leads to insulin resistance and full-blown type 2 diabetes.

Worldwide, more than 200 million people have type 2 diabetes, and close to 20 million people in the United States have been diagnosed with the disorder. The new studies suggest that people with an inherited predisposition to type 2 diabetes might have variations in the gene for GnT-4a, said the researchers.

Marth and his colleagues began their studies hoping to learn more about the function of protein glycosylation in the pancreas. They focused on the function of GnT-4a, in part, because it is highly expressed in the pancreas. GnT-4a is a type of enzyme known as a glycosyltransferase that attaches sugar-like molecules called glycans to proteins in a process called glycosylation. Glycans are essential for the proper function of many proteins.

GnT-4a was found to maintain glucose transporters on the surface of beta cells in the pancreas. Those transporters, such as Glut-2, play a crucial role in allowing the beta cell to sense how much glucose is in the blood. Transport of glucose across the cell membrane into pancreatic beta cells triggers insulin secretion.

The new studies showed that in the absence of sufficient GnT-4a enzyme, Glut-2 lacks an attached glycan that is required for it to be expressed at the cell membrane. Without that glycan, Glut-2 leaves the cell surface and becomes internalized, where it can no longer transport glucose into the cell. In turn, this failure impairs insulin secretion, causing type 2 diabetes in the mice.

What was really astounding to us, however, was that when we fed normal mice a high-fat diet, we saw this same mechanism of pathogenesis with attenuation of GnT-4a RNA levels, reduced Glut-2 glycosylation, and loss of cell surface Glut-2 expression, said Marth. This finding may explain the loss of Glut-2 commonly observed in type 2 diabetes. In addition, transcriptional control of GnT-4a expression may underlie the pathogenesis of type 2 diabetes in human mature onset diabetes of the young (MODY), and perhaps in response to leptin signaling deficiency in db mice.

In addition, variations in susceptibility to type 2 diabetes may result from inherited differences in the gene for GnT-4a that may ultimately affect its level or activity. These findings could have important clinical implications because reduced GnT-4a expression has been observed by other researchers in tissue samples from humans with diabetes. If you could somehow stimulate production of this enzyme, you might be able to render animals, and perhaps humans, resistant to high-fat diet-induced diabetes, said Marth.

To explore such possible clinical applications, Marth and his colleagues are now testing whether over-expression of the GnT-4a gene in transgenic mice makes them resistant to diabetes induced by a high-fat diet or by transcriptional factor mutations that cause MODY.
If our findings can be applied to humans, they should give us important insights into how type 2 diabetes may be prevented and treated, he said.

While a deficiency of insulin can cause diabetes, too much insulin can also be harmful, and has been found to contribute to the pathogenesis of cancer, cardiovascular disease, ovarian diseases, and Alzheimer's disease. It may be that suppressing insulin production to some degree could be beneficial in such disorders, and that could theoretically be achieved by inhibiting the GnT-4a glycosyltransferase, Marth said.