Unearthing a path leading to diabetes

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A molecular mechanism that links diet, obesity and diabetes involves depletion of specialized ‘transporter proteins’, a Japanese–American team has found. Transporter proteins deliver glucose to so-called ‘beta cells’ of the pancreas, which produce the hormone insulin to help the body regulate its sugar levels. The work opens the way to new treatments for diabetes since ensuring sufficient numbers of glucose transporter (Glut) proteins on their outer surface could improve beta cell function.

In both humans and animals, there is a widespread and accepted connection between high-fat diets, obesity and susceptibility to type 2 (or adult onset) diabetes (Fig. 1). Until now, however, the causal links were not clear, particularly at a molecular level, explains team member Kazuaki Ohtsubo from the RIKEN Advanced Science Institute in Wako, Japan.

A hallmark of the condition is a drop in the effectiveness of insulin in lowering blood sugar levels, known as insulin resistance. Previous work by other researchers had determined that type 2 diabetes is accompanied by a loss of sensitivity of beta cells to increasing glucose levels. Rising levels of glucose normally trigger secretion of insulin and are detected by greater amounts of sugar moving into beta cells. A decrease in Glut proteins, hence a lower capacity for glucose transport, could therefore explain defective insulin secretion. Interestingly, mice that lack the enzyme GnT-4a, which catalyzes the linkage of Glut proteins to the cell surface, develop type 2 diabetes. In earlier work, Ohtsubo also showed that a high-fat diet can induce a deficiency of GnT-4a.

To investigate these earlier findings in detail, Ohtsubo and his colleagues from the University of California, USA, investigated the sequence of molecular events in pancreatic beta cells of mice and humans. They found that high levels of fatty acids led to nuclear exclusion of the proteins that facilitate transcription of the genes for GnT-4a and Glut. The resulting deficiency of the GnT-4a enzyme led to many of the symptoms of diabetes. This could be alleviated in mice by adding the human gene for GnT-4a. The researchers also observed that the molecular pathways activated in the mice that developed type 2 diabetes were similar to those that were active in human type 2 diabetes.

“We are already searching for small chemical compounds which activate the expression of GnT-4a in pancreatic beta cells under high-free fatty acids conditions,” says Ohtsubo. “These compounds could improve beta

cell function and should be good candidates for new types of drugs for diabetes."

More information: Ohtsubo, K., et al. Pathway to diabetes through attenuation of pancreatic beta cell glycosylation and glucose transport. Nature Medicine 17, 1067–1075 (2011).

Ohtsubo, K., et al. Dietary and genetic control of glucose transporter 2 glycosylation promotes insulin secretion in suppressing diabetes. Cell 123, 1307–1321 (2005).

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