Single enzyme is necessary for development of diabetes

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An enzyme called 12-LO promotes the obesity-induced oxidative stress in the pancreatic cells that leads to pre-diabetes, and diabetes. 12-LO's enzymatic action is the last step in the production of certain small molecules that harm the cell, according to a team from Indiana University School of Medicine, Indianapolis. The findings will enable the development of drugs that can interfere with this enzyme, preventing or even reversing diabetes. The research is published ahead of print in the journal *Molecular and Cellular Biology*.

Nearly 40 percent of Americans—more than 120 million people—have diabetes or pre-diabetes. Diabetes results when the pancreas fails to produce sufficient insulin to remove sugar from the blood.

"We surmised that when individuals eat high fat foods and become overweight, the beta cells of their pancreases fail to produce sufficient insulin," says principal investigator Raghavendra Mirmira. In earlier studies, these researchers and their collaborators at Eastern Virginia Medical School showed that 12-LO (which stands for 12-lipoxygenase) is present in these cells only in people who become overweight.

The harmful small molecules resulting from 12-LO's enzymatic action are known as HETEs, short for hydroxyeicosatetraenoic acid. HETEs harm the mitochondria, which then fail to produce sufficient energy to enable the pancreatic cells to manufacture the necessary quantities of insulin.

For the study, the investigators genetically engineered mice that lacked the gene for 12-LO exclusively in their pancreas cells. Mice were either fed a low-fat or high-fat diet.

Both the control mice and the knockout mice on the high fat diet developed obesity and insulin resistance. The investigators also examined the pancreatic beta cells of both knockout and control mice, using both microscopic studies and molecular analysis. Those from the knockout mice were intact and healthy, while those from the control mice showed oxidative damage, demonstrating that 12-LO and the resulting HETEs caused the beta cell failure.

Mirmira notes that fatty diet used in the study was the Western Diet, which comprises mostly saturated—"bad"—fats. Based partly on a recent study of related metabolic pathways, he says that the unsaturated and mono-unsaturated fats—which comprise most fats in the healthy, relatively high fat Mediterranean diet—are unlikely to have the same effects.

"Our research is the first to show that 12-LO in the beta cell is the culprit in the development of pre-diabetes, following high fat diets," says Mirmira. "Our work also lends important credence to the notion that the beta cell is the primary defective cell in virtually all forms of diabetes and pre-diabetes."

More information: The manuscript can be found online at mcb.asm.org/content/early/2014 … 157-14.full.pdf+html . The final version of the article is scheduled for the October 2014 issue of *Molecular and Cellular Biology*.

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