MicroRNA derails protein that blocks insulin production

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Diabetes, a disease affecting nearly 26 million Americans, results when insulin fails to ferry glucose into cells, causing sugar to accumulate in the blood. Xiaoqing Tang has shed light on the insulin production process.

(Medical Xpress)—Work by Michigan Technological University biologist Xiaoqing Tang is yielding new insights into how a tiny snippet of genetic material can promote healthy insulin production in mice.

Her work may eventually lead to new therapies for the treatment of

diabetes, a disease that affects nearly 26 million Americans and causes myriad health problems, including heart disease, kidney failure and stroke. Diabetes results when the pancreas does not produce or release enough insulin into the blood stream or when cells fail to respond to the hormone.

The genetic material in question is a microRNA molecule called miR-30d, which is the same in mice and people. MicroRNA, or miRNA, attaches to long RNA molecules and prevents them from making proteins.

Proteins are the building blocks of life, but they can also cause serious problems; think of the plaques that develop in the brains of Alzheimer's patients.

One such protein is a tumor necrosis factor, which is involved in cell death and can trigger the production of another problematic protein, called MAP4K4, which blocks the formation of insulin when cells are under adverse conditions. MAP4K4 throws a wrench into the works by interfering with production of an important protein named MafA that binds to DNA and is an essential part of the insulin-making pathway.

In a series of experiments, Tang and her research team showed how miR-30d can counteract the tumor necrosis factor–triggered production of MAP4K4 and help the pancreas make more insulin.

First, they compared pancreas cells from diabetic mice with those of wild mice and found that the diabetic cells have much less miR-30d.

Second, using genes they created in their lab, they made cells that produce extra amounts of miR-30d. Those cells doubled the amount of the good protein MafA and generated much more insulin, showing that miR-30d works at least in part by activating MafA in the pancreas.

Finally, they added the tumor necrosis factor to those cells with the extra miR-30d. Unlike regular cells, which had MafA production blocked by the tumor necrosis factor, the super cells managed to keep on producing MafA, though not as much as before.

"What we found with miR-30d is that it can increase cells' ability to make insulin by activating MafA," Tang said. "We've also shown that the tumor necrosis factor–triggered MAP4K4 is a direct target of miR-30d. Based on our data, we think miR-30d probably plays multiple roles, both in enhancing insulin production and in protecting cells from the inflammatory effects of tumor necrosis factor."

Their latest research was published online Sept. 7 in *The Journal of Biological Chemistry*. The article, "MicroRNA-30d Induces Insulin Transcription Factor MafA and Insulin Production by Targeting Mitogen-Activated Protein 4 Kinase 4 in Pancreatic Beta Cells," was authored by Tang, Xiaomin Zhao and Ramkumar Mohan of Michigan Tech; and Sabire Ozcan of the University of Kentucky.

Tang is now studying transgenic mice that generate extra amounts of miR-30d. "We want to induce diabetes and see if the process slows down in the transgenic mice," she said. "If that happened, it would be great."

The study is in its early stages, but preliminary results are intriguing. The transgenic mice are smaller and leaner than wild mice. Yet they don't seem to have extra insulin in their blood.

"We still don't understand why insulin is low in the blood of the transgenic mice." she said. "It may mean that insulin gets into cells from the blood very quickly. Or, the beta cells in the pancreas may sense that they don't need to produce much insulin. Or maybe it's another process all together. A mouse is much more complicated than a cell line."