Scientists make insulin-producing cells self-replicate

April 29 2013

(Medical Xpress)—Scientists have discovered a hormone that causes the body's insulin-producing factories, beta cells, to churn out more of themselves. Having enough insulin is critical to regulating the amount of sugar in the blood.

The hormone, a protein that the researchers named betatrophin, boosts beta cell division in mice 17-fold, without affecting the proliferation of other cell types. The discovery may pave the way for a new therapy for diabetes—in particular type 2 diabetes, which is characterized by a gradual failure or loss of beta cells.

"There's a real chance that this hormone could be used to treat diabetics," says study author Howard Hughes Medical Institute (HHMI) Investigator Douglas Melton, who is at Harvard University. His team's results, based on studies in mice, were published online in the journal *Cell* on April 25, 2013.

The hope is that using betatrophin to stimulate production of beta cells may one day be an improvement over today's standard therapies—anti-diabetes drugs or multiple daily injections of insulin—which Melton says do not control blood sugar as well as functional beta cells.

Pancreatic beta cells divide sluggishly, and their slow turnover makes them a precious commodity in the body. Their loss or failure in diabetes affects 171 million people worldwide.

For more than 10 years, Melton has been leading an effort to turn stem cells into beta cells as a potential treatment. While most of his lab members have worked to repurpose embryonic and induced pluripotent stem cells into beta cells, one postdoctoral fellow in his lab, Peng Yi, wanted to study how beta cell mass is regulated normally.

Yi created a new mouse model of diabetes by giving healthy mice a peptide drug (S961) that blocks their insulin receptors—most of which are found in the liver, skeletal muscle, and brain. With no functioning receptors, even if beta cells produce insulin, the hormone has no effect.

"We had this simple idea: if you provide S961 to a mouse, the animal is either going to make more insulin from its existing beta cells or it's going to make more beta cells," Melton says. A 2000 study from another team at Harvard Medical School, including HHMI investigator Gerald Shulman at Yale, provided some hints, showing that genetically inhibiting insulin receptors in the liver caused pancreatic beta cells to proliferate, presumably to compensate for the inhibition.

Indeed, Yi found that injecting S961 into the mice caused their beta cells to divide by an unprecedented 12-fold. The effect went away shortly after researchers stopped administering the drug. When the group tried adding S961 to beta cells in a dish, however, the drug had no effect, suggesting that the drug acts indirectly to make beta cells divide in the body.

The scientists then looked at gene expression in tissues known to be involved in metabolism—liver, white fat, and skeletal muscle—after giving S961 to mice. That's when they got lucky: only one gene was expressed more than usual in the liver and white fat: Gm6484. In humans, the gene (called C19orf80) is active mainly in the liver.

Melton's team found that expression of Gm6484 was also elevated in the

livers of mouse models of diabetes, and in healthy pregnant mice. Pregnancy prompts beta cells to divide to meet the growing food intake of the mom-to-be.

"Best of all, when we express the gene in the liver, its natural site of expression, it does quite an amazing thing," he says. "It boosts beta cell replication more than anything anyone has ever observed," says Melton. "It does so fast, and it does it specifically. The only cells in the body that divide are the beta cells."

These effects make the protein a promising potential therapy for type 2 diabetes, Melton says. Doctors might be able to give betatrophin to patients with diabetes periodically to increase beta cell production, bypassing the need for frequent insulin injections. However, the hormone needs further study to determine if it is safe and effective in humans, as well as whether it can be manufactured on a large scale, Melton says.

For individuals with type 1 diabetes, a disease in which the immune system destroys beta cells, the betatrophin's potential as a therapy is harder to predict, Melton says. "I can imagine using the hormone in new-onset patients to boost the number of beta cells they have left and couple that with an immunosuppressant," Melton says. "In mice that works quite well. But many things that work in mice don't work in humans," he cautions.

Melton's group is working to find betatrophin's receptor to understand its exact mechanism of action. "I'm 99 percent confident we'll get the receptor soon and then the interesting part would be [finding out] where the receptor is expressed," he says. It could be in other tissues besides the beta cells—for example, the hypothalamus, a part of the brain that receives signals related to blood sugar status and regulates hunger.

As his lab continues that work, Melton has partnered with Evotec and Janssen Pharmaceuticals to bring betatrophin to the clinic. "We're counting on our partners to make [the] soluble protein in large amounts for testing in animals and then humans," Melton says, adding that these first steps will take at least a year.

More information: Abstract: Developmental Biology and Regenerative Medicine of the Pancreas

Provided by Howard Hughes Medical Institute