Bariatric surgery successes lead to type 2 diabetes treatment

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Bethany Cummings, assistant professor of biomedical sciences at the College of Veterinary Medicine and senior author on the new paper in Cell Reports. Photo by the College of Veterinary Medicine. Credit: Cornell University

Bariatric surgery has long yielded almost immediate health benefits for patients with type 2 diabetes, and new findings on the reasons for remission may be the key to developing drug alternatives to surgery.

"One of the things that bariatric surgery does is cause type 2 diabetes remission," said Bethany Cummings, assistant professor of biomedical sciences at the College of Veterinary Medicine and senior author on the paper in *Cell Reports*. "This has given rise to a field dedicated to figuring out how exactly it does that."

There are several types of bariatric surgery, all of which reduce the size of the stomach in some way. Cummings' research focused on vertical sleeve gastrectomy, in which the stomach is reshaped into a tube. Her paper is the first of its kind to be tissue-specific and inducible, which means her lab's mouse model contains no genetic variables that could lead to errors in the results.

Type 2 diabetes develops due to two issues: islet dysfunction in the pancreas, and insulin resistance that's generally associated with obesity. Pancreatic islets produce important hormones for the body, including insulin. If they aren't functioning correctly, insulin can't move glucose out of the blood.

"The switch between pre-diabetic to diabetic comes down to the islet," said Darline Garibay, first author on the paper and a graduate student in Cummings' lab.

The islets comprise a delicate balance of alpha cells and beta cells. Alpha cells produce the hormone glucagon, which pushes glucose into the blood and promotes type 2 diabetes, and beta cells produce insulin, which pushes glucose out of the blood and protects against type 2 diabetes. When a pancreatic islet functions normally, it secretes both hormones into the blood stream. With type 2 diabetes, the islet functions

abnormally and is unable to push enough insulin out, so the blood stream becomes saturated with excess glucose and has nothing to balance it.

Beta cells get help producing insulin from the hormone glucagon-like peptide-1 (GLP-1), which is classically thought to be produced only in the gut, not the pancreas. Alpha cells typically make glucagon, but can make GLP-1 instead, though a way to control this important pathway is unknown.

Since GLP-1 numbers rise dramatically in the blood after bariatric surgery, Cummings' research group focused on GLP-1 receptor signaling in the improvements observed after surgery. Her investigation showed that bariatric surgery has a surprising effect: increasing the expression of GLP-1 in the alpha cell. They also found that the presence of a GLP-1 receptor in the beta cell increased the occurrence of the GLP-1 hormone in the alpha cell - essentially changing its identity from a cell that promotes diabetes to a cell that can fight diabetes. Cummings' lab thinks that this is a paracrine process, meaning there is an unknown factor secreted from the beta cell that signals locally to convince the alpha cell to stop producing glucagon and switch to making GLP-1 instead.

No dangerous amounts of glucose in the blood stream means no type 2 diabetes.

"Basically, there's a way to switch the alpha cell from making a bad hormone into making a good hormone," said Cummings, though she's not recommending that people rush to get bariatric surgery, which can be risky and expensive, just for these effects.

To further this research into GLP-1, the U.S. Department of Defense awarded Cummings' lab a Medical Discovery Award to figure out what factor or factors may act to switch what alpha cells produce.

"The ultimate goal here is to define how the surgery works so we can develop a drug that mimics the effect of surgery. Developing such a drug will bypass the risk and expense of bariatric surgery to make the benefits of this surgery more widely available," said Cummings.

More information: β Cell GLP-1R Signaling Alters α Cell Proglucagon Processing after Vertical Sleeve Gastrectomy in Mice, *Cell Reports* (2018). DOI: https://doi.org/10.1016/j.celrep.2018.03.120

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