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Decade of effort yields diabetes susceptibility gene: Tomosyn-2 regulates insulin secretion

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Ten years of meticulous mouse breeding, screening, and record-keeping have finally paid off for Alan Attie and his lab members.

The University of Wisconsin–Madison researchers' efforts, published Oct. 6 in the journal *PLoS Genetics*, pinpointed a gene that confers diabetes susceptibility in obese mice.

They also showed that the protein coded by the gene, called tomosyn-2, acts as a brake on insulin secretion from the pancreas.

"It's too early for us to know how relevant this gene will be to human diabetes," says Attie, a UW–Madison biochemistry professor, "but the concept of negative regulation is one of the most interesting things to come out of this study and that very likely applies to humans."

In a properly tuned system, insulin secreted into the blood after eating helps maintain blood sugar at a safe level. Too little insulin (as in type 1 diabetes) or insulin resistance (as in type 2 diabetes) leads to high blood sugar and diabetic symptoms. Too much insulin can drive blood glucose dangerously low and lead to coma or even death in a matter of minutes.

"You can imagine that if you're in a fasted state, you don't want to increase your insulin, so it's very important to have a brake on insulin secretion," says Angie Oler, one of the lead authors. "It needs to be stopped when you're not eating and it needs to start again when you do eat."

The group honed in on tomosyn-2 while searching for genes that contribute to diabetes susceptibility in obese animals.

Why study fat mice?

"It takes more insulin to achieve the same glucose-lowering effect in an obese person than it does in a lean person. If you can produce that extra insulin – and most people do – you'll be okay. You will avoid diabetes at the expense of having to produce and maintain a higher insulin level," Attie explains. "Most of the type 2 diabetes that occurs in humans today would not exist were it not for the obesity epidemic."

But an insufficient insulin response leads to diabetes, and the same is true in mice.

Painstaking genetic analyses and comparisons of obese diabetes-resistant and diabetes-susceptible mouse strains ultimately revealed a single amino acid difference that destabilizes the tomosyn-2 protein in the diabetes-resistant mice, effectively releasing the brake on insulin secretion and allowing those animals to release enough insulin to avoid diabetes.

The researchers also confirmed that the human form of tomosyn-2 inhibits insulin secretion from human pancreatic beta cells.

Though diabetes is highly unlikely to be caused by a single gene, identifying important biological pathways can suggest clinically useful targets. "This study shows the power of genetics to discover new mechanisms for a complex disease like type 2 diabetes," says postdoctoral fellow Sushant Bhatnagar, a co-lead author of the paper.

"Now we know there are proteins that are negative regulators of insulin secretion. Very likely they do the same thing in human beta cells, and it

motivates us to move forward to try to figure out the mechanisms behind that negative regulation," Attie says.

More information: Bhatnagar S, Oler AT, Rabaglia ME, Stapleton DS, Schueler KL, et al. (2011) Positional Cloning of a Type 2 Diabetes Quantitative Trait Locus; Tomosyn-2, a Negative Regulator of Insulin Secretion. PLoS Genet 7(10): e1002323. doi:10.1371/journal.pgen.1002323. www.plosgenetics.org/article/i … journal.pgen.1002323

Provided by University of Wisconsin-Madison