Discovery of insulin switches in pancreas could lead to new diabetes drugs

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Researchers at the Salk Institute have discovered how a hormone turns on a series of molecular switches inside the pancreas that increases production of insulin.

The finding, published today in the Proceedings of the National Academy of Sciences, raises the possibility that new designer drugs might be able to turn on key molecules in this pathway to help the 80 million Americans who have type 2 diabetes or pre-diabetic insulin resistance.

The molecular switches command pancreatic beta islet cells, the cells responsible for insulin, to grow and multiply. Tweaking these cells might offer a solution to type 1 diabetes, the form of diabetes caused by destruction of islet cells, and to type II diabetes, the form caused by insulin resistance.

"By understanding how pancreatic cells can be encouraged to produce insulin in the most efficient way possible, we may be able to manipulate those cells to treat or even prevent diabetes," says the study's lead author, Marc Montminy, a professor in the Clayton Foundation Laboratories for Peptide Biology at Salk.

Such new agents might increase the functioning of beta islet cells even in people who have not developed diabetes.

"The truth is that as we grow older, these islet cells tend to wear out,"

Montminy says. "The genetic switches just don't get turned on as efficiently as they did when we were younger, even if we don't develop diabetes. It's like using a garage door opener so many times, the battery wears out. We need a way to continually refresh that battery."

Type II diabetes is caused by an inability for insulin to stimulate muscles to take up glucose, a kind of sugar, from the bloodstream after eating. Age is a risk factor for diabetes, as is obesity, genetic predisposition and lack of physical exercise.

Montminy and two researchers in his lab, Sam Van de Velde, a post-doctoral research associate, and Megan F. Hogan, a graduate student, set out to study how glucagon-like peptide-1 (GLP-1), a hormone produced in the gastrointestinal tract, promotes islet cell survival and growth.

The question is important, not only to understanding basic insulin biology, but also because it would help explain how a drug approved to treat diabetes in 2005 actually works.

That drug, exenatide (Byetta), is a synthetic version of extendin-4, a hormone found in the saliva of the Gila monster lizard. Extendin-4 is similar to GLP-1 in humans, but is much longer acting. "The Gila monster hibernates most of its life, feeding only twice a year, so it needs a way of storing food really well, which means its insulin has to be very efficient," says Montminy.

GLP-1 has a very short duration because enzymes in the bloodstream break it down quickly after it activates insulin production, he says. Patients using exenatide, on the other hand, need to inject it only twice a day.

As helpful as that drug is, Montminy reasoned that if he could pinpoint the various switches that GLP-1 turns on to promote insulin secretion, it

might be possible to identify drug targets that might be even more efficient for human use than exenatide.

The researchers set out to identify the various players in the molecular pathway that is activated when GLP-1 docks onto its receptor on the surface of islet cells. In his previous work, Montminy had already discovered that one of the first switches activated is CREB, which turns on other genes.

In this study they defined other players "downstream" of CREB — discoveries that turned out to be surprising. Two of the molecules, mTOR and HIF, are heavily implicated in cancer development, Montminy says. For example, mTOR is a critical sensor of energy in cells, and HIF works inside cells to reprogram genes to help cells grow and divide.

"Turning on switches inside a cell is a bit like running a relay race," Montminy says. "GLP-1 activates CREB, which passes the baton to mTOR, and then HIF takes over to help islet cells withstand the stresses that cause wear and tear, such as aging. It stands to reason that mTOR and HIF would be involved in helping islet cells to remain healthy because they are involved in cell growth — in this case, growth of islet cells."

These findings suggest it may be possible to activate these molecular players independently to restore insulin production, Montminy says. A drug could directly activate the HIF switch, for example, bypassing the prior steps in the pathway: GLP-1, CREB and mTOR. That might not only increase production of insulin from existing islet cells, but also promote growth of new islet cells.

The findings have other clinical implications as well. Understanding that mTOR is involved in insulin secretion helps explain why some transplant

patients develop diabetes. Rapamycin, a drug often used to prevent organ rejection, suppresses mTOR activity, and so probably undermines insulin production.

Knowing that activating HIF also may help islet cells grow could be useful in efforts to transplant islet cells in patients with type 1 diabetes.

Provided by Salk Institute