

Scientists show how insulin-producing cells may fail in diabetes, how they might someday be restored

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Two new studies led by UC San Francisco (UCSF) scientists shed new light on the nature of beta cells, the insulin-producing cells in the pancreas that are compromised in diabetes.

The first suggests that some cases of diabetes may be caused when beta cells are deprived of oxygen, prompting them to revert to a less mature state that renders them incapable of producing insulin. The second study demonstrates that acinar cells, pancreatic cells that do not normally produce insulin, can be converted to functional beta cells, a potential new avenue for treating the disease.

In the first study, led by Sapna Puri, PhD, a scientist in the laboratory of Matthias Hebrok, PhD, director of the UCSF Diabetes Center, a gene known as VHL was selectively deleted from beta cells in mice. Insulin production in these beta cells was sharply reduced, and over time the mice developed the physiological equivalent of type 2 diabetes. Puri and Hebrok were joined in the study by Haruhiko Akiyama, MD, PhD, of Kyoto University, who provided a critical mouse model for the work.

Type 2 diabetes, which usually emerges in adulthood but is becoming increasingly common in childhood, is generally thought to arise when tissues become resistant to the effects of insulin, causing higher levels of glucose to circulate in the blood. Type 1 diabetes, diagnosed in childhood, is an autoimmune disease in which [pancreatic beta cells](#) are

attacked and damaged by the immune system.

Despite the fact that much research on type 2 diabetes is focused on [insulin resistance](#), the team behind the first new study suggests that a decline in the function of beta cells over time may be a factor in many cases, such as in the subset of lean adults who develop diabetes.

"Some humans with a high body mass index have well-performing beta cells, and some lean people have poorly performing beta cells," said Hebrok, senior author of a paper describing the research in the December 1, 2013 issue of *Genes & Development*. "This mouse is a model of lean humans who develop type 2 diabetes."

During the development of the pancreas, changes in gene expression cause some cells to differentiate into beta cells, but when the researchers examined the VHL-deprived beta cells they found the cells had "de-differentiated." Critical proteins that are always found in mature, functional beta cells were absent, and conversely, a protein known as Sox9, which is only seen in beta cells before they are fully developed, was robustly expressed in the VHL-deprived cells.

"Levels of markers of mature cells go down in these cells, and markers that shouldn't be there go up," Hebrok said.

VHL is a vital cellular oxygen-sensor. In low-oxygen conditions, VHL unleashes intracellular pathways that make compensatory metabolic changes to protect the cell. If these metabolic adjustments fail, alternative pathways prompt the cell to self-destruct.

With its targeted deletion of VHL from beta cells, the research team was emulating conditions of oxygen deprivation in just one cell type, said Hebrok. "We made beta cells 'believe' they are hypoxic, without actually reducing the amount of oxygen."

Even modest weight gains in individuals with subpar beta cells may increase demand on the cells for insulin to a point that they begin to exceed their capacity, Hebrok said. Whether oxygen starvation or metabolic changes within the beta cells are the key drivers during the development of diabetes in some patients remains to be discovered.

"The beta cell is a highly sophisticated cell that produces tremendous amounts of insulin in a tightly regulated way," said Hebrok, "Starving it of oxygen turns a Porsche into a VW Beetle, a high-octane race car into a car that you now have to fuel with low octane—it can still get from A to B, but it can't get there as well as it should."

Though researchers and physicians have drawn broad categories of "pre-diabetic" and "diabetic" when classifying patients, Hebrok believes that many cases of diabetes are the result of steady, long-term declines in the function of already compromised beta cells as they cope with an increasing demand for insulin.

"What we are unraveling here is a different way of looking at how diabetes occurs," said Hebrok. "It's not that you're perfectly fine and then you're pre-diabetic and then you're diabetic and then your beta cells die. Instead it's a slippery slope where the beta cell function erodes over time."

The work was funded by grants from the National Institutes of Health and the Juvenile Diabetes Research Foundation.

In the second study, published in the November 17 issue of *Nature Biotechnology*, researchers were able to restore normal insulin and glucose levels in mice with no functional beta cells by transforming other pancreatic cells into "beta-like" cells.

Led by Luc Baeyens, a new postdoctoral fellow in the laboratory of

Michael S. German, MD, professor of medicine and associate director of the UCSF Diabetes Center, the work was completed as part of Baeyens's research in the laboratory of Harry Heimberg, PhD, at Vrije Universiteit Brussel, in Brussels, Belgium.

Mice were first injected with a beta-cell-specific toxin that caused them to display symptoms of diabetes. Five weeks later, the diabetic mice were implanted with miniature pumps that continuously administered two signaling molecules known as cytokines for seven days.

Treatment with the two cytokines, epidermal growth factor and ciliary neurotrophic factor, restored glucose and insulin to normal levels in the mice, and the mice maintained normal blood sugar control eight months later when the study concluded.

In additional experiments the group showed that the cytokine treatment had exerted its effects by "reprogramming" acinar cells—[pancreatic cells](#) that normally secrete digestive enzymes rather than insulin—and causing them to take on the properties of beta cells, including glucose sensing and insulin secretion.

Previous work had shown that certain transcription factors delivered by viruses could reprogram [acinar cells](#) in mice, but the work by Baeyens and colleagues is the first demonstration that acinar-to-beta cell reprogramming is possible in a living animal through pharmacological treatment. Because viral delivery can be both risky and difficult, the new research represents a promising approach to therapy for [type 1 diabetes](#), or for cases of [type 2 diabetes](#) marked by beta cell dysfunction.

"Type 1 [diabetes](#) patients would greatly benefit from pharmacological therapies that create new beta cells, provided that the current findings in mouse models could be translated into the identification of druggable targets in the human pancreas, and provided we could put a stop to the

ongoing autoimmune destruction of the [beta cells](#)." Baeyens said. "In the short run, this model could serve as a platform to identify and study new compounds with therapeutic potential. In the long run, despite these encouraging results, we are still quite a long way from taking this research from the bench to the bedside."

Provided by University of California, San Francisco

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