Resetting the clock in diabetes

By Lev Osherovich, Senior Writer

A **Columbia University** team has evidence that pancreatic islet β cells do not die in mouse models of type 1 diabetes and type 2 diabetes but rather dedifferentiate into stem cell-like precursors.¹ The findings could explain why diabetes rapidly resolves in obese patients who undergo bariatric surgery and could argue for developing strategies to turn these dedifferentiated cells back into β cells to restore insulin secretion in diabetic patients.

β Cells secrete insulin, which promotes the packaging of sugar into glycogen and results in the build-up of energy reserves. In both forms of diabetes, the inability to produce insulin leads to numerous metabolic, vascular and neurological problems.

Although the two forms of diabetes have different root causes—autoimmunity in the case of type 1 and excess metabolic activity in the case of type 2—both culminate in β cell dysfunction and degeneration.

It is generally accepted that once β cells are lost, the only way to boost insulin levels is to regularly inject the hormone—the standard of care for type 1 diabetes—or to restore missing β cells with regenerative therapies.

Now, a team led by Domenico Accili, professor of medicine and director of the Columbia University Diabetes and Endocrinology Research Center, has found that rather than dying off, β cells can actually remain intact in mouse models of advanced diabetes, albeit in a quiescent state.

“The key result here, which is applicable to both type 1 and type 2 diabetes, is that β cells aren’t dead,” said Accili. “They’re present in the pancreas under a different guise.”

Devolution

Accili’s team made the discovery while characterizing a mouse with knockout of *forkhead box O1* (*Foxo1*), a transcription factor involved in stress response in multiple tissue types. Those mice had multiple abnormalities in food intake and glucose homeostasis.²

In the new study, Accili’s team examined how pancreas-specific deletion of *Foxo1* affected disease progression in mouse models of diabetes.

Initially, pancreas-specific *Foxo1* knockout mice had normal pancreatic activity. However, as the animals aged they showed loss of β cell mass, lower insulin secretion and higher levels of the glucose-releasing hormone glucagon compared with wild-type controls.

Fluorescent labeling studies of the *Foxo1* knockouts’ pancreas indicated that the β cells were still present but had reverted to an

undifferentiated state. These dedifferentiated cells expressed markers associated with pluripotent or stem cell-like characteristics but were unable to secrete insulin.

Over time, the dedifferentiated cells converted into a variety of pancreatic cell types other than β cells. The team found similarly dedifferentiated β cells in two other models of type 2 diabetes—an obese mouse and a mouse lacking insulin receptors in key tissues—and in a chemically induced model of type 1 diabetes.

Results were reported in *Cell*.

Are we not mice?

Accili’s findings raise the possibility that dedifferentiated β cells may be present in the pancreas of patients with diabetes. The challenge will be finding such cells and showing that they are a result of disease and can be reverted to their normal state.

“This paper makes people rethink whether cell death is the main cause of diabetes or whether there is something going on with these weird dedifferentiated cells,” said Douglas Melton, professor in the Department of Stem Cell & Regenerative Biology at **Harvard University** and co-director of the **Harvard Stem Cell Institute**.

“Accili’s group provides compelling evidence that dedifferentiation of functional β cells into a quiescent state leads to reduction of β cell mass and function,” said Hui Tian, VP of research at **NGM Biopharmaceuticals Inc.** “It remains to be tested whether this phenomenon can be observed in other animal models, and, more importantly, in humans.”

NGM is conducting discovery-stage research to identify targets to regenerate β cells in type 1 and type 2 diabetes.

Melton and Tian said determining whether dedifferentiated β cells are present in humans will require developing imaging tools that detect changes in β cells *in vivo*.

One way to find dedifferentiated cells would be histological studies of pancreatic biopsies from patients, but intact *ex vivo* tissue samples are difficult to obtain.

“The challenge for human studies has always been the availability of high-quality pancreatic specimens with enough sample size,” said Tian.

“We lack the ability to interrogate the status of β cells in a living person,” said Melton. “You can’t do a biopsy because the pancreas is an extremely fussy organ, and you can’t just go in there and remove tissue. You need some kind of imaging method to see cells undergoing dedifferentiation.”

Whip into shape

If β cell dedifferentiation indeed occurs in humans, the challenge will be to reverse the process. Accili suspects this could be done by manipulating metabolic conditions or developmental cues known to affect β cell differentiation.

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**—Hui Tian,
NGM Biopharmaceuticals Inc.**

One hypothesis is that changes in diet or food absorption could be enough to restore β cell functioning.

“We’ve known since the 1970s that type 2 diabetes is reversible by fasting,” said Accili. His team hopes to test whether restoration of β cell identity plays a role in recovery from diabetes brought about by severe dietary restriction.

The study raises the possibility that the recovery of β cells from a dedifferentiated state could account for the rapid restoration of insulin secretion in obese type 2 diabetes patients after bariatric surgery.

“It’s a tantalizing hypothesis that these patients may have dedifferentiated progenitor cells present that are now reactivated by bariatric surgery,” noted Tian.

Separately from its work on β cell regeneration, NGM is conducting discovery-stage research to elucidate the mechanisms underlying remission of diabetes following bariatric surgery and identify protein and peptide hormones involved in the process.

Accili said another idea is that developmental pathways such as wingless-type MMTV integration site (WNT) and NOTCH signaling that induce β cells from undifferentiated precursors during embryogenesis could be manipulated to restore β cell identity.

His team is now conducting cell culture screens for compounds that promote redifferentiation of β cell precursors and has filed a patent on these screening methods.

Melton noted that in type 1 diabetes, any efforts to restore β cells from a dedifferentiated state will still need to be accompanied

by immunomodulatory therapy to prevent the autoimmune attack.

He said dedifferentiation in type 1 diabetes might in fact be beneficial, hiding β cells from complete destruction by the immune system during an early stage of disease. It may, he said, be desirable to accelerate the process of dedifferentiation to protect the β cells until autoimmunity can be brought under control.

“If you can make cells dedifferentiate quickly, you might not attract the attention of immune cells during the so-called honeymoon period” before the onset of a full autoimmune assault on β cells, said Melton.

According to Accili, Columbia has filed for patents covering biomarkers of dedifferentiated β cells. Those patents are available for licensing.

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