CLINICAL IMPLICATIONS OF BASIC RESEARCH

Beta-Cell Dedifferentiation and Type 2 Diabetes

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Type 2 diabetes results from a combination of insulin resistance and dysfunction of insulin-producing pancreatic beta cells. Insulin deficiency is thought to be caused by both beta-cell dysfunction and decreased beta-cell mass. Reduced beta-cell mass has been attributed to enhanced beta-cell apoptosis and perhaps failure of beta-cell proliferation. Consequently, many research efforts are aimed toward the restoration of functional beta-cell mass by preventing beta-cell death and inducing replication.

Increased glucagon secretion from islet alpha cells has also been observed in type 2 diabetes, and its central role in metabolic dysregulation has recently been emphasized.[1] Hyperglucagonemia is thought to result from decreased paracrine inhibition of alpha cells by locally secreted insulin, although a relative increase in alpha-cell mass has also been postulated.

Talchai and colleagues[2] recently offered a provocative explanation for both beta-cell failure and alpha-cell hyperfunction in type 2 diabetes. They examined the role of the key transcription factor Foxo1 in beta cells. Beta-cell expression of Foxo1 is markedly decreased in severe hyperglycemia. To study this phenomenon, Talchai et al. genetically modified mice so that their beta cells could not express Foxo1. These mice were generally healthy; however, aging or multiple pregnancies (conditions that presumably increase metabolic pressure on beta cells) caused hyperglycemia, an apparent dramatic reduction of beta-cell mass, and increased numbers of alpha cells. In addition, expression of the proinsulin processing enzyme Pcsk1 (proprotein convertase subtilisin/kexin type 1) was reduced in beta cells of the engineered mice after stress; this led to an increase in the secretion of biologically inactive proinsulin, which has also been observed in uncontrolled type 2 diabetes. Thus, Foxo1 deletion in beta cells provides a new model for stress-induced diabetes.

There was a surprising outcome when Foxo1 deletion was combined with permanent genetic labeling of beta cells. This experiment showed that Foxo1-deficient beta cells did not die but rather had lost expression of key beta-cell genes such as those encoding insulin, glucose transporter 2, glucokinase, and major transcription factors (Fig. 1). Moreover, Foxo1-deficient beta cells often gained expression of other islet hormones such as glucagon; this may explain the apparent increase in alpha-cell mass. These results suggest that the apparent loss of insulin-positive cells does not reflect simple degranulation of beta cells that have undergone long-term stimulation but rather a deeper loss of cell identity.

A similar phenomenon of massive beta-cell dedifferentiation was described previously in cultured human and mouse islets,[3,4] albeit not in the context of type 2 diabetes. It also was reported that early in the evolution of autoimmune diabetes in nonobese diabetic mice, some beta cells lost insulin expression and evaded immune destruction[5]; it is not clear whether such beta cells underwent changes similar to those described by Talchai et al. Their results also resonate with recent evidence of islet-cell plasticity, in which alpha and beta cells can interconvert under certain conditions.

Talchai et al. conclude that loss of Foxo1 causes beta-cell dysfunction and diabetes not by reducing the numbers of beta cells but by triggering the loss of beta-cell identity. In other words, this is a model of diabetes resulting from beta-cell dedifferentiation. Talchai and colleagues then described evidence of beta-cell dedifferentiation and loss of Foxo1 activity in two other mouse models of type 2 diabetes (leptin-receptor–deficient *db*/*db* mice and mice bearing muscle- and fat-specific deletion of the insulin receptor); this suggests that dedifferentiation might be a general mechanism of beta-cell failure in type 2 diabetes. Genetic lineage tracing studies can definitively determine whether beta cells dedifferentiate in these models. Talchai et al. further suggest that beta-cell dedifferentiation involves reversal to a multipotent state resembling embryonic endocrine progenitors and perhaps even pluripotent stem cells, although the evidence of this is more controversial.

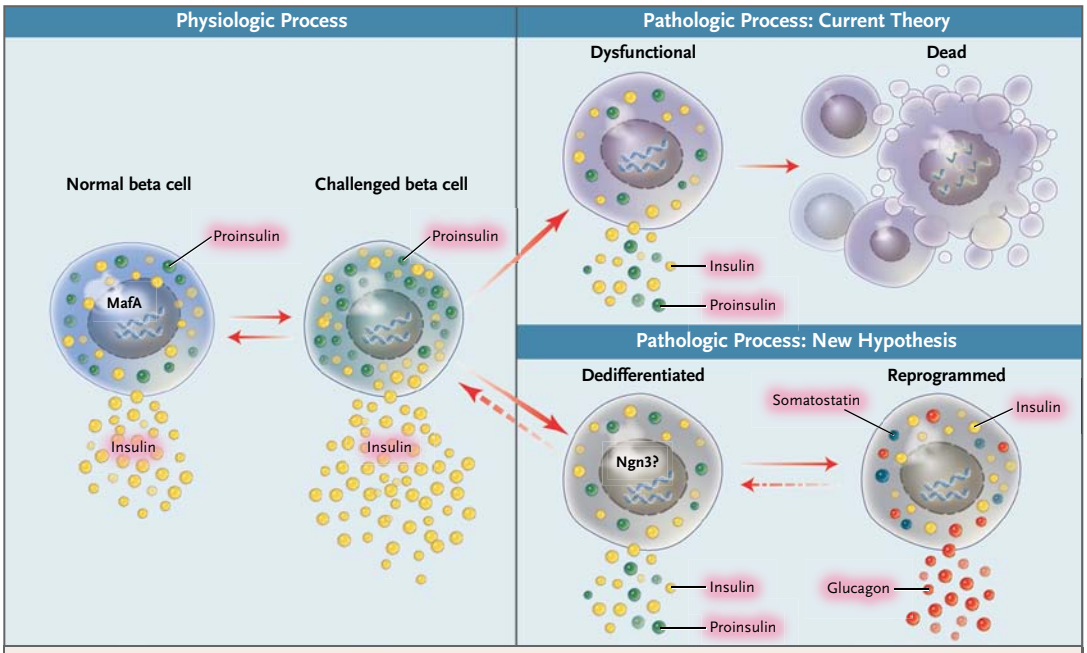

Figure 1. Redifferentiation — The Road to Future Therapy for Type 2 Diabetes?

Beta-cell dedifferentiation, rather than death, may be the mechanism responsible for beta-cell failure in type 2 diabetes. When normal beta cells (far left) are challenged by mild hyperglycemia or insulin resistance, they produce and secrete more insulin, thus maintaining euglycemia. Current thinking (upper right) suggests that oxidative stress, endoplasmic-reticulum stress, or both results in beta-cell dysfunction, which, among other things, results in increased secretion of incompletely processed proinsulin. If unchecked, this process may trigger apoptosis. Talchai et al.[2] propose that stressed beta cells may undergo dedifferentiation, decreasing expression of beta-cell–specific genes, including transcription factors (such as MafA) and the enzyme that processes proinsulin; this may explain increased proinsulin secretion in type 2 diabetes (lower right). Dedifferentiation may also involve gained expression of embryonic progenitor-cell markers such as Ngn3. Later on, these cells begin to express non–beta-cell hormones such as somatostatin and glucagon.

The findings reported by Talchai et al. raise fascinating questions. First, does beta-cell dedifferentiation occur in humans? If so, does it play a role in the pathogenesis of type 2 diabetes? Answering this question is a challenging task that will require innovative approaches to trace the fate of human beta cells once they have lost identity markers. Second, what triggers beta-cell dedifferentiation? The authors propose a pathway leading from chronic hyperglycemia through Foxo1 inactivation to beta-cell dedifferentiation (and even acquisition of multipotent progenitor-cell markers), but the exact molecular components of this pathway remain to be worked out. Third, can dedifferentiation be avoided or reversed? The last question presents the clearest therapeutic implication of these findings: in the future, will there be a new class of type 2 diabetes therapies based on the prevention or reversal of beta-cell dedifferentiation? It is tantalizing to think that the findings of Talchai et al. may be translated into "beta-cell identity drugs."

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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