

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Bulking Up on Beta Cells**

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Current diabetes therapies provide suboptimal glycemic control, fueling efforts to develop strategies to restore the functional mass of insulin-secreting beta cells in the pancreases of patients with diabetes. This feat can be accomplished either by halting or slowing the death of beta cells or by increasing their proliferation. The adaptive proliferation of adult beta cells is possible in response to increased insulin resistance (e.g., during pregnancy¹ or as a consequence of inhibiting insulin signaling in the liver²), but the proliferative response is modest.

Now, Yi et al.³ describe a hormone that increases beta-cell proliferation by a factor far greater than that in any previous studies. They first rendered mice acutely insulin-resistant by infusing them for a week with an insulin-receptor antagonist called S961. This insulin resistance immediately invoked a specific and large increase (by a factor of >10) in beta-cell proliferation, which was associated with the activation of positive regulators of the cell cycle, including cyclins and adenovirus E2 promoter factors (E2Fs), and the repression of cell-cycle inhibitors. Consequently, beta-cell numbers tripled within a week, whereas the size of individual cells remained unchanged. Because the addition of S961 to beta cells *ex vivo* had no effect, Yi et al. posited that S961 had an indirect effect on beta-cell proliferation.

The investigators then obtained gene-expression profiles of tissues involved in metabolic regulation (liver, white fat, and skeletal muscle) to identify putative mediators of the beta-cell response to S961. One gene, which the investigators called the “betatrophin” gene, was up-regulated in the liver and white fat of animals exposed to S961 (Fig. 1). The sequence of this gene, which is also known as the hepatocellular carcinoma–associated protein TD26 gene in humans, is highly conserved across mammals.

Although betatrophin is expressed in the liver

and white fat of mice, it is predominantly restricted to the liver in humans; it is also detectable in plasma, consistent with the action of a secreted protein. Hepatic betatrophin expression is dramatically up-regulated in other models of insulin resistance associated with increased beta-cell proliferation and mass, including in mice during pregnancy and in those with type 2 diabetes that lack leptin (*ob/ob*) or the leptin receptor (*db/db*). However, the protein does not seem to be up-regulated during beta-cell replication after experimental ablation of beta cells, implying that betatrophin induction contributes to compensatory beta-cell proliferation in response to increased metabolic demand but not during injury-induced regeneration.

To test for a beta-cell proliferative effect *in vivo*, Yi and colleagues transiently expressed mouse betatrophin in the liver. This induced an increase in beta-cell proliferation by a factor of 17 to 33, which resulted in a tripling of the beta-cell mass in 8 days and was accompanied by reduced fasting glucose levels and augmented glucose clearance. During this process, beta cells remained functionally normal, despite their overwhelming proliferative recruitment. Finally, to exclude the possibility that the beta-cell proliferative response could be indirectly attributed to betatrophin-induced insulin resistance, Yi et al. found that insulin tolerance was unaffected by hepatic betatrophin expression.

In this study, Yi et al. provide compelling evidence to support the hypothesis that betatrophin is a novel liver-derived hormone promoting compensatory beta-cell proliferation through a mechanism that is independent of insulin resistance. There have been previous hints of such a hepatic cue — for example, in studies of liver insulin receptor knockout (LIRKO) mice, which have a liver-specific deficiency in the insulin receptor along with beta-cell hyperplasia.² Ostensibly, Yi et al. recapitulated this deficiency pharmacolog-

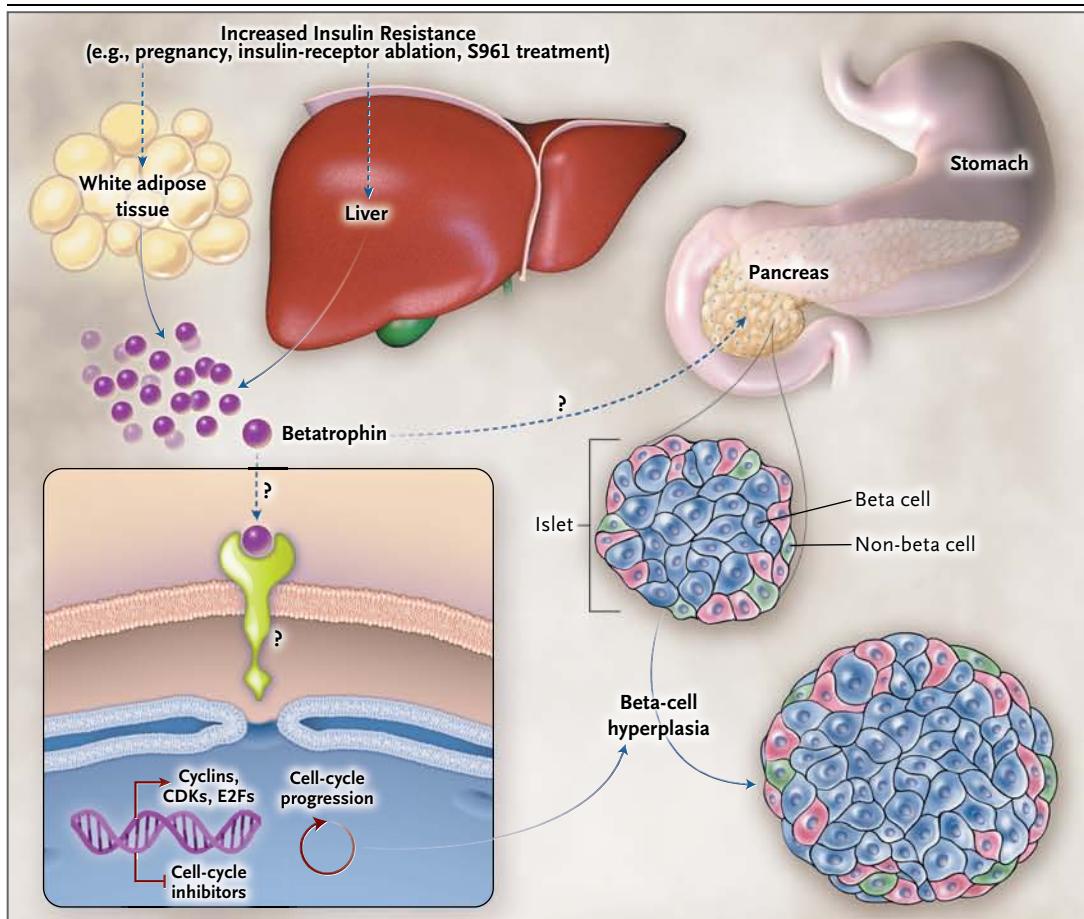


Figure 1. Bumping Up Beta-Cell Numbers.

A recent study by Yi et al.³ showed that the expression of a hormone called betatrophin is induced in white fat and the liver in response to increased metabolic demand, in the form of elevated insulin resistance. In mice, insulin resistance can develop during pregnancy, in those deficient in a hepatic insulin receptor, or after the administration of the insulin-receptor antagonist S961. As a secreted protein, betatrophin induces a dramatic increase in beta-cell proliferation, which is associated with increased expression of positive inducers of the cell cycle, including various cyclins, cyclin-dependent kinases (CDKs), and adenovirus E2 promoter factors (E2Fs), whereas the expression of cell-cycle inhibitors is decreased. Consequently, the beta-cell population enters active mitosis, resulting in a rapid augmentation of beta-cell numbers and mass. Rates of proliferation of other types of endocrine cells (as well as of pancreatic exocrine acinar and ductal cells) remain unaffected by betatrophin.

ically through the administration of S961. However, because beta-cell replication is abrogated in LIRKO mice that are also deficient in insulin-receptor expression in beta cells,⁴ it remains unclear how the beta cells of S961-treated mice are capable of compensatory growth, since S961 should also block insulin-receptor function in beta cells. The exact dose of S961 that is administered may be important here. Demonstration of betatrophin as the principal driver of increased beta-cell proliferation and mass in LIRKO mice and in other states of insulin resis-

tance (e.g., pregnancy in mice and in *ob/ob* and *db/db* mice) could be achieved with the use of the existing betatrophin knockout mouse.⁵ Betatrophin ablation would be predicted to abrogate such compensatory beta-cell proliferation.

Arguably, the magnitude of increased beta-cell proliferation in response to S961 or betatrophin is the most striking finding of Yi et al. Their results dwarf the reported increases in beta-cell proliferation by a factor of 3 to 4 during pregnancy¹ and by a factor of 6 in LIRKO mice.⁴ This extreme potency is compatible with

the therapeutic administration of recombinant betatrophin peptide to augment beta-cell mass, not only in patients with type 2 diabetes but also in patients with recently diagnosed juvenile diabetes, in whom such therapy might be efficacious in halting or even reversing beta-cell loss if autoimmunity can be controlled. Indeed, it is almost inevitable that betatrophin will enhance beta-cell mass more effectively in young patients with diabetes, given that compensatory beta-cell proliferation decreases sharply with age. Yi et al. studied relatively young (8-week-old) mice; the effect of betatrophin in older animals warrants assessment. Finally, and most notably, the mechanism through which betatrophin drives beta-cell proliferation — whether directly or indirectly — remains an unknown. Elucidating the mechanism of action, including the identity of the

betatrophin receptor, should support the translation of this discovery into clinical practice.

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

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