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Insulin Resistance Compensation: Not Just a Matter of β-Cells?

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COMMENTARY

The global epidemic of type 2 diabetes is largely secondary to insulin resistance induced by obesity and sedentary lifestyles. Most insulin-resistant subjects are able to increase β-cell secretion to meet the increased insulin demand and do not develop diabetes. However, when β-cell compensation fails, type 2 diabetes develops (1,2). Understanding the mechanisms of this compensatory response is of fundamental importance to elucidate the pathophysiology of type 2 diabetes and has implications for the treatment of the disease.

The capacity of β-cell mass to increase in response to insulin resistance is well established in rodents, where it has been able to prevent diabetes even in extreme conditions (3). In humans, β-cell mass expansion has been shown in normal physiological growth (4) and in insulin-resistant conditions such as pregnancy (5) and obesity (6–10). However, β-cell mass increment is more modest in obese humans than in rodents, has not been confirmed in all ethnic backgrounds (11), and shows a large variability among subjects (10,12). Current imaging techniques are not sensitive enough to accurately measure β-cell mass in vivo, and ethical considerations preclude obtaining pancreatic samples from living subjects. Thus, human β-cell mass has been determined in autopsied pancreata. The cross-sectional nature of the studies, the potential interference of pre- and postmortem processes, and the absence of concomitant or even previous assessment of insulin resistance and insulin secretion are significant limitations of the available morphological studies.

In the current issue, Mezza et al. (13) present a detailed analysis of islet function, insulin resistance, and islet morphology in 18 nondiabetic patients requiring a pancreatoduodenectomy (~50% pancreatectomy) to treat a tumor of the ampulla of Vater. One week before surgery a hyperinsulinemic-euglycemic clamp, a hyperglycemic clamp followed by acute stimulation with L-arginine, and a mixed-meal test were performed. Based on the hyperinsulinemic-euglycemic clamp, patients were divided into more insulin-sensitive and more insulin-resistant. At surgery, a pancreatic sample was collected, and the full metabolic study was repeated ~40 days after surgery when 77% of the insulin-resistant subjects but none of the insulin-sensitive subjects had developed diabetes. Mean islet size and fractional insulin, glucagon, and somatostatin areas were higher in insulin-resistant subjects. β-Cell replication, apoptosis, and individual β-cell size were similar in insulin-resistant and insulin-sensitive subjects, suggesting that these factors did not contribute to increase β-cell mass. In contrast, increased islet neogenesis was suggested in insulin-resistant subjects based on higher β-cell and islet densities and on indirect markers of neogenesis that are compatible with a ductal origin of new β-cells. Insulin-resistant subjects showed a dramatic increment of fractional α-cell area that correlated inversely with insulin sensitivity, a reduced β-/α-cell ratio, and an increased percentage of cells double-positive for insulin and glucagon. Glucagon-like peptide 1 (GLP-1) expression, colocalized with glucagon, was identified in the pancreas in both groups, and GLP-1 secretion correlated positively with the α-cell area and negatively with insulin sensitivity.

The simultaneous and comprehensive functional study and morphological analysis of islets in pancreas from living subjects is a major strength of the study. The increased β-cell mass in insulin-resistant subjects is in line with current concepts about β-cell plasticity and compensation for insulin resistance. Among the several possible origins of the increased β-cell mass (Fig. 1), Mezza et al. support a role for islet neogenesis that some previous studies have also suggested (14). The increased

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See accompanying article, p. 994.

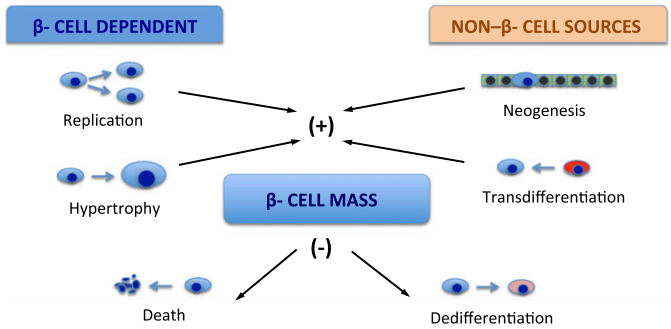

Figure 1—Adult β-cell mass expansion in response to increased insulin demand, such as that generated by insulin resistance, may take place based on preexisting β-cells—by enhanced β-cell replication and/or increased individual β-cell size—or new β-cells could be generated from other cell sources, such as neogenesis from ductal cells or transdifferentiation from acinar cells or α-cells. In diabetic patients, β-cell mass reduction can result from increased apoptotic cell death, and recently β-cell dedifferentiation and conversion into other endocrine non–β-cells of the islets has been described in diabetic mice.

percentage of cells double-positive for the duct marker CK19 and insulin indicates that neogenetic β-cells could be of ductal origin. Nevertheless, in the absence of direct markers, islet cell neogenesis cannot be confirmed (14). The identity of the circulating signals that drive the compensatory β-cell response to insulin resistance is of fundamental interest. A dominant role has been proposed for glucose (15), but other factors have been identified in rodents (16). This question was not addressed in the current study.

The sixfold increment in α-cell area in insulin-resistant subjects of a higher magnitude than that of β-cells and the proposed role of pancreatic α-cells in GLP-1 secretion and in β-cell mass compensation generate new questions about α-cell involvement in insulin resistance and in the evolution toward type 2 diabetes. Could the increased α-cell area be part of the compensatory response to insulin resistance? The authors suggest that transdifferentiation of α-cells into β-cells (17) could increase β-cell mass, and speculate that GLP-1 secretion by α-cells (18) would have beneficial paracrine effects on islets and pancreatic progenitor cells. On the other hand, β-cell dedifferentiation and conversion into other islet endocrine cell types was recently described in diabetic mice (19). It is intriguing to consider whether β-cell dedifferentiation and conversion into α-cells could occur in insulin-resistant subjects and play a role in the progressive loss of β-cell function and mass that leads to the development of diabetes. However, at this time, caution should be used when interpreting the α-cell results: α-cell area was unusually low in the insulin-sensitive group (less than 7% of the β-cell area); glucagon secretion was not increased in the insulin-resistant group, despite the higher α-cell area; and in other studies, increased α-cell mass has not been identified in obese subjects (12,20). The cross-sectional nature of the morphological study, the small number of patients in each group, and the assessment of cell mass as fractional area instead of absolute cell mass are additional limitations of the study.

In summary, the results of Mezza et al. (13) strongly support the capacity of human β-cells to respond to the increased demands imposed by insulin resistance, and they provide indirect evidence suggesting that neogenesis from duct cells contributed to increased β-cell mass. The increased α-cell area identified in the normoglycemic insulin-resistant subjects, as well as the involvement of GLP-1, if confirmed, could open new possibilities to prevent the evolution to type 2 diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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