Linking the Genetics of Type 2 Diabetes With Low Birth Weight

A Role for Prenatal Islet Maldevelopment?

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Diabetes develops if pancreatic β-cells fail to provide sufficient amounts of insulin at a given degree of insulin resistance. In type 1 diabetes, the extent of β-cell loss at the time of disease onset has been estimated to be ~60–70% (1,2), while studies in patients with type 2 diabetes and individuals with impaired fasting glucose have reported β-cell deficits of ~65 and ~50%, respectively (3). However, while impaired islet cell mass and function seem to determine the development of diabetes to a large extent, individual risk undoubtedly also depends on other parameters, such as obesity and insulin resistance (4).

Over the years, increasing evidence has accumulated that shows that, in addition to these established risk factors, low birth weight is also associated with a greater risk of developing type 2 diabetes later in life (5,6). The causes underlying this association have been debated, and fetal malnutrition has been proposed as a potential mechanism (7,8).

Freathy et al. (9), as reported in this issue of *Diabetes*, have now tested the alternative hypothesis (the fetal insulin hypothesis) that genetic variants predisposing to type 2 diabetes might also reduce birth weight by altering intrauterine insulin secretion or action. Using fetal DNA from 7,986 mothers and 19,200 offspring from four European studies, the authors provide convincing evidence for a link between two recently identified type 2 diabetes loci (*CDKAL1* and *HHEX-IDE*) and reduced birth weight, with a mean difference in birth weight of 80 g between carriers of four type 2 diabetes risk alleles and individuals carrying none of these risk alleles.

What are the common factors that confer coincident risk of type 2 diabetes and low birth weight? Although alterations in both insulin secretion and insulin action are theoretically possible, a number of points seem to support the hypothesis that impairments in early β-cell development lead to fetal malnutrition and predispose individuals to development of type 2 diabetes later in life. Indeed, β-cell mass has been increasingly recognized as a central cause of type 2 diabetes over the years (10). Thus, even though obesity and insulin resistance clearly increase the likelihood of developing diabetes (11), a substantial percentage of obese individuals remain free of diabetes throughout life, and, in turn, pancreas transplantation has been shown to restore normoglycemia even in insulin-resistant patients with type 2 diabetes (12). The importance of β-cell mass for individual type 2 diabetes risk has been further highlighted by the results of recent genome-wide scans that have uniformly linked the likelihood of developing type 2 diabetes to genetic defects in insulin secretion (13–15). In particular, the two loci that were related to low birth weight in this study (*CDKAL1* and *HHEX-IDE*) have been shown to be associated with significant impairments in β-cell function (16,17). Therefore, the most likely explanation for the association between low birth weight and the risk for type 2 diabetes seems to be a genetically determined maldevelopment of β-cells leading to insufficient insulin secretion. The intrauterine insulin deficiency may then impair fetal growth (18), while insufficient insulin secretion later in life may confer an increased risk of developing type 2 diabetes. Consistent with such reasoning, autopsy studies in 46 children aged between 2 weeks and 21 years have revealed a more than fivefold variation in pancreatic β-cell area between children of similar age (19). Taken together, the findings of these and the recent genetic studies indicate that pre- and postnatal maldevelopment of islets leading to insufficient insulin secretion may be an important, yet underappreciated, risk constellation for the subsequent manifestation of type 2 diabetes.

These studies suggest that we reconsider our current thinking of the pathogenesis of type 2 diabetes; three different concepts seem to emerge (Fig. 1*A*). The insulin resistance concept proposes that islet β-cells increase their insulin secretion in response to declining peripheral insulin action until a point of β-cell exhaustion and manifestation of hyperglycemia (20) (Fig. 1*A*). Based on this hypothesis, insulin resistance triggers β-cell failure through an increased secretory demand. According to the β-cell apoptosis concept, β-cell mass declines because of an increased rate of β-cell apoptosis (Fig. 1*B*) (3). The loss of islet β-cells leads to impairments in insulin secretion, thereby promoting the manifestation of hyperglycemia. The islet malformation concept is based on the association between the genetic risk for type 2 diabetes and low birth weight, suggesting a genetic constellation associated with impaired islet β-cell development (Fig. 1*C*) (9). As a consequence, β-cell mass fails to expand and grow to a normal extent, which subsequently leads to impaired insulin secretion and manifes-

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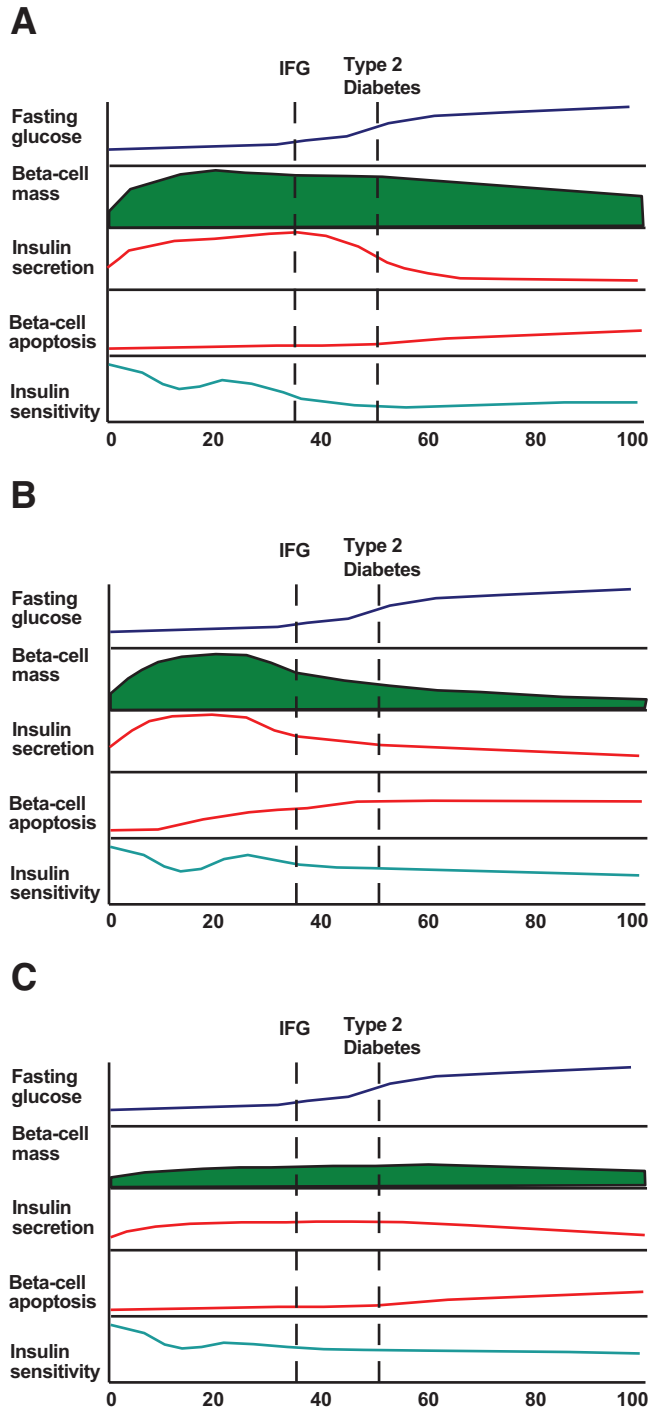

FIG. 1. Three hypotheses for the pathogenesis of type 2 diabetes. *A*: The insulin resistance concept proposes that islet β-cells increase their insulin secretion in response to declining peripheral insulin action until a point of β-cell exhaustion and manifestation of hyperglycemia. *B*: The β-cell apoptosis concept suggests that β-cell mass declines because of an increased rate of β-cell apoptosis, thereby leading to impairments in insulin secretion (3). *C*: The islet malformation concept suggests a genetic constellation associated with impaired islet β-cell development. As a consequence, β-cell mass fails to grow to a normal extent, thereby leading to impaired insulin secretion.

tation of hyperglycemia. In reality, the pathogenesis of type 2 diabetes likely involves a combination of these three mechanisms, with the respective importance of each pathway varying substantially between different individuals.

Taken together, the fetal insulin hypothesis has provided a strong link between genetic β-cell defects, low birth weight, and the risk of type 2 diabetes. Accordingly, the deficit in β-cell mass typically found in patients with type 2 diabetes may not only be secondary to an increased rate of apoptosis but may also be the consequence of abnormal islet cell development and growth. The findings by Freathy et al. (9) therefore significantly extend our knowledge on the pathogenesis of type 2 diabetes and will certainly foster future work aiming to explore the role of islet maldevelopment in the development of diabetes.

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