Mary, Mary, Quite Contrary, How Do Your β-Cells Fail?

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The dogma regarding the pathogenesis of type 2 diabetes has evolved over the last decade to view the islet β-cell as the final determinant of whether glucose tolerance is normal or abnormal (1). While obesity and insulin resistance have reached epidemic proportions around the world, the presence of an appropriate compensation of insulin secretion ("healthy β-cells") allows daylong glycemia to be indistinguishable from metabolically normal individuals (2). In turn, pre-diabetes and type 2 diabetes result from progressive β-cell dysfunction (3). As such, an army of researchers worldwide is searching for the pathogenic basis of this β-cell dysfunction, along with strategies of when, and how, to intervene. What has resulted is a reasonably good mapping of the natural history of the β-cell dysfunction, plus a lengthy list of potential mechanisms. Most are based on animal studies; therefore, homing in on the operative mechanisms in humans remains a challenge. Still, there is high confidence within the β-cell research arena that we are on the right track to identifying the molecular details of β-cell compensation and failure.

Figure 1 shows the proposed stages of β-cell dysfunction. It begins early, perhaps at birth, with β-cells that are programmed to be at risk to fail ("susceptible β-cells"). Indeed, the recent genome-wide scans have identified many susceptibility genes for type 2 diabetes that likely impact the development and ongoing homeostasis of the mass of β-cells, as well as insulin secretion and synthesis (4). Although direct evidence is lacking, many are betting that a lowered mass of normally functional β-cells, from genetics or environmentally based imprinting during fetal or early life, will end up being a common cause of susceptible β-cells, based on animal (5,6) and human (Kumar et al. [7]) studies posthemipancreatectomy showing a predilection for diabetes. Eventually, β-cell dysfunction (actually failed β-cell compensation) occurs when the subject is still normally glucose tolerant, resulting in a slow rise in glycemia (8). Whether this reflects dysfunctional β-cells, a loss of β-cells, or both is unknown. By the onset of pre-diabetes, defective β-cell function (glucose unresponsivesness and impaired insulin pulsatility) and a lowered β-cell mass are both found and worsen with time (1). Many mechanisms for the β-cell dysfunction and death are being studied, such as glucotoxicity, glucolipotoxicity, oxidative or endoplasmic reticulum stress, amyloid infiltration, inflammation, and so on.

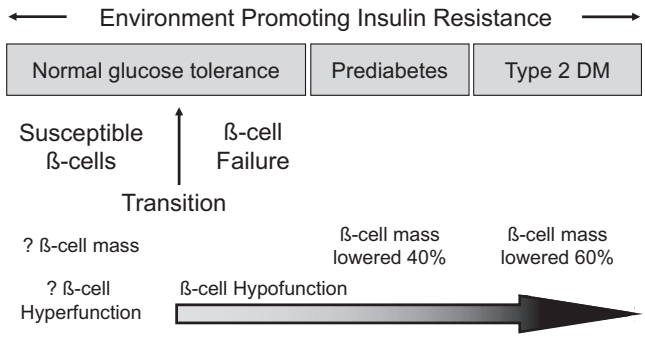

FIG. 1. Proposed schema for the pathogenesis of type 2 diabetes that incorporates the available literature on β-cell mass and function through the evolution from normal glucose tolerance to overt type 2 diabetes.

However, there is one stage of this sequence called "transition" (i.e., the time when insulin secretion switches from successful to failed compensation) that has gone relatively unstudied. In this issue of *Diabetes*, the article by Chakravarthy et al. (9) may provide important insight into this event, although that was not the original intent. They intensively studied a mouse model of intrauterine growth retardation (IUGR) due to haploinsufficiency for fatty acid synthase (FAS), noting modest hyperglycemia on a standard diet at 12 months of age and even worse hyperglycemia after fat feeding compared with the wild-type mice. The reason was defective insulin secretion and a falling β-cell mass. Importantly, this propensity to diabetes came without the postnatal catch-up in body weight and insulin resistance that characterize most other models of IUGR, which allowed the authors to conclude that β-cells were programmed for failure by events related to the IUGR. The story became even more interesting when they looked earlier (at 3 months) and found an opposite phenotype. The FAS heterozygous mice were hypoglycemic/hyperinsulinemic on a standard diet, with a larger β-cell mass and insulin secretion that was hyperresponsive to glucose, when they were more insulin sensitive than age-matched wild-type mice. Furthermore, the FAS haploinsufficient mice compensated better to fat feeding than did wild-type mice in terms of a greater increase in β-cell mass and insulin secretion; plus, there were lower-than-normal glucose values during a glucose challenge. So, early on there was super β-cell compensation, and later there was failed compensation.

The authors concluded that they had discovered a body weight–sensing mechanism during fetal development that regulates β-cell mass. As such, growth retardation feeds back to enhance β-cell mass and insulin secretion to augment whole-body fat and protein deposition. They supported this conclusion with a second mouse model of IUGR, also with enhanced insulin sensitivity (muscle-specific uncoupling protein-1 transgenic mice), that showed the same early increases in β-cell mass and

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function. Finally, they concluded that it was the initial β-cell hyperfunction that programmed the β-cells for later failure (i.e., creating susceptible β-cells).

It is impossible to know, from this study, about the plausibility of the proposed fetal size–sensing regulatory system for β-cell mass and function. No biological details for such an effect are known in mammals, and one can envision fairly profound metabolic changes in fatty acid homeostasis and cellular metabolism in the studied mice. Instead, the concept of β-cell hyperfunction programming β-cells for later failure (termed "β-cell overwork" or "β-cell exhaustion") is supported by studies over several decades from many investigators (10), although the relevant literature is often forgotten. Hansen and Bodkin (11) performed seminal studies that mapped the stages to type 2 diabetes in rhesus monkeys, finding that β-cell hyperresponsiveness for insulin was the first identifiable event preceding obesity and insulin resistance. We studied Zucker fatty rats that are obese and normoglycemic and noted that the compensatory increase in β-cell mass started well before the time reported by others for the onset of insulin resistance (12). Studies in humans have shown that insulin hypersecretion precedes insulin resistance in nondiabetic obese juveniles (13), and a high fasting insulin level independent of insulin resistance was shown to be an important risk factor for type 2 diabetes in Pima Indians (14). Moreover, intervention studies (15–18) using inhibitors of insulin secretion (diazoxide, novel ATP-sensitive K^+ channel openers, and somatostatin), so-called "β-cell rest strategies" that have shown paradoxical improvements in β-cell function in animals and humans with type 2 diabetes, have been highly influential for the β-cell overwork concept. Indeed, one wonders if the improved β-cell function after aggressive blood glucose control using insulin that originally led to the glucose toxicity concept (19,20) might more correctly stem from β-cell rest.

A key question is how to distinguish healthy β-cell compensation versus unhealthy increases in β-cell function. Again, the study by Chakravarthy et al. (9) may provide an important clue, as the 3-month-old FAS haploinsufficient mice were mildly hypoglycemic basally and during the glucose challenge after fat feeding. In other words, the enhanced β-cell mass and function, at this early time point, were neither appropriate nor normally regulated but instead resulted in a condition that is reminiscent of the honeymoon period in type 1 diabetes, another state of failing β-cells. Whether there is a comparable phase in human type 2 diabetes is unknown, although it was commonly believed by clinicians years ago that ~20% of individuals presenting with type 2 diabetes had gone through a prior period of reactive postmeal hypoglycemia.

Thus, extensive literature supports that enhanced β-cell function (and likely mass) is an early stage, and likely causative event, in the progression to β-cell failure and type 2 diabetes. What is needed now is a better understanding of the biology that links β-cell hyperfunction to eventual failure, followed by the development of targeted pharmaceuticals in order to test the concept of β-cell rest for the prevention and treatment of early type 2 diabetes.

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