Targeting β-cell functions in therapy for type 2 diabetes

Recently, Leahy *et al*. issued a "consensus statement" in regard to targeting β-cell function in therapy for type 2 diabetes that recommends continued multidisciplinary efforts to realign treatment of type 2 diabetes to preserve β-cell function by early intervention. This might be applicable not only for obese type 2 diabetes in Europe and America, but also for lean type 2 diabetes in Asia. To establish evidence, development of non-invasive measurements of β-cell mass for longitudinal observation during long duration of diabetes is critical. In addition, studies that clarify the development of β-cell dysfunction with regard to both mass reduction and functional impairment are required for the development of novel strategies to preserve β-cell function by treatment of type 2 diabetes.
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Leahy *et al.*[1] recently issued a consensus statement that recommends targeting β-cell function for therapy in type 2 diabetes. The consensus is based on recent studies showing that declining β-cell function, a pathogenesis of type 2 diabetes, begins early in the disease's natural history, accelerates markedly after reaching a compensatory threshold, drives the progression of the disease and is potentially reversible, particularly in the early stages. They concluded that continued multidisciplinary effort to realign treatment of type 2 diabetes to preserve β-cell function by early intervention is both necessary and important.

In a longitudinal study of obese Pima Indians by Weyer *et al.*[2], failure to augment β-cell function to compensate for increased insulin demand as a result of decreased insulin sensitivity, due to weight gain for example, was found to be involved in deterioration of glucose homeostasis in type 2 diabetes. It is important to determine whether or not this pathogenesis is also applicable to lean type 2 diabetes in Asia. Sato *et al.*[3] showed, by a cross-sectional study using the oral glucose tolerance test, that β-cells begin to deteriorate during normoglycemia with a minimal elevation of fasting plasma glucose in Japanese subjects. In our previous cross-sectional study, endogenous insulin secretion shown by indices of serum C-peptide immunoreactivity (CPR) levels was negatively correlated with years from diagnosis, suggesting progressive deterioration of β-cell function over several decades of diabetes exposure in Japanese type 2 diabetes[4]. Interestingly, body mass index (BMI) was positively correlated with indices of CPR, suggesting that increased insulin resistance positively affects endogenous insulin secretion, even in lean type 2 diabetes. However, the positive effect of BMI on endogenous insulin secretion is weaker in patients with longer duration of diabetes than in those with shorter duration, suggesting a decrease in the capacity to compensate insulin secretion against insulin resistance by disease duration and that early intervention might be necessary, even in lean type 2 diabetes.

A previous study using streptozotocin-treated mini-pigs showed that β-cell function *in vivo* is closely related to β-cell mass, even when only slightly reduced[5]. A decrease in β-cell mass in type 2 diabetes compared with that in normal subjects is shown by cross-sectional studies using specimens of autopsies or surgical operations, but longitudinal studies are absent. In a cross-sectional study using specimens derived from autopsies, β-cell mass in individuals showed extreme variability and markedly overlapped in normal subjects and patients with type 2 diabetes, despite the significant average decrease in β-cell mass in type 2 diabetes[6]. These results show that measurement of β-cell mass at one time point in an individual cannot predict progression to type 2 diabetes and that longitudinal observation is necessary. Trials to find useful probes to visualize β-cell mass *in vivo* continue[7]. Such non-invasive methods, if realized, will be valuable to clarify the relationship between function and mass of β-cells during the natural course of type 2 diabetes

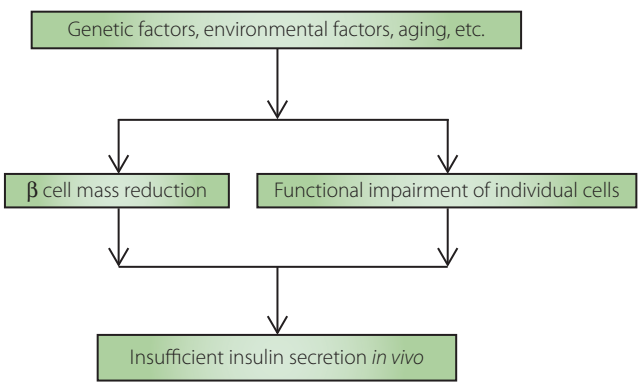

Figure 1 | Pathogenesis of type 2 diabetes mellitus.

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in longitudinal studies and to evaluate the effects of early intervention.

In the consensus statement, Leahy *et al.* stressed the importance of basic research to elucidate the nature and mechanisms of β-cell failure in type 2 diabetes. Understanding the molecular basis of β-cell proliferation and apoptosis is required to realize clinical application of early intervention to preserve β-cell mass. Unlike in rodents, a 50% pancreatectomy does not prompt β-cell regeneration in adult humans[8]; the difference between the mechanisms of β-cell replication in human and rodents has been shown[9]. Many beneficial effects of incretin on the preservation of rodent β-cells have been proposed, but thorough evaluation of the effects in human β-cells is required. Furthermore, extreme variability of β-cell mass in humans shows that the pathogenesis of type 2 diabetes is derived from functional impairment of insulin secretion, as well as from reduction of β-cell mass (Figure 1). Indeed, glucose-specific impairment of insulin secretion is characteristic in type 2 diabetes; the insulin response to intravenous administration of arginine is preserved, whereas the insulin response to intravenous administration of glucose is severely impaired in patients with type 2 diabetes[10]. Results from diabetic rodent and human islets show that decreased glucose-stimulated insulin secretion in diabetes is derived, at least in part, from impaired metabolism–secretion coupling in β-cells; impaired glucose metabolism and adenosine triphosphate (ATP) production in β-cells causes a decrease in glucose-stimulated insulin secretion. We propose that ATP production in β-cells is impaired by endogenous overproduction of reactive oxygen species (ROS) and by diminished hyperpolarization of mitochondrial membrane potential as a result of overexpression of uncoupling protein and a nuclear factor[11,12]. Interestingly, an increase in the intracellular cAMP level by GLP-1 receptor agonist ameliorates impaired ATP production by suppressing endogenous ROS generation in diabetic β-cells, which suggests that incretin therapy might have an important role in recovering impaired metabolism-secretion coupling[11]. Studies to elucidate the mechanism of β-cell dysfunction, including mass reduction and functional impairment, will contribute to establishing novel strategies to preserve β-cell function in treatment of type 2 diabetes.

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REFERENCES

1. Leahy JL, Hirsch IB, Peterson KA, *et al.* Targeting β-cell function early in the course of therapy for type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010; 95: 4206–4216.
2. Weyer C, Bogardus C, Mott DM, *et al.* The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104: 787–794.
3. Sato Y, Komatsu M, Katakura M, *et al.* Diminution of early insulin response to glucose in subjects with normal but minimally elevated fasting plasma glucose. Evidence for early β-cell dysfunction. *Diabet Med* 2002; 19: 566–571.
4. Funakoshi S, Fujimoto S, Hamasaki A, *et al.* Analysis of factors influencing pancreatic β-cell function in Japanese patients with type 2 diabetes: association with body mass index and duration of diabetic exposure. *Diabetes Res Clin Pract* 2008; 82: 353–358.
5. Larsen MO, Rolin B, Wilken M, *et al.* Measurements of insulin secretory capacity and glucose tolerance to predict pancreatic β-cell mass in vivo in the nicotinamide/streptozotocin Göttingen minipig, a model of moderate insulin deficiency and diabetes. *Diabetes* 2003; 52: 118–123.
6. Rahier J, Guiot Y, Goebbels RM, *et al.* Pancreatic β-cell mass in European subjects with type 2 diabetes. *Diabetes Obes Metab* 2008; 10(Suppl 4): 32–42.
7. Mukai E, Toyoda K, Kimura H, *et al.* GLP-1 receptor antagonist as a potential probe for pancreatic β-cell imaging. *Biochem Biophys Res Commun* 2009; 389: 523–526.
8. Menge BA, Tannapfel A, Belyaev O, *et al.* Partial pancreatectomy in adult humans does not provoke β-cell regeneration. *Diabetes* 2008; 57: 142–149.
9. Fiaschi-Taesch N, Bigatel TA, Sicari B, *et al.* Survey of the human pancreatic β-cell G1/S proteome reveals a potential therapeutic role for cdk-6 and cyclin D1 in enhancing human β-cell replication and function in vivo. *Diabetes* 2009; 58: 882–893.
10. Fujimoto S, Nabe K, Takehiro M, *et al.* Impaired metabolism-secretion coupling in pancreatic β-cells: role of determinants of mitochondrial ATP production. *Diabetes Res Clin Pract* 2007; 77(Suppl 1): S2–S10.
11. Mukai E, Fujimoto S, Sato H, *et al.* Exendin-4 suppresses Src activation and reactive oxygen species production in diabetic GK rat islets in an Epac-dependent manner. *Diabetes* 2011; 60: 218–226.
12. Yoshihara E, Fujimoto S, Inagaki N, *et al.* Disruption of TBP-2 ameliorates insulin sensitivity and secretion without affecting obesity. *Nat Commun* 2010; 1: art. no. 127.