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COMMENTARY

Inceptor intercepts insulin signaling in pancreatic β-cells

Insulin resistance and pancreatic β-cell failure are two major pathological mechanisms in type 2 diabetes mellitus. It is known that at the very least, β-cell failure involves a decrease in glucose-responsive insulin secretion and a decrease in cell volume. β-Cell failure worsens over time, causing a deterioration of glucose tolerance in patients with type 2 diabetes. Therefore, the ideal treatment of type 2 diabetes should suppress the development of β-cell failure and improve deteriorated β-cell function. Many antidiabetic drugs are currently used clinically, but none have the aforementioned characteristics. As a basis for developing such drugs, it is necessary to elucidate the mechanisms underlying the regulation of both β-cell volume and glucose-responsive insulin secretion by β-cells. This knowledge will eventually contribute to the establishment of new methods to maintain normal β-cell function in patients with type 2 diabetes.

While hepatic neural circuits and humoral factors from liver are reported to be involved in the regulation of β-cell function[1,2], signals induced by insulin and insulin-like growth factor (IGF)-1 receptor expressed in β-cells play important roles in maintaining β-cell mass and normal glucose responsive insulin secretion. This importance has been supported by numerous studies that used mice deficient in the genes for the insulin receptor, IGF-1 receptor, and their downstream molecules that are essential for signal transduction, such as insulin receptor substrate-2 and protein kinase B[3]. The signals from insulin and the IGF-1 receptor are known to enhance insulin secretory capacity and increase β-cell volume. A simple interpretation regarding the importance of the molecules related to insulin receptor signaling in pancreatic β-cells is that insulin secreted from β-cells binds to insulin receptors in an autocrine or paracrine manner, and then the signals from the insulin receptors enhance β-cell function. However, several findings conflict with this idea.

In many types of cells, such as hepatocytes, insulin binding to the insulin receptor leads to clathrin- or caveolin-mediated endocytosis, and the insulin receptor is desensitized[4]. As concentration of insulin around pancreatic β-cells is thought to be high, it is conceivable that insulin receptor desensitization occurs readily in these cells. No data have proven this, but even if it is true, it is unknown if insulin would efficiently stimulate insulin receptor signaling in pancreatic β-cells. Furthermore, a phenomenon known as feedback inhibition of insulin has been reported, in which endogenous insulin secretion is suppressed by exogenous insulin administration[5]. It has also been reported that β-cell volume is increased in insulin gene knockout mice[6]. These data suggest that insulin inhibits insulin secretion and decreases β-cell mass, and that the effect of insulin is contrary to that of insulin receptor stimulation, as estimated by the deficiency of essential molecules in the insulin receptor signal transduction pathway. To solve this mystery, it is essential to elucidate the factors affecting insulin receptor signaling.

Very recently, Ansarullah *et al.*[7] identified ELAPOR1 as a molecule that regulates the insulin and IGF-1 receptor signaling pathways in pancreatic β-cells. ELAPOR1 is strongly expressed in the pancreas at E 14.5, and is a single-pass, type I transmembrane protein containing a cysteine-rich domain that resembles domains in growth factor receptors, such as the insulin receptor and IGF-1 receptor. In addition, ELAPOR1 contains the mannose 6-phosphate receptor domain, which is similar to the domain present in the IGF-2 receptor. Although ELAPOR1 is known to be expressed in secretory cells of endocrine glands and the hypothalamic–pituitary–gonadal axis, in the pancreas its expression is observed in both endocrine and exocrine tissues. To investigate the physiological role of ELAPOR1, Ansarullah *et al.*[7] generated systemic ELAPOR1 gene-deficient mice, as well as tamoxifen-induced, β-cell-specific, ELAPOR1 gene-deficient mice. Intriguingly, the pancreatic islets of these mice showed enhanced phosphorylation of the insulin receptor and IGF-1 receptor, and also showed insulin-responsive protein kinase B. In addition, these mice showed enhanced glucose-responsive insulin secretion, increased pancreatic β-cell proliferation and volume, and amelioration of glucose tolerance. These data suggest that ELAPOR1 functions as a negative regulator of insulin and IGF-1 receptor signaling in pancreatic β-cells. Regarding the IGF-2 receptor, a protein containing the mannose 6-phosphate receptor domain is involved in the trafficking of proteins from the trans-Golgi network to endosomes and eventually to lysosomes. As expected, ELAPOR1 is localized in the Golgi-endoplasmic reticulum-lysosomal compartment in β-cell lines. In addition, ELAPOR1 contains a consensus-binding motif for the activating protein-2 adaptor complex that is involved in clathrin-mediated endocytosis. Indeed, ELAPOR1 colocalizes clathrin in clathrin-coated pits, and is shown to be involved in clathrin-mediated endocytosis. Furthermore, Ansarullah *et al.* showed that through this

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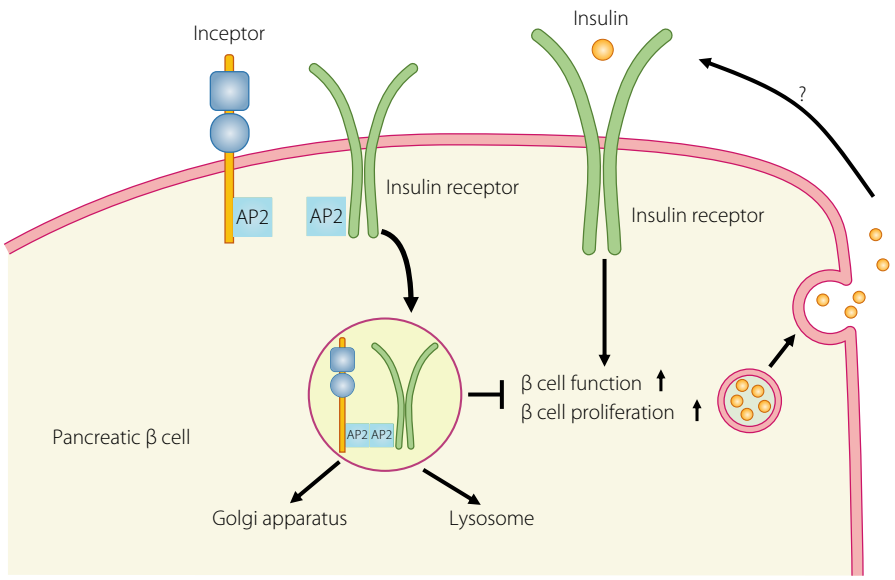

Figure 1 | Inceptor regulates β-cell function. The signal pathway from insulin and insulin-like growth factor-1 receptors has been shown to be essential for the maintenance of normal β-cell function. Activating protein (AP)-2 binding protein inceptor enhances internalization of insulin receptor in β-cells, thus, suppressed expression of inceptor enhances β-cell function.

process, ELAPOR1 binds to the activating protein-2 protein complex to promote clathrin-mediated endocytosis of insulin and the IGF-1 receptor, and, thus, ELAPOR1 is a key molecule for insulin receptor desensitization. Because of the features of ELAPOR1, Ansarullah *et al.*[7] renamed this molecule the insulin inhibitory receptor, or "inceptor" (Figure 1).

These findings are very important, but there remain many unanswered questions. For example, systemic inceptor gene-deficient mice die shortly after birth. What is the reason for this? In addition, whereas insulin signals are known to negatively regulate autophagy, the islets of inceptor gene-deficient mice show upregulation of genes related to autophagy and mitophagy. What is the mechanism involved? The physiological role of inceptor is still far from clear, and the discovery of inceptor alone has not shown specific details regarding insulin action in pancreatic β-cells. However, this discovery might be the starting point for achieving a full understanding of insulin receptor signaling in β-cells.

DISCLOSURE

HW discloses honoraria for lectures for Mitsubishi Tanabe Pharma, Dainippon Sumitomo Pharma, Sanwa Kagaku, Takeda, Sanofi, Kowa, Merck Sharp & Dohme, Boehringer Ingelheim, Eli Lilly and Novo Nordisk, and research activities for Takeda, Boehringer Ingelheim, Kissei Pharma, Novo Nordisk, Mitsubishi Tanabe Pharma, Lifescan Japan, Dainippon Sumitomo Pharma, Kyowa Kirin and Merck Sharp & Dohme.

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