New factors secreted from islets expand β-cell mass

A common feature and critical culprit of type 2 diabetes is a decline in β-cell function accompanied by functional impairment of individual cells and reduction of β-cell mass. From the point of view of treatment based on the pathophysiology of disease, improvement of β-cell function and increase in β-cell mass are the main targets for the treatment of diabetes.

The use of glucagon-like peptide-1 (GLP-1)-based therapy has increased in recent years. Given that GLP-1 stimulates glucose-dependent insulin response and increases pancreatic β-cell mass at least in diabetic rodents, GLP-1-based compounds appear to have good profiles for treatment of type 2 diabetes mellitus. However, some of the GLP-1 mimetic compounds increase heart rate and sometimes cause gastrointestinal side-effects. Accordingly, it is important to continue to search for new drugs that preserve and enhance β-cell function and mass.

Recently, Stephens *et al.*[1] found that TLQP-21, a peptide secreted from pancreatic β-cells, preserves and enhances functional β-cells. Another study found that overexpression of Nkx6.1, a transcription factor essential for β-cell differentiation[2], enhanced glucose-stimulated insulin secretion and β-cell replication[3]. In that study, they showed that Nkx6.1 strongly upregulates the expression of the prohormone VGF. *Vgf* was initially identified as a nerve growth factor-inducible transcript in PC12 cells[4], and its expression is limited to neurons and various endocrine cells including pancreatic β-cells[5]. VGF is a prohormone that is converted to several peptides by prohormone convertases (PC) 1/3 and PC2. Among these peptides, TLQP-21 has gained interest for its effect in increasing energy expenditure after intracerebroventricular injection. In support of its importance, the amino acid sequence of the TLQP-21 peptide is identical in rats and mice, and also highly conserved in humans. However, the role of TLQP-21 in β-cells had not been investigated yet.

In their studies, Stephens *et al.*[1] showed increased release of TLQP-21 by glucose from islets. In addition, short-term administration of TLQP-21 in rats resulted in immediate amelioration of glucose intolerance with enhanced insulin secretion. Furthermore, long-term treatment of Zucker Diabetic Fatty rats with TLQP-21 improved glucose homeostasis by increasing β-cell mass. In addition, TLQP-21 increased cyclic adenosine monophosphate (cAMP) and insulin release in isolated isles, and prevented islet cell death through the protein kinase A (PKA)/insulin-like growth factor 1 receptor (IGF1R)/phosphoinositide 3-kinase (PI3K) pathway (Figure 1). These results suggest that the actions of TLQP-21 on β-cells are similar to GLP-1. However, different from GLP-1, TLQP-21 did not slow gastric emptying nor induced tachycardia. Thus, TLQP-21 might be beneficial in patients who show side-effects to treatment with GLP-1 mimetics.

The action of TLQP-21 is an example that hormones secreted from β-cells, other than insulin, regulate β-cell function. In this regard, the actions of TLQP-21 are similar to serotonin. Serotonin is a neurotransmitter known to regulate sex drive, sleep, mood and also appetite. Recent

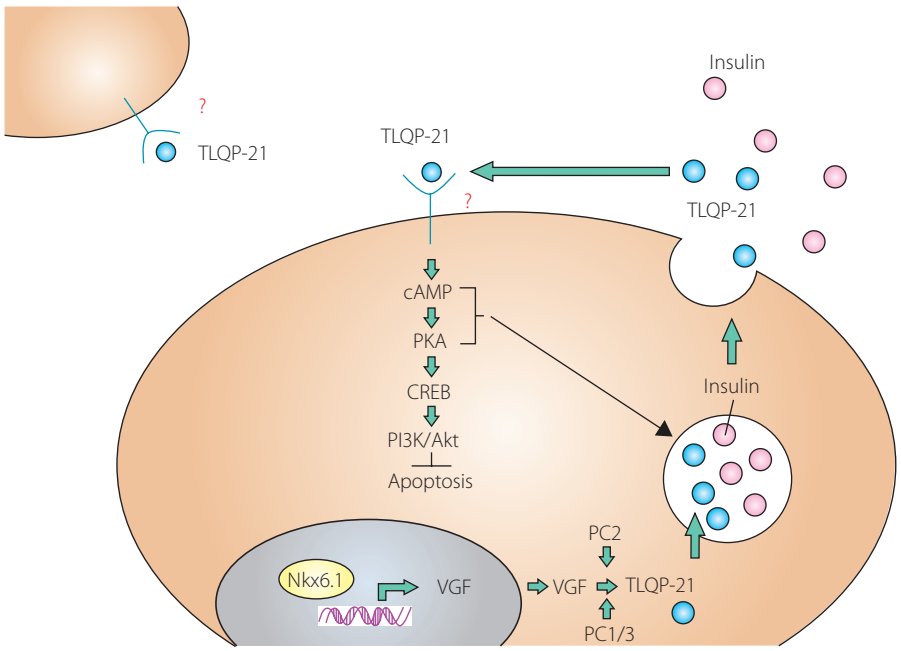

Figure 1 | Schematic diagram of the TLQP-21 signal pathway involved in enhancement of insulin secretion and β-cell expansion. cAMP, cyclic adenosine monosphosphate; CREB, cyclic adenosine monosphosphate responsive element binding protein; PC1/3, prohormone convertase 1/3; PC2, prohormone convertase 2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A.

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studies described the involvement of serotonin in the adaptive expansion of β-cell mass during pregnancy through lactogenic hormones. During pregnancy, β-cell mass increases to compensate insulin resistance. Kim *et al.*[6] showed that lactogenic signals increase the transcription of tryptophan hydroxylase, which is the rate-limiting enzyme in the synthesis of serotonin, resulting in the expression of serotonin in β-cells. The secretion of serotonin by β-cells during pregnancy promotes β-cell replication through its autocrine or paracrine effect. Among the receptors for serotonin, 5-hydroxytryptamine 2b (Htr2b) seems to mediate the effects of serotonin on β-cell mass expansion. In addition to serotonin and TLQP-21, there might be other peptides secreted from β-cells that enhance the expansion of β-cells.

Although it had been thought that GLP-1 is produced by L cells rather than α-cells, recent data have shown that GLP-1 is produced by α-cells during exercise and the state of insulin resistance[7]. Exercise and the state of insulin resistance are associated with high plasma concentrations of interleukin-6 (IL-6). Administration of IL-6 or high IL-6 plasma concentrations in response to exercise promotes the expression of PC1/3 in α-cells, which stimulates the production of GLP-1 by pancreatic α-cells. Consequently, enhanced GLP-1 secretion in islets improves insulin secretion and ameliorates glucose intolerance.

Considered together, we believe that compounds secreted from islets other than the major hormones are potentially suitable targets for the treatment of type 2 diabetes. With regard to TLQP-21 actions, the receptors that mediate the cell signal have not yet been identified. Identification of the cell signal pathway should provide important information for the development of new drugs for type 2 diabetes.

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