Neuronautin and glucose-induced stress in pancreatic β-cells

Type 2 diabetes is caused by peripheral insulin resistance and impaired insulin secretion. However, pancreatic β-cell failure, which results in impaired insulin secretion, is especially important in Asian populations. Although many scientists are investigating the mechanisms of pancreatic β-cell failure, many of these studies are focused on “glucose toxicity.” Glucose has been called “a most important partner” for the induction of insulin secretion in pancreatic β-cells through an increase in cellular adenosine triphosphate levels, whereas glucose has also been described as “a most troublesome enemy” that causes various forms of stress, including oxidative stress and endoplasmic reticulum (ER) stress, in pancreatic β-cells.

When pancreatic β-cells are exposed to high levels of glucose for a long period of time, pancreatic and duodenal homeobox 1 and MAFF bZIP transcription factor A expression is decreased, resulting in a reduction of insulin secretion and pancreatic β-cell mass. This is one of the mechanisms underlying the induction of oxidative stress by pancreatic β-cell failure. When the demand for insulin is increased by hyperglycemia, a large amount of proinsulin is synthesized in pancreatic β-cells; thereafter, proinsulin is folded in the ER. The accumulation of misfolded proinsulin causes ER stress and induces the expression of chaperones for the adaptation to ER stress (i.e., the adaptive unfolded protein response [UPR]). Furthermore, in response to excessive ER stress, pancreatic β-cells activate ER-associated protein degradation and translational attenuation as a defense mechanism. When these responses fail to reduce ER stress, pancreatic β-cells undergo apoptosis (i.e., the terminal UPR).

However, there is no doubt that glucose is an essential source of energy for pancreatic β-cells. Sharma et al. reported that the UPR regulates the number of pancreatic β-cells when insulin demand is increased by glucose load. Glucose stimulation to the islets of mice increases the expression of binding protein, a marker of the UPR. They showed that pancreatic β-cells in which binding protein expression is increased are more likely to proliferate in vivo. In addition, they also showed that the UPR is essential for the glucose-induced proliferation of pancreatic β-cells in vivo and ex vivo, and the activating transcription factor 6 pathway is an important signal in this process. This phenomenon is also observed in human pancreatic β-cells; therefore, their report suggested that glucose stimulation is very important for the proliferation of pancreatic β-cells.

In a recent report, Millership et al. showed that the expression of neuronatin (Nnat), an imprinted gene, is highly induced by glucose stimulation and processes proinsulin to proinsulin through the activation of the signal peptidase complex (SPC) in pancreatic β-cells. They generated and analyzed mice lacking Nnat expression globally and specifically in β-cells, and reported that both types of mice show impaired glucose-stimulated insulin secretion and elevated blood glucose levels during an oral glucose tolerance test. Furthermore, they confirmed that mature insulin and proinsulin content is decreased, whereas unprocessed proinsulin content is increased in Nnat-deficient islets. To investigate the association between Nnat and the accumulation of proinsulin, the authors identified novel interaction partners of Nnat in mouse insulinoma 6 cells using an affinity purification/mass spectroscopy approach. They found that there is an interaction between Nnat and three components of the SPC (SEC11A, SPC51 and SPC52). Their report suggested that Nnat is localized across the ER membrane and regulates glucose-induced insulin secretion through the translocation of proinsulin into the ER by its interaction with the SPC. Nnat expression was found to be regulated by glucose treatment. As Nnat expression is increased in the islets of mice with acute feeding or high-fat feeding, it was considered that Nnat has a role in increasing the levels of mature insulin in response to insulin demand. Thus, Nnat is considered an important regulator of glucose homeostasis under physiological conditions.

Nnat expression is reportedly regulated by micro-ribonucleic acid (miR)-708. In pancreatic β-cells, miR-708 expression is controlled by glucose treatment. Thus, miR-708 expression is reduced under hyperglycemic conditions and is increased in the hypoglycemic state. This result shows an inverse correlation between the expression of miR-708 and Nnat, and helps to explain why Nnat activates the processing of
preproinsulin in the hyperglycemic state. Furthermore, miR-708 expression is regulated by CCAAT/enhancer-binding protein (CHOP), an ER stress-induced transcription factor. CHOP expression is induced by the terminal UPR, and causes cell growth arrest and apoptosis. CHOP is considered to be an important factor for pancreatic β-cell failure, and CHOP-induced miR-708 expression in pancreatic β-cells suppresses Nnat expression under the condition of ER stress (Figure 1). Consequently, prolonged ER stress might induce a reduction of mature insulin content and a decrease in insulin secretion through the impaired processing of preproinsulin. Under pathological conditions, such as ER stress, pancreatic β-cell failure might be alleviated by suppressing miR-708 expression or increasing Nnat expression. Nnat is an essential molecule to maintain glucose homeostasis under physiological conditions, whereas Nnat is expected to be a target molecule for therapy under pathological conditions.

In addition to miR-708, other micro-ribonucleic acids (miRNAs) are reportedly associated with the UPR, especially miR-211 and miR-17, which increase survival by targeting CHOP and caspase-2, respectively (Figure 1). Although there is no current treatment for ER stress, which is a high risk factor for pancreatic β-cell failure, miRNAs might be a notable factor. Recently, dedifferentiation has drawn attention as a mechanism of pancreatic β-cell failure caused by glucose-induced stress. Prolonged hyperglycemia leads β-cells to dedifferentiate, resulting in a decrease in β-cell mass and an increase in α-cell mass. Previous reports have shown that Nnat or miRNAs affect insulin secretion or proliferation in pancreatic β-cells, while the relationship between Nnat/miRNAs and dedifferentiation remains to be elucidated fully. Further investigation is required to uncover the role of Nnat in pancreatic β-cells.

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Figure 1 | Schematic representation of the relationship between neuronatin (Nnat) and glucose-induced endoplasmic reticulum (ER) stress in pancreatic β-cells. Nnat induced by glucose stimulation processes preproinsulin to proinsulin. In the adaptive unfolded protein response (UPR), activating transcription factor (ATF) 6 promotes cell proliferation, and spliced X-box binding protein 1 (XBP1), induced by activated inositol requiring enzyme 1 (IRE1), suppresses cell death. However, when exposed to excessive ER stress, ATF4-induced CHOP and the increase in caspase-2 caused by micro-ribonucleic acid (miR)-17 suppression causes cell death in the terminal UPR. Furthermore, Nnat expression is suppressed by CCAAT/enhancer-binding protein homologous protein (CHOP)-induced miR-708, resulting in the reduction of mature insulin content and glucose-stimulated insulin secretion. These pathways might explain the mechanism of ER stress-induced pancreatic β-cell failure involved in impaired insulin secretion and in reduced β-cell mass. eIF-2α, eukaryotic initiation factor-2α; PERK, protein kinase RNA-like endoplasmic reticulum kinase; SPC, signal peptidase complex.
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