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Asahara, Shun-ichiro

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COMMENTARY

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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 MAF 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 preproinsulin 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.*[1] 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.*[2] showed that the expression of neuronatin (*Nnat*), an imprinted gene, is highly induced by glucose stimulation and processes preproinsulin 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 preproinsulin content is increased in *Nnat*-deficient islets. To investigate the association between *Nnat* and the accumulation of preproinsulin, 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, SPCS1 and SPCS2). Their report suggested that *Nnat* is localized across the ER membrane and regulates glucose-induced insulin secretion through the translocation of preproinsulin into the ER by its interaction with the SPC. *Nnat* in pancreatic islets 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[3]. 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

*Corresponding author. Shun-ichiro Asahara
Tel.: +81-78-382-5861
Fax: +81-78-382-2080
E-mail address: asahara@med.kobe-u.ac.jp
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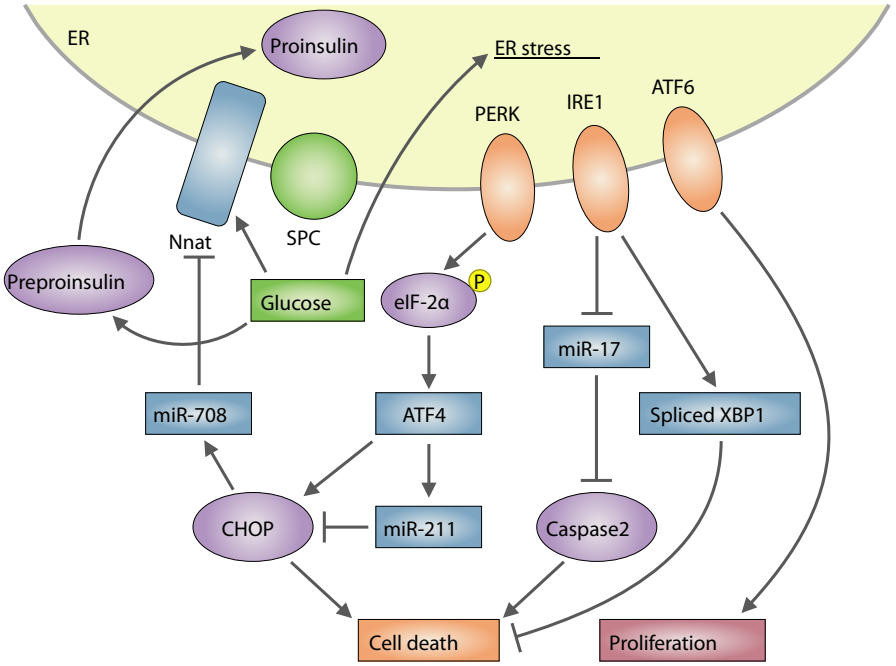

Figure 1 | Schematic representation of the relationship between neuronatin (*Nnat*) and glucose-induced endoplasmic reticulum (ER) stress in pancreatic β-cells. *Nnat* induced by glucose stimulation processes preproinsulin to proinsulin. In the adaptive unfolded protein response (UPR), activating transcription 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.

preproinsulin in the hyperglycemic state. Furthermore, *miR-708* expression is regulated by CCAAT/enhancer-binding protein homologous 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)[4]. 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[5]. 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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DISCLOSURE

The author declares no conflict of interest.

Shun-ichiro Asahara*
Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

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