Review

ER Stress and β -Cell Pathogenesis of Type 1 and Type 2 Diabetes and Islet Transplantation

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Endoplasmic reticulum (ER) stress affects the pathogenesis of diabetes. ER stress plays important roles, both in type 1 and type 2 diabetes, because pancreatic β -cells possess highly developed ER for insulin secretion. This review summarizes the relationship between ER stress and the pathogenesis of type 1 and type 2 diabetes. In addition, the association between islet transplantation and ER stress is discussed.

Key words: β -Cells; Endoplasmic reticulum (ER) stress; Islet transplantation

ER STRESS IN DIABETES

Diabetes mellitus is a devastating disease, and the World Health Organization (WHO) expects that the number of diabetic patients worldwide will increase to 300 million by 2025. Type 1 diabetes results from autoimmune-mediated destruction of insulin-secreting β -cells of the pancreas, whereas type 2 diabetes is associated with systemic insulin resistance and reduced insulin secretion by β -cells. Type 1 diabetes develops when β -cells are selectively disrupted by autoimmune and/or inflammatory processes. Type 2 diabetes occurs when both functional defects and reduced β -cell mass contribute to β -cell dysfunction. Apoptosis in β -cells is detected in both type 1 diabetes and type 2 diabetes (4). Hyperlipidemia and hyperglycemia are likely causes of β -cell apoptosis (8,20,27,34). Pancreatic β -cells produce insulin in response to fluctuations in blood glucose levels. There is a constant demand from the body for insulin biosynthesis and secretion, so baseline endoplasmic reticulum (ER) stress levels are high in these cells. Evidence suggests that cellular stress caused by the accumulation of unfolded and misfolded proteins in the ER is related to β -cell dysfunction and death during

the development and progression of type 1 and type 2 diabetes (9,10,32).

The ER is an organelle that has several important functions, such as posttranslational modification, folding and assembly of newly synthesized secretory proteins, and storing cellular calcium (Ca^{2+}). Pancreatic β -cells possess a highly developed ER, required for the folding, export, and processing of newly synthesized insulin. Human preproinsulin is synthesized in the cytoplasm, translocated into the lumen of the ER, and cleaved to produce proinsulin. Proinsulin undergoes protein folding in the lumen of the ER. Properly folded proinsulin is then delivered to the Golgi apparatus and packed into secretory granules (23). The conversion of proinsulin to insulin takes place in the secretory granules, and mature insulin is released by exocytosis (28). ER homeostasis must be maintained in order for secretory proteins to fold properly. Various conditions that disturb ER function result in stress that causes the accumulation of misfolded proteins in the ER (2,28,42). ER function can be impaired by viral infections, environmental toxins, inflammatory cytokines, and mutant protein expression, as well as by physiological processes

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such as aging and the large biosynthetic load placed on the ER such as due to insulin production in response to blood glucose fluctuations.

Cells have a self-protective mechanism, known as the ER stress response or unfolded protein response (UPR), that allows them to survive under ER stress conditions. That mechanism involves [1] translational attenuation, which reduces synthesis of new protein and prevents further accumulation of unfolded proteins; [2] upregulation of the genes encoding ER chaperone proteins to increase protein folding activity and to prevent protein aggregation; [3] proteosomal degradation of misfolded proteins following their regulated extrusion from the ER; and [4] apoptosis in the event of persistent stress (28,29). The UPR either protects β -cells or promotes their death, depending on the nature of the stress condition. The UPR induces apoptosis when ER function is severely impaired. Signaling from the ER is initiated by ER-localized stress sensors, protein kinase RNA (PKR)-like ER kinase (PERK), activating transcription factor (ATF)6, and inositol-requiring kinase (IRE)1, which remain inactive under nonstress conditions due to association of their ER luminal domains with binding protein (BiP) (3). Apoptosis is induced by ATF4 transcriptional activation of the gene for cytidine-cytidine-adenosine-adenosine-thymidine (CCAAT)/enhancer-binding protein (C/EBP) homologous protein (CHOP) (24,39) and by activation of c-Jun N-terminal kinase 1 (JNK1) and caspase-12 (2,28,42).

ER Stress and Type 1 Diabetes

Pancreatic β -cells are the target of an autoimmune assault in type 1 diabetes, with invasion of the islets by mononuclear cells in an inflammatory reaction termed "insulinitis," leading to loss of most β -cells after prolonged periods of disease (16). Both animal models and human type 1 diabetes show that β -cell apoptosis coincides with expression of cytokines such as interleukin (IL)-1 β , interferon (IFN)- γ , and tumor necrosis factor (TNF)- α by the infiltrating immune cells and inducible nitric oxide (NO) synthase (iNOS) by both β -cells and immune cells (14,36). However, the complete mechanisms causing β -cell destruction have not been clarified. Recent studies have proposed that the mechanism of cytokine-induced β -cell death involves ER stress. β -cells are characterized by highly developed ER, which is important for insulin secretion. β -Cells represent one of the tissues most susceptible to ER stress (2). The baseline of ER stress in β -cells is higher than that of other cell types due to their exposure to frequent energy fluctuations, constant demand of insulin biosynthesis, and secretion (10). Viral infections, environmental stresses, as well as NO are insults to the β -cell that can lead to excessive, unresolved ER stress, thus triggering an apoptotic cascade (23).

Oydomari et al. revealed the mechanism of β -cell damage by ER stress. They used mouse insulinoma 6 (MIN6) cells, a mouse β -cell-derived cell line. They showed that CHOP, a C/EBP homologous protein, is induced by a NO donor and leads to apoptosis. They concluded that NO depletes ER Ca^{2+} , causes ER stress, and leads to β -cell apoptosis. Ca^{2+} is required for the protein binding and chaperoning ability of ER chaperones (25). Severe ER Ca^{2+} depletion will impair the quality of ER protein folding and trigger CHOP expression and apoptosis. Cardozo et al. reported that production of NO leads to the attenuation of the sarcoendoplasmic reticulum pump Ca^{2+} ATPase2b (SERCA2b) and consequently the reduction of Ca^{2+} in the ER. This Ca^{2+} depletion leads to severe ER stress and the induction of the proapoptotic transcription factor CHOP. They suggested that IL-1 β and IFN- γ -induced decrease in SERCA2b expression, with subsequent depletion of ER Ca^{2+} and activation of the ER stress pathway, is a potential contributory mechanism to β -cell death (5). In addition, Wang et al. suggested that the IL-1 β -induced depletion of ER Ca^{2+} and activation of the ER stress via the JNK pathway are potential mechanisms that contribute to β -cell death (38).

On the other hand, there are studies that suggest that the PERK-ATF4-CHOP ER stress-signaling pathway is not required for cytokine-induced β -cell death (1). Although more studies and new insights are expected to clarify the mechanism of β -cell apoptosis in type 1 diabetes, it is clear that ER stress plays important roles in β -cell dysfunction.

ER Stress and Type 2 Diabetes

Resistance to insulin action in peripheral tissues, such as adipose tissue, muscle, and liver, is one of the primary presenting features of type 2 diabetes. This insulin resistance leads to the hyperproduction of insulin in the β -cell. Hyperglycemia and type 2 diabetes develop in patients who are unable to sustain this compensatory response of the β -cell. This high insulin production exceeds the ER folding capacity and leads to severe, chronic hyperactivation of the UPR, inducing β -cell apoptosis. This phenomenon is associated with chronic activation of IRE1 during consistent insulin biosynthesis, which leads to activation of the IRE1-JNK proapoptotic signaling pathway (37). ER stress has been proposed to be the cellular/molecular mechanism linking obesity with insulin resistance (6). Ozcan et al. showed that obesity can cause ER stress. It leads to the suppression of insulin receptor signaling through hyperactivation of JNK and subsequent serine phosphorylation of insulin receptor substrate-1 (IRS-1) (26). Several studies have indicated that ER stress is an early consequence of nutrient excess and a cause for the development of insulin resistance and inflammation. Chronic excess nutrient intake has been shown to cause

ER stress, as well as insulin resistance and inflammation in the adipose tissue of ob/ob mice and in mice with high-fat diets (11).

CHOP is also induced by ER stress and has a central role in its apoptotic execution pathways. A recent study revealed that systemic deletion of CHOP induced abdominal obesity and hepatic steatosis, with normal glucose tolerance and insulin sensitivity, and revealed lower levels of proinflammatory cytokines and less infiltration of immune cells into fat and liver. It indicated that insulin resistance is not induced by fat accumulation, but rather by the inflammation induced by ectopic fat, and CHOP may take important role in inflammation that induce insulin resistance (21). Free fatty acids (FFAs) might also be responsible for the ER stress response observed in the hepatocytes or adipocytes of obese mice (22,26), while simultaneously disturbing pancreatic β -cell function and viability. Furthermore, Laybutt demonstrated that the proapoptotic fatty acid palmitate triggers a comprehensive ER stress response in MIN6 cells, as well as the activation of genes involved in ER stress, in islets from db/db mice and from human type 2 diabetes subjects (18). In addition, Sage et al. suggested that ER stress was elevated in monocytes isolated from individuals with metabolic syndrome (31). Monocytes play an important role in causing insulin resistance and vascular complications. These findings suggest that there is an association between both acute and chronic hyperglycemia and ER stress in humans.

ER STRESS AND ISLET TRANSPLANTATION

Controlling the blood glucose level is therefore critical for preventing vascular complications in diabetes and maintaining the function of β -cells. However, it is difficult to achieve the optimal control. The Third National Health and Nutrition Examination Survey (NHANES III) showed that only 50% of diabetics achieve a glycated hemoglobin (HbA1c) level of less than 7%. The only way to ensure the long-term health of diabetic patients is to maintain constant normoglycemia. However, despite intensive insulin therapy, most individuals with type 1 diabetes are unable to maintain a blood glucose level in the optimal range. In addition, intensive insulin therapy is associated with an increased risk of hypoglycemia. Pancreatic islet transplantation has emerged as one of the most promising therapeutic approaches for improving glycometabolic control in type 1 diabetic patients (12). The "Edmonton Protocol" introduced several modifications to the transplantation procedure, such as the use of a steroid-free immunosuppression regimen and transplantation of a mean islet mass of 11,000 IEQ/kg of a patient's weight (33). Clinical islet transplantation activity has dramatically increased all over the world. However, the Edmonton group showed that only 7.5% of the 65 patients who received islet transplantation achieved insulin independence, although the majority of

patients (82%) presented graft survival (C-peptide positivity) (30). Islet transplantation still faces major challenges, especially those related to cell loss during the process of islet isolation and the losses related to the graft site, apoptosis, allorejection, autoimmunity, and immunosuppression. In addition, glucose toxicity (40) and the abnormal transplant environment (17) are likely to contribute to the dysfunction of transplanted β -cells. Chronic hyperglycemia causes excess ER stress that induces β -cell apoptosis (9,41). Understanding the transplant environment is therefore important for understanding the molecular mechanism of glucose toxicity of β -cells.

Kennedy et al. reported that human β -cells in a transplant site show UPR changes in gene expression that protect against the proapoptotic effects of unfolded proteins (15). They evaluated the expression of genes involved in ER stress in β -cell-enriched tissue obtained with laser capture microdissection (LCM) from frozen sections of pancreases obtained from nondiabetic subjects at surgery (control) and from human islets transplanted into imprinting control region-severe combined immunodeficient (ICR-SCID) mice. The transplanted β -cells were exposed to mild hyperglycemia since mice have higher glucose levels than humans. RNA was extracted from the LCM specimens and microarray analysis was performed. The transplanted β -cells showed a UPR. Many genes of the IRE1 pathway that provide protection against the harmful effects of ER stress were observed to be activated, thus increasing the expression of ER chaperones and ER-associated protein degradation (ERAD) proteins. The IRE1 pathway is important in insulin biosynthesis in which transient increases in insulin production lead to IRE1 activation (37). However, the chronic activation of IRE1 during prolonged increases in insulin biosynthesis may lead to β -cell death through IRE1-mediated activation of JNK (19). However, two genes known to contribute to apoptosis, CHOP and JNK, were downregulated in this study. It is striking that β -cells in a transplant site exhibit UPR with changes that should help the cells adapt to unfolded proteins and to resist apoptosis.

Another factor that causes ER stress in transplanted β -cells is immunosuppressants. Johnson et al. showed that 24-h exposure to FK506 (tacrolimus) or mycophenolate mofetil (MMF), but not rapamycin, impairs glucose-stimulated insulin secretion in human islets. FK506 also could have acute and direct effects on islet function, whereas MMF does not. Increased cleaved caspase-3 protein levels are a hallmark of β -cell apoptosis. Caspase-3 cleavage is increased by FK506, MMF, and rapamycin (13). As CHOP is the transcriptional factor that plays an essential role in β -cell apoptosis (24), MMF and rapamycin induced CHOP expression. However, treating human islets with the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide ameliorates the immunosuppressant-

induced defects in glucose-stimulated insulin release (13). The GLP-1 receptor agonist was reported to significantly reduce biochemical markers of islet ER stress in vivo. This suggests that GLP-1 receptor signaling directly modulates the ER stress response leading to promotion of β -cell adaptation and survival (43). In addition, GLP-1 receptor agonists protect β -cells against FFAs through the induction of the ER chaperone BiP and the antiapoptotic protein JunB, which mediate β -cell survival under lipotoxic conditions (7). Another report revealed that chronic GLP-1 analog liraglutide treatment increased the expression of antioxidant genes and reduced ER stress-related genes in β -cells of db/db mice (35).

Islet transplantation is one of the promising therapeutic approaches for type 1 diabetic patients. Future investigations must clarify the pathophysiology of transplanted β -cells. A better understanding of ER stress and its management is therefore required in order to maintain the transplanted β -cell function.

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