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Stress hypERactivation in the beta-cell

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In pancreatic β-cell, the endoplasmic reticulum (ER) is the crucial site for insulin biosynthesis, as this is where the protein-folding machinery for secretory proteins is localized. Perturbations to ER function of the β-cell, such as a high demand for insulin secretion, can lead to an imbalance in protein homeostasis and lead to ER stress. This stress can be mitigated by an adaptive, cellular response, the Unfolded Protein Response (UPR). UPR activation is vital to the survival of β-cells, as these cells represent one of the most susceptible tissues for ER stress, due to their highly secretory function. However, in some cases, this response is not sufficient to relieve stress, leading to apoptosis and contributing to the pathogenesis of diabetes. Recent evidence shows that ER stress plays a significant role in both type 1 and type 2 diabetes. In this review, we outline the mechanisms of ER stress-mediated β-cell death and focus on the role of ER stress in various forms of diabetes, particularly a genetic form of diabetes called Wolfram Syndrome.

Introduction

Pancreatic β-cells have the specialized function of regulating glucose homeostasis by synthesizing and secreting the hormone insulin. Newly synthesized insulin is not immediately functional—it must be folded into its proper three-dimensional structure. The endoplasmic reticulum (ER) has an essential role in the processing and assembly of insulin, with its complex of chaperones, such as immunoglobulin heavy chain-binding protein (BiP) and foldases, such as protein disulfide isomerase (PDI).

The sensitive folding environment of the ER can be disrupted by physiological processes, such as post-prandial insulin biosynthesis which places a heavy load on the ER, as well as a pathological exposure to viruses, toxins, cytokines and mutant protein expression. ER stress occurs when the ER exceeds its folding capacity with such disruptions, leading to an overall dysregulation of protein homeostasis, reflected as reduced maintenance of the quality and quantity of protein and an accumulation of unfolded/misfolded proteins that cannot be processed through the secretory pathway. This stress elicits an ER-to-nucleus signaling cascade, the Unfolded Protein Response (UPR), which mitigates stress in three distinct manners: (1) enhancement of folding activity through increased chaperone/foldase expression, (2) reduction of ER workload through general translational attenuation and (3) clearance of protein aggregation and residual unfolded proteins through ER-associated protein degradation (ERAD). When the UPR does not adequately reduce stress and return the cell to a state of protein homeostasis, the cell undergoes apoptosis.

β-cell apoptosis has recently been shown not only to be a component of type 1 diabetes, but also type 2 diabetes. In type 1 diabetes, β-cells are selectively destroyed by a combination of autoimmune and inflammatory processes leading to an absolute insulin deficiency, whereas in type 2 diabetes, resistance to insulin in peripheral tissues accompanied by a reduction in insulin secretion contributes to relative insulin deficiency.

The UPR has three master transducers which serve to mitigate stress: inositol requiring 1 (IRE1), PKR-like kinase (PERK), and activating transcription factor 6 (ATF6). The ER chaperone BiP binds to each of these to maintain them in an inactive state until ER stress is present (i.e., unfolded and misfolded proteins accumulate in the ER lumen) (Fig. 1). IRE1α, is a type 1 ER transmembrane kinase that has endoribonuclease activity. Mammalian cells have two isoforms, IRE1α and IRE1β, which both have functions as sensors of the UPR. IRE1α is ubiquitously expressed, while the β isomorph is uniquely expressed in the epithelial cells of the gastrointestinal tract. When unfolded or misfolded proteins accumulate in the ER, IRE1α dimerizes and undergoes trans-autophosphorylation to become active. Activation of its kinase domain leads to activation of its endoribonuclease function, whereby the mRNA of the transcription factor X-box protein binding 1 (XBP1) is unconditionally spliced. Spliced XBP1 translocates to the nucleus where it upregulates a variety of UPR target genes encoding ERAD components, as well as foldases such as PDI.

PERK, also a type 1 ER transmembrane kinase, senses stress in its N-terminal luminal domain. When released from BiP, PERK dimerizes and undergoes trans-autophosphorylation. Activated PERK, directly phosphorylates the α subunit of eukaryotic initiation factor 2 (eIF2α), its only identified target. This in turn inhibits general protein synthesis, while preferentially increasing

Key words: ER stress, UPR, diabetes, β-cell, Wolfram syndrome, WFS1
translation of UPR target mRNAs, such as activating transcription factor 4 (ATF4).12

ATF6, on the other hand, is a type II ER transmembrane transcription factor, which is released from the ER membrane when ER stress is present. It then transits to the Golgi where it is cleaved by S1 and S2 proteases, a process called regulated intramembrane proteolysis (RIP).13 The processed form of ATF6 translocates to the nucleus where it upregulates UPR genes primarily involved in protein folding, such as BiP.14

It is of much interest that there is extensive crosstalk between the three UPR pathways. For example, IRE1 null cells are still able to induce chaperones in response to stress,15 while a loss of ATF6α (one of the two ATF6 isoforms), leads to diminished activation of ERAD components which were originally thought to be IRE1-dependent.16 Additionally, there is convergence of the ATF6α and PERK pathways, in which there is a mutual control of a subset of targets such as C/BEP-homologous protein (CHOP), BiP, and protein kinase inhibitor of 58 kDa (p58IPK).17 These types of cross-talks were probably evolved by high eukaryotes to enhance survival during times of severe ER stress. The extent of the overlap between pathways and feedback loops could interestingly be dependent on cell type, with highly secretory cells, such as pancreatic β-cells, illustrating a greater communication between pathways.

**Protein Homeostasis in the β-Cell**

Insulin is secreted by the β-cell in response to acute hyperglycemia which occurs post-prandially. This secretory response stimulates the biosynthesis and translation of the precursor proinsulin in the ER, in which there is approximately a 10-fold increase in synthesis from a low-glucose (<3 mM) to higher glucose concentrations.18,19 Preproinsulin is synthesized in the cytoplasm and co-translationally translocated into the ER. Preproinsulin’s signal peptide is cleaved in the ER to generate proinsulin, which then undergoes precise folding in the lumen of the ER, where three disulphide bonds are formed. Once proinsulin is properly folded, it is transported to the Golgi and packaged into secretory granules, where it is processed to yield mature insulin.20

β-cells, due to their heavy engagement in insulin secretion,21 have been found to be very sensitive to disruptions in ER homeostasis.22 This is reflected in the fact that these cells have a highly developed ER and a high expression of ER stress transducer proteins such as IRE1α, PERK, total XBP1, GRP94 and BiP.23-27 Thus, while β-cells have a robust ER signaling system, they are sensitive to disruptions in a system that is already at capacity. These cells are exposed to frequent energy fluctuations (i.e., intermittent changes in blood glucose levels), and thus require precise and proper folding of proinsulin to respond to such changes. Thus, any imbalance between the load of insulin translation placed on the ER and the ER folding capacity will lead to ER stress and a disruption in protein homeostasis in these cells.

The IRE1-XBP1 signaling pathway is important for ER expansion,28 and the IRE1α isoform is highly expressed in the pancreas.29 β-cells have been shown to have a baseline phosphorylation of IRE1α, illustrating the high activity of the UPR in these cells. Suppression of IRE1 activity inhibits proinsulin biosynthesis, while activation enhances insulin biosynthesis in an XBP1-independent manner.27 While the downstream targets of this unique IRE1 pathway have yet to be identified, it is known that the ER-resident oxidoreductase, endoplasmic oxidoreductin 1 (ERO1α) is upregulated. ERO1α is an activator of PDI, which is critical in catalyzing the formation of disulphide bonds during protein folding in the ER.30 Thus, IRE1 activation may enhance insulin biosynthesis through the upregulation of ERO1α which in turn is responsible for the vital formation of the three disulphide bonds in proinsulin through PDI activation.

PERK is also highly expressed in islets.31 PERK activation (i.e., phosphorylation) negatively regulates insulin biosynthesis.31 In PERK null mouse islets, high glucose treatment-induced insulin biosynthesis was enhanced compared to control littermate islets.24 In β-cell-specific PERK null mice, a connection has been made between the expression of PERK and β-cell development and proliferation.32 PERK mutations are also the cause of a genetic form of diabetes called Wolcott-Rallison syndrome.33 Thus, the IRE1 pathway (positive regulator) and PERK pathway (negative regulator) work together to precisely regulate insulin output, again highlighting the importance of the UPR in the β-cell.

Recently, it has been demonstrated that ATF6 may also have a function in regulating insulin. Under ER stress, ATF6 is activated, leading to a decrease in insulin gene expression.34 This suggests that ATF6 may have dual functions: positive regulation of chaperones and negative regulation of insulin promoter activity. The involvement of the UPR triad (i.e., IRE1, PERK and ATF6) in β-cell proteostasis and insulin biosynthesis illustrates...
the extensive crosstalk in the UPR network which precisely regulates protein secretion.

**HypERactivation of the UPR**

There are two protein quality control outputs of the UPR: homeostatic and apoptotic. The goal of the UPR is to restore protein homeostasis, however, this may involve apoptosis to ensure that highly stressed cells do not produce damaged (i.e., misfolded) secretory proteins. Indeed, ER stress can be classified into two groups: physiological and pathological. Physiological stress occurs when there is a high demand for protein load. This is acute stress that is readily mitigated by the UPR. One example of this is acute post-prandial ER stress in the β-cell—there is a high demand for insulin biosynthesis following food intake which increases the folding load of the ER. This stress is actually favorable to the β-cell.27

When ER stress is severe or prolonged such that it cannot be resolved by the UPR, cell death occurs by apoptosis.28,29 This prolonged stress can be attributed to an insufficient UPR response, or hyperactivation of a component of the UPR (i.e., the UPR is not properly regulated). There are at least three pathways involved in ER stress-dependent apoptosis which culminate in the activation of the effector cysteine protease, caspase-3: (1) transcriptional activation of CHOP which represses Bcl-2,37 (2) activation of the effector cysteine protease caspase-12: (3) activation of CHOP which represses Bcl-2,37 (2) activation of the effector cysteine protease, caspase-3,37 and (3) activation of JNK by IRE1-dependent recruitment of the adaptor protein, TRAF2.38

Physiological ER stress in the β-cell is beneficial and leads to the highly-regulated activation of insulin biosynthesis.27 This is attributable to acute hyperglycemia. This physiological stress can also be referred to as Stimulus-Coupling Adaptation to ER Folding (SCAF). In this state, the downstream apoptotic factors of the UPR are not activated. However, exposure of these cells to chronic, prolonged hyperglycemia induces pathological ER stress which impairs ER function. This leads to β-cell dysfunction and eventually cell death because this pathological stress leads to hyperactivation of the UPR. An example of this can be seen when β-cells are treated with an inhibitor of eIF2α dephosphorylation, salubrinal.41 Persistent activation of the PERK-eIF2α pathway is deleterious to these cells, most likely due to the inhibition of general translation. Hyperactivation of IRE1, as measured by its chronic phosphorylation, also leads to cell death via the JNK pathway42 and the degradation of mRNAs encoding key stress signaling regulators, such as chaperones.43 Thus, hyperactivation of any of the UPR triad pathways is detrimental, even the ATF6 pathway which controls the expression of the pro-apoptotic CHOP transcription factor.14,44 In addition to treatment of β-cells with chronic high glucose, there are other causes of pathological ER stress in the cells: exposure to long-chain free fatty acids (e.g., palmitate),45,46 hyperinsulinemia which occurs in the pre-diabetic stage,47 glucose deprivation,48 islet amyloid polypeptide (IAPP) expression49 and exposure to inflammatory cytokines such as IL-1β and IFNγ.50

One may consider that through the evolution of the β-cell, there should have been the development of a robust defense mechanism against ER stress-mediated apoptotic outcomes. However, because of the constant demands of insulin biosynthesis, this has rendered the β-cell dependent on a highly efficient UPR. Recent findings show that β-cells are highly susceptible to ER stress-mediated apoptosis and this can be a cause of diabetes.51,52

**Wolfram Syndrome: A Model of ER Stress-Mediated β-Cell Death**

Current evidence suggests that ER stress is one of the molecular mechanisms of β-cell dysfunction contributing to the pathogenesis of diabetes.41,45,55 The relationship of ER stress and diabetes can clearly be seen in a rare, autosomal recessive form of juvenile diabetes, Wolfram syndrome.

The first report of this disease was documented in 1938 when Wolfram and Wagener analyzed eight siblings, four of which had a combination of juvenile diabetes and optical atrophy.54 This disease has been characterized as having four cardinal components: diabetes insipidus, diabetes mellitus, optic atrophy and deafness, of which only diabetes mellitus and optical atrophy are required to make a diagnosis.55-58 Diabetes mellitus typically becomes symptomatic in the first decade of life, with a mean age of 6, while optic atrophy follows in the second decade (mean age of 12).59,60 Of the other symptoms, 73% of patients develop diabetes insipidus, 62% develop sensorineural deafness, 58% develop renal tract complications, and 62% develop neurological defects.59 A high percentage of patients also present
with urinary tract abnormalities and neuropsychiatric impairment, while powdered cataract and retinopathy can also be seen in a fraction of these patients. While generally considered a rare disease in most countries, for example in the UK the prevalence is 1/770,000, some countries like Japan and Lebanon have higher incidences.

The nuclear gene responsible for this syndrome which spans 33.4 kb of genomic DNA was identified by two separate groups in 1998 and named WFS1. To date, there are over 130 distinct mutations in WFS1 identified in patients. While there has been no descript mutational hotspot noted, most are located in the region which encodes the transmembrane and C-terminal domain of the protein, exon 8. A majority of patients are compound heterozygotes for two mutations, most of which have one mutation that alters the C-terminal tail. Even mutations of the last seven amino acids of the C-terminal lead to a full disease phenotype, suggesting that this region may be important to the function of WFS1.

In a survey of patient mutations, 35% were missense, 25% nonsense, 21% frameshift, 13% inframe deletions/insertions and 3% splice-site. It is challenging to make conclusive genotype-phenotype relationships, although severely inactivating mutations, for example a premature stop codon, seem to elicit more severe symptoms than mildly inactivating ones, such as missense mutations, and mutations outside of exon 8 typically present with a more mild phenotype.

WFS1 mutations in patients with Wolfram syndrome thus lead to a loss-of-function of WFS1. It must be noted that the heterogeneity of this disease has led to the recent discovery of another locus for this disease, WFS2/Miner1/CISD2, which accounts for only a fraction of Wolfram syndrome cases.

WFS1 is a 100 kDa glycosylated protein that is localized to the ER membrane. Its N-terminal is cytoplasmic, while its C-terminal is located in the ER lumen. The C-terminal of WFS1 is highly conserved in the mouse, rat and human. N-glycosylation is its only predicted post-translational modification and it is projected to have nine transmembrane domains. There is evidence which suggests that WFS1 may function as a calcium channel; ectopic expression of WFS1 produces an increase in calcium concentration in the cytosol and exhibits cation-selective channel activities in the ER membrane. This suggests that WFS1 may function in ER calcium homeostasis. WFS1 may also regulate ion homeostasis of the canalicular reticulum. Hence, inactivation or suppression of WFS1 may cause an imbalance in ER calcium homeostasis.

While ubiquitously expressed, WFS1 is highly expressed in the pancreas. Although Wolfram syndrome patients are generally not obese, nor do they have insulitis, postmortem studies reveal a selective loss of β-cells in their pancreatic islets. In line with this, WFS1 is not only highly expressed in β-cells, but is localized to these cells in the pancreas, with no detectable expression in the various other pancreatic cell types.

While it was known that the loss of β-cells in patients is not auto-immune related, the cause of cell death has been elusive until recently. WFS1 has been shown to be a component of IRE1 and PERK signaling and is important in the maintenance of ER homeostasis, particularly in β-cells. It has also been reported that glucose-induced cytosolic calcium production is lower in the islets of WFS1 knockout mice as compared to controls. Suppression of WFS1 leads to high levels of ER stress in β-cells, suggesting that WFS1 protects β-cells against ER stress and, conversely, chronic ER stress is caused by a loss-of-function of WFS1 protein. Together, these findings suggest that a lack of functional WFS1 causes abnormal calcium homeostasis in the ER, elicits ER stress, and triggers apoptosis in pancreatic β-cells. This suggests that Wolfram syndrome can be attributed to chronic, unresolved ER stress in the β-cell.

The precise function of WFS1 in ER stress signaling has remained somewhat elusive. However, there is several lines of evidence which suggest that WFS1 may be a multi-functional protein. For example, it was reported that the C-terminal and transmembrane domains of WFS1 interact with the Na+/K+ ATPase β1 subunit. WFS1 mutations thus disrupt this interaction which is speculated to decrease α1 and β1 sodium pump subunit expression in β-cells leading to cell dysfunction. The question remains whether this interaction is a result of ER stress and is it primary or secondary to the pathology of Wolfram syndrome. In addition, WFS1 can bind the Ca2+/CaM complex, which suggests that WFS1 may modulate the actions of Ca2+ as an intracellular second messenger. Impairment of binding of this complex may also cause a loss-of-function of WFS1. There is also preliminary evidence that WFS1 regulates a key transcription factor of the UPR, ATF6, through the ubiquitin-proteasome pathway. Higher expression of WFS1 in β-cells, prevents hyperactivation of ER stress signaling.
in these cells which are particularly sensitive to disruption of ER homeostasis and dysregulation of the UPR. Thus, WFS1 has a role in protecting β-cells from premature death by acting as an ER stress signaling suppressor.

Interestingly, WFS1 may also have a role in insulin biosynthesis and secretion. WFS1 expression is induced during glucose-induced insulin secretion. This data, along with the localization of WFS1 to the β-cell, suggests that WFS1 is an important component of proinsulin folding and processing in the ER of the β-cell. The role of WFS1 as a regulator of the ATF6 branch of the UPR may also be related to its role in regulating insulin biosynthesis and/or secretion, demonstrating the multi-functional aspect of this protein. Indeed, activation of ATF6 by ER stress has been shown to decrease insulin gene expression. ATF6 polymorphisms and haplotypes are also associated with impaired glucose homeostasis and type 2 diabetes. Thus, this raises the possibility that the interaction between WFS1 and ATF6 not only functions as a method to regulate the UPR, but also insulin biosynthesis: by restricting ATF6 activation, WFS1 prevents ATF6-mediated suppression of insulin gene expression.

Studying rare diseases, such as Wolfram syndrome, can help lead to answers to more common diseases, because there is a single genetic defect which can allow researchers to focus on the function of a gene or protein that is often involved in common diseases. Indeed, a link can be made between Wolfram syndrome and common diseases as a gene or protein that is often involved in common diseases. This could be defined as a cell-type specific UPR transducer. Together, the current research on WFS1 demonstrates that indeed there is a link between ER stress and the pathogenesis of various forms of diabetes: genetic, type 1 and type 2. Thus, WFS1 may be an important target for diabetes prevention and/or therapy. Currently, a patient registry has been initiated by Dr. Alan Permutt’s group at Washington University to better define the natural history of this disease and find further links between ER stress and common forms of diabetes.

**Type 1 and Type 2 Diabetes and the ER Stress Connection**

Genetic forms of diabetes, such as Wolfram syndrome, are just the tip of the iceberg when it comes to linking ER stress with the metabolic syndrome. There is recent evidence which links type 1 diabetes and ER dysfunction. The production of pro-inflammatory cytokines by phagocytes, such as monocytes and macrophages, plays a key role in the pathogenesis of this disease. This includes the production of TNFα, IL-12, IL-1β and IFNγ. These cytokines have been shown to decrease ER calcium and cause severe ER stress and ER stress-mediated apoptosis in β-cells. In addition, IFNγ and IL-1β in β-cells induce the production of nitric oxide (NO). This in turn leads to β-cell failure and apoptosis, thus NO also plays an important role in the pathogenesis of type 1 diabetes. There is evidence that this NO-induced β-cell apoptosis is mediated by ER stress signaling. NO production leads to a reduction of ER calcium levels through the attenuation of the sarcoendoplasmic reticulum Ca2+-ATPase2b (SERCA2b), causing β-cell reactive killer T cells which can add further insult by destroying any remaining islets.

There is a further connection which links ER stress and the UPR with type 2 diabetes. Reduction of β-cell mass is a contributing component of the pathogenesis of this form of the disease. Insulin resistance is a primary feature which leads to hyperinsulinemia in the β-cell. This high insulin production overwhelms the ER folding capacity and leads to severe, chronic hyperactivation of the UPR, inducing β-cell apoptosis. This has been seen with chronic activation of IRE1 during prolonged periods of insulin biosynthesis which leads to activation of the IRE1-JNK pro-apoptotic signaling pathway. CHOP and glycogen synthase kinase 3 (GSK3β) may also promote the progression of type 2 diabetes via ER stress-mediated β-cell death. Evidence which supports this ER connection includes the data which shows the ER density and volume are over two-fold higher in human diabetic β-cells than non-diabetic β-cells and diabetic islets cultured in high glucose demonstrate an induction of BiP and spliced XBP1, which was not noted in non-diabetic counterparts. There is also a deeper link between the insulin resistance feature of type 2 diabetes and ER stress. Glucolipotoxicity (i.e., the exposure of the β-cell to chronic
high glucose and long-chain free fatty acids) has recently been shown to lead to excessive ER stress which may perpetuate the cycle of β-cell exhaustion and the strain already placed on the ER of the β-cell by hyperinsulinenia. In addition, ER stress is involved in insulin resistance of the liver, muscle and adipose.

Figure 4. Nitric oxide production and ER stress-mediated apoptosis. Nitric oxide production in the β-cell due to exposure of inflammatory cytokines, can cause apoptosis of the β-cell through two pathways: (1) ER stress-mediated and (2) non-ER stress-mediated. In the ER stress mediated pathway, nitric oxide causes calcium depletion from the ER, leading to the accumulation of unfolded and misfolded proteins (i.e., ER stress) and the activation of the pro-apoptotic gene, CHOP.

Figure 5 summarizes the link between ER stress and the different forms of diabetes.

Future Perspectives

There is abundant evidence to support the role of ER stress and stress signaling in the physiological function of the β-cell, as well as the pathogenesis of different forms of diabetes. This has been exquisitely demonstrated through studies of monogenic forms of diabetes such as Wolfram syndrome. Such studies have allowed researchers to better understand components of the UPR pathway and their functions, as well as the importance of ER stress signaling in the pancreatic β-cell. This has been highlighted by the link between the functional absence of a UPR component, such as WFS1, and ER stress-mediated β-cell death.

There are several aspects of ER stress signaling which need to be further investigated in order to appreciate the role of this pathway in the pathogenesis of diabetes. This will also answer the question whether components of the UPR, such as WFS1, would make “druggable” targets for the treatment of various forms of diabetes—this would address the issue of whether β-cells can be protected from hyper- or hypo-activation of ER stress signaling pathways without compromising their primary function as glucose sensors and regulators. The areas of research which need future exploration include: (1) understanding the mechanisms of the UPR in regulating insulin biosynthesis and secretion, (2) understanding the mechanisms of UPR activation in the β-cell by glucolipotox and (3) further defining the key regulators, pathways, and crosstalk of UPR-mediated apoptosis specific to the β-cell. Such research will further strengthen the link between ER stress, β-cell death, and the pathogenesis of diabetes.

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Figure 5. Summary of the link between ER stress and different forms of diabetes. The three forms of diabetes: genetic, type 1 and type 2 can all be linked to ER stress and UPR-mediated apoptosis of the β-cell.

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