Section 6: β-Cell Survival

Endoplasmic Reticulum Stress and the Development of Diabetes

A Review

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The early steps of insulin biosynthesis occur in the endoplasmic reticulum (ER), and the β-cell has a highly developed and active ER. All cells regulate the capacity of their ER to fold and process client proteins and they adapt to an imbalance between client protein load and folding capacity (so-called ER stress). Mutations affecting the ER stress–activated pancreatic ER kinase (PERK) and its downstream effector, the translation initiation complex eukaryotic initiation factor 2 (eIF2), have a profound impact on islet cell development, function, and survival. PERK mutations are associated with the Wolcott-Rallison syndrome of infantile diabetes and mutations that prevent the α-subunit of eIF2 from being phosphorylated by PERK, block β-cell development, and impair gluconeogenesis. We will review this and other rare forms of clinical and experimental diabetes and consider the role of ER stress in the development of more common forms of the disease. *Diabetes* 51 (Suppl. 3):S455–S461, 2002

Most secreted and integral membrane proteins of eukaryotic cells are translocated cotranslationally into the lumen of the endoplasmic reticulum (ER). The lumen of the ER provides a specialized environment for posttranslational modification and folding of secreted, transmembrane, and resident proteins of the various compartments of the endomembrane system. Properly folded proteins, assembled as needed into oligomeric structures, will eventually be cleared for exit from the ER and progress down the secretory pathway, whereas unfolded/malfolded proteins will eventually be disposed of by an ER-associated protein degradation machine (1). The load of ER client proteins that cells process varies considerably depending on cell type and physiological state, and cells adapt to this variation by modulating both the capacity of their ER to process clients and the load of client proteins synthesized. Disequilibrium between ER load and folding capacity is referred to heuristically as ER stress, and the ability to adapt to physiological levels of ER stress is important to all cells, but especially to professional secretory cells. This also holds true for the insulin-producing β-cell, which must process various and sometimes large amounts of ER client proteins.

ER stress is triggered by an increase in synthesis of client proteins, and it also occurs in the course of several pathophysiological states. Hypoxia and hypoglycemia, exposure to natural and experimental toxins that perturb ER function, and a variety of mutations that affect the ability of client proteins to fold all cause ER stress (2,3). Consequently, it is likely that ER stress and the cellular response to it play a role in the pathophysiology of numerous human diseases (4).

The case for implicating ER stress in disease is strongest in a relatively small subset of genetic disorders in which mutations in the coding region of highly expressed ER client proteins directly perturbs their folding and causes ER stress. Most disease-causing mutations that perturb folding interfere with the production of the encoded protein and result in a loss-of-function phenotype transmitted as a recessive trait. Common forms of cystic fibrosis, hemophilia, and hypercholesterolemia are all a result of this genetic mechanism, and whereas protein malfolding may lead to some ER stress, it is unlikely to play a dominant role in their pathogenesis. Less commonly, the malfolded protein exerts its effect in a dominant fashion, and the resultant phenotype is a consequence not of deficiency of the mutant gene product but of the ability of the malfolded protein to perturb the function of the cell that produces it. The liver disease caused by the Z allele of α1-antitrypsin and the peripheral neuropathy caused by mutations in the P0 protein in certain cases of Charcot-Marie-Tooth disease are examples of this genetic mechanism in action. Recently, Koizumi and colleagues (5) discovered that a rare mutation in the mouse *Ins-2* gene can interfere with β-cell function by a similar mechanism.

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ATF, activating transcription factor; eIF2, eukaryotic initiation factor 2; ER, endoplasmic reticulum; GCN2, general control non-depressed 2; ISR, integrated stress response; MHC, major histocompatibility complex; PERK, pancreatic ER kinase; SREBP, sterol regulatory element binding protein; TRAF2, tumor necrosis factor receptor–associated factor 2; XBP-1, X-box binding protein 1.

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This finding called attention to the β-cell's susceptibility to ER stress.

Independently, Julier and colleagues (6) discovered that the Wolcott-Rallison syndrome of infantile diabetes, a disorder characterized by early destruction of pancreatic β-cells, is caused by mutations in the *EIF2AK3* gene, which encodes for pancreatic ER kinase (PERK), a major ER stress transducer in mammalian cells. PERK knockout produced the identical phenotype in mice and established that attenuated ER stress responses may severely compromise β-cell survival (7). *WFS1*, a mutation that causes a rare heritable form of diabetes known as Wolfram syndrome (8), encodes an ER resident protein with some homology to proteins that are known to play an important role in degradation of malfolded ER proteins in yeast and nematodes (9), further supporting a link between ER homeostasis and the health of the β-cell.

These findings shed new light on earlier studies in which targeted overexpression of major histocompatibility complex (MHC) class II proteins in transgenic mouse islets was noted to cause β-cell destruction without evidence of inflammation (10). At the time, it was suggested that the overexpressed MHC proteins were impairing β-cell function by a nonspecific mechanism (11). It now seems plausible that ER stress may have been part of that process. Finally, recent findings from Mori and colleagues (12) suggest that ER stress may have a role in the death of islet cells exposed to nitric oxide, an effector molecule implicated in the pathogenesis of type 1 diabetes. Here we will briefly review the organization of ER stress–responsive signaling pathways active in mammalian cells and attempt to relate them to pathophysiological mechanisms operating in rare and more common forms of diabetes.

Components of the mammalian ER stress response. In mammalian cells, the ER stress response has three functional components. The first component is the early and transient attenuation of protein biosynthesis. This protective mechanism acutely reduces the translocation of new client proteins into the ER lumen and prevents overloading of the organelle. The second component is the activation of genes encoding components of the ER protein translocation, folding, export, and degradation machinery. This component acts to upregulate the capacity of the ER to fold client proteins and to degrade malfolded ones. Because it entails synthesis of new proteins and lipids, it has an inherent latency and follows in sequence the recovery in protein biosynthesis. The third component is the induction of programmed cell death. This response is believed to lead to elimination of cells that have sustained irreparable levels of damage caused by ER stress. It has the longest latency of the three functional components and is mediated by dedicated effectors with surprising specificity for ER stress.

Regulation of protein synthesis by ER stress. Protein synthesis is rapidly repressed in cells experiencing ER stress. This is due to decreased activity of the eukaryotic initiation factor 2 (eIF2) complex, which normally recruits charged initiator methionyl tRNA to the 40S ribosomal subunit. The eIF2 complex is rendered less active because stress-induced phosphorylation of its α-subunit on serine 51 converts it from a substrate to an inhibitor of eIF2B, the GTP exchange factor for eIF2. Only the GTP-bound form of eIF2 can participate in translation initiation, and therefore, eIF2α phosphorylation evolved as a major mechanism for reducing translation initiation and protein synthesis in eukaryotes (13).

ER stress–mediated eIF2α phosphorylation is carried out by PERK (also known as PEK), an ER resident protein whose effector eIF2α kinase domain lies on the cytoplasmic side of the ER membrane and whose stress-sensing domain lies on the opposite side of the membrane in the ER lumen (14,15). Like other transmembrane protein kinases, PERK is activated by oligomerization in the plane of the membrane. In unstressed cells, the binding of the ER chaperone BiP to its lumenal side holds PERK in an inactive complex. As client proteins accumulate in the ER lumen, the PERK-BiP complex is disrupted, and PERK oligomerizes and is activated by *trans*-autophosphorylation. Phosphorylated, activated PERK then phosphorylates eIF2α, attenuating translation initiation and protein synthesis (16,17).

The *PERK* knockout demonstrated its crucial role in controlling protein synthesis in ER-stressed cells. Decreased protein synthesis and polysome dissociation observed in ER-stressed cultured wild-type cells is completely absent from similarly treated $PERK^{-/-}$ cells (18). Furthermore, the mutant cells were markedly hypersensitive to treatment with agents that cause ER stress, such as tunicamycin and thapsigargin (18). The $PERK^{-/-}$ cells exhibited increased activity in a parallel ER stress pathway mediated by IRE1 (18). This latter observation suggests that part of the hypersensitivity of the mutant cells may be caused by overloading of their stressed ER with client proteins, a fate the wild-type cells avoid by attenuating client protein synthesis as part of their ER stress response. PERK is expressed at especially high levels in professional secretory cells, such as islet β-cells (14), and PERK signaling is particularly important to the normal function and survival of these cells (see below).

Regulated gene expression by ER stress. Evidence for a specific ER stress response was first provided by the observation that agents that cause ER stress activate genes encoding ER localized chaperones but not cytosolic chaperones (19). This signaling pathway came to be known as the unfolded protein response (or UPR), and genetic screens in the yeast *Saccharomyces cerevisiae* first delineated its components. The proximal, stress-sensing component is a type 1 ER resident protein encoded for by the *IRE1* gene (20,21). IRE1 proteins have lumenal domains with considerable similarity to those of PERK proteins, and IRE1, too, is under negative regulation by BiP binding (16,17,22). The effector domain of IRE1 is also a protein kinase, but its only known substrate is IRE1 itself (23). Once activated by transautophosphorylation, the type 1 ER transmembrane protein kinase (Ire1p) cleaves a preformed substrate mRNA at two specific locations, resulting in removal of an intron (24–27). The two ends of the cleaved mRNA are ligated together by tRNA ligase (28), and the mRNA modified by this nonconventional splicing encodes a transcription factor, Hac1p, that binds to and activates the promoters of many ER stress–inducible target genes in yeast.

The gene expression program activated in ER-stressed yeast was explored using expression microarrays. The

genes upregulated by the response were found to encode not only known ER chaperones and disulfide exchange factors (these would contribute directly to folding and processing of ER client proteins) but also structural components of the ER protein translocation machinery, enzymes that maintain the oxidative environment in the ER, enzymes involved in lipid and oligosaccharide biosynthesis, and components of the machinery that degrades malfolded ER proteins. Surprisingly, components of the secretory pathway that function downstream of the ER were also upregulated during ER stress, and all of these responses in yeast were *IRE-* and *HAC1*-dependent (29,30). These observations suggest that yeast determine the magnitude of the secretory apparatus they must maintain by monitoring the load on their ER; in other words, ER stress upregulates the entire secretory apparatus.

There are two mammalian IRE1 proteins, and both participate in ER stress signaling. IRE1α is broadly expressed, whereas IRE1β is expressed selectively in foregut-derived epithelium (31,32). However, in mammals, unlike yeast, IRE1-mediated signaling controls only part of the gene expression program induced by ER stress (33). A clue to the nature of the IRE1-mediated gene expression program was provided recently with the identification of a mammalian HAC1-like mRNA substrate of IRE1. It turns out that ER stress–mediated activation of mammalian IRE1 results in the splicing of the X-box binding protein 1 (XBP-1) mRNA (34–36) and that splicing controls the expression of XBP-1 protein (34). XBP-1 is a transcription factor expressed at high levels in cells actively engaged in protein secretion (37). In the B-cell lymphoid lineage, XBP-1 is required for plasma cell development with the associated elaboration of an active ER and secretory apparatus (38). Together, these findings suggest that physiological levels of ER stress, acting through an IRE1- and XBP-1–dependent signaling pathway, upregulate the secretory apparatus in mammalian cells. This hypothesis predicts that defective signaling in this pathway would affect other professional secretory cells, such as islet β-cells. Unfortunately, because of the embryonic lethality of IRE1α$^{-/-}$ and *XBP-1*$^{-/-}$ mouse embryos, testing this prediction must await the development of conditional mutant alleles of these genes.

Alongside the IRE1 pathway, mammalian cells have two other known signal transduction pathways for activating ER stress–induced gene expression. Mori and colleagues (39) have identified two similar transcription factors, activating transcription factor (ATF)-6α and ATF6β, that are activated by regulated intramembrane proteolysis in ER-stressed cells. In unstressed cells, ATF6 is retained in an inactive form by association with ER membranes, and ER stress activates a proteolysis step that liberates the NH_2-terminus of these proteins from the ER membranes, whence they migrate to the nucleus and activate ER stress–inducible target genes (39,40). Proteolytic processing of ATF6 is dependent on the same set of proteases that process the related sterol-regulated transcription factors sterol regulatory element binding protein (SREBP)-1 and SREBP2 (41). Interestingly, mammalian cells with mutations in the site-2 protease that processes both ATF6s and SREBPs have a profound defect in activating the BiP gene, a classic target gene of the ER stress response (41). This observation suggests that in mammalian cells, ATF6 plays a major role in ER stress–induced gene expression.

Perhaps surprisingly, the third pathway for activating ER stress–induced gene expression is mediated by PERK. Phosphorylation of eIF2α and the resulting decrease in eIF2 activity does not affect the translation of all mRNAs equally; some mRNAs are spared the general repression of translation initiation, whereas others are translationally induced. In unstressed cells, the mRNA encoding for the transcription factor ATF4 is basally repressed. However, under stress, when eIF2α is phosphorylated, ATF4 translation is de-repressed, and the encoded protein accumulates in the nucleus. Thus, in the context of ER stress, activation of ATF4 and downstream gene expression is PERK dependent (42). Other eIF2α kinases (e.g., general control non-depressed 2 [GCN2]) can couple ATF4 activation to amino acid starvation (42), and the pathway can also be activated by a variety of toxins and conditions that induce oxidative stress, although the kinase(s) implicated in the latter circumstance has not yet been identified. Because this gene expression pathway can integrate signaling by a variety of unrelated stresses, we refer to it as the integrated stress response (ISR).

The scope of the gene expression program activated by the ISR has not yet been defined, but in the context of the ER stress response (in which PERK activation and the ISR are an important part), it plays a role in activating both classic target genes (such as BiP and XBP-1 itself) and others (such as GADD34 and CHOP/GADD153) that serve more general functions in stress responses (34,42,43). A homologous pathway, known as the general control response, adapts yeast to amino acid starvation (44). As we shall discuss below, the gene expression program activated by the mammalian ISR may have retained that special link to intermediary metabolism.

ER stress–induced cell death. Among the responses to ER stress, the least well understood is the induction of programmed cell death. Proper function of the ER is required for expression of secreted proteins and cell surface receptors that could play important roles in cell survival. Therefore, the death of cells exposed to conditions perturbing ER function was never particularly surprising. However, it has recently been recognized that cells possess genes that activate cell death pathways specifically under conditions of prolonged ER stress. These new findings imply that in a multicellular organism, there may be some advantage to eliminating cells that have sustained high levels of ER stress. At present we do not understand how this advantage might play out. In some circumstances, death of severely stressed cells may be part of a regeneration cycle that allows recovery of organ function.

Caspase-12 is constitutively localized to ER membranes and undergoes activating cleavage specifically in ER-stressed cells. Most importantly, *Caspase-12*$^{-/-}$ mice and cultured cells experienced significantly less cell death when exposed to toxins that cause ER stress (45). This finding is especially important because Caspase-12 belongs to the Caspase-1 family of upstream caspases that activate the downstream effector caspases that promote cell death. It appears, therefore, that cells have evolved a specific caspase to couple ER stress to common cell death pathways. Several processes have been suggested as con-

tributing to Caspase-12 activation in ER-stressed cells. *m*-Calpain, a cysteine protease activated by perturbed calcium homeostasis in ER-stressed cells, may directly cleave and activate Caspase-12 (46). Caspase-7, which is recruited to the ER in stressed cells, may likewise cleave and activate Caspase-12 (47). Finally, ER stress–activated IRE1 may lead to clustering of Caspase-12 at the ER membranes by recruitment of tumor necrosis factor receptor–associated factor 2 (TRAF2) proteins, which interact with both IRE1 and Caspase-12 (48). Recruitment of TRAF2 to activated, phosphorylated IRE1 also activates c-Jun NH_2-terminal kinases in mammalian cells (49), providing an additional plausible link from ER stress to cell death (50).

Another mediator of programmed cell death in ER-stressed cells is the transcription factor CHOP. CHOP expression is transcriptionally upregulated by the ISR (42,51), and the protein also undergoes activating phosphorylation by stress-activated p38 mitogen-activated protein kinase (52). *CHOP*$^{-/-}$ cells are resistant to ER stress–induced death (53,54), whereas CHOP overexpression promotes cell death (55). Identification of specific CHOP target genes has not shed light on the role of the transcription factor in promoting cell death (56). However, it has been suggested recently that CHOP promotes cell death by downregulating the expression of B-cell leukemia/lymphoma 2 (Bcl2), which causes the accumulation of reactive oxygen species (54). Finally, a recent article suggests that the stress-activated c-Abl tyrosine kinase is redistributed from the ER to mitochondria in ER-stressed cells and that ER stress–induced apoptosis is attenuated in c-Abl–deficient cells (57).

ER stress and β-cell function

Lessons from the Akita mouse. The Akita mouse harbors a spontaneous mutation that causes early-onset nonobese diabetes. Diabetes, which is transmitted as a semidominant trait, is caused by a missense mutation, *Ins2*^{C96Y}, which replaces a highly conserved cysteine with tyrosine. This precludes formation of one of the two disulfide bonds normally present in proinsulin-2, and the mutant proinsulin is retained in the ER. Diabetes develops because the mice are unable to produce enough insulin. However, loss of insulin production by the mutant allele alone is unlikely to have a major impact on insulin biosynthesis because rodents have two insulin genes (*Ins1* and *Ins2*), and loss of both copies of *Ins2* has no metabolic consequences (58).

The Akita mouse is born with normal-appearing islets. Hyperglycemia and falling insulin production correlate with a progressive decrease in β-cell mass. The ER of affected β-cells distends and contains elevated levels of BiP. Another ER stress marker, *CHOP*, is also activated in the β-cells, suggesting that the mutant, malfolded proinsulin-2 protein is causing ER stress (5,59). Proinsulin-2 is a major ER client protein in the β-cell, and it is hardly surprising, therefore, that its malfolding would cause ER stress. A recent report indicates that ER stress is not merely an incidental finding but is directly implicated in the death and dysfunction of the β-cell in the Akita mouse.

When the Akita mutation was introduced into a *CHOP*$^{-/-}$ background, islet cell destruction and hyperglycemia were delayed in onset (59). The *CHOP* knockout reduces cell death by ER stress of any cause (53); therefore, its ability to impact the phenotype of the Akita mutation indicates that "undifferentiated" ER stress plays an important role in the pathogenesis of islet dysfunction in the Akita mouse. It is also clear from the experiments of Oyadomari et al. (59) that CHOP activation is not the only mechanism by which the Akita mutation impacts islet function, because the *CHOP* knockout merely delayed the onset of diabetes in the heterozygous *Ins2*$^{C96Y/+}$ mouse and had no measurable impact on the phenotype of the more severely affected homozygous *Ins2*$^{C96Y/C96Y}$ mice.

Lessons from mutations that affect eIF2α phosphorylation. The Wolcott-Rallison syndrome of infantile diabetes, pancreatic hypoplasia, and osteodystrophy is caused by homozygous loss-of-function mutations in the *EIF2AK3/PERK* gene (6). Mice in which the *PERK* gene had been knocked out also develop a similar clinical syndrome (7). The mice are born with nearly normal islets of Langerhans, but over the first few weeks of life, they experience a progressive destruction of β-cells. When explanted from prediabetic *PERK*$^{-/-}$ mice and placed in culture, the islets synthesize and process proinsulin normally and secrete the mature hormone. Remarkably, when switched from culture in low glucose to high glucose, the mutant islets increase insulin production more vigorously than wild-type islets (7).

Glucose is known to stimulate insulin biosynthesis (60,61). The differences noted between wild-type and mutant islets are therefore consistent with a scenario whereby glucose-mediated stimulation of proinsulin biosynthesis promotes some ER stress because it imposes a load on the folding and protein processing machinery of the ER. In the wild-type mouse, this induces a rectifying pathway consisting of PERK activation, eIF2α phosphorylation, and reduced client protein synthesis. This important mechanism for modulating protein synthesis is lost in the *PERK*$^{-/-}$ islets such that protein synthesis is unresponsive to the stress on the folding apparatus of the ER. As a consequence, ER client proteins (e.g., proinsulin) are translocated into the lumen of the ER in excess of the folding capacity of the organelle. The chaperone reserve in the stressed ER has been exceeded; therefore, these initially unfolded client proteins may now progress down folding pathways that would never otherwise be used. The consequence, we speculate, is the production of novel toxic configurations of proteins that may damage the islet. In keeping with this model, electron microscopy reveals the accumulation of electron-dense material in the ER and distorted organelle morphology in the *PERK*$^{-/-}$ islets (7).

PERK was first identified as a protein kinase that is abundantly expressed in rat islets of Langerhans and was even named pancreatic enriched kinase (PEK) (14). Since then, however, it has been established that PERK is expressed at some level in all cells, and it is especially enriched in secretory cells (7,62). It is likely, therefore, that alterations noted in the endocrine pancreas also affect the exocrine pancreas, liver, and possibly the osteoblasts in the *PERK*$^{-/-}$ mouse, accounting for the full spectrum of the mutant phenotype.

The above model for the pathophysiological events that take place in *PERK* mutant islet cells emphasizes the role of loss of translational control. However, phosphorylated

eIF2α (the downstream effector of PERK) controls not only translation but also activates a gene expression program referred to as the ISR (42). Preliminary results from our laboratory suggest that some of the downstream genes in this response may promote survival in stressed cells (H.P.H., unpublished observations). It is thus conceivable that reduced activity of these survival genes also plays a role in the death of β-cells both in *PERK*$^{-/-}$ mice and in the Wolcott-Rallison syndrome.

The gene expression program controlled by eIF2α phosphorylation is likely to have complex effects on islet cell development, survival, and function. Mice that are homozygous for a point mutation in eIF2α, which converts serine 51 (the residue phosphorylated by PERK and other eIF2α kinases) to an alanine (*eIF2α*^{S51A}), predictably lose the ability to control translation and activate downstream gene expression programs in response to activation of the upstream kinases. Remarkably, these mice survive to the end of gestation; however, they are born with islets of Langerhans that have a severely reduced complement of insulin-producing β-cells (63). These observations suggest that eIF2α phosphorylation may have a role not only in protecting β-cells from ER stress, but also in islet development. Furthermore, the homozygous *eIF2α*^{S51A} mouse has abnormalities in intermediary metabolism, such as reduced liver glycogen stores and impaired gluconeogenesis (63). In yeast, eIF2α phosphorylation coordinates metabolism and amino acid availability (44). The broad defect in metabolic regulation in the homozygous *eIF2α*^{S51A} mouse suggest that this link between metabolism and eIF2α phosphorylation might be preserved in mammals (64).

PERK is not the only eIF2α kinase activated in islets of Langerhans. GCN2 is also abundantly expressed in these cells, and the homozygous *eIF2α*^{S51A} mouse is refractory to both kinases. The normal development of islets in the *PERK*$^{-/-}$ mice and the severe abnormalities noted in the homozygous *eIF2α*^{S51A} mouse suggest that GCN2 activity may have an important role in islet development. At present, amino acid limitation is the only known upstream activator of GCN2; however, it is possible that other activating signals may control this kinase in the context of islet development.

An additional complication related to understanding the role of eIF2α phosphorylation in cell physiology concerns its role in CHOP activation. Activity of the ISR is an absolute requirement for CHOP induction by ER stress (42), and CHOP promotes cell death by ER stress (53,54). Therefore, signaling through PERK protects cells from ER stress while at the same time activating potential cell death–promoting functions. The genetic analysis of *PERK*$^{-/-}$ and *CHOP*$^{-/-}$ tells us that under normal conditions, the survival effects predominate, but it is possible that under extreme stress, the death-promoting effects of the ISR may be more important.

Other observations on a possible role for ER stress in diabetes. The Wolfram syndrome is a rare genetic disorder transmitted as a recessive trait, in which insulin-dependent diabetes is associated with diabetes insipidus and neurodegeneration. Recently, loss-of-function mutations in the *WFS1* gene have been linked to the Wolfram syndrome (8,65). The product of *WFS1*, wolframin, is an ER resident protein (9) with some sequence similarity to SEL-1 and Hrd3p, proteins that play an important role in degrading malfolded ER proteins in *Caenorhabditis elegans* and yeast, respectively. Both vasopressin-producing neurons (66) and myelin-producing oligodendrocytes (67) are affected in ER stress diseases; it is therefore possible to reconcile the pleotrophic features of the Wolfram syndrome by postulating that Wolframin plays a role in ER-associated degradation of malfolded proteins.

Nitric oxide is believed to be an important effector of β-cell death in type 1 diabetes. It has recently been shown that nitric oxide treatment of cultured β-cells causes ER stress, presumably by depleting ER calcium stores through inhibition of the sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pump. Remarkably, CHOP plays an important role in nitric oxide–mediated death of these cells (12). These observations, made on cultured cells, suggest that ER stress may also play a role in the loss of β-cells in type 1 diabetes. The *EIF2AK3/PERK* gene maps to a locus that is implicated in the development of type 1 diabetes in Scandinavians (68). It is interesting, therefore, to speculate on the possibility that variation in the activity of PERK, which is an important defender against ER stress, may modify the consequences of an immune attack on the β-cell.

CONCLUSIONS

Firm genetic evidence implicates ER stress and defective ER stress signaling in the developing of rare forms of experimental and clinical diabetes. These and other lines of evidence suggest that the insulin-secreting β-cell may be especially sensitive to the adverse affects of perturbed ER function. Whereas the role of ER stress in the pathophysiology of common forms of diabetes remains unknown, the analysis of islets of Langerhans from *PERK*$^{-/-}$ mice supports a model whereby ER stress is linked to the secretory activity of the β-cell, in so much as insulin secretion must be matched with insulin biosynthesis. Thus, the level of ER stress in the β-cells would be increased in physiological hypersecretory states such as insulin resistance. In insulin-resistant humans, glucose intolerance develops only after the endocrine pancreas fails to keep up with the increased demand for insulin. It is reasonable to ask, therefore, whether prolonged ER stress might contribute to the degradation of β-cell function that precedes metabolic decompensation in the insulin-resistant patient and whether variation in the activity of signaling pathways that counteract ER stress may modulate the diabetic phenotype in such individuals.

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