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A Reevaluation of the Role of the Unfolded Protein Response in Islet Dysfunction: Maladaptation or a Failure to Adapt?

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Endoplasmic reticulum (ER) stress caused by perturbations in ER homeostasis activates an adaptive response termed the unfolded protein response (UPR) whose function is to resolve ER stress. If unsuccessful, the UPR initiates a proapoptotic program to eliminate the malfunctioning cells from the organism. It is the activation of this proapoptotic UPR in pancreatic β-cells that has been implicated in the onset of type 2 diabetes and thus, in this context, is considered a maladaptive response. However, there is growing evidence that β-cell death in type 2 diabetes may not be caused by a maladaptive UPR but by the inhibition of the adaptive UPR. In this review, we discuss the evidence for a role of the UPR in β-cell dysfunction and death in the development of type 2 diabetes and ask the following question: Is β-cell dysfunction the result of a maladaptive UPR or a failure of the UPR to adequately adapt? The answer to this question is critically important in defining potential therapeutic strategies for the treatment and prevention of type 2 diabetes. In addition, we discuss the potential role of the adaptive UPR in staving off type 2 diabetes by enhancing β-cell mass and function in response to insulin resistance.

The endoplasmic reticulum (ER) is an extensive network of tubular membranes within the cytoplasm of the cell that serves as a site for the synthesis of lipids, phospholipids, steroids, and almost all secreted and membrane proteins. Thus, the maintenance of the ER is essential for preserving cellular function and viability. Disruption in ER homoeostasis caused by, for example, the depletion of ER calcium, perturbations in the ER redox state, and/or the accumulation of misfolded proteins within the ER results in what is commonly referred to as "ER stress" (Appendix 1). This stress is sensed by ER transmembrane proteins that activate the unfolded protein response (UPR), an adaptive response whose function is to restore ER homeostasis and thus alleviate ER stress (Fig. 1) (for reviews, see refs. 1–4). This is achieved by *1*) decreasing the ER synthetic load through inhibiting protein synthesis, *2*) clearing the ER of misfolded proteins by increasing the expression of components of ER-associated degradation (ERAD), which translocates misfolded proteins out of the ER for subsequent proteosomal degradation, and *3*) enhancing the synthesis and folding capacity of the ER by stimulating an increase in both ER mass and function.

The canonical transducers of the UPR are three ER transmembrane proteins: PKR-like ER kinase (PERK), a serine–threonine kinase; inositol-requiring enzyme 1 (IRE1), which has both serine–threonine kinase and RNA endonuclease activity; and activating transcription factor 6 (ATF6) (Fig. 1). PERK phosphorylates the α subunit of eukaryotic translation initiation factor 2 (eIF2α) (5,6) and in vitro can phosphorylate nuclear factor (erythroid-derived 2)–related transcription factor (Nrf2) (7), although there is limited evidence that Nrf2 can be phosphorylated by PERK in vivo. The phosphorylation of eIF2α inhibits protein synthesis thus reducing ER protein folding load. However, it also promotes an increase in protein translation from a subset of mRNAs including that encoding activating transcription factor 4 (ATF4) (Appendix 2) (8–10). This in turn increases the expression

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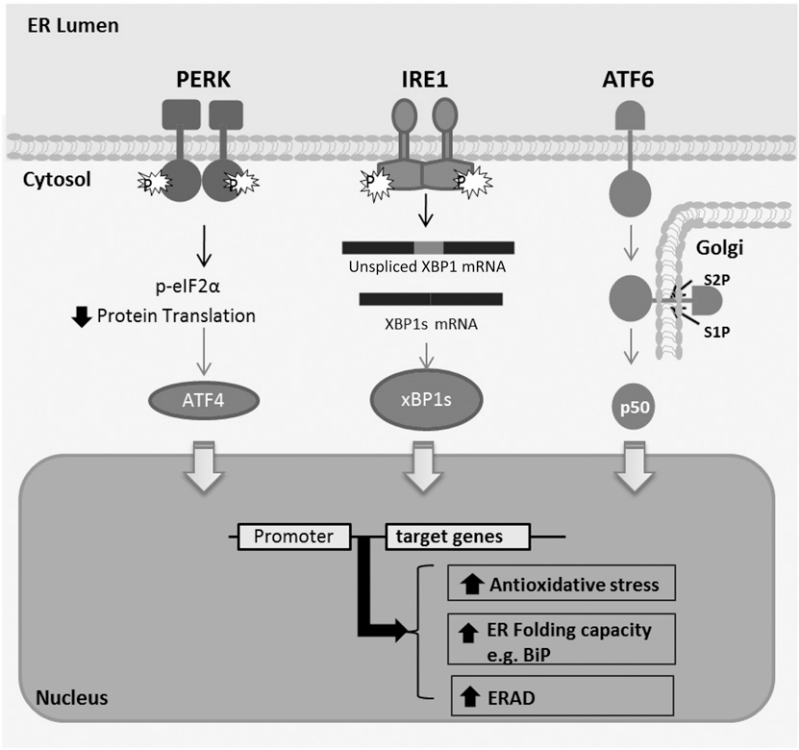

Figure 1—A simplified overview of the adaptive UPR. PERK, IRE1, and ATF6 signal to the nucleus through the action of the transcription factors ATF4, XBP1s, and ATF6, which bind to response elements (e.g., the antioxidant response element, the amino acid response element, the UPR element, and the ER stress response element) within promoters to induce transcription of mRNAs whose products are important in increasing ER folding capacity, increasing ERAD, and reducing oxidative stress.

of mRNAs involved in amino acid metabolism, maintaining redox state and combating oxidative stress (11). There are two isoforms of IRE1 in mammalian cells, IRE1α and IRE1β (for review, see ref. 12), although most research investigating the role of IRE1 in the UPR has focused on IRE1α. IRE1α catalyzes the removal of a 26-bp sequence from the mRNA encoding the bZIP transcription factor XBP1 (X-box binding protein 1) resulting in a frame shift and the production of a transcriptionally active "spliced" form of XBP1 (XBP1s) (12,13). XBP1s enhances the expression of mRNAs encoding proteins that increase folding capacity, such as the ER chaperones BiP and GRP94, and promote ERAD, such as ER-degradation–enhancing α-mannosidase–like protein (EDEM) (14). IRE1α/XBP1 promotes insulin-stimulated proinsulin synthesis in β-cells (15,16). Although there are also two isoforms of ATF6, ATF6α and ATF6β, it is ATF6α that has been implicated in UPR induction. ATF6α activation is initiated by the unmasking of a Golgi localization signal by the dissociation of BiP. This allows ATF6 to translocate to the Golgi where it is cleaved by site-1 protease (S1P) and site-2 protease (S2P) resulting in the release of a 50-kD N-terminal fragment (p50) encoding a bZIP transcription factor. p50 has overlapping functions with and compensatory functions to those of XBP1s (17).

If the activation of the UPR is unable to restore ER homeostasis, the UPR switches from an adaptive to a proapoptotic program mediated primarily by the chronic activation of IRE1α and/or PERK (3,12). Chronic PERK activation causes the ATF4-dependent increase in the expression of the proapoptotic protein C/EBP homologous protein (CHOP), otherwise known as DNA damage–inducible transcript 3 (DDIT3) and growth arrest and DNA damage–inducible 153 (GADD153). Chronic IRE1α activation leads to the recruitment of tumor necrosis factor receptor–associated factor 2 (TRAF2) (18) and the activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases (MAPK) (18), resulting in the increased expression of proapoptotic proteins. Prolonged IRE1α activation also promotes apoptosis by degrading mRNAs encoding essential cell-survival proteins through a process called regulated IRE1α-dependent decay or RIDD (19). In addition, both PERK and IRE1α can promote the expression of proinflammatory cytokines (20–22). This proapoptotic response is important in clearing malfunctioning cells from the organism. However, the death of nonreplenishing cells that have a critical function, such as pancreatic β-cells, can have deleterious consequences on the organism. Thus, in this specific context the UPR is maladaptive ("maladaptive" as defined by an adaptation more harmful than helpful to the organism) (Appendix 3). It is this feature of the UPR that has gained it a great deal of notoriety in its proposed role in the pathogenesis of type 2 diabetes, the focus of this review.

ER STRESS AND THE UPR IN THE DEVELOPMENT OF β-CELL DYSFUNCTION IN TYPE 2 DIABETES

Obesity is often associated with a decrease in insulin sensitivity in skeletal muscle, liver, and adipose tissues. However, the majority of people who are obese and insulin resistant do not develop diabetes. This is because of a compensatory increase in insulin secretion maintained through an increase in both β-cell function and mass (23). This is referred to as β-cell adaptation or β-cell compensation, and there is mounting evidence that ER stress and the induction of an adaptive UPR play an important role in this. However, if the β-cells are unable to adequately compensate and/or are unable to sustain a compensatory phenotype, this leads to relative insulin deficiency and ultimately to the onset of diabetes. This "failure" of the β-cells is initially characterized by the development of β-cell dysfunction exemplified by a loss of first-phase insulin secretion and defective proinsulin processing but ultimately by a decrease in β-cell mass primarily due to β-cell death. It has been proposed that this deterioration in β-cell function and loss of viability is caused by the rate of proinsulin synthesis exceeding the processing and folding capacity of the ER, which leads to the accumulation of unfolded/unprocessed proinsulin (1,6,24,25) resulting in chronic ER stress and the activation of a proapoptotic UPR. However, it has also been proposed, on the basis of experimental evidence, that ER stress in pancreatic β-cells can be caused by the following: the formation of islet amyloid, a common feature of human type 2 diabetes; chronic exposure to elevated levels of free fatty acids and/or glucose, a hallmark of obesity and insulin resistance; and/or elevated levels of proinflammatory cytokines, another common feature of obesity (26–29).

β-Cell Compensation: A Positive Role for the UPR

With increased demand for insulin there is a need to increase secretory capacity by increasing both the mass of β-cells and the processing capacity of individual β-cells to synthesize and secrete insulin. Notably, there is evidence that the UPR plays a positive role in these important compensatory adaptations. Transgenic animal models in which the UPR is compromised provide evidence that the UPR is important in β-cell compensation. For example, β-cell and hypothalamic IRE1α knockout mice, when placed on a high-fat diet (HFD) to promote obesity and insulin resistance, have reduced β-cell mass due to a reduced rate of β-cell replication possibly caused by a decrease in XBP1s-dependent expression of cyclin D1, a critical regulator of cell-cycle progression (30). However, these results have yet to be confirmed using β-cell–specific IRE1α knockout mice.

As IRE1α/XBP1 is also required for glucose-stimulated insulin synthesis (15,16), increased activation through this pathway may be important in increasing β-cell function. ATF6α may also be important in β-cell compensation, as ATF6α null mice placed on an HFD have exacerbated glucose intolerance due to a reduction in insulin secretion compared with their wild-type HFD-fed controls (31). Moreover, in vitro studies on dispersed mouse or human islets indicate that increased β-cell proliferation in response to an increase in insulin demand is mediated by the activation of ATF6 (32). However, β-cell–specific deletion of ATF6α in mice has no discernible effect on β-cell development or function (33), and human carriers of Atf6α "hypomorphic" mutations have only been characterized to have achromatopsia, a cone photoreceptor defect (34). Thus, the role of ATF6α in β-cell function is unclear.

β-cell–specific ablation of PERK in mice results in the development of diabetes (6,35) likely due to a reduction in β-cell proliferation and neonatal β-cell expansion (35), whereas the conditional deletion of PERK in adult mice has been reported to cause increased β-cell death (32). However, PERK's role in β-cell compensation in these transgenic mouse models has not been explored, although mice carrying a nonphosphorylatable mutant of eIF2α (PERK's primary and perhaps only substrate) in β-cells develop glucose intolerance due to β-cell failure likely caused by an inability to mount an effective UPR (25).

Studies of rodent models of obesity and insulin resistance also provide evidence that ER stress and the activation of an adaptive UPR are important in β-cell compensation (Table 1). The *ob/ob* mice are leptin deficient and consequently rapidly become obese and severely insulin resistant; however, they do not develop diabetes because of successful β-cell compensation sustained through an increase in both β-cell function and mass. In islets isolated from these mice, the expression of markers of an adaptive UPR increases between 6 and 16 weeks of age (36), which is concomitant with an increase in β-cell mass and function. Likewise, the islets isolated from Zucker and female Zucker diabetic fatty (ZDF) rats or prediabetic *db/db* mice, genetic models of obesity and β-cell compensation, have increased expression of markers of the adaptive UPR compared with their lean controls (36,37). The story is similar with HFD-fed mice, which are considered a more physiologically relevant model of insulin resistance–associated β-cell compensation (38), as their islets also have increased expression of markers of an adaptive UPR compared with their lean controls (29,39). Notably, increased CHOP expression is observed in many of these models of β-cell adaptation (Table 1), indicating that levels of CHOP expression per se are poor markers of a maladaptive UPR (Appendix 2).

The activation of the UPR in all of these animal models is presumably in response to an increase in insulin resistance and the demand for insulin. Congruent with this presumption, hyperglycemia induced by glucose infusion in Wistar rats activates an adaptive UPR in islets, as determined by increased expression of XBP1s and the ER chaperones BiP and GRP94 (40). Similarly, mild hyperglycemia imposed on human islets when transplanted into mouse recipients also results in the activation of an adaptive UPR (41). These effects on the UPR are likely due to

Table 1—Studies in which changes in ER stress/UPR activation were determined in animal models of insulin resistance and type 2 diabetes

Animal models of insulin resistance and β-cell compensation

Model	Evidence for ER stress/ongoing UPR activation	Markers of an adaptive UPR	Maladaptive UPR (CHOP expression)
Prediabetic *db/db* mouse (6 weeks) (36)	↑ XBP1s	↑ BiP, p58, Erp72, Fkbp11, Grp94	↑
Zucker fatty rat (37)		↑ BiP, HYOU1	↑
fZDF rat (37)		↑ BiP	↑
HFD-fed mouse (29,39,83)	↑ XBP1s (29,83) ↔ P-eIF2α (39)	↑ BiP (29,39) ND (83)	ND (29) ↑ (83) ↔ (39)
ob/ob mouse (36)	↑ XBP1s	↑ BiP, p58, Erp72, Fkbp11, Grp94	ND
HFD-fed rats (27)	↑ P-PERK	↑ BiP	ND

Animal models of β-cell failure and type 2 diabetes

Model	ER stress/UPR activation	Markers of an adaptive UPR	Maladaptive UPR (CHOP expression)
db/db mouse (16 weeks) (36)	↓ XBP1s	↓ BiP, Grp94, Erp72, Fkbp11 compared with levels in prediabetic mice	↓ Compared with levels in prediabetic mice
HFD-fZDF rat (37)	↔ P-eIF2α, P-IRE1	↔ / ↓	↔

ND, no data. P-eIF2α, phosphorylated eIF2α; P-IRE1, phosphorylated IRE1; P-PERK, phosphorylated PERK.

an increased demand for insulin rather than hyperglycemia per se (32,42). Indeed, a reduction in insulin synthesis has been shown to reduce ER stress in mice (42).

The activation of an adaptive UPR increases insulin processing and secretory capacity, and there is good evidence to support the notion that this protects β-cells from the detrimental effects of ER stress. For example, the overexpression of the ER chaperone BiP in β-cells protects mice against HFD-induced diabetes (39). Conversely a reduction in BiP expression as a result of C/EBPβ-mediated downregulation of ATF6 is associated with diabetes (43). Moreover, administration of pharmacological chaperones such as tauroursodeoxycholic acid, 4-phenylbutyrate (PBA), and the more recently discovered azoramide can restore rodent islet function both in vitro and in vivo (32,36,40,44–46). In humans, PBA has also been shown to partially alleviate lipid-induced β-cell dysfunction (47).

β-Cell Dysfunction and Death in Type 2 Diabetes: Maladaptation or a Failure to Adapt?

Pharmacological induction of ER stress in both clonal pancreatic β-cell lines and human or rodent islets of Langerhans using agents such as thapsigargin or tunicamycin results in β-cell death (48–50). Similarly, incubation of clonal β-cell lines or isolated islets with the long-chain saturated free fatty acid palmitate also causes ER stress, UPR activation, and ultimately cell death (50–53). In vivo, the expression of misfolding mutants of insulin that causes chronic ER stress also causes β-cell death in mice and in humans resulting in permanent neonatal diabetes (54). CHOP clearly plays an important role in ER stress–induced β-cell death (26,55,56). For example, in the Akita mouse, a model of diabetes that expresses a misfolding mutant of insulin resulting in chronic ER stress, the ablation of CHOP delays diabetes onset (56,57). In summary, chronic unresolvable ER stress in vitro or in vivo can cause β-cell dysfunction and death through the activation of a proapoptotic UPR. However, there is limited evidence that in the development of type 2 diabetes, β-cell dysfunction and death is caused by chronic ER stress and the induction of a proapoptotic UPR. The *db/db* mice, a well-characterized model of type 2 diabetes, are defective in leptin signaling and as a consequence rapidly develop obesity and insulin resistance. Despite initial β-cell compensation, these mice develop diabetes because of a decline in β-cell function and mass. Surprisingly, the expression of XBP1s and ATF4, proximal markers of IRE1 and PERK activation, respectively, and surrogate markers of ER stress, are reduced in islets isolated from diabetic 16-week-old *db/db* mice compared with prediabetic 6-week-old *db/db* mice (36). Similarly, in islets isolated from diabetic HFD-fed obese female ZDF (HFD-fZDF) rats, another well-characterized rodent model of type 2 diabetes, there is no detectable increase in the phosphorylation status of eIF2α and IRE1 compared with age-matched obese prediabetic fZDF rats (37). In addition, the expression of markers of an adaptive UPR are also either significantly decreased or show a tendency toward a decrease in animal models of diabetes, and surprisingly this is invariably associated with no change or a decrease in CHOP expression (an indicator of the activation of a proapoptotic UPR) (36,37) (Table 1).

Tellingly and in line with what was observed in studies using rodents, the expression of 691 out of 692 ER-associated genes, many of which are markers of ER stress and the UPR, was unchanged in β-cell–enriched samples isolated from human subjects with diabetes compared

with BMI-matched control subjects without diabetes (58). However, ER distension, a morphological indicator of ER stress, was detected in β-cells isolated from subjects with diabetes (58). Interestingly, the expression of BiP, XBP1s, and CHOP was lower in cultured islets isolated from subjects with type 2 diabetes compared with those isolated from subjects without diabetes (58). Similarly, in a separate study, the expression of XBP1s and ATF6 and the phosphorylation of eIF2α were all found to be decreased in islets within pancreata isolated from subjects with type 2 diabetes compared with non–BMI-matched controls (59). However, increased nuclear localization of CHOP has been reported in islets from subjects with type 2 diabetes compared with BMI-matched controls (60). Given the challenges associated with these types of studies using human tissue, it is difficult to interpret the data and thus reach a conclusion with any confidence. However, evidence for chronic ER stress and/or activation of a proapoptotic UPR in islets from subjects with diabetes is clearly limited.

There is considerable evidence that a failure to mount an effective UPR has marked deleterious consequences to both β-cell function and viability. For example, Wolcott-Rallison syndrome, a rare human autosomal recessive genetic disorder caused by the impairment of or loss-of-function mutations in PERK, is characterized by early-onset diabetes due to pancreatic β-cell failure (61). Similarly, the ablation of PERK in mice results in the selective death of β-cells and the development of diabetes (24). Likewise, conditional deletion of IRE1α from the β-cells of mice results in glucose intolerance caused by a reduction in insulin content (15,30,62) and β-cell failure primarily due to reduced antioxidative capacity (15). Increased unspliced XBP1 (XBP1u) protein may also play a role, as it has been reported to inhibit ER function (63) and autophagy (64).

β-Cells from autophagy-deficient mice also have a compromised UPR, and when crossed onto *ob/ob* mice, the mice develop diabetes due to ineffective β-cell compensation (65). This correlates with a reduction in the adaptive UPR and surprisingly a decrease in the expression of proapoptotic CHOP (65), a classical yet nonspecific marker of chronic ER stress (Appendix 2). A decrease in ER folding capacity by the genetic ablation or reduction of the expression of ER chaperones such as $p58^{IPK}$ and BiP in β-cells can also lead to β-cell dysfunction and death (39,66).

Interestingly, β-cells of mice carrying a nonphosphorylatable form of eIF2α and hence have a defective UPR develop ER stress and death coincident with the induction of oxidative stress (20), as do β-cells of mice with $p58^{IPK}$ deletion (66). Deletion of IRE1α in β-cells also leads to increased oxidative stress and the development of β-cell dysfunction (15). Notably, the administration of antioxidants reduces ER stress in vivo and preserves β-cell function in mouse models of diabetes (40,66,67). Thus, a decrease in the UPR activation decreases β-cell resistance to oxidative stress. In addition, β-cell damage and death caused by, for example, increased oxidative stress would inevitably lead to inflammation that can itself induce both oxidative and ER stress (29) and thus exacerbate the development of β-cell dysfunction and death (Fig. 2).

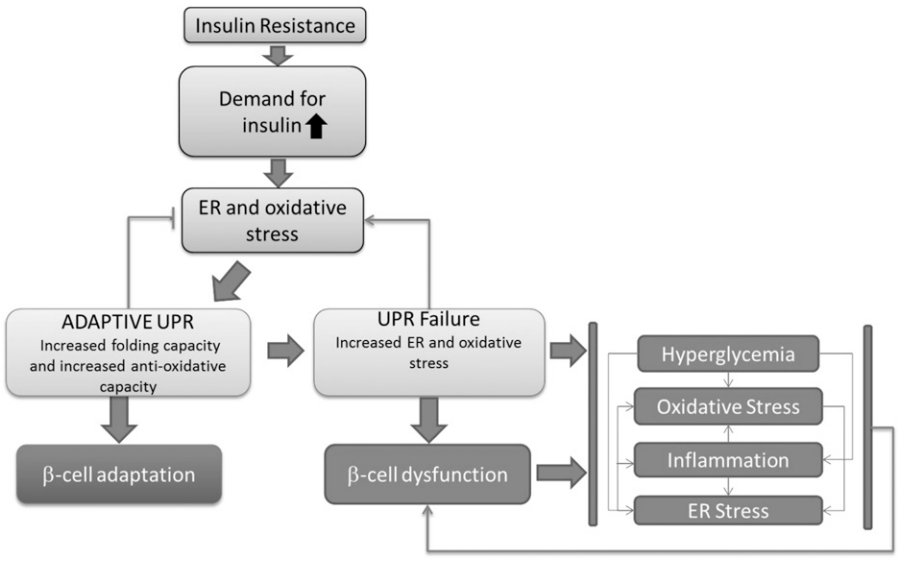

Figure 2—Schematic showing the role of the UPR in β-cell compensation or failure in type 2 diabetes. An increase in the demand for insulin can cause ER and oxidative stress. This activates an adaptive UPR that, if effective, relieves stress and promotes β-cell adaptation. However, failure to mount a successful UPR can result in increased ER and oxidative stress, which can lead to an inflammatory response. All of this can promote the development of β-cell dysfunction and death leading to hyperglycemia. Hyperglycemia promotes oxidative stress, inflammation, and ER stress. ER stress can promote oxidative stress and inflammation, inflammation can promote ER stress and oxidative stress, and oxidative stress can promote ER stress and inflammation. Thus, a vicious cycle ensues, ultimately resulting in reduced β-cell mass and the onset of diabetes.

The decrease in the adaptive UPR observed in β-cells from diabetic animals could be a consequence of hyperglycemia, as the expression of many adaptive UPR genes including the ER chaperones BiP and Grp94 are downregulated in mouse islets transplanted into diabetic mice compared with those transplanted into nondiabetic control animals (68). Furthermore, normalization of glycemia in these diabetic mice restores the expression of markers of an adaptive UPR in transplanted islets. Thus, it is possible that chronic hyperglycemia not only increases the demand for insulin resulting in the activation of the UPR but ultimately compromises the adaptive UPR. There is evidence from studies of *db/db* mice that the activation of JNK may play an important role in switching off an adaptive UPR (69). Decreased expression of markers of an adaptive UPR are coincident with increased JNK activation in islets from *db/db* mice, and the inhibition of JNK in islets isolated from *db/db* mice improves adaptive UPR gene expression and reduces cell death (69). CHOP may also play a role in inhibiting the adaptive response. Mice deleted of *Chop* display improved glycemic control and expanded β-cell mass in genetic and diet-induced models of insulin resistance, and this is associated with increased expression of adaptive UPR genes (67). Thus, the balance between the adaptive UPR and CHOP may be critically important in the regulation of β-cell function and survival during ER stress (Fig. 2).

Genetic evidence that a defective UPR may be an important predisposing factor for the development type 2 diabetes in humans is somewhat limited, although genome-wide association studies have implicated polymorphisms within the *ATF6* gene with type 2 diabetes in both Pima Indians and Dutch Caucasians (70,71). Moreover, polymorphisms within the Wolfram syndrome 1 (*WFS1*) gene, a negative regulator of ER stress (72), have also been associated with increased risk of type 2 diabetes (73).

CONCLUSIONS AND FUTURE PERSPECTIVES

There is mounting evidence that β-cell dysfunction and death in type 2 diabetes is caused by the inactivation of the UPR and, as a consequence, the failure of the β-cell to adequately adapt rather than by the more commonly proposed model of chronic ER stress and the activation of a proapoptotic UPR. Although chronic unresolvable ER stress can lead to β-cell death through activation of a proapoptotic UPR, which may be beneficial under certain physiological or pathological conditions, it is unclear whether β-cells are exposed to such severe stress in type 2 diabetes. During the development of type 2 diabetes, islets are subjected to a slow and gradual increase in the demand for insulin with obesity and decreasing insulin sensitivity, and this occurs over several years. It is likely that this translates into cycles of UPR activation and adaptation with relatively small changes in demand provoking a transient and subtle activation of an adaptive UPR. This would result in small but effective increases in ER folding and processing capacity thus alleviating ER stress.

Despite clear evidence for the activation of an adaptive UPR in both obese insulin-resistant rodents and humans, the evidence that β-cell failure and death are mediated by the activation of a proapoptotic UPR is limited. However, there is evidence for a decrease in the expression of markers of an adaptive UPR in islets undergoing β-cell failure in rodent models of type 2 diabetes and in human subjects with type 2 diabetes. Moreover, UPR dysfunction is known to lead to β-cell dysfunction and/or the inability of β-cells to adequately compensate in the face of an increase in the demand for insulin. Thus, β-cell dysfunction and death in type 2 diabetes may be caused by a failure of the UPR to adequately adapt rather than the activation of a proapoptotic and, in this context, maladaptive UPR (Appendix 3). However, further investigation is required to establish this.

As much of the work on the role of ER stress in β-cell failure in type 2 diabetes has been conducted in rodent islets, it is important to consider whether there are significant differences between how rodent and human islets respond to ER stress. On the basis of several in vitro studies, it is unlikely that there are fundamental differences in the mechanism of UPR activation or in islet resilience to ER stress (26,50,74). However, one important difference that may impact on islet survival is the ability of islets to adapt to increased demand (for reviews, see refs. 75,76). Rodent β-cell mass readily increases in response to increased demand primarily through proliferation, thus decreasing insulin secretory demand per β-cell and presumably relieving ER stress. Indeed, decreased insulin production relieves ER stress and interestingly promotes β-cell replication in mice (42). In contrast, although human islet mass has been shown to increase in adults who are obese, these changes are small compared with the changes observed in mice and are primarily mediated by an increase in β-cell size rather than number (77). Therefore, one may predict that human β-cells are more likely to be subjected to a comparatively greater demand for insulin and thus be more susceptible to ER stress, which in turn may lead to a greater propensity to develop β-cell dysfunction and death.

Other important unresolved questions are *1*) what leads to the failure of the adaptive UPR and *2*) if β-cell death is not caused by the activation of a proapoptotic UPR, then what is it caused by? There is evidence that "UPR failure" may be caused by the activation of stress-activated signaling pathways, whereas β-cell death appears to be mediated by a culmination of stresses of which oxidative stress plays a particularly critical role. As there have been a number of reports demonstrating the importance of the UPR in limiting oxidative stress (e.g., refs. 11,15,25), it is not surprising that one consequence of UPR failure is an increase in oxidative stress. Notably, the administration of antioxidants reduces ER stress and preserves β-cell function (40,66,67), thus showing therapeutic potential. Another important question is whether it is possible to intervene therapeutically to

promote further adaptation. Clearly, increasing ER folding capacity through the administration of pharmacological chaperones in rodent models of diabetes has beneficial effects (32,36,40,44–46,78), and there is some evidence that it is also beneficial in humans (47). Thus, the identification and an evaluation of the efficacy of drugs that increase ER folding capacity and/or reduce oxidation stress is an important avenue of pharmacological exploration.

APPENDIX

1. Experimentally, ER stress is most often defined by its consequences, i.e., the morphological distension of the ER and/or the activation of the UPR. Thus, the UPR is not a measurement of ER stress per se but rather an indication that the cells have encountered or are encountering ER stress. Unfortunately, ER stress infers a pathophysiological perturbation of the ER despite the fact that physiological changes in ER homeostasis also activate the UPR. This causes much confusion, as experimental evidence of UPR activation is often provided as evidence of pathology.
2. Stresses other than ER stress caused by, for example, nutrient limitation, infection, inflammation, increased reactive oxygen species, and/or DNA damage can also increase ATF4 expression through increased phosphorylation of eIF2α mediated by one of three alternative eIF2α kinases, namely GCN2, HRI, and PKR. Thus, it is worth noting that the phosphorylation of eIF2α or an increase in the expression of its downstream effectors such as ATF4 and CHOP is not in and of itself evidence for UPR activation or indeed ER stress.
3. It is conceivable that if cells were irreversibly dysfunctional, then their elimination would be considered beneficial. This may be the case with some β-cells in the latter stage of type 2 diabetes, but there is no clear evidence for this. On the other hand, many studies have demonstrated the reversibility of β-cell dysfunction in type 2 diabetes, including with bariatric surgery (79) and the normalization of glycemia with intensive insulin treatment (80,81) or pharmacotherapy (82). Thus, rather than being terminally dysfunctional, β-cells in type 2 diabetes likely represent a functional reserve. Therefore, in this context the elimination of dysfunctional β-cells under chronic ER stress conditions is defined as maladaptive.

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