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Endoplasmic reticulum stress and pancreatic beta cell death

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Summary

In pancreatic β cells, the endoplasmic reticulum (ER) is an important cellular compartment for insulin biosynthesis, which accounts for half of total protein production in these cells. Protein flux through the ER must be carefully monitored to prevent dysregulation of ER homeostasis and stress. ER stress elicits a signaling cascade known as the unfolded protein response (UPR) which influences both cellular life and death decisions. β cell loss is a pathological component of both type 1 and type 2 diabetes, and recent findings suggest that ER stress is involved. In this review, we address the transition from the physiological ER stress response to the pathological response and explore the mechanisms of ER stress-mediated β cell loss during the progression of diabetes.

Protein homeostasis in the β cell

The endoplasmic reticulum (ER) is the synthesis and folding site for membrane and secretory proteins, and is responsible for several important cellular functions including Ca^{2+} storage and cell signaling. In the β cell, the ER has an essential role in the assembly and processing of insulin. The ER houses a specialized environment, including complexes of chaperones and foldases, as well as high fidelity quality control mechanisms to ensure the crucial maintenance of ER homeostasis in these cells. ER homeostasis is defined as the unique equilibrium between the cellular demand for protein synthesis and the ER folding capacity to promote protein transport and maturation. β cells often undergo conditions that cause a disruption to ER homeostasis: fluctuations in blood glucose levels lead to a high demand for insulin biosynthesis via increasing both insulin transcription and translation [1, 2]. Glucose rapidly stimulates up to a 20-fold increase in insulin synthesis and total protein synthesis [3]. It has been proposed that this increase in proinsulin biosynthesis generates a heavy load of unfolded/misfolded proteins in the ER lumen [4]. This disruption in homeostasis and accumulation of unfolded and misfolded proinsulin in the ER lumen, causes ER stress [5]. Metabolic dysregulation associated with obesity, such as excess

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nutrients and insulin resistance, has also been implicated in the secretory burden of the β cell leading to ER stress and severely compromising cell function [6, 7]

ER stress is sensed by the luminal domains of three ER transmembrane proteins: Inositol Requiring 1 (IRE1), PKR-like ER kinase (PERK), and Activating Transcription Factor 6 (ATF6). Once activated, these stress sensors transduce a complex ER-to-nucleus signaling cascade termed the unfolded protein response (UPR) [8] (Figure 1). The UPR regulates several downstream effectors that function in adaptation, feedback control, and cell fate regulation [9]. Initially the UPR triggers the adaptive response: enhancement of folding activity through upregulation of molecular chaperones and protein processing enzymes. This is followed by reduction of ER workload through translational attenuation and mRNA degradation, and an increase in the expression of ER-associated protein degradation (ERAD) and autophagy components to promote clearance of unwanted proteins.

IRE1 is an ER transmembrane kinase with endoribonuclease activity. In response to ER stress, IRE1 oligomerizes and undergoes transautophosphorylation, leading to activation of its endoribonuclease activity and unconventional splicing of transcription factor X-box protein binding 1 (XBP1) mRNA, which regulates chaperone and ERAD protein expression.

Like IRE1, PERK is a transmembrane kinase which dimerizes and autophosphorylates when stress is sensed. Its main function is to regulate protein synthesis through phosphorylation of the α subunit of eukaryotic initiation factor 2 (eIF2 α). This inhibits general protein synthesis, while preferentially increasing translation of selected UPR mRNAs such as activating transcription factor 4 (ATF4), which is involved in regulating genes important for resting ER homeostasis.

ATF6, the third UPR transducer, is unique in that it is part of a family of ER transmembrane sensors which function in a cell-/tissue-specific manner. For example, one family member, cAMP responsive element-binding protein 3-like protein 1 (OASIS), is a putative ER stress sensor in astrocytes [10, 11]. Unlike IRE1 and PERK, ATF6 is a transcription factor which gets shuttled to the Golgi for its ER stress-mediated activation. Translocation of the processed form of ATF6 to the nucleus results in the upregulation of UPR homeostatic effectors involved in protein folding, processing, and degradation.

All three UPR transducer responses are critical in β cells to alleviate ER stress and restore ER homeostasis, ensuring the proper production of high quality proteins, especially insulin, which accounts for approximately half of total protein production in these cells [12]. This sensitive stress-sensing program, the UPR, has built-in feedback control mechanisms to switch off the UPR master regulators and their downstream targets, thus preventing harmful UPR hyperactivation [13]. The UPR, therefore, is not only responsible for regulating the expression and activation of adaptation/survival effectors, but it can also promote cell death [9, 14–16]. It is also evident that conditions associated with severe ER stress can compromise β cell function [7].

Causes of ER-stressed β cells

There are several proposed physiological, environmental, and genetic causes of ER stress activation specific for β cells (Figure 2). One form of physiological stress, which can become a pathological stress, occurs when these cells are exposed to high glucose [17]. Under high glucose conditions, increased insulin biosynthesis can overwhelm the ER folding capacity, causing an imbalance in homeostasis and leading to ER stress. Both acute (1–3 hours) and chronic (≥ 24 hours) high glucose (≥ 16.7 mM) have been shown to induce activation of IRE1 α in vivo and in isolated rat and mouse islets [18, 19]. In one study, transient activation of IRE1 α by high glucose was shown to enhance proinsulin biosynthesis

via minimal splicing of XBP-1, whereas other studies have shown that prolonged activation of IRE1 α by chronic high glucose, a pathological condition, leads to insulin mRNA degradation, profuse XBP-1 splicing, and induction of pro-apoptotic effectors, such as Jun N-terminal kinase (JNK) and C/EBP homologous protein (CHOP), causing β cell dysfunction and death [19–22]. It should be noted that the handling of primary rodent islets seems to be critical in determining the level of UPR activation from chronic, high glucose treatment [18]. In *in vivo* rodent models, exposure of islets to a hyperglycemic environment causes suppression of genes needed to optimize glucose-induced insulin secretion and maintain β cell differentiation [23]. In rodent diabetic db/db islets, there is also evidence of ER stress signaling activation [24]. Chronically elevated glucose, referred to as glucose toxicity, is associated with increases in reactive oxygen species (ROS) which can also induce ER stress, in addition to other cellular effects [25–27]. Chronically elevated ER stress, therefore, may also play a role in glucose toxicity which contributes to potentially irreversible β cell damage leading to diabetes. However, while ER stress seems to somehow be involved in chronic hyperglycemia, it must be noted that the cellular response to glucotoxicity is complicated. Interestingly, tribbles homolog 3 (TRB3), may be the link between glucotoxicity and ER stress-mediated apoptosis. TRB3, which inhibits Akt/PKB signaling, is upregulated in hyperglycemic Goto-Kakizaki rat islets and has been implicated in ER stress-induced apoptosis, as well as negative regulation of insulin exocytosis [28, 29].

Free fatty acids (FFAs), specifically long-chain FFAs, have also been implicated in induction of ER stress in β cells [13, 30]. Treatment of rodent islets with the saturated FFA, palmitate, causes ER distension as well as activation of all three UPR stress sensors. Overexpression of the ER-resident chaperone, binding immunoglobulin protein (BiP), in β cells protects against FFA-induced lipo-apoptosis [24]. The mechanism behind this ER stress-induced lipo-apoptosis is complicated and may involve several factors, including depletion of ER calcium levels [31]. It has also been proposed that FFAs, such as palmitate, reduces ER-to-Golgi trafficking, contributing to ER stress through protein overload in the ER lumen [32]. Other proposed mechanisms include alterations in ATP-citrate lyase expression, as well as carboxypeptidase E (CPE) levels. The UPR may also contribute to FFA-induced β cell death through upregulation of the proapoptotic effector CHOP, and activation of JNK and caspase-12 [33]. Interestingly, a study in human islets showed that ER stress is involved in lipotoxicity, but not in gluco-lipotoxicity. Palmitate treatment led to severe ER stress and induction of apoptosis, but the palmitate-induced ER stress response was not modified by high glucose concentrations [34].

Inflammatory cytokines such as interleukin-1 β (IL-1 β) and γ -interferon (IFN- γ), can also cause ER stress and UPR activation in β cells [35]. While it is controversial whether or not cytokine-induced β cell death is dependent or independent of ER stress signaling, IL-1 β in combination with IFN- γ has been shown to induce nitric oxide (NO) in β cells, leading to β cell dysfunction and death in type 1 diabetes [36, 37]. It has been shown that NO-induced β cell apoptosis is mediated by ER stress [38]. NO production decreases expression of the sarcoendoplasmic reticulum pump Ca²⁺ ATPase 2b (SERCA2b), leading to a decrease in Ca²⁺ in the ER. This Ca²⁺ depletion causes a high level of ER stress in β cells which may play a role in cytokine-induced cell death in type 1 diabetes [35, 39].

Hypoxia has also been shown to cause ER stress in β cells. The ER lumen maintains an oxidizing environment to promote disulfide bond formation in newly synthesized proteins, which is particularly important for proinsulin which requires three disulphide bonds for proper folding [40]. In addition, the ER has high concentrations of ATP, which contributes to the folding efficiency of molecular chaperones. Hypoxia negatively impacts both ER redox potential and ATP concentrations, causing ER stress. Islets are normally highly vascularized, which is important for their ability to quickly secrete insulin in response to

changes in blood glucose levels [41]. Hypoxia-mediated ER stress may play a role in the death of transplanted pancreatic islets [15]. Transplanted islet grafts experience hypoxia for several days post-transplantation. In addition, they are less vascularized and have a lower oxygen tension than endogenous islets in the pancreas, even after revascularization is complete, thus rendering them susceptible to hypoxia-mediated ER stress [42–44]. In addition to islet graft loss by immunological factors, a substantial portion of the transplanted cells are no longer able to cope with the deleterious effects of hypoxia and eventually undergo apoptosis. Indeed, a recent study shows that human islet grafts transplanted into SCID mice exhibited signs of ER stress, which was thought to be a protective response [45]. It was speculated that the majority of islet cells would have a protective ER stress response, while a subgroup of vulnerable cells undergo apoptosis due to activation of the proapoptotic UPR branch. Thus, ER stress-mediated β cell death may play an important role in death of transplanted islets.

It has been shown that β cell failure is also associated with mutations in murine and human proinsulin that cause misfolding and accumulation of proinsulin in the ER lumen [46, 47]. Expression of mutant insulin has been associated with ER stress activation. The Akita diabetic mouse model carries a mutation in the insulin 2 gene [48], which results in a cysteine⁹⁶ to tyrosine substitution. Cysteine⁹⁶ is involved in the formation of one of the three disulfide bonds between the A and B chains of mature insulin [49]. These mice develop diabetes, which may result from both β cell dysfunction and death, as this mutation causes incorrect folding of proinsulin in the ER of β cells [50, 51]. Recent genetic studies have uncovered several mutations in the human insulin gene, specifically mutations occurring in critical regions of proinsulin folding, termed *MIDY* (*M*utant *I*NS-gene-induced *D*iabetes of *Y*outh) that result in early-onset diabetes and may lead to impairment of normal proinsulin folding. While these mutants induce ER stress and the UPR, it remains controversial whether this alone is sufficient to activate apoptosis [52–54]. Interestingly, one of the mutations found is the exact mutation from the Akita mouse [21].

It is also hypothesized that misfolded islet amyloid precursor protein (IAPP) may accumulate in the β cell ER lumen and cause ER-induced apoptosis [55, 56]. Islet amyloid expression is a common characteristic in type 2 diabetes and may play a role in β cell dysfunction and death during the progression of the disease [57]. Islet amyloid is composed of a 37-residue amyloidogenic polypeptide derived from IAPP. IAPP spontaneously forms ER membrane-damaging sheets of amyloid [58]. While one study has shown a disconnect between human IAPP and ER stress [59], others have shown that high expression of human IAPP induces ER stress and subsequent death of β cells [55, 60]. Therefore, IAPP could be one of the links between ER stress and β cell death in type 2 diabetes.

Life and death decisions

The ultimate cell fate decision of life or death is dependent on the nature and severity of ER stress that the β cell is exposed to. Thus, there are two types of ER stress conditions: resolvable and unresolvable. When ER stress can be resolved, the UPR promotes β cell survival. In contrast, under unresolvable ER stress conditions, the UPR activates death effectors, leading to β cell apoptosis.

When β cells are exposed to conditions that induce mild ER stress (e.g. physiological exposure to glucose fluctuations following a meal), the ER can facilitate stress mitigation and restore protein homeostasis, thus “priming” cells for future ER stress insult and promoting cell survival. It has been shown that IRE1 α and PERK are the primary transducers for regulating insulin production under these conditions, thus promoting activation of UPR pro-survival pathways [4, 5, 19, 61, 62]. Unresolvable ER stress

conditions occur when an insufficient UPR response fails to restore ER homeostasis, leading to the induction of pro-apoptotic pathways. This can be attributed to several factors from genetic mutations to chronic exposure to high glucose, as well as dysregulation of the UPR itself. Thus, the UPR behaves like a binary switch between life and death in β cells.

This binary switch is regulated by the three master UPR transducers: IRE1, PERK, and ATF6. Both adaptive/survival and death effectors are simultaneously expressed during UPR activation, and it is the delicate balance between these effectors which determines the fate of the cell (Figure 3).

The IRE1-XBP1 pathway regulates the expression of homeostatic components of the UPR such as chaperones and components of the ERAD machinery. In addition to cleavage of XBP1, IRE1 also plays a role in the cleavage of other ER-associated mRNAs, such as insulin mRNA, thus relieving the workload placed on the ER [20, 63–66]. In β cells, mild activation of IRE1 is particularly important for enhancement of insulin biosynthesis. While this may be an XBP1-independent process, other components of this pathway, such as oxidoreductase endoplasmic oxidoreductin 1 (ERO1) enzymes may also be involved [3]. ERO1 enzymes are responsible for oxidizing protein disulphide isomerase (PDI) during disulfide bond formation and appear to be important for proinsulin folding. Recent studies show that disruption of the pancreatic-selective isoform of ERO1, ERO1 β , compromises oxidative folding of proinsulin and leads to glucose intolerance in mice [67]. Enhancement of insulin biosynthesis is an adaptive mechanism, which is beneficial not only to β cell function, but also survival. While IRE1 has a role in promoting cell survival, it acts as a binary switch and has additional functions in promoting cell death through two mechanisms: (1) endoribonuclease activity and (2) kinase activity. IRE1's endoribonuclease function may regulate cell death by downregulating mRNAs involved in β cell homeostasis and survival, such as the redox protein, PDI, the ER-resident chaperone, BiP, while its kinase function plays a role in activation of UPR death effectors [66, 68]. There are two IRE1-dependent pathways which promote cell death through its kinase activity: (1) phosphorylation of JNK via IRE1-dependent recruitment of TNF-receptor-associated factor 2 (TRAF2) and (2) activation of murine caspase-12 (caspase-4 and caspase-11 in humans) [69, 70]. In β cells, chronic hyperglycemia leads to IRE1 hyperactivation and consequent activation of UPR death effectors [19]. This hyperactivation leads to higher levels of XBP1 splicing, which may be harmful to the cell. It has been shown that overexpression of spliced XBP1 can suppress insulin expression and inhibit β cell function, ultimately leading to cell death [71].

PERK also acts as a binary switch in the UPR. PERK is highly expressed in β cells and its activation negatively regulates insulin biosynthesis. PERK's role in attenuating protein production has been shown to protect β cells from ER stress-mediated apoptosis. Complimentary to its role in protecting the cell by initiating a global reduction in protein synthesis, PERK also has been found to upregulate an anti-apoptotic effector, apoptosis antagonizing transcription factor (AATF), which is responsible for mediating β cell survival in part through transcriptional regulation of AKT1 [72]. PERK, however, can also activate proapoptotic effectors. Reducing PERK activity has been shown to ameliorate the progression of the insulin Akita mutant mice towards diabetes [73]. It has been shown that continuous activation of eIF2 α induces β cell apoptosis, through ATF4 activation [13]. ATF4 promotes cell death under conditions of unresolvable ER stress through transcription of CHOP [74, 75]. CHOP promotes cell death through five outputs: (1) promoting hyper-oxidizing environment in the ER, (2) increasing the client protein load in the ER through GADD34 activation, (3) increasing the expression of the proapoptotic Bcl-2 family member PUMA, (4) increasing the expression of the Akt inhibitor, TRB3, and (5) activating calcium release through inositol 1,4,5-triphosphate receptor [76–80]. Thus, like IRE1, PERK also plays a critical role in balancing life and death decisions.

The third binary switch of the UPR, ATF6, serves a protective role and promotes cell survival by increasing the folding capacity of the ER. However, like IRE1 and PERK, ATF6 can also act as a binary switch between survival and death, which in part may be determined by one of its downstream effectors, CHOP. In β cells, hyperactivation of ATF6 suppresses insulin gene expression and has been shown to cause β cell dysfunction and death [81]. The exact mechanism for this suppression of insulin expression is currently unknown.

It is clear that each of the UPR master transducers must be under tight control due to their dual roles as regulators of both survival and cell death. ER stressors trigger both protective and proapoptotic outputs simultaneously, so the question is how cell fate is determined by the UPR? This is where the distinction of resolvable and unresolvable ER stress comes into play. When ER stress is resolvable, the master regulators and their downstream effectors are properly switched off, thus restoring ER homeostasis. However, this stress becomes unresolvable when this feedback regulation is bypassed, resulting in hyperactivation of the UPR. This hyperactivation redirects the cell into an apoptotic fate, via upregulation of death effectors. Important targets involved in this feedback process include BiP, GADD34, p58^{IPK}, RACK1, and WFS1 [39–43]. The ER-resident chaperone, BiP, binds to IRE1, PERK, and ATF6 to keep them in an inactive state in the ER membrane. As mentioned previously, GADD34 restores translation by dephosphorylating eIF2 α , thus turning off the PERK pathway. Another regulator of the PERK pathway is p58^{IPK}, which inhibits eIF2 α signaling. Interestingly, *Dnajc3* (p58^{IPK}) knockout mice exhibit a gradual onset of hyperglycemia associated with an increase in apoptosis of islet cells. Receptor of activated protein kinase C 1 (RACK1) has been recently shown to be an important regulator of the IRE1 pathway. With mild ER stress, such as acute glucose treatment of β cells, RACK1 recruits protein phosphatase 2A (PP2A) to IRE1, thereby turning off its activation. Wolfram syndrome 1 (WFS1), on the other hand, plays an important role in regulating the third master regulator, ATF6. WFS1 prevents ATF6 activation by recruiting ATF6 to the proteasome for ubiquitin-mediated degradation. It has been shown that a lack of functional WFS1, leads to hyperactivation of ATF6 signaling, inducing β cell death [43].

UPR survival outputs (i.e. the feedback regulators), if functioning properly, outweigh any of the death effectors, thus favoring cell survival. This may be due to the increased mRNA and protein stability of these feedback targets over apoptotic proteins, which provides the cell with an opportunity to adapt to stress. Further research is needed to better understand what is the exact turning point which favors the apoptotic fate and how the UPR can bypass the feedback regulation put in place to prevent this from occurring.

ER stress-mediated diabetes: Genetic evidence

Clinical and genetic evidence suggest that ER stress is one of the molecular mechanisms involved in β cell dysfunction and death which occurs in diabetes. In diet-induced and genetic rodent models of insulin resistance, it has been shown that knockout of the proapoptotic ER stress gene, CHOP, improves glycemic control and expansion of β cell mass [82].

This relationship of ER stress-induced β cell dysfunction and death was first revealed in a form of hereditary diabetes, the Wolcott-Rallison syndrome. In this syndrome, inactivating mutations in the *EIF2AK3* gene encoding PERK have been reported [44]. It has become evident that PERK plays a critical role in the life of the β cell, as in *Eif2ak3* (PERK) knockout models, β cells fail to expand during neonatal development due to decreased proliferation, causing diabetes [45][61]. PERK is also important for β cell differentiation, as *Eif2ak3* knockout islets are deficient in key markers of differentiation [61]. Interestingly, when *Eif2ak3*^{−/−} islets are cultured in high glucose, insulin production is more vigorous

than wild type islets, promoting ER stress and the accumulation of electron dense material in the ER lumen [4]. As mentioned previously, phosphorylation of PERK's primary target, eIF2 α , is essential to regulating the UPR and insulin synthesis. In agreement with this, mice carrying a heterozygous mutation in the phosphorylation site of eIF2 α (*Eif2s1^{+/tm1Rjk}*) show severe β cell deficiency and develop diabetes when fed a high-fat diet. These mice show abnormal β cell ER morphology, defective insulin trafficking, and reduced secretory granule number [5]. Thus, dysregulation in the UPR contributes to diabetes found in patients with Wolcott-Rallison syndrome most likely through a loss in β cell mass caused by a lack in β cell proliferation and potentially a vulnerability to ER stress-induced apoptosis.

Permanent neonatal diabetes or *MIDY* is another example of the involvement of excessive ER stress in diabetes. This form of diabetes, which occurs within the first month of life, can be caused by several types of mutations, including mutations in the critical regions of preproinsulin. Mouse models of this disease, the Munich and Akita mouse which both have dominant missense mutations in the *Ins2* (insulin) gene, reveal that progressive hyperglycemia associated with the mutations is accompanied by elevated levels of ER stress markers such as BiP and CHOP [46, 48]. While these mutants exhibit high levels of ER stress and develop diabetes, as previously mentioned, it is controversial whether this alone is sufficient to activate apoptosis [52, 54].

Wolfram syndrome, a rare disorder characterized by diabetes mellitus and optical atrophy, is another example of a genetic link between ER stress and β cell death and diabetes [46]. Here there is a selective loss of β cells which has been attributed to mutations in *WFS1*, a gene encoding an ER transmembrane protein that is localized to β cells. It has recently been shown that *WFS1* is a key feedback regulator of the ATF6 branch of the UPR. Presumably, patients with Wolfram syndrome have UPR hyperactivation in their β cells, leading to cell death. Recent genome-wide association studies reveal *WFS1* polymorphisms are associated with impaired β cell function and risk for type 2 diabetes [83–85]. Thus, *WFS1* seems to be a β cell-specific prosurvival component of the UPR.

ER stress: Link between β cell loss and impaired function in common forms of diabetes

Recent evidence indicates that β cell death is a major pathogenic component in most forms of diabetes [30]. Type 1 diabetes is a condition of absolute insulin deficiency due to β cell death by autoimmunity. Type 2 diabetes is a condition of relative insulin deficiency due to β cell dysfunction and death as the combined consequence of increased circulating glucose, saturated fatty acids, and inflammation. Despite *in vitro* and *in vivo* findings in rodent models which show a link between ER stress and β cell dysfunction and death, the role of ER stress-induced diabetes in humans remains controversial. In some of the genetic forms of diabetes outlined above, such as Wolfram syndrome and permanent neonatal diabetes, protein misfolding and dysregulated ER homeostasis can contribute to β cell death. Evidence of ER stress in the β cells of patients with type 2 diabetes has also been documented in several studies [24, 56]. However, the extent of UPR induction in patients seems to be variable. Autopsy samples from type 2 diabetic patients exhibit higher levels of ER stress, while isolated islets only show signs of ER stress when cultured at high glucose, raising the possibility of multiple factors playing a role in β cell death, including oxidative stress [86, 87]. Gene profiling studies also do not show a marked difference in ER stress levels in type 2 diabetic patients, however, this could be a sign of chronic compensation [88, 89].

One more factor must be kept in mind when looking at the relationship between ER stress and diabetes: the role of β cell dysfunction. It has been reported that patients with impaired fasting glucose, a group at high risk of developing overt diabetes, have a 40% deficit in

relative β cell volume compared with comparable obese control subjects with normal fasting glucose concentration, while patients with overt diabetes had a 60% deficit [90]. This has also been documented in other studies, however it remains unclear whether or not the decline in β cell mass by itself can cause diabetes, as human studies have proven to be somewhat variable [91, 92]. The question remains whether it is a decline in β cell mass, deteriorating β cell function, or both which cause type 2 diabetes. Despite this, it is intriguing to think that the tipping point between pre-diabetes and overt diabetes could lie in an additional 20% loss of β cells. Interestingly, it has been shown that β cell mass further declines with duration of clinical diabetes [92]. We propose that ER stress-mediated β cell dysfunction plays an important role in the transition from pre-diabetes to overt diabetes, since this further decline in cell mass is likely not to be the cause of diabetes in the absence of β cell dysfunction. When patients have lost 40 % of β cells, increased workload for production of insulin on residual β cells may cause chronic ER stress, leading to translational attenuation of proinsulin and degradation of insulin mRNA. This “adaptive” response exacerbates chronic hyperglycemia, leading to unresolvable ER stress and ER stress-mediated apoptosis (Figure 4).

UPR: Target for diabetes therapy

We propose that discovering methods that could reduce ER stress to a tolerable state and/or modulating the UPR to preferentially activate survival over death pathways could lead to novel and efficient therapeutic modalities for diabetes. Glucagon-like peptide 1 (GLP-1) is a good candidate for targeting this type of therapy. As described above, mild activation of the UPR by tolerable ER stress or specific activation of anti-apoptotic pathways of the UPR has beneficial effects on β cell function and survival. GLP-1, which is a gut-derived peptide secreted from intestinal L-cells after a meal, has numerous physiological actions, including enhancement of β cell growth and survival [93]. GLP-1 is also a physiological activator of the UPR. Activation of GLP-1 signaling improves β cell function and survival through the mild activation of the UPR [19, 94]. We predict that other endogenous factors, like GLP-1, or chemical compounds that can mildly activate the UPR could be used to increase the viability of β cells.

Conclusions and future directions

The prevalence of diabetes has risen dramatically world-wide. In type 1 diabetes, it has been established that β cell death is a major pathogenic component. Recent discoveries in human genetics have revealed that genes important for β cell survival, proliferation, and function are also involved in type 2 diabetes [95–100]. These findings point to the importance of developing therapies able to preserve or restore depleted numbers of β cells for type 1 and type 2 diabetes. Increasing clinical, experimental, and genetic evidence indicates that ER stress and the UPR has a role in β cell dysfunction and death during the progression of type 1, type 2, and genetic forms of diabetes. It is currently believed that the UPR behaves as a binary switch between life and death of the β cell. The complete understanding of how the UPR regulates cell fate will provide us with new insights into mechanisms of β cell death and shed light on future diabetes prevention or treatment. Prevention of diabetes could be improved by preventing unresolvable ER stress in β cells. It would also be important to study the associations between single nucleotide polymorphisms (SNPs) of the UPR genes and individuals’ predispositions to β cell death and diabetes. Advances in pharmacogenomics may allow us to target critical molecules regulating the UPR binary switch for preventing β cell death. We propose that understanding and regulation of the UPR binary switch in β cells will lead to a novel therapeutic modalities and prevention for most forms of diabetes.

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Figure 1. The ER stress signaling network

There are three main regulators of the unfolded protein response (UPR): IRE1, PERK, and ATF6. Each of these stress transducers activates downstream targets which mitigate ER stress.

Figure 2. Causes of ER stress in the β cell

There are several causes of ER stress in the β cell ranging from physiological stress, such as high glucose levels which follow meal intake, to pathological causes such as the expression of mutant insulin protein.

Figure 3. The balance between death and survival

The UPR acts as a binary switch between cell survival and death decisions when ER stress is present in the cell. Mild stress induces a regulated UPR, in which survival effectors outweigh death effectors, leading to adaption and survival of the cell. When severe stress is present, on the other hand, the UPR becomes hyperactivated, a situation in which the death effectors outweigh survival effectors, ultimately leading to apoptosis.

Figure 4. ER stress: The tipping point between β cell death and dysfunction

ER stress mediated β cell dysfunction plays an important role in the transition from a pre-diabetic state to an overt diabetic state. In the pre-diabetic state some β cell loss has already occurred and residual β cells have to work harder to keep up with insulin output. This leads to additional ER stress, causing β cell dysfunction. This dysfunction is the tipping point leading to additional cell loss and the progression to a diabetic state.