

Review Article

Role of the Unfolded Protein Response in β Cell Compensation and Failure during Diabetes

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Pancreatic β cell failure leads to diabetes development. During disease progression, β cells adapt their secretory capacity to compensate the elevated glycaemia and the peripheral insulin resistance. This compensatory mechanism involves a fine-tuned regulation to modulate the endoplasmic reticulum (ER) capacity and quality control to prevent unfolded proinsulin accumulation, a major protein synthesized within the β cell. These signalling pathways are collectively termed unfolded protein response (UPR). The UPR machinery is required to preserve ER homeostasis and β cell integrity. Moreover, UPR actors play a key role by regulating ER folding capacity, increasing the degradation of misfolded proteins, and limiting the mRNA translation rate. Recent genetic and biochemical studies on mouse models and human UPR sensor mutations demonstrate a clear requirement of the UPR machinery to prevent β cell failure and increase β cell mass and adaptation throughout the progression of diabetes. In this review we will highlight the specific role of UPR actors in β cell compensation and failure during diabetes.

1. Introduction

Type 2 diabetes (T2D) mellitus is a chronic metabolic disease with “epidemic” proportions. Its global prevalence was estimated to be 6.4% worldwide (285 million adults in 2010) and is predicted to rise to approximately 7.7% (439 million) by 2030 [1]. T2D is a multifactorial disorder resulting from an interaction between genetic and environmental conditions (sedentary lifestyle and Western diet) and characterized by a peripheral insulin resistance, hyperglycaemia, and pancreatic β cell dysfunctions. Two defects have been reported during diabetes development, a gradual deterioration of β cell functions and a reduction in pancreatic β cells mass. β cell failure is not limited to T2D but is rather a common feature of all forms of diabetes, including the autoimmune type 1 diabetes (T1D), autosomal dominant onset diabetes of young (MODY), Wolfram syndrome, and Wolcott-Rallison syndrome (WRS).

In the early stage of diabetes development, the response of pancreatic islets challenged by nutrients and/or insulin resistance is a hypersecretion of insulin to maintain normoglycaemia. To this end, an adaptive and compensatory response of β cells is required. The process of β cell compensation is a combination of β cell mass expansion and an increase of acute glucose-stimulated insulin secretion. Postmortem analyses of pancreas of nondiabetic obese patients show an increase of β cell volume, implying postnatal plasticity of β cell mass. Moreover the β cell compensation process is associated with an improved capacity of the secretory machinery to support increased insulin production. Subsequently, the production of large amounts of insulin by compensating islet β cells places a continuous demand on the ER for proper protein synthesis, folding, trafficking, and secretion. When the folding capacity of the ER is exceeded, misfolded or unfolded proteins accumulate in the ER lumen, resulting in ER stress.

The cytoprotective response to ER stress is the unfolded protein response (UPR). Paradoxically, UPR signalling activation leads to opposite cell fates, that is, adaptation/survival versus death. Increasing evidence links the endoplasmic reticulum (ER) stress to β cell deterioration and apoptosis [2, 3]. Recent experiments performed in db/db mice and ob/ob mice models at different times of disease progression revealed that the maintenance (or suppression) of adaptive UPR is associated with β cell compensation (or failure) in obese mice [4]. Moreover, Engin et al. recently showed a progressive loss of UPR mediator expression before the onset of diabetes in NOD mice [5]. The administration of the chemical chaperone tauroursodeoxycholic acid to rescue the deleterious ER stress response improved pathophysiological signs of diabetes with a recovery of β cell survival and adaptation to stress [5]. In addition, the authors showed a decline of the UPR mediator in both experimental models and T2D human islets, suggesting that decreased expression of β cell UPR actors can play a central role in β cell compensation and subsequently T2D occurrence [6].

2. The UPR Pathway

Three canonical ER resident molecules mediate UPR response, namely, protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6), which are maintained inactive by their association with the immunoglobulin heavy chain-binding protein (BiP, GRP78) in normal conditions (Figure 1(a)). The accumulation of unfolded proteins in the ER leads to the release of PERK, IRE, and ATF6 and their subsequent activation [7, 8]. The downstream signalling effectors from these pathways converge to the nucleus and activate UPR target genes, finally reducing the ER input (Figure 1(a)). Their action is bipartite, with an acute programme that attenuates the ER workload and a latent transcriptional one that builds ER capacity.

PERK is a type 1 ER transmembrane kinase with a stress sensing luminal N-terminal domain. During ER stress PERK phosphorylates the α -subunit of eIF2- α on serine 51 leading to a delivery inhibition of the initiator methionyl-tRNA_i to the ribosome and ultimately resulting in global protein translation attenuation [9] (Figure 1(a)). This phosphorylation event directly contributes to the reduction of ER stress and protects cells from ER stress-mediated apoptosis [10]. Intriguingly, the mRNA transcription of UPR target genes is selectively activated by eIF2 α phosphorylation, as these polycistronic mRNAs have inhibitory upstream open reading frames (uPRFs) and are thus preferentially translated by the ribosome. These include the bZIP transcription factor 4 (ATF4) that acts as a regulator of UPR target genes such as C/EBP-homologous protein (CHOP) and growth arrest and DNA damage inducible gene 34 (GADD34), as well as genes involved in the redox balance and amino acid synthesis [11]. GADD34 interacts with the catalytic subunit of protein phosphatase (PP1c) and controls the level of eIF2- α phosphorylation by a negative feedback loop [12], allowing the restoration of an UPR basal state once ER stress is resolved.

IRE1 is a central regulator of UPR. Like PERK, IRE1 is also a type 1 transmembrane kinase with an N-terminal luminal domain that senses ER stress signalling. Two homologues of IRE1 have been described, IRE1 α and IRE1 β . IRE1 α is expressed ubiquitously, showing high expression levels in the pancreas and placenta [13], whereas IRE1 β is only expressed in the intestinal epithelium and lung [14]. IRE1 possesses kinase as well as endoribonuclease activities. Once the ER stress is triggered, IRE1 activates its RNase domain through its dimerization and transautophosphorylation and causes an unconventional splicing by the removal of 26-nucleotide intron from the X-box binding protein 1 (XBP1) mRNA (Figure 1(a)). The subsequent spliced XBP1 (XBP1s) mRNA encodes a leucine zipper transcription factor with a high transcriptional activity that upregulates genes encoding ER protein chaperones, ER associated protein degradation (ERAD), and lipid biosynthetic enzymes [15, 16]. IRE1 has also a non-specific RNase activity that degrades mRNAs localized near the ER membrane, thereby reducing protein import into the ER lumen [17]. High levels of ER stress also activate the kinase activity of IRE1 and initiate a signalling cascade of apoptosis signal-regulating kinase 1 (ASK1)/cJun amino terminal kinase (JNK), which can participate in the apoptotic cell fate [18].

ATF6 is an ER located type 2 transmembrane protein with a basic leucine zipper DNA binding domain (Figure 1(a)). Two ubiquitously expressed isoforms of ATF6 have been described, ATF6 α and ATF6 β [19]. Under ER stress conditions, ATF6 α translocates from the ER to the Golgi apparatus, where it is cleaved by Site-1 protease and Site-2 protease (S1P/S2P). The newly generated cytosolic fragment migrates to the nucleus and activates UPR gene transcription [20, 21]. The exclusive or the combined action of cleaved ATF6 α and XBP1s is able to activate all three ER stress response elements: ERSE, UPRE, and ERSE2 [22]. ATF6 β was first described as a repressor of ATF6 α [23]. However, mouse embryonic fibroblasts generated from ATF6 β null mice did not show altered UPR gene induction, suggesting a minor role for ATF6 β in ER stress response [24]. In contrast, ATF6 α null mice have a significant alteration in their UPR gene expression profile, suggesting a central role for ATF6 α in ER protein quality control and protection against ER stress [24]. As the double ATF6 α/β knockdown is lethal, the authors suggested that ATF6 α and ATF6 β provide a complementary function during early development [24]. Moreover ATF6 activity is regulated by the Wolfram syndrome 1 (WFS1) protein, which targets ATF6 to the E3 ubiquitin ligase HRD1, consequently resulting in its ubiquitination and proteasomal degradation [25]. A number of other ER stress transducers that share a high sequence homology with ATF6 have been identified, such as Luman, OASIS, BBF2H7, CREBH, and CREB4 (reviewed in [26]). However, despite their structural similarities, each ATF6 homolog seems to have specific functions in UPR regulated processes in specific organs and tissues [26].

2.1. β Cells Compensation and UPR Actors. β cell is a highly specialized secretory cell which responds to elevated postprandial glycaemia by increasing mRNA proinsulin translation and insulin secretion [27]. The periodic waves of proinsulin mRNA translation generate biosynthetic loads that

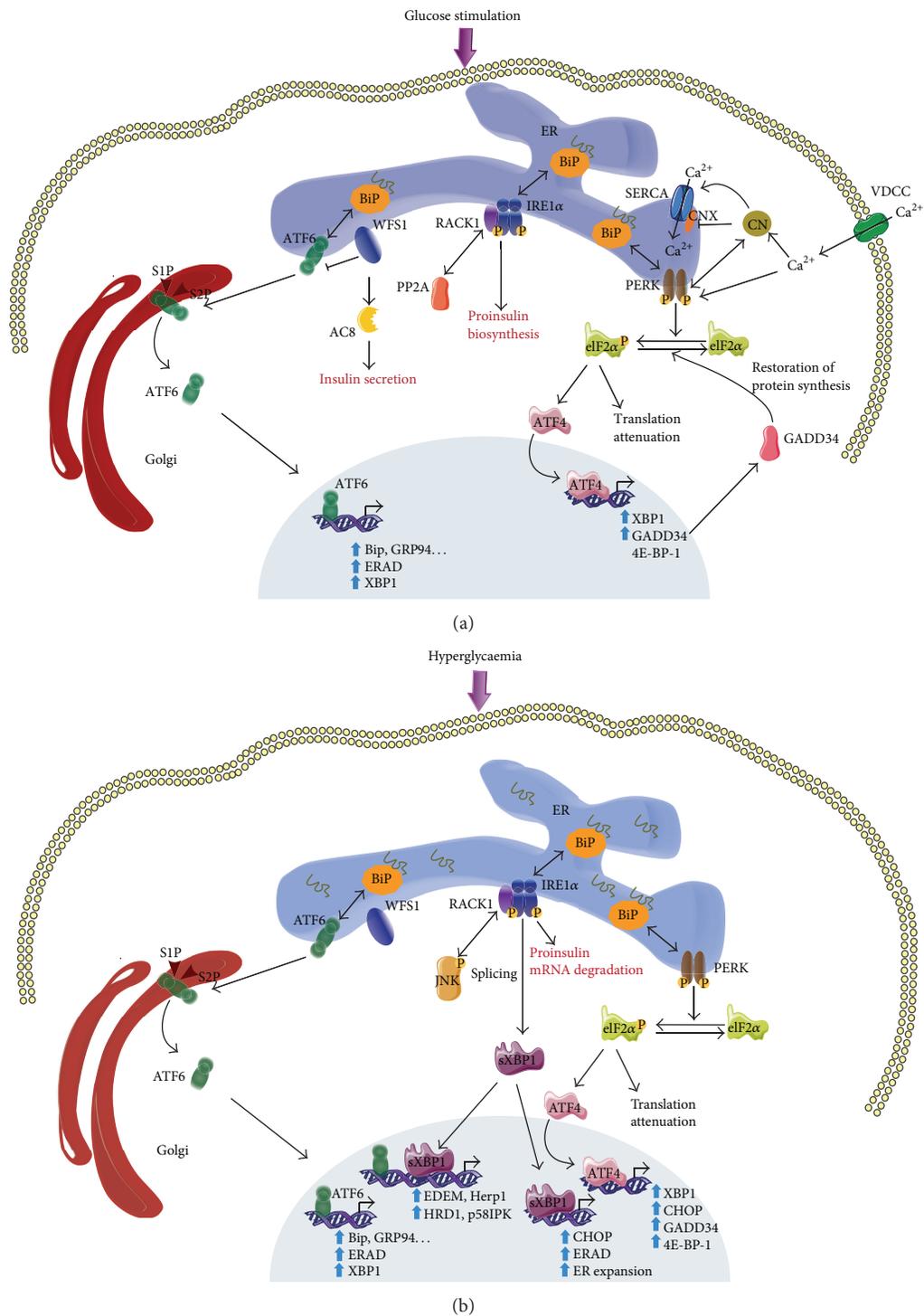


FIGURE 1: Physiological and physiopathological UPR activated pathways in β cells. (a) Under physiological conditions, increased proinsulin synthesis in response to postprandial glucose activates UPR to reduce ER stress and to promote β cell adaptation. The UPR triggers transcription of folding protein (BiP, GRP94,...), protein quality control (ERAD), UPR retrocontrol protein (GADD34), and attenuates protein translation (eIF2 α). Additionally, the UPR regulates calcium homeostasis via PERK, promotes proinsulin synthesis via IRE1 α , and increases insulin secretion via a WFS1-AC8 pathway. (b) Under physiopathological conditions, the UPR is hyperactivated leading to IRE1 α hyperphosphorylation, which in turn induces proinsulin mRNA degradation, JNK pathway activation, and XBP1 mRNA splicing. XBP1s alone or in synergy with ATF6 lead to expression of ER chaperon (Herp1, EDEM, HRD1, p58IPK, and ERAD) and subsequent ER expansion. Both ATF4 and sXBP1 increase CHOP mRNA expression. Under these conditions the UPR feedback is deregulated.

induce UPR. To manage this burden imposed by proinsulin synthesis, β cells increase their ER size, as exemplified during diabetes development. In the prediabetic state, β cell must adapt its ER machinery to the new hyperglycaemic environment, promoting β cell compensation. The use of genetically modified mouse models and genetic studies from human diabetic patients demonstrated that UPR actors support this adaptation as well as β cell compensatory mechanism [4, 28].

2.2. Insulin Mutants and β Cells Compensation. Misfolding of proinsulin is associated with ER stress and severe dysfunctions leading to a massive destruction of β cells. *In vivo* evidences were observed in both Akita and Munich mice carrying cysteine residues mutations that interfere with disulphide bond formation [29, 30]. Interestingly, inactivation of the UPR induced proapoptotic Chop gene delayed the onset of diabetes in heterozygous Akita mice, suggesting a key role for CHOP in ER stress-mediated β cell apoptosis [30]. Diabetes of youth (MIDY) is a syndrome caused by a heterozygous mutation of the coding sequence of proinsulin leading to an autosomal-dominant and insulin-deficient diabetes [31]. This mutation has been shown to be the second most common cause of permanent neonatal diabetes related to ER stress [32, 33]. In line with these observations, inducible expression of the human analogue proinsulin C96Y mutation of Akita mice in rat insulinoma-1 (INS-1) caused ER stress and cell apoptosis. However, upregulation of UPR and ERAD seems to have a protective effect [34]. *In vivo* expression of the same proinsulin mutant driven by the weak *Ins1* promoter induced both ER stress and pancreatic compensation [35]. Altogether these data demonstrate a clear link between misfolding of proinsulin and ER stress induction.

2.3. PERK-eIF2 α -ATF4 Pathway in β Cells Compensation. Loss of function mutation in the EIF2AK3 gene-encoding PERK was associated with WRS, which has been confirmed by the functional characterisation of *Perk* knockout mice [36]. Embryonic development of these mice is normal but they exhibit a postnatal growth retardation, skeletal dysplasia, and progressive loss of β cells, associated with defects in ER secretory machinery and proinsulin folding [37, 38]. However, generation of β cell specific *Perk* knockout mice revealed that β cell death was not increased, but rather β cell proliferation and differentiation were repressed during the embryonic and postnatal state [39]. Other studies on these mice models demonstrated an impaired ER to Golgi anterograde trafficking, retrotranslocation out of the ER, and proteasomal degradation, showing requirement of PERK for ER and Golgi integrity and processing of ATF6 [40]. In contrast to the first rapport, specific β cell inducible *Perk* deletion in mice showed a rapid progression of insulin dependent diabetes regardless of mice age [41]. The authors showed, on the one hand, that this phenotype was due to an increased β cell proliferation after the induction of PERK deletion due to the increased activation cyclin D-dependent kinase activity. On the other hand, they showed a significant increase in β cell death, associated with an activation of other UPR actors and a disturbance in calcium homeostasis [41]. Moreover, a recent work

demonstrated that PERK, in concert with calcineurin, regulates ER calcium reuptake through calnexin interaction and a negative regulation of the sarcoplasmic endoplasmic reticulum calcium ATPase pump (SERCA) [42] (Figure 1(a)). PERK thus appears to sense glucose by direct sensing of ER calcium levels, raising the possibility that the primary function of PERK in β cell is to modulate proinsulin quality control and trafficking.

Within the β cell, phosphorylation of eIF2 α is mostly PERK dependent in ER stress conditions (Figure 1(b)). Mice harbouring a homozygote knock-in mutation at the PERK-mediated phosphorylation site (Ser51Ala) of eIF2 α display a severe β cell deficiency detectable in late stage embryos and die within 18 h after birth as a consequence of hyperglycaemia associated with defective neoglucogenesis [43]. Heterozygote mice development is normal; however, when challenged with a high fat diet, they develop severe obesity, glucose intolerance, and impaired insulin release. In this genetic context reduced insulin content, fewer granules, ER distension, and a prolonged association of proinsulin with BiP have been observed. Thus, eIF2 α phosphorylation is required for UPR to prevent β cell failure when insulin demand is increased. These findings demonstrate a central role of eIF2 α phosphorylation in β cell adaptation during compensation [44]. The generation of conditional homozygote ser51Ala eIF2 α mutation in β cell confirmed this observation. These mice exhibit a high rate of β cell apoptosis, likely caused by hypoinsulinemia, severe glucose intolerance, and hyperglycaemia. Furthermore, the authors showed ER distension and mitochondrial damage associated with a lower basal expression of the majority of UPR genes and β cell antioxidant responsive genes. Altogether these data indicate that the correct UPR and antioxidant response controlled by PERK-eIF2 α signalling are required for β cell adaptation and survival [45].

Phosphorylation of eIF2 α leads to attenuate global translation of most mRNA although translation of ATF4 is selectively stimulated in this context [11] (Figure 1(b)). The role of ATF4 in insulin secretion and β cell survival is controversial. Pioneer studies showed that *Atf4* knockout mice on a 129SV genetic background are lean, hypoglycaemic, and resistant to diet-induced obesity, probably as a result of increased energy expenditure. However, no effect was observed on plasma insulin level when mice were fed with normal diet, whereas insulin levels were shown to be lower in *Atf4* null mice compared to wild-type mice when fed with a high fat diet [46, 47]. Paradoxically, other studies using *Atf4* KO mice on C57BL6/J genetic background demonstrated that these mice are hypoglycaemic and hyperinsulinemic with an increased β cell mass and function. The phenotype of these mice could be secondary to an overexpression of osteocalcin in osteoblasts, a bone derived secreted molecule promoting insulin secretion and insulin sensitivity [48]. The genetic background may explain the differences observed in these *Atf4* null mice models. The role of ATF4 in insulin synthesis and β cell adaptation to ER stress remains unclear, and further studies using a β cell specific *Atf4* KO mouse model may be useful to answer this question.

ATF4 activation by eIF2 α also leads to the transcription of eIF4-E binding protein (4E-BP-1), a well-documented gene

involved in β cells adaptation to stress [49]. In fact, translation attenuation by eIF2 α phosphorylation is transient, subsequently leading to the feedback dephosphorylation by GADD34, whereas 4E-BP1 suppresses prolonged translation by the inhibition of cap-dependent translation [49, 50]. β cell specific 4e-bp1 KO mice are normal without any metabolic disorder when fed normal diet but are insulin resistant and show β cell defects under high fat diet due to induced ER stress [49, 51, 52]. Moreover, the inactivation of 4e-bp1 gene in Min6 cell line results in sensitization to ER stress and increased β cell loss and hyperglycaemia in diabetic mouse models [49]. These findings suggest a central role of 4E-BP1 in β cell adaptation to ER stress. In contrast, other groups indicated that suppression of 4E-BP1 expression is involved in beneficial effects of high-density lipoproteins on β cells survival [53], suggesting that the role of ATF4 in β cell compensation might depend on several cellular interactions.

2.4. IRE1 α -XBP1 Pathways in β Cells Compensation. IRE1 α is the major isoform expressed in the pancreas and plays a central role in β cell adaptation to ER stress (Figure 1(b)). IRE1 α is required for embryonic development as demonstrated by the embryonic lethality of global IRE1 α KO mice. IRE1 α plays a crucial role in insulin biosynthesis. The generation of IRE1 α conditional KO mice revealed that IRE1 α deletion caused mild hyperinsulinemia and hyperglycaemia and a lower body mass under normal diet [54]. Physiological activation of UPR by glucose results in IRE1 α phosphorylation, without increasing XBP1 mRNA splicing. Moreover, knockdown of IRE1 α in INS-1 insulinoma cell line resulted in decreased proinsulin biosynthesis or insulin content without impacting global protein synthesis or insulin secretion, suggesting a beneficial effect of IRE1 α activation by transit exposure to glucose in β cells [55]. However, chronic exposure to high glucose leads to hyperphosphorylation of IRE1 α , which in turn results in selective degradation of proinsulin mRNA [56]. This may be part of the β cell protective mechanism from apoptosis under chronic hyperglycaemia induced ER stress. This adaptative mechanism combined to UPR activation may explain the reduced insulin secretion in type 2 diabetic patients in the absence of β cell death. IRE1 α dephosphorylation is mediated by proteins phosphatase A2 (PP2A) through ternary complex containing the scaffold protein RACK1 (receptor for activated C kinase 1). Under glucose stimulation or ER stress, RACK1 mediates IRE1 α , RACK1, and PP2A complex formation and promotes IRE1 α dephosphorylation by PP2A, thereby inhibiting IRE1 α activation and attenuating IRE1 α -dependent increase in insulin production. Moreover, IRE1 α activation is increased and RACK1 abundance is decreased in db/db mice [57]. The endoplasmic activity of IRE1 α is also involved in the activation of a key metabolic enzyme, AMP-activated kinase (AMPK), in response to nitric oxide (NO) and ER stress in β cells [58]. AMPK is a holoenzyme activated by changes in AMP/ATP ratio, shifting from glucose to the use of lipids as an energy source in order to respond to cellular demand [59]. Activated AMPK by GTPase dynamin related protein 1 (DRP1) phosphorylation prevents ER and mitochondrial alteration in stressed β cells [60]. In addition IRE1 α

modulates nuclear factor κ light chain enhancer (NF- κ B) target gene expression and IL-1 β activation under mild ER stress, which could contribute to chemokine-induced β cell death [61].

Upon UPR mediating IRE1 α activation, XBP1 splicing is the major event. Several reports indicated that XBP1s target genes and its downstream effect are cell specific and might be dependent on the activating pathways. Like IRE1 α , XBP1 deficient mice died between 10.5 and 14.5 day after birth because of cardiac myocyte defects [62]. Heterozygous Xbp1 mice exhibited significant increase in body mass associated with a progressive hyperinsulinemia and glucose intolerance when fed with a high fat diet [63]. These mice showed increased ER stress and decreased insulin receptor expression in the liver. The β cell-specific deletion of XBP1 in mice resulted in a modest hyperglycaemia and glucose intolerance caused by decreased insulin secretion [64]. The loss of XBP1 markedly decreased the number of insulin granules and impaired proinsulin processing. Further analysis revealed that XBP1 deficiency not only participated in the ER stress in β cells but also caused constitutive hyperactivation of its upstream activator, IRE1 α , which could degrade a subset of mRNAs encoding proinsulin-processing enzymes [64]. In summary, β cell defects in XBP1 mutant mice result from a combined effect of XBP1 suppression on canonical UPR and its negative feedback activation of IRE1 α . Altogether these findings suggest a dual and opposite role for IRE1 α in β cells. A precise regulated feedback circuit involving IRE1 α and its product XBP1s is required to achieve optimal insulin secretion and glucose control. In contrast, sustain production of XBP1s leads to inhibition of PDX1 and MAFA expressions, promoting β cells dysfunction and apoptosis [54].

2.5. ATF6 Pathways in β Cell Compensation. Both ATF6 isoforms are required for positive regulation of UPR. However, the transcriptional activity of ATF6 β is lower than that of ATF6 α . The double knockdown of the two isoforms caused an embryonic lethality demonstrating overlapping functions of ATF6 α and ATF6 β , which are essential for embryonic development [24]. ATF6 α KO mice demonstrated a severe hypoglycaemia suggesting that suppression of ATF6 α increased insulin sensitivity [65]. Treatment of these mice with a pharmacological ER stress inducer leads to liver dysfunction and steatosis [66]. Furthermore, when fed with a high fat diet, ATF6 α null mice developed insulin resistance associated with impaired insulin secretion and lower insulin content, reinforcing the idea of a key role of ATF6 α in β cells adaptation and insulin resistance [65]. Recently, a basal expression of active ATF6 α was demonstrated to be essential for β cell survival even under unstressed conditions. Interestingly, specific functions of ATF6 α have been revealed depending on its interaction with XBP1. When ATF6 α is acting alone, it induces the expression of a cluster of genes involved in protein folding such as BiP and GRP94. When it heterodimerizes with XBP-1 they are modulating the expression of specific class of target genes, such as genes involved in protein degradation (EDE1, Herpud1, HRD1, and p58IPK) [24]. In contrast, a deleterious effect of active ATF6 α overexpression on

β cell function and expression of insulin, PDX1, and MAFA in INS-1 cells was shown [67]. Interestingly, some reports demonstrated that some ATF6 variants are associated with type 2 diabetes and new onset diabetes after transplantation (NODAT), suggesting potential links between ATF6 α and human diabetes pathophysiology [68, 69]. It is important to note that, from the myriad of ATF6 homolog described until now, only old astrocyte specifically induced substance (OASIS) was identified in β cell [70]. However, microarray analysis of INS-1 β cell line overexpressing the active form of OASIS showed its implication in extracellular matrix production and protein transport but not in the classical ER stress response [70].

A great interest has been focused on the ATF6 α negative regulator WFS1 because of its association with the Wolfram syndrome, a rare genetic disorder [71, 72]. Loss of function mutation in the *wfs1* gene encoding wolframin protein caused neurodegenerative disorders characterised by juvenile onset diabetes mellitus, optic atrophy, and hearing impairment [73, 74]. WFS1 KO mice exhibit an activated ER stress especially in β cells, leading to β cell loss through impaired cell cycle progression and increased apoptosis [75]. Conditional WFS1 knockdown in β cell induced diabetes as a result of enhanced ER stress and apoptosis [76]. Moreover WFS1 is essential for glucose and glucagon-like peptide 1 (GLP1) stimulated AMP production and regulation of insulin biosynthesis and secretion [77]. Under glucose stimulation, WFS1 translocates from the ER to plasma membrane, where it stimulates cyclic adenosine monophosphate [73] synthesis through an interaction with adenylyl cyclase 8 (AC8), which subsequently promoted insulin secretion [77] (Figure 1(a)). A recent report using induced pluripotent stem (iPS) cells to create β cells from individuals with Wolfram syndrome confirmed these observations. In this study, WFS1 deficient β cells showed increased levels of UPR genes and decreased insulin content, leading to β cell dysfunctions as previously described in mouse models [78].

2.6. The UPR/ER Stress Induction of β Cell Apoptosis. As discussed above, the UPR regulates both survival and death effectors. It is now clear that the three unfolded protein sensors—IRE1 α , PERK, and ATF6—influence the life-death decision. The inability of UPR outputs to restore homeostasis may generate continuous signalling from these sensors, tipping the balance in favour of apoptosis. The ER might actually serve as a site where apoptotic signals are generated and integrated to elicit the death response. ER stress leads to apoptosis by activating both mitochondrial dependent and independent pathways. Several stimuli have been linked to ER stress-induced apoptosis including hyperglycaemia, exposure to long-chain free fatty acids (e.g., palmitate) [79–81], hyperinsulinemia occurring in the prediabetic stage [82], glucose deprivation [83], islet amyloid polypeptide (IAPP) expression [84], and exposure to inflammatory cytokine [85]. Players involved in the cell death response include PERK/elf2 α -dependent transcriptional induction of proapoptotic transcription factor CHOP which represses Bcl-2 [86], IRE1-mediated activation of ASK1/JNK [18], and cleavage and activation of procaspase 12 (caspase 4 in humans) [87, 88].

CHOP has retained a special attention as a central mediator of apoptosis. Its expression is low under physiological condition but is strongly induced upon ER stress [89]. The induction of CHOP is regulated by ATF4 [11, 90] and ATF6 [91–93] and its role in ER stress-induced apoptosis was demonstrated both *in vitro* and *in vivo* [94]. Mice lacking CHOP are protected from renal toxicity of the ER stressor tunicamycin, an inhibitor of glycosylation [94]. CHOP deletion promotes β cells survival in both genetic and diet-induced insulin resistant mice models [30, 92]. Pancreatic β cells are also sensitive to oxidative stress, but β cells from CHOP knockout mice are protected and maintain insulin secretion under oxidative stress [92, 95]. Moreover, islets from these mice showed resistance to NO, a chemical agent implicated in β cells disruption in type 1 diabetes [96]. In contrast, CHOP deficiency in a genetic background of nonobese diabetic mice (NOD-Chop $^{-/-}$) did not affect the development of insulinitis, diabetes, and β cells apoptosis [97]. Interestingly, CHOP knockout mice on a C57BL/6 background showed a different phenotype, with abdominal obesity and hepatic steatosis, while preserving normal glucose tolerance and insulin sensitivity [98].

Under ER stress CHOP positively regulates the expression of genes involved in apoptosis including GADD34 [50, 99], the ER oxidoreductin 1 α (ERO1 α) [100], death receptor 5 (DR5) [101], and the pseudokinase tribbles related 3 (TRB3) [102]. As shown for CHOP deletion, genetic inactivation of these genes protected against β cell ER stress-induced apoptosis [100, 103–105]. Additionally, CHOP represses the expression of the antiapoptotic gene Bcl2 and enhances oxidant injury [106]. Finally, deletion of CHOP was reported to prevent the cytokine-mediated cleavage of caspase 9 and caspase 3 and subsequent β cells apoptosis by reducing cytokine-induced NF- κ B activity and the expression of key NF- κ B target genes involved in apoptosis and inflammation [107].

ER stress-mediated apoptosis can also be signalled through IRE1 α dependent activation of JNK pathway [18]. IRE1 α interacts with TBF receptor associated factor 2 (TRAF2) and ASK1 mediating JNK phosphorylation [18, 108]. The analysis of ASK1 deficient mice showed that ASK1 loss of function attenuated insulin resistance, cardiac inflammation and fibrosis, vascular endothelial dysfunction, and remodelling induced by diet-induced obesity [109]. Moreover, deletion of ASK1 in homozygous Akita mice protected β cells from ER induced apoptosis and delayed the onset of diabetes [110]. The IRE1 α /TRAF2 complexes also contributes to ER stress-induced apoptosis by promoting the clustering of procaspase-12 and its activation by cleavage in response to ER stress [111]. In addition, the IRE1 α /TRAF2 complex interacts with IKK, an inhibitor of NF- κ B, mediating its activation and promoting cell apoptosis in response to ER stress [112, 113]. Finally, members of Bcl2 family including BAX, BAK, BIM, and PUMA have been reported to directly interact with IRE1 α demonstrating a physical link between members of the core apoptotic pathway and the UPR [114, 115]. In contrast, IRE1 α forms a stable protein complex with Bax inhibitor-1 (BI-1) protein, suppressing cell death [116]. The IRE1 α /BI-1 association decreased the ribonuclease activity of IRE1 α and seemed to be required for early adaptive responses against ER

stress-induced apoptosis [116]. The control of IRE1 α activity appears to be central in the mechanism protecting β cells from ER stress-induced apoptosis. Further studies are needed to understand the various aspect of IRE1 α regulation and the contribution of the others actors of UPR in the ER stress-induced apoptosis.

2.7. The UPR in Human Diabetes. Clear evidence of the existence of ER stress in human β cells has been reported in the last decade [2, 3, 6, 117]. First analysis of islets from human T2D patients showed an ER extension but modest signs of ER stress marker in human pancreatic samples and isolated islets. However, glucose stimulation induced increased UPR in T2D islets cells [3]. Some markers of ER stress are increased in T1D human islets with partial ER stress [117, 118]. A recent report shows an alteration in the expression of specific branches of UPR mediators in T2D β cells [6]. These findings support the hypothesis of a decline in β cell adaptation/compensation during the progression of diabetes in human.

3. Conclusion

The β cell has a marked capacity to adapt to environment changes by increasing its mass and function. Diabetic signs occur when this adaptative mechanism fails to compensate for the increasing insulin demand. Activation of UPR actors is triggered in the early stage of the compensatory mechanism and may play a central role in β cell adaptation and subsequent functions. Further studies are required to understand the physiological significance and the direct implication of ER stress and UPR in the early stage of diabetes physiopathology. Moreover, the relationships among UPR actors, their activation, and β cell fate (adaptation/survival versus β cell dysfunction/apoptosis) remain to be fully clarified. Theoretically, the size of β cell mass is controlled by a balance between proliferation and apoptosis. Either increase of β cell apoptosis or decrease in β cell adaptation and compensation could, therefore, reduce the β cell mass in T2D patients. Studies carried out during diabetes development are required to better understand the mechanism of compensatory capacity and subsequent β cell loss in humans. This is of particular interest, since it could have beneficial impact for the treatment of metabolic diseases such as diabetes.

It is important to note that most UPR molecules have an adaptive function in β cells. Their role in the switch from survival to apoptosis is clearly demonstrated *in vitro* and in animal models but it remains unclear whether the same mechanisms occur in human β cell. Isolating and culturing primary β cells may be very stressful and do not perfectly reflect the *in vivo* context. Therefore the use of alternative method such as immunohistochemistry is powerful to determine the role of each branch of UPR in diabetes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

- [1] J. E. Shaw, R. A. Sicree, and P. Z. Zimmet, "Global estimates of the prevalence of diabetes for 2010 and 2030," *Diabetes Research and Clinical Practice*, vol. 87, no. 1, pp. 4–14, 2010.
- [2] S. G. Fonseca, M. Burcin, J. Gromada, and F. Urano, "Endoplasmic reticulum stress in β -cells and development of diabetes," *Current Opinion in Pharmacology*, vol. 9, no. 6, pp. 763–770, 2009.
- [3] P. Marchetti, M. Bugliani, R. Lupi et al., "The endoplasmic reticulum in pancreatic beta cells of type 2 diabetes patients," *Diabetologia*, vol. 50, no. 12, pp. 2486–2494, 2007.
- [4] J. Y. Chan, J. Luzuriaga, M. Bensellam, T. J. Biden, and D. R. Laybutt, "Failure of the adaptive unfolded protein response in islets of obese mice is linked with abnormalities in beta-cell gene expression and progression to diabetes," *Diabetes*, vol. 62, no. 5, pp. 1557–1568, 2013.
- [5] F. Engin, A. Yermalovich, T. Ngyuen et al., "Restoration of the unfolded protein response in pancreatic beta cells protects mice against type 1 diabetes," *Science Translational Medicine*, vol. 5, no. 211, Article ID 211ra156, 2013.
- [6] F. Engin, T. Nguyen, A. Yermalovich, and G. S. Hotamisligil, "Aberrant islet unfolded protein response in type 2 diabetes," *Scientific Reports*, vol. 4, article 4054, 2014.
- [7] A. Bertolotti, Y. Zhang, L. M. Hendershot, H. P. Harding, and D. Ron, "Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response," *Nature Cell Biology*, vol. 2, no. 6, pp. 326–332, 2000.
- [8] S. Nadanaka, H. Yoshida, and K. Mori, "Reduction of disulfide bridges in the lumenal domain of ATF6 in response to glucose starvation," *Cell Structure and Function*, vol. 31, no. 2, pp. 127–134, 2006.
- [9] H. P. Harding, Y. Zhang, and D. Ron, "Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase," *Nature*, vol. 397, no. 6716, pp. 271–274, 1999.
- [10] H. P. Harding, Y. Zhang, A. Bertolotti, H. Zeng, and D. Ron, "Perk is essential for translational regulation and cell survival during the unfolded protein response," *Molecular Cell*, vol. 5, no. 5, pp. 897–904, 2000.
- [11] H. P. Harding, I. Novoa, Y. Zhang et al., "Regulated translation initiation controls stress-induced gene expression in mammalian cells," *Molecular Cell*, vol. 6, no. 5, pp. 1099–1108, 2000.
- [12] Y.-Y. Lee, R. C. Cevallos, and E. Jan, "An upstream open reading frame regulates translation of GADD34 during cellular stresses that induce eIF2 α phosphorylation," *The Journal of Biological Chemistry*, vol. 284, no. 11, pp. 6661–6673, 2009.

- [13] W. Tirasophon, A. A. Welihinda, and R. J. Kaufman, "A stress response pathway from the endoplasmic reticulum to the nucleus requires a novel bifunctional protein kinase/endoribonuclease (Ire1p) in mammalian cells," *Genes & Development*, vol. 12, no. 12, pp. 1812–1824, 1998.
- [14] A. Bertolotti, X. Wang, I. Novoa et al., "Increased sensitivity to dextran sodium sulfate colitis in IRE1 β -deficient mice," *The Journal of Clinical Investigation*, vol. 107, no. 5, pp. 585–593, 2001.
- [15] A.-H. Lee, E. F. Scapa, D. E. Cohen, and L. H. Glimcher, "Regulation of hepatic lipogenesis by the transcription factor XBP1," *Science*, vol. 320, no. 5882, pp. 1492–1496, 2008.
- [16] H. Yoshida, T. Matsui, A. Yamamoto, T. Okada, and K. Mori, "XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor," *Cell*, vol. 107, no. 7, pp. 881–891, 2001.
- [17] J. Hollien and J. S. Weissman, "Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response," *Science*, vol. 313, no. 5783, pp. 104–107, 2006.
- [18] F. Urano, X. Wang, A. Bertolotti et al., "Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1," *Science*, vol. 287, no. 5453, pp. 664–666, 2000.
- [19] K. Haze, T. Okada, H. Yoshida et al., "Identification of the G13 (cAMP-response-element-binding protein-related protein) gene product related to activating transcription factor 6 as a transcriptional activator of the mammalian unfolded protein response," *Biochemical Journal*, vol. 355, part 1, pp. 19–28, 2001.
- [20] K. Haze, H. Yoshida, H. Yanagi, T. Yura, and K. Mori, "Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress," *Molecular Biology of the Cell*, vol. 10, no. 11, pp. 3787–3799, 1999.
- [21] M. Hong, S. Luo, P. Baumeister et al., "Underglycosylation of ATF6 as a novel sensing mechanism for activation of the unfolded protein response," *The Journal of Biological Chemistry*, vol. 279, no. 12, pp. 11354–11363, 2004.
- [22] K. Yamamoto, H. Yoshida, K. Kokame, R. J. Kaufman, and K. Mori, "Differential contributions of ATF6 and XBP1 to the activation of endoplasmic reticulum stress-responsive cis-acting elements ERSE, UPRE and ERSE-II," *Journal of Biochemistry*, vol. 136, no. 3, pp. 343–350, 2004.
- [23] D. J. Thuerauf, L. Morrison, and C. C. Glembotski, "Opposing roles for ATF6 α and ATF6 β in endoplasmic reticulum stress response gene induction," *The Journal of Biological Chemistry*, vol. 279, no. 20, pp. 21078–21084, 2004.
- [24] K. Yamamoto, T. Sato, T. Matsui et al., "Transcriptional induction of mammalian ER quality control proteins is mediated by single or combined action of ATF6 α and XBP1," *Developmental Cell*, vol. 13, no. 3, pp. 365–376, 2007.
- [25] S. G. Fonseca, S. Ishigaki, C. M. Osowski et al., "Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells," *The Journal of Clinical Investigation*, vol. 120, no. 3, pp. 744–755, 2010.
- [26] R. Asada, S. Kanemoto, S. Kondo, A. Saito, and K. Imaizumi, "The signalling from endoplasmic reticulum-resident bZIP transcription factors involved in diverse cellular physiology," *Journal of Biochemistry*, vol. 149, no. 5, pp. 507–518, 2011.
- [27] N. Itoh and H. Okamoto, "Translational control of proinsulin synthesis by glucose," *Nature*, vol. 283, no. 5742, pp. 100–102, 1980.
- [28] O. Omikorede, C. Qi, T. Gorman et al., "ER stress in rodent islets of Langerhans is concomitant with obesity and beta-cell compensation but not with beta-cell dysfunction and diabetes," *Nutrition & Diabetes*, vol. 3, article e93, 2013.
- [29] N. Herbach, B. Rathkolb, E. Kemter et al., "Dominant-negative effects of a novel mutated Ins2 allele causes early-onset diabetes and severe β -cell loss in Munich Ins2C95S mutant mice," *Diabetes*, vol. 56, no. 5, pp. 1268–1276, 2007.
- [30] S. Oyadomari, A. Koizumi, K. Takeda et al., "Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes," *The Journal of Clinical Investigation*, vol. 109, no. 4, pp. 525–532, 2002.
- [31] J. Støy, E. L. Edghill, S. E. Flanagan et al., "Insulin gene mutations as a cause of permanent neonatal diabetes," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 38, pp. 15040–15044, 2007.
- [32] E. L. Edghill, S. E. Flanagan, A.-M. Patch et al., "Insulin mutation screening in 1,044 patients with diabetes mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood," *Diabetes*, vol. 57, no. 4, pp. 1034–1042, 2008.
- [33] M. Liu, I. Hodish, L. Haataja et al., "Proinsulin misfolding and diabetes: mutant INS gene-induced diabetes of youth," *Trends in Endocrinology and Metabolism*, vol. 21, no. 11, pp. 652–659, 2010.
- [34] T. Hartley, M. Siva, E. Lai, T. Teodoro, L. Zhang, and A. Volchuk, "Endoplasmic reticulum stress response in an INS-1 pancreatic β -cell line with inducible expression of a folding-deficient proinsulin," *BMC Cell Biology*, vol. 11, article 59, 2010.
- [35] I. Hodish, A. Absood, L. Liu et al., "In vivo misfolding of proinsulin below the threshold of frank diabetes," *Diabetes*, vol. 60, no. 8, pp. 2092–2101, 2011.
- [36] M. Delépine, M. Nicolino, T. Barrett, M. Golamaully, G. Mark Lathrop, and C. Julier, "EIF2AK3, encoding translation initiation factor 2- α kinase 3, is mutated in patients with Wolcott-Rallison syndrome," *Nature Genetics*, vol. 25, no. 4, pp. 406–409, 2000.
- [37] P. Zhang, B. McGrath, S. Li et al., "The PERK eukaryotic initiation factor 2 α kinase is required for the development of the skeletal system, postnatal growth, and the function and viability of the pancreas," *Molecular and Cellular Biology*, vol. 22, no. 11, pp. 3864–3874, 2002.
- [38] H. P. Harding, H. Zeng, Y. Zhang et al., "Diabetes mellitus and exocrine pancreatic dysfunction in *Perk* $^{-/-}$ mice reveals a role for translational control in secretory cell survival," *Molecular Cell*, vol. 7, no. 6, pp. 1153–1163, 2001.
- [39] W. Zhang, D. Feng, Y. Li, K. Iida, B. McGrath, and D. R. Cavener, "PERK EIF2AK3 control of pancreatic β cell differentiation and proliferation is required for postnatal glucose homeostasis," *Cell Metabolism*, vol. 4, no. 6, pp. 491–497, 2006.
- [40] S. Gupta, B. McGrath, and D. R. Cavener, "PERK (EIF2AK3) regulates proinsulin trafficking and quality control in the secretory pathway," *Diabetes*, vol. 59, no. 8, pp. 1937–1947, 2010.
- [41] Y. Gao, D. J. Sartori, C. Li et al., "PERK is required in the adult pancreas and is essential for maintenance of glucose homeostasis," *Molecular and Cellular Biology*, vol. 32, no. 24, pp. 5129–5139, 2012.
- [42] R. Wang, B. C. McGrath, R. F. Kopp et al., "Insulin secretion and Ca²⁺ dynamics in beta-cells are regulated by PERK (EIF2AK3) in concert with calcineurin," *The Journal of Biological Chemistry*, vol. 288, no. 47, pp. 33824–33836, 2013.

- [43] D. Scheuner, B. Song, E. McEwen et al., "Translational control is required for the unfolded protein response and in vivo glucose homeostasis," *Molecular Cell*, vol. 7, no. 6, pp. 1165–1176, 2001.
- [44] D. Scheuner, D. Vander Mierde, B. Song et al., "Control of mRNA translation preserves endoplasmic reticulum function in beta cells and maintains glucose homeostasis," *Nature Medicine*, vol. 11, no. 7, pp. 757–764, 2005.
- [45] S. H. Back, D. Scheuner, J. Han et al., "Translation attenuation through eIF2 α phosphorylation prevents oxidative stress and maintains the differentiated state in beta cells," *Cell Metabolism*, vol. 10, no. 1, pp. 13–26, 2009.
- [46] J. Seo, E. S. Fortuno III, J. M. Suh et al., "Atf4 regulates obesity, glucose homeostasis, and energy expenditure," *Diabetes*, vol. 58, no. 11, pp. 2565–2573, 2009.
- [47] C. Wang, Z. Huang, Y. Du, Y. Cheng, S. Chen, and F. Guo, "ATF4 regulates lipid metabolism and thermogenesis," *Cell Research*, vol. 20, no. 2, pp. 174–184, 2010.
- [48] T. Yoshizawa, E. Hinoi, Y. J. Dae et al., "The transcription factor ATF4 regulates glucose metabolism in mice through its expression in osteoblasts," *The Journal of Clinical Investigation*, vol. 119, no. 9, pp. 2807–2817, 2009.
- [49] S. Yamaguchi, H. Ishihara, T. Yamada et al., "ATF4-mediated induction of 4E-BP1 contributes to pancreatic β cell survival under endoplasmic reticulum stress," *Cell Metabolism*, vol. 7, no. 3, pp. 269–276, 2008.
- [50] I. Novoa, H. Zeng, H. P. Harding, and D. Ron, "Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2 α ," *Journal of Cell Biology*, vol. 153, no. 5, pp. 1011–1021, 2001.
- [51] O. le Bacquer, E. Petroulakis, S. Paglialunga et al., "Elevated sensitivity to diet-induced obesity and insulin resistance in mice lacking 4E-BP1 and 4E-BP2," *The Journal of Clinical Investigation*, vol. 117, no. 2, pp. 387–396, 2007.
- [52] K. Tsukiyama-Kohara, F. Poulin, M. Kohara et al., "Adipose tissue reduction in mice lacking the translational inhibitor 4E-BP1," *Nature Medicine*, vol. 7, no. 10, pp. 1128–1132, 2001.
- [53] J. P tremand, N. Bulat, A.-C. Butty et al., "Involvement of 4E-BP1 in the protection induced by HDLs on pancreatic β -cells," *Molecular Endocrinology*, vol. 23, no. 10, pp. 1572–1586, 2009.
- [54] T. Iwawaki, R. Akai, and K. Kohno, "IRE1 α disruption causes histological abnormality of exocrine tissues, increase of blood glucose level, and decrease of serum immunoglobulin level," *PLoS ONE*, vol. 5, no. 9, Article ID e13052, 2010.
- [55] K. L. Lipson, S. G. Fonseca, S. Ishigaki et al., "Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1," *Cell Metabolism*, vol. 4, no. 3, pp. 245–254, 2006.
- [56] K. L. Lipson, R. Ghosh, and F. Urano, "The role of IRE1 α in the degradation of insulin mRNA in pancreatic β -cells," *PLoS ONE*, vol. 3, no. 2, Article ID e1648, 2008.
- [57] Y. Qiu, T. Mao, Y. Zhang et al., "A crucial role for RACK1 in the regulation of glucose-stimulated IRE1 α activation in pancreatic β cells," *Science Signaling*, vol. 3, no. 106, article ra7, 2010.
- [58] G. P. Meares, K. J. Hughes, A. Naatz et al., "IRE1-dependent activation of AMPK in response to nitric oxide," *Molecular and Cellular Biology*, vol. 31, no. 21, pp. 4286–4297, 2011.
- [59] N. B. Ruderman, D. Carling, M. Prentki, and J. M. Cacicedo, "AMPK, insulin resistance, and the metabolic syndrome," *The Journal of Clinical Investigation*, vol. 123, no. 7, pp. 2764–2772, 2013.
- [60] J. D. Wikstrom, T. Israeli, E. Bachar-Wikstrom et al., "AMPK regulates ER morphology and function in stressed pancreatic beta-cells via phosphorylation of DRP1," *Molecular Endocrinology*, vol. 27, no. 10, pp. 1706–1723, 2013.
- [61] M. Miani, M. L. Colli, L. Ladriere, M. Cnop, and D. L. Eizirik, "Mild endoplasmic reticulum stress augments the proinflammatory effect of IL-1 β in pancreatic rat beta-cells via the IRE1 α /XBP1s pathway," *Endocrinology*, vol. 153, no. 7, pp. 3017–3028, 2012.
- [62] T. Masaki, M. Yoshida, and S. Noguchi, "Targeted disruption of CRE-Binding factor TREB5 gene leads to cellular necrosis in cardiac myocytes at the embryonic stage," *Biochemical and Biophysical Research Communications*, vol. 261, no. 2, pp. 350–356, 1999.
- [63] U.  zcan, Q. Cao, E. Yilmaz et al., "Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes," *Science*, vol. 306, no. 5695, pp. 457–461, 2004.
- [64] A.-H. Lee, K. Heidtman, G. S. Hotamisligil, and L. H. Glimcher, "Dual and opposing roles of the unfolded protein response regulated by IRE1 α and XBP1 in proinsulin processing and insulin secretion," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 21, pp. 8885–8890, 2011.
- [65] M. Usui, S. Yamaguchi, Y. Tanji et al., "Atf6 α -null mice are glucose intolerant due to pancreatic β -cell failure on a high-fat diet but partially resistant to diet-induced insulin resistance," *Metabolism*, vol. 61, no. 8, pp. 1118–1128, 2012.
- [66] K. Yamamoto, K. Takahara, S. Oyadomari et al., "Induction of liver steatosis and lipid droplet formation in ATF6 α -knockout mice burdened with pharmacological endoplasmic reticulum stress," *Molecular Biology of the Cell*, vol. 21, no. 17, pp. 2975–2986, 2010.
- [67] H.-Y. Seo, D. K. Yong, K.-M. Lee et al., "Endoplasmic reticulum stress-induced activation of activating transcription factor 6 decreases insulin gene expression via up-regulation of orphan nuclear receptor small heterodimer partner," *Endocrinology*, vol. 149, no. 8, pp. 3832–3841, 2008.
- [68] F. Thameem, V. S. Farook, C. Bogardus, and M. Prochazka, "Association of amino acid variants in the activating transcription factor 6 gene (ATF6) on 1q21-q23 with type 2 diabetes in Pima Indians," *Diabetes*, vol. 55, no. 3, pp. 839–842, 2006.
- [69] S. Fougeray, M.-A. Lorient, V. Nicaud, C. Legendre, E. Thervet, and N. Pallet, "Increased body mass index after kidney transplantation in activating transcription factor 6 single polymorphism gene carriers," *Transplantation Proceedings*, vol. 43, no. 9, pp. 3418–3422, 2011.
- [70] R. N. Vellanki, L. Zhang, M. A. Guney, J. V. Rocheleau, M. Gannon, and A. Volchuk, "OASIS/CREB3L1 induces expression of genes involved in extracellular matrix production but not classical endoplasmic reticulum stress response genes in pancreatic β -cells," *Endocrinology*, vol. 151, no. 9, pp. 4146–4157, 2010.
- [71] G. Boutzios, S. Livadas, E. Marinakis, N. Opie, F. Economou, and E. Diamanti-Kandarakis, "Endocrine and metabolic aspects of the Wolfram syndrome," *Endocrine*, vol. 40, no. 1, pp. 10–13, 2011.
- [72] T. G. Barrett, S. E. Bunday, A. R. Fielder, and P. A. Good, "Optic atrophy in Wolfram (DIDMOAD) syndrome," *Eye*, vol. 11, no. 6, pp. 882–888, 1997.

- [73] K. Cryns, T. A. Sivakumaran, J. M. W. van den Ouweland et al., "Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease," *Human Mutation*, vol. 22, no. 4, pp. 275–287, 2003.
- [74] F. Khanim, J. Kirk, F. Latif, and T. G. Barrett, "WFS1/wolframin mutations, wolfram syndrome, and associated diseases," *Human Mutation*, vol. 17, no. 5, pp. 357–367, 2001.
- [75] T. Yamada, H. Ishihara, A. Tamura et al., "WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic β -cells," *Human Molecular Genetics*, vol. 15, no. 10, pp. 1600–1609, 2006.
- [76] A. C. Riggs, E. Bernal-Mizrachi, M. Ohsugi et al., "Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis," *Diabetologia*, vol. 48, no. 11, pp. 2313–2321, 2005.
- [77] S. G. Fonseca, F. Urano, G. C. Weir, J. Gromada, and M. Burcin, "Wolfram syndrome 1 and adenylyl cyclase 8 interact at the plasma membrane to regulate insulin production and secretion," *Nature Cell Biology*, vol. 14, no. 10, pp. 1105–1112, 2012.
- [78] L. Shang, H. Hua, K. Foo et al., " β -cell dysfunction due to increased ER stress in a stem cell model of Wolfram syndrome," *Diabetes*, vol. 63, no. 3, pp. 923–933, 2014.
- [79] E. Karaskov, C. Scott, L. Zhang, T. Teodoro, M. Ravazzola, and A. Volchuk, "Chronic palmitate but not oleate exposure induces endoplasmic reticulum stress, which may contribute to INS-1 pancreatic β -cell apoptosis," *Endocrinology*, vol. 147, no. 7, pp. 3398–3407, 2006.
- [80] D. A. Cunha, P. Hekerman, L. Ladrière et al., "Initiation and execution of lipotoxic ER stress in pancreatic β -cells," *Journal of Cell Science*, vol. 121, no. 14, pp. 2308–2318, 2008.
- [81] M. Cnop, B. Abdulkarim, G. Bottu et al., "RNA-sequencing identifies dysregulation of the human pancreatic islet transcriptome by the saturated fatty acid palmitate," *Diabetes*, 2013.
- [82] H. Wang, G. Kouri, and C. B. Wollheim, "ER stress and SREBP-1 activation are implicated in B-cell glucolipotoxicity," *Journal of Cell Science*, vol. 118, no. 17, pp. 3905–3915, 2005.
- [83] S. G. Carlson, T. W. Fawcett, J. D. Bartlett, M. Bernier, and N. J. Holbrook, "Regulation of the C/EBP-related gene gadd153 by glucose deprivation," *Molecular and Cellular Biology*, vol. 13, no. 8, pp. 4736–4744, 1993.
- [84] C.-J. Huang, C.-Y. Lin, L. Haataja et al., "High expression rates of human islet amyloid polypeptide induce endoplasmic reticulum stress-mediated β -cell apoptosis, a characteristic of humans with type 2 but not type 1 diabetes," *Diabetes*, vol. 56, no. 8, pp. 2016–2027, 2007.
- [85] A. K. Cardozo, F. Ortis, J. Storling et al., "Cytokines downregulate the sarcoendoplasmic reticulum pump Ca^{2+} ATPase 2b and deplete endoplasmic reticulum Ca^{2+} , leading to induction of endoplasmic reticulum stress in pancreatic β -cells," *Diabetes*, vol. 54, no. 2, pp. 452–461, 2005.
- [86] A. L. Anding, J. S. Chapman, D. W. Barnett, R. W. Curley Jr., and M. Clagett-Dame, "The unhydrolyzable fenretinide analogue 4-hydroxybenzylretinone induces the proapoptotic genes GADD153 (CHOP) and Bcl-2-binding component 3 (PUMA) and apoptosis that is caspase-dependent and independent of the retinoic acid receptor," *Cancer Research*, vol. 67, no. 13, pp. 6270–6277, 2007.
- [87] R. V. Rao, E. Hermel, S. Castro-Obregon et al., "Coupling endoplasmic reticulum stress to the cell death program. Mechanism of caspase activation," *The Journal of Biological Chemistry*, vol. 276, no. 36, pp. 33869–33874, 2001.
- [88] J. Hitomi, T. Katayama, Y. Eguchi et al., "Involvement of caspase-4 in endoplasmic reticulum stress-induced apoptosis and $\text{A}\beta$ -induced cell death," *Journal of Cell Biology*, vol. 165, no. 3, pp. 347–356, 2004.
- [89] X.-Z. Wang, B. Lawson, J. W. Brewer et al., "Signals from the stressed endoplasmic reticulum induce C/EBP-homologous protein (CHOP/GADD153)," *Molecular and Cellular Biology*, vol. 16, no. 8, pp. 4273–4280, 1996.
- [90] Y. Ma, J. W. Brewer, J. A. Diehl, and L. M. Hendershot, "Two distinct stress signaling pathways converge upon the CHOP promoter during the mammalian unfolded protein response," *Journal of Molecular Biology*, vol. 318, no. 5, pp. 1351–1365, 2002.
- [91] Y. Adachi, K. Yamamoto, T. Okada, H. Yoshida, A. Harada, and K. Mori, "ATF6 is a transcription factor specializing in the regulation of quality control proteins in the endoplasmic reticulum," *Cell Structure and Function*, vol. 33, no. 1, pp. 75–89, 2008.
- [92] B. Song, D. Scheuner, D. Ron, S. Pennathur, and R. J. Kaufman, "Chop deletion reduces oxidative stress, improves β cell function, and promotes cell survival in multiple mouse models of diabetes," *The Journal of Clinical Investigation*, vol. 118, no. 10, pp. 3378–3389, 2008.
- [93] T. Okada, H. Yoshida, R. Akazawa, M. Negishi, and K. Mori, "Distinct roles of activating transcription factor 6 (ATF6) and double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK) in transcription during the mammalian unfolded protein response," *Biochemical Journal*, vol. 366, part 2, pp. 585–594, 2002.
- [94] H. Zinszner, M. Kuroda, X. Wang et al., "CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum," *Genes & Development*, vol. 12, no. 7, pp. 982–995, 1998.
- [95] Y. Ariyama, Y. Tanaka, H. Shimizu et al., "The role of CHOP messenger RNA expression in the link between oxidative stress and apoptosis," *Metabolism*, vol. 57, no. 12, pp. 1625–1635, 2008.
- [96] S. Oyadomari, K. Takeda, M. Takiguchi et al., "Nitric oxide-induced apoptosis in pancreatic β cells is mediated by the endoplasmic reticulum stress pathway," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 19, pp. 10845–10850, 2001.
- [97] T. Satoh, N. Abiru, M. Kobayashi et al., "CHOP deletion does not impact the development of diabetes but suppresses the early production of insulin autoantibody in the NOD mouse," *Apoptosis*, vol. 16, no. 4, pp. 438–448, 2011.
- [98] M. Maris, L. Overbergh, C. Gysemans et al., "Deletion of C/EBP homologous protein (Chop) in C57Bl/6 mice dissociates obesity from insulin resistance," *Diabetologia*, vol. 55, no. 4, pp. 1167–1178, 2012.
- [99] E. Kojima, A. Takeuchi, M. Haneda et al., "The function of GADD34 is a recovery from a shutoff of protein synthesis induced by ER stress: elucidation by GADD34-deficient mice," *The FASEB Journal*, vol. 17, no. 11, pp. 1573–1575, 2003.
- [100] S. J. Marciniak, C. Y. Yun, S. Oyadomari et al., "CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum," *Genes & Development*, vol. 18, no. 24, pp. 3066–3077, 2004.

- [101] H. Yamaguchi and H.-G. Wang, "CHOP is involved in endoplasmic reticulum stress-induced apoptosis by enhancing DR5 expression in human carcinoma cells," *The Journal of Biological Chemistry*, vol. 279, no. 44, pp. 45495–45502, 2004.
- [102] N. Ohoka, S. Yoshii, T. Hattori, K. Onozaki, and H. Hayashi, "TRB3, a novel ER stress-inducible gene, is induced via ATF4-CHOP pathway and is involved in cell death," *The EMBO Journal*, vol. 24, no. 6, pp. 1243–1255, 2005.
- [103] D. A. Cunha, M. Igoillo-Esteve, E. N. Gurzov et al., "Death protein 5 and p53-upregulated modulator of apoptosis mediate the endoplasmic reticulum stress-mitochondrial dialog triggering lipotoxic rodent and human beta-cell apoptosis," *Diabetes*, vol. 61, no. 11, pp. 2763–2775, 2012.
- [104] Y. Y. Jang, N. K. Kim, M. K. Kim et al., "The effect of tribbles-related protein 3 on ER stress-suppressed insulin gene expression in INS-1 cells," *Korean Diabetes Journal*, vol. 34, no. 5, pp. 312–319, 2010.
- [105] C. W. Liew, J. Bochenski, D. Kawamori et al., "The pseudokinase tribbles homolog 3 interacts with ATF4 to negatively regulate insulin exocytosis in human and mouse β cells," *The Journal of Clinical Investigation*, vol. 120, no. 8, pp. 2876–2888, 2010.
- [106] K. D. McCullough, J. L. Martindale, L.-O. Klotz, T.-Y. Aw, and N. J. Holbrook, "Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state," *Molecular and Cellular Biology*, vol. 21, no. 4, pp. 1249–1259, 2001.
- [107] F. Allagnat, M. Fukaya, T. C. Nogueira et al., "C/EBP homologous protein contributes to cytokine-induced pro-inflammatory responses and apoptosis in beta-cells," *Cell Death & Differentiation*, vol. 19, no. 11, pp. 1836–1846, 2012.
- [108] H. Nishitoh, A. Matsuzawa, K. Tobiume et al., "ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats," *Genes & Development*, vol. 16, no. 11, pp. 1345–1355, 2002.
- [109] E. Yamamoto, Y.-F. Dong, K. Kataoka et al., "Olmesartan prevents cardiovascular injury and hepatic steatosis in obesity and diabetes, accompanied by apoptosis signal regulating Kinase-1 inhibition," *Hypertension*, vol. 52, no. 3, pp. 573–580, 2008.
- [110] K. Yamaguchi, K. Takeda, H. Kadowaki et al., "Involvement of ASK1-p38 pathway in the pathogenesis of diabetes triggered by pancreatic β cell exhaustion," *Biochimica et Biophysica Acta*, vol. 1830, no. 6, pp. 3656–3663, 2013.
- [111] T. Yoneda, K. Imaizumi, K. Oono et al., "Activation of caspase-12, an endoplasmic reticulum (ER) resident caspase, through tumor necrosis factor receptor-associated factor 2-dependent mechanism in response to the ER stress," *The Journal of Biological Chemistry*, vol. 276, no. 17, pp. 13935–13940, 2001.
- [112] P. Hu, Z. Han, A. D. Couvillon, R. J. Kaufman, and J. H. Exton, "Autocrine tumor necrosis factor alpha links endoplasmic reticulum stress to the membrane death receptor pathway through IRE1 α -mediated NF- κ B activation and down-regulation of TRAF2 expression," *Molecular and Cellular Biology*, vol. 26, no. 8, pp. 3071–3084, 2006.
- [113] M. F. Tonnesen, L. G. Grunnet, J. Friberg et al., "Inhibition of nuclear factor- κ B or Bax prevents endoplasmic reticulum stress- but not nitric oxide-mediated apoptosis in INS-1E cells," *Endocrinology*, vol. 150, no. 9, pp. 4094–4103, 2009.
- [114] C. Hetz, P. Bernasconi, J. Fisher et al., "Proapoptotic BAX and BAK modulate the unfolded protein response by a direct interaction with IRE1 α ," *Science*, vol. 312, no. 5773, pp. 572–576, 2006.
- [115] D. A. Rodriguez, S. Zamorano, F. Lisbona et al., "BH3-only proteins are part of a regulatory network that control the sustained signalling of the unfolded protein response sensor IRE1 α ," *The EMBO Journal*, vol. 31, no. 10, pp. 2322–2335, 2012.
- [116] F. Lisbona, D. Rojas-Rivera, P. Thielen et al., "BAX Inhibitor-1 is a negative regulator of the ER stress sensor IRE1 α ," *Molecular Cell*, vol. 33, no. 6, pp. 679–691, 2009.
- [117] I. Marhfour, X. M. Lopez, D. Lefkaditis et al., "Expression of endoplasmic reticulum stress markers in the islets of patients with type 1 diabetes," *Diabetologia*, vol. 55, no. 9, pp. 2417–2420, 2012.
- [118] M. G. Hartman, D. Lu, M.-L. Kim et al., "Role for activating transcription factor 3 in stress-induced β -cell apoptosis," *Molecular and Cellular Biology*, vol. 24, no. 13, pp. 5721–5732, 2004.



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