Endoplasmic reticulum stress and the unfolded protein response in pancreatic islet inflammation

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Abstract

Insulin-secreting pancreatic β-cells are extremely dependent on their endoplasmic reticulum (ER) to cope with the oscillatory requirement of secreted insulin to maintain normoglycemia. Insulin translation and folding rely greatly on the unfolded protein response (UPR), an array of three main signaling pathways designed to maintain ER homeostasis and limit ER stress. However, prolonged or excessive UPR activation triggers alternative molecular pathways that can lead to β-cell dysfunction and apoptosis. An increasing number of studies suggest a role of these pro-apoptotic UPR pathways in the downfall of β-cells observed in diabetic patients. Particularly, the past few years highlighted a cross talk between the UPR and inflammation in the context of both type 1 (T1D) and type 2 diabetes (T2D). In this article, we describe the recent advances in research regarding the interplay between ER stress, the UPR, and inflammation in the context of β-cell apoptosis leading to diabetes.

Key Words
- pancreatic beta cells
- inflammation
- unfolded protein response
- NF-kB
- diabetes

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Introduction

The endoplasmic reticulum (ER) is an intracellular organelle responsible for several crucial features of cellular homeostasis, such as protein maturation and transport and Ca^{2+} homeostasis (Ellgaard & Helenius 2003, Walter & Ron 2011). Therefore, maintaining the ER homeostasis is crucial for proper cellular function and cells have developed an adaptive response to the disruption of this homeostasis named the unfolded protein response (UPR). The UPR encompasses an array of signaling pathways mediated by the action of three signaling proteins named inositol-requiring protein 1α (IRE1α), protein kinase RNA (PKR)-like ER kinase (PERK), and activating transcription factor 6 (ATF6) (Walter & Ron 2011).

Upon ER stress, IRE1α autophosphorylates leading to alternate splicing and translation of the active form of the transcription factor XBP1 (XBP1s), which stimulates the expression of chaperones and components of the ER-associated protein degradation (ERAD) pathway (Pincus *et al.* 2010, Walter & Ron 2011). Moreover, IRE1α selectively degrades mRNAs (RIDD, regulated IRE1-dependent decay), thereby decreasing the ER protein load (Maurel *et al.* 2014). PERK also undergoes autophosphorylation and activation upon ER stress, leading to phosphorylation of the eukaryotic initiation factor 2α (eIF2α) and decreased general translational activity, reducing ER protein overload (Walter & Ron 2011). However, PERK-mediated eIF2α

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phosphorylation also triggers selective induction of ATF4 (Lu *et al.* 2004). Moreover, PERK directly phosphorylates and activates the nuclear erythroid 2 p45-related factor 2 (NRF2) by disrupting the NRF2–KEAP1 (Kelch-like ECH-associated protein 1) complex (Cullinan & Diehl 2006). Both NRF2 and ATF4 induce the expression of antioxidant genes, which counteracts the increase in reactive oxygen species (ROS) due to the boosted oxidation/reduction reactions during UPR-stimulated protein folding (Harding *et al.* 2003, Malhotra & Kaufman 2007, Hybertson *et al.* 2011). However, PERK/ATF4 can initiate pro-apoptotic responses via upregulation of the C/EBP homologous protein (CHOP) (McCullough *et al.* 2001, Oyadomari *et al.* 2002*a*,*b*, Oyadomari & Mori 2004). Activation of the third UPR branch, the transcription factor ATF6, is mediated via cleavage by site-1 and site-2 proteases (SP1 and SP2) in the Golgi. Cleaved ATF6 regulates the expression of several genes encoding chaperones, ERAD components, and XBP1 (Hetz 2012). Notably, the three UPR branches may be independently and differentially activated depending on the type and duration of ER stress and the cell type (Cardozo *et al.* 2005, Gomez *et al.* 2008, Engin *et al.* 2013). However, it remains unclear how this differential activation is coordinated.

The UPR can be divided into two distinct phases: the initial or the adaptive phase and the second or the maladaptive phase. While the first phase is characterized by cell survival and restoration of ER homeostasis by the mechanisms described above, the second phase is initiated under conditions of irreversible ER stress and results in the activation of pro-inflammatory responses and cell death (for more details of cell death pathways activated during ER stress, please see reviews of Tabas & Ron 2011, Gorman *et al.* 2012, Cao & Kaufman 2014).

Glucose homeostasis depends on a tightly regulated secretion of insulin by the pancreatic β-cells. The ever-changing demand for insulin production and secretion in response to nutrient stimulation relies greatly on the ER, to ensure synthesis and proper folding of pro-insulin (Back *et al.* 2009, Hassler *et al.* 2015). As a result, β-cells are exquisitely sensitive to additional ER pressure and accumulating evidence indicate a major role of the UPR in the context of β-cell demise leading to diabetes (Brozzi & Eizirik 2016, Hasnain *et al.* 2016).

This article focuses on (1) the signal transduction pathways involved in the UPR and their connections to inflammation, (2) the specific role of the UPR in pancreatic β-cell survival in the context of diabetes, (3) the interplay between UPR signaling and inflammation in pancreatic β-cells, and (4) the potential ER stress-targeting therapies to treat diabetes.

UPR and inflammation

The pro-inflammatory signaling pathways initiated downstream of the UPR are mainly coordinated via activation of the nuclear factor κB (NF-κB) and activating protein (AP)-1 transcription factors (Hotamisligil 2010, Garg *et al.* 2012). NF-κB is a major modulator of inflammatory responses controlled by the IκB kinase (IKK) complex formed by IKKβ, IKKα, and IKKγ (Shih *et al.* 2011). When stimulated, the IKK complex leads to phosphorylation and degradation of the inhibitory κB (IκB) protein, allowing NF-κB dimers to migrate to the nucleus and induce the expression of several cytokines and chemokines (Shih *et al.* 2011). During ER stress, NF-κB can be induced due to PERK-mediated attenuation of protein translation, leading to decreased levels of IκB proteins and consequent increase of NF-κB (Fig. 1) (Deng *et al.* 2004). IRE1α may also trigger NF-κB activation by binding to the tumor necrosis factor (TNF)-receptor associated factor 2 (TRAF2), which activates the IKK complex (Kaneko *et al.* 2003, Hu *et al.* 2006) (Fig. 1). Loss of either IRE1α or PERK reduces NF-κB during ER stress, indicating a synergistic effect of these kinases on NF-κB activity (Tam *et al.* 2012). In addition, two studies have shown that ATF6 stimulates NF-κB activity downstream of AKT phosphorylation (Yamazaki *et al.* 2009, Rao *et al.* 2014).

AP1 is a dimer composed of transcription factors from different families of proteins such as JUN, FOS, ATF, and MAF (Davis 2000). The diversity of AP1 dimers implicates this transcription factor in different cellular responses. Thus, AP1 modulates inflammation by upregulating the expression of cytokines, chemokines, and other pro-inflammatory molecules (Angel *et al.* 2001, Shaulian & Karin 2001, Eferl & Wagner 2003). Several pro-inflammatory genes have binding sites for both AP1 and NF-κB (Angel *et al.* 2001). During ER stress, AP1 activation can be initiated downstream of IRE1α, via TRAF2-mediated JNK phosphorylation (Fig. 1) (Urano *et al.* 2000). Moreover, both NF-κB and AP1 signaling may be activated by ROS generated during ER stress (Garg *et al.* 2012).

Besides NF-κB and AP1, the UPR may trigger pro-inflammatory responses via XBP1s and ATF4, since these transcription factors were shown to stimulate the expression of pro-inflammatory cytokines and chemokines, such as TNF, IL6, IL8, C-X-C motif ligand 2 (CXCL2), and C-X-C motif ligand 3 (CXCL3) in endothelial cells during UPR (Gargalovic *et al.* 2006). ATF4 was also shown to contribute to LPS-induced C–C motif ligand 2 (CCL2) production in endothelial cells and retina and IL6 in macrophages (Iwasaki *et al.* 2014, Huang *et al.* 2015).

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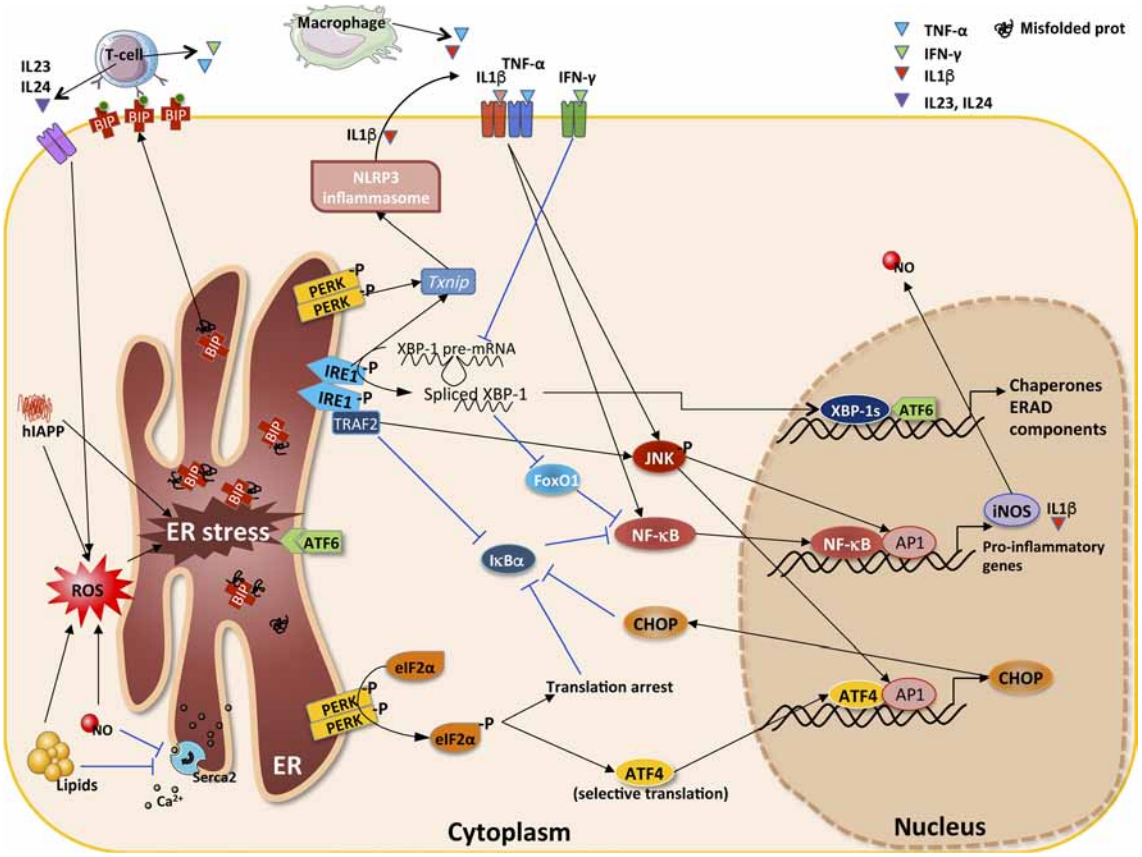

Figure 1
Schematic representation of the possible cross talks between UPR and pro-inflammatory pathways in pancreatic β-cells under ER stress. Pro-inflammatory cytokines (IL1β, TNF, IFN, IL23, and IL24), lipids (free fatty acids), IAPP aggregates, and *Serca2* blockers induce ER stress by diverse mechanisms such as NO formation, ROS production, and ER calcium depletion leading to UPR activation in pancreatic β-cells. UPR-mediated activation of IRE1α (by its dimerization and phosphorylation) may lead to the recruitment of the adaptor protein tumor necrosis factor receptor-associated factor 2 (TRAF2) leading to activation of NF-κB (via IκBα degradation) and JNK. JNK activation in turn increases AP1 activity and both AP1 and NF-κB migrate to the nucleus to induce expression of pro-inflammatory genes. Under pro-inflammatory stimulation, JNK (via AP1) upregulates CHOP expression, consequently increasing IκBα degradation, NF-κB activation and elevated NO production further potentiating ER stress responses. Furthermore, IRE1α induces the alternative splicing of XBP1s, which may increase NF-κB activation via its inhibitory effect on FOX01. Finally, IRE1α increases degradation of miRNA that targets *Txnip*, leading to increased activation of the NLRP3 inflammasome and IL1β production, under certain conditions. Activation of the PERK arm in ER-stressed β-cells might activate NF-κB via ATF4-mediated increase in the expression of CHOP. Moreover, PERK inhibits general protein translation (via phosphorylation and activation of eIF2α), which may also increase NF-κB activation, due to inhibition of *de novo* IκBα expression. Finally, PERK was also shown to contribute to the activation of the NLRP3 inflammasome and IL1β release. Furthermore, cytokine-induced ER stress stimulates translocation of citrullinated BiP to the plasma membrane where it may activate the immune system, thereby contributing to the inflammatory response in the islets. This ER stress-mediated inflammatory state contributes to the maintenance of ER stress and probably leads to β-cell demise. Additional information and supporting references are provided in the text.

Furthermore, XBP1s is implicated in synergistic production of type 1 interferons (IFNs), for example, IFN-β or IFN-α, in response to combination of ER stress and Toll-like receptor (TLR) signaling in macrophages (Martinon *et al.* 2010, Zeng *et al.* 2010).

Both the UPR and inflammation are important protective cellular/tissue responses that when deregulated can lead to cellular damage. In line with this, UPR dysfunction is involved in many autoimmune and inflammatory disorders, such as diabetes (Hotamisligil 2010, Kaser & Blumberg 2010, Oslowski & Urano 2011*a*, Chaudhari *et al.* 2014).

Pancreatic β-cell susceptibility to ER stress

The two main forms of diabetes are T1D and T2D. T1D is primarily caused by an autoimmune attack leading to β-cell destruction and insulin deficiency (Seino *et al.* 2010). T2D is triggered by the combination of insulin resistance and impaired β-cell function and survival, mostly secondary

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to metabolic factors through a process referred to as glucolipotoxicity (Seino *et al.* 2010). Both pathologies are characterized by decreased β-cell mass secondary to apoptosis; however, β-cell loss is more marked in T1D and is a relative late event in T2D, probably contributing to secondary failure of oral therapies (Christoffersson *et al.* 2016, Hara *et al.* 2016). In T1D, pro-inflammatory cytokines are early mediators of β-cell apoptosis, while in T2D a combination of high glucose, cholesterol, and free fatty acid (FFA) levels contribute to β-cell death. Cytokines, high glucose, and FFAs induce ER stress in β-cells (Eizirik *et al.* 2008, Cnop *et al.* 2010, Brozzi & Eizirik 2016). CHOP and BiP levels are increased in islets from individuals with T1D as compared with nondiabetic individuals (Marhfour *et al.* 2012). In islets from T2D patients, an increased ER density together with augmented levels of CHOP and the ER chaperones BiP and DNAJC3 (also known as p58IPK) was observed as compared with nondiabetic controls (Huang *et al.* 2007, Laybutt *et al.* 2007, Marchetti *et al.* 2007). These studies suggest an involvement of the ER stress pathways in the development of both T1D and T2D.

β-cells are unique due to their capacity to sense blood glucose and to respond to changeable demands in insulin secretion. An increase in insulin production, up to 20-fold induced by glucose, is a common physiological response of β-cells that results in an intense trafficking of proteins through the ER (Eizirik *et al.* 2008). Therefore, β-cells express high levels of the UPR transducers IRE1α and PERK, which are necessary for strict quality control of pro-insulin synthesis and to limit oxidative stress induced during the insulin folding, a process that could lead to β-cell failure (Lipson *et al.* 2006, Eizirik *et al.* 2008, Back *et al.* 2009, Oslowski & Urano 2011*a*, Hassler *et al.* 2015). Thus, β-cell exposure to intermittent physiological levels of high glucose increases pro-insulin production with a controlled and regulated UPR activation, which contributes to proper β-cell function and survival (Oslowski & Urano 2011*a*). However, chronic exposure to hyperglycemia induces prolonged activation of the IRE1α pathway leading to β-cell apoptosis (Lipson *et al.* 2006, 2008, Elouil *et al.* 2007, Pirot *et al.* 2007*a*, Hou *et al.* 2008, Han *et al.* 2009, Jonas *et al.* 2009). Sustained activation of ATF6 also contributes to β-cell dysfunction via inhibition of the insulin promoter activity and induction of β-cell death (Seo *et al.* 2008). Similarly, persistent XBP1s production hampers β-cell function, eventually leading to apoptosis (Allagnat *et al.* 2010). Sustained PERK activation/eIF2α phosphorylation contributes to β-cell apoptosis via inhibition of protein translation leading to decreased levels of the anti-apoptotic protein MCL1 and by inducing the pro-apoptotic protein CHOP (Oyadomari *et al.* 2002*b*, Scheuner *et al.* 2005, Cnop *et al.* 2007, Song *et al.* 2008, Allagnat *et al.* 2011, 2012).

Several studies in animal models demonstrated a prominent role for the different UPR pathways on β-cell survival and function (Eizirik *et al.* 2008, Volchuk & Ron 2010). Moreover, mutations in diverse genes leading to β-cell ER stress contribute to the development of diabetes in humans (Inoue *et al.* 1998, Delepine *et al.* 2000, Stoy *et al.* 2007, Colombo *et al.* 2008, Polak *et al.* 2008, Liu *et al.* 2015, Sun *et al.* 2015). These results suggest that tight control of ER homeostasis is crucial to maintain β-cell function and survival.

Inflammation induces ER stress in pancreatic β-cells

Type 1 diabetes

The most evident role of inflammation-induced ER stress in pancreatic β-cells is in the context of T1D (Brozzi & Eizirik 2016). At early stages of the disease, T-cells, macrophages, dendritic cells, and natural killer cells surround the islets in a process called insulitis (Eizirik *et al.* 2009). During insulitis, β-cells are exposed to pro-inflammatory cytokines and free radicals, such as interleukin-1β (IL1β), TNF, IFN-γ, interleukin-17 (IL17), and NO secreted by these infiltrating immune cells, inducing a first wave of β-cell apoptosis (Eizirik *et al.* 2009). Cytokine-mediated β-cell death is a complex phenomenon involving NO production, activation of the diverse transcription factors (e.g., NF-κB and STAT1), MAP kinases (e.g., JNK), and ER stress that culminate in the induction of the intrinsic pro-apoptotic pathway (Eizirik *et al.* 2009, Gurzov & Eizirik 2011). In addition, pro-inflammatory cytokines stimulate the expression and secretion of cytokines and chemokines by the β-cells themselves, initiating a pro-inflammatory dialog between β-cells and the immune system (Eizirik *et al.* 2009, Grieco *et al.* 2011). This contributes to massive T-cell infiltration within the islets and final β-cell destruction (Eizirik *et al.* 2009, Grieco *et al.* 2011). Recent evidences suggest that ER stress is also involved in the pro-inflammatory responses induced by cytokines in β-cells (see below, ER stress-induced inflammation in pancreatic β-cells).

Increased expression of ER stress markers is observed in insulitis-positive and cell-containing islets of T1D patients (Marhfour *et al.* 2012). In line with these results, virus-inducible autoimmune diabetes in the diabetes-resistant BB (BBDR) rat is accompanied by an

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activation of the IRE1α/XBP1 pathway preceding insulitis and a later increase in CHOP expression and caspase 3 activation coinciding with diabetes development (Yang *et al.* 2013). Moreover, expression of ER stress markers and β-cell dysfunction appear before the development of hyperglycemia in nonobese diabetic (NOD) mice, in which a clear increase in the expression of NF-κB target genes is observed (Tersey *et al.* 2012). These results indicate, *in vivo*, a cross talk between inflammatory signaling and ER stress induction that probably contributes to diabetes onset.

Exposure of rat primary β-cells to IL1β + IFN-γ *in vitro* decreases the expression of Serca2b, the main Ca^{2+} pump driving Ca^{2+} influx into the ER, leading to ER Ca^{2+} depletion and activation of the UPR in rat pancreatic β-cells (Cardozo *et al.* 2005). Cytokine-induced ER stress in rat primary β-cells is a consequence of NF-κB-mediated NO production, since inhibition of NO prevents Serca2b downregulation, splicing of XBP1 and CHOP upregulation (Fig. 1) (Cardozo *et al.* 2005). By contrast, in mouse β-cells/islets, cytokine-mediated Serca2b downregulation and UPR activation are independent of NO production (Chan *et al.* 2011). However, in these β-cells, the free radical contributes to the activation of pro-apoptotic responses by upregulating CHOP and decreasing the expression of ER chaperones (Chan *et al.* 2011). In human β-cells, pro-inflammatory cytokines also induce ER stress responses (Allagnat *et al.* 2012, Brozzi *et al.* 2015) and, similar to mouse β-cells, this effect is independent of NO production (Brozzi *et al.* 2015). The factors inducing ER stress in cytokine-treated human β-cells remain to be determined.

Cytokine-induced UPR in β-cells is characterized by a strong activation of the PERK-ATF4-CHOP pathway and a defective induction of ER chaperones, probably due to the lack of ATF6 activation and a modest increase in XBP1 splicing (Rasschaert *et al.* 2003, Cardozo *et al.* 2005, Ortis *et al.* 2010). Moreover, IFN-γ potentiates IL1β-induced death of a rat insulinoma cell line (INS-1E cells) by decreasing the expression of spliced *Xbp1* mRNA and several ER chaperones (Fig. 1) (Pirot *et al.* 2006). Cytokine-mediated NO production was shown to inhibit the expression of the ER chaperones, foldases, and degradation enhancers, decreasing the capacity of a mouse insulinoma cell line (MIN6) cells and primary mouse β-cells to alleviate ER stress (Chan *et al.* 2011). In line with these *in vitro* results, the levels of XBP1s and ATF6 are diminished in islets from T1D patients and two mouse models of T1D (NOD and RIP-LCMV-GP (rat insulin promoter–lymphocytic choriomeningitis virus–glycoprotein)) (Engin *et al.* 2013). Interestingly, administration of the chemical chaperone TUDCA increases ATF6 expression and decreases β-cell death, islet inflammation, and development of diabetes in these mouse models (Engin *et al.* 2013). These results indicate that a defective expression of ER chaperones may contribute to β-cell susceptibility to ER stress and cell death in T1D.

Type 2 diabetes

Obesity, a major risk factor for T2D, is characterized by systemic low-grade chronic inflammation in the form of increased circulating levels of pro-inflammatory cytokines such as TNF, IL1β, and IL6 and lower levels of anti-inflammatory adipokines such as adiponectin and omentin (Pereira & Alvarez-Leite 2014). In line with this, elevated circulating levels of pro-inflammatory cytokines characterize the early (or pre-clinical) stages of T2D and exhibit a graded increase with the disease progression (Duncan *et al.* 2003, Grossmann *et al.* 2015). Interestingly, recent studies also suggest links between inflammation and ER stress in T2D patients at the level of the immune system. Thus, peripheral blood mononuclear cells (PBMCs) of T2D patients express higher levels of BiP, CHOP, and thioredoxin-interacting protein (TXNIP), and lower levels of IκBα and NRF2 (Lenin *et al.* 2015, Mozzini *et al.* 2015), suggesting chronic ER stress in PBMCs and increased pro-inflammatory signals in those patients. Whether these relatively low levels of circulating cytokines affect β-cell survival *in vivo* remains unclear, although they seem to affect the secretory function of INS1E cells *in vitro* (Eizirik 1991, Zhang & Kim 1995, Kiely *et al.* 2007). FFAs may also activate TLR2 and TLR4 in mouse islets, leading to the expression of pro-inflammatory factors via NF-κB (Eguchi *et al.* 2012, Pal *et al.* 2012, Yin *et al.* 2014). This local inflammation probably contributes to increased recruitment of immune cells, particularly macrophages, in the vicinity of islets in T2D patients, promoting a pro-inflammatory environment and UPR activation (Eguchi & Manabe 2013, Cucak *et al.* 2014). Islets from T2D patients produce amyloid polypeptide (hIAPP), which aggregates to form amyloid fibrils. Interestingly, extracellular hIAPP aggregation provokes ER stress and impairs the ubiquitin–proteasome pathway in INS-1 cells (Haataja *et al.* 2008). Thus, while lipids, via Ca^{2+} modulation and ROS generation, are probably the major cause of ER stress, β-cell dysfunction, and apoptosis in T2D (reviewed in (Cnop *et al.* 2010)), lipid-induced inflammation together with adipose-tissue-mediated low-grade inflammation likely contribute to ER stress and to the progression of the disease (Fig. 1).

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Recently, Hasnain *et al.* (2014) provided a direct evidence for the role of inflammation in ER stress induction in T2D. Thus, they showed that IL23 and IL24 are increased in islets of T2D patients, and that blocking these cytokines partially reduced oxidative and ER stress in the islets and improved glucose tolerance in obese mice (Fig. 1) (Hasnain *et al.* 2014). The authors further demonstrated that administration of IL22, a cytokine that decreases ROS formation, was able suppress ER stress and improve islet function, leading to the restoration of glucose homeostasis in these animals (Hasnain *et al.* 2014). Overall, there is a growing amount of evidence suggesting that inflammation contributes to UPR induction and β-cell fate in both T1D and T2D.

ER stress-induced inflammation in pancreatic β-cells

ER stress, NF-κB, and JNK signaling

Although this research area is not yet well developed, different lines of evidence support a role for the UPR in inducing and/or amplifying inflammatory responses in pancreatic β-cells. They are mainly focused on the transcription factor NF-κB, a key regulator of pro-inflammatory responses in these cells (Cardozo *et al.* 2005, Ortis *et al.* 2010, 2012). Microarray analysis of INS-1E cells exposed to the Serca2 blocker and ER stress inducer cyclopiazonic acid (CPA) demonstrated modulation of pro-inflammatory genes, some of them which are NF-κB dependent (Pirot *et al.* 2007*a*). Thus, CPA-treated INS-1E cells express increased levels of the chemokines, CXCL1 and CXCL2; the cytokines IL1β, TNF, TNF ligand superfamily member 1 (TNFSF1, previously known as TNF-β), and IFN-γ receptor; and decreased levels of IL6, IL15, and CCL5 (Pirot *et al.* 2007*a*). Later studies showed that CPA and another Serca2 blocker, namely thapsigargin, induce NF-κB activation in INS-1E cells and human islets (Tonnesen *et al.* 2009, Igoillo-Esteve *et al.* 2010). Notably, NF-κB activation and expression of its downstream genes induced by the Serca2 inhibitors are of a much lower magnitude than that observed in β-cells treated with pro-inflammatory cytokines (Pirot *et al.* 2007*a*, Tonnesen *et al.* 2009, Igoillo-Esteve *et al.* 2010). While TNF and IL1β induce a strong NF-κB activation due to binding to their respective receptors (Shih *et al.* 2011), the mechanisms linking Serca2 inhibition with NF-κB activation in β-cells were not fully investigated. Translational attenuation does not seem to be the main mechanism since salubrinal, a selective inhibitor of eIF2α dephosphorylation, did not modify CPA-mediated NF-κB activation in human islet cells (Igoillo-Esteve *et al.* 2010). However, thapsigargin was shown to potentiate cytokine-mediated NF-κB activation and pro-inflammatory gene expression by increasing IκBα protein degradation in MIN6 cells (Chan *et al.* 2012). ER calcium depletion is probably an important trigger of NF-κB activation in β-cells, since tunicamycin, an agent inducing ER stress via inhibition of protein glycosylation (Oslowski & Urano 2011*b*) does not induce or potentiate NF-κB activation in MIN6 and rat primary β-cells (our own unpublished data) (Chan *et al.* 2011). A subsequent study by Miani *et al.* (2012) showed that INS-1E cells or primary rat β-cells exposed to a low concentration of CPA are sensitized to IL1β-mediated pro-inflammatory responses. Thus, expression of NF-κB downstream genes such as *FAS*, *CCL2*, *CXCL1*, and *iNOS*, as well as NO production were higher in β-cells pre-exposed to CPA, as compared with cells treated with IL1β alone. This effect was due to a XBP1-mediated degradation of the NF-κB-inhibitor fork head boxO1 (FoxO1) protein (Fig. 1), suggesting pro-inflammatory properties of XBP1 (Miani *et al.* 2012). However a recent article showed that IRE1α/XBP1 ablation in adult mouse islets leads to increased levels of IL1β, iNOS, and CXCL2 after exposure to high glucose (Hassler *et al.* 2015). The authors suggest that this increase in pro-inflammatory gene expression occurs downstream of elevated ROS formation in *Ire1α*$^{-/-}$ islets and is not a direct effect of XBP1 on these genes (Hassler *et al.* 2015). Therefore, the outcome of the pro- or anti-inflammatory effects of XBP1 in β-cells seems to be context dependent and defined by the balance between its anti-apoptotic/anti-oxidative responses versus its direct pro-inflammatory signaling. This is in agreement with data obtained in other tissues showing that while XBP1 deficiency may stimulate inflammation (Kaser *et al.* 2008), XBP-1 signaling may also directly induce pro-inflammatory responses (Smith *et al.* 2008, Martinon *et al.* 2010, Zeng *et al.* 2010, Hu *et al.* 2011, Ziogas *et al.* 2015).

The transcription factor CHOP is induced upon ER stress downstream of the PERK pathway (Fig. 1) (Oyadomari & Mori 2004). CHOP contributes to rodent and human β-cell apoptosis and its expression is upregulated in islets from both T1D and T2D patients (Laybutt *et al.* 2007, Cunha *et al.* 2008, Allagnat *et al.* 2012). Besides its pro-apoptotic role, recent studies revealed a pro-inflammatory role for CHOP in different disease models, including myocardial inflammation (Miyazaki *et al.* 2011), lung damage induced by LPS (Endo *et al.* 2005), chemical hepatocarcinogenesis (DeZwaan-McCabe *et al.* 2013), and high fat diet-induced diabetes (Maris *et al.* 2012). Other

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studies have also shown that CHOP positively regulates the expression of pro-inflammatory cytokines such as IL1β and IL8 and chemokines such as CCL2 in different tissues (Kodama *et al.* 2005, Endo *et al.* 2006, Cucinotta *et al.* 2008, Suyama *et al.* 2008, Namba *et al.* 2009). In INS-1E cells and rat primary β-cells CHOP contributes to NF-κB activation by promoting IκBα degradation and subsequent p65 translocation to the nucleus (Fig. 1) (Allagnat *et al.* 2012). This leads to an increased expression of key NF-κB target genes involved in apoptosis and inflammation, including *iNOS*, *FAS*, *IRF7*, *IL15*, *CCL5*, and *CXCL10* (Allagnat *et al.* 2012). The mechanisms by which CHOP regulates NF-κB activation are not yet clear. Moreover, the impact of *CHOP* knockdown in *in vivo* models of T1D is controversial. Thus, backcrossing NOD mice with *Chop*$^{-/-}$ mice did not prevent or delayed diabetes incidence (Satoh *et al.* 2011). However, *Chop*$^{-/-}$ mice are protected against multiple low-dose streptozotocin (MLDSZT)-induced diabetes (Ariyama *et al.* 2008). The observed protection against MLDSZT, however, suggests that *Chop* deletion may favor β-cell survival in a model where inflammation plays a key role, as suggested by the previously described protection afforded by inhibiting NF-κB expression in β-cells from MLDSZT-treated mice (Eldor *et al.* 2006).

In summary, when activated by pro-inflammatory cytokines, the transcription factor NF-κB regulates UPR responses of β-cells. However, the UPR positively regulates NF-κB activity and pro-inflammatory responses, increasing apoptotic signaling and expression of pro-inflammatory cytokines and chemokines that may contribute to β-cell demise (Fig. 1).

As mentioned above, JNK is another player linking ER stress to inflammation in other cell types. In β-cells, IL1β + IFN-γ-mediated JNK activation is partially mediated by IRE1α (Fig. 1) (Brozzi *et al.* 2014). Although the pro-apoptotic role for JNK in β-cells is well established (Bonny *et al.* 2001, Nikulina *et al.* 2003), few studies have evaluated and demonstrated a pro-inflammatory role for JNK in these cells (Hou *et al.* 2011, Tan *et al.* 2013, Lawrence *et al.* 2015). One of the mechanisms by which JNK contributes to ER stress-mediated inflammation in β-cells is by upregulating CHOP expression (Fig. 1) (Pirot *et al.* 2007*b*, Allagnat *et al.* 2012). Further studies are necessary to evaluate the role of JNK in β-cell mediated-pro-inflammatory responses.

ER stress, IL1β, and the inflammasome

Although controversial, it has been proposed that exposure of mouse or human islets to high glucose concentrations induces production of IL1β contributing to β-cell apoptosis and constitutes a common mechanism for β-cell death in both T1D and T2D (Cnop *et al.* 2005, Mandrup-Poulsen *et al.* 2010). IL1β production is mediated via the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which in turn can be activated via increased expression of TXNIP (Yoshihara *et al.* 2014). The chemical ER stressor, thapsigargin, was shown to upregulate *Txnip* mRNA in INS-1E cells, mouse, and human primary islets leading to activation of the NLRP3 inflammasome and release of IL1β, contributing to β-cell death (Lerner *et al.* 2012, Oslowski *et al.* 2012). While *Txnip* induction is directly modulated by PERK (Oslowski *et al.* 2012), IRE1α exhibits an indirect effect on *Txnip* via IRE1α-mediated degradation of a repressive microRNA (Fig. 1) (Lerner *et al.* 2012). However, a subsequent study failed to observe protection of mouse NLRP3$^{-/-}$ or caspase-1$^{-/-}$ islets against ER stress, glucose, or glucolipotoxicity-mediated cell death (Wali *et al.* 2014). Moreover, genetic activation of NLRP3 specifically in mouse β-cells did not induce IL1β expression/production or increased cell death in response to glucolipotoxicity stimuli (Wali *et al.* 2014). The latter results contradict a role for IL1β or NLRP3 inflammasome in high-glucose- and/or ER stress-mediated β-cell death and are consistent with other studies that failed to show a role for IL1β under these conditions (Kharroubi *et al.* 2004, Cnop *et al.* 2005, McKenzie *et al.* 2010). Notably, IL1β alone does not induce apoptosis in primary β-cells (Eizirik & Mandrup-Poulsen 2001, Cardozo *et al.* 2005). Therefore, further studies are necessary to clarify the role of ER stress in IL1β production and its involvement in β-cell death in diabetes.

ER stress and antigen presentation

In T1D, initiation and progression of the disease is related to the presence of β-cell-specific autoantibodies (van Belle *et al.* 2011). Notably, the majority of β-cell autoantigens recognize proteins produced in the ER (van Belle *et al.* 2011). Pro-inflammatory cytokines induce both ER stress and assembly of the MHC complex in the organelle (Rasschaert *et al.* 2003, Cardozo *et al.* 2005). Therefore, it is plausible that cytokine-mediated UPR could influence post-translational modification of proteins, leading to production and presentation of potential autoantigens. It was previously shown that ER calcium depletion drives the translocation of ER-resident proteins BiP, GRP94, and calreticulin in the plasma membrane (Peters & Raghavan 2011), which may have pro- or anti-inflammatory outcomes depending on the protein and cellular context (Panayi & Corrigall 2006, Peters & Raghavan 2011, Raghavan *et al.* 2013,

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Pockley *et al.* 2014). A recent publication showed that cytokines and ER stressors induce translocation of BiP to the plasma membrane in INS-1E, MIN6 cells, and mouse islets (Rondas *et al.* 2015). Interestingly, pro-inflammatory cytokines, but not ER stressors, induced BiP citrullination in INS-1E cells (Rondas *et al.* 2015). Citrullinated BiP induced production of autoantibodies that stimulated effector T-cells in pre-diabetic NOD mice (Fig. 1) (Rondas *et al.* 2015). The presence of citrullinated proteins correlates with activation of the immune system in autoimmune diseases (Blass *et al.* 2001, Shoda *et al.* 2011) and increased response to citrullinated GAD65 peptides is observed in T1D patients (McGinty *et al.* 2014). Another evidence that ER stress response may influence β-cell antigen presentation is delayed appearance of autoantibodies observed in NOD mice knockout for *Chop* (Satoh *et al.* 2011). However, the mechanism leading to this delayed antibody response was not investigated in this study (Satoh *et al.* 2011). A recent elegant publication showed that β-cells transfer antigenic epitopes to antigen presenting cells via a direct membrane contact (Vomund *et al.* 2015). This is a novel mechanism, however, not specific for 'diabetic' β-cells, since it was observed in both diabetic and nondiabetic mice and in nondiabetic humans. Interestingly, high glucose increased the transfer of epitopes (Vomund *et al.* 2015). The mechanism for this increase has not been yet investigated, but it would be interesting to verify whether it is not due to high glucose-induced ER stress. Further work is necessary to clarify the role for ER stress in the process of autoantibody production in patients with T1D and its consequences on β-cell autoimmunity (Marre *et al.* 2015).

ER stress-targeting therapies

As described above, several studies support an important role for ER stress in the pathogenesis of T1D and T2D. Therefore, the development of strategies to prevent or alleviate ER stress in β-cells may prove useful for prevention and/or treatment of these diseases. Approaches targeting the UPR for therapeutic purposes remain largely in their infancy, but several strategies aimed at improving ER function in pancreatic β-cells are emerging (Fig. 2).

Targeting the chaperone capacity of the cells

One strategy to alleviate ER stress in β-cells relies on the use of chemical chaperones. Two compounds, in particular 4-phenyl butyric acid (4-PBA) and taurine-conjugated ursodeoxycholic acid (TUDCA), show promising results regarding diabetes therapy. As mentioned above, TUDCA administration at the pre-diabetic stage reduces diabetes incidence in the NOD and RIP-LCMV-GP mouse models of T1D and this reduction is accompanied by improved survival and preserved insulin secretion (Engin *et al.* 2013). *In vitro*, TUDCA inhibits eIF2α phosphorylation and restores thapsigargin-induced β-cell dysfunction in porcine islets (Fig. 2) (Lee *et al.* 2010), while 4-PBA ameliorates palmitate-induced GSIS inhibition in primary rat islet cells (Choi *et al.* 2008). Besides β-cell dysfunction, ER stress also contributes to insulin resistance in T2D (Salvado *et al.* 2015). Both PBA and TUDCA alleviate ER stress in obese mice, restoring insulin sensitivity and normoglycemia (Ozcan *et al.* 2006). Importantly, these compounds also improved insulin sensitivity in obese subjects (Kars *et al.* 2010, Xiao *et al.* 2011). However, no evidence of improved β-cell function was provided in these studies and despite these encouraging results, additional research is required to better clarify by which mechanism these compounds are acting, verify their specificity, and explore their long-term benefit and safety.

Another potential strategy is to increase the folding capacity of the ER by enhancing endogenous chaperone expression in β-cells. Valproic acid (VPA), a drug widely used for the treatment of epilepsy and mood disorders (Chen *et al.* 2014), has been shown to increase the expression of BiP, reduce expression of CHOP, and protect from ER stress-induced neuronal cell death in various rat models (Fig. 2) (Wang *et al.* 1999, Bown *et al.* 2002, Penas *et al.* 2011, Zhang *et al.* 2011, Lee *et al.* 2014). Interestingly, Huang *et al.* recently demonstrated that VPA protects rat INS-1 cells from palmitate-induced ER stress and apoptosis via GSK-3β inhibition, independent of ATF4/CHOP pathway (Huang *et al.* 2014). Notably, GSKβ3 inhibition also protects β-cells against both chemical ER stress- and cytokine-mediated β-cell apoptosis (Srinivasan *et al.* 2005, Fukaya *et al.* 2016). One of the possible mechanisms could be stabilization of the anti-apoptotic protein MCL1, since inhibition of GSK3β hampers cytokine-mediated MCL1 degradation and protects INS-1E and human β-cells against apoptosis (Meyerovich K, Ortis F, Allagnat F and Cardozo AK unpublished observations). Further studies are required to extend these findings in animal models and explore the potential efficacy of VPA and/or GSK3β inhibition on β-cell death *in vivo*.

Studies carried out in neuronal cells suggest that the BiP inducer X (BIX) compound protects against ER stress-induced neuronal cell death in mice (Fig. 2)

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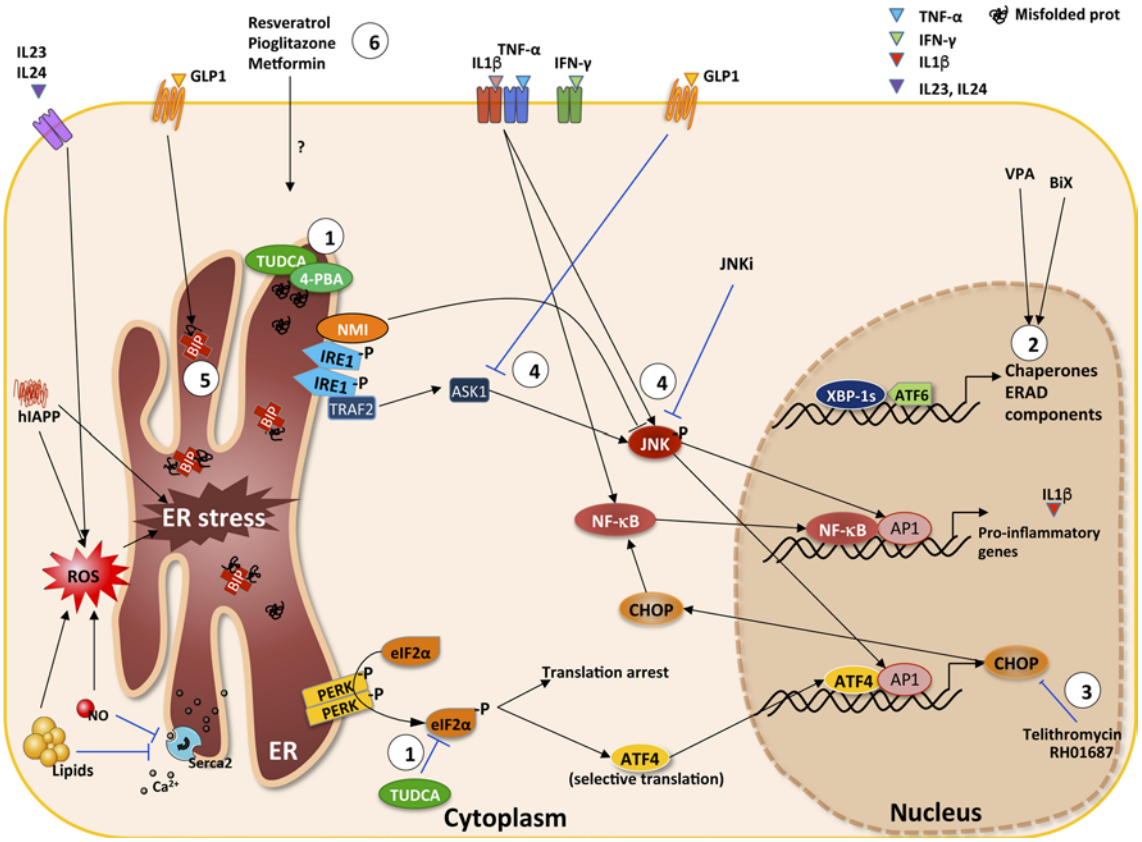

Figure 2
ER stress-targeting therapies. Several strategies to improve ER function in pancreatic β-cells are emerging. (1) The use of the chemical chaperones 4-phenyl butyric acid (4-PBA) and taurine-conjugated ursodeoxycholic acid (TUDCA) show promising results regarding diabetes therapy, although their mode of action remains largely unknown. (2) Several compounds such as valproic acid (VPA) or BiP inducer X (BiX) may promote the expression of endogenous chaperones, thereby reducing ER stress and apoptosis. (3) Two novel compounds, namely telithromycin and RH01687, were shown to inhibit CHOP and promote β-cell function and survival during ER stress. (4) Strategies aimed at blocking pro-apoptotic UPR pathway such as ASK1 or JNK activity downstream of IRE1α have been shown to protect against ER stress-mediated cell death. Notably, the anti-apoptotic properties of GLP1 are partly mediated by reduced ER stress through actions on ASK1 and the transcription factor JunB downstream JNK (5). GLP1 may also stimulate BiP expression. (6) Finally, other anti-diabetic therapies such as pioglitazone, metformin, or resveratrol have been shown to reduce ER stress in β-cells through unknown mechanisms.

(Kudo *et al.* 2008, Inokuchi *et al.* 2009). Whether or not this compound might be of interest for the treatment of diabetes, in general, and the survival of pancreatic β-cells, in particular, remains to be assessed.

Targeting the UPR

The PERK-eIF2α pathway plays a central role in the UPR pro-apoptotic signaling (Laybutt *et al.* 2007, Song *et al.* 2008, Allagnat *et al.* 2012). Thus, salubrinal, a compound preventing eIF2α dephosphorylation and driving CHOP expression, increases the sensitivity of rat and human pancreatic β-cells to fatty-acid-induced ER stress and apoptosis (Cnop *et al.* 2007, Ladriere *et al.* 2010). Moreover, upregulation of CHOP and downregulation of the anti-apoptotic protein MCL1 contributes to ER stress-mediated β-cell apoptosis downstream of PERK (Laybutt *et al.* 2007, Allagnat *et al.* 2012). Therefore, compounds that prevent eIF2α phosphorylation and subsequently CHOP expression might prove useful for the treatment of diabetes. However, salubrinal protects neuronal cells from ER stress-induced cell death (Boyce *et al.* 2005, Fullwood *et al.* 2012), suggesting the need for cell-specific therapies when targeting UPR pathways. Recently, the screening of a bank of compounds identify telithromycin and RH01687 as potential anti-apoptotic molecules targeting CHOP and reducing tunicamycin-induced apoptosis and restoring the insulin secretion *in vitro* in βTC6 and MIN6 (Fig. 2) (Tran *et al.* 2014). Further studies are necessary to extend those findings in primary cells and *in vivo* and test whether such molecules do not have adverse effects on other organs.

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Another possibility to block CHOP expression is to act on another upstream regulator, that is, JNK (Allagnat *et al.* 2012, Gurzov *et al.* 2012). As mentioned above, the kinase JNK plays a central role in ER stress and pancreatic β-cell dysfunction (Bonny *et al.* 2001, Nikulina *et al.* 2003). Besides CHOP, JNK may activate other pro-apoptotic proteins such as BID, BIM, and death protein 5 (DP5), while inhibiting anti-apoptotic proteins such as BCL2 and MCL1 (Dhanasekaran & Reddy 2008, Gurzov *et al.* 2009, Allagnat *et al.* 2011, Santin *et al.* 2011). Moreover, JNK activation resulting from ER stress contributes to insulin resistance in insulin-stimulated cells and organs, such as liver and adipose tissue (Kaneto *et al.* 2006). Therefore, compounds targeting JNK activation may have a positive impact on multiple organs in the context of T2D. The cell-permeable peptide inhibitor of JNK (Fig. 2) (1) prevents islet apoptosis after isolation (Noguchi *et al.* 2005), (2) improves islet grafts survival (Noguchi *et al.* 2008), and (3) prevents ER stress-induced CHOP expression in rat INS-1E cells (Allagnat *et al.* 2012, Gurzov *et al.* 2012). Further studies are required to test the potential of this JNK inhibitor *in vivo*.

Cytokine-induced JNK activation is at least partially mediated via the IRE1α pathway. However, targeting IRE1α is not ideal since this protein is also responsible for activation of *Xbp1*- and *Ire1*α-knockout mice are not viable (Zhang *et al.* 2005). The best alternative is to interfere with IRE1α downstream signaling leading to JNK activation. It was recently shown that N-MYC interactor (NMI) protein negatively modulates IRE1α-dependent activation of JNK and apoptosis in rodent and human pancreatic β-cells (Brozzi *et al.* 2014), thus NMI could be pointed as a potential target. IRE1-mediated JNK activation is also downstream of the apoptosis signal-regulated kinase 1 protein (ASK1). Interestingly, ASK1 is activated by ER stress in MIN6 cells *in vitro* and ASK1 deficiency *in vivo* decreases β-cell apoptosis and delays the onset of diabetes in Akita mice (Yamaguchi *et al.* 2013). Therefore, chemical inhibitors of ASK1 might provide cytoprotection in the context of ER stress.

Existing treatments of T2D that reduce ER stress

One of the most promising avenues for the treatment of diabetes relies on GLP1 receptor agonists such as liraglutide and exenatide (reviewed in (Madsbad 2016)) and inhibitors of the dipeptidyl peptidase-4 (DPP4) peptidase responsible for rapid degradation of GLP1 (reviewed in Li *et al.* 2015, Deacon & Lebovitz 2016, Nauck 2016). The anti-apoptotic properties of GLP1 in β-cells are well known and they are at least partially mediated by reduced ER stress through actions on several targets including BiP, ASK1, SIRT1, and the transcription factors C/EBPs and JunB (Fig. 2) (Yusta *et al.* 2006, Tsunekawa *et al.* 2007, Cunha *et al.* 2009, Kwon *et al.* 2009, Widenmaier *et al.* 2009, Oh *et al.* 2013, Kim *et al.* 2015).

Other existing treatments of T2D such as the insulin sensitizers Metformin and Pioglitazone are known to improve insulin sensitivity partly by reducing ER stress in the liver and peripheral tissues (Fig. 2) (Singh *et al.* 2015). Pioglitazone was recently shown to reduce ER stress in *Wfs1*-deficient mice (Yamada *et al.* 2006), a genetic model for ER stress-mediated β-cell loss and diabetes, thus almost preventing the onset of diabetes in those mice (Akiyama *et al.* 2009). Pioglitazone also protects rat insulin-secreting cells from thapsigargin-induced cell death (Hara *et al.* 2014). Similarly, Metformin partially protects INS-1 cells from palmitate-induced ER stress and cell death (Simon-Szabo *et al.* 2014). The fact that current T2D therapies act, at least partly, through modulation of UPR pathways underscores the central role of ER stress in β-cell dysfunction and death.

An array of additional molecules with anti-oxidant properties improve several circulating markers of T2D such as fasting blood glucose, HbA1c, insulin, and lipid (LDL and triglycerides) levels (Azadmehr *et al.* 2014, Szkudelski & Szkudelska 2015). Among them resveratrol was shown to protect against ER stress-driven cell dysfunction in the context of obesity-related disorders and diabetes (Andrade *et al.* 2014, Guo *et al.* 2015). However, further studies are required to better characterize the molecular mechanisms regulating the effects of resveratrol in β-cells.

Conclusions

Research on the UPR is a relatively new field and although its role on β-cell function, dysfunction, and survival is well studied, the role of the UPR in β-cell pro-inflammatory responses is just beginning to be elucidated. Thus, 'sterile' (non-inflammatory/chemically induced) UPR activation is able to induce pro-inflammatory responses in β-cells. However, β-cell exposure to pro-inflammatory cytokines released in and from the islets in both T1D and T2D induces UPR responses that in turn may potentiate inflammation and contribute to β-cell death. The mechanisms by which the UPR modulates inflammation are not completely clarified, but the available data indicates that it is context-dependent. Recent studies showing that manipulating UPR responses may decrease inflammatory responses and reduced diabetes developments in animal models of both T1D and T2D indicate that these

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pathways are of relevance and can be used as new targets for interventional therapies to prevent these diseases.

As discussed in this article, ER stress and disrupted UPR are likely to play a central role in the pathophysiology of diabetes, not only at the β-cell level, but also in the liver, muscle, adipose tissue, and immune system. Therefore, approaches aimed at reducing ER stress might have beneficial effects on multiple organs. However, one should keep in mind that certain strategies to protect β-cells might have detrimental effects in other tissues. The studies indicating that current therapies for treating T2D alleviate ER stress and the fact that existing molecules already used to treat other pathologies may also reduce ER stress in β-cells provide exciting opportunities to advance the treatment of diabetes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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