PERK in the life and death of the pancreatic β-cell

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Abstract

To ensure cellular survival to ER (endoplasmic reticulum) stress, PERK [PKR (double-stranded-RNA-dependent protein kinase)-like ER kinase], an ER transmembrane kinase, is activated as part of the unfolded protein response. PERK is highly expressed in pancreatic β-cells and is essential in the β-cell’s development, differentiation and function. However, chronic activation of PERK can induce cell death, and its activation has been implicated in both Type 1 and Type 2 diabetes. This short review aims to provide an insight into our current understanding of the role of PERK in the life and death of the β-cell.

Introduction

The β-cell’s primary function is to synthesize and secrete insulin in response to glucose in order to maintain normoglycaemia. This places a huge demand on the β-cell’s highly developed ER (endoplasmic reticulum) to synthesize, fold and process large quantities of insulin. Failure of the ER to cope with this demand would result in the accumulation of unfolded proteins, ER stress, decreased β-cell function and ultimately cell death. In order to alleviate ER stress and promote cell survival, an adaptive response, known as the UPR (unfolded protein response), is activated, resulting in decreased ER folding load, increased ER folding capacity and the clearance of misfolded proteins from the ER (reviewed in [1]). Transducers of this UPR, which are highly expressed in β-cells, include three ER transmembrane proteins: PERK [PKR (double-stranded-RNA-dependent protein kinase)-like ER kinase], IRE1 (inositol requiring enzyme-1) [an endonuclease required for the splicing and activation of XBP-1 (X-box-binding protein-1)] and ATF6 (activating transcription factor-6) (see Figure 1a). PERK phosphorylates the α-subunit of eIF2α (eukaryotic initiation factor-2α), which inhibits protein synthesis and hence decreases ER protein folding load. Moreover, phosphorylated eIF2α, through up-regulating the expression of ATF4, increases the expression of proteins important in amino acid metabolism and combating oxidative stress. PERK also promotes cell survival by phosphorylating and activating Nrf2 (nuclear factor-erythroid 2 p45 subunit-related factor 2), which results in an increase in mRNAs encoding proteins important in maintaining redox homeostasis. The activation of IRE1 and ATF6 leads to an increase in the expression of foldases, chaperones and proteins important in ERAD (ER-associated degradation). Collectively, the activation of PERK, IRE1 and ATF6 (i.e. the UPR) is clearly intended to alleviate ER stress and hence promote cell survival. Yet, the prolonged activation of the UPR can ultimately lead to programmed cell death.

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PERK and β-cell proliferation and differentiation

PERK plays a critical role in the life of the β-cell as β-cells from PKO (PERK-knockout, pancreas-specific PKO and endocrine-pancreas-specific PKO) mice fail to expand during neonatal development due to decreased proliferation, resulting in reduced β-cell mass and the development of frank diabetes [2,3]. These effects of knocking-out PERK on the β-cell are possibly mediated through the phosphorylation state of eIF2α, as homozygous Ser-51 to alanine (S51A) ‘knock-in’ mice (therefore creating a non-phosphorylatable eIF2α) also show severe β-cell deficiency [4]. The failure of the β-cells to expand in PKO neonates may be due to decreased expression of mRNAs important in G1- and M-phase progression of the cell cycle [3]. Studies from PKO mice also revealed that PERK is important in β-cell differentiation, as, during the earliest stages of β-cell neogenesis, the expression of key markers of differentiation, such as insulin mRNAs, are reduced in PKO mice compared with WT mice [3]. Moreover, islets from PKO mice fail to develop normal islet architecture and the β-cells exhibit abnormal ER morphology. Together, these manifestations result in impaired glucose-stimulated insulin secretion [3]. Importantly, β-cell-specific loss of PERK in mice after the critical neonatal period of β-cell proliferation does not lead to reduced β-cell mass, and the resultant βPKO (β-cell-specific PKO) mice maintain glucose homeostasis [3]. However, the effects of this βPKO on β-cell function and survival under pathophysiological conditions that induce ER stress, such as during insulin resistance where there is increased demand for insulin or during periods of elevated NEFAs (non-esterified fatty acids) as seen in obesity-induced diabetes, are currently unknown. Intriguingly, however, heterozygous eIF2α S51A ‘knock-in’ mice, fed on a high-fat diet, show abnormal β-cell ER morphology, defective insulin

Key words: diabetes, double-stranded RNA-dependent protein kinase (PKR)-like ER kinase (PERK), endoplasmic reticulum stress, eukaryotic initiation factor-2α (eIF2α), pancreatic β-cell, unfolded protein response.

Abbreviations used: ATF, activating transcription factor; eIF2α, eukaryotic initiation factor-2α; ER, endoplasmic reticulum; JNK, c-Jun N-terminal kinase; NEFA, non-esterified fatty acid; IRE1, inositol requiring enzyme-1; PKR, double-stranded RNA-dependent protein kinase; PERK, PKR-like ER kinase; PKO, PERK-knockout; βPKO, β-cell-specific PKO; WT, wild-type; UPR, unfolded protein response; XBP-1, X-box-binding protein-1.

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PERK and the UPR

Figure 1

(a) Upon ER stress, PERK and IRE1 are activated by homo-oligomerization and autotransphosphorylation. ATF6 is transported into the Golgi where it is cleaved releasing its activation domain, which then translocates to the nucleus. These events (see text for details) lead to the alleviation of ER stress and hence increased cell survival. (b) The prolonged activation of the UPR results in induction of apoptosis via PERK-dependent and possibly ATF6-dependent decrease in Bcl-2. IRE1 activation can also lead to apoptosis via the recruitment of TRAF2 [TNF (tumour necrosis factor)-receptor-associated factor 2] and ASK1 (apoptosis signal-regulating kinase 1) resulting in JNK activation, which phosphorylates and inactivates Bcl-2. FFA = NEFA.

trafficking and a reduced number of secretory granules [5], indicating that eIF2α phosphorylation protects β-cells from the deleterious effects of chronically raised circulating NEFAs.

PERK and glucose-stimulated protein synthesis

In β-cells, glucose rapidly stimulates a specific increase in insulin synthesis (up to 20-fold within 1 h) and an increase in total protein synthesis (reviewed in [6]). These changes are regulated in part by PERK-dependent phosphorylation of eIF2α at a low glucose concentration ([7], and M.L. Powell, E. Gomez and T.P. Herbert, unpublished work) and probably play an important role in maintaining β-cell mass and ensuring the replenishment of secreted insulin. PERK-dependent eIF2α phosphorylation at low glucose also up-regulates the expression of a specific subset of proteins including the transcription factor ATF4, which probably promotes cell survival [8,9]. Islets isolated from PKO newborns have a higher rate of insulin synthesis at high glucose than WT neonatal islets [2]. However, there is no evidence that PERK activity is increased at high glucose concentration. Therefore it is more likely that the basal activity of PERK suppresses insulin synthesis to limit ER load.

PERK in the death of the β-cell

The prolonged activation of PERK, as part of the UPR, can induce apoptosis and is implicated in the pathophysiology of a number of diseases including diabetes [1]. UPR-induced cell death can occur via one of several apoptotic pathways (reviewed in [10]) (see Figure 1b). For example, chronic PERK activation increases the expression of CHOP [CCAAT/enhancer-binding protein]-homologous protein] via ATF4, which blocks the expression of the anti-apoptotic protein Bcl-2, whereas prolonged IRE1 activation results in the phosphorylation of the MAPK (mitogen-activated protein kinase) JNK (c-Jun N-terminal kinase), which in turn phosphorylates and inactivates Bcl-2.

In Type 1 diabetes, β-cells are the target of an autoimmune attack by invasion of the islets by mononuclear cells in an inflammatory reaction termed ‘insulitis’, leading to the β-cell death. This is likely to be mediated by cytokines secreted from macrophages and T-cells, which result in an increase in NO (nitric oxide). Interestingly, NO and cytokines induce ER stress, chronic activation of the UPR and apoptosis in clonal pancreatic β-cell lines [11,12]. These effects have been reported to be mediated by the inhibition of SERCA2b (sarcoplasmic/endoplasmic-reticulum Ca2+-ATPase 2b) expression, a calcium ATPase that pumps calcium into the ER, resulting in ER calcium depletion and the accumulation of misfolded proteins within the ER [12].

The development of Type 2 diabetes occurs when pancreatic β-cells fail to compensate for insulin resistance in peripheral tissues due to defects in insulin secretion or loss of β-cell mass. Elevated levels of NEFAs have been shown to be cytotoxic to β-cells in obesity-associated diabetes models as well as in normal β-cells. Interestingly, these cytotoxic effects may be mediated through the activation of the UPR as incubation of a number of pancreatic clonal β-cell lines with the NEFA palmitate can result in the activation of PERK and the phosphorylation of eIF2α, increased XBP-1 splicing and the transient activation of ATF6 [13,14]. Moreover, the
expression of mRNAs associated with ER stress is elevated in pancreatic sections from humans suffering from Type 2 diabetes and in islets from db/db mice that develop a disease resembling Type 2 diabetes [14].

Conclusions and future perspectives

PERK activity is essential for the development and differentiation of the islet and probably plays a key role in β-cell survival and the regulation of protein synthesis. Yet, PERK activation can also induce β-cell apoptosis and is implicated in the pathogenesis of diabetes. Therefore a key focus for future research must be to extend our understanding of the role of PERK and its mode of regulation in the β-cell in order to develop new strategies to alleviate ER stress and/or PERK/UPR-induced apoptosis.

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