Endoplasmic reticulum stress in disease: mechanisms and therapeutic opportunities

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ABSTRACT

Various stresses, which impair ER (endoplasmic reticulum) function, lead to an accumulation of unfolded or misfolded proteins. ER stress triggers many rescuer responses, including a UPR (unfolded protein response). Increasing evidence has suggested that ER stress is involved in neurodegenerative diseases (Alzheimer’s disease, Parkinson’s disease and cerebral ischaemic insults), cancer, obesity and diabetes. In the present review, we consider the importance of ER stress under pathological conditions in mammals. Furthermore, we discuss the therapeutic potential for treatment targeting ER stress.

INTRODUCTION

Cells respond to a stressful environment by adapting to maintain homeostasis. The ER (endoplasmic reticulum) is an important organelle responsible for the folding and sorting of proteins. Stress which impairs ER function leads to an accumulation of unfolded or misfolded proteins (ER stress) (Figure 1). This accumulation of unfolded proteins is toxic to cells and, to adapt, cells activate the UPR (unfolded protein response) [1,2]; however, when ER stress is excessive or prolonged, cells undergo apoptosis. In recent years, ER stress has been implicated in neurodegenerative diseases (Alzheimer’s disease, Parkinson’s disease and cerebral ischaemic insult), cancer, obesity and diabetes (Figure 1). This has led to the proposal of a new therapeutic approach targeting ER stress. A better understanding of ER stress may help to clarify the molecular mechanisms and appropriate pharmacological treatment of ER-stress-related disease. Thus, in the present review, we describe the basic mechanisms of ER stress and related diseases. Furthermore, we discuss the therapeutic opportunities in targeting ER stress.

ER STRESS

The accumulation of unfolded or misfolded proteins in the ER triggers the UPR (Figure 2). The UPR acts to alleviate ER stress by: (i) increasing folding capacity, (ii) inhibiting general protein translation, and (iii) promoting the degradation of misfolded proteins [2,3]. However, if the response is unable to rescue cells, the ER stress

Key words: apoptosis, cancer, neurodegenerative disease, endoplasmic reticulum, obesity, stress response, unfolded protein response.

Abbreviations: AR-JP, autosomal recessive juvenile parkinsonism; ATF, activating transcription factor; BiP, immunoglobulin heavy-chain-binding protein; BIX, BiP inducer X; CHOP, CCAAT/enhancer-binding protein-homologous protein; eIF, eukaryotic initiation factor; ER, endoplasmic reticulum; ERAD, ER-associated protein degradation; GADD34, growth-arrest and DNA-damage-inducible protein 34; GRP78, glucose-regulated protein of 78 kDa; HSP90, heat-shock protein 90; IRE1, inositol-requiring protein 1; JAK, Janus kinase; OASIS, old astrocyte specifically induced substance; Pael-R, Parkin-associated endothelin receptor-like receptor; 4-PBA, 4-phenyl butyric acid; PDI, protein disulfide-isomerase; PI3K, phosphoinositide 3-kinase; PKR, double-stranded-RNA-dependent protein kinase; PERK, PKR-like ER kinase; PTP1B, protein tyrosine phosphatase 1B; RIP, regulated intramembrane proteolysis; SOCS3, suppressor of cytokine signalling 3; STAT, signal transducer and activator of transcription; TUDCA, taurine-conjugated ursodeoxycholic acid; uORF, upstream open reading frame; UPR, unfolded protein response; UTR, untranslated region; VEGF, vascular endothelial growth factor; XBP1, X-box-binding protein 1.

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Stress signals, which impair ER function, would lead to an accumulation of unfolded or misfolded proteins. Increasing evidence has suggested that ER stress is involved in Alzheimer's disease, Parkinson's disease, cancer, obesity and diabetes. Will eventually lead to apoptosis via an increase in the expression of CHOP (CCAAT/enhancer-binding protein-homologous protein), an apoptotic transcription factor [4,5], or the activation of ER-specific caspases (Figure 2).

To date, three ER-resident proteins have been identified as sensors of ER stress: IRE1 (inositol-requiring protein 1), PERK [PKR (double-stranded-RNA-dependent protein kinase)-like ER kinase] and ATF6 (activating transcription factor 6). The initial activation of these three sensors has been suggested to be dependent on the dissociation of GRP78 (glucose-regulated protein of 78 kDa) in response to ER stress [6,7]. GRP78 is an ER chaperone protein that uses ATP to promote folding and prevent the aggregation of proteins in the ER. After dissociation, IRE1 and PERK are activated by luminal-domain-mediated homodimerization and autophosphorylation [6]. On the other hand, ATF6 undergoes RIP (regulated intramembrane proteolysis), which results in the accumulation of cleaved fragments of cytoplasmic domains that enter the nucleus to regulate gene transcription [8].

IRE1 is a type 1 transmembrane serine/threonine receptor protein kinase which functions as a sensor for misfolded/unfolded proteins in the ER lumen. Activated IRE1 induces the splicing of XBP1 (X-box-binding protein 1) mRNA by cleaving off its intron [9,10]. XBP1 translated from the spliced mRNA functions as a transcription factor specific for ER-stress-related genes such as the GRP78 gene (HSPA5).

PERK is a type 1 transmembrane protein kinase that resides in the ER and transmits stress signals in response to the perturbation of protein folding [11]. When activated, PERK phosphorylates the α subunit of eIF2 (eukaryotic initiation factor 2) and decreases eIF2 activity, resulting in translational repression [11,12]. The decrease in eIF2 activity, however, promotes the translation of ATF4 and activates the CHOP promoter, which results in the production of CHOP protein [13–15]. Furthermore, recent observations suggest that 4E-BP1 (eIF4E-binding protein 1), a suppressor of the mRNA 5' cap-binding protein eIF4E, was increased by an ATF4-mediated pathway, which contributed to survival against ER stress in pancreatic β-cells [16]. The translation of ATF4 mRNA during cellular stress was reported to involve uORFs (upstream open reading frames).
frames) [17]. uORFs within the 5′-UTR (untranslated region) of the mRNA are responsible for the sensitivity of the translation of ATF4 to the phosphorylation of eIF2α. Under basal conditions, the translation of both uORFs in the 5′-UTR leads to a failure of initiation at the start codon. When the amount of active eIF2 complex is limited, scanning through the second inhibitory uORF allows initiation at the start codon of ATF4 to occur. Considering the feedback inhibition of the phosphorylation of eIF2α, it was reported [18,19] that GADD34 (growth-arrest and DNA-damage-inducible protein 34) expression depends on stress-induced eIF2α kinases, and that GADD34-mediated dephosphorylation of eIF2α in a negative-feedback loop would promote recovery from translational repression.

ATF6 is a type 2 transmembrane protein that undergoes RIP. ER stress activates ATF6 by translocating it from the ER to Golgi complex, where it is cleaved by the Golgi-resident serine proteases S1P and S2P (site 1 and site 2 proteases respectively) [7,20,21]. The cleaved 50-kDa cytoplasmic b-ZIP (basic leucine zipper)-containing fragment moves to the nucleus and activates the transcription of UPR targets such as GRP78, CHOP and XBP1 [10,20,22,23]. Interestingly, OASIS (old astrocyte specifically induced substance), which is similar to the ATF6 family, has been identified as a transducer of ER stress in astrocytes [24]. Furthermore, CREBH (cAMP-response-element-binding protein H) has been identified as a RIP-regulated liver-specific transcription factor that is cleaved upon ER stress [25]. These observations suggest that cell- or tissue-type-specific UPR signalling exists under ER stress.

Unfolded or misfolded proteins that accumulate in the ER are trapped and transported to the cytoplasm. ERAD (ER-associated protein degradation) requires the retrograde transport of these proteins from the ER to the cytoplasm through translocons. The proteins are then degraded by the ubiquitin–proteasome system [26,27]. The mechanisms that determine cell fate during ER stress are not well understood. Previously, we observed that the phosphorylation of Akt was up-regulated in response to short-term exposure to ER stress, whereas it was down-regulated after long-term exposure [28]. The activation of PI3K (phosphoinositide 3-kinase)/Akt pathways promotes cell survival. Interestingly, ER-stress-induced apoptosis has been reported to be mediated by reduced insulin signalling [29]. It was found that ER-stress-induced apoptosis was associated with an attenuation of phospho-Akt and phospho-GSK3β (glycogen synthase kinase 3β) expression, and was inhibited by the co-treatment of cells with IGF1 (insulin-like growth factor 1). Thus, from these results, we proposed that Akt monitors cell status under ER stress, functioning as a ‘check point’ of cell death or survival [28]. Indeed, we also observed that the inactivation of PI3K induced the expression of CHOP, an ER-stress-related apoptotic transcription factor [30]. In addition, PI3K-inhibitor-induced CHOP expression was mediated through a 4-(2-aminoethyl)-benzenesulfonyl fluoride-sensitive serine protease [31]. Similar to these results, it has been proposed that IRE1 signalling affects cell fate during ER stress [32]. In that report, the authors found that the time course of the activation of the UPR branch of IRE1, ATF6 and PERK differed in response to ER stress. They observed that IRE1 activity was quickly attenuated despite the persistence of ER stress, whereas the attenuation of ATF6 and PERK activity were delayed. On the other hand, when IRE1 activity was sustained artificially, cell survival was enhanced, suggesting a link between the duration of UPR branch signalling and cell fate under ER stress. Overall, it is important to analyse further the mechanisms that determine whether a cell lives or dies in response to ER stress.

### ER STRESS AND NEURODEGENERATIVE DISEASES

#### Alzheimer’s disease

Alzheimer’s disease is characterized by a progressive decline of cognitive functions [33]. Many findings suggest that one of its major causes is an accumulation of amyloid β-peptide in cerebral neuritic plaques. In addition, apoptosis is observed in the affected brain. Interestingly, amyloid β-peptide-mediated neuronal cell death (apoptosis) was reported to be mediated through the ER-specific activation of caspase 12 in mice [34]. Thus caspase 12 is suggested to be involved in Alzheimer’s disease; however, a subsequent analysis of human caspase 12 revealed deleterious mutations resulting in the production of a premature form [35]. From these observations, the authors concluded that caspase 12 is not involved in Alzheimer’s disease. On the other hand, caspase 12 polymorphisms have been reported in human subjects, and caspase 12 has been suggested to be involved in immune functions [36,37]. It was found that a longer caspase 12 variant led to less cytokine production than the shorter form in response to a bacterial component, lipopolysaccharide. Furthermore, preliminary studies have indicated that there is no correlation between the longer and shorter forms of caspase 12 in patients with Alzheimer’s disease [36]. Thus these observations raise the possibility that caspase 12 is not involved in the disease in humans. Therefore what is the mediator of the ER-stress-induced apoptosis observed in patients with Alzheimer’s disease? Hitomi et al. [38] reported that caspase 4 is involved in amyloid β- and ER-stress-induced cell death in humans. They found that caspase 4 is activated by amyloid β or ER stress and that a reduction in caspase 4 by RNAi (RNA interference) decreased ER-stress-induced cell death. Thus it is possible that caspase 4 is involved in
ER-stress-induced cell death observed in patients with Alzheimer’s disease.

Homocysteine is formed upon the demethylation of methionine, and an elevated level of homocysteine is associated with Alzheimer’s disease [39]. Interestingly, homocysteine induces ER stress [40–42], and HERP (homocysteine-induced ER-stress-responsive protein) [43] has been shown to enhance presenilin-mediated amyloid β production [44].

Overall, these observations suggest that ER stress is involved in Alzheimer’s disease; however, more studies are needed to fully understand the significance of ER stress in the disease.

**Parkinson’s disease**

Parkinson’s disease is a neurodegenerative disorder involving the selective loss of dopaminergic neurons in the substantia nigra pars compacta as well as other regions of the brain. The disease is characterized by progressive motor disturbances such as tremors, akinesia and rigidity. An analysis using post-mortem samples of brain tissue from patients with Parkinson’s disease has revealed the activation of the UPR, suggesting the involvement of ER stress [45].

Studies of the familial type of Parkinson’s disease have led to the discovery of genes responsible for the disease. For example, AR-JP (autosomal recessive juvenile parkinsonism) has been reported to result from mutations of PARK2 (encoding Parkin) [46]. Subsequent analysis revealed that Parkin is a RING-type E3 ubiquitin-protein ligase, and that its overexpression suppressed ER-stress-induced dopaminergic cell death [47]. Furthermore, a putative G-protein-coupled integral membrane polypeptide, named the Pael-R (Parkin-associated endothelin receptor-like receptor), has been reported to be a substrate of Parkin, and the accumulation of Pael-R reportedly leads to dopaminergic neuronal death in AR-JP [48]. In addition, a mutation in SNCA (encoding α-synuclein) has been identified in patients with Parkinson’s disease [49]. The mutant type of α-synuclein decreases proteasome activity, which leads to cell death [50,51]. Furthermore, the A53T mutation of α-synuclein increased ER stress in neuronal cells [52].

These observations suggest that ER stress is involved in the familial type of Parkinson’s disease.

The causes of sporadic Parkinson’s disease are not well understood either. Interestingly, 6-OHDA (6-hydroxydopamine), MPP+ (1-methyl-4-phenylpyridinium) and rotenone, widely used to generate models of Parkinson’s disease, have been shown to induce ER stress in neuronal cells [53,54]. On the other hand, dopamine itself has been suggested to play a role in sporadic Parkinson’s disease, and exposure to dopamine leads to an increase in ER stress proteins prior to cell death [55].

PDI (protein disulfide-isomerase) is an ER-localized protein involved in the formation of disulfide bonds to yield the native forms of proteins [56,57]. As it is located in the ER and its expression is up-regulated in response to ER stressors, such as tunicamycin (an inhibitor of N-glycosylation) and A23187 (a calcium ionophore), PDI is involved in ER stress [58]. S-nitrosylated PDI has been suggested to be involved in protein misfolding and neurodegeneration [59]. It was found that the S-nitrosylation of PDI results in inhibition of its enzymic activity. Importantly, PDI was S-nitrosylated in the brains of patients with sporadic Parkinson’s and Alzheimer’s diseases. Overall, the authors concluded that PDI would prevent neurotoxicity associated with ER stress and protein misfolding, but NO would block this protective effect in neurodegenerative disorders through the S-nitrosylation of PDI. The possibility that the S-nitrosylation of PDI is involved in ER stress and neurodegenerative diseases should be studied further.

**ER STRESS AND CANCER**

Conditions that induce ER stress, such as hypoxia, nutrient deprivation and changes in pH (acidosis), are frequently encountered in tumour cells [60]. An altered UPR has been reported in several tumour cells, including gastric tumour [61], hepatocellular carcinoma [62] and breast cancer [63] cells. In addition, VEGF (vascular endothelial growth factor), a pro-angiogenic factor, has been shown to be up-regulated through ATF4 during ER stress [64]. Homocysteine- or DTT (dithiothreitol)-induced ER stress increased VEGF at the mRNA level through ATF4 in the retinal pigment epithelial cell line ARPE-19. Furthermore, VEGF was shown to be secreted in response to ER stress [65]. These results suggest that ER stress is involved in cancer; however, as ER stress activates both cell survival and apoptotic pathways, it is necessary to distinguish which branch of the UPR is involved in cancer. Interestingly, XBPI and GRP78 have been shown to be involved in tumour progression [66,67], which suggests that some types of the UPR promote tumorigenesis. HSP90 (heat-shock protein 90) is a molecular chaperone involved in the conformational maturation of proteins, such as mutated p53, Raf-1, Akt, Bcr-Abl and ErbB2, and previous studies have suggested that agents that inhibit HSP90 have anticancer properties [68,69]. Geldanamycin is a benzoquinone ansamycin which binds to and inhibits HSP90 activity [70,71]. Interestingly, Hendershot and co-workers [72] have found that geldanamycin up-regulates the expression of ER chaperones and CHOP, and we have found that geldanamycin induces CHOP expression through a 4-(2-aminoethyl)-benzenesulfonyl fluoride-responsive serine protease [73]. Moreover, HSP90 associates with PERK and IRE1α, ER-resident transmembrane protein kinases [74]. Thus it is suggested...
that HSP90 is involved in ER stress. Furthermore, these observations provide a mechanistic insight into cancer, i.e. the possible involvement of ER stress.

**ER STRESS AND OBESITY (DIABETES)**

Increasing evidence has suggested that obesity is associated with physiological changes, such as Type 2 diabetes, cardiovascular disease and hypertension. However, the molecular mechanism of obesity is not well understood. To identify novel genes involved in obesity, Friedman and co-workers [75] identified the hormone ‘leptin’. Leptin is an important circulating signal for repressing food intake and body weight through its actions in the brain [75–79]. Leptin activates the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) tyrosine kinases through the Ob-Rb leptin receptor [80–82]. Leptin receptors (Ob-R) are found in many tissues in several alternatively spliced forms [81,83–85], and STAT3 protein in the hypothalamus and brain stem [86,87]. As leptin represses food intake and enhances energy expenditure, it was initially suspected to be useful in treating obesity [88]; however, although a high-fat diet evoked a sustained increase in circulating levels of leptin in mice, the animals did not show a decrease in food intake [89]. Furthermore, the effect of leptin therapy in obese patients was modest [90], and most forms of obesity are unresponsive to circulating levels of leptin. These results led to the notion that ‘leptin resistance’ was a cause of obesity. Thus elucidating the mechanisms responsible for ‘leptin resistance’ may be beneficial for treating obesity. Recently, we found that one of the mechanisms of leptin resistance is mediated through ER stress [42]. We observed that ER-stress-inducing reagents inhibited the leptin-induced phosphorylation of STAT3 (Figure 3). It has been reported that SOCS3 (suppressor of cytokine signalling 3) [91,92] or PTP1B (protein tyrosine phosphatase 1B) [93,94] are involved in leptin resistance. We revealed that ER stress-induced leptin resistance would be mediated through PTP1B but not through SOCS3 [42]. Moreover, we have found that homocysteine, which induces ER stress [41,43], evoked leptin resistance both in vitro and in vivo [42]. Importantly, a high-fat diet (which induces obesity) has been reported to induce ER stress in the hypothalamus, as evaluated by PERK phosphorylation [95]. Thus these results raise the possibility that ER stress is linked to leptin resistance, which results in obesity (Figure 4); however, further analysis is necessary to test this possibility.

Interestingly, Özcan et al. [96] found that obesity causes ER stress and this, in turn, leads to insulin resistance and Type 2 diabetes. They observed that Xhp1-deficient mice developed insulin resistance. These results suggest that ER stress is a key factor involved in both obesity and diabetes. Regarding the involvement of
diabetes in ER stress, several reports have been published. Eif2ak3 (PERK)-deficient mice have been shown to have a dysfunction in the exocrine pancreas, resulting in diabetes [97]. Furthermore, EIF2AK3 gene mutations have been observed in patients with Wolcott–Rallison syndrome, an autosomal-recessive disorder characterized by insulin-dependent diabetes at a young age [98]. Moreover, hyperglycaemia in the diabetic Akita mouse was found to be accompanied by CHOP expression and the apoptosis of $\beta$-cells, and targeted disruption of the Ddit3 (CHOP) gene delayed the onset of diabetes in this model [99]. In addition, the deletion of CHOP has been shown to reduce oxidative stress, improve $\beta$-cell function and promote cell survival in multiple mouse models of diabetes [100]. These results suggest that ER stress is involved in diabetes and that several ER-stress-related genes are involved in these processes.

**THERAPEUTIC POTENTIAL FOR ER-STRESS-RELATED DISEASES**

As ER stress is involved in several diseases, a drug that targets it would be useful. Recently, Kudo et al. [101] identified BIX (BiP (immunoglobulin heavy-chain-binding protein) inducer X), which induced ER-mediated expression of the chaperone BiP (GRP78). They found that BIX reduced ER-stress-induced neuroblastoma cell death. Moreover, BIX reduced the area of infarction due to focal cerebral ischaemia in mice. The protective effect of BIX is due to the induction of GRP78 expression, which may increase the ER folding capacity.

Inhibition of proteasome activity would result in the accumulation of ERAD substrates in the ER. Indeed, proteasome inhibitors have been shown to induce ER stress in myeloma cells [102]. Bortezomib (PS-341) is a new class of anticancer drug that selectively inhibits 26S proteasome activity [103]. Inhibition of the proteasome with bortezomib induces ER stress [104,105], which would be crucial to its activity in human cancer therapy.

ER stress promotes the phosphorylation of eIF2$\alpha$, which results in translational repression. Interestingly, salubrinal, a selective inhibitor of the dephosphorylation of eIF2$\alpha$ (which inhibits GADD34 phosphatase activity), has been reported to protect PC12 neuronal cells from ER stress [106]. Similarly, salubrinal has been shown to protect against cell death induced by the glutamate receptor agonist kainic acid (ER stress) [107] or the A53T $\alpha$-synuclein mutant [52]. Thus salubrinal-induced eIF2$\alpha$ phosphorylation is expected to play a protective role against ER stress. However, inconsistent observations have been reported regarding the physiological role of eIF2$\alpha$ in regulating cell viability. PERK-mediated phosphorylation of eIF2$\alpha$ would play a cytoprotective role [97,108], and the phosphorylation of eIF2$\alpha$ has been suggested to promote $\beta$-cell survival [109]. In addition, an
ATF4-mediated integrated stress response initiated by the phosphorylation of eIF2α has been shown to protect cells against oxidative stress [110]; however, PKR-mediated phosphorylation of eIF2α has been shown to promote apoptosis [111, 112]. Furthermore, the phosphorylation of eIF2α enhances apoptosis in response to inhibition of the proteasome [113]. Regarding the pharmacological effect of salubrinal on β-cells, it potentiated fatty-acid-induced ER stress and apoptosis [114]. This result contrasts with its effect on PC12 neuronal cells, where it inhibited cell death [106]. At present, the reasons for these discrepancies concerning the physiological role of eIF2α and the pharmacological actions of salubrinal are not well understood. ER stress activates a negative-feedback pathway to decrease eIF2α phosphorylation [115]. Interestingly, activation of the GLP1 (glucagon-like peptide 1) receptor has been shown to accelerate the recovery from ER-stress-mediated translational repression and improve β-cell function following the induction of ER stress [116]. Thus it is possible that the temporary phosphorylation of eIF2α would inhibit the ER-stress-induced accumulation of unfolded or misfolded proteins. However, in the late phase of ER stress (when unfolded proteins are cleared), cells would escape from apoptosis by inhibiting the phosphorylation of eIF2α. It is possible that the magnitude and duration of the phosphorylation affect cell viability. In addition, differences would exist due to the cell type or tissues examined. It is important to clarify these issues in future analyses. Furthermore, special attention should be paid to the discovery/use of a new drug which can target eIF2α.

Small molecules known as chemical chaperones have been shown to inhibit the aggregation of proteins. Such a drug would be effective in ameliorating ER-stress-induced protein aggregation. Indeed, Özcan et al. [117] have reported that chemical chaperones, such as 4-PBA (4-phenyl butyric acid) and TUDCA (taurine-conjugated Ursodeoxycholic acid), reduced ER stress and restored glucose homeostasis in a mouse model of Type 2 diabetes. Furthermore, we found that 4-PBA reduced ER-stress-induced leptin resistance [42]. Moreover, Zhang et al. [95] have reported that TUDCA reduced high-fat diet-induced ER stress in the hypothalamus. These studies have shed light on previously unknown mechanisms of obesity and diabetes, and suggest the usefulness of chemical chaperones for obesity (leptin-resistance) and diabetes (insulin-resistance) associated with ER stress.

CONCLUSIONS

In recent years, knowledge regarding the mechanisms of the UPR and ER-stress-related diseases has rapidly accumulated. However, many unanswered questions still remain. Investigations of the mechanisms and pharmacological actions of ER stress are important in providing new mechanistic insights and developing novel targets for ER-stress-related diseases. We believe that a more complete understanding of ER stress will open up promising avenues for the development of clinically useful drugs.

While this paper was under review, an important article entitled 'Endoplasmic reticulum stress plays a central role in development of leptin resistance' [118] was published. We believe that its findings will support the hypothesis that ER stress is involved in 'leptin resistance' [42, 95].

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