Role of Endoplasmic Reticulum in Non-communicable Diseases

ABSTRACT

Endoplasmic reticulum (ER) is a large membrane-bound organelle that provides high fidelity quality control in protein synthesis, maturation and transport. There are two distinct types of ER that differ in structure and function: smooth ER and rough ER. The complex function of the ER can be significantly influenced by various factors both inside the cell and in its microenvironment. Disturbances in ER protein folding capacity result in accumulation of misfolded proteins in the ER lumen and in activation of ER stress. The unfolded protein response normally has pro-survival functions and protects cells by providing the reestablishment of protein processing and cellular homeostasis. However, prolonged and excessive ER stress results in activation of apoptotic pathways. Therefore, the persistent protein misfolding initiates apoptotic cascades that are now known to play fundamental roles in the pathogenesis of multiple human diseases including diabetes, atherosclerosis and neurodegenerative diseases. With the improved understanding of the underlying molecular mechanisms, therapeutic interventions that target the ER stress response would be potential strategies to treat various diseases driven by prolonged ER stress.

KEYWORDS ER stress, unfolded protein response (UPR), neurodegenerative disease, liver disease, atherosclerosis, diabetes, cancer

INTRODUCTION

Endoplasmic reticulum structure and function

The endoplasmic reticulum (ER) is a large membrane-bound organelle that functions to support the biosynthesis of membrane and secretory proteins, which account for approximately one-third of all proteins in a eukaryotic cell. It consists of interconnected, branching membranous tubules, vesicles and cisternae that provide a distinct sub-cellular compartment with different functions. The ER has a central role in producing, processing and transporting biochemical compounds for use inside and outside of the cell. Its membrane is the site of production of all the transmembrane proteins and lipids for most of the cells. The ER is a specialised organelle that has crucial roles in cell homeostasis and survival, which include protein folding, lipid biosynthesis and calcium storage and redox homeostasis.

There are two distinct types of ER that differ in structure and function: smooth ER and rough ER. The rough ER is so named because the cytoplasmic surface is covered with ribosomes. The smooth ER appears smooth since its cytoplasmic surface lacks ribosomes. The lumen of the ER is the major site for proper protein folding and contains molecular chaperones and folding enzymes including glucose-regulated protein 78 (GRP78) [binding immunoglobulin protein (BiP)], Grp94, protein disulfide isomerase (PDI), calnexin and calreticulin. Only properly folded proteins are exported to the Golgi organelle, while incompletely folded proteins are retained in the ER to complete the folding process or are delivered to the cytosol to undergo ER-associated degradation.

Under physiologic conditions, there is an equilibrium between ER protein load and folding capacity. The ER contains a quality control mechanism called chaperones. These special proteins attach themselves to newly synthesised proteins and assist them in folding into their native conformations. Chaperones also keep misfolded proteins in the ER to be broken down.
Types of endoplasmic reticulum

There are two distinct forms of ER, rough and smooth ER that differ in structure and function. Rough ER is studded with ribosomes on its outer surface and plays an important role in protein synthesis, secretion, folding, posttranslational modification and transport. Rough ER is particularly abundant in secretory cells, such as antibody-producing plasma cells and insulin-secreting β cells. A large fraction of the cytosol is occupied by rough ER. Sarcoplasmic reticulum is a specialised form of the ER in muscle cells and functions to sequester and release large amounts of calcium to effect muscle contractions and relaxation.

Smooth ER lacks ribosomes and it is not primarily involved in protein synthesis, but plays a central role in lipid synthesis, cholesterol synthesis, steroid hormones synthesis and detoxification of endogenous and exogenous substances, metabolism of carbohydrates and regulation of calcium homeostasis. In the liver also, enzymes in the smooth ER metabolise and detoxify hydrophobic chemicals, such as drugs and carcinogens and direct them for secretion from the body.

ENDOPLASMIC RETICULUM STRESS

The ER plays an important role in the quality control of proteins by regulating their synthesis, folding and trafficking. ER homeostasis depends on a balance between protein synthesis and folding. ER is a highly dynamic organelle, and its complex functions can be significantly influenced by many of the parameters both inside the cell and in its microenvironment. For example, the availability of oxygen (hypoxia) or glucose (hypoglycemia), hyperthermia, acidosis, depletion of calcium levels, mutations, insufficient chaperone capacity or cellular energy to promote chaperone–protein interaction and other factors can impact and disturb proper functioning of the ER, resulting in ER stress and impacting protein folding in the lumen of the ER.

Pharmacological agents also interfere with protein secondary modifications or calcium homeostasis can also induce the accumulation of unfolded proteins (Fig. 1). These unfolded proteins continue to burden the ER; the cell will undergo proteotoxicity and subsequent cell death. However, the cell has an integrated stress response programme specific to conditions resulting in unfolded protein accumulation known as the unfolded protein response (UPR). The ER stress factors are depicted in Fig. 1.

Unfolded protein response

Accumulation of misfolded proteins in the ER lumen causes ER stress and activation of a signal response termed the UPR. The UPR consists of a group of ER protein who work closely together. Those proteins act as molecular sensors and regulators of the UPR. The aim of the UPR is to alleviate ER stress and restore ER homeostasis and initiate a cascade of events leading to:

- A transient decrease in overall translation, reducing ER folding load
- An increase in the amount of ER chaperones to augment the folding capacity of the ER
- An increase in translation of genes associated with ER-associated degradation, to increase the number of irreversibly misfolded proteins that are degraded
- If the stress is chronic and too severe for the cell to recover, the UPR triggers apoptosis

There are three ER transmembrane proteins transduce UPR signaling: double stranded RNA-activated kinase (PKR)-like ER kinase (PERK), inositol requiring ER-to-nucleus signal kinase (inositol requiring enzyme 1 (IRE1)) and activating transcription factor 6 (ATF6). All three of these stress sensors associate with GRP78/BiP in their inactive states. When ER homeostasis is perturbed, GRP78 is thought to preferentially interact with the unfolded/misfolded proteins, thus dissociating from the UPR transducers. This hypothesis is
supported by evidence that GRP78 is released from all three transducers with the accumulation of misfolded proteins. When unfolded proteins accumulate in the ER lumen, however, they are dissociated from GRP78, activated by dimerization, phosphorylation or translocation to the Golgi, and then induce signals to attenuate translation or up regulate adaptive UPR target gene expression.

Another theory stipulates that the luminal domain of IRE1 may be capable of directly binding unfolded proteins, which may change its quaternary structure and induce autophosphorylation and UPR initiation. ATF6 released from GRP78 is trafficked to the Golgi where its cytosolic fragment is cleaved and migrates to the nucleus to further regulate transcription of UPR-responsive genes, including chaperones. Finally, if the stress is chronic and severe, the UPR signals can result in cell apoptosis. UPR exerts its adaptive effects via three arms of action as shown in the Fig. 2.

The three ER-resident transducers induce the ER chaperones to enhance folding capacity and activate the pathway for ER-associated protein degradation (ERAD) to reduce the accumulation of unfolded proteins. The UPR pathway maintains ER homeostasis to ensure cell survival. When severe ER stress results in excessive or prolonged UPR activation, cells are unable to resolve the protein-folding defect or restore ER homeostasis via the adaptive UPR pathway. In these circumstances, the pro-apoptotic UPR mediated by CHOP (CCAAT/enhancer binding protein homologous protein) or caspase 12 is induced to ensure cell death.

Fig. 2  Pathways of unfolded protein response.
IRE-1α pathway

The IRE-1α protein is a type one transmembrane protein approximately 100 kDa weight and has two domains; serine/threonine kinase domain and an endoribonuclease domain. IRE1 regulates the transcriptional induction of genes encoding ERAD components. The dissociation of the ER sensory protein BiP causes IRE-1α to oligomerise. This oligomerisation activates IRE-1α mRNAase domain which is located in the cytosolic side of the ER membrane. IRE-1α mRNAase splice the mRNA of X-box binding protein 1 (XBP1)5,12. This spliced mRNA is translated and the resulting protein translocates to the nucleus to induce an increased rate of expression of ER chaperone proteins, ERAD proteins, lipid synthesis proteins and ER biogenesis proteins. IRE1 signaling and XBP1 splicing are particularly important in highly secretory cells where the protein folding machinery is continuously engaged with a high amount of nascent proteins13.

In addition to splicing a number of mRNAs, a second function of IRE1 is to activate a signaling cascade involved in controlling cell fate with regard to cell death. The activated IRE1 recruits tumour necrosis factor receptor (TNFR)-associated factor 2 (TRAF2), which results in the downstream activation of apoptosis signal-regulated kinase 1 (ASK1) and c-Jun N-terminal kinase (JNK)14. The JNK activity during prolonged ER stress inhibits anti-apoptotic members of the BCL-2 (B-cell lymphoma 2) family of proteins. On the other hand, JNK phosphorylates and activates pro-apoptotic BH3-only proteins, such as BID (BH3 interacting domain death agonist) and Bim (BCL-2-interacting mediator of cell death). Combined, these events lead to oligomerization of B-cell leukemia/lymphoma (BCL-2)-associated X protein and BCL2 homologous antagonist killer, resulting in permeabilization of the outer mitochondrial membrane and execution of the intrinsic apoptotic process15.

ATF6 pathway

The second arm of the UPR is the ATF6 protein. In response to ER stress, ATF6 is released from BiP and is translocated to the Golgi apparatus for cleavage by resident proteins S1P (site 1 protease) and S2P (site 2 protease). The cleaved ATF6 is released into the cytosol to enter the nucleus and regulate gene expression. ATF6 pathway activation results in the up regulation of the ER chaperone proteins7.

Upon translocation to the nucleus, ATF6 stimulates expression of a number of genes whose protein products contribute to protein folding, protein secretion and ERAD, thereby supporting the cell’s effort to cope with ER stress and accumulated misfolded/unfolded proteins16. For example, ATF6-regulated genes include GRP78 and GRP94, PDI, XBP1 and CHOP. Besides ATF6, a number of other ER-transmembrane basic leucine zipper domain protein transcription factors have been described in recent years that are also regulated by intramembrane proteolysis.

PERK pathway

PERK is the third arm protein of the UPR. PERK is a sensor molecule residing on the ER membrane and is responsible for the most immediate response to ER stress, attenuation of overall translation17. The molecular structure of PERK is similar to that of IRE1, but the cytosolic domain of the PERK contains only the kinase domain. In the absence of ER stress, PERK is an inactive monomer, whereas PERK becomes an active oligomer upon ER stress, like IRE1. The mechanism of activation is similar to that of IRE-1α as both possess a serine/threonine kinase domain protruding into the cytoplasm. Once BiP dissociates, PERK is activated by oligomerisation and autophosphorylation.

This active form of PERK causes the phosphorylation of the α-subunit of eukaryotic translational initiation factor 2 (eIF2α) protein in the cytoplasm. This phosphorylation inactivates eIF2α which results in attenuation of global proteins translation. Thus decreasing the protein folding load on the ER chaperon proteins5,7.

Besides eIF2α, nuclear factor-erythroid 2-related factor 2 (Nrf2) represents a second immediate substrate for phosphorylation by PERK. Upon activation, this basic leucine zipper transcription factor migrates to the nucleus where it activates genes encoding antioxidant proteins and detoxifying enzymes. Because ER stress may involve the accumulation of reactive oxygen species (ROS), thereby promoting a state of oxidative stress, Nrf2 plays a critical role in fighting such perturbations in redox homeostasis. The importance of this defensive role of Nrf2 has been further emphasised by findings that Nrf2-deficient cells displayed greatly increased cell death following exposure to ER stress18.

ER STRESS AND DISEASES

Dysfunction of the UPR or prolonged ER stress disturbs ER homeostasis, leading to many human diseases such as neurodegenerative disease, metabolic disease, inflammatory disease and diabetes mellitus, atherosclerosis, liver diseases and cancer (Table 1).

ER stress and neurodegenerative disease

ER stress and the UPR signaling are closely linked with many neurodegenerative diseases, including Parkinson’s disease (PD), Huntington’s disease (HD) and Alzheimer’s disease (AD). In a large number of neurodegenerative diseases, the accumulation of misfolded proteins is a common and toxic feature such proteins includes amyloid β (Aβ), which is produced by processing of amyloid precursor protein (APP) in AD, polyglutamine is a product of CAG repeat of nucleotide expressions in poly Q disease such as HD and the mutant form of superoxide dismutase 1 (SOD1), which is found in familial amyotrophic lateral sclerosis (ALS)19.
Role of ER in non-communicable diseases

Alzheimer’s disease

AD is the most common form of neurodegenerative disease, resulting in progressive decline of intellectual and social abilities and productivity. AD is accompanied by a tremendous amount of cell injury and neuron loss in various parts of the brain, including the hippocampus and neurocortex. AD is a disorder characterised by formation of insoluble fibrous protein aggregates in the brain. AD is caused by accumulation of β-amyloid and hyper-phosphorylated Tau protein deposition in intracellular neurofibrillary tangles (NFTs) (i.e. induction of ER stress). AD patients suggest that the PERK-eIf2α pathway is hyperactive, which implying that ER stress is activated.

Parkinson’s disease

PD is second neurodegenerative disorders next to AD. This disease has been characterised by selective loss of dopaminergic neurons and the presence of Parkin, α-synuclein and ubiquitin accumulation of protein aggregates (Levy bodies, LBs) in a distinct brain region. Patients with juvenile-onset PD show hereditary mutations in the ER-associated E3 ubiquitin ligase Parkin. This Parkin has also been closely associated with ER stress-induced cell death. Accumulation of misfolded proteins during PD induces ER stress thereby upregulating UPR. ER stress can lead to oxidative damage by inducing the function of oxidative protein folding enzymes such as endoplasmic reticulum oxidoreductin-1. This enzyme participates in protein disulfide bond formation during protein refolding in the ER in order to relieve ER stress. In addition, HD, prion-based diseases, polyglutamine disease, transmissible spongiform encephalopathies, amyotrophic lateral sclerosis and neuronal storage disease are other neurodegenerative disorders in which ER stress plays a role in their pathophysiology.

ER stress and metabolic disease

The ER is an important role for protein quality control but also for lipid and glucose metabolism. Perturbations

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in ER homeostasis can result in the dysregulation of lipid and glucose metabolism in the liver and adipose tissue, leading to a number of metabolic diseases such as hepatic steatosis, diabetes and dyslipidemia. ER stress is also known to contribute to lipogenesis and inactive lipoprotein secretion\textsuperscript{21}.

**Diabetes**

ER stress plays a role in the pathogenesis of diabetes, contributing to pancreatic β-cell loss and insulin resistance\textsuperscript{22}. The β cells have a function in secreting large amounts of insulin and other glycoprotein, so they possess an extremely well-developed ER. This secretory function of β cells may explain why mice lacking PERK are likely to have diabetes, undergoing apoptosis of their β cells and suffering from progressive hyperglycemia with ageing\textsuperscript{23}. In Wolcott-Rallison Syndrome, PERK gene mutations occur where the ER cannot fold new proteins entering in it, leading to the accumulation of misfolded proteins, excessive stress generation and finally to cell death\textsuperscript{24}.

Obesity induces T2D, a metabolic disorder characterised by a combination of insulin resistance, dysregulated hepatic glucose production and inadequate insulin secretion by pancreatic β cells. Several molecular, genetic and biochemical factors cause the loss of metabolic homeostasis in type 2 diabetes. At the molecular level, it involves perturbations in insulin signaling, such as reduced insulin receptor function and reduced post-insulin receptor phosphorylation steps. ER stress parameters such as phosphorylation of PERK and IRE1 are increased in the liver and adipose tissues of T2D animals\textsuperscript{25,26}.

ER stress parameters including Grp78, XBP1 spliced, phospho-eIF2α and phospho-JNK are increased in the liver and adipose tissues of obese insulin-resistant non-diabetic humans and these parameters are significantly reduced after weight loss\textsuperscript{27}.

**ER stress and inflammatory disease**

Numerous recent studies have revealed that the UPR pathways contribute inflammatory signaling to assist in the recovery from tissue damage. In inflammatory diseases, such as inflammatory bowel disease, the ER stress-induced inflammation exacerbates disease progression. Induction of UPR, ROS production, Ca\textsuperscript{2+} release from the ER as well as activation of nuclear factor κ light-chain enhancer of activated B cells (NF-kB) and of JNK can additionally trigger the inflammation\textsuperscript{28}.

NF-kB is involved in the regulation of genes that are responsible for stress and growth and can regulate both pro-apoptotic and antiapoptotic genes, depending on the stimulus. Under prolonged ER stress, NF-kB initiates apoptosis, thereby shifting the outcome of the compensatory mechanism from an adaptive one to a maladaptive one\textsuperscript{29}.

**ER stress and cardiovascular disease**

The role of ER stress in heart diseases is quite well known. Pressure overload by transverse aortic constriction induces the expression of ER chaperones and ER stress in cardiomyocytes\textsuperscript{30}. Since cellular Ca\textsuperscript{2+} homeostasis is also crucial for both ER and cardiomyocyte-specific functions, ER stress events and cardiovascular diseases are very closely related.

**ER stress and heart disease**

ER stress is involved in heart-related diseases. Pressure overload by transverse aortic constriction induces expression of ER chaperones and ER stress-induced apoptosis of cardiac myocytes, leading to cardiac hypertrophy. ER chaperones, especially GRP78, underline the phenomenon of preconditioning in the heart, in which exposure to a transient episode of brief ischemia provides subsequent protection from a sustained ischemic challenge. Reduced blood flow resulting from arterial occlusion or cardiac arrest is closely associated with tissue hypoxia and hypoglycemia that cause protein misfolding and ER stress\textsuperscript{31}.

**ER stress and atherosclerosis**

Atherosclerosis is a disease that is associated with arteries harden and narrow because of the accumulation of fatty substances, cholesterol, cellular waste, Ca\textsuperscript{2+} and other substances in the arterial inner lining, leading to heart attack or stroke\textsuperscript{32}.

Elevated triglycerides and hypercholesterolemia induces ER stress in vascular cells. UPR is induced in endothelial cells by oxidised lipids, and UPR components ATF4 and XBP1 have been involved in ER stress-induced cytokine generation through these vascular cells. Similarly, addition of macrophages with cholesterol was shown to induce ER stress, enhancing expression of cytokines in presence of CHOP induction, which further implicates the UPR in the atherosclerosis mechanism. Abnormal deposition of free cholesterol in coronary arteries is toxic to many different vascular cell types, including macrophages, endothelial cells and smooth muscle cells. This condition leads to apoptosis of vascular cells, which is believed to promote atherosclerosis\textsuperscript{33}.

**ER stress and cancer**

The link between the UPR and cancers has been amply established as the UPR is highly activated in a number of cancers. Under regular homeostatic conditions, the majority of normal cells do not experience ER stress. The expression of GRP78 and other glucose-regulated proteins are induced during tumour growth. During tumourigenesis, the high proliferation index of cancer cells requires increased activities of ER protein folding, assembly and transport, a condition that can induce physiological ER stress\textsuperscript{34}. Following initiation of malignancy, poor
vascularisation in tumours results in hypoxia, hypoglycemia and acidosis. All these processes are strong inducers of UPR pathways. In addition, some cancer cells express mutant proteins that cannot be correctly folded and activate UPR. Unlike normal cells, most cancer cells express chronically elevated baseline ER stress levels, as indicated by permanently increased expression of GRP78.34

One of the pro-survival functions of GRP78 is to alleviate the transcription of pro-apoptotic CHOP-mediated pathways, which is achieved via binding of GRP78 and subsequent inactivation of the ER transmembrane signaling components PERK, IRE1 and ATF6. However, during conditions of prolonged stress, GRP78 remains bound to misfolded proteins in the lumen of the ER in order to repair them, and therefore permanently dissociated from the UPR proteins that continue to stimulate expression of CHOP. As a consequence, CHOP expression remains increased under these conditions, thus leading to apoptosis.35

Elevated Grp78 level has been reported to correlate well with higher pathologic grade, recurrence rate and poor prognosis in patients with breast, liver, prostate, colon and gastric cancers and suppression of GRP78 inhibited the proliferation of cancer cells.46

ER STRESS AND THERAPEUTIC IMPLICATIONS

A large number of studies have focused on therapeutic approaches utilizing chemical chaperones to stabilise misfolded proteins, improve the ER folding capacity and suppress ER retention of these misfolded proteins. Chemical or pharmaceutical chaperones are a group of low-molecular weight compounds that have been proposed to increase ER folding capacity by facilitating proper folding and decreasing the accumulation and aggregation of misfolded proteins in the ER lumen.37,38 For example, in mouse models, 4-phenyl butyrate (4-PBA) and taurine-conjugated deoxycholic acid (TUDCA) have been shown to provide benefit for numerous ER stress-related diseases including T2D, atherosclerosis and leptin resistance. However, their precise ER stress-relieving properties remain unknown.

Increases the expression of ER chaperones such as Grp78 and Grp94 and has beneficial effects in vitro models of neurodegenerative diseases.39 In addition, a recent report showed that a specific inducer of Grp78/ BiP called BiP inducer X (BIX) has beneficial effects in focal ischemia-stroke mouse models, further providing evidence that approaches aimed at enhancing the protective arms of the UPR may be beneficial in ER stress-related disorders and additional studies are needed to determine the mechanisms responsible for this improvement.

Several studies have focused on survival signaling in the UPR, such as signaling of the PERK-eIF2α pathway. For example, salubrinal is a compound that inhibits dephosphorylation of eIF2α, delays the recovery of protein translation and protects cells from ER stress. Salubrinal induces a marked eIF2α phosphorylation and inhibitory effects of free fatty acids on protein synthesis and insulin release. This selective activation of the PERK-eIF2α pathway, but not IRE1 and ATF6 pathway, leads to a marked induction of activating transcription factor 4 (ATF4) and CHOP, resulting in β-cell apoptosis.41 However, it is difficult to develop therapeutic approaches specifically targeting ER stress because UPR signaling exerts dual biological functions related to both survival and apoptosis.

Therapeutic induction of ER stress-induced apoptosis may be beneficial in killing cancer cells. As an example, inhibition of proteasome activity, which degrades misfolded proteins, induces ER stress in cancer cells. For example, bortezomib which is a selective proteasome inhibitor used for killing multiple myeloma cells and provides antitumour activity in the treatment of pancreatic cancer.42

CONCLUSION

A significant increase in our understanding of the role of ER stress in the regulation of cell homeostasis has been achieved. ER stress, considered as both a cause and consequence of metabolic disturbances, results in UPR activation. Under ER stress, cells recognise perturbations of ER homeostasis and direct the UPR signal to either survival or apoptosis pathways, depending on the intensity of ER stress. Survival pathways such ATP6, IRE1α-XPB1, PERK-eIF2α-ATF4 and ERAD restore the ER capacity through transcriptional activation of genes related to the refolding and maturation of misfolded proteins. However, prolonged or severe ER stress directs cell death through an apoptosis pathway such as IRE1-ASK1-JNK or PERK-eIF2α-ATF4-CHOP. In contrast, dysfunction of the UPR pathway or chronic ER stress, may contribute to the pathogenesis of numerous human diseases. Therefore, in future an understanding of the cause of protein misfolding, aggregation and genetic environmental susceptibility induced ER stress. In addition, new therapeutic agents must be carefully tested in appropriate mouse models to avoid possible adverse effects of ER stress-associated diseases.

REFERENCES