The Egyptian Journal of Medical Human Genetics 19 (2018) 59–68

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The Egyptian Journal of Medical Human Genetics

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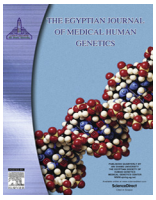

Review

The endoplasmic reticulum stress response in disease pathogenesis and pathophysiology

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ARTICLE INFO

Article history:
Received 5 June 2017
Accepted 2 July 2017
Available online 12 July 2017

Keywords:
Endoplasmic reticulum
ER stress response
Hormesis
Unfolded protein response
ER overload response

ABSTRACT

The minute experience of disease progression happens in the cell. Whereas recent researches have focused separately on disease, molecular mechanisms reveal the coincidence of pathways that provide guided benefit to biomedicine. Interestingly, taken-for-granted mechanisms like endoplasmic reticulum (ER) quality control or ion exchange and cell polarity indeed play major roles in epidemiologically relevant problems like viral infection, tumorigenesis and other chronic disorders. The ER synthesizes proteins destined for the nucleus and Golgi, as well as cell-surface receptors needed for cell-to-cell communication. This is therefore the target of viral infection in making the cell susceptible to receptor-mediated invasion, and is usually affected in tumor cells to promote cell insensitivity. Any aberrations therefore, such as protein unfolding, are acted upon by molecular chaperones and prevented from leaving the ER. These proteins are essential for cell survival, and intuitively the ER must activate stress responses to evade immediate cell dysfunction as the cell processes lag behind. This review will discuss mainly the ER and its role in the pathogenesis and pathophysiology of epidemiologically-relevant diseases, as well as updates on mechanisms related to the ER stress response.

Contents

1. Introduction

Disease begins and ends with the cell. Cellular homeostasis is of vital importance, and has been shown to progress to senescence and cell death should the protein machinery be consistently perturbed. However, the cell must not be thought of as passive. In the event of cellular stress, genes that promote tolerance and

Peer review under responsibility of Ain Shams University.
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http://dx.doi.org/10.1016/j.ejmhg.2017.07.004
1110-8630/

survival are upregulated, until the cell can no longer compete with such an extremity [1]. Since physiologic functions rely heavily on homeostasis, it is not surprising that other aberrations such as Ca^{2+} dysregulation, chronic inflammation, nutrient deficiency and inappropriate extracellular ionic strength all contribute and possibly induce stress in cells [2–4]. While there are manifold pathways that describe the role of homeostasis in pathogenesis, the endeavour of unifying published concepts to profoundly describe disease is of greater significance. In achieving a comprehensive understanding of a given disorder, it is important to recognize the multi-factorial and multi-faceted nature of cell functions. For instance, considering inflammation in the context of cell regulation would lead to the role of T cells in immunological tolerance at anatomic places where a pool of antigens are expected to be, such as in the digestive tract [5–7]. Likewise, stress-induced inflammation brought by cell necrosis even in the absence of a pathogen may be realized as plausible [8,9]. To this end, the review will highlight cross-talks between Ca^{2+} transport and the ER stress response, which will be related to the pathogenesis and pathophysiology of certain medical conditions.

2. The ER stress response

The endoplasmic reticulum (ER) regulates the flow of macromolecules such as lipids, proteins and carbohydrates needed in maintaining cell function. Accordingly, it is mandatory to maintain homeostasis [10], and in cases where it is not, the organelle initiates several pathways directed toward restoration, some of which are not yet well-elucidated.

In usual cases, the effect of perturbation is aberrant protein folding. Such mechanisms that the ER employs to regulate this unwanted process are both preventive and modulatory in nature. The ER recognizes peptides being newly synthesized through the signal recognition particle (SRP) which causes an arrest in elongation and resumes being directed to the translocon in what is called co-translational translocation [11,12]. Proper protein folding is ensured by chaperones such as calreticulin and membrane-bound calnexin as an orchestrated quality control point in the ER [13]. Inhibitors targeting vital points in the glycoprotein biosynthesis have been used to understand further the underlying mechanisms for ER function, some of which are tunicamycin, an *N*-glycosylation inhibitor; thapsigargin and 2,5-di-*t*-butyl-1,4-benzohydroquinone (BHQ), which inhibit the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), and castanospermine and 1-deoxynojirimycin for glucosidase I and II inhibition, among others [14]. Through these, it was found that persistently unfolded proteins are targeted for either ER-associated (ERAD) or autophagic degradation [15]. Intuitively, misfolding and degradation of proteins must be addressed if the cell is to survive.

3. Unfolded protein response (UPR)

The unfolded protein response is a well-known ER pathway against challenges of stress. In physiologic conditions, the dsRNA-activated protein kinase (PKR)-like ER kinase (PERK) is stabilized by heat shock protein 90 (HSP90) and immunoglobulin heavy chain binding protein (BIP); however, ER stress permits the release, dimerization and autophosphorylation of PERK, which then phosphorylates the eukaryotic initiation factor 2 (eIF2) complex at the Ser51 position leading to a cascade of events to attenuate protein synthesis. Phosphorylated eIF2 has a manifold greater affinity for GDP that would prevent re-initiation of translation due to lack of eIF2B-mediated GTP exchange for reformation of the eIF2-GTP-$tRNA_{met}$ complex [16,17]. In this event, attenuation of mRNA translation occurs with a concomitant upregulation of genes translating anti-stress proteins and amino acid transporters, such as the activating transcription factor 4 (ATF4). This protein interacts with the ER and upregulates ER stress response genes associated with both cell survival and apoptosis, with the matter of time in question (Fig. 1).

In persistent accumulation of errors, ATF4 upregulates the transcription of genes encoding C/EBP homologous protein (CHOP)/GADD153 that activates ER-mediated apoptosis [18,19], probably through repression of the B-cell lymphoma 2 (Bcl2) gene and sensitization of cells to the persistent stress [3,20]. These are followed by the upregulation of Bcl-2-like protein 11 (BIM) [21] that together with BH3-only proteins preferentially activate Bcl-2-associated X protein (BAX) to cause mitochondrial damage [22–24]. As to how ATF4 executes such a time-sensitive response, the PERK-dependent miR-211 inhibit the expression of CHOP until apoptosis is deemed necessary [25]. Further, it is important to acknowledge the short turnover of both CHOP and ATF4 – requiring the presence of chronic ER stress to activate the apoptotic signals [26].

When ER stress is activated, BIP dissociates from the inositol-requiring kinase 1 (IRE1) to permit IRE1 detection of protein misfolding [27,28], although BIP-independent detections have also been proposed [29]. Having both endoribonuclease (ERN) and serine-threonine kinase (STK) activities, the oligomerization at the ER membrane and autophosphorylation at S724 of IRE1 allows the ERN-mediated splicing and expression of X-box binding protein 1 (Xbp1) mRNA [10,30,31]. Xbp1 is a transcription factor that together with nuclear factor Y (NF-Y) upregulate chaperone and protein degradation genes for error fixation [32,33] while also upregulating $P58^{IPK}$ that binds to the kinase domain of PERK. Should the kinase domain of PERK be blocked, PERK activity would decrease – permitting the expectation that the protein load of ER would increase [34]. This downregulation of PERK activity has a duality: in events that stress is relieved this would cease attenuation of protein synthesis and homeostasis is achieved; however, in persistent ER stress, the PERK-dependent miR-211 would cease to attenuate CHOP expression which may eventually lead to further stress and apoptosis [35,36] (Fig. 1). This activity of IRE1 is therefore essential in the later phase of the UPR [34,37]. What is of interest to many diseases is the activity of IRE1α, which is present in every cell, and constitutes the most conserved UPR cascade found in eukaryotes – permitting *in vivo* studies to shed significant light on the ER stress response [10,38].

Definitively, the kinase domain of IRE1 serves pro-apoptotic functions in late-phase UPR. Its interactions with proteins lead to the activation of procaspase-12 and the apoptosis signal regulating kinase 1 (ASK1), eventually leading to c-Jun N-terminal kinase-mediated cell death [39–41]. However, Lin, Walter and Yen proposed that IRE1 also contributes directly to apoptosis by possible downregulation of other mRNAs committed to ensuring survival [10]. Nonetheless, consensus remains elusive.

4. ER overload response (EOR)

Interestingly, EOR is one among others that bridge the gap between the ER stress response and the regulation of Ca^{2+}. For it to occur, Ca^{2+} must be released from the ER followed by ROS production, both of which lead to the activation of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) [42]. It is far less studied than the UPR, but its action can apply from acute to chronic disease. In releasing Ca^{2+} stores from the ER lumen to the cytosol, ROS production eventually leads to the activation of NF-κB, which is a sequence-specific transcription factor that is a key point in cell proliferation, inflammation and hence cell survival [43,44] (Fig. 2A). Being a principal calcium storage and signalling

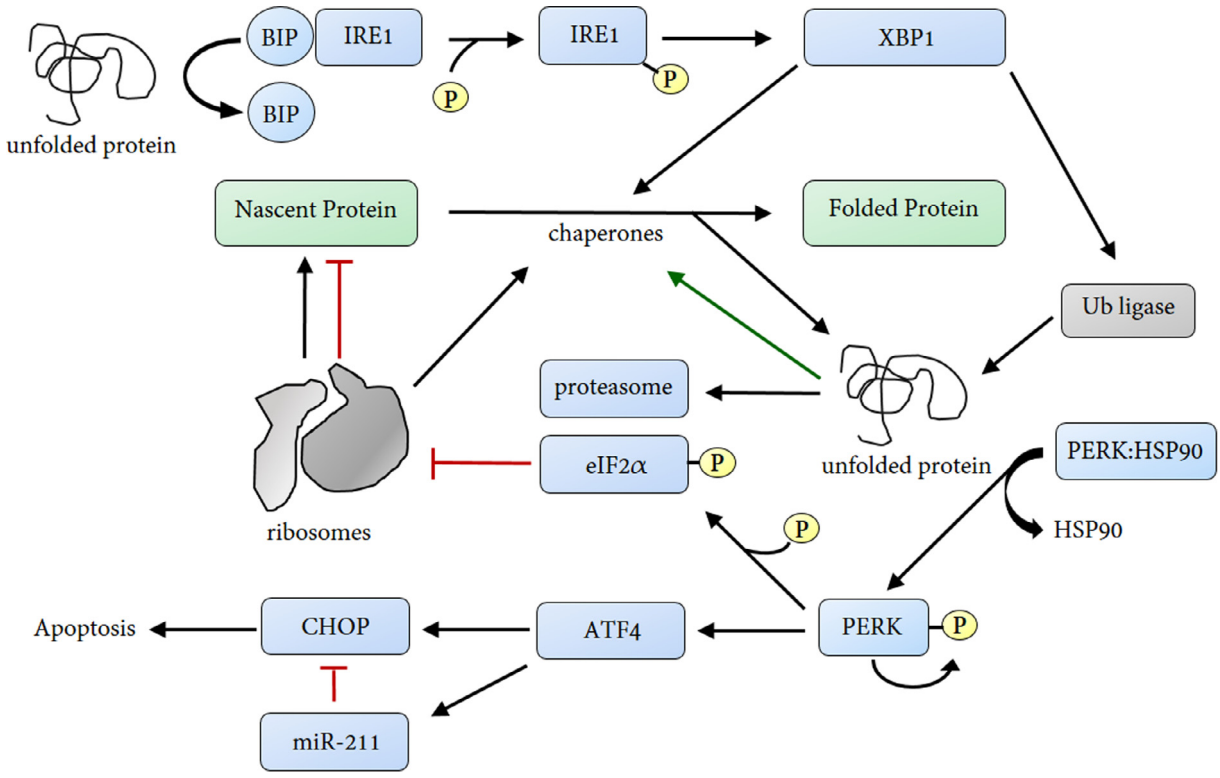

Fig. 1. The unfolded protein response (UPR) activates pathways dedicated to cell survival and cell death. In the presence of aberrations, HSP90 dissociates from PERK that then phosphorylates eIF2α to attenuate protein translation. Likewise, it activates ATF4 that induces the transcription of CHOP – an apoptotic signal, and miR-211 that controls it. miR-211 acts as a molecular switch, which downregulates during persistent stress, allowing CHOP to accumulate and mediate apoptosis. On the other hand, unfolded proteins activate IRE1 that upon autophosphorylation induces splicing of Xbp1, which assists protein folding and degradation.

site, the ER is very sensitive to any processes that tip the balance of Ca^{2+} homeostasis, which is why ionophores, glycosylation inhibitors, toxins and unfolded proteins – all of which lead to ER lumen Ca^{2+} depletion – trigger the ER stress response. During viral transformation or glucose deprivation, transcription of glucose-regulated protein (GRPs) is upregulated. These GRPs are Ca^{2+}-binding chaperone proteins, which by so binding perturbs Ca^{2+} homeostasis and leads to the EOR [45,46]. Compared to the UPR, the EOR seems to be more specialized in detecting Ca^{2+} perturbations. Recently, Wang et al. showed that TMCO1 encodes for an ER transmembrane protein that acts as a Ca^{2+}-load-activated-Ca^{2+} channel (CLAC) in preventing luminal Ca^{2+} excess (Fig. 2B), coupling with the Ca^{2+}-release-activated-Ca^{2+} channel (CRAC) to refill the ER lumen with Ca^{2+} [47]. Further, the EOR specializes in activating pathways leading to inflammation and cell proliferation (via NF-κB) to promote cell survival, which is in stark contrast to UPR. While the demarcation between UPR and EOR is unclear, one must give way to the other in order to prevent redundancy in mechanistic logic. We can infer that the UPR leads to a defence state, while the EOR leads to an attack state.

5. The ER stress response in Alzheimer's and Parkinson's diseases

Ca^{2+} transport is an important process in all types of cells of an organism, with no less emphasis on its role in cognitive function and neurotransmission. The most widely accepted view of Alzheimer's disease (AD) is that it is a tauopathy – characterized by hyperphosphorylated tau that is a grand hallmark of this disease [48–50]. Another are Aβ aggregates, originally deriving from proteolysis of the amyloid precursor protein (APP) by β- and γ-secretases in preparation for carbohydrate modifications in the ER. Since the precursor protein APP normally does not misfold in the ER, it is not prevented from leaving the organelle. Katayama et al. showed that by mutating the Presenilin-1 subunit of γ-secretase, IRE1 function in cell cultures was interfered [51]. Since IRE1 is essential for the transcription of chaperones, this mutation may partly explain why Aβ continues to misfold in those whose γ-secretases have undergone mutation. Further, amyloidogenesis seem to play a role in the UPR. By upregulating the expression of APP, the expression of CHOP is enhanced, and since CHOP is vital for apoptosis, then APP expression can lead to neuronal cell death [52]. From here, it may be inferred that by reducing the capability of cells to address protein misfolding and attenuating signals that favour cell death, amyloidogenesis and β-amyloid aggregation together lead to the death of neurons that are pathological hallmarks of dementia. Indeed, by using γ-secretase inhibitors, Takahashi et al. showed that CHOP mRNA transcription decreased [53].

What is critical is that the continued presence of Aβ aggregates activate the UPR, and subsequent luminal Ca^{2+} release to activate the EOR and other related pathways for cell survival also activates GSK-3-β, which is a major tau kinase [54]. By so doing, an increase in deposition of aggregates not only would lead to signals that favour neuronal cell death but also to the hyperphosphorylation of tau that causes the collapse of associated microtubules (Fig. 3A) – leading to more unfolded proteins and eventually more apoptosis [55]. Further, the activated UPR that leads to eIF2α phosphorylation to attenuate protein synthesis has also been shown to increase the mRNA transcripts of BACE-1, which is a β-secretase that leads to the production of more Aβ [56]. Meanwhile, continued Ca^{2+} depletion leads to the EOR, which then activates NF-κB. This explains in part why inflammation is a critical part of AD pathophysiology and progression [57,58], since NF-κB activation leads to cytokine production and subsequent recruitment of microglial cells [59]. However, since processing of APP can happen in

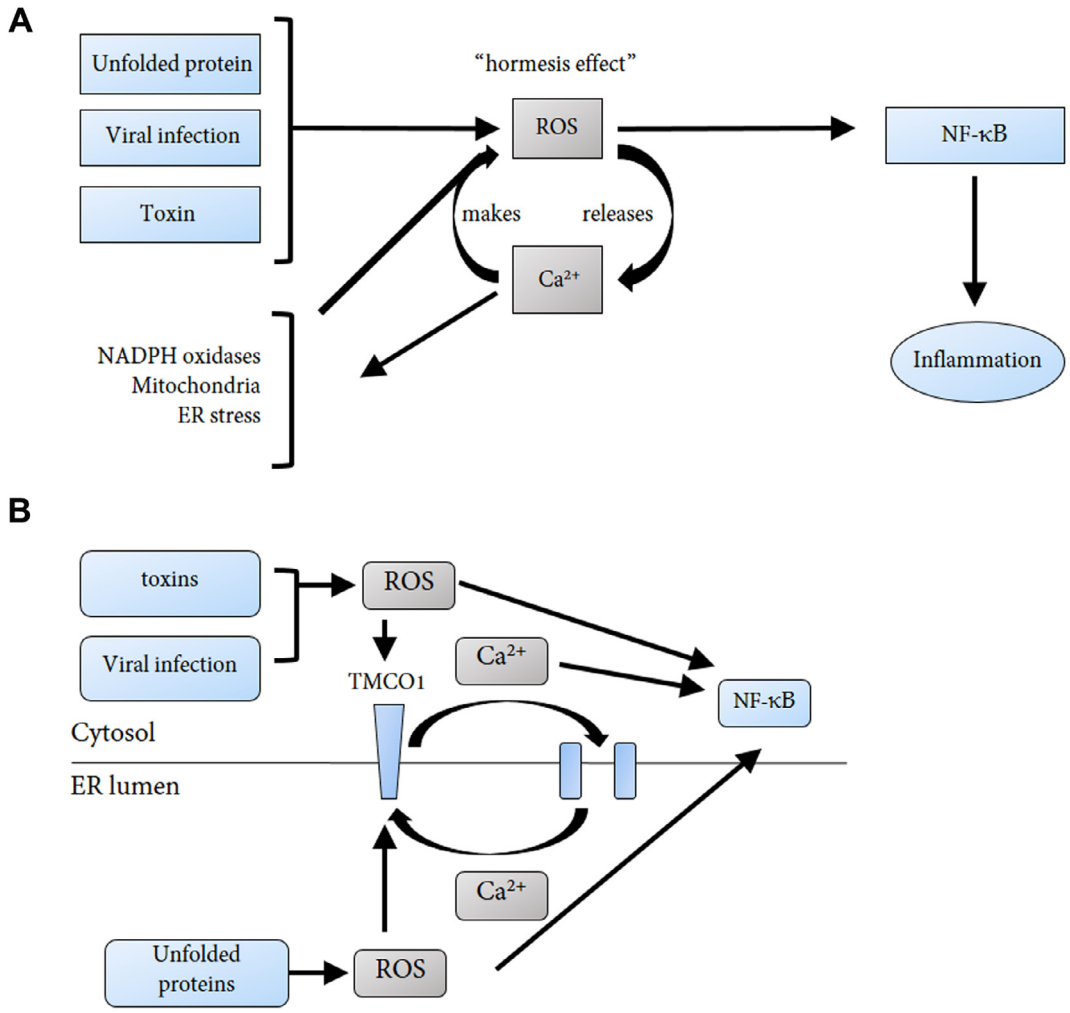

Fig. 2. The ER Overload Response (EOR) as a response to homeostatic perturbations. (A) Normal processes in oxidative phosphorylation and cell-cell communication provide reactive oxygen species (ROS) and Ca^{2+} at basal levels. In perturbations due to infection, toxins, or unfolded proteins, ROS production exceeds threshold, releasing calcium stores into the cytosol and triggering the EOR to upregulate NF-κB, which leads to inflammation. (B) In reality, Ca^{2+} transport is a homeostatic process. In the absence of perturbation, Ca^{2+} is released from the ER and refilled to serve cell signalling and signal transduction purposes. In the event of ROS overproduction, TMCO1, a recently discovered Ca^{2+} ion channel in the ER, might be affected to perturb this equilibrium, leading to Ca^{2+} in the cytosol which when coupled with ROS above threshold will activate the EOR.

many places in the cell such as the Golgi and the lysosome, it remains unclear where the main target for preventing aggregation should be [59].

In Parkinson's disease (PD), the trigger responses are said to be more profound, especially since it involves two cell types – neurons and myocytes. Being the most common neurodegenerative disease second to AD, PD requires much attention, especially since drugs designed to alleviate it often cause more harm long-term. Genome-wide association studies (GWAS) for Japanese and European ancestries revealed the possible roles of leucine-rich repeat kinase 2 (LRRK2) – a kinase implicated in loss of dopaminergic (DA) neurons – and α-synuclein – proteins whose aggregates constitute the Lewy bodies – in the pathogenesis and pathophysiology of PD [60,61]. In addition, a certain protein termed Pael-R (Parkin-associated endothelin receptor-like receptor), which is a G-protein coupled receptor, has been shown to unfold spontaneously when upregulated. This Pael-R is a substrate of Parkin, which is then ubiquitinated and destined for proteasomal degradation. Hence, mutations in the Parkin gene may lead to accumulation of Pael-R, which may trigger the UPR. In fact, Pael-R-induced neuronal cell death is observed in autosomal recessive juvenile parkinsonism, or AR-JP [60,62].

Studies have shown that α-synuclein affects Rab1, a protein involved in trafficking components from the ER to the Golgi. Further, α-synuclein directly interacts with nascent ATF6, effectively preventing its association with COPII vesicles that generally transfers proteins to the Golgi (Fig. 3B). These have certain implications: (1) interfering with the Rab protein could lead to accumulation of unfolded proteins in the ER, and (2) inhibition of ATF6 would generally stop the ERAD, triggering the cell to signal apoptosis [63]. What is interesting in PD is that it resembles the 'minor-lethal' requirements of the EOR. Mercado et al. found that by developmental ablation of Xbp1, which is a transcription factor modulating chaperone production, DA neurons were found to be more resistant to 6-hydroxydopamine (6-OHDA) – a neurotoxin. This hormesis effect is striking, in that a little of something bad can actually prime the cells to resist more of the worst to come [64]. Lastly, it is important to realize that myocytes share the same stress responses in PD. This is most clearly seen in PD therapy that involves dopamine agonists or dopaminergic drugs such as L-DOPA. Administration of these drugs mimics dopamine signalling or produces dopamine, and since neither addresses DA neurodegeneration, a typical PD patient would eventually need a higher dose overtime. As the dosage of L-DOPA increases, an

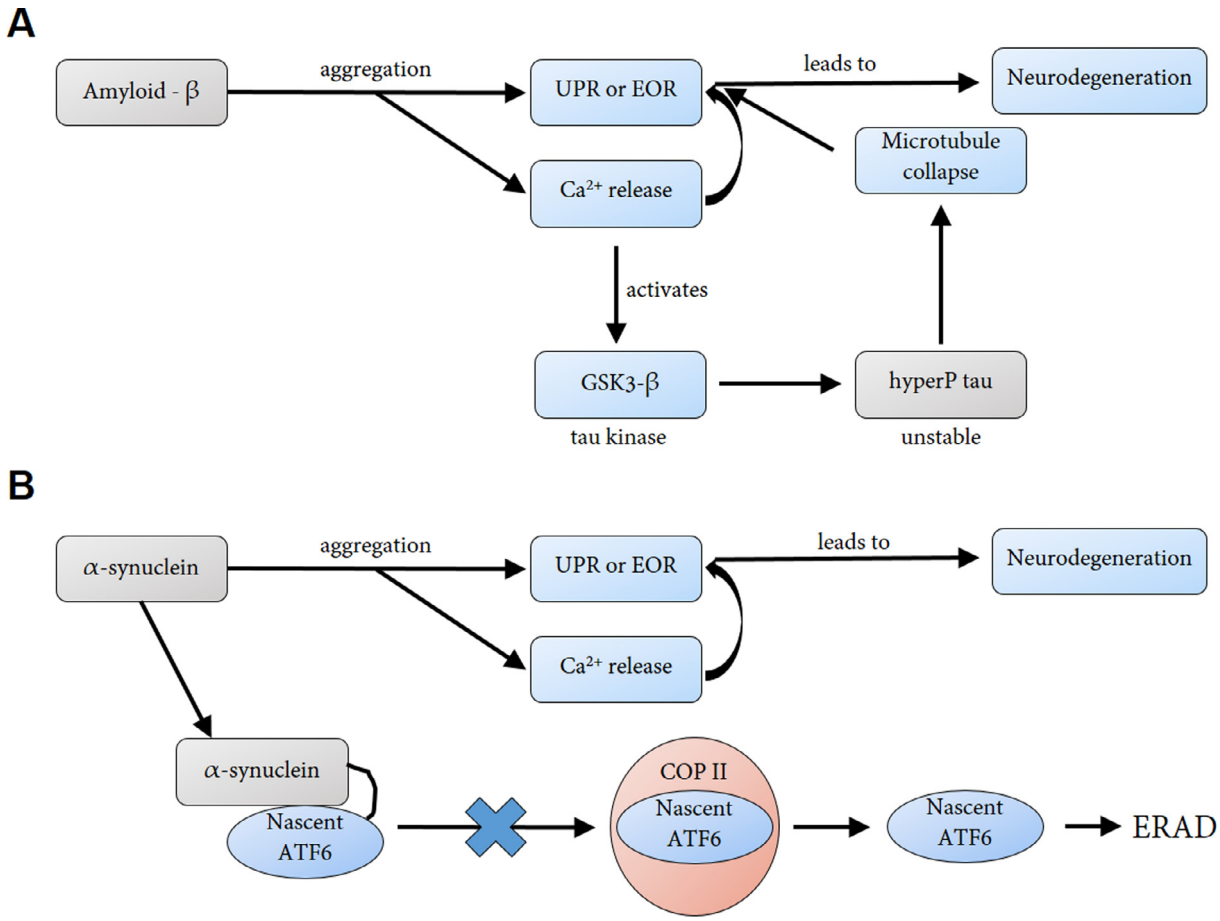

Fig. 3. The ER stress response actively participates in the pathogenesis and pathophysiology of Alzheimer's (AD) and Parkinson's diseases (PD). (A) In AD, the production of amyloid-β and its subsequent tendency to aggregate activates the ER stress response, which may either be the UPR, the EOR, or both. Perturbations deplete Ca^{2+} stores from the ER lumen, which positively feedbacks the ER stress. In the process, GSK3-β is hyperactivated, hyperphosphorylating tau proteins leading to microtubule collapse. This loop of protein unfolding persistently promotes inflammation, promoting death signals from the UPR that culminate in neurodegeneration. (B) In PD, aggregation of α-synuclein activates the ER stress response, which when persistently activated will result to inflammation and neurodegeneration. Unfortunately, α-synuclein also associates with nascent ATF6, preventing its delivery to the Golgi via COPII vesicles. Loss of mature ATF6 will lead to neurodegeneration.

overload of Ca^{2+} release in myocytes lead to what is called L-DOPA-induced dyskinesia (LID). Depletion of luminal Ca^{2+} stores to favour muscle contraction would then trigger ER stress. Triggering EOR, as shown previously, results to the activation of NF-κB, and we hypothesize that this explains in part why PD patients who experience LID or related dystonias also experience muscle inflammation and atrophy.

It may be tempting to think that ER stress is solely caused by aberrations in the ER, but this is often not the case. Recently, Celardo and colleagues showed that defective mitochondria may also initiate the UPR. By inhibiting pink1 and parkin – a kinase and an E3 ligase, respectively – in *D. melanogaster*, mitochondria became dysfunctional, and these dysfunctional mitochondria led to the UPR by forming mitofusin bridges with the ER. If mitofusin contacts are reduced, even if the amount of defective mitochondria remains unchanged, the PERK signalling pathway and hence the UPR would subsequently be attenuated [65]. In this light, it is important to realize that aberrations in organelles that interact with the ER may also trigger the ER stress response, which points out to the ER as being central to cell pathobiology.

6. The ER stress response in diabetes mellitus

Diabetes mellitus is a chronic disease divided into two types. Type 1 (T1D) is an autoimmune disorder that leads to the destruction of pancreatic β-cells and subsequent deficiency in insulin production, while type 2 (T2D) is a complex mixture of metabolic conditions leading to insulin resistance and eventual impaired insulin secretion [66,67].

The islet of Langerhans comprise about 2% of the pancreas by mass, and 60% of these are insulin-secreting. When glucose associates with β-cells after a full meal, insulin will only be produced and secreted after ROS generation and stimulation of Ryanodine receptors, followed by luminal Ca^{2+} release and subsequent increase in intracellular Ca^{2+} stores. This response constitutes the glucose-stimulated insulin secretion (GSIS) response, leading to insulin release to relevant tissues such as muscle cells that are in need of continuous energy source [68]. Therefore, any perturbations in Ca^{2+} transport will prevent insulin secretion, and persisting high blood glucose will lead to inflammation and destruction of the β-cells. Profoundly, a hyperglycemic environment promotes the formation of advanced glycation end products (AGEs), which is a spontaneous chemical reaction forming Schiff-base Amadori products. Aside from the glycation of plasma proteins that induce apoptosis of β-cells, we hypothesize that membrane proteins of β-cells also form AGEs, similar to what happens to red blood cells during hyperglycemia. When these happen, AGEs can act as ligands to RAGEs that are receptors constitutively expressed on immune cells to detect microbes, or to RAGEs expressed on β-cell membranes (Fig. 4). In fact, RAGE deficiency in mice has been shown to impair

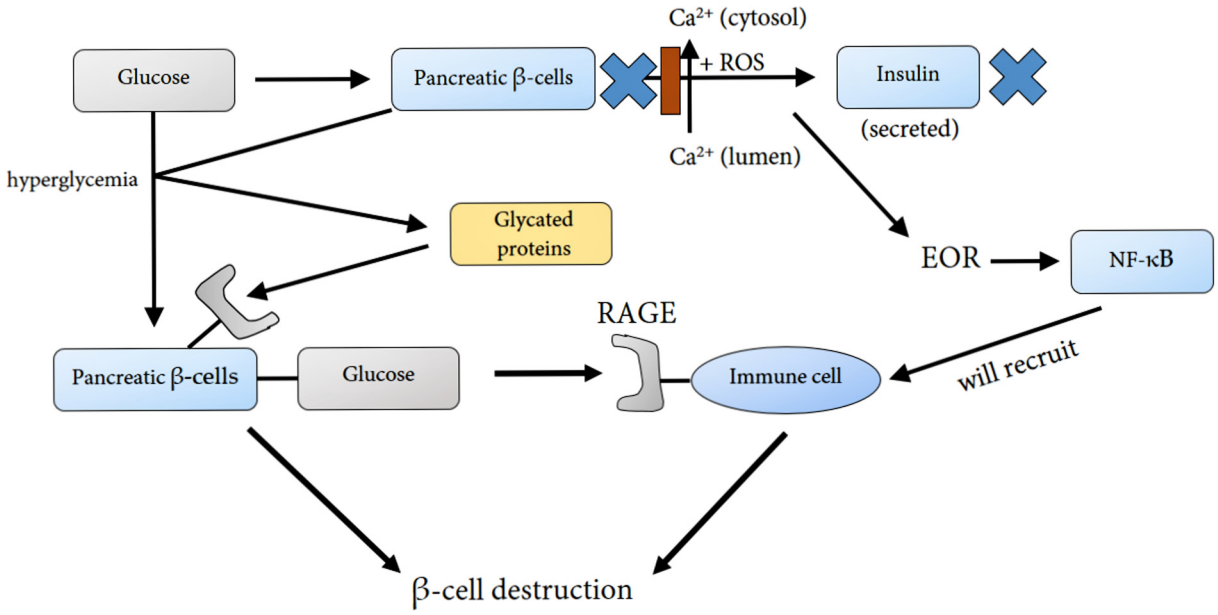

Fig. 4. The ER stress response is partly responsible for pancreatic β-cell destruction. When aberrations in the Ca^{2+} ion channel or insulin insensitivity occur, insulin release and action will not be possible. These result to persistent hyperglycemia, which forces β-cells to produce more insulin eventually leading to its wastage. The reactive oxygen species (ROS) produced from these aberrations drives the EOR, which upregulates NF-κB to recruit immune cells to the β-cell location. Unfortunately, persistent high blood glucose drives the Maillard reaction to form advanced glycation end products (AGEs) with either plasma proteins or possibly membrane proteins of β-cells. RAGE receptors on β-cells will recognize glycated plasma proteins and induce apoptosis. The RAGE receptor in immune cells will also recognize the AGEs bound to pancreatic β-cells, leading to their destruction. The persistent hyperglycemia and persistent recruitment of immune cells via the EOR perpetuates this cycle, contributing to the severity of diabetes mellitus type 1.

bacterial clearance, indicating its role in pro-inflammatory response. From here, it can be inferred that AGE formation can trigger inflammation, which is characteristic of the autoimmune response in T1D [69]. Indeed, the AGE-RAGE interactions in diabetes mellitus have been shown to lead to diabetic nephropathy and retinopathy as well [70].

Due to genetic factors which are usually the cause of T1D, aberrations in translation or posttranslational modifications of proteins lead to their unfolding, which may then trigger the ER stress response [67]. When this couples with Ca^{2+} release and ROS production prior to insulin release, the EOR response activates – leading to the activation of NF-κB that will subsequently lead to inflammation. In T2D, insulin resistance either by mutations in the insulin receptors or in the vesicular proteins transporting the receptors to the cell surface lead to an increase in β-cell workload. In this event, the persistent hyperglycemia promotes ROS generation and Ca^{2+} release, depleting the ER Ca^{2+} stores and triggering ER stress. Eventually, UPR promotes attenuation of protein synthesis, which would lead to a downregulation of insulin production and eventually the depleted Ca^{2+} promoted by hyperglycemia would cause β-cell exhaustion and ER-induced apoptosis [66,71]. Further, any mutations in the Ca^{2+} ion channels would lead to accumulation of proteins and ROS in the β-cell, likewise triggering the UPR or EOR. Indeed, both Ca^{2+} transport and the ER stress response is critical in the pathogenesis and pathophysiology of diabetes types 1 and 2, and can therefore be targets for therapy.

7. The ER stress response in viral infection and T-cell exhaustion

Quality control in the cell is a relatively taken-for-granted concept in microbial infection. Normally, it is intuitive that cell senescence or death depends upon exertion of microbial toxins or hijacking the cell machinery as in viral infections. With quality control in mind, this perception is shifted to recognize that cells respond not only to detect and eliminate pathogen invasion but also to limit damage and promote repair [72]. Of course, this ER stress response forms a large barricade for intracellular pathogens that aim to hijack the cell machinery for its survival. By attenuating protein synthesis, for instance, viruses are confronted with a problem of how they can multiply. Further, activation of the EOR would lead to cytokine production – such as IFN-γ – that will inhibit viral replication. Thus, the ER is a major barricade for infection, so much so that viruses have evolved to tap into this defence mechanism and stop it from protecting the host cell. In times of viral infection, BIP associates with PERK, ATF6 and IRE-1 to attenuate protein synthesis and mark ER-localized proteins for degradation. PERK will phosphorylate eIF2α to stop translation; ATF6 will translocate to the Golgi where upon cleavage would upregulate chaperone proteins; IRE-1 would then facilitate formation of a mature Xbp-1, and together would mark new protein for degradation [73].

Viruses have an arsenal of techniques to manipulate this defence. For instance, hepatitis C virus stimulates the ATF6 pathway, but inhibits that of IRE-1-Xbp (Fig. 5A). By so doing, chaperone proteins can help viral proteins to assemble, without being marked for degradation [74]. On the other hand, the herpes simplex virus encodes a protein whose $\gamma_1$34.5 region is homologous to the GADD34 protein. This protein is a component of the PERK pathway that relieves translation attenuation. Since the herpes protein is camouflaged to look like GADD34, it activates the PERK pathway to inhibit CHOP via PERK-dependent miR-211, allowing the cell to survive. Then, herpes blocks the phosphorylation of eIF2α, allowing normal translation kinetics [75].

It only gets more striking in the case of HIV infection. During infection, HIV induces ATF4 expression. Since ATF4 is involved in a time-sensitive response for either cell survival or death, ATF4 can trigger HIV replication in the survival phase of the UPR, and has been suggested to play a role in shifting viral latency to active replication mediated by the Tat protein [76]. In terms of translation, Tat protein effectively competes with eIF2 for phosphorylation by and inhibits the activation of RNA-activated kinase (PKR), leading to reactivation of translation processes [77]. Further, the

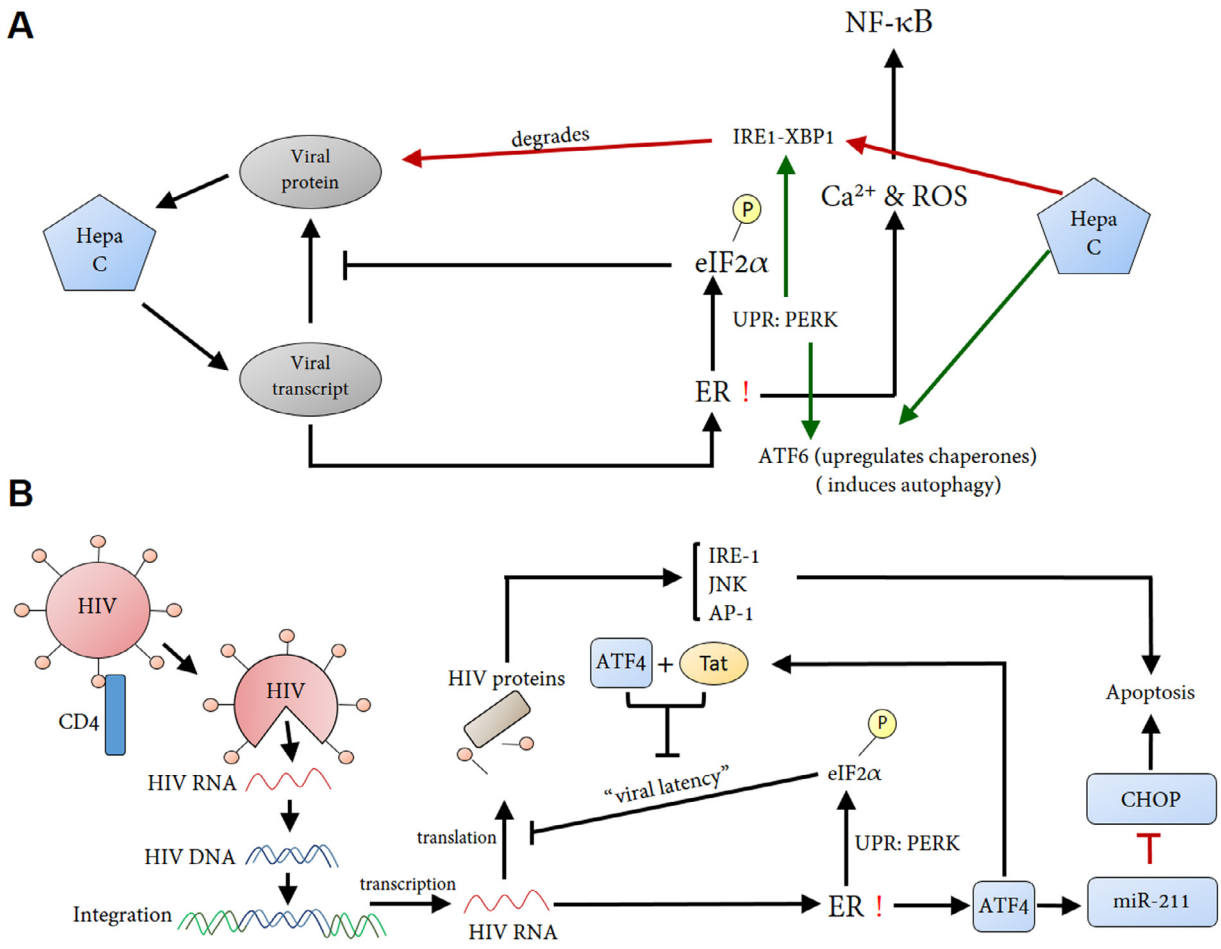

Fig. 5. Viruses have evolved mechanisms to evade the ER stress response. (A) In Hepatitis C (Hepa C) infection, the PERK pathway activates ATF6, which upregulates chaperones assisting viral protein assembly. IRE1 is directly inhibited by Hepa C, preserving the viral proteins. Activation of NF-κB is partly responsible for liver inflammation common to this infection. (B) In HIV infection, the synergistic action of both ATF4 and the HIV Tat protein activates viral replication and inhibits phosphorylation of eIF2α, ending viral latency. HIV protein gp120 also upregulates pro-apoptotic proteins IRE-1, JNK and AP-1, tipping the balance between CHOP and miR-211 to instruct apoptosis and to assist HIV progression to AIDS.

gp120 protein of HIV-1 induces IRE1, JNK and AP-1, leading to cell apoptosis that can contribute to HIV progression to AIDS [78] (Fig. 5B).

Meanwhile, IL-2 induces the splicing of Xbp-1 in $CD8^+$ T-cells, which in turn is critical for their differentiation into cytotoxic T-cells [79]. Since $CD4^+$ T-cells are the usual targets of HIV, aberrations in these cells induce the ER stress response, which would lead to translation attenuation. However, as many viruses have evolved to hijack this defence, HIV continues to replicate and translate proteins in the lymphocyte. This eventually exhausts the cell, leading to its destruction. Continuous destruction of $CD4^+$ T-cells deplete MHC class II-restricted T-cells that subsequently depletes precursors for T-helper cells (T_H), which is critical for cell-mediated immunity (CMI). As this happens, HIV also downregulates MHC class I in infected CD4s, preventing detection by $CD8^+$ T-cells. Further, cytokine production is altered in such a way that stimulation of $CD8^+$ T-cells would lead to anergy [80]. In chronic HIV infection without antiretrovirals, the high viral load is seen concomitantly with a persistent elevation in $CD8^+$ T-cell count which implies a prolonged activity of these T_Cs. Actually, too much attention has been placed on recovery of $CD4^+$ T-cell count, while CD8 activity has been largely neglected [81]. It must be realized that this points out to a missing link in effective HIV therapy. Through some mechanism, HIV is able to activate $CD8^+$ T-cells chronically. Too long an activation (perhaps by cytokines) would deplete the Ca^{2+} stores which are released to activate the EOR for pro-inflammatory responses and cytokine production, leading to T-cell exhaustion and eventual cell death. Overtime, the number of naïve $CD8^+$ T-cells are depleted, and the T_Cs undergo anergy as the chronic HIV infection persists. Lastly, it has been shown that Tat stimulates an abnormal hyper-activation of human dendritic cells (DCs), macrophages, as well as differentiation of $CD8^+$ T-cells into T_Cs [82,83]. In this way, HIV Tat is seen to promote inflammation and exhausted $CD8^+$ T-cells and innate immune cells while depleting $CD4^+$ T-cell count and hence differentiated B-cell count in the process.

8. The ER stress response in tumorigenesis and cancer

Finally, it is noteworthy that the ER has a significant contribution in tumorigenesis and cancer, especially since the pathophysiology of neoplasms include uncontrolled proliferation and synthesis of proteins required to support this immense growth. Intuitively, this growth must manipulate the ER. Activation of ER stress has been shown to render tumor cells more resistant to cellular insults due to cell survival promotion, while inhibiting the signals that determine inflammation and cell apoptosis [84]. The most known of the genes involved is Bcl-2, which is the first pro-survival gene discovered in the ER stress response [85]. In

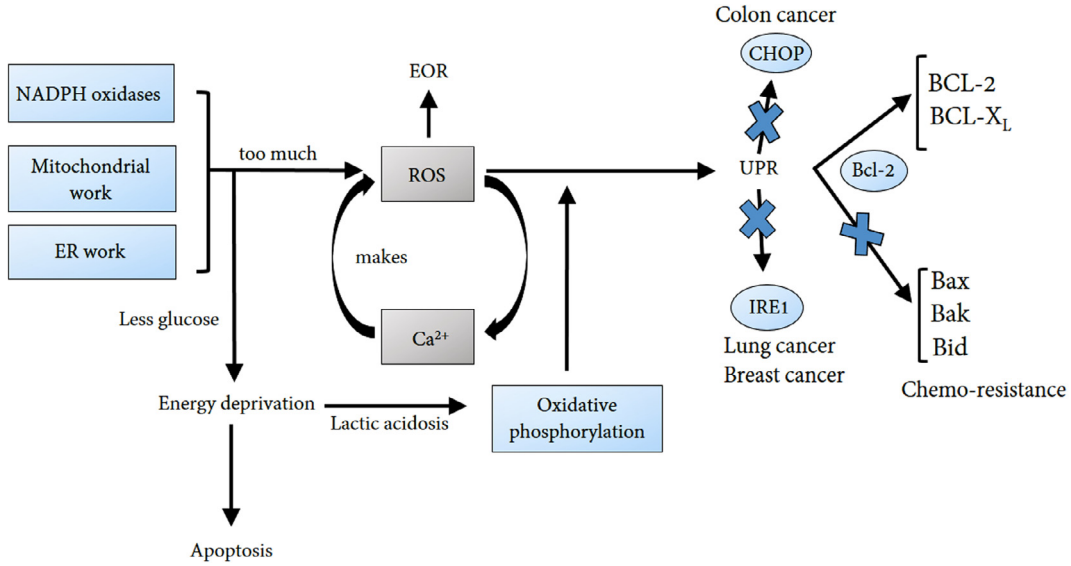

Fig. 6. The ER stress response participates in tumorigenesis and cancer. In tumor progression, the immense metabolism of cells lead to overproduction of ROS and Ca^{2+} release, activating the EOR responsible for local inflammation in many cancers. Lowering glucose intake is thought to deprive these tumors of energy, leading to their apoptosis. However, in the presence of lactic acidosis, tumors are able to shift their metabolism to oxidative phosphorylation, allowing survival and the persistent activation of the UPR/EOR. In some cases of colon cancer, CHOP production is lost, leading to tumor survival. Meanwhile, mutations in IRE1 is associated with lung and breast malignancies. Lastly, mutations in death signals of the Bcl-2 family of oncogenes promote survival, and is common to tumors resistant to chemotherapeutic agents.

tumorigenesis, Bcl-2 is involved in chromosomal translocations and increased transcription rates in malignancies such as non-Hodgkin's lymphoma and cancer of the lungs. This is made possible by the loss of miRNAs that impose a threshold on the pro-survival logic, as well as hypomethylations that promote permissiveness of the Bcl-2 gene to transcription. This process, however, is not at all simplistic. The Bcl-2 family of oncogenes are divided into two – those that promote survival and those that promote death. Previously mentioned to promote survival are Bcl-2 and Bcl-X_L, which are induced during ER stress to promote survival. Meanwhile, those that promote apoptosis are BAX and Bcl-2 homologous antagonist killer (BAK), and either BAX or BAK can act as a sufficient trigger for cell death when the cell can no longer address its perturbations [85,86] (Fig. 6). Both stimulate the outer membrane permeabilization of the mitochondria, which leads to cytochrome *c* release and the activation of caspases. Meanwhile, the dysfunctional mitochondria may produce mitofusin bridges that will trigger the PERK pathway in a deadly combination ultimately favoring apoptosis. Indeed, one of the reasons why some tumors resist chemotherapy is because of an overexpression of anti-apoptotic Bcl-2 oncogenes, and in a similar manner any mutations in the apoptotic proteins BAX or BAK would lead to loss of death signals that will allow cancer cells to resist treatment and continue its proliferation [85] (Fig. 6).

Interestingly, the Bcl-2 family of oncogenes is not the sole player in cancer. Previously, we have described that in times of ER stress, IRE-1 is activated to promote differential splicing of nascent Xbp-1 into mature Xbp-1. This pathway is actually upregulated by cancer cells – especially in fibrosarcoma and lung carcinoma – during hypoxic stress, whereas colon cancer cells upregulate the PERK pathway to indirectly inhibit the transcription of CHOP (Fig. 6). By so doing, chaperones will combat cell stress-induced unfolding, which would render tumor cells resistant to the consequences of immense metabolism. Further, in a hypoglycemic environment, tumors increase anaerobic glycolysis to produce a lot of lactate that will decrease the pH of the cell. This will lead to acidosis, and itself being a perturbation in normal proton concentrations would trigger the UPR to activate the Bcl-2 family of oncogenes for survival [87–90]. Indeed, by regulating the IRE1-Xbp-1 pathway, Rajapaksa and colleagues were able to demonstrate a decreased survival rate of breast cancer cells *in vitro* [91]. Further, by removing lactate, tumor cells were not able to survive a hypoglycemic environment (0.5 mM) – indicating the role of UPR in tumor survival [92].

9. Conclusion

Being a common denominator among all cell types, the ER governs mechanisms to ensure cell survival, integrity and function. Therefore, it may also be a common target in diseases that seem unrelated to one another – neurodegenerative disease, diabetes, infection or cancer. Recent studies on the ER stress response shed some light on a strong link between these cell-specific diseases, and permitted guided benefit to biomedicine due to its broadly applicable molecular pathways. Indeed, we are entering an era where, in profound understanding of the basic science governing various diseases, addressing the need to discover new drugs and therapeutic approaches beyond one's expertise is permitted. The ER stress response is a set of molecular mechanisms that acts to promote cell survival by upregulating chaperones to assist protein folding, proteins to direct persistently unfolded proteins for degradation, and transcription factors to bias transcription to certain genes for survival, while generally attenuating translation of proteins for normal cell function. Further, the ER activates NF-κB to promote inflammation, in cases where immune cells are needed. In some cases, the ER stress response fails, and leads to disease. Still in others, viruses evade the response to effectively continue viral replication. Indeed, the ER stress response is the organelle that bridges the gap among these diseases.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to thank Dr. Salvador Eugenio Caoili of the University of the Philippines Manila for his valuable ideas in the discussion of the ER stress response.

References

[1] Rathore S, Datta G, Kaur I, Malhotra P, Mohmmed A. Disruption of cellular homeostasis induces organelle stress and triggers apoptosis like cell-death pathways in malaria parasite. Cell Death Dis 2015;6:e1803.
[2] Yerbury J, Stewart E, Wyatt A, Wilson M. Quality control of protein folding in extracellular space. EMBO Rep 2005;6(12):1131–6.
[3] Chakrabarti A, Chen AW, Varner JD. A review of the mammalian unfolded protein response. Biotechnol Bioeng 2011;108(12):2777–93.
[4] Kotas M, Medzhitov R. Homeostasis, inflammation, and disease susceptibility. Cell 2015;160(5):816–27.
[5] van Parjis L, Perez VL, Abbas AK. Mechanisms of peripheral T cell tolerance. Novartis Found Symp 1998;215:5–14.
[6] Abbas AK, Lohr J, Knoechel B, Nagabhushanam V. T cell tolerance and autoimmunity. Autoimmun Rev 2004;3(7–8):471–5.
[7] van Wijk F, Cheroutre H. Mucosal T cells in gut homeostasis and inflammation. Expert Rev Clin Immunol 2010;6(4):559–66.
[8] Rock K, Kono H. The inflammatory response to cell death. Annu Rev Pathol 2008;3:99–126.
[9] Chovatiya R, Medzhitov R. Stress, inflammation, and defense of homeostasis. Mol Cell 2014;54(2):281–8.
[10] Lin JH, Walter P, Yen TS. Endoplasmic reticulum stress in disease pathogenesis. Annu Rev Pathol 2008;3:399–425.
[11] Saraogi I, Shan SO. Molecular mechanism of co-translational protein targeting by the signal recognition particle. Traffic 2011;12:535–42.
[12] Zimmerman R, Eyrisch S, Ahmad M, Helms V. Protein translocation across the ER membrane. Biochim Biophys Acta 2010;1808:912–24.
[13] Moremen KW, Molinari M. N-linked glycan recognition and processing: the molecular basis of endoplasmic reticulum quality control. Curr Opin Struct Biol 2006;16:592–9.
[14] McLaughlin M, Vandenbroeck K. The endoplasmic reticulum protein folding factory and its chaperones: new targets for drug discovery? Br J Pharmacol 2011;162(2):328–45.
[15] Araki K, Nagata K. Protein folding and quality control in the ER. Cold Spring Harb Perspect Biol 2011;3(11):a007526.
[16] Siekierka J, Manne V, Ochoa S. Mechanism of translational control by partial phosphorylation of the [alpha] subunit of eukaryotic initiation factor 2. Proc Natl Acad Sci USA 1984;81:352–6.
[17] Das S, Ghosh R, Maitra U. Eukaryotic translation initiation factor 5 functions as a GTPase-activating protein. J Biol Chem 2001;276:6720–6.
[18] Harding HP, Novoa I, Zhang Y, Zeng H, Wek R, Schapira M, et al. Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol Cell 2000;6(5):1099–108.
[19] Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, et al. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. Genes Dev 2004;18(24):3066–77.
[20] Gotoh T, Terada K, Mori M. Hsp70-Dnaj chaperone pairs prevent nitric oxide-mediated apoptosis in raw 264.7 macrophages. Cell Death Differ 2001;8:357–66.
[21] Puthalakath H, O'Reilly LA, Gunn P, Lee L, Kelly PN, Huntington ND, et al. ER stress triggers apoptosis by activating BH3-only Bim. Cell 2007;129 (7):1337–49.
[22] Czabotar PE, Colman PM, Huang DC. Bax activation by Bim? Cell Death Differ 2009;16(9):1187–91.
[23] Sarosiek KA, Chi X, Bachman JA, Sims JJ, Montero J, Patel L, et al. BID preferentially activates BAK while BIM preferentially activates BAX, affecting chemotherapy response. Mol Cell 2013;51(6):751–65.
[24] Wang M, Kaufman R. The impact of the endoplasmic reticulum protein-folding environment on cancer development. Nat Rev Cancer 2014;14:581–97.
[25] Chitnis NS, Pytel D, Bobrovnikova-Marjon E, Pant D, Zheng H, Maas NL, et al. MiR-211 is a pro-survival microRNA that regulates chop expression in a PERK-dependent manner. Mol Cell 2012;48(3):353–64.
[26] Rutkowski DT, Arnold SM, Miller CN, Wu J, Li J, Gunnison KM, et al. Adaptation to ER stress is mediated by differential stabilities of pro-survival and pro-apoptotic mRNAs and proteins. PLoS Biol 2006;4(11):e374.
[27] Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D. Dynamic interaction of bip and er stress transducers in the unfolded-protein response. Nat Cell Biol 2000;2:326–32.
[28] Sidrauski C, Walter P. The transmembrane kinase ire1p is a site-specific endonuclease that initiates mrna splicing in the unfolded protein response. Cell 1997;90:1031–9.
[29] Liu CY, Wong HN, Schauerte JA, Kaufman RJ. The protein kinase/endoribonuclease ire1 alpha that signals the unfolded protein response has a luminal n-terminal ligand-independent dimerization domain. J Biol Chem 2003;277:18346–56.
[30] Calfon M, Zeng H, Urano F, Till JH, Hubbard SR, Harding HP, et al. IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. Nature 2002;415(6867):92–6.
[31] Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell 1997;107:881–91.
[32] Lee AH, Iwakoshi NN, Glimcher LH. XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. Mol Cell Biol 2003;23:7448–59.
[33] Shaffer AL, Shapiro-Shelef M, Iwakoshi NN, Lee AH, Qian SB, Zhao H, et al. XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. Immunity 2004;21:81–93.
[34] Yan W, Frank C, Korth M, Sopher B, Novoa I, Ron D, et al. Control of PERK eIF2α kinase activity by the endoplasmic reticulum stress-induced molecular chaperone $P58^{IPK}$. Proc Natl Acad Sci USA 2002;99(25):15920–5.
[35] Lagides WC, Knoblaugh SE, Morton JF, Korth MJ, Sopher BL, Baskin CR, et al. Pancreatic β-cell failure and diabetes in mice with a deletion mutation of the endoplasmic reticulum molecular chaperone gene P58IPK. Diabetes 2005;54 (4):1074–81.
[36] Szegezdi E, Logue S, Gorman A, Samali A. Mediators of endoplasmic reticulum stress-induced apoptosis. EMBO Rep 2006;7(9):880–5.
[37] Malhotra JD, Kaufman RJ. The endoplasmic reticulum and the unfolded protein response. Semin Cell Dev Biol 2007;18:716–31.
[38] Hetz C, Glimcher LH. Fine-tuning of the unfolded protein response: assembling the ire1 alpha interactome. Mol Cell 2009;35:551–61.
[39] Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, Harding HP, et al. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Science 2000;287(5453):664–6.
[40] Nishitoh H, Matsuzawa A, Tobiume K, Saegusa K, Takeda K, Inoue K, et al. ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats. Genes Dev 2002;16 (11):1345–55.
[41] Barr RK, Bogoyevitch MA. The c-Jun N-terminal protein kinase family of mitogen-activated protein kinases. Int J Biochem Cell Biol 2001;33 (11):1047–63.
[42] Pahl HL, Baeuerle PA. The ER-overload response: activation of NF-kappa B. Trends Biochem Sci 1997;22(2):63–7.
[43] Lawrence T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harb Perspect Biol 2009;1(6):a001651.
[44] Kong L, Li S, Huang M, Xiong Y, Zhang Q, Ye L, et al. The roles of endoplasmic reticulum overload response induced by HCV and NS4B protein in human hepatocyte viability and virus replication. PLoS One 2015;10(4):e0123190.
[45] Kaufman RJ. Stress signalling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. Genes Dev 1999;13:1211–33.
[46] Lee AS. Mammalian stress response: induction of the glucose-regulated protein family. Curr Opin Cell Biol 1992;4:267–73.
[47] Wang Q-C, Zheng Q, Tan H, Zhang B, Li X, Yang Y, et al. TMCO1 is an ER Ca^{2+} load-activated Ca^{2+} channel. Cell 2016;165(6):1454–66.
[48] Guo JL, Narasimhan S, Changolkar L, He Z, Stieber A, Zhang B, et al. Unique pathological tau conformers from Alzheimer's brains transmit tau pathology in nontransgenic mice. J Exp Med 2016;213(12):1–20.
[49] Nilson AN, English KC, Gerson JE, Whittle TB, Crain CN, Xue J, et al. Tau oligomers associate with inflammation in the brain and retina of tauopathy mice and in neurodegenerative diseases. J Alzheimer's Dis 2017;55 (3):1083–99.
[50] Manalo RV, Silvestre MA, Barbosa AZA, Medina PM. Coconut (Cocos nucifera) ethanolic leaf extract reduces amyloid-β (1–42) aggregation and paralysis prevalence in transgenic Caenorhabditis elegans independently of free radical scavenging and acetylcholinesterase inhibition. Biomedicines 2017;5(2):17.
[51] Katayama T, Imaizumi K, Sato N, Miyoshi K, Kudo T, Hitomi, et al. Presenilin-1 mutations downregulate he signalling pathway of the unfolded protein response. Nat Cell Biol 1999;1:479–85.
[52] Copanaki E, Schürmann T, Eckert A, Leuner K, Müller WE, Prehn JH, et al. The amyloid-precursor protein potentiates CHOP induction and cell death in response to ER Ca^{2+} depletion. Biochim Biophys Acta 2007;1773:157–65.
[53] Takahashi K, Niidome T, Akaike A, Kihara T, Sugimoto H. Amyloid precursor protein promotes endoplasmic reticulum stress-induced cell death via C/EBP homologous protein-mediated pathway. J Neurochem 2009;109:1324–37.
[54] Resende R, Ferreiro E, Pereira C, Oliveira CR. ER stress is involved in Abeta-induced GSK-3beta activation and tau phosphorylation. J Neurosci Res 2008;86:2091–9.
[55] Endres K, Reinhardt S. ER-stress in Alzheimer's disease: turning the scale? Am J Neurodegener Dis 2013;2(4):247–65.
[56] O'Connor T, Sadleir KR, Maus E, Velliquette RA, Zhao J, Cole SL, et al. Phosphorylation of the translation initiation factor eIF2α increases BACE I levels and promotes amyloidogenesis. Neuron 2008;60:988–1009.
[57] Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. Nature 2008;454:455–62.
[58] Kaser A, Blumberg RS. Endoplasmic reticulum stress in the intestinal epithelium and inflammatory bowel disease. Semin Immunol 2009;21:156–63.
[59] Salminen A, Kauppinen A, Suuronen T, Kaarniranta K, Ojala J. ER stress in Alzheimer's disease: a novel neuronal trigger for inflammation and Alzheimer's pathology. J Neuroinflamm 2009;6(41):1–13.
[60] Omura T, Kaneko M, Okuma Y, Matsubara K, Nomura Y. Endoplasmic reticulum stress and Parkinson's disease: the role of HRD1 in averting apoptosis in neurodegenerative disease. Oxid Med Cell Longev 2013;239854:1–7.
[61] Li J-Q, Tan L, Yu J-T. The role of the LRRK2 gene in Parkinsonism. Mol Neurodegener 2014;9:47.
[62] Takahashi R, Imai Y. Pael receptor, endoplasmic reticulum stress, and Parkinson's disease. J. Neurol. 2003;250(Suppl. 3):III25–9.

[63] Credle JJ, Forcelli PA, Delannoy M, Oaks AW, Permaul E, Berry DL, et al. Alpha-synuclein-mediated inhibition of ATF6 processing into COPII vesicles disrupts UPR signalling in Parkinson's disease. Neurobiol Dis 2015;76:112–25.
[64] Mercado G, Castillo V, Vidal R, Hetz C. ER proteostasis disturbances in Parkinson's disease: novel insights. Front Aging Neurosci 2015;7(1):39.
[65] Celardo I, Costa AC, Lehmann S, Jones C, Wood N, Mencacci NE, et al. Mitofusin-mediated ER stress triggers neurodegeneration in *pink1/parkin* models of Parkinson's disease. Cell Death Dis 2016;7:e2271.
[66] Back SH, Kaufman RJ. Endoplasmic reticulum stress and type 2 diabetes. Annu Rev Biochem 2012;81:767–93.
[67] O'Sullivan-Murphy B, Urano F. ER stress as a trigger for β-cell dysfunction and autoimmunity in type 1 diabetes. Diabetes 2012;61(4):780–1.
[68] Llanos P, Contreras-Ferrat A, Barrientos G, Valencia M, Mears D, Hidalgo C. Glucose-dependent insulin secretion in pancreatic β-cell islets from male rats requires Ca^{2+} release via ROS-stimulated ryanodine receptors. PLoS One 2015;10(10):e0140198.
[69] Gkogkolou P, Böhm M. Advanced glycation end products: Key players in skin aging? Dermatoendocrinology 2012;4(3):259–70.
[70] Sakurai S, Yonekura H, Yamamoto Y, Watanabe T, Tanaka N, Li H, et al. The AGE-RAGE system and diabetic nephropathy. J Am Soc Nephrol 2003;14 (Suppl. 3):S259–63.
[71] Araki E, Oyadomari S, Mori M. Endoplasmic reticulum stress and diabetes mellitus. Intern Med 2003;42(1):7–14.
[72] Pillich H, Loose M, Zimmer K-P, Chakraborty T. Diverse roles of endoplasmic reticulum stress sensors in bacterial infection. Mol Cell Pediatr 2016;3:9.
[73] He B. Viruses, endoplasmic reticulum stress, and interferon responses. Cell Death Differ 2006;13:393–403.
[74] Tardif KD, Mori K, Siddiqui A. Hepatitis C virus subgenomic replicons induce endoplasmic reticulum stress activating an intracellular signaling pathway. J Virol 2002;76:7453–9.
[75] He B, Gross M, Roizman B. The $\gamma_1$34.5 protein of herpes simplex virus 1 complexes with protein phosphatase 1α to dephosphorylate the alpha subunit of the eukaryotic translation initiation factor 2 and preclude the shutoff of protein synthesis by double-stranded RNA-activated protein kinase. Proc Natl Acad Sci USA 1997;94:843–8.
[76] Borsa M, Ferreira PLC, Petry A, Ferreira LGE, Camargo MM, Bou-Habib DC, et al. HIV infection and antiretroviral therapy lead to unfolded protein response activation. Virol J 2015;12:77.
[77] Brand SR, Kobayashi R, Mathews MB. The tat protein of human immunodeficiency virus type 1 is a substrate and inhibitor of the interferon-induced, virally activated protein kinase, PKR. J Biol Chem 1997;272:8388–95.
[78] Shah A, Vaidya NK, Bhat HK, Kumar A. HIV-1 gp120 induces type-1 programmed cell death through ER stress employing IRE1α, JNK and AP-1 pathway. Sci Rep 2016;6:18929.
[79] Kamimura D, Bevan M. Endoplasmic reticulum stress regulator XBP-1 contributes to effector $CD8^+$ T cell differentiation during acute infection. J Immunol 2008;181(8):5433–41.
[80] Gulzar N, Copeland KF. $CD8^+$ T-cells: function and response to HIV infection. Curr HIV Res 2004;2(1):23–37.
[81] Cao W, Mehraj V, Kaufmann DE, Li T, Routy J-P. Elevation and persistence of CD8 T-cells in HIV infection: the Achilles heel in ART era. J Int AIDS Soc 2016;19(1):20697.
[82] Haij NB, Planès R, Leghmari K, Serrero M, Delobel P, Izopet J, et al. HIV-1 tat protein induces production of proinflammatory cytokines by human dendritic cells and monocytes/macrophages through engagement of TLR4-MD2-CD14 complex and activation of NF-κB pathway. PLoS One 2015;10(6):e0129425.
[83] Nicoli F, Finessi V, Sicurella M, Rizzotto L, Gallerani E, Destro F, et al. The HIV-1 tat protein induces the activation of $CD8^+$ T cells and affects *in vivo* the magnitude and kinetics of antiviral responses. PLoS One 2013;8(11):e77746.
[84] Cubillos-Ruiz JR, Bettigole SE, Glimcher LH. Tumorigenic and immunosuppressive effects of endoplasmic reticulum stress in cancer. Cell 2017;168(4):692–706.
[85] Yip KW, Reed JC. Bcl-2 family proteins and cancer. Oncogene 2008;27:6398–406.
[86] Wang X, Olberding KE, White C, Li C. Bcl-2 proteins regulate ER membrane permeability to luminal proteins during ER stress-induced apoptosis. Cell Death Differ 2011;18:38–47.
[87] Tsai YC, Weissman AM. The unfolded protein response, degradation from the endoplasmic reticulum, and cancer. Genes Cancer 2010;1(7):764–78.
[88] Vandewynckel Y-P, Laukens D, Geerts A, Bogaerts E, Paridaens A, Verhelst X, et al. The paradox of the unfolded protein response in cancer. Anticancer Res 2013;33(11):4683–94.
[89] Urra H, Dufey E, Avril T, Chevet E, Hetz C. Endoplasmic reticulum stress and the hallmarks of cancer. Trends Cancer 2016;2(5):252–62.
[90] Cubillos-Ruiz JR, Mohamed E, Rodriguez P. Unfolding anti-tumor immunity: ER stress responses sculpt tolerogenic myeloid cells in cancer. J Immunother Cancer 2017;5(5):1–10.
[91] Rajapaksa G, Nikolos F, Bado I, Clarke R, Gustafsson JÅ, Thomas C. ERβ decreases breast cancer cell survival by regulating the IRE1/XBP-1 pathway. Oncogene 2015;34(31):4130–41.
[92] Xie J, Wu H, Dai C, Pan Q, Ding Z, Hu D, et al. Beyond Warburg effect – dual metabolic nature of cancer cells. Sci Rep 2014;4:4927.