Review

The endoplasmic reticulum stress response in disease pathogenesis and pathophysiology

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A B S T R A C T

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.

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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
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 endeavor 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-elicited.

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-β-butyryl-1,4-benzohydrolquinone (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 P58ipk 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
site, the ER is very sensitive to any processes that tip the balance of Ca²⁺ homeostasis, which is why ionophores, glycosylation inhibitors, toxins and unfolded proteins – all of which lead to ER lumen Ca²⁺ depletion – trigger the ER stress response. During viral transformation or glucose deprivation, transcription of glucose-regulated protein (GRPs) is upregulated. These GRPs are Ca²⁺-binding chaperone proteins, which by so binding perturbs Ca²⁺ homeostasis and leads to the EOR [45,46]. Compared to the UPR, the EOR seems to be more specialized in detecting Ca²⁺ perturbations. Recently, Wang et al. showed that TMCO1 encodes for an ER transmembrane protein that acts as a Ca²⁺-load-activated-Ca²⁺ channel (CLAC) in preventing luminal Ca²⁺ excess (Fig. 2B), coupling with the Ca²⁺-release-activated-Ca²⁺ channel (CRAC) to refill the ER lumen with Ca²⁺ [47]. Further, the EOR specializes in activating pathways leading to inflammation and cell proliferation (via NF-kB) 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

Ca²⁺ 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 Ca²⁺ release to activate the EOR and other related pathways for cell survival also activates GSK-3β, 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 Ca²⁺ depletion leads to the EOR, which then activates NF-kB. This explains in part why inflammation is a critical part of AD pathophysiology and progression [57,58], since NF-kB activation leads to cytokine production and subsequent recruitment of microglial cells [59]. However, since processing of APP can happen in
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 vesicles that generally transfer 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
overload of Ca\textsuperscript{2+} release in myocytes lead to what is called L-DOPA-induced dyskinesia (LID). Depletion of luminal Ca\textsuperscript{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 \textit{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\textsuperscript{2+} release and subsequent increase in intracellular Ca\textsuperscript{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\textsuperscript{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

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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\textsuperscript{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 further 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.
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 insulin 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 ejection 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 γ;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 and inhibits the activation of RNA-activated kinase (PKR), leading to reactivation of translation processes [77]. Further, the
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 depletes MHC class II-restricted T-cells that subsequently depletes precursors for T-helper cells (T_{h1}), 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].
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-XL, 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.

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