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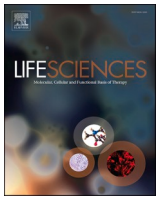

Review article

Cellular battle against endoplasmic reticulum stress and its adverse effect on health

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ABSTRACT

The endoplasmic reticulum (ER) is a dynamic organelle and a reliable performer for precisely folded proteins. To maintain its function and integrity, arrays of sensory and quality control systems enhance protein folding fidelity and resolve the highest error-prone areas. Yet numerous internal and external factors disrupt its homeostasis and trigger ER stress responses. Cells try to reduce the number of misfolded proteins via the UPR mechanism, and ER-related garbage disposals systems like ER-associated degradation (ERAD), ER-lysosome-associated degradation (ERLAD), ER-Associated RNA Silencing (ERAS), extracellular chaperoning, and autophagy systems, which activates and increase the cell survival rate by degrading misfolded proteins, prevent the aggregated proteins and remove the dysfunctional organelles. Throughout life, organisms must confront environmental stress to survive and develop. Communication between the ER & other organelles, signaling events mediated by calcium, reactive oxygen species, and inflammation are linked to diverse stress signaling pathways and regulate cell survival or cell death mechanisms. Unresolved cellular damages can cross the threshold limit of their survival, resulting in cell death or driving for various diseases. The multifaceted ability of unfolded protein response facilitates the therapeutic target and a biomarker for various diseases, helping with early diagnosis and detecting the severity of diseases.

1. Introduction

The endoplasmic reticulum (ER) is a convoluted and peculiar single membrane-bound intracellular organelle found only in eukaryotes. The ER rises from the nuclear envelope, continues as peripheral cisternae and tubules, and extends throughout the cell's cytoplasm. To meet the different demands of eukaryotic cells, distinct territories of ER become highly specialized and have various shapes and architecture. Cells with a high capacity to secrete proteins, especially pancreatic beta cells, lymphocytes, acinar cells, and adrenal cells, have considerable numbers of ribosomes attached to the ER sheets [1]. The ER pattern in neuronal architecture plays a significant role in pre-and postsynaptic signaling via

Abbreviations: UPR, unfolded protein response; hPSCs, human pluripotent stem cell; GRP 78, Glucose Regulated Protein 78; BIP, binding immunoglobulin protein; HSP 70, heat shock protein 70; HSP 40, heat shock protein 40; ERQC, endoplasmic reticulum quality control system; IRE1α, Inositol requiring transmembrane kinase/endoribonuclease 1α; PERK, PER-like ER kinase; ATF6, activating transcription factor-6; XBP 1, X box-binding protein; ERAD, endoplasmic reticulum associated degradation system; RIDD, Regulated IRE1 α Dependent Decay; IRAK2, Interleukin-1 Receptor Associated Kinase-2; TRAF2, tumor necrosis factor receptor-associated factor 2; JNK, C-jun NH2-terminal kinase; eIF 2α, eukaryotic translation initiator factor 2α; ATF4, activating transcription factor 4; CRE, cAMP response element; CHOP, CAAT/enhancer-binding protein (C/EBP) homologous protein; RPAP2, RNA Polymerase II Associated protein 2; DR5, Death Receptor 5; ERO1L, endoplasmic reticulum oxidoreductin like-1 like protein; ROS, Reactive Oxygen Demand; SIRT1, Sirtuin-1; ERAS, endoplasmic reticulum associated RNA silencing; ERLAD, ER-to-lysosome-associated degradation; PDI, protein disulfide isomerase; BCL2, B-cell leukemia/lymphoma 2 protein; TEX264, testis expressed gene 264; ATL3 308, atlastin GTPase 3; RTN3L, reticulon 3; MAMs, mitochondria-associated membranes; IP3R, Inositol 1,4,5-trisphosphate (IP3) receptors; RyRs, ryanodine receptors; SERCA, Sarcoplasmic/ER Ca2 + 356 ATPase; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; DAMPS, damage-associated molecular patterns; TLR 9, Toll like Receptor; TRAIL, tumor-necrosis factor related apoptosis inducing ligand; VDACs, voltage-dependent anion channels; NFκB, Nuclear Factor Kappa B; IKK, Ikappa B kinase; AP-1, activator protein 1; LC 3, 1A/1B-Light chain 3; DNAJB11, DNAJ homolog subfamily B member 11; MANF, mesencephalic astrocyte derived neutrophic factor; FOXO1, Forkhead box protein 01; Sdf2L1, stromal cell derived factor 2 like 1; Vps34, vacuolar protein sorting 34; COPD, chronic obstructive pulmonary disease; PCOS, polycystic ovary syndrome; HRD1, human ubiquitin ligase; Pael-R, Parkin-associated endothelin receptor-like receptors; 3-MCPD, 3-chloro-1, 2-propanediol; CRELD2, cysteine rich with epidermal growth factor (EGF)-like domains 2; TXNDC5, thioredoxin domain containing 5.

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Ca^{2+}, and ER present in the Human pluripotent stem cell (hPSCs) are structurally underdeveloped [2]. Several dynamic properties of ER are accountable for its unique functions. They are a net-like structure that acts as a communication hub and maintains tight contact with other subcellular organelles. Large surface areas are responsible for calcium storage and metabolic processes like glucanogenesis, drug metabolism & lipid synthesis [3]. The ribosomes embedded in the rough endoplasmic reticulum are central to protein synthesis. The oxidative microenvironment is an excellent platform for post-translational modifications, disulfide bond formation, protein folding & maturation. Finally, apt protein folding is tightly regulated and supported by the quality control agents in the ER. Numerous chaperones, like calnexin, calreticulin, glucose-regulated protein 78 (GRP 78)/binding immunoglobulin protein (Bip) and heat shock proteins (HSP 70 and HSP 40), enzymes that require glycosylation (glycosidase and transferase) and disulfide bond formation (protein disulfide isomerase) are the critical components of the endoplasmic reticulum quality control system (ERQC) [4]. The teamwork of ER and ER quality control systems successfully renovates the nascent protein into its native form. ER acts as a quality control system for the secretory proteins, especially the checkpoints, which selectively set aside only precisely folded proteins, and abnormal proteins are degraded (by autophagy and ubiquitin proteasomes) or returned to the chaperones for refolding. Even though the highest error-prone step in the gene expression process is protein folding, ER is an excellent protein folding and maturation factory for most of the secretory proteins and all the membrane proteins in the eukaryotic cell [5]. Here, we critically review the current knowledge about ER stress, novel mechanisms of terminal UPR, and its adverse effects on health.

2. ER stress signaling - UPR

The efficiency and fidelity of apt protein folding are vital for ER homeostasis; these are constantly adjusted by integrating various environmental and cellular signals like genetic insults/abnormalities, the error-prone nature of protein folding, organismal aging, and an impaired protein quality control system. These are primarily governed by oxidative, metabolic, pathological, & proteotoxic stresses, imbalanced calcium levels, energy deficiency, inflammatory stimulation, and defective autophagy [6–14]. All of which directly or indirectly impact ER homeostasis, eventually leading to the accumulation and aggregation of misfolded proteins in the ER lumen, causing ER stress. Upon ER stress, the cell triggers a spectrum of intrinsic signaling pathways to cope with protein folding alterations, collectively called the unfolded protein response (UPR). The UPR signaling pathways are initiated by the activation of ER-localized sensory proteins IRE1α (Inositol-requiring transmembrane kinase/endoribonuclease 1α), PERK (PKR –like ER kinase), and ATF6 (activating transcription factor 6) and act as an effective warrior against ER stress. Generally, sensory protein activities are hindered by the bounded chaperone BiP. The accumulation of misfolded proteins frees them, activates all three sensory proteins, and controls the ER function by regulating various transducers. Initially, UPR tries to reestablish ER homeostasis via various pro-survival activities called adaptive UPR but prolonged or overwhelming ER stress conditions, UPR fails to restore ER homeostasis, so its signals are continuously emitted and eventually converted into terminal UPR/maladaptive UPR leading to disease or cell death via hyperactivation of UPR pathways [15–17].

2.1. IRE1α

IRE1α is a bilingual protein with serine/threonine kinase and endoribonuclease domains. Upon ER stress, it dimerizes and trans-autophosphorylates the juxtapose kinase domain, subsequently activating the site-specific endoribonuclease. The endoribonuclease enzyme initiates excision of the 26-nucleotide intron from the mRNA encoding the transcription factor X box-binding protein 1 (XBP1). The active form of XBP1 translocates to the nucleus and upregulates the spectrum of gene expression involved in prosurvival events, such as quality control, maintaining ER homeostasis, ERAD, and autophagy or promoting cell death through apoptosis. Upon XBP1 deficiency, IRE1α turned on RIDD (Regulated IRE1α Dependent Decay) mechanism to reduce ER stress [18,19] RIDD can lessen the burden of ER stress through the RNase of IRE1α. It rapidly cleaves the mRNA at the specific cleavage site (consensus sequence CUGCAG motif in stem-loop structure) and halts the protein production that challenges the ER. During ER stress, IRAK2 (Interleukin-1 Receptor-Associated Kinase-2) acts as a regulator and amplifies the IRE1α expression to resolve the unfolded protein [20]. [21], exposed a novel anti-apoptotic factor, EI24, which is ER transmembrane protein and plays a dual role; IRE1α-mediated UPR activation and regulating the calcium homeostasis in the lumen of ER. At normal conditions, the EI24 protein binds with the kinase domain of IRE1α and inhibits its activity. Upon stressed condition, it dissociates, activates IRE1α, and binds to the IP3R1 to prevent excessive calcium leakage [22].

Upon unresolved ER stress (terminal/maladaptive UPR) conditions, activated IRE1α collaborates with the cytosolic adapter proteins TRAF2 and activates various stress signals like inflammatory and cell death pathways [23]. Increasing IRE1α -JNK signaling stimulates the proapoptotic factors BID and BIM and elevates programmed cell death. Cytosolic TRAF2 bounded with the activated IRE1α and phosphorylated the C-jun NH2-terminal kinase (JNK). JNK phosphorylation induces inflammatory genes to be expressed via the activator protein 1 (AP-1). They induce inflammation by promoting cytokines, chemokines, and other proinflammatory molecules [24]. There is some evidence that IRE1α forms a complex with the cytosolic IKK through TRAF2 and subsequently phosphorylates the IκB and activates NFκB. IRE1α and XBP1 knockout mice studies revealed that IRE1α is critical for both embryonic and placental development [25]. The IRE1α inhibition studies demonstrated that IRE1α has other crucial functions, including delaying the malignant progression of cancer & increasing the survival rates [26–28], activating inflammasomes [29] and reducing pain in PGE_2-regulated mouse models of pain in mice [30]. XBP1-deficient mice have a significant bacterial burden during infection compared to wild-type mice; this clearly shows the role of XBP1 in the immune system of mammals [31].

2.2. PERK

PERK is a serine/threonine kinase protein, and it undergoes dimerization, trans-autophosphorylation, and further oligomerization to activate. And concomitantly phosphorylate the downstream substrate eukaryotic translation initiator factor-2α (eIF2α) at the serine 51 subunit. It transiently attenuates the protein synthesis owing to a lower amount of GTP. It temporarily halts the release of newly synthesized protein and a continuous accumulation of unfolded proteins, thus reducing ER stress. On the other hand, higher levels of phosphorylated eIF2α repress most of the mRNAs but promote the expression of ATF4. ATF4 (Activating Transcription Factor 4) binds to the cAMP response element (CRE) and promotes the expression of ER stress-mediated proteins such as ATF3 and CHOP [1]. CHOP is a critical intermediator of ER stress-induced apoptosis. Hyperactivation of PERK potentially induces NF-κB mediated inflammation. Generally, PERK activates eIF2α-mediated attenuation of translation which inhibits the synthesis of IκBα. Insufficient NF-κB inhibitor IκBα triggers inflammation [32]. Chang et al. studies revealed that the unresolved ER stress persists in the PERK activity but paradoxically attenuates IRE1α. PERK activates eIF2α and subsequently induces RPAP2 (RNA polymerase II-associated protein 2). This activated RPAP2 suppresses the IRE1α activity by dephosphorylation [33] (Fig. 1). As a result, it impaired RIDD mechanisms and derepressed the DR5/TRAIL expression. The well-known fact is that upon the initial period of ER stress, RIDD mechanisms encounter proapoptotic signals like DR5/TRAIL mRNA. Upregulated TRAIL activates the FADDosome complex (caspase-8, FADD, and RIPK1), which triggers

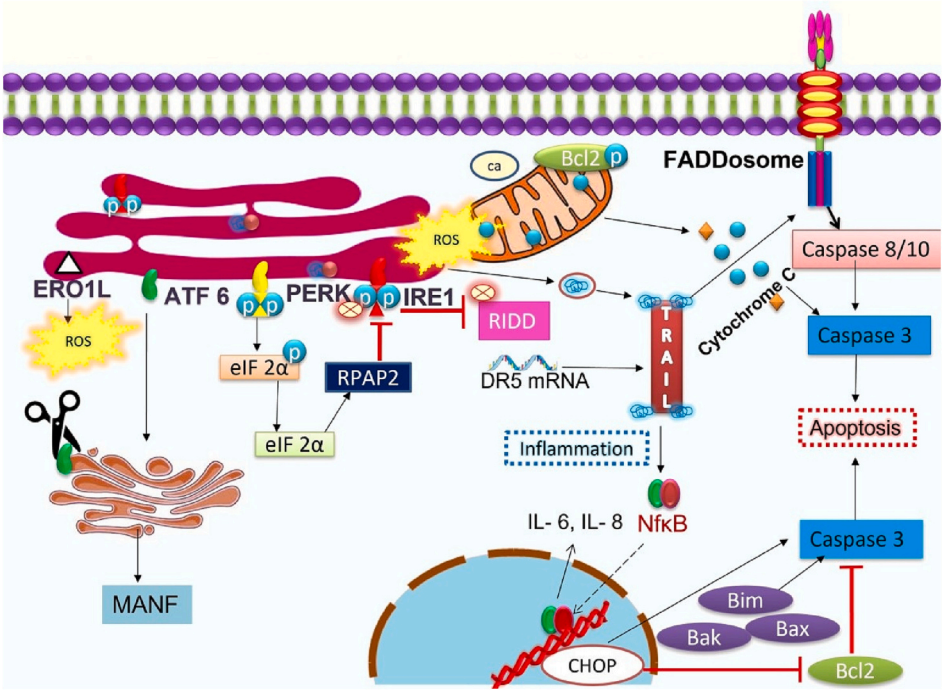

Fig. 1. Overview of the terminal UPR/maladaptive UPR mechanisms. Overwhelming or prolonged misfolded protein accumulation in the ER lumen ultimately causes terminal UPR. In such conditions, PERK transmembrane protein overexpresses the RPAP2, which dephosphorylates the IRE1α and inhibits its activity. IRE1α suppression ultimately impaired the RIDD mechanisms and de-repress the TRAIL/DR5 mRNA synthesis. Unfolded proteins can act as a ligand and bind directly to the TRAIL protein, activating the FADDosome complex (caspase-8, FADD, and RIPK1), mediating the NF-kB pathway, resulting in the expression of inflammatory cytokines (IL-6 & IL-8). Finally activates apoptosis via the induction of the caspase 3 enzyme or disrupts the equilibrium of the mitochondrial protein Bcl-2 to release the cytochrome C. Prolonged ER stress activates the ER lumen protein ERO1L to leak H_2O_2, increasing ROS in the cytoplasm. MANF is an ER lumen chaperone overexpressed by the ATF6 transmembrane protein responsible for the refolding nature of the misfolded proteins.

the NFκB pathway and subsequent activation of cytokines [34,35]. Adding credence to this idea, Lam et al. studies revealed that the unfolded proteins could act as a ligand to bind the TRAIL receptor intracellularly and promote apoptosis [36]. Recent studies show that the tight control of PERK-eIF2α signaling is essential for normal, long-lasting synaptic plasticity, cognitive function, & memory development and induces the antioxidant gene (glutathione S transferase) regulation [37,38]. Impaired PERK-eIF2α drives neurodegeneration, attenuates microglial activation, skeletal dysplasia, hyperglycemia, and reduces beta-cell proliferation [39–43]. Recent studies revealed that the BZW1 protein act as an adaptor for the PERK protein and facilitates the phosphorylation of eIF2α, promoting the Warburg effect via HIF1α and c-Myc translation [44].

2.3. ATF6

ATF6 is a type II transmembrane protein constructed by two isoform proteins, such as ATF6α and ATF6β. Upon ER stress, detachment of BIP/GRP78 unmasks the Golgi-localization signal, which translocates the ATF6 from ER to Golgi. In Golgi, ATF6 undergoes proteolysis by the endopeptidase enzymes such as S1P I (Site-1 protease) and S2P (Site-2 protease). Consequently, the active ATF6 transcription factor is released by the dissection of ATF6 from the juxta membrane site. The activated ATF6 bound to an ER stress response element in the nuclease and triggered the range of proteins involved in the UPR machinery. In unresolved ER stress (terminal UPR) conditions, ATF6 sensory protein upregulates the ER-localized chaperone MANF activity and reduces the misfolded protein secretion [45]. ATF6 knockout studies exposed early embryonic lethality in mice [46]. Novel endoplasmic reticulum oxidoreductin-1-like (ERO1L) protein is responsible for disulfide bond formation in the newly synthesized protein. Upon ER stress conditions, ERO1L promotes a hyper oxidizing environment in the ER lumen, resulting in H_2O_2 leakage and cytotoxic ROS in the cytoplasm [47].

3. Terminal UPR adaptations

It is well known that prolonged or overwhelming ER stress leads to terminal UPR results in apoptosis and tissue/organ damage. Knowing the molecular switches that govern how the UPR selects the stress adaptations over apoptosis is crucial. A deficiency of ER stress adaptations leads to apoptosis and is associated with various human diseases. Recent studies revealed that misfolded proteins accumulation in the ER lumen selectively activates the N^6-adenosine-methyltransferase-14 (METTL14) expression and promotes chop mRNA decay by its 3′ UTR N^6-methyladenosine (m^6A) [48]. Hyperactivation of unfolded protein response induces the Sirtuin (SIRT1), suppressing the ER stress-induced apoptosis via regulating the PERK activity [49]. SIRT1 interacts with the eIF2α and deacetylates it, reducing the proapoptotic protein CHOP expression [50]. SIRT1 plays a positive role in various ER-induced organ damages via promoting autophagy, decreasing apoptosis, regulating the sensors of UPR, decreasing the S-nitrosylation effect of protein disulfide isomerase (PDI) protein, and increasing the expression of FOXO1, HSP70, ORP150, and HSP40 [50–52].

4. Mis-folded protein degradation system

ER has evolved to resolve the accumulation of misfolded proteins in critical ways through protein degradation mechanisms like ER-phagy (selective autophagy for ER, which turns over the damaged ER in bulk) and ERAD. The ER-cytosol-associated ERAD system degrades unassembled and misfolded proteins in ER. However, the significant biosynthetic compartment ER lacks the degradation system, but the UPR mechanisms control the expression of many ERAD proteins. Misfolded proteins in the ER lumen will be recognized by the ER chaperones (calnexin, calreticulin, and protein disulfide isomerases), further retrotranslocating to the cytosol via the Hrd1-SEL1L channel, and finally degraded by the 26 s proteosomes [53] (Fig. 2).

Recent studies revealed that the ERAD deficient (lacking the Sel1L-Hrd1 protein complex) mice were cold-sensitive, exhibited mitochondrial dysfunction, and developed podocytopathy [185]. The ERAD process is vital for nephrin maturation and kidney glomerular filtration task [54]. Xu et al. studies show that the Sel1L-Hrd1 protein expressions are too high in stem cells and that inhibiting the activity of the *sel1l* gene destroys stem cell identity [55], which state that the ERAD mechanisms act as safeguards against genotoxic and proteotoxic stress and maintain a healthy pool of stem cells. Sdf2l1 is an ER-resident protein that acts as

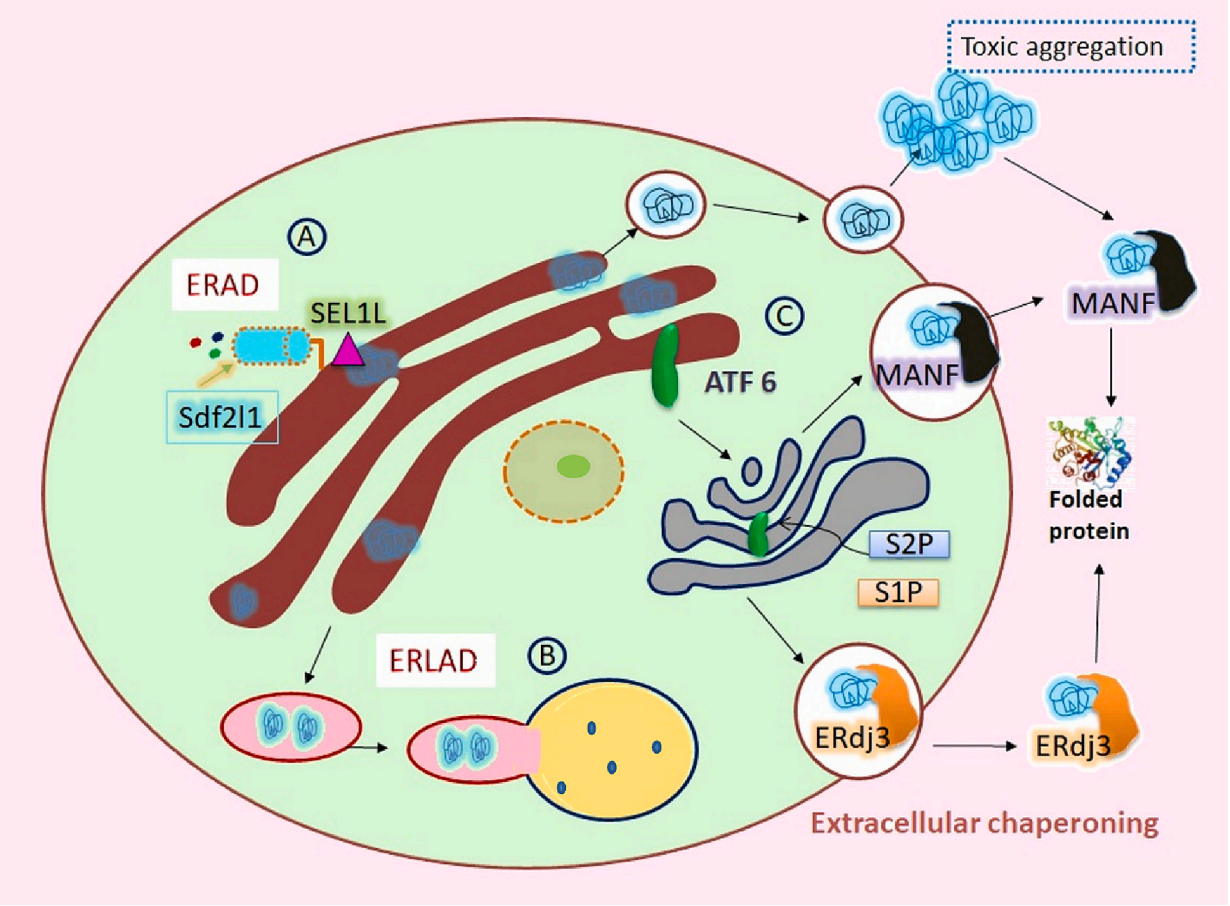

Fig. 2. ER-related garbage disposals systems.
A: The ER chaperones recognized the unresolved misfolded proteins in the ER lumen, which were translocated to the cytosol via the transmembrane protein SEL1L, mediating proteosomal degradation of the misfolded proteins. Sdf2l1 acts as a regulator of the ERAD pathway. B: ERLAD is an alternative method of degrading misfolded mutant proteins. In the ERLAD method, ERAD-resistant misfolded proteins were segregated in the subdomain of ER with the help of ER chaperone calnexin. It formed a single membrane vesicle with aggregated misfolded proteins. It fuses with the lysosome and mediates the degradation process. C: Acute ER stress leads to the secretion of misfolded proteins in the extracellular space. In order to resolve these toxic aggregates of misfolded proteins, the cell activates the ATF6 signaling protein, which gets activated by the splicing process in the Golgi and upregulates the extracellular chaperones such as MANF and ERdj3. These chaperones were segregated or co-segregated to the misfolded proteins and resolved the misfolded nature of the protein.

a chaperone and regulates ERAD; that expression is correlated with sXBP1 during obesity and diabetic conditions [56].

4.1. ER-to-lysosome-associated degradation (ERLAD)

ER-to-lysosome-associated degradation (ERLAD) is a novel misfolded protein degradation mechanism that uses lysosomes to degrade the aggregated proteins in the ER lumen [57,58]. ERLAD system degrades mainly the proteasome-resistant (ERAD resistance) proteins like dysferlin mutants, serpin mutants, and alpha1 antitrypsin (AT) variants [9,10]. ERLAD pathways are initiated by the accumulation of misfolded polymers in the ER lumen and are segregated in the ER subdomains by the chaperone calnexin and the LC3 lipidation machinery. Immediately single membrane ER-derived vesicles formed with the intervention of ER-phagy receptor FAM134B. ER-derived vesicles were fused with the lysosome with the help of ER-resident SNARE STX17 and the lysosome-resident SNARE VAMP8 proteins (Fig. 2). It favors the release of the aggregated proteins into the lysosomes for clearance [9].

4.2. ER-associated RNA silencing (ERAS)

Numerous cell survival mechanisms were developed in cells to maintain ER homeostasis during stressful conditions. A novel post-transcriptional silencing of the ER-associated mRNA turnoff mechanism, ERAS, was recently discovered by Efstathiou et al. It works through RNA silencing machinery like argonaute protein RDE-1/AGO2 mediated mRNA degradation [59,60]. The ERAS mechanisms work together with the ERAD and protect the cell from ER stress-associated cellular damages by maintaining ER homeostasis and reducing protein flux and tissue integrity. Even though ERAD and ERLAD mechanisms effectively work against chronic ER stress, it has a lacuna in slower and time-consuming activation against the misfolded protein load [61]. The novel ERAS mechanisms swiftly work against ER stress via selectively degraded mRNA releases from the ribosomes attached to the ER and reduce the protein flux. The other mRNA degrading mechanisms, such as RIDD, differ entirely from ERAS. RIDD reduces the ER stress burden with the help of IRE1α and cleaves the mRNA at the specific cleavage site to reduce protein production.

5. Extracellular chaperoning

Cells deploy a variety of catabolic roots to cope with the error proneness of protein folding. The eminent ER quality control mechanisms, such as the UPR system and the misfolded protein degradation system (ERAD and ERLAD), effectively work against the misfolded protein accumulations in the ER lumen. Yet, several factors, such as genetics, aging, and environment, disrupt the appropriate protein folding mechanisms. Such conditions unequivocally increased the

secretion of misfolded proteins in the extracellular space. Satpute-Krishnan et al. studies revealed that severe ER stress activates the direct secretion of some amount of misfolded proteins in the extracellular membrane before they activate the lysosome-mediated degradation mechanisms or when the ERAD system is in a saturated condition [61]. Misfolded proteins in the extracellular space are related to various diseases like Alzheimer's, Glomerulonephritis, Down's syndrome, Spongiform encephalopathies, and Creutzfeldt–Jakob [62,63]. Cells develop an extracellular chaperoning system to resolve the misfolded protein aggregation in the extracellular space. Generally, most of the chaperones in the ER, like BIP (GRP78), PDI, and GRP94, contain a C-terminal KDEL-ER retention sequence that acts as a signal to keep the chaperone in the ER [64]. However, specific chaperones like ERdj3 lack KDEL sequences and are reported as secretory chaperones [65]. Some chaperones like MANF (mesencephalic astrocyte-derived neurotrophic factor) have a KDEL sequence; due to the ER stress, the affinities of the KDEL sequence receptors were altered, leading to the secretion of those protein chaperones in the extracellular space [66].

Upon ER stress, ATF6 plays a significant role in preventing extracellular protein aggregation through the upregulation and secretion of the ER-resident HSP40 ERdj3/DNAJB11 and MANF chaperones [67,68] (Fig. 2). Recent studies revealed that the MANF is a novel redox-sensitive chaperone, enhancing protein folding and increasing myocyte viability during reductive ER stress [45]. Secreted ERdj3 binds to misfolded proteins or co-secreted with the unfolded proteins in the extracellular space, inhibits protein aggregation, and attenuates proteotoxicity of the disease-associated toxic protein (Fig. 2). Recent studies showed that ERdj3 chaperone participates in Z mutation of the alpha-1-antitrypsin gene (ZAAT) trafficking network, and the depletion of the ERdj3 increased the rate of ZAAT degradation [10]. ERdj3-SDF2L1 complex increases the chaperoning activity of ERdj3 and inhibits the misfolded protein aggregation [65,69].

6. ER-phagy

Autophagy is one of the essential cell survival mechanisms, activated upon cellular stress to establish cellular homeostasis and aid in the lysosomal degradation of unfolded/misfolded proteins, aggregated proteins, and damaged subcellular organelles. During ER stress, activated sensory proteins and calcium-mediated signaling regulates ER-phagy [70–72]. A novel autophagy-inducing agent, sertraline, is bound to the mitochondrial VDAC1 (voltage-dependent anion channel 1) and induces autophagy via the AMPK-mTOR pathway [73]. Upon ER stress, activated IRE1α bounded with TRAF2 & apoptosis signal-regulating kinase-1 (ASK1) to the stress kinases JNK. Activated JNK phosphorylates Bcl-2, disrupts the Beclin-1/Bcl-2 complex, and forces the Beclin-1 to release. The released Beclin-1 forms the complexes with vacuolar protein sorting 34 (Vps34), which leads to vesicular nucleation. In addition, XBP-1 and IRE1α RNase domains also trigger autophagy through the upregulated expression of Beclin-1 [72]. Activated PERK induces the expression of ATF4, a pivotal transducer to induce the ATG 12 and CHOP proteins. These induce a range of proteins (MAP1LC3B, BECN1, ATG3, ATG12, ATG13, ATG16L1, RETREG1, and TEX264) involved in autophagy [74,75] (Fig. 3). Activated sensory protein ATF6α initiates autophagy by elevated expression of AKT [76,77]. Autophagy deficiency causes impaired skin repair, proliferation, migration, and suppressed fibroblast activation in keratinocyte cells [186] and decreases glutathione released by the astrocyte [78]. Excessive cell degradation may lead to the loss of specific enzymes in the lysosome, leading to lysosomic storage diseases. Recent studies revealed

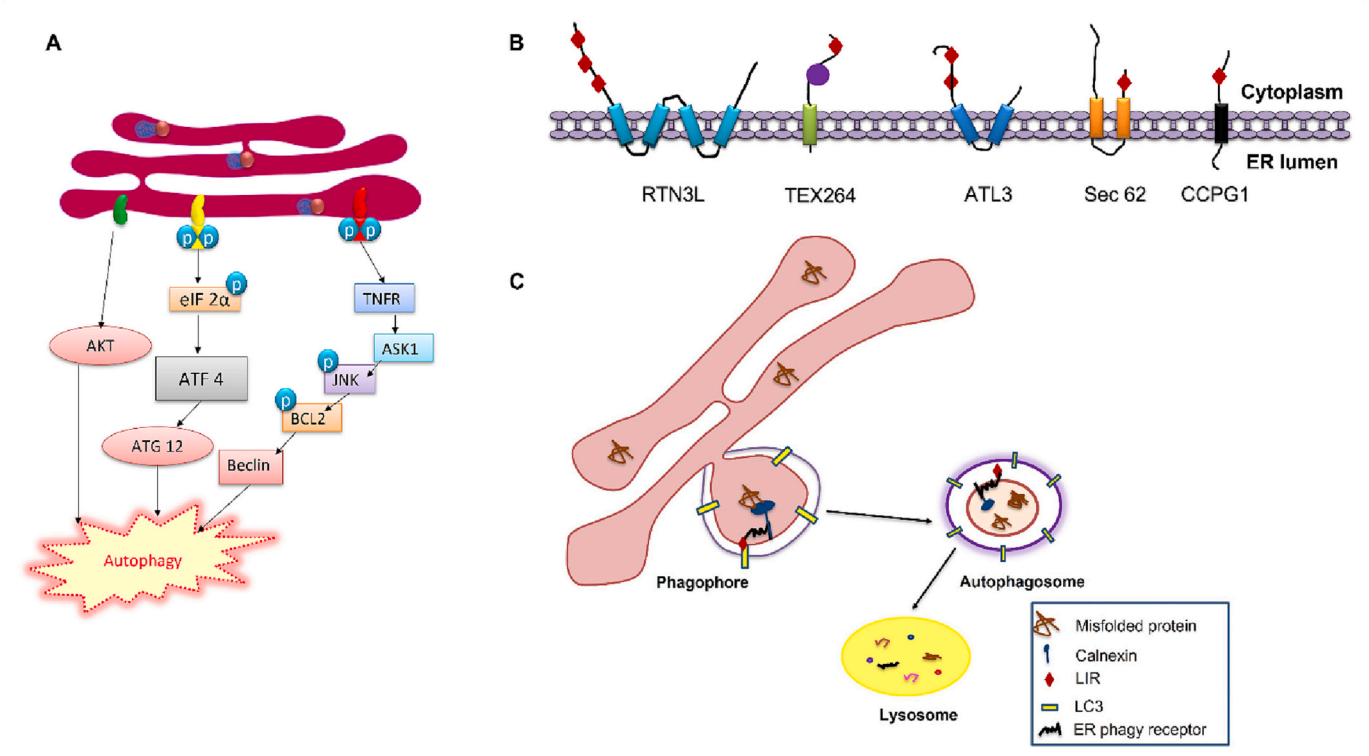

Fig. 3. ER-phagy

A: Overview of the ER stress-mediated autophagy. Sensory proteins IRE1, PERK, and ATF6 activate autophagy via the sequential activation of various proteins. B: Structure of mammalian ER-phagy receptors. ER-phagy receptors are ER transmembrane proteins containing LC3 (or GABARAP)-interacting region (LIR), which can bind to autophagosomal LC3/GABARAP family proteins. C: Mode of ER-phagy mechanisms: During the recovery phase of ER stress, misfolded proteins were accumulated at the ER exit site. With the help of ER-phagy receptors, the autophagosomes cover the selective subdomains. ER-phagy receptors have fragmentation activity and cleave the ER portion into fragments during sequestration into an autophagosome. Finally, it fuses with the lysosome and degrades the accumulated misfolded proteins.

that dysfunctional lysosomal storage impaired the synaptic structure [79]. Gaucher's disease is caused by the excessive degradation of the mutant protein β-glucocerebrosidase and subsequent insufficient lysosomal function [80].

6.1. ER-phagy receptors

ER-phagy receptors/adaptors facilitate ER-phagy and mediate the degradation of ER in specific regions. Recent studies revealed that, during ER-phagy, a range of ER-localized surface proteins, like CCPG1 (cell cycle progression 1), TEX264 (testis expressed gene 264), ATL3 (atlastin GTPase 3), RTN3L (reticulon 3) and FAM134B act as specific autophagy receptors of LC3/GABARAP-interacting regions and hire ER-phagy machinery [81]. ER -phagy receptors are accountable for the specific degradation of the ER portion [82] and prevent the hyper-accumulation of misfolded proteins in the ER lumen [82]. FAM134B is an ER-shaping protein responsible for the curved sheet in ER. Over-expression of this protein leads to fragmentation of ER. Also, it enhances the degradation of sec61B protein in the ER sheets, whereas the down-regulation of this protein is responsible for the expansion of ER [81,83,84]. Mutant FAM134B causes impaired nociception, autonomic dysfunction, and autonomic neuropathy via apoptosis in dorsal root ganglion neurons [85]. Recent studies state that the coreceptor calnexin recognized the misfolded proteins and interacted with the ER-phagy receptor FAM134B [86]. ATL3 and RTN3L ER-phagy receptor is found in the tubular region of ER and is responsible for tubular degradation [87,88]. ATL3 is an ER fusion protein, defects in this protein cause neurodegeneration [89]. Recent findings suggest that the ATL3 protein is required for the virion genome maturation and virus production [90]. A novel ER-phagy receptor, TEX264 is a single-pass transmembrane ER-resident protein that uses LC3 interacting region (LIR) to traffic into ATG8-positive puncta and initiates ER-phagy via the formation of the three-way ER tubule junction and subsequently fuses with a lysosome [91,92]. The central role of the ATG8 in the growing autophagosome is autophagosome's maturation and expansion. It directly binds to the cargo receptors in the lysosome and is also involved in DNA repair [93]. TEX264 receptor is present throughout the ER network, and the increasing or decreasing rate of TEX264 protein results in the altered ER-phagy flux [94]. TEX264 knockout studies revealed that it could affect cell migration in the Hela cells by regulating SNX27- mediated Itgα 5 receptor membrane recycling [95]. CCPG1 is an ER-localized transmembrane protein that helps to degrade peripheral ER. ER stress-mediated unfolded protein response induced the CCPG1 ER-phagy receptor and mediates ER-phagy [96,97].

7. Calcium signaling in ER and mitochondria

ER lumen is the dynamic reservoir of calcium. Calcium is one of the vital signal transducers associated with proteins and mediates several functions and, in addition, acts as a buffering system. Calcium participation in the brain is essential for various intracellular and extracellular processes and brain functions, including neuronal excitability, plasticity, synaptic transmission, and memory formation [98]. ER-mitochondrial crosstalk is an excellent adaptive mechanism for handling environmental stress through calcium and ROS signaling. ER interacts closely with the mitochondria by the mitochondrial reticular branched network in the cytosol termed mitochondria-associated membranes (MAMs). ER transmits Ca_2^+ signals via the MAMs region to the mitochondria, which regulate numerous functions like metabolism, energy production, and apoptosis in the cell [99]. Inositol 1,4,5-trisphosphate (IP3) receptors (IP3R) and ryanodine receptors (RyRs) are the chief effectors of the ER Ca_2^+ release machinery. The FK506-binding protein binds with the RYR receptor, acts as a RyR stabilizer, and suppresses calcium leaks or excessive calcium release [100]. The released Ca_2^+ entered the mitochondrial intermembrane space through the voltage-dependent anion channels (VDACs) [101]. 75-kDa glucose-regulated protein (GRP75) acts as an interacting protein between IP3R and VDACs to transfer Ca_2^+ [102]. VDACs are a class of mitochondrial channel proteins that forms large voltage-gated pores in the outer mitochondrial membrane sites and are extensively abundant in the ER-mitochondrial contact sites. The mitochondrial calcium uniporter (MCU) complex is responsible for the rapid transport of Ca_2^+ into the matrix of mitochondria. The type II calcium pump, Sarcoplasmic/ER Ca_2^+ATPase (SERCA) uniporter, is present in the ER membrane and helps to uptake the Ca_2^+ back to the ER lumen [8]. The SERCA pump's crucial role in calcium maintenance represents an attractive target for proteins that regulate cell death. Fine-tuned calcium levels are regulated by calcium-binding and buffering proteins such as calretinin, calcineurin, calmodulin, and calbindin. The different molecular players (transcription factors) and the upstream signaling pathways also regulate Ca_2^+ signaling in the MAMs region. Chronic ER stress permits the calcium release from the ER and consequently increases it in the mitochondrial matrix; these overloaded calcium accumulations can dramatically alter mitochondrial functions like ATP production and subsequently increase ROS production. Accumulating Ca_2^+ and ROS triggers mPTP (mitochondrial permeability transition pore) opening leading to mitochondrial permeability via the leakage of mitochondrial-derived factors, such as mtDNA (mitochondrial DNA), cytochrome C, DAMPS (damage-associated molecular patterns), and dsRNA, which induce the activation of TLR9 which leads to NFκB mediated inflammasome formation. It is responsible for the various pathological challenges and triggers mitophagy and subsequent apoptosis (Fig. 1).

A range of interacting proteins was located in the MAM region to facilitate ER-mitochondrial contact and accountable for their interchangeable contents. ER-localized VABP and Bap31 interacted with the OMM protein PTPIP51 (tyrosine phosphatase-interacting protein-51) and FIS1 (mitochondrial fission 1 protein), respectively [103]. Recent studies show that FUNDC1 is an outer mitochondrial membrane protein that binds with the ER-resident IP3R2 protein. The disturbance of FUNDC1 leads to poor interaction between ER & mitochondria and limits the calcium level in both mitochondria and cytosol. Over-expression of *fundc1* raises calcium levels [104]. Current findings suggest that the ER stress transducer IRE1α is also located in the MAM region and interacts with the vital calcium channel IP3R2. IRE1α deficiency altered mitochondrial physiology and energy metabolism [105].

8. ER stress in health and diseases

The life of an individual organism is stressful in a natural ecosystem. Live cells exposed continuously to different stresses significantly altered the cell's health and life span. Stress-mediated signaling pathways are interlinked, evolutionarily conserved, and played a cardinal role in maintaining homeostasis. Rapid ongoing climate change & global warming, and labor-intensive workers in hot and humid environments forced live cells frequently encounter heat stress [106]. It induces a variety of illnesses like a decline in male fertility, heatstroke, and metabolic disorders. In recent investigations, it has become clear that heat stress damages the different cells of the testis and brain by inducing ER stress [107], oxidative stress, and subsequent apoptosis. The studies of Liu et al. demonstrated that heat stress induces ER stress and inhibits heat shock responses through the translational block in the heat-stressed rat. Heat shock protein (HSP) is a molecular chaperone that protects the cell from heat-induced damages like misfolding and protein degradation and the refolding nature of the damaged proteins. Recent studies showed ER stress is the primary pathology of the common endocrine disorder, polycystic ovary syndrome (PCOS). ER stress inhibitors effectively reduce interstitial fibrosis and collagen deposition in the ovary [108,109].

8.1. Lung diseases

Prolonged cigarette smoking causes the primary pathology of

chronic obstructive pulmonary disease (COPD), mainly affected by imbalanced proteolytic and inflammatory responses, increased oxidative & nitrosative stress, increased apoptotic cells, and decreased proliferation [110,111]. Epithelial ER stress increases lung fibrosis risk and causes idiopathic pulmonary fibrosis [112]. ER stress-associated genes like *EIF2AK3*, *HSPA5*, and *DDIT3* polymorphisms are related to a high risk of lung cancer [113]. Recent studies revealed that ER stress inhibitors like PI3K and 4-phenyl-butyric acid (4-PBA) effectively work against the pulmonary fibrosis and lung injury models, respectively [114,115]. Cisplatin, in combination with the ER stress inhibitors like 4-phenyl-butyric acid (4-PBA) or tauroursodeoxycholic acid sodium (TUDC) treatment, enhances apoptosis in lung cancer cells [116]. Quercetin, a well-known anti-inflammatory flavonoid compound, protects the sepsis-induced acute lung injury (ALI) via the SIRT1/AMPK pathways and suppresses ER stress, oxidative stress, and mitochondrial dysfunction [117]. Natural compounds like crassolide, pendulone, and lathyrol have an effective anti -tumor activity against lung cancer cells via inducing ER stress pathways and oxidative stress pathways and subsequent apoptosis [118–120]. ER stress-associated severe eosinophilic and neutrophilic inflammation plays a crucial role in the pathogenesis of asthma in patients of the lungs [121].

8.2. Diabetes

Chronic Endoplasmic Reticulum stress is the primary pathology for developing type 2 diabetes [122]. The long-term overexpression of mutant proinsulin proteins accumulated in the ER lumen perturbs the ER-Golgi trafficking, leading to ER stress, increased inflammatory responses, and finally induces beta cell death by apoptosis [123]. Recent studies exposed the adaptive plasticity properties of beta cells against reversible chronic ER stress. Beta cells lost their function and identity during stressed conditions via transcriptional and translational reprogramming and regained their property when they recovered from the stress [21]. Glucose fluctuation is more harmful than sustained hyperglycemia and promotes apoptosis by triggering ER stress signaling pathways in diabetic rats [124]. ER stress and inflammation are the central pathology of diabetic retinopathy (DR). It triggers ATF6-related ER stress via its susceptibility gene transcription factor 7 like 2 (TCF7L2) [125]. Recent studies state that tauroursodeoxycholic acid (TUDCA) is a dynamic therapeutic agent against diabetic complications of vascular and neurodegenerative changes in the retina. The receptor TGR5 plays a significant role in retinal ER stress and neurovascular dysfunction in diabetic retinopathy [126]. A novel bioactive compound lactucaxanthin, acts as a therapeutic compound against the diabetic retinopathy condition [127].

8.3. Liver diseases

ER stress is associated with multiple liver pathologies such as liver ischemia, drug toxicity, alcohol associated liver diseases, viral hepatitis, and liver cancer [15]. Chronic ER stress is the central pathogenesis of non-alcoholic fatty liver diseases, and recent studies state that NRF2-mediated SIRT3 induction protects the hepatocyte cell from chronic ER stress [128]. The high-risk heavy metal cadmium induces liver damage by activating the PERK-eIF2α-ATF4-CHOP signaling pathway and subsequent ferroptosis [129]. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease. ER stress acts as primary pathology and an upstream signal for liver ferroptosis in NAFLD conditions. The natural compound acacetin reduces the serum cholesterol, aspartate aminotransferase, alanine aminotransferase levels, triglycerides, and suppresses the increased body weight in a high-fat diet mouse model [130]. Citrinin, a secondary metabolite, mainly induces cell arrest and liver injury by activating ROS and ER stress signaling pathways [131]. A recent study stated that the main dietary flavonoid avicularin attenuated lead-induced damages like hepatic inflammation and hepatic glucose metabolism via ER stress and inflammatory pathways [132].

8.4. Heart diseases

Chronic ER stress and oxidative stress critically impact cardiomyocytes function and result in cardiac hypertrophy, dilated cardiomyopathy, ischemic heart diseases, arrhythmias, and heart failure [133,134]. RyR and the calcium-releasing channels are crucial for cardiac muscle contraction, and the oxidation of the RyR channel or calcium leak via hyperphosphorylated protein kinase A causes heart failure and triggers ventricular arrhythmias [135,136]. The active component of traditional Chinese medicine, Echinacoside, reduces cardiomyocyte pyroptosis by suppressing NADPH/ROS/ER stress [137]. The compounds like ferulic acid, pterostilbene, and tyrosol protect cardiomyocytes and mice hearts from cardiac alterations induced by chronic ER stress by reducing cardiomyocyte apoptosis [138]. Dapagliflozin (DAPA), a hypoglycemic drug, inhibits sodium-glucose cotransporter 2 (SGLT2) and reduces glucose reabsorption by kidneys. Recent studies revealed that DAPA drug work against heat failure via inhibits ER stress response through the PERK-eIF2α-CHOP pathway [139]. The primary pathology for the Pulmonary Arterial Hypertension (PAH) condition is inflammation and ER stress. The ER stress chaperone GRP78 is protective through extracellular signaling [140].

8.5. Neurodegenerative diseases

Accumulating misfolded proteins in the brain is the primary pathology of neurodegenerative diseases like Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and prion-related diseases [141,142]. Overwhelming or prolonged ER stress fails to clear the accumulation of unfolded proteins in the brain, and the neuronal cells are sensitive to protein accumulation. Parkinson's disease is related to ER stress-mediated neuronal death. Accumulation and aggregation of α-synuclein in the lumen of the ER cause Parkinson's disease and induce ER stress via abnormal interactions with the Chaperones, impairment of UPR signaling, inhibiting the trafficking of secretory proteins from ER to Golgi and Suppressing the ERAD-mediated system [143,144]. Human ubiquitin ligase (HRD1) is a translocon protein involved in the ERAD degradation process, and its upregulation decreased Parkinson-associated neuronal cell death. HRD1 translocon protein promotes the degradation of Parkin-associated endothelin receptor-like receptors (Pael-R) [145]. Extracellular aggregation and accumulation of toxic beta-amyloid protein in the brain is the primary cause of Alzheimer's disease [146,147]. Huntington's disease is majorly caused by the expansion of the polyglutamine (poly Q) tract in huntingtin protein, and it mainly causes by the leakage of calcium from the RyR channel [100]. Amyotrophic lateral sclerosis (ALS) is a common motor neurodegenerative disease caused by unresolved ER stress [148]. Components of all three UPR pathways and PDI chaperone expressions are increased in the spinal cord of amyotrophic lateral sclerosis patients [148,149].

8.6. Infectious diseases

Upon viral infection, the sudden necessity to process more viral proteins beyond the standard folding capacity of the host cell is the foremost reason for the tremendous stress potential of ER and its protein folding machinery [150,151]. The ultimate goal of the virus is to utilize the stress-induced protein production of the host cell for replication and progeny production without damaging its habitat (host cell). It is well known that unresolved ER stress can lead to cell death. For this reason, the virus synthesizes the host shutoff protein NS1 and limits the host protein production to buffer the ER stress [152]. Bacteria and their virulence factors, such as lipopolysaccharides (LPS), Shiga, cholera toxins, streptolysin O, and streptolysin S, can induce unfolded protein responses in host cells [7,153]. A recent study revealed that the 3-

Chloro-1, 2-propanediol (3-MCPD) is a food-borne toxic substance that stimulates ER stress response via PERK-ATF4-CHOP and IRE1α signaling and also increases mitochondrial dysfunction and overexpression of the apoptotic initiator protein caspase 12 [154].

9. Disease biomarkers and therapeutic targets

UPR components were used as potential disease biomarkers and therapeutic targets. Changes in UPR and ER stress markers in blood, urine, and tissue biopsy samples can indicate the severity of the disease and be a diagnostic tool for diseases. They can be utilized as biomarkers for a variety of diseases in humans. Molecular transcription factors can also be a potential marker for various diseases. ER chaperones like MANF, ERdj3, ERdj4, PDIA3, and ER stress-dependent highly soluble proteins such as CRELD2 and angiogenin are biomarkers and valuable tools for early diagnosis in kidney-related diseases [67,155]. Overexpression of MUC5B is the most potent risk factor and a marker for Idiopathic pulmonary fibrosis diseases [112]. ERO1L is highly expressed in Pancreatic ductal and lung adenocarcinoma, a novel biomarker and a promising target for cancer therapy [156,157]. Increased activation of UPR and ER chaperone Bip levels is high in the Alzheimer's disease affected patients' brains [158,159]. ATF6 and PDI chaperone expressions are higher in the cerebrospinal fluids of ALS and act as potential biomarkers of ALS disease [148,149]. The thioredoxin domain containing 5 (TXNDC5) is upregulated in the fibrotic liver. It is a biomarker and a possible therapeutic target for liver fibrosis [160].

Perturbation in UPR signaling branches plays a significant role in developing multiple human diseases. Targeting the UPR branch may contribute to developing novel, ground-breaking treatment strategies. IRE1α activity has the potential to influence cellular fate and act as a therapeutic target [161]. Cancer cells experience a nutrient shortage or hypoxia with high metabolic and protein folding demand, which induces ER stress, and to overcome this situation, it adapts IRE1α signaling mechanisms and acts as a new therapeutic target to abrogate tumor progression. Recent studies reported that IRE1α is a potential target against cancer like glioblastoma [162,163], breast cancer [164,165], neuroblastoma [166]. Chemical compounds modulate IRE1's activity by targeting its kinase or RNase domains [184]. In order to prevent XBP1 splicing, the chemical compound targets RNase activity directly at lysine 907, the catalytic residue of RNase [162]. Inhibitors that inhibit IRE1 kinase work by competitively binding to the active site and displacing ATP, preventing the kinase trans-autophosphorylation reactions. ATP competitive inhibitors have two different effects; some increase RNA splicing, while others inhibit RNase activity. STF-083010 is a cell-permeable compound that explicitly targets the IRE1 RNase domain by disrupting the IRE1-XBP1 activity without affecting its kinase activity [167]. MKC8866, OICR464, 4μ8C, salicylaldehydes, and B-109 are examples of IRE1 RNase inhibitors [168,169]. GSK2850163 is a novel IRE1 RNase and kinase inhibitor. APY29 and Sunitinib are IRE1 modulators that inhibit transphosphorylation but activate RNase activity [170,171].

Overactivation of PERK is responsible for various diseases, so pharmacological modulators of PERK may significantly reduce the pathology. GSK2656157 is a novel PERK-eIF2α inhibitor; it dephosphorylates the eIF2α and inhibits the PERK- eIF2α signaling pathway [172].

Calnexin is ER chaperone that helps to refold the mutant protein iduronate 2-sulfatase (IDS) in the ER lumen and acts as a potent target for mucopolysaccharidosis type II (MPS II) diseases. Chaperone base treatments were the best therapeutic targets for Alzheimer's disease [147]. Glucose-regulated protein 78 (GRP78) is a potential target of betulinic acid in inhibiting aerobic glycolysis and mediating suppression of breast cancer [173]. Tousson-Abouelazm et al. state that podocyte injury is associated with the secretion of the extracellular chaperone MANF and ERdj3 into the urine. It reflects the intensity of ER stress in glomerulonephritis [174]. GRP78 and PDI are potent markers for epithelial ovarian cancer [175]. Recent findings state that a loss-of-function variant of proprotein convertase subtilisin/kexin type 9 (PCSK9) acts as a co-chaperone and increases the GRP78 and 94 chaperones in liver cells to encounter ER stress [176]. This may be a novel approach to protecting liver cells from ER stress.

IRAK2 is an IRE1 regulatory gene that acts as a new drug target for various diseases like pancreatic ductal adenocarcinoma [20,177]. Recent studies exposed the activation of SIRT1-dependent deacetylation as a specific target for heart diseases [51]. Phenolic compounds like ferulic acid, pterostilbene, and tyrosol suppress ER stress hyperactivity via the activation of SIRT1-dependent deacetylation of the translation initiation factor eIF2α and antioxidant activity [138]. Resveratrol is an eminent Sirt1 activator that prevents various heart diseases without altering blood pressure [178].

HRD1 is a potential target for Parkinson's disease, and the upregulation of this gene increased the degradation rate of Parkinson-associated receptor Pael-R [145]. ER resident molecule Sdf2l1 (stromal cell-derived factor 2 like 1) is a therapeutic target and a sensitive biomarker in obesity-associated diseases [56]. ATL3 ER-phagy receptor is a perfect drug target for flaviviral-associated diseases [90]. Ryanodine receptor (RyR) is a ubiquitous, intracellular calcium-releasing channel. Its function was crucial for many organelles, especially the heart, skeletal muscle, and synaptic transmission in the brain. RyR is a crucial target for neurodegenerative diseases, especially Huntington's [100,179,180]. RyR inhibitors are neuroprotective and improve motor behavior [100,146]. Rycal drug S107 can cross the blood-brain barrier and heal the calcium leakage in the RyR2 channel [181]. TRAIL is a promising target against cancer treatments [182]. Recent studies investigated the combination of TRAIL and OTG inhibitors' therapeutic efficiency against cancer cells. OTG inhibitors, OSMI-1, played a prominent role in inducing ER stress and blocking the NFκB signal pathway [183].

10. Conclusion

UPR compounds in the Endoplasmic reticulum regulate the delicate balance between health and diseases, and it is also an indispensable tool for cellular communication that extends beyond the intracellular space. ER has the potential to be used as a preventive, diagnostic, and therapeutic tool for various diseases. Boosting the ER protein production capacity with therapeutic agents is crucial to resolving ER stress-associated diseases. ER stress is necessary for the development and physiological function of the innate immune system, so assessing the side effects is crucial while targeting ER stress therapies.

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Credit authorship contribution statement

SD, PR wrote the manuscript; PR, SD conceived and designed the study.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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