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Review

Broad Roles of Endoplasmic Reticulum Stress Sensors Activated by Diverse Pathophysiological Stimuli

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Abstract

The endoplasmic reticulum (ER) stress response is a critical cellular program that maintains proteostasis and membrane homeostasis through the activation of the ER stress sensor proteins inositol-requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and old astrocyte specifically induced substance (OASIS) family proteins. These sensors, canonically understood as transducers of the unfolded protein response (UPR), respond to the accumulation of misfolded proteins in the ER lumen as a result of ER luminal Ca^{2+} depletion, defective disulfide bond formation, dysregulated glycosylation, or inhibition of ER-associated degradation. However, recent conceptual advances have reshaped understanding of these classical mechanisms, by revealing multiple non-canonical pathways that operate independently of luminal proteotoxicity. Emerging evidence highlights the roles of ER stress sensors in integrating diverse stimuli, including the integrated stress response, lipid bilayer stress, mitochondria-ER contact, and the DNA damage response. Herein, we discuss how these ER stress sensors function as multidimensional signaling hubs for proteotoxic, metabolic, and genomic stresses, and consequently modulate pathophysiological cellular outcomes. Finally, we examine current knowledge regarding both canonical and non-canonical modes of ER stress sensor activation, and we discuss how these mechanisms expand the functional scope of ER stress signaling in physiological regulation and diseases.

Keywords: endoplasmic reticulum (ER); ER stress sensors; unfolded protein response (UPR)

1. Introduction

The endoplasmic reticulum (ER) is a multifunctional organelle dedicated to the synthesis, folding, and quality control of secretory and membrane proteins. To ensure the production of functional proteins, the ER maintains a luminal environment characterized by high Ca^{2+} levels, a specialized oxidative redox state, and an abundant pool of molecular chaperones. Traditionally, any disruption of this homeostasis was understood to result in the accumulation of misfolded proteins, in a process termed ER stress. ER stress triggers the unfolded protein response (UPR), a signaling network governed by the ER stress sensors inositol-requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6). However, accumulating evidence indicates that these ER-resident sensors are not only activated by proteotoxic stress but also serve as integrative hubs for diverse cellular pathways associated with non-canonical events, including the integrated stress response (ISR), lipid bilayer stress (LBS), and the DNA damage response (DDR). Furthermore, the spatial organization of these sensors at mitochondria-associated membranes (MAMs) facilitates critical organelle crosstalk, thereby coordinating cellular bioenergetics and translation with the functional state of ER. Understanding these non-canonical pathways is essential for unraveling the pathomechanisms underlying a broad spectrum of human diseases. In this review, we summarize the functions of ER stress sensors in both canonical and non-canonical UPR signaling, and explore how their dysregulation contributes to pathogenesis.

2. Literature Review

2.1 UPR Activation by the Major ER Stress Sensors IRE1, PERK, and ATF6

The ER, the largest intracellular membrane system, functions as a central hub for Ca^{2+} storage, protein folding and maturation, lipid biosynthesis, metabolic regulation, and intracellular signaling [1]. To preserve ER homeostasis, eukaryotic cells use specialized ER stress sensor proteins that monitor the protein folding environment of the ER lumen. These sensors detect the accumulation of unfolded or misfolded proteins, and initiate a series of adap-

tive signaling pathways collectively termed the UPR [2]. Although the UPR in metazoans is evolutionarily conserved with respect to that in protozoa, it exhibits higher complexity [3]. This system coordinates transcriptional, translational, and post-translational systems that restore ER homeostasis by enhancing protein folding ability, through attenuating global protein synthesis and promoting ER-associated degradation (ERAD) [4].

The three principal ER stress sensors, IRE1, PERK, and ATF6, are evolutionarily conserved transmembrane proteins characterized by an ER stress-sensing domain and cytosolic effector region [5,6,7,8]. Under homeostasis, these sensors are maintained in an inactive state through their association with the ER chaperone binding immunoglobulin protein (BiP/GRP78/HSPA5). Under ER stress, BiP preferentially binds unfolded or misfolded proteins. Therefore, BiP dissociation from ER stress sensors permits their activation [9].

2.1.1 IRE1

IRE1 is composed of an N-terminal ER luminal domain, transmembrane segment, cytosolic serine/threonine kinase domain, and endoribonuclease (RNase) domain (Fig. 1, Ref. [10,11]). Mammals possess two IRE1 isoforms: ubiquitously expressed IRE1α and tissue specific IRE1β, which localizes predominantly to the mucosal epithelium of the gastrointestinal tract, where it plays a specialized role in regulating the mucosal barrier and inflammatory responses [12,13]. Although IRE1α is ubiquitously expressed, its expression is particularly high in secretory cells, such as pancreatic β cells, hepatocytes, and plasma cells, whose protein folding demands are high [13,14]. The physiological importance of IRE1 is emphasized by findings that *Ire1α*-deficient mice exhibit embryonic lethality (between E12 and E14) due primarily to impaired liver development, and defects in placental vascularization or B lymphocyte differentiation [15,16].

Under normal conditions, IRE1 is maintained in an inactive monomeric state through its association with BiP at the ER luminal domain. After unfolded proteins accumulate in the ER lumen, dissociation of BiP from the IRE1 luminal domain facilitates IRE1's dimerization or higher-order oligomerization [9,17], thus leading to autophosphorylation of its cytosolic kinase domains and activation of its RNase domain. Activated IRE1 catalyzes unconventional splicing of X-box binding protein 1 (*Xbp1*) mRNA [18]. Excision of a 26-nucleotide intron induces a translational frameshift in *Xbp1* resulting in the production of the spliced form of XBP1 (XBP1s). XBP1s translocates to the nucleus, where it upregulates a diverse gene network involved in chaperone production, lipid synthesis, and ERAD [19]. Beyond *Xbp1* splicing, hyper-activated oligomerization of IRE1 induces the broader RNase activity known as regulated IRE1-dependent decay (RIDD) [20]. Through RIDD, IRE1 degrades a subset of ER-localized or secretory protein mRNAs and microRNAs, thereby decreasing the global protein folding load and ER stress [20]. However, unresolved ER stress can drive RIDD toward degradation of mRNAs essential for cell survival and ultimately promote apoptosis through pro-inflammatory signaling pathways such as the c-Jun N-terminal kinases (JNK) pathway [21] (Fig. 2).

2.1.2 PERK

PERK is composed of an ER luminal sensing domain, transmembrane domain, serine/threonine kinase domain, and cytosolic regulatory domain (Fig. 1). Although PERK is ubiquitously expressed, it is highly expressed in the pancreas [22]. Loss of function mutations in PERK cause Wolcott-Rallison syndrome, a rare autosomal recessive disorder characterized by early-onset diabetes due to severe pancreatic β cell dysfunction and skeletal abnormalities [23]. Similarly, *Perk*-deficient mice show progressive diabetes and exocrine pancreatic insufficiency, thus emphasizing PERK's essential role in maintaining secretory cell viability [24].

Under homeostatic conditions, PERK, like IRE1, is kept inactive through its association with BiP at the ER luminal domain [9]. Under ER stress, BiP dissociation leads to the dimerization and/or oligomerization of PERK with autophosphorylation of the ER luminal domains [9]. Activated PERK phosphorylates substrates, primarily eukaryotic initiation factor 2α (eIF2α), and consequently inhibits assembly of the ternary complex formed by eIF2 with guanosine triphosphate and-methionine transfer RNA (eIF2-GTP-Met-tRNA) [22,25]. The resulting global attenuation of protein translation decreases the influx of nascent polypeptides into the stressed ER lumen (Fig. 2).

Paradoxically, eIF2α phosphorylation selectively enhances the translation of specific mRNAs. ATF4 is a basic leucine zipper-type (bZIP) transcription factor that regulates the expression of UPR target genes important for stress recovery [26]. ATF4 also promotes dephosphorylation of eIF2α through the induction of a negative feedback regulator growth arrest and DNA damage-inducible protein 34 (GADD34) [27]. This reverse regulation is mediated by the presence of upstream open reading frames (uORFs) in the 5′ untranslated region (UTR) of the mRNA. Under normal conditions, ribosomes translate the uORFs and dissociate before reaching the coding sequence. When eIF2α is phosphorylated, delayed translation re-initiation allows ribosomes to bypass the inhibitory ORFs and initiate translation at the actual start codon [28]. ATF4 then translocates to the nucleus and regulates the expression of genes involved in amino acid metabolism and transport, antioxidant stress responses, and apoptosis induction via the upregulation of CCAAT/enhancer-binding protein-homologous protein (CHOP/GADD153) during chronic or terminal stress [26].

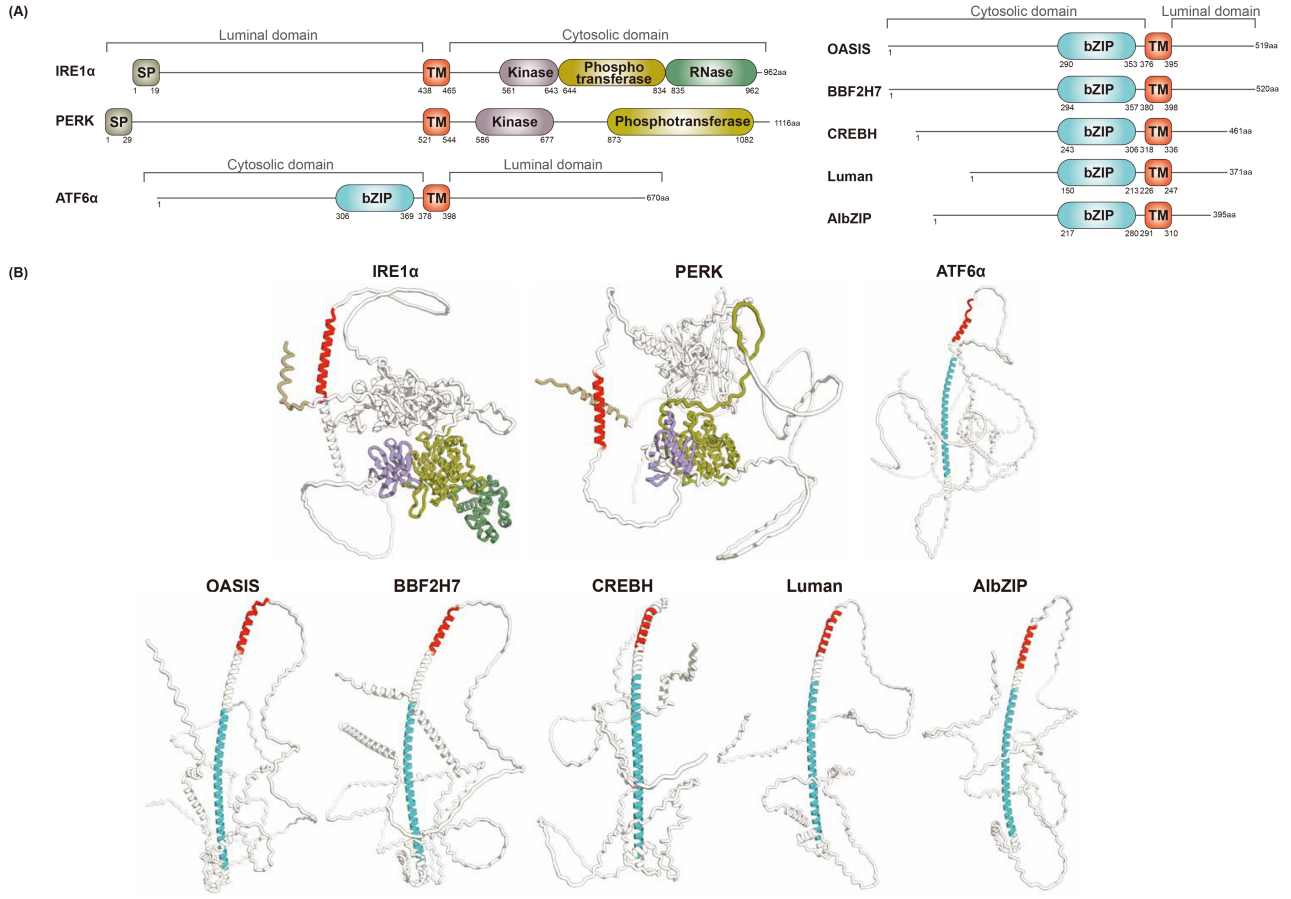

Fig. 1. Structures of endoplasmic reticulum (ER) stress sensors. (A) Linear representation of the domain organization of ER stress sensors (numbers indicate amino acid position from InterPro [10]). SP, signal peptide domain; TM, transmembrane domain; Kinase, phosphorylase kinase domain. (B) Three-dimensional structures predicted by AlphaFold [11]. The color-coding of the domains matches the colors' linear representation in panel A (ocher: SP domain, red: TM domain, purple: Kinase domain, yellow: phosphotransferase domain, green: RNase domain, cyan: bZIP domain, created with CueMol2 (http://www.cuemol.org/en/)).

2.1.3 ATF6

ATF6, a type II transmembrane glycoprotein, is a transcription factor that is composed of an ER luminal regulatory domain, transmembrane domain, and bZIP domain (Fig. 1) [5]. Mammals ubiquitously express two isoforms, ATF6α and ATF6β, which have partially redundant but indispensable roles, as evidenced by the embryonic lethality at E8.5 in double knockout animals [29]. ATF6α is particularly highly expressed in the liver, cardiac muscles, and brain. Studies of ATF6α conditional deficiency in the brain have revealed critical roles of ATF6α in neurodevelopment and synapse formation [30].

The activation mechanism of ATF6 is distinct from those of IRE1 and PERK. Under homeostatic conditions, ATF6 is inactivated through association with BiP at the ER luminal domain and the formation of intermolecular disulfide bonds, thus resulting in dimerization or oligomerization within the ER lumen [5,31,32]. Under ER stress, BiP dissociation unmasks both disulfide bond cleavage by protein disulfide isomerase family A member 5 (PDIA5) and Golgi localization signals within ATF6 [32,33,34]. The monomerization of ATF6 facilitates its packing into coat protein complex II (COPII) vehicles for transport from the ER to the Golgi apparatus [34]. Within the Golgi membrane, ATF6 undergoes sequential intramembrane proteolysis by two specific proteases, site-1 and site-2 proteases (S1P and S2P), which are involved in regulated intramembrane proteolysis (RIP) [5,31]. This proteolytic cleavage releases the cytosolic 50 kDa N-terminal fragment (N-ATF6), which translocates to the nucleus. In the nucleus, N-ATF6 forms a complex with NF-Y and acts as a transcription factor by binding specific DNA sequences called ER stress response elements (ERSE, CCAAT-N9-CCACG), thus inducing the transcription of molecular ER chaperones (e.g., *Bip/Grp78* and *Grp94*) and ERAD components (e.g., Protein sel-1 homolog 1 (*Sel1l*), Homocysteine-responsive endoplasmic reticulum-resident ubiquitin-like domain member 1 protein (*HERP1/HERPUD1*), and E3 ubiquitin-protein ligase synoviolin (*Hrd1/Syvn1*)) [29,35,36]. Additionally, ATF6 heterodimerizes with XBP1s and subsequently binds the

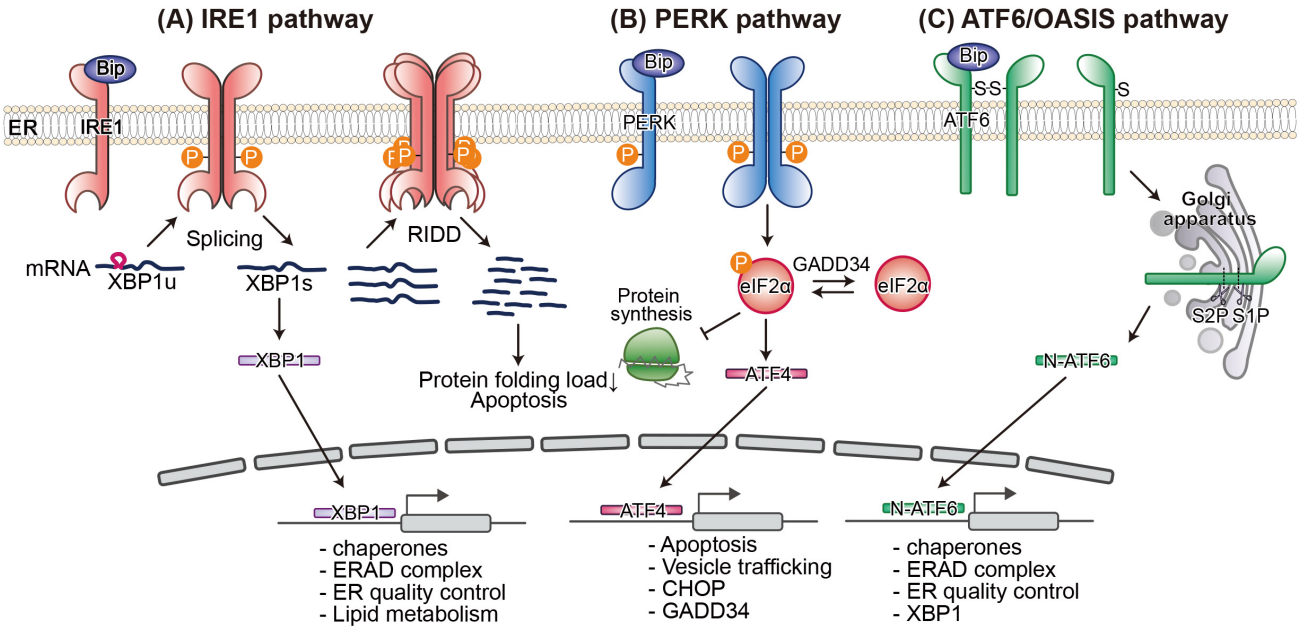

Fig. 2. Activation of ER stress sensors by pathological stimuli. Scheme of the major ER stress responses involving inositol-requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK), and activating transcription factor 6 (ATF6). These three ER stress sensors bind binding immunoglobulin protein (BiP) under homeostatic conditions. (A) In the IRE1α pathway, after BiP dissociates, IRE1 undergoes dimerization, autophosphorylation, and subsequent x-box binding protein 1 (XBP1) mRNA splicing or regulated IRE1-dependent decay (RIDD)-mediated mRNA degradation. (B) PERK activation results in attenuation of global protein synthesis via eukaryotic initiation factor 2α (eIF2α) phosphorylation. Phosphorylated eIF2α selectively permits the translation of ATF4 mRNA, which encodes a transcription factor. (C) In the ATF6 pathway, reduction of disulfide bonds promotes ATF6's monomerization and transport to the Golgi apparatus, where it is sequentially cleaved by site-1 and site-2 proteases (S1P and S2P). This processing releases the active cytosolic fragment N-ATF6, which in turn translocates to the nucleus and induces gene expression. Similar to ATF6, OASIS family proteins follow the same translocation and activation pathway under ER stress conditions. At the bottom of the figure, general unfolded protein response (UPR) outcomes are summarized.

UPR element (UPRE, TGACGTGG/A), thereby enhancing the expression of genes involved in ER quality control and degradation, such as ER degradation-enhancing α-mannosidase-like protein 1 (*EDEM1*) and Degradation in endoplasmic reticulum protein 2 (*DERL2*), which protect against neurodegeneration [18,36] (Fig. 2).

2.2 Tissue-Specific Non-Canonical ER Stress Sensors: The OASIS Family Proteins OASIS, BBF2H7, AIbZIP, Luman, and CREBH

Beyond the three major UPR sensors, the old astrocyte specifically induced substance (OASIS) family of transmembrane containing transcription factors, also known as the cyclic adenosine monophosphate (cAMP) response element binding protein 3 (CREB3) family, has been identified. This family comprises old astrocyte specifically induced substance (OASIS/CREB3L1), box-B binding factor 2 human homolog on chromosome 7 (BBF2H7/CREB3L2), Luman (CREB3), cAMP-responsive element-binding protein H (CREBH/CREB3L3), and Androgen-induced basic leucine zipper protein (AIbZIP/CREB3L4) [37]. From an evolutionary perspective, molecules potentially related to ATF6 and OASIS family proteins are found in organisms more complex than *C. elegans*. Architecturally, all OASIS family proteins resemble ATF6, as type II transmembrane proteins that undergo RIP at the Golgi apparatus in response to ER stress. However, unlike the ubiquitously expressed major ER stress sensors, OASIS family members exhibit distinct tissue-specific expression patterns and have specialized physiological roles.

2.2.1 OASIS (CREB3L1)

OASIS was originally identified in long-term cultured astrocytes [38]. This protein is expressed predominantly in astrocytes and osteoblasts [39,40]. Structurally, the ER luminal domain of OASIS differs from that of classical ER stress sensors, because it does not rely on the canonical BiP-dissociation mechanism to sense generalized proteotoxic stress [41]. Under physiological conditions, OASIS, but not ATF6, is constitutively degraded via the ubiquitin-proteasome pathway. However, under ER stress conditions, OASIS escapes proteasomal degradation and undergoes RIP; subsequently, its N-terminal fragment translocates to the nucleus and acts as a transcription factor [41].

In the central nervous system, OASIS is essential for promoting differentiation and maintaining astrocyte homeostasis under mild ER stress [42]. Its transcriptional targets include glial cell missing-1 (Gcm1), a DNA-binding protein that facilitates astrocyte differentiation from neural precursor cells by promoting demethylation of the promoter of glial fibrillary acidic protein, a canonical astrocyte marker. In bone tissue, OASIS plays a critical role in the high secretion of type I collagen (Col1) during bone formation. OASIS directly binds the promoter of the *Col1* gene, which encodes a major bone matrix protein, and stimulates its transcription [40,43]. Accordingly, *Oasis*-deficient mice exhibit severe osteopenia caused by diminished Col1 protein production [40,43].

2.2.2 BBF2H7 (CREB3L2)

BBF2H7 is widely expressed in several tissues and has particularly high expression in the cartilage, lung, brain, ovary, spleen, and testis [44]. BBF2H7 transcriptionally regulates the COPII component Sec23a, which is essential for vesicle budding from the ER [45]. In addition, BBF2H7 plays a specialized role in notochord vacuolization via the transcriptional regulation required for enlargement of COPII vesicles; this adaptation is necessary for the massive export of Col2 from the ER [45]. BBF2H7 null mutants show severe chondrodysplasia due to defective cartilage formation; this defect results from accumulation of cartilage matrix proteins within the ER lumen caused by impaired anterograde COPII-mediated transport [45]. The regulation of anterograde protein transport by BBF2H7 is also critical for melanogenesis. After synthesis in the ER lumen, Tyrosinase, the master regulator of melanin production, is trafficked from the ER into melanosomes via BBF2H7-mediated COPII transport and subsequently promotes melanin pigmentation [46,47]. Additionally, BBF2H7 fine-tunes hedgehog signaling. After RIP-mediated cleavage, the C-terminal luminal region of BBF2H7 is secreted to the extracellular space, where it interacts with Indian hedgehog (IHH) and its receptor, Patched-1, thereby promoting differentiation from proliferative to hypertrophic chondrocytes [44,48,49]. The regulation of hedgehog signaling by secreted C-terminal BBF2H7 is also involved in the growth of neuronal axon [49]. Beyond its developmental roles, BBF2H7 has cytoprotective functions in the central nervous system, by protecting neurons against ER stress-induced apoptosis. Under conditions of proteasome inhibition, BBF2H7 forms a heterodimer with ATF4 and subsequently regulates the expression of sorting nexin 3 (SNX3), a key component of the retromer complex involved in endosome-to-Golgi trafficking, thus further highlighting its role in maintaining neuronal protein homeostasis [50].

2.2.3 CREBH (CREB3L3)

CREBH is expressed predominantly in the liver and small intestine [51,52]. Its transcription is dynamically induced by metabolic cues such as fasting, fatty acids, and peroxisome proliferator–activated receptor-α (PPARα). CREBH is therefore a crucial regulator of nutrient and energy metabolism [53,54,55]. CREBH is indispensable in maintaining systemic lipid homeostasis. *Crebh*-deficient mice exhibit severe hypertriglyceridemia due primarily to impaired expression of apolipoproteins required for triglyceride clearance. Beyond lipid regulation, CREBH coordinates hepatic lipid oxidation and glucose homeostasis through synergistic cooperation with PPARα and the metabolic hormone fibroblast growth factor 21 (FGF21) [56]. In contrast, loss of CREBH exacerbates hepatic steatosis and accelerates progression to nonalcoholic steatohepatitis under metabolic stress conditions [57].

2.2.4 Luman (CREB3)

Luman is broadly expressed in various tissues, and is highly expressed in the liver and nervous system [58]. Luman was originally identified through its interaction with host cell factor (HCF), a protein involved in herpes simplex virus replication [59]. Activated Luman under ER stress targets the promoter region of *Herp*, a ubiquitin-like integral ER membrane protein involved in ERAD [60]. Luman also plays a role in maintaining mitochondrial homeostasis through the regulation of Ca^{2+} and adenosine triphosphate (ATP) production [61].

During early stages of osteoclast differentiation, Luman undergoes RIP and nuclear translocation in response to receptor activator of nuclear factor kappa-B ligand (RANKL) signaling, where it induces expression of dendritic cell-specific transmembrane protein (DC-STAMP), a key factor in osteoclast cell-cell fusion and subsequent maturation [62]. Luman also directly interacts with DC-STAMP, and regulates its subcellular localization and protein stability [62].

In the nervous system, induction of ER stress and activation of sensors in distal dendrites has been suggested to be important for maintaining nerve function [63,64]. Luman also plays a role as a retrograde injury signal. After axonal damage in sensory neurons, Luman is synthesized, cleaved, and activated within axons. The activated fragment subsequently undergoes retrograde transport to the nucleus, where it governs neurons' intrinsic regenerative ability [58].

2.2.5 AIbZIP (Androgen-Induced bZIP Protein/CREB3L4)

AIbZIP is expressed primarily in the prostate and malignant tissue [65,66]. AIbZIP was originally identified as an androgen responsive gene in prostate cancer cell lines [66]. Notably, AIbZIP exhibits unique biochemical properties from those of other OASIS family members. Whereas

other OASIS family proteins are cleaved in response to pharmacological ER stress inducers, AIbZIP is resistant to the ER stress inducer Brefeldin A; therefore, its activation requires specific physiological stimuli or post-translational modifications rather than general ER-to-Golgi trafficking disruption [67].

2.3 Classical Pathological Stimuli Activating ER Stress Sensors

In general, diverse intra- and extracellular stimuli compromise protein folding ability in the ER lumen and subsequently activate ER stress sensors. This section summarizes the major pathological stimuli and phenomena inducing pathological ER stress.

2.3.1 Impaired Chaperone Function Caused by ER Luminal Ca^{2+} Depletion

The ER lumen is the major intracellular Ca^{2+} store, and high luminal Ca^{2+} concentrations are essential for the proper activity of ER-resident chaperones, including BiP, calreticulin, and calnexin [68]. Both excessive increases and decreases in ER luminal Ca^{2+} levels compromise chaperone-mediated protein folding and lead to rapid accumulation of misfolded proteins. Experimentally, Thapsigargin, A23187, and Ionomycin are widely used to induce robust ER stress by depleting ER Ca^{2+} stores. Even under physiological conditions, Ca^{2+} levels within the ER are dynamically regulated and transiently decreased by receptor stimulation or cellular excitation. Spatiotemporally controlled Ca^{2+} release through inositol 1,4,5-trisphosphate receptors (IP_3Rs) or ryanodine receptors occurs during neuronal activity, muscle contraction, and periods of high secretory demand, such as in pancreatic β cells [69,70]. Moreover, because the IRE1-XBP1 axis is activated during physiological synaptic activity [63], Ca^{2+} depletion appears to contribute to ER stress sensor activation even under normal physiological conditions.

2.3.2 Disruption of Redox Balance and of Disulfide Bonds

The ER lumen maintains the particular oxidative environment required for proper protein folding through the formation of disulfide bonds catalyzed by protein disulfide isomerases (PDIs), which relay electrons from nascent polypeptides to the terminal acceptor via the endoplasmic reticulum oxidoreductase (ERO1)-catalyzed oxidation cycle [71]. This redox state is sensitive to cellular metabolic conditions and oxygen availability. Mechanistically, this redox state acts as a fundamental regulator of ER stress sensor activation through specific thiol-based modifications. For instance, a shift toward a more reducing environment or reactive oxygen species (ROS) accumulation induces cysteine sulfenylation in the IRE1α kinase activation loop [72]. This modification functions as a redox switch that physically obstructs trans autophosphorylation.

Structural alterations in ATF6α, in contrast to ATF6β, are particularly sensitive to the reductive capacity of the ER. When the ER environment becomes more reducing, intermolecular disulfide bridges in ATF6, which aid in dimerization or oligomerization, are cleaved. The resulting monomeric ATF6α undergoes a conformational change that facilitates its recruitment into COPII vesicles [31]. Hypoxia or metabolic perturbations disrupt ER redox homeostasis, and consequently decrease the efficiency of disulfide bond formation and cause protein misfolding. Chipurupalli et al. [73] have demonstrated that the PERK-eIF2α-ATF4 signaling pathway confers a survival advantage to tumor cells under hypoxic environments. Additionally, hypoxia induces XBP1 mRNA and protein expression, and XBP1 deficiency suppresses tumor growth [74]. To model this scenario, reducing agents such as dithiothreitol (DTT) are commonly used to disrupt the oxidative environment and cause a robust and ER stress response.

2.3.3 Dysregulation of Protein Glycosylation

N-linked glycosylation, a hallmark of ER protein processing, provides essential signals for the calnexin/calreticulin folding cycles [75]. Productive folding of N-glycosylated proteins in the ER depends on the lectin-like molecular chaperones calnexin and calreticulin, both of which recognize monoglucosylated N-glycans and facilitate polypeptide folding. Experimentally, Tunicamycin is widely used to block N-acetylglucosamine transfer, thus resulting in the accumulation of hypoglycosylated proteins in the ER lumen. This defect also places excessive demand on the ERAD system [76]. Importantly, although the overall activation mechanisms of ER stress sensors are similar to those mentioned above, proteomics analysis has demonstrated differential downstream gene expression after tunicamycin vs. thapsigargin treatment [77]. These differences in expression arise from expression biases and dysregulation of protein glycosylation that not only induce the general UPR but also affect the ER stress sensors themselves. For example, *Xbp1s* regulates N-glycan maturation pathways [78,79]. Tunicamycin treatment has revealed differences in proteolytic kinetics between ATF6α and ATF6β [80,81]. In addition, N-glycosylation of ATF6β is required for proteolytic cleavage and dysregulates the transcriptional activation of ATF6α [82], thereby regulating the strength and duration of ATF6-dependent induction of gene expression. Under low glucose conditions, which impair N-glycosylation and induce the UPR, ATF4 and ATF6 primarily regulate the expression of genes involved in lipid and amino acid homeostasis, as well as cell death in lung cancer cells [83]. Physiologically, alterations in glucose metabolism, such as those occurring during starvation-refeeding transitions or hyperglycemic conditions, impair the efficiency of N-linked glycosylation and increase the burden of misfolded proteins in the ER [84]. In metabolically active cells, including pancreatic β cells and hepato-

cytes, such changes in glycosylation efficiency can induce a mild and adaptive UPR that maintains metabolic homeostasis [85].

2.3.4 Inhibition of ERAD and Proteasomal Degradation

The ERAD pathway mediates the retro-translocation of misfolded proteins from the ER lumen into the cytosol, where they are degraded by the 26S proteasome [86]. The accumulation of unfolded proteins within the ER lumen caused by the factors described above can overwhelm the ERAD machinery. Therefore, either an excessive influx of aberrant proteins or downregulation of ERAD components can trigger ER stress. Indeed, proteasome inhibitors such as MG132 are frequently used to block this clearance system, thus leading to the accumulation of misfolded proteins in both the ER lumen and the cytosol. Physiologically, ERAD plays a key role in major histocompatibility complex class I (MHC-I) quality control by mediating the efficient disposal of the misfolded MHC-I heavy chains frequently arising from defective peptide loading. This process involves a specialized dislocation mechanism in which the SEL1L/HRD1 complex ubiquitinates luminal residues of the heavy chain before its full extraction into the cytosol [87].

2.3.5 Mutated Protein Accumulation in the ER

Excessive accumulation of mutated ER luminal or secretory proteins that do not fold properly can also induce ER stress, which is often accompanied by ER luminal expansion. For example, the Akita mouse, which carries a mutation in the *Insulin 2* gene, is widely used as a diabetes model [88]. In this model, mutant proinsulin is trapped and accumulates within the ER lumen because of defective maturation, and subsequently induces ER stress characterized by increased activation of ATF6, upregulation of ER chaperones such as BiP and Grp94, and induction of CHOP [89,90].

Similarly, mutant Col1, particularly variants containing glycine substitutions, folds slowly and improperly, thus resulting in prolonged ER retention, excessive post-translational modification, and intracellular accumulation. These defects overload the ER folding and modification capability, and lead to ER dysfunction and UPR activation. Cells expressing mutant Col1 show ultrastructural abnormalities associated with collagen retention, including ER dilation, altered cisternal thickness, and vacuolization [91].

In addition, intracellular antigenic proteins are degraded into peptides by various cytosolic proteasomes and subsequently transported into the ER lumen. For example, overexpression of certain MHC-I alleles, such as Human leukocyte antigen (HLA-B27), correlates with the accumulation of misfolded heavy chains and the magnitude of UPR activation, a process central to the pathogenesis of spondyloarthritis [92].

2.4 Non-Canonical Stimuli Activating ER Stress Sensor Proteins

Accumulating evidence in recent decades indicates that ER stress sensors are triggered via multiple non-canonical pathways, independently of the accumulation of misfolded or unfolded proteins in the ER lumen. These alternative mechanisms link the signaling derived from the sensors to diverse cellular responses, including metabolic shift, lipid imbalance, organelle crosstalk, and genotoxic stress, thereby positioning ER stress sensors as integrative hubs for cellular homeostasis.

2.4.1 Integrated Stress Response

Whereas classical ER stress induces the phosphorylation of eIF2α through the ER-resident sensor PERK, the ISR is a conserved adaptive pathway that coordinates translational control in response to a wide range of intracellular and extracellular stresses through eIF2α phosphorylation. The ISR is regulated by four distinct eIF2α kinases: PERK, general control nonderepressible 2 (GCN2), protein kinase R (PKR), and heme-regulated inhibitor (HRI). Each kinase responds to specific stress cues, including ER stress (PERK), amino acid deprivation (GCN2), viral infection and double-stranded RNA (PKR), and oxidative stress or heme deficiency (HRI) (Fig. 3A) [93].

Remarkably, PERK itself can be activated within the broader framework of the ISR through mechanisms not strictly dependent on the accumulation of unfolded or misfolded proteins in the ER lumen. In addition to UPR, PERK is also activated by ISR-related cellular responses initiated by the immune system or extracellular cues, including nutrient imbalance, mitochondrial stress, and cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway [94,95,96]. Similarly to the ER stress response, PERK activation within the ISR leads to eIF2α phosphorylation and subsequently rapid global attenuation of cap-dependent translation. However, the activation mechanisms of PERK differ from those of the canonical UPR. For example, STING directly binds and activates the intracellular C-terminal region of the PERK kinase domain [94]. The STING-PERK-eIF2α signaling pathway differs from the canonical STING-TANK-binding kinase 1-interferon regulatory factor 3 (STING-TBK1-IRF3) pathway. The STING-PERK interaction facilitates the translation of specific mRNAs associated with inflammatory and survival signaling. Extracellular cues such as Semaphorin-3A lead to remodeling of the local proteome, in a process mediated by mTOR and Extracellular signal-regulated kinases 1 and 2 (ERK-1/2) [95]. This initial burst of protein synthesis overloads the ER, thereby selectively activating the downstream PERK pathway without triggering other canonical UPR branches [94]. This specific signaling cascade enhances eIF2B activity through the local translation and dephosphorylation of its subunit, thereby counteracting the inhibitory effect of PERK-mediated eIF2α phosphoryla-

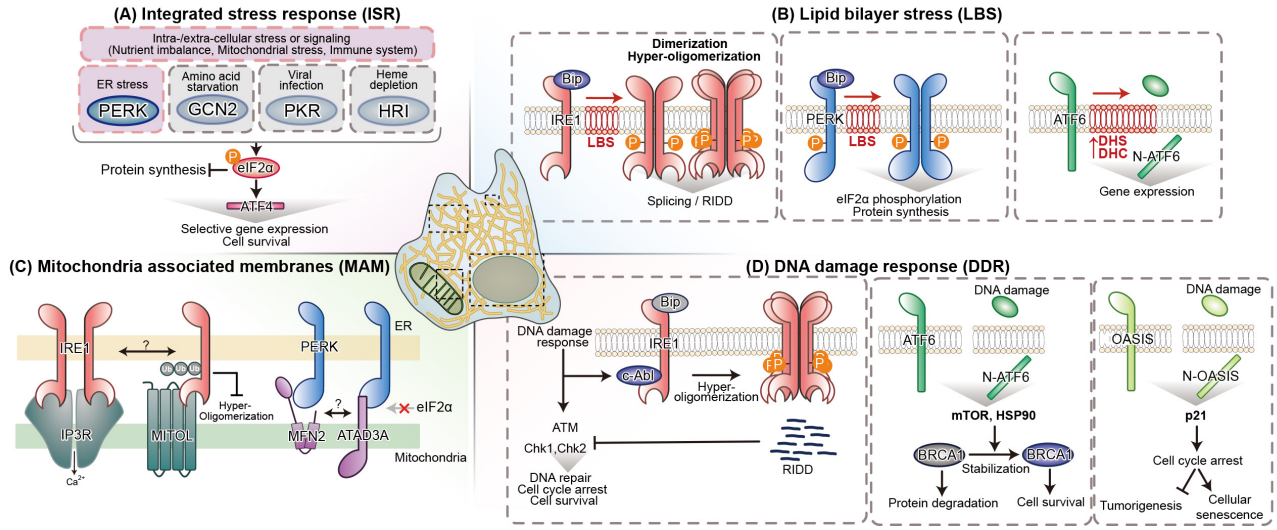

Fig. 3. Schematic diagram of activation of ER stress sensors by non-canonical stimulation via ISR, LBS, MAMs, and the DDR. (A) The ISR, involving four upstream eIF2α kinases, PERK, general control nonderepressible 2 (GCN2), protein kinase R (PKR), and heme-regulated inhibitor (HRI), is triggered by distinct cellular stresses. Activation of these kinases leads to phosphorylation of eIF2α, and ultimately results in global attenuation of protein synthesis or translation of stress adaptive mRNAs such as ATF4. (B) LBS induces the dimerization or hyper-oligomerization of IRE1, and the phosphorylation of PERK. Alterations in the relative abundance of sphingolipid intermediates activate ATF6. (C) At MAMs, a direct interaction between inositol 1,4,5-trisphosphate receptors (IP_3Rs) and IRE1 regulates mitochondrial Ca^{2+} influx. Ubiquitination of IRE1 by mitochondrial ubiquitin ligase (MITOL) suppresses IRE1 hyper-oligomerization. In addition, the interaction between mitofusin-2 (MFN2) and PERK regulates the mitochondria-ER contact site (MERCS) architecture. The physical interaction of ATPase family AAA domain-containing protein 3A (ATAD3A) with PERK competes for PERK-eIF2α binding. (D) Under DDR conditions, IRE1 hyper-oligomerization via c-Abl interaction triggers RIDD's modulation of Chk1/2 and ataxia-telangiectasia mutated (ATM) signaling, thus supporting cell survival. Activation of ATF6 stabilizes breast cancer type 1 susceptibility protein (BRCA1) and sustains mammalian target of rapamycin (mTOR) and heat shock protein 90 (HSP90) expression. old astrocyte specifically induced substance (OASIS) induces *p21*-mediated cell cycle arrest, thereby suppressing tumorigenesis and promoting cellular senescence.

tion and ultimately sustaining global translation. This specialized translational control facilitates precise axon navigation and terminal branching in retinal ganglion cells. Through this mechanism, PERK functions as a critical integrative node linking ER-resident stress sensing to cytosolic and metabolic stress responses, thereby expanding the functional scope of ER stress signaling beyond the classical UPR driven by luminal protein misfolding. Future studies are expected to provide deeper insights into the precise mechanistic regulation of PERK during the ISR.

2.4.2 Lipid Bilayer Stress

Aberrant physical properties of the ER membrane, including lipid compositions, membrane fluidity, stiffness, and packing, directly influence the activation of ER stress sensors via various proteotoxic stress mechanisms. These lipid-driven perturbations are referred to as LBS (Fig. 3B).

Alterations in ER lipid composition, particularly the balance between phosphatidylethanolamine (PE) and phosphatidylcholine (PC), are directly sensed by the transmembrane domains of IRE1 and PERK [97,98]. Mechanistically, IRE1 has an amphipathic helix that senses lipid bilayer properties, such as lipid packing density, and subsequently modulates its own oligomerization and activation [99,100,101]. Similarly, multiple lipid conditions, such as impaired fatty acid desaturation, elevated sterol levels, and inositol depletion, activate IRE1 signaling [102,103,104,105].

Membrane stiffening, often caused by elevated cholesterol or saturated fatty acids, is also a non-canonical trigger of the ER-to-Golgi translocation of ATF6. Notably, sphingolipid intermediates, such as dihydrosphingosine (DHS) and dihydroceramide (DHC), selectively activate ATF6, but not IRE1 or PERK; therefore, specific lipid composition is a key regulator of ATF6 signaling [106]. These sphingolipid intermediates, which are normally present in low abundance, are elevated under ER stress conditions and activate ATF6 through a conserved transmembrane motif (VXXFIXXNY). This motif resembles the sphingomyelin-binding motif of p24, a key component of COPI-coated vesicles, thus suggesting a structural basis for lipid-dependent protein sorting [107].

Beyond lipid sensing, OASIS has emerged as a unique regulator of nuclear envelope stress and genomic integrity

[108]. Unlike other family members, OASIS specifically accumulates at sites of nuclear envelope damage, such as those induced by mechanical stress or cellular senescence, in its full-length form rather than as a cleaved transcription factor. At these damage sites, OASIS colocalizes with the linker of nucleoskeleton and cytoskeleton (LINC) complex (SUN2/Nesprin-2) and endosomal sorting complex required for transport complex III (ESCRT-III repair machinery, and it stabilizes the nuclear architecture in regions of lamina depletion. By acting as a structural scaffold, OASIS restores nuclear morphology and directly suppresses nuclear envelope stress-induced DNA damage, through a non-canonical pathway that safeguards genome integrity independently of traditional ER stress signaling.

2.4.3 Organelle Membrane Contact Sites

MAMs are specialized contact sites between the ER and mitochondria that play central roles in Ca^{2+} flux, lipid transfer, and the regulation of mitophagy or apoptosis [109]. MAMs are highly dynamic structures that undergo remodeling in response to pharmacological and metabolic triggers. Mitochondrial stress induced by doxycycline treatment or inhibition of mTOR signaling by rapamycin increases mitochondria-ER contact site (MERCS) formation, and leads to increased mitochondrial Ca^{2+} uptake and oxidative metabolism, often accompanied by upregulation of ER stress associated transcripts, including *Chop* [96,110]. Therefore, MAM remodeling is an adaptive stress response that couples ER stress signaling to mitochondrial metabolic reprogramming. Increasing evidence highlights a tight functional link between MAMs and ER stress sensor proteins, and both IRE1α and PERK have been identified as key residents of these contact sites (Fig. 3C).

2.4.3.1 IRE1 as a Physical Scaffold and Signaling Hub at MAMs. At MAMs, IRE1α plays a dual role by promoting cell survival by splicing of *Xbp1* mRNA while also transmitting apoptotic signals under excessive stress conditions [111,112]. IRE1α at MAMs increases mitochondrial Ca^{2+} uptake and bioenergetics through physical interaction with IP_3Rs, thereby maintaining proper mitochondrial morphology and regulating the distance of MERCS [113]. Critically, these functions can be categorized into (i) a structural role, wherein IRE1α serves as a physical tether stabilizing the MAM architecture, and (ii) a signaling role, wherein IRE1α modulates Ca^{2+} flux and bioenergetics via interaction with IP_3Rs. Beyond this structural scaffolding role, IRE1α deficiency alters the molecular compositions of MAMs and cellular metabolism independently of its canonical ER functions. Moreover, IRE1α activity at MAMs is fine-tuned by the mitochondrial ubiquitin ligase (MITOL), which ubiquitinates IRE1α at lysine 481 and subsequently prevents hyper-oligomerization, RIDD, and apoptosis [114,115]. Although both IP3R and MITOL are key regulators of MERCS formation, further investigations are required to indicate whether IRE1 serves as a molecular and functional hub for these MAM components.

2.4.3.2 PERK as a Protector of Mitochondrial Proteins and Structural Scaffold at Membrane Contact Sites. During the adaptive UPR, PERK promotes MERCS assembly, and consequently facilitates mitochondrial adaptations and autophagy [96]. (i) Structurally, the interaction with PERK and MAM-associated proteins such as mitofusin-2 (MFN2) or mitochondrial protein ATPase family AAA domain-containing protein 3A (ATAD3A) promotes the physical assembly of MERCS [116,117]. Beyond this physical scaffold function, (ii) interaction with ATAD3A competitively limits eIF2α binding to PERK, thereby protecting mitochondrial translation against global translational repression and ensuring sustained expression of essential mitochondrial proteins during ER stress [116]. Given that MFN2 and ATAD3A are found on mitochondria, PERK might cooperate with these factors in regulating or protecting mitochondrial structures under the adaptive UPR.

Beyond MAMs, PERK also acts as a structural scaffold at ER-plasma membrane contact stress [118]. Under ER Ca^{2+} store depletion, PERK undergoes dimerization, thus enabling direct interaction with the actin regulator filamin A (FLNA). This PERK-FLNA axis modulates F-actin dynamics and the scaffolding function of the cytoskeleton, and juxtaposes the ER and the plasma membrane. This structural reorganization is essential for the translocation of tethering proteins, such as stromal interaction molecule 1 (STIM1) and extended-synaptotagmin 1 (E-Syt1), to the cell surface, and it enables efficient inter-organelle communication and Ca^{2+} signaling.

2.4.3.3 CREBH as a Regulator of MAM Function. An expansion of the UPR concept is the mitochondrial UPR, a mitochondrial stress response to disrupted mitochondrial proteostasis [119]. CREBH regulates the expression of genes involved in mitochondrial homeostasis, thus serving as a critical link between hepatic MAM expansion and increased energy metabolism. Notably, CREBH regulates ATF4 and ATF5, transcriptional regulators of the mitochondrial UPR, by directly binding their promoters in a manner independent of the ER UPR. By regulating the mitochondrial UPR, CREBH ensures that mitochondrial function remains aligned with hepatic metabolic state.

2.4.4 DNA Damage Response

The DDR is an evolutionarily conserved mechanism that ensures genomic integrity by recognizing DNA lesions and initiating signaling cascades that coordinate DNA repair [120]. ER stress sensors, through functional coupling with DDR pathways, enable bidirectional communication between ER-centered signaling and nuclear genome maintenance [121,122,123]. This coordination influences DNA repair, cell cycle arrest, and apoptosis—processes central to

the progression of cancers, such as multiple myeloma, and therapeutic resistance [121,124,125,126].

At the molecular level, ER stress sensors physically and functionally interact with key DDR components, such as ataxia-telangiectasia mutated (ATM), ataxia-telangiectasia and Rad3-related (ATR), p53, checkpoint kinase (Chk) 1, and Chk2. Under DNA damage, the non-receptor tyrosine kinase c-Abl directly binds and induces hyper-oligomerization of IRE1α, and triggers RIDD of mRNAs encoding DDR-related factors, such as PPP2CA-scaffolding A subunit (Ppp2r1a) and RuvB like AAA ATPase1 (Ruvbl1) [121]. The degradation of these transcripts prevents dephosphorylation of activated Chk1 and Chk2, and eventually promotes cell survival. ATF6 also contributes to genome protection by supporting breast cancer type 1 susceptibility protein (BRCA1) stability (Fig. 3D). In cancer cells, ATF6α sustains mTOR signaling and HSP90 expression, prevents BRCA1 degradation, and promotes resistance to DNA-damaging agents. Inhibition of ATF6α sensitizes tumor cells by increasing the accumulation of DNA damage (Fig. 3D) [127]. Beyond activating major ER stress sensors, DNA damage induces the expression and activation of OASIS, which promotes cellular senescence through transcriptional induction of p21 in a p53-independent manner [128].

Finally, organismal studies have revealed that DNA damage activates the UPR as an adaptive response independent of protein misfolding [129]. In *C. elegans*, sublethal DNA damage suppresses protein skinhead-1 (SKN-1) signaling, and leads to altered lipid metabolism and increased levels of unsaturated phosphatidylcholine. This lipid remodeling activates the IRE1/XBP1 branch via lipid mediated stress. These findings underscore a broader physiological principle in which nuclear genotoxic stress reprograms ER homeostasis by altering the lipid bilayer environment, thus further bridging the conceptual gap between LBS and the DDR.

2.5 Pathogenesis Due to Perturbation of ER Stress Sensors

This section discusses the pathological consequences of ER stress sensor dysregulation. Although these sensors are essential for homeostasis, their aberrant activation or chronic perturbation contributes to a spectrum of human diseases as diverse as neurodegeneration, metabolic disorders, and cancer [130,131,132]. By examining both canonical and non-canonical signaling contexts, we highlight how ER stress sensors serve as critical determinants of disease progression and potential therapeutic targets.

The pathological onset of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis (ALS), has been attributed to triggering of ER stress sensors [131,133]. In some cases, ER sensors themselves contribute directly to the formation of neurotoxic aggregates. For example, the BBF2H7 derived peptide, whose sequence is located between the S1P and S2P cleavage sites, co-aggregates with amyloid-β and subsequently enhances neurotoxicity [134]. The critical role of ER folding is further highlighted in metabolic and developmental disorders such as Wolcott-Rallison syndrome, in which *Perk* mutations lead to profound neonatal diabetes and epiphyseal dysplasia [23,135]. Similarly, OASIS deficiency is indispensable for osteoblast differentiation and bone formation [136], whereas BBF2H7 plays roles in chondrocyte differentiation and proliferation, and the efficient secretion of extracellular matrix proteins.

In the harsh microenvironment of solid tumors, cancer cells hijack canonical UPR signaling, thereby adapting to hypoxia and nutrient deprivation, enhancing survival, and promoting malignancy [137]. Moreover, ATF6 pathways coordinate with the DDR by forming a bidirectional crosstalk exploited for survival and therapy resistance in aggressive cancers. In both hematological and solid malignancies, c-Myc-dependent IRE1α-XBP1s signaling and ATF6-mTOR pathways sustain DDR components such as BRCA1 and radiation-sensitive protein 51 (RAD51) [126,127]. Additionally, increasing evidence implicates the activation of non-canonical ER stress sensors in tumorigenesis. Members of the OASIS family play key roles in cancer pathogenesis. OASIS has been identified as a functional tumor suppressor. When activated by the DDR, OASIS induces *p21* expression and cell cycle arrest [128]. Clinically, OASIS exhibits dual functionality by acting as a tumor suppressor in metastatic breast and bladder cancers [138], but promoting tumor growth and immune evasion in pancreatic adenocarcinoma through stromal remodeling and decreased $CD8^+$ T cell infiltration [139]. In contrast, BBF2H7 and AIbZIP function predominantly as potent oncogenic drivers. BBF2H7 promotes metastasis via SREBP1-mediated lipid regulation and immune resistance by suppressing T cell activity through paracrine hedgehog signaling [140,141]. Enhanced AIbZIP expression in malignant tissues promotes cell-cycle progression by promoting degradation of the cyclin-dependent kinase inhibitor p27, and consequently accelerating cell proliferation and malignant progression [142,143].

Non-canonical activation of ER stress sensors by ISR, LBS, MAMs, and the DDR has emerged as a critical pathological foundation across multiple disease contexts. Both the cGAS-STING and PERK-eIF2α pathways have been implicated in the pathogenesis of cardiovascular diseases such as ischemic cardiomyopathy and atherosclerosis. Consequently, the integration of these pathways into a unified ISR, cGAS-STING-PERK-eIF2α axis might critically contribute to these pathophysiologies [94,144]. Aberrant LBS has been implicated in the pathogenesis of metabolic, ischemic, and neurodegenerative diseases. For example, ER membrane stiffening caused by the accumulation of saturated fatty acids in diabetic kidney disease differentially modulates UPR signaling [145]. Whereas the PERK-eIF2α-ATF4 axis promotes cell death, IRE1α signaling has

Table 1. Comprehensive comparison of canonical vs. non-canonical ER stress responses and diseases.

Stimuli	Trigger	Activated sensors	Diseases	Reference
		Classical ER stress		
Ca^{2+} depletion Redox imbalance Dysglycosylation Inhibition of ERAD Mutated protein accumulation	Accumulation of unfolded proteins BiP dissociation	IRE1 PERK ATF6 OASIS family	Wolcott-Rallison syndrome O steogenesis imperfecta Neurodegenerative disease multiple cancer	Delépine et al., 2000 [23] Symoens et al., 2013 [136] Hetz et al., 2017 [131] Zhang et al., 2024 [130]
		Non-canonical ER stress		
Integrated Stress Response	Extracellular cues (Semaphorin-3A) Mitochondrial stress cGAS-STING	PERK	Cardiovascular Diseases	Wan et al., 2024 [144]
Lipid Bilayer Stress	Alterations in ER lipid composition (PE, PC) Impaired fatty acid desaturation Elevated sterol level inositol depletion	IRE1, PERK IRE1	Diabetic Kidney Disease Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis	Pérez-Martí et al., 2022 [145] Sozen et al., 2022 [105]
	Membrane stiffness (DHS, DHC) Nuclear envelope stress	ATF6 OASIS	Achromatopsia No report	Tam et al., 2018 [106] Kamikawa et al., 2021 [108]
Organelle contact site	Mitochondria-ER contact site	IRE1 PERK CREBH	Ischemic Injury Cardiovascular Diseases	Li et al., 2024 [146] Tao et al., 2025 [117]
	Plasma membrane-ER contact site (ER Ca^{2+} store depletion)	PERK	No report	
DNA damage response	Binding with c-Abl and IRE1α Alter lipid remodeling	IRE1α	Multiple myeloma	Arena et al., 2022 [126]
	Protect from DNA damage (BRCA1 stability) p21 transcriptional induction	ATF6 OASIS	Colon cancer Tumorigenesis	Benedetti et al., 2022 [127] Saito et al., 2023 [128]

ERAD, ER-associated degradation; PE, phosphatidylethanolamine; PC, phosphatidylcholine; DHS, dihydrosphingosine; DHC, dihydroceramide; CREBH, cAMP-responsive element-binding protein H.

an essential protective role. Findings that ATF6 achromatopsia (ACHM) mutants, which are unresponsive to proteotoxic stress, remain activatable by LBS stimuli [106], suggest that lipid-driven signaling can bypass defects in classical UPR pathways. Disruption of MAM architecture contributes to pathogenesis through Ca^{2+} dyshomeostasis and mitochondrial dysfunction. These perturbations trigger aberrant activation of PERK and/or IRE1α and subsequent cell death in cardiovascular diseases and ALS, and diabetic cognitive impairment [117,146]. Loss of Luman leads to elevated mitochondrial Ca^{2+} levels, and consequently increases basal mitochondrial respiration, ATP production, and ROS accumulation. In agreement with these metabolic alterations, *Luman*-deficient mice exhibit elevated energy expenditure without changes in energy intake, thus resulting in protection against weight gain from a high-fat diet, hyperglycemia, and tissue lipid accumulation [147]. Interestingly, male *Luman*-deficient mice resist hepatic lipid accumulation and glucose intolerance, whereas female deficient mice are protected against lipid accumulation in skeletal muscle.

Understanding of this non-canonical ER stress activation, which extends beyond canonical ER roles, suggests that these sensors might provide promising targets for precision medicine in diseases in which traditional proteostatic sensing is impaired.

3. Conclusions

The understanding of the ER stress response has evolved from a reactive "damage control" system to a proactive regulatory network essential for cellular and organismal homeostasis. Whereas classical UPR pathways are triggered by proteotoxic stress, accumulating evidence highlights the physiological and pathological importance of non-canonical triggers, including ISR, LBS, signal transduction at MAMs, and the DDR. These stimuli collectively position ER stress sensors as integrative signaling hubs that link ER function to cellular metabolism, organelle crosstalk, and genome integrity (Table 1, Ref. [23,105,106,108,117,126,127,128,130,131,136,144,145,146]).

Despite these advancements, several fundamental questions remain to be resolved. Although the structural basis of canonical activation is well studied, the precise molecular and activation mechanisms of ER stress sensors by non-canonical stimuli require further investigation. Advanced imaging techniques and multi-omics for each stimulus may address future challenges. Additionally, identifying endogenous chemical chaperones or small molecules that selectively modulate specific sensor arms without disrupting global ER function is a major research frontier.

Understanding molecular mechanisms and identifying compounds that selectively regulate ER stress sensors activity has the potential to enable disease treatment applications. However, several challenges remain to be overcome. Several UPR modulators are currently in clinical trials for cancer, such as MKC8866 (targeting IRE1) and HC-5404-FU (targeting PERK) [148]. Although these agents suppress the proliferation of cancer cells via the inhibition of their kinase activities, achieving high target specificity and minimizing off-target toxicity remain critical challenges. Elucidating more detailed mechanisms by which these compounds change the sensor activities is essential for resolving those issues. In conclusion, by bridging local ER quality control and systemic physiological demands, ER stress sensors establish the ER as a central decision-making organelle. Elucidating these non-canonical activation mechanisms should therefore provide critical insights into molecular pathogenesis, such as neurological, metabolic, or oncological diseases, and ultimately enable the identification of novel therapeutic targets.

Author Contributions

KF: Conceptualization, funding acquisition, design of the manuscript structure, writing, review and editing, creating the figures. HK: review and editing, creating the figures. TT: review and editing, creating the figures. YK: design of the manuscript structure, review and editing. KI: design of the manuscript structure, review and editing. AS: conceptualization, funding acquisition, design of the manuscript structure, writing, review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

Osaka Medical Research Foundation is the affiliated institution of Dr. Kazunori Imaizumi, and this relationship did not influence the judgments in data interpretation or manuscript writing. The other authors declare no conflict of interest.

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