IRE1: ER stress sensor and cell fate executor

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Abstract

Cells operate a signaling network termed unfolded protein response (UPR) to monitor protein-folding capacity in the endoplasmic reticulum (ER). IRE1 is an ER transmembrane sensor that activates UPR to maintain ER and cellular function. While mammalian IRE1 promotes cell survive, it can initiate apoptosis via decay of anti-apoptotic microRNAs. Convergent and divergent IRE1 characteristics between plants and animals underscore its significance in cellular homeostasis. This review provides an updated scenario of IRE1 signaling model, discusses emerging IRE1 sensing mechanisms, compares IRE1 features among species, and outlines exciting future directions in UPR research.

Keywords
unfolded protein response; ER stress; IRE1; cell fate; protein quality control; membrane trafficking system

ER stress and unfolded protein response

The membrane trafficking system maintains operation of approximately one-third of the eukaryotic proteome. Most secretory proteins first enter the ER for folding and assembly. To maintain the fidelity of ER functions, cells coordinate a protein quality control system with a signaling network termed unfolded protein response (UPR) [1-6]. UPR is triggered by ER transmembrane sensors upon ER stress, a cellular condition referring to the accumulation of unfolded proteins in the ER (Figure 1) [7, 8]. The adaptive response occurring at the initial phase of UPR aims to rebalance the protein-folding homeostasis [2, 3, 9-12]. If cells fail to recover from ER stress, UPR represses the adaptive response and triggers apoptosis [1, 3, 4, 7, 13, 14]. The inositol-requiring enzyme (IRE1) is the only identified ER stress sensor in yeast and essential for UPR in animals and plants [15-18] (Figure 1). As an ER transmembrane protein, IRE1 monitors ER homeostasis through an ER luminal stress-sensing domain and triggers UPR through a cytoplasmic kinase domain and an RNase domain [15, 16]. Upon ER stress, IRE1 RNase is activated through conformational change, autophosphorylation, and higher order oligomerization [19-21]. Mammalian IRE1 initiates diverse downstream signaling of the UPR either through unconventional splicing of the transcription factor Xbp-1 or and through posttranscriptional modifications via Regulated IRE1-Dependent Decay (RIDD) of multiple substrates [15, 16, 22-25]. In addition, PERK
and ATF6 function as two distinct mammalian ER stress sensors to cope with complex UPR scenarios [7, 26] (Figure 1). Similar to IRE1, PERK and ATF6 are ER transmembrane proteins that contain an ER luminal stress-sensing domain and a cytoplasmic enzymatic domain. To prevent a further increase in protein-folding demand in the ER, PERK transiently inhibits general protein translation through phosphorylation of eukaryotic initiation factor 2 (eIF2α). Phosphorylated eIF2α can also selectively activate translation of mRNAs including ATF4 transcription factor to regulate UPR target genes [27]. ER stress triggers relocation of ATF6 from the ER to the Golgi where it undergoes proteolytic cleavage. The cleaved transcription factor domain of ATF6 enters the nucleus for UPR regulation [28-30] (Figure 1).

The main molecular mechanisms underlying IRE1 unconventional splicing are conserved in eukaryotes. In budding yeast, mammals, and plants, there is only one transcription factor identified as a splicing target of IRE1 (Figure 1). The stem-loop structure and cleavage site of the IRE1 splicing substrate are conserved among species. In contrast, RIDD appears more divergent in eukaryotes. In yeast, RIDD is only operated in fission yeast *Schizosaccharomyces pombe*, but not in budding yeast *Saccharomyces cerevisiae* [31]. Intriguingly, RIDD-mediated decrease in protein-folding demand is the only identified mechanism of UPR in fission yeast [31]. While plant RIDD may potentially degrade a significant portion of mRNAs encoding secretory proteins [32], it is undetermined whether plant RIDD processes various substrates to direct UPR outputs like mammalian RIDD. Unlike mammalian UPR, plant PERK orthologs have not been yet identified; however, two functional homologs of ATF6, bZIP28 and bZIP17, exist in plants [33] (Figure 1). Moreover, a component of G-protein complex, AGB1, is essential for plant UPR [17] while an alternative G-protein-coupled receptor is involved in noncanonical UPR in *C. elegans* [34]. Due to large members of the mammalian G-protein complex, its roles in classical UPR might be more challenging to reveal. While IRE1 and ATF6 arms are partially conserved between plants and animals, it is interesting to establish the degree of UPR diversification between the two species.

This review presents the latest advances and viewpoints on IRE1-dependent UPR research. We focus on the recent groundbreaking discoveries that define IRE1 as a master regulator in cell fate determination under ER stress. IRE1 was long considered as a positive regulator in cell survival. Thus, the repression of IRE1 was believed to potentiate apoptosis. The recent identification of novel IRE1 regulatory events reveals that IRE1 signaling is persistent during ER stress. Namely, IRE1 can no longer be considered simply as a driving force for cell survival, but rather as an administrator/executor of cell fate determination under ER stress. Through presentation of the recent evidence establishing that IRE1 triggers diverse signaling, we delineate current IRE1-signaling models. It has also become clear that IRE1 monitors cellular homeostasis beyond the protein-folding status in the ER; therefore, the functional relevance of the UPR within physiological processes will be discussed. Finally, we will compare convergent and divergent features of IRE1 between plants and mammals to provide an integrated view of IRE1 in multicellular eukaryotes.

**IRE1 signaling in cell fate determination**

Life-versus-death determination is constantly scrutinized and tightly controlled. Prevalence of malfunctioning cells due to irremediable ER stress contributes to significant diseases, including cancer and diabetes. Conversely, over-commitment to cell death may result in organ damage or cell degenerative diseases [35-39]. To reach optimal fitness under ER stress, cell fates are determined through tight coordination of adaptive and apoptotic responses [37, 40, 41]. In mammals, PERK-eIF2α-ATF4 regulates the transcription factor CHOP to activate ER stress-triggered apoptosis. In parallel, IRE1 controls cell fate
determination through mitogen protein kinase JNK under ER stress [3, 7, 8, 42] (Figure 1). In contrast, while ER stress can play a role in programmed cell death in plants [43], very little is known about ER stress-induced cell death in plants [17, 32, 44]. Furthermore, lack of sequence homologs of most mammalian apoptosis regulators in plants hints that divergent mechanisms of ER stress-induced cell death exist among organisms.

**Revised model of IRE1α signaling network in mammals**

The mammalian genome encodes two isoforms of IRE1, IRE1α and IRE1β. The IRE1α is expressed ubiquitously and IRE1α knockout mice exhibit embryonic lethality. On the contrary, the IRE1β expression is restricted and IRE1β knockout mice are viable [45, 46]; therefore, most mammalian UPR research conducts on the IRE1α. IRE1α was identified as a positive regulator for cell survival. It was believed that IRE1α signaling was terminated during irremediable ER stress to enable apoptosis [1, 2, 7, 15, 47, 48]. Nevertheless, recent studies have challenged this concept by showing that IRE1α persistsently adjusts protein-folding capacity, actively directs UPR signaling, and executes cell fate determination [49, 50] (Figure 2). IRE1α employs splicing and RIDD to direct cell fate throughout ER stress. Despite Xbp-1 being the only identified IRE1α splicing target, numerous types of RNA are proven to be RIDD substrates [22, 49, 50]. Even though the significance of RIDD targets is not completely understood, some RIDD events are critical for IRE1α-dependent cell fate determination. During the adaptive response, IRE1α conducts RIDD on mRNAs encoding ER-translocating proteins to prevent further increases in protein-folding demand in the ER [50]. To augment protein-folding ability, IRE1α splices the transcription factor Xbp-1 mRNA to induce the transcription of ER quality control components. If attempts to restore ER homeostasis fail, IRE1α ceases to splice Xbp-1 mRNA. Alternatively, IRE1α represses adaptive responses and activates apoptosis through RIDD [49, 50]. During the transition phase, occurring between the adaptive and apoptotic response, RIDD increases ER stress intensity through degradation of selective UPR target genes including ER protein chaperone BiP [50]. Once ER stress intensity reaches its threshold, RIDD initiates apoptosis through repression of anti-apoptotic pre-microRNAs [49]. Caspase-2 (CASP2) is a proapoptotic protease essential for apoptosis execution [51]. Upregulation of CASP2 is an indicator of apoptotic initiation. Through decay of anti-Casp2-pre-microRNAs (miRs), IRE1α activates apoptosis through upregulation of Casp2 (Figure 2) [49]. A close association of IRE1α activity and cell fate determination has been proposed for years [1, 2, 7, 15, 47, 48]. These findings provide direct evidence that IRE1α is a molecular switch and apoptosis executioner during ER stress [49]. It was previously proposed that the attenuation of IRE1α activity allows cells to initiate apoptosis [1, 2, 7, 15, 47, 48]. The identification of the IRE1α-Casp2 pathway elaborates an intriguing IRE1α signaling model: IRE1α-Xbp-1 is active in the adaptive phase and attenuated in the apoptotic phase. In parallel, activation of IRE1α-Casp2 event initiates cell death in the apoptotic phase (Figure 3).

**Is mammalian IRE1α the only major trigger of ER stress-induced apoptosis?**

IRE1α is necessary and sufficient to trigger apoptosis while PERK and ATF6 are dispensable in the apoptosis activation [49]. Nonetheless, it cannot be excluded that distinct ER stress sensors may serve as major executioners of cell death in a context-specific manner. Using chemical genetic tools, the regulatory roles of the phosphor-transfer and RNase activity of IRE1α in UPR can be examined separately. The phosphor-transfer function is dispensable for Xbp-1 mRNA splicing and upregulation of CASP2 expression; however, it is required for the subsequent CASP2 cleavage and apoptosis activation, indicating that IRE1α-phosphor-transfer function is essential for cell fate switch during ER stress [49, 50]. Notably, the phosphor-transfer function is mostly studied through an in vitro conditional IRE1α induction that mimics ER stress. While this experimental system is valuable to distinguish phosphor-transfer and RNase function of IRE1α it is important to
note that ATF6 and PERK are not activated through ER stress. A potentially compromised
crosstalk among UPR arms raises a possibility that the IRE1α induction system might not
completely resemble a genuinely biological scenario of ER stress. Hence, careful data
interpretation from the conditional induction system and integration of in vivo analyses are
necessary to determine whether IRE1α is the master trigger in ER stress-induced apoptosis.

The substrate specificity of mammalian IRE1α

While the four identified IRE1α-cleaved microRNAs, miR-17, miR-34a, miR-96, and
miR-125b repress the common substrate Casp2, TXNIP is another target of miR-17 [52].
TXNIP is involved in cell death and was selected to potentially regulate ER stress-induced
apoptosis based on its rapidly elevated expression under severe ER stress. Similar to the
IRE1α mutation, TXNIP mutation leads to compromised apoptosis activation, indicating
that TXNIP is essential for ER stress-induced apoptosis [52, 53]. While PERK-eIF2α
activates TXNIP transcription, IRE1α increases TXNIP expression by degradation of
miR-17. Accordingly, it is conceivable that each of four IRE1α-cleaved microRNAs might
have specific substrates such as TXNIP. Based on this scenario, IRE1α might differentially
degradate its individual target microRNA for fine-tuning of UPR. Another interesting feature
of mammalian RIDD is that distinct substrates comprise a degree of sequence similarity
within the cleavage site, whereas the flanking sequences of the cleavage sites are relatively
divergent [49, 54]. This suggests that the cleavage mechanisms are likely to be conserved
while the flanking sequence determines the specificity of substrate recognition. This
scenario would support the hypothesis that IRE1α adjust its RNase substrate specificity to
activate diverse UPR. The flexibility of IRE1α to target different substrates might rely on
combinations of phosphorylation status, conformational changes, and physical associations
with IRE1α regulators. As alterations of IRE1α substrate specificity lead to opposite cell
fates [50], further understanding of IRE1α substrate preferences will reveal how IRE1α
coordinates cellular homeostasis to determine cell fate under ER stress. Currently the target-
switch of RIDD has only been reported in animals. Therefore, in order to gain a deeper
understanding of UPR evolution in eukaryotes, further studies are needed to determine
whether similar mechanisms exist in yeast and plants.

Plant IRE1 in ER stress response and cell fate determination

Despite the conservation of IRE1 among eukaryotes, divergent IRE1-dependent regulatory
events have also been observed between plants and mammals. These evolutionarily
converged and divergent mechanisms are likely the reason for different ER stress and cell
fate phenotypes observed between plants and mammals. Unlike mammalian IRE1 isoforms,
the two Arabidopsis IRE1 isoforms are expressed ubiquitously with a limited tissue-specific
expression pattern [55, 56]. There is no significant defect of UPR in single mutants of
Arabidopsis IRE1A or IRE1B while Arabidopsis ire1 double mutants display compromised
ER stress tolerance and a UPR activation phenotype [17, 18]. These observations indicate
that the two Arabidopsis IRE1 homologues share partially overlapping function during the
UPR. Evidence for established, dominant or specific roles of individual Arabidopsis IRE1
isoforms during UPR and cell fate regulation need to be further elucidated. Notably, it is
experimentally undetermined that viable Arabidopsis ire1b are knockouts or partial loss-of-
function mutants. Failure to recover a homozygous plant of putative IRE1B knockout hints
that Arabidopsis IRE1B might be an essential gene similar to mammalian IRE1α [57].
Interestingly, although mammalian IRE1α is essential for UPR in goblet cells, in other cell
types, there is no detectable defect in UPR target gene induction in a mammalian ire1 double
mutant likely due to partially overlapping function with ATF6 and PERK [46, 58]. In
contrast, although two functional homologs of ATF6, bZIP28 and bZIP17, exist in
Arabidopsis [33] (Figure 1), Arabidopsis ire1 double mutants exhibit dramatic reduction of
UPR target gene activation [17, 18]. These data indicate that the UPR is partially diversified
between mammals and plants. On the contrary, similar IRE1 features are also observed between plants and mammals. For instance, ire1 and xbp1-1 mutants display differential phenotypes despite both being essential genes. Likewise, the mutant of Arabidopsis IRE1 splicing target, bZIP60, shows comparable ER stress tolerance with the wild type plants as opposed to Arabidopsis ire1 double mutant [17], supporting the hypothesis that the function of Arabidopsis IRE1 is not restricted to unconventional splicing like mammalian IRE1.

Interestingly, mutations of IRE1 in plants and mammals lead to opposite effects in ER stress-induced cell death phenotypes [17, 18, 32]. Ire1α−/− mouse embryonic fibroblasts (MEFs) exhibit a greater survival rate than Ire1α+/+ MEFs under ER stress, supporting that mammalian IRE1 is an apoptosis executioner. Contrarily, Arabidopsis ire1 double mutants display compromised ER stress tolerance, instead of a greater survival rate [17, 18]. Consistently, DNA fragmentation and ion leakage are enhanced in the Arabidopsis ire1 double mutant during ER stress [32], suggesting that plant IRE1 might not function as an apoptosis executioner like its mammalian counterpart. Nevertheless, it cannot be excluded that the differences are related to dissimilar experimental settings: mammalian UPR research is mostly conducted in cell culture, while intact organisms are used in plant UPR studies. Moreover, except potential roles in protein loading reduction under ER stress [32], biological significance of the plant RIDD in cell fate determination is unknown. Further experimental validation will reveal whether the plant RIDD could process multiple substrates to control cell fate decisions similar to that seen in mammals.

Shared components of UPRosome and apoptosis

IRE1 activation is tightly controlled by its interacting protein complex termed UPRosome [15]. Most UPRosome components are involved in apoptosis, supporting that intense crosstalk exists between IRE1 activity and apoptosis activation (Table 1). Specifically, although UPRosome comprises multiple components, loss-of-function mutation of the single component, such as PARP16, Bi-1, Aip-1, PTP-1B, NMHCIIB, Jab1, Nck1, and Ask1, is sufficient to alter the IRE1 splicing activity or apoptosis activation [59-66] (Table 1). Moreover, IRE1 interactors mutants displaying either elevated or declined IRE1 splicing activity can show enhanced apoptosis, indicating that a precise activation level of IRE1 splicing is important for cell survival [59-66]. This further suggests IRE1 activation is controlled by a signaling network that maintains a delicate equilibrium of adaptive and apoptotic responses. A subtle imbalance of the equilibrium could disturb cellular homeostasis and thus alter cell fate determination [59-76]. Furthermore, the observation that a single mutation of UPRosome leads to significant defects in IRE1 signaling hints that IRE1 is differentially regulated in a context-specific manner (Table 1). Because UPRosome analyses are conducted under various conditions, systematic and comparable analyses of UPRosome members will connect each hub and thus give a clearer view of IRE1 signaling network.

IRE1 sensing mechanisms

ER stress-sensing mechanisms are intensively studied in yeast and animals [77]. The ER stress sensors are silent through physical association with BiP, the most abundant ER-resident chaperone. Dissociation with BiP or interaction with unfolded proteins is the major trigger of IRE1 activation. Yeast IRE1 is activated through association with unfolded proteins rather than disassociation with BiP [78]; however, the physical interaction of BiP is a fine-tuning mechanism to ensure that yeast IRE1 is appropriately activated [79]. Unlike yeast IRE1, the activation mechanisms of mammalian IRE1 rely on its disassociation of BiP as opposed to a direct interaction with unfolded proteins [80]. The differences in activation mechanisms between yeast and mammalian IRE1 can be partially explained by the
dissimilarity in protein structure within the sensor domain [15]. Surprisingly, a recent study revealed that mammalian IRE1 \( \beta \) tends to interact with unfolded proteins like yeast IRE1 and it is unable to associate with BiP [81]. Accordingly, it is possible that, like yeast IRE1, binding of unfolded proteins is the primary trigger of mammalian IRE1 \( \alpha \) activation. Despite intense studies in mammals and yeast, the plant IRE1 sensing mechanisms are completely undefined. Further structural and functional analyses in plant IRE1 will be instrumental to reveal ER stress sensing mechanisms in plants.

**Cell-type specific sensing mechanisms: the role of mammalian IRE1\( \beta \)**

How the cellular homeostasis is maintained in a cell-type specific manner is a fundamental question of cell biology. It has been recently shown that IRE1 \( \beta \) is essential for UPR specifically in goblet cells [46]. In goblet cells, IRE1 \( \beta \) is dispensable for Xbp-1 splicing and BiP induction. Instead, IRE1 \( \beta \) mutation leads to enhance ER stress intensity evidenced by higher level of Xbp-1 splicing and BiP induction. Moreover, IRE1 \( \beta \) \(-/-\) mice display a distended ER phenotype potentially due to over accumulation of Mucin2 (MUC2), the most prominent protein secreted from goblet cells. This suggests that IRE1 \( \alpha \) controls MUC2 expression in goblet cells. Thus, IRE1 \( \beta \) mutation leads to MUC2 overload in the ER and in turns trigger ER stress [46]. RIDD was proposed to be the mechanism underlying IRE1 \( \beta \) regulation on MUC2 level in goblet cells [46]. The cell-type-specific target of IRE1 \( \beta \) provides a molecular explanation as to how the UPR maintains a dynamic and specific secretory ability in multicellular organisms. Consistent with the notion that unfolded proteins trigger IRE1 \( \alpha \) activation, IRE1 \( \beta \) might physically interact with specific types of unfolded protein. In the case of goblet cells, IRE1 \( \beta \) might specifically monitor the MUC2 level in the ER and adjusts its loading into the ER through RIDD. Based on this scenario, the mammalian ER stress sensors might distinguish the type of unfolded proteins accumulated in the ER and trigger differential UPR signaling. More specifically, if the unfolded proteins are dispensable for cell survival, ER stress sensors could repress the expression of unfolded proteins through RNA decay or translational repression. Conversely, if unfolded proteins are essential for cellular function, the UPR might preferentially augment the expression of chaperones to recover the production of unfolded proteins. While the ER stress duration and intensity are considered major factors in the apoptosis threshold, the type of misfolded protein might be also critical for determination of UPR signaling outputs.

**Sensing mechanisms beyond protein-folding homeostasis**

Emerging evidence shows that IRE1 monitors cellular homeostasis beyond sensing unfolded protein accumulation. For instance, CRY1/CRY2-mediated circadian rhythm regulates IRE1 \( \beta \) activity in the liver [82], suggesting that IRE1 \( \alpha \) coordinates ER function to cope with circadian-related physiological processes. These observations provide a link between the IRE1 \( \alpha \)-dependent UPR, circadian regulation, and liver metabolic processes. More importantly, because circadian rhythm has a substantial influence on UPR activation, time course studies of the UPR will require diligent experimental design and appropriate controls to avoid biases. Recently, lipid homeostasis is proven to impact the UPR activation through an unconventional sensing mechanism as the unfolded-protein-sensing domain of IRE1 \( \alpha \) and PERK is dispensable for lipid-dependent UPR activation [83]. All together, these observations support that the UPR perceives physiological and cellular signaling beyond ER protein folding homeostasis. Although it is unclear whether plant IRE1 senses signaling beyond protein-folding capacity, an *Arabidopsis ire1* double mutant displaying a root-specific phenotype under unstressed conditions hints that plant IRE1 also integrates physiological signals to maintain specific secretory activity [17]; however, this hypothesis is still awaiting experimental validation.
Concluding remarks

Significant progress on defining IRE1 mechanisms has been achieved. We now know that IRE1 activities are coordinated at a systemic level to cope with dynamic secretion activity. While in vitro experimental systems and conditional IRE1 induction approaches reveal groundbreaking discoveries in the basic UPR knowledge [49, 50, 84-87], we are still far from a comprehensive understanding of UPR in intact organisms. The lethality of the mammalian IRE1 α mutant represents a challenge to gaining insights into the IRE1 function in vivo. In contrast, the viability of plant IRE1 mutants enables in vivo analyses to reveal its roles in organ growth, pathogen defense, and abiotic stress responses [17, 33, 88, 89]. Moreover, with the ease of building high order plant mutants, in vivo phenotypic analyses show that Arabidopsis IRE1 and a conserved component of the G protein complex display a synergistic effect in both plant UPR activation and growth regulation. The study underscores that the UPR network can be built in intact organisms using plants as a model system [17]. With more systematic and quantitative studies of UPR in vivo, there are certainly significant findings ahead that will decipher the dynamic UPR maps close to a genuinely physiological scenario.

Acknowledgments

We thank Dr. Danielle Loughlin for helpful comments and suggestions. We apologize to those authors whose work could not be cited owing to space constraints. This work was supported by grants from the National Institutes of Health (R01 GM101038-01) and NASA (NNX12AN71G).

References


- IRE1 α degrades anti-Casp2 microRNA to initiate cell death.
- The phosphor-transfer function of IRE1 α is essential for cell fate determination.
- IRE1 perceives developmental cues and protein folding homeostasis distinctly.
- Alterations of IRE1 α substrate specificity determine cell fates.
- Conserved and unique features between plant and mammalian IRE1.
Figure 1. Overview of UPR arms in eukaryotes

The IRE1 arm is conserved in eukaryotes. IRE1 unconventionally splices bZIP transcription factors, Xbp-1, bZIP60, and Hac1 mRNA in mammals, plants, and yeast respectively. The spliced bZIP transcription factor enters into the nucleus to regulate UPR target genes. In addition, two distinct arms mediated by PERK and ATF6 regulate mammalian UPR. ATF6 is an ER transmembrane transcription factor. ER stress triggers the relocation of ATF6 from the ER to the Golgi apparatus where it is undergone proteolytic cleavage. Subsequently, the transcription factor domain of ATF6 enters into the nucleus to modulate transcription of UPR target genes. Two functional homologues of ATF6, bZIP17 and bZIP28, exist in plants. PERK, an ER transmembrane protein kinase is identified only in animals. Upon ER
stress, PERK phosphorylates eukaryotic initiation factor 2 (eIF2α), which leads to a transient inhibition of general protein translation and selective translation of the transcription factor ATF4. Under irremediable ER stress, PERK-eIF2α-ATF4-CHOP and IRE1-JNK initiate apoptosis in mammals. Moreover, the beta subunit of the heterotrimeric G protein complex, AGB1, is essential for the plant UPR. Although the G protein complex is conserved in eukaryotes, its significance in UPR is unclear in other eukaryotic organisms. Color code: blue - eukaryotes; black - mammals; green - plants; red - yeast.
Figure 2. IRE1α regulatory mechanisms during ER stress

Mammalian IRE1α is repressed through a physical interaction with BiP when demand and capacity of protein folding is balanced in the ER. A dissociation of IRE1α from BiP due to an elevated level of unfolded protein in the ER leads to activation of IRE1α. The IRE1α activating processes include its auto-phosphorylation, conformational change, and higher order assembly. IRE1α directs cell fate decision through unconventional splicing and Regulated IRE1-Dependent Decay (RIDD). To prevent increasing demand of ER protein folding, IRE1α conducts RIDD to degrade the transcripts of ER-translocating proteins. In parallel, IRE1α unconventionally splices the transcript of Xbp-1 transcription factor. The spliced XBP-1 enters into the nucleus to transcriptionally reprogram UPR target genes.
including ER chaperones. Under irremediable ER stress, IRE1 α ceases to splice Xbp-1 mRNA. Instead, IRE1 α operates RIDD on selective UPR target genes including BiP to enhance the ER stress intensity. Once the ER stress intensity reaches its threshold, IRE1 α represses anti- Casp2 microRNA, miR-17, miR-34a, miR-96, and miR-125b through RIDD. IRE1 α-mediated degradation of anti- Casp2 microRNAs leads to activation of apoptotic initiator Casp2 and subsequently triggers the mitochondrion-dependent apoptosis.
Figure 3. Updated model of IRE1α and PERK signaling in cell fate determination during ER stress

The UPR signaling aimed for cell survival is considered an adaptive response during ER stress. Under irremediable ER stress, UPR represses the adaptive response and triggers an apoptotic response. IRE1α and PERK are two ER stress sensors that decrease ER protein folding demand through mRNA decay and translational inhibition, respectively. Both PERK and IRE1α signaling appear to persist throughout ER stress. IRE1α differentially triggers diverse UPR according to need. In the adaptive phase, to increase protein folding capacity, IRE1α-mediated Xbp-1 mRNA splicing is activated for transcriptional regulation of UPR target genes. In a transition phase between the adaptive and apoptotic responses, the signaling mediated by IRE1α-Xbp-1 is attenuated. In parallel, IRE1α increases ER stress intensity through mRNA decay of selective UPR target genes including ER chaperones. During the apoptotic phase, IRE1α-Casp2 signaling is activated to initiate cell death.
Table 1

Interacting proteins of IRE1

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