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Quality Control in the Endoplasmic Reticulum: Crosstalk between ERAD and UPR pathways

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Abstract

Endoplasmic reticulum (ER)-associated degradation (ERAD) and the unfolded protein response (UPR) are two key quality-control machineries in the cell. ERAD is responsible for the clearance of misfolded proteins in the ER for cytosolic proteasomal degradation, while UPR is activated in response to the accumulation of misfolded proteins. It has long been thought that ERAD is an integral part of UPR because expression of many ERAD genes is controlled by UPR; however, recent studies have suggested that ERAD has a direct role in controlling the protein turnover and abundance of IRE1 α , the most conserved UPR sensor. Here, we review recent advances in our understanding of IRE1 α activation and propose that UPR and ERAD engage in an intimate crosstalk to define folding capacity and maintain homeostasis in the ER.

Introduction

The ER is a major protein folding compartment that actively monitors the biosynthesis, assembly, and trafficking of most secretory and membrane proteins [1]. Thousands of distinct gene products flux through the ER, many of which control normal physiology, and are linked to human health and disease [2]. To maintain protein homeostasis, cells must ensure the fidelity of protein folding and maturation. However, certain physiological and pathological conditions can lead to an imbalance between protein-folding demand and the folding capacity, resulting in an accumulation of misfolded proteins in the ER, with resultant ER stress [2,3]. To maintain ER homeostasis, cells have evolved protein quality-control systems through the action of different pathways, including the UPR, ERAD, and autophagy.

ER-resident proteins are mainly cleared by ERAD for proteasomal degradation in the ER, while protein aggregates in the ER may be cleared by autophagy [4–6]. The SEL1L-HRD1 protein complex represents the most conserved ERAD machinery in mammals with SEL1L being the cofactor for the E3 ligase HRD1 (reviewed in [4,5,7]). Ubiquitinated ERAD substrates by the action of HRD1 and SEL1L are extracted from the ER membrane to the cytosol, a process referred to as ‘retrotranslocation’ or ‘dislocation’. This process is coupled

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to the energy derived from ATP hydrolysis by the AAA ATPase VCP/p97 (Cdc48 in yeast) and its cofactors [8–10]. The accumulation of misfolded proteins in the ER triggers UPR by activating three main UPR sensors, IRE1 α , PERK and ATF6, on the ER membrane (reviewed in [3,11]). They subsequently initiate signaling pathways to enhance protein folding and degradation, and attenuate protein translation. While the functions of UPR and autophagy have been extensively characterized both *in vitro* and *in vivo*, we are only just beginning to appreciate the physiological importance of ERAD *in vivo* [7].

While the ER quality-control systems are integrated to assist and monitor protein folding and/or degradation, thereby maintaining ER homeostasis under different physiological cues, the crosstalk among these quality control systems has not yet been fully investigated. Here, we first review the history and major advances in the ERAD and UPR fields, and then highlight recent advances in our understanding of the functions of IRE1 α and SEL1L-HRD1, with a focus on their crosstalk.

Historic Perspectives

During the early 1990s, Peter Walter at University of California, San Francisco and Kazutoshi Mori at Kyoto University independently identified an ER-to-nucleus signaling pathway known as the UPR, mediated by an ER membrane protein called ERN1 or inositol requiring enzyme 1 (IRE1) in budding yeast [12–14]. Soon after, they reported identification of a gene encoding the IRE1-specific substrate HAC1, a transcription factor [15–17]. Later, the Kaufman group at the University of Michigan and the Ron group at New York University cloned the mammalian homolog IRE1 α [18,19]. In addition to IRE1 α , two other major sensors of ER stress, the pancreatic eIF2 α kinase (PEK) or protein kinase R (PKR)-like ER kinase (PERK), and the activating transcription factor 6 (ATF6), were later identified in worms and mammals by the Shi/Wek and Mori groups, respectively [20,21]. Among the three UPR signaling branches, IRE1 α is the most conserved ER stress sensor, from budding yeast to humans.

Around the same time when yeast IRE1 was identified, several laboratories were in a race to identify the mysterious proteolytic system(s) for ER proteins. In 1988–1991 Jennifer Lippincott-Schwartz and Richard Klausner at the National Institutes of Health showed that the degradation of unassembled subunits of T cell receptor (TCR) occurs at a site closely associated with the ER, through a lysosome-independent mechanism [22,23]. Shortly after, work by the Dieter Wolf group helped to define a set of misfolded proteins, including a mutated version of a soluble protein carboxypeptidase Y (CPY*), as the first ERAD substrate in yeast [24]. These findings later contributed to the establishment of a concept of protein quality control in the ER. During the period 1992–1997, several laboratories showed that the degradation of ER proteins, including TCR subunits [25], cystic fibrosis transmembrane conductance regulator [26,27], mutant α 1-antitrypsin [28], yeast carboxypeptidase [29], prepro-alpha factor [30], and MHC class I heavy chains [31,32], all required the ubiquitin-proteasome pathway in the cytoplasm. In 1996, Ardythe McCracken and Jeffrey Brodsky at University of Pittsburgh termed this specialized destruction process ‘ERAD’ [33]. Around the same time, Randy Hampton at University of California, San Diego performed a genetic screen in budding yeast of the turnover of HMG-CoA reductase

(HMGCR), a rate-limiting enzyme involved in cholesterol biosynthesis, which led to the identification a group of proteins termed ‘Hrd’ (HMG-CoA reductase degradation) [34]. This family includes the E3 ligase Hrd1p and its cofactor Hrd3p [35]. Dieter Wolf at Universität Stuttgart independently performed a similar screen for mutants defective in ERAD using CPY* in budding yeast, which led to discovery of the genes in the Hrd1 pathway, such as *Der1* and *Der3/Hrd1* [36,37]. These two nonbiased studies indicated that HRD1 has a role in the degradation of both membrane and ER luminal proteins.

Notably, before the identification of yeast Hrd1p/Hrd3p, the Greenwald group at Columbia University identified *Caenorhabditis elegans* SEL-11 (Hrd1p homolog) and SEL-1 (Hrd3p homolog) as negative regulators of LIN12/NOTCH-like protein, which were later proposed to regulate LIN12 turnover [38–40]. In 1997, the mammalian homolog of SEL-1 was cloned and named ‘SEL1L’ by Ida Biunno [41]; in 2002, the human *HRD1* gene was first cloned from HEK293 cDNA as a homolog to yeast Hrd1p by the Nomura group at Hokkaido University [42]. Concurrently, HRD1 was also termed as Synoviolin by the Nakajima group in 2003 because it was cloned from rheumatoid synovial cells [43]. Its upregulation in synovial tissues from patients with rheumatoid arthritis has implicated HRD1 in arthropathy [43]. However, neither HRD1 nor SEL1L were not recognized as ERAD components until 1–2 years later, when the Wiertz and Ploegh groups at Leiden University Medical Center and Harvard Medical School demonstrated the requirement of human HRD1 and SEL1L, respectively, in ERAD complex formation and model substrate degradation [44,45].

Key breakthroughs and major events related to IRE1 α UPR and SEL1L-HRD1 ERAD are shown in Figure 1. Here, we highlight recent advances in our understanding of the function of IRE1 α and the SEL1L-HRD1 protein complex, focusing on their crosstalk. Readers are referred to several recent excellent reviews on the topics related to ERAD [5,7,46,47] and UPR [3,11] in general.

IRE1 α of UPR

IRE1 α is a type I transmembrane protein with molecular weight of 110 KDa, containing an N-terminal luminal sensor domain as well as cytosolic kinase and RNase domains. Under basal conditions, IRE1 α is present largely in an inactive state, and is found associated with the ER **chaperone** (see Glossary) **BiP/Grp78** (reviewed in [11]). Upon activation, IRE1 α self-associates into dimers or higher-order oligomers, [48,49], leading to *trans*-autophosphorylation of the IRE1 α kinase domain and, subsequently, the activation of the RNase domain. Activated IRE1 α initiates the unconventional mRNA splicing of X-box binding protein (XBP1), generating a frameshift that encodes a potent transcription factor, XBP1s. XBP1s activates the transcription of a subset of UPR-related genes linked to protein folding, secretion, ERAD, and lipid synthesis [50–54]. In addition, IRE1 α may be involved in a promiscuous RNA degradation process known as regulated IRE1-dependent decay (RIDD), for ER-localized mRNAs, ribosomal RNA, and miRNAs [55].

Below, we discuss recent findings on the newly identified IRE1 α binding proteins **HSP47** and **ERdj4** (Figure 2). Other IRE1 α interactors or regulators, such as BAX, BAK, BI-1, AIP1, NMIIB, RACK1, PKA, PP2A, PARP16, and others, have been reviewed extensively elsewhere and will not be discussed here [11].

HSP47

In resting cells, inactive IRE1 α is found associated with BiP, one of several abundant ER chaperones in the ER [56]. During ER stress, BiP is recruited to misfolded proteins, accompanied by IRE1 α activation (Figure 2). While BiP was the first protein found to interact with the luminal domain of inactive IRE1 α , the detailed events regulating IRE1 α activation in the ER lumen have remained unclear.

A recent study by Sepulveda *et al.* [57] uncovered ER chaperone HSP47 as a novel IRE1 α regulator. The authors identified HSP47 as a binding partner of IRE1 α in a mass spectrometry-based immunoprecipitation proteomics screen of epitope-tagged IRE1 α in mouse embryonic fibroblasts (MEFs). Overexpression of HSP47 in MEFs not only enhanced XBP1 mRNA splicing and transcription of several XBP1s-dependent UPR target genes, but also increased the RIDD activity of IRE1 α during ER stress. Indeed, further analyses demonstrated that HSP47 positively regulates IRE1 α activity (as shown by its oligomerization and phosphorylation), while not altering the total IRE1 α protein levels. Conversely, downregulation of HSP47 delays IRE1 α activation and attenuates XBP1 mRNA splicing.

Mechanistically, the authors showed that HSP47 directly competes with BiP for binding to the luminal domain of IRE1 α . Under ER stress, BiP dissociates from IRE1 α with a concurrent increase in IRE1 α -HSP47 association (Figure 2). Once disengaged from IRE1 α to interact with misfolded proteins, BiP may have only limited ability to return due to IRE1 α occupancy by HSP47. Similarly, HSP47 binding may accelerate and stabilize IRE1 α oligomerization, leading to rapid IRE1 α activation. Analysis of the binding kinetics of HSP47 and BiP with the dimerization-defective IRE1 α -D123P mutant (aspartic acid at position 123 mutated to proline [58]) revealed that the IRE1 α -D123P mutant constitutively interacts with BiP but not HSP47 and, hence, is largely unresponsive to ER stress. Furthermore, *in vivo* analysis of *Drosophila melanogaster* with HSP47 knockdown challenged by pharmacological ER stress demonstrated the importance of HSP47 in IRE1 α activation and signaling. Future studies are needed to further dissect the competitive relationship between BiP and HSP47 in IRE1 α activation and to delineate the physiological significance of HSP47 in the activation of the other UPR sensors, PERK and ATF6.

ERdj4

The Ron laboratory reported the identification of the ER **co-chaperone** ERdj4 as a cofactor for BiP to cooperatively regulate IRE1 activation [59]. When ATP is bound, BiP exhibits low affinity for IRE1 α [59]. ATP hydrolysis then switches BiP into a closed conformation to stabilize the binding. Similar to all HSP70s, the intrinsic ATPase activity of BiP is weak, but **J-protein** co-chaperones, such as ERdj4, accelerate ATP hydrolysis to augment the efficiency of substrate recognition and BiP binding [60,61]. Biochemical studies using purified recombinant proteins showed that ERdj4 recruits BiP and stimulates the ATPase activity of BiP while directly binding to IRE1 α . Moreover, the initial weak binding of BiP to IRE1 α luminal domain (IRE1^{LD}) became stronger and more stable following ERdj4 J-domain-stimulated ATP hydrolysis, leading to the disruption of IRE1^{LD} dimer to its monomeric form. Given the report that ERdj4 is a downstream target of XBP1s [62], the

'ERdj4-IRE1 α ' axis may represent a negative feedback to fine-tune IRE1 α activation and signaling. In line with this notion, ERdj4 deficiency has been shown to cause constitutive ER stress with increased XBP1 mRNA splicing in mice [63], mimicking XBP1 overexpression [64].

Previously, it has been reported that **protein disulfide isomerase** family 6 (PDIA6) limits IRE1 α activity by converting oligomeric IRE1 α back to the monomeric form through the cycle of formation and breakage of disulfide bonds between IRE1 α and PDIA6 [65]. Thus, we speculate that ERdj4 attenuates IRE1 α activation by facilitating BiP binding, following IRE1 α deoligomerization by PDIA6 (Figure 2).

Outstanding Questions

All three IRE1 regulators discussed in this section, HSP47, ERdj4, and PDIA6, are IRE1 α -XBP1 targets, which raises interesting questions of how these factors work together (cooperatively or competitively) or independently, to regulate the activation state of IRE1 α during basal and stress conditions. Given that the IRE1 α -BiP complex is still detected in ERdj4-depleted cells, other ERdj proteins may function similarly to help repress IRE1 α activation [59]. Indeed, similar to ERdj4 deficiency, deletion of ERdj2 in Chinese hamster ovary (CHO) cells results in an induction of IRE1 α RNase activity as measured by a flow cytometry-based reporter assay [59]. Moreover, deletion of ERdj2 also strongly activates the CHOP reporter (a downstream effector of PERK pathway), suggesting that ERdj proteins also regulate PERK activation. It remains to be tested whether the actions of ERdj proteins are conserved for all or only some branches of the UPR.

SEL1L-HRD1 ERAD

ERAD has a critical role in the maintenance of the integrity of the ER proteome by constantly monitoring the folding of polypeptides under normal and stress conditions [4]. Proteins that fail to achieve, or lose, proper folding status are directed for clearance ('quality' control), and this mechanism has also been deployed to eliminate excessive copies of certain proteins ('quantity' control) [66]. ERAD occurs in a multistep process comprising recognition, extraction, and ubiquitination of ER proteins for cytosolic proteasomal degradation. To accomplish such coordinated processes, several ERAD components are organized into distinct functional networks [67,68]. In a simplified model of ERAD, chaperones and lectins (e.g., BiP, EDEM, ERdj, OS9, XTP3B, etc.) within the ER lumen recognize unfolded nascent polypeptide sub-strates [69–74] and hand them over to membrane-embedded ERAD adaptors (e.g., SEL1L, Erlins, Insigs, etc.) [45,75–79], when then undergo retrotranslocation through a putative channel (candidates includes HRD1, DER1, and DFM1) followed by polyubiquitination [80–82]. Once exposed in the cytosol, VCP/p97 and its helper proteins provide the energy source for substrate extraction from the ER membrane [8,83–86].

A dozen of ERAD E3 ligases that have been identified to date, including HRD1, GP78, TRC8, TEB4/MARCH6, RNF5/Rma1, RNF170, RNF185, and TMEM129. HRD1 (also known as SYVN1) is the best characterized [44,87–95]. SEL1L is an indispensable adaptor of HRD1 because it has an essential role in HRD1 stability and likely also substrate

recruitment [74–76,96–98]. In yeast, Hrd3p is also indispensable for Hrd1p function by stabilizing Hrd1p, but Hrd1p overexpression can bypass Hrd3 requirement [84,99]. In mammals, the relationship between SEL1L and HRD1 is likely to be more complicated depending on cell types and substrates [67], and requires further investigation.

In recent years, the generation and characterization of cell-type specific SEL1L- or HRD1-deficient mouse and cellular models have provided unprecedented insights into the physiological significance of ERAD, and have led to the identification of several endogenous substrates, including IRE1 α , B cell development-specific pre-B cell receptor (pre-BCR) and Fas, peroxi-some proliferator activator receptor γ b coactivator β (PGC1 β), B lymphocyte-induced maturation protein 1 (BLIMP1), p53, NF-E2-related factor 2 (NRF2), and, recently, the prohormones, pro-arginine-vasopressin (proAVP) and pro-opiomelanocortin (POMC) in neuroendocrine cells [96,100–110].

Germline deletion of *SEL1L* or *HRD1* in mice leads to embryonic lethality around embryonic day 11–14 [111,112], while acute deletion of either gene in adult mice leads to premature death within ~3 weeks [96,105]. Subsequent characterization of cell type-specific SEL1L [96,100–102,106,107] and HRD1 [103–105,110,113] deletion in adipocytes, immune cells, enterocytes, and AVP and POMC neurons has revealed the significance of SEL1L-HRD1 ERAD in a cell type- and substrate-specific manner *in vivo* [7]. For example, mice with SEL1L or HRD1 deficiency in adipocytes exhibit lipodystrophy and postprandial hyperlipidemia [100,105]. Mice with SEL1L ablation in AVP neurons progressively develop polyuria and polydipsia, both characteristic of diabetes insipidus [107]. Mice with SEL1L ablation in POMC neurons develop hyperphagia and obesity even when fed a low-fat chow diet [108]. These studies underscore the pathophysiological importance of SEL1L-HRD1 ERAD in health and disease. For a detailed discussion of this topic, readers are referred to a recent review [7].

Similarly, germline deletion of some ERAD components, such as Derlin-1 [114], Derlin-2 [115], or Ube2j1 [116], but not others (Derlin-3 and HERP [114]), leads to embryonic or perinatal lethality. These findings demonstrate the importance of ERAD in development and normal physiology.

IRE1 α Degradation by SEL1L-HRD1 ERAD

In a proteomic analysis of isolated microsomes, IRE1 α was found to accumulate in SEL1L-deficient MEFs without any change in gene transcription [101]. Further studies revealed that IRE1 α protein stability is controlled by ERAD both *in vivo* and *in vitro* under basal conditions, which occurs in an HRD1-, SEL1L- and OS9-dependent manner (Figure 3, Key Figure). Interestingly, BiP is also required for IRE1 α ERAD because depletion of BiP causes dissociation of IRE1 α from ERAD components, stabilizing IRE1 α . Under ER stress, both BiP and SEL1L-HRD1 are released from IRE1 α , attenuating IRE1 α degradation and promoting IRE1 α stabilization and/or activation. It remains unclear whether dissociation of BiP and ERAD components from IRE1 α under stress conditions is sequentially linked or coordinated. Whether ERAD-dependent proteasomal degradation of IRE1 α requires cytosolic ERAD apparatus, such as p97, remains to be experimentally tested. However,

given the well-established role of p97 in substrate retrotranslocation and extraction from the ER membrane [5], SEL1L-HRD1-mediated IRE1 α degradation is likely p97 dependent.

Deletion of either SEL1L or HRD1 in various tissues and cell types, including enterocytes, pancreas, adipose tissue, and MEFs, results in a profound 10–100-fold increase in IRE1 α protein, while its mRNA levels are largely unchanged [101]. Moreover, the level of phosphorylated IRE1 α as well as its RNase enzymatic activity as measured by *Xbp1* mRNA splicing are moderately elevated in ERAD-deficient cells under basal conditions, pointing to a key role of ERAD in the restraint of IRE1 α hyperactivation. Although protein levels are highly elevated in the absence of SEL1L-HRD1 ERAD, IRE1 α protein does not form detergent-insoluble aggregates as has been seen with some other ERAD substrates, and the IRE1 α branch of the UPR remains responsive to ER stress [101]. This finding suggests that, in ERAD-deficient cells, a majority of accumulated IRE1 α remains in a BiP-bound form. Whether accumulated IRE1 α in ERAD-deficient models triggers XBP1s-independent effect(s) remains to be determined.

It is not clear whether IRE1 α is subjected to ERAD-mediated quality control (due to an intrinsic propensity to misfold) or quantity control (when its protein level becomes disproportionately high). These two events are not necessarily mutually exclusive because SEL1L-HRD1 ERAD is unlikely to sense the abundance of ER proteins, but rather the folding or maturation state of its substrates. Together with the observation that IRE1 α interacts extensively with ER chaperones, as discussed above, we propose that newly synthesized IRE1 α protein may be misfolding prone and may be recognized and targeted for proteasomal degradation by SEL1L-HRD1 ERAD machinery (Figure 3). Under stress conditions, dimerization or oligomerization of IRE1 α may result in the stabilization of IRE1 α , which is accompanied by the dissociation of BiP. Alternatively, the presence of an excessive amount of misfolded proteins during stress out-competes IRE1 α for ERAD, leading to its stabilization. The regulated degradation of IRE1 α by ERAD adds another example of proteins subjected to a regulated quality and/or quantity control, in addition to the best-studied precedent of HMG-CoA reductase (HMGCR), the turnover of which is controlled in response to cellular sterol levels [34,79].

It remains mysterious how endogenous ERAD substrates are recognized and selected. Molecular chaperones and ER lectins are essential components of the process because of their ability to directly bind folding intermediates. Analysis of chaperone-peptide interactions using a peptide library *in vivo* has revealed that ERdj4 (and ERdj5) specifically binds to aggregation-prone sequences exhibiting substrate-binding patterns distinct from that of BiP [117]. Speculatively, the IRE1 α luminal domain may expose a putative aggregation-prone region (probably the same or adjacent region that engages IRE1 α dimerization and/or oligomerization) to serve as a recognition element for ERdj4. Given that previous studies have implicated ERdj4 in substrate recruitment for ERAD (e.g., epithelial sodium channel and surfactant protein C [118,119]), we speculate that ERdj4, together with BiP and other chaperones, may be involved in IRE1 α ERAD. Hence, ERdj4 may develop two strategies to restrain IRE1 α signaling, one through ERAD and the other through BiP-mediated inactivation. Proteomics-based identification and validation of additional IRE1 α adaptors and modulators in the context of IRE1 α ERAD will further advance our understanding of

this fundamental degradative event. It is unclear whether ERAD controls the IRE1 protein stability in yeast. If the pathway is conserved, yeast genetic screens will be useful to identify genes involved in IRE1 ERAD.

Feedback Loop between UPR and ERAD in Health and Disease

SEL1L and HRD1 are transcriptionally regulated by the IRE1 α -XBP1 signaling pathway [120]. An increase in ERAD activity can alleviate ER stress and restore ER homeostasis by promoting the clearance of unfolded and/or unwanted proteins. Thus, the discovery of regulated IRE1 α ERAD represents a unique feedback mechanism. Limiting the amplitude and duration of IRE1 α activity at basal levels is critical to maintain cellular homeostasis because aberrant activation of IRE1 α can have deleterious outcomes, such as cell death [121]. Impaired ERAD function may alter ER homeostasis not only by affecting the clearance of misfolded proteins in general, but also by upregulating IRE1 α activation. Abnormal accumulation and signaling of IRE1 α due to impaired ERAD function may be causally linked to the disease pathogenesis.

IRE1 α heterozygosity in the intestinal epithelium partially rescued the colitis caused by treatment with the dextran sodium sulfate in enterocyte-specific SEL1L-deficient mice, suggesting that ERAD deficiency in the pathogenesis of experimental colitis is due, at least in part, to a failure to limit excessive IRE1 α (level and activity) [101]. However, defects associated with SEL1L-deficient Paneth cells, a secretory cell type in the small intestine, were not rescued by the loss of IRE1 α [102]. In addition, a mutation S658P (serine at position 658 to proline) in the *SEL1L* gene (a mutation located in one of the Sell1-like-repeats in the ER lumen close to the transmembrane domain) has been identified in canines with early-onset cerebellar ataxia [122]. Although the molecular mechanism underlying the SEL1L-S658P mutation remains unclear, the increased expression of several UPR genes, including *XBPI*, *ERdjs*, *ATF6*, *CHOP*, and ERAD components, suggests that UPR is elevated in response to a SEL1L defect. It will be of interest to determine the extent to which the SEL1L-S658P mutation leads to loss of function of SEL1L-HRD1 ERAD and, consequently, elevated IRE1 α protein levels and signaling.

A loss-of-function mutation within Fam8A1, a component of the SEL1L-HRD1 protein complex [67,123], was identified during the analysis of whole-exome sequencing in 238 families (928 individuals) with autism spectrum disorder (ASD) [124]. It would be interesting to determine whether the Fam8A1 mutation associated with ASD is linked to SEL1L-HRD1 ERAD and, thus, possibly leads to dysregulated IRE1 α signaling. Since dysfunction of the UPR and ERAD pathways independently has been reported in association with many human diseases, including neurodegenerative diseases, cancer, diabetes mellitus, ischemia, and infectious diseases, it will be important to determine whether the two pathways contribute cooperatively or synergistically contribute to disease initiation and progression [6]. Even more interesting would be to determine whether IRE1 α inhibitors, such as 8866 and MKC-3946, could have beneficial effects in ERAD-associated animal models and human diseases [125,126].

By contrast, loss of function of IRE1 α may also contribute to disease pathogenesis. The human somatic cancer-associated IRE1 α -P830L mutant (proline at position 830 to leucine at the kinase/RNase junction) [127] has a shorter biological half-life than that of wild-type IRE1 α because the mutant protein is structurally unstable [128]. The mutant is unable to form oligomers and autophosphorylates upon ER stress, and, thus, is defective in UPR activation. Although the biochemical mechanism underlying the action of IRE1 α -P830L in cancer has not been systematically examined, no-to-low activation of IRE1 α protein can cause disease, as shown in the case of diffuse large B cell lymphoma, in which impaired *IRE1a* gene expression is linked to cancer development [129]. Further investigation of the interplay between IRE1 α -P830L, ERAD, and the role of BiP in this process will provide new insights into the importance of crosstalk between ERAD and UPR in disease pathogenesis.

Concluding Remarks and Future Perspectives

Recent studies have revealed that IRE1 α and SEL1L-HRD1 ERAD, the two principal ER quality-control machineries, function in an independent and yet cooperative manner in maintaining a healthy ER proteome and cellular function. The notion that IRE1 α is subject to negative feedback regulation by SEL1L-HRD1 ERAD *in vivo* provides an enlightening perspective into the maintenance of ER homeostasis by ER quality-control machineries in health and disease. Maintaining an optimal physiological concentration of IRE1 α by ERAD is an important regulatory checkpoint that fine-tunes ERfolding capacity and ER homeostasis. The effect of ERAD on UPR may not be limited to IRE1 α , because an *in vitro* study has shown that SEL1L-HRD1 ERAD is also responsible for the turnover of ATF6 [130]; however, the extent to which this process occurs *in vivo* and its physiological significance remain unknown (see Outstanding Questions). Future studies will help gain a better understanding of the crosstalk between ERAD and UPR in different physiological and pathological settings, such as aging, cancer, metabolic syndrome, and neurodegeneration.

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Glossary

BiP/GRP78:

an ER-resident HSP70 chaperone that regulates both protein folding and quality control of unfolded proteins.

Chaperones:

a functionally related group of proteins assisting protein folding in the cell under physiological and stress conditions. They recognize and bind non-native proteins, thus preventing aggregation, and couple ATP binding/hydrolysis to the folding process. Repeated

cycles of client binding and release ensure proper client folding. Typical chaperone members include HSP70 and HSP90.

Co-chaperones:

assist chaperones in protein folding and other functions. Co-chaperones catalyze the hydrolysis of ATP to ADP on their respective chaperones, which then undergo a large conformational change to either bind to their substrates with higher affinity or aid in the release of the substrate following protein folding.

HSP47:

an ER luminal chaperone involved in collagen maturation and trafficking as well as the activation of the UPR sensor IRE1 α .

J-protein (also called DnaJ):

defined by the presence of a J domain that can regulate the activity of the HSP70 family, including BiP; is known to be involved in the ERAD. ERdj4 may also be involved in the regulation of IRE1 α activity.

Protein disulfide isomerase (PDI):

a member of the thioredoxin superfamily of redox proteins with three catalytic activities: thiol-disulfide oxidoreductase, disulfide isomerase, and a redox-dependent chaperone. The disulfide isomerase function of PDIA6 has been reported to be important for limiting UPR signaling.

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Outstanding Questions

What are pathological conditions causally linked to aberrant UPR and/ or compromised ERAD function?

What are the physiological functions and significance of the crosstalk between SEL1L-HRD1 ERAD and IRE1 α UPR in a tissue-and cell type-specific manner?

How does the crosstalk between ERAD and UPR affect ER homeostasis in health and disease? Does an imbalance in the crosstalk contribute to disease initiation and progression?

Does the effect of ERAD on UPR go beyond of IRE1 α ?

Highlights

The UPR sensor IRE1 α and SEL1L-HRD1 ERAD are the two most conserved branches of ER quality-control mechanisms.

IRE1 α activation is controlled by different modulators, such as newly identified ERdj4, HSP47, and SEL1L-HRD1 ERAD.

SEL1L-HRD1 ERAD targets IRE1 α for proteasomal degradation to restrain IRE1 α signaling under basal condition.

Crosstalk between UPR and ERAD is critical for the maintenance of ER homeostasis under physiological and pathological conditions.

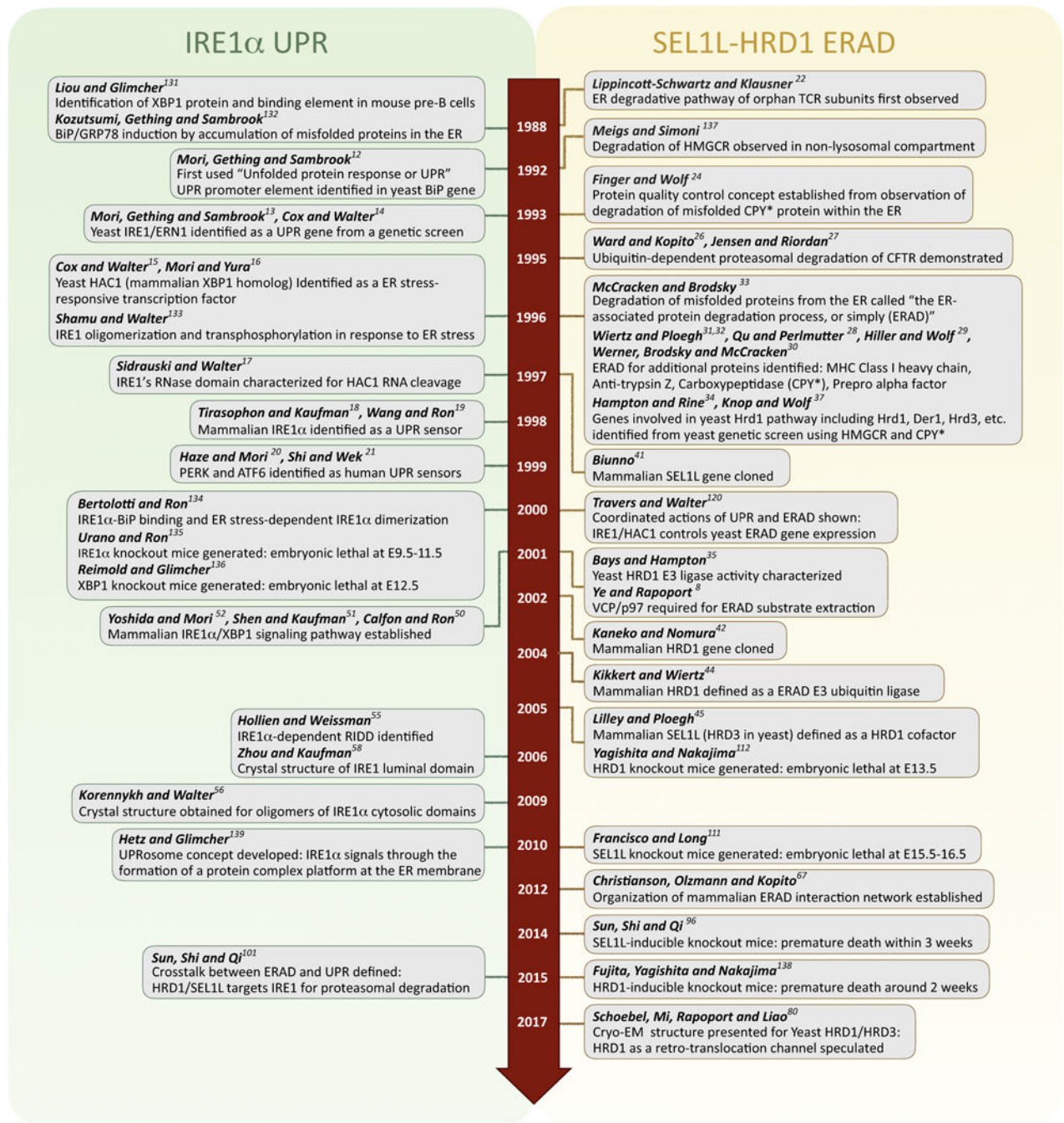


Figure 1. Timeline for Key Discoveries in the SEL1L-HRD1 Endoplasmic Reticulum (ER)-Associated Degradation (ERAD) and Inositol-Requiring Enzyme 1 (IRE1)- α Unfolded Protein Response (UPR) Fields.

A chronology of notable events throughout the history of IRE1 α UPR (A) and HRD1-SEL1L ERAD (B) over the past three decades [8,12–22,24,26–35,37,42,44,45,50–52,55,56,58,67,80,96,101,111,112,120,131–139].

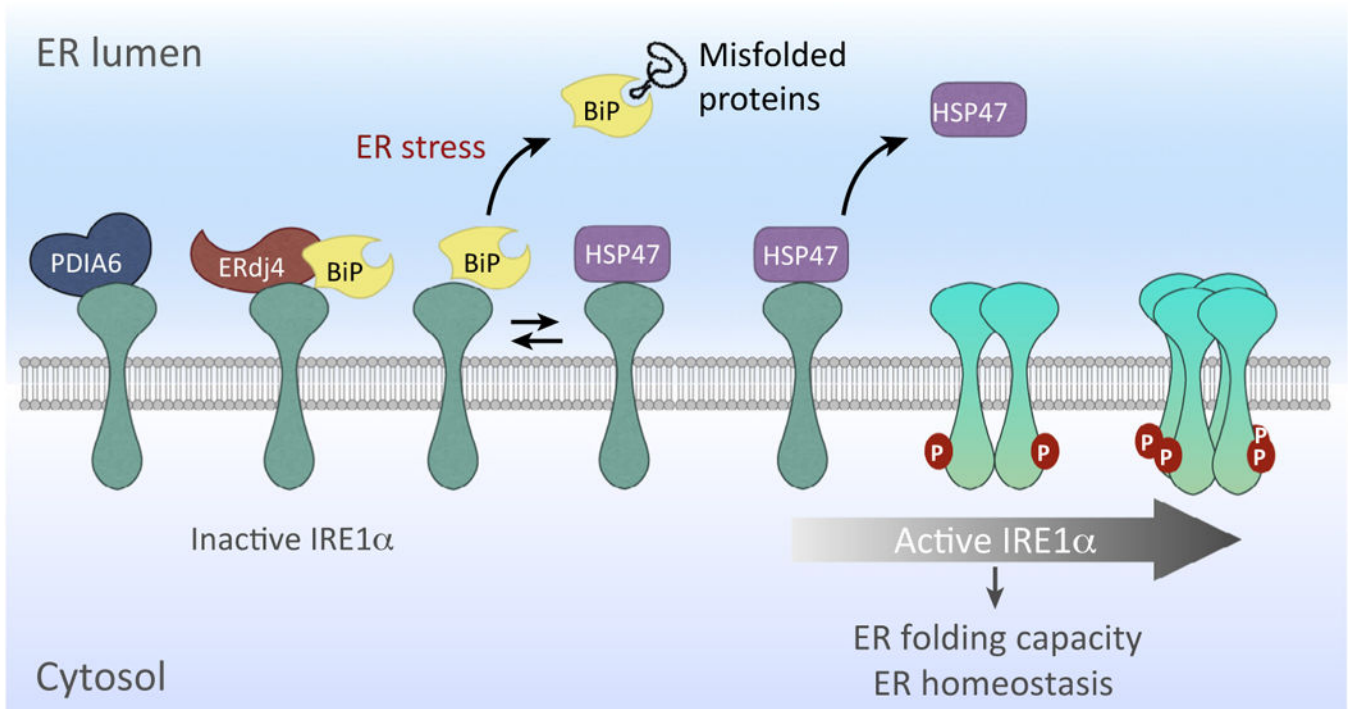


Figure 2. Regulators of Inositol-Requiring Enzyme 1 (IRE1)- α Activation.

The activity of IRE1 α is regulated through the binding of several cofactors that modulate its inhibition [BiP, ERdj4, and protein disulfide isomerase (PDI)-A6] and activation (HSP47). IRE1 α is maintained as a monomer in a repressed state under basal conditions through an association with BiP. The endoplasmic reticulum (ER) chaperone HSP47 binds to IRE1, enhancing its activation by displacing BiP, which facilitates IRE1 α dimerization/oligomerization for activation. Following activation, IRE1 α oligomers are converted to monomers by association with PDIA6. ERdj4 represses IRE1 α by recruiting BiP.

Key Figure

Crosstalk between Endoplasmic Reticulum (ER)-Associated Degradation (ERAD) and Unfolded Protein Response (UPR)

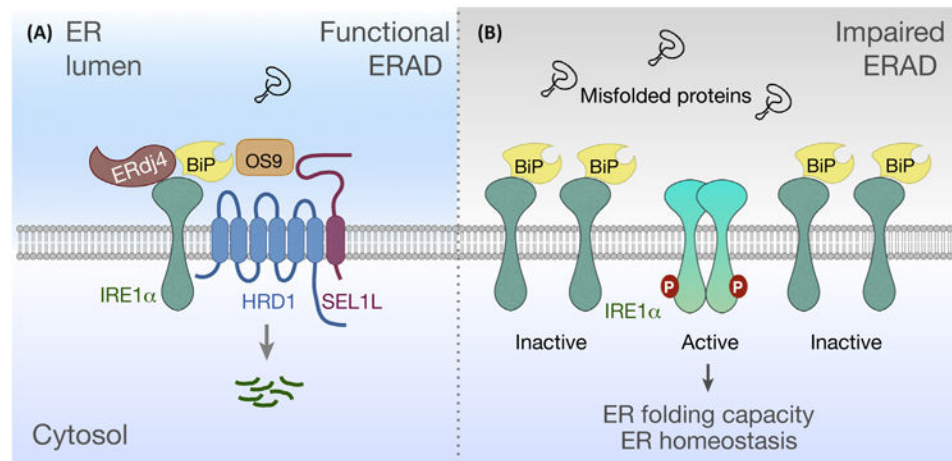


Figure 3.

Inositol-requiring enzyme 1 (IRE1)- α is degraded via SEL1L-HRD1 ERAD, a process that depends on HRD1, SEL1L, OS9, and BiP (A). ERAD deficiency results in IRE1 α accumulation, leading to its activation under basal conditions (B).