Published in final edited form as:
Physiol Rev. 2012 April ; 92(2): 537–576. doi:10.1152/physrev.00027.2011.

THE DELICATE BALANCE BETWEEN SECRETED PROTEIN FOLDING AND ENDOPLASMIC RETICULUM-ASSOCIATED DEGRADATION IN HUMAN PHYSIOLOGY

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Abstract

Protein folding is a complex, error-prone process that often results in an irreparable protein by-product. These by-products can be recognized by cellular quality control machineries and targeted for proteasome-dependent degradation. The folding of proteins in the secretory pathway adds another layer to the protein folding "problem," as the endoplasmic reticulum maintains a unique chemical environment within the cell. In fact, a growing number of diseases are attributed to defects in secretory protein folding, and many of these by-products are targeted for a process known as endoplasmic reticulum-associated degradation (ERAD). Since its discovery, research on the mechanisms underlying the ERAD pathway has provided new insights into how ERAD contributes to human health during both normal and diseases states. Links between ERAD and disease are evidenced from the loss of protein function as a result of degradation, chronic cellular stress when ERAD fails to keep up with misfolded protein production, and the ability of some pathogens to coopt the ERAD pathway. The growing number of ERAD substrates has also illuminated the differences in the machineries used to recognize and degrade a vast array of potential clients for this pathway. Despite all that is known about ERAD, many questions remain, and new paradigms will likely emerge. Clearly, the key to successful disease treatment lies within defining the molecular details of the ERAD pathway and in understanding how this conserved pathway selects and degrades an innumerable cast of substrates.

I. INTRODUCTION

A. The Folding Problem: Inefficiency and Inaccuracy During Protein Folding

Accurate protein folding is key for biological function, but this process is hampered by the fact that folding is chemically complex. In eukaryotes, the translation of mRNAs occurs on 80S ribosomes, which are either free in the cytoplasm or tethered to the endoplasmic reticulum (ER), giving the organelle a studded or rough appearance by electron microscopy. As a nascent protein emerges from the ribosome exit tunnel, the polypeptide must adopt a functional conformation out of a huge number of possible conformations. It was originally

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

thought that protein folding followed a direct pathway and was dictated by the sum of the interactions that can form between amino acids, including ion pairs, van der Waals forces, hydrophobic interactions, and hydrogen bonding. However, decades of biophysical and computational research have yielded the more sophisticated view that protein folding is instead a nonlinear process. Proteins can navigate through a number of different energy landscapes, which may adopt a funnel-like shape with the lowest energy (folded) state at the bottom of the funnel. Folding information is mainly present in the amino acid side chains, but involves both local and distant interactions and is driven largely by the need to isolate hydrophobic residues within the protein core (105). However, even this view may be naive, as protein folding must occur in a complex, highly crowded environment that has been estimated to reach concentrations as high as 300 mg/ml in the cytoplasm (118). Thus intra-molecular interactions impinge on the efficiency of protein folding in the cell.

To prevent illegitimate inter- and intramolecular interactions, and to protect hydrophobic amino acid side chains as they emerge from the ribosome, folding is aided by a class of proteins known as molecular chaperones. Based on their propensity to bind short peptides with hydrophobic character (47, 133), molecular chaperones guard against misfolding and aggregation. In most cases, molecular chaperones do not increase the rate of folding, but rather increase the number of productive interactions and prevent misguided interactions, thus augmenting folding efficiency (106).

Heat shock proteins (Hsp) of ~90, 70, and 40 kDa represent three important classes of chaperones (59, 60, 89, 274, 450, 573). Hsp70s have a substrate-binding pocket and a low ATPase activity, which is stimulated by the interaction with Hsp40 cochaperone partners that contain an ~70 amino acid motif known as the J-domain. Hsp70s are highly conserved and are critical for protein folding, protein translocation, protein degradation, and the assembly and disassembly of protein complexes. The Hsp40s also bind substrates and via their interaction with Hsp70 are thought to hand-off substrates to Hsp70s. Because Hsp40s enhance the basal ATPase activity of Hsp70s, and because Hsp70 in the ADP-bound state exhibits a higher affinity for peptide substrates, the transfer of substrate to Hsp70 results in a tight Hsp70-peptide complex. Ultimately, a member of a diverse class of nucleotide exchange factors helps release ADP from Hsp70, which in turn frees the peptide substrate. Thus the Hsp70-Hsp40 complex helps to control and maintain the solubility of proteins that may otherwise aggregate.

The interaction of Hsp90s with substrates is mediated through more than one domain in this dimeric chaperone (464, 520). In this case, the relationship between ATP hydrolysis and substrate binding and release is more complex, and a nucleotide-free state may be an important intermediate in the chaperone cycle. It is generally accepted, though, that Hsp90s usually function at later steps in the protein folding pathway than Hsp70s and Hsp40s.

Given the complexity of protein folding, it is not difficult to imagine that one of many problems may arise. For example, nascent polypeptides may aggregate due to unwanted interactions amongst hydrophobic amino acid side chains. It has been estimated that as many as one-third of all newly synthesized proteins may be degraded in some cell types, presumably due to problems during their synthesis or folding (438). Protein misfolding and

aggregation are actually quite common and are responsible for a number of human pathologies, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and α1-antitrypsin deficiency (22). Protein aggregation can lead to the formation of amyloid deposits in tissues throughout the body. Even though the proteins that result in amyloid fibril production are quite varied, the fibrils share many general structural features, suggesting a common fate amongst many aggregated products. However, the propensity of a given polypeptide to form amyloids is highly sensitive to the cellular environment (see, for example, Ref. 106).

B. The Trafficking Problem: Difficulty Transiting Throughout the Secretory Pathway

Nearly one-third of all newly synthesized proteins are targeted to the ER, which is the first step in the delivery of these proteins for trafficking to other organelles of the secretory pathway or to the extracellular space (157). As a nascent secreted protein emerges from the ribosome exit tunnel, it presents an NH_2-terminal hydrophobic signal sequence to the aqueous environment of the cytoplasm. Signal sequences do not follow a strict consensus, but are generally ~20–30 residues in length and contain 3 common features: a basic motif, a hydrophobic core, and a short polar region (196). The emerging signal sequence is then captured by a ribonucleoprotein complex known as the signal recognition particle (SRP), which consists of six proteins and a single RNA (242, 422, 547). One of the SRP subunits binds GTP, which is required for the particle to function. SRP has two general roles: *1*) translational arrest, which provides a window of opportunity for the ribosome-nascent chain complex to "find" the ER membrane, and *2*) targeting and release of the nascent peptide to the ER membrane translocation complex (see FIG. 1). At the ER membrane, SRP associates with the heterodimeric SRP receptor, which stimulates SRP's hydrolysis of GTP (389). SRP is then released from the ribosome-nascent chain complex and translation resumes, resulting in the insertion of the nascent peptide into the translocation pore, or "translocon."

Protein translocation occurs through the Sec61 complex (365, 408). In mammalian cells, the three subunits of the Sec61 complex (alpha, beta, and gamma) provide an aqueous pore through which proteins can be inserted either into the ER lumen or, if hydrophobic membrane-spanning segments are encountered, directly into the lipid bilayer of the ER (FIG. 1, *A* AND *B*). Insertion of membrane-spanning domains is thought to occur through the opening of the translocon and lateral movement into the hydrophobic environment of the membrane. Several studies indicate that the translocon is quite flexible and may accommodate multiple transmembrane helicies at once during the insertion of polytopic membrane proteins (457). During translocation, the hydrophobic signal sequence is cleaved by the signal sequence peptidase complex, which is intimately associated with the ER membrane (473). Upon insertion into the ER space, translocating proteins also interact with chaperones to promote folding and undergo cotranslational modifications, as discussed below.

Protein targeting and translocation were originally thought to be highly efficient, but there is now evidence to the contrary. Given the fact that signal sequences are quite diverse, it is not surprising that they are sometimes interchangeable and can tolerate certain alterations (see, for example, Ref. 234). However, signal sequence diversity is now known to be important

for targeting, translocation, and signal sequence cleavage efficiency (196). For example, the signal sequence of the ER lectin calreticulin is somewhat inefficient, resulting in a cytosolic population of this chaperone in addition to an abundant ER pool. Chimeric proteins containing the signal sequence of calreticulin or prolactin, another well-characterized secretory protein, were used to demonstrate inefficient translocation of chimeras containing the calreticulin signal sequence both in vitro and in vivo (447). In addition, the use of a translocation reporter that was appended onto a variety of signal sequences suggested that up to 50% of some other proteins that normally enter the secretory pathway are inefficiently targeted to and inserted into the ER (291). Whether this represents the need to retain a cytosolic pool of some secreted proteins or an inherently inefficient targeting system is not completely clear.

Signal sequence inefficiency has been proposed as the underlying mechanism for the pathophysiology of a neurodegenerative condition caused by prion protein (PrP), a glycoprotein of unknown function that resides on the cell surface. Prion diseases can be sporadic, genetic, or infectious and result in the accumulation of misfolded PrP and fatal neurodegeneration (392). During PrP synthesis, the protein is cotranslationally inserted into the ER and is modified with a glycophosphatidylinositol anchor that initially tethers PrP to the ER membrane and ultimately to the cellular plasma membrane. By examining the biogenesis of disease-causing mutations in PrP, it was suggested that PrP pathogenesis was the result of inefficient maturation in the ER, followed by “retrotranslocation” and aggregation in the cytosol (317). However, subsequent studies indicated that the cytoplasmic accumulation of PrP is not due to retrotranslocation (110, 401). Instead, the inefficiency of the PrP signal sequence results in the formation of either a cytoplasmic (^{cy}PrP) form or a transmembrane (^{Ctm}PrP) form of the protein (71). Of note, ^{Ctm}PrP accumulates as a stable species, and its expression correlates with neurodegeneration in mice and humans (197, 198). Consistent with these data, disease-causing mutations that result in the accumulation of ^{Ctm}PrP can be rescued by increasing the efficiency of signal sequence insertion (400). These results highlight the sensitivity of protein homeostasis and disease to subtle differences in protein synthesis, targeting, and/or translocation efficiency. In further support of this view, silent mutations in a multidrug resistance transporter that simply change the protein’s translation rate, but leave the amino acid sequence unchanged, alter the transporter’s substrate specificity (249).

C. Protein Modification in the Unique Environment of the ER

Coincident with translocation, nascent proteins encounter the ER’s unique environment, which contrasts sharply with other organelles in its chemical properties and protein composition. Chemically, the ER is more oxidizing and is calcium-rich. The oxidizing potential favors the formation of disulfide bonds, and calcium serves as a necessary cofactor for many chaperones and is vital for cellular signaling. In addition, the ER is packed with proteins that aid the folding of other proteins, that catalyze ER-specific posttranslational modifications, and that form the protein quality control machinery. Unique posttranslational modifications also occur in the ER. After signal sequence cleavage, translocating proteins may be modified with sugar moieties on specific Asn side chains via a process known as *N*-

linked glycosylation, and as noted above, they may acquire disulfide bonds. Each of these modifications contributes to a protein's native fold (14, 56, 190, 256, 455).

Disulfide bonds are formed through the oxidation of pairs of free thiols on cysteine residues. Disulfide bonds help stabilize a protein, which may be especially important if a protein is to be secreted into the harsh extracellular milieu or into the lysosome, which is acidic. Sometimes disulfide bonds serve as the only link between proteolytically cleaved subunits, such as in cholera toxin (582) or insulin (see below) and help maintain the stability of oligomeric secreted proteins, such as immunoglobulins (80). The incorrect acquisition or maintenance of disulfide bonds can give rise to a form of the clotting disease, von Willebrand disease (435), and the connective tissue disorder, Marfan disease (543).

The enzymes that catalyze the formation of disulfide bonds are generally referred to as protein disulfide isomerases (PDIs). PDIs can also function during the isomerization of disulfide bonds. The mammalian ER contains 20 different PDI family members, which are characterized by the presence of one or more thioredoxin-like domains (190). During protein folding, disulfide bonds are formed and incorrectly formed bonds must be broken; therefore, cycles of PDI action are vital during protein folding. The family was first named for PDI, which was the first protein shown to have the ability to form disulfide bonds on ER proteins (61, 161, 511). Interestingly, PDI possesses both oxidoreductase activity as well as a chaperone-like activity, both of which are essential for the folding/secretion of many proteins, including procollagen trimers (20).

ER calcium concentrations range from 100 to 300 μM, which is in stark contrast to the cytoplasmic calcium concentration (10 to 100 nM; Refs. 65, 165). ER calcium release is mediated through inositol 1,4,5-trisphosphate receptors (IP_3R), which open upon binding to the second messenger IP_3. Plasma membrane excitation by various signaling proteins, including hormones, growth factors, and neurotransmitters, results in phospholipase C-mediated cleavage of a plasma membrane phospholipid to generate IP_3 (42). The wave of released calcium is critical for numerous cellular events, such as muscle contraction, exocytosis, cell proliferation, the immune response, transcriptional activation, and apoptosis (43, 69). Of note, following activation by certain signals, IP_3R levels are downregulated by ERAD as a mechanism to attenuate the response to IP_3 signaling (551). Released calcium is reconcentrated by sarco/endoplasmic reticulum Ca^{2+}-ATPases (SERCAs), which couple the free energy of ATP hydrolysis to pump calcium against its concentration gradient back into the ER (393). Many ER chaperones, including the PDIs and BiP (also known as Grp78), Grp94 (an ER lumenal Hsp90 homolog), calnexin, and calreticulin (see above), bind calcium and are thought to help buffer calcium levels, in addition to their roles in protein folding (85). The importance of ER calcium became even more evident when it was discovered that disturbing ER calcium stores altered the secretion of several proteins (306). Not surprising, many diseases, including spinocerebellar ataxia, heart disease, and Darier's disease, have been directly linked to defects in IP_3 receptor and SERCA function (54, 346, 355).

As introduced above, another posttranslational modification that occurs in the ER during protein translocation is the addition of sugar moieties guided by the consensus signal Asn-X-Ser/Thr. The sugar is transferred to the Asn side chain, and thus this event is termed *N*-

linked glycosylation. *N*-glycans not only protect proteins and stabilize protein structure/interactions, but they mediate the interaction with quality control lectins in the ER, such as calnexin and calreticulin (also see below). Therefore, *N*-linked glycans are intimately involved in early protein folding events. A large number of diseases are also linked to the improper glycosylation of secreted proteins. Currently, there are 16 known genetic diseases that arise either from improper assembly or processing of *N*-glycans, and these are collectively known as congenital disorders of glycosylation (226, 265). For example, individuals with mutations in *ALG6*, which encodes glucosyltransferase I, have hyptonia, strabism, seizures, and low circulating levels of certain glycoproteins, including the coagulation inhibitors protein C and anti-thrombin.

The acquired *N*-glycan is composed of two *N*-acetylglucosamines, nine mannoses, and three glucose moieties, which are transferred by the oligosaccharyltranferase complex (OGT) en bloc from a precursor to the Asn side chain (14, 194, 372). Following enzymatic cleavage to remove two of the three glucose residues, the nascent glycoprotein can interact with the lectin-like chaperones calnexin and calreticulin. Protein interaction with calnexin and calreticulin is maintained until cleavage of the final glucose residue, following which a "decision" about folding status must be made. If still unfolded, glycoproteins can rebind calnexin/calreticulin after being reglucosylated by UDP-glucose:glycoprotein glycosyltransferase. This gives the protein more time to attain a folded conformation. However, if the protein fails to fold soon enough, the stochastic removal of mannose residues by ER mannosidases triggers the selection of the misfolded protein for degradation by the ERAD pathway. A particularly important player in these events is the ER degradation enhancing α-mannosidase-like protein I, EDEM1. EDEM1 has been proposed to interact with a specific glycan conformation produced by glycan trimming during repeated folding cycles, and/or functions as a "timer" for degradation by trimming the mannoses on the glycoprotein so that the substrate is committed for degradation (84, 87, 357, 395). However, recent studies have challenged this view, by demonstrating that EDEM1 can interact with misfolded substrates regardless of their glycosyation state (87, 169). A reconciling of these two contrasting views is provided by the observation that under low expression of EDEM1, the ERAD of a misfolded version of the asialoglycoprotein receptor (H2a) requires glycan trimming, whereas under high expression of EDEM1, mannose trimming is not required. Furthermore, overexpression of EDEM1 stimulates the ERAD of a nonglycosylated version of H2a, suggesting a dual role for EDEM1 that is perhaps regulated by cellular EDEM1 levels (411).

In addition to diseases that arise directly from defects in *N*-linked glycosylation, the importance of glycosylation in human health and disease is underscored by the fact that cellular stress results from defects in protein glycosylation. Experimentally, this is best evidenced by the fact that tunicamycin, a fungal metabolite, prevents *N*-glycosylation by inhibiting early steps in the assembly of the glycan chain (390). Treatment with tunicamycin results in a build-up of misfolded glycoproteins within the ER and the induction of the unfolded protein response (UPR). Diseases as diverse as diabetes, neurodegeneration, heart and kidney disease, and cancer have been linked to UPR induction (93, 207, 327, 478, 585).

In at least some cases, disease progression arises from the fact that prolonged UPR activation triggers apoptosis (301, 323, 417, 581).

D. Strategies to Deal With Misfolded Proteins: The UPR

As discussed in the preceding sections, many problems can occur during protein targeting to the ER and subsequent folding events. Protein misfolding is detrimental as it results in a loss of native protein function and can lead to a toxic gain of function due to aggregation. Misfolded proteins in the ER also induce the UPR. Fortunately, cells evolved two main strategies to clear unwanted proteins from the secretory pathway: ERAD, which is the main focus of this review, and autophagy, which is beyond the scope of this article, but is discussed briefly in subsequent sections. If these degradative processes fail to effectively remove misfolded and aberrant proteins from the ER, then UPR induction becomes critical to maintain cellular homeostasis.

The UPR is a conserved cellular stress response that triggers the activation of three signal transduction pathways. The net effect of UPR activation is general translational repression coupled with an expansion of the ER's folding and degradative capacity. First hints of the UPR's existence arose from the observation that various stress conditions, including glucose starvation, inhibition of glycosylation, and treatment of mammalian cells with calcium ionophores, increased the expression of two ER-localized chaperones, BiP and Grp94 (270). Data from this study indicated that the presence of unfolded proteins in the ER was the primary trigger for the response. The identification of a stress response element in the promoter of the yeast BiP homolog (262, 339) and subsequent genetic approaches led to the identification of a conserved, ER-localized kinase, inositol-requiring protein 1 (Ire1; Refs. 88, 338). During ER stress, Ire1 activation initiates the cleavage of an intron from the message encoding a transcription factor, Hac1 (in yeast) or XBP1 (in mammals), which removes a translational inhibitory region. The protein product activates the transcription of genes that encode chaperones and enzymes required for ER protein folding, factors required for ERAD, lipid biosynthetic enzymes to enlarge the ER, and components that augment ER-to-Golgi protein trafficking (302, 358, 495). Subsequent work indicated that the mammalian UPR included the actions of two additional ER components, PERK and ATF6, which respectively activate down-stream responses that inhibit protein synthesis and activate stress-responsive and proapoptotic genes.

Two models have been proposed to describe how unfolded proteins activate the Ire1 branch of the UPR. First, Ire1 interacts with BiP, an ER luminal Hsp70 that participates in both protein folding and degradation processes (44). The Ire1-BiP interaction may act as a sensor of ER protein folding status. Accumulation of misfolded proteins would titrate BiP away from Ire1, thereby allowing for Ire1 dimerization, phosphorylation, and activation of its ribonuclease domain and splicing activity. In support of this model, it was demonstrated that diffusion of BiP within the ER lumen inversely correlates with the levels of misfolded proteins in the ER (278). In the second model, Ire1 directly binds to misfolded proteins via a peptide-binding pocket. These data, based on a crystal structure of yeast Ire1 and by the fact that mutations in the peptide-binding pocket compromise UPR induction, suggest that Ire1 and the UPR are activated directly by misfolded proteins (91). However, it is less obvious

whether the mammalian Ire1 homolog also accommodates unfolded polypeptides (588). In the end, it is likely that UPR activation proceeds via some combination of the two models (248), and indeed, there is evidence that BiP modulates UPR efficiency, Ire1 localization, and signal duration (382).

E. Strategies to Deal With Misfolded Proteins: ERAD

Several of the UPR targets are genes encoding proteins that facilitate ERAD, which in principle provides the most rapid and direct means to clear the ER of potentially toxic proteins. In general, ERAD can be broken down into four steps: substrate recognition, ubiquitination, retrotranslocation to the cytosol, and proteasome-mediated degradation. In addition to clearing misfolded proteins from the ER due to cell stress and degrading proteins that are mutated and misfolded, the ERAD pathway is also used to regulate the levels of specific enzymes and lipid carriers. These include 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the rate-determining step in cholesterol biosynthesis, and apolipoprotein B, which is required for the assembly of cholesterol-containing liposomes (131, 183). Defects in the metabolically-regulated destruction of these ER residents lead to a variety of diseases linked to lipid homeostasis and atherosclerosis. For all of these reasons, ERAD is vital for human health, and increasing evidence links this pathway to many diseases (TABLE 1). But, before embarking on a discussion of select ERAD-associated diseases, we will begin with a discussion of some of the key findings that have defined the ERAD pathway since its discovery. We will also provide an overview of the steps and describe the key players in the pathway that are highlighted in the remaining sections of this review.

Early studies on the assembly of the T-cell receptor (TCR) were the first to hint at the existence of what is now known as ERAD. Klausner and colleagues (303) discovered that unassembled alpha, beta, and delta subunits of the heptameric TCR were degraded in a nonlysosomal compartment. It was hypothesized that degradation either was occurring by an ER-resident protease or in another prelysosomal compartment. Further evidence for pre-Golgi degradation came from studies examining other mammalian proteins, including a subunit of the asialoglycoprotein receptor, HMG-CoA reductase, unassembled immunoglobulin light chains, and cytochrome *P*-450 (151, 333, 546). In addition to these reports using mammalian cell systems, parallel work in the budding yeast *Saccharomyces cerevisiae* also hinted at the existence of a novel, lysosome-independent degradation pathway. For example, translocation defects elicited by a temperature-sensitive mutant of Sec61, a translocon component, were found to be rescued by deletion of the gene encoding Ubc6; Ubc6 is a ubiquitin-conjugating enzyme that is integrated into the yeast ER membrane (461). These data suggested a role for the cytoplasmic proteasome in the turnover of a misfolded ER membrane protein, i.e., the Sec61 mutant. Soon after, the proteasome-dependent degradation of immature wild-type and mutant forms of the cystic fibrosis transmembrane conductance regulator (CFTR) was reported in mammalian cells (also see sect. II*A*). The requirement for the delivery of an aberrant soluble protein in the ER to the cytoplasm emerged from studies on misfolded yeast secretory proteins, pro-alpha factor, and CPY*. Using both in vitro and genetic tools, these proteins were found to be retrotranslocated from the ER and destroyed by the proteasome (201, 330, 540). The

retrotranslocation and degradation of soluble proteins from the mammalian ER was also observed (394). Ultimately, it quickly became clear that ERAD and most of the core requirements that underlie the mechanism of this pathway are conserved from yeast to humans.

ERAD begins with the recognition of a misfolded protein by molecular chaperones (FIG. 2). ERAD substrates can present a misfolded lesion either in the ER lumen, ER membrane, or cytoplasm, which will influence the types of chaperones with which they interact (55). BiP, which was introduced above, is an ER luminal Hsp70 that was discovered by virtue of its stable binding to immunoglobulin (Ig) heavy chains (174). As with other Hsp70s (see above), the binding of BiP to newly synthesized proteins occurs through exposed hydrophobic surfaces on the client protein, an event that obscures these aggregation-prone surfaces as the protein attempts to attain its natively folded state. However, if folding is delayed or if the protein is terminally misfolded, extended chaperone interaction may serve one of two functions: *1*) the prolonged prevention of aggregation and maintenance of an unfolded substrate and/or *2*) a more elaborate process in which the misfolded protein is shuttled to other chaperones and/or to the ERAD machinery. Evidence for the second function came from a study demonstrating that BiP and Grp94 bound to Ig light chains (Ig λ). BiP associated with both reduced and oxidized forms of Ig λ, whereas Grp94 bound primarily to the oxidized form, suggesting that the chaperones interact with Ig λ in a sequential fashion (334). BiP also bound more tightly to nonsecreted forms of Ig λ (259). Evidence for the first function came from a study examining the degradation of soluble yeast substrates. In yeast that have a temperature-sensitive allele in the gene encoding BiP, the substrates aggregated at high temperatures; the same phenomenon was observed when the Hsp40 cochaperone partners were mutated (351). Together, these studies highlight how chaperones work together during different stages of protein folding/degradation.

N-glycans, which bind to chaperone-like lectins in the ER, play an essential role in protein folding and in ERAD. The funneling of glucose-trimmed glycoproteins into the calnexin-calreticulin folding cycle, which is governed by OGT, is in competition with exit from the cycle and degradation. As discussed above, exit from the cycle is triggered by the action of ER mannosidases. In mammalian cells, ERManI and EDEM1 and their isozymes trim the mannose residues on specific branches of the glycan structure, preventing reglucosylation while simultaneously promoting substrate retrotranslocation and degradation (204). As expected, then, modulation of ER mannosidase levels has a direct effect on the efficiency of degrading specific substrates, such as a mutant form of the protein that causes anti-trypsin deficiency (205, 325, 357; see sect. II*E*). Interestingly, the yeast homolog of EDEM1 is in a complex with PDI, and a similar interaction has been observed in mammalian cells between EDEM1 and the ER oxidoreductase ERdj5 (84, 154, 176, 421). These observations may indicate that substrate selection is linked to the acquisition of a protein's proper disulfide bonds. In accordance with this view, a PDI homolog also associates with calnexin (386).

Protein ubiquitination is critical to target most substrates to the proteasome (129). The ubiquitin chain is usually attached onto a Lys residue on the misfolded protein, although recent data indicate that some ERAD substrates contain ubiquitin chains on Ser or Thr residues (223, 452, 530). Protein ubiquitination occurs via a three-step process that is

mediated by a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin ligase (E3), which catalyzes the final transfer of ubiquitin to the substrate. It is thought that the E3 ligase provides substrate specificity, and accordingly, E3s are the most abundant of the three classes, with over 500 putative ligases identified in mammalian cells (500). Key E3s involved in ERAD are Hrd1, gp78, RMA1, TEB4, and CHIP (29, 103, 123, 188, 236, 245, 272, 326, 574). On the basis of the chemical and structural diversity of ERAD substrates, it is likely that additional E3s that contribute to this pathway will emerge.

After initial E3-mediated ubiquitin attachment, ubiquitin chain extension ("polyubiquitination") occurs by the covalent modification of additional ubiquitin monomers onto a Lys residue in a previously linked ubiquitin. This forms an extended isopeptide-linked polyubiquitin chain. In some cases, the cooperative extension of a polyubiquitin chain is mediated by another group of enzymes, the E4s, which augment ERAD efficiency (261, 345, 405).

A chain of four ubiquitins must be appended onto a substrate for efficient proteasome interaction (396, 491), and polyubiquitin chains are distinguished based on the residue upon which the chain is built. In other words, the type of linkage can determine the fate of the ubiquitinated substrate. Initially, a polyubiquitin chain built upon Lys-48 isopeptide linkages was assumed to be specific for proteasomal degradation, whereas a Lys-63 polyubiquitin chain served as a nonproteasomal signal for endocytosis and DNA repair (83). However, proteomic studies revealed that several other ubiquitin linkages (Lys-6, -11, -27, -29, and -33) exist in cells and that both Lys-48- and -11-linked chains are appended onto ERAD substrates (557). Future research will continue to unravel the functions of different linkages and mixed linkages that exist. Nevertheless, it is clear that proteins with extended polyubiquitin chains can be found in intracellular inclusions in neurodegenerative diseases, suggesting that inefficient proteasome degradation is linked to the disease phenotype (see Section II*B*).

After or during polyubiquitination, the ERAD substrate must be delivered, or retrotranslocated to the proteasome. While the existence or identity of a retrotranslocation channel in the ER membrane remains contested, several putative channels have been considered. These include Sec61, which is the translocation channel, the Derlins, which are a family of polytopic membrane proteins intimately linked to some ERAD substrates and components of the ERAD machinery, and Hrd1, which is a polytopic E3 ubiquitin ligase. The use of Sec61 as a retrotranslocation channel initially seemed most logical. In yeast it was found that Sec61 mutants prevented the ERAD of some substrates (381, 385) and that an ERAD substrate formed disulfide bonds with Cys residues in Sec61 en route to its degradation (443). This result suggested that the protein was unfolded and retrotranslocating through Sec61. Another ERAD substrate, apolipoprotein B, clearly retrotranslocates through the Sec61 channel when it is cotranslationally targeted for ERAD (370). Cholera toxin also appears to utilize Sec61 to leave the mammalian ER during its journey from the plasma membrane, back through the secretory pathway, and ultimately into the cytoplasm (433; also see sect. II*D*). However, another yeast ERAD substrate depended on the functions of both Sec61 and a yeast Derlin homolog (548). The contribution of Derlin is consistent with findings that antibodies against this protein thwart the retrotranslocation of a model substrate

from mammalian ER vesicles (518) and that a dominant negative form of Derlin disrupts the viral-induced retrotranslocation and degradation of MHC class I molecules (see sect. II*F*). Moreover, Derlin recruits Cdc48/p97 (299, 567), which provides the energy required to drive ERAD substrates from the ER (see below). To add to an already complex situation, yeast Derlin interacts with the E3 ligase Hrd1, which has itself been implicated in the retrotranslocation of both ER luminal proteins and in the degradation of HMG-CoA reductase (70, 152). TEB4 and the yeast homolog Doa10 may act similarly (402, 477). Together, these studies highlight the enigmatic nature of the retro-translocation process and suggest that one of many proteins/complexes may provide the channel required for ERAD, or that the channel may be composed of several different proteins.

For most ERAD substrates, the mechanical force necessary to remove proteins from the ER lumen or membrane is provided by the cytoplasmic AAA^+ ATPase p97 (also known as valosin-containing protein, VCP, or Cdc48 in yeast). p97/Cdc48 functions in several cellular processes, including cell division, membrane fusion, and the processing of membrane-associated transcription factors (26). In fact mutations in this protein give rise to the complex syndrome, inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia (538). A role for p97/Cdc48 in proteasome-dependent degradation first emerged from a yeast genetic screen (158). Given its diverse activities, it makes sense that Cdc48 interacts with a wide range of partners that provide specificity for this ATPase's energy-coupled functions (439). Thus, during ERAD, a complex containing p97/Cdc48, Npl4, and Ufd1 is required to extract soluble and integral membrane polyubiquitinated substrates from the ER for degradation (31, 227, 398, 566). p97/Cdc48 also interacts with E3 ligases, placing it in an ideal position to aid in the retrotranslocation of polyubiquitinated proteins (28, 587).

Following extraction, proteins must be ushered to the 26S proteasome, but with the exception of two cytosolic proteins in yeast (397), the identities of the factors that participate in this step are not clear. Membrane proteins pose a formidable challenge as some of these substrates can be retrotranslocated intact (152, 211, 287, 345, 545); therefore, the hydrophobic membrane-spanning domains are exposed to the aqueous environment of the cytoplasm and must be protected. A recent study suggests that a protein complex that participates in the recognition of tail-anchored proteins at the ribosome may help maintain membrane proteins in a soluble form en route to the proteasome; however, this complex does not seem to recognize membrane-spanning regions of its associated substrates (528), which are probably the regions most prone to aggregate.

ERAD substrate proteolysis occurs in the cytoplasm via the action of the 26S proteasome (129). The proteasome is a large (~2.5 MDa) protein complex that can be subdivided into two main assemblies: the 20S core particle and the 19S regulatory particle (also known as the 19S "cap" or PA700). The polyubiquitin tag on a substrate is recognized either by subunits in the proteasome cap and/or by proteasome-associated proteins (213, 436). After recognition, substrates must be deubiquitinated by deubiquitinating enzymes (DUBs). For example, the Rpn11 subunit in the 19S cap deubiquitinates proteasome substrates, which is a prerequisite for degradation and is important for maintaining high levels of free ubiquitin (328, 514, 565). DUBs have also been proposed to remove ubiquitin linkages from

substrates as they are threaded through p97/Cdc48 (120) and a large-scale proteomic analysis identified a DUB, USP13, that associates with p97/Cdc48 and two p97/Cdc48 partners; USP13 knock-down stabilized an ERAD and a cytosolic ubiquitinated substrate, suggesting that this DUB regulates p97/Cdc48 function (465). In contrast, if DUBs interact with the substrate prior to proteasome association, they can trim ubiquitin chains and delay substrate degradation.

The 20S proteasome core contains three distinct proteolytic activities: trypsin-like, chymotrypsin-like, and caspase-like. The net result of proteasome-mediated degradation is the generation of small, ~2–30 amino acid peptides that can be further processed by other cellular proteases (251). Several proteasome inhibitors have been discovered, which target different activities of the proteasome and have proven useful in determining the contribution of the ubiquitin-proteasome system (UPS) (82, 513) in the regulation of cellular pathways, including ERAD. For example, acetyl-Leu-Leunorleucinal (ALLN) and Cbz-Leu-Leu-leucinal (MG-132) are reversible inhibitors of the chymotrypsin-like activity (147, 409) and laid the foundation for the discovery of proteasome inhibitors that are used clinically, i.e., Bortezomib (see sect. III*A*).

II. SPECIFIC EXAMPLES OF PATHOLOGIES LINKED TO ERAD

In this section, we focus on six examples of how ERAD is directly linked to human health and disease. We also provide a table (TABLE 1) that includes 67 diseases that have been connected to the ERAD pathway. Because the pace of research on newly discovered rare diseases is rapid, and because there are many disease-relevant proteins for which there are insufficient data to be classified as being ERAD-linked, the table is not exhaustive. Our goal is instead to illustrate the diverse nature of the diseases linked to this pathway. To be included in TABLE 1, there had to be a demonstration of a protein's ER retention/impaired trafficking together with either proteasome-dependent degradation and/or polyubiquitination.

A. Cystic Fibrosis and Other Diseases of ATP-Binding Cassette Transporters

The first disease unambiguously linked to the ERAD pathway was cystic fibrosis (CF). CF is caused by defects in a chloride transporter, the CFTR. Mutations in CFTR alter salt and water balance across a variety of epithelia, and as a result, the main clinical features of CF are delayed growth due to digestive and nutrient-related disorders, severe constipation, and mucus build-up in the lungs, which results in recurring and prolonged infections. Over 1,000 disease-causing alleles have been reported in *CFTR*, and it is estimated that 1 in 29 Caucasian Americans carry a mutant CF allele (2, 4). Currently approved treatments are only supportive and focus on reducing the number and duration of lung infections and on providing diet supplementation to meet the patient's nutritional needs. Unfortunately, the average life expectancy for a CF patient is ~35 years, a value that has increased significantly during the past three decades. Due to the devastating nature of this disease and its prevalence, a large research effort is devoted to uncovering the molecular mechanisms underlying CF. These efforts include studies on CFTR channel activity and regulation, CFTR folding in the early secretory pathway, and CFTR trafficking through the secretory

pathway. Studies to identify modifiers of the disease phenotype have also been undertaken (see, for example, Ref. 30).

CFTR is a member of the ATP-binding cassette (ABC) family of transporters, which as their name implies couple ATP hydrolysis to solute transport. While CFTR is perhaps the most widely recognized member of the ABC family, other diseases are also attributed to mutated ABC family members (see TABLE 1). In general, ABC transporters are multipass integral membrane proteins that contain two membrane-spanning domains (MSD), each followed by a nucleotide-binding domain (NBD). However, CFTR is unique among ABC transporters in that it functions as an ion channel and possesses a regulatory (R) domain lying between NBD1 and the second MSD. CFTR channel opening is regulated in part by protein kinase A-mediated phosphorylation of the R domain and is tightly coupled to nucleotide binding to the NBDs (148, 250, 407).

Based on its size (1,480 amino acids) and complex domain organization, even the wild-type form of CFTR encounters a significant number of hurdles during synthesis. In fact, CFTR begins to fold cotranslationally, even though post-translational folding events must also take place before the protein achieves its native conformation (112, 113, 244, 257, 489, 490). To aid in folding, and to select misfolded species for ERAD, nascent CFTR engages both cytoplasmic and ER luminal chaperones (15, 309, 331, 472, 531, 564, 580). In addition, as portions of the protein enter the ER, nascent CFTR is *N*-glycosylated, producing an immature ER-localized form, termed “band B.” This species interacts with the lectin-like chaperones that reside in the ER, i.e., calnexin and calreticulin (124, 125, 162, 184, 360, 383, 414). After folding and upon ER exit, the core glycan structure is further elaborated in the Golgi apparatus, which decreases CFTR’s electrophoretic mobility on a polyacryl-amide gel and leads to the presence of “band C.” This species is most commonly designated as the mature form and can be found at the plasma membrane. Consistent with its many folding hurdles, as much as 45–80% of wild-type CFTR is degraded during or soon after synthesis (77, 229, 315, 535), although under some conditions and in some epithelial cells the wild-type protein may mature quite well (512).

The most common disease-causing mutant allele in *CFTR* is a deletion of a phenylalanine at position 508 (ΔF508). This mutation causes virtually all of the protein to misfold or prevents folding, which in either case leads to its degradation (77). However, the mutation only partially reduces channel function (94, 191). Computational and structural evidence suggest that the ΔF508 mutation disrupts the interaction between NBD1 and a cytoplasmic loop within MSD2 (446), and consistent with these data, earlier cross-linking experiments suggested that the ΔF508 mutation alters MSD packing (75). Interestingly, “rescued” forms of ΔF508-CFTR that reach the plasma membrane are also subject to protein quality control and are targeted for lysosomal degradation by some of the same chaperones and ubiquitin ligases that act during ERAD (see below; Ref. 359). Although ~90% of CF patients possess at least one ΔF508 allele, another disease-causing mutation in CFTR is G551D, which results in a channel gating defect rather than in a trafficking defect (111, 182).

Early studies revealed that ΔF508-CFTR was only present as band B (77). This result suggested that the protein had not been processed by Golgi-resident enzymes and that the

disease was linked to an ER quality control phenomenon. Consistent with this hypothesis, Ward and Kopito (535) showed that both the immature wild-type form of CFTR and the ΔF508 mutant form of CFTR were degraded soon after translation, and thus before lysosomal delivery. Indeed, ΔF508-CFTR levels were unaffected by inhibitors of lysosomal proteases, and degradation was insensitive to treatment with the fungal toxin Brefeldin A (BFA) (315), which prevents ER to Golgi trafficking. Even though a role for the UPS in destroying secretory pathway proteins had not yet been observed, parallel studies by the Kopito and Riordan labs (229, 536) next demonstrated that the proteolysis of ER resident forms of CFTR required the activity of the cytoplasmic 26S proteasome. Together, these data established the first direct link between a disease caused by a mutated protein and ERAD.

As with most proteasome-targeted proteins, CFTR is polyubiquitinated once it is selected for degradation. By using a cell-free assay, it was found that ΔF508-CFTR polyubiquitination occurs cotranslationally while the nascent chains are associated with the ribosome (425). Moreover, polyubiquitinated ΔF508-CFTR can accumulate in an insoluble form when the activity of the proteasome is compromised (231). These data suggested that the amelioration of CF-linked maladies would require a more elaborate treatment than simply inhibiting ΔF508-CFTR degradation (see sect. III*A*). In fact, nonspecific “chemical chaperones,” osmolytes that improve the protein folding environment in the cell, partially repaired the ΔF508-CFTR folding defect such that band C and channel activity became evident (57, 208, 426, 583; also see sect. III*A* and TABLE 2). Incubating cells at low temperature similarly repaired the ΔF508-CFTR folding defect, consistent with ΔF508 exhibiting the features of a classical temperature-sensitive, folding-compromised mutant (100).

Since then, much work has been devoted to characterizing the ubiquitination machinery that mediates ΔF508-CFTR quality control. Establishing a specific E3 ubiquitin ligase for ΔF508-CFTR was not trivial, as mammals encode up to 500 of these enzymes (see above), often with overlapping specificities and partially redundant functions (129). To date, three E3 ligases are the best candidates as being implicated directly in the ERAD of CFTR. These include the cytoplasmic protein CHIP and the integral ER membrane proteins RMA1 and gp78 (170, 332, 340). Since folding defects may occur at any one of several points during CFTR synthesis, it is not surprising that more than one E3 facilitates the ubiquitination of CFTR. However, it is unclear how these E3s coordinately target CFTR for degradation. One possibility is that different E3s work in a sequential manner to ubiquitinate CFTR, e.g., co- and posttranslationally. Evidence for this scenario comes from studies in which the overexpression of either RMA1 or CHIP decreased the levels of wild-type CFTR; however, RMA1 and CHIP showed different preferences for mutant forms of CFTR. Namely, CFTR containing mutations within NBD1 are more sensitive to RMA1, whereas CFTR with an NBD2 truncation is more sensitive to CHIP expression (574). These data suggest that RMA1 acts on CFTR cotranslationally, recognizing early folding defects with the assistance of select chaperones (see below), whereas CHIP and Hsp70 (332) recognize folding defects as CFTR translation is completed.

During protein quality control, chaperone and E3 function are tightly intertwined (329, 345; and see below). Therefore, the targeting of chaperones that are associated with E3 ligases

may either facilitate the degradation of the misfolded protein, as suggested above, or prevent the premature degradation of CFTR. Thus chaperone modulation may provide a means to fold ΔF508-CFTR so that it can escape ERAD and ultimately function, albeit less efficiently, at the plasma membrane. In fact, an effective scheme to rescue ΔF508-CFTR was recently achieved by altering the activity of an Hsp40 cochaperone, which functions at the same step as RMA1. The chaperone, DNAJB12, is ER-associated, and decreasing DNAJB12 levels by siRNA increases CFTR folding efficiency (170, 560). When DNAJB12 was silenced in combination with a small molecule corrector, Corrector 4a (Corr-4a), which partially rescues ΔF508-CFTR maturation (375; also see sect. III*A*), a strong synergistic effect on CFTR maturation was evident (170). These data emphasize the importance of targeting both the degradation and folding machineries to achieve maximal, therapeutic effects.

Molecular chaperones act as ERAD gatekeepers, closely monitoring protein folding and regulating the decision between folding and degradation (59, 350). It remains mysterious how the same chaperone can engage in protein folding and degradation processes. One possibility is that the amount of time a client protein interacts with the chaperone is critical for this decision. In this model, as a protein folds, exposed chaperone-binding sites can go through several cycles of binding and release. But, as a protein attains its final conformation, these sites are obscured and the protein is released from the ER and traffics to the Golgi. If, however, binding sites remain accessible to chaperones for extended periods of time, then the bound chaperone may recruit the degradation machinery. Notably, chaperones have been suggested to act as bridging factors between misfolded proteins and E3 ligases (329, 345), and in support of this model, Hsp70 and Hsp40s regulate the degradation of ΔF508-CFTR together with the E3 ligases CHIP andRMA1 (also see above; Refs. 170, 332). In further support of this model, cytosolic Hsp70 interacts with ΔF508-CFTR longer than wild-type CFTR (564), and an enhanced interaction between ΔF508-CFTR and an Hsp70-Hsp40 chaperone pair was observed (331).

It is also mysterious how a distinct chaperone may exhibit a “profolding” versus “prodegradative” effect on different substrates. Studies in yeast show that Hsp70 acts in a prodegradative manner during CFTR quality control (584), but the cytoplasmic Hsp90 plays an important role in maintaining the solubility of NBD1 and facilitating CFTR folding (571). Specifically, perturbation of Hsp90 function, either by genetic ablation in yeast or chemical inhibition in mammalian cells, accelerates the degradation of CFTR or both CFTR and ΔF508-CFTR, respectively (309, 571). For other substrates, Hsp90 promotes ERAD (173). In mammals, the ATPase activity of Hsp90 is intrinsically low, but the cochaperone Aha1 binds to and stimulates Hsp90 ATPase activity (369). Since Hsp90 promotes CFTR folding, one might predict that increased levels of Aha1 might further promote CFTR maturation. Unexpectedly, an increase in Aha1 accelerated CFTR degradation, and decreasing Aha1 levels rescued ΔF508-CFTR folding/maturation (268, 531). One explanation for this result is that a slow rate of Hsp90 cycling benefits CFTR maturation, but by accelerating this cycle, CFTR maturation is compromised because the protein is delivered too soon to the degradation machinery. Ultimately, it is likely that additional chaperones and

cochaperones, which might themselves become therapeutic targets to treat CF, will be discovered that augment ΔF508-CFTR maturation.

In addition to CFTR, other ABC transporters have been identified as substrates for ERAD, including the multidrug resistance proteins, P-glycoprotein, and the breast cancer resistance protein (BCRP) (see TABLE 1). P-glycoprotein and BCRP are members of the MDR/TAP and White subfamilies of ABC transporters, respectively (96). A key function of the multidrug resistance proteins is ATP-dependent export of xenobiotics, such as those administered as chemotherapeutics. Drug resistance is a major clinical problem, impacting the effective treatment of many diseases, especially cancer. In fact, sequencing studies have found that BCRP variants can have dramatic effects on protein levels and methotrexate transport, a measure of BCRP activity (222). This finding suggests that the variants affect either protein biosynthesis or trafficking. In particular, cells containing one of two alleles, F208S and S441N, produce comparable amounts of mRNA compared with those expressing wild-type BCRP, but have reduced protein levels. It was also shown that the mutant proteins produced by these variants remain sensitive to endoglycosidase H (endo H). In higher eukaryotic cells, as *N*-glycosylated proteins transit through the Golgi, their glycans are processed by Golgi α-mannosidase II, which renders glycoproteins insensitive to endo H. Therefore, prolonged sensitivity to endo H is indicative of ER retention. Furthermore, both the F208S and S441N mutants are ubiquitinated, and protein levels increase when cells are incubated with MG-132, a proteasome inhibitor that was noted above (343). These data strongly suggest that the BCRP variants are retained in the ER and targeted for ERAD. While no diseases are directly caused by mutant forms of these transporters, correlations between polymorphisms and patient responses to chemotherapeutics have been documented (222). Therefore, the importance of understanding the mechanisms that regulate the expression of multidrug transporters should not be underestimated. This knowledge may help predict how a patient will respond to chemotherapeutics. In addition, new strategies to combat drug-resistant tumors may be developed.

B. Neurodegenerative Disorders

Several disorders result from the accumulation of ERAD substrates in neuronal cells. Neuronal cells have a relatively low regenerative capacity and an age-dependent decrease in their ability to withstand cellular stress, rendering them particularly sensitive to toxic aggregates that result in apoptosis (516). In general, neurodegenerative diseases cause mental impairment and movement disorders, such as those seen in Alzheimer's disease (AD). In AD, the accumulation of an incorrectly processed form of the amyloid precursor protein, termed amyloid beta (Aβ) is thought to be linked to the neurodegenerative phenotype in AD. Accumulation of Aβ has been proposed to result in neurodegeneration due to mitochondrial dysfunction, oxidative stress, disruption of synaptic transmission, disruption of axonal trafficking, and/or general membrane disruption (92, 445). While the specific molecular defect due to Aβ accumulation remains to be determined, the pathology of this disease highlights the sensitivity of neuronal cells to aggregating or aggregation-prone proteins. Although there are several examples of neurodegenerative diseases that follow the typical ERAD paradigm (protein misfolding, followed by proteasome-dependent

degradation; TABLE 1), we focus our discussion here on two neurodegenerative diseases linked to the ERAD machinery in a somewhat atypical fashion.

Huntington's disease (HD) results from abnormally high numbers (>35) of polyglutamine (polyQ) repeats in the huntingtin (Htt) protein. In HD, the length of the CAG codon repeats in *HTT* positively correlates with an increased propensity of Htt aggregate formation. In line with this observation, the length of the CAG repeat in *HTT* also directly correlates with the age of onset and disease severity in HD patients (469). The disease is inherited in an autosomal dominant pattern and afflicts nearly 1 in 10,000 Americans (10). In adult-onset HD, patients present with a combination of behavioral changes, movement disorders, and progressive dementia (8, 591). The native function of Htt is poorly understood, and the unusual nature of the link between HD and ERAD stems from the fact that Htt is a cytoplasmic protein, instead of a secretory protein.

An early hint that the UPS might be connected to the pathogenesis of HD came from a study demonstrating that HD inclusions in brain sections from affected individuals are immunoreactive for ubiquitin (104). A possible, functional link between HD and the UPS was provided by the Kopito lab, which showed that the UPS is less active in cells expressing polyQ Htt. Specifically, as the length of the polyQ repeat increased beyond a threshold that correlates with disease presentation, the ability of the proteasome to degrade a fluorescent reporter in cells was inhibited (34). These data provided one mechanistic explanation for why HD develops: the generation of Htt polyQ aggregates decreases UPS activity, which will then lead to a further accumulation of unprocessed UPS substrates and an escalation of aggregate toxicity. However, it is still debated whether the HD aggregates are a secondary effect of the disease or are the cause of neurodegeneration (24, 246, 427, 459). Thus misfolded Htt preaggregates might also accumulate, which may initiate disease onset.

Nevertheless, support for the UPS inhibition model comes from a study examining the levels of K48 ubiquitin-linked, proteasome-directed peptides present in an Htt polyQ-expressing cell line and in tissue taken from a mouse model for HD. In both experimental systems, there was a significant increase in the amount of K48 ubiquitinated peptides present in samples containing an Htt reporter with 150 polyQ repeats (37). Furthermore, K48 chain accumulation correlated strongly with proteasome inhibition. However, it was possible that the increase in K48 linked chains resulted from the accumulation of polyubiquitinated Htt aggregates, rather than from global impairment of the proteasome. To test for global impairment, the levels of other ubiquitin chain linkages, i.e., K11 and K63, were examined. Both the levels of K11 and K63 ubiquitin chains increased in the presence of either MG-132 or the 150 polyQ repeat form of Htt, which points toward wholesale dysregulation of the UPS (37).

Do ERAD substrates also accumulate under these conditions? The answer appears to be yes, as Duennwald and Lindquist (114) found that the concentration of several well-characterized ERAD substrates increases in the presence of aggregation-prone Htt. The accumulation of these ERAD substrates may arise from direct proteasome inhibition, as suggested above, and/or from the observed colocalization of p97/Cdc48 to the Htt inclusions. Also, a recent study reported an in vitro interaction between Htt polyQ aggregates and the ER-resident E3

ubiquitin ligase gp78, which is required for the ERAD of several substrates (230, 247, 297, 340); Htt aggregates block the association of gp78 with polyubiquitinated proteins and with p97/Cdc48 (563).

If ERAD substrates accumulate, one might predict that the UPR is induced in the presence of polyQ Htt. In fact, the connection between a long-term UPR induction and apoptosis (see sect. I*D*) might explain at least in part the neurodegenerative phenotype in HD. Indeed, expression of polyQ Htt in yeast activates the UPR and is synthetically lethal when combined with other inducers of ER stress, such as tunicamycin, the inhibitor of *N*-linked glycosylation (114). Studies in mammalian cells show that polyQ Htt induces cell stress, increases chaperone levels, and results in the conversion of IRE1 and PERK into their active, phosphorylated forms (114, 269, 353). Together, these data strongly suggest that polyQ Htt aggregates alter the activity of the ERAD machinery and induce the UPR, further contributing to cytotoxicity. This is not to say that Htt polyQ preaggregates don't also contribute to the disease (427, 458, 459), and in fact, it has been proposed that the mechanism of pathogenesis of HD stems from disruption of other pathways, either through aberrant interactions or by loss of Htt function. For example, Htt localizes to the Golgi, endosomes, and vesicular carriers, among other locations in cells. If Htt function in axonal trafficking is blocked due to polyQ Htt, this could lead to decreased synaptic transmission and cell death (159). Together, future therapies for HD may need to focus on addressing the cytotoxicity associated with ER stress.

Another example of a neurological disease linked to the ERAD pathway is Parkinson's disease (PD). PD is a member of the family of movement disorders and results from the loss of dopaminergic neurons. PD occurs in ~1–2% of the population, usually developing after 60 years of age. Patients with PD present with four main categories of symptoms: tremors, bradykinesia, rigidity, and postural instability (11). The probability of developing PD increases with age and either can be sporadic or arise from specific genetic mutations. For instance, mutations in *PARK2*, which encodes the E3 ubiquitin ligase Parkin, lead to an autosomalrecessive form of early-onset PD. Parkin is normally localized to the cytoplasm, which with the exception of CHIP (see above) is generally atypical for E3 ligases that participate in ERAD. However, it was demonstrated that Parkin is induced by the UPR (218). In addition, a candidate for a Parkin substrate is the Parkin-associated endothelin receptor-like receptor PaelR (217). PaelR, also known as GPR37, is a putative G protein-coupled receptor that is highly expressed in the central nervous system, but for which no endogenous ligands have been found (290). The connection between PaelR and PD is supported by the observation that PaelR accumulates in Lewy bodies, which are electrondense inclusions that serve as a histological indicator of PD (342). Furthermore, PaelR is polyubiquitinated in cells and can be ubiquitinated by Parkin in vitro. In addition, the proteasome-dependent degradation of PaelR is stimulated by Parkin overexpression (217). Finally, PaelR accumulates in a detergent-insoluble fraction in cells treated with a proteasome inhibitor or with ER stressors, indicating that PaelR has a natural propensity to misfold under stress conditions. These data indicate that Parkin mediates the quality control of PaelR.

Another connection between Parkin and ERAD was provided by the observation that Parkin function may be supplanted by another E3 required for the ERAD of select substrates in mammals, Hrd1 (41, 79, 206, 223). Modulation of Hrd1 levels changes PaelR levels, and Hrd1 expression can protect against PaelR-induced cell death (361). Furthermore, Hrd1 is expressed in dopaminergic neurons throughout the mouse brain, providing additional evidence that Hrd1 and Parkin function might be coordinated (362). However, Parkin has also been implicated in mitophagy, a process in which mitochondria are engulfed and destroyed via an autophagy-related pathway (239, 572). It was found that the mitochondrial serine/threonine kinase PINK1 accumulates on damaged mitochondria and in turn recruits Parkin. Parkin ubiquitinates the mitochondria fusion-promoting factor mitofusin. This results in the degradation of mitofusin via a p97/Cdc48-dependent ERAD-like process. Mitofusin degradation then triggers mitophagy (368). This pathway appears to be important for the pathogenesis of PD, as mutations in PINK1 can also cause inherited PD. However, the relationship and relative importance between the mitochondrial and ER functions of Parkin remain to be determined. But, in the past few years, communication between mitochondria and the ER has been established. Mitochondria directly interact with the ER, and this interaction is important for many processes, including lipid transfer, calcium signaling, and cell death (384). Also, some factors that comprise the ERAD machinery also function to recognize, extract, and destroy components that reside in the mitochondrial membrane (86, 199, 558). A recent study revealed that Parkin is not only upregulated by ER stress, but also by mitochondrial stress (50). Surprisingly, however, the cytoprotective effect associated with Parkin expression may occur independent of the proteasome. These collective data highlight the enigmatic nature of Parkin's true function and the need to further examine Parkin's role at the interface between ERAD and disease.

C. Metabolic Disease

Diabetes mellitus is a metabolic disease in which individuals either produce too little insulin or are unable to respond properly to insulin, resulting in hyperglycemia. In general, diabetes can be broken into two main classes based on the underlying cause of the disease and/or the conditions surrounding the onset of the symptoms. Type 1 diabetes accounts for ~5–10% of all cases and is usually diagnosed at a young age. Type 1 diabetes results from immune system-mediated destruction of pancreatic β-cells, thereby decreasing the levels of insulin. In contrast, type 2 diabetes accounts for the majority of cases (90–95%) and results primarily from insulin resistance due to a decreased ability of target cells to respond to insulin (25). Diabetic individuals can present with a range of both short-term and long-term symptoms, including blindness, heart disease, kidney failure, and the need for limb amputation due to poor circulation (6). Classification of patients into type 1 or type 2 is sometimes difficult due to a large number of disease modifiers (25). For the purpose of this review, we will focus on the genetic factors that can cause diabetes and have been directly linked to ERAD.

Normally, the peptide hormone insulin is produced by pancreatic β-cells and stimulates the clearance of blood glucose by muscle, fat, and liver cells (356). Clearance is achieved via interaction with insulin receptors on these cells, thereby initiating a signaling cascade. Pancreatic β-cells are specialized in that they have a highly elaborated secretory system that

is designed to synthesize and export large amounts of insulin under hyperglycemic conditions. In fact, insulin production in these cells accounts for 50% of total protein synthesis under stimulated conditions (440, 470). Insulin biosynthesis begins with the cotranslational insertion of a 110 amino acid preproinsulin into the ER. Subsequent removal of the signal sequence from this precursor generates the 86 amino acid peptide proinsulin. In the oxidizing environment of the ER, proinsulin acquires three disulfide bonds. Following export to the Golgi complex, further proteolytic processing of proinsulin results in the production of mature insulin that is then packaged into secretory granules.

The demand placed on the biosynthetic and folding machinery by insulin production has been suggested to result in increased amounts of ER stress in β-cells (515). As discussed earlier, unresolved activation of the UPR can lead to apoptosis, and heterozygous mice that are unable to activate one leg of the UPR, which is mediated by PERK, become diabetic and glucose intolerant (432). And, *XBP-1*$^{+/-}$ mice, in which UPR signaling is only partially inhibited, develop insulin resistance (367). Thus, as anticipated, β-cell apoptosis is relevant for both type 1 and type 2 diabetes, and ER stress may play a significant role in cell death and insulin deficiency (135). These events suggest the presence of a positive-feedback loop: stressed β-cells are destroyed, which in turn potentiates the disease due to a decreased ability to produce insulin. Consistent with a link between insulin production, the UPR, and diabetes, ER stress is increased in the diabetic Akita mouse model. In this case, the disease arises from the expression of a single copy of an insulin mutant (Ins2C96Y) that is unable to form an intrachain disulfide bond (16, 21). Interestingly, the levels of both wild-type insulin and Ins2C96Y are increased in the presence of MG-132, which implies that even native insulin is subject to misfolding and proteasome-dependent degradation (16). Further support for a role for ER stress in the pathogenesis of diabetes comes from the finding that guanabenz, a small molecule, rescues cells from death resulting from exposure to ER stressors, including tunicamycin and expression of Ins2C96Y. Investigation into the mechanism of action of guanabenz revealed that rescue was due to an enhancement of UPR-mediated translational attenuation (501). This finding represents a novel approach to mitigate ER stress and may be useful in treating metabolic syndromes associated with misfolded insulin variants or other peptide hormones.

The data described above suggest that allelic variants of insulin in humans may contribute to the “normal” levels of ER stress in β-cells, a phenomenon that may push these cells over the edge and lead to apoptosis and diabetes. In support of this model, several point mutations in the insulin gene have been identified in patients with neonatal diabetes. The identified mutations result in the ER accumulation of proinsulin and an accompanying secretion defect (371). Interestingly, one of the naturally occurring mutations, C96Y, is the same one found in the Akita mouse (523). Other studies with the Akita model demonstrated robust Hrd1-dependent ubiquitination of Ins2C96Y, directly implicating the ERAD pathway in the pathogenesis of genetically linked diabetes (16). A mouse model with inducible expression of Ins2C96Y confirmed the relationship between ER stress, increased apoptosis, and diabetes. Of note, the apoptotic response was increased either by proteasome inhibition or by downregulation of a member of the Hrd1 complex (186). Therefore, ERAD plays an important role in mitigating the stress incurred upon expression of misfolded insulin.

Diabetes-causing mutations have also been identified in the insulin receptor (IR), which target the mutant receptor for ERAD. IR is synthesized as an immature form, which must then undergo posttranslational modifications that include *N*-glycosylation, dimerization, and proteolytic cleavage (534). Substitution of the highly conserved His at position 209 with Arg prevents receptor dimerization and reduces transport to the cell surface (233). A decrease in the levels of mutant IR precursors over time suggested that the protein was degraded. Further analysis of the H209R and another IR variant, F382V, revealed that these mutants exhibit an enhanced interaction with BiP, indicative of increased ER retention and perhaps recognition for degradation (12). Two additional IR variants, D1179E and L1193W, were identified in patients with insulin resistance and which result in decreased surface expression coupled with increased degradation of the pro-receptor form (220). Further study revealed that pro-receptor levels increased upon the addition of proteasome inhibitors (219). In addition, the mutant forms of IR associated with cytosolic Hsp90 to a greater extent than wild-type IR. To define the role of Hsp90 in IR degradation, anti-Hsp90 antibodies were microinjected into cells transfected with mutant IR. This treatment increased the amount of the mutant IR (219), suggesting that cytosolic Hsp90 enhances the degradation of mutant IR. In contrast, chemical inhibition of Hsp90 increased the proteasome-dependent degradation of wild-type immature forms of IR, suggesting that this chaperone also facilitates the formation of early biogenic intermediates of the receptor (399).

D. Bacterial Toxins and ERAD

Pathogenic bacteria, including *Vibrio cholera, Bordetella pertussis, Shigella dysenteriae*, and Shiga toxigenic *Escherichia coli*, infect hundreds of millions of people each year. Combined, these infections result in millions of deaths annually (391). For example, *Vibrio cholera* is a serious threat in developing nations and is estimated to infect 3–5 million persons each year, resulting in ~100,000 deaths (1). Infectious outbreaks occur primarily in these nations due to poor sanitation and inadequate medical care. Patients infected with pathogenic variants of *Vibrio cholera* present with abrupt-onset watery diarrhea and dangerous levels of fluid loss. If not properly treated, death can result within hours.

The key to *Vibrio cholera*'s virulence begins with the secretion of AB5 protein complexes, which alter host cellular homeostasis. The AB5 toxin family consists of four subfamilies based on the method of toxin entry into the host cell via the B subunit and upon the enzymatic activity of the A subunit. Cholera toxin (CTx) is composed of a B-homopentamer and disulfide-linked A1 (catalytic) and A2 (linking) domains. The AB5 holotoxin is internalized from the apical plasma membrane of enterocytes following cell surface interaction with gangliosides. After entry into endosomes, CTx is trafficked in a retrograde manner to the Golgi, possibly due to its association with the ganglioside. Further retrograde trafficking of CTx to the ER occurs via the KDEL receptor, which recognizes the KDEL ER retrieval signal in the A2 subunit. Once in the ER, the catalytic A1 subunit (CTA1) disassociates from the A2B5 subunits, due to the action of ER oxidoreductases (289, 466, 509). CTA1 is then retrotranslocated from the ER to the cytoplasm where it folds and catalyzes the addition of an ADP-ribosyl group onto the G_s subunit of adenylate cyclase. This results in constitutive activation of adenylate cyclase, increased cAMP production, and

continuous activation of CFTR (509). Overactive CFTR causes diarrhea and the resulting water and electrolyte loss.

Retrotranslocation of CTA1 from the ER to the cytoplasm appears to follow an ERAD-like pathway. As observed during ERAD, the toxin must first be recognized prior to retrotranslocation. Interestingly, recognition involves the ERresident PDI. PDI does not function as an oxidoreductase in the CTA1 unfolding reaction, but rather as a "redox-dependent chaperone" (499). In one model, PDI directs CTA1 unfolding, which was found to depend on another ER oxidoreductase, Ero1α (136, 137, 336). Ero1α helps PDI cycle between the reduced (toxin binding) and oxidized (toxin releasing) states. In another model, CTA1 spontaneously unfolds once dissociated from PDI (482). Unlike other ERAD substrates, CTA1 retrotranslocation is p97/Cdc48-independent (267). What then is the driving force for CTA1's retrotranslocation from the ER to the cytosol? One possibility is that CTA1 is extracted by the 19S cap of the proteasome, which is sufficient for the removal of pro α-factor from yeast (284) and mammalian (518) vesicles. However, data directly supporting a role for the 19S cap in CTA1 dislocation are currently lacking. Yet another hypothesis is that spontaneous refolding of CTA1 in the cytosol ratchets CTA1 through a retrotranslocon, while simultaneously helping CTA1 avoid recognition by the cytosolic quality control machinery. Evidence in support of yet another model derives from the fact that the cytosolic chaperone Hsp90 interacts with CTA1 in an ATP-dependent manner and is required for the ER dislocation of CTA1 (483). Finally, treatment of cells with the multifunctional drug 4-phenylbutyric acid (PBA) inhibits cholera intoxication (482). In contrast to its other modes of action (see sect. III*A*), PBA may stabilize the tertiary structure of CTA1 since the compound increases the thermal stability of CTA1, as assessed by circular dichroism and fluorescence spectroscopy. Cell lines treated with PBA also exhibited reduced translocation of CTA1 from the ER to the cytoplasm and were spared CTA1 intoxication (482).

There are three proteins that have been implicated as the retrotranslocon for CTA1. In 2000, Schmitz et al. (433) used a cell-free system to examine the role of Sec61 in CTA1 retrotranslocation. They showed that CTA1 can be retrotranslocated from CTA1-loaded microsomes, but this process was inhibited by the addition of a ribosome nascent chain complex to block Sec61 (433). In contrast, the retrotranslocation of CTA1 subunit was facilitated by Derlin-1 in human embryonic kidney cells. CTA1 interacted with Derlin-1, and reduced CTA1 retrotranslocation was evident in cells expressing a dominant-negative version of Derlin-1 (39). Derlin-1 also interacts with PDI, which could provide for a convenient mechanism to hand CTA1 from the holotoxin to the retrotranslocon. Recently, the interaction of CTA1 with the E3 ligases gp78 and Hrd1 were noted (40). Besides functioning as an E3, Hrd1 has been implicated in the retrotranslocation of HMG-CoA reductase (152, 424) and CPY* (70) in yeast (see sect. I*E*). Consistent with these data, downregulation of Hrd1 or the use of dominant-negative mutants of Hrd1 attenuated CTA1 retrotranslocation. Interestingly, the dominant-negative form of Derlin-1 also blocked the interaction of CTA1 with gp78 and Hrd1, suggesting that CTA1 interacts with Derlin-1 prior to the E3 ligases (40). These collective data support a role for multiple, putative channels in

CTA1 retrotranslocation, although it is unclear if they act together, sequentially, or redundantly.

After retrotranslocation, it is unknown how CTA1 escapes polyubiquitination and proteasome-dependent degradation, which is the typical fate of ERAD substrates. It was hypothesized that CTA1 avoids polyubiquitination because it has only two lysines, which may be inaccessible to modification by the E3s (193, 410). Direct ubiquitination of CTA1 has not been observed, and one study demonstrated that CTA1 retrotranslocation continues in a lysine-less version of CTA1. However, as noted in section I*E*, ubiquitination has been noted on noncanonical sites such as Ser or Thr (67, 223, 452, 530). Therefore, the role of the E3 ligases and ubiquitination during CTA1 retrotranslocation remain uncertain. An alternate possibility is that polyubiquitinated CTA1 may be acted upon by a deubiquitinating enzyme that rescues proteins from being degraded. Or, the rapid refolding of CTA1 in the cytoplasm (see above) may obscure residues that might otherwise be ubiquitinated. This model is supported by data showing rapid acquisition of trypsin resistance upon release from PDI (410). Overall, these studies reveal that CTA1 intoxication requires a functional ERAD machinery and that CTA1 masquerades as an ERAD substrate, albeit one with unique features. But, because the AB5 toxins are structurally similar and seem to have evolved similar mechanisms to coopt the ERAD machinery, understanding the factors and processes required for CTx toxicity might provide useful targets for the treatment of symptoms resulting from other pathogenic bacteria harboring AB5 toxins. In fact, ricin (a plant AB5 toxin produced by *Ricinus comminus*) may spontaneously unfold once dissociated from PDI in the ER (33, 467) and also appears to forego ubiquitination after its retrotranslocation through either Sec61 or a Hrd1-based retrotranslocon (97, 293, 453). Since ricin is synthesized within eukaryotic cells, rather than in bacteria like CTx, it is glycosylated in the ER (102). This may explain some of the observed differences between the fates of ricin and CTA1, such as the interaction between ricin and EDEM1, and a measurable amount of degradation of ricin toxin in the cytoplasm, presumably due to its failure to efficiently translocate into the ER or completely refold after its retrotranslocation (453, 460, 541).

E. Serpinopathies

The family of serine protease inhibitors (serpins) is responsible for a class of diseases known as the serpinopathies (164). These diseases result from mutations in serpin family members, including α1-antitrypsin (AT), neuroserpin, antithrombin, and β2-antiplasmin. Mutant serpins can adopt altered, unstable conformations, leading to loss of native protein function and in some cases the acquisition of a toxic gain-of-function aggregate or polymer. The net outcomes are a group of pathologies that result in lung and liver disease, dementia, and blood clotting deficiencies.

Members of the serpin family share >30% sequence homology, as well as a conserved tertiary structure. Mutations in *SERPINA1*, which encodes the prototypical serpin α1-AT result in AT deficiency. Approximately 1 in 2,000 people of Northern European descent is homozygous for disease-causing alleles of AT (307). AT-deficient patients may present with chronic obstructive pulmonary disease (COPD) and can develop cirrhosis (3). Among individuals affected by AT deficiency, nearly 1–2% develop COPD symptoms, which is

exacerbated by smoking. Liver disease is more common, with 10% of infants being born with jaundice and up to 50% of homozygous adults (over the age of 50) with some evidence of cirrhosis at death (116). This observation highlights the progressive nature of AT deficiency and the need for early diagnosis. Current treatment for AT-associated COPD relies on intravenous enzyme replacement therapy (3). It is much more difficult, to treat cirrhosis that results from polymer accumulation, and the only viable option is a liver transplant. Therefore, a significant body of research has been devoted to uncovering the pathways that degrade misfolded AT in hopes of developing therapies to reduce polymer formation and/or increase protein clearance in the liver.

AT is a 394-amino acid protein that is synthesized primarily in hepatocytes, and in the ER it becomes *N*-glycosylated. AT functions both in the bloodstream where it inhibits neutrophil-derived proteases and in lung tissue where it regulates elastase. The wild-type protein, known as the “M” allele, binds to and is cleaved by these proteases, thereby inducing a conformational change that inactivates them (117, 212). The most common disease-causing variant of AT is termed the Z variant (E342K), ATZ, based on its slower migration on an isoelectric focusing gel relative to ATM. Due to its inherent instability and the loss of an intramolecular salt bridge, ATZ self-associates and forms dimers and higher order polymers within the ER in hepatocytes. As a result, serum levels are only ~10–15% of wild-type levels (308, 378, 456). In essence, ATZ self-assembly underlies the two main pathologies associated with AT deficiency: *1*) AT deficiency is a loss-of-function disease as a consequence of increased elastase activity, which results in the destruction of connective tissue in the lung; and *2*) AT deficiency is a gain-of-function disease from the accumulation of toxic aggregates in the liver, which can lead to hepatitis, cirrhosis, and an increased risk for hepatocellular carcinoma (379).

Early work in mammalian cells and in a yeast model demonstrated that ATZ degradation requires the activity of the proteasome, pointing toward a role for ERAD in clearing soluble forms of ATZ from the secretory pathway. First, ATZ degradation was significantly delayed in a yeast strain lacking the chymotrypsin-like activity of the proteasome (540) and in a strain in which proteasome assembly was defective (442). Second, the half-life of ATZ expressed in human skin fibroblasts was increased threefold in the presence of a proteasome inhibitor (394). The proteasome is also required for the degradation of a naturally occurring truncated version of AT, null Hong Kong (NHK) (304). Surprisingly, it remains unclear whether mutant AT is ubiquitinated prior to degradation, although gp78 may be involved in ATZ turnover (451) and NHK resides in a Hrd1-containing complex (79). Moreover, a dominant-negative Hrd1 construct decreased the ubiquitination of NHK in HeLa cells (260), and ATZ solubility and degradation were enhanced by Hrd1 overexpression (522).

Other work demonstrated that ATM interacts with calnexin during its maturation (366); therefore, it is not surprising that lectins play an important role in the ERAD of misfolded forms of AT. ATZ was shown to interact with calnexin in patient fibroblasts transfected with the ATZ gene (554), and a similar interaction was demonstrated for NHK (282). Ongoing studies using NHK have yielded additional insights into the machinery required to degrade misfolded forms of AT. For example, calnexin-bound NHK appears to be transferred in a sequential manner to EDEM1 (see sect. I*E*) and then perhaps to the retrotranslocon (357).

Another study suggested that EDEM1's role during NHK degradation is cell-type specific, and ERManI may instead be the critical "timer" that choses NHK for degradation (553). Nevertheless, EDEM1 and the ERManI can act synergistically to trigger the degradation of NHK (205). NHK also binds two other lectins, XTP3-B and OS-9, which with BiP (66) act early in the pathway for ERAD substrate selection (79, 206).

Increasing evidence indicates that autophagy may play a complementary role to ERAD to destroy difficult-to-manage proteins (275). Because the autophagic pathway can remove large aggregates and even significant portions of damaged ER, one might imagine that autophagy could clear higher order ATZ polymers. Early evidence for this hypothesis came from studies examining ATZ polymer residence by immunoelectron microscopy. As predicted, ATZ was found not only in the ER but also in autophagosomes (486). Notably, chemical disruptors of autophagy stabilized ATZ, albeit rather modestly compared with proteasome inhibition (394, 486). This evidence was corroborated through the use of the yeast model, in which it was shown that autophagy became necessary to degrade ATZ but only when the protein was overexpressed and aggregated (276). Ultimately, the importance of the autophagic pathway and the fate of ATZ were demonstrated in mouse models (235). This model proved essential for the testing of small molecules that might one day improve the pathologies associated with AT deficiency (see sect. III*A*). Overall, the level of ATZ expression and components that regulate autophagy may represent genetic modifiers of AT deficiency. The identification of genetic modifiers for AT is vital given that <10% of ATZ homozygotes develop clinically relevant liver disease in childhood (476).

Surprisingly, there are some serpin family members that do not exhibit serine protease inhibitor activity but instead function as chaperones. Hsp47 resides in the ER and aids in the assembly of procollagen into a triple-helical form of procollagen (320). Mutations in Hsp47 compromise chaperone function, but at this point, the mutations do not appear to result in toxic polymerization (78). Instead, the loss of Hsp47 function manifests as osteogenesis imperfecta due to delayed secretion of procollagen trimers. Patient fibroblasts have virtually no detectable levels of Hsp47 protein; however, treatment with MG-132 increases Hsp47 levels, suggesting that the ERAD pathway plays a role in this form of the disease. In contrast, aggregates that arise in the ER directly from mutant forms of procollagen and that also cause osteogenesis imperfecta are destroyed by autophagy (221).

It should be mentioned that in addition to the serpinopathies described here, three other mutant forms of serpins exist that are ER retained (23, 503). Defects in these proteins lead to thyroxine binding globulin deficiency, alpha-1-antichimotrypsin deficiency, and type I hereditary angioedema. It remains unknown whether the mutant proteins are targeted for ERAD and/or autophagy, but based on the fates of other mutant serpins (273), it is likely that these pathways will contribute to their turnover.

F. Viruses and ERAD

In addition to bacteria, select viruses have also evolved ways to subvert host cells by capitalizing on ERAD-associated activities. Immune surveillance for virally infected cells requires the presentation of viral peptides by MHC-I molecules to cytotoxic T cells. The generation of viral peptides is accomplished by proteasome processing and cleavage by

other proteases, which is followed by loading onto MHC-I in the ER and trafficking to the cell surface (98, 107). MHC-I biosynthesis is complex, requiring disulfide bond formation, *N*-linked glycosylation, heterodimerization, and peptide loading, and the failure to properly assemble these complexes can result in ERAD (74). In one example, the turnover of MHC-I molecules was accelerated by infection with human cytomegalovirus (HCMV) (32). HCMV is a herpes-type virus that can cause persistent, latent infections, but is usually only life-threatening in immunocompromised individuals. For those individuals, HCMV leads to mononucleosis-like symptoms, including fatigue, joint stiffness, and muscle pain, but the virus can also target specific organs, such as the eyes, lungs, gastrointestinal tract, and brain (5).

The study of MHC-I downregulation contributed significantly to early investigations of ERAD. Two viral genes were identified, US2 and US11, that direct newly synthesized MHC-I molecules to the ERAD pathway (232, 544, 545). Other early studies also demonstrated retrotranslocation of full-length MHC-I into a cytoplasmic pool in the presence of US11 (128, 449, 544). The retrotranslocated, or “dislocated” material, was deglycosylated, which may be important to feed the protein into the proteasome (203, 292). HCMV-induced degradation of MHC-I also required polyubiquitination, but interestingly ubiquitination does not occur on the cytoplasmic tail of MHC-I, which suggested that ubiquitination was occurring on the luminal domain of MHC-I (144). Thus the protein must form a hairpin across the ER membrane, and at least partial retrotranslocation is required for MHC-I ubiquitination. It is not surprising, then, that BiP plays a role in the US2- and US11-mediated degradation of MHC-I (195).

Interestingly, there are differences between the machinery used by US2 and US11, such as in the involvement of Derlin for US11 retrotranslocation, but not for US2 (299). In contrast, there is a requirement for signal peptide peptidase (SPP) for US2-mediated retrotranslocation (313), which at first glance is somewhat surprising given the fact that US2 is a type I membrane protein with a noncleavable signal sequence (156). However, a recent study found SPP in a complex together with PDI (285). These data suggest that substrate recruitment by SPP can occur independently of signal sequence cleavage. More generally, SPP may be important to clip integral membrane spans of select ERAD substrates, and consistent with this view a misfolded region in an integral membrane protein associated with SPP (90).

Other differences between US2 and US11 deserve mention. US2-induced ubiquitination of MHC-I has been attributed to the mammalian E3 ligase TRC-8 (468). By comparison, US11-dependent polyubiquitination of MHC-I appears to be facilitated by Hrd1 (189, 448). However, a recent study demonstrated that Hrd1 contributes to the physiological regulation of unfolded MHC-I but is dispensable for degradation induced by the presence of US11 (63). Together, the discovery of US2 and US11 has helped shed light on the molecular details underlying various facets of the ERAD pathway.

Another example in which the ERAD pathway has been co-opted by a virus is provided by the human immunodeficiency virus (HIV), which downregulates several aspects of host immunity, including CD4 function. HIV is spread through transmission of body fluids and

results in a gradual decrease in CD4+ T cells. Ultimately, this can progress into acquired immune deficiency syndrome (AIDS) once the patient's CD4 T-cell count has dropped below 200 cells/mm^3. HIV-AIDS has reached epidemic proportions, affecting ~33 million individuals worldwide, and has caused over 25 million deaths (7). At first glance, the effect of HIV on MHC-I is unlike that of HCMV, since MHC-I is cleared from the cell surface and degraded through the action of the HIV protein Nef. However, the presence of CD4 at the cell surface, which is the primary cell surface receptor for the virus, also hinders HIV because it inhibits virus budding, interferes with assembly of the HIV virion, and can trigger a CD4+ T-cell immune response (314). To overcome these barriers, HIV expresses the Vpu protein. Vpu was first shown to induce the rapid degradation of CD4 in a prelysosomal compartment (549), and eventually Vpu-induced CD4 degradation was demonstrated to be dependent on a functional UPS (437). Interestingly, Vpu is a tail-anchored protein that interacts with the COOH terminus of the β-transducin repeat containing protein, β-TrCP (324). Through its F-box domain, an E3 Skp1-Cullin1-F-box (SCF) ligase is recruited to β-TrCP and therefore to CD4 (142). Normally, the $SCF^{\beta\text{-}TrCP}$ complex does not participate in ERAD. Consistent with CD4 being "tricked" into becoming an ERAD substrate, recent data indicate that CD4 downregulation by Vpu also requires the p97/Cdc48 complex (46, 319).

Coronavirus and hepatitis C virus also interact with the ERAD machineries, but in very different ways from those discussed above. Coronaviurses (CoV) are RNA viruses that infect mammals, including humans, resulting in respiratory infections, i.e., severe acute respiratory syndrome (SARS) (376). Recently, it was shown that CoV replication occurs in virally induced membranous compartments that are enriched for EDEM1 and OS-9 (404). The importance of concentrating EDEM1 and OS-9 in these non-ER compartments is unknown, but among other possibilities, these data suggest a need to downregulate ERAD for efficient CoV replication. In line with this possibility, hepatitis C virus (HCV) replication was recently linked to the ERAD pathway. Specifically, ubiquitination of an HCV protein is increased by EDEM 1 or EDEM 3 overexpression, while viral replication is increased by treatment EDEM1 or EDEM3 siRNA (419).

III. CONCLUDING REMARKS

A. Current Experimental Treatments and Prospects for Future Therapies

As evidenced from the previous sections and TABLE 1, the ERAD pathway has been implicated in the underlying mechanisms of several diseases. But, because of the many factors that facilitate ERAD substrate selection and degradation, and because of diverse mechanisms by which different substrates may be destroyed, the treatment of ERAD-related diseases will be no simple task. In addition, any therapeutic treatments must take into account the proteostasis network within a cell, which comprises all of the factors that influence protein fate, such as synthesis, folding, degradation, and trafficking (363, 388). Even though these are still the "early days" for ERAD therapeutics, a growing number of approaches have been explored to correct ERAD-linked disease (TABLE 2). These approaches have had varying degrees of success for a number of reasons. For example, the proteostasis network is cell type specific, and cell toxicity is always problematic since modulation of ERAD may have secondary effects on the UPR and consequently lead to

apoptosis. In addition, as described in the preceding sections, other degradative pathways, such as autophagy, may act complementary to ERAD. Therefore, autophagy may compensate for chemical inhibition of the ERAD pathway. In this section, we will discuss select examples of recent therapeutic strategies as they have applied to cystic fibrosis, a lysosomal storage disease, AT deficiency, and familial transthyretin amyloid disease.

Because the ΔF508-CFTR folding and trafficking defects were rescued by incubating cells at a lower temperature (94, 100, 111) (see sect. II*A*), the destruction of the diseasecausing protein appeared to be a temperature-sensitive process. Consistent with this fact, temperature-dependent aggregation of wild-type CFTR can even be observed in vitro (162). Unfortunately, low temperature incubation of affected tissues in CF is not a viable therapeutic option. However, these data do suggest that modulating kinetic and/or thermodynamic aspects of the folding problem associated with ΔF508-CFTR may be sufficient to keep the protein from being selected for ERAD.

The most obvious approach to reduce the degradation of ΔF508-CFTR, thereby allowing the protein more time and perhaps a better environment in which to fold, is to inhibit the proteasome. Some of the most common proteasome inhibitors used are MG-132 (Cbz-Leu-Leu-leucinal), ALLN (acetyl-Leu-Leu-norleucinal), and lactacystin (a natural product isolated from a fungus; Refs. 49, 147). Refined proteasome inhibitors are currently used in the clinic and have shown efficacy in the treatment of late-stage multiple myeloma (434). These compounds acts as pseudosubstrates of the proteasome and inhibit the chymotryptic-like activity or both the chymotryptic- and tryptic-like activities (in the case of lactacystin; Ref. 283). Unfortunately, proteasome inhibition with ALLN or lactacystin shifted wild-type CFTR from a soluble form to a detergent-insoluble form (536). These results suggested that strategies to augment the folding and trafficking of ΔF508-CFTR must rescue the immature protein before it has been committed for degradation, since this pool is aggregation-prone once ubiquitinated.

Providing aid to the endogenous chaperone-assisted folding machinery in the cell has been considered as an attractive, alternate strategy to rescue ΔF508-CFTR and other conformationally challenged, disease-causing proteins. One means to achieve this outcome is via the administration of chemical chaperones. Chemical chaperones were first defined as osmolytes that provide a more favorable milieu in which a protein can fold, often by simply increasing the strength of the intramolecular hydrophobic bonds that are buried within a protein. Chemical chaperones may also more globally affect the cellular proteostasis network, thus leading to a more favorable folding/trafficking environment. Other chemical chaperones directly bind to the misfolded protein and have been termed “pharmacological chaperones” (51, 363, 505). These compounds lower the protein’s free energy state, which may help the protein fold, escape ERAD, and/or limit aggregation. For ΔF508-CFTR, one chemical chaperone that has been examined is curcumin. Curcumin is a component of turmeric and is derived from the plant *Curcuma longa*. Curcumin is something of a panacea, having been studied as a treatment for diseases from cancer to inflammatory bowel disease as a result of its in vitro effects as an anti-inflammatory, anti-oxidant, proapoptotic, and anti-cancer agent (119). Initial reports indicated that curcumin was able to rescue the ΔF508-CFTR trafficking defect and some disease-related phenotypes in a CF mouse model (115).

However, the inability to reproduce some of these results casts doubt on curcumin's efficacy for CF (321, 462, 533). These findings do not preclude the use of curcumin to treat CF, as the compound may function at different steps in CFTR biogenesis or work more effectively for other CFTR mutants (38, 529, 577).

More successful attempts to chemically correct ΔF508-CFTR were achieved by the outcomes of high-throughput screens for small molecules that increase ΔF508-CFTR activity at the cell surface. In one case, this led to the isolation of Corr-4a, which is a bisaminomethylbithiazole derivative (375). Although the mechanism of action of this compound is unknown, there is some evidence that Corr-4a binds directly to CFTR (532). More recent results suggest that Corr-4a rescues ΔF508-CFTR by repairing MSD2-related folding defects (171). Another ΔF508-CFTR corrector that was isolated through a high-throughput screen, Vertex-325 (508), may bind directly to NBD1 in CFTR (576). These combined data are consistent with evidence that the ΔF508 mutation disrupts interactions between NBD1 and MSD2 (446). Another compound, Vertex-770, rescues the gating defect in a less common CFTR mutant (G551D) that leads to disease (507). More likely than not, this potentiator also binds directly to CFTR to increase the channel's open probability. Overall, there is continued interest in performing functional screens for small molecule modulators of ΔF508-CFTR, and in the end, the best therapeutic outcome may be through a combined application of drugs that restore both the folding/trafficking defect associated with the protein, as well as its reduced channel activity.

Chemical chaperones have also been used to treat lysosomal storage diseases (LSDs), such as Gaucher disease (GD). GD results from a deficiency in glucocerebrosidase (GC), a lysosomal enzyme that normally breaks down the glycosphingolipid glucosylceramide. The inability to metabolize glucosylceramide affects many organs, resulting in hepatomegaly, splenomegaly, anemia, thrombocytopenia, bone lesions, and in some cases central nervous system (CNS) deficiencies (45, 211, 430). Some of the allelic variants that cause GD have been linked to ERAD, including N370S, G202R, and L444P (431). While enzyme replacement therapy has been successful for some LSDs, this strategy is ineffective for GD, presumably due to poor targeting of the exogenous enzyme to macrophages (430). This problem has been partially overcome by the development of a tagged version of GC that is recognized by a macrophage receptor; however, the modified enzyme is ineffective for patients with CNS symptoms due to its inability to cross the blood-brain barrier (578). Because reduced temperature also appears to rescue the G202R and L444P mutants (431), several chemical chaperones have been examined that increase the folding and trafficking efficiency of GC variants, some of which bind to GC's active site as a pseudosubstrate (578). Unfortunately, one of the most common GC mutations, L444P, is largely unresponsive to chemical chaperones, as the mutation is not in the active site.

To circumvent the special problem associated with L444P, proteasome inhibitors and a proteostasis regulator were examined. The proteostasis regulator is celastrol, which is used in traditional Chinese medicine and induces the heat shock response and the UPR (341, 542). Surprisingly, both MG-132 and celastrol repaired the mutant GC, but lactacystin was insufficient to rescue L444P, in spite of the fact that the measured proteasome inhibition by MG-132 and lactacystin was indistinguishable (341). The explanation for this difference

may stem from the finding that MG-132 and celastrol alter the expression of 400–500 genes, suggesting that the proteostatic network was affected. Among these genes were several factors regulated by the heat shock response and UPR, the latter of which is required for the effect of MG-123 and celastrol. Notably, upon treatment with celastrol, the L444P GC mutant now became receptive to treatment with chemical chaperones, and combining these treatments resulted in synergistic rescue (341). This study highlights the importance of considering the off-target, but potentially beneficial effects of a compound. In other observations, the accumulation of glucosylceramide has been noted to increase calcium efflux from the ER (264, 305, 377). As calcium is an important cofactor for components of the ER folding machinery (see above), increased efflux has been hypothesized to further impair the ER's folding capacity. Indeed, altering ER calcium levels by inhibiting efflux, or by the overexpression of SERCAs, which increase ER calcium, increases the processing and activity of L444P GC (364, 521). In addition, it was noted that calcium modulation combined with proteostasis modulation yields synergistic rescue. These studies demonstrate the delicate nature of the ER folding environment and reinforce the benefit of combining therapeutic approaches.

Another compound for which a known and off-target, but desired, effect is evident is PBA. PBA is an FDA-approved drug for the treatment of urea cycle disorders due to its ability to function as a nitrogen scavenger (58). PBA has also been explored for the treatment of sickle cell anemia, β-thalassemia, and various malignancies (387). Thus it was something of a surprise that PBA administration led to measureable rescue of ΔF508-CFTR in several different cell types, including patient-derived epithelial cells (415). In a clinical trial examining the use of PBA to treat CF, a partial rescue of CFTR activity in nasal airway epithelium was observed, supporting continued research on the mechanism of action of this compound (416). In fact, a proteomic analysis of the outcome of PBA treatment revealed, among other changes, increases in BiP and Hsp70 and Hsp90, and a downregulation of the constitutively expressed Hsp70 (Hsc70) and a subunit of the 26S proteasome (454). Thus PBA may exert a desired effect on several key players in the protein folding and ERAD pathways. This effect is most likely mediated by the ability of PBA to inhibit histone deacetylases (HDAC) (76, 406). Histone acetylation and deacetylation are important regulators of gene expression (68, 175, 406). A second FDA-approved drug, suberoylanilide hydroxamic acid (SAHA), is also an HDAC inhibitor, and is currently used to treat cutaneous T-cell lymphoma and is in clinical trials for the treatment of other forms of lymphoma (288, 322). SAHA was recently shown to rescue ΔF508-CFTR channel activity to ~28% of wild-type levels in primary airway epithelial cells. The silencing of specific HDACs led to the identification of HDAC7 as a key mediator of ΔF508-CFTR rescue. Perhaps not surprisingly, HDAC7 silencing broadly altered the transcriptional profile in the epithelial cells and influenced the levels of many genes implicated in CFTR folding and trafficking (215).

The pleiotropic effects of HDAC inhibitors are likely responsible for their effectiveness in ameliorating disease phenotypes associated with other ERAD-targeted proteins, including ATZ. PBA increases the secretion of ATZ from patient-derived fibroblast cells expressing ATZ and in mice engineered to produce human ATZ (64). Unfortunately, PBA was ineffective in a clinical trial aimed at increasing serum AT levels, likely due to the difficulty

in delivering an optimal dose to the affected tissues (484). However, another FDA-approved drug, carbamazepine (CBZ), was examined in a model for ATZ-associated liver disease. CBZ has been used to treat epilepsy and has applications as a mood stabilizer because of its effects on inositol (487, 550). Because of the effects on IP_3 levels, CBZ also enhances autophagy and the clearance of polyQ HTT aggregates (423). Recently, CBZ was shown to enhance the degradation of both soluble and insoluble ATZ in a mouse model (200). These data make CBZ an attractive candidate to treat AT-associated liver disease.

In our last example, we discuss one of the rare cases in which knowledge about protein structure led to the design of an effective therapeutic that is being used in the clinic. Transthyretin (TTR) is a secreted protein that functions as a tetramer to transport thyroid hormone and retinol-binding protein in the bloodstream. Certain disease-causing variants of TTR, such as D18G, are secreted inefficiently because they are retained in the ER and degraded by ERAD (444). As might be expected, this variant binds to BiP to a much greater extent than wild-type TTR or to the variants that result in disease through an ERAD-independent mechanism (463). Other unstable TTR variants escape ERAD but form serum amyloid fibrils that can lead to cardiomyopathy, familial amyloid polyneuropathy, and CNS amyloidosis (180). On the basis of extensive biophysical studies, TTR amyloidosis was shown to arise due to a kinetic destabilization of secreted TTR tetramers into monomers, which then form fibrils (181). Therefore, molecules that stabilize the tetramer should have therapeutic potential. After X-ray crystallography was used to determine the key features by which amyloid inhibitors bind to TTR, computational analysis guided the design of more potent and specific small molecule inhibitors of TTR amyloidosis (255). Further refinement led to the discovery of a halogenated benzoxazole, compound 20, which bound tightly to TTR and prevented fibril formation (403). Compound 20, now referred to as Tafimidis, is currently used to treat familial transthyretin amyloid diseases (9).

B. Summary and Future Questions

The purpose of this review was to highlight key factors that direct ERAD substrates for degradation and to provide select examples on the number of unique ways in which ERAD can impact human physiology and disease. For more specific details and for a more inclusive list, we have provided TABLE 1. However, we are quite aware that this table is incomplete and that in the future many more diseaseassociated ERAD substrates will be added. In other cases, the data linking a particular disease-associated protein to the ERAD pathway are not definitive, but are only suggestive. Many proteins are only loosely associated with various aspects of ER quality control, but their residence in the ER and proteasome-dependent degradation have not been studied. We hope that our work will lead to a more in-depth investigation into potential connections to ERAD and stimulate future research efforts. Given the nearly infinite number of conformations that a secreted protein can adopt, especially when all possible mutant forms are considered, it is not surprising that the list is already relatively long. We suspect that the table will grow as additional secreted proteins are characterized and as ill-characterized genes encoding secreted proteins are better defined. We also hope that our work will raise important questions about how current and future research efforts can best be directed to treat these conditions. In the era of personal genomics, care must be taken to accurately define the underlying effects of disease-

causing mutations that result in protein misfolding. And, as promising therapeutics are examined for their effects on a variety of disease models, secondary effects on the ERAD pathway will need to be examined. As TABLE 2 demonstrates, compounds that can control for effects on the fates of ERAD substrate are already in-hand for these efforts.

Acknowledgments

C. J. Guerriero gives special thanks to Emily Guerriero for critical reading of the manuscript and support during its preparation as well as to the members of the Brodsky lab for many helpful discussions.

GRANTS

The study of ERAD in our laboratory is supported by grants from the National Institutes of Health (GM-75061) and via the Pittsburgh Center for Kidney Research (DK-79307) as well as from the Cystic Fibrosis Foundation (BRODSK08XX0) (to J. L. Brodsky). C. J. Guerriero is supported by a National Institutes of Health National Research Service Award F32 individual postdoctoral fellowship (GM-903642).

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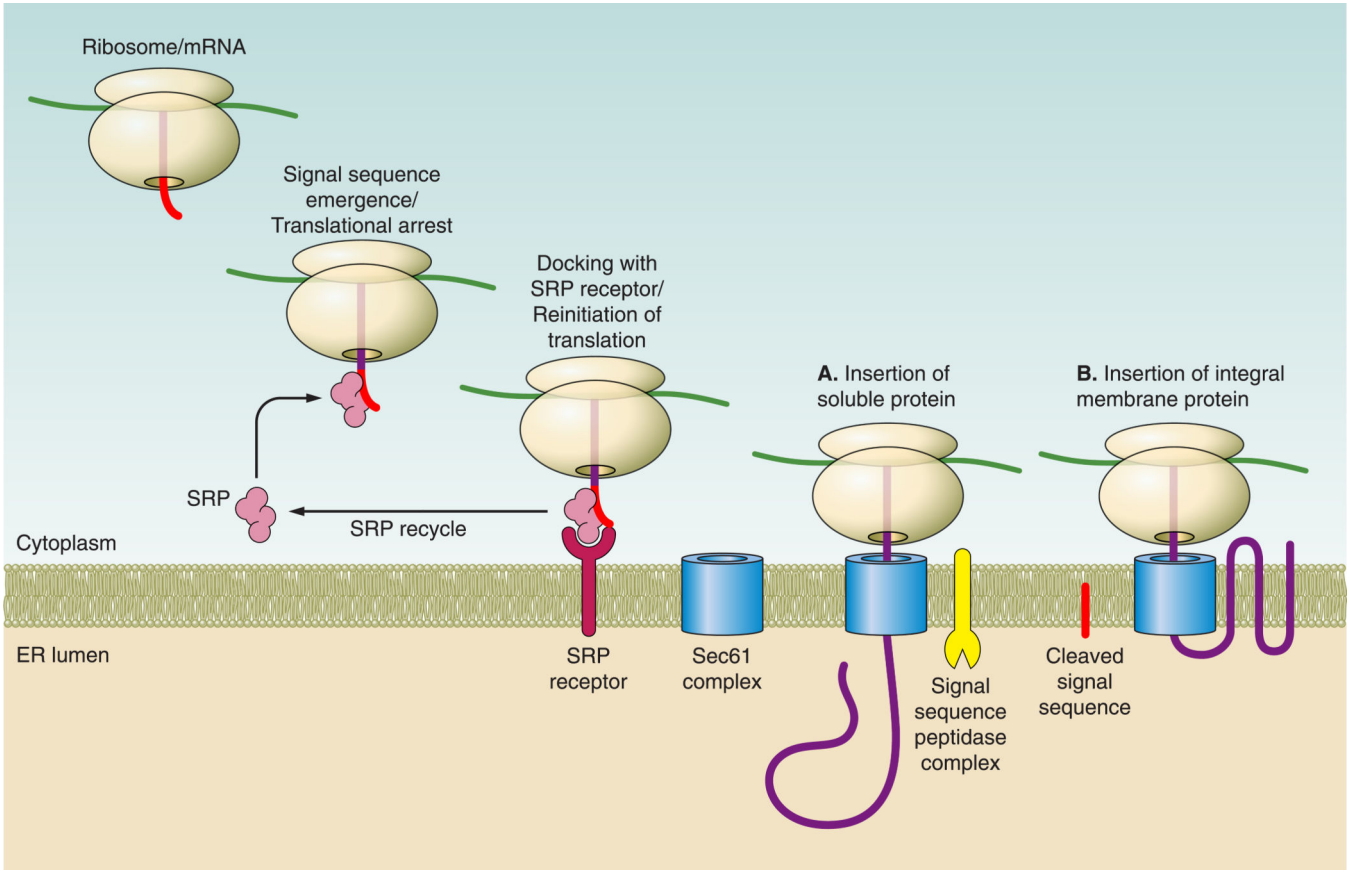

FIGURE 1. Protein targeting to the endoplasmic reticulum

As a nascent secretory protein emerges from the ribosome exit tunnel, it presents a hydrophobic signal sequence that is recognized by the signal recognition particle (SRP). Binding of SRP to the signal sequence slows translation and targets the ribosome-nascent chain complex to the ER membrane via its interaction with the dimeric SRP receptor. Following release, SRP is recycled and translation resumes. A nascent soluble protein (*A*) is translocated into the ER lumen, and an integral membrane protein (*B*) is incorporated into the membrane by the Sec61 translocation complex, and for all soluble proteins and some membrane proteins the hydrophobic signal sequence is cleaved by the ER localized signal peptidase complex.

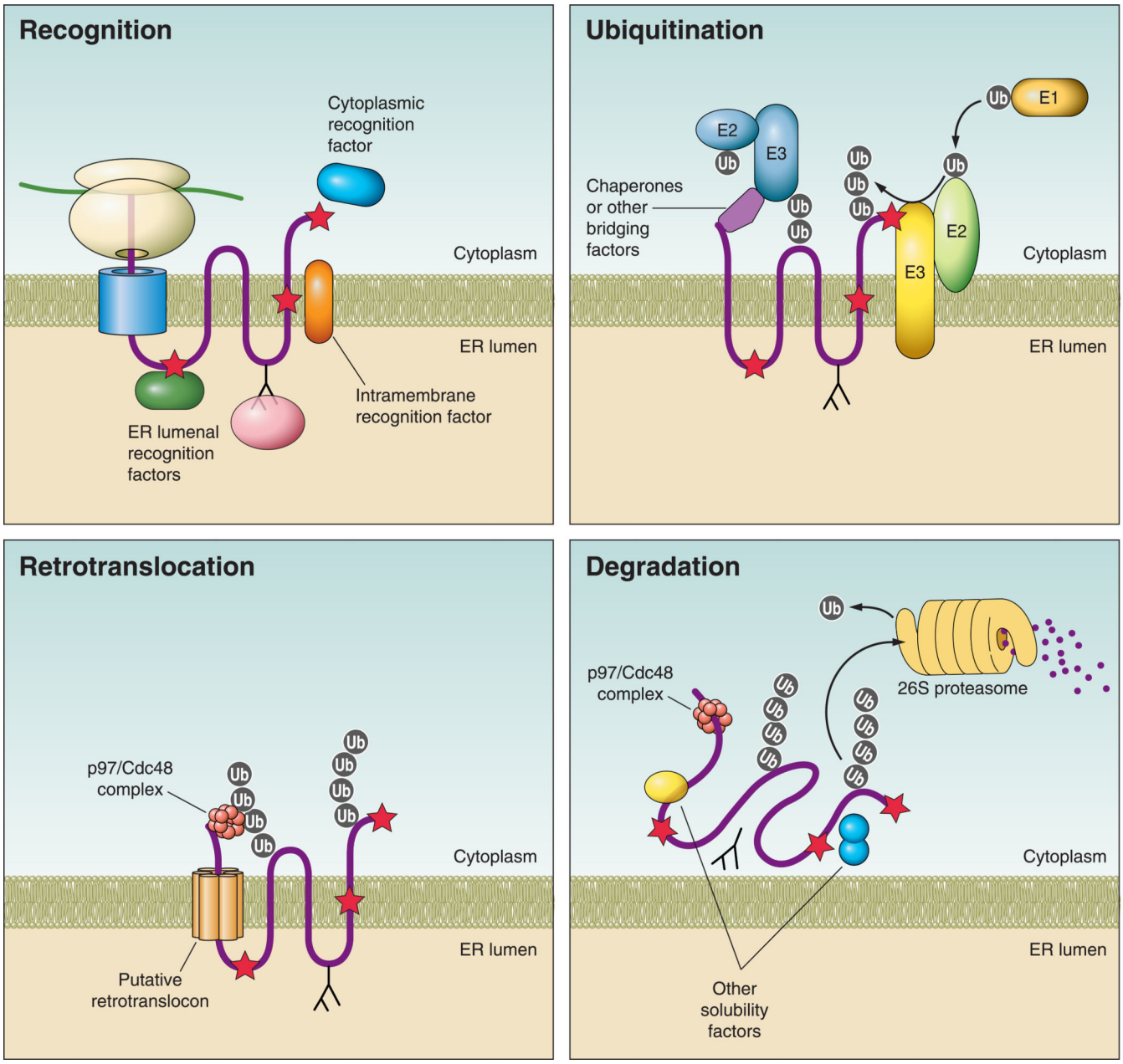

FIGURE 2. Steps in endoplasmic reticulum-associated degradation (ERAD)

Recognition: during protein synthesis and translocation, a misfolded region (red star) may reside in a protein's cytoplasmic, ER luminal, or transmembrane domains. Recognition is mediated by ER luminal or cytoplasmic chaperones, as depicted, depending on the location of the folding lesion. For glycoproteins, lectins (pink) interact with *N*-glycans and in some cases they monitor the folding status of the protein. *Ubiquitination:* following recognition, the ubiquitination machinery is recruited to the misfolded substrate, either directly within the membrane or by interactions with cytoplasmic chaperones. A ubiquitin activating enzyme (E1) transfers ubiquitin (gray circle) to an active site cysteine in a ubiquitin conjugating enzyme (E2) in an ATP-dependent process. The ubiquitin is then transferred most

commonly to a lysine residue on a client protein via a ubiquitin ligase (E3). Ubiquitination at the ER membrane can occur via cytoplasmic or ER-localized E3 ligases, both of which are shown. *Retrotranslocation:* for polytopic membrane proteins (pictured), retrotranslocation may occur by removal of the protein through a channel (retrotranslocon) and/or by removal of the protein and the surrounding membrane (not pictured). In either case, retrotranslocation almost always depends on the p97/Cdc48 complex, which includes Ufd1 and Npl4 and interacts with ubiquitin and misfolded regions on a substrate. p97/Cdc48 provides the mechanical force via ATP hydrolysis for substrate removal. *Degradation:* following retrotranslocation, misfolded proteins are ushered to the 26S proteasome and must be kept soluble to prevent aggregation. *N*-glycans are clipped by *N*-glycanse (not pictured), and ubiquitin moieties are removed by deubiquitinating enzymes either in the cytosol or in the proteasome cap. The proteasome contains three peptidase activities, trypsin-like, chymotrypsin-like, and caspase-like, which cleave proteins into short peptide fragments.

Table 1

Disease-related proteins degraded by ERAD or linked to ERAD

Chromosomal Locus	Gene	Protein	Disease	Reference Nos.	Class
Cardiovascular					
2p24–23	*APOB*	Apolipoprotein B (Apo B)	A-beta-lipoproteinemia	(62, 297, 298, 568)	S
Xq22	*GLA*	Alpha-galactosidase A (alpha-Gal A)	Fabry disease	(179, 559)	S
7q36.1	*KCNH2*	Human ether-a-go-go-related gene (HERG) voltage-gated potassium channel	Congenital long QT syndrome	(146, 163, 519, 589, 590)	S
19p13.3	*LDLR*	Low-density lipoprotein receptor (LDLR)	Familial hypercholesterolemia	(228, 286, 295)	S
2q13–14	*PROC*	Protein C	Protein C deficiency	(240, 241, 352, 494)	S
3q11.2	*PROS1*	Protein S	Protein S deficiency	(502)	S
1q23–25.1	*SERPINC1*	Antithrombin	Type I antithrombin deficiency	(492, 493)	S
17p13	*SERPINF2*	Alpha-2-antiplasmin (A2AP)	Alpha 2-plasmin inhibitor deficiency	(81, 352)	S
12p13.3	*VWF*	von Willebrand factor (vWF)	von Willebrand’s disease type IIA	(17, 18, 48, 316)	S
Digestive					
10q24	*ABCC2*	Multidrug resistance protein 2 (MRP2)	Dubin-Johnson syndrome	(187, 243)	S
2q24	*ABCB11*	Bile salt export pump (BSEP)	Progressive familial intrahepatic cholestasis type II (PFIC II)	(192, 335, 524)	S
13q14.3	*ATP7B*	Copper transporting P-type ATPase	Wilson disease	(95, 185, 214, 506)	S
18q21–22	*ATP8B1*	FIC1 aminophospholipid-transporting ATPase	Progressive familial intrahepatic cholestasis type II (PFIC I)	(134, 374, 506)	S
4q28	*FGB*	Fibrinogen	Hereditary hypofibrinogenemia	(53, 277, 555, 556)	S
6p21.3	*HFE*	Hemochromatosis	Hereditary hemochromatosis	(63, 517)	S
10q11.2	*RET*	RET tyrosine kinase	Hirschprung disease	(253, 254)	S
Endocrine					

Chromosomal Locus	Gene	Protein	Disease	Reference Nos.	Class
11p15.1	*ABCC8*	Sulfonylurea receptor 1 (SUR1)	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)	(481, 561, 562)	S
3q13	*CASR*	Calcium-sensing receptor (CasR)	Familial hypocalciuric hypercalcemia (FHH) in heterozygotes	(209, 210, 380)	S
3q13	*CASR*	Calcium-sensing receptor (CasR)	Neonatal severe hyperparathyroidism (NSHPT) in homozygotes	(209, 210, 380)	S
11p15.5	*INS*	Proinsulin	Neonatal diabetes (type 1)	(16, 186, 371)	S
19p13.3–13.2	*INSR*	Insulin receptor	Insulin resistance syndrome (type 2 diabetes)	(12, 219, 233, 399)	S
3p22–21.1	*PTH1R*	Parathyroid hormone receptor (PTHR)	Parathyroid hormone resistance	(19)	S
Immune					
19p13.3	*Elane*	Neutrophil elastase	Severe congenital neutropenia (SCN)	(347)	S
17q23.1	*MPO*	Myeloperoxidase (MPO)	Hereditary myeloperoxidase deficiency	(99)	S
Integumentary					
4q21.21	*ANTXR2*	Anthrax toxin receptor 2	Hyaline fibromatosis syndrome	(101)	S
6p21.3	*HLA-A*	Major histocompatibility complex I heavy chain (MHC1), viral E3 MIR1	Kaposi’s sarcoma	(67)	C
11q14–21	*TYR*	Tyrosinase (TYR)	Oculocutaneous albinism	(27, 178, 475, 537)	S
Multisystemic					
16p13.1	*ABCC1*	P-glycoprotein	Implications for cancer treatment	(312)	S
4q22	*ABCG2*	Breast cancer resistance protein	Implications for cancer treatment	(145, 343, 344, 474)	S
20p13	*AVP*	Vasopressin precursor protein	Autosomal dominant neurohypophysial diabetes insipidus (ADNDI)	(140, 225, 349)	S
2p12	*EIF2AK3*	Eukaryotic translation initiation factor 2-alpha kinase 3 (PERK)	Walcott-Rallison syndrome (WRS)	(172)	S/D
15q21.1	*FBN1*	Fibrillin 1	Marfan syndrome	(73, 543)	S
6p21.3	*HLA-A*	MHC1, viral proteins US2 and US11	Cytomegalovirus (CMV) infection	(232, 300, 468, 544, 545)	C

Chromosomal Locus	Gene	Protein	Disease	Reference Nos.	Class
12q13.13	*RNF41*	Neuregulin receptor degradation protein 1 (Nrdp1)	Breast and other cancers	(141)	M
14q32.1	*SERPINA1*	Alpha-1-antitrypsin (AT)	Alpha-1-antitrypsin deficiency	(394, 485)	S
9p13.3	*VCP*	Cdc48/p97/valosin-containing protein (VCP)	Inclusion body myopathy associated with Paget's disease of bone (IBMFPD)	(72, 496, 539)	M
Musculoskeletal					
17q21.33	*COL1A1*	Type I procollagen pro-alpha 1 chain	Osteogenesis imperfecta	(132, 221, 279)	S
2p13.3	*DYSF*	Dysferlin	Limb girdle muscular dystrophy type 2B/Miyoshi myopathy (LBMD2B/MM)	(78, 143)	S
7q21	*SGCA*	Sarcoglycan alpha subunit	Limb girdle muscular dystrophy type 2D(LBMD2D)	(143, 153)	S
7q21.3	SGCE	Sarcoglycan epsilon subunit	Myoclonus-dystonia syndrome (MDS)	(121)	S
11q13.5	*SERPINH1*	Heat shock protein 47 (Hsp47)	Osteogenesis imperfecta	(78)	S
Nervous					
1p36	*ATP13A2*	ATPase type 13A2 cation transporter	Kufor-Rakeb syndrome (KRS)/Parkinsons disease 9	(504)	S
14q21	*ATXN3*	Ataxin 3	Machado-Joseph disease/spinocerebellar ataxia type 3	(527, 570, 586)	S
11q13	*BSCL2*	Seipin	Silver's syndrome/distal hereditary motor neuropathy type V	(224)	S
5q34	*GABRA1*	Gamma aminobutyric acid receptor (GABAR) alpha 1	Juvenile myoclonic epilepsy	(52, 149)	S
5q34	*GABRA1*	Gamma aminobutyric acid receptor (GABAR) alpha 1	Childhood absence epilepsy (CAE)	(238)	S
5q34	*GABRG2*	Gamma aminobutyric acid receptor (GABAR) gamma 2	Generalized epilepsy with febrile seizures plus (GEFS+)	(237)	S
1q21	*GBA*	Glucocerebrosidase (GC)	Gaucher disease	(35, 341, 412)	S
Xq13.1	*GJB1*	Connexin 32 (Cx32)	X-linked Charcot-Marie-Tooth disease (CMTX)	(258, 420, 510)	S
15q24.1	*HEXA*	Beta-hexosaminidase alpha subunit	Tay-Sachs	(281, 318, 341)	S
4p16.3	*HTT*	Huntingtin	Huntington's disease	(34, 114, 563)	D
18q11–12	*NPC1*	Niemann-Pick type C 1 (NPC1), sterol transporting protein	Niemann-Pick type C disease	(155, 525)	S

Chromosomal Locus	Gene	Protein	Disease	Reference Nos.	Class
6q25.2–27	*PARK2*	Parkin	Autosomal recessive juvenile Parkinsonism (AR-JP)	(361, 368, 413)	M
Xq22	*PLP1*	Proteolipid protein (PLP) DM20 (splice isoform)	Pelizaeus-Merzbacher disease (PMD)/spastic paraplegia type 2 (SPG-2)	(166, 271)	S
17p12	*PMP22*	Peripheral myelin protein 22 (PMP22)	Charcot-Marie-Tooth disease type 1A	(138, 139, 418)	S
3q21–24	*RHO*	Rhodopsin	Retinitis pigmentosa	(167, 168, 216, 266)	S
3q26.1	*SERPINI1*	Neuroserpin	Familial encephalopathy with neuroserpin inclusion bodies (FENIB)	(273, 569)	S
9q34	*TOR1A*	Torsin A	Early-onset torsion dystonia	(160, 348)	S
Respiratory					
7q31.2	*CFTR*	Cystic fibrosis transmembrane conductance regulator (CFTR)	Cystic fibrosis (CF)	(229, 536)	S
8q21	*SFTPC*	Surfactant protein C (SP-C)	Interstitial lung disease	(108, 526)	S
Urinary					
12q12–13	*AQP2*	Aquaporin 2	Nephrogenic diabetes insipidus (NDI)	(202, 480)	S
Xq28	*AVPR2*	V2 vasopressin receptor 2 (V2R)	Nephrogenic diabetes insipidus (NDI)	(441)	S
4q21.1	*PKD2*	Polycystin 2	Autosomal dominant polycystic kidney disease type 2 (ADPKD)	(150, 296)	S
17q21–22	*SLC4A1*	Kidney chloride/bicarbonate anion exchanger (kAE1)	Autosomal recessive renal tubular acidosis	(252)	S
Toxins					
		Cholera toxin A1 subunit (*Vibrio cholerae)*	Cholera	(410, 488, 499)	C
		Exotoxin A (*Pseudomonas aeruginosa)*	Respiratory/urinary tract infections	(13, 263)	C
		Pertussis toxin (*Bordetella pertussis*)	Whooping cough	(552)	C
		Ricin A chain (*Ricinus communis)*	Ricin poisoning	(294, 453, 460)	C
		Shiga toxin (SHT) (*Shigella dysenteriae)*	Shigellosis	(575)	C

Chromosomal Locus	Gene	Protein	Disease	Reference Nos.	Class
		Shiga-like toxins (SLT-I and -II) (*Escherichia coli*)	Hemolytic uremic syndrome (HUS)	(280)	C

The proteins listed in the table are either ERAD substrates (S), proteins that are part of the ERAD machinery (M), mutant proteins that result in a defect in ERAD (D), or proteins that coopt ERAD to subvert host immunity and cause disease (C). Inclusion in the table requires a clear demonstration of the involvement of ERAD. For ERAD substrates (S), a mutant form of the protein must have been shown to be degraded in a proteasome-dependent manner coupled with either ER retention and/or ubiquitination. Common abbreviations for each protein and disease are indicated in parentheses. In some cases, a single mutant protein is known to result in multiple forms of a disease, and this is denoted by a forward slash separating the two pathologies in the disease column.

Table 2

Select experimental compounds used to rescue disease-related ERAD substrates

Protein	Compound	Reference Nos.
Alpha-1-antitrypsin (AT)		
	Carbamazepine (CBZ)	200
	4-Phenylbutyric acid (PBA)	64
Alpha-D-galactosidase (α-Gal A)		
	1-Deoxy-galactonojirimycin (DGJ)	36, 122, 179
Aquaporin 2 (APQ2)		
	Dimethyl sulfoxide (DMSO)	479
	Glycerol	479
	Trimethylamine-*N*-oxide (TMAO)	479
Beta-hexosaminidase alpha subunit		
	Bisnaphthalimide	497
	Celastrol	341
	DMSO	497
	N-acetylglucosamine thiazoline	318, 498
	Nitro-indian-1-one	497
	Pyrrolo[3,4-d]pyridazin-1-one	497
	Pyrimethamine	318
Cystic fibrosis transmembrane conductance regulator (CFTR)		
	Benzoquinolizinium compounds	109, 471
	Betaine	583
	Corrector-4a	170, 171, 532
	Curcumin	38, 115, 529, 577
	Glycerol	57, 426
	MG-132	229, 536
	Myo-inositol	208, 583
	S-nitrosoglutathione	208, 579
	PBA	415, 416, 454
	Suberoylanilide hydroxaic acid (SAHA)	215
	Sorbitol	208
	Taurine	208, 583
	TMAO	57, 130, 208
Glucocerebrosidase (GC)		
	Celastrol	341
	Dantrolene	364, 521
	Diltiazem	364
	N-(*n*-nonyl)deoxynojirimicin (DNJ)	428, 429
	MG-132	341, 521

Protein	Compound	Reference Nos.
Human ether-a-go-go-related gene (HERG) protein		
	Astemizole	126, 127, 590
	Cisapride	127, 590
	Methanesulfonanilide, E-4031	127, 590
P-glycoprotein (P-gp)		
	Capsaicin	311
	Corrector-4a	533
	Curcumin	533
	Cyclosporin	310, 311, 533
	Verapamil	310, 311
	Vinblastine	310, 311
Rhodopsin		
	11-*cis*−7-ring retinal	354
Sulfonylurea receptor 1 (SUR1)		
	Diazoxide	373
Transthyretin (TTR)		
	Benzoxazole, Tafimidis	403
	Diclofenac	255
	Flufenamic acid	255
	Resveratrol	255
Tyrosinase		
	LLnL (proteasome inhibitor)	177
V2 vasopressin receptor (V2R)		
	SR121463A (V2R antagonist)	337

Several different classifications of small molecules have been used to rescue ERAD substrates, including pharmacological and chemical chaperones, and proteostatic regulators, such as heat-shock and stress-inducing agents, transcriptional regulators, ion channel inhibitors, and proteasome inhibitors. However, in some cases precise placement into these groups is difficult as the exact mechanism of action is unknown and/or the compound may have multiple effects (see text for additional details). The references included in the table are those that demonstrate a connection between the protein and ERAD and are not necessarily the first studies to describe the molecular basis of a particular disease.