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Chaperoning Endoplasmic Reticulum–Associated Degradation (ERAD) and Protein Conformational Diseases

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Misfolded proteins compromise cellular homeostasis. This is especially problematic in the endoplasmic reticulum (ER), which is a high-capacity protein-folding compartment and whose function requires stringent protein quality-control systems. Multiprotein complexes in the ER are able to identify, remove, ubiquitinate, and deliver misfolded proteins to the 26S proteasome for degradation in the cytosol, and these events are collectively termed ER-associated degradation, or ERAD. Several steps in the ERAD pathway are facilitated by molecular chaperone networks, and the importance of ERAD is highlighted by the fact that this pathway is linked to numerous protein conformational diseases. In this review, we discuss the factors that constitute the ERAD machinery and detail how each step in the pathway occurs. We then highlight the underlying pathophysiology of protein conformational diseases associated with ERAD.

PROTEIN FOLDING, MOLECULAR CHAPERONES, AND PROTEOSTASIS

The birth of a protein begins in the cytoplasm with the emergence of a polypeptide chain from the ribosome exit tunnel. For a protein to attain its native conformation, it must navigate a complex folding landscape and endure the relentless surveillance of quality-control pathways. The information for a protein's tertiary structure is contained within its primary amino acid sequence (Anfinsen 1973), yet the growing polypeptide does not exit the ribosome in isolation. Rather, it emerges into a crowded environment filled with other proteins, lipid membranes, and cellular metabolites, which can alter the folding pathway. In addition, exposed hydrophobic side chains in soluble proteins must be shielded from solvent, whereas integral membrane proteins and proteins that enter the secretory pathway are directed to the endoplasmic reticulum (ER). Moreover, translated regions may need to interact with more carboxy-terminal regions before the native structure is attained, leaving unfolded polypeptide chains to linger in solution (van den Berg et al. 1999; Frydman 2001; Braselmann et al. 2013). Consequently, proteins are initially deposited in an energetically unfavorable environment, and there is a strong propensity to reach an unproductive or deleterious energy minimum that can give rise to toxic protein aggregates (Hartl et al. 2011).

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To overcome these challenges, a conserved and extensive network of proteins, known as molecular chaperones, are dedicated to ushering newly translated polypeptides through the folding and maturation process. Molecular chaperones also aid in the identification and elimination of polypeptides that are unable to fold (Klaips et al. 2018). Collectively, the group of diverse factors that maintain these protein homeostatic systems is known as the proteostasis network (Sala et al. 2017). Although there is an enormous investment of cellular resources dedicated to maintaining proteostasis, some protein-folding errors are unrecognized or the machinery that comprises the proteostasis network malfunctions. In turn, some misfolded proteins are prematurely captured and destroyed before they can fold. These phenomena lie at the heart of several protein conformational diseases in humans and have been implicated in cellular and organismal aging (Labbadia and Morimoto 2015; Higuchi-Sanabria et al. 2018).

In this review, we will first briefly discuss the biogenesis of proteins in the ER and the major chaperone classes that engage nascent polypeptides. We will then review the individual steps in the ER-associated degradation (ERAD) pathway and highlight how chaperones and other factors facilitate these steps. We conclude with a discussion of select diseases associated with this pathway.

MOLECULAR CHAPERONES PLAY CRITICAL ROLES DURING PROTEIN BIOGENESIS IN THE ER

The ER is the entry point to the secretory pathway and assembles integral membrane proteins in eukaryotes (Fig. 1). Soluble ER-directed proteins contain a signal sequence at the amino terminus. During signal sequence emergence from the ribosome, this short peptide is recognized and bound by the signal recognition particle (SRP), a ribonucleoprotein complex, which temporarily interrupts translation and directs the ribosome to the ER membrane after docking to the SRP receptor (Saraogi and Shan 2011). The SRP–SRP receptor interaction positions the polypeptide at the translocation channel, which is composed of the trimeric Sec61 protein complex along with several regulatory subunits (Rapoport 2007). After SRP dissociates, translation continues, and Sec61 allows passage of the polypeptide into the ER or, for membrane proteins, into the ER bilayer by virtue of a lateral gate in Sec61 (Osborne et al. 2005). The signal sequence is cleaved inside the ER by signal peptidase. In contrast, the first transmembrane helix (TMH) in integral membrane proteins often serves as a signal sequence and in most cases is not cleaved (Shao and Hegde 2011).

Proteins that enter the ER progress through several maturation steps that require the addition, formation, and/or modification of sugar moieties, *cis–trans* prolyl isomers, disulfide bonds and—for integral proteins—the adoption of complex transmembrane topologies (Braakman and Bulleid 2011). An Hsp70 molecular chaperone, known as BiP (Gething 1999), is a central player in ER homeostasis. Hsp70s have two allosterically linked functional domains, a substrate-binding domain that interacts with short stretches of hydrophobic residues, and an ATP-binding domain that drives a conformational change in the protein via ATP hydrolysis to regulate substrate-binding affinity (Hageman et al. 2011; Zhuravleva et al. 2012; Zuiderweg et al. 2013). By associating with exposed hydrophobic patches, Hsp70s, like BiP, shield a polypeptide from aggregating until productive intramolecular interactions occur (Mayer and Bukau 2005; Otero et al. 2010; Young 2010; Mayer 2013). This is especially important given the vectorial nature of protein translocation. In fact, BiP has also been shown to augment protein translocation (Brodsky et al. 1995; Matlack et al. 1999) as well as ERAD, as discussed below. More recently, the reversible oligomerization of BiP was found to be associated with the unfolded protein load in the ER (Preissler et al. 2015), and oxidation of a key cysteine in the chaperone regulates its activity in response to oxidative stress (Wang et al. 2014). These data indicate that the activity of this chaperone also responds to the ER environment.

The peptide binding and release cycle of Hsp70 is intrinsically slow but is stimulated by Hsp40 cochaperones (Kampinga and Craig

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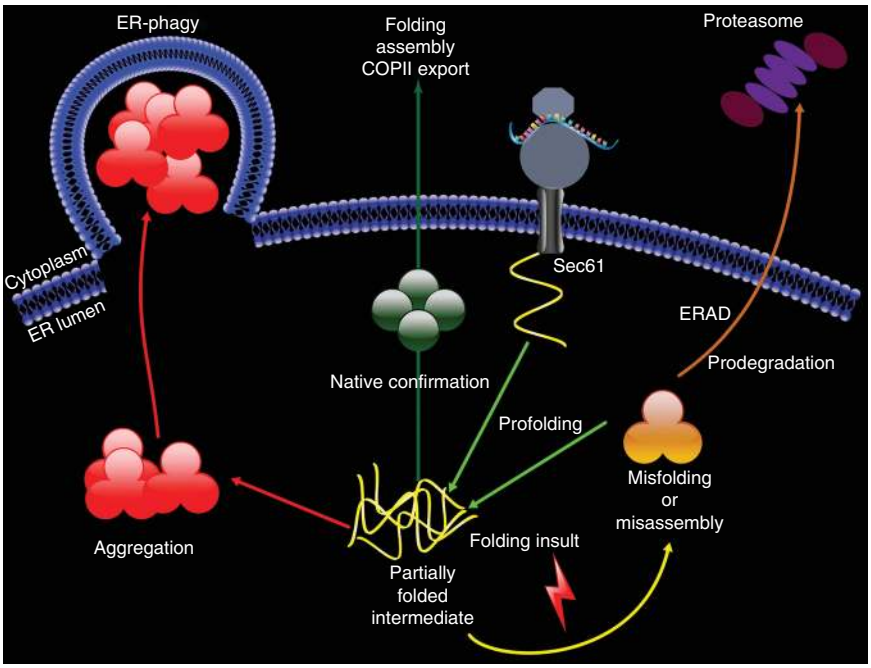

Figure 1. Nascent polypeptide biogenesis in the endoplasmic reticulum (ER). After docking at the ER membrane on the Sec61 translocation channel, the ribosome cotranslationally translocates a polypeptide (in yellow) into the ER lumen. Chaperones, including Hsp70s, Hsp40s, NEFs, lectins, disulfide isomerases, and peptidyl proline isomerase, act as "profolding" factors (see text for details). If the polypeptide acquires its native conformation and—as shown in one example, oligomerizes (in green)—it traffics from the ER in COPII vesicles. Genetic mutations, errors in transcription or translation, defects in the acquisition of posttranslational modifications, and/or ER stress can result in misfolding or a misassembled intermediate (in orange). If the substrate is unable to fold, "prodegradation" chaperones facilitate ER-associated degradation (ERAD). In contrast, partially folded intermediates can aggregate (in red) and are instead cleared by ER-phagy. One route for this pathway leads to the formation of an "omegasome," as depicted (Simonsen and Stenmark 2008). For simplicity, only a soluble ER lumenal protein is presented.

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2010; Kityk et al. 2018) and by nucleotide exchange factors (NEFs) (Bracher and Verghese 2015), both of which also reside in the ER and facilitate protein folding and quality control. Hsp40s can also bind and deliver substrates to Hsp70. Recent data indicate that Hsp40s in the ER aid in the assembly of oligomeric membrane proteins (Li et al. 2017), regulate protein translocation (Schorr et al. 2015), and differentially recognize unique motifs in nascent polypeptides, some of which are aggregation-prone (Behnke et al. 2016).

As noted above, the activity of Hsp70 chaperones is also enhanced by NEFs, and in the ER several members of this family are important during early steps in protein biogenesis. NEFs in the Hsp110/170 family resemble Hsp70 in that they contain an ATP-binding domain as well as a substrate-binding domain, but they also harbor an extended carboxy-terminal motif and acidic insertions in the substrate-binding domain (Liu and Hendrickson 2007). Like Hsp70s and Hsp40s, members of this family bind protein substrates and prevent aggregation (Park et al. 2003; Goeckeler et al. 2008; Behnke and Hendershot 2014), but the importance of this activity—at least for the cytosolic homologs—is unclear (Garcia et al. 2017). Nevertheless, conserved ER NEFs liberate bound ADP from BiP (Steel et al. 2004; Andréasson et al. 2010; Hale et al. 2010). This event drives substrate release not only because the exchange of

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bound ADP with ATP lowers peptide affinity, but because some NEFs possess a peptide-like motif that displaces the BiP-associated substrate (Rosam et al. 2018). Another recent finding is that the Sil1 NEF in yeast acts as a BiP reductant, thereby altering its substrate-binding properties after an oxidative stress has been resolved (Siegenthaler et al. 2017).

Nearly all secreted proteins contain disulfide bonds, which are formed in the more oxidizing environment of the ER and stabilize native conformations (Frand et al. 2000; Tu and Weissman 2004). To this end, protein disulfide isomerases (PDIs) catalyze the formation of disulfide bonds in nascent polypeptides (Feige and Hendershot 2011) and can associate with other chaperones, such as BiP, which deliver substrates to the PDIs (Jessop et al. 2009). One PDI family member, ERdj5, is both an Hsp40 and a PDI family member. Unlike other PDIs, ERdj5 is a reductase and helps unfold proteins before ERAD (see below) (Ushioda et al. 2008).

Most secreted and membrane proteins contain glycans, which are added cotranslationally by the action of the ER oligosaccharyltransferase (Aebi et al. 2010; Cherepanova et al. 2016). Glycosylation occurs on an asparagine in the N-X-(S/T) consensus site and serves several purposes, such as stabilizing the protein and preventing aggregation. As discussed in the next paragraph, glycans also engage ER chaperone-like lectins, which monitor protein folding (Caramelo and Parodi 2007; Pearse and Hebert 2010). Finally, glycans mediate cell–cell contact and signaling cascades when positioned on cell surface proteins.

Soon after the addition of the core glycan, which is composed of $Glc_3Man_9(GlcNAc)_2$, two of the three outer glucose residues are trimmed by glucosidases (Deprez et al. 2005). The monoglucosylated glycan is then recognized by two calcium-binding lectins, calnexin (CNX), an integral ER membrane protein associated with Sec61, and calreticulin (CRT), an ER lumenal protein (Schrag et al. 2001). Both CNX and CRT act as chaperones, stabilizing ER proteins, promoting folding, and recruiting other folding components, such as PDIs. Removal of the final glucose by another glucosidase results in release from CNX/CRT and, potentially, transport of a folded protein from the ER. However, the folding status of the released substrate is assessed by the UDP glucose glycosyltransferase (UGGT) (Sousa and Parodi 1995; Trombetta and Helenius 2000; Taylor et al. 2004; Ritter et al. 2005). If the protein has not yet folded, UGGT adds back a single glucose to the appended glycan so CNX/CRT can rebind, allowing for additional cycles of protein folding.

Another rate-limiting step during protein folding is *cis–trans* isomerization of prolines (Reimer et al. 1998), which is catalyzed by the peptidyl-prolyl isomerases (PPIs) (Schmid et al. 1993; Gothel and Marahiel 1999). Spontaneous isomerization of proline is too slow to support protein folding, and specific prolines may need to isomerize multiple times before a native conformation is achieved. Consistent with their role in protein folding, one PPI associates with both a PDI as well as a chaperone-like lectin that facilitates protein folding in the ER (Kozlov et al. 2017).

Finally, the ER in most eukaryotes contains an Hsp90 homolog, known as Grp94. Cytosolic and nuclear Hsp90s are best known for their role in the maturation of transcription factors, protein kinases, and cell surface receptors (Pratt et al. 2008; Taipale et al. 2012), which has spurred interest in the development of Hsp90 inhibitors in cancer. In the cytoplasm, Hsp70 and Hsp90 interact through a cofactor known as Hop that also regulates their activity (Johnson et al. 1998; Alvira et al. 2014). Surprisingly, however, the ER lacks a Hop homolog, and there is a relatively small number of known Grp94 substrates (Ansa-Addo et al. 2016).

Overall, molecular chaperones assemble into large multifunctional complexes, which augment protein folding and other processes (Freilich et al. 2018; Joshi et al. 2018). This is especially critical in the ER, which receives, sorts, and posttranslationally modifies one-third of the eukaryotic proteome. However, the efficiency of the ER-folding machinery is not foolproof, and when errors in posttranslational modification occur or mutations compromise protein folding, aberrant species must be removed or cellular homeostasis will fail. Somewhat surprisingly, some

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of the same chaperones dedicated to the folding of nascent polypeptides in the ER also become essential recognition components of the degradation machinery (Brodsky 2007). However, by associating with proteins during folding, chaperones are in a prime position to identify when a protein has failed to reach its native state. The switch from a profolding to a prodegradative function may be based on interactions with different motifs in the protein or by differential association with cofactors. The mechanism of how this switch is made is not understood, but, as discussed above, glycosylation can act as a switch (Roth and Zuber 2017). Notably, slow-acting mannosidases interrupt CNX/CRT binding and impart a time frame for folding (Liu et al. 1999; Kanehara et al. 2007). Specifically, after the initial removal of mannose, an unfolded protein becomes a substrate for the ER degradation-enhancing mannosidase (EDEM) (Molinari et al. 2003; Oda et al. 2003; Clerc et al. 2009). EDEM binding results in further glycan processing and ERdj5 recruitment (see above), which breaks disulfide bonds in preparation for ERAD (Ushioda et al. 2008; Ninagawa et al. 2014). At this point, the commitment to degradation has been made and EDEM hands a substrate to the OS9 or XTP3-B lectin, which escorts it to the ERAD machinery (Christianson et al. 2008; van der Goot et al. 2018). There is also evidence of spatial separation of the mannosidases, which allow folding attempts to occur before mannose trimming (Pan et al. 2013; Benyair et al. 2015). Nevertheless, some proteins in the ER are not glycosylated. In some of these cases, the lectins still function as ER quality-control gatekeepers, and in other cases alternate mechanisms of substrate recognition exist or recognition is mediated by BiP (Brodsky et al. 1999; Okuda-Shimizu and Hendershot 2007; Ushioda et al. 2013).

ENDOPLASMIC RETICULUM QUALITY CONTROL AND ERAD

The clearance or repair of misfolded proteins in the ER depends on ERAD as well as the unfolded protein response (UPR) and ER-phagy (Fig. 1). The UPR has been reviewed in detail elsewhere (see, for example, Karagöz et al. 2018; Preissler and Ron 2018), but in brief this transcriptional response is activated by the accumulation of misfolded proteins in the ER and triggered by integral ER membrane sensors. The UPR mitigates stress by slowing general protein translation, thus reducing the protein load in the ER while simultaneously up-regulating factors that facilitate the folding or clearance of misfolded species, including ERAD-requiring factors (Travers et al. 2000). However, continued ER stress shifts the UPR from a protective to a proapoptotic pathway, which underlies the pathology of numerous diseases. In contrast, ER-phagy selectively removes portions of the ER after the UPR has been resolved (Schuck et al. 2014) or more directly targets substrates via recently identified ER-phagy receptors (Smith and Wilkinson 2017). Select ERAD substrates become substrates for ER-phagy when overexpressed (Kruse et al. 2006b; Ishida et al. 2009), but to date it is unclear whether these substrates are targeted for autophagy after retrotranslocation and aggregation in the cytoplasm or through encapsulation of ER fragments (Fig. 1).

ERAD takes place in distinct yet coordinated steps (Fig. 2). First, misfolded substrates are recognized, which is followed by substrate tagging via the conjugation of a polyubiquitin motif. Acquisition of this motif serves as a signal for the energy-dependent extraction of the substrate from the ER as well as its subsequent delivery to the proteasome (Meusser et al. 2005; Vembar and Brodsky 2008; Araki and Nagata 2011; Smith et al. 2011; Ruggiano et al. 2014; Pisoni and Molinari 2016; Berner et al. 2018).

ERAD substrates are recognized by molecular chaperones and the chaperone-like lectins discussed above. Chaperone-based recognition takes advantage of surface-exposed, hydrophobic polypeptides that should be sequestered within the protein interior. Early results implicated BiP as a partner of misfolded or orphaned proteins in mammalian cells (Bole et al. 1986; Knittler et al. 1995), and later genetic studies in yeast directly implicated BiP in ERAD substrate selection (Plemper et al. 1997; Brodsky et al. 1999; Kabani et al. 2003). The contributions of Hsp40 partners (Nishikawa et al. 2001) and NEFs (Buck et al. 2013; Williams et al. 2015)

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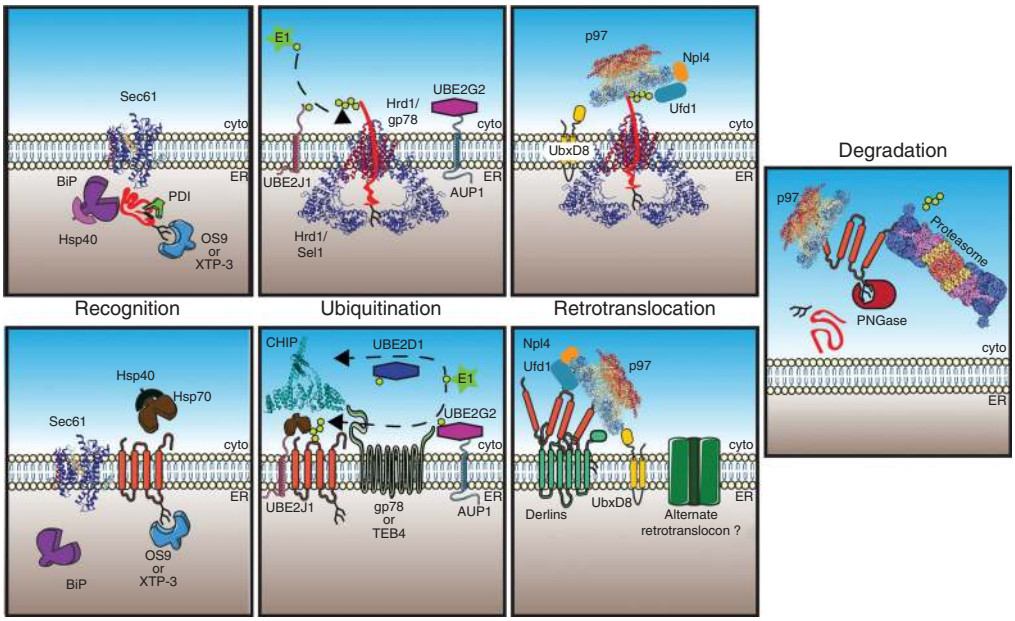

Figure 2. Endoplasmic reticulum-associated degradation (ERAD) of lumenal and integral membrane substrates. (*Top*) During translocation through Sec61 (RCSB PDB 3JC2), a soluble ERAD substrate (in red) encounters BiP, which aids in polypeptide folding and translocation across the membrane. BiP activity is enhanced by ER lumenal Hsp40s. The polypeptide can be modified by the formation of disulfide bonds by protein disulfide isomerases (PDIs) and by addition of *N*-linked glycans, which are bound by lectins such as OS9 or XTP-3 (in mammals). If the polypeptide fails to fold, it is transferred to Hrd1. The E3 ligase/RING domain of Hrd1 is located in the cytoplasm, so lumenal substrates must be partially retrotranslocated for ubiquitin conjugation, which occurs via an enzymatic cascade that includes an E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme such as UBE2G2/AUP1 or UBE2J1), and E3 (ubiquitin ligase such as Hrd1 or gp78), which build a polyubiquitin chain (lime hexagons) on the substrate. AUP1 tethers the E2 to the ER membrane and functions analogously to Cue1 in yeast. Following ubiquitination, the substrate is bound by the p97 (RCSB PDB 5C1A) complex, which is recruited to the membrane by UbxD8 and interacts with the substrate via ubiquitin-binding partners Ufd1 and Npl1. (*Bottom*) Integral membrane ERAD substrates (in orange) may also interact with BiP, but also have access to cytoplasmic chaperones such as Hsp70-Hsp40 that recognize folding lesions. Cytoplasmic lysines are then polyubiquitinated by E3 ligases such as TEB4, gp78, and/or CHIP (cyan, RCSB PDB 2C2L) in mammals. The p97–Ufd1–Npl1 heterotrimer is recruited by UbxD8 and, in some cases, Derlin family members, which facilitate retrotranslocation. The nature of the retrotranslocon channel (green) for membrane proteins is not established. Finally, the retrotranslocated protein can be deglycosylated by PNGase, followed by delivery to the 26S proteasome (RCSB PDB 4CR2), deubiquitinated by components in the 19S particle (purple/blue), and proteolyzed in the 20S core particle (yellow/salmon).

during BiP-mediated selection and the maintenance of substrate solubility underscores the importance of chaperone-based complexes in promoting both folding and ERAD.

In the second step, the identified substrate is ubiquitinated. Ubiquitin is a 76-amino-acid protein that forms isopeptide-linked polyubiquitin chains, which serve as a signal for proteasome-mediated degradation during ERAD (Preston and Brodsky 2017). Ubiquitin is primed for addition to misfolded proteins by an enzymatic cascade starting with a ubiquitin-activating enzyme (E1). Next, ubiquitin becomes covalently linked to a ubiquitin-conjugating enzyme (E2) before a ubiquitin ligase (E3) catalyzes the final transfer of ubiquitin to exposed lysine residues in the targeted substrate (Deshaies and Joazeiro 2009; Finley 2009). In yeast, where ERAD was first defined and has been extensively studied, there are two ER-localized E3 ligases associated

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with this pathway, Hrd1 (Wilhovsky et al. 2000) and Doa10 (Swanson et al. 2001), but the contributions of other E3s were uncovered more recently (Kohlmann et al. 2008; Stolz et al. 2013; Foresti et al. 2014). As anticipated, based on the greater number of potential ERAD substrates, the list of ERAD-contributing E3s in mammals is significantly longer (Claessen et al. 2012; Olzmann et al. 2013a).

Based on the specific site of the misfolded lesion within a protein, different branches of the ERAD pathway have been described (Huyer et al. 2004; Vashist and Ng 2004; Carvalho et al. 2006; Denic et al. 2006). These distinctions are most clearly defined in yeast but are somewhat blurred in mammalian cells (Bernasconi et al. 2010). Nevertheless, the term ERAD-L has been used to designate a soluble protein within the ER lumen or an ER membrane–associated protein with a misfolded domain facing the lumen. Hrd1 is the E3 ubiquitin ligase used for ERAD-L. Other factors that recognize and transfer substrates from lumenal chaperones to Hrd1 or stabilize the Hrd1 complex include the Derlins (Knop et al. 1996), Usa1 (Horn et al. 2009; Carroll and Hampton 2010) or HERP in mammals (Okuda-Shimizu and Hendershot 2007), and Hrd3 (or Sel1 in mammals) (Gardner et al. 2000; Mueller et al. 2008; Vashistha et al. 2016). Hrd3 interacts with BiP as well as an Hsp40 partner and even shows chaperone-like properties (Mehnert et al. 2015), which may help retain a misfolded protein in solution before retrotranslocation.

An ER membrane protein with a misfolded cytoplasmic-facing domain is inaccessible to ER resident chaperones. In this case, recognition requires cytoplasmic chaperones, and a different E3 ligase, Doa10, is used along with a distinct set of E2-conjugating enzymes and cofactors in yeast (Vashist and Ng 2004; Carvalho et al. 2006; Ravid et al. 2006). This route is known as ERAD-C, and the recognition and ubiquitination of ERAD-C substrates depends on Hsp70 and Hsp40 partners (Youker et al. 2004; Han et al. 2007; Nakatsukasa et al. 2008). More recently, the yeast cytosolic protein disaggregase, Hsp104, was shown to enhance the degradation of an aggregation-prone ERAD-C substrate (Preston et al. 2018). Based on the diversity of potential ERAD-C substrates (i.e., membrane proteins with cytoplasmic domains), it is likely that other recognition factors exist.

The identification of integral membrane proteins with folding lesions within the lipid bilayer is especially problematic as no classical chaperones have been identified that possess this activity. However, a single-pass transmembrane protein with low hydrophobicity was transiently displaced into the ER lumen in which BiP could bind and facilitate ERAD (Feige and Hendershot 2013). For more firmly anchored membrane proteins, the Hrd1 ubiquitin ligase, along with the associated Hrd3 cofactor, appears to bind and then ubiquitinate these ERAD-M substrates (Sato et al. 2009). Nevertheless, based on the complex nature of membrane proteins, which deposit domains in three unique chemical environments (i.e., the ER, the lipid bilayer, and the cytosol), it is likely that most misfolded integral membrane proteins will follow more than one of these three ERAD pathways (see, for example, Buck et al. 2010).

Once selected, ERAD substrates are transported or retrotranslocated from the ER lumen or membrane back to the cytosol where they are delivered to and degraded by the 26S proteasome. Initially, it was assumed that an ER resident protease handled misfolded ER proteins (Needham and Brodsky 2013), but it subsequently became evident that aberrant soluble and even membrane proteins are retrotranslocated to the cytosol for disposal (Hiller et al. 1996; McCracken and Brodsky 1996; Wiertz et al. 1996; Plemper et al. 1997; Nakatsukasa et al. 2008; Garza et al. 2009). Initially, the Sec61 translocation channel was the best candidate for a retrotranslocation channel (Pilon et al. 1997; Romisch 1999), and more recently an ER metalloprotease was shown to help clear substrates that become trapped in Sec61 caused by the premature folding of a cytoplasmic domain (Ast et al. 2016). Hrd1 is involved in the destruction of similar substrates (Rubenstein et al. 2012). Other work suggested that the Derlins might be the retrotranslocation channel, or at least act as a major contributor to retrotranslocation (Lilley and Ploegh 2004; Ye et al. 2004;

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Wahlman et al. 2007; Greenblatt et al. 2011; Mehnert et al. 2014). However, more recent data are consistent with Hrd1 acting as both a ligase and a retrotranslocation channel, at least for soluble substrates (Baldridge and Rapoport 2016; Schoebel et al. 2017). It also remains possible that integral membrane proteins are extracted directly from the lipid bilayer or are somehow solubilized within the bilayer and retrotranslocated without the aid of a channel (Avci and Lemberg 2018).

The force to pull substrates from the ER is provided by the AAA-ATPase Cdc48 in yeast or the homologous p97 protein in mammals (Bays et al. 2001; Rabinovich et al. 2002; Ye et al. 2004). Hexameric, chaperone-like AAA-ATPase ring structures form components of multichaperone complexes and proteolytic machines. In general, this class of proteins act as force-generating engines in numerous energy-dependent processes, such as protein degradation and disaggregation and DNA and lipid remodeling (Mogk et al. 2008; Sauer and Baker 2011; van den Boom and Meyer 2018). Cdc48/p97 functions in a complex with Ufd1 and Npl4, which recognize polyubiquitinated substrates and bind several components at the ER membrane (Stolz et al. 2010; Buchberger et al. 2015; Neal et al. 2018). The appended polyubiquitin chain not only marks the substrate for proteasome-dependent degradation, but Cdc48 uses this motif as a handle (and the ER membrane as an anchor) for substrate retrotranslocation by coupling ATP hydrolysis to drive the motor. Only a few substrates can be extracted in a ubiquitin-independent manner, and in this case AAA-ATPases in the proteasome are sufficient (Lee et al. 2004). A recent study also reported that more hydrophobic transmembrane domains were less efficiently retrotranslocated, suggesting that degradation at the ER, perhaps via clipping by integral membrane proteases (Loureiro et al. 2006; Fleig et al. 2012), contributes to retrotranslocation/degradation (Guerriero et al. 2017). Other recent data indicate that polyubiquitinated substrates are threaded through the Cdc48 core after partial deubiquitination (Bodnar and Rapoport 2017). Whether species with shorter polyubiquitin chains interact efficiently with the proteasome or whether another round of polyubiquitination is needed is unknown.

After a polyubiquitinated substrate is removed from the ER, it is delivered to the proteasome with the help of the Rad23 and Dsk2 shuttling factors (Medicherla et al. 2004). In some cases, appended glycans are removed by a protein *N*-glycanase (PNGase) before proteasome delivery (Hirayama et al. 2015). Rad23 also interacts with this enzyme (Kim et al. 2006), suggesting that delivery is coupled with glycan removal, which might otherwise impede proteasome entry. The proteasome has a barrel-like catalytic core housing two copies of three unique proteases (Voges et al. 1999; Bard et al. 2018), and entry into a narrow aperture at the end of the barrel is regulated by the 19S "cap," which itself recognizes ubiquitinated substrates and possesses deubiqutinating enzymes as a substrate is fed into the proteasome core for degradation (Finley 2009; Liu and Ye 2012).

REGULATION OF PROTEIN ABUNDANCE BY ERAD

The ER serves as a portal for residents of the ER, Golgi, lysosome, and plasma membrane, as well as secreted proteins. Included among this diverse group of substrates are hormones, enzymes, cell surface receptors, and nutrient and ion transporters and channels. This positions the ER as a potential regulator of downstream pathways (Halperin et al. 2014). Indeed, ERAD is implicated not only in quality control but in quantity control (Printsev et al. 2017). For example, HMG-CoA reductase catalyzes the rate-limiting step in cholesterol biosynthesis and is the target of cholesterol- lowering statins (Goldstein and Brown 1990). The appearance of sterol end products or biosynthetic intermediates leads directly to the acquisition of a structurally disordered form of the enzyme, which triggers ubiquitination and ERAD (Jo and Debose-Boyd 2010; Wangeline et al. 2017). Other enzymes in the sterol and lipid droplet biosynthetic pathway are also regulated by ERAD (Foresti et al. 2013; Olzmann et al. 2013b; Ruggiano et al. 2016). Another example of regulated degradation occurs when the ERAD pathway is hijacked by a

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viral pathogen. The human cytomegalovirus (HCMV) genome encodes several proteins that reduce surface expression of major histocompatibility class I (MHC-1), thus disabling of the host immune response. MHC-1 degradation is induced via an ERAD-like pathway that requires select HCMV gene products. A similar situation exists after HIV infection (Morito and Nagata 2015; van den Boomen and Lehner 2015). Interestingly, none of these processes require molecular chaperones, consistent with the idea that ERAD-mediated quality and quantity control can proceed via distinct routes.

In contrast, the metabolic regulation of apolipoprotein B (ApoB), a protein component of chylomicrons, very low-density lipoproteins (VLDLs), and LDLs (Fisher and Ginsberg 2002), is chaperone-dependent. When lipid availability is limited, the cotranslational translocation of ApoB through Sec61 is halted and the protein is instead routed for ERAD in an Hsp70, Hsp90, and PDI-dependent manner (Fisher et al. 1997; Gusarova et al. 2001; Grubb et al. 2012); the PDIs also play a role in ApoB lipidation (Wang et al. 2015). Interestingly, the Hsp110 chaperone, which shows substrate-binding activity and functions as an NEF (see above), protects ApoB, potentially acting as a holdase as the protein translocates into the ER (Hrizo et al. 2007).

ERAD SUBSTRATE RECOGNITION

As outlined above, ERAD substrate recognition requires chaperones and chaperone-like lectins, but the biochemical and biophysical features of a misfolded protein or an orphaned subunit that are sufficient for ERAD targeting are poorly defined. Simply exposing hydrophobic motifs favors chaperone binding, but whether the chaperone now plays a profolding or prodegradative role clearly requires other events, which were discussed in the previous section. Nevertheless, the presence of an aggregation-prone domain was recently shown to support ERAD-C targeting (Preston et al. 2018), and studies on a related substrate indicated that aggregation propensity influences whether a substrate is delivered to the ERAD or lysosomal/vacuolar degradation pathway (Sun and Brodsky 2018). However, aggregation propensity for many ERAD-L substrates may be less relevant as the ER has an unusually robust capacity to prevent protein aggregation compared with the cytosol (Rousseau et al. 2004; Vincenz-Donnelly et al. 2018). Thus, the ER provides a protective environment in which most aggregation-prone proteins remain soluble for recognition by chaperones and lectins. Nevertheless, several proteins can still aggregate or illegitimately oligomerize in the ER and undergo ER-phagy (Kruse et al. 2006a,b; Ishida et al. 2009).

PROTEIN CONFORMATIONAL DISEASES AND ERAD

In principle, proteins can adopt a stunning array of conformations during folding—estimated to be as high as 10^{300} (Levinthal 1969; Karplus 1997)—and given the diverse conformations of secreted proteins and the preponderance of genetic mutations it is not unreasonable to imagine that many of the ~6700 secretory proteins in humans may be a harbinger of disease. To date, 64 diseases in which the conformationally defective protein is destroyed by ERAD are known (Table 1). For inclusion, a mutant protein associated with a human disease must be retained in the ER and stabilized by treatment with a proteasome inhibitor and/or is polyubiquitinated. In contrast to a more extensive previous list (Guerriero and Brodsky 2012), we excluded toxins that masquerade as ERAD substrates and diseases associated with the ERAD-like action of viral pathogens.

The manifestation of a protein conformational diseases depends on how a mutation alters the structure and function of the gene product. Loss-of-function mutations that lead to conformational diseases usually result in protein misfolding and/or defects in multiprotein complex assembly. For proteins that enter the ER, the most common outcome is ERAD.

A mutant form of the cystic fibrosis transmembrane conductance regulator (CFTR) was the first disease-causing/loss-of-function protein linked to ERAD (Cheng et al. 1990; Jensen et al. 1995; Ward et al. 1995). CFTR is a member of the ATP-binding cassette (ABC) family,

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Table 1. Resource list in which disease-associated proteins are destroyed ERAD

Chromosomal locus	Gene	Protein	Disease	References
Receptors				
11p15.1	*ABCC8*	Sulfonylurea receptor 1 (SUR1)	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)	Taschenberger et al. 2002; Yan et al. 2005, 2010
4q21.21	*ANTXR2*	Anthrax toxin receptor 2	Hyaline fibromatosis syndrome	Deuquet et al. 2009, 2011
Xq28	*AVPR2*	V2 vasopressin receptor 2 (V2R)	Nephrogenic diabetes insipidus (NDI)	Schwieger et al. 2008
3q13	*CASR*	Calcium-sensing receptor (CasR)	Familial hypocalciuric hypercalcemia (FHH) in heterozygotes	Huang et al. 2006; Pidasheva et al. 2006; Huang and Breitwieser 2007
3q13	*CASR*	Calcium-sensing receptor (CasR)	Neonatal severe hyperparathyroidism (NSHPT) in homozygotes	Huang et al. 2006; Pidasheva et al. 2006; Huang and Breitwieser 2007
5q34	*GABRA1*	γ-amino butyric acid receptor (GABAR) α1	Juvenile myoclonic epilepsy	Gallagher et al. 2007; Bradley et al. 2008
5q34	*GABRA1*	γ-amino butyric acid receptor (GABAR) α1	Childhood absence epilepsy (CAE)	Kang et al. 2009b
5q34	*GABRG2*	γ-amino butyric acid receptor (GABAR) γ2	Generalized epilepsy with febrile seizures plus ($GEFS^+$)	Kang et al. 2009a
4q13.2	*GNRHR*	Gonadotropin-releasing hormone (GnRH) receptor	Hypogonadotropic hypogonadism	Brothers et al. 2004; Houck et al. 2014
19p13.3-13.2	*INSR*	Insulin receptor	Insulin resistance syndrome (type 2 diabetes)	Kadowaki et al. 1991; Accili et al. 1992; Imamura et al. 1998; Ramos et al. 2007
19p13.3	*LDLR*	Low-density lipoprotein receptor (LDLR)	Familial hypercholesterolemia	Lehrman et al. 1987; Jensen et al. 1997; Li et al. 2004
3p22-21.1	*PTH1R*	Parathyroid hormone receptor (PTHR)	Parathyroid hormone resistance	Alonso et al. 2011
10q11.2	*RET*	RET receptor tyrosine kinase	Hirschprung disease	Kjaer and Ibáñez 2003; Kjaer et al. 2010
3q21-24	*RHO*	Rhodopsin	Retinitis pigmentosa	Illing et al. 2002; Griciuc et al. 2010a,b
Transporters				
7q21.1	*ABCB4*	ATP-binding cassette, subfamily B, member 4 (MDR3)	Progressive familial intrahepatic cholestasis type 3 (PFIC3)	Delaunay et al. 2009; Gautherot et al. 2012; Gordo-Gilart et al. 2016; Park et al. 2016
2q24	*ABCB11*	Bile salt export pump (BSEP)	Progressive familial intrahepatic cholestasis type II (PFIC II)	Hayashi et al. 2005; Mochizuki et al. 2007; Wang et al. 2008
16p13.1	*ABCC1*	P-glycoprotein	Implications for cancer treatment	Loo and Clarke 1998

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Table 1. *Continued*

Chromosomal locus	Gene	Protein	Disease	References
10q24	*ABCC2*	Multidrug resistance protein 2 (MRP2)	Dubin–Johnson syndrome	Hashimoto et al. 2002; Keitel et al. 2003
4q22	*ABCG2*	Breast cancer resistance protein	Implications for cancer treatment	Nakagawa et al. 2008, 2009; Furukawa et al. 2009; Sugiyama et al. 2011
13q14.3	*ATP7B*	Copper transporting P-type ATPase	Wilson disease	Harada et al. 2001; Huster et al. 2003; de Bie et al. 2007; van der Velden et al. 2010
1p36	*ATP13A2*	ATPase type 13A2 cation transporter	Kufor–Rakeb syndrome (KRS)/ Parkinson's disease 9	Ugolino et al. 2011
Channels				
12q12-13	*AQP2*	Aquaporin 2	Nephrogenic diabetes insipidus (NDI)	Tamarappoo et al. 1999; Hirano et al. 2003
7q31.2	*CFTR*	Cystic fibrosis transmembrane conductance regulator (CFTR)	Cystic fibrosis (CF)	Jensen et al. 1995; Ward et al. 1995
7q36.1	*KCNH2*	Human ether-a-go-go-related gene (HERG) voltage-gated potassium channel	Congenital long QT syndrome	Zhou et al. 1998, 1999; Furutani et al. 1999; Gong et al. 2005; Walker et al. 2010
11q24.3	*KCNJ1*	Renal outer medullary potassium channel (ROMK)	Bartter syndrome	O'Donnell et al. 2017a,b
11p15.5-15.4	*KCNQ1*	Potassium voltage-gated channel subfamily Q member 1	Long QT syndrome	Gouas et al. 2004; Dahimene et al. 2006; Peroz et al. 2009; Huang et al. 2018
4q21.1	*PKD2*	Polycystin 2	Autosomal dominant polycystic kidney disease type 2 (ADPKD)	Liang et al. 2008; Gao et al. 2010
3p22.2	*SCN5A*	Cardiac sodium channel (SCN5A)	Brugada syndrome	Baroudi et al. 2002, 2004; Lin et al. 2008; Shao et al. 2009; Clatot et al. 2012
17q21-22	*SLC4A1*	Kidney chloride/bicarbonate anion exchanger (kAE1)	Autosomal recessive renal tubular acidosis	Kittanakom et al. 2004; Patterson and Reithmeier 2010; Chu et al. 2014
Secreted/other				
2p24-23	*APOB*	Apolipoprotein B (Apo B)	A-β-lipoproteinemia	Yeung et al. 1996; Liao et al. 1998; Liang et al. 2003; Burnett et al. 2007
20p13	*AVP*	Vasopressin precursor protein	Autosomal-dominant neurohypophyseal diabetes insipidus (ADNDI)	Ito and Jameson 1997; Nijenhuis et al. 1999; Friberg et al. 2004
11q13	*BSCL2*	Seipin	Silver's syndrome/distal hereditary motor neuropathy type V	Ito and Suzuki 2007

Continued

Table 1. *Continued*

Chromosomal locus	Gene	Protein	Disease	References
17q21.33	*COL1A1*	Type I procollagen pro-α1 chain	Osteogenesis imperfecta	Lamandé et al. 1995; Fitzgerald et al. 1999; Ishida et al. 2009
2p13.3	*DYSF*	Dysferlin	Limb girdle muscular dystrophy type 2B/ Miyoshi myopathy (LBMD2B/MM)	Fujita et al. 2007
19p13.3	*Elane*	Neutrophil elastase	Severe congenital neutropenia (SCN)	Kollner et al. 2006; Grenda et al. 2007; Xia and Link 2008; Nanua et al. 2011; Nustede et al. 2016
2p12	*EIF2AK3*	Eukaryotic translation initiation factor 2α kinase 3 (PERK)	Walcott–Rallison syndrome (WRS)	Gupta et al. 2010
15q21.1	*FBN1*	Fibrillin 1	Marfan syndrome	Whiteman and Handford 2003; Chao et al. 2010
4q28	*FGB*	Fibrinogen	Hereditary hypofibrinogenemia	Xia and Redman 1999, 2001; Brennan et al. 2000; Kruse et al. 2006b
1q21	*GBA*	Glucocerebrosidase (GC)	Gaucher disease	Ron and Horowitz 2005; Mu et al. 2008; Bendikov-Bar et al. 2011
Xq13.1	*GJB1*	Connexin 32 (Cx32)	X-linked Charcot–Marie–Tooth disease (CMTX)	VanSlyke et al. 2000; Kleopa et al. 2002; Sakaguchi et al. 2011
Xq22	*GLA*	α-Galactosidase A (α-Gal A)	Fabry disease	Yam et al. 2006; Hamanaka et al. 2008
15q24.1	*HEXA*	β-Hexosaminidase α subunit	Tay-Sachs	Lau and Neufeld 1989; Maegawa et al. 2007; Mu et al. 2008
6p21.3	*HFE*	HFE protein	Hereditary hemochromatosis	Waheed et al. 1997
11p15.5	*INS*	Proinsulin	Neonatal diabetes (type 1)	Allen et al. 2004; Hartley et al. 2010; Park et al. 2010
17q23.1	*MPO*	Myeloperoxidase (MPO)	Hereditary myeloperoxidase deficiency	DeLeo et al. 1998
18q11-12	*NPC1*	Niemann–Pick type C1 (NPC1), sterol transporting protein	Niemann–Pick type C disease	Gelsthorpe et al. 2008; Wang et al. 2011
19q13.1	*NPHS1*	Nephrin mutations unfold and ER stress	Congenital nephrotic syndrome of the Finnish type	Liu et al. 2001, 2004; Drozdova et al. 2013
1q25.2	*NPHS2*	Podocin mutations unfold and ER stress	Focal segmental glomeulonecrosis (FCGS)	Roselli et al. 2004; Fan et al. 2009; Serrano-Perez et al. 2018
Xq22	*PLP1*	Proteolipid protein (PLP) DM20 (splice isoform)	Pelizaeus–Merzbacher disease (PMD)/ spastic paraplegia type 2 (SPG-2)	Gow et al. 1998; Krämer-Albers et al. 2006

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Table 1. *Continued*

Chromosomal locus	Gene	Protein	Disease	References
17p12	*PMP22*	Peripheral myelin protein 22 (PMP22)	Charcot–Marie–Tooth disease type 1A	Ryan et al. 2002; Fortun et al. 2005, 2007
2q13-14	*PROC*	Protein C	Protein C deficiency	Katsumi et al. 1996, 1998; Tokunaga et al. 1996; Nishio et al. 2008
3q11.2	*PROS1*	Protein S	Protein S deficiency	Tsuda et al. 2006
14q32.1	*SERPINA1*	α-1-Antitrypsin (AT)	α-1-Aantitrypsin deficiency	Qu et al. 1996; Teckman et al. 2001
Xq22.2	*SERPINA7*	Thyroxine-binding globulin (TBG)	Thyroxine-binding globulin deficiency	Miura et al. 1994a,b; Soheilipour et al. 2016
1q23-25.1	*SERPINC1*	Antithrombin	Type I antithrombin deficiency	Tokunaga et al. 1997, 2003
17p13	*SERPINF2*	α-2-Antiplasmin (A2AP)	α-2-Plasmin inhibitor deficiency	Chung et al. 2000; Nishio et al. 2008
11q13.5	*SERPINH1*	Heat shock protein 47 (Hsp47)	Osteogenesis imperfecta	Christiansen et al. 2010
3q26.1	*SERPINI1*	Neuroserpin	Familial encephalopathy with neuroserpin inclusion bodies (FENIB)	Kroeger et al. 2009; Ying et al. 2011
8q21	*SFTPC*	Surfactant protein C (SP-C)	Interstitial lung disease	Dong et al. 2008; Wang et al. 2009
9q34	*TOR1A*	Torsin A	Early onset torsion dystonia	Giles et al. 2008; Li et al. 2014; Zacchi et al. 2014, 2017
18q12.1	*TTR*	Transthyretin (TTR)	Familial amyloid polyneuropathy	Sekijima et al. 2005; Sato et al. 2007; Susuki et al. 2009
8q24.22	*TG*	Thyroglobulin	Congenital hypothyroid goiter	Guaraldi et al. 1991; Medeiros-Neto et al. 1996; Hishinuma et al. 1999; Kim et al. 2008
11q14-21	*TYR*	Tyrosinase (TYR)	Oculocutaneous albinism	Halaban et al. 2000; Svedine et al. 2004; Watabe et al. 2004; Ballar et al. 2011
16p12.3	*UMOD*	Uromodulin	Medullary cyst kid disease/familial juvenile hyperuricemic nephropathy	Rampoldi et al. 2003; Bernascone et al. 2006; Williams et al. 2009; Schaeffer et al. 2017
12p13.3	*VWF*	von Willebrand factor (vWF)	von Willebrand's disease type IIA	Lyons et al. 1992; Allen et al. 2000, 2001; Bodó et al. 2001

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which are made-up of two membrane-spanning domains, each with six TMHs and two cytoplasmic nucleotide-binding domains (NBDs). CFTR is unique among ABC transporters in that it is a chloride channel and contains a regulatory domain between NBD1 and MSD2. The topological complexity of CFTR combined with extensive co- and posttranslational folding result in a substantial amount of the wild-type protein and essentially all of the F508del disease-causing mutant allele being targeted for ERAD (Jensen et al. 1995; Ward et al. 1995; Kleizen et al. 2005; Thibodeau et al. 2005, 2010; Du and Lukacs 2009; Khushoo et al. 2011). In addition to the common F508del variant, ~120 other disease-causing mutations have been identified in *CFTR* (Sosnay et al. 2013), many of which also affect protein folding (Veit et al. 2016). F508del CFTR is recognized by Hsp70, Hsp40, small HSPs, and PPIs, and is then polyubiquitinated and delivered to the proteasome (Meacham et al. 1999, 2001; Youker et al. 2004; Grove et al. 2011; Hutt et al. 2012).

Cystic fibrosis patients are faced with pathologies in multiple organ systems, including the respiratory and gastrointestinal tracts and the reproductive and endocrine systems, which is caused by increased viscosity of lumenal secretions (Rowe et al. 2005; Cutting 2015). In the 29 years since the *CFTR* gene was identified (Kerem et al. 1989; Riordan et al. 1989; Rommens et al. 1989), small molecules that facilitate F508del CFTR biogenesis have been actively sought. Early work focused on nonspecific chemical chaperones that enhance the cellular folding environment (Brown et al. 1996; Sato et al. 1996; Howard et al. 2003). In addition, simply subjecting cells to low-temperature increased F508del CFTR maturation and cell surface activity, presumably by decreasing kinetic barriers during folding (Denning et al. 1992). More recently, combinations of a folding "corrector" and a channel potentiator significantly increased F508del CFTR surface expression and activity (Van Goor et al. 2009, 2011). This drug combination was approved by the Food and Drug Administration (FDA) in 2015, and even with some positive outcomes the effects in patients have shown limited efficacy and give rise to unwanted side effects (Horsley and Barry 2017). Improved corrector–potentiator combinations will undoubtedly be forthcoming. In theory, the addition of an ERAD inhibitor might further improve the efficacy of these therapeutics (Chung et al. 2016).

Under some circumstances, misfolded conformers may overwhelm or even escape the detection of quality-control pathways, resulting in a toxic gain-of-function phenotype. For example, transthyretin (TTR) is secreted into the vitreous humor by retinal pigment epithelial cells, the cerebrospinal fluid by the choroid plexus, and the bloodstream by the liver (Hamilton and Benson 2001). More than 135 mutations in TTR have been identified, which vary in their amyloidogenicity and, in turn, the age of onset and disease presentation (Connors et al. 2003; Hammarström et al. 2003; Sekijima et al. 2005). Some mutant TTR variants escape ERAD and form amyloids in the heart and peripheral nerves, which presents as TTR cardiomyopathy, familial amyloid polyneuropathy, or central nervous system amyloidosis. Mutations that destabilize the TTR tetramer are more prone to oligomerize (Hammarström et al. 2002). Interestingly, the D18G variant is one of the most highly aggregation-prone TTR forms in vitro, but gives rise to a mild disease phenotype, likely because of the protective effect of ERAD (Hammarström et al. 2003; Sekijima et al. 2003, 2005). Another TTR mutant, A25T is secreted more efficiently, and recent data indicate that an ER lumenal Hsp40 chaperone, ERdj3, escorts the mutant protein through the secretory pathway, potentially suppressing ERAD and extracellular aggregation (Genereux et al. 2015). Although a drug that stabilizes the TTR tetramer shows efficacy for some mutant alleles (Klabunde et al. 2000; Bulawa et al. 2012; Rappley et al. 2014), these data highlight a more general role for chaperones as therapeutic targets (Lindquist and Kelly 2011; Brandvold and Morimoto 2015; Li et al. 2016).

CONCLUDING REMARKS

In this review, we introduced ER quality-control pathways, highlighted the molecular chaperones and other factors required for protein folding in the ER as well as ERAD, and provided a resource

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list in which disease-associated proteins are destroyed by ERAD (Table 1). Given the magnitude of coding variations in human genome databases (Telenti et al. 2016)—and the astronomical number of possible mutations that might compromise protein folding—it is possible that any protein that enters the ER might ultimately be included in this list.

One category of disease-causing substrates we predict will increasingly be linked to ERAD is ion channels. Ion channels present cells with multiple folding challenges as they are large, show complex topologies, form hetero- or homo-oligomers, and/or contain charged residues within their membrane-spanning domains, which allows for ion permeation or voltage sensing (Green 1999). For example, the epithelial sodium channel, ENaC forms a heterotrimer of homologous α, β, and γ subunits (Buck and Brodsky 2018). In some cells, the β and γ subunits are constitutively produced and are targeted for ERAD, whereas the α subunit is only synthesized after aldosterone secretion. When expressed individually, each subunit is degraded in an Hsp40-dependent manner (Buck et al. 2010). In contrast, only the orphaned α subunit is degraded in an Lhs1/Grp170-dependent manner (Buck et al. 2013). Mutations in ENaC that alter ERAD and lead to salt-wasting have not yet been identified, but based on these complex regulatory and folding pathways—and because the assembled channel can still be degraded by ERAD (Staub et al. 1997; Valentijn et al. 1998; Malik et al. 2001)—we anticipate that syndrome-associated ENaC polymorphisms will be identified. Similarly, loss-of-function mutations in the thiazide-sensitive NaCl cotransporter, NCC, cause the salt-wasting disorder Gitelman syndrome (Simon et al. 1996). One Gitelman-causing NCC mutation truncates the cytoplasmic tail of the protein, which binds more readily to Hsp70 and Hsp40 (Donnelly et al. 2013). Future work will be required to determine whether this mutant and any of the other ∼40 disease-causing mutants is more efficiently targeted for ERAD, as these data suggest.

Although drugs have been identified to treat both loss-of-function (e.g., CFTR) and gain-of-function (e.g., TTR) diseases, these examples represent the exception rather than the rule. Thus, another important future goal is to find chemical—or better, pharmacological—chaperones that facilitate the folding of mutant proteins and prevent ERAD. Proteostasis modulators such as 4-phenylbutyric acid, celastrol, verapamil, and suberoylanilide hydroxamic acid (SAHA) have been used with some success (see Kelly 2018), and in one study the combined administration of SAHA and an ERAD inhibitor led to synergistic, corrective effects on a mutant ion channel (Han et al. 2015). One hopes that other examples of this approach will soon follow.

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