Title

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Permalink

https://escholarship.org/uc/item/5356f48q

Journal

The Journal of Membrane Biology, 250(4)

ISSN

0022-2631

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Publication Date

2017-08-01

DOI

10.1007/s00232-016-9931-0

Peer reviewed

Membrane Protein Quantity Control at the Endoplasmic Reticulum

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Abstract

The canonical function of the endoplasmic reticulum-associated degradation (ERAD) system is to enforce quality control among membrane-associated proteins by targeting misfolded secreted, intra-organellar, and intramembrane proteins for degradation. However, increasing evidence suggests that ERAD additionally functions in maintaining appropriate levels of a subset of membrane-associated proteins. In this 'quantity control' capacity, ERAD responds to environmental cues to regulate the proteasomal degradation of specific ERAD substrates according to cellular need. In this review, we discuss in detail seven proteins that are targeted by the ERAD quantity control system. Not surprisingly, ERAD-mediated protein degradation is a key regulatory feature of a variety of ER-resident proteins, including HMG-CoA reductase, cytochrome P450 3A4, IP$_3$ receptor, and type II iodothyronine deiodinase. In addition, the ERAD quantity control system plays roles in maintaining the proper stoichiometry of multi-protein complexes by mediating the degradation of components that are produced in excess of the limiting subunit. Perhaps somewhat unexpectedly, recent evidence suggests that the ERAD quantity control system also contributes to the regulation of plasma membrane-localized signaling receptors, including the ErbB3 receptor tyrosine kinase and the GABA neurotransmitter receptors. For these substrates, a proportion of the newly synthesized yet properly folded receptors are diverted for degradation at the ER, and are unable to traffic to the plasma membrane. Given that receptor abundance or concentration within the plasma membrane plays key roles in determining signaling efficiency, these observations may point to a novel mechanism for modulating receptor-mediated cellular signaling.

Keywords

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Introduction

Plasma Membrane Protein Degradation

Plasma membrane-embedded proteins serve as the interface of cells with their environment, playing critical roles in anchoring cells to their neighbors and extracellular matrix components, in partitioning ions, metabolites and macromolecules to the cell interior, and in receiving and interpreting extracellularly derived growth and homeostatic cues. To maintain the fidelity of these processes, the quantities of receptors and transporters within the plasma membrane must be very tightly regulated. While transcriptional control of the genes encoding plasma membrane proteins provides one level of regulation, over the last two decades it has become appreciated that protein degradation mechanisms can have a profound impact on the levels of plasma membrane proteins, and that disruptions in these mechanisms can lead to disease.

Liddle syndrome, a rare autosomal dominant genetic disorder characterized by early and often severe hypertension, illustrates the critical importance of the degradation of even a single plasma membrane protein in maintaining physiological homeostasis (Snyder 2002; Rotin and Kumar 2009). The epithelial sodium channel (ENaC) is localized to the apical plasma membrane of renal tubule epithelial cells, and plays key roles in sodium ion homeostasis and blood pressure maintenance by mediating sodium reabsorption. Liddle syndrome patients carry an allele encoding ENaC with alterations that decouple the channel from the protein degradation mechanisms that keep its levels in check. The resulting hyper-accumulation of ENaC protein leads to excessive sodium reabsorption, increased extracellular volume, and elevated blood pressure. Similarly, dysregulated quantity control of specific cell surface proteins has been implicated in a variety of genetic and acquired disorders, from cystic fibrosis via the underproduction of cystic fibrosis transmembrane conductance regulator (CFTR; Lukacs and Verkman 2012) to cancer via the overproduction of receptor tyrosine kinases (Carraway 2010).

Canonically, plasma membrane and secreted proteins are degraded following their endocytosis and trafficking to the lysosome. However, increasing evidence points to the possibility that the levels of some plasma membrane proteins are normally regulated by degradation at the endoplasmic reticulum. Perhaps not surprisingly, the mechanisms underlying plasma membrane protein quantity control by the ER appear to involve the same ubiquitin–proteasome machinery as those that govern the quality control of newly synthesized plasma membrane proteins.

Ubiquitination and the ERAD Pathway

The ubiquitin–proteasome system (UPS) is a crucial eukaryotic pathway that recycles unwanted or misfolded proteins to regulate systems important to cell growth, survival, and cellular homeostasis. The events that commit a protein to degradation begin with the addition of the soluble 8.6 kDa protein ubiquitin to the target protein substrate to be degraded. Ubiquitin is first covalently linked to an E1 ubiquitin-activating enzyme in an ATP-dependent manner, passed on to an E2-conjugating enzyme, and lastly, via a substrate-specific E3 ubiquitin ligase, the ubiquitin is covalently added to the substrate (Glickman and

Ciechanover 2002). Additional ubiquitin proteins (donor) modify the primary ubiquitin (recipient) via the recipient N-terminus or one of its seven lysine residues to form polyubiquitin chains (Komander and Rape 2012). The addition of a minimum of four linked ubiquitin molecules to a substrate, via the lysines at the 48th or 11th residues on the recipient ubiquitin, is a signal recognized by the 26 proteasome, thus leading the substrate to degradation (Finley 2009).

The UPS exists in the cytosol and nuclei of eukaryotic cells. However, membrane proteins and proteins existing within organelle lumens also become misfolded or unnecessary, thus requiring disposal by the UPS. This problem is solved in the endoplasmic reticulum (ER) by a pathway called endoplasmic reticulum-associated degradation (ERAD) in which misfolded ER luminal or transmembrane proteins are recognized by their hydrophobicity and glycosylation state by molecular chaperones, simultaneously ubiquitinated and withdrawn from the ER via a retrotranslocation mechanism, and degraded by the cytosolic proteasome (Meusser et al. 2005).

Newly synthesized proteins at the ER experience the addition of an N-linked oligosaccharide ($Glc_3Man_9\_GlcNAc_2$) during translation. The glycosylated protein is recognized by ER-resident chaperones calnexin and calreticulin, which assist in ensuring the proper folding of their substrate. After the terminal glucose molecules are completely removed from the oligosaccharide by glucosidases that associate with the chaperones, the folded protein can exit the ER. However, if the protein is not appropriately folded, the enzyme UDP-glucose:glycoprotein glucosyltransferase (UGGT) can add more glucose molecules to the oligosaccharide, and the protein is again incorporated into the calnexin/calreticulin folding cycle. If the misfolded substrate cannot reach its native conformation, degradation-enhancing α-mannosidase-like lectins (EDEMs) shuttle the substrate to a retrotranslocon, a proteinaceous channel responsible for the formation of the pore necessary to allow ERAD substrates to exit from the ER. Once the substrates reach the retrotranslocon, their N-linked oligosaccharides are removed, and they are simultaneously ubiquitinated and withdrawn from the organelle. Ubiquitination is facilitated by ER-associated or membrane-bound E2 ubiquitin-conjugating enzymes and E3 ubiquitin ligases. This ubiquitination allows the recognition of the substrate by the hexameric AAA-ATPase Cdc48p/p97/VCP, or by VCP-associated cofactors Npl4 and Ufd1, and ATP is hydrolyzed to provide mechanical energy to remove the substrate from the organelle and facilitate its transfer to the cytosolic 26S proteasome (Meusser et al. 2005; Gregersen et al. 2006; Hegde and Ploegh 2010).

ERAD has often been described in a way that highlights its role in quality control of misfolded substrates (Gregersen et al. 2006); however, mounting evidence suggests that ERAD, or an auxiliary pathway that employs ERAD components, may play a role in the physiological quantity control of proteins (Hegde and Ploegh 2010). In this review, we define quantity control substrates of ERAD as those that are not constitutively misfolded, such as the variant chloride channel CFTR F508 (Lukacs and Verkman 2012) responsible for cystic fibrosis, not degraded as a result of infection, such as the T cell surface glycoprotein CD4 (Magadan et al. 2010), and are not themselves protein components of infectious organisms, such as the hepatitis C envelope protein (Saeed et al. 2011). We provide a comprehensive list of known quantity control substrates (Table 1), and delve into

the details and physiological context surrounding the degradation of well-studied proteins subject to this type of regulation. Our discussion will begin with ER-resident proteins whose quantities are governed by elements of the ERAD pathway, and then we will explore examples of plasma membrane residents that experience ER-localized quantity control.

ER-Resident Substrates

HMG-CoA Reductase

The most widely studied example of quantity control by ERAD is 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR). HMGR is an ER-localized enzyme that functions as the rate-limiting step of the mevalonate pathway, catalyzing the formation of mevalonate from 3-hydroxy-3-methyl-glutaryl-CoA. Given its importance in the mevalonate pathway and the biosynthesis of a diverse collection of molecules such as prenyl groups, dolichol, ubiquinone, and sterols including cholesterol, it is of no surprise that HMGR is regulated at three different levels: transcription, translation, and protein degradation (Goldstein and Brown 1990; Petras et al. 1999; Jo and Debose-Boyd 2010).

Sterol and non-sterol signals can induce the ER-localized degradation of HMGR protein. Treatment of cells with mevalonic acid reduces HMGR protein levels independent of its exit from the ER. HMGR degradation occurs despite treatment with Brefeldin A, a fungal antibiotic that prevents ER to Golgi trafficking, and the deletion of genes involved in ER to Golgi transport (Chun et al. 1990; Hampton and Rine 1994). Proteasomal inhibition blocks mevalonate-induced degradation and stabilizes ER-localized HMGR (Lecureux and Wattenberg 1994). Treatment of cells with farnesol, a downstream product of the mevalonate pathway, induces HMGR protein degradation in a squalene synthase- and sterol-dependent manner (Meigs et al. 1996; Song et al. 2005a), and this sterol-dependent degradation has been shown to occur in vitro with ER membranes isolated from sterol-pretreated cells (Moriyama et al. 2001). HMGR degradation does not require the lysosome or the vacuole in yeast (Inoue et al. 1991; Hampton and Rine 1994), and in mammalian cells, sterol-stimulated HMGR degradation is unaffected by lysosomal inhibition (Tanaka et al. 1986), reinforcing the notion that the degradation of physiologically active HMGR occurs at the ER.

The degradation of HMGR involves several proteins integral to the ERAD pathway. Hrd1 is a transmembrane ER-localized RING E3 ligase that promotes the ubiquitination and degradation of misfolded proteins in a quality control ERAD pathway (Vashist and Ng 2004; Carvalho et al. 2010). However, Hrd1, in conjunction with the Ubc7 E2 ubiquitin-conjugating enzyme, also plays a role in eliminating HMGR in a Hrd1 RING domain-dependent fashion (Kikkert et al. 2004). Interestingly, it has been suggested that on binding to sterols, HMGR undergoes a conformational shift from a stable to misfolded conformation, allowing its Hrd1-mediated ubiquitination and degradation to proceed, thus forcing quantity control to occur via a quality control mechanism (Gardner et al. 2001; Shearer and Hampton 2005). However, from a lack of experiments showing endogenous HMGR to be sensitive to Hrd1 knockdown, some believe that the function of Hrd1 toward HMGR is non-specific, and that Gp78, an ER-localized E3 ligase bearing significant homology to Hrd1, is responsible for the physiological and specific control of HMGR protein levels (Song et al. 2005b;

DeBose-Boyd 2008). Sterol binding causes HMGR to associate with the transmembrane Insig-1/2 proteins that in turn recruit Gp78 (Song et al. 2005a, b; Leichner et al. 2009; Jo et al. 2011). After GP78-mediated ubiquitination, HMGR is recognized by VCP and the VCP cofactor Ufd1, which transfer HMGR to the proteasome (Song et al. 2005b; Cao et al. 2007) surprisingly in the absence of a protein channel (Garza et al. 2009), perhaps by enhancing ER exit through lipid droplets (Hartman et al. 2010; Jo et al. 2013).

Apolipoprotein B

Apolipoprotein B (ApoB) is an essential secreted protein component of triacylglycerol-rich lipoproteins such as the chylomicrons, VLDL, IDL, and LDL particles responsible for the extracellular transport of lipids, triglycerides, and cholesterol. The classification of ApoB particles depends on the type of ApoB protein present (either full length ApoB100 or the proteolytically cleaved ApoB48), particle size, and relative quantities of cholesterol and triglycerides (Sniderman et al. 2010; Olofsson and Boren 2012). LDL particles are composed of ApoB100, up to 75 % cholesterol, and are responsible for the initiation of plaques that are characteristic of atherosclerosis, created by the affinity of the basic amino acids in ApoB100 for the proteoglycans of artery walls (Boren et al. 1998).

The maturation of ApoB into lipoprotein particles requires the translocation of the protein during synthesis from the ER membrane into the lumen. However, up to half of membrane-embedded ApoB is constitutively degraded at the ER during translocation (Ginsberg and Fisher 2009). Within 10 min of synthesis, ApoB is highly ubiquitinated (Chen et al. 1998). Blocking ER exit with Brefeldin A does not affect ApoB degradation, and once ApoB reaches the Golgi network, it is spared from destruction (Sato et al. 1990; Furukawa et al. 1992), suggesting that the protein is degraded while it is localized at the ER. Furthermore, ApoB in isolated ER can still be degraded while ApoB in isolated Golgi cannot (Furukawa et al. 1992). ApoB degradation can be enhanced as a result of insulin and LDL treatment, while oleate, a component of LDL, decreases ER-localized ApoB degradation and enhances its secretion. None of the aforementioned stimuli affect ApoB mRNA levels (Sato et al. 1990; Dixon et al.,1991; Furukawa et al. 1992; Qiu et al. 2005).

The translocation of ApoB is slow due to its large hydrophobic beta-sheets (Yamaguchi et al. 2006), providing ApoB an opportunity to associate with cytoplasmic chaperones such as Hsp70 and Hsp90 that enhance degradation (Gusarova et al. 2001). Bip is an ER luminal chaperone that also contributes to the destruction of ER-localized ApoB, mostly targeting the protein when it is poorly lipidated (Qiu et al. 2005). On the other hand, luminal chaperone calnexin and cytosolic Hsp110 can protect ApoB from degradation (Chen et al. 1998; Hrizo et al. 2007). Although ApoB co-immunoprecipitates with Hrd1 (Rutledge et al. 2009), Gp78 is the ligase responsible for ubiquitinating ApoB (Liang et al. 2003; Fisher et al. 2011). Knockdown of Gp78 decreases the cytosolic availability of ApoB and increases the secretion of VLDL particles from cells (Fisher et al. 2011), indicating that the ApoB spared from degradation is well folded and functional. The VCP ATPase interacts with ApoB; knockdown of VCP stabilizes intracellular ApoB protein and prevents its release into the cytosol (Fisher et al. 2008). It has also been shown that the putative ERAD retrotranslocon protein Derlin-1 and the UBXD8 cofactor are involved in the degradation of

a lipidated population of ApoB that resides in a hybrid ER/lipid droplet "crescent" (Suzuki et al. 2012).

A handful of other ApoB degradation mechanisms exist along its secretory route, including one that targets a population of ApoB that has already been translocated into the lumen of the ER. ApoB was shown to interact with ER-60, an ER luminal protein disulfide isomerase that also harbors cysteine protease activity (Adeli et al. 1997). The overexpression of ER-60 can elicit ApoB degradation independently of both the proteasome and ER-60 isomerase function, but dependent on its innate protease function (Qiu et al. 2004; Rutledge et al. 2013). Secondly, ApoB can experience increased degradation from ER stress, an event triggered by the increase of misfolded proteins at the ER. ER stress induces the unfolded protein response (UPR) which transcriptionally upregulates chaperones and components of the UPS and ERAD pathways (Hetz 2012). Glucosamine and high doses of oleate, surprisingly, can induce ER stress, thus affecting the ER-localized degradation of ApoB during and post-translocation (Pan et al. 2004; Qiu et al. 2005; Ota et al. 2008).

Cytochrome P450 3A4

Cytochrome P450 3A4 (CYP3A4) is part of the cytochrome P450 (CYP) superfamily of oxidizing enzymes, comprising as much as 30 % of all cytochrome P450 proteins in liver. Its primary cellular function is to remove endo- and xenobiotics such as drugs, atmospheric pollutants, smoke, and dietary compounds from the body (Shimada et al. 1994; Ortiz de Montellano 2005; Narjoz et al. 2009). With the N-terminus embedded in the cytosolic surface of the ER, the C-terminus of CYP3A4 is catalytically responsible for the metabolism and disposal of over 50 % of clinically relevant drugs, including widely prescribed anticancer agents such as tamoxifen, docetaxel, and imatinib (Ortiz de Montellano 2005; Rochat 2005), while also mediating many adverse food–drug and drug–drug interactions (Ogu and Maxa 2000; Fujita 2004).

Although reactivity with substrates can alter their conformation and stability, CYP proteins also undergo constitutive turnover via either proteasomal or lysosomal pathways, or a combination of both (Roberts 1997; Liao et al. 2006). CYP3A4 is degraded while localized at the endoplasmic reticulum by the 26S proteasome in the absence of external signals (Roberts 1997). However, in the presence of 3,5-dicarbethoxy-2,6-dimethyl-4-ethyl-1,4-dihydropyridine (DDEP), which mimics a subset of cytochrome substrates by modifying the heme group of CYP3A4, turnover is enhanced regardless of blockage ER to Golgi trafficking with Brefeldin A or inhibition of the lysosome, thus indicating ER-localized degradation (Wang et al. 1999).

In yeast, vacuolar (lysosomal) ligases, Hrd1 and Ubc6, and the ER-localized yeast E3 ligases Doa10/TEB4 and Rsp5p [homolog of Nedd4 and Itch (Dunn and Hicke 2001)], are dispensable for CYP3A4 degradation. Ubc7, anchored to the ER by Cue1p, and VCP, with Ufd1 and Npl4 cofactors, are required (Murray and Correia 2001; Liao et al. 2006; Faouzi et al. 2007). An in vitro analysis using mammalian components indicates the involvement of Ubc7 and Gp78, but less of UbcH5a and CHIP, and not TEB4 or Hrd1, in the ubiquitination of CYP3A4 (Pabarcus et al. 2009). In cultured rat hepatocytes, both Gp78 and CHIP knockdowns lead to increases in basal CYP3A4 protein levels, correlating with decreased

ubiquitination. Gp78 knockdown abolishes DEPP-induced degradation, indicating that at least Gp78 is also responsible for stimulated CYP3A4 turnover (Kim et al. 2010). Additionally, the stabilized CYP3A4 is found to be functional as microsomes from cells treated with Gp78 or CHIP knockdown have increased capability to catalyze the 7-*O*-debenzylation of 7-benzyloxy-4-trifluoromethylcoumarin (BFC), a diagnostic CYP3A functional probe, to 7-hydroxy-4-trifluoromethylcoumarin (HFC; Kim et al. 2010).

CYP3A4 is phosphorylated by protein kinase A and protein kinase C, and this phosphorylation event enhances in vitro ubiquitination of the cytochrome. Serine/threonine mutants of CYP3A4 incapable of undergoing phosphorylation are more stable in yeast and mammalian cells (Wang et al. 2009a). The phosphorylation of CYP3A4 enhances the in vitro ubiquitination of the cytochrome by Gp78 and CHIP (Wang et al. 2012b), highlighting the importance of phosphorylation in the ER-localized degradation of CYP3A4.

IP3 Receptor

Inositol 1,4,5-trisphosphate receptor (IP_3R) is an ER-localized, transmembrane protein that allows the release of Ca^{2+} from intracellular stores by binding its ligand, the second messenger inositol 1,4,5-trisphosphate (IP_3). IP_3R is conserved among many species and is expressed ubiquitously in animal tissues, although mammals have three different isoforms of IP_3R which differ in their distribution (Higo et al. 2005). Due to the wide-reaching effects of Ca^{2+}, the receptor regulates a variety of cellular processes such as division, proliferation, apoptosis, fertilization, development, behavior, memory, and learning (Furuichi and Mikoshiba 1995; Bosanac et al. 2002). Additionally, IP_3R acts as a scaffold for a plethora of binding partners. Thus, it is said that the receptor participates in a "macro signal complex," perhaps as the center of an ER-localized hub of cellular signaling (Mikoshiba 2007).

In addition to regulation of its activity by ATP, phosphorylation, and Ca^{2+}, nascent IP_3R is constitutively turned over at the ER (Khan and Joseph 2003). IP_3R can also be degraded as a result of activation, for example, from treatment with carbachol which binds muscarinic acetylcholine receptors at the cell surface and stimulates phospholipase C and IP_3 production (Wojcikiewicz and Nahorski 1991). Stimulated increases in IP_3 induce IP_3R ubiquitination and degradation without changes in mRNA levels (Wojcikiewicz et al. 1994, 1999). This downregulation requires luminal Ca^{2+}, persistent elevation of IP_3 levels, and occurs despite Brefeldin A treatment or disruption of the lysosome, indicating that degradation of IP_3R occurs while it is localized at the ER (Wojcikiewicz et al. 1994; Wojcikiewicz and Oberdorf 1996; Alzayady and Wojcikiewicz 2005). Overexpression of dominant-negative Ubc7, but not dominant-negative Ubc6, prevents carbachol-stimulated ubiquitination and degradation of IP_3R (Webster et al. 2003). IP_3R stimulation induces the formation of a receptor complex with VCP and its cofactors Ufd1 and Npl4. Furthermore, knockdown of VCP prevents the carbachol-stimulated ubiquitination and degradation of IP_3R, and overexpression of VCP in VCP-depleted cells rescues receptor degradation (Alzayady et al. 2005).

Almost immediately after activation, but necessarily prior to ubiquitination and degradation, IP_3R forms a complex with the transmembrane proteins SPFH1 and SPFH2. SPFH1/2 exists in a complex with several ERAD components in carbachol-unstimulated cells, including

VCP. Knockdown of SPFH2 decreases IP$_3$R ubiquitination and degradation, decreases IP$_3$R interaction with VCP, and increases Ca^{2+} mobilization, indicating that the ERAD mediated by SPFH1/2 plays a physiological role in regulating IP$_3$R levels after activation, and the IP$_3$R spared from degradation is well folded and functional (Pearce et al. 2007, 2009; Wang et al. 2009b). In the absence of carbachol, the SPFH1/2 complex interacts with the transmembrane E3 ubiquitin ligase RNF170 which, after stimulation, is responsible for ubiquitinating IP$_3$R in an RNF170 RING domain-dependent fashion (Lu et al. 2011). Knockdown of RNF170 spares endogenous IP$_3$R from destruction in both resting and carbachol-stimulated cells (Lu et al. 2011).

Type II Iodothyronine Deiodinase

Type II iodothyronine deiodinase (D2) is a single-pass transmembrane, ER-localized selenoprotein whose catalytic activity converts thyroxine (T4) to the biologically active hormone triiodothyronine (T3). D2 also converts T4 and T3 to the biologically inactive molecules reverse triiodothyronine (rT3) and diiodothyronine (T2), respectively (Arrojo e Drigo and Bianco 2011; Arrojo e Drigo et al. 2013a). Out of the three iodothyronine deiodinase enzymes, D2 has the highest affinity for the T4 substrate and is the predominant form in adult tissues (Arrojo e Drigo and Bianco 2011). Once T4 is converted to T3 on the surface of the ER, it is able to diffuse into the nucleus to activate the thyroid hormone receptor (TR) that can act either as a homodimer or as the more potent TR/retinoid X receptor (RXR) heterodimer to induce transcriptional changes in genes involved in development, growth, neural differentiation, and metabolic regulation (Brent 2012; Kliewer et al. 1992).

The D2 substrate T4 and the inactive product rT3 decrease the half life of endogenous D2 protein, while proteasomal inhibition blocks rT3-induced D2 degradation (Steinsapir et al. 1998). rT3 stimulation increases ectopic D2 ubiquitination in microsomes as opposed to cytosolic cellular fractions, suggesting that stimulated degradation occurs at the ER (Gereben et al. 2000). In yeast cells lacking Ubc6 and Ubc7, but not Ubc1, ectopic D2 protein is less ubiquitinated, stabilized, and more active, pointing to a properly folded D2 that was spared from degradation by ERAD (Botero et al. 2002). However, in HEK cells, dominant-negative Ubc6 and Ubc7 must be expressed together to stabilize ectopic D2 in rT3-treated and rT3-untreated cells, suggesting some functional redundancy between the E2 ubiquitin-conjugating enzymes in the degradation of D2. Overexpressed wild-type E2s, either alone or in combination, do not have an effect on D2 (Dentice et al. 2005). Furthermore, D1 and D3 are unaffected by the expression of wild-type or dominant-negative E2s in combination, signifying the specificity of D2 as an ERAD substrate (Dentice et al. 2005).

In mammalian cells, the Hedgehog-inducible ubiquitin E3 ligase WSB-1 contributes to the destruction of ectopic D2 by participating in a complex alongside elongin B, elongin C, Cul5, and Rbx1 (Dentice et al. 2005). Knockdown of WSB-1 increases D2 protein levels and activity, and overexpression of WSB-1 increases the ubiquitination of and destabilizes D2 (Dentice et al. 2005). In yeast, the Hrd1 E3 ligase is dispensable in D2 regulation; however, deletion of the transmembrane E3 ligase Doa10/TEB4 stabilizes D2 levels comparably to

Ubc6 or Ubc7 deletion (Ravid et al. 2006). In T4-stimulated or unstimulated mammalian cells, the knockdown of TEB4 decreases ubiquitination of ectopic D2, correlating with increased D2 protein levels and activity, with D1 remaining unaffected (Zavacki et al. 2009). The activity of endogenous D2 also increases in the presence of TEB4 knockdown, signifying that the endogenous D2 is well folded and functional (Zavacki et al. 2009). The expression of TEB4 and WSB-1 differs somewhat between tissues, indicating that the E3 ligase responsible for the degradation of D2 may be tissue specific (Zavacki et al. 2009). Lastly, VCP is responsible for retrotranslocating D2, making it available for cytosolic proteasomal degradation (Arrojo e Drigo et al. 2013b).

D2 is expressed in the brown adipose tissues (BAT) of small mammals and is responsible for generating a response to cold temperatures as the transcription of thermogenin, also known as uncoupling protein 1 (UCP1), is induced by T3. Once active, UCP1 is responsible for decreasing the proton gradient necessary for ATP generation during oxidative phosphorylation, thus dissipating the electrochemical proton potential as heat and uncoupling oxidation from ATP synthesis (Nedergaard et al. 2001; Cannon and Nedergaard 2011; Borecky and Vercesi 2005). Interestingly, cold exposure of BAT rapidly induces transcription of ER-localized VDU1 deubiquitinase which is capable of deubiquitinating and stabilizing ectopic D2 but not D1, signifying that the sparing of D2 from ER-localized degradation is physiologically relevant (Curcio-Morelli et al. 2003).

Plasma Membrane Resident Substrates

ErbB3

The transmembrane ErbB3 receptor tyrosine kinase is essential for the proper development of neural, cardiac, and mammary tissues in addition to contributing to the maintenance of an array of tissues in the adult (Riethmacher et al. 1997; Erickson et al. 1997; Jackson-Fisher et al. 2008; Stern 2008). Overexpression of ErbB3 has been linked to hyperactivity of the receptor and increased downstream signaling, contributing to tumor malignancy and therapeutic resistance in a number of cancer types (Engelman and Cantley 2006; Stern 2008; Hamburger 2008; Baselga and Swain 2009). While the hyperactivity of ErbB family members HER2/ErbB2 and EGFR has been traced to genetic amplification, the same has not been found in the case of ErbB3 overexpression. ErbB3 transcript levels in tumor and normal tissues are equivalent despite tumors experiencing marked increases in ErbB3 protein, this being indicative of a failure in a potent post-transcriptional mechanism of ErbB3-negative regulation (Lemoine et al. 1992; Sibilia et al. 2007; Baselga and Swain 2009; Hynes and MacDonald 2009; Amin et al. 2010).

Nrdp1 is a RING-type E3 ubiquitin ligase that was discovered in a yeast 2-hybrid screen, pulled out by the intracellular domain of ErbB3 (Diamonti et al. 2002), and provides an essential avenue for steady-state maintenance of ErbB3 protein levels (Yen et al. 2006; Printsev et al. 2014). Nrdp1 co-localizes and physically associates with newly synthesized ErbB3 at the ER, affecting the ubiquitination and degradation of the nascent receptor. Disruption of ErbB3 exit from the ER with Brefeldin A does not disrupt Nrdp1-mediated ectopic receptor ubiquitination or degradation. Nrdp1 knockdown stabilizes the nascent form of endogenous ErbB3, and overexpression of Nrdp1 decreases the protein levels of the

endogenous receptor during Brefeldin A treatment. Furthermore, the stabilized ErbB3 resulting from Nrdp1 knockdown enhances the ability of cells to bind and respond to neuregulin (NRG1) growth factor, indicating that the receptor spared from degradation by Nrdp1 is properly folded and fully functional (Yen et al. 2006; Fry et al. 2011).

The canonical ERAD substrate CFTR F508 has been shown to be rapidly degraded at the ER shortly after translation due to its improperly folded state (Lukacs and Verkman 2012). After recognition by the Hsp70 chaperone, CFTR F508 is ubiquitinated by the E3 ligases Gp78 and CHIP, prior to withdrawal from the membrane by VCP (Meacham et al. 2001; Morito et al. 2008; Brodsky and Skach 2011). However, CFTR F508 is unaffected by Nrdp1 overexpression, signifying that Nrdp1 is specific to ErbB3 in an ERAD-like quantity control pathway. On the other hand, the dominant-negative form of VCP blocks the ability of Nrdp1 to induce ErbB3 degradation while leaving ubiquitination of ErbB3 unaffected. This signifies that VCP functions downstream of Nrdp1 to transfer ubiquitinated ErbB3 from the ER to the proteasome as a shared component between quantity and quality control ERAD (Fry et al. 2011).

GABA Receptors

The neurotransmitter γ-Aminobutyric acid (GABA) is responsible for the reduction of neuronal excitability by binding GABA receptors, an action that prevents further action potentials and neurotransmitter release. GABA induces neuronal chloride uptake and potassium release, resulting in a net negative charge in the transmembrane potential usually associated with membrane hyperpolarization. $GABA_A$ receptor ($GABA_AR$), the major site of action of barbiturates and benzodiazepines, is a fast-acting ligand-gated ion channel; GABA binding to $GABA_AR$ induces the opening of its chloride ion-selective pore to allow neuronal chloride uptake. $GABA_B$ receptor ($GABA_BR$) is slower acting and engages second messenger systems via $G\alpha_{i/o}$-type GTP-binding proteins (Gassmann and Bettler 2012); GABA binding to presynaptic $GABA_BR$ represses Ca^{2+} influx, and binding to postsynaptic $GABA_BR$ opens K^+ channels, creating a hyperpolarized postsynaptic neuron and an inhibitory postsynaptic potential (Bettler et al. 2004). The GABA receptors are widely expressed in the central nervous system, and have been implicated in a variety of disorders including epilepsy, anxiety, depression, insomnia, spasticity, stress, schizophrenia, obsessive compulsive disorder, addiction, and pain (Gassmann and Bettler 2012; Bettler et al. 2004; Bowery et al. 2002).

Regulation of neuronal cell surface levels of both $GABA_AR$ and $GABA_AR$ appears important to their function, and evidence has accumulated that each is post-translationally regulated at the endoplasmic reticulum. It has been demonstrated that chronic blockade of neuronal activity increases $GABA_AR$ ubiquitination and proteasome-dependent degradation at the endoplasmic reticulum, while increasing neuronal activity has the opposite effect (Saliba et al. 2007, 2008). The net result is the activity-dependent augmentation of cell surface receptor levels to regulate the efficacy of synaptic inhibition and contribute to homeostatic synaptic plasticity.

The degradation of $GABA_BR$ has largely been described as activation-induced lysosomal degradation after internalization at the plasma membrane (Benke 2010). However, there is

some evidence that there is also post-translational, physiologically relevant regulation that occurs at the ER. In neurons, proteasomal inhibition and the inhibition of VCP cause an accumulation of endogenous GABA_BR. Correspondingly, a decrease of GABA_BR is observed with the proteasome activator betulinic acid and the inhibition of a deubiquitinase implicated in ERAD (Nagai et al. 2009; Zemoura et al. 2013). The overexpression of dominant-negative VCP increases GABA_BR protein levels and their presence and activity at the plasma membrane (Zemoura et al. 2013). The degradation of GABA_BR is thought to be accomplished via its interactions with Hrd1 and VCP (Zemoura et al. 2013). However, the receptor also interacts with Rpt6, an ATPase component of the 19S regulatory particle of the proteasome required for the ER-localized degradation of GABA_BR (Zemoura and Benke 2014). Enhancing neuronal activity causes decreases in GABA_BR levels, corresponding with the receptor's increased association with Rpt6, which can be reversed by inhibiting VCP (Zemoura and Benke 2014), indicating a physiological role for the ERAD of GABA_BR.

Quantity Control in the Maintenance of Protein Complex Stoichiometry

There exists a subset of ERAD substrates that are efficiently synthesized but are degraded when there is a dearth of interaction partners that would form a functional complex with the substrate. These substrates qualify as quantity control regulated for the reason that if their numbers exceed than the correct stoichiometry, they are considered by the cell to be in excess. Despite the possibility that these substrates are being engaged by ERAD due to misfolding or exposed hydrophobic domains in the absence of their interaction partners, their undesirable presence implies that degradation fulfills cellular quantity control.

The transmembrane major histocompatibility complex (MHC) class I heavy chain complexes with β2-microglobulin and an 8–10 amino acid peptide generated by the proteasome from the degradation of endogenous and foreign proteins. Once complete, the MHC complex is trafficked to the plasma membrane to present the peptide antigen to T cells. MHC-I heavy chain is degraded as a result of viral infection in order to suppress the recognition of infected cells (Barel et al. 2006; Wang et al. 2013). However, in the absence of β2-microglobulin and peptide, without participation in a fully formed MHC, the class I heavy chain is degraded by the proteasome in an Ubc6- and Hrd1-dependent manner (Hughes et al. 1997; Burr et al. 2011). Likewise, the yeast Matα2 transcriptional repressor (Johnson et al. 1998; Laney and Hochstrasser 2003; Ravid et al. 2006), yeast SREBP1 transcription factor (Hughes et al. 2009), pTα and CD3δ subunits of the T cell receptor complex (Ishikura et al. 2010; Lerner et al. 2007), and the monocarboxylate transporter targeting protein CD147 (Tyler et al. 2012) are downregulated by ERAD in the absence of their oligomerization partners.

Conclusions

In this review, we have delved into the details surrounding the degradation of several well-known quantity control substrates of ERAD, underscoring the molecular mechanisms by which environmental conditions engage ERAD to target proteins for degradation. In addition, we have attempted to create a comprehensive list of such substrates characterized thus far; it is likely that this list will expand dramatically in the future. Given how little is

known about the degradation of many of these substrates—identities of the proteins that constitute the destruction complexes, which substrate-specific adapter proteins mediate the connection to ERAD, and what cellular or environmental signals can induce degradation—many potential future research avenues are possible. As the list of quantity control ERAD substrates continues to grow, and the underlying mechanisms become discerned, these pathways may become targets for those aiming to alter protein stability in order to achieve a therapeutic or otherwise physiologically relevant outcome.

A key point that has begun to emerge over the last several years is that ER-based degradation mechanisms can play substantial roles in dictating the quantities of membrane-associated proteins at a variety of organelles, including those involved in cellular signaling and homeostasis. It makes a lot of sense that the engagement of ERAD contributes to the quantity control ER-localized proteins, and even to the maintenance of proper stoichiometries of non-ER protein complexes. But why might it be advantageous for a cell to have ERAD govern the quantities of monomeric plasma membrane proteins, for example, the ErbB3 receptor tyrosine kinase? One possibility is that in some cases appearance of receptors at the cell surface at an inappropriate time may compromise cell function. Growth factor ligands for many receptor tyrosine kinases are frequently deposited on the extracellular matrix, and hence are constitutively present. Thus, to regulate signaling, access of the receptor to the cell surface must be restricted when signaling is not needed, and enhanced upon cellular stress where growth signaling might promote cell survival under adverse conditions. Nrdp1 could carry out this function by efficiently coupling ErbB3 to the ERAD machinery under conditions where growth factor signaling is either not needed or is deleterious, while its suppression by stressors could allow ErbB3 accumulation and survival signaling (Carraway 2010). Overall, it is likely that the few examples given here are just the tip of the iceberg; in the future, the notion of limiting receptor access to the cell surface via ERAD-mediated proteolytic degradation could become a predominant theme in signal transduction.

Acknowledgments

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Table 1

Quantity control substrates of ERAD

Organism	Substrate	Localization	Biological role	Regulation	UPS	Key refs.
Mammalian	HMGR	ER membrane	Sterol, isoprenoid synthesis	Sterols	Hrd1, Gp78, Ubc7, Insig1/2	Chun et al. (1990), Song et al. (2005b), Cao et al. (2007), Jo et al. (2011)
Mammalian	ApoB	Secreted	LDL, VLDL formation	Oleic acid, LDL, insulin	Gp78, Derlin-1, UBXD8, ER-60	Sato et al. (1990), Adeli et al. (1997), Liang et al. (2003), Suzuki et al. (2012)
Mammalian	CYP3A4	ER membrane	Drug metabolism	DDEP (catalysis)	Ubc7, Cue1p, CHIP, Gp78, UbcH5a	Roberts (1997), Pabarcus et al. (2009), Kim et al. (2010), Wang et al. (2012b)
Mammalian	IP3R	ER membrane	Calcium signaling	Calcium, IP3	SPFH1/2, RNF170, Ubc7	Khan and Joseph (2003), Pearce et al. (2007), Lu et al. (2011)
Mammalian	D2	ER membrane	Thyroid hormone activation	T4, rT3	WSB-1, TEB4	Steinsapir et al. (1998), Dentice et al. (2005), Zavacki et al. (2009)
Mammalian	ErbB3	Plasma membrane	Receptor tyrosine kinase	?	UbcH5, Nrdp1	Fry et al. (2011), Hatakeyama et al. (2016)
Mammalian	GABA$_B$R	Plasma membrane	Inhibitory neurotransmission	Neuronal activity	Hrd1, Rpt6	Zemoura et al. (2013)
Mammalian	MHC-I	Plasma membrane	Antigen presentation	Stoichiometry	Ubc6, Hrd1	Hughes et al. (1997), Burr et al. (2011)
Yeast	Matα2	Nucleus	Differentiation	Stoichiometry	Ubc6, Ubc7, Doa10	Johnson et al. (1998), Ravid et al. (2006)
Yeast	SREBP1	ER membrane, nucleus	Hypoxic transcription factor	Stoichiometry	Ubc7, Hrd1	Hughes et al. (2009)
Mammalian	pTα	Plasma membrane	T cell receptor complex	Stoichiometry	Hrd1	Ishikura et al. (2010)
Mammalian	GABA$_A$R	Plasma membrane	Inhibitory neurotransmission	Neuronal activity	Plic-1	Saliba et al. (2008)
Mammalian	CD147	Plasma membrane	Transporter localization	Stoichiometry	Hrd1	Tyler et al. (2012)
Yeast	Erg3p	ER membrane	Sterol Synthesis	Catalysis	Hrd1	Jaenicke et al. (2011)
Mammalian	DGAT2	ER membrane	Triacylglycerol synthesis	?	Gp78	Choi et al. (2014)
Mammalian	Nrf2	Cytosol, nucleus	Oxidative response transcription factor	ER stress	Hrd1	Wu et al. (2014)
Mammalian	GGT	Plasma membrane	Glutathione metabolism	ER stress	–	Ravuri et al. (2013)
Mammalian	UGT8	ER membrane	Sphingolipids metabolism	Sterols	Insig1	Hayashi et al. (2012)
Mammalian	SUR1/Kir6.2	Plasma membrane	Potassium channels	?	Derlin-1	Wang et al. (2012a)
C. elegans	PAT-3	Plasma membrane	Laminin receptor	?	RNF121, Derlin-1, SCFFbx2	Darom et al. (2010)
Mammalian	WFS1	ER membrane	ER stress	?	Smurf1	Guo et al. (2011)
Mammalian	Pael-R	Plasma membrane	Prosaposin receptor	?	Hrd1	Omura et al. (2006)

Organism	Substrate	Localization	Biological role	Regulation	UPS	Key refs.
Mammalian	ATF6	ER membrane, nucleus	ER stress response	ER stress	SEL1L, Xbp1u	Horimoto et al. (2013)
Mammalian	Cav1.2	Plasma membrane	Voltage-dependent calcium channel	–	RFP2, Derlin-1	Altier et al. (2011)