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Review

Mechanisms of productive folding and endoplasmic reticulum-associated degradation of glycoproteins and non-glycoproteins

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ABSTRACT

Background: The quality of proteins destined for the secretory pathway is ensured by two distinct mechanisms in the endoplasmic reticulum (ER): productive folding of newly synthesized proteins, which is assisted by ER-localized molecular chaperones and in most cases also by disulfide bond formation and transfer of an oligosaccharide unit; and ER-associated degradation (ERAD), in which proteins unfolded or misfolded in the ER are recognized and processed for delivery to the ER membrane complex, retrotranslocated through the complex with simultaneous ubiquitination, extracted by AAA-ATPase to the cytosol, and finally degraded by the proteasome.
Scope of review: We describe the mechanisms of productive folding and ERAD, with particular attention to glycoproteins versus non-glycoproteins, and to yeast versus mammalian systems.
Major conclusion: Molecular mechanisms of the productive folding of glycoproteins and non-glycoproteins mediated by molecular chaperones and protein disulfide isomerases are well conserved from yeast to mammals. Additionally, mammals have gained an oligosaccharide structure-dependent folding cycle for glycoproteins. The molecular mechanisms of ERAD are also well conserved from yeast to mammals, but redundant expression of yeast orthologues in mammals has been encountered, particularly for components involved in recognition and processing of glycoproteins and components of the ER membrane complex involved in retrotranslocation and simultaneous ubiquitination of glycoproteins and non-glycoproteins. This may reflect an evolutionary consequence of increasing quantity or quality needs toward mammals.
General significance: The introduction of innovative genome editing technology into analysis of the mechanisms of mammalian ERAD, as exemplified here, will provide new insights into the pathogenesis of various diseases.

1. Introduction

Approximately one-third of total cellular proteins are synthesized on ribosomes attached to the endoplasmic reticulum (ER). Newly synthesized secretory and transmembrane proteins gain their appropriate three-dimensional structure in the ER with assistance from ER-localized molecular chaperones (ER chaperones) [1,2]. Only folded proteins are allowed to proceed to the next compartment of the secretory pathway, the Golgi apparatus. In the ER, they often undergo posttranslational modification which facilitates folding. This is carried out by folding enzymes; examples include oxidoreductase-mediated disulfide bond formation [3,4], and oligosaccharyltransferase-mediated transfer of an oligosaccharide with 14-sugar (2.37 kDa) units in the cases of yeast and mammals from dolichol to an Asn residue in the consensus sequence (Asn-X-Thr/Ser; X: any amino acid except Pro) [5–7]. This *N*-glycan is composed of three glucoses, nine mannoses and two *N*-acetylglucosamines, and referred to $Glc_3Man_9GlcNAc_2$ (G3M9) (Fig. 1A). Importantly, a particular number of glucose residues, namely $Glc_1Man_9GlcNAc_2$ (G1M9), becomes a signal to facilitate glycoprotein folding (Fig. 1B). This signal is decoded by lectin-type ER chaperones complexed with an oxidoreductase.

However, even after assistance from ER chaperones and folding enzymes, proteins are sometimes unable to attain their tertiary or quaternary structures due to intrinsic difficulty in folding, the absence of partner proteins required for assembly, or genetic mutation, among others [8–10]. Still unfolded or misfolded proteins are dealt with by the ER-associated degradation (ERAD) system, in which such proteins are recognized, processed, and delivered to the retrotranslocation channel (retrotranslocon) for transport back to the cytosol, where they are degraded by the ubiquitin-proteasome system (Fig. 1C) [11–13]. This degradation machinery is basically conserved from yeast to mammals to maintain ER homeostasis. If this quality control system is not functional,

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the cell becomes vulnerable to accumulation of misfolded proteins in the ER, culminating in apoptosis [14–16].

Depending on the position of lesions in the substrate, ERAD is categorized into three pathways: ERAD-L for proteins with defects in ER luminal regions; ERAD-M for proteins with defects in membrane regions [17–19]; and ERAD-C for membrane proteins in the ER with defects in the cytosol (Fig. 1C) [20,21]. Each degradation pathway requires different components [20,22]. Yeast ERAD-L requires the E3 ligase Hrd1, a multi-spanning transmembrane protein operating with its accessory proteins, including Hrd3. Yeast ERAD-M also requires the Hrd1 complex, although a subset of accessory proteins essential for ERAD-L is dispensable. Yeast ERAD-C requires the E3 ligase Doa10 [17,20,21,23], a multi-spanning transmembrane protein. ERAD-L is further divided into ERAD-Ls for soluble ER proteins and ERAD-Lm for ER membrane proteins with defects in luminal regions [24]. Interestingly, in the case of ERAD-L of misfolded glycoproteins, a particular branch structure of *N*-glycan, namely $Man_7GlcNAc_2$ (M7A), as well as M6 and M5, all of which expose a terminal α1,6-linked mannosyl residue

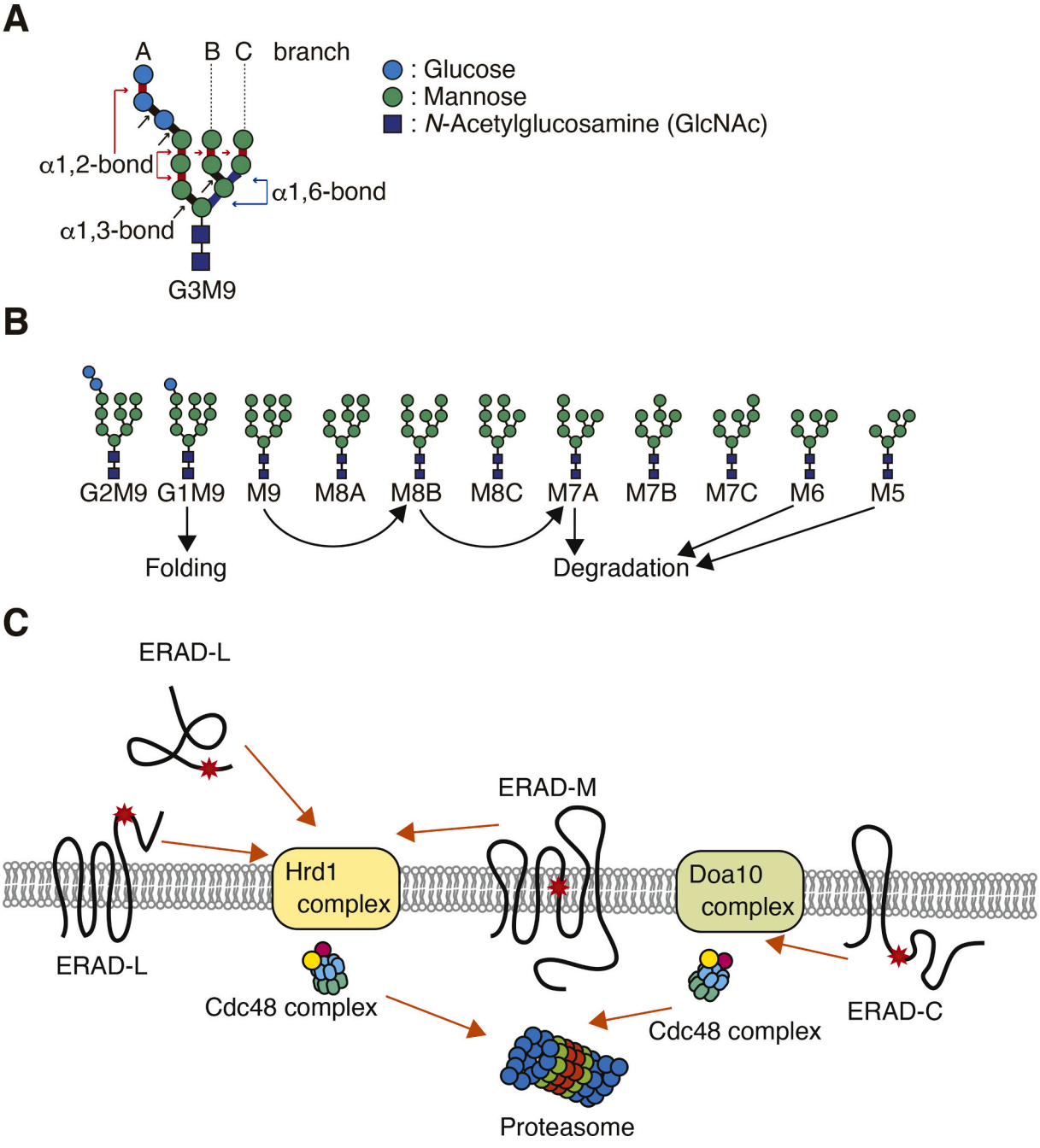

Fig. 1. Structures of *N*-glycans and three pathways in yeast ERAD.
(A) Structure of $Glc_3Man_9GlcNAc_2$ (G3M9) composed of the A, B and C branches. α1,2-bond, α1,3-bond and α1,6-bond are indicated by red, black and blue bars and arrows, respectively.
(B) Structures of various *N*-glycans producible in the ER and the codes embedded in several *N*-glycans.
(C) Yeast ERAD is divided into ERAD-L (substrates with defects in luminal region), ERAD-M (defects in membrane region) and ERAD-C (defects in cytosolic region). The ERAD-L and -M pathways utilize the Hrd1 complex, whereas the ERAD-C pathway utilizes the Doa10 complex. The Cdc48 complex extracts substrates from the Hrd1 and Doa10 complexes, and the proteasome digests extracted polypeptides.

produced via M9 and M8B from G1M9, becomes signals for degradation (Fig. 1B). These signals are decoded by a specific lectin(s). It should be noted that while M8C and M7B also expose terminal α1,6-linked mannosyl residues, they are rarely produced in the ER of either yeast [25] or mammals [26] and do not serve as signals for degradation.

This review focuses on the molecular mechanisms of productive folding and ERAD-L of glycoproteins and non-glycoproteins by comparison of yeast and mammalian systems, as schematically summarized in Fig. 2 (yeast) and Fig. 3 (mammal). It should be noted that whenever we refer to a gene product, the name in yeast is written first, followed by a slash mark and the name(s) in mammals.

2. Productive folding

Folding of non-glycoproteins in the ER is assisted by the "chaperone cycle (cycle of substrate binding and release)". Hsp70-type ER chaperone Kar2 [27]/BiP [28,29] is composed of the ATP-bound form and ADP-bound form, in which the substrate binding site is open and closed,

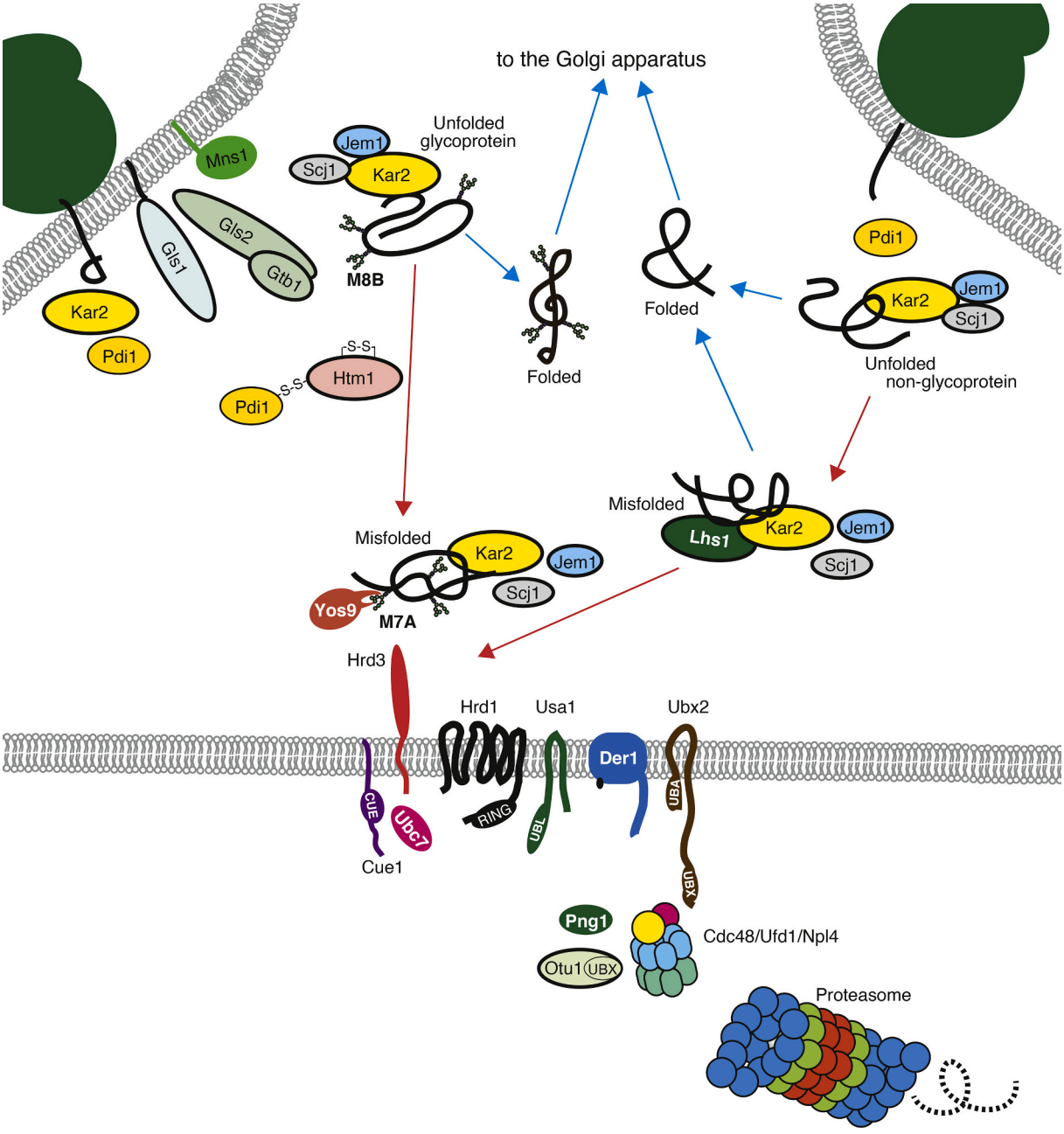

Fig. 2. Schematic view of folding and degradation of soluble glycoproteins and non-glycoproteins in yeast.
Left and right ribosomes synthesize glycoproteins and non-glycoproteins, respectively. Two glucosidases, Gls1 and Gls2-Gtb1, trim *N*-glycan of newly synthesized glycoproteins to produce M9, which is immediately trimmed by Mns1 to M8B. Kar2 cooperates with co-chaperones Jem1 and Scj1 to assist in productive folding. Properly folded glycoproteins are transported to the Golgi apparatus. In contrast, unfolded or misfolded glycoproteins are captured by Htm1-Pdi1 for removal of the outermost mannose at the C branch to produce M7A, which is recognized by Yos9, and retrotranslocated into the cytosol through the Hrd1 complex at the ER membrane. In the Hrd1 complex, Hrd3 accepts substrates; Usa1 recruits Der1; and Cue1 recruits Ubc7, an ubiquitin-conjugating E2 enzyme. Ubx2 binds to the Cdc48 complex, which extracts polyubiquitinated substrates from the ER membrane. After the actions of Otu1, a de-ubiquitinating enzyme, and Png1 for removal of *N*-glycan, polypeptides are degraded by the proteasome in the cytosol. Newly synthesized non-glycoproteins interact with the Kar2 complex, including Jem1 and Scj1, and/or Lhs1 to facilitate folding and degradation. Misfolded non-glycoproteins are degraded via the Hrd1 complex.

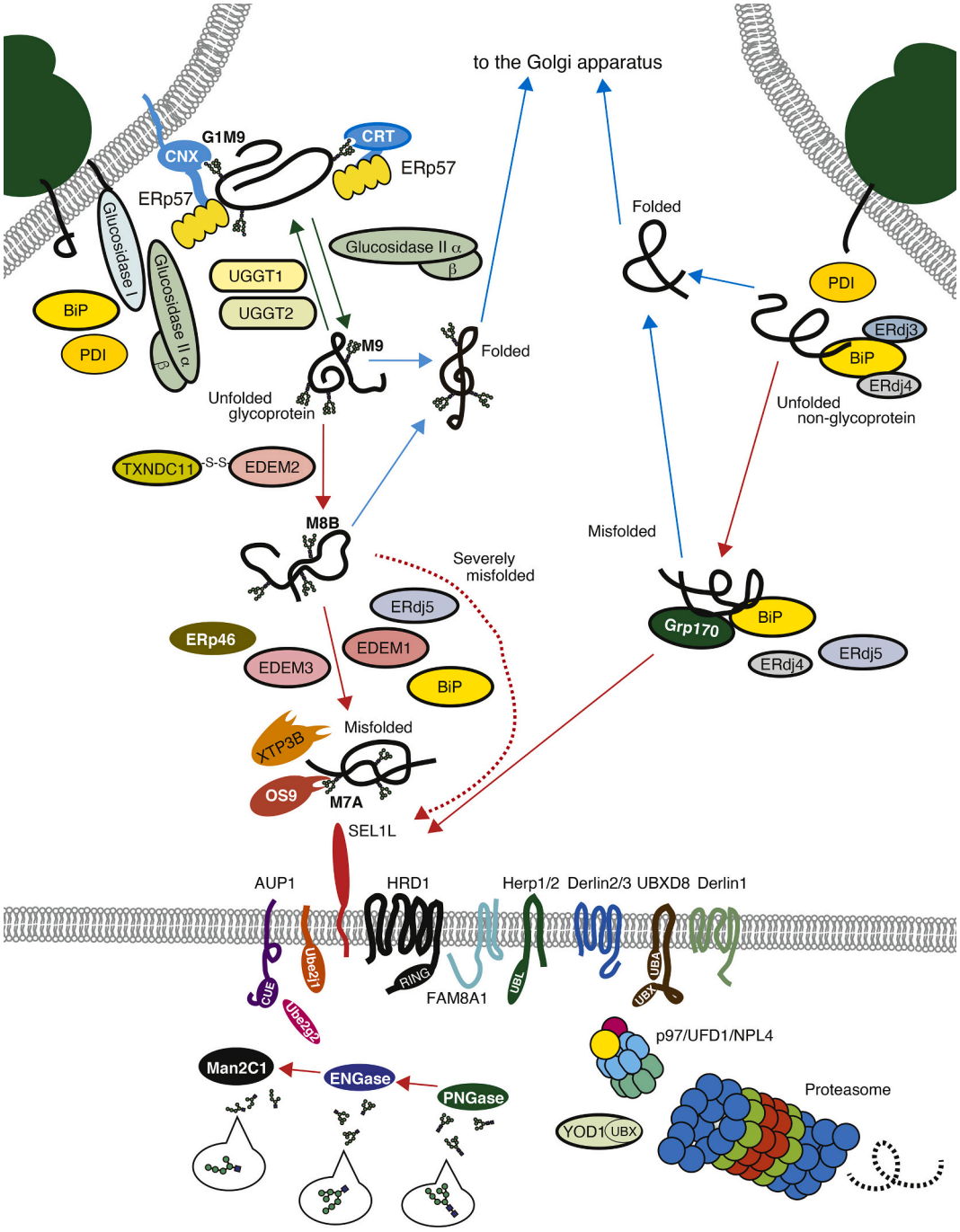

Fig. 3. Schematic view of folding and degradation of soluble glycoproteins and non-glycoproteins in mammals.
Left and right ribosomes synthesize glycoproteins and non-glycoproteins, respectively. Glucosidase I embedded in the ER membrane and soluble Glucosidase II, composed of two (α and β) subunits, sequentially trim glucoses of *N*-glycan on newly synthesized glycoproteins to produce G1M9, which is recognized by lectin chaperones CNX or CRT complexed with ERp57, an oxidoreductase. Glucosidase II again acts on the *N*-glycan to produce M9. If a protein is not correctly folded, UGGT1 or UGGT2 reglucosylates it to again create the substrate for CNX or CRT. The protein, with its native structure, is transported to the Golgi apparatus. However, proteins which cannot be folded into the correct three-dimensional structure are recognized first by EDEM2-TXNDC11 for removal of the outermost mannose on the B chain from M9 to produce M8B, and second by EDEM3 or EDEM1 for further removal of mannoses from M8B. *N*-glycan exposing an α1,6-linked mannosyl residue, such as M7A, M6 or M5, is captured by OS9 or XTP3B. On the ER membrane, E3 ubiquitin ligase HRD1 associated with SEL1L mediates retrotranslocation of ERAD substrates. Herp1/2 and Derlin2/3 are located proximal to the HRD1 complex. UBXD8 and AUP1 have similar domain structures to yeast Ubx2 and Cue1, respectively, and their requirements for degradation are substrate-dependent. FAM8A1 contributes to the assembly of the HRD1 complex. Polyubiquitinated substrates are extracted by the p97 complex from the retrotranslocon, deubiquitinated by YOD1, and digested by the proteasome. During these processes, PNGase-mediated deglycosylation produces free oligosaccharides in the cytosol, which are processed by ENGase and Man2C1. Severely misfolded glycoproteins are subjected to the non-gpERAD pathway via an unknown mechanism (denoted with a dashed line). Folding and degradation of non-glycoproteins are mediated by BiP, co-chaperones and/or Grp170. Misfolded non-glycoproteins are degraded via the HRD1 complex.

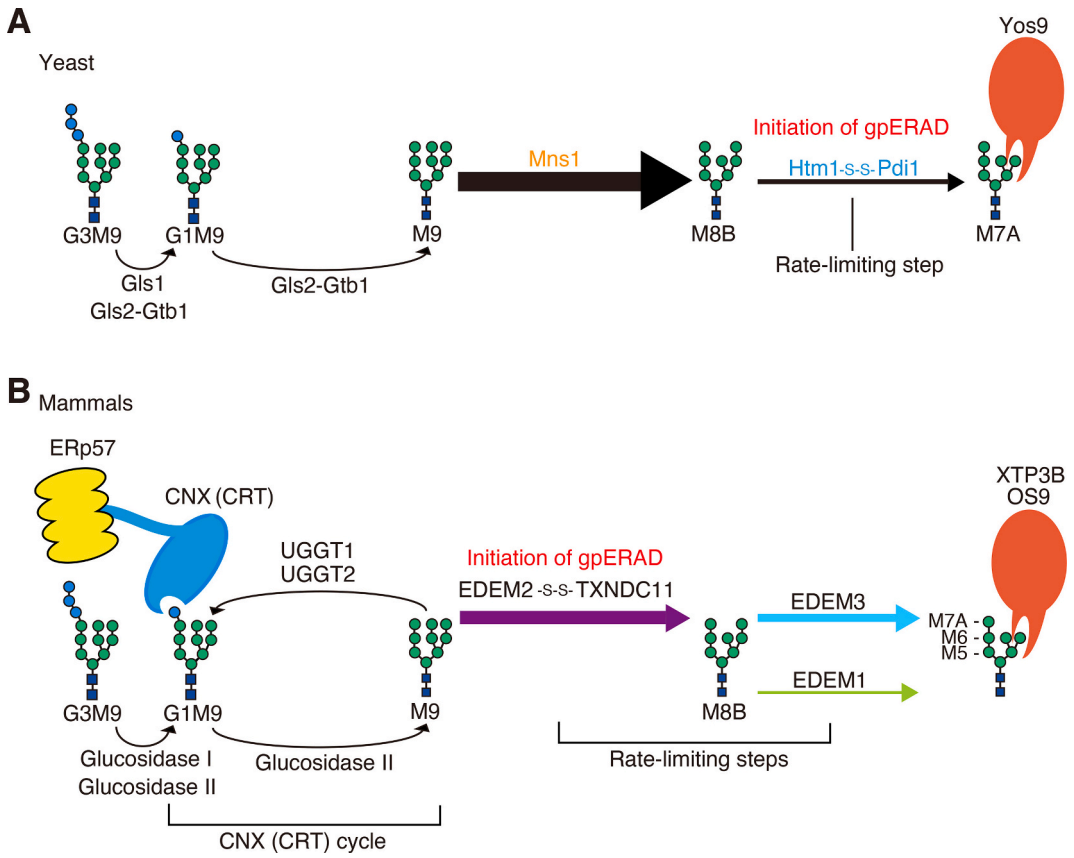

Fig. 4. *N*-glycan trimming processes for folding and degradation of glycoproteins
(A) N-glycan trimming processes in yeast. As trimming from M8B to M7A is not rapid, gpERAD starts at this step.
(B) CNX (CRT) cycle and N-glycan trimming processes in mammals. As trimming from M9 and from M8B is not rapid, gpERAD starts with trimming from M9.

respectively [28]. A substrate containing a hydrophobic region exposed on the surface binds to the ATP-bound form, which is converted to the ADP-bound form by co-chaperone-mediated stimulation of intrinsic ATPase activity to grab the substrate. The ADP-bound form is converted to the ATP-bound form by the action of nucleotide exchange factor (NEF) Lhs1 [30–32]/Grp170 [33–36] to release the substrate [37], which folds spontaneously according to Anfinsen's dogma. Still unfolded substrate containing a hydrophobic region exposed on the surface binds to the ATP-bound form again. This cycle continues until the folding is completed. Disulfide bond formation catalyzed by protein disulfide isomerase Pdi1 [38,39]/PDI family proteins [3,4,40–42] also helps productive folding.

If the time required for this folding process is extended beyond a certain limit, the chaperone cycle is terminated in yeast but probably not in mammals by Pmt1-Pmt2-mediated *O*-mannosylation of the substrate [43,44], which increases solubility and suppresses interaction with ER chaperones [45–49]. The function of mammalian BiP is regulated via AMPylation catalyzed by FIC (filamentation induced by cyclic AMP) domain protein adenyltransferase (FICD) at the site of the substrate binding domain. AMPylated BiP is inactive; it dissociates from substrate 6-fold faster than unmodified BiP, and is insensitive to co-chaperone-mediated stimulation of intrinsic ATPase activity [50–53].

In addition to the chaperone cycle and disulfide bond formation, folding of glycoproteins in the ER - although possibly not all these glycoproteins [54] - is assisted by the "calnexin (CNX)/calreticulin (CRT) cycle" in mammals [55–59]. *N*-glycan (G3M9) attached to newly synthesized protein is converted to G2M9 by the action of Gls1 [60,61]/glucosidase I [5,55,62]. G2M9 is recognized by malectin in mammals [63,64], which may serve as a first checkpoint, given that its overexpression attenuated secretion of a misfolded glycoprotein (NHK; see next section for details) [65–67]. G2M9 is converted to G1M9 by the action of Gls2 (catalytically active α subunit) complexed with Gtb1 (β subunit) [68,69]/glucosidase II, consisting of the catalytically active α subunit and β subunit (Fig. 4A and B) [70–73]. G1M9 can now be recognized by the lectin-type chaperone Cne1/CNX (transmembrane protein) or CRT (soluble protein). Folding of the protein moiety is assisted by a 1:1 complex of a lectin-type chaperone and ERp57, an oxidoreductase [74–77], and is followed by conversion of G1M9 to M9 by the action of Gls2-Gtb1/glucosidase II. If the protein moiety is folded, the substrate is transported to the Golgi apparatus. If the protein moiety is not fully folded, M9 is converted to G1M9 via re-addition of glucose by the action of UDP-glucose:glycoprotein glucosyltransferase 1 (UGGT1) [78–81] or UGGT2 [82,83], which is able to distinguish the folding status of the substrate. Folding of the substrate with G1M9 is assisted again by the complex of a lectin-type chaperone and ERp57. This process is called the CNX (CRT) cycle [55,59] (Fig. 4B). Of note, the glucosidase II-mediated conversion of G1M9 to M9 is significantly slower than that of G2M9 to G1M9 in mammals [84,85], allowing time for the action of CNX or CRT. The CNX cycle is terminated by ERAD (see below). Although yeast Cne1 works as a lectin-type chaperone toward G1M9

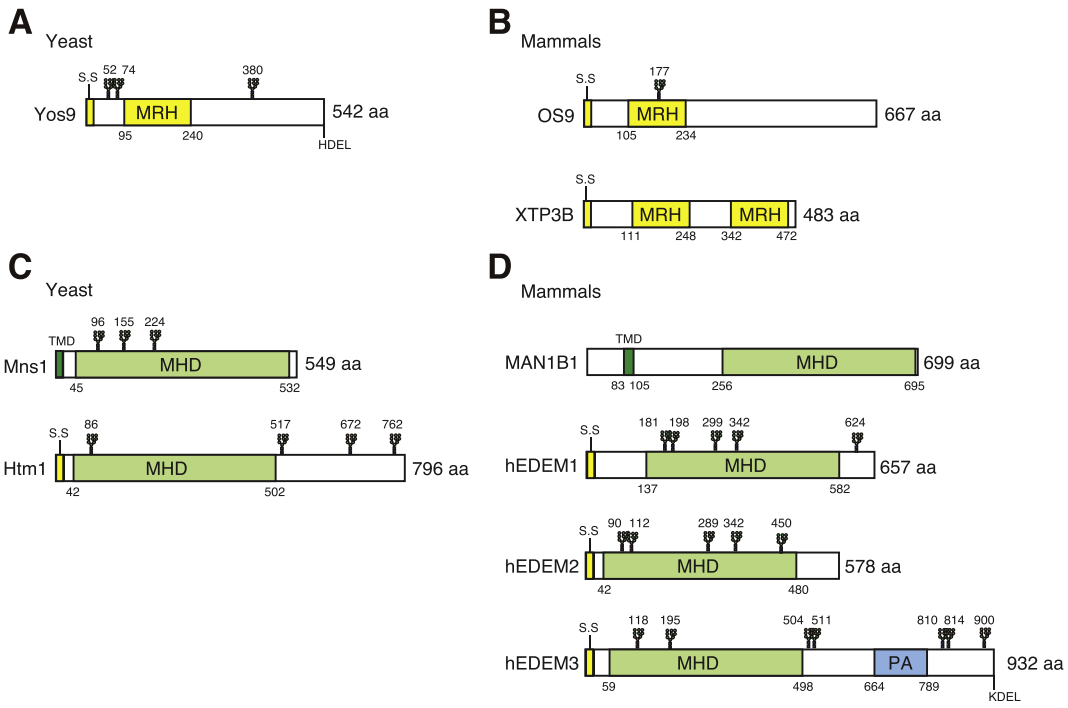

Fig. 5. Schematic structures of lectins and α1,2-mannosidases involved in gpERAD.
(A) Yeast lectin Yos9. (B) Mammalian lectins OS9 and XTP3B. (C) Yeast α1,2-mannosidases Mns1 and Htm1. (D) Mammalian α1,2-mannosidases MAN1B1 and EDEM1/2/3. s.s and PA denote signal sequence and protease-associated domain, respectively. Potential *N*-glycosylation sites are also shown with amino acid numbers.

[86–90], the Cne1 cycle is not effective in yeast, because the conversion of G1M9 to M9 by Gls2-Gbt1 is rapid [91], and because yeast (*Saccharomyces Cerevisiae*) does not have a functional orthologue of UGGTs.

3. Luminal events in ERAD-L pathway

3.1. gpERAD versus non-gpERAD

The ERAD-L pathway degrades soluble and membrane proteins with luminal defects. A feature of the luminal events in the ERAD-L pathway is the presence or absence of *N*-glycan, whose structure plays a crucial role in selecting targets for degradation, as mentioned above. Substrates with *N*-glycan are degraded via the glycoprotein ERAD (gpERAD) pathway while those without *N*-glycan are degraded via the non-glycoprotein ERAD (non-gpERAD) pathway.

The gpERAD-Ls model substrate widely used in yeast is the G255R mutant of carboxypeptidase yscY (CPY; formally Prc1), designated as CPY* [92,93]. CPY possessing four *N*-glycosylation sites folds properly in the ER and functions as one of the major soluble proteases in the vacuole. In contrast, misfolded CPY* is retained in the ER and subjected to gpERAD. Interestingly, the *N*-glycan located C-terminal to the lesion of CPY* appears to act as a destruction signal, given that the fourth *N*-glycan at the position of Asn368 is essential for degradation [94,95], although it is not clear how far this rule can be applied.

gpERAD is more efficient than non-gpERAD in yeast. The half-life of CPY* is ~30 min, whereas that of CPY* without four *N*-glycans (CPY*0000) is ~90 min [95]. Similarly, the vacuolar proteinase A (PrA) is a soluble protein which possesses two *N*-glycosylation sites, and PrA with the deletion of 55–91 aa and 295–331 aa, called PrA*Δ295–331, is degraded more rapidly than its non-glycosylated version, ngPrA*Δ295–331; indeed, 90% of PrA*Δ295–331 and 60% of ngPrA*Δ295–331 are degraded within 30 min [96].

In contrast to the case in yeast, non-gpERAD appears to be more effective than gpERAD in mammals. A truncated soluble variant designated as RI_{332} of ribophorin I, a type I transmembrane protein in the ER, is an gpERAD-Ls substrate with one *N*-glycosylation site. Its non-glycosylated form, termed RI_{332}-Thr, is degraded much faster than RI_{332} [97]. The null Hong Kong (NHK) variant, one of the most frequently used gpERAD-Ls substrates, is a soluble protein with three *N*-glycosylation sites. NHK contains a C-terminal large truncation due to a frame shift mutation of the α1 proteinase inhibitor. Its non-glycosylated form is called NHK-QQQ. Of note, the half-life of NHK is 3 h, whereas that of NHK-QQQ 1 h [98–100].

3.2. N-glycan recognition in gpERAD

As described in the Introduction, M7A, M6 and M5 become signals for the degradation of misfolded glycoproteins, owing to the exposed α1,6-linked mannosyl residue present in their C branch (Figs. 1A, 4A and B). They are decoded by a lectin-type ERAD component Yos9 [101–105]/OS9 [24,106,107] containing a mannose 6-phosphate receptor homology (MRH) domain (Fig. 5A and B). Indeed, purified full length Yos9 binds to free oligosaccharides of M8C, M7A, M6, M5 and M3 [105] and the purified MRH domain of OS9 binds to those of M8C, M7A, M7B, M6 and M5 [108,109], all of which expose an α1,6-linked mannosyl residue (Fig. 1B), as determined by frontal affinity chromatography which detects binding with weak affinity [110,111].

Yos9 is essential for the degradation of various gpERAD substrates, such as CPY*, PrA*Δ295–331, KHN and KWW (KHN and KWW are ERAD-L substrates containing four *N*-glycosylation sites; KHN is a soluble protein to which a single-pass transmembrane domain is attached to produce KWW) [101–104]. The function of Yos9 is to inspect the substrates on the Hrd1 complex to determine whether they have an appropriate *N*-glycan structure for degradation [112,113]. Yos9 has also been shown to retain misfolded proteins (CPY* variants) in the ER independently from its function as a lectin [114].

In mammals, OS9 is involved in the degradation of gpERAD substrates such as NHK [108,115] and CD147. CD147 is the first endogenous ERAD-Lm substrate possessing three *N*-glycosylation sites [116]. Further, OS9 prevents the secretion of aberrant proteins such as NHK

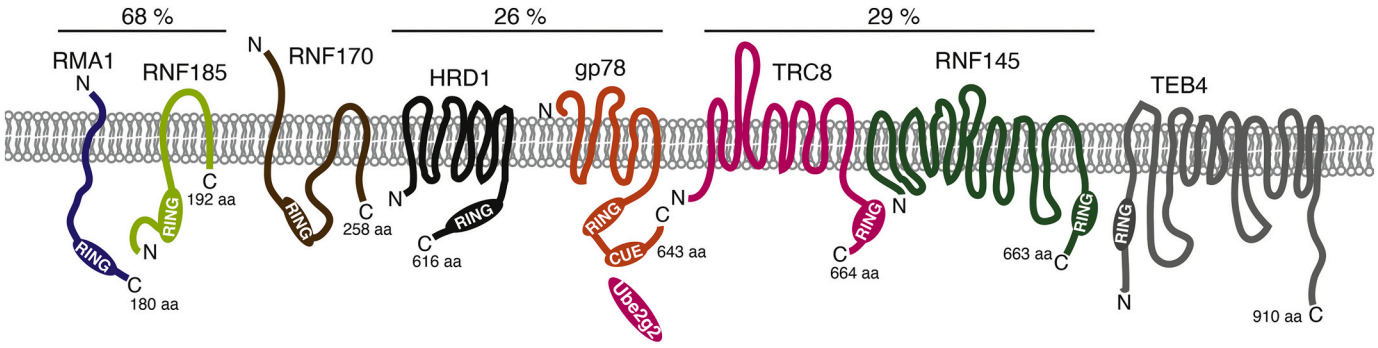

Fig. 6. Mammalian E3 ligases contributing to ERAD.
HRD1 and gp78 are the two mammalian orthologues of yeast Hrd1. TEB4 (MARCH-6) is the single mammalian orthologue of yeast Doa10. Through evolution, various E3s have become involved in ERAD. % of amino acid identity is denoted for paralogous genes.

[117]. The crystal structure of the MRH domain of OS9 indicates the importance of the continuous double tryptophan (WW) motif to its function as a lectin [118].

XTP3B is another orthologue of yeast Yos9 and has two MRH domains (Fig. 5B) [119]. Examination of the two purified MRH domains in XTP3B showed that recognition of *N*-glycan requires the C-terminal MRH2 domain, but not the N-terminal MRH1 domain [120]. The function of XTP3B in gpERAD yet remains unclear. Overexpression of XTP3B inhibited degradation of NHK, consistent with the finding that MRH2 weakly associates with M9, but not with *N*-glycans exposing an α1,6-linked mannosyl residue [121]. However, its knockdown did not show any effect on the turnover of NHK [115] or CD147 [116]. Double knockdown of OS9 and XTP3B significantly inhibited gpERAD of BACE476Δ and CD3-δ-ΔTM (soluble glycoproteins possessing four and three *N*-glycosylation sites, respectively), compared with OS9 single knockdown [24]. This inhibition was not reproducible in the cases of NHK [115] and CD147 [116] (soluble and transmembrane glycoproteins, respectively).

Recently, CRISPR/Cas9-mediated genome editing successfully produced OS9-knockout (KO), XTP3B-KO and OS9/XTP3B-double KO (DKO) cells [100]. Analysis revealed that degradation of CD147 proceeded normally in OS9-KO and XTP3B-KO cells but was blocked in DKO cells, indicating that OS9 and XTP3B play a redundant role in degradation of CD147, albeit that rescue experiments indicated the importance of MRH1 but not MRH2 of XTP3B, contrary to the biochemical experiments mentioned above. Curiously, however, although degradation of NHK was significantly delayed in DKO cells, similarly to the case of CD147, degradation of NHK was only slightly delayed in OS9-KO cells but became slightly faster in XTP3B-KO cells. Furthermore, OS9 and XTP3B are also involved in non-gpERAD in a non-redundant manner: XTP3B inhibited non-gpERAD of NHK-QQQ by binding to the *N*-glycan attached to N431 of SEL1L (a partner protein of HRD1), the only site bearing high mannose-type *N*-glycans trimmed to M7-M5 among the five *N*-glycosylation sites (N195, N217, N272, N431 and N608). This inhibition was antagonized by OS9. The molecular basis of these substrate-dependent differences in behavior remains to be resolved.

3.3. Mannose trimming from N-glycan

3.3.1. Mannose trimming from N-glycan in yeast

ER-localized α1,2-mannosidases trim M9 to M8B and then to M7A to produce the destruction signal (Fig. 4A and B). In yeast, M9 is trimmed to M8B by Mns1 [91,122,123], which belongs to glycoside hydrolase family 47 and has a mannosidase homology domain (MHD) to hydrolyze α1,2-linked mannosyl residue (Fig. 5C) [124,125]. Purified Mns1 converts almost all M9 to M8B present on both denatured proteins and free oligosaccharides in vitro. Accordingly, *N*-glycan on newly synthesized protein is immediately trimmed to M8B by the sequential actions of Gls1, Gls2-Gtb1, and Mns1 without productive folding [126]. Thus, M8B is the major form of oligosaccharide in yeast [126,127], as confirmed by whole-cell *N*-glycan profiling [127].

M8B is trimmed to M7A by Htm1 containing the MHD (Fig. 5C). Htm1 exerts its enzymatic activity only when it forms a disulfide bonding-mediated complex with Pdi1 [25,127]. Purified Htm1-Pdi1 complex certainly but weakly converts M8B to M7A on glycoprotein but not on free oligosaccharide in vitro, consistent with the abundant presence of M8B in yeast as mentioned above. This means that trimming from M8B is the rate-limiting step in yeast gpERAD (Fig. 4A). Pdi1 associates with C-terminal cysteine residues of Htm1, which in turn facilitates introduction of an intramolecular disulfide bond between two cysteine residues (C65 and C445) in the MHD of Htm1 [128]. This complex prefers a non-native to a native protein conformation, implying that gpERAD substrates are selected during this trimming step [129,130].

3.3.2. Mannose trimming from N-glycan in mammals

In mammals, the specific enzymes responsible for sequential mannose trimming long remained in the dark and were only recently identified. The primary α1,2-mannosidase candidate for trimming of M9 to M8B in the ER was MAN1B1 (previously called ER mannosidase I), as it is the single mammalian orthologue of yeast Mns1. MAN1B1 is a type II transmembrane protein with a short cytosolic region, a single transmembrane domain and a large luminal region containing the MHD (Fig. 5D). Overexpressed MAN1B1 showed co-localization with CRT [131], as well as accelerated disposal of NHK by stimulating the trimming of *N*-glycan [132]. Its recombinant protein converted free oligosaccharides from M9 to M8B in vitro [131,133], requiring calcium for its activation [134]. Compared with endogenous protein level (estimated to be ~2.3 μg/ml) [135,136], however, highly concentrated recombinant MAN1B1 (~500 μg/ml) [135] produced M6 or M5 from M9 in vitro, and knockdown of MAN1B1 increased untrimmed *N*-glycan and decreased M6 and M5, as shown by whole-cell *N*-glycan profiling [137]. Despite the proposal that overexpressed MAN1B1 was localized in the ER quality compartment (ERQC) in high concentration under proteasome inhibition [137,138], it was clearly shown that endogenous MAN1B1 was co-localized with Golgi apparatus markers such as GM130, GPP130 and Giantin [139,140] and modified by Golgi-specific *O*-glycosylation [139,141]. These results suggest that MAN1B1 might not be the specific enzyme for the conversion of M9 to M8B conducted in the ER. Interestingly, endogenous MAN1B1 in the Golgi apparatus may contribute to ERAD separately from its enzymatic activity via interaction with γ-COP, the gamma subunit of coat protein complex I (COPI), to retrieve ERAD substrates back to the ER [141,142].

Similarly to the case of MAN1B1, EDEM (ER degradation enhancing α-mannosidase-like protein) family proteins, which contain the MHD domain and consist of EDEM1, EDEM2 and EDEM3 (Fig. 5D), were

previously considered the primary α1,2-mannosidase candidates for trimming of M8B to M7A in the ER. This is because they are the three mammalian orthologues of yeast Htm1 and because overexpressed EDEM1 accelerated degradation of NHK [143]. However, since EDEM1 did not show detectable mannosidase activity in vitro, it was originally proposed that EDEM1 worked as a lectin that recognizes *N*-glycan during gpERAD [143], and also that EDEM1 acted as an acceptor of a substrate from the CNX (CRT) cycle [144,145] and then delivers it to the HRD1 complex via its MHD domain-mediated recognition of *N*-glycan on SEL1L [146]. To the contrary, however, findings showed that overexpressed EDEM1 accelerated mannose trimming from the A branch, namely from M9 to M8A and from M8B to M7C [147], as well as from the C branch, namely from M9 to M8C and from M8B to M7A [148] (see Fig. 1B). These findings supported the mannosidase activity of EDEM1.

EDEM2 and EDEM3 were discovered by homology searches using the EDEM1 sequence. Although overexpressed EDEM2 accelerated gpERAD of NHK [149] and BACE476 (a transmembrane protein possessing four *N*-glycosylation sites) [150], recombinant EDEM2 did not exhibit mannosidase activity toward M9 or M8 on free oligosaccharide in vitro [149]. In contrast, overexpressed EDEM3 increased the mobility of NHK during SDS-PAGE, reflecting a potential for mannosidase activity [151]. Thus, the question of whether EDEM family proteins work as an α1,2-mannosidase or lectin during gpERAD was long a subject of debate.

The turning point in the field came with the development of innovative genome-editing techniques [152–154]. Genetic (gene knockout) analyses of four candidates of gpERAD α1,2-mannosidase were conducted, using both conventional homologous recombination in chicken DT40 cells and transcriptional activator-like effector nuclease-mediated genome editing in human HCT116 diploid cells. Whole-cell *N*-glycan profiling revealed that M9 was drastically accumulated in EDEM2-KO cells, quite unexpectedly, and that while M8B was increased to a larger extent in EDEM3-KO cells and to a smaller extent in EDEM1-KO cells, M9 was only slightly increased in MAN1B1-KO cells. Accordingly, gpERAD substrates migrated more slowly in EDEM2-KO cells than in WT or MAN1B1-KO cells during SDS-PAGE. Thus, EDEM2 is required for the conversion of M9 to M8B, and EDEM3 and EDEM1 are required for the conversion of M8B to M7A, implying that all EDEM family proteins have α1,2-mannosidase activity [26]. This means that glycoproteins for degradation can be elaborately selected two times, firstly by EDEM2 and secondly by EDEM3 or EDEM1 (Fig. 4B).

Nonetheless, this new model needed to be proved by unambiguous demonstration of in vitro mannosidase activity of EDEM family proteins, particularly of EDEM2. In a timely fashion, genome-wide CRISPR/Cas9-mediated forward genetic screen and gene-trap haploid mutagenesis screen both identified TXNDC11 (thioredoxin domain containing 11), an oxidoreductase, as a gene product required for degradation of the major histocompatibility complex (MHC) class I molecule, a gpERAD substrate, in addition to EDEM2, EDEM1 and PDI. TXNDC11 is an ER-resident protein which contains five thioredoxin (Trx)-like domains [155,156]. Interaction of TXNDC11 with EDEM2 and EDEM3 raised expectations that TXNDC11 plays a critical role in expression of EDEM2's mannosidase activity, similar to that of Pdi1 in expression of Htm1's mannosidase activity. However, subsequent studies apparently failed to show expected mannosidase activity in vitro using EDEM2 immunoprecipitated from cultured cells overexpressing EDEM2 or those overexpressing both EDEM2 and TXNDC11 [157], probably due to insufficient recovery of the complex in immunoprecipitates; of note, TXNDC11 containing a hydrophobic region in its N-terminus was expressed as a transmembrane protein when translated from Met1.

The key to progress in this field was analysis of non-reducing SDS-PAGE. Approximately 75% of endogenous EDEM2 in HCT116 cells was covalently disulfide-bonded to TXNDC11, which was essential for EDEM2 to carry out the first mannose trimming step in the cell. Most importantly, M9 on free oligosaccharide was clearly converted to M8B by an EDEM2-TXNDC11 complex purified as soluble proteins using an alternative translational initiation of TXNDC11 [158]; it turned out that the hydrophobic region in the N-terminus functioned as a signal sequence when TXNDC11 was translated from Met58. This was the first clear demonstration of in vitro α1,2-mannosidase activity toward free oligosaccharide among EDEM family proteins, which include Htm1. Thus, the notion that EDEM2 catalyzes the first mannose trimming step and thereby initiates gpERAD is now firmly supported by both genetic and biochemical analyses.

In the case of EDEM3, TCRα with three *N*-glycosylation sites migrated faster during SDS-PAGE after incubation with purified EDEM3, indicative of EDEM3's mannosidase activity. This effect appeared to be enhanced by co-overexpression in the cell of EDEM3 and ERp46, a member of the PDI family with three Trx domains [159]. It remains to be determined whether ERp46 is an essential component for mannosidase activity of endogenous EDEM3.

Given findings that lectin-type cargo receptor VIP36 or VIPL prefers untrimmed or less trimmed *N*-glycan, such as M9, M8B, M8C and M7A [160], whereas ERGIC53 can bind to various *N*-glycan forms including M6 and M5 [160,161] for transport from the ER to the Golgi apparatus, determination of the exact route(s) by which *N*-glycan is trimmed from M8B to M5 (with no α1,2-linked mannosyl residue) in vitro and in the cell by EDEM1 and EDEM3 requires further analysis.

3.4. Delivery of gpERAD substrates to the Hrd1/HRD1 complex

In yeast, Yos9, Kar2 and Hrd3 (a partner of Hrd1) can form a complex in the ER lumen, whereas Yos9 and Hrd3 can recruit both misfolded glycoproteins such as CPY* and misfolded non-glycoproteins such as CPY*0000, independently of each other [113]. This effect is consistent with the subsequent finding [114], as mentioned above. Kar2 can maintain the solubility of ERAD substrates as a chaperone. Taken together, gpERAD substrates appear to have two routes to reach the retrotranslocon. The first is that gpERAD substrate bound to Kar2 binds to Yos9 after mannose trimming to M7A, and the three-protein complex binds to Hrd3 for subsequent degradation via Hrd1. The second is that gpERAD substrate bound to Kar2 directly binds to Hrd3 after mannose trimming to M7A and Yos9 joins the three-protein complex for subsequent degradation via Hrd1.

In mammals, because OS9 and XTP3B bind to SEL1L (the single mammalian orthologue of yeast Hrd3) via their MRH domains [100,115], similar two routes appear to operate for delivery of gpERAD substrates to the HRD1 complex, albeit that OS9 - but not XTP3B - prefers GRP94, an ER chaperone of the Hsp90 family [115].

However, extensive studies on EDEM1 have challenged this scenario. As mentioned above, EDEM1 binds to SEL1L via its MHD domain [146], suggesting that EDEM1 can directly deliver gpERAD substrates to the retrotranslocon after conducting mannose trimming to M7A. Furthermore, multiple modes were identified for EDEM1 to interact with ERAD substrates as well as with ERAD components, namely glycan-dependent interaction with SEL1L, thiol-dependent as well as weak protein-protein interaction with NHK, and intrinsically disordered region (located at the N-terminus and C-terminus of EDEM1)-mediated interactions with ERdj5 and the gpERAD substrate tyrosinase [162]. These findings support the role of EDEM1 as a hub in gpERAD.

Nevertheless, given that EDEM3 also binds to SEL1L [26,163] and plays a major role in mannose trimming from M8B to M7A [26], a conclusive understanding of the mechanisms by which misfolded glycoproteins are delivered to the retrotranslocon requires extensive comparative analysis using EDEM1, EDEM3, OS9 and XTP3B.

3.5. Non-gpERAD mediated via Kar2/BiP complex

In yeast, degradation of not only soluble non-glycosylated substrates but also glycosylated substrates depends on Kar2 [96,164,165], and Scj1 or Jem1 [166], as non-glycosylated ngPrA*Δ295–331 [96] and glycosylated CPY* [165,166] were not degraded in yeast cells carrying a mutation of Kar2 or in yeast cells lacking both Scj1 and Jem1, although

Lhs1 appeared to be involved only in non-gpERAD (degradation of non-glycosylated form of the epithelial Na^+ channel, ENaC [167]). Notably, Slp1-Emp65 binds to unfolded proteins and decreases erroneous degradation of actively folding soluble proteins such as CPY by 20–30% [168].

In mammals, co-chaperones of BiP [169,170], namely DnaJ-like proteins ERdj4 and ERdj5, facilitated degradation of the Akita (Cys96-Tyr) mutant of insulin (a soluble non-glycoprotein) and surfactant protein C (a non-glycosylated integral membrane protein) [171]. Grp170 [33,37,172,173] facilitated non-gpERAD (Akita mutant of insulin), but probably not gpERAD. These findings indicate the importance of the chaperone cycle in non-gpERAD, but not in gpERAD. Further, Grp170 prevented aggregation of mutant proinsulin and promoted secretion of properly folded proinsulin [174]. Native but unstable or somewhat unfolded glycoproteins, such as ATF6 (see below for details) and CD147, were degraded only via the gpERAD pathway, whereas glycoproteins possessing a severely misfolded region, such as NHK, were targeted to the non-gpERAD machinery as well (Fig. 3, broken arrow) [99,100,156]. Elucidation of this molecular basis may provide an answer to an important question of how *N*-glycans or any other mechanisms prevent misfolded glycoproteins from entering non-gpERAD until the determinant mannose residue is exposed.

3.6. Reduction of ERAD-L substrates

Disulfide bonding can be a conformational obstacle to the dislocation of substrates to the cytosol [175]. In yeast, several paralogues of Pdi1 are candidates of such reductase [4,38,176], but the mechanism by which disulfide bonds are reduced prior to retrotranslocation remains an open question. It was first reported in mammals that ERdj5 accepted ERAD substrates from EDEM1 and cleaved their disulfide bonds through the reductase activity present in its C-terminal Trx domains [177,178]. Nevertheless, as ERdj5-KO mice are healthy, other molecules are likely to play a redundant role [179]. PDI is known to play a critical role not only in the oxidation of various substrates for folding, but also in the reduction of substrates. For example, PDI reduced Akita mutant proinsulin [180–182] and the hedgehog precursor to allow retrotranslocation [183], but its universality is not established. Although TMX4, a transmembrane Trx-like protein 4 localizing at the ER, interacted with CNX and showed reductase activity in an ER redox environment in vitro, its role in the cell is not determined [184]. Of the five predicted Trx-like domains in TXNDC11, only Trx5 has a complete CXXC motif and exhibits reductase activity in vitro [155]. However, since most of the first cysteine in the CXXC motif in Trx5 are occupied to produce stable disulfide bonding with EDEM2 in HCT116 cells [158], it seems difficult to consider that TXNDC11 would work as a reducing enzyme.

4. Retrotranslocation from ER to cytosol

4.1. E3 ligase Hrd1/HRD1 complex

A pivotal component of the ERAD-L pathway which functions at the ER membrane is the Hrd1 [185–187]/HRD1 [12,24,188,189] complex (Figs. 2 and 3). Hrd1/HRD1 is a multi-spanning membrane protein with a cytosolic RING finger domain which mediates the ubiquitination of retrotranslocated substrates. The critical component of the Hrd1/HRD1 complex is Hrd3 [113,190,191]/SEL1L [107,115,192–194], a single-pass transmembrane protein containing a large luminal region. Hrd3/SEL1L works as an acceptor of substrates onto the Hrd1 complex [112,115,190,192,195–197]. Several yeast analyses have now largely established that the Hrd1-Hrd3 complex itself is the retrotranslocation channel by which substrates are brought back from the ER to the cytosol [198]. Oligomerized Hrd1 directly interacts with substrates undergoing ERAD, as shown by photocrosslinking [199]. The structure of the Hrd1-Hrd3 complex revealed by Cryo-EM showed that Hrd1 has eight transmembrane domains, five of which assemble to form an aqueous channel [200]. Hrd1 has two substrate binding sites, namely a low-affinity luminal site and a high-affinity cytosolic site, and it is these which drive the movement of substrates. Its pore - required for the retrotranslocation of substrates - is opened by auto-ubiquitination of Hrd1 and closed by deubiquitination [191,201]. Proteoliposome containing purified Hrd1 transfers soluble [202] and transmembrane substrates [191] outside of the lipid bilayer.

4.2. E3 ligase gp78 and ERAD-Lm in mammals

HRD1 and its paralogue gp78 (Fig. 6) have been shown to be essential for the degradation of ERAD-Lm substrates such as BACE476 and NHK_{BACE}, namely NHK artificially attached to the transmembrane region of BACE, but SEL1L was considered unnecessary for the degradation of these substrates [24]. However, the category of ERAD-Lm has been broadened by findings concerning the degradation-requirements of endogenous ATF6 [203–205]. ATF6, a type II transmembrane protein possessing three *N*-glycosylation sites, is constitutively subjected to gpERAD with a half-life of 2 h and its degradation requires SEL1L [206]. Furthermore, endogenous IRE1, an ERAD-Lm substrate, also requires SEL1L for its destruction [207]. Now, ERAD-Lm substrates are classified into three subgroups: class I, requiring neither mannose trimming nor SEL1L (BACE457, TCR-α); class II, requiring mannose trimming but not SEL1L (CD3-δ, CD147); and class III, requiring both mannose trimming and SEL1L (ATF6, IRE1) [206,207]. Moreover, gp78 has its own specific substrates; examples are CD3-δ, a transmembrane protein with three *N*-glycosylation sites which fails to assemble in the absence of its partner proteins [10,208]; and Insig-1, a multi-spanning membrane protein which is required for the retention of SREBP-SCAP complex at the ER [209–211]. Functionally, gp78 is coupled with the soluble E2 ligase Ube2g2, which is recruited to the Cue domain of gp78 (Fig. 6) [212–218].

4.3. Hrd1/HRD1 accessory proteins

Usa1 [18,219,220]/Herp1, Herp2 [18,221–223], which possesses an N-terminal ubiquitin-like domain (UBL) and a hairpin-like transmembrane region, is critical to both ERAD-L and -M, and contributes to oligomerization of Hrd1/HRD1. HRD1 oligomerization is also mediated by FAM8A1 [223,224]. The N-terminal region of Usa1 binds to the cytosolic part of Hrd1, while its C-terminal region binds to Der1 for recruitment to the Hrd1 complex. Der1 - constituting the retrotranslocon with Hrd1 - is required for degradation of CPY* by transferring substrates into the cytosol [18,196,225–227]. N-terminal acetylation of Der1 by Nat3 is required for stability of Der1 [228].

Mammalian Derlin1, Derlin2 and Derlin3, the three orthologues of yeast Der1, are inactive members of the rhomboid intramembrane protease family [195,229,230]. Derlin1 and Derlin2 are expressed ubiquitously, whereas Derlin3 is expressed at specific tissues such as placenta and pancreas [231]. Derlin1 is characteristically different from Derlin2 and Derlin3. Derlin1, which consists of six transmembrane regions, was found to be involved in virally induced degradation of MHC class I through the interaction with the human cytomegaloviral protein US11 [229,230,232]. It promotes ERAD using the active site of the rhomboid domain to induce retrotranslocation of ERAD-Ls substrates [233,234] and enhances ubiquitylation of the epithelial Na^+ channel (ENaC), whose subunits require assembly for folding [235]. Derlin1, but not Derlin2, facilitates the retrotranslocation of cholera toxin [236]. In contrast, Derlin2 and Derlin3 are highly homologous and play a redundant role in the degradation of various ERAD-Ls substrates, such as proinsulin [237], the cleaved form of C-terminal SHH [238], RI_{332} [239], and BACEΔ476, as well as the ERAD-Lm substrate ATF6 [222]. Derlin2 appears to be present at a higher level than Derlin1 in the HRD1-SEL1L complex, supporting findings that Derlin2 and Derlin3 participate in the function of the HRD1-SEL1L complex [195,222,238]. SEL1L-dependent ERAD-Ls and -Lm substrates require Derlin2/3 and Herp1/

2 for degradation [222].

4.4. E2 ligases involved in ERAD-L

Yeast Hrd1 primarily utilizes Ubc7 and, less frequently, Ubc6 or Ubc1 as an E2 ubiquitin-conjugating enzyme for its activation [187,240]. Ubiquitination of misfolded MHC I is mediated by HRD1 and Ube2j1 but not Ube2j2 [241] in mammals, both of which are orthologues of yeast Ubc6 [242]. Cue1 [240,243–246]/AUP1 [107,247], a type II membrane protein with a large cytosolic region, recruits E2 enzymes via its CUE domain to cause the elongation of polyubiquitin. AUP1 is involved in the degradation of RI_{332}, NHK [247], Insig-1 and HMG-CoA reductase [215,248].

4.5. E3 ligases localizing at the ER membrane in mammals

In mammals, several ERAD-related E3 ligases are localized at the ER membrane, including RMA1 (RNF5), RNF185, RNF170, TRC8 (RNF139), RNF145, and TEB4 (MARCH-6) (Fig. 6). These E3 ligases appear to be involved in ERAD-M or -C pathways by degrading specific substrates.

RMA1 is a single-pass transmembrane protein which is involved in the degradation of the pathogenic mutant ΔF508 of cystic fibrosis transmembrane conductance regulator (CFTR), together with Ube2j1, VIMP, Derlin1 and gp78 [230,249–253]. RNF185, with two C-terminal transmembrane domains, works with its paralogue RMA1 to degrade CFTR [254,255]. RNF170, with three transmembrane domains, interacts with activated IP_3 receptors to catalyze ubiquitination [256]. TRC8 is a multi-spanning membrane protein which mediates the degradation of MHC class I [257], Insig-1, Insig-2 [258] and misfolded human ether a go-go-related gene (hERG), a potassium channel with a disease mutation at Gly601Ser [259]. RNF145 is a multi-spanning membrane protein (described as having fourteen transmembrane regions [260]) which shares 29% amino acid identity with TRC8 by BLAST search and, together with gp78 and HRD1, facilitates the degradation of HMG-CoA reductase, indicating redundancy in the function of ER-membrane E3 ligases [215,260–262].

TEB4 (MARCH-6) is the orthologue of yeast Doa10 [263,264], which plays a pivotal role in ERAD-C, and is involved in the degradation of transmembrane proteins having a large cytosolic region, such as HMG-CoA reductase [265], iodothyronine deiodinase [266] and lanosterol 14 α-demethylase [267]. A pathological mutant form of NPC1, I1061T/I1061T, which has a multi-pass transmembrane domain, is also degraded by TEB4 [268], whereas TRC8 and TEB4 are required for the degradation of the tail-anchored protein heme oxygenase-1 [269]. In mammals, ERAD-M and -C are not clearly distinguished, except for the case of CHIP E3 ubiquitin ligase, which engages only in ERAD-C and utilizes cytosolic Hsp70 to recognize folding defects of CFTR [250,270,271].

5. Extraction and degradation in cytosol

ERAD-L, -M and -C pathways are integrated into a cytosolic homohexamer Cdc48 [272–276]/p97 (VCP) [230,277], AAA-ATPase, complexed with Ufd1/UFD1 and Npl4/NPL4, which extracts polyubiquitinated substrates from the retrotranslocon [12,230]. The Cdc48/p97 complex, which is recruited to the Hrd1/HRD1 complex by Ubx2 [278,279]/UBXD8 [280–282] via its ubiquitin regulatory X (UBX) domain, conducts the unfolding of a broad range of substrates through the initial unfolding of ubiquitin attached to the substrate [283]. The function of UBXD8 in recruitment of the p97 complex to the ER membrane might be largely replaced by the Derlin family proteins in mammals [107,195,230]. Furthermore, Otu1 [202,284,285]/YOD1 [284], a de-ubiquitinating enzyme recruited onto the Cdc48/p97 complex via its UBX domain, facilitates cleavage of the polyubiquitin chain and substrate release.

N-glycan is a structural obstacle to proteasomal degradation and is thus removed in the cytosol by Png1 [5,286–289]/PNGase [5,290] via interaction with the proteasomal subunit Rad23 [291] prior to polypeptide digestion. In yeast, profiling of the free oligosaccharides generated mostly by Png1 revealed that half of them are generated via the ERAD-L pathway, but that M8B was unexpectedly the most abundant, even though it does not act as a signal for degradation [292,293]. This implies that a portion of glycoproteins is degraded irrespective of the *N*-glycan structure. In mammals, after deglycosylation by PNGase, ENGase hydrolyses a reducing terminal *N*-acetylglucosamine of free oligosaccharides [294,295]. Man2C1 subsequently cleaves specific α1,2-, α1,3- and α1,6-linked mannosyl residues [296,297]. Both the polypeptide and its *N*-glycan, which are originally localized in the ER lumen, are finally digested by the cytosolic machinery.

6. Concluding remarks

Since its discovery in the mid-1990s, ERAD (ERAD-L currently) has fascinated numerous researchers, as it consists of three interesting steps, namely 1) recognition and processing, 2) retrotranslocation and simultaneous ubiquitination, and 3) extraction and degradation by the proteasome. Understanding of the molecular mechanisms of ERAD-L has made great progress using yeast as a model system. Thanks to the power of yeast genetics, many components have been identified, including Mns1 and Htm1 for step 1; Yos9, Hrd1, Hrd3, Usa1, Der1, Ubx2, Cue1, and Ubc7 for step 2; Cdc48, Ufd1, Npl4, and Otu1 for step 3 (Fig. 2).

Analysis of the mechanisms of mammalian ERAD-L has been primarily based on the findings in yeast ERAD-L, but redundant expression of yeast orthologues in mammals has been encountered (Fig. 3). This may reflect an evolutionary consequence of increasing needs in the quantity or quality (i.e. requirement of fine-tuning) of the productive folding and ERAD toward mammals. Knockout of Derlin1 [298], Derlin2 [239] or HRD1 [189] in mice causes embryonic lethality at stage E7, E13.5 or E13.5, respectively, while that of gp78 exhibits age-related non-alcoholic steatohepatitis [299], indicating that even the diverged components have non-overlapping and essential functions. An important exception is the Cdc48/p97 complex in the cytosol, which functions in step 3. Polypeptides retrotranslocated from the ER are already fated for degradation, raising the possibility that diverged genes and complicated degradation processes are not necessary. Interestingly, some ERAD components are utilized for other purposes. For example, UBXD8 [280–282] and AUP1 [247,300,301] work at lipid droplets to recruit p97 and Ube2g2, respectively.

Analysis of redundant components of mammalian ERAD-L was based on knockdown or overexpression. Recently, however, the advent of extremely innovating genome editing technology has changed the world, as described in the sections of *N*-glycan recognition [100] and mannose trimming [26]. Mammalian cultured cells can now be handled like yeast cells. This technology opens the way to exciting new insights into the mechanisms of ERAD; and given its involvement in the pathogenesis of more than 60 diseases - including Alzheimer's, Parkinson's, Huntington's diseases and amyotrophic lateral sclerosis [302] – the need for such discovery is urgent and clear.

Declaration of Competing Interest

None.

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Appendix table

Table 1
List of yeast components and their mammalian counterparts involved in productive folding and ERAD [303–349].

Components (Yeast)	Note	Components (Mammals)	Note
Kar2	Chaperone [27, 303], translocation [304-306] non-gpERAD [96], gpERAD [165]	BiP	Chaperone [37, 303], translocation [307, 308], inactivated by AMPylation [52], non-gpERAD [169, 170]
Lhs1	Chaperone [309], NEF [30], translocation [31, 32], non-gpERAD [30, 167]	Grp170	Chaperone [35, 36], NEF [33], translocation [34], non-gpERAD [172, 173]
–	–	FICD	Inactivates BiP by AMPylation [50, 52]
Scj1	Co-chaperone, Hsp40 [310], gpERAD [166], non-gpERAD [96]	ERdj1 (DNAJC1)	Translational regulator [28]
		ERdj2 (Sec63L)	Translocation, complexed with Sec61 and Sec62 [311]
		ERdj3 (DNAJB11)	Co-chaperone, recruits substrates to BiP [312, 313]
		ERdj4 (DNAJB9)	Co-chaperone [314], non-gpERAD [171]
–	–	ERdj5 (DNAJC10)	Co-chaperone, non-gpERAD [171], reductase [177, 178, 315]
Jem1	Co-chaperone, Hsp40 [316], gpERAD [166], non-gpERAD [96]	ERdj6 (p58, DNAJC3)	Co-chaperone, Hsp40, in cytosol [317] and ER [318]
Pmt1	*O*-mannosylation [319, 320]	POMT1	*O*-mannosylation [321-323]
Pmt2	*O*-mannosylation, heterodimerized with Pmt1 [320]	POMT2	*O*-mannosylation [321-323]
Gls1 (Cwh41)	Transmembrane protein [61], glucosidase I [60, 324]	MOGS	Transmembrane protein, complexed with Sec61 and glucosidase I [55, 62, 325, 326]
Gls2	Glucosidase II α subunit [70]	GANAB (GIIα)	Glucosidase II α subunit (a catalytic subunit) [73, 327]
Gtb1	Glucosidase II β subunit [68]	PRKCSH (GIIβ)	Glucosidase II β subunit with MRH domain and ER localization signal [71, 327]
–	–	Malectin	Lectin recognizing G2M9 [63, 64]
Cne1	Lectin chaperone [87, 328]	Calnexin (CNX)	Lectin chaperone recognizing G1M9 [55, 329]
		Calreticulin (CRT)	Lectin chaperone recognizing G1M9 [55, 329]
–	–	ERp57 (PDIA3)	Complexed with CNX or CRT [75] promoting formation of disulfide bonds [74]
–	– (in *Saccharomyces cerevisiae*)	UGGT1	Reglucosylates M9 to produce G1M9 [78-81]
		UGGT2	Reglucosylates M9 to produce G1M9 [82, 83]
Yos9	Lectin with MRH domain recognizing a terminal α1,6-linked mannosyl residue [105], retention of misfolded proteins [114]	OS9	Lectin with MRH domain recognizing a terminal α1,6-linked mannosyl residue [109], complexed with GRP94 [115], retention of misfolded proteins [117]
		XTP3B	Lectin with two MRH domains [120] recognizing a terminal α1,6-linked mannosyl residue [100], prevention of ERAD in certain cases [100, 121]

Mns1	Transmembrane protein [123, 127, 330-332], ER mannosidase, *N*-glycan trimming from M9 to M8B [91, 122, 123]	MAN1B1 (ERmanI)	Transmembrane protein, mannosidase [131, 133, 135], endogenous protein localized at Golgi [139, 140], *N*-glycan trimming from M9 [131, 333]
Htm1	ER mannosidase, *N*-glycan trimming from M8B to M7A [25, 127], complexed with Pdi1 via disulfide bond [25, 127, 128]	EDEM1	ER mannosidase, *N*-glycan trimming from M8B to M7A [26, 157], induced by ER stress [143], soluble or transmembrane protein [334]
		EDEM2	ER mannosidase, *N*-glycan trimming from M9 to M8B [26, 158]
		EDEM3	ER mannosidase, *N*-glycan trimming from M8B to M7A [26, 159]
–	–	TXNDC11	Required for mannosidase activity of EDEM2 [158], complexed with EDEM2 via disulfide bond [155, 158] and EDEM3 [155], alternative translational initiation sites [158]
–	–	ERp46	Oxidoreductase [335], enhances mannosidase activity of EDEM3 [159]
Pdi1	Oxidoreductase [38], complexed with Htm1 via disulfide bond [25, 127, 128]	PDI (P4HB)	Oxidoreductase [3], reductase [180-182]
Hrd1	Multi-spanning transmembrane protein, E3 ligase [186], central component for ERAD-L, retrotranslocation channel [191, 196, 200-202]	HRD1 (Synoviolin)	Multi-spanning transmembrane protein, E3 ligase [188], central component for ERAD-L, required for stabilization of SEL1L [98]
		gp78 (AMFR)	E3 ligase [209] with Cue domain [249], ERAD-Lm [24]
Hrd3	Acceptor of substrates onto Hrd1 complex [113], required for stabilization of Hrd1 [190], stimulates Hrd1 E3 activity [336]	SEL1L	Acceptor of substrates onto HRD1 complex [115]
–	–	FAM8A1	Required for oligomerization of HRD1, recruits Herp1 to HRD1 complex [223, 224]
Usa1	Required for oligomerization of Hrd1, recruits Der1 to Hrd1 complex [18, 219, 220]	Herp1 (HERPUD1)	Similar domain structure with Usa1 [18], induced by ER stress [337], upregulates HRD1-mediated ubiquitination [338], recruits Derlin2 to HRD1 [221]
		Herp2 (HERPUD2)	Overlapping role with Herp1 [221, 222], expressed constitutively, recruits Derlin2 to HRD1 [221]
Der1	Rhomboid superfamily member [339], ERAD-L, constitutes retrotranslocon with Hrd1 [196, 227], N-terminal acetylation [228]	Derlin1	Rhomboid superfamily member [339], recruits p97 [229, 230]
		Derlin2	Rhomboid superfamily member [339], assembled with HRD1 complex [195, 238], recruits p97 [195]
		Derlin3	Rhomboid superfamily member [339], overlapping role with Derlin2 [221, 222], expressed in specific tissues [231]
Dfm1	Rhomboid superfamily member with SHP box motif that binds Cdc48 [19, 340, 341], ERAD-M [19, 339]	RHBDL4	Active rhomboid protease involved in intramembrane proteolysis [342, 343], interacts with p97 [342, 344]
Ubc1	E2 ligase for Hrd1 [154]	-?	-?
Ubc6	E2 ligase for Hrd1 [187]	Ube2j1	E2 ligase for HRD1 [241]
		Ube2j2	E2 ligase [241]
Ubc7	Main E2 ligase for Hrd1 [187, 240]	Ube2g2	E2 ligase, recruited to CUE domain of gp78 [212-216]
Cue1	Recruits Ubc7 to Hrd1 complex [240, 244, 245]	AUP1	Recruits Ube2g2 to E3 [301], associated with HRD1 and gp78 [248], ERAD-L [107, 215, 247, 248], localized at ER and lipid droplet [247]

Cdc48	Extracts ubiquitinated substrates [272, 273]	p97 (VCP)	Extracts ubiquitinated substrates [272, 277]
Npl4	Cofactor of Cdc48 [272]	NPL4	Cofactor of p97 [272]
Ufd1	Cofactor of Cdc48 [272]	UFD1	Cofactor of p97 [272]
Ubx2	Recruits Cdc48 complex to Hrd1 complex via UBX domain [278, 279]	UBXD8	Recruits p97 complex to HRD1 complex via UBX domain [281, 282, 345], localized at ER and lipid droplet [280]
–	–	TRC8 (RNF139)	E3 ligase at ER membrane [257, 259, 261, 269, 346]
–	–	RNF145	E3 ligase at ER membrane playing partially redundant role with HRD1 and gp78 [215, 260, 262]
–	–	RNF170	E3 ligase at ER membrane [256]
–	–	RMA1 (RNF5)	E3 ligase at ER membrane [250, 251], cooperates with gp78 [249]
–	–	RNF185	E3 ligase at ER membrane [215, 255, 260, 262, 347]
Doa10	E3 ligase for ERAD-C [20, 21, 23]	TEB4 (MARCH6)	E3 ligase at ER membrane for ERAD-C or -M [263-266, 269, 347]
Otu1	De-ubiquitinating enzyme [202]	OtuB1	Inhibition of ubiquitination in response to DNA damage [348], not involved in ERAD
		YOD1	De-ubiquitinating enzyme for ERAD [284], functional orthologue of yeast Otu1
Png1	Removes *N*-glycan at cytosol [286-288]	PNGase (Ngly1)	Removes *N*-glycan at cytosol [290, 349]
–	–	ENGase	Processes *N*-glycan removed from ERAD substrates [294, 295]
–	–	Man2C1	Processes *N*-glycan further after ENGase [296, 297]

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