Endoplasmic reticulum-associated degradation of glycoproteins in plants

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Quality control and maintenance of protein homeostasis in the endoplasmic reticulum (ER) require the expression of molecular chaperones that assist protein folding and the recognition and elimination of non-native proteins by proteolytic degradation (Hegde and Ploegh, 2010; Smith et al., 2011). Many soluble and membrane-bound proteins are glycoproteins and the recognition of specific protein-bound sugar residues by lectins as well as the processing of the protein-bound oligosaccharides by glycosylation enzymes are crucial events during protein folding and ER-quality control processes (Helenius and Aebi, 2004). Nascent polypeptides that enter the ER are frequently glycosylated at asparagine residues in Asn-X-Ser/Thr consensus sequences. This type of protein glycosylation (termed N-glycosylation) occurs co-translationally in the ER by transfer of the oligosaccharide precursor (Figure 1A). Immediately after the transfer the two terminal glucose residues are cleaved off by α-glucosidase I and II and the resulting polypeptides with monoglycosylated glycan structures are subjected to folding and modifications involving the formation of disulfide bridges, assembly of subunits to multi-protein complexes, and glycosylation. During these processes incompletely folded, terminally misfolded, and unassembled proteins can accumulate which endanger the cellular homeostasis and subsequently the survival of cells and tissues. Consequently, organisms have developed a quality control system to cope with this problem and remove the unwanted protein load from the ER by a process collectively referred to as ER-associated degradation (ERAD) pathway. Recent studies in Arabidopsis have identified plant ERAD components involved in the degradation of aberrant proteins and evidence was provided for a specific role in abiotic stress tolerance. In this short review we discuss our current knowledge about this important cellular pathway.

Keywords: endoplasmic reticulum, protein degradation, protein quality control, ubiquitin–proteasome, protein glycosylation

In all eukaryotes the endoplasmic reticulum (ER) has a central role in protein folding and maturation of secretory and membrane proteins. Upon translocation into the ER polypeptides are immediately subjected to folding and modifications involving the formation of disulfide bridges, assembly of subunits to multi-protein complexes, and glycosylation. During these processes incompletely folded, terminally misfolded, and unassembled proteins can accumulate which endanger the cellular homeostasis and subsequently the survival of cells and tissues. Consequently, organisms have developed a quality control system to cope with this problem and remove the unwanted protein load from the ER by a process collectively referred to as ER-associated degradation (ERAD) pathway. Recent studies in Arabidopsis have identified plant ERAD components involved in the degradation of aberrant proteins and evidence was provided for a specific role in abiotic stress tolerance. In this short review we discuss our current knowledge about this important cellular pathway.

ERAD of glycoproteins in yeast and mammalian cells

In different eukaryotic cells, glycosylated and non-glycosylated ER-luminal as well as integral membrane proteins have been identified as ERAD substrates. Based on the location of the misfolded lesion in the protein that is subjected to disposal, ERADL (lesion in the luminal region), ERADC (defect in the cytoplasmic region), and ERADM (defect in transmembrane domain) substrates have been distinguished (Vashist and Ng, 2004; Bernasconi et al., 2010). Analysis of individual components of the ERAD complex and a recent systematic investigation of the ERAD interaction network and substrate-specific degradation pathways (Denic et al., 2006; Sato et al., 2009; Christianson et al., 2012) revealed that the yeast and mammalian ERAD complexes use a highly adaptive mechanism to remove different classes of substrate proteins. In yeast, the membrane-bound DOA10 E3 ubiquitin ligase complex is involved in degradation of ERADc substrates, while the HRD complex is required for disposal of ERADL and ERADM substrates. The HRD pathway is also a core ERAD route for degradation of non-native proteins in mammals. Central to this complex is the membrane-spanning HRD1 E3 ubiquitin ligase, which forms a stoichiometric complex with the membrane-anchored SEL1L (HRD3 in yeast). SEL1L is a type I membrane protein with a luminal tetratricopeptide repeat containing domain that is involved in binding and recognition of misfolded proteins (Gauss et al., 2006; Iida et al., 2011).

Abbreviations: ER, endoplasmic reticulum; ERAD, endoplasmic reticulum-associated degradation; MRH, mannose-6-phosphate receptor homology; UPR, unfolded protein response.
Another well-characterized component of the yeast HRD1 ERAD complex is the mannose-6-phosphate receptor homology (MRH) domain containing protein YOS9 (Bhamidipati et al., 2005; Kim et al., 2005; Szathmary et al., 2005). This luminal lectin interacts with HRD3 and together they perform proofreading of glycosylated ERAD substrates by recognition of a bipartite signal that is composed of a certain non-native protein conformation and the specific glycan signal (Hebert et al., 2010; Hosokawa et al., 2010). In the prevalent model, YOS9 or its mammalian counterparts OS9 and XTP3-B act as glycan-dependent sensors of client proteins and bind through their MRH-domain to an exposed α1,6-mannose residue at the C-branch of N-glycans on substrates destined for degradation (Figure 1A; Quan et al., 2008; Clerc et al., 2009; Hosokawa et al., 2009). In addition to the glycan-dependent
binding it has also been shown that these MRH-domain proteins can bind to misfolded polypeptide segments and associate with the membrane-embedded ubiquitin ligase (Bhamidipati et al., 2005; Bernasconi et al., 2008; Christianson et al., 2008).

**ERAD of Glycoproteins in Plants**

In sharp contrast to mammals and yeast, glycan-dependent ERAD pathways are poorly described in plants (Vitale and Boston, 2008; Liu and Howell, 2010b; Ceriotti, 2011). A first evidence for ER-retention and degradation of misfolded glycoproteins in plants has come from a study on an assembly defective form of phaseolin, which is the major storage protein of common bean and contains two N-glycosylation sites (Pedrazzini et al., 1997). The ER-to-cytosol disposal route has also been described for a soluble GFP-form fused to the P-domain of maize calreticulin (Brandizzi et al., 2003). Another well-characterized ERAD substrate is the catalytic chain of the plant toxin ricin (RTA) from *Ricinus communis*. RTA is glycosylated and upon retrotranslocation to the cytosol, the protein is deglycosylated and eventually degraded in tobacco protoplasts (Di Cola et al., 2001). Proteasome inhibitors like clastolactacystin beta-lactone and MG132 stabilized RTA, but the mannose trapping inhibitor 1-deoxymannojirimycin had no effect on protein levels (Di Cola et al., 2005; Marshall et al., 2008) strongly indicating that this glycoprotein is degraded by a non-glycan-dependent ERAD pathway and thus does not represent a glycoprotein ERAD substrate. Interestingly, RTA and *R. communis* agglutinin (RCA), another ERAD substrate, are degraded in a ubiquitin-independent way and retrotranslocation and degradation are uncoupled. RTA and RCA disposal require the cytosolic ATPase CDC48 (Marshall et al., 2008), that acts as a molecular machine and provides the force to pull proteins out of the ER membrane to the proteasome. Expression of a dominant negative mutant of the *Arabidopsis* ATPase CDC48A, which is impaired in ATPase function (CDC48A QQ), causes also the accumulation of the non-glycosylated ERAD substrate MLO-1, which is a mutated form of the barley powdery mildew resistance O (MLO) protein (Müller et al., 2005). The integral membrane protein MLO-1 has a lesion in one of the cytoplasmic loops (ERADc substrate) and is therefore highly unstable when expressed in *Arabidopsis*. MLO-1 is polyubiquitylated and degraded in a proteasome-dependent way and data from expression of MLO-1 in yeast provide evidence that the disposal of misfolded MLO proteins is dependent on the HRD1 ubiquitin ligase complex.

Two mutated forms of the brassinosteroid receptor kinase BRASSINOSTEROID INSENSITIVE 1 (BRI1) have been classified as glycoprotein ERAD substrates (Hong et al., 2008, 2009). BRI1 is a plasma membrane protein that is subjected to receptor internalization and eventually degraded in the vacuole (Russinova et al., 2004). BRI1 contains a single-pass transmembrane domain and 14 N-glycosylation sites in its N-terminal extracellular brassinosteroid binding domain (Li and Chory, 1997). The two mutated receptor variants BRI1-5 (C69Y mutation, ERADL substrate) and BRI1-9 (S662F mutation, ERAD2 substrate) display a subtle change in their structural conformation that retains them in the ER by different protein quality control mechanisms (Jin et al., 2007, 2009; Hong et al., 2008). Pharmacological inhibition of mannose trimming using the highly specific class I α-mannosidase inhibitor kifunensine stabilizes both BRI1-5 and BRI1-9, resulting in their partial leakage to the plasma membrane and suppression of the severe growth phenotype of bri1-5 and bri1-9 mutants (Hong et al., 2008, 2009). In addition, the bri1-5 and bri1-9 growth defects are also rescued by the alg12 mutant, which lacks the specific mannosyltransferase that transfers the α1,6-mannose to the C-branch during the assembly of the oligosaccharide precursor (Hong et al., 2009). These findings are hallmarks of glycan-dependent ERAD processes and reveal that recognition of a defined mannose residue plays also a crucial role for the degradation of aberrant glycoproteins in plants.

Recently, the first members of the *Arabidopsis* ERAD complex have been discovered (Liu et al., 2011; Su et al., 2011). Mutants deficient in the homologs of the membrane-bound cargo receptor SEL1L/HRD3 and the E3 ubiquitin ligase HRD1 can suppress the dwarf phenotype of bri1-5 and bri1-9 plants. sel1l/hrd3 mutants accumulate BR1-5 and BRI1-9 proteins and analysis of their glycosylation status revealed the presence of processed endoglycosidase H-insensitive N-glycans on a small portion of the mutant BRI1 variants. These data suggest transport of functional BRI1 variants to the plasma membrane resulting in the rescue of the dwarf phenotypes of bri1-5 and bri1-9. A similar phenotypic suppression of the bri1-9 phenotype and BRI1-9 accumulation was observed for a mutant (*hrd1a hrd1b*) with T-DNA insertions in both copies of the *Arabidopsis* HRD1 homolog (Su et al., 2011). Moreover, stabilization of the non-glycosylated ERADc substrate MLO-1 was detected in sel1l/hrd3 plants (Liu et al., 2011) indicating that the HRD1–SEL1L/HRD3 complex is involved in degradation of glycosylated as well as non-glycosylated proteins (Table 1).

In another recent study the putative *Arabidopsis* homolog of YOS9 termed OS9 was identified and characterized with respect to its role in degradation of misfolded glycoproteins (Hüttner et al., 2011).
Apart from degradation of aberrant proteins the ERAD machinery plays also a major role in physiological regulation of protein turnover and constitutive degradation of processed polypeptide fragments in yeast and mammalian cells (Kikkert et al., 2004; Chen et al., 2011; Jaenicke et al., 2011). The identification of plant ERAD components allows now to address the question whether ERAD in plants has in addition to the removal of non-native proteins also a similar function in regulation of protein turnover. Remarkably, none of the three Arabidopsis ERAD mutants (sel1l/hrd3, hrd1a hrd1b, os9) displays an obvious phenotype under normal growth conditions. However, all three mutants are less tolerant toward salt stress, with hrd1a hrd1b being more affected than sel1l/hrd3 and os9 (Liu et al., 2011; Hüttner et al., 2012; Figure 1C). In regard to that, all three ERAD components are upregulated by chemicals like tunicamycin that result in the accumulation of misfolded proteins and induce the unfolded protein response (UPR; Martínez and Chrispeels, 2003; Kamauchi et al., 2005; Nagashima et al., 2011; Su et al., 2011; Hüttner et al., 2012). Current models predict a relationship between salt stress response and UPR induction. High salt concentrations may result in the accumulation of misfolded or unfolded proteins in the ER leading to the activation of salt stress responsive and UPR pathway genes (Liu et al., 2007, 2011; Che et al., 2010; Liu and Howell, 2010a). Under such adverse environmental conditions, the ERAD complex could alleviate ER stress by removal of misfolded proteins, while in the absence of a functional ERAD pathway the growth/survival of plants is impaired (Figure 1C; Liu et al., 2011; Hüttner et al., 2012).

In a recent study, the ubiquitin conjugating enzyme UBC32 has been identified as another component involved in ERAD (Cui et al., 2012). UBC32 deficiency resulted in the accumulation of BR1-5/BR1-9 proteins and subsequent suppression of the bri1-5 and bri1-9 phenotypes. UBC32, which is homologous to yeast UBC6, is very likely a component of the plant DOA10 complex (Cui et al., 2012). Interestingly, the stabilization of BR1 variants and suppression of their growth defect indicates overlapping client proteins with the HRD1–SEL1L/HRD3–OS9 complex. However, there is a major difference with respect to the salt stress response as the ubc32 mutants are more tolerant to salt stress and overexpression of UBC32 results in increased salt-sensitivity. These findings suggest that UBC32 is either a negative regulator of the pathway or has additional unknown functions that are unrelated to the degradation of misfolded proteins under ER stress situations. Further investigation of the pathways and complexes is required to solve this discrepancy.

Based on the finding that ubc32 seedlings are more sensitive to brassinosteroids in a hypocotyl elongation assay it has been proposed that there is a link between ERAD, the salt stress response, and brassinosteroid signaling due to a direct effect of UBC32 on BR1 (Cui et al., 2012). However, no evidence was provided that wild-type BR1 protein levels are altered in ubc32 or UBC32 overexpression lines. Other studies have shown that native BR1 is not subjected to ERAD and does not interact with ERAD components (Hong et al., 2008, 2009; Su et al., 2011; Hüttner et al., 2012). Consequently, it might in fact be that UBC32 is involved in processes that indirectly affect brassinosteroid signaling. In this context we would like to emphasize that the identified ERAD substrates BR1-5 and BR1-9 are artificial clients, which are valuable tools to examine the plant ERAD pathway and its components, but do not provide any direct insights into the function of the ERAD complex under physiological conditions. To investigate the regulatory function of the ERAD complex it is essential to identify endogenous target proteins that are degraded via this pathway. A recent proteomics approach in yeast has discovered 85 proteins...
that were significantly more abundant in a mutant with a defiency in HRD1 (Jaenicke et al., 2011) indicating that the core ERAD pathway plays an important role for protein turnover under non-ER stress conditions.

**CHALLENGES AND PERSPECTIVES**

The main shortcoming of ERAD research in plants is the lack of suitable client proteins to investigate individual steps and discover novel aspects of the pathway. For example, no luminal glycoprotein ERAD substrate has been identified so far and it is still not entirely clear how ER-retained glycoprotein ERAD substrates are degraded as ubiquitination and translocation to the cytoplasm remains to be shown. Binding of SEL1L/HRD3 and OS9 to the misfolded BRI1-5 and BRI1-9 proteins suggests that these ERAD components have a direct role in targeting of substrates for disposal (Su et al., 2011; Hüttner et al., 2012). However, apart from this proposed direct effect we cannot rule out that BRI1-5/BRI1-9 protein accumulation or ER-retention are altered by an unknown mechanism in the absence of a functional ERAD pathway. The nature of the glycan signal and its generation are also still poorly understood and no endogenous glycoprotein substrates are known. In conclusion, the recent identification of plant ERAD components is a major breakthrough since it enables now the concerted search for interacting proteins and new ERAD substrates that undergo glycan-mediated degradation in the ER. Moreover, the controversial data regarding the salt stress tolerance suggests a complex regulation and interaction of ERAD with other ER stress-induced pathways, like the UPR, that have to be discovered in the future.

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