Endoplasmic reticulum-related E3 ubiquitin ligases: Key regulators of plant growth and stress responses

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ABSTRACT
Accumulating evidence has revealed that the ubiquitin proteasome system plays fundamental roles in the regulation of diverse cellular activities in eukaryotes. The ubiquitin protein ligases (E3s) are central to the proteasome system because of their ability to determine its substrate specificity. Several studies have demonstrated the essential role of a group of ER (endoplasmic reticulum)-localized E3s in the positive or negative regulation of cell homeostasis. Most ER-related E3s are conserved between plants and mammals, and a few plant-specific components have been reported. In this review, we summarize the functions of ER-related E3s in plant growth, ER-associated protein degradation and ER-phagy, abiotic and biotic stress responses, and hormone signaling. Furthermore, we highlight several questions that remain to be addressed and suggest directions for further research on ER-related E3 ubiquitin ligases.

Keywords: E3 ligase, plant endoplasmic reticulum, UPS, ERAD, stress response

INTRODUCTION
The ubiquitin proteasome system (UPS) plays a central role in the regulation of protein stability by degrading soluble or short-lived normal and abnormal proteins in eukaryotic cells. The UPS has been demonstrated to regulate cell homeostasis and function and to coordinate plant growth and stress responses. It participates in cell cycle progression, transcriptional regulation, abiotic and biotic stresses, hormonal responses, root growth, photomorphogenesis, and floral homeosis (Ingvardsen and Veierskov, 2001; Xie et al., 2002; Kurepa and Smalle, 2008; Kurepa et al., 2013; Liu et al., 2013; Yu et al., 2016). The UPS is a serial cascade process of protein ubiquitination and degradation. Substrate proteins destined for degradation are tagged with 76-residue ubiquitin and then hydrolyzed by the 26S proteasome. Substrate ubiquitination involves three steps catalyzed by three different enzymes or enzyme complexes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin protein ligase (E3).

Among these enzymes, E3s are the most expanded components and play an essential role in recognizing targets and later transferring ubiquitin to targets. For example, there are approximately 1400 E3s in the Arabidopsis genome and a similar number in other plants. The plant E3 ubiquitin ligases are classified into four main types: really interesting new gene (RING), U-box, homologous to the E6-AP carboxyl terminus (HECT), and Cullin-RING ligases (CRLs) (Chen and Hellmann, 2013). Such large numbers of E3s indicate that E3s determine the specific protein targets for ligation and strictly regulate different cellular processes.

The endoplasmic reticulum (ER) is the largest membrane-bound organelle, and it is a major site for the biosynthesis of proteins and lipids and for their subsequent distribution. Many ER-embedded or cytosolic proteins have different functions in ER homeostasis and participate in plant development. With more extensive research, a number of E3 ligases have been identified in plants and have been well summarized (Zhang et al., 2019a; Sun et al., 2019; Xu and Xue, 2019; Ban and Estelle, 2021). Here, we mainly summarize recent advances in our understanding of how ER-related E3 ligases function in stress responses, hormone signaling, and plant growth and development, as well as future directions for research on the outstanding questions that await investigation in this field.
THE ROLES OF ER-RELATED E3S IN PLANTS

ER-related E3s function in ERAD and ER-phagy

The balance of protein synthesis and degradation in the ER, as well as the degradation of dysfunctional ER domains, is termed ER turnover and ensures cellular homeostasis and function. The ER is the major site for the biosynthesis of soluble and integral membrane proteins and most lipids. After being synthesized in the ER, they are transported to different locations and then fulfill their functions. The folding and processing capacities of the ER are finite and limited. When the demand for protein folding exceeds the capacity of the ER, the accumulation of misfolded or unfolded proteins can lead to a status called ER stress. It minimizes the accumulation of unfolded/misfolded proteins by increasing the transcription of genes involved in protein folding, vesicle trafficking, proteasome-mediated protein degradation, and autophagy (Goldberg, 2003; Liu and Howell, 2010). ER-associated protein degradation (ERAD) is one of the ways by which the UPS eliminates misfolded or unfolded proteins (Liu and Howell, 2016).

Most of the current knowledge about ERAD was obtained from yeast and mammals. The degradation of misfolded proteins in the ER involves several distinct steps. In the recognition step, E3s embedded in the ER membrane cooperate with accessory recognition factors to recognize misfolded proteins. Next, proteins are exported to the cytosol through a retrotranslocation pore formed by HMG-CoA REDUCTASE DEGRADATION 1 (HRD1). The substrate is subsequently ubiquitylated by three different enzymes or enzyme complexes, E1, E2, and E3, at the cytosolic face of the ER. Finally, the substrate is removed from the membrane and degraded by the 26S proteasome (Hirsch et al., 2009). Arabidopsis CDC48, an AAA-ATPase, provides the driving force for the retrotranslocation of ERAD substrates (Begue et al., 2019), similar to the roles of Cdc48/p97 in mammalian cells and yeast (Ye et al., 2001; Tsai et al., 2002). The HRD1 complex and the DEGRADATION OF ALPHA2 10 (Doa10) complex are two major complexes in the ERAD system (Sun et al., 2021). The ERAD component E3s play a core and critical role in both complexes. In recent years, more E3s that participate in ERAD have been identified in plants; however, studies of E3s involved in plant ERAD are very limited compared with those in yeast and mammals (Liu and Li, 2014; Sun et al., 2021). Most plant E3s are homologs of yeast and mammals, but some are specific to plants.

AthRD1A and AthRD1B, encoded by At3g16090 and At1g65040, are ER membrane-localized E3s that contain the RING domain and are homologs of Hrd1p in yeast and HRD1 in mammals (Kosarev et al., 2002). AthRD1B is upregulated by dithiothreitol (DTT) and tunicamycin (Tm), which can trigger ERAD (Kamauchi et al., 2005). AthRD1A and AthRD1B function redundantly in ERAD of bri1-9 protein, which is a mutated brassinosteroid (BR) receptor known as brassinosteroid-insensitive 1 (BRI1) that shows defects in ER retention. A genetic screen of suppressors of Arabidopsis bri1-9 revealed that EBS5 (HRD3A) can interact with and recognize bri1-9-GFP (Su et al., 2011). EBS7, a plant-specific protein, was also identified by screening suppressors of bri1-9; it can interact with AthRD1A and may regulate AthRD1A stability (Liu et al., 2015). AtOS9, an ER luminal lectin, can recognize an asparagine-linked glycan on misfolded proteins (Su et al., 2012). A series of exciting studies show that loss of AtOS9/EBS6, EBS5/HRD3A, EBS7, and AthRD1, which belong to the HRD1 complex, can restore BR sensitivity in the bri1-9 mutant allele (Su et al., 2011, 2012; Liu et al., 2015). AthRD1s also regulate the abundance of the E2 ubiquitin-conjugating enzyme UBC32, which works in the DOA10 complex (Chen et al., 2016). Arabidopsis DOA10, also named ECRIFERUM9 (CER9), encodes a putative RING domain-containing E3 ubiquitin ligase that is localized in the ER and is similar to Doa10 in yeast and TEB4 in human (Zhao et al., 2014). The ERAD pathway operates at a relatively low capacity under standard growth conditions, and the ERAD factors are degraded by either the lysosome or the proteasome through a process termed ERAD tuning. The regulation of UBC32 by the HRD1 complex is conserved between plants and mammals (Chen et al., 2016, 2017). MAKIBISHI 1 (MKB1), an ER-anchored ERAD-type E3 ubiquitin ligase in the legume Medicago truncatula and a homolog of mammalian RMA1, negatively regulated the stability of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), the major rate-limiting enzyme in steroid biosynthesis (Pollier et al., 2013). Although different E3 ligases, yeast HRD and mammalian gp78, are involved in the proteasome-dependent turnover of HMGR (Song et al., 2005b; Garza et al., 2009), the regulatory mode of HMGR is highly conserved in eukaryotic cells. Therefore, ERAD is also used to degrade folded proteins in a highly regulated manner.

A new plant-specific E3 ligase, EMR (ERAD-mediating RING finger protein), was identified in Arabidopsis. EMR is localized on the ER membrane facing the cytosol and forms a complex with UBC32. Moreover, EMR is involved in plant ERAD of AtOS9 and mildew resistance locus O-12 (MLO12), a mutant of the barley powdery mildew (Park et al., 2019). The emr mutant is tolerant to ER stress, and EMR upregulated in wild-type plants under ER stress may influence BR signaling to modulate the plant stress response. Medicago falcata MSTMIR is another ER membrane-anchored RING finger E3 ubiquitin ligase that is highly conserved in leguminous plants but lacks homologs in yeast or mammals. MSTMIR responds to ER stress and is an active ERAD component that degrades the substrate MiCPY* and interacts with MtUBC32 and MtSec61γ, a protein translocator subunit (Zhang et al., 2019b). The ER-related E3s discussed above include a few E3 homologs found in yeast and mammals, as well as two plant-specific E3s. It is interesting that two plant-specific E3s can interact with UBC32. ERAD substrates such as mutated BR1 and MLO have been found in plants, but most of the reviewed E3s have unknown specific targets that are important for E3 functions. More work needs to be done to identify the specific targets of E3s, thereby clarifying the ERAD process.

Under severe ER stress, misfolded or unfolded proteins that accumulate in the ER and dysfunctional ER membranes can be degraded in the vacuole or recycled by ER-phagy (Liu et al., 2012). ER-phagy is a type of autophagy that is mediated by a series of autophagy-related proteins (ATGs) and is required for degrading or recycling unwanted cell components. Therefore,
ER-related E3s: Key players in plants

ER-phagy, along with the UPR and ERAD pathways, plays an essential role in maintaining ER homeostasis. In the last few years, great progress has been made in understanding plant ER-phagy (Zeng et al., 2019; Bao and Bassham, 2020; Qi et al., 2021). However, progress on the function of ER-related E3s in plant ER-phagy is very limited. Two Arabidopsis LUNAPARK proteins localized at three-way ER junctions, LNP1 and LNP2, are reported to work as ubiquitin ligases and stabilize the formation of the tubular ER. The ER becomes a dense tubular network in inp1-1 Inp2-1 mutant cells, and inp1-1 Inp2-1 mutants have shorter root hairs and smaller cotyledons and leaves than wild-type plants. LNPs can be recruited by an atlastin GTPase root hair defective (RHD3) to the newly formed three-way ER junctions in plant cells. Subsequently, LNPs promote the ubiquitination and subsequent 26S proteasomal degradation of RHD3, as well as selective autophagic degradation, and the nascent three-way ER junctions are stabilized. Therefore, two E3 ligase LNPs are required for normal cell development and for the maintenance of the tubular ER network (Sun et al., 2020).

ER-related E3s in environmental stress

Stress is a limiting factor that affects plant growth and crop production. As sessile organisms, plants often encounter various environmental stimuli, including abiotic and biotic stresses, such as drought, salt, heat, ion imbalances, fungi, bacteria, and viruses. Previous work has demonstrated that these environmental factors induce a great deal of misfolded proteins and disturb the balance of the ER, leading to ER stress (Liu and Howell, 2010, 2016). At the same time, plants have evolved a number of mechanisms to adapt to environmental stress through changes at the morphological, physiological, and molecular levels (Verslues et al., 2006; Yu et al., 2013). Research in recent years has shown the indispensable roles of ER-related E3s in plant response to environmental stress.

Functions in abiotic stress

The function of E3s in plant response to drought stress has been well studied. In 2012, Lu et al. (2012) cloned CER9 by mapping the cer9-1 mutation and predicted that it encodes a Dof10-like protein. They observed that the cer9 mutant displayed enhanced resistance to drought stress, with increased stomatal closure, more total stem cutin monomers, lower transpiration efficiency, extreme changes in leaf wax, and altered ultrastructure of the cuticular membrane in leaves and stems. Three homologs of human RING membrane-anchor 1 (Rma1) were identified in Arabidopsis: AtRma1, AtRma2, and AtRma3. Although all three proteins have a conserved structure containing transmembrane domain (TM) and RING domain, they may have different functions. A promoter GUS assay showed that AtRma1 and AtRma3 were predominantly expressed in most tissues, whereas AtRma2 was expressed only in the root tips and leaf hydathodes of Arabidopsis (Son et al., 2009). Drought stress-induced CaRma1H1 in hot pepper (Capsicum annuum) is a homolog of the human RING ER membrane-anchored E3 ligase Rma1, and CaRma1H1 is also a homolog of AtRma1 (Lee et al., 2009). Overexpression of CaRma1H1 in Arabidopsis and tomato can enhance plant tolerance to drought stress (Lee et al., 2009; Seo et al., 2012). Both CaRma1H1 and AtRma1 were shown to interact with and ubiquitinate PIP2, a plasma membrane aquaporin and one of the most abundant water channel proteins in Arabidopsis, thereby inhibiting PIP2 trafficking from the ER to the plasma membrane and impairing the response to dehydration (Lee et al., 2009). Another study reported that GpDSR7, which encodes a novel E3 ligase, is involved in the drought stress tolerance of Grimmia pilifera, an ancient bryophyte. GpDSR7 functions as a RING-type E3 ligase anchored to the ER membrane. GpDSR7 is induced by various abiotic stresses, and its overexpression in Arabidopsis conferred a higher water content and greater survival ratio under drought stress (Li et al., 2016). Two other RING E3s, ZmXerico1 and ZmXerico2, were identified based on their high induction by drought stress in maize. Overexpression of ZmXerico1 and ZmXerico2 in Arabidopsis and maize confers ABA hypersensitivity and improves water use efficiency, and their overexpression in maize is associated with increased ABA levels and decreased levels of the ABA degradation products diphasic acid and phaseic acid. ZmXerico1 is localized in the ER and controls ABA homeostasis by regulating the protein stability of ER-localized ABA 8’-hydroxylase (Brugiere et al., 2017).

In addition to drought stress, high soil salinity is another severe abiotic stress that damages plant growth and affects crop productivity. SpRing, a RING-type and ER-localized E3, is expressed in all tissues of wild tomato and is induced by salt, drought, and osmotic stresses (Qi et al., 2016). SpRing functions as a positive regulator of salt tolerance because silencing of SpRing leads to increased salt stress sensitivity and greater H2O2 accumulation, and overexpression of SpRing in Arabidopsis enhances salt tolerance during seed germination and early seedling development (Qi et al., 2016). The expression of MSTMIR was also induced by salt, and it relieved ER stress during salt stress by interacting with MtUBC32 and MtSec61β. However, salt stress-related substrates of MSTMIR have not been found in Medicago (Zhang et al., 2019b). RING finger-type E3 salt- and drought-induced RING finger1 (SDIR1) is localized on the ER membrane and participates in the drought response in Arabidopsis thaliana (Zhang et al., 2007). SDIR1-overexpressing lines exhibit enhanced ABA-induced stomatal closure and drought tolerance in Arabidopsis, and similar results have been obtained in rice and maize (Zhang et al., 2008; Gao et al., 2011; Xia et al., 2012). Zhang et al. (2015) found that SDIR1 modulated the stability of the target SDIR1-INTERACTING PROTEIN1 (SDIRIP1) through the UPS and regulated the plant salt response. Similar to SDIR1, CaRma1H1 functions in the plant response to both drought and salt stresses (Seo et al., 2012).

Mutants with ERAD defects show increased sensitivity to various environmental stresses (Huttner and Strasser, 2012). Some studies have reported that ERAD components are involved in heat and selenium (Se) stresses. For example, hrd1a hrd1b is sensitive to Se stress (Van Hoewyk, 2018). DOA10 and AthRD1 play a redundant role in plant response to heat stress, and mutation in DOA10 or AthRD1 can increase plant tolerance to heat treatment (Li et al., 2017). However, the detailed mechanism remains to be investigated.

Functions in biotic stress

Little evidence is available regarding ER-related E3s that are associated with disease resistance in plants. Ascencio-Ibañez et al. (2008) analyzed Arabidopsis microarray data associated with the response to cabbage leaf curl virus (CaLCuV) infection.
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Among the 5365 genes differentially expressed in infected rosette leaves, DOA10 is one of the genes that influence the pathogen response and cell cycle (Menges et al., 2002). Nonetheless, the function of DOA10 in plant response to CaLCuV infection is not well understood.

The ATL family, a specific family of RING finger E3 ligases, is characterized by rapid induction after elicitor treatment and a structure that includes a highly conserved RING-H2 zinc-finger domain and at least one TM domain (Serrano et al., 2006). Many ATL genes participate in the defense-response pathway in plants (Katoh et al., 2003; Navarro et al., 2004; Hondo et al., 2007; Du et al., 2010; Mukoko Bopopi et al., 2010; Guzman, 2012). Arabidopsis toxicos en levadura 9 (ATL9), also known as ATL2G, is a member of the ATL gene family. ATL9 expression is induced by wounding, abiotic stress, and chitin, a pathogen-associated molecular pattern (PAMP). Its induction by chitin is dependent on NAPDH oxidase activity, but it is not induced by treatment with known defense hormones such as salicylic acid, jasmonate, or ethylene. ATL9 is reported to be an ER-localized E3 that acts against the biotrophic fungal pathogen Golovinomyces cichoracearum. Microarray data for atgl identified some candidate genes that may act downstream of ATL9 in chitin-mediated defenses. However, no further evidence indicates which gene encodes a substrate of ATL9 (Berrocal-Lobo et al., 2010). ATL9 is unique among the ATL family because it contains a PEST domain; it is suspected to be involved in ERAD because its RING and PEST domains are exposed to the ER lumen (Berrocal-Lobo et al., 2010). Deng et al. (2017) demonstrated that the PEST domain and the RING domain contribute to the short half-life of ATL9, which is degraded by the UPS. All domains, including TM, RING, and PEST, are important for the resistance of ATL9 to fungal pathogens. In the future, it will be important and helpful to identify specific targets of ATL9 during the defense response, as this will assist us in understanding the precise role of this E3 ligase in biotic stress.

The U-box-type E3 CMPG1–V was reported to be induced in the leaves and stem of Haynaldia villosa upon inoculation with the fungus Blumeria graminis f. sp. tritici (Bgt). CMPG1–V possesses E3 ligase activity and is localized in the nucleus, ER, plasma membrane, and partially in the trans-Golgi network (TGN)/early endosome (EE) vesicles. CMPG1–V contributes to the defense responses to Bgt in powdery mildew of wheat, particularly to broad-spectrum disease resistance, which is associated with an increased expression of salicylic acid-responsive genes and H2O2 accumulation in plants (Zhu et al., 2015).

Most of the E3s related to stress can be induced by stress and are expressed in numerous organs and tissues at various developmental stages to perform their functions. Plants with mutated E3s often exhibit stress-related phenotypes. It is interesting that all E3 ligases that have been shown to function in stress response belong to the RING-type or are U-box E3 ligases, and it is therefore worth checking whether other types of E3 ligases can also participate in stress response.

ER-related E3s function in hormone signaling pathways

Plant hormones play an important role in regulating responses to different stresses, such as high salinity and drought, and developmental processes, such as germination and flowering. Hormones function as a response signal to activate a series of hormone-dependent responses. Increasing evidence has shown that E3s play an essential role in hormone perception and/or signaling pathways through protein degradation by the UPS. Many researchers have put in much effort and provided clear summaries of these pathways (Chen and Hellmann, 2013; Yu et al., 2016; Serrano et al., 2018). Here, we summarize the role of ER-related E3s that function in hormone pathways.

The plant hormone ABA plays a role in various pathways, such as stress response and plant development. SDIR1 was reported to target SDIRIP1 and to be a positive regulator of ABA signaling. Although SDIRIP1-GFP is localized to the chloroplast, the interaction between SDIR1 and SDIRIP1 may occur in the cytosol and be associated with the ER. SDIR1 functions upstream of the ABA response genes ABF3/ABF4/ABIS; however, SDIRIP1 specifically regulates the expression of ABIS (Zhang et al., 2007, 2015). Unlike SDIR1, CER9 is a negative regulator of ABA biosynthesis and ABA-mediated seed germination, and the expression of CER9 is induced by ABA. Introduction of the abI-1, abI-3, or abI-103 mutation completely or partially eliminated the ABA hypersensitivity of cer9, indicating that CER9 is an upstream regulatory factor of these ABA-responsive genes. Nevertheless, the substrates of CER9 in the ABA signaling pathway have not been reported (Zhao et al., 2014). ABA transport is important for plant response to environmental stress, and it is therefore strictly regulated under standard growth conditions. NRT1.2/NPF4.6, an ABA transporter, was phosphorylated by C-terminally encoded peptide receptor 2 (CEP2R) at serine 292, then ubiquitinated and degraded through both 26S proteasomal and vacuolar degradation pathways. Furthermore, the three E2 ubiquitin-conjugating enzymes UBC32, UBC33, and UBC34 were shown to interact with NRT1.2/NPF4.6 in the ER and modulate its ubiquitination (Zhang et al., 2021). Whether ER-related E3 ligase(s) are involved in the ubiquitination requires further investigation.

BR is another important hormone that regulates plant development. As mentioned above, AtHRD1A and AtHRD1B can participate in the ERAD process of mutated BRI1 in Arabidopsis, protecting the cell from ER stress, balancing the BR signaling pathway, and ensuring normal plant growth (Su et al., 2011). The degradation of mutated BRI1 by EMR is similar to the degradation promoted by AtHRD1A and AtHRD1B under standard growth conditions, and knockdown of EMR in the bRI-5 background partially enhances BR signaling by changing the amount of misfolded BRI1 and the phosphorylation status of BES1 under strong ER stress (Park et al., 2018).

The hormone ethylene, the simplest alkene (C2H4), functions in numerous plant processes, including seed germination, seedling growth, organ development, leaf abscission, fruit ripening, and stress responses (Iqbal et al., 2017; Dou et al., 2018; Munne-Bosch et al., 2018; Bak et al., 2019; Kieber and Schaller, 2019). In recent years, the ethylene signaling pathway has been clearly established in Arabidopsis, and the mechanism of ethylene signaling is conserved in flowering plants such as rice, maize, soybean, poplar, and tomato (Sauter et al., 2002; Hu et al., 2017; Ibort et al., 2018; Ji et al., 2018; Zhang et al., 2018). The RING-type E3 ligase SDIR1 is an important modulator of ethylene signaling. EIN3-binding F-box protein 1 (EBF1) and EBF2 negatively mediate the stability of the transcription factors that regulate ethylene responses.
factor ethylene insensitive 3 (EIN3) to tune ethylene signaling (Gagne et al., 2004). SDIR1 expression is induced by elevated ambient temperatures, thus enabling SDIR1 to target EBF1/EBF2 for ubiquitination and subsequent degradation by the 26S proteasome to promote EIN3 accumulation and regulate the ethylene response at different ambient temperatures (Hao et al., 2021).

**ER-related E3s function in plant growth and development**

Some proteins described above are also involved in plant growth and development. Transcriptome analyses have shown that CER9 and HRD1B are among the genes whose expression changes during pollen germination and tube growth in Arabidopsis (Wang et al., 2008). Mutations in E3s can cause plant growth defects, and various studies have described the phenotypes of these mutants. The cer9 mutant exhibited delayed germination, which was independent of seed coat permeability (Lu et al., 2012; Zhao et al., 2014). CER9 also plays an essential role in root development. A genetic screen performed for second-site suppressor mutations of the dry2/sud1 Defects1 (SUD1) was identified and also named CER9. Primary root lengths were doubled in dry2/sud1 compared with dry2, and the number of lateral roots was decreased. The sud1 mutation was shown to suppress the root defects of dry2 by down-regulating the activity of HMGR, the major rate-limiting enzyme in steroid biosynthesis. However, protein gel blot analyses indicated that SUD1 did not exert its function by regulating HMGR protein levels, and SUD1 may produce the direct monoubiquitination of HMGR, thereby increasing its activity (Doblas et al., 2013). Therefore, SUD1 is a positive regulator of HMGR activity in the isoprenoid biosynthetic pathway, unlike other E3s such as HRD1 and gp78 in animals that control the protein stability of HMGR (Nadav et al., 2003; Kikkert et al., 2004; Song et al., 2005a, 2005b; Menzies et al., 2018). Therefore, it is not surprising that the Doa10-like protein participates in lipid biosynthesis. CER9 was shown to affect leaf cuticle lipid metabolism and influence wax composition in the cutin biosynthesis pathway (Lu et al., 2012). Interestingly, the stability of HMGR in the legume M. truncatula was negatively regulated by a homolog of mammalian RMA1, MAKIBISHI 1 (MKB1). Knockdown of MKB1 in M. truncatula hairy roots produced roots with caltrop-like structures that differed from control roots (Poliier et al., 2013).

**CONCLUDING REMARKS AND FUTURE PERSPECTIVES**

In the past 10 years, great progress has been made in functional research on plant ER-related E3s, which play crucial roles in plant growth and stress responses (Table 1). Most of the E3s reviewed above are RING-type E3s that target their substrates in a positive or negative manner. Thus, RING-type E3s play a key role in the balance of ER proteins and the maintenance of the ER network, although large numbers of RING E3s remain uncharacterized. The E3s reviewed above mostly contain TM regions and anchor in the ER membrane. TM regions may be associated with the function of E3s in ER dynamic equilibrium and plant development. Many ER-related E3s are conserved between plants and mammals, and plant-specific components have been reported. Furthermore, the function of some E3 genes is not limited to just one pathway but may involve different pathways (Figure 1) (Berrocal-Lobo et al., 2010; Deng et al., 2017). Current progress on ER-related E3s is based mainly on genetic and biochemical research in the model plants Arabidopsis and rice, and little is known in other plants. Therefore, the functions of many ER-related E3s still remain to be identified and investigated in different plants, which is useful for studying the mechanism of E3 ligases. With the development of genome sequencing technology, more ER-related E3 proteins will be identified. Furthermore, it is a challenge to perform functional studies on the E3s, as they belong to a large family and have high functional overlap. New powerful techniques such as CRISPR-Cas9 will help to analyze their functions by generating different mutants of gene families.

The conjugation of ubiquitin to substrates can alter the stability or non-degradative process of the proteins. Most of the reviewed E3s promote the ubiquitination and degradation of their substrates. However, SUD1 in Arabidopsis modulates HMGR activity but does not regulate HMGR protein levels (Doblas et al., 2013). The UPS and ER-phagy are two major proteolytic systems that use ubiquitin as a selective marker; they cooperate and influence each other to modulate cellular homeostasis during plant development and response to stresses (Marshall et al., 2015; Marshall and Vierstra, 2018; Qi et al., 2020; Su et al., 2020). Although the relationship between the UPS and ER-phagy has been revealed in mammals, little is known in plants.

Increasing evidence has shown the importance of ER-related E3 proteins in plant growth and development, response to stress, and hormone signaling; however, there is much to learn about these proteins, including the identification of their substrates. It is still a significant challenge to define the E3-substrate interaction because of the transient and rapid interaction between E3 ligases and their substrates. Although the yeast two-hybrid screen and IP-MS (immunoprecipitation followed by mass spectrometry) are two commonly used methods to identify interacting proteins, many ER-related E3s have no known substrates, and several substrates localize in the ER without corresponding E3s. Proximity labeling MS, developed recently, is a sensitive and powerful method for characterizing protein–protein interactions; it has been used extensively in animal systems to identify protein interaction networks, and successes have been achieved in plants in recent years (Kim et al., 2014; Uezu et al., 2016; Lobinger et al., 2017; Conlan et al., 2018; Khan et al., 2018; Das et al., 2019; Hsu et al., 2019; Yang et al., 2021). The application of different high-throughput approaches will deepen our understanding of ER-related E3s and provide answers to outstanding questions in this field.

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| Name                 | Origin     | Localization | Biological function                  | Targets                             | References                      |
|---------------------|------------|--------------|--------------------------------------|-------------------------------------|---------------------------------|
| HRD1                | A. thaliana| NA           | ERAD                                 | mutated BRI1/UBC32                 | Su et al., 2011; Chen et al., 2016 |
|                     |            |              | heat                                 | UN                                  | Li et al., 2017                 |
|                     |            |              | Se                                   | UN                                  | Van Hoewyk, 2018                |
| EMR                 | A. thaliana| ER           | ERAD                                 | AtOS9/MLO-12                        | Park et al., 2018                |
|                     |            |              | BR signaling                         | mutated BRI1                        | Park et al., 2018                |
| MfSTMIR             | M. falcata | ER           | ERAD                                 | MiCPY*                              | Zhang et al., 2019b              |
|                     |            |              | salt                                 | UN                                  | Zhang et al., 2019b              |
| CER9/SUD1/DOA10     | A. thaliana| NA           | root development                     | HMGR                                | Doblas et al., 2013              |
|                     |            |              | ABA signaling                        | UN                                  | Zhao et al., 2014                |
|                     |            |              | drought                              | UN                                  | Lu et al., 2012                  |
|                     |            |              | heat                                 | UN                                  | Li et al., 2017                  |
| CaRma1H1            | Hot pepper | ER           | drought and salt                     | PIP2                                | Seo et al., 2012                 |
| Rma1                | A. thaliana| ER           | drought and salt                     | PIP2                                | Lee et al., 2009                 |
| ZmXerico1           | Zea mays   | ER           | ABA homeostasis and drought          | ABA 8’-hydroxylase                  | Brugiere et al., 2017            |
| SDIR1               | A. thaliana| ER           | ABA signaling and salt               | SDIRIP1                             | Zhang et al., 2015               |
|                     |            |              | drought                              | UN                                  | Zhang et al., 2007               |
|                     |            |              | ethylene response                    | EBF1/EBF2                           | Hao et al., 2021                 |
| OsSDIR1             | Oryza sativa| NA         | drought stress                       | UN                                  | Gao et al., 2011                 |
| GpDSR7              | G. pilifera| ER           | drought stress                       | UN                                  | Li et al., 2016                  |
| SpRing              | S. lycopersicum| ER| salt stress                           | UN                                  | Qi et al., 2016                  |
| ATL9                | A. thaliana| ER           | defense response                     | UN                                  | Berrocal-Lobo et al., 2010; Deng et al., 2017 |
| CMPG1–V             | T. aestivum| ER, nucleus PM, TGN/EE vesicles     | defense response                     | UN                                  | Zhu et al., 2015                 |
| LNP1/2              | A. thaliana| ER           | maintenance of tubular ER network    | RHD3                                | Sun et al., 2020                 |
| MKB1                | M. truncatula| ER     | root development ERAD                | HMGR                                | Pollier et al., 2013             |

Table 1. Plant ER-related E3s with their known functions and targets
NA: not available; UN: unknown; PM: plasma membrane; TGN/EE: trans-Golgi network/early endosome.
ER-related E3s: Key players in plants

Figure 1. ER-related E3 ubiquitin ligases play crucial roles in plant growth and stress responses.

The left portion of the circle shows ER-related E3 ubiquitin ligases that function in plant growth and development. The stability of HMGR is negatively regulated by MKB1 in the legume *M. truncatula*. LNP1 and LNP2 (*A. thaliana*) promote the degradation of RHD3 through ubiquitination to stabilize the formation of the tubular ER for normal plant development. SUD1 (*A. thaliana*) may directly monoubiquitinate HMGR, thereby increasing its activity. The E3 ubiquitin ligase involved in NRT1.2/NPF4.6 (*A. thaliana*) ubiquitination has not been found. The right portion of the circle shows the E3-substrate pairs involved in plant response to stress. MtCPY and Pip2 are the substrates of E3 ubiquitin ligases MtSSTMIR (*M. falcata*) and Rma1 (*A. thaliana*), respectively, and UBC32 and brl1-5 are the substrates of the known ER-anchored E3 ubiquitin ligase HRD1 (*A. thaliana*). Sub1 indicates the substrates of SDR1 (*A. thaliana*), SDRIP1, EBF1, and EBF2. Sub2 indicates the substrates of EMR (*A. thaliana*), AtOS9, brl1-5, and MLO-12. Sub3 indicates the substrate of ZmXerico1, ABA 8’-hydroxylase.

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