Plant Physiology and Biochemistry 145 (2019) 227–236

Contents lists available at ScienceDirect

Plant Physiology and Biochemistry

journal homepage: www.elsevier.com/locate/plaphy

Review

Protein partners of plant ubiquitin-specific proteases (UBPs)

Ruihua Wu[b,1], Wenqing Zheng[b,1], Jinyi Tan[b], Rana Sammer[b], Liang Du[a,b,*], Cunfu Lu[b,**]

[a] Beijing Advanced Innovation Center for Tree Breeding by Molecular Design, Beijing Forestry University, Beijing, 100083, China
[b] College of Biological Sciences and Technology, Beijing Forestry University, Beijing, 100083, China

ARTICLE INFO

Keywords:
UBP
Ubiquitin
Ubiquitination
Deubiquitination
Protein partners

ABSTRACT

As one type of deubiquitinases (DUBs), ubiquitin-specific proteases (UBPs) play an extensive and significant role in plant life involving the regulation of plant development and stress responses. However, comprehensive studies are still needed to determine the functional mechanisms, which are largely unclear. Here, we summarized recent progress of plant UBPs' functional partners, particularly the molecular mechanisms by which UBPs work with their partners. We believe that functional analyses of UBPs and their partners will provide new insights into protein deubiquitination and lead to a better understanding of the physiological roles of UBPs in plants.

1. Introduction

All organisms have evolved a sophisticated armory of proteins for the regulation of critical cellular signaling events. Many cellular processes are tightly controlled by the post-translational modifications (PTMs) of target proteins, and as one type of PTM, protein ubiquitination is involved in many physiological events including DNA repair, cell-cycle control, stress response, immune response, endocytosis, and vesicle trafficking (Clague et al., 2012; Isono and Nagel, 2014; Pickart, 2004; Vierstra, 2009; Zhou et al., 2017). Generally, ubiquitination, the covalent attachment of the small protein modifier ubiquitin to a substrate protein (Chou et al., 2017), and deubiquitination, the removal of ubiquitin, often antagonistically regulate the ubiquitination level of target proteins, and are strictly controlled at multiple steps during cellular processes (Katz et al., 2010; Neutzner and Neutzner, 2012; Vierstra, 2009; Wilkinson, 2000).

When being ubiquitinated, ubiquitin C-terminus Gly and the ε-amino group of Lys of the target protein form a conjugation through an isopeptide between them. The ubiquitin molecules by themselves or in conjugation with proteins are also ligated to additional Ub residues to produce branched polyubiquitin chain assemblies (Hershko and Ciechanover, 1998). In a hierarchical cascade, the covalent attachment of Ub to proteins is catalyzed by the action of a series of ubiquitinating enzymes (UBEs): Ub-activating enzyme (E1), Ub-conjugating enzyme (E2), and Ub ligase (E3) (Hershko and Ciechanover, 1998). The fate of ubiquitinated proteins mainly depends on the length and linkage type of the Ub moiety. On the one hand, a protein with four or more Ub moieties linked via K29 or K48 is generally targeted for degradation by the 26S proteasome; on the other hand, ubiquitination via K63- linkage is thought to be involved in the regulation of target protein activity in signaling (de Poot et al., 2017). In addition to the above two cases, a number of plasma membrane proteins, and proteins involved in intracellular sorting and trafficking are attached to only one Ub moiety (Hershko and Ciechanover, 1998; Pickart, 2004; Vierstra, 2009). On the contrary, another event of comparative importance related to Ub is protein deubiquitination which is carried out by deubiquitinases/deubiquitinating enzymes (DUBs). DUBs is a large protein family divided into five groups based on characteristic catalytic domains: the ubiquitin-specific protease (USP/UBP), the ubiquitin C-terminal hydrolase (UCH), the ovarian tumor domain protease (OTU), the Machado–Joseph Disease protein domain protease (MJD), and the JAMM (JAB1/MPN/Mov34) motif protease (JAMM) (Komander et al., 2009; Reyes-Turcu et al., 2009). Except for the JAMM, which are zinc-dependent metalloproteases, all DUB belong to cysteine proteases (Komander et al., 2009; Nijman et al., 2005; Reyes-Turcu et al., 2009). Generally, DUBs recognize substrates anchored with monoubiquitin and polyubiquitin chain assemblies, and selectively cleave them (Katz et al., 2010; Neutzner and Neutzner, 2012; Sahtoe and Sixma, 2015; Soboleva and Baker, 2004; Wilkinson, 2000; Wolberger, 2014). Factually, protein ubiquitination which is essential for many cellular processes is dynamically regulated both by UBEs and DUBs (Fig. 1). In plants, UBPs form the largest subfamily of DUBs. For example, in *Arabidopsis thaliana,* there are 27 putative UBP members, accounting more than half of the total DUBs (Liu et al., 2008; Yan et al., 2000). All UBP proteins

---

[*] Corresponding author. Beijing Advanced Innovation Center for Tree Breeding by Molecular Design, Beijing Forestry University, Beijing, 100083, China.
[**] Corresponding author.
E-mail addresses: duliang@bjfu.edu.cn (L. Du), lucunfu@bjfu.edu.cn (C. Lu).
[1] Ruihua Wu and Wenqing Zheng contributed equally to this work.

https://doi.org/10.1016/j.plaphy.2019.08.032
Received 26 March 2019; Received in revised form 16 July 2019; Accepted 31 August 2019

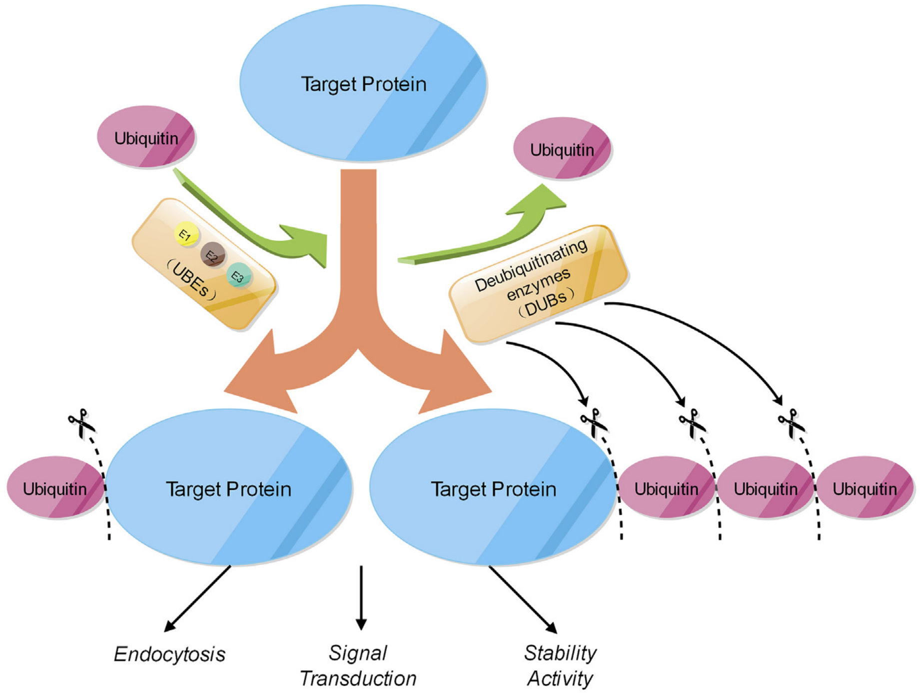

Fig. 1. Protein ubiquitination, deubiquitination and basic physiological functions. The UBEs (E1, E2, E3) and DUBs function antagonistically to control the ubiquitination state of target protein and subsequently regulate different cellular processes. During the process, the ubiquitin molecule is added to or removed from the target protein as a recyclable tag which is also vital to the ubiquitin pool homeostasis.

characteristically contain a specific UCH domain, with two short but well-conserved motifs, called cysteine (Cys) and histidine (His) boxes, which are the key parts of two triads of catalytic sites (Cys in the cysteine box, and His and Asp/Asn in the Histidine box) (Varshavsky, 1998; Yan et al., 2000). Recently, many cellular processes have found to be controlled by some UBP members, demonstrating an important role of UBPs in plant life. Here we briefly reviewed the recent progress on plant functional partners of UBPs that would be beneficial for the illustration of UBP roles in plants development and stress responses, aiming to touch upon the research trend of plant UBPs in the future.

1.1. UBPs in plants

During the plant life cycle, growth and development are strictly controlled by many factors to cope with multiple abiotic or biotic stresses. Recent data have shown that UBPs might function in the whole life cycle of plants (Fig. 2). Based on a comparison of similar sequences of Arabidopsis UCH domains (specific in UBP proteins, also called UBP domains, including both conserved Cys- and His-boxes), a total of 23 UBP genes were identified in the *Physcomitrella patens* moss genome, 18 in *Selaginella moellendorffii* lycophyte genome, 25 in the *Oryza sativa* monocot genome, and 14 in three green algae genomes (Fig. 3).

In *Arabidopsis thaliana*, based on sequence similarity and genomic organization, especially referring to the typical Cys- and His-box signature motifs, 27 UBP proteins are clustered into 14 sub-families (Wilkinson, 1997; Yan et al., 2000). For most UBP members, the basic structures of UBP genes are established in early land plants and conserved within subfamilies. In addition, most members within a subfamily have common non-UBP protein motif compositions or conserved amino acids, whereas members of different subfamilies show variations in protein domains (Table 1). The unique protein motif compositions of each subfamily differentiate the subfamily classifications and, more importantly, provide evidence for functional divergence among UBP subfamilies. Most members of the same subfamily have common protein motif compositions. However, beyond the three highly conserved catalytic residues, all UBPs share low sequence similarities and possess variant domain compositions, which imply diversity in their localization, substrate specificity and physiological function (Amerik and Hochstrasser, 2004; Clague et al., 2012; Isono and Nagel, 2014; Nijman et al., 2005). UBP-like activities are capable of cleaving ubiquitin attached to the target proteins via a peptide or an iso-peptide linkage, even without ATP support (Sullivan et al., 1990). Both Cys- and His-boxes are required for the deubiquitinating activities of UBPs, although the Cys-box is more conserved than the His-box (Doelling et al., 2001; Yan et al., 2000). Additionally, some less conserved motifs also exist in plant UBPs, including MATH, zinc-fingers (two types: Zf-MYND or Zf-UBP), Domain present in ubiquitin-specific proteases (DUSP), UBQ, Ub associated domains (UBA) and Ub-like domains (UBL) (Liu et al., 2008; Yan et al., 2000) (Table 1). These motifs might be involved in differentiating the specific functions of different members, promising plant UBPs the potential to participate in a broad range of cellular processes.

1.2. Plant UBP functional partners

It has long been acknowledged that some ubiquitin ligases (E3) rely on scaffolds and adaptors to deliver substrates to the catalytically active macromolecular complex. Similarly, as deubiquitinases (DUBs), UBPs may also acquire their substrates by binding the target protein in a conjugate or by associating with other partners in macromolecular complexes found to bind ubiquitin directly (Atanassov et al., 2011). Especially, in yeasts or animals, many UBPs have been shown to associate physically with E3, and function together to regulate ubiquitin-related pathway (de Poot et al., 2017; Sowa et al., 2009; Wolberger, 2014). The substrate specificity of UBP proteins in yeasts and animals has been determined by a variety of methods, while few are reported in plants (Loch and Strickler, 2012; de Poot et al., 2017; Sahtoe and Sixma, 2015; Sowa et al., 2009; Wolberger, 2014).

To date, Several plant UBP members (mostly from research results of *Arabidopsis thaliana*) have been elucidated, shedding light on their important roles in plant life. However, the detailed biological roles of most UBPs remain unknown. To identify substrates or functional partners is the key step in exploring UBP molecular function. Here we summarized the functional partners of UBPs with a view to exploring more details of molecular mechanisms of plant UBPs. Among the plant UBP partners, some are biological substrates, some are activity regulators of UBPs, and some are ones with the unknown relationship with UBPs (Table 2). The followings chosen for discussion here are UBPs whose functional partners have been identified.

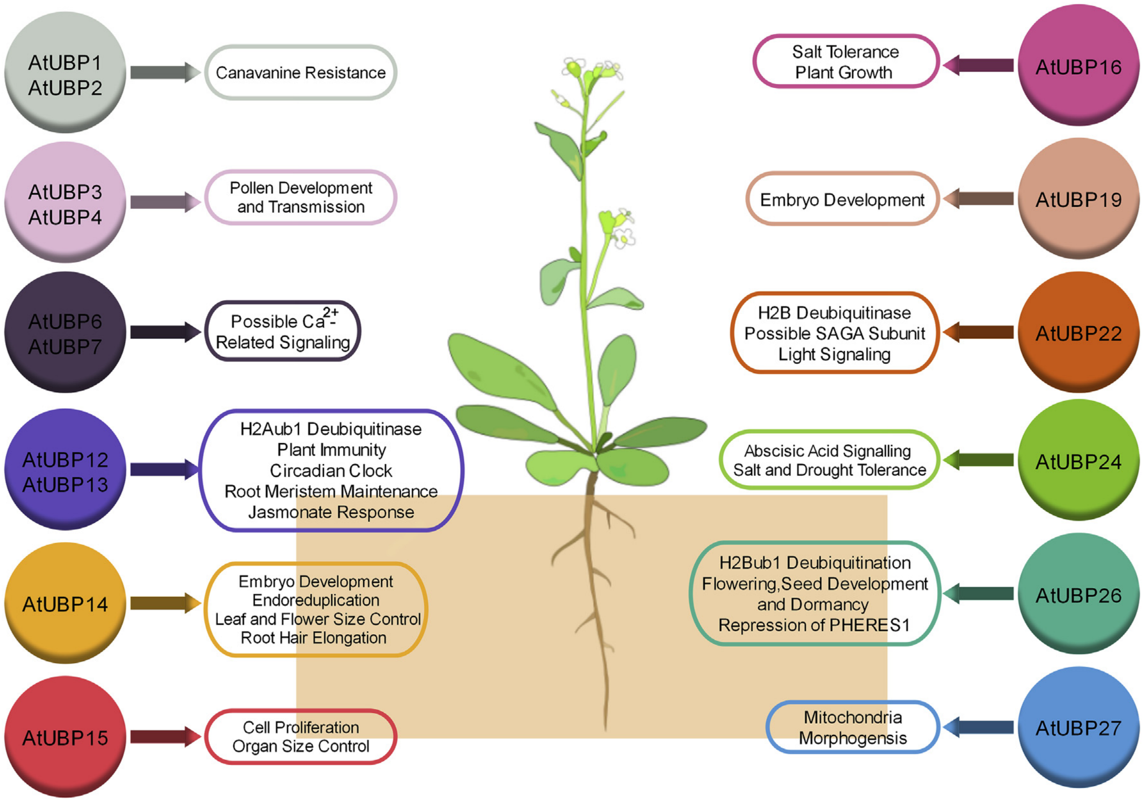

Fig. 2. Biological functions of UBPs in plants. The plant UBPs function in various cellular process of development, such as cell proliferation, seed dormancy, embryo and pollen development, circadian clock. They also involved in stress responses, such as plant immunity, salt and drought tolerance.

1.2.1. *UBP6*

The Arabidopsis UBP6 is a DUB that has been implicated in canavanine stress response and regulation of seedling early growth (Byeong et al., 2005; Moon et al., 2009). UBP6 interacts with CaM proteins and is possibly involved in the Ca^{2+}-mediated protein degradation by the 26S proteasome in plants (Byeong et al., 2005). Similarly, human USP14 (homolog of the Arabidopsis UBP6) is also found to be associated with the 26S proteasome, indicating a role in protein degradation (Leggett et al., 2002).

- **CaM protein**: Ca^{2+} acts as a secondary messenger that regulates multiple cellular processes triggered by external stimuli (Mcainsh and Hetherington, 1998; Reddy et al., 2001; Trewavas and Malhó, 1998). As one Ca^{2+} sensor, calmodulin (CaM) widely exists among all eukaryotes. Although there is no catalytic activity itself, the CaM transduces various Ca^{2+}-mediated signals to its effector proteins, CaM-binding proteins (CaMBPs) (Bender and Snedden, 2013; Hoeflich and Ikura, 2002; Poovaiah et al., 2013; Schulz et al., 2013; Snedden and Fromm, 2010). It has been shown that UBP6 binds directly to CaM, raising the possibility of UBP6-CaM cooperation in Ub-dependent protein degradation and/or stabilization in plants (Byeong et al., 2005). Does UBP6 target CaM to degradation directly? Or, does the UBP6 act as an effector of CaM to deliver Ca^{2+} related signaling? In fact, it is rarely reported about the DUB-Ca^{2+} signaling functional cross. The physical association of UBP6 and CaM provides an interesting clue to explore more details of the mechanism for DUB in the regulation of protein deubiquitination or protein stability via association with interacts Ca^{2+} signaling in the future.

1.2.2. *UBP12/13*

Arabidopsis UBP12 and UBP13 are the only two homologous proteins in the subgroup 5 of plant UBP family. They act as a deubiquitinase of monoubiquitinated H2A (H2Aub1), and function in the regulation of plant immunity, circadian clock, root meristem maintenance and jasmonate response (An et al., 2018; Cui et al., 2013; Derkacheva et al., 2016; Ewan et al., 2011; Jeong et al., 2017). In humans, USP7 shares a high similarity to Arabidopsis UBP12 and UBP13, and functions in tumor suppressor regulation by p53, which is a special class of transcription factors, involved in the various cellular stresses and induced cellular responses, such as cell cycle arrest, DNA repair, apoptosis and aging (Nicholson et al., 2011).

- **LHY/CCA1/TOC1**: These plant circadian clock genes differentiated their expression at a different time of day. For example, *LHY* and *CCA1* genes are highly expressed in the morning and their encoding proteins bind to the promoter of *TOC1* (evening gene) to repress its expression (Alabadí et al., 2001). In turn, the *TOC1* gene regulates the expression of *CCA1* and *LHY* as a repressor (Gendron et al., 2012; Huang et al., 2012). In the *ubp12w ubp13-3* double mutant, the circadian periods of *LHY* and *TOC1* expression were shortened and the transcription level of *TOC1* was obviously increased, suggesting that UBP12 and UBP13 are essential for proper circadian rhythm (Cui et al., 2013). Interestingly, UBP12 and UBP13 are also circadian controlled (Cui et al., 2013), proposing a complex network regulation between *UBP12/13* and circadian clock genes. While being circadian controlled, they regulate the circadian rhythm of clock genes, including *LHY*, *CCA1*, and *TOC1*, and also regulate photoperiodic flowering through a CO-dependent pathway (Cui et al., 2013). It has been known that CO protein degradation is promoted by at least two ubiquitin E3 ligases: HOS1 and COP1 (Jang et al., 2008; Lazaro et al., 2012). Thus, UBP12 and UBP13 might act in circadian and photoperiodic flowering by altering the ubiquitin-proteasome degradation pathway antagonistically with E3 ligase as DUBs.
- **H2A/LHP1/PcG target genes**: The highly conserved polycomb

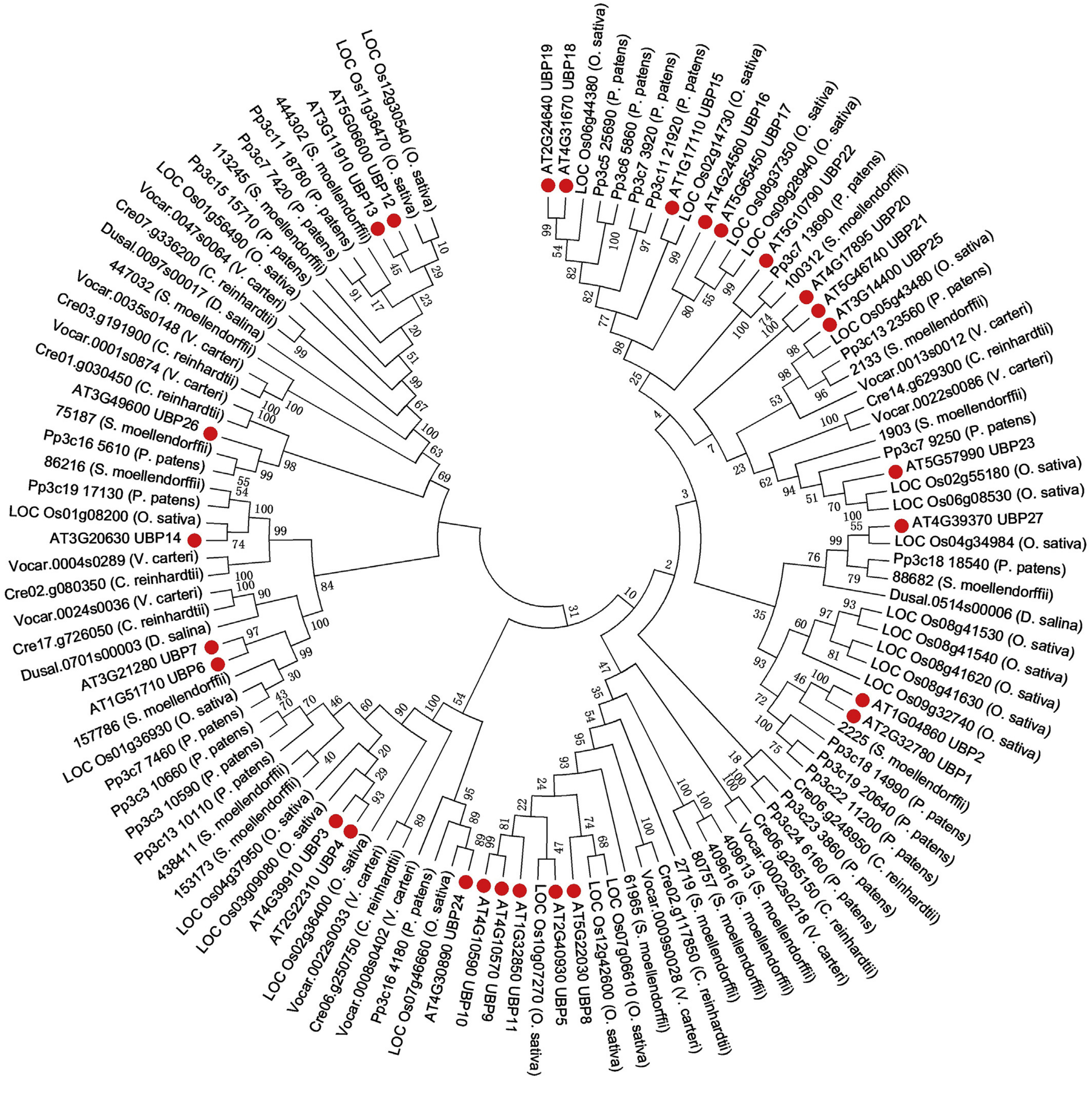

Fig. 3. Phylogenetic tree of UBPs in plants. Phylogeny of UBP proteins from Arabidopsis, Physcomitrella patens, Selaginella moellendorffii, Oryza sativa and three green algae. The red dots represent the UBP members in Arabidopsis thaliana. The tree was generated with Clustal X 2.0 software using the neighbor-joining (N-J) method.

group (PcG) proteins are a large family that epigenetically represses gene expression related to development by modulating the histone modification state (Chittock et al., 2017). As two of the three major complexes involved in such state modification, PRC1 and PRC2 are involved in gene repression through monoubiquitination of H2A to monoubiquitinated H2A (H2Aub1), and function in the deposition of trimethylation of histone 3 on lysine 27 (H3K27me3) as a repressive epigenetic mark, respectively (Calonje, 2014; Hengbin et al., 2004; Jiang and Berger, 2017; Mozgova et al., 2015). It shows that *in vitro* UBP12 and UBP13 physically associate with a PcG related protein LHP1, which may connect PRC1 and PRC2 and mediates the repression of some PcG genes by affecting local H2Aub1 and H3K27me3 levels (Derkacheva et al., 2016). As the UBP12 has H2Aub1 deubiquitination activity *in vitro* and *in vivo* (Derkacheva et al., 2016), raising the high possibility that UB12 (and UBP13) factually acting as the deubiquitinases of H2Aub1.

- **RGFR1:** This is a receptor of ROOT MERISTEM GROWTH FACTOR 1 (RGF1), which is an important peptide hormone that modulates root growth. Generally, the RGF1 binds to the RGFR1 to transduce a signal to regulate the expression of two transcription factors, PLETHORA 1 and 2 (PLT1/2), to finally influence root meristem development (Aida et al., 2004; Siligato, 2014; Yo et al., 2010). UBP13 interacts directly with RGFR1 to counteract the ligand-induced ubiquitination and degradation of RGFR1, suggesting that UBP13

Table 1
Characterization of AtUBPs and their functions.

Sub-family	Name/ID	Non-UBP domains	Function	Reference
1	UBP1 (AT2G32780)	Zf-UBP	canavanine resistance	Yan et al. (2000)
	UBP2 (AT1G04860)	Zf-UBP	canavanine resistance	Yan et al. (2000)
2	UBP3 (AT4G39910)	–	pollen development and transmission	Doelling et al., 2007
	UBP4 (AT2G22310)	–	pollen development and transmission	Doelling et al., 2007
3	UBP5 (AT2G40930)	DUSP	–	–
	UBP8 (AT5G22030)	–	–	–
	UBP9 (AT4G10570)	DUSP	–	–
	UBP10 (AT4G10590)	DUSP	–	–
	UBP11 (AT1G32850)	DUSP	–	–
4	UBP6 (AT1G51710)	UBL	possible Ca^{2+}- related signaling,	Byeong et al. (2005); Moon et al. (2009)
	UBP7 (AT3G21280)	UBL	possible Ca^{2+}- related signaling	Moon et al. (2009)
5	UBP12 (AT5G06600)	MATH	H2Aub1 deubiquitinase, plant immunity, circadian clock, root meristem maintenance, JA response	An et al. (2018); Cui et al. (2013); Derkacheva et al. (2016); Ewan et al. (2011); Jeong et al. (2017)
	UBP13 (AT3G11910)	MATH	H2Aub1 deubiquitinase, plant immunity, circadian clock, root meristem maintenance, JA response	An et al. (2018); Cui et al. (2013); Derkacheva et al. (2016); Ewan et al. (2011); Jeong et al. (2017)
6	UBP14 (AT3G20630)	Zf-UBP, UBA	embryo development endoreduplication, leaf and flower size control, root hair elongation (Pi availability)	Doelling et al. (2001); Li et al. (2010); Tzafrir et al. (2002); Xu et al. (2016)
7	UBP15 (AT1G17110)	Zf-MYND	cell proliferation, organ size control	Du et al. (2014); Liu et al. (2008),
	UBP16 (AT4G24560)	Zf-MYND	salt tolerance, plant growth (partially redundantly with UBP15)	Liu et al. (2008); Zhou et al. (2012)
	UBP17 (AT5G65450)	Zf-MYND	–	–
	UBP18 (AT4G31670)	Zf-MYND	–	–
	UBP19 (AT2G24640)	Zf-MYND	embryo development	Liu et al. (2008)
8	UBP20 (AT4G17895)	–	–	–
	UBP21 (AT5G46740)	–	–	–
9	UBP22 (AT5G10790)	Zf-UBP	H2Bub1 deubiquitinase, SAGA subunit, light signaling	Nassrallah et al. (2018)
10	UBP23 (AT5G57990)	–	–	–
11	UBP24 (AT4G30890)	–	abscisic acid signaling, salt and drought tolerance	Zhao et al. (2016)
12	UBP25 (AT3G14400)	–	–	–
13	UBP26 (AT3G49600)	DUSP, UBL	H2Bub1 deubiquitination, flowering, seed development and dormancy, repression of *PHERES1*	Schmidz et al., 2009; Sridhar et al. (2007); Luo et al. (2008)
14	UBP27 (AT4G39370)	–	mitochondria morphogenesis	Pan et al. (2014)

(and UBP12) are components of the RGFR1 signaling pathway and are crucial for root meristem maintenance (An et al., 2018). By their deubiquitinating activity, the UBP12 and UBP13 stabilize the RGFR1 to maintain root cell sensitivity to RGF1 for meristem maintenance (An et al., 2018).

- **MYC2:** It is a putative transcription factor that acts as a master switch integrating diverse signals to mediate plant development and stress responses (Goossens et al., 2017; Kazan and Manners, 2013). Recently, it has been found that JA-mediated phenotypes are also associated with the MYC2 protein level (Chico et al., 2014; Schmiesing et al., 2016; Shin et al., 2012), which is affected by different conditions, i.e. dark, far-red light, red light, and blue light, or hormones (such as MeJA and SA) (Chico et al., 2014; Schmiesing et al., 2016). Moreover, MYC2 protein levels are negatively controlled by PUB10-mediated ubiquitination in JA responses (Jung et al., 2015). *in vitro,* the UBP12 and UBP13 interact with MYC2 and remove ubiquitin from polyubiquitinated MYC2, thus, it is possible that the UBP12/13 could elevate MYC2 levels by deubiquitinating the polyubiquitinated transcription factor from being degraded in the jasmonate response (Jeong et al., 2017).

1.2.3. UBP14

The Arabidopsis UBP14 is involved in the regulation of embryonic development (Doellinget al., 2001; Tzafrir et al., 2002), root hair elongation in the absence of phosphate (Li et al., 2010), and organ growth by affecting ploidy level in cells (Xu et al., 2016). Its protein sequence has a high similarity to humans USP5/IsoT and yeast Ubp14, which function in recycling monomeric Ub by dismantling unanchored poly-Ub chains (Avvakumov et al., 2012; Dayal et al., 2009).

- **APC/C/UVI4/CCS52A1/CYC2A2;3/CDKB1;1**: In all eukaryotes, the Anaphase-Promoting Complex/Cyclosome (APC/C) is a multisubunit E3 ubiquitin ligase complex, selectively targets mitotic cyclins for ubiquitination during degradation to control mitotic progression (Marrocco et al., 2010; Pesin and Orrweaver, 2008). CYCA2;3 and CDKB1;1 act downstream components of the APC/C and function together to inhibit the switch from the mitotic cell cycle to the endocycle (Boudolf et al., 2009). Increasing expression of the two genes leads to ectopic cell division and represses the endocycle (Boudolf et al., 2009; Imai et al., 2006). The APC/C activity is regulated dynamically. On one hand, it is activated by some subunits, such as the docking factor APC10/Doc1 and the Cell Cycle Division 20 (CDC20)/Fizzy or CDH11/Fizzy-related (FZR) activator subunits (Pesin and Orrweaver, 2008). In *Arabidopsis thaliana*, the CCS52A1/FZR2, CCS52A2/FZR1, and CCS52B are three CDH11/FZR-related proteins involved in the regulation of endoreplication onset and progression (Breuer et al., 2012; Lammens et al., 2008; Zachary et al., 2009). On the other hand, the APC/C function is prevented by some inhibitory proteins. For instance, in mammalian and *Xenopus laevis* cells, the Early Mitotic Inhibitor 1 (Emi1) inhibits APC/CCDH1 activity coupled with DNA replication in mitotic progression (Di Fiore and Pines, 2007). In *Arabidopsis thaliana*, the UV-B-Insensitive 4 (UVI4) has been proposed as a functional homolog of Emi1, and interacts with CCS52A1 to suppress the endocycle by inhibiting CYCA2;3 degradation (Hase et al., 2006; Heyman et al., 2011; Iwata et al., 2011). It is found that the Arabidoposis UBP14 physically interacts UVI4 and represses endoreduplication in plant cells. Meanwhile, the UBP14 functions antagonistically with CCS52A1, although UBP14 does not interact with CCS52A1 in the regulation of endocycle (Xu et al., 2016). It also found that the UBP14 positively influences the stability of CYCA2;3 and CDKB1;1, two downstream components of the APC/C (Xu et al., 2016). For the opposite role of the UBP14 (a DUB) and APC (an E3 complex) in the protein ubiquitination, it is possible that they act together through

Table 2
UBP partners and associated comments.

UBPs	Partners	Role of partners			Comments
		Substrate	Regulatory	Unclear or others	
UBP6	Calmodulin			✓	UBP6 interacts with CaM, possibly involved in Ub-dependent protein degradation and/or stabilization (Byeong et al., 2005).
UBP12/UBP13	LHY/CCA1/TOC1		✓		UBP12 and UBP13 redundantly modulate the circadian rhythm of clock genes, including *LHY*, *CCA1*, and *TOC1*, and regulate photoperiodic flowering through a CO-dependent pathway (Derkacheva et al., 2016).
	LHP1/PcG			✓	UBP12 and UBP13 associate with LHP1 to regulate the expression of PcG target genes (Derkacheva et al., 2016).
	H2A	✓			UBP12 and UBP13 deubiquitinate H2Aub1 to regulate circadian clock and photoperiodic flowering time (Cui et al., 2013).
	RGFR1	✓			UBP12 and UBP13 deubiquitinate RGFR1, as components of the RGFR1 signaling pathway which is crucial for root meristem maintenance (An et al., 2018).
	MYC2	✓			UBP12 and UBP13 prevent MYC2 from being degraded by deubiquitination, and maintain cellular sensitivity to JA (Jeong et al., 2017).
UBP14	UVI4			✓	UBP14 physically associates with UVI4 (an inhibitor of the APC/C ubiquitin ligase) to repress endoreduplication (Xu et al., 2016).
	CCS52A1	✓			UBP14 functions antagonistically with CCS52A1 (an activator of APC/C) to regulate endoreduplication (Xu et al., 2016).
	CYCA2;3/CDKB1;1	✓			UBP14 positively regulates the stability of CYCA2;3 and CDKB1;1 (Xu et al., 2016).
UBP15	DA1		✓		The stability of UBP15 is negatively regulated by DA1 (Du et al., 2014; Dong et al., 2017).
UBP16	SHM1	✓			UBP16 stabilizes SHM1 by removing the conjugated ubiquitin and modulates sodium transport activity (Zhou et al., 2012)
UBP22	SGF11/ENY2			✓	UBP22, SGF11 and ENY2 potentially form a trimeric DUBm in a highly conserved complex SAGA involved in the deubiquitination of H2Bub1. (Nassrallah et al., 2018).
	H2B	✓			UBP22 deubiquitinates H2Bub1 as a component of SAGA complex (Nassrallah et al., 2018).
UBP24	ABI2		✓		UBP24 acts upstream of ABI2 and participates in salt tolerance (Zhao et al., 2016).
UBP26	H2B	✓			UBP26 is required for deubiquitination of H2Bub1 (possible substrate), involved in the transcriptional activation of *FLC* and repression of *PHE1* (Luo et al., 2008; Schmitz et al., 2009; Sridhar et al., 2007).
UBP27	DRP3			✓	UBP27 modulates DRP3 in an indirect manner by reducing the association of DRP3 with mitochondria resulting in change of mitochondrial morphology (Pan et al., 2014).

the interaction with UVI4 (a partner of APC/C) to balance the protein ubiquitination or degradation for the downstream components in the control of endoreduplication.

1.2.4. *UBP15/SOD2*

The Arabidopsis UBP15 acts downstream of DA1 controlling organ size and plant growth by affecting cell proliferation (partially redundant with UBP16 and UBP17) (Du et al., 2014; Liu et al., 2008).

- **DA1:** DA means "big" in Chinese (Li et al., 2008). The DA1 is a putative ubiquitin receptor with a plant-specific LIM-domain and has multiple functions in regulating organ size and abiotic stress response (Li et al., 2008; Zhao et al., 2014). *DA1* expression is induced by abscisic acid (ABA), indicating the potential involvement of DA1 in ABA-related abiotic stress responses (Li et al., 2008). DA1 controls final organ size and acts maternally to affect seed growth by restricting cell proliferation in the integuments (Du et al., 2014; Li et al., 2008; Xia et al., 2013). Additionally, it demonstrates that DA1 and its two homologs, DA1-related 1 (DAR1) and DA1-related2 (DAR2) function in a common pathway with TCP14/15 to regulate endoreduplication by modulating the stability of TCP14/15 which promote cell proliferation and represses endoreduplication (Peng et al., 2015). Moreover, DA1 interacts and destabilizes DA2, Big Brother (BB), and UBP15 to control final organ size (Du et al., 2014; Xia et al., 2013). DA1 is a putative ubiquitin receptor implying its role in ubiquitination and degradation of its targets by the 26S-related proteasome. However, recently it has revealed that DA1 acts as a ubiquitin-activated peptidase. It is monoubiquitinated and activated by two E3s, BB and DA2; in turn, the activated DA1 cleaves and destabilizes BB and DA2 (Dong et al., 2017). In addition, DA1 peptidase activity is also required to cleave TCP15, TCP22, and UBP15, indicating that DA1 peptidase activity coordinates cell proliferation, endoreplication and differentiation by targeting different regulatory protein destruction (Dong et al., 2017).

1.2.5. *UBP16*

As mentioned above, the Arabidopsis UBP16 functions partially redundantly with UBP15 and UBP17 in plant growth (Liu et al., 2008). Meanwhile, UBP16 is responsible for salt tolerance by regulating the activity of PM Na^+/H^+ antiports (Zhou et al., 2012).

- **SHM1:** The Serine Hydroxymethyltransferase 1 (SHM1) is the major Serine Hydroxymethyltransferase (SHMT) isozyme that plays a critical role in plant salt tolerance (Mcclung et al., 2000; Somerville and Ogren, 1981). When *SHM1* mutates, leaf mitochondrial SHMT activity is undetectable and photorespiratory Gly metabolism related to Serine is significantly reduced (Somerville and Ogren, 1981). UBP16 interacts with SHM1 and targets ubiquitinated-SHM1 as a substrate of deubiquitination, to prevent its degradation. Consistent with the situation in *shm1*, the SHMT activity is reduced by the UBP16 mutation, indicating that the low protein level of SHM1 is essential for the SHMT activity.

1.2.6. *UBP22*

Similar to the homolog DUB (USP22) in human, the Arabidopsis UBP22 is thought to be part of an atypical SAGA-like DUB module (DUBm) which is responsible for the deubiquitination of mono-ubiquitinated H2B (H2Bub1) (Nassrallah et al., 2018; Zhang et al., 2008; Weake and Workman, 2008). In *Arabidopsis thaliana*, the abundance of UBP22 is regulated by DE-ETIOLATED 1 (DET1) during dark/light transitions (Nassrallah et al., 2018).

H2B/SGF11/ENY2: Dynamic H2B ubiquitination is required for heterochromatic histone H3 methylation and DNA methylation, resulting in the regulation of gene expression (Sridhar et al., 2007). The H2B ubiquitination level is tuned by DUBm in a highly conserved complex SAGA (Spt–Ada–Gcn5–Acetyl transferase) that is thought to control the transcription of approximately 10% of genes, particularly the stress-related genes (Helmlinger and Tora, 2017; Lee et al., 2000). In yeast, DUBm is an independent structure functionally composed of the ubiquitin protease 8 (Ubp8) catalytic subunit (Ingvarsdottir et al., 2005), the SAGA-associated factor 11 (Sgf11) nucleosome-binding subunit (Ingvarsdottir et al., 2005; Lee et al., 2005), the small protein Sus1, ubiquitin-binding subunit (Rodríguez Navarro et al., 2004), and Sgf73 that forms the bridge with core SAGA modules (Kohler et al., 2008; Lee et al., 2009). Although there is no a predictable plant Sgf73-like subunit in *Arabidopsis thaliana*, the orthologous proteins of yeast Sgf11, Ubp8, and Sus1 are SGF11, UBP22, and ENY2, respectively (Moraga and Aquea, 2015). SGF11, ENY2, and UBP22 potentially form a trimeric DUBm *in planta* without an ortholog of Sgf73. It has been found that the UBP22 physically associates with SGF11 but ENY2, although robust interaction exists between SGF11 and ENY2, both of which are the two other members of DUBm. In contrast with yeast and animal DUBm, the plant lack the Sgf73-like subunit that connects the DUBm and the core SAGA modules, thus the Arabidopsis DUBm only comprises three subunits (SGF11, ENY2, and UBP22) and appears to function independently as a major deubiquitinase of H2Bub1 (Nassrallah et al., 2018).

1.2.7. UBP24

The Arabidopsis UBP24 is a negative regulator of ABA signaling upstream of ABI2 (Zhao et al., 2016). It is interesting that the *ubp24* mutant seedlings are hypersensitive to ABA and salt stress, though their stomatal closure is less sensitive to ABA (Zhao et al., 2016).

- **ABI2:** As a member of protein phosphatases type 2C (PP2Cs), the ABI2 interacts with the positive regulator SnRK2 in the absence of ABA, and then phosphorylates transcription factors to activate ABA-responsive gene expression (Fujii et al., 2009; Ma et al., 2009). In the presence of ABA, the receptors PYR1/PYLs/RCAR are activated by binding to ABA, and trigger the release of SnRK2 from PP2C-SnRK2, resulting in phosphorylation of bZIP family transcription factors (ABF/ABRE/ABI5) and activation of ABA-induced gene expression (Fujii et al., 2009; Ma et al., 2009; Park et al., 2009). In addition, ABI2 also integrates signals of ABA and auxin through its suppression by FERONIA (FER) which is a positive regulator of auxin-promoted growth (Yu et al., 2012). In the presence of ABA, UBP24 functions upstream of ABI2, and negatively regulates phosphatase activity of PP2C, demonstrating a regulatory role of UBP24 in response to ABA and salt stress in plants (Zhao et al., 2016). There is no evidence for how the UBP24 regulates the activity of PP2C, however, the current research results could support the idea that the UBP24 modulates the activity of PP2C indirectly via the FER-mediated auxin signaling pathway.

1.2.8. UBP26/SUP32

The Arabidopsis UBP26 is required for deubiquitination of H2Bub1 (similar to the function of UBP22), subsequently affecting H3 methylation and DNA methylation (Sridhar et al., 2007). It also found that the UBP26 is required for seed development and the repression of PHERES1 (PHE1) (Luo et al., 2008).

- **H2B/PHE1:** The UBP26 can deubiquitinate H2B, which is required for heterochromatic histone H3 and DNA methylation (Sridhar et al., 2007). The *FIS* genes encode PcG proteins and function in H3K27me3 modification at the locus of *PHE1* to regulate seed development (Grossniklaus and Paro, 2014; Makarevich et al., 2006). In the *ubp26* mutant, the *PHE1* gene shows higher activity in terms of transcription and a lower level of H3K27me3 at its locus, suggesting that *UBP26* has a role in seed dormancy and repression of *PHE1* (Luo et al., 2008). Although the UBP26 is essential for deposition of H3K27me3 at the *PHE1* locus, no direct evidence shows the relationship between *UBP26* and *FIS* genes in the regulation of PHE1 methylation and function.

1.2.9. UBP27

The Arabidopsis UBP27 is identified as a mitochondrial outer membrane protein with a N_{in}–C_{out} topology and plays a role in mitochondrial morphogenesis possibly by modulating the function of organelle division proteins (Pan et al., 2014).

- **DRP3**: The DRP3A (ADL2a) and DRP3B (ADL2b) are well conserved dynamic-related proteins (DRPs), both orthologs of Dnm1/Drp1, and are involved in mitochondrial morphogenesis and peroxisome fission (Arimura, 2017; Arimura and Tsutsumi, 2002; Arimura et al., 2008, 2004; 2017; Fujimoto et al., 2009; Logan et al., 2004; Mano et al., 2004; Yoshinaga et al., 2006; Zhang and Hu, 2009). The UBP27 modulates DRP3 in an indirect manner by reducing the association of DRP3 and mitochondria (Pan et al., 2014), possibly by facilitating the recycling of DRP3 proteins from mitochondria to the cytosol, yet it remains unclear whether UBP27 interacts directly or indirectly to deubiquitinate DRP3.

2. Conclusion

Although characterization of UBP proteins in different plant model organisms has been accelerated, our understanding of their functions remains limited. Protein partners shed light on possible molecular mechanisms underlying the possible functions of UBP proteins in the regulation of cellular events in plants.

In yeasts and animals, it is found that many UBPs associate with E3 ligases which always ubiquitinate themselves. Therefore, deubiquitination of E3 ligases to maintain their stabilization is a major aspect of UBP physiology and, reciprocally, E3s may ubiquitinate their UBP partners to destabilize them. Additionally, UBPs and E3 ligases in complex commonly function to coordinate ubiquitination of the same substrate (Komander et al., 2009). For example, in yeasts and animals, USP8 and Nrdp1 (E3 ligase) are in a functional complex, antagonistically acting in the regulation of ubiquitination level and stabilization of DRDP1 (Wu et al., 2004). Similarly, USP19 stabilizes KPC (also known as RNF123), an E3 ligase required for the ubiquitination of cyclin-dependent kinase inhibitor p27Kip1, to support cell proliferation (Lu et al., 2009). In the case of USP7, it interacts with E3 ligase partner MDM2 and their common substrate p53 to function in DNA repair and apoptosis (Zaman et al., 2013). These evidences raise the possibility that UBP and E3 commonly form a complex in the regulation of substrate ubiquitination level. In plants, the H2B ubiquitination level seems to be coordinated by both a UBP (UBP22) and an E3 complex (DET1-related) (Nassrallah et al., 2018); however, a “UBP/USP-E3” complex has not been extensively found in plants thus far. Therefore, in the future, identification of the E3 partners of plant UBPs, will be beneficial for the dissecting plant UBP-mediated biological mechanisms.

The UBPs modulate the H2A and H2B ubiquitination levels, which affect H3 methylation and related gene transcription significantly, implying the role of UBPs in the crosstalk of histone epigenetic modification and gene expression by deubiquitination of H2Aub1 and H2Bub1, future advances of this cooperation in plants may be expected (March and Farrona, 2017). Indeed, the role of different plant UBPs in H2Aub1 and H2Bub1 deubiquitination and DNA methylation associated with transcriptional regulation is appearing (Talbert and Henikoff, 2017). In plants, UBP12 and UBP13 work with LHP1, which mediate H2A monubiquitination and H3 trimethylation, respectively, to regulate the expression of some PcG target genes (Derkacheva et al., 2016). In yeast and animal, the H2B ubiquitination is thought to control the transcription of a few stress-related genes and its level is tuned by DUBm in two highly conserved complex SAGA and Sir, in which the corresponding DUB subunit are Ubp8/USP22 and Ubp10 (Gardner et al., 2005; Helmlinger and Tora, 2017; Lee et al., 2000). In plants, both UBP22 and UBP26 are involved in H2Bub1 deubiquitination, however, the sequence similarity of UBP22/26 and Ubp8/10 is very low. Accordingly, the responsible DUBs for H2Bub1 deubiquitination might differentiate in an early time. Additionally, the yeast Ubp8 and Ubp10 show high similarity in their protein sequence, while that of UBP22 and UBP26 is quite low. So it will also be a challenge to identify the functional relationship between UBP22 and UBP26 in the crosstalk with H2B deubiquitination in the future work.

Funding

This study was financially supported by the National Key Research and Development Program of China (Grant No. 2018 YFD0600101), the Fundamental Research Funds for the Central Universities [Grant No. BLX201418], and the National Natural Science Foundation of China [Grant No. 31501168].

Contributions of authors

Liang Du and Cunfu Lu designed the work; Ruihua Wu and Liang Du wrote the manuscript; Wenqing Zheng constructed charts; Jinyi Tan and Rana Sammer reviewed the manuscript.

Acknowledgments

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

References

Aida, M., Beis, D., Heidstra, R., Willemsen, V., Blilou, I., Galinha, C., Nussaume, L., Noh, Y.S., Amasino, R., Scheres, B., 2004. The PLETHORA genes mediate patterning of the Arabidopsis root stem cell niche. Cell 119, 109–120.

Alabadí, D., Oyama, T., Yanovsky, M.J., Harmon, F.G., Más, P., Kay, S.A., 2001. Reciprocal regulation between TOC1 and LHY/CCA1 within the Arabidopsis circadian clock. Science 293, 880–883.

Amerik, A.Y., Hochstrasser, M., 2004. Mechanism and function of deubiquitinating enzymes. Biochim. Biophys. Acta 1695, 189–207.

An, Z., Liu, Y., Ou, Y., Li, J., Zhang, B., Sun, D., Sun, Y., Tang, W., 2018. Regulation of the stability of RGF1 receptor by the ubiquitin-specific proteases UBP12/UBP13 is critical for root meristem maintenance. Proc. Natl. Acad. Sci. 115, 1123–1128.

Arimura, S., 2017. Fission and fusion of plant mitochondria, and genome maintenance. Plant Physiol. 176, 152–161.

Arimura, S., Tsutsumi, N., 2002. A dynamin-like protein (ADL2b), rather than FtsZ, is involved in Arabidopsis mitochondrial division. Proc. Natl. Acad. Sci. 99, 5727–5731.

Arimura, S.I., Aida, G.P., Fujimoto, M., Nakazono, M., Tsutsumi, N., 2004. Arabidopsis DYNAMIN-LIK PROTEIN 2a (ADL2a), like ADL2b, is involved in plant mitochondrial division. Plant Cell Physiol. 45, 236–242.

Arimura, S.i., Fujimoto, M., Doniwa, Y., Kadoya, N., Nakazono, M., Sakamoto, W., Tsutsumi, N., 2008. Arabidopsis ELONGATED MITOCHONDRIA1 is required for localization of DYNAMIN-RELATED PROTEIN3A to mitochondrial fission sites. Plant Cell 20, 1555–1566.

Arimura, S.I., Kurisu, R., Sugaya, H., Kadoya, N., Tsutsumi, N., 2017. Cold treatment induces transient mitochondrial fragmentation in *Arabidopsis thaliana* in away that requires DRP3A but not ELM1 or an ELM1-like homologue. ELM2. Int. J. Mol. Sci. 18, 2161.

Atanassov, B.S., Koutelou, E., Dent, S.Y., 2011. The role of deubiquitinating enzymes in chromatin regulation. FEBS Lett. 585, 2016–2023.

Avvakumov, G.V., Walker, J.R., Xue, S., Allali-Hassani, A., Asinas, A., Nair, U.B., Fang, X., Zuo, X., Wang, Y.X., Wilkinson, K.D., Dhe-Paganon, S., 2012. Two ZnF-UBP domains in isopeptidase T (USP5). Biochemistry 51, 1188–1198.

Bender, K.W., Snedden, W.A., 2013. Calmodulin-related proteins step out from the shadow of their namesake. Plant Physiol. 163, 486–495.

Boudolf, V., Lammens, T., Boruc, J., Van Leene, J., Van Den Daele, H., Maes, S., Van Isterdael, G., Russinova, E., Kondorosi, E., Witters, E., Jaeger De, G., Inze, D., Veylder De, L., 2009. CDKB1;1 forms a functional complex with CYCA2;3 to suppress endocycle onset. Plant Physiol. 150, 1482–1493.

Breuer, C., Morohashi, K., Kawamura, A., Takahashi, N., Ishida, T., Umeda, M., Grotewold, E., Sugimoto, K., 2012. Transcriptional repression of the APC/C activator CCS52A1 promotes active termination of cell growth. EMBO J. 31, 4488–4501.

Byeong, C.M., Man, S.C., Yun, H.K., Min, C.K., Mi, S.C., Chan, Y.P., Jae, H.Y., Sung, C.K., Sang, M.L., Chae, O.L., Moo, J.C., Woo, S.C., 2005. Arabidopsis UBIQUITIN-SPECIFIC PROTEASE 6 (AtUBP6) interacts with calmodulin. FEBS Lett. 579, 3885–3890.

Calonje, M., 2014. Prc1 marks the difference in plant pcg repression. Mol. Plant 7, 459–471.

Chico, J.M., Fernandez-Barbero, G., Chini, A., Fernandez Calvo, P., Diez Diaz, M., Solano, R., 2014. Repression of jasmonate-dependent defenses by shade involves differential regulation of protein stability of MYC transcription factors and their JAZ repressors in *Arabidopsis*. Plant Cell 26, 1967–1980.

Chou, E.C., Latwiel, S., Miller, T.C., Müller, C.W., 2017. Molecular architecture of polycomb repressive complexes. Biochem. Soc. Trans. 45, 193–205.

Clague, M.J., Coulson, J.M., Urbe, S., 2012. Cellular functions of the DUBs. J. Cell Sci. 125, 277–286.

Cui, X., Lu, F., Li, Y., Xue, Y., Kang, Y., Zhang, S., Qiu, Q., Cui, X., Zheng, S., Liu, B., Xiu, X., Cao, X., 2013. UBIQUITIN-SPECIFIC PROTEASES UBP12 and UBP13 act in circadian clock and photoperiodic flowering regulation in *Arabidopsis*. Plant Physiol. 162, 897–906.

de Poot, S.A.H., Tian, G., Finley, D., 2017. Meddling with fate: the protea somal deubiquitinating enzymes. J. Mol. Biol. 429, 3525–3545.

Derkacheva, M., Liu, S., Figueiredo, D.D., Gentry, M., Mozgova, I., Nanni, P., Tang, M., Mannervik, M., Köhler, C., Hennig, L., 2016. H2A deubiquitinases UBP12/13 are part of the Arabidopsis polycomb group protein system. Nat. Plants 2, 16126.

Di Fiore, B., Pines, J., 2007. Emi1 is needed to couple DNA replication with mitosis but does not regulate activation of the mitotic APC/C. J. Cell Biol. 177, 425–437.

Doelling, J.H., Yan, N., Kurepa, J., Walker, J., Vierstra, R.D., 2001. The ubiquitin-specific protease UBP14 is essential for early embryo development in *Arabidopsis thaliana*. Plant J. 27, 393–405.

Dong, H., Dumenil, J., Lu, F., Na, L., Vanhaeren, H., Naumann, C., Klecker, M., Prior, R., Smith, C., McKenzie, N., Saalbach, G., Chen, L., Xia, T., Gonzalez, N., Seguela, M., Inze, D., Dissmeyer, N., Li, Y., Bevan, M.W., 2017. Ubiquitylation activates a peptidase that promotes cleavage and destabilization of its activating E3 ligases and diverse growth regulatory proteins to limit cell proliferation in *Arabidopsis*. Genes Dev. 31, 197–208.

Du, L., Li, N., Chen, L., Xu, Y., Li, Y., Zhang, Y., Li, C., Li, Y., 2014. The ubiquitin receptor DA1 regulates seed and organ size by modulating the stability of the ubiquitin-specific protease UBP15/SOD2 in *Arabidopsis*. Plant Cell 26, 665–677.

Ewan, R., Pangestuti, R., Thornber, S., Craig, A., Carr, C., O'Donnell, L., Zhang, C., Sadanandom, A., 2011. Deubiquitinating enzymes AtUBP12 and AtUBP13 and their tobacco homologue NtUBP12 are negative regulators of plant immunity. New Phytol. 191, 92–106.

Fujii, H., Chinnusamy, V., Rodrigues, A., Rubio, S., Antoni, R., Park, S.Y., Cutler, S.R., Sheen, J., Rodriguez, P.L., Zhu, J., 2009. In vitro reconstitution of an abscisic acid signalling pathway. Nature 462, 660–664.

Fujimoto, M., Arimura, S.I., Mano, S., Kondo, M., Saito, C., Ueda, T., Nakazono, M., Nakano, A., Nishimura, M., Tsutsumi, N., 2009. Arabidopsis dynamin-related proteins DRP3A and DRP3B are functionally redundant in mitochondrial fission, but have distinct roles in peroxisomal fission. Plant J. 58, 388–400.

Gardner, R.G., Nelson, Z.W., Gottschling, D.E., 2005. Ubp10/Dot4p regulates the persistence of ubiquitinated histone H2B: distinct roles in telomeric silencing and general chromatin. Mol. Cell. Biol. 25, 6123–6139.

Gendron, J.M., Pruneda-Paz, J.L., Doherty, C.J., Gross, A.M., Kang, S.E., Kay, S.A., 2012. Arabidopsis circadian clock protein, TOC1, is a DNA-binding transcription factor. Proc. Natl. Acad. Sci. 109, 3167–3172.

Goossens, J., Mertens, J., Goossens, A., 2017. Role and functioning of bHLH transcription factors in jasmonate signalling. J. Exp. Bot. 68, 1333.

Grossniklaus, U., Paro, R., 2014. Transcriptional silencing by polycomb-group proteins. Cold Spring Harb. Protoc. 6, a019331.

Hase, Y., Trung, K.H., Matsunaga, T., Tanaka, A., 2006. A mutation in the uvi4 gene promotes progression of endo-reduplication and confers increased tolerance towards ultraviolet B light. Plant J. 46, 317–326.

Helmlinger, D., Tora, L., 2017. Sharing the SAGA. Trends Biochem. Sci. 42, 850–861.

Hengbin, W., Liangjun, W., Hediye, E.B., Miguel, V., Paul, T., Jones Richard, S., Yi, Z., 2004. Role of histone H2A ubiquitination in Polycomb silencing. Nature 431, 873–878.

Hershko, A., Ciechanover, A., 1998. The ubiquitin system. Annu. Rev. Biochem. 67, 425–479.

Heyman, J., Van den Daele, H., De Wit, K., Boudolf, V., Berckmans, B., Verkest, A., Kamei, C.L.A., De Jaeger, G., Koncz, C., De Veylder, L., 2011. Arabidopsis ULTRAVIOLET-B-INSENSITIVE4 maintains cell division activity by temporal inhibition of the anaphase-promoting complex/cyclosome. Plant Cell 23, 4394–4410.

Hoeflich, K.P., Ikura, M., 2002. Calmodulin in action : diversity in target recognition and activation mechanisms. Cell 108, 739–742.

Huang, W., Pérez-García, P., Pokhilko, A., Millar, A.J., Antoshechkin, I., Riechmann, J.L., Mas, P., 2012. Mapping the core of the Arabidopsis circadian clock defines the network structure of the oscillator. Science 336, 75–79.

Imai, K.K., Ohashi, Y., Tsuge, T., Yoshizumi, T., Matsui, M., Oka, A., Aoyama, T., 2006. The a-type cyclin CYCA2;3 is a key regulator of ploidy levels in Arabidopsis endoreduplication. Plant Cell 18, 382–396.

Ingvarsdottir, K., Thompson, N.J., Emili, A., Hughes, T.R., Greenblatt, J.F., Berger, S.L., 2005. H2B ubiquitin protease Ubp8 and Sgf11 constitute a discrete functional module within the *Saccharomyces cerevisiae* SAGA complex. Mol. Cell. Biol. 25, 1162–1172.

Isono, E., Nagel, M.K., 2014. Deubiquitylating enzymes and their emerging role in plant biology. Front. Plant Sci. 5, 56.

Iwata, E., Ikeda, S., Matsunaga, S., Kurata, M., Yoshioka, Y., Criqui, M.C., Genschik, P., Ito, M., 2011. GIGAS CELL1, a novel negative regulator of the anaphase-promoting complex/cyclosome, is required for proper mitotic progression and cell fate determination in *Arabidopsis*. Plant Cell 23, 4382–4393.

Jang, S., Marchal, V., Panigrahi, K.C., Wenkel, S., Soppe, W., Deng, X.W., et al., 2008. Arabidopsis COP1 shapes the temporal pattern of CO accumulation conferring a photoperiodic flowering response. EMBO J. 27, 1277–1288.

Jeong, J.S., Jung, C., Seo, J.S., Kim, J.K., Chua, N.H., 2017. The deubiquitinating enzymes UBP12 and UBP13 positively regulate MYC2 levels in jasmonate responses. Plant Cell 29, 1406–1424.

Jiang, D., Berger, F., 2017. DNA replication-coupled histone modification maintains polycomb gene silencing in plants. Science 35, 1146–1149.

Jung, C., Zhao, P., Seo, J.S., Mitsuda, N., Deng, S., Chua, N.H., 2015. PLANT U-BOX PROTEIN10 regulates MYC2 stability in *Arabidopsis*. Plant Cell 27, 2016–2031.

Katz, E.J., Isasa, M., Crosas, B., 2010. A new map to understand deubiquitination. Biochem. Soc. Trans. 38, 21–28.

Kazan, K., Manners, J., 2013. MYC2: the master in action. Mol. Plant 6, 686–703.

Kohler, A., Schneider, M., Ghislain, G.C., Nehrbass, U., Hurt, E., 2008. Yeast Ataxin-7 links histone deubiquitination with gene gating and mRNA export. Nat. Cell Biol. 10, 707–715.

Komander, D., Clague, M.J., Urbé, S., 2009. Breaking the chains: structure and function of the deubiquitinases. Nat. Rev. Mol. Cell Biol. 10, 550–563.

Lammens, T., Boudolf, V., Kheibarshekan, L., Zalmas, L.P., Gaamouche, T., Maes, S., Vanstraelen, M., Kondorosi, E., La Thangue, N.B., Govaerts, W., 2008. Atypical E2F activity restrains APC/CCCS52A2 function obligatory for endocycle onset. Proc. Natl. Acad. Sci. 105, 14721–14726.

Lazaro, A., Valverde, F., Piñeiro, M., Jarillo, J.A., 2012. The Arabidopsis E3 ubiquitin ligase HOS1 negatively regulates CONSTANS abundance in the photoperiodic control of flowering. Plant Cell 24, 982–999.

Lee, T.I., Causton, H.C., Holstege, F.C.P., Shen, W., Hannett, N., Jennings, E.G., Winston, F., Green, M.R., Young, R.A., 2000. Redundant roles for the TFIID and SAGA complexes in global transcription. Nature 405, 701.

Lee, K.K., Laurence, F., Swanson, S.K., Washburn, M.P., Workman, J.L., 2005. The deubiquitylation activity of Ubp8 is dependent upon Sgf11 and its association with the SAGA complex. Mol. Cell. Biol. 25, 1173–1182.

Lee, K.K., Swanson, S.K., Florens, L., Washburn, M.P., Workman, J.L., 2009. Yeast Sgf73/Ataxin-7 serves to anchor the deubiquitination module into both SAGA and Slik (SALSA) HAT complexes. Epigenet. Chromatin 2, 2.

Leggett, D.S., Hanna, J., Borodovsky, A., Crosas, B., Schmidt, M., Baker, R.T., Walz, T., Ploegh, H., Finley, D., 2002. Multiple associated proteins regulate proteasome structure and function. Mol. Cell 10, 495–507.

Li, Y., Zheng, L., Corke, F., Smith, C., Bevan, M.W., 2008. Control of final seed and organ size by the DA1 gene family in *Arabidopsis thaliana*. Genes Dev. 22, 1331–1336.

Li, W.F., Perry, P.J., Prafulla, N.N., Schmidt, Wolfgang, 2010. UBIQUITIN-SPECIFIC PROTEASE 14 (UBP14) is involved in root responses to phosphate defciency in *Arabidopsis*. Mol. Plant 3, 212–222.

Liu, Y., Wang, F., Zhang, H., He, H., Ma, L., Deng, X., 2008. Functional characterization of the Arabidopsis ubiquitin-specific protease gene family reveals specific role and redundancy of individual members in development. Plant J. 55, 844–856.

Loch, C.M., Strickler, J.E., 2012. A microarray of ubiquitylated proteins for profiling deubiquitylase activity reveals the critical roles of both chain and substrate. Biochim. Biophys. Acta 1823, 2069–2078.

Logan, D.C., Scott, I., Tobin, A.K., 2004. ADL2a, like ADL2b, is involved in the control of higher plant mitochondrial morphology. J. Exp. Bot. 55, 783–785.

Lu, Y., Adegoke, O.A.J., Nepveu, A., Nakayama, K.I., Bedard, N., Cheng, D., Peng, J., Wing, S.S., 2009. USP19 deubiquitinating enzyme supports cell proliferation by stabilizing KPC1, a ubiquitin ligase for p27Kip1. Mol. Cell. Biol. 29, 547–558.

Luo, M., Luo, M., Buzas, D., Finnegan, J., Helliwell, C., Dennis, E.S., Peacock, W.J., Chaudhury, A., 2008. UBIQUITIN-SPECIFIC PROTEASE 26 is required for seed development and the repression of PHERES1 in *Arabidopsis*. Genetics 180, 229–236.

Ma, Y., Szostkiewicz, I., Korte, A., Moes, D., Yang, Y., Christmann, A., Grill, E., 2009. Regulators of PP2C phosphatase activity function as abscisic acid sensors. Science 324, 1064–1068.

Makarevich, G., Leroy, O., Akinci, U., Schubert, D., Clarenz, O., Goodrich, J., Grossniklaus, U., Köhler, C., 2006. Different polycomb group complexes regulate common target genes in *Arabidopsis*. EMBO Rep. 7, 947–952.

Mano, S., Nakamori, C., Kondo, M., Hayashi, M., Nishimura, M., 2004. An *Arabidopsis* dynamin-related protein, DRP3A, controls both peroxisomal and mitochondrial division. Plant J. 38, 487–498.

March, E., Farrona, S., 2017. Plant deubiquitinases and their role in the control of gene expression through modification of histones. Front. Plant Sci. 8, 2274.

Marrocco, K., Bergdoll, M., Achard, P., Criqui, M.C., Genschik, P., 2010. Selective proteolysis sets the tempo of the cell cycle. Curr. Opin. Plant Biol. 13, 631–639.

Mcainsh, M.R., Hetherington, A.M., 1998. Encoding specificity in Ca^{2+} signalling systems. Trends Plant Sci. 3, 32–36.

Mcclung, C.R., Hsu, M., Painter, J.E., Gagne, J.M., Karlsberg, S.D., Salomé, P.A., 2000. Integrated temporal regulation of the photorespiratory pathway. Circadian regulation of two *Arabidopsis* genes encoding serine hydroxymethyltransferase. Plant Physiol. 123, 381–391.

Moon, Y.K., Hong, J.P., Cho, Y.C., Yang, S.J., An, G., Kim, W.T., 2009. Structure and expression of OsUBP6, an UBIQUITIN-SPECIFIC PROTEASE 6 homolog in rice (*Oryza sativa L.*). Mol. Cells 28, 463–472.

Moraga, F., Aquea, F., 2015. Composition of the SAGA complex in plants and its role in controlling gene expression in response to abiotic stresses. Front. Plant Sci. 6, 1–9.

Mozgova, I., Köhler, C., Hennig, L., 2015. Keeping the gate closed: functions of the polycomb repressive complex PRC2 in development. Plant J. 83, 121–132.

Nassrallah, A., Rougée, M., Bourbousse, C., Drevensek, S., Fonseca, S., Iniesto, E., Ait-Mohamed, O., Deton-Cabanillas, A.F., Zabulon, G., Ahmed, I., Stroebel, D., Masson, V., Lombard, B., Eeckhout, D., Gevaert, K., Loew, D., Genovesio, A., Breyton, C., Jaeger, G., Rubio, V., Barneche, F., 2018. DET1-mediated degradation of a SAGA-like deubiquitination module controls H2Bub homeostasis. Elife 7, 1–19.

Neutzner, M., Neutzner, A., 2012. Enzymes of ubiquitination and deubiquitination. Essays Biochem. 52, 37–50.

Nijman, S.M.B., Luna-Vargas, M.P.A., Velds, A., Brummelkamp, T.R., Dirac, A.M.G., Sixma, T.K., Bernards, R., 2005. A genomic and functional inventory of deubiquitinating enzymes. Cell 123, 773–786.

Pan, R., Kaur, N., Hu, J., 2014. The Arabidopsis mitochondrial membrane-bound ubiquitin protease UBP27 contributes to mitochondrial morphogenesis. Plant J. 78, 1047–1059.

Park, S.Y., Fung, P., Nishimura, N., Jensen, D.R., Fujii, H., Zhao, Y., Lumba, S., Santiago, J., Rodrigues, A., Chow, T.F., 2009. Abscisic acid inhibits type 2C protein phosphatases via the PYR/PYL family of START proteins. Science 324, 1068–1071.

Peng, Y., Chen, L., Lu, Y., Wu, Y., Dumenil, J., Zhu, Z., Bevan, M.W., Li, Y., 2015. The ubiquitin receptors DA1, DAR1, and DAR2 redundantly regulate endoreduplication by modulating the stability of TCP14/15 in *Arabidopsis*. Plant Cell 27, 649–662.

Pesin, J.A., Orrweaver, T.L., 2008. Regulation of APC/C activators in mitosis and meiosis. Annu. Rev. Cell Dev. Biol. 24, 475–499.

Pickart, C.M., 2004. Back to the future with ubiquitin. Cell 116, 181–190.

Poovaiah, B., Du, L., Wang, H., Yang, T., 2013. Recent advances in calcium/calmodulin-mediated signaling with an emphasis on plant-microbe interactions. Plant Physiol. 163, 531–542.

Reddy, V., Ali, G., Reddy, A., 2001. Calcium: silver bullet in signaling. Plant Sci. 160, 381–404.

Reyes Turcu, F.E., Ventii, K.H., Wilkinson, K.D., 2009. Regulation and cellular roles of ubiquitin-specific deubiquitinating enzymes. Annu. Rev. Biochem. 78, 363–397.

Rodríguez Navarro, S., Fischer, T., Luo, M.J., Antúnez, O., Brettschneider, S., Lechner, J., Jose, E.P.O., Reed, R., Hurt, E., 2004. Sus1, a functional component of the SAGA histone acetylase complex and the nuclear pore-associated mRNA export machinery. Cell 116, 0–86.

Sahtoe, Sixma, 2015. Layers of DUB regulation. Trends Biochem. Sci. 40, 456–467.

Schmiesing, A., Emonet, A., Gouhier-Darimont, C., Reymond, P., 2016. Arabidopsis MYC transcription factors are the target of hormonal salicylic acid/jasmonic acid cross talk in response to pieris brassicae egg extract. Plant Physiol. 170, 2432–2443.

Schulz, P., Herde, M., Romeis, T., 2013. Calcium-dependent protein kinases: hubs in plant stress signaling and development. Plant Physiol. 163, 523–530.

Shin, J., Heidrich, K., Sanchezvillarreal, A., Parker, J.E., Davis, S.J., 2012. TIME FOR COFFEE represses accumulation of the MYC2 transcription factor to provide time-of-day regulation of jasmonate signaling in *Arabidopsis*. Plant Cell 24, 2470–2482.

Siligato, R., 2014. PLETHORA gradient formation mechanism separates auxin responses. Nature 515, 125–129.

Snedden, W.A., Fromm, H., 2010. Calmodulin as a versatile calcium signal transducer in plants. New Phytol. 151, 35–66.

Soboleva, T. a, Baker, R.T., 2004. Deubiquitinating enzymes: their functions and substrate specificity. Curr. Protein Pept. Sci. 5, 191–200.

Somerville, C., Ogren, W., 1981. Photorespiration-deficient mutants of Arabidopsis thaliana lacking mitochondrial serine transhydroxymethylase activity. Plant Physiol. 67, 666–671.

Sowa, G., Westrick, E., Rajasekhar, A.G., Woods, B., Leckie, S., Coelho, P., Vo, N., Studer, R., Kang, J., 2009. Identification of Candidate Serum Biomarkers for Intervertebral Disk Degeneration in an Animal Model, vol. 1. pp. 536–540.

Sridhar, V.V., Kapoor, A., Zhang, K., Zhu, J., Zhou, T., Hasegawa, P.M., Bressan, R. a, Zhu, J., 2007. Control of DNA methylation and heterochromatic silencing by histone H2B deubiquitination. Nature 447, 735–738.

Sullivan, M.L., Callis, J., Vierstra, R.D., 1990. High performance liquid chromatography resolution of ubiquitin pathway enzymes from wheat germ. Plant Physiol. 94, 710–716.

Talbert, PB., Henikoff, S., 2017. Histone variants on the move: substrates for chromatin dynamics. Nat. Rev. Mol. Cell Biol. 18 (2), 115–126.

Trewavas, A.J., Malhó, R., 1998. Ca^{2+} signalling in plant cells: the big network!. Curr. Opin. Plant Biol. 1, 428.

Tzafrir, I., McElver, J.A., Liu, Cm, Yang, L.J., Wu, J.Q., Martinez, A., Patton, D.A., Meinke, D.W., 2002. Diversity of TITAN functions in Arabidopsis seed development. Plant Physiol. 128, 38–51.

Varshavsky, A., 1998. The ubiquitin system. Annu. Rev. Biochem. 22, 383–387.

Vierstra, R.D., 2009. The ubiquitin-26S proteasome system at the nexus of plant biology. Nat. Rev. Mol. Cell Biol. 10, 385–397.

Wilkinson, K.D., 1997. Regulation of ubiquitin-dependent processes by deubiquitinating enzymes. FASEB J. 11, 1245–1256.

Wilkinson, K.D., 2000. Ubiquitination and deubiquitination: targeting of proteins for degradation by the proteasome. Semin. Cell Dev. Biol. 11, 141.

Wolberger, C., 2014. Mechanisms for regulating deubiquitinating enzymes. Protein Sci. 23, 344–353.

Wu, X., Yen, L., Irwin, L., Sweeney, C., Carraway, K., 2004. Stabilization of the E3 ubiquitin ligase Nrdp1 by the deubiquitinating enzyme USP8. Mol. Cell. Biol. 24, 7748–7757.

Xia, T., Li, N., Dumenil, J., Li, J., Kamenski, A., Bevan, M.W., Gao, F., Li, Y., 2013. The ubiquitin receptor DA1 interacts with the E3 ubiquitin ligase DA2 to regulate seed and organ size in *Arabidopsis*. Plant Cell 25, 3347–3359.

Xu, Y., Jin, W., Li, N., Zhang, W., Liu, C., Li, C., Li, Y., 2016. UBIQUITIN-SPECIFIC PROTEASE 14 interacts with ULTRAVIOLET-B INSENSITIVE 4 to regulate endoreduplication and cell and organ growth in *Arabidopsis*. Plant Cell 28, 1200–1214.

Yan, N., Doelling, J.H., Falbel, T.G., Durski, A.M., Vierstra, R.D., 2000. The ubiquitin-specific protease family from *Arabidopsis*. At UBP1 and 2 are required for the resistance to the amino acid analog canavanine 1. Plant Physiol. 124, 1828–1843.

Yo, M., Mari, O.O., Ayaka, M., Yoshikatsu, M., 2010. Secreted peptide signals required for maintenance of root stem cell niche in *Arabidopsis*. Science 329 (5995), 1065–1067.

Yoshinaga, K., Fujimoto, M., Arimura, S.I., Tsutsumi, N., Uchimiya, H., Kawai-Yamada, M., 2006. The mitochondrial fission regulator DRP3B does not regulate cell death in plants. Ann. Bot. 97, 1145–1149.

Yu, F., Qian, L., Nibau, C., Duan, Q., Kita, D., Levasseur, K., Li, X., Lu, C., Li, H., Hou, C., Li, L., Buchanan, B.B., Chen, L., Cheung, A.Y., Li, D., Luan, S., 2012. FERONIA receptor kinase pathway suppresses abscisic acid signaling in *Arabidopsis* by activating ABI2 phosphatase. Proc. Natl. Acad. Sci. 109, 14693–14698.

Zachary, L.R., Ziyu, L., Patrick, H.M., Christopher D, D., 2009. FZR2/CCS52A1 expression is a determinant of endoreduplication and cell expansion in *Arabidopsis*. Plant Physiol. 149, 874–884.

Zaman, M.M., Nomura, T., Takagi, T., Okamura, T., Jin, W., Shinagawa, T., Tanaka, Y., Ishii, S., 2013. Ubiquitination-deubiquitination by the TRIM27-USP7 complex regulates tumor necrosis factor alpha-induced apoptosis. Mol. Cell. Biol. 33, 4971–4984.

Zhang, X., Hu, J., 2009. Two small protein families, DYNAMIN-RELATED PROTEIN3 and FISSION1, are required for peroxisome fission in *Arabidopsis*. Plant J. 57, 146–159.

Zhang, X., Varthi, M., Sykes, S., Phillips, C., Warzecha, C., Zhu, W., Wyce, A., Thorne, A., Berger, S., Mcmahon, S., 2008. The putative cancer stem cell marker USP22 is a subunit of the human SAGA complex required for activated transcription and cell-cycle progression. Mol. Cell 29, 102–111.

Zhao, M., He, L., Gu, Y., Wang, Y., Chen, Q., He, C., 2014. Genome-wide analyses of a plant-specific LIM-domain gene family implicate its evolutionary role in plant diversification. Genome Biol. Evol. 6, 1000–1012.

Zhao, J., Zhou, H., Zhang, M., Gao, Y., Li, L., Gao, Y., Li, M., Yang, Y., Guo, Y., Li, X., 2016. UBIQUITIN-SPECIFIC PROTEASE 24 negatively regulates abscisic acid signaling in *Arabidopsis thaliana*. Plant Cell Environ. 39, 427–440.

Zhou, H., Zhao, J., Yang, Y., Chen, C., Liu, Y., Jin, X., Chen, L., Li, X., Deng, X., Schumaker, K.S., Guo, Y., 2012. UBIQUITIN-SPECIFIC PROTEASE16 modulates salt tolerance in *Arabidopsis* by regulating Na^+/H^+ antiport activity and serine hydroxymethyltransferase stability. Plant Cell 24, 5106–5122.

Zhou, H., Zhao, J., Cai, J., Patil, S.B., 2017. UBIQUITIN-SPECIFIC PROTEASES function in plant development and stress responses. Plant Mol. Biol. 94, 565–576.