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Roles of SUMO in Plants

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Abstract

The covalent conjugation of SUMO (Small Ubiquitin-related MOdifier) protein to its substrates regulates numerous cellular processes, including protein stability and activity in eukaryotes as well as in plants. In this present review, we summarize biochemical aspects of SUMO conjugation and deconjugation and the functions of SUMO and sumoylation-related proteins in *Arabidopsis* and other plants. In particular, we provide an overview of the roles of the SUMO in widely different biological processes including the ABA response, floral induction, pathogen defense, abiotic stresses and hormone signaling. Furthermore, we explore the possible roles of SUMO in embryo and seed development.

Key words: SUMO, Sumoylation, embryo, seed

Introduction

One of the main ways that protein function becomes diversified is through post-translational addition or removal of chemical groups. Amongst these modifiers, Ubls (ubiquitin-like proteins), such as SUMO (small ubiquitin-related modifier), are known to be key regulators of a range of biological functions. SUMO, which is approximately 100 amino acids in length, has also been named as Sentrin and Smt, UBL1, PIC1, GMP1 or SMT3C (Muller et al. 2001; Muller et al. 2004; Gill 2003; Melchoir et al. 2003; Seeler and Dejean 2003; Verger et al. 2003; Johnson 2004). SUMO has a compact core sequence and variable N-terminal and C-terminal sequences (Bayer et al. 1998). It has only about a 20% similarity to ubiquitin but is similar to ubiquitin in three dimensional structure (Bayer et al. 1998).

SUMO was first identified as a peptide conjugated to RanGAP1, a nuclear pore complex, which promotes nucleocytoplasmic trafficking (Matunis et al. 1996). Sumoylation is an ubiquitin-like protein (UBL) conjugation process that catalyzes the attachment of SUMO to a target substrate (Kerscher et al. 2006), a process that occurs both in the nucleus and in the cytoplasm. Similar to ubiquitin, SUMO proteins are covalently and reversibly conjugated to specific lysine residues of target proteins. However, sumoylation does not target proteins for proteosomal degradation and can stabilize its target protein by blocking ubiquitination of the same lysine residue (Desterro et al. 1998). Recently, it has become clear that sumoylation is involved in diverse biological pathways (Johnson 2004; Hay 2005; Cheng et al. 2006; Gutierrez and Ronai 2006; Montpetit et al. 2006; Nowak and Hammerschmidt 2006; Makhnevych et al. 2007; Seufert et al. 1995; Nacerddine et al. 2005). For instance, sumoylation has been shown to be associated with DNA repair, subcellular localization, stress response and chromatin structural maintenance. In addition, it has been shown that sumoylation is involved in certain human diseases and cell viability (Kim et al. 2006; Moschos et al. 2006; Johnson et al. 1997; Fraser et al. 2000; Nacerddine et al. 2005; Saracco et al. 2007). In particular, SUMO modification of transcription factors is necessary for various developmental, hormonal and environmental responses (Hay 2005; Verger et al. 2003; Lois et al. 2003; Kurepa et al. 2003; Miura et al. 2005; Miura et al. 2007).

Based on genome sequence data, factors involving in SUMO conjugation and deconjugation are conserved in the plant kingdom including *Arabidopsis* (Kurepa et al. 2003; Novatchkova et al. 2004), implying the importance of post-translational modification by sumoylation in regulatory signaling pathways.

In this article we discuss the present state of our knowledge of sumoylation in plants.

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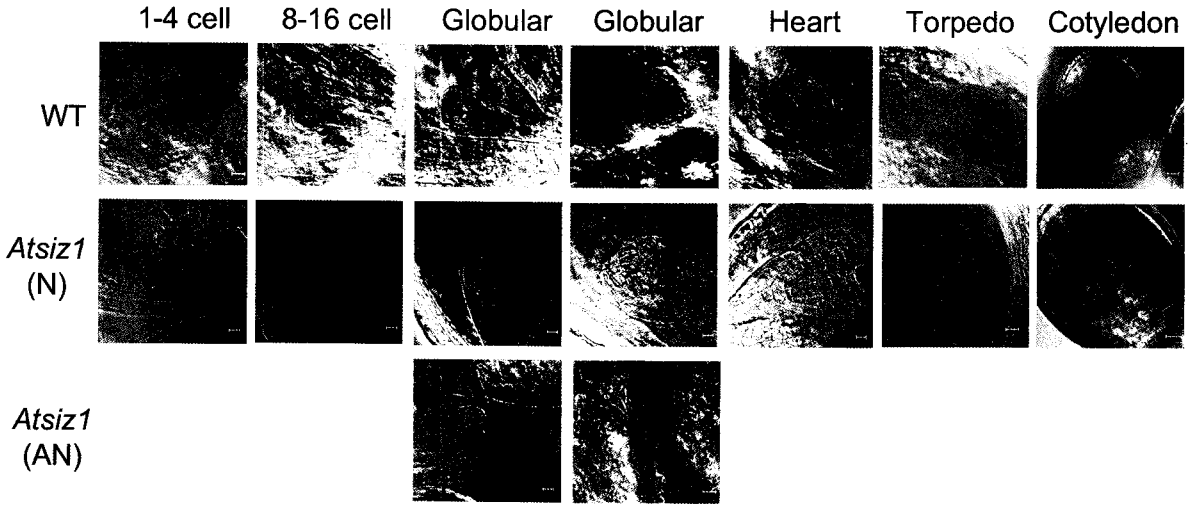

Fig. 1. The pattern of embryo development of the *Atsiz1* mutant from 1-4 cells to the cotyledon stage. The embryo development of the *Atsiz1* mutant was arrested at the globular stage although some embryos of the mutant developed normally. Embryos were examined and photographed by differential interference contrast (DIC) microscopy. Bar, 10 μm.

Post-translational modification by SUMO

Sumoylation

There are eight different SUMO isoforms in *Arabidopsis* and these are clustered into five subfamilies (Kurepa et al. 2003; Lois et al. 2003). Sumoylation proceeds in a stepwise manner comprising three biochemical events referred to as SUMO E1 activation, E2 conjugation, and E3 ligation, respectively (Johnson 2004; Seeler and Dejean 2003).

The first step in sumoylation is the production of mature SUMO which is generated from precursor proteins of ~95-111 amino acids by SUMO peptidase, which recognizes a carboxyl-terminal diglycine (GG) motif and which deletes about 10 amino acids directly after the GG motif. Secondly, SUMO is then activated by an E1 heterodimer that catalyzes ATP hydrolysis to form SUMO-AMP. By comparison to the ubiquitin activation step which uses a single E1 enzyme (UBA1), SUMO activation is driven by a SAE1 (SUMO activating enzyme 1)-SAE2 (SUMO activating enzyme 2) heterodimer, where the SAE1 and SAE2 are equivalent to the N- and C-terminal halves of UBA1, respectively. Subsequently, a high-energy thioester bond between the sulfhydryl group of the catalytic cysteine (C) residue in SAE2 and the carboxyl group of G in SUMO is formed. Thirdly, after activation, SUMO is transferred from SAE2 to a C residue in SCE1 (SUMO conjugating enzyme 1, E2 enzyme) to form a SUMO-SCE1 thioester complex. Fourthly, SUMO is transferred to a substrate protein by the formation of an isopeptide bond between the SUMO carboxyl-terminal G and the μ-amino group of lysine in the SUMO consensus tetrapeptide ψKXE/D (where ψ is a large hydrophobic residue, K is the acceptor lysine, X is any amino acid and E/D denotes glutamate or aspartate). This is induced by E3 SUMO ligases, which are SCE1-interacting proteins.

SIZ/PIAS (SIZ1 and NFI1/SIZ2) of budding yeast and PIAS in animals were the first identified and characterized SUMO E3 ligases (Hay et al. 2005; Johnson 2004; Johnson and Gupta 2001; Kahyo et al. 2001; Sharrocks 2006). Three types of E3 SUMO ligases including SIZ1, RanBP2 (Ran binding protein 2) and Pc2 (polycomb family 2) have now been identified and many types of sumoylation systems have been described in animals, fungi and yeast (Johnson and Gupta 2001; Kahyo et al. 2001; Pichler et al. 2002; Rose and Meier 2001; Kagey et al. 2003).

Although a homogeneous sumoylation system has recently been described in plants, several results showing roles of SUMO and E3 SUMO ligases have been reported (Colby et al. 2006). In *Arabidopsis* AtSIZ1, a homologue of SIZ1 is the sole protein that is known to function as an E3 SUMO ligase in the sumoylation reaction (Miura et al. 2005; Jin et al. 2008).

SUMO conjugation and its biological function in plants

1. Responses to abiotic stresses

Similar to other post-translational modifications, sumoylation is involved in the regulation of numerous cellular functions. Although investigations are still at an early stage, several results have been reported in plant studies. SUMO conjugation was induced by heat stress or after treatment with H_2O_2 or ethanol, implying that SUMO must be involved in the response against abiotic stress and protection of plant cells from such stress (Saracco et al. 2007; Kurepa et al. 2003; Miura et al. 2005; Yoo et al. 2006).

In eukaryotic systems including animals, the heat shock factor (HSF) is sumoylated at high temperatures and its modification controls the expression of heat shock protein (HSP), thus conferring tolerance (Hilgarth et al. 2004; Hietakangas et al.

2006). In plant systems, heat tolerance may be controlled by a similar HSF system. In so far as is known, most of the abiotic stress responses are modulated by the E3 SUMO ligase AtSIZ1 in plants. This may give rise to tolerance against heat stress, even if it does not seem to activate HSF regular expression (Saracco et al. 2007; Miura et al. 2005). Based on the amino acid sequence, downstream of the SUMO consensus site, there are two types of SUMO conjugation: PDSM (phosphorylation-dependent sumoylation motif) and NDSM (negatively charged amino acid-dependent sumoylation motif)(Anckar and Sistonen, 2007). In PDSM, the target protein would first be phosphorylated at a serine residue located within a 7-amino-acid region downstream of a consensus ψKXE motif ψKXEX$_{1-7}$SP (where $\psi$is a large hydrophobic residue, K is the acceptor lysine and X is any amino acid, X$_{1-7}$ is any amino acid, S is serine and P is proline). The lysine is then sumoylated, the process being phosphorylation-dependent. In NDSM, negatively charged residues are found predominantly within a 10-amino-acid region downstream of the SUMO consensus motif ψKXEXXX$_{3-6}$ (where ψ is a large hydrophobic residue, K is the acceptor lysine, X is any amino acid and X$_{3-6}$ is aspartate or glutamate) and sumoylation of the target substrate depends on the extended amino acids.

Overall there are different types of stress that induce trimerization and phosphorylation of animal HSF1 and these facilitate its sumoylation (Hong et al. 2001; Hietakangas et al. 2003; Hietakangas et al. 2003).

In *Arabidopsis*, the transcription factor ICE1 (inducer of CBF/DREB1 expression 1) mediates a freezing tolerance (Miura et al. 2007; Chinnusamy et al. 2003). ICE1 is first sumoylated by AtSIZ1 and its modification represses the expression of MYB15 which is a negative regulator of CBF3/DREB1A. This leads to the expression of CBF3/DREB1A and its downstream genes, resulting in the tolerance. Sumoylation of ICE1 is protected from degradation by a 26S proteosome complex through HOS1 (high expression of osmotically responsive genes1, RING-type E3 ubiquitin ligase) activity, its activity being thereby stabilized (Ulrich 2005; Miura et al. 2007; Dong et al. 2006). Pi deficiency responses are also controlled by sumoylation. Sumoylation of PHR1, a MYB transcription factor, by AtSIZ1-dependent process may repress the expression of the transporter (PHT1;4) and phosphatase (AtPS2) genes, causing the inhibition of phosphate uptake (Miura et al. 2007; Rubino et al. 2001). Thus, AtSIZ1 appears to be an important regulator of the Pi-starvation response in plants. In addition, SUMO conjugates are accumulated in dehydration, through AtSIZ1-dependent processes. The AtSIZ1 mutant *Atsiz1-3* shows a much higher sensitivity to drought stress, suggesting a critical role of AtSIZ1 in the drought stress response through the regulation of gene expression (Catala et al. 2007).

2. Hormonal responses

The ABA response is regulated by sumoylation. Overexpression of AtSUMO1 reduces the sensitivity to the inhibition effect of root growth by ABA while co-suppression of AtSCE1 shows the opposite effect (Lois et al. 2003). In addition, transcript levels of the stress-inducible genes, RDA29A and AtPLC1, were increased in AtSUMO1- and AtSUMO2-overexpressing plants (Lois et al. 2003), supporting a role for ABA as a stress hormone in the stress-induced sumoylation process. Auxin signaling may be also regulated by sumoylation. AtSIZ1 negatively regulates phosphate uptake that causes the redistribution of auxin in the root (Miura et al. 2007, Nacry et al. 2005; Jain et al. 2007), resulting in the stimulation of primary root growth and lateral root development.

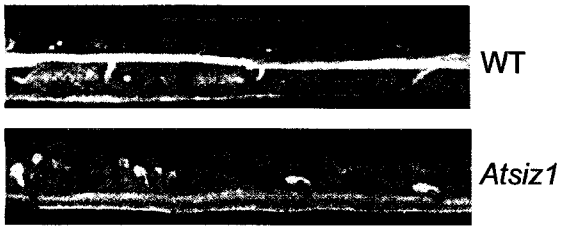

Fig. 2. The developmental pattern and phenotype of the *Atsiz1* mutant seeds.

Further, SA (salicylic acid) accumulates in the siz1 mutant, this being suppressed by the expression of the NahG gene encoding for SA hydrolase in the siz1 mutant (Lee et al. 2007a and 2007b), suggesting that AtSIZ1 is involved in SA signal transduction.

3. Defense barrier against pathogen attack

Infection of *Trichoderma viride* into the tobacco and tomato leaf induces ethylene production and cell death by expression of xylanase, while SUMO overexpression, or co-expression of SUMO and xylanase, inhibit ethylene formation and cell death (Hanania et al. 1999). These results suggest that xylanase may control the level of the sumoylated proteins in the plant defense system. XopD of the bacterial pathogen *Xanthomonas campestris* hydrolyzes *Arabidopsis* and tomato SUMO precursor proteins and decreases the level of SUMO conjugates in plant extracts *in vitro* (Hoston et al. 2003; Chosed et al. 2007). Interestingly, XopD has specific activity only for plant SUMO precursor proteins. The introduction of the virulence effector AvrXv4 into plant cells lowers the level of SUMO conjugates (Roden et al. 2004). PopP2, an effector protein of *Ralstonia solanacearum*, directly interacts with the *Arabidopsis* TIR-NBS-LRR type R protein RRS1, suggesting that PopP2 may desumoylate the R protein (Deslandes et al. 2003). Moreover, AtSIZ1 may negatively regulate SA signaling by scavenging of SA, although it is not known whether it involves SA synthesis and catabolism (Lee et al. 2007a). This finding implies that E3 SUMO ligase directly regulates innate plant immunity by infection of viral and bacterial pathogens but not by fungal pathogens.

4. Control of flowering and seed development

ESD4 encodes a SUMO-specific protease that only has SUMO isopeptidase activity for desumoylation (Miura et al. 2003). The esd4 mutant plant showed early flowering and contained an increased level of SUMO-conjugates (Miura et al. 2003). An Atsiz1 mutant also showed early short-day flowering, implying that AtSIZ1 and ESD4 both are negative regulators of

Table 1. The embryo development of the *Atsiz1* mutant. The embryo developmental stages correspond to the cell number or morphology of the embryo proper.

Silique	Number of Seeds at Each Embryo Development Stage					
	1-4 Cells	8-16 Cells	Globular	Heart	Torpedo	Cotyledon
WT						
1	30	27	-	-	-	-
2	16	30	-	-	-	-
3	4	31	18	-	-	-
4	5	29	29	2	-	-
5		15	35	11	2	-
6	-	-	35	19	7	-
7	-	-	19	39	5	-
8	-	-	4	16	35	12
9	-	-	-	-	9	50
10	-	-	-	-	-	58
Atsiz1						
1	15	7	3	-	-	-
2	12	7	7	-	-	-
3	3	5	17	-	-	-
4	2	9	14	10	-	-
5	3	1	10	19	2	-
6	1	6	-	7	18	-
7	2	4	9	9	22	-
8	2	3	7	3	24	-
9	-	6	-	1	21	10
10	1	5	3	2	16	11

flowering even if they have otherwise opposite functions (Murtas et al. 2003; Reeves et al. 2002). These results also suggest that they may, directly or indirectly, down-regulate expression or activity of the FLC (Flowering Locus C), an *Arabidopsis* MADS-box transcription factor and a central floral repressor. AtSIZ1 acts up-stream of FLD (Flowering Locus D), an activator of flowering (Jin *et al.* 2008). Sumoylation of FLD by AtSIZ1 induces deacetylation of histones in the FLC chromatin and thereby represses FLC expression (Jin et al. 2008). The embryonic development of the *Atsiz1* mutant was arrested after fertilization at the globular stage (Figure 1), although some embryos of the mutant developed normally (Table 1). This causes abnormal growth, resulting in an abortion rate of approximately 50% of the mature seeds (Figure 2). It is therefore clear from current data that sumoylation and desumoylation are an important post-translation modification processes for flowering control and seed development. More recently, *in vitro* interaction analysis revealed that FLC interacts with AtSIZ1 (Park et al. unpublished), implying that FLC activity might be regulated by sumoylation.

Conclusion

The modification of target proteins by small polypeptides, including SUMO, appears to be an important regulatory mechanism in biological processes, particularly since post-translational modification *via* ubiquitin has been identified. In plants, our knowledge is still rudimentary and it remains to be determined how sumoylation and desumoylation is involved in signaling networks, although a few signal transduction pathways are known and it seems that the SUMO protein functions as in other organisms including animals. We anticipate that sumoylation- and desumoylation-related regulators will be identified within a short period of time, leading to further additions to the list of SUMO functions. Further investigations should lead to new insight into the role of sumoylation and desumoylation in plant development.

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