Towards understanding the multifaceted role of SUMOylation in plant growth and development

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Post-translational modifications (PTMs) play a critical role in regulating plant growth and development through the modulation of protein functionality and its interaction with its partners. Analysis of the functional implication of PTMs on plant cellular signalling presents grand challenges in understanding their significance. Proteins decorated or modified with another chemical group or polypeptide plays a significant role in regulating physiological processes as compared to non-decorated or non-modified proteins. In the past decade, SUMOylation has been emerging as a potent PTM influencing the adaptability of plants to growth, in response to various environmental cues. Deciphering the SUMO mediated regulation of plant stress responses and its consequences is required to understand the mechanism underneath. Here, we will discuss the recent advances in the role and significance of SUMOylation in plant growth, development and stress response.

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Introduction

Being sessile organisms, plants are constantly exposed to a wide variety of environmental stresses such as biotrophic and necrotrophic infections, salinity, drought. In order to adapt to their immediate environment, plants have evolved different mechanisms that includes the initiation of complex signalling pathways that crosstalk with each other. Different phytohormones like auxins, gibberellins, brassinosteroids, abscisic acid, salicylic acid and jasmonic acid have been studied and play a significant role in plant growth and development. Additionally, phytohormones also play major roles in mediating plant defence responses against pathogens and abiotic stresses (Bari and Jones 2009). Different hormones are responsible for the regulation of different stress responses, for instance ABA is involved in regulating drought, salinity, cold and heat stress (Zhang et al. 2006). Salicylic acid and Jasmonic acid are known to be involved in providing responses in plant defence against biotrophic/hemibiotrophic and necrotrophic pathogens respectively (Wasternack and Hause 2013). The phytohormone auxin is involved in plant growth and patterning. Polar auxin transport has importance in various developmental aspects, such as vascular tissue development, tissue regeneration, apical dominance or flower and fruit development (Sorefan et al. 2009). It is important to remember that hormone responses *in situ* are not solely the result of linear pathways, but rather the output of multiple pathway integration and interdependence. These hormones imply an exchange of information between them, referred to as "cross-talk", that directly or indirectly affects a wide variety of biological outputs (Mundy et al. 2006, Chandler 2009). The interaction between signalling components modulate the hormonal cross-talk and determine the plant response during biotic and abiotic stress. These responses need to be adjusted in reaction to the changing environment, this can be achieved by regulating the abundance and activity of proteins involved in the signalling pathways. These protein components might be the targets for post-translational modifications.

Posttranslational modifications of proteins are a central feature of the hormone signal transduction pathways that regulate the expression of target genes bringing about the response. Optimal regulation of protein activity, stability, localisation and its interactions are required for cellular homeostasis. To maintain the homeostasis post-translational modification (PTM) of proteins plays a critical role. PTMs are either through conjugation of small chemical group as is the case for phosphorylation, acetylation and methylation or via covalent attachment of another polypeptide such as ubiquitination and SUMOylation. Among the various post-translational modifications (PTMs), SUMOylation, a versatile regulatory process, has emerged as a major molecular process that participates in various biotic and abiotic stress responses (Chinchilla et al. 2007). SUMO conjugation (SUMOylation) and deconjugation

(deSUMOylation) is a dynamic and reversible PTM and is used to regulate many processes with central roles in development including signal transduction, protein subcellular localisation, protein aggregation and the epigenetic control of transcription (Conti et al. 2008, Park et al. 2010, Catala et al. 2007, Lois et al. 2003). These PTMs are known to work independently as well as cross talk with other PTMs. PTMs have been studied in great detail in animals but has been explored to a lesser extent in plants. In order to harness the potential of PTMs in crop improvement and generate stress tolerant crops that can withstand the rapidly changing global environment, better understanding of the process is essential. SUMOylation involves conjugation of approximately 100-115 amino acid polypeptides called Small Ubiquitin MOdifier (SUMO) to lysine residues of target proteins (Hanaina et al., 1999). It is an essential PTM in eukaryotes that provides a dynamic regulatory ability that enable plants to rapidly respond to environmental cues. SUMOylation affects the protein stability, subcellular localisation and protein-protein interactions.

SUMO and its machinery

Several ubiquitin related proteins have been identified. Depending on their identities with ubiquitin they have been divided into two groups: closely related to ubiquitin (>35% identities) and remotely related to ubiquitin (<20% identities). SUMO belongs to the second group of proteins and has the ability to conjugate to other proteins in a ubiquitin like fashion (Loeb and Haas 1994). In 1995, first SUMO homologue, suppressor of mif two 3 (Smt3) was identified in a screen for suppressors of a temperature-sensitive allele of MIF2 in yeast (Meluh and Koshland 1995). Later on, several human and mouse homologs were identified (Chen et al. 1998). In 1996, Matunis and Blobel discovered that RanGAP1 covalently attaches to a novel ubiquitin related protein named GAP modifying protein 1 (GMP1; Matunis et al. 1998) and later it was called SUMO1 (Mahajan et al. 1997). In plants, SUMO was first identified in tomato. Eight highly conserved orthologs of SUMO have been identified in Arabidopsis using bioinformatic approaches among which only SUMO 1, 2, 3 and 5 are expressed, although only under specific conditions and at specific times. Among the various isoforms SUMO1 and 2 are the most closely related isoforms sharing 83% amino acid sequence identity, whereas SUMO 9 is considered to be a pseudogene. Besides Arabidopsis, SUMO families have been identified in many different crop plants such as rice, maize, wheat, sorghum, and poplar spp. SUMO plays a critical role during plant growth and development and regulates plant responses (Ross et al. 2002, Stade et al. 2002, Kurepa et al. 2003, Lois et al. 2003, Gill 2005, Miura et al. 2005, Catala et al. 2007, Conti et al. 2008, Reed et. al. 2010, Park et al. 2010, van den Burg et. al. 2010).

Similar to ubiquitination, SUMO is covalently attached to the proteins through an ATP dependant cascade of sequential reactions. It involves the action of E1- SUMO activating enzyme (SAE1/2), E2-SUMO conjugating enzyme (SCE) and E3 SUMO ligase enzymes (Geiss-Friedlander and Melchoir 2007, Jentsch and Psakhye 2013, Ulrich 2009). SUMO interacts non-covalently with E1 and E2 enzymes during the process of SUMO conjugation (Louis and Lima 2005). This process results in the linking of SUMO to its substrate on the lysine residue through a diglycine motif (Fig. 1). E3 SUMO ligases are not always required for conjugating SUMO to its targeting proteins. Therefore, it raises the question on the functional significance of SUMO E3 ligases (Wilkinson and Henley 2010). In Arabidopsis, only two E3 ligases have been identified named as HIGHPLOIDY2 (HPY2) and SAP and Miz1 (SIZ1). Depending on the SUMOylation consensus site at the SUMO N-terminal, target proteins can be SUMO conjugated with a single SUMO in most cases or with multiple SUMOs to build a poly-SUMO chain on the target protein (Aguilar-Martinez et al. 2015, Bylebyl et al. 2003, Knipscheer et al. 2007, Capili and Lima et al. 2007). SIZ1, SP-ring finger protein, has been shown to be involved in flowering (Jin et al. 2008, Son et al. 2014), seed germination (Kim et al. 2016), epigenetic regulation (Kim et al. 2016), nutrient utilisation (Park et al. 2011), freezing tolerance (Miura et al. 2007, Gou et al. 2017), defence response (Lee et al. 2006, Hammoudi et al. 2018), photomorphogenesis (Lin et al. 2016), iron deficiency (Zhou et al. 2019) and phosphate deficiency (Miura et al. 2005). Recent studies showed that SIZ1 plays an important role in the accumulation and stability of seed storage proteins through its E3 ligase activity and mediates methylation of histone proteins (Kwak et al. 2019, Miura et al. 2020). Overexpression of SIZ1 can regulate heat/drought tolerance and responses to phosphate and nitrogen in rice, tomato and cotton (Mishra et al. 2018, Zhang et al. 2017, Zhang et al. 2018). The diverse potential of SUMO conjugating enzymes can be utilised in crop improvement. SUMO conjugation and deconjugation both are highly dynamic and well-balanced during normal cellular activities.

SUMO proteases

Ubiquitin-like proteases (ULPs) and ULP-like proteases are cysteine family proteases that are responsible for SUMO maturation and for the release of SUMO from their targets, the process is called deSUMOylation, via their endopeptidase and isopeptidase activities respectively. (Benlloch and Lois, 2018, Yates et al. 2016, Garrido et al. 2018, Verma et al. 2018). These ULPs recognise a carboxyl-terminal diglycine (GLyGly) motif in SUMO proteins and remove about ten amino acids after the GlyGly motif, thereby exposing the motif for conjugation to target proteins (Jonson, 2004, Melchoir et.

al. 2003, Park et. al. 2011). The SUMO proteases also function to cleave the terminal glycine of SUMO conjugates and the substrate, releasing free SUMO from the target protein, which is then ready for further SUMO conjugation cycles (Muller et. al. 2001, Yates et. al. 2016). SUMO proteases constitute the most numerous family among members of the SUMOylation machinery and display specificity for SUMO isoform and substrate (Chosed et. al. 2006, Colby et. al. 2006). The Arabidopsis genome has identified seven SUMO-specific proteases, namely EARLY IN SHORT DAYS 4 (ESD4), ULP1a/ ESD4 LIKE SUMO PROTEASE (ELS1), ULP1b, ULP1c/ OVERLY TOLERANT TO SALT 2 (OTS2), ULP1d/OTS1, ULP2a and ULP2b (Kurepa et. al, 2003, Colby et. al. 2006, Miura et. al. 2007, Miura and Hasegawa 2010, Hermkes et. al. 2011, Kong et al. 2016, Liu et al. 2017). All the SUMO proteases identified to date have peptidase activity that cleaves SUMO1/2/3 isoforms in vitro (Chosed et al. 2006, Conti et al. 2008).

As evident, the number of identified SUMO proteases is higher than the number of SUMO conjugating enzymes. (Yates et al. 2016, Garrido et al. 2018, Castro et al. 2018). Due to the subcellular localisation, spatial restriction and regulatory domains with in proteases they are thought to provide specificity to maintain the pool of SUMO conjugated and deconjugated form of target proteins.

All identified ULPs are cysteine proteases with a conserved histidine (H), aspartic acid (D) and cysteine (C) catalytic triad (Kurepa et al. 2003, Rawling et al. 2008, Morrell and Sadanandom 2019). They are classified into three different classes: the ULP/SENP (Ubiquitin-like protease/sentrin-specific protease) family, the Desi (deSUMOylating isopeptidase) family, and USPL1 (Ubiquitin specific peptidase-like protein). The first SUMO protease identified was ubiquitin-like specific protease1 (ULP1) from yeast (*Saccharomyces cerevisiae*) (Li and Hochstrasser 1999). Later on, by comparing the amino acid sequence from the catalytic domain of ULP1, a second yeast SUMO protease (ULP2) was identified (Li and Hochstrasser 2000). SUMO proteases have been identified based on amino acid sequence conservation to yeast ULP1 or ULP2, eight consensus group have been found and six have been characterised (Hickey et al. 2012, Kurepa et al. 2003, Lois 2010, Conti et al. 2008, Hermkes et al. 2011, Liu et al. 2017). The Desi proteases belong to the evolutionary distinct family of cysteine proteases (Shin et al. 2003). Recently, we have characterised the role and significance of Desi SUMO proteases in Arabidopsis during pathogen triggered immunity (PTI; Orosa et al. 2018) but its orthologs have not been identified in lower eukaryotes such as yeast. The USPL1 class of SUMO protease, has only been identified in metazoan vertebrates and invertebrates.

Different members of the ULP family exhibit substrate specificity for SUMO processing as well as cleavage of SUMO conjugates. Analysis with both full length and the catalytic core of ULP1 reveals

variability in the regulatory N-terminal domain of the proteases (Chosed et al. 2006) and their role varies from one protein to the other. The regulatory (N-terminal) domain of the SUMO protease is required for both peptidase and/or isopeptidase activities and the regulatory domain also plays a significant role in activity of the catalytic (C-terminal) domain by either inhibiting or activating the catalytic activity (Chosed et al. 2006).

Potential of SUMO proteases in regulating plant growth and development

Understanding how plants quickly respond to environmental cues is an important question in plant biology to develop biotic or abiotic stress resilience in crops. As global climate change brings more frequent and extreme weather, plants also need to quickly adapt to the environmental conditions. Contrary to animals, plants cannot escape from these environmental constraints. To overcome these environmental stresses, plants have developed biochemical and molecular mechanisms. Phytohormones such as auxin, gibberellin, jasmonic acid, salicylic acid and abscisic acid play a pivotal role and coordinate with different signalling pathways during response to environmental stimuli. These hormones are important in nearly every aspect of plant growth and development from embryogenesis to senescence. They are small endogenous signalling molecules which are fundamental to plant phenotypic plasticity. SUMO has gained huge attention over the last decade after the discovery of its ability to modulate the function of protein without affecting its kinetics. Recent studies show that SUMOylation enables plants to respond through either modulating hormone signalling pathways or by rapidly moderating protein function.

Aforementioned studies demonstrate that cellular localisation of SUMO proteases take part in regulation of different SUMOylated proteins. Additionally, it is observed that SUMO proteases provide another layer of specificity through substrate recognition and cleavage (Orosa et al. 2018, Orosa-Puente et al. 2018, Srivastava et al. 2020). These proteases are responsible to maintain the cellular level of SUMOylated and nonSUMOylated form of proteins. During biotic stress, the cellular levels of these SUMO proteases are altered and change the balance between SUMO modified and non-modified proteins. Recent studies implicated the role of different SUMO proteases in various signalling cascades that are involved in regulating both directly or indirectly plant responses to different biotic and abiotic stresses (Fig. 2).

The SUMOylation status of proteins regulate protein stability and its interaction ability with their partners. It also alters the subcellular localisation of proteins. It is also involved in chromatin remodelling and conformational changes in target proteins. Recent studies suggest that SUMO

proteases play a critical role in various aspects of plant growth and defence. SUMO1 and SUMO2 have been linked to the regulation of salicylic acid mediated defence signalling against biotrophic infection in *Arabidopsis thaliana.* Salicylic acid has been studied to induce the degradation of the SUMO protease OTS1/2 that results in accumulation of SUMO1/2 conjugates (Bailey et. al., 2016). SUMO has been established to have a role in mediating the FLS2 mediated innate immunity responses. Flagellin induces the degradation of plasma membrane localised SUMO protease Desi3a thus enhancing FLS2 SUMOylation to promote BIK1 dissociation and trigger intracellular immune signalling (Orosa et. al., 2018). SUMO also mediates necrotrophic infections as these Arabidopsis pathogens have been shown to promote degradation of the nuclear localised SUMO protease OTS1/2 and hence increase SUMOylation of JAZ proteins resulting in its accumulation, thereby inhibiting JA signalling (Srivastava et. al., 2018). SUMOylation has been studied to influence plant responses to abiotic stress as well. Salt stress causes degradation of the SUMO protease OTS1 in Arabidopsis (Conti et. al., 2008) as well as in rice (Srivastava et. al., 2016) but causes accumulation of the cytoplasm localised SUMO protease ULP1a (Srivastava et. al., 2020). SUMOylation not only affects plant's responses to stresses but also regulates plant growth. Roots branch when in contact with water by using the hydropatterning response. Hydropatterning is dependent on the auxin response factor ARF7. ARF7 induces asymmetric expression of its target gene LBD16 in lateral root founder cells. This differential expression pattern is regulated by posttranslational modification of ARF7 with the SUMO protein. SUMOylation negatively regulates ARF7 DNA binding activity. ARF7 SUMOylation is required to recruit the Aux/IAA repressor protein IAA3. Blocking ARF7 SUMOylation disrupts IAA3 recruitment and hydropatterning. SUMO-dependent regulation of the auxin response controls root branching patterning in response to water availability (Orosa et. al., 2018). The SUMO pathway regulates these responses by cross-talking with different hormonal signalling pathways that include gibberellic acid signalling (Conti et al. 2014), jasmonic acid signalling (Srivastava et al. 2018), auxin signalling (Orosa-Puente et al. 2018), brassinosteroid signalling (Srivastava et al. 2020) and ABA signalling (Wang et al. 2018). Recent studies have been carried out in studying the role of SUMO proteases in light signalling pathways. It has been shown that SUMOylation of PHYB is enhanced by red light and displays a diurnal pattern in plants grown under light/ dark cycles and inhibits binding to PIF5. SUMOylation of phyB negatively regulates light signalling and is partly mediated by the SUMO protease OTS1 (Sadanandom et al. 2015). SUMO has also been studied to modulate the activity of COP1, master repressor of photomorphogenesis. The SUMO E3 ligase SIZ1 physically interacts with COP1 and mediates the SUMOylation of COP1. Thus, SUMO helps in maintaining the homeostasis of COP1 activity, ensuring

proper photomorphogenic development in changing light environments (Lin et al. 2016). The FAR RED ELONGATED HYPOCOTYL 1 (FHY1) is also SUMOylated in response to far-red light (FR). FR exposure promotes SUMOylation of FHY1, accelerating its degradation. ARABIDOPSIS SUMO PROTEASE 1 (ASP1) interacts with FHY1 in the nucleus under FR and facilitates its deSUMOylation. Continuous FR inhibits ASP1 accumulation, perhaps contributing to the desensitization of FR signalling (Qu et al. 2020). Red light and far red light promote the SUMOylation of phyB and FHY1 respectively, that modulates their interaction with their key interacting partner(s) and their stability (Sadanandom et al. 2015; Qu et al. 2020).

Conclusions and further perspectives

Post-translational modification, especially SUMOylation, of proteins has been receiving a lot of attention in the last decade. A wide range of proteins that are involved in varied physiological process have been identified to be SUMOylated and this knowledge is still expanding. SUMOylation displays functional diversity, ranging from roles in plant development, growth, fertilisation, cellular signalling and biotic and abiotic responses to regulating the fate of proteins. Nonetheless, a lot of factors still need to be investigated. Conclusively, by bringing together the cutting-edge techniques to answer biological questions, especially in relation to SUMOylation, such as how SUMO proteases identify substrates and how they attain the substrate specificity, is still lacking in the field. Various studies have been carried out to identify the significance of SUMO conjugating and deconjugating enzymes but the underlying mechanism in substrate selection is still lacking. Proteomic strategies to identify specific SUMO protease targets and their SUMO isoforms needs to be explored and studied in Arabidopsis SUMO research. The SUMO proteases identified to date act only on SUMO 1 and 2. SUMO proteases that target other SUMO proteins are yet to be discovered. Additionally, there is limited studies about SUMO proteases in crop plants, hence there are potentially many SUMO proteases in crops yet to be discovered. As SUMOylation plays a role in a variety of physiological processes and influences multiple hormones, the studies need to be replicated in crop plants. Although some work has already been done in crops, there is much to be explored and the field needs to be studied more, so that the SUMO machinery can be utilised for generating more resilient crops that might improve crop productivity. This new information will open novel avenues in the crop improvement program. Answering these questions in the field of SUMO research will expand our understanding.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Figure Legends

Fig. 1. A schematic representation of protein SUMOylation. SUMO proteases cause SUMO maturation followed by SUMO conjugation using E1, E2 and E3 conjugating enzymes. The

final/crucial step is deSUMOylation where SUMO proteases cleave off the SUMO, setting the substrate and the SUMO free, where the latter starts another cycle of SUMO conjugation.

Fig. 2. A schematic interpretation of the recent discoveries of the role of SUMOylation controlling different hormone signaling pathways. SUMOylation has an impact on jasmonic acid, gibberellic acid, auxin signalling, light signalling, brassinosteroid signalling, salicylic acid and abscisic acid signaling.