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Plant Cell Signaling : SUMO is under the influence of steroids and salt

Grégory Vert

How do plants reduce growth when facing high salinity ? A new study provides insight into how salt stress impinges on the plant steroid hormone signaling pathway to dampen plant growth.

Plants are growing in a constantly changing environment and, unlike most animals, cannot run away from adverse conditions. Instead, plants adjust their growth and development using an intricate network of internal signals to ensure completion of their life cycle. Among these, brassinosteroids (BRs), the polyhydroxylated steroid hormones of plants, have been the focus a lot of attention during the past two decades. The main actors driving the perception and signal transduction of BRs in plant cells have now been identified in the model plant *Arabidopsis*, mostly through intensive genetic and biochemical approaches. A complex cascade of phospho/dephosphorylation events conveys the BR signal from the cell surface to the nucleus where it culminates in the regulation of gene expression by the BRASSINAZOLE RESISTANT (BZR) family of transcription factors [1]. BZR proteins are absolutely essential to BR signaling and more generally to plant growth and development [2]. Their precise regulation in time and space is therefore central and at the node of many pathways ultimately impacting on plant growth. The best characterized regulatory mechanism targeting BZR proteins is a BR-regulated phospho/dephosphorylation coupled to a ubiquitin-mediated degradation by the 26S proteasome that has been brought to light with BZR1 and BZR2, the founding members of the BZR family. In the resting state, plant cells phosphorylate BZR proteins using the GSK3/SHAGGY kinase BIN2 [1]. This results in the cytosolic localization and destabilization of BZR proteins, thus shutting down BR genomic responses. When plant cells perceive BRs, BIN2 is inactivated and degraded [3, 4], allowing the dephosphorylation of BZR proteins by PP2A phosphatases [5]. Dephosphorylated BZR proteins in turn accumulate in the nucleus where they bind to target promoters to fire BR genomic responses [1]. Recently, additional BR-dependent and -independent mechanisms directly controlling the activity of BZR proteins

were identified. These convey responses to both endogenous (strigolactones) and exogenous (light, dark, drought, starvation, pathogens) cues and allow to translate various inputs into BZR-dependent responses and growth [6-13]. Overall, the precise molecular mechanisms by which external conditions impact on plants growth are slowly emerging. A new study by Srivastava et al published in this issue of Current Biology now sheds light on the regulation of BZR1 by another post-translational modification, SUMOylation, and examines its shared contribution to BR signaling and plant responses to salt stress [14].

SUMO is a covalent and reversible modification of proteins that has the remarkable capacity to modify their activity, subcellular localization, interaction with partner proteins or even stability [15]. SUMO drives numerous developmental, and responses to biotic and abiotic stress responses in plants, as highlighted by the myriad of phenotypes displayed by mutants impaired in SUMO attachment or removal [16]. A strong link with salt stress was uncovered with the characterization of the OVERLY TOLERANT TO SALT OTS1/2 SUMO proteases for which an *ots1/2* double mutant harbors extreme sensitivity to salt, with shorter roots than wild-type plants in high salt [17]. The targets of OTS1/2 driving salt stress responses are however still unknown. In their new study, Srivastava et al reveal that another SUMO protease named ULP1a is also required for salt stress responses, but contrary to *ots1/2*, *ulp1a* mutant fails to reduce root growth upon high salt [14]. Provided that *ulp1a* takes up similar amount of salt, this clearly argues for an active shut down of root growth in young seedlings upon stress rather than acute toxicity of salt at that stage. A first clue to the mechanism underlying such lack of growth suppression by *ulp1a* upon salty growth conditions is the finding that *ulp1a* shows increased BR signaling evidenced by the misregulation of typical BR-feedback regulated genes or its resistance to the BR biosynthesis inhibitor brassinazole. The real beauty in this story is the identification of the SUMO target of ULP1a connecting BR signaling to salt stress. Using *in silico* analysis, the authors identified two high-confidence and highly conserved lysine residues likely serving as SUMO sites within BZR1 protein. BZR1 protein is then elegantly shown to be a SUMO substrate *in vitro* and *in vivo*, with lysine residues K280 and K320 being necessary for SUMO attachment to BZR1. In addition, ULP1a catalyzes the deSUMOylation of BZR1, whereas OTS1 is largely unable to do so. Altogether, this work convincingly adds up BZR1 to the growing list of SUMO-regulated plant proteins and identifies ULP1 as a BZR1 deSUMOylating enzyme.

Since ULP1a certainly possesses many targets in plant cell, the fact that *ulp1a* displays salt- and BR-related phenotypes is definitely not enough to decipher the true contribution of

BZR1 SUMOylation in these processes. The authors therefore generated transgenic plants expressing a SUMO-defective variant of BZR1, BZR1^{2K/R}, where both target lysines are substituted to arginines. Detailed analyses of BZR1 and BZR1^{2K/R} highlight several defects in typical readouts of BR signaling. First, the BZR1^{2K/R} protein fails to accumulate in the nucleus and shows reduced dephosphorylation following BR treatment in contrast to BZR1. Second, BZR1^{2K/R}-expressing plants show increased sensitivity to brassinazole in root growth assays and harbor increased expression of the BR biosynthetic genes *DWF4* and *CPD*. Finally, BR treatment promotes a rapid SUMOylation of BZR1 associated with the degradation of ULP1a. Remains to be clarified if such increase in SUMO-BZR1 only results from reduced deSUMOylation activity through ULP1a degradation or whether there is also a concomitant increase in SUMO conjugation on BZR1. Regardless, altogether these observations undoubtedly point to the requirement for BZR1 SUMOylation to promote BR signaling and responses, making of SUMO a new post-translational modification in the BZR landscape. What makes this story so exciting is the identification of the precise molecular mechanism underlying BZR1 SUMO/deSUMOylation. By co-expressing the wild-type or SUMO-defective BZR1 in plant cells, the authors indeed show that BZR1^{2K/R} has greater affinity for BIN2. The SUMO/deSUMOylation of BZR1 therefore appears as a BR-dependent molecular switch controlling the recruitment of BIN2.

It may seem unclear why plants need to control BZR1 activity using SUMOylation, phosphorylation, degradation, and nuclear shuttling but the most likely explanation resides in the enhanced possibility to connect signaling modules to impinge on BZR1 activity and to fine tune BR-dependent growth. This is well exemplified by the new report of Srivastava et al where salt stress is shown to build up the levels of ULP1a by stabilizing the corresponding protein [14]. Salty conditions therefore yield increased levels of deSUMOylated BZR1, thus putting the brakes on BR-dependent growth to accommodate unfavorable conditions. It is also noteworthy that other BR-regulated transcription factors are known to be SUMOylated [18, 19]. BZR2 was recently shown to interact with and to be SUMOylated by the SUMO E3 ligase SIZ1 at residue K302 that is also shared by BZR1 [19]. Surprisingly though, BZR2 SUMOylation appears to be independent of BRs, suggesting different mechanisms of SUMO/deSUMOylation and possibly different function compared to BZR1. Accordingly, decoration of BZR2 with SUMO negatively regulates BR signaling. To date, the 88%-identical BZR1 and BZR2 proteins were thought to have mostly redundant functions but their SUMO regulation may confer specificity in their regulation of BR responses. Future work will therefore be needed to clarify if SIZ1 and ULP1a act on both BZR1 and BZR2, and how

the SUMOylation of BZR1 and BZR2 at nearby residues yields radically opposed BR signaling outputs. In addition, burning questions about how BRs or salt regulate BZR1 SUMOylation come to mind. How do plants sense salt in the regulation of plant growth? How does salt stress signaling lead to the stabilization of UPL1a? Do BRs and salt control the same E3 ubiquitin ligase in opposite manner to regulate UPL1a levels or are different E3s at stake? Although many questions are still to be answered about BRs, salt and SUMO, this study is a first step towards the creation of crop plants better handling the ever-increasing salinization of arable lands or that can accommodate naturally saline soils.

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Figure 1. Schematic representation of the model proposed by Srivastava et al.

(A) Salt negatively regulates plant growth through the downregulation of brassinosteroid (BR) signaling *via* the ULP1 SUMO protease. (B) Plant growth is reduced under low BRs or high salt as a result of the stabilization of ULP1a and the deSUMOylation of BZR1. DeSUMOylated BZR1 has increased affinity for BIN2, yielding inactive phosphorylated

BZR1. (C) BR perception or low salt conditions promote growth through reduction in SUMO-BZR1 levels and dephosphorylation by PP2A. S, SUMO ; P, phosphate.