Roots branch towards water by post-translational modification of transcription factor ARF7

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Abstract:

Plants adapt to heterogeneous soil conditions by altering their root architecture. For example, roots branch when in contact with water using the hydropatterning response. We report that hydropatterning is dependent on auxin response factor ARF7. This transcription factor induces asymmetric expression of its target gene *LBD16* in lateral root founder cells on the side of the root in contact with water. This differential expression pattern is regulated by post-translational 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. We conclude that SUMO-dependent regulation of auxin response controls root branching pattern in response to water availability.

119 words

One Sentence Summary:

Auxin hormone signaling links root branching with water availability.

69 characters

The soil resources plants require like water are often distributed heterogeneously (*1*). To aid foraging, root development is responsive to the spatial availability of soil signals (*2, 3*). MicroCT imaging revealed soil-water contact impacts root architecture, causing lateral roots to form when roots are in direct contact with moisture (*4, 5*). This adaptive branching response is termed hydropatterning (*4, 5*). In this current study we report the molecular mechanism controlling hydropatterning, revealing core components of the auxin response machinery are targets for post-translational regulation.

The hydropatterning response can be mimicked *in vitro* by growing seedling roots vertically on the surface of agar plates (Fig. 1A)(*4*). Opposite sides of a root are either in contact with moisture (directly with the plate or via the meniscus) or exposed to air (Fig. S1). To visualize whether primordia preferentially form on the side in contact with moisture, we transferred a root including the gel it was growing on, into a Light Sheet Fluorescence Microscope to image young primordia and measure their angle of outgrowth with respect to the agar surface (Fig. S1). This revealed lateral roots preferentially emerge from the side of the root in contact with moisture (Fig. 1A).

What causes new primordia to form on the water-contact side of a root? Seedlings exposed to a hydropatterning stimulus exhibit an auxin response gradient across the root radius (*4*). Auxin regulates lateral root development (*6*). Auxin responsive gene expression is regulated by a family of transcription factors termed auxin response factors (ARF) (*7*). The model plant *Arabidopsis thaliana* contains five *ARF* transcriptional activating genes termed *ARF5, 6, 7, 8* and *19* (*8*). To determine which ARF gene(s) controls hydropatterning, we phenotyped loss of function alleles. ARF7 mutants (*8*, *9*) were all impaired (Fig. 1A,B, C & S2), whereas hydropatterning was normal

in mutants of other ARF family members tested (Fig. S3). Hence, hydropatterning appears ARF7 dependent.

ARF7 regulates lateral root initiation (*8*, *10*, *11* reviewed in *6*). Network inference, ChIP-PCR validation and transcriptomic studies have revealed that ARF7 controls the auxin-dependent expression of lateral root regulatory genes such as *LBD16* (Fig. S4)(*12*). Like *ARF7*, *LBD16* loss of function alleles *lbd16-1* and *lbd16-2* exhibit a hydropatterning defect (Fig. S5). ARF7 may therefore control hydropatterning in an *LBD16*-dependent manner. *LBD*-like genes are differentially expressed in maize during hydropatterning (5). To determine whether *LBD16* is differentially expressed in response to a hydropatterning stimulus by ARF7, we monitored spatial expression of a *gLBD16-GFP* reporter (*13*). LBD16-GFP was first detected in the elongation zone (Fig. 1D; Movie S1) in a subset of cells (termed xylem pole pericycle [XPP] founder cells from which primordia originate), consistent with this reporter being an early marker for lateral root development (*13*). In Arabidopsis lateral roots originate from pericycle cells positioned above either xylem pole (*6*). We tested whether *gLBD16-GFP* was differentially expressed in XPP cell files closest to the agar. To mark which side of a root was exposed to air, we overlaid samples with low melting point agar containing fluorescent beads, then imaged from multiple angles employing light-sheet microscopy (Fig. S6-8). Reconstructed root images revealed preferential *gLBD16-GFP* expression in XPP cell nuclei earlier on one side of WT roots (Fig. 1E). Asymmetric *gLBD16-GFP* expression was disrupted in *arf7-1* (Fig. 1E, F), consistent with the mutant's hydropatterning defect (Fig. 1C). Quantification of *LBD16-GFP* distribution in WT and *arf7-1* revealed this reporter was differentially expressed in an ARF7-dependent manner (Fig. S8A-D, F). To test whether asymmetric *LBD16* expression is essential for hydropatterning, the constitutive 35S promoter was used to drive *LBD16* expression in *lbd16* (Fig. S9). *35S:LBD16* expression failed to

rescue the *lbd16* hydropatterning defect (in contrast to *LBD16:LBD16-GFP*). Hence, asymmetric *LBD16* expression is essential for hydropatterning.

We next tested whether LBD16-dependent hydropatterning was controlled via differential ARF7 expression using transcriptional and translational *ARF7pro::ARF7-VENUS* reporters (Fig. S10, S11). In contrast to *gLBD16-GFP* (Fig. 1E, F), ARF7 reporters did not exhibit differential expression in LR stem cells (Fig. 1G). To test whether ARF7 was a target of post-translational regulation, ARF7 was constitutively expressed (using the 35S promoter) in *arf7-1*. This revealed *35S:ARF7* could rescue *arf7-1* hydropatterning (Fig. 1C, S12). Hence, ARF7 appears to control hydropatterning via a post-translational (rather than transcriptional) mechanism.

ARF7 contains post-translational regulatory motifs including 4 putative sites for addition of Small Ubiquitin MOdifier (SUMO) proteins at lysine residues (K104, K151, K282 and K889) (Fig. 2A). SUMO, unlike ubiquitin, can modify the function (rather than abundance) of target proteins (*14*). We confirmed ARF7 is a target for SUMOylation by co-expressing GFP and HA tagged ARF7 and SUMO sequences (Fig. 2B). Addition of SUMO to ARF7 is abolished after replacing lysine for arginine in all four ARF7 SUMOylation motifs (in *gARF7-*$^{4K/R}$; Fig. 2B).

To test the importance of ARF7 SUMOylation for LR development and hydropatterning, we expressed SUMOylatable gARF7 and non-SUMOylatable *gARF7-*$^{4K/R}$ transgenes in *arf7-1*. Bioassays revealed *arf7* hydropatterning could be rescued by wild type *gARF7* (Fig. 2C, D, S13) but not by *gARF7-*$^{4K/R}$ (Fig. 2E, F, S14). Nevertheless, *gARF7-*$^{4K/R}$ (like *gARF7*) remained capable of restoring *arf7* lateral root density to a WT level (Fig. 2F). Hence, ARF7-$^{4K/R}$ remained functional, but unable to regulate hydropatterning. Quantification of *LBD16-GFP* distribution in *gARF7* versus *gARF7-*$^{4K/R}$ *arf7-1* revealed this reporter was only differentially expressed in the

presence of SUMOylatable ARF7 (Fig. S8A-C, E, G). We conclude ARF7 SUMOylation is required for hydropatterning.

How does SUMOylation modify ARF7 activity? ARF7 is rapidly SUMOylated following auxin treatment (Fig. 2G). One ARF7 SUMOylation site (K151) is located within the DNA binding domain (Fig. 2A)(*15*). SUMOylation may attenuate auxin-induced ARF7 DNA binding activity. Time course ChIP-PCR analysis revealed ARF7 transiently interacts with the *LBD16* promoter following auxin treatment (Fig. S15). Furthermore, ChIP-PCR assays performed on *LBD16* and *LBD29* target promoters detected higher DNA binding by ARF7-$^{4K/R}$-GFP than WT ARF7-GFP (Fig. S16). Hence, SUMOylation negatively regulates ARF7 DNA binding activity.

ARF7 transcriptional activity is negatively regulated by Aux/IAA repressor proteins (*16*). Aux/IAAs such as IAA3/SHY2 and IAA14/SLR control ARF7 activity during LR development (*16*, *17*). Like *arf7-1*, *IAA3* loss of function allele *shy2-31* causes a LR hydropatterning defect (Fig. 3A, S17). Thus we tested whether interactions between ARF7, IAA3/SHY2 and IAA14/SLR were SUMO dependent. Pull down assays revealed ARF7-GFP interacted with IAA3/SHY2 and IAA14/SLR proteins (Fig. S18). In contrast, non-SUMOylatable ARF7-$^{4K/R}$ largely failed to pull down IAA3/SHY2. However, both forms of ARF7 interacted with IAA14/SLR (Fig. S19). Hence, interaction between ARF7 and IAA3/SHY2 (but not IAA14/SLR) depends on the residues that regulate ARF7 SUMOylation.

Bioinformatic analysis revealed *IAA3/SHY2* (but not *IAA14/SLR*) contained a SUMO interaction motif (SIM) (Fig. 3B). With its SIM domain mutated, interaction between IAA3 and WT ARF7 was abolished (Fig. 3C). Nevertheless, the IAA3 SIM mutant protein could interact with the TIR1 auxin receptor and TPL transcriptional repressor (Fig. S19, S20). Hence, mutating the SIM site differentially affects IAA3's ability to interact with SUMOylated ARF7, but not other partners.

To assess the functional importance of the *IAA3* SIM sequence *in planta*, we engineered transgenic plants overexpressing *shy2-2* with or without SIM sequences. We examined the impact of the SIM sequence on the suppression of root branching characteristic of *shy2-2* mutant plants *(18),* a phenotype not dependent on hydropatterning. We drove overexpression of the *shy2-2* gene with the endodermal-specific CASP promoter. More root branching is evident in roots of plants expressing *CASP:shy2-2* without the SIM sequence than in plants expressing *CASP:shy2-2* with the SIM sequence (Fig. 3D). Thus overexpression of shy2-2 in endodermis can block ARF7-dependent lateral root development, but only if the SIM sequence is included.

SUMO modifiers are added and removed from target roteins by E3 ligases and SUMO proteases, respectively. In *Arabidopsis*, OTS1 and OTS2 proteases cleave off SUMO from nuclear localized proteins (*19*). Pull down assays revealed ARF7 is a direct target for OTS1 (Fig. S21). Our bioassays revealed the *ots1 ots2* mutant exhibits a hydropatterning defect (Fig. S22). Hence, hydropatterning appears dependent on OTS1 and OTS2 function. These SUMO proteases are labile when plants are exposed to abiotic stress, causing their SUMOylated target proteins to accumulate (*19*, *20*). Indeed, transiently exposing *gARF7-GFP* seedlings to 20' outside an agar plate resulted in a rapid increase in ARF7 SUMOylation (Fig. 2H). Hence, it is the absence (rather than the presence) of water that stimulates this post-translational response. Modelling suggests a substantial differential in water potential is generated across the air and contact axis of the root (*5*). We hypothesize this triggers SUMOylated ARF7 on the air side of roots to recruit IAA3 and create a transcriptional repressor complex, thereby blocking auxin responsive gene expression associated with lateral root initiation (Fig. 3E). Conversely, since IAA3 cannot be recruited by non-SUMOylated ARF7 in root cells on the contact side, this population of transcription factors can induce expression of genes like *LBD16* to trigger organ initiation (Fig. 3E).

Our study has revealed how environmental inputs modulate the auxin response machinery. The SUMO-mediated post-translational regulation of auxin signalling operates on top of the specificity provided from distribution of the hormone itself and the expression patterns of individual regulatory components. Thus auxin regulation controls root branching pattern in response to water availability, building a root architecture that optimizes access to water.

~1520 words (main text)

Legends

Fig. 1. Arabidopsis root branching towards water is ARF7 dependent (A, B) Cross section schematic of a root growing on agar. Lateral root primordia outgrowth angle (yellow lines) in respect to the agar surface quantified from 3D light-sheet microscopy images of wildtype (A) and *arf7-1* (B) plants. (C) Hydropatterning bioassay of wildtype (WT), *arf7* and *arf7* overexpressing ARF7 (*p35S::ARF7*). Data shown is mean values ± S. E. Statistical differences were analysed on the percent of emerged LRs emerging towards either contact or air using an Anova, Tukey HSD test ($P<0.05$); statistically similar groups are indicated using the same letter. (D) Confocal image of Arabidopsis root tip expressing *gLBD16-GFP*. Grey boxed area highlights onset of LBD16-GFP expression in the elongation zone. (E, F, G) Maximum intensity projections of radial re-slices obtained from LSFM-Multiview imaging show the gene expression pattern of LBD16-GFP in wildtype (E) and, *arf7* (F) and *ARF7::ARF7-Venus* (G) on the contact versus air sides. The number under the (E) and (F) displays the index of asymmetry. Positive values correspond to an earlier expression beginning on the contact side, negative values show asymmetry towards the air side. Details explained in Fig. S1, 6-8. Scale bars 50um.

Fig. 2. ARF7 SUMOylation regulates hydropatterning and DNA binding affinity (A) Schematic of ARF7 domains and four predicted SUMO sites K104, K151, K282 and K889. (B) Replacing all ARF7

SUMO site lysine with arginine residues in ARF7-GFP(4*K/R) blocks SUMOylation with HA-SUMO1 (but not WT ARF7 or single SUMO K104) in transient expression assays. (C-D) Bioassays reveal 2 independent transgenic lines expressing WT gARF7 can rescue *arf7-1* hydropatterning (C) and LR density defects (D), n LR=196/78/292/231 n Plants=7/5/10/9. (E-F) Bioassays reveal 3 independent transgenic lines expressing gARF7(4*K/R) cannot rescue *arf7-1* hydropatterning (E) but does restore LR density (F), n LR=374/268/198/286/206 n Plants=12/16/8/11/8. Data is mean values ± S. E. and statistics performed as Fig. 1C. (G) Immunoprecipitation reveals ARF7-GFP [but not ARF7-GFP(4*K/R)] is rapidly SUMOylated 15' after NAA treatment. (H) Immunoprecipitation reveals ARF7-GFP [but not ARF7-GFP(4*K/R)] is rapidly SUMOylated 20' after seedlings were removed from their agar plates.

Fig. 3 SHY2 interacts with ARF7 in a SUMO-dependent manner to control hydropatterning

(A) Bioassay reveals *IAA3/SHY2* mutant allele *shy2-31* does not exhibit a hydropatterning response. Data shown is mean ± S. E. Letters indicate a significant difference compared to WT (L*er*) roots based on Student *t* test ($p<0.05$), n LR=208/604 n Plants=7/19. (B) The *IAA3* (but not *IAA14*) sequence contains a putative SUMO-Interaction-Motif (SIM), suggesting IAA3 could bind SUMOylated ARF7. (C) Transient expression of IAA3/SHY2-HA(WT-SIM) or IAA3/SHY2-HA(SIM mutant) with ARF7-GFP or ARF7-GFP(4*K/R), followed by immunoprecipitation and western analysis, revealed IAA3 interacts with ARF7 in a SIM and SUMO-dependent manner. (D) Phenotyping Arabidopsis seedlings expressing *shy2-2* ± SIM using the endodermal *CASP1* promoter, revealed *CASP1:shy2-2* (WT) blocks LR branching (upper tier) whereas *CASP1:shy2-2* (non-SIM) branch normally (lower tier). Seedlings are from six independent lines termed SIM containing *CASP1:shy2-2* (WT L1, L2 and L3) and non-SIM containing *CASP1:shy2-2* (SIML1, L2 and L3) (E) Schematic summarizing SUMO-dependent ARF7 model for hydropatterning, where on the air side of the root ARF7 is SUMOylated, resulting in an interaction with IAA3 that inhibits LR initiation. On the contact side of the root, ARF7 is not SUMOylated, enabling the transcriptional factor to activate expression of genes involved in LR initiation.

References and Notes:

1. A. Hodge, The plastic plant: root responses to heterogeneous supplies of nutrients. *New Phytol.* **162**, 9–24 (2004).

2. B. D. Gruber, R. F. H. Giehl, S. Friedel, N. von Wirén, Plasticity of the Arabidopsis Root System under Nutrient Deficiencies. *Plant Physiol.* **163**, 161–179 (2013).

3. E. C. Morris *et al.*, Shaping 3D Root System Architecture. *Curr. Biol.* **27** (2017).

4. Y. Bao *et al.*, Plant roots use a patterning mechanism to position lateral root branches toward available water. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 9319–24 (2014).

5. N. E. Robbins, J. R. Dinneny, Growth is required for perception of water availability to pattern root branches in plants. *Proc. Natl. Acad. Sci. U. S. A.* **115**, E822–E831 (2018).

6. J. Lavenus *et al.*, Lateral root development in Arabidopsis: fifty shades of auxin. *Trends Plant Sci.* **18**, 450–458 (2013).

7. T. Ulmasov, J. Murfett, G. Hagen, T. J. Guilfoyle, Aux/IAA proteins repress expression of reporter genes containing natural and highly active synthetic auxin response elements. *Plant Cell*. **9**, 1963–71 (1997).

8. Y. Okushima *et al.*, Functional Genomic Analysis of the AUXIN RESPONSE FACTOR Gene Family Members in Arabidopsis thaliana: Unique and Overlapping Functions of ARF7 and ARF19. *Plant Cell*. **17**, 444–463 (2005).

9. R. Harper *et al.*, The NPH4 locus encodes the auxin response factor ARF7, a conditional regulator of differential growth in aerial Arabidopsis tissue. *Plant Cell*. **12**, 757–770 (2000).

10. M. A. Moreno-Risueno *et al.*, Oscillating Gene Expression Determines Competence for Periodic Arabidopsis Root Branching. *Science (80-.).* **329**, 1306–1311 (2010).

11. B. Péret *et al.*, Auxin regulates aquaporin function to facilitate lateral root emergence. *Nat. Cell Biol.* **14**, 991–998 (2012).

12. J. Lavenus *et al.*, Inference of the Arabidopsis Lateral Root Gene Regulatory Network Suggests a Bifurcation Mechanism That Defines Primordia Flanking and Central Zones. *Plant Cell*. **27**, 1368–1388 (2015).

13. T. Goh *et al*., The establishment of asymmetry in *Arabidopsis* lateral root founder cells is regulated by LBD16/ASL18 and related LBD/ASL proteins. *Development*. **139**, 883-93 (2012).

14. E. S. Johnson, Protein Modification by SUMO. *Annu. Rev. Biochem.* **73**, 355–382 (2004).

15. D. R. Boer *et al.*, Structural basis for DNA binding specificity by the auxin-dependent ARF transcription factors. *Cell*. **156**, 577–89 (2014).

16. T. Goh, H. Kasahara, T. Mimura, Y. Kamiya, H. Fukaki, Multiple AUX/IAA-ARF modules regulate lateral root formation: the role of Arabidopsis SHY2/IAA3-mediated auxin signalling. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **367**, 1461–8 (2012).

17. K. Swarup *et al.*, The auxin influx carrier LAX3 promotes lateral root emergence. *Nat. Cell Biol.* **10**, 946–954 (2008).

18. J. E. M. Vermeer *et al.*, A spatial accommodation by neighboring cells is required for organ initiation in arabidopsis. *Science (80-.).* **343** (2014).

19. L. Conti *et al.*, Small Ubiquitin-like Modifier Protein SUMO Enables Plants to Control Growth Independently of the Phytohormone Gibberellin. *Dev. Cell*. **28**, 102–110 (2014).

20. L. Conti *et al.*, Small ubiquitin-like modifier proteases OVERLY TOLERANT TO SALT1 and -2 regulate salt stress responses in Arabidopsis. *Plant Cell*. **20**, 2894–908

(2008).

21. T. Nakagawa *et al.*, Improved Gateway Binary Vectors: High-Performance Vectors for Creation of Fusion Constructs in Transgenic Analysis of Plants, doi:10.1271/bbb.70216.

22. S. J. Clough, A. F. Bent, Floral dip: a simplified method for Agrobacterium-mediated transformation of Arabidopsis thaliana. *Plant J.* **16**, 735–43 (1998).

23. M. M. Goodin, R. G. Dietzgen, D. Schichnes, S. Ruzin, A. O. Jackson, pGD vectors: versatile tools for the expression of green and red fluorescent protein fusions in agroinfiltrated plant leaves. *Plant J.* **31**, 375–383 (2002).

24. J. D. Nelson, O. Denisenko, P. Sova, K. Bomsztyk, Fast chromatin immunoprecipitation assay. *Nucleic Acids Res.* **34**, e2 (2006).

25. H. Cho *et al.*, A secreted peptide acts on BIN2-mediated phosphorylation of ARFs to potentiate auxin response during lateral root development. *Nat. Cell Biol.* **16**, 66–76 (2014).

26. D. von Wangenheim, R. Hauschild, J. Friml, Light sheet fluorescence microscopy of plant roots growing on the surface of a gel. *J. Vis. Exp.* **2017** (2017).

27. S. Preibisch *et al.*, Efficient Bayesian-based multiview deconvolution. *Nat. Methods*. **11**, 645–648 (2014).

28. S. Preibisch, S. Saalfeld, J. Schindelin, P. Tomancak, Software for bead-based registration of selective plane illumination microscopy data. *Nat. Methods*. **7**, 418–419 (2010).

Acknowledgments: We acknowledge Tom Guilfoyle for insightful discussions and dedicate this manuscript in his memory. We thank Jennifer Dewick for assisting submitting this manuscript.

Funding: This work was supported by the awards from the Biotechnology and Biological Sciences Research Council [grant numbers BB/G023972/1, BB/R013748/1, BB/L026848/1, BB/M018431/1, BB/PO16855/1, BB/M001806/1]; European Research Council (ERC) FUTUREROOTS Advanced grant 294729; ERC SUMOrice Consolidator grant 310235; Leverhulme Trust grant RPG-2016-409; ANR 2014-CE11-0018 Serrations grant; AuxID PICS grant from the CNRS; a joint INRA/University of Nottingham PhD grant to J. T.; JEMV is supported by the Swiss National Science Foundation (PP00P3_157524 and 316030_164086) and the Netherlands Organization for Scientific Research (NWO 864.13.008). H.F was supported by a Grant-in-Aid for Scientific Research on Priority Areas (19060006) from the MEXT, Japan.

Author contributions: B.O.P, N.L, D. W, J.B., K.H., H.F., J.E.M.V., T.V., J.D., A.F., A.B., A.S. and M.B. designed experiments; B.O.P, N.L, D. W, J.B, A.K.S., K.H., J.T., R.B., E.M., M.S., B.K. and T.G. performed experiments; and B.O.P, N.L, D.W, A.B., A.S. and M.B. wrote the manuscript.

Competing interests: "Authors declare no competing interests." **Data and materials availability:** No restrictions are placed on materials, such as materials transfer agreements. All data is available in the main text or the supplementary materials. All data, code and materials used in the analysis are available to other researchers.

Materials and Methods

Figures S1-S18

Tables S1-S2

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References supplement

(*21*)(*22*)(*23*)(*24*)(*25*)(*26*)(*27*, *28*)