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Commentary

DVL/RTFL small peptides function as integrative hubs for hormonal crosstalk and crop improvement

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Abstract

The recent identification of DEVIL/ROTUNDIFOLIA-like (SiDVL/RTFL) peptides from foxtail millet (*Setaria italica*) as negative regulators of auxin signaling has provided important insights into how small peptides orchestrate root development. Wang *et al*. (2024) demonstrate that SiDVLs are proposed to suppress root growth through a dual mechanism involving transcriptional upregulation of Aux/IAA repressors and post-translational downregulation of PIN auxin efflux carriers. Previous studies have revealed that DVL/RTFL peptides physically interact with BRASSINOSTEROID-SIGNALING KINASEs (BSKs) and redundantly regulate root stem-cell maintenance under abiotic stress via abscisic acid (ABA) signaling, may function as emerging integrative hubs as central hubs that integrate auxin, brassinosteroid (BR), and ABA pathways. This commentary discusses how these findings advance our understanding of peptide-hormone interactions, particularly the novel role of DVLs in coordinating growth and stress responses. We also discuss preliminary evidence suggesting that DVL overexpression enhances drought and salt tolerance, highlighting the translational potential of DVL-BSK modules for climate-resilient agriculture.

Keywords: Small peptides, DVL/RTFL, Hormone signaling

Introduction: Rethinking the Role of Small Peptides in Hormone Networks

Small signaling peptides have emerged as crucial regulators of plant development and environmental adaptation, often acting in parallel with classical phytohormones to fine-tune cellular responses [1]. Among these, the DEVIL/ROTUNDIFOLIA (DVL/RTFL) family defines a unique class of non-secreted peptides and is conserved across land plants [2,3]. Initially characterized for their effects on leaf morphology and cell proliferation in *Arabidopsis thaliana* [4,5], the functional repertoire of DVLs has since expanded to include regulation of nodulation [6], stem cell maintenance [7], and BR signaling [8].

In a study using foxtail millet (*Setaria italica*), Wang *et al*. show that DVL peptides suppress auxin signaling in roots, offering fresh insights into DVL functional research [9]. This work is particularly significant because foxtail millet possesses remarkable tolerance to drought, salinity, and nutrient deficiency [10], traits intrinsically linked to root architecture. The authors demonstrate that *SiDVL* overexpression attenuates auxin responses despite elevated endogenous indole-3-acetic acid (IAA) levels, revealing a complex feedback loop that cannot be explained by simple linear models of auxin-controlled growth. Recent studies have identified DVL/RTFL peptides as physical interactors of BSKs, a family of receptor-like cytoplasmic kinases that serve as central points where multiple hormone pathways converge [8,11]. These findings suggest that DVLs not only serve as auxin antagonists, but also help coordinate growth, immune responses, and stress adaptation, making them promising candidates for crop improvement.

Mechanistic Innovation: Dual Targeting of Signaling and Transport

What stands out in Wang *et al*.'s work is their finding that SiDVLs affect two key aspects of auxin balance: the transcriptional processes driving auxin signaling and the directional transport system. Together, these findings suggest that DVL peptides influence auxin response at both the transcriptional and transport levels.

In the canonical auxin signaling pathway, Aux/IAA transcriptional repressors are degraded via the TIR1/AFB ubiquitin-ligase complex, thereby releasing AUXIN RESPONSE FACTOR (ARF) activity [12]. Wang *et al*. observed significant upregulation of multiple *Aux/IAA* genes (*IAA1*, *IAA5*, *IAA19*, *IAA30*, and *IAA32*) in *SiDVL*-overexpressing lines, which correlated with diminished DR5 reporter activity. This transcriptional amplification of negative regulators represents a mechanism distinct from the well-characterized auxin-related peptide signals such as C-TERMINALLY ENCODED PEPTIDES (CEPs) or RAPID ALKALINIZATION FACTORS (RALFs), which typically modulate signaling through receptor-like kinase-mediated phosphorylation cascades [13,14]. The molecular basis for SiDVL-mediated *Aux/IAA* induction remains unclear. One possible explanation is that, given that DVLs lack canonical DNA-binding domains, their effects likely involve indirect transcriptional regulation, potentially through the modulation of chromatin accessibility or interference with ARF-binding sites. Notably, the study reveals that mutation of conserved cysteine or isoleucine residues within the RTFL domain abolishes auxin insensitivity in yeast, suggesting that structural integrity is essential for interaction with downstream effectors [9].

Additionally, SiDVLs reduce the protein abundance of the auxin efflux carriers PIN1, PIN2, and PIN7. The PIN family orchestrates directional auxin transport through dynamic subcellular trafficking [15], and their reduced accumulation would logically impair acropetal and basipetal auxin fluxes in the root meristem. This observation is consistent with the observed shortening of both the meristematic zone and elongation zone, as compromised PIN function disrupts the auxin maximum required for cell division and elongation [16]. Interestingly, the authors observed that PINs seem to be internalized more frequently through vesicle trafficking when DVL levels are elevated. This raises the possibility that DVLs might interact with the endomembrane system or regulate ADP-ribosylation factor (ARF) guanine nucleotide exchange factor (ARF-GEF) machinery required for PIN recycling, although future studies will be required to test this hypothesis [17,18].

DVL-BSK Interaction: A Molecular Hub for Hormone Crosstalk

While the inhibitory effects of DVLs on auxin signaling are well established, recent studies reveal that DVL/RTFL peptides physically interact with BSK family proteins, thereby extending their regulatory reach to BR signaling and plant immunity. These findings suggest that DVLs may function as emerging integrators of multiple hormonal inputs. Shade-induced RTFL18 peptides directly interact with BSK3 and BSK6 to suppress BR signaling and reduce PIF4 protein stability, thereby acting as negative regulators of the shade avoidance syndrome in Arabidopsis [8]. Parallel studies further expand the functional scope of DVL-BSK interactions. S-acylation (palmitoylation) of the RTFL4 (ROT4) mediates its plasma membrane localization and interaction with BSK5, which disrupts the association between BSK5 and the immune receptor PEP RECEPTOR 1 (PEPR1) complex to activate plant immune signaling, thereby establishing a mechanistic link between non-secreted and secreted peptide pathways in immunity [11].

The convergence of DVLs on BSKs is especially noteworthy because BSKs serve as versatile signaling hubs. BSKs are cytoplasmic receptor-like kinases that transduce signals not only from the BR receptor BRI1, but also from pattern recognition receptors (PRRs) involved in immunity [19,20]. By competitively binding to BSKs, DVLs may function as molecular switches, a model that will require direct experimental validation in future studies, that redirect cellular resources from growth-related processes toward defense and stress responses.

The Hormonal Paradox: DVLs as Key Regulators Balancing Growth and Stress

One surprising finding is that IAA levels remain high even when auxin signaling is blocked. The authors demonstrate that *SiDVL*-overexpressing lines exhibit 2–3-fold higher IAA levels than wild-type (WT) plants, accompanied by upregulation of biosynthetic genes (*TAA1* and *YUCCAs*). This is best interpreted as a compensatory response aimed at restoring signaling balance by overcoming the block, rather than a dysregulated accumulation of hormone, but it cannot fix the root growth defects. This indicates that functional signaling is more important than absolute hormone levels for development.

When viewed through the lens of DVL-BSK interactions, this paradox gains broader significance. BSKs are known as positive regulators of BR signaling, which promotes cell elongation and growth. By sequestering BSKs, DVLs simultaneously dampen both auxin responses via transcriptional repression of ARF targets and BR responses via inhibition of BSK-mediated BES1/BZR1 activation. This dual inhibition explains the dwarfed phenotype of DVL-overexpressing plants and suggests that DVLs may act as gatekeepers that shift the hormonal balance from growth promotion to growth arrest. Consistent with this model, preliminary data from our laboratory show that SiDVL overexpression in foxtail millet enhances drought and salt tolerance but comes at the cost of reduced pollen fertility (C. A. Wu, unpublished observations). This trade-off aligns with the established roles of BSKs in stress responses [21]. We propose that under abiotic stress increased *DVLs* expression may divert BSKs from growth-promoting pathways toward stress-protective processes.

Evolutionary and Agricultural Perspectives

The foxtail millet genome harbors 27 *DVL* members, distributed in clusters suggestive of tandem duplication events [9]. Although overexpression of *SiDVL1*, *SiDVL3*, and *SiDVL8* in Arabidopsis caused comparable phenotypes, including reduced stature, rounded leaves, and shortened roots, subtle quantitative differences in organ-specific effects suggest functional diversification. The observation that *SiDVL* transgenic lines produce larger seeds than WT plants, despite vegetative dwarfism, is particularly noteworthy. This decoupling of vegetative and reproductive growth metrics suggests that DVLs might differentially modulate source-sink relationships, potentially through altered phloem loading or carbon partitioning [22].

Unlike secreted peptides, such as CEPs [23,24], which can be exogenously applied to reshape root system architecture, functional utilization of DVLs likely requires genetic manipulation. However, the non-secreted nature of DVLs may prove advantageous for precision breeding, as their cell-autonomous action minimizes pleiotropic effects on neighboring tissues and allows for precise spatiotemporal control via synthetic promoters. Nevertheless, it is important to acknowledge potential trade-offs, such as reduced fertility under certain conditions, and the need for field-level validation before these findings can be translated into practical breeding programs. The complexity of translating signaling modules into agronomic traits should not be underestimated.

Future investigations should explore whether *DVLs* can be engineered for tissue-specific or inducible expression. For example, restricting *DVL* expression to the root cap or quiescent center could localize growth inhibitory effects to discrete soil layers. Furthermore, elucidating the receptors of DVLs remains a critical priority. The failure of SiDVLs to restore auxin sensitivity in yeast strains deficient in plant-specific receptor components indicates that DVL signal perception relies on molecular modules unique to plants, potentially including members of the leucine-rich repeat receptor kinase (LRR-RLK) family. For climate-resilient agriculture, the capacity to fine-tune DVL-BSK interaction modules also carries transformative potential.

Unresolved Questions and Future Directions

Although Wang *et al*. and recent BSK-interaction studies provide a framework for DVL function, several critical questions warrant investigation: 1) Receptor Identity and Subcellular Dynamics: As non-secreted peptides localized to the plasma membrane via S-acylation [11], DVLs likely compete with BRI1 and PRRs for BSK recruitment. How do membrane microdomains organize these competitive interactions? Do they interact directly with intracellular auxin signaling components, or do they require membrane-localized receptors to initiate endocytic cascades affecting PIN stability? 2) Functional Redundancy in Native Contexts: Arabidopsis *dvl* mutants display no obvious phenotypes due to functional redundancy [5,7]. What is the phenotypic consequence of multiplex CRISPR editing of *DVL* clusters in foxtail millet? Such experiments would clarify whether *DVLs* are essential for the stress tolerance that characterizes this crop. 3) Interaction with ABA Signaling: The authors note that *SiDVLs* respond to ABA treatment and previous work links *AtDVLs* to ABA-mediated root stem cell maintenance [7]. The mechanistic intersection of DVL-mediated auxin inhibition and ABA signaling, potentially through the ABI4-CYCB1;1 module [25], offers a promising direction for studying hormone crosstalk. 4) Crop-Specific Optimization: How can the DVL-BSK module be engineered in cereals to maximize the "drought tolerance and fertility" trade-off? The observation that SiDVLs overexpression enhances stress tolerance suggests that natural variation in *DVL* expression levels or BSK-binding affinities may underlie the exceptional resilience of this crop.

Conclusion

The work by Wang *et al*. provides evidence supporting the role of DVL/RTFL peptides as negative regulators of auxin signaling, revealing a sophisticated regulatory layer in which small peptides concurrently dampen transcriptional responses and compromise polar transport. The identification of BSKs as direct DVL interactors fundamentally expands this framework, suggesting that DVLs may function as emerging integrative contributors coordinating growth (auxin and BR), defense (immunity), and stress responses. This dual-action mechanism provides a molecular explanation for the pleiotropic growth defects associated with *SiDVL*-overexpression, including the intriguing combination of dwarfism, stress tolerance, and altered fertility. As we work toward developing climate-resilient crops, understanding how natural peptide modules like SiDVLs balance growth and stress through BSK-mediated hormone interactions will be essential. Future research should examine how DVL-BSK interactions vary in strength and timing, and apply these fundamental insights to develop gene-editing approaches that improve root architecture and stress tolerance in cereals. Foxtail millet, with its broad genetic diversity and physiological adaptations to stress, provides an excellent system for such studies. It may reveal how ancient *C4* grasses adapted their roots to survive in harsh environments.

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Author Contributions

C.Y. Wang and C.A. Wu designed and wrote the paper.

Declaration of Interests

The authors declare that they have no competing interests.

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