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DELLA and SCL3 balance gibberellin feedback regulation by utilizing INDETERMINATE DOMAIN proteins as transcriptional scaffolds

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Abbreviations: FD, FLOWERING LOCUS D; FT, FLOWERING LOCUS T; GA, gibberellin; GAI, GA INSENSITIVE; GID1, GIBBERELLIN INSENSITIVE DWARF1; IDD, INDETERMINATE DOMAIN; RGA, REPRESSOR of ga1-3; RGL, RGA-LIKE; SCL3, SCARECROW-LIKE3; SCR, SCARECROW; SHR, SHOOT-ROOT; TFL1, TERMINAL FLOWER1

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DELLA proteins are key negative regulators in the phytohormone gibberellin's (GA) signaling. In addition to this role, the DELLA proteins upregulate the gene expression levels of the positive regulators in GA signaling, such as GA 20-oxidase, GA receptor, and a transcriptional regulator, SCARECROW-LIKE3 (SCL3), which enables the regulation of GA feedback. Since DELLAs lack a known DNA binding domain, other transcription factor(s) that recruit DELLAs to DNA are essential for this regulation. Recently, we showed that the INDETERMINATE DOMAIN family proteins serve as transcriptional scaffolds to exert the transactivation activity of DELLAs. This finding and further analyses regarding the function of SCL3 indicate that the balance of the DELLAs and SCL3 protein levels (both are GRAS proteins) regulates downstream gene expression through IDDs binding to DNA. Here, we review the regulatory system in plants similar to ours and also discuss the interactive network between GRAS and IDD proteins.

Gibberellin (GA) is a plant hormone that modulates various processes involved in plant growth, organ development, and environmental responses. These include leaf expansion, flowering time, seed germination, stem elongation, and the development of flowers, fruit, and seeds.[1] In the past few decades, several protein components involved in GA signaling have been identified. Among these, DELLA proteins are the key negative regulators in GA signaling. GA is perceived by a GA-receptor, GID1, and then elicits the degradation of DELLAs,[2-4] resulting in a de-repressed GA signaling state. DELLA proteins are characterized by a DELLA/TVHYNP motif at the N-terminus and a GRAS domain (named after its first 3 members: GA INSENSITIVE [GAI], REPRESSOR of ga1–3 [RGA], and SCARECROW [SCR]) at the C-terminus, placing DELLAs within the GRAS family of transcriptional regulators. The DELLA subfamily is highly conserved among angiosperms, gymnosperms, and ferns, but not in *Physcomitrella patens*, a model organism for mosses (bryophytes). *Arabidopsis* has 5 DELLAs, GAI, RGA, RGA-LIKE (RGL)1, RGL2, and RGL3, whereas, rice has one DELLA, SLENDER RICE1.[1,5]

DELLAs, lacking a known DNA-binding domain, are thought to act as transcriptional regulators in 2 ways.[6] To interact with DNA-binding domains of transcription factors and inhibit the expression of their target genes, or to interact with other transcription factors as transcriptional co-activators to promote the expression of downstream genes. In the latter case, the downstream genes include the positive regulators in GA signaling, such as GA biosynthetic enzymes, GA 3-oxidase and GA 20-oxidase, GA receptor GID1, and transcriptional regulators, such as SCL3, which are involved in GA feedback regulation. In this context, the principal question was how DELLAs positively regulate gene expression levels. Recently, we identified

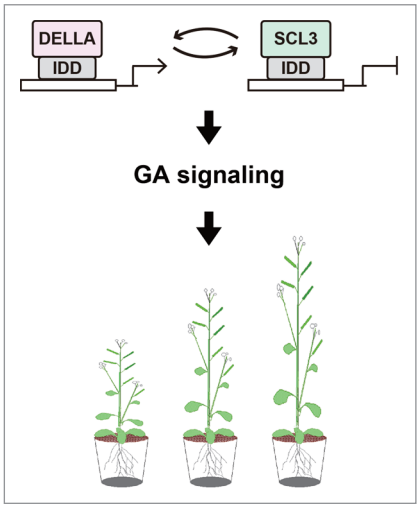

Figure 1. The co-activator/co-repressor exchange system, consisting of DELLA, SCARECROW-LIKE3 (SCL3), and INDETERMINATE DOMAIN (IDD) proteins, regulates the feedback loop in gibberellin signaling.

certain members of the IDD transcription factor family, AtIDD3, –4, –5, –9, and –10, that can act as transcriptional scaffolds, which mediate between DELLAs and the promoter sequence of the downstream genes.[7] They interact with both the GRAS domain of RGA and the promoter sequence of the DELLA-target gene, *SCARECROW-LIKE3* (*SCL3*).[8,9] The IDD protein family is characterized by a highly conserved N-terminal domain containing 4 zinc finger motifs that bind to DNA and 2 C-terminal short motifs.[10] Although an IDD protein was first isolated as the causal factor for a late-flowering mutant of maize,[11] the diverse physiological functions of IDDs have been revealed in *Arabidopsis* and rice, including the regulation of auxin signaling and flowering time, as well as gravitropic responses.[12-16] Our experiments indicated that RGA and the IDDs synergistically upregulate the expression of *SCL3*. Plants overexpressing AtIDD3 fused with SRDX, a plant specific repression domain, partially mimicked the GA-deficient plant, suggesting that the AtIDD3-SRDX protein causes DELLA's loss of transactivation activity in the feedback loop of GA signaling.

Additionally, we focused on the function of the SCL3 protein. SCL3, like the DELLAs, possesses a GRAS domain at its C-terminus and belongs to the GRAS family.[17] Based on the sequence similarity between DELLAs and SCL3, we hypothesized that SCL3 can also interact with IDDs. The interaction between SCL3 and the IDDs was expected to inhibit DELLA-IDD interactions based on previous genetic studies that showed SCL3 functions antagonistically to the DELLAs.[9,18] In fact, we demonstrated the interaction between SCL3 and IDD proteins, and we also revealed that RGA and SCL3 competitively interact with AtIDD3. Furthermore, we demonstrated that the competitive relationship reflects the transcriptional regulation of their downstream genes, such as *SCL3*.

In the conclusion of our recent paper, we proposed that DELLAs, SCL3, and IDDs constitute a "co-activator/co-repressor exchange regulation system" to fine-tune GA feedback regulation (**Fig. 1**). In this model, DELLAs act as co-activators binding to the promoter of the downstream genes, including *SCL3*, through the transcriptional scaffolds, IDDs. After increasing *SCL3* transcription, accumulated SCL3 protein acts as a co-repressor, leading to an increased level of the SCL3-IDD complex, and then, it reduces the expression of downstream genes, including itself. Such a regulatory system, in which a transcription factor regulates positively or negatively the downstream genes depending on its interactions with co-activators or co-repressors, respectively, is well studied in animals;[19] however, it has been rarely reported in plants. To our knowledge, *Arabidopsis* is proposed to have a similar system for regulating flowering time and for the development of the inflorescence meristem. FLOWERING LOCUS T (FT), a key positive regulator that induces flowering, and its homolog TERMINAL FLOWER1 (TFL1), which antagonizes FT's function, seem to act as mediators to recruit co-activators and co-repressors, respectively, through interactions with the DNA-binding complex, which consists of 14-3-3 and FLOWERING LOCUS D (FD).[20] When flowering is induced, FT moves from leaves to the shoot apical meristem and then excludes TFL1 from the 14-3-3-FD complex. This results in the formation of the FT-14-3-3-FD transactivation complex that promotes the expression of downstream genes.[20] Considering this, the co-regulator exchange system may be not limited to the GA signaling pathway but may be widely used in other signaling pathways in plants.

We found physical and genetic relationships between the GRAS proteins, DELLAs and SCL3, and the IDD family proteins, AtIDD3, –4, –5, –9, and –10. Previous research on GRAS and IDD proteins also found interactions between them. GRAS family members, SCR and SHOOT-ROOT (SHR), and IDD family members, AtIDD3 and AtIDD10, regulate each other's expression levels and can form complexes to regulate root development.[21,22] The interaction between SHR and AtIDD4 has been reported,[23] as has the interaction between DELLAs and AtIDD1, which regulates seed dormancy.[24] These results, and ours, illustrate the importance of the emerging common theme, the interaction and transcription network between GRAS and IDD proteins that is likely involved in multiple signaling pathways and many aspects of physiological events in plants.[24]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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