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REVIEW

Molecular basis and evolutionary pattern of GA–GID1–DELLA regulatory module

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Abstract The tetracyclic diterpenoid carboxylic acids, gibberellins (GAs), orchestrate a broad spectrum of biological programs. In nature, GAs or GA-like substance is produced in bacteria, fungi, and plants. The function of GAs in microorganisms remains largely unknown. Phytohormones GAs mediate diverse growth and developmental processes through the life cycle of plants. The GA biosynthetic and metabolic pathways in bacteria, fungi, and plants are remarkably divergent. In vascular plants, phytohormone GA, receptor GID1, and repressor DELLA shape the GA–GID1–DELLA module in GA signaling cascade. Sequence reshuffling, functional divergence, and adaptive selection are main driving forces during the evolution of GA pathway components. The GA–GID1–DELLA complex interacts with second messengers and other plant hormones to integrate environmental and endogenous cues, which is beneficial to phytohormones homeostasis and other biological events. In this review, we first briefly describe GA metabolism pathway, signaling perception, and its second messengers. Then, we examine the evolution of GA pathway genes. Finally, we focus on reviewing the crosstalk between GA–GID1–DELLA module and phytohormones. Deciphering mechanisms underlying plant hormonal interactions are not only beneficial to addressing basic biological questions, but also have practical implications for developing crops with ideotypes to meet the future demand.

Keywords Gibberellin · Receptor GID1 · Repressor DELLA · Molecular interaction · Evolutionary behavior

Introduction

Diterpenoid acids gibberellins (GAs) were first isolated from the necrotrophic fungus *Gibberella fujikuroi* which causes rice '*Bakanae*' disease, characteristic of elongated seedlings, slender leaves, and stunted roots (Tamura 1991). Actually, GAs are biosynthesized not only in fungi, but also in bacteria and plants. There is evidence supporting that GAs production in microorganisms is involved in plant immune responses (Navarro et al. 2008). In plants, phytohormones GAs modulate diverse biological events, from seed dormancy and germination, embryogenesis, plant stature determination, floral organ morphogenesis, fertility, and flowering time to fruit development (Rodrigues et al. 2012).

Over the past decade, tremendous research efforts have been made to elucidate the mechanisms of GA metabolism and signaling. The GA metabolic process is triggered at multiple hierarchical levels. For one thing, bioactive GAs are synthesized through diverse enzymes and intermediates (Silverstone et al. 1997; Williams et al. 1998; Fleet et al. 2003; Sun 2008; Yamaguchi 2008). For another, GAs deactivation is mediated by both genetic and epigenetic factors (Varbanova et al. 2007; Sun 2008; Yamaguchi 2008). In the GA signaling cascade, phytohormone GA, receptor GID1 together with repressor DELLA constitute a GA–GID1–DELLA regulatory module to integrate environmental and endogenous cues, which is beneficial to the enhancement

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of stress tolerance, higher fertility, and yield benefits (Murase et al. 2008; Shimada et al. 2008; Plackett et al. 2012; Saville et al. 2012). In this review, we first briefly introduce GA metabolism pathway, signaling perception, and its second messengers. After the description, we aim to unravel the evolution of GA pathway genes. Finally, we highlight recent findings of interactions between the GA–GID1–DELLA complex and phytohormones, including abscisic acid (ABA), auxin (Aux), brassinosteroids (BRs), cytokinins (CKs), ethylene (ET), jasmonic acid (JA), and salicylic acid (SA).

GA metabolism and signaling perception

GA metabolism

The GA biosynthetic and metabolic pathways are diversified in nature. In bacteria, a diterpenoid operon is responsible for GA biosynthesis, which contains ferredoxin-, alcohol dehydrogenase-, *trans*-geranylgeranyl diphosphate synthase (GGPS)-, terpene synthases-, and cytochrome P450 mono-oxygenases (P450s)-encoding genes (Morrone et al. 2009).

In fungi, a single bifunctional *ent*-copalyl diphosphate synthase (CPS)/*ent*-kaurene synthase (KS) enzyme functions in the conversion of precursor *trans*-geranylgeranyl diphosphate (GGPP) to *ent*-kaurene (Kawaide et al. 1997). P450s combined with desaturase are necessary for the conversion of intermediates to bioactive GAs. The 13-hydroxylation of GA_7 to GA_3 is the last step in the production of GA_3 (Tudzynski et al. 2003).

In vascular plants, GAs are biosynthesized from precursor GGPP catalyzed by three types of enzymes, including terpene synthases (TPSs), P450s, and 2-oxoglutarate-dependent dioxygenases (ODDs) (Fig. 1a), reviewed in Yamaguchi (2008). The conversion of GGPP to *ent*-kaurene is promoted by two monofunctional TPSs, CPS and KS. *ent*-kaurene is converted to intermediate GA_{12} through two P450s *ent*-kaurene oxidase (KO) and *ent*-kaurenoic acid oxidase (KAO). Inactive precursor GA_{12} is then converted to bioactive GAs by GA 20-oxidase (GA20ox) and GA 3-oxidase (GA3ox) enzymes which belong to ODDs. The GAs deactivation is through 2β-hydroxylation catalyzed by another ODD enzyme GA 2-oxidase (GA2ox). In addition, GAs turnover could be achieved through epoxidation and methylation modifications (Zhu et al. 2006; Varbanova et al. 2007).

GA signaling perception

The DELLA proteins, member of GRAS (for GAI, RGA, and SCARECROW) superfamily, serve as negative regulators in the GA signaling cascade. Rice *GA INSENSITIVE DWARF1* (*GID1*) was identified as a GA receptor, which marks a milestone in the investigation of GA perception (Ueguchi-Tanaka et al. 2005). The GA–GID1–DELLA module has been proposed to decipher the molecular mechanisms of GA perception (Fig. 1b). Briefly, when the GA level is low, receptor GID1 is not bound by GA. Repressor DELLAs bind with target genes and inhibit genes transcription. When the GA level is high, GA combines with a pocket of receptor GID1 and causes GID1 conformation change, which makes it possible to interact with the N-terminal domain of DELLAs and form the GA–GID1–DELLA complex. The DELLA proteins are polyubiquitinated by $SCF^{SLY1/GID2}$ E3 ubiquitin ligase and then proteolyzed via the 26S proteasome. The DELLA degradation relieves the suppression of GA-responsive genes (Hedden 2008; Murase et al. 2008; Shimada et al. 2008).

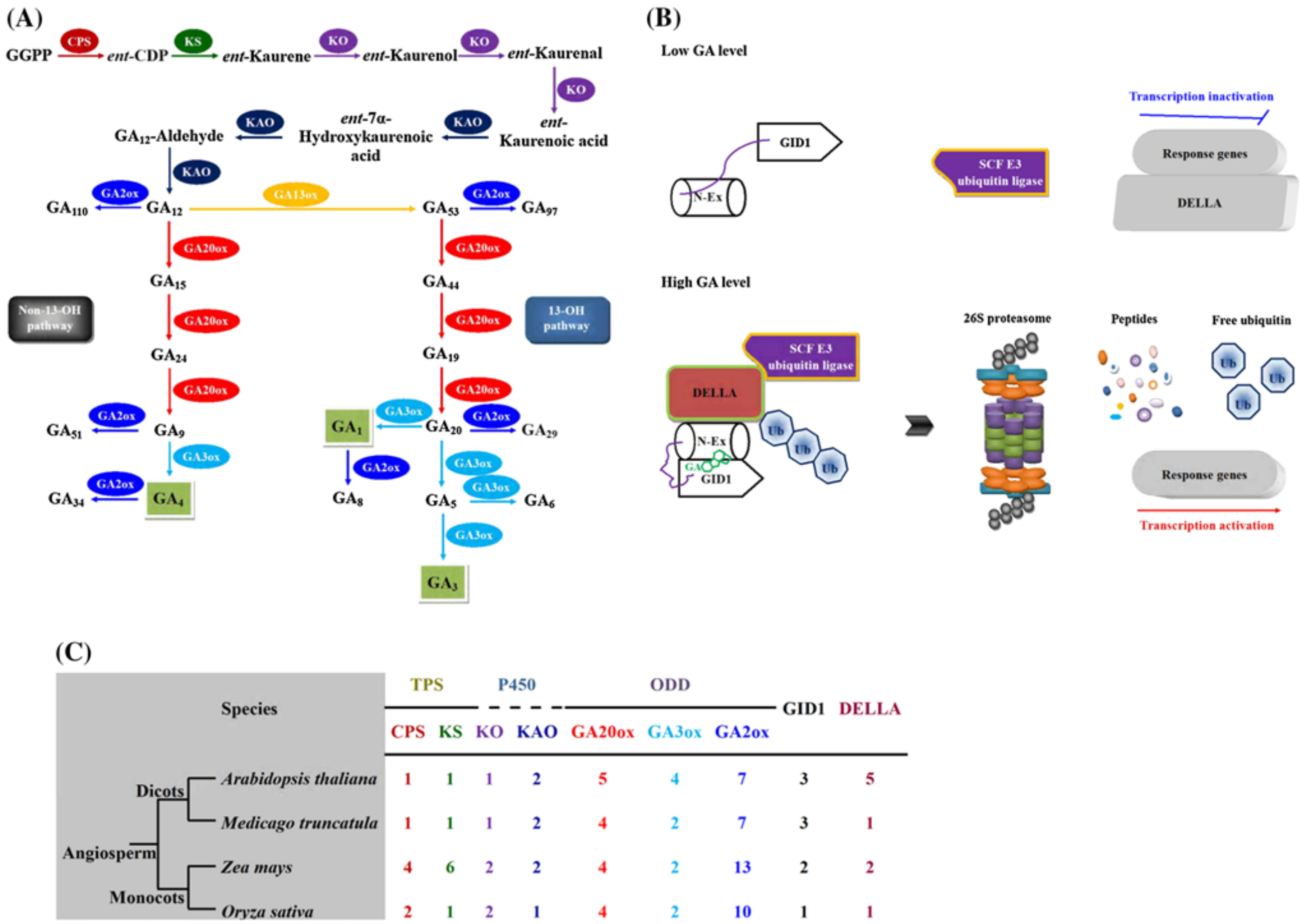
Intriguingly, *Arabidopsis* GA receptor AtGID1B can interact with DELLA in a GA-independent manner similar to that of rice OsGID1 substitution mutant (Yamamoto et al. 2010). Sun (2011) believes that GA-dependent and GA-independent GIDs may separately respond to a certain developmental or environmental stimulations.

GA and its second messengers

The environmental conditions and plant hormones are effectively linked by second messengers, which can finely tune diversified biological programs. Second messengers Ca^{2+}, guanosine 3′,5′-cyclic monophosphate (cGMP), and nitric oxide (NO) have been proved to be involved in the GA signaling transduction. In rice aleurone cells, Ca^{2+} binds to calmodulin (CAM) and forms the Ca^{2+}/CAM complex. The Ca^{2+}/CAM complex regulates the intracellular Ca^{2+} level and functions in the GA signaling through modulating the expression of GA-responsive Ca^{2+}-ATPase gene (Chen et al. 1997). As a second messenger, cGMP timely responds to GA stimulation and plays an important role in GA-dependent transcriptional regulation (Bastian et al. 2010). During *Arabidopsis* seed germination, NO acts upstream of GA and modulates both GA biosynthesis and signaling pathways (Bethke et al. 2007). There is evidence demonstrating that NO antagonizes GA in controlling light-regulated photomorphogenesis by increasing the content of DELLA proteins (Lozano-Juste and León 2011).

Evolutionary patterns of GA pathway components

The conversion of GGPP to *ent*-kaurene in vascular plants is catalyzed by monofunctional TPSs. There appears no *TPS-like* gene in green algae (Table S1). Plant TPSs



Species		CPS	KS	KO	KAO	GA20ox	GA3ox	GA2ox	GID1	DELLA
		TPS	TPS	P450	P450	ODD	ODD	ODD		
Angiosperm – Dicots	*Arabidopsis thaliana*	1	1	1	2	5	4	7	3	5
	Medicago truncatula	1	1	1	2	4	2	7	3	1
Angiosperm – Monocots	*Zea mays*	4	6	2	2	4	2	13	2	2
	Oryza sativa	2	1	2	1	4	2	10	1	1

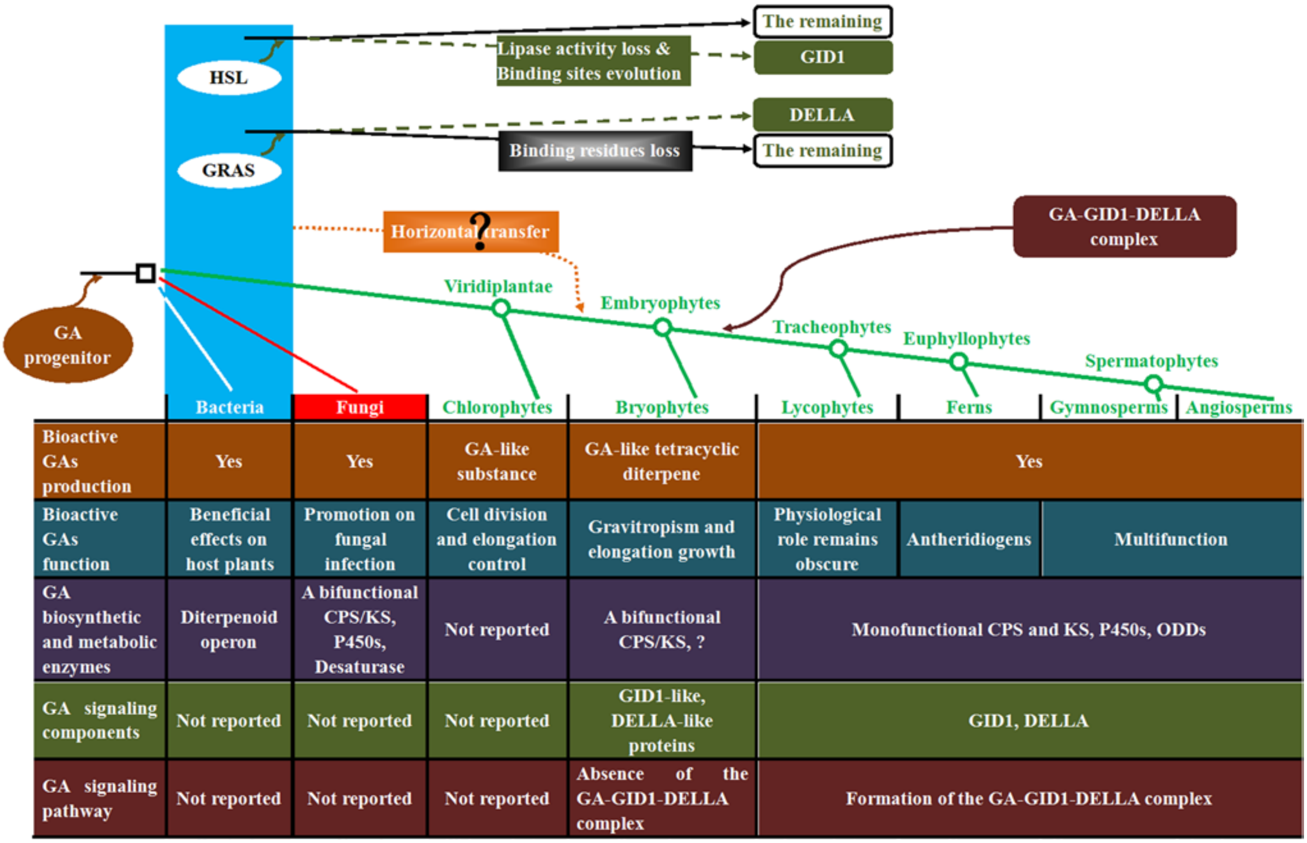
Fig. 1 GA metabolism and signaling perception in vascular plants. **a** GA metabolism pathway. Phytohormones GAs are biosynthesized from precursor GGPP which is converted to *ent*-kaurene by CPS and KS enzymes. The *ent*-kaurene is converted to GA_{12} via KO and KAO enzymes. GA_{12} is then converted to bioactive GAs through GA20ox and GA3ox enzymes. The GAs deactivation is catalyzed by GA2ox enzymes. **b** GA signaling perception. The carboxy-terminal core domain of receptor GID1 shapes a GA-binding pocket. The NH_2-terminal extension domain (simplified as N-Ex in Figure) forms a lid of the pocket. Plant hormones GAs are positioned in the cavity in receptor GID1. When the GA level is low, receptor GID1 is not bound by GA. The DELLA proteins inhibit the expression of GA-responsive genes. When the GA level is high, GA combines with GID1 and forms the GA–GID1–DELLA complex. The DELLA proteins are ubiquitinated by $SCF^{SLY1/GID2}$ E3 ubiquitin ligase and proteolyzed through the 26S proteasome. The DELLA degradation relieves the suppression of GA-responsive genes. **c** Number of GA pathway genes. Detailed information of GA pathway genes is presented in Table S1

originated from the larger diterpene synthase whose internal domain loss produces the precursor of TPSs (Hillwig et al. 2011). Evolutionary patterns of TPSs involved in general and specialized metabolisms are divergent. In general metabolism, TPS in moss remains bifunctional with sequence divergence from the ancestral gene. Subfunctionalization of ancestral gene after duplication gives rise to two monofunctional TPSs, CPS and KS in vascular plants. In specialized metabolism, the production of bifunctional TPSs in vascular plants is ascribed to neofunctionalization of duplicated ancestral gene (Keeling et al. 2010). The diversification of TPS family is mainly ascribed to sequence reshuffling and functional divergence. De novo and re-sequencing of multiple species using next-generation sequencing technologies are helpful for the elucidation of sequence atlas in genome scale, which will shed new insights into the TPS family evolution.

The *ent*-kaurene is converted to GA_{12} via KO and KAO enzymes. The KO- and KAO-like proteins were identified in algae and moss (Table S1). The catalytic steps of P450 enzymes are shared in fungi and plants, suggesting the convergent evolution of P450-mediated GA biosynthetic pathways in nature.

The pathways downstream from GA_{12} in vascular plants are catalyzed by three types of enzymes GA20ox, GA3ox, and GA2ox which belong to ODDs. Compared with enzymes TPSs and P450s, GA20ox, GA3ox, and GA2ox enzymes are relatively diversified. Some GA20ox, GA3ox, and GA2ox enzymes may be directly or indirectly responsible for GA responses, others may be recruited for other biological events. The ODD-like sequences from algae and moss were identified and positioned in distinct clades of the dendrogram (Table S1, Figure S1c), their exact role in biological systems remains to be investigated. The P450s and desaturase instead of ODD enzymes are responsible for the conversion of intermediate to bioactive GAs in fungi. In addition, the final step in the production of GA_3 in fungi is 13-hydroxylation (Tudzynski et al. 2003). The GA biosynthetic and metabolic pathways in fungi and vascular plants have evolved independently (Fig. 2), reviewed in Hedden et al. (2002).

Overall structure of rice nuclear GA receptor OsGID1 is similar to that of a hormone-sensitive lipase (HSL) family member AeCXE1 from kiwi fruit. The GA receptor GID1 originated from one member of the HSL family and evolved to adapt to the GA signaling pathway by sequence reshuffling (Murase et al. 2008; Shimada et al. 2008). The DELLA proteins, member of GRAS superfamily, are master repressors of the GA signaling. The GRAS family contains DELLA proteins, which is regarded as unique in plants. Based on bioinformatic evidence, Zhang et al. (2012) hypothesized that GRAS proteins could first appear in bacteria and are horizontally transferred to land plant. Undoubtedly, further experimental data should be collected to test the hypothesis. By homologous searching, GID1- and DELLA-like proteins were detected in moss (Table S1). However, there is still no bioactive GAs and functionally orthologous GID1–DELLA components reported in moss, although the GA-like tetracyclic diterpene was identified in moss (Von Schwartzenberg et al. 2004). Moreover, the GA–GID1–DELLA complex was found in spikemoss (Hayashi et al. 2010). The GID1-mediated GA signaling cascade appeared after the divergence of vascular plants from the moss (Hirano et al. 2007). The GA–GID1–DELLA signaling pathway is gradually shaped



	Bacteria	Fungi	Chlorophytes	Bryophytes	Lycophytes	Ferns	Gymnosperms	Angiosperms
Bioactive GAs production	Yes	Yes	GA-like substance	GA-like tetracyclic diterpene	Yes			
Bioactive GAs function	Beneficial effects on host plants	Promotion on fungal infection	Cell division and elongation control	Gravitropism and elongation growth	Physiological role remains obscure	Antheridiogens	Multifunction	
GA biosynthetic and metabolic enzymes	Diterpenoid operon	A bifunctional CPS/KS, P450s, Desaturase	Not reported	A bifunctional CPS/KS, ?	Monofunctional CPS and KS, P450s, ODDs			
GA signaling components	Not reported	Not reported	Not reported	GID1-like, DELLA-like proteins	GID1, DELLA			
GA signaling pathway	Not reported	Not reported	Not reported	Absence of the GA-GID1-DELLA complex	Formation of the GA-GID1-DELLA complex			

Fig. 2 Production, function, and evolution atlas of GA. The GAs and GA-like compounds are produced in bacteria, fungi, and plants, which play diverse roles in nature. In bacteria, diterpenoid operon is responsible for GA biosynthesis. In fungi and moss, a bifunctional CPS/KS enzyme functions in the GA production. P450 and desaturase enzymes are involved in the conversion of intermediates to bioactive GAs in fungi. In vascular plants, monofunctional CPS and KS, P450s, as well as ODDs participate in the GA biosynthesis. The GID1-mediated GA signaling cascade appeared after the divergence of vascular plants from moss. The HSL, as progenitor of receptor GID1, together with GRAS, as progenitor of repressor DELLA, may first emerge in bacteria and is horizontally transferred to land plants. Ancestors of GID1 and DELLA evolved to adapt to the GA signaling pathway by sequence reshuffling and functional divergence

by modifications of DELLA and GID proteins (Yasumura et al. 2007).

Crosstalk between GA–GID1–DELLA module and phytohormones

The GA–GID1–DELLA regulatory module is fine-tuned by various feedback loops. On one hand, GAs regulate the expression of GA–GID1–DELLA components, such as biosynthetic ODD genes *GA20ox* and *GA3ox*, receptor *GID1*, and repressor *DELLA* (Middleton et al. 2012). On the other hand, DELLA proteins modulate the transcription of GA biosynthetic and receptor genes (Zentella et al. 2007). Of note, GA–GID1–DELLA module interacts with various phytohormones in the maintenance of homeostasis in plant life (Fig. 3).

GAs and ABA

Phytohormones, GAs and ABA, antagonistically function in guiding the transition from embryogenesis to seed germination (Gómez-Cadenas et al. 2001). Physiological mechanisms of the antagonistic relationship between GAs and ABA have recently been elucidated. During rice seed germination, ascorbic acid (ASC) has been proved to mediate the antagonism (Ye and Zhang 2012). Molecular basis of the crosstalk between GAs and ABA remains largely unknown, although there is evidence indicating that APETALA 2 (AP2)-like transcription factor gene *OsAP2-39* mediates GAs' interactions with ABA in rice. Overexpression of *OsAP2-39* leads to an increase in endogenous ABA levels through up-regulating of ABA biosynthetic gene *OsNCED-I*. The *Elongation of Upper most Internode*

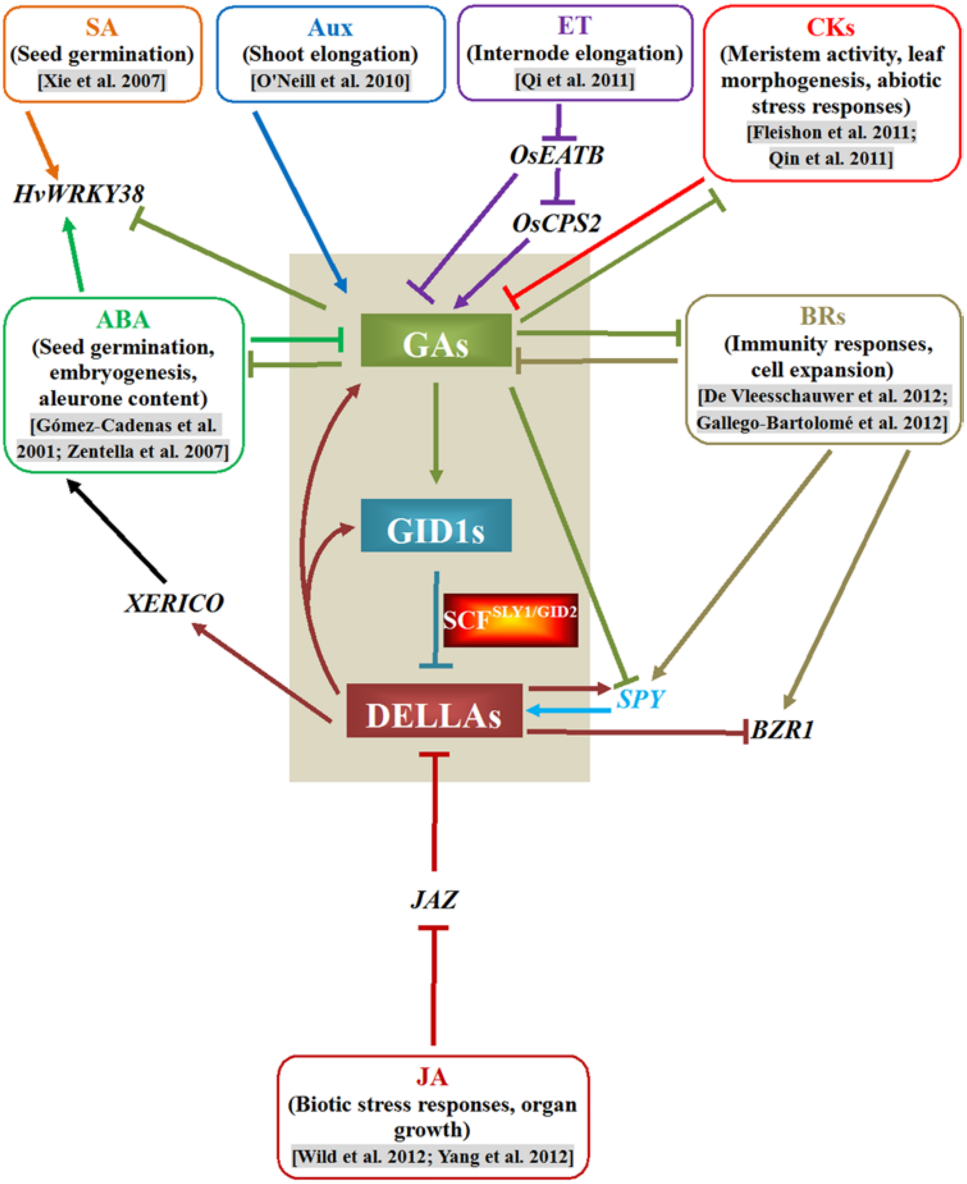


Fig. 3 Crosstalk between GA–GID1–DELLA module and phytohormones. Synergistic and antagonistic interactions between GAs and other phytohormones abscisic acid (ABA), auxin (Aux), brassinosteroids (BRs), cytokinins (CKs), ethylene (ET), jasmonic acid (JA), and salicylic acid (SA) are mediated by various effectors *BRASSINAZOLE RESISTANT1* (*BZR1*), *HvWRKY3*, *JA ZIM-domain* (*JAZ*), *OsCPS2*, *OsEATB* (for rice *E*RF protein *a*ssociated with *t*illering and panicle *b*ranching), *SPINDLY* (*SPY*), and *XERICO*. In addition, GA–GID1–DELLA module is fine-tuned by feedback loops. GAs regulate the expression of GA biosynthetic genes, receptor *GID1*, and repressor *DELLA*. DELLA proteins modulate the transcription of GA biosynthetic and receptor genes. *Arrows* denote positive regulation, and *T bars* indicate negative regulation

(*EUI*) gene encoding enzyme that deactivates bioactive GAs is simultaneously up-regulated in *OsAP2-39* overexpression line. *OsAP2-39* gene acts as orchestrator to maintain the homeostasis of GAs and ABA in rice (Yaish et al. 2010).

The DELLA proteins modulate GA-related processes by regulating the ABA pathway. An ubiquitin E3 ligase gene *XERICO* serves as target for DELLA proteins and is involved in ABA metabolism. The DELLA promotes the expression of *XERICO* and then enhances ABA levels (Zentella et al. 2007). The DELLA proteins may represent a hub for the maintenance of GAs/ABA balance in response to abiotic stress.

GAs and Aux

The synergistic crosstalk between GAs and Aux has been observed in many developmental processes (O'Neill et al. 2010). Genetic basis of the interplay between GAs and Aux has been elucidated by surveying the behavior of Aux transport in GA-defective mutant. Aux transport is severely inhibited in GA-defective mutant. The reduction of Aux transport mainly attributes to a decrease in the levels of PIN-FORMED (PIN) proteins, promoters of Aux transport. GAs govern the Aux efflux through an adjustment in PIN proteins abundance (Willige et al. 2011). Moreover, GAs regulate the transcription of Aux signaling gene *Auxin Response Factor7* (*ARF7*), which converges the GA–Aux crosstalk during fruit development (de Jong et al. 2011).

GAs and BRs

The crosstalk between phytohormones GAs and BRs is involved in biotic stress responses (De Vleesschauwer et al. 2012). Genetic mechanisms of the interplay between GA and BR signaling cascades have been dissected at the transcriptional level. Transcription factor BRASSINAZOLE RESISTANT1 (BZR1) triggers the expression of BR-responsive genes, whose regulatory activity is directly repressed by *Arabidopsis* DELLA protein GA INSENSITIVE (GAI). The GA and BR signaling pathways are integrated by the crosstalk between DELLA protein GAI and modulator BZR1 (Gallego-Bartolomé et al. 2012). The interaction between another *Arabidopsis* DELLA protein REPRESSOR OF GA1-3 (RGA) and BZR1 has been confirmed by two independent groups (Bai et al. 2012; Li et al. 2012).

Evidently, multiple *Arabidopsis* DELLA proteins are involved in the interactions between GA and BR signaling. A total of five DELLA proteins GAI, RGA, RGA-LIKE 1 (RGL1), RGL2, and RGL3 are in the *Arabidopsis* genome (Table S1). Exact role of the remaining three DELLA proteins in the convergence of *Arabidopsis* GA and BR pathways warrants future elucidation.

GAs and CKs

The mutual antagonistic interactions between plant hormones GAs and CKs have been well characterized. On one hand, GAs suppress the CK signaling in a DELLA-independent way. On the other hand, CKs affect the GA signaling (Fleishon et al. 2011). The *SPINDLY* (*SPY*) gene serves as a repressor in the GA signaling. In contrast, *SPY* positively regulates CK responses. *SPY* serves as a key regulator in the GA–CK crosstalk which occurs early in the CK signaling and relates to abiotic stress adaption (Qin et al. 2011).

GAs and ET

Plant hormones GAs and ET participate in diverse biological processes, such as seed germination, nodulation, emergence, plant height determination, and submergence responses (Dubois et al. 2011; Ferguson et al. 2011). Plant hormone ET inhibits plant growth through the modulation of GAs levels via altering the expression of GA biosynthetic and metabolic genes (Kim et al. 2012). A recent study has demonstrated that an interaction between GAs and ET, which is mediated by one member of AP2/ethylene-responsive element binding factor (ERF) family, restrains rice internode elongation by decreasing transcript levels of GA biosynthetic gene *OsCPS2* (Qi et al. 2011). Moreover, ET triggers plant growth by regulating the status of DELLA proteins (Achard et al. 2003). Evidently, the crosstalk between ET and GAs could be achieved by regulating GAs abundance and/or the stability of DELLA proteins.

GAs and JA

The crosstalk between *Arabidopsis* GA and JA signaling is mediated by the interaction between DELLA protein RGL3 and JA signaling repressor JA ZIM-domain 1 (JAZ1), which inhibits the transcription of JA-responsive genes through binding to a basic helix-loop-helix (bHLH) transcription factor *MYC2*, the important transcriptional activator of JA responses (Wild et al. 2012). Similarly, GAs interaction with JA during plant defense over growth is also mediated by the crosstalk between DELLA protein and JA signaling repressor JAZ. The coronatine insensitive 1 (COI1) is a component of the SCF E3 ubiquitin ligase. JA promotes the degradation of JAZ1 through interaction with COI1. Besides, JA delays GA-mediated DELLA degradation. JA signaling repressor JAZ9 represses the crosstalk between DELLA protein RGA and growth-promoting transcription factor PHYTOCHROME-INTERACTING FACTOR3 (PIF3). The COI1, JAZ, DELLA, and PIF modulators cooperatively function in JA-mediated defense over growth (Yang et al. 2012). Collectively, GA and

JA pathways are interconnected to form a complicated network, which needs to be dissected by an integrative approach in the future.

GAs and SA

Phytohormone SA, similar to JA, plays fundamental role in inducible defenses against biotic and abiotic stress (An and Mou 2011). Moreover, SA inhibits GA-induced seed germination by inducing the expression of barley *HvWRKY38* gene (Xie et al. 2007). During *Arabidopsis* seed germination and seedling establishment, exogenous application of bioactive GA_3 counteracts inhibitory effects of abiotic stress by the enhancement of SA levels through promoting the expression of *isochorismate synthase1* and *nonexpressor of PR1* genes, which is necessary for SA biosynthesis and function, respectively. In addition, overexpression of GA-responsive gene *FsGASA4*, one member of GA_3 stimulated in Arabidopsis (GASA) family, results in a decrease in GA-dependent growth and an increase in endogenous SA levels. The crosstalk between GA and SA pathways may play a central role in abiotic stress responses (Alonso-Ramírez et al. 2009).

Conclusions and perspectives

Phytohormones GAs are vital in various aspects of plant growth and development. Diversified exogenous and endogenous cues are recruited by the GA–GID1–DELLA regulatory module at multiple hierarchical levels, which are required for meeting the constantly changing conditions with high plasticity and flexibility. Current challenge is to dissect the converging node of complicated GA-involved network using fruitful omic-based and systems biology approaches. Furthermore, plant hormones, GA, ABA, Aux, BRs, CKs, ET, JA, SA, and Strigolactones pathways are interwoven to establish a complex network in the modulation of plant growth and development. Elucidation of mechanisms underlying plant hormonal network is important yet challenging opportunities for biologists.

Molecular modification based on our deepening knowledge of GA-related network opens new avenues for positively affecting plant stature without penalty on yield and other agronomic values of crops. The most well-known example is the success of 'Green Revolution' which mainly attributes to plant stature manipulation via the utility of GA homeostasis genes *semidwarf1* (*sd1*) and *Reduced height* (*Rht*) (Khush 2001). However, over the past decades, 'Green Revolution' genes *sd1* and *Rht* have been extensively used to breed modern semidwarf cultivars. Extensive use of limited dwarf resources undoubtedly results in genetic bottleneck and vulnerability. To overcome this problem, mining, breeding values estimation, molecular mechanisms elucidation, and application of novel dwarf germplasms based on an integrative approach are urgent. With the flourishing of next-generation sequencing and high-throughput metabolite profiling platforms, molecular breeding and improvement with a goal of bolstering global food security is promising through the modulation of GA-related pathways.

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