



# Gibberellin signaling in plants – the extended version

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The plant hormone gibberellin (GA) controls major aspects of plant growth such as germination, elongation growth, flower development, and flowering time. In recent years, a number of studies have revealed less apparent roles for GA in a surprisingly broad set of developmental as well as cell biological processes. The identification of GA receptor proteins on the one end of the signaling cascade, DELLA proteins as central repressors of the pathway and transcription regulators such as the phytochrome interacting factors and the GATA-type transcription factors GNC and CGA1/GNL on the current other end of the signaling cascade have extended our knowledge about how GA and DELLAs regulate a diverse set of plant responses.

**Keywords:** gibberellin, bHLH, DELLA protein, GATA transcription factor, jasmonate ZIM domain protein, phytochrome interacting factor, receptor, signal transduction

## GIBBERELLINS

The diterpenoid substances of the gibberellin (GA) class were first described and isolated in the 1920s and 1930s based on the property of a compound isolated from the rice pathogenic fungus *Gibberella fujikuroi* to induce strong elongation growth and other disease symptoms in rice. After their identification as causative agent of this so-called *bakanae* (foolish seedling) disease, it was later discovered that GAs are also synthesized by plants where they promote a number of important developmental processes besides elongation such as germination and flowering. In the following decades, GA biology gained particular attention because it was recognized that interfering with GA signaling by chemical or genetic means could be used to modulate plant growth and most importantly to control crop yield and quality (Peng et al., 1999; Rademacher, 2000; Hedden, 2003).

The mechanisms that underlie GA action in plant growth control have mainly been revealed through studies conducted in rice, *Arabidopsis* and other model species such as pea and tomato. There, the analysis of mutants with defects in GA biosynthesis and signaling as well as the availability of chemical GA biosynthesis inhibitors has allowed the identification of the molecular components that control GA response during germination (Lee et al., 2002; Cao et al., 2005; Penfield et al., 2006; Piskurewicz et al., 2008, 2009; Piskurewicz and Lopez-Molina, 2009), during hypocotyl elongation and hook formation (Achard et al., 2003, 2007b; Alabadi et al., 2004; Djakovic-Petrovic et al., 2007), in chlorophyll and anthocyanin accumulation (Jiang et al., 2007; Richter et al., 2010; Cheminant et al., 2011), in flower development and in flowering time control (Cheng et al., 2004; Tyler et al., 2004; Achard et al., 2007a) as well as in fertilization (Chhun et al., 2007). More recently, less apparent roles for GAs could be elucidated such as roles in cell proliferation (Achard et al., 2009), hypocotyl xylem expansion (Ragni et al., 2011), phosphate starvation response (Jiang et al., 2007), pathogen responses (Navarro

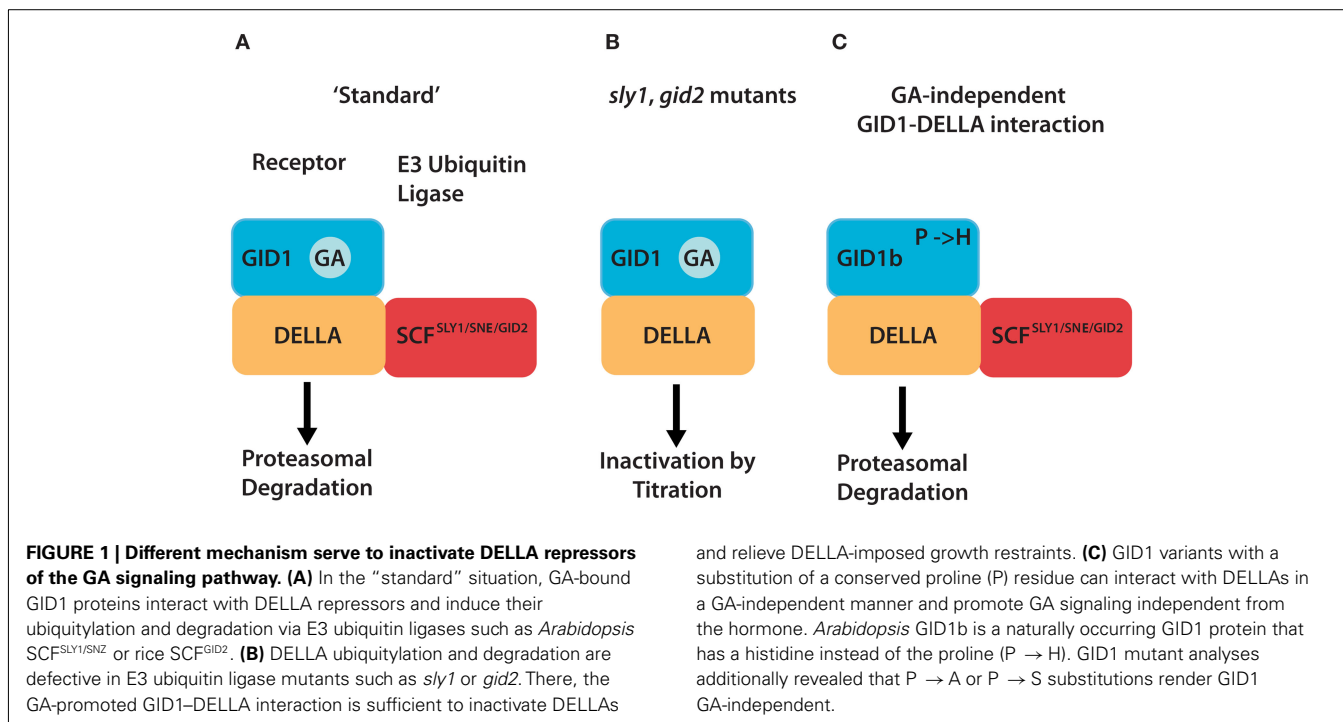
et al., 2008), oxidative stress response (Achard et al., 2008), and the response to abiotic environmental cues (Achard et al., 2006).

In order to keep the complexity of the present minireview to an appropriate level, this review almost exclusively summarizes molecular results from rice and *Arabidopsis thaliana*, where the wealth of genetic resources has enabled gaining the most valuable insights into GA biology and signaling.

## GA SIGNAL TRANSDUCTION – THE BASICS

The discovery of the GA receptor based on the rice *gibberellin insensitive dwarf1* (*gid1*) mutant in 2005 represented a major breakthrough in the understanding of the signaling pathway of this hormone (Ueguchi-Tanaka et al., 2005). While rice has only one *GID1* gene, *Arabidopsis* has three functional *GID1* orthologs, and the loss of all three *Arabidopsis GID1* genes is required for a complete loss of GA response (Griffiths et al., 2006; Willige et al., 2007). Following hormone binding, the soluble *GID1* proteins interact with the DELLA growth repressors such as SLENDER RICE1 (SLR1) in rice (Ikeda et al., 2001) and GIBBERELLIC ACID INSENSITIVE (GAI; Peng et al., 1997), REPRESSOR-OF-*ga1-3* (RGA; Silverstone et al., 1998), and RGA-LIKE1 (RGL1), RGL2, and RGL3 in *Arabidopsis* (Lee et al., 2002; Wen and Chang, 2002; Cheng et al., 2004). In the absence of GA, these DELLA proteins repress germination, growth, and other GA-dependent processes. In the presence of GA, the *GID1* interaction induces DELLA degradation via the rice SCF<sup>GID2</sup> (SKP1-CULLIN-F-BOX complex with the F-box protein subunit *GID2*; Sasaki et al., 2003; Gomi et al., 2004) or the *Arabidopsis* SCF<sup>SLY1</sup> or SCF<sup>SNE</sup> (SCF complexes with the F-box protein subunit SLEEPY1 or SNEEZY; McGinnis et al., 2003; Dill et al., 2004; Fu et al., 2004; Dohmann et al., 2010; Arizumi et al., 2011) E3 ubiquitin ligases and the 26S proteasome (Figure 1A).

In monocot and dicot species with only one DELLA protein, such as rice or tomato, the activity of GA signaling or the



progression of GA response can be judged based on the abundance of the DELLA protein and GA responses can be completely uncoupled from GA signaling in *DELLA* gene mutants (Itoh et al., 2002; Bassel et al., 2004). In species with multiple DELLA proteins, such as *Arabidopsis*, the latter statement is complicated by the fact that homeostasis mechanisms are in place that regulate the overall abundance of the functionally redundant DELLA proteins via negative feedback mechanisms that at least in part function via GA biosynthesis (Peng et al., 1997). E.g., *Arabidopsis* mutants and transgenic lines that accumulate the DELLA protein RGA have reduced levels of the DELLA protein RGA when compared with wild type plants (Willige et al., 2007). At the same time it is known that the expression of GA biosynthesis genes is upregulated in such backgrounds and that reduced RGA levels are the consequence of increased GA-dependent protein turnover.

DELLA proteins are typically but not exclusively inactivated by protein degradation. Besides proteasomal degradation, it was shown that the GA-induced interaction with the GID1 receptors is sufficient to inhibit DELLA activity (Ariizumi et al., 2008; Ueguchi-Tanaka et al., 2008). This inactivating mechanism allows to explain the comparatively mild phenotypes of rice *gid2* and *Arabidopsis sly1* mutants, E3 ubiquitin ligase subunit mutants that accumulate very high levels of DELLA proteins. In these mutants, these inhibitory GA-induced GID1–DELLA protein interactions can still take place while DELLA ubiquitylation and proteasomal degradation are blocked (Figure 1B).

In addition, the analysis of a rice *gid1* mutant suppressor mutation revealed that GID1 GA receptor variants exist that can interact with DELLAs in a GA-independent (or GA-hypersensitive) manner (Yamamoto et al., 2010). Biochemical and physiological data suggest that the substitution of a specific proline residue in GID1, e.g., by a serine or alanine allows interactions with the DELLA SLR1 in the absence of GA and that this mutant GID1 variant

can therefore suppress GA-deficiency phenotypes (Figure 1C). Interestingly, one of the three GID1 proteins from *Arabidopsis*, GID1b, can also interact with DELLAs in a GA-independent manner (Griffiths et al., 2006; Nakajima et al., 2006). Intriguingly, the critical proline residue identified in rice GID1 corresponds to a histidine in *Arabidopsis* GID1b (but to proline in GID1a and GID1c). Even more so, the GID1b–DELLA protein interaction becomes entirely GA-dependent when the respective histidine of GID1b is replaced by a proline (Yamamoto et al., 2010). It can thus be postulated that GA-independent GA receptor function may be an integral part of GA signaling, in at least some plant species, where it may serve to fine tune GA-signal transduction by promoting GA-independent DELLA inactivation mechanisms.

### GA SIGNAL TRANSDUCTION – THE EXTENDED VERSION

The biochemical role of DELLA proteins as biological repressors of GA responses has been enigmatic for an entire decade (Peng et al., 1997). In recent years, however, several studies have elucidated the identity of DELLA-interaction partners and have allowed biochemical modes of action for DELLA function to be proposed. These studies revealed that the hypothesis about their predicted role as transcriptional regulators was correct, while at the same time, the hypothesis about them functioning as DNA-binding proteins most likely is incorrect.

### CROSS-TALK WITH THE PHYTOCHROME INTERACTING FACTORS (PIFs)

Phytochrome interacting factors (PIFs) are a subfamily of basic helix-loop-helix (bHLH) transcription factors that are characterized by the AP domain, a domain for the binding of the light-activated Pfr conformer of phytochromes (Leivar and Quail, 2010). DELLAs interact with and regulate the activity of PIF3 and PIF4 (De Lucas et al., 2008; Feng et al., 2008), and they may also

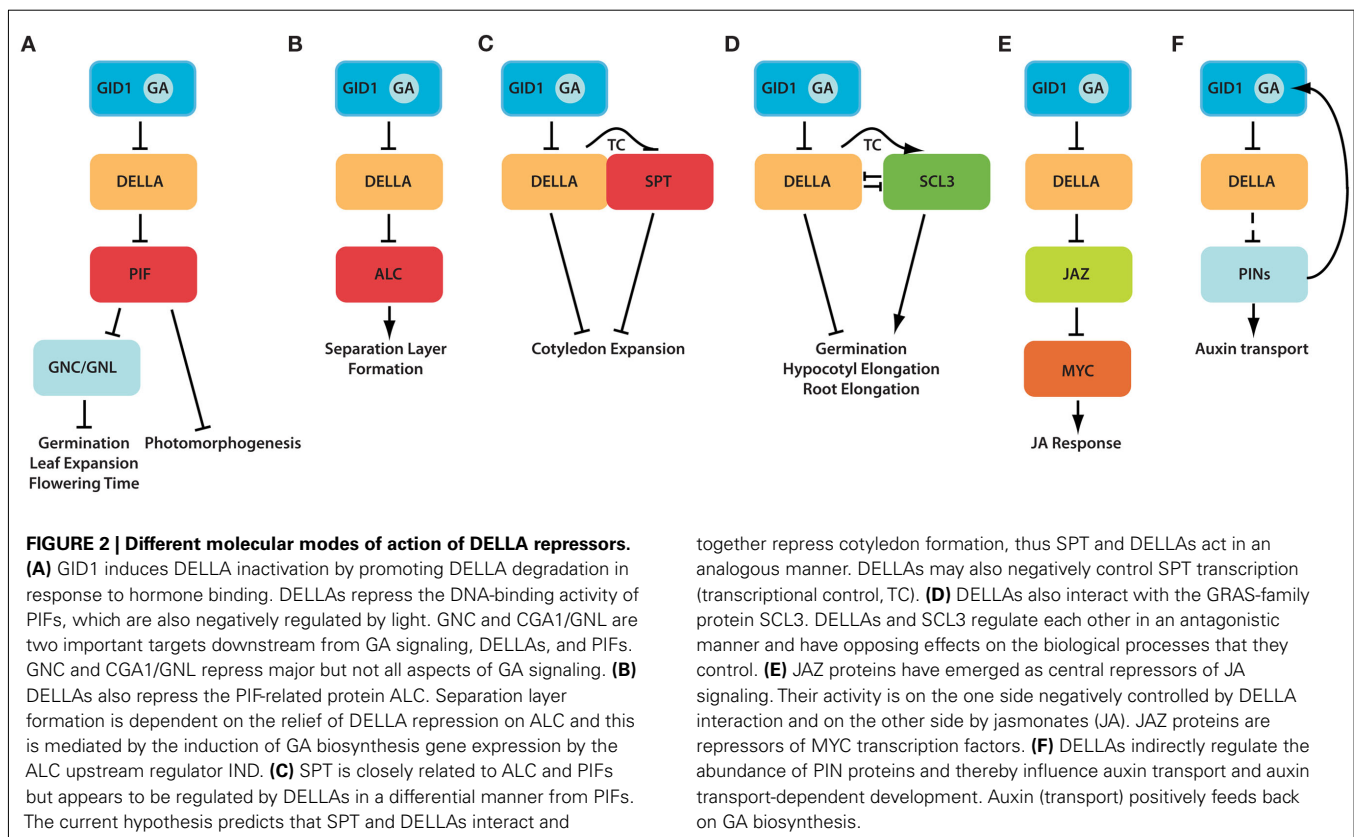
regulate the activity of other PIFs (Gallego-Bartolome et al., 2010). Through these interactions, DELLAs seemingly prevent PIFs from binding to their cognate promoter binding sites, and they thereby interfere with the transcriptional activity of PIFs and ultimately their biological function, e.g., in promoting hypocotyl elongation (**Figure 2A**; De Lucas et al., 2008; Feng et al., 2008). Importantly, PIFs also integrate light signaling through their interaction with activated phytochrome, and this is followed by their proteasomal degradation. The effect of DELLA-dependent repression on PIF function is therefore most obvious in – but not necessarily restricted to – the dark where the effect of GA and DELLAs on PIF activity can be studied in the absence of the destabilizing effect of light on PIFs. The proposed DELLA–PIF interaction in the dark can very nicely explain the apparent photomorphogenic phenotype of dark-grown *pif* mutant seedlings (Leivar et al., 2008, 2009; Shin et al., 2009) or of seedlings with increased DELLA abundance and consequently increased DELLA-mediated PIF inactivation (De Lucas et al., 2008; Feng et al., 2008). Since it is known that GA levels decline when dark-grown seedlings are transferred to the light (Achard et al., 2007b), the resulting DELLA stabilization should lead to a repression of PIF function that is then followed by the light-induced PIF degradation. In the light, PIF proteins – albeit present at low levels – are expected to retain functionality in the light-grown seedling and plant. PIFs, namely PIF1, have also been proposed to directly promote the expression of the DELLA genes *GAI* and *RGA*, and to indirectly repress GA biosynthesis gene expression, and to thereby contribute to the homeostasis of the GA signaling pathway (Oh et al., 2007).

### SIGNALING DOWNSTREAM OF PIFs

The two functionally homologous GATA family transcription factors GLUCOSE NITROGEN CARBON (GNC) and CYTOKININ-INDUCED GATA FACTOR1/GNC-LIKE (CGA1/GNL) were identified as putative GA pathway regulators based on their transcriptional regulation by GA. The expression of *GNC* and *GNL* is repressed by PIFs and their transcriptional regulation by GA and PIFs was found to require the *GID1* GA receptors and DELLA degradation (**Figure 2A**; Richter et al., 2010). *GNC* and *CGA1/GNL* repress a range of well-established GA responses including germination, elongation growth, and flowering, and they promote greening. *GNC* or *CGA1/GNL* overexpression results in plant growth as well as gene expression phenotypes that largely phenocopy GA-deficiency as well as *PIF* gene deficiency. Most importantly, the loss of *GNC* and *CGA1/GNL* function partially suppresses the phenotype of the GA-deficient *ga1* mutant. Based on these criteria, it can be postulated that *GNC* and *GNL* are major GA pathway regulators downstream of the DELLAs and the PIFs. Since the expression of these two GATA factors is also controlled – possibly via the PIFs – by light, glucose, nitrogen, and cytokinin, it may be argued that *GNC* and *CGA1/GNL* are central integrators of growth controlling signals (Bi et al., 2005; Naito et al., 2007).

### CROSS-TALK WITH ALCATRAZ (ALC)

The PIF-related bHLH protein ALCATRAZ (ALC) was initially discovered based on its role in the formation of the separation layer of the valve margin in *Arabidopsis* siliques (Rajani and Sundaresan, 2001). ALC contains a DELLA-binding domain but



lacks the AP-binding site for phytochrome interaction (Leivar and Quail, 2010). The transcription factor INDEHISCENCE (IND) is an upstream regulator of ALC and it induces the expression of a critical GA biosynthesis gene in the separation layer where ALC functionality is essential (Arnaud et al., 2010). In analogy to the interaction of DELLAs with PIF3 and PIF4, genetic, and protein–protein interaction studies clearly suggest that DELLAs also interact with ALC and that GA relieves the DELLA-imposed repression on ALC by promoting DELLA proteolysis and thereby allowing proper valve margin development (Figure 2B).

#### CROSS-TALK WITH SPATULA (SPT)

SPATULA (SPT) is the closest homolog of ALC in *Arabidopsis* and, similarly to PIFs and ALC, SPT is able to bind the DELLAs RGA and GAI (Gallego-Bartolome et al., 2010). SPT was identified based on its role in septum, style, and stigma development in the flower (Alvarez and Smyth, 1999). SPT was subsequently also shown to control germination in response to cold temperature in *Arabidopsis* seeds and to repress cotyledon expansion (Penfield et al., 2005; Josse et al., 2011). In the context of DELLA function and GA signaling, the role of SPT as a repressor of cotyledon expansion is important (Josse et al., 2011). In contrast to the antagonistic DELLA–PIF and DELLA–ALC interactions, DELLAs and SPT function in an analogous manner as repressors of cotyledon elongation (Figure 2C; Josse et al., 2011). Loss-of-function mutants of *SPT* as well as of *DELLAs* have enlarged cotyledons and this phenotype is enhanced in mutants lacking *SPT* as well as *DELLAs*. Interestingly, DELLA abundance is negatively correlated with SPT abundance, suggesting that a homeostasis mechanism is in place that controls the overall abundance of the DELLA and SPT repressors. Since GA treatment cause an increase in *SPT* transcript abundance also when *SPT* gene expression is under control of an overexpression promoter, it was postulated that an *SPT* transcript stabilizing mechanism is responsible for the accumulation of SPT in the presence of GA (Josse et al., 2011). At present, it remains to be seen whether such a regulation requires the interaction between DELLAs and SPT and which other molecular players contribute to this interaction.

#### CROSS-TALK WITH SCARECROW-LIKE3 (SCL3)

The five *Arabidopsis* DELLA proteins belong to the superfamily of GRAS (GAI, RGA, SCARECROW) transcription regulators that in *Arabidopsis* additionally includes SCARECROW (SCR) and 27 SCARECROW-like (SCL) proteins (Pysh et al., 1999; Lee et al., 2008). The DELLA domain and the adjacent VHYNP domain allow to distinguish the DELLAs from the remaining SCR/SCL proteins (Pysh et al., 1999; Willige et al., 2007). A number of studies have tried to understand the evolutionary and functional relationship between SCR/SCL proteins and DELLAs. *SCL3* attracted the attention of GA biologists because its transcription was repeatedly found to be strongly repressed by GA and to be induced by DELLAs (Willige et al., 2007; Zentella et al., 2007). Genetic analyses of *SCL3*-deficient mutants have allowed positioning *SCL3* into the GA signaling pathway. *SCL3* and DELLA (RGA) interact and *SCL3* positively regulates GA responses (Heo et al., 2011; Zhang et al., 2011). The primary effect of the interaction between *SCL3* and DELLA is antagonistic, however, this appears to be

more complicated because DELLA induces the transcription of its *SCL3* antagonist and, inversely, because *SCL3* possibly stabilizes its DELLA antagonist by modulating GA biosynthesis (Figure 2D).

#### CROSS-TALK WITH THE JASMONIC ACID (JA) PATHWAY

Gene expression studies and pathobiological assays had suggested that GA controls JA-responsive gene expression (Cao et al., 2006; Hou et al., 2008) and JA-mediated plant immune responses (Navarro et al., 2008). In an analysis of the underlying molecular causes it was found that GA attenuates the JA-induced expression of a number of JA-responsive genes (Hou et al., 2010). The expression of these genes is dependent on the transcription activators MYC2, MYC3, and MYC4 and their negative regulators, the dimerizing jasmonate ZIM domain proteins (JAZ; Chini et al., 2007; Fernandez-Calvo et al., 2011). Via NINJA proteins, JAZ proteins are linked to the TOPLESS(-RELATED) corepressors (Pauwels et al., 2010) and the repressive activity of JAZs is relieved in the presence of JA by their proteasomal degradation via the E3 ligase SCF<sup>COI1</sup> (Thines et al., 2007). It was recently shown that the DELLA proteins RGA, GAI, RGL1, and RGL2 directly bind to and thereby inhibit the (representative) JAZ proteins JAZ1, JAZ3, and JAZ9 (Hou et al., 2010). Hierarchically, JA-mediated JAZ degradation has thus to be seen as the major control element of the pathway, while DELLAs modulate JA responses by repressing JAZ activity (Figure 2E).

#### CROSS-TALK WITH AUXIN TRANSPORT

Most of the DELLA-dependent regulatory events that have been identified so far involve a cascade of – typically repression – events that ultimately lead to gene expression changes that – somehow – are responsible for GA-mediated growth control. Few of these signaling events allow hypothesizing about how GA controls growth at the cell biological level. At least two reports link GA signaling to auxin transport and these findings help at least in part to explain how the GA signal is influenced by or is influencing transport of the plant hormone auxin and ultimately plant growth. Auxin transport controls organ initiation and development as well as tropic responses: auxin is synthesized in the shoot apex and transported toward the root tip via the activity of PIN-FORMED (PIN) auxin efflux carriers. When the shoot and consequently the shoot-derived auxin source is removed, roots cease to grow and fail to respond properly to GA. This reduced GA-responsiveness can be suppressed when the auxin indole-3-acetic acid (IAA) is applied to the site of shoot removal. Genetic and cell biological analyses showed that the cessation of root growth correlates with the accumulation of DELLAs (RGA) in the root and is suppressed in *DELLA* gene loss-of-function mutants (Fu and Harberd, 2003). Thus, auxin and auxin transport may control DELLA abundance and control (root) growth. At the same time it was recently found that GA controls auxin transport and PIN protein abundance (Willige et al., 2011). GA promotes the degradation of the auxin efflux carriers PIN1 and PIN2, at least in root tips and inflorescence stems, possibly by increased targeting of these transporter proteins for degradation in the vacuole (Vieten et al., 2007; Willige et al., 2011). At the physiological level, the downregulation of PIN proteins as observed in GA and GA signaling-deficient mutants correlates with a reduction in auxin transport in inflorescence

stems, defective embryo development and reduced root gravitropism. Since GA-dependent changes in PIN protein abundance do not correlate with GA-dependent changes in *PIN* gene transcription, and since PIN protein abundance at the same time is increased when PIN protein degradation is blocked, it has to be argued that GA controls PIN abundance at the post-translational level (**Figure 2F**; Willige et al., 2011).

## OPEN QUESTIONS

This review provides an overview of the current knowledge on the mechanisms governing GA signaling. Certainly, it has become clear that especially in recent years major advances have been made in understanding the molecular mode of action of the DELLA proteins as key repressors of the pathway. A number of obvious questions remain to be answered, some of which have already been phrased in the above paragraphs. At least two additional major issues that have puzzled the GA signaling field for some time will require clarification in the near future: the O-Linked *N*-acetylglucosaminyltransferase (OGT) SPINDLY (SPY) was identified repeatedly as a major repressor of GA signaling (Jacobsen and Olszewski, 1993; Wilson and Somerville, 1995; Jacobsen et al., 1996; Shimada et al., 2006). SPYs repression function in *Arabidopsis* GA signaling was recapitulated in other plant species including tomato and rice (Greb et al., 2002; Shimada et al., 2006). Most importantly, *spy* mutant alleles fully suppress GA-deficiency as well as defects in GA signaling and this phenotype can best be

explained by a direct control of DELLA repressor activity by SPY-mediated O-Linked *N*-acetylglucosamine-modification. A proof for this or an alternative mode of action urgently needs to be brought about.

Several reports have identified DELLA proteins as phosphoproteins. Although it had initially been claimed that this modification is essential for the proteasomal degradation of DELLAs (Sasaki et al., 2003; Gomi et al., 2004), this view was subsequently corrected (Itoh et al., 2005). On the other side, *in vitro* data using pharmacological inhibitors suggest that phosphoregulation may be involved in DELLA protein turnover (Wang et al., 2009). Thus, it remains to be seen whether and how DELLA phosphorylation regulates DELLA activity. The mutation of predicted phosphorylation sites in *Arabidopsis* RGL2 impairs GA-induced protein degradation but whether or not this effect is ultimately due to changes in RGL2 phosphorylation rather than RGL2 functionality could not be fully clarified (Hussain et al., 2005, 2007). The recently identified casein kinase, CKI, is a candidate kinase that may phosphorylate DELLAs and regulate their activity *in vivo* to control flowering time in rice (Dai and Xue, 2011). Further experiments will bring light into the identity of the *in vivo* targets of this kinase and may identify further kinases that interfere with DELLA activity.

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