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REVIEW

How Plants Make and Sense Changes in Their Levels of Gibberellin

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To cope with constantly changing environments, plants employ versatile mechanisms. Gibberellins (GAs) are a class of well-characterized plant hormones that enable plastic growth and developments in higher plants throughout their life cycles. Several key components of GA metabolism and signaling have now been revealed through elegant molecular genetics analyses powered by genomics information from *Arabidopsis* and rice. Here, we highlight recent findings concerning the molecular mechanisms by which plants control their bioactive GA levels and sense/respond to changes in gibberellin concentrations.

Keywords: Arabidopsis, gibberellins, hormone, metabolism, signaling

GIBBERELLINS AND PLANTS

Various aspects of growth and development are highly plastic in higher plants throughout their life cycles. After changes in their external/endogenous environment are perceived, plants respond to such stimuli by adopting appropriate developmental alterations. Plant hormones play central roles in these physiological/molecular/developmental fluctuations (Davies, 2004). Gibberellins (GAs) comprise a large group of tetracyclic diterpenoid carboxylic acids. Among the over 135 different GAs from natural sources (http://www.plant-hormones.info/gibberellins.htm), only certain members function as bioactive GAs to control seed germination, stem elongation, trichome differentiation, leaf expansion, floral induction and development, seed set, and fruit formation (Richards et al., 2001). Recent detailed analyses of the GA-responsive transcriptome as well as studies of mutants have demonstrated the involvement of GAs in biotic/abiotic stress tolerance (Ogawa et al., 2003; Magome et al., 2004; Achard et al., 2006; Cao et al., 2006). Indeed, a variety of endogenous/external stimuli affect the bioactive-GA level as well as GA-signaling (Yamaguchi and Kamiya, 2000; Hay et al., 2004; Fleet and Sun, 2005; Swain and Singh, 2005; Zhao et al., 2007). Here, we review recent findings that illuminate the way in which plants can detect changes in their endogenous GA levels and modulate their developmental programs.

REGULATORY MECHANISMS OF BIOACTIVE-GA LEVELS

Over the past decade, our knowledge of the process by which plants produce bioactive GA has been greatly advanced via genetic analysis of GA-deficient mutants, particularly in *Arabidopsis* (Fig. 1). As a result, most of the genes involved in GA metabolism have been identified (Hedden and Phillips, 2000; Yamaguchi and Kamiya, 2000; Olszewski et al., 2002). Biologically active GAs are synthesized from geranylgeranyl diphosphate that is converted to ent-kaurene, which in turn is oxidized to ent-kaurenoic acid. This is further oxidized to GA_{12}, which is subject to oxidative modification at C-20, and then to 3-β hydroxylation, thus producing biologically active GA_1 and GA_4. Hydroxylation of C-2 by GA 2-oxidases (GA2ox) inactivates the biologically active GAs (Hedden and Phillips, 2000). Modifications to GA levels in response to endogenous/external stimuli involve changes in gene expression for either two GA-biosynthetic enzymes -- GA20 oxidase and GA3 oxidase -- or a GA-catabolic enzyme, GA2 oxidase. These stimuli include light quality, low temperatures, photoperiod, and several plant hormones, e.g., GA itself, auxins, brassinosteroids, and polyamines (Chiang et al., 1995; Wu et al., 1996; Cowling et al., 1998; Yamaguchi et al., 1998; Xu et al., 1999; Ross et al., 2000; Bouquin et al., 2001; Alcázar et al., 2005).

Other, currently unknown, processes also may modulate GA levels. Novel classes of GA-deactivation mechanisms and their corresponding enzymes have been characterized using genetics approaches. In addition to GA 2β-hydroxylation by GA2 oxidase, GA-methylation by GAMT1/GAMT2 functions to deactivate bioactive GA in *Arabidopsis* (Varbanova et al., 2007). Likewise, a cytochrome p450 monooxygenase, EUI (ELONGATED UPPERMOST INTERNODE) enzyme, catalyzes 16,17-epoxidation of non-13-hydroxylated GAs to reduce bioactive GA_4 in rice (Zhu et al., 2006). Reversible GA-glycosylation also has been characterized (Schneider et al., 1992), although the corresponding enzymes remain to be determined. Data from our recent work on a novel GA-sensitive dominant dwarf mutant in *Arabidopsis*, designated as *gibberellin-sensitive dwarf1* (*gsd1-1*), suggest that GSD1 represents a novel regulatory locus to modulate the bioactive GA level, but without affecting the expression of known GA-metabolic enzymes (Lee and Soh, unpublished results; Soh, 2006).

Several regulatory factors that control GA biosynthesis at particular developmental stages have been identified in plants. These include a basic leucine zipper protein of tobacco, RSG (for REPRESSION OF SHOOT GROWTH) (Fukazawa et al., 2000; Ishida et al., 2004); the KNOX homeodomain protein, NTH15 (*Nicotiana tabacum homeobox 15*); a MADS domain protein, AGL15 (AGAMOUS-LIKE 15); an

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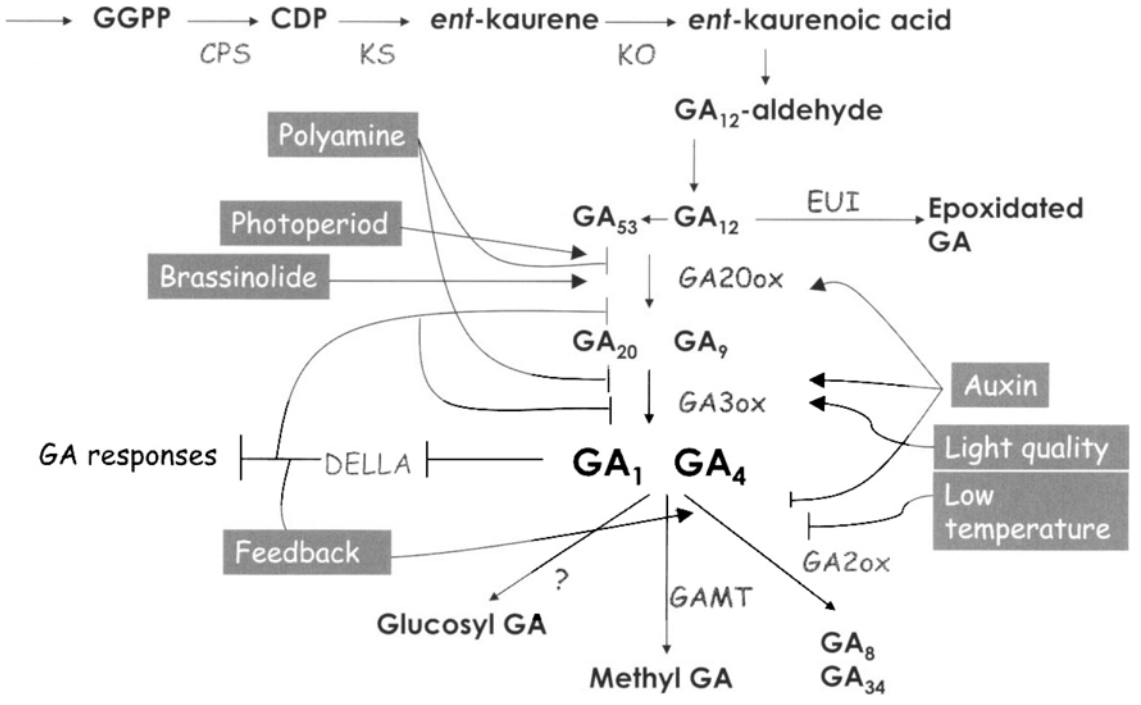

Figure 1. Regulation of GA biosynthesis and inactivation in *Arabidopsis*. Geranylgeranyl diphosphate (GGDP), ent-copalyl diphosphate (CDP), ent-copalyl diphosphate synthase (CPS), ent-kaurene synthase (KS), ent-kaurene oxidase (KO), GA 20-oxidase (GA20ox), GA 3-oxidase (GA3ox), GA 2-oxidase (GA2ox), GA methyltransferase (GAMT), ELONGATED UPPERMOST INTERNODE (EUI).

AT hook protein, AGF1; a basic helix-loop-helix protein, SPATULA; and two AP2-type transcription factors, DDF1 (DWARF AND DELAYED FLOWERING1) and DDF2 (DWARF AND DELAYED FLOWERING2) (Tanaka-Ueguchi et al., 1998; Magome et al., 2004; Wang et al., 2004; Penfield et al., 2005; Matsushita et al., 2007). Nevertheless, it is still poorly understood how plants regulate those factors to control the expression of GA-metabolic genes. Significant progress has been made into how plants initiate changes in their GA levels in response to light quality during *Arabidopsis* seed germination. When treated with red light, gibberellin content is increased in the imbibed seeds, thereby inducing germination (Borthwick et al., 1952; Toyomasu et al., 1993; Yamaguchi et al., 1998; Oh et al., 2006). After red light is perceived, photo-transformed Pfr-phytochrome enters the nucleus (Nagatani, 2004), where phytochrome binds with PIL5(PIF3-LIKE5)/PIF1 (PHYTOCHROME-INTERACTING FACTOR1) (Huq et al., 2004; Oh et al., 2004). As a result, phytochrome appears to direct the proteasome-mediated degradation of PIL5 (Oh et al., 2006). Light-independent germination in the *pil5* mutant indicates that PIL5 acts as a negative regulator of germination. Indeed, PIL5 seems to repress the expression of *GA3ox1/GA3ox2*, but induces that of *GA2ox2* (Oh et al., 2006). Thus, red-light promotion of seed germination involves the de-repression of PIL5 on GA-biosynthetic/catabolic genes. It is interesting to note that a "relief of restraint" working mode also is adopted, as seen in the light-induced enhancement of GA levels as well as activation of the GA-signaling pathway (Fig. 2). We expect that integrated functional genomics and proteomics analyses will soon provide more comprehensive knowledge of the mechanisms by which the level/activity of GA-metabolic enzymes are controlled by specific endogenous/external stimuli at the molecular level.

GA PERCEPTION AND SIGNALING

Seminal progress has been made toward understanding how GA is perceived and its signal is integrated into developmental programs. Molecular genetics/reverse genetics approaches have been fruitful in identifying the GA-signaling components in rice and *Arabidopsis*. Although genetic analyses are hampered by functional redundancy as well as by the essential roles of GA in seed germination, and pollen and seed development (Swain and Singh, 2005), functional genomics and reverse genetics technologies provide important clues about GA-signaling in higher plants. It is interesting to note that a recurring theme of plant developmental regulation, i.e., the relief of restraint via protein degradation (Callis and Vierstra, 2000; Hellmann and Estelle, 2002; Vierstra, 2003) is also adopted in GA-signaling.

GA receptors

Molecular cloning of a GA-insensitive dwarfing mutant in rice, *OsGID1*, has revealed that this gene encodes a nuclear soluble protein that resembles a hormone-sensitive lipase (HSL) (Ueguchi-Tanaka et al., 2005). Biochemical analysis has shown that this protein can bind a physiologically active form of GA. All of these results demonstrate its functioning as a bona-fide GA receptor. Three members of the OsGID1 homologues, AtGID1a through c, exist in *Arabidopsis* (Nakajima et al., 2006). Based on their genetic and biochemical

functional characterization, they were shown to act as GA receptors, playing partially overlapping roles in a subset of GA-responsive growth and development (Griffiths et al., 2006). Even in the presence of GA, the triple knockout mutants of *AtGID1a-c* genes exhibit germination defects, dark-green leaves, dwarf stem growth, and poorly developed floral organs. GID1 interacts with the DELLA domain of DELLA proteins, repressors of GA-dependent responses, in a GA-dependent manner in both rice and *Arabidopsis* (Ueguchi-Tanaka et al., 2005; Griffiths et al., 2006).

DELLA protein, a target of the GA receptor

Genetic analysis of *Arabidopsis* has identified a group of repressor proteins in GA-signaling. These are called DELLA proteins. Koornneef et al. (1985) have isolated a dominant mutation, *gai-1*, that causes GA-insensitive dwarfism in *Arabidopsis*. Molecular cloning of the *GAI* locus has revealed that the *gai-1* allele is a gain-of-function allele that lacks 17 amino acids in its N-terminal region, the so-called DELLA domain (Peng et al., 1997). The loss-of-function *rga* mutants have been identified as suppressors of GA-deficient mutants (Silverstone et al., 1997). Molecular analysis of the *RGA* locus has shown that *GAI* and *RGA* comprise a subfamily, i.e., the *DELLA* genes, within the *GRAS* family of transcriptional regulators (Silverstone et al., 1998). *Arabidopsis* contains five *DELLA* protein genes: *GAI, RGA, RGL1, RGL2*, and *RGL3* (Dill and Sun, 2001). Their genetic characterization and functional analysis has demonstrated that, except for *RGL3*, these genes have partially overlapping functions in repressing GA-regulated plant growth and development (Dill and Sun, 2001; King et al., 2001; Lee et al., 2002; Cheng et al., 2004; Tyler et al., 2004; Cao et al., 2005). In particular, GAI and RGA are the major repressors of GA-dependent vegetative growth and floral induction; RGL2 represses GA-dependent seed germination, with its functioning being enhanced by GAI and RGA; and RGA, RGL1, and RGL2 play major roles in flower development. For example, the quadruple mutant of *GAI, RGA, RGL1*, and *RGL2* completely suppress *ga1-3*, the null allele of the *GA1* locus, which exhibits severe GA-deficient phenotypes throughout various developmental stages (Cheng et al., 2004; Tyler et al., 2004; Cao et al., 2005). Thus, these four DELLA proteins act as central negative regulators, repressing GA-dependent germination, stem elongation, leaf expansion, and flower/seed development. It is also noteworthy that DELLA proteins function as GA-signaling repressors in other plant species, such as maize, barley, rice, wheat, grape, and *Brassica rapa* (Peng et al., 1999; Ikeda et al., 2001; Boss and Thomas, 2002; Chandler et al., 2002; Muangprom at al., 2005). This indicates the functional conservation of DELLA proteins in GA-signaling among higher plants.

It is largely unknown how DELLA proteins repress the GA-dependent response. Along with nuclear localization, the existence of a GRAS domain in the DELLA proteins (which contains potential protein-protein motifs -- two Leu heptad repeat motifs), suggests that these proteins might interact with other transcriptional regulators (Sun and Gubler, 2004). Recent microarray experiments have revealed a distinct DELLA-dependent transcriptome, depending on the developmental context (Cao et al., 2006). For example, although DELLA proteins repress similar cellular events (e.g., cell-wall loosening and cell elongation) during germination and floral development, a unique transcriptome is controlled by DELLA proteins in the course of GA-dependent germination and flower formation. These results implicate the involvement of differential transcriptional factors in DELLA-mediated repression of specific subsets of GA-responsive genes, depending on certain developmental context. Identification of the transcriptional complex that mediates DELLA-dependent repression would shed light on the ways in which plants control specific GA-responsive transcriptomes according to their differential development.

Role of GID1 in the degradation of DELLA proteins

Except for RGL1, the DELLA proteins undergo 26S proteasome-mediated proteolysis that is activated by gibberellin (Dill et al., 2001; Silverstone et al., 2001; Fu et al., 2002; Wen and Chang, 2002; Sasaki et al., 2003; Dill et al., 2004; Fu et al., 2004). Molecular identification of *SLEEPY1* (*SLY1*) has provided critical clues that enhance our understanding of how GA-signaling pathways are controlled. *SLY1* was originally identified from a suppressor screening of the *abi1-1 (ABA-insensitive1-1)* mutant during the germination process (Steber et al., 1998). Physiological analysis has shown that SLY1 acts as a positive regulator of GA-signaling. Molecular cloning of the *SLY1* gene has revealed that it encodes an F-box protein, a component of the SCF E3 ubiquitin ligase complex (McGinnis et al., 2003). This SCF^{SLY1} complex directly targets DELLA proteins to 26S proteasome-dependent proteolysis (Dill et al., 2004; Fu et al., 2004). Interestingly, the interaction between SLY1 and the DELLA proteins is enhanced or activated by GA. Recent elegant analysis has illustrated the role of GA and its receptor GID1 in the proteolysis of those DELLA proteins. Three hybrid experiments have demonstrated that the interaction of RGA with SLY1 is further promoted by GA-bound GID1 (Griffiths et al., 2006). Thus, GA-GID appears to facilitate the targeting of DELLA proteins to SCF^{SLY1}-dependent ubiquitination via direct interaction with the DELLA proteins (Fig. 2). The working model is also supported by the existence of a novel type of gain-of-function allele of the DELLA protein from *Brassica rapa*. A mutant form of that protein, BRRGA1-D, functions as a GA-insensitive repressor by preventing its interaction with SLY1. *Brrga1-d* contains a missense mutation in the GRAS domain, indicating that this domain of the DELLA proteins mediates not only repressive functioning but also interaction with SLY1 for degradation (Muangprom et al., 2005). Thus, whichever form of the mutant DELLA proteins that cannot interact with GA-GID1 or SLY1 remains stable even in the presence of gibberellin. It is noteworthy that plants utilize very similar strategies to sense different concentrations of auxin or gibberellin by promoting the destruction of repressor proteins, Aux/IAA or DELLA proteins, respectively (Dharmasiri et al., 2005; Kepinski and Leyser, 2005; Ueguchi-Tanaka et al., 2005).

Future challenges

Despite the growth in our understanding of GA-signaling, several important questions remain to be addressed.

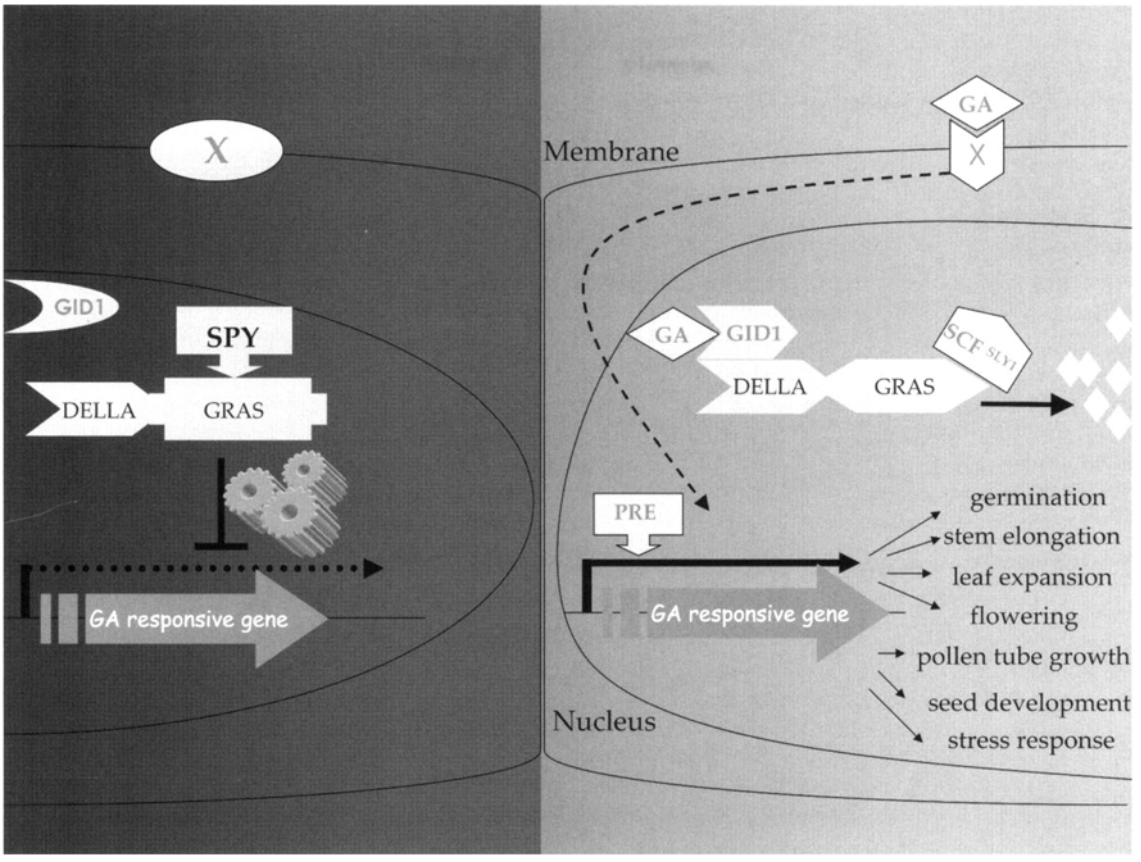

Figure 2. A working model of GA-signaling in *Arabidopsis*. In the absence of GA (left side), DELLA proteins act to repress downstream expression of GA-responsive gene. DELLA proteins not recognized by SLEEPY1 (SLY1) remain stable as repressors of GA-responsive gene expression. SPINDLY (SPY) may enhance repressive functioning of DELLA proteins. In the presence of GA (right side), GA-bound GID1 (GA receptor) interacts with DELLA proteins, triggering unknown structural changes that facilitate interaction between DELLA proteins and SLY1, a component of the SCF^{SLY1} E3 ubiquitin ligase complex. Once DELLA proteins are targeted to 26S proteasome-mediated proteolysis, downstream gene expression can occur, leading to GA-dependent responses that include germination, stem elongation, leaf expansion, and flowering. PACLUBUTRAZOL RESISTANCE (PRE) proteins may aid GA-responsive gene expression as positive regulator of GA-signaling. Membrane-localized GA receptor (X) remains to be identified.

Are there other GA receptors besides GID1? Although GID1 proteins have been characterized as bona fide GA receptors in both rice and *Arabidopsis* (Griffiths et al., 2006), an intriguing question remains concerning the existence of other such receptors, e.g., those that are membrane-bound. The hypothesis that GA-signaling might involve membrane-bound receptors and/or membrane-bound signaling components, such as heterotrimeric G-protein/G-protein-coupled receptors, is supported by considerable experimental evidence (Jones et al., 1998; Ashikari et al., 1999; Ueguchi-Tanaka et al., 2000; Ullah et al., 2002; Chen et al., 2004). Moreover, it should be noted that some GA-dependent responses, including seed development and pollen formation/germination, appear normal in the *Arabidopsis gid1a-c* triple mutant (Griffiths et al., 2006). These processes may involve a different class of GA receptors. In potato, gibberellin triggers the nuclear localization of a positive GA-signaling component, PHOR1 (Amador et al., 2001). Taken together, it is conceivable that GA receptors other than nuclear GID1 may function for a subset of GA-dependent responses.

Are there any other modulators of SLY1-mediated DELLA degradation? The basal level of DELLA proteins is significantly higher in the *sly1* mutant than for *ga1-3* or the *gid1a-c* triple mutant (Dill et al., 2004; Griffiths et al., 2006). It is assumed that stimuli other than GA may facilitate SLY1-mediated degradation of DELLA proteins. Indeed, two different plant hormones, auxin and ethylene affect the stability of those proteins (Achard et al., 2003; Fu and Harberd, 2003). Thus, DELLA proteins appear to act as integrators of multiple plant hormones. We must still determine how auxin and ethylene influence the GA-induced destruction of DELLA proteins. In a similar manner, other biotic/abiotic stimuli may control the stability of those proteins. It is noteworthy that the DELLA-dependent transcriptome includes genes implicated in biotic/abiotic stress-resistance (Cao et al., 2006).

Are there any other targets of GID1a-c besides DELLAs? Although the DELLA proteins appear to be largely responsible for the massive changes in gene expression driven by GA, some sets of the GA-responsive transcriptome are not altered by quadruple mutants of those proteins (Ogawa et al., 2003; Cao et al., 2006). For example, the *gid1a-c* triple mutant of GA receptors exhibits more severe phenotypes

than *sly1-10*, even though the level of DELLA proteins in *sly1-10* is higher than in the triple mutant (Griffiths et al., 2006). These results indicate that GA receptors may have other regulatory functions through a DELLA-independent pathway.

What are the roles for kinase(s)/phosphatase(s) in conjunction with the DELLA proteins? DELLA proteins are possibly phospho-proteins (Sasaki et al., 2003; Hussain et al., 2005). Treatment with protein phosphatase inhibitors blocks the GA-induced degradation of DELLA proteins (Fu et al., 2002; Hussain et al., 2005). Moreover, the results of functional analysis, combined with site-directed mutagenesis of DELLA proteins, has suggested that their phosphorylation is an important regulatory process not only for DELLA-degradation but also for their repressive functioning (Hussain et al., 2005). Identification of the protein kinases/phosphatases involved in the phosphorylation of DELLA proteins would provide important insight into the regulation of DELLA-functioning.

What are the signaling-network and biochemical functions of other players implicated in GA-signaling? Previous genetic analysis has identified several classes of components that affect GA-induced growth and development. However, those elements have been poorly characterized. Positive signaling components include a CHD3 chromatin remodeling factor (PICKLE); a Katanin-like microtubule-associated protein, LUE1; and non-DNA binding helix-loop-helix proteins (i.e., PRE proteins) (Ogas et al., 1999; Bouquin et al., 2003; Lee et al., 2006). A diverse family of transcriptional factors, e.g., the GAMYB proteins (Gocal et al., 2001; Gubler et al., 2002; Diaz et al., 2002), a MADS protein AGL20/SOC1 (Moon et al., 2003), SQUAMOSA-PROMOTER-BINDING-PROTEIN-LIKE8 (SPL8) (Zhang et al., 2007), and a bHLH protein NAN-JANG-I (Kim et al., 2005), have been described as mediating a subset of GA-dependent growth processes. Notably, the overexpression of *PRE* genes suppresses most of the developmental defects in a GA-deficient mutant, *ga2-201* (Lee et al., 2006). Together with DELLA-mediated repression of this *PRE* gene expression, our results imply that the PRE proteins are early targets of the DELLA-dependent repression of GA responses (Fig. 2).

Negative regulators of GA-signaling include microRNA *miR159*, SHORT INTERNODE (SHI), and SPINDLY (SPY). The first, *miR159*, targets and directly cleaves the mRNA that encodes GAMYB-related proteins. These are involved in GA-dependent floral induction and anther development (Achard et al., 2004). *SHI* encodes a RING-finger protein whose overexpression causes GA-insensitive dwarf plants (Fridborg et al., 1999), while *SPY* encodes an *O*-linked *N*-acetylglucosamine transferase (OGT), in which a loss-of-function mutation partially suppresses all aspects of the GA-deficient syndrome in *ga1* mutants (Jacobsen and Olszewski, 1993; Jacobsen et al., 1996). Observations of the pleiotropic effects in the *spy* mutant imply that its functions may be related to the early events of GA-signaling (Swain et al., 2001, 2002). SPY appears to enhance the repressive functioning of DELLA proteins (without affecting DELLA-degradation), by altering the phosphorylation status of the DELLA proteins (Shimada et al., 2006; Silverstone et al., 2007). It should be noted that SPY is also involved in other biological processes, e.g., the brassinosteroid pathway, cytokinin responses, and components of the circadian clock (Tseng et al., 2004; Greenboim-Wainberg et al., 2005; Shimada et al., 2006). Moreover, the synthetic lethal phenotypes of the double mutant of SPY and its homologue SECRET AGENT (SEC) indicate that these gene products may have broader functions than previously thought (Hartwek et al., 2002). It is still unclear about the molecular target of SPY-associated OGT activity in GA-signaling.

Together with the functional characterization of these GA-signaling components, a possible molecular network and/or cross-talk among them should be investigated to improve our understanding of how GA signals are relayed and integrated in other developmental programs.

CONCLUDING REMARKS

With the aid of molecular genetics studies, we are now in the middle of an exciting phase that will enhance our knowledge of how plants alter their GA level and respond to different concentrations of gibberellin. Further refined and integrated approaches that employ gain-of-function mutant-screening, reverse-genetics analysis, microarrays, proteomics, and metabolomics approaches will unveil the missing pieces and fill the gaps in our understanding of various regulatory components/mechanisms. As exemplified by the recent discovery that the 'green revolution' genes of rice and wheat are related to GA metabolism and signaling (Peng et al., 1999; Hedden, 2003; Sakamoto et al., 2003; Sun and Gubler, 2004), additional comprehensive data will provide novel opportunities for generating genetically engineered crop varieties with increased yield and productivity.

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