Journal of Experimental Botany, Vol. 60, No. 4, pp. 1085–1092, 2009
doi:10.1093/jxb/ern301 Advance Access publication 28 November, 2009

Journal of Experimental Botany
www.jxb.oxfordjournals.org

REVIEW PAPER

Releasing the brakes of plant growth: how GAs shutdown DELLA proteins

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Received 29 September 2008; Revised 24 October 2008; Accepted 3 November 2008

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Abstract

Bioactive gibberellins (GAs) are tetracyclic diterpenoid plant hormones that promote important processes of plant growth and development, such as seed germination, growth through elongation, and floral transition. Thus, mutant plants that are affected in GA biosynthesis or signalling exhibit altered seed germination and, at the adult stage, are dwarf and dark green and also show delayed flowering. The components of the GA metabolism and signalling pathways are reviewed here and recent findings regarding the regulation and possible mode of action of DELLA proteins are discussed.

Key words: *Arabidopsis*, DELLA, ROS, gibberellins, ubiquitin.

Components of the GA metabolism and signalling pathways

By biochemical and genetic approaches most of the genes encoding GA biosynthesis and deactivating enzymes have been identified (recently reviewed in Yamaguchi, 2008). Given the number of GAs (more than 100 but only a few are biologically active) and their multiple roles in plant development (Richards *et al.*, 2001; Sun and Gubler, 2004), the regulation of the GA levels is likely to be complex. Accordingly, many steps in the GA metabolism pathway are controlled by enzymes belonging to small multigenic families, with each member having a specific pattern of expression. In particular, GA biosynthesis is tightly regulated through the modulation of the expression of members of two gene families encoding GA 20-oxidases (GA20ox) and GA 3-oxidases (GA3ox) that catalyse the final steps in the synthesis of bioactive GAs (Chiang *et al.*, 1995; Phillips *et al.*, 1995) (Fig. 1A). By a series of oxidation steps, these enzymes lead to the formation of the two main bioactive GAs, GA_4 and GA_1. However, homeostasis of GAs also depends on GA deactivation pathways. Hence, the major route known to deactivate bioactive GAs, is the 2β-hydroxylation, catalysed by the GA 2-oxidases (GA2ox) (Thomas *et al.*, 1999; Schomburg *et al.*, 2003; Rieu *et al.*, 2008). In Arabidopsis, two main groups have been characterized: the C_{19}- and C_{20}-GA2ox. The C_{19}-GA2ox (including AtGA2ox1, -2, -3, -4, and -6) have been shown to hydroxylate C_{19}-GAs substrates, including the bioactive GAs (GA_4 and GA_1) and their immediate precursors (GA_9 and GA_{20}) (Rieu *et al.*, 2008). In contrast, C_{20}-GA2ox (AtGA2ox7 and -8) accept only C_{20}-GAs (GA_{12} and GA_{53}, precursors of bioactive GAs) as substrates, rendering them unable to be converted to bioactive GAs (Schomburg *et al.*, 2003). The C_{20}-GA2ox probably plays a role in depleting pools of precursor GAs.

Recent work has revealed two other GA deactivation pathways. One of them, identified in rice, occurs through epoxidation and is catalysed by a P450 mono-oxygenase, CYP714D1 (Zhu *et al.*, 2006), whereas another pathway elucidated in *Arabidopsis* involves GA methylation (catalysed by the SABATH methyl transferases GAMT1 and GAMT2) and may be more specific for seed development (Varbanova *et al.*, 2007).

In addition, the expression of genes encoding enzymes involved in the later steps of the GA metabolism pathway is subject to regulation by GA itself. Indeed, bioactive GA

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homeostasis is maintained by feedback regulation of genes involved in GA metabolism and, for that, an active GA response pathway is necessary (Hedden and Phillips, 2000; Olszewski *et al.*, 2002; Yamaguchi, 2008). Thus, in mutants deficient in bioactive GA production or signalling, the transcript level of GA biosynthetic genes (*GA20ox* and *GA3ox*) is high, whereas the expression of catabolic genes (*GA2ox*) is low. Accordingly, the converse situation is observed in mutants with increased GA levels or enhanced GA signalling. The molecular level of this feedback mechanism is still poorly understood, but it was recently proposed that DELLA proteins (GA-regulated factors, see below), most probably with the help of unknown DNA binding proteins, contribute in establishing GA homeostasis by direct feedback regulation of the expression of *GA3ox1* and *GA20ox2* genes (Zentella *et al.*, 2007). It is noteworthy that, in rice, the YABBY1 transcription factor may act downstream of DELLA to regulate GA metabolic gene expression (Dai *et al.*, 2007).

The GA signalling pathway has now been unravelled in both *Arabidopsis* and rice (Fig. 2). This pathway is fairly simple, taking into account its limited number of components. Key regulators of the GA signalling pathway are the nuclear-localized growth repressing DELLA proteins (DELLAs) (Peng *et al.*, 1997; Silverstone *et al.*, 1998; Dill and Sun, 2001; King *et al.*, 2001), a subset of the GRAS family of transcriptional regulators (Bolle, 2004). Whereas rice has only one DELLA protein (SLENDER RICE1 [SLR1]), the *Arabidopsis* genome encodes five DELLAs (GA-INSENSITIVE [GAI], REPRESSOR OF GA1-3 [RGA], RGA-LIKE1 [RGL1], RGL2, and RGL3), that all share the DELLA-motif in their N-terminal domain, as well as the C-terminal GRAS conserved domain (Peng *et al.*, 1997; Ikeda *et al.*, 2001; Silverstone *et al.*, 2001; Lee *et al.*, 2002; Wen and Chang, 2002). Genetic analyses have revealed both distinct but also overlapping functions for individual DELLAs in the regulation of plant development (Lee *et al.*, 2002; Cheng *et al.*, 2004; Tyler *et al.*, 2004; Achard *et al.*, 2006). Hence, RGA and GAI repress stem elongation (Dill and Sun, 2001; King *et al.*, 2001), RGL2 inhibits seed germination (Lee *et al.*, 2002) and RGA, RGL1, and RGL2 together regulate floral development (Cheng *et al.*, 2004; Tyler *et al.*, 2004, Yu *et al.*, 2004).

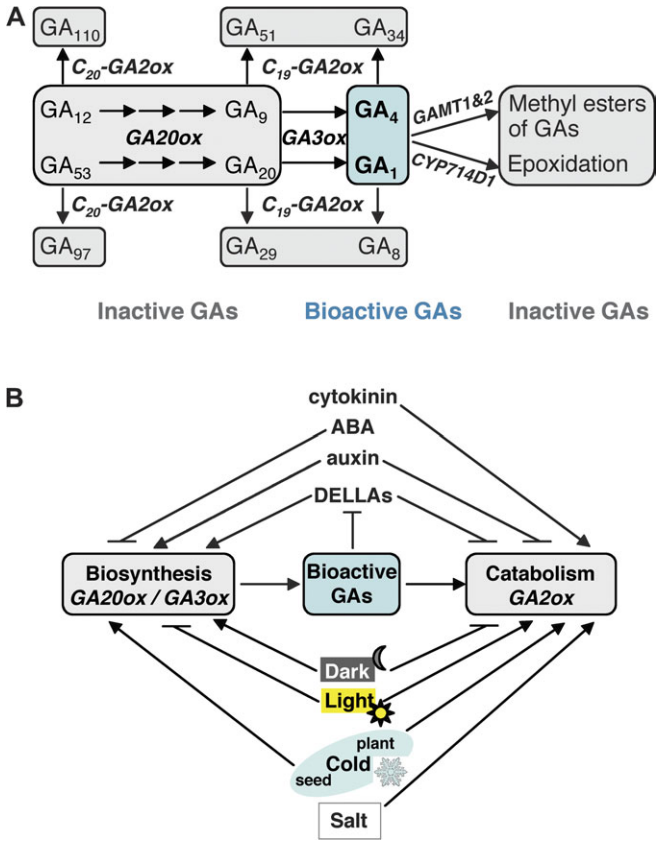

Fig. 1. Control of GA homeostasis. (A) Levels of biologically active GAs (GA_4 and GA_1) are under the control of GA biosynthetic enzymes (GA20ox [GA 20-oxidases] and GA3ox [GA 3-oxidases]) and GA deactivating enzymes (GA2ox [GA 2-oxidases], GAMT1&2 [SABATH methyltransferases] and CYP7141D [P450 mono-oxygenase]). (B) Expression levels of GA biosynthesis and catabolism genes are regulated by multiple hormonal and environmental inputs.

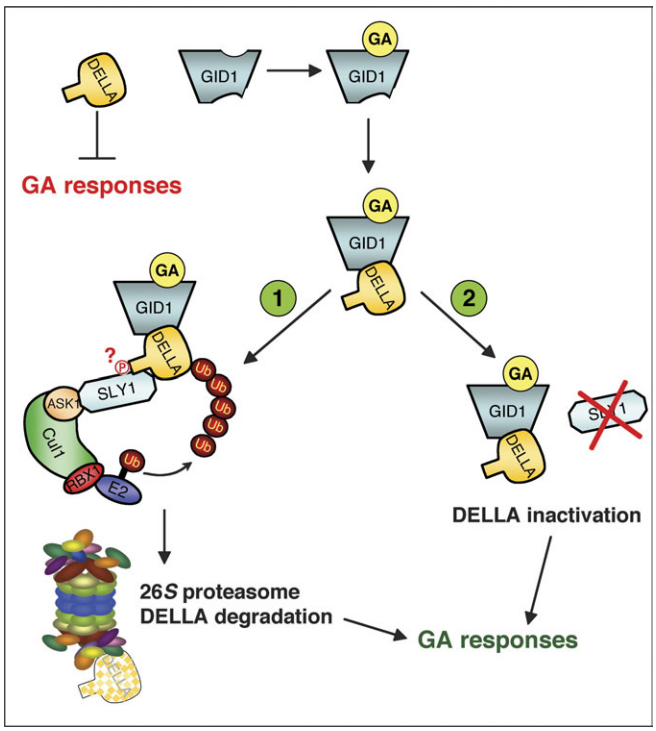

Fig. 2. Model of the GA signalling pathway. In the absence of bioactive GAs, DELLAs repress GA responses. In the presence of bioactive GAs, the receptor GID1 is bound by GA, thus promoting its interaction with a DELLA protein. The GA-GID1-DELLA trimeric complex is then targeted by an SCF E3 ligase (1), triggering the DELLA ubiquitinylation and degradation by the 26*S* proteasome. DELLAs can also be inactivated via a proteolysis-independent pathway in the absence of the F-box AtSLY1/OsGID2 (2). The degradation or eventual inactivation of DELLAs relieves DELLA-mediated repression of GA responses.

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According to the relief of restraint model (Harberd *et al.*, 1998; Dill and Sun, 2001; King *et al.*, 2001; Silverstone *et al.*, 2001; Harberd, 2003), DELLAs restrain plant growth, whereas GA promotes growth by overcoming DELLA-mediated growth restraint.

The GA-signal is perceived by a soluble GA receptor with homology to human hormone-sensitive lipase, GA-INSENSITIVE DWARF1 (GID1) (Ueguchi-Tanaka *et al.*, 2005). There is a single *GID1* gene in rice, but three orthologues in *Arabidopsis* with overlapping functions (Nakajima *et al.*, 2006). The binding of bioactive GAs to GID1 promotes an interaction between GID1 and the DELLA-domain of DELLAs (Griffiths *et al.*, 2006; Ueguchi-Tanaka *et al.*, 2007; Willige *et al.*, 2007). The DELLA motif is essential for this interaction, because its deletion in GAI and RGA results in an inability to interact with GID1, despite the presence of GA (Griffiths *et al.*, 2006; Willige *et al.*, 2007).

Subsequently, the binding of DELLA by GID1-GA enhances the affinity between DELLAs and a specific SCF E3 ubiquitin–ligase complex, $SCF^{SLY1/GID2}$, involving the F-box proteins AtSLY1 and OsGID2 in *Arabidopsis* and rice, respectively (McGinnis *et al.*, 2003; Sasaki *et al.*, 2003; Griffiths *et al.*, 2006; Willige *et al.*, 2007). In turn, $SCF^{SLY1/GID2}$ promotes the ubiquitinylation and subsequent destruction of DELLAs by the 26*S* proteasome (McGinnis *et al.*, 2003; Sasaki *et al.*, 2003; Dill *et al.*, 2004; Fu *et al.*, 2004). According to the current model (Fig. 2), DELLAs restrain plant growth, whereas GA promotes growth by targeting DELLAs for destruction. This model is, however, difficult to reconcile with the fact that Arabidopsis *sly1* mutant seeds can germinate despite a high content of RGL2 protein, the DELLA specifically repressing seed germination (Ariizumi and Steber, 2007). Thus DELLA's degradation does not always seem to be required for GA action.

Many levels of regulation to control DELLA protein accumulation and activity

DELLA gene transcription

The expression levels of several *DELLA* genes are known to differ at various developmental stages. Whereas *RGA* and *GAI* are highly expressed in most tissues, *RGL1*, *RGL2*, and *RGL3* are mainly expressed in germinating seeds, young seedlings, and flowers; indicating that these GA-negative signalling components might be transcriptionally regulated (Tyler *et al.*, 2004). Indeed, it is found that, in the dark, the light-labile transcription factor PHYTOCHROME-INTERACTING FACTOR3-LIKE5 (PIL5), promotes the transcription of *GAI* and *RGA* genes by binding directly to their promoters through a G-box element (Oh *et al.*, 2007). Upon light irradiation, activated phytochromes induce PIL5 degradation, leading to decreased levels of GAI and RGA proteins. This transcriptional repression of *GAI* and *RGA* plays an important role in promoting seed germination in response to light. In another study, it was reported that low temperature specifically enhances *RGL3* transcript levels thereby improving freezing tolerance (Achard *et al.*, 2008*a*). Hence it is likely that various environmental factors in addition to light or temperature modulate GA-responses via a direct effect on *DELLA* transcript levels.

DELLA protein abundance and activity

DELLA proteins are also regulated by changes in their protein stability. When bioactive GA levels are low, DELLAs are relatively stable. By contrast, when bioactive GA levels are high, DELLA proteins are ubiquitinylated and rapidly degraded by the 26*S* proteasome (see above). Thus, DELLA protein abundance is inversely related to the amount in bioactive GAs.

GA metabolism is tightly regulated by both developmental and environmental stimuli (for a review see Yamaguchi, 2008). Recent studies propose that GA signalling permits flexible and appropriate modulation of plant growth in response to changes in natural environments (Fig. 1B). The stress-response hormones ethylene and abscisic-acid (ABA) reduce GA contents and thus enhance DELLA accumulation (Achard *et al.*, 2006, 2007*a*; Penfield *et al.*, 2006). Such plants may actively slow their rate of growth when the environmental conditions become less favourable. Light also modulates GA content. Dark-grown hypocotyls contain relatively high levels of transcripts encoding the GA biosynthesis enzymes (*GA20ox1* and *GA3ox1*) and low levels of transcripts encoding the GA deactivating enzymes (*GA2ox1*). Conversely, when grown in continuous light, hypocotyls contain, respectively, high and low amounts of *GA2ox1* and *GA20ox1* transcripts. Thus in dark-grown hypocotyls, the relatively high level of bioactive GAs targets DELLAs for destruction and promotes hypocotyl growth. Conversely, light favours DELLA accumulation, thus promoting repression of hypocotyl growth (Achard *et al.*, 2007*b*). As a consequence, light-mediated regulation of DELLA protein abundance contributes significantly to the shade-avoidance responses (Djakovic-Petrovic *et al.*, 2007). Temperature is another factor controlling GA levels. During imbibition of *Arabidopsis* seeds, low temperature activates GA biosynthesis via the up-regulation of *GA3ox1* gene transcripts (Yamauchi *et al.*, 2004). This increase in GA levels plays an essential role in breaking seed dormancy, probably by enhancing the destruction of RGL2, the main DELLA restraining seed germination (Lee *et al.*, 2002). Surprisingly, low temperature provokes the opposite effect at a later stage of plant development. At the rosette stage, cold (via the cold-inducible transcription factor CBF1/DREB1b) enhances *GA2ox3* and *GA2ox6* transcript levels and thus decreases the amount in the bioactive GAs GA_4 and GA_1 (Achard *et al.*, 2008*a*). As a consequence, a reduction in GA content results in an increase in the accumulation of DELLAs (by increasing their stability), thus restraining plant growth. It was shown that this pathway contributes significantly to cold acclimation responses. Thus cold gives opposite effects on GA production depending on the developmental stage. Finally, salt reduces bioactive GA contents via an increase in *GA2ox7*

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transcript levels (Magome *et al.*, 2008). Under salinity stress, *Arabidopsis* plants highly express DWARF AND DELAYED-FLOWERING1 (DDF1), an AP2 transcription factor closely related to the CBF/DREB1 family, which binds to the DRE-like motifs present in the *GA2ox7* promoter. This salt-mediated reduction in bioactive GA levels results in an increase in DELLA accumulation, thereby represses plant growth and improves stress protection (Magome *et al.*, 2004, 2008; Achard *et al.*, 2006). Remarkably, because CBF1 and DDF1 belong to the same family of transcription factor and both modulate DELLA stability through the regulation of the GA deactivating enzymes, it is likely that a large number of these DREB factors interfere with the GA pathway.

Despite the fact that regulation of DELLA activity by means of their stability is a key feature for the GA pathway, recent findings in *Arabidopsis* and rice further indicate that DELLA repression can also be shutdown by a proteolysis-independent mechanism (Ariizumi *et al.*, 2008; Ueguchi-Tanaka *et al.*, 2008) (Fig. 2). In support of such a scenario, GID1 ectopic expression could rescue the *sly1/gid2* F-box mutant phenotypes without decreasing DELLA protein content. These results indicate that derepression of DELLA repressive activity can be accomplished by GA and GID1 alone and does not require F-box (SLY1/GID2) function. The exact contribution of this pathway in wild-type plants, however, still remains to be elucidated.

Post-translational modifications

DELLA proteins are modified by at least two types of post-translational modifications: phosphorylation and *O*-Glc-Nac modification. Phosphorylated forms of DELLAs have been identified in both *Arabidopsis* and rice (Sasaki *et al.*, 2003; Fu *et al.*, 2004; Gomi *et al.*, 2004; Hussain *et al.*, 2005, 2007; Itoh *et al.*, 2005). The role of phosphorylation in the control of DELLA protein accumulation and activity is still unclear. Consistent with the dogma for SCF E3 ligases, it appears that phosphorylated DELLAs display a higher binding affinity to their respective F-box proteins (Sasaki *et al.*, 2003; Gomi *et al.*, 2004; Fu *et al.*, 2004). Conversely, phosphorylation of SLR1, the DELLA in rice, is independent of its degradation in response to GA (Itoh *et al.*, 2005). Moreover, by mutating putative Ser/Thr residues, which could serve as phosphorylation sites, it was proposed that the phosphorylation of *Arabidopsis* RGL2 stabilizes, rather than destabilizes, this DELLA protein in BY2 cell cultures (Hussain *et al.*, 2005).

DELLA proteins are also suspected of being modified by SPINDLY (SPY), an *O*-linked *N*-acetylglucosamine (GlcNac) transferase (OGT) (Olszewski *et al.*, 2002; Silverstone *et al.*, 2007). In animal cells, OGTs usually modify target proteins by glycosylation of Ser/Thr residues, which either interfere or compete with kinases for phosphorylation sites (Wells *et al.*, 2001). In Arabidopsis, SPY acts as a negative regulator of GA signalling as its mutation suppresses GA deficiency as well as the gain of function *gai-1* and *rgaΔ17* mutations (Jacobsen and Olszewski, 1993; Jacobsen *et al.*, 1996; Peng *et al.*, 1997; Silverstone *et al.*, 2007). Although it has not been biochemically demonstrated, *O*-Glc-Nac modification might increase DELLA activity.

Finally, how and where do DELLAs function?

One of the most interesting questions, still poorly understood, is the molecular mechanism of DELLA protein action. DELLAs are nuclear-localized proteins, which have been proposed to act as transcriptional regulators, though they do not carry a proven DNA binding domain. Microarray studies have recently revealed several DELLA-dependent GA-regulated genes (Cao *et al.*, 2006; Zentella *et al.*, 2007; Achard *et al.*, 2008*b*; Hou *et al.*, 2008). At least in *Arabidopsis*, based on chromatin immunoprecipitation (ChIP) studies, evidence for the association of one DELLA, RGA, with target gene promoters has been provided (Zentella *et al.*, 2007). However it is unclear whether DELLAs associate with target DNA sequences directly or via other, still unknown, DNA binding proteins (Fig. 3).

A major breakthrough was recently achieved regarding DELLA action on the light control of hypocotyl elongation (de Lucas *et al.*, 2008; Feng *et al.*, 2008). It was previously known that light inhibits hypocotyl cell elongation in a DELLA-dependent manner, whereas GAs have an opposite effect (Alabadi *et al.*, 2004; Achard *et al.*, 2007). This process is largely dependent on the PHYTOCHROME INTERACTING FACTORS (PIFs), subfamily members of related basic helix–loop–helix (bHLH) transcription factors. PIFs (such as PIF3 and PIF4) are known to activate the expression of genes with a role in cell elongation by directly binding to G-box elements present in the promoter of these genes. The work of de Lucas *et al.* (2008) and Feng *et al.* (2008) elegantly demonstrated that, in the absence of GAs, DELLAs interact with the bHLH DNA-recognition domain of PIFs and, as a consequence, sequester them into inactive complexes unable to bind DNA (Fig. 3). In addition, PIFs are also inactivated by degradation mediated by the light-activated Pfr form of phyB (Al-Sady *et al.*, 2006). By contrast, in etiolated seedlings exhibiting higher levels of endogenous GAs, DELLAs are degraded via $SCF^{SLY1/GID2}$ (see above) and therefore PIFs are released and can mediate their control of hypocotyl elongation. Such a model is reminiscent of auxin signalling, where auxin promotes the degradation of AUX/IAA repressors via SCF^{TIR1}, releasing the activity of AUXIN RESPONSE FACTORS (ARFs), the transcription factors mediating auxin signalling (reviewed in Parry and Estelle, 2006). It will be interesting to investigate whether DELLAs sequester only a subclass of PIFs or whether this mechanism applies to all members of the PIF family or even to other bHLH transcription factors, which may explain the broad function of DELLAs in many different developmental processes.

Recent work has indicated an important function of DELLAs under both abiotic and biotic environmental stress conditions (Achard *et al.*, 2006, 2008*a*, *b*; Navarro

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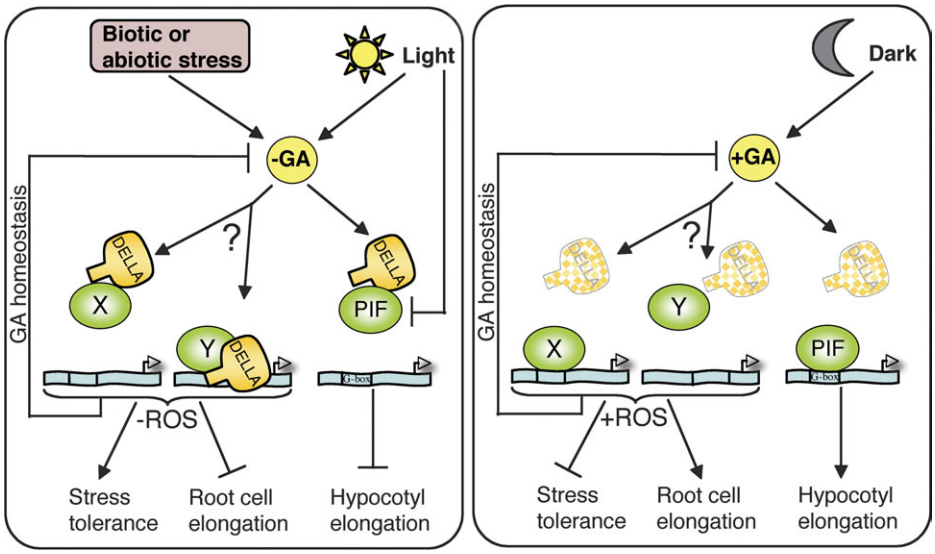

Fig. 3. Model of DELLAs action in GA homeostasis, light signalling, and stress responses. Extreme growth conditions or light exposition reduce bioactive GA levels and thus enhance DELLA accumulation. Increased DELLA accumulation represses PIF transcriptional activity by sequestering them into inactive forms, thereby inhibiting hypocotyl elongation. Light also directly targets PIFs degradation by the 26S proteasome pathway. Moreover, by interacting with putative unknown factors (X or Y), DELLAs repress ROS accumulation (through the increase of gene transcripts encoding ROS scavenging enzymes), and hence enhance stress tolerance and restrain root cell elongation. Finally, enhanced DELLA accumulation feedback controls the level of GA metabolism enzymes to ensure GA homeostasis. Inversely, when bioactive GA levels are high (e.g. in the dark), the degradation of DELLAs releases a DELLA-mediated GA-response restraint.

et al., 2008). Thus, it was found that salt stress, inducing DELLA protein stabilization, restricts plant growth which, in turn, is beneficial for plant survival (Achard *et al.*, 2006). Moreover, DELLA protein accumulation after cold treatment also confers higher freezing tolerance to *Arabidopsis* plants (Achard *et al.*, 2008*a*). Interestingly, a possible molecular mechanism explaining how DELLAs could promote plant survival under adverse conditions has been highlighted (Achard *et al.*, 2008*b*; Fig. 3). Microarray analysis revealed that DELLAs restrain stress-induced reactive oxygen species (ROS) accumulation by acting on the ROS scavenging system. Hence, stress-induced DELLA accumulation elevates the expression of ROS detoxification enzymes such as the Cu/Zn-superoxide dismutases (CSDs) and catalases, thus reducing ROS accumulation. As a consequence, ROS-inducing cell death is delayed, thereby promoting stress tolerance. Moreover, the modulation of ROS levels by DELLAs protects plants from pathogen-induced cell death (Achard *et al.*, 2008*b*), although it is thought that DELLAs also modulate other plant hormones during plant immune responses (Navarro *et al.*, 2008).

Interestingly, ROS are also known to play important roles in plant biology as second messengers, and in particular, like GAs, ROS control root cell expansion (reviewed in Gapper and Dolan, 2006). Hence, in a recent work, Achard *et al.* (2008*b*) showed that DELLAs regulate root hair growth, at least in part via a ROS-dependent mechanism. However, the precise way by which GA-mediated regulation of ROS levels acts as a biological signal in plants remains unclear.

Finally, it remains unclear whether the GA/DELLA pathway promotes growth at the cellular, tissue or organ levels. Indeed, despite all our knowledge on the key role of DELLAs in controlling plant growth and development, the site of action of these growth regulators still remains unknown. In a recent work, Ubeda-Tomas *et al.* (2008) addressed this gap by investigating the mechanism of GA action in *Arabidopsis* root. To identify the tissue in which GA-dependent degradation of DELLA is required to promote growth, expression of *gai* [a non-degradable mutant form of GAI (Peng *et al.*, 1997)] was targeted to specific root tissues using tissue-specific promoters. Whereas expression of *gai* in either epidermal, cortical or stele tissues had no effect on root growth, expression of *gai* solely in the endodermis significantly reduced root growth (Ubeda-Tomas *et al.*, 2008). Thus the endodermis represents the primary GA-response tissue regulating root growth. A fascinating challenge will be to investigate whether this mechanism of GA-action is specific to the root or is general to the entire plant.

Still many questions with no answers

Although considerable progresses has been made in elucidating the molecular basis of GA signalling, we are still far from having the complete picture of how GAs modulate plant growth under normal and stress conditions. Many questions still remain to be resolved. Is GID1 the only class

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of GA receptors in plants? How important is the proteolysis-independent mechanism of DELLA inactivation in GA signalling? What are the exact contributions of phosphorylation and *O*-Glc-Nac modifications on DELLAs and how do they affect protein stability and/or activity? Are there functional relationships between both modifications? In addition to PIF3 and PIF4, how many other bHLH transcription factors do DELLAs negatively regulate? And how general is this mechanism in plants? What is the contribution of ROS signalling in the GA-mediated regulation of plant growth?

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique and the Agence Nationale de la Recherche Grant 07-JCJC-0118.

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