Gibberellin Receptor and Its Role in Gibberellin Signaling in Plants

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Abstract

Gibberellins (GAs) are a large family of tetracyclic, diterpenoid plant hormones that induce a wide range of plant growth responses. It has been postulated that plants have two types of GA receptors, including soluble and membrane-bound forms. Recently, it was determined that the rice *GIBBERELLIN INSENSITIVE DWARF1* (*GID1*) gene encodes an unknown protein with similarity to the hormone-sensitive lipases that has high affinity only for biologically active GAs. Moreover, GID1 binds to SLR1, a repressor of GA signaling, in a GA-dependent manner in yeast cells. Based on these observations, it has been concluded that GID1 is a soluble receptor mediating GA signaling in rice. More recently, *Arabidopsis thaliana* was found to have three GID1 homologs, AtGID1a, b, and c, all of which bind GA and interact with the five *Arabidopsis* DELLA proteins.

Contents

INTRODUCTION

Gibberellin (GA) is a well-known phytohormone that affects a wide range of plant growth, development, and environmental responses, including seed germination, stem elongation, leaf expansion, pollen maturation, and induction of flowering (reviewed in 7). Recently, the GA receptor GIBBERELLIN INSENSITIVE DWARF1 (GID1) was identified by a combination of biochemical and genetic techniques (42, 69). Because of the identification of the GA receptor, the molecular mechanisms of GA perception and signal transduction are much better understood. In this article, we review the history of attempts to identify receptor candidates for GA, the biochemical and physiological characteristics of the GID1 GA receptor, and its roles in GA signaling.

BIOCHEMICAL SEARCH FOR THE GIBBERELLIN RECEPTOR

Because GAs are relatively hydrophobic molecules, they are believed to be able to transverse plant cell plasma membranes by passive diffusion. In the early stages of the study of GA perception, some researchers expected that GA perception occurs by a mechanism similar to hydrophobic steroid hormones in mammalian cells. In accordance with this concept, Johri & Varner (27) showed that the composition of RNA in isolated nuclei from pea seedlings changed before and after the application of GA. Much later, Sechley & Srivastava (56) reported a similar effect of GA on nuclear transcription rates in cucumber hypocotyls. Further, Witham & Hendry (75) pointed to the possibility of direct interactions between double-stranded DNA and GA based on computer modeling.

In contrast to the idea that GA molecules directly affect gene transcription, there were many attempts to identify proteins with GA-binding activity [GA-binding protein (GBP)]. Stoddart et al. (61) first reported detection of GA-binding activity in crude protein extracts from lettuce hypocotyls. Since this first observation of GBP, a number of GBPs have been proposed as GA receptor candidates (**Table 1**). Once a GBP has been detected and reported, the candidate protein is tested to see if it meets the four criteria of a GA receptor. GA receptors must reversibly bind GA, have GA saturability and high affinity for biologically active GAs, and must have reasonable ligand specificity for biologically active GAs.

Thus far, two GA-responsive systems have been used to detect GBPs: promotion of stem elongation and induction of hydrolytic enzymes in aleurone layers of cereal seed. The stem elongation assay has been used to identify GA-binding activity in the soluble protein fractions of pea epicotyls and cucumber

Table 1 Gibberellin-binding proteins in various plant materials

Materials	Site	MW (kDa)	Amount (pmol/mg)	Method	Ref.
Lettuce hypocotyl	CW	n.d.	n.d.	SDG	(61)
Wheat aleurone	n.d.	n.d.	0.45	UC	(26)
Pea epicotyl	CY	60/500	n.d.	GPC/EQD	(62)
Pea epicotyl	CY	40–70/600	0.9	GPC	(32)
Cucumber hypocotyl	CY	n.d.	0.4	GPC/EQD	(30)
Cucumber hypocotyl	CY	n.d.	0.4	DEAE filter	(29)
Cucumber hypocotyl	CY	n.d.	0.4	DEAE filter	(76)
Maize leaf sheath	CY	40–90/500	n.d.	GPC	(31)
Cucumber hypocotyl	CY	n.d.	0.25	DEAE filter	(77)
Bean epicotyl	N/CH	80–100	330	PEI filter	(66)
Mung bean hypocotyl	CY	150–200	65	Salting-out	(41)
Oat aleurone	MC	60[a]	n.d.	Photoaffinity	(20)
Maize mesocotyl	CY	n.d.	0.62	Salting-out	(53)
Oat aleurone	CY	50[a]	n.d.	Photoaffinity	(72)
Pea epicotyl	CY	n.d.	0.66	DEAE filter	(38)
Pea epicotyl	CY	40–110	0.21	DEAE filter	(37)
Rice leaf	CY	47[a]	n.d.	LB	(34)
Adzuki bean epicotyl	CY	25–40	0.0001	GPC	(43)
Oat aleurone	MC	18/68[a]	n.d.	Photoaffinity	(39)

[a]Estimation under denatured condition (SDS-PAGE).

CH, chloroplast; CW, cell wall; CY, cytosol or soluble fraction; DEAE, diethylaminoethyl; EQD, equilibrium dialysis; GPC, gel-permeation column; LB, ligand blotting; MC, microsome or membrane-bound fraction; n.d., no data or not described clearly; N, nuclear; PEI, polyetyleneimine; SDG, sucrose density-gradient centrifugation; UC, ultracentrifugation.

hypocotyls (29, 30, 32, 76), although none of these GBPs has been further characterized (31, 37, 38, 77). Komatsu et al. (34) identified a soluble GBP from rice leaves by detecting a GA-binding activity for membrane-blotted proteins. The GBP was homologous to RuBisCO activase (ribulose-1,5-biphosphate carboxylase/oxygenase activase) and was phosphorylated in the presence of Ca^{2+}, Mg^{2+}, ATP, and GA. They suggested that a Ca^{2+}-dependent protein kinase (CDPK) might be involved in the signaling pathway from this GBP (57). Nakajima et al. (43) also detected GA-binding activity in the soluble protein fraction from adzuki bean (*Vigna angularis*) seedlings by using a gel-permeation column. Further studies have revealed that this GBP in the partially purified fraction fulfills all four of the GA receptor criteria (47, 48).

Using the GA-dependent induction of aleurone hydrolytic enzymes, Jelsema et al. (26) first reported GBP activity in wheat seed aleurone homogenates. Later, the researchers in the United Kingdom demonstrated that α-amylase can be induced in aleurone protoplasts in a GA-dependent manner. Moreover, such induction occurs even with the application of GA derivatives that cannot pass through the plasma membrane (2, 18). Gilroy & Jones (14) also reported that there was no induction of α-amylase when GA was injected into the cytoplasm of barley aleurone protoplasts. These biochemical experiments strongly suggested that the GA-perception site is outside the plasma membrane and, consequently, that at least one GA receptor is in the plasma membrane of aleurone cells. Based on these observations, Hooley and his colleagues attempted to identify a

GA receptor located on the plasma membrane of oat aleurone cells using a photoaffinity-labeled GA, and succeeded in detecting two GBPs: a 60-kDa protein localized in the microsomal fraction (20), and a 50-kDa protein in the cytosolic fraction (19, 72). Two other GBPs of 68/18 kDa were also detected in the plasma membrane fraction from oat aleurone by the same photoaffinity-labeling method (39). Even though partial amino acid sequences for the 18-kDa GBP have been identified, there is no further information about these GBPs.

There is an alternative biochemical approach for isolating receptor candidates using an immunological method. Hooley et al. (17, 19) prepared antisera raised against a monoclonal antibody for GA (i.e., anti-idiotypic antibodies) that competes with GA molecules for binding to the parental monoclonal antibody. The anti-idiotypic antibodies inhibit GA action in aleurone protoplasts, suggesting that the anti-idiotypic antibodies bind to the GA-interacting domains of GA receptor(s). An oat cDNA library was screened using these antibodies and a ubiquitin gene was isolated as a candidate, though there was no report of its GA-binding activity (52).

DELLA PROTEIN IS A KEY REGULATOR IN GIBBERELLIN SIGNALING

Derepression of the repressed state is currently considered to be the key step of GA action in the GA signaling pathway. In this model, DELLA subfamily proteins of the GRAS superfamily play an important role in the negative control of GA signaling. Members of the GRAS family, which was originally defined by the presence of the conserved domains VHIID and RVER of GAI, RGA, and SCR in *Arabidopsis thaliana* (51), are thought to function as transcription factors, although there is as yet no direct evidence. Members of the DELLA subfamily contain the conserved amino acid motifs DELLA (hence its name) and TVHYNP near their N-terminal portion.

DELLA proteins are highly conserved in *Arabidopsis* (GAI, RGA, RGL1, RGL2, RGL3) (9, 35, 49, 59, 73), and in several crop plants, including rice (SLR1) (22), wheat (Rht) (50), barley (SLN1) (5), maize (d8) (50), and grape (VvGAI) (3). The wheat DELLA gene *Rht* is well known for its contribution to increases in crop yield in the "green revolution" wheat breeding program of the middle of the twentieth century. Gain-of-function mutations in this gene family result in dwarfism and reduced GA response, whereas loss of function results in the GA-constitutive response phenotype, even in the presence of GA-biosynthesis inhibitors. For example, loss-of-function mutants of rice *SLR1* show a slender phenotype with an elongated stem and leaf, and reduced root number and length (22, 24). Also, GA-inducible α-amylase is produced in embryo half-seeds in the absence of GA application. These *slr1* phenotypes are typical of plants treated with exogenous GA, even though levels of endogenous GA are lower than in wild-type plants. Moreover, the GA-overdose phenotype of *slr1* is not affected by the GA-biosynthesis inhibitor uniconazol (22). Barley *sln1* loss-of-function mutants also have a similar GA-constitutive response phenotype (5), indicating that DELLA proteins function as negative regulators in GA signaling.

In contrast to the clear GA-overdose phenotype in the loss-of-function mutants of rice and barley, loss of DELLA protein functions in *Arabidopsis* does not induce an obvious GA-overdose phenotype. Among the five DELLA proteins, RGA plays the most prominent role in stem elongation, leaf expansion, and induction of flowering. Its loss-of-function alleles partially suppress most of the phenotype of the GA-deficient mutant *ga1-3*, except for seed germination and floral development (60). The loss-of-function *gai* allele, *gai-t6*, has wild-type features, but has slightly increased resistance to a GA-biosynthesis inhibitor, paclobutrazol, in vegetative growth (49). The ambiguous phenotypes of loss-of-function *Arabidopsis*

mutants are due to the functional redundancy of five DELLA proteins. For example, *RGA* and *GAI* encode proteins sharing 82% amino acid identity (59, 60). A double knockout of *RGA* and *GAI* produces a clearer phenotype of the GA-constitutive phenotype, including increased stem elongation and early flowering in the wild-type background, and also suppresses the severely dwarfed phenotype (9, 33) and stunted root growth (11) in the GA-deficient mutant *ga1-3*. The absence of *RGA* and *GAI* was not sufficient to rescue the *ga1-3* mutant from abnormal germination or flower development, suggesting that other DELLA proteins, besides RGA and GAI, have decisive functions in GA-dependent germination and flower development (9, 33). RGL1 and RGL2 have been reported to be involved in seed germination (35, 68, 73). More recently, by preparing triple and quadruple knockout mutants in the *ga1-3* background, Cao et al. (4) reported that RGL2 is the predominant repressor of seed germination, and that GAI, RGA, and RGL1 are functional enhancers of RGL2 and tuners for environmental conditions. RGA and RGL2 also have been reported to act dominantly in floral development, and RGL1 can function as a minor repressor (68, 81).

In contrast to the GA-constitutive phenotype of loss-of-function mutations in DELLA proteins, dominant alleles in the *Arabidopsis gai* (49), wheat *Rht* (50), and maize *D8* loci (50) confer a GA-insensitive phenotype with characteristic dwarfism. These dominant alleles have in-frame deletions in their conserved N-terminal domains, such as DELLA and TVHYNP, resulting in constitutive DELLA protein function. Similarly, transgenic rice plants that produce a SLR1 protein truncated in the DELLA or TVHYNP domain have a dominant dwarf phenotype similar to the spontaneous mutants (24). All of these mutants and transgenic plants show GA-insensitive characters, suggesting that the N-terminal region that includes the DELLA and TVHYNP domains functions in the perception of an upstream GA signal. Further

domain analysis of the rice DELLA protein SLR1 has shown that the C-terminal region containing the VHIID, PFYRE, and SAW domains, which are shared with other GRAS family proteins, is involved in the suppressive function of DELLA proteins against GA action. The proteins also contain leucine-heptad repeats (LHR), which may mediate protein-protein interaction, and Ser/Thr residues, which may be involved in the regulation of their repression activity. It has been proposed that the activity or stability of DELLA proteins is regulated by *O*-GlcNAc modification or phosphorylation via the action of SPINDLY (SPY), which is another negative regulator of GA signaling, or kinase with the Ser/Thr residues as the target site (67).

F-BOX-DEPENDENT DEGRADATION OF DELLA PROTEINS IS A KEY EVENT IN GIBBERELLIN SIGNALING

All available evidence indicates that DELLA proteins are subject to GA-dependent proteolysis via the ubiquitin-proteasome pathway. The model of DELLA protein degradation by 26S-proteasome-mediated proteolysis was first suggested by the observation that the level of a barley DELLA protein, SLN1, increases in the presence of 26S proteasome inhibitors (12). This model was later greatly substantiated by the cloning of F-box genes from rice (*OsGID2*) and *Arabidopsis* (*AtSLY1*) (40, 55). Loss-of-function mutation of *OsGID2* or *AtSLY1* results in GA-insensitive phenotypes of the host plant. Positional cloning of these mutated genes revealed that *OsGID2* and *AtSLY1* are orthologous and encode F-box domain-containing proteins. An F-box protein is a component of the SCF complex, which is named for its Skp1, cullin, and F-box protein subunits. The SCF complex catalyses the transfer of ubiqutin from E2 to the target protein (13). Rbx1 is another component of the SCF complex and binds to the C terminus of cullin

and to the E2 ubiquitin conjugating enzyme. Adding a polyubiquitin chain to the target protein induces degradation of the target protein by the 26S proteasome, which is a large protein degradation complex. F-box proteins contain an F-box domain, which is usually located at their N terminus and involved in interaction with Skp1, and also generally contain interaction domains with target proteins at the C terminus, such as WD40 repeats and leucine-rich repeats. OsGID2 and AtSLY1 contain F-box domains at the N termini, as do other F-box proteins, but they lack known protein-protein interaction domains at their C termini. However, OsGID2 and AtSLY1 share conserved amino acid sequences not only at their N termini but also within their C-terminal regions, and deletions of the conserved C-terminal regions cause a loss of function (40, 55). Yeast two-hybrid assays and in vivo immunoprecipitation experiments demonstrate that OsGID2 is a component of the SCF complex through interaction with one of the rice Skp1-like proteins, OsSkp15 (15). *Arabidopsis* has an *AtSLY1* homologous gene, *SNE*, which can functionally replace *AtSLY1* in the knock-down plants of the *SLY1* function by its antisense construct, suggesting that *SNE* has at least partial overlapping function with *SLY1* (63).

Several lines of evidence support the notion that the target of SCF^{GID2} and SCF^{SLY1} are the DELLA proteins, SLR1 and RGA, respectively. First, high levels of SLR1 and RGA protein accumulation are observed in *gid2* and *sly1* mutant plants. Second, double mutants carrying rice *gid2-1/slr1-1* and *Arabidopsis sly1-10/rga-24* show the *slr1* and *rga* phenotypes (10, 55). This suggests that the GA-insensitive phenotype of *gid2* or *sly1* depends on the function of SLR1 or RGA. Finally, SLY1 interacts directly with RGA and GAI via their C-terminal GRAS domains in yeast two-hybrid and in vitro pull-down assays (10). The direct interaction between DELLA proteins and SLY1 was confirmed by the observation that the product of the gain-of-function allele of *SLY1*, *gar2/sly1-d*, has higher

affinity for RGA and GAI than does the wild-type SLY1 protein. In contrast, OsGID2 does not interact directly with SLR1 in yeast cells (H.Tsuji, unpublished results). Recombinant GID2 protein produced in *Escherichia coli* interacts with SLR1 in rice crude extracts in vitro (23), indicating that additional components are required for GID2-SLR1 interaction in rice cells.

Biochemical studies in yeast and mammals have shown that the interaction of F-box proteins with protein substrates depends on modifications such as phosphorylation (8), glycosylation (80), and hydroxylation (25). There are some supportive observations that the GA-induced degradation of DELLA proteins depends on their phosphorylation. For instance, treatment with protein Tyr kinase inhibitors, such as genistein and Tyrophostin B46, blocked the GA-induced degradation of SLN1 in barley seedlings (12). Furthermore, the level of phosphorylated SLR1 increases in response to GA signaling in rice seedlings, and phosphorylated SLR1 binds to recombinant glutathione S-transferase (GST)-GID2 (15, 55). On the other hand, more recent observations suggest that phosphorylation of DELLA proteins is not directly involved in GA-induced degradation (23). For example, exogenously applied GA induces both phosphorylated and nonphosphorylated forms of SLR1 with similar induction kinetics in *gid2* cells. Both phosphorylated and nonphosphorylated SLR1 proteins are degraded by GA treatment with a similar half-life in rice wild-type cells, and both proteins interact with recombinant GST-GID2. Furthermore, Ser/Thr phosphatase inhibitors effectively block RGL2 degradation in tobacco BY2 cells, but Ser/Thr kinase inhibitors have no visible effect, suggesting that the default state of RGL2 is in a phosphorylated form in BY2 cells (21). Transgenic rice plants containing RNAi or an antisense construct for rice *SPY*, which is another negative regulator of GA signaling, alter the phosphorylation state of SLR1 without changing the SLR1 level (58). This also indicates that the amount of SLR1 is not

controlled by its phospholylation state. To make sense of all of these apparently contradicting observations, it could be that the phosphorylation of DELLA proteins does not directly lead to their degradation and could be independent of their interaction with F-box proteins.

GID1 IS A SOLUBLE GIBBERELLIN RECEPTOR AND DIRECTLY INTERACTS WITH THE RICE DELLA PROTEIN, SLR1, IN A GIBBERELLIN-DEPENDENT MANNER

The rice *gid1* recessive mutant shows a typical GA-insensitive phenotype (69). A *gid1-1/slr1-1* double mutant exhibits the slr1 phenotype, indicating that SLR1 is epistatic to GID1. GA treatment does not diminish the amount of SLR1 in *gid1-1* plants like the *gid2* mutant. Although the GA-insensitive phenotype of *gid1* is similar to *gid2* mutants, there are some differences, namely that *gid1* dwarfism is more severe than that of *gid2*, and that the amount of accumulated SLR1 in *gid1* is lower than in *gid2*. The *gid1* phenotype is thus similar to the GA-deficient mutant *cps*, indicating that *GID1* functions upstream from *SLR1* in the GA signaling pathway, but not in SLR1 degradation.

GID1 protein fused with a GST tag (GST-GID1) binds to 16,17-dihydro-GA$_4$ with a reasonable dissociation constant (K_d) of 1.4×10^{-6} M. The ligand specificity of GST-GID1 for various GAs in vitro is generally consistent with the physiological activity of GAs. That is, biologically active GAs generally have higher binding affinity whereas biologically inactive GAs have lower affinity. However, GA$_4$-binding affinity to GID1 is about 20 times higher than GA$_3$, but the physiological activity of GA$_4$ is lower than that of GA$_3$. This discrepancy between the GA-GID1-binding affinity in vitro and physiological activity in planta has been attributed to differences in the stability of GA$_4$ and GA$_3$ in planta. In this case, GA$_4$ is rapidly inactivated by a GA-inactivating enzyme, GA 2-oxidase (54). This hypothesis is confirmed by the observation that SLR1 degradation starts at a much lower concentration of GA$_4$ than GA$_3$ in rice culture cells that contain no bioactive GA or GA 2-oxidase activity (M. Ueguchi-Tanaka, unpublished results). The GA-perception activity of GID1 in vivo is also confirmed by the GA-hypersensitive phenotype of transgenic rice plants that overproduce GID1.

GID1 encodes an unknown protein with similarity to the hormone-sensitive lipase (HSL) family, including the conserved HSL motifs HGG and GXSXG (45). The importance of this GXSXG motif is confirmed by the severe phenotype of *gid1-1* carrying a single amino acid exchange of the first G for D in the motif. Furthermore, GA binding is completely abolished by the deletion of its shared regions with the HSL family, indicating that the entire conserved region between GID1 and HSL is essential for GA binding (M. Ueguchi-Tanaka, unpublished results). However, GID1 may not have a lipase activity, because GID1 shares only two of the three conserved amino acid residues essential for HSL activity. The third residue, H, is replaced by V, which is essential for forming the catalytic triad in the HSL family. Furthermore, recombinant GID1 does not hydrolyze an artificial substrate for HSL, *p*-nitrophenyl acetate. The cellular localization of GID1 is predicted to be mainly in nuclei and its localization does not change with the endogenous GA level (69).

GID1 interacts with SLR1 in a GA-dependent manner in yeast two-hybrid assays (69). This indicates that the GA-GID1 complex interacts directly with SLR1 and probably transduces the GA signal to SLR1. The GA-binding activity of GID1 is increased about threefold in the presence of SLR1 (M. Ueguchi-Tanaka, unpublished results). This enhanced GA binding is caused by the decreased dissociation rate between GID1 and GA although its association rate is not affected
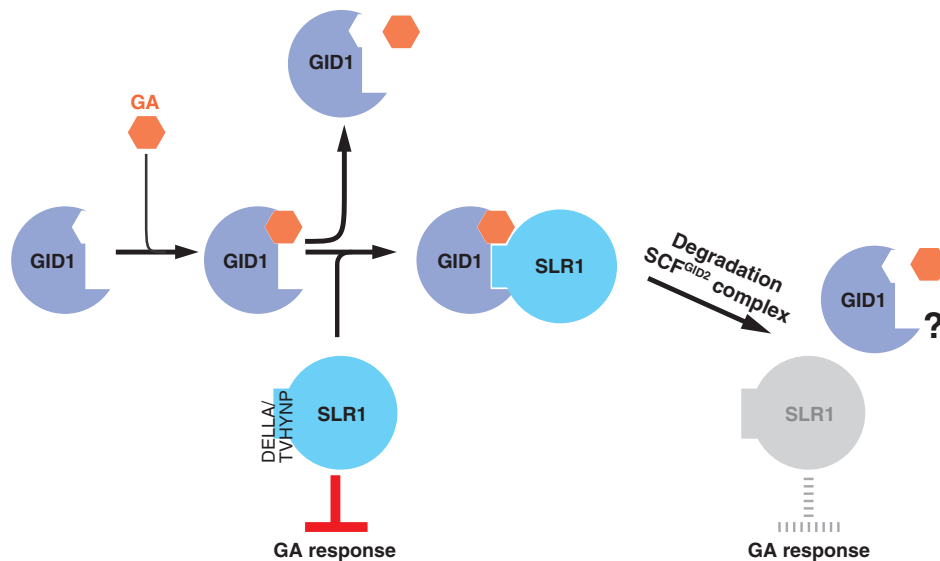
Figure 1

Model of gibberellin signaling in rice. Under low GA concentrations, SLR1 represses the GA responses. Under high GA concentrations, a soluble receptor, GID1, binds to GA; however, the binding is unstable and easily dissociates from the other. The GID1-GA complex specifically interacts with SLR1 at the site of DELLA and TVHYNP domains. The triple complex composed of GID1-GA-SLR1 is stable and does not easily dissociate. The triple complex is in turn targeted by the SCF^{GID2} complex and the SLR1 protein is degraded by the 26S proteosome, which releases the repressive state of GA responses.

by SLR1 (M. Ueguchi-Tanaka, unpublished results). Thus, SLR1 stabilizes the interaction between GID1 and GA. Domain analysis of SLR1 using a yeast two-hybrid assay revealed that the DELLA and TVHYNP domains are essential for its GA-dependent interaction with GID1 (M. Ueguchi-Tanaka, unpublished results). Deleting the Leu-heptad domain, or the conserved regions of the GRAS family such as the VHIID, PFYRE, and SAW domains, does not result in a complete loss of GID1 interaction. These observations indicate that the N-terminal portion of SLR1 is essential and sufficient for the GA-dependent interaction between GID1 and SLR1. This hypothesis has also been confirmed in vitro. Based on these observations, Ueguchi-Tanaka et al. proposed a model of GA perception mediated by GID1 (**Figure 1**). When GID1 binds GA, the GA-GID1 complex can interact with SLR1 probably by some conformational change. The region containing the

DELLA/TVHYNP domains of SLR1 and the conserved HSL regions of GID1 are essential for the interaction between GID1 and SLR1. The association and dissociation of GID1 and the GA molecule occur rapidly in the absence of SLR1, but when the GID1-GA complex interacts with SLR1, the GID1-GA complex is greatly stabilized. The stabilized trio-complex consisting of GA, GID1, and SLR1 might be a target of GID2, leading to the degradation of SLR1 by 26S proteasomes through ubiquitination of the SCF^{GID2} complex.

GIBBERELLIN PERCEPTION AND THE GID1-DELLA INTERACTION IN *ARABIDOPSIS*

Three genes, *AtGID1a* (*At3g05120*), *AtGID1b* (*At3g63010*), and *AtGID1c* (*At5g27320*), have been predicted to be GA receptors in *Arabidopsis* based on their

structural similarity to the rice GA receptor (42). Like rice GID1, the *AtGID1* protein products have a high affinity only for biologically active GAs, especially for GA_4. Among these four GA receptors, only AtGID1b has a strong pH dependency and about a four-times-higher affinity for GA (K_d for 16,17-dihydro-GA_4 $= 4.8 \times 10^{-7}$ M), setting it apart biochemically from the other receptors. Phylogenic analysis also supports the uniqueness of AtGID1b, and AtGID1a and AtGID1c are classified within the same group as rice GID1, whereas AtGID1b is located in an independent subgroup.

As *Arabidopsis* has three *GID1*s and five DELLA proteins (RGA, GAI, and RGL1, 2, and 3), 15 GID1/DELLA combinations are possible. A yeast two-hybrid analysis confirmed that the GA-dependent interaction between AtGID1s and AtDELLAs occurs in all 15 combinations with different affinities in each combination. This suggests that there are combinatorial biases for AtGID1-DELLA in the complicated GA-signal transduction of *Arabidopsis*, but unambiguous biological differences for each combination have not been observed. However, it is possible that preferential interactions between a specific AtGID1 and AtDELLA occur in each GA-dependent biological event, because all five DELLA proteins are differentially involved in GA-dependent events, as mentioned previously. Precise analysis on the AtGID1/AtDELLA interaction in planta should be examined for each GA-dependent event, because of the possibility of modifying the interaction between AtGID1s and AtDELLAs, including the DELLA protein modification (21, 64), the presence of SLY1, or combining DELLA proteins under completive conditions. The affinity of the AtGID1c-GA interaction was increased about 100-fold by RGA or GAI, suggesting that the GID1-GA complex is stabilized by DELLA proteins (42). The expression of each *AtGID1* in rice *gid1* mutants rescued its GA-insensitive dwarf phenotype, demonstrating that AtGID1s function as GA receptors in rice, and suggesting that a common GA signaling pathway operates in both rice and *Arabidopsis* (42).

IS GID1 THE SOLE GIBBERELLIN RECEPTOR IN PLANTS?

As previously described, several experiments using the induction of α-amylase expression in cereal aleurone cells indicate that binding of GA to a plasma membrane–localized receptor is required for GA signaling. On the other hand, the GA-dependent α-amylase induction hardly occurs in *gid1* aleurone cells (69). In terms of GA perception, cereal aleurone cells are unusual, because these cells cannot produce bioactive GA themselves but can only perceive transported GAs produced in the embryo, while almost all rice cells except aleurone cells also can synthesize bioactive GAs (28). Under such situations, it is possible that cereal aleurone cells may have gained an additional, unique GA-perception system besides the constitutive GID1-DELLA-mediated GA-perception system. Another supporting bit of evidence for the presence of a plasma membrane–localized receptor is the involvement of trimeric G proteins in GA signaling (1, 70). In animal cells, trimeric G proteins function as mediators from hormone receptors, which carry a membrane-spanning structure and are localized within the plasma membrane, to the cytosolic signaling pathway. By analogy, involvement of trimeric G protein in GA signaling would suggest that GA is perceived by a membrane-localized receptor. It is now known that the trimeric G proteins are involved not only in GA signaling but also in various kinds of signal pathways, such as ABA (46), auxin (71), brassinosteroids (6), and pathogen-resistance (36). Thus, the dwarfism of G protein–deficient mutants may not be simply caused by a defect in GA signaling. Actually, rice *d1* Gα mutants show a semidwarf phenotype similar to GA-related mutants, but the global morphology of the *d1* plants is not the same as that of rice GA-deficient mutants (M. Ashikari, unpublished

results). The involvement of trimeric G proteins in GA signaling should be reviewed with care to eliminate the effects of other signaling pathways.

Hartweck & Olszewski (16) raised the question of whether GA responses are always mediated by degradation of DELLA proteins based on the observation that the fastest GA response, an increase in calcium concentration, occurs in wheat aleurone cells during the 2–5 min following GA treatment, whereas the fastest documented GA-dependent decrease in a DELLA protein occurs 5–10 min after GA treatment. According to the time course of GA-induced responses of barley and wheat aleurone cells, which was deduced from the results of several independent experiments, the response of SLN1 degradation to GA treatment is a little faster than calcium uptake (65). Either way, it will be necessary to precisely examine the time course of GA signaling and response events under the same experimental conditions. As GA perception by GID1 directly transmits to DELLA proteins and continuously induces the degradation of DELLA proteins to release the suppressive state of GA action, if there is some level of GA action(s) not accounted for by the DELLA protein degradation mechanism, the presence of an alternative GA receptor would be the primary candidate. Because DELLA proteins and GID1 are specifically and preferentially localized in nuclei, GA signaling mediated by the GID1/DELLA system should be directly linked with the regulation of transcription.

In this context, GA actions not involved in transcriptional regulation would need to be known to address whether there is GA signaling independent from the GID1/DELLA pathway.

Establishing when the GID1/DELLA-mediated GA-perception system evolved is an alternative way to answer the above question. Some tree ferns contain GA_1 and GA_4 as the dominant bioactive GA forms (78, 79), and the lycophyte *Selaginella moellendorffii*, which is a member of one of the oldest lineages of vascular plants (74), contains some homologous genes to the angiosperm GID1, DELLA, and GID2 proteins (M. Matsuoka, unpublished results), suggesting that moniliforms with true leaves may also use the GID1/DELLA-mediated GA-perception system. However, genes encoding these homologous proteins in a model moss plant, *Physcomitrella patens*, which as a member of the bryophytes diverged from the ancestors of vascular plants early in land plant evolution, around 430 mya (44), are not detected, and it is also unknown whether this plant uses GAs as a growth regulator (M. Matsuoka, unpublished results). This suggests that the growth hormone GA and the GID1/DELLA-perception system may have been established in ancestors of vascular plants soon after divergence from bryophytes at an early stage of land plant evolution, although direct evidence that the *S. moellendorffii* homologous genes actually function in GA signaling should be confirmed.

SUMMARY POINTS

1. The biochemical search for GA receptors has gone on for a long time, and through these experiments it has been postulated that there are two types of GA receptors, including soluble and membrane-bound forms.

2. Degradation of DELLA proteins is the key step of the GA signaling pathway. DELLA protein degradation causes derepression of the repression state of GA action. The DELLA protein is degraded by 26S proteasome-mediated proteolysis, whereas an F-box protein specific for DELLA protein degradation is necessary for SCF targeting to DELLA protein.

3. The single rice GID1 protein, which is similar to the hormone-sensitive lipases, was identified as a soluble GA receptor by its affinity to GAs, specific interactions with bioactive GAs, and the GA-hypersensitive response of GID1 overproducing plants. *Arabidopsis* has three GID1 proteins, which have similar characteristics to the rice protein.

4. Binding of GA with GID1 induces interaction of the DELLA protein to the GA-GID1 complex in yeast cells. Furthermore, the DELLA protein promotes the binding of GA with GID1 by stabilizing the GA-GID1 complex. Interaction between GID1 and DELLA proteins suggests that the GA-perception signal mediated by GID1 is transduced to the DELLA protein directly and probably induces its degradation, mediated by the F-box protein.

5. Several lines of evidence suggest the presence of a plasma membrane–bound GA receptor. Further studies are necessary to determine whether an alternative GA receptor is actually located on the plasma membrane.

FUTURE ISSUES

1. The X-ray and nuclear magnetic resonance (NMR) analyses of GID1 are important to gain the three-dimensional (3D) structure of the GA receptor. The information of the 3D structure of GID1 alone and interacting with GA will hint at the molecular mechanism of formation of the GID1-GA-DELLA trio complex.

2. Is the GID1-GA-DELLA trio complex targeted by an F-box, GID2/SLY1, directly for degradation of DELLA protein? If so, what is the molecular mechanism for direct interaction between DELLA and F-box? If not, what is protein necessary for DELLA protein degradation?

3. It is necessary to clarify the molecular function of DELLA proteins. When DELLA proteins are transcription factors, as expected, what are their target genes?

4. Identification and isolation of alternative GA receptor localized on the plasma membrane are necessary.

ACKNOWLEDGMENTS

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