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Gibberellin Metabolism and Signaling: Targets for Improving Agronomic Performance of Crops

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Gibberellins (GAs) are a class of tetracyclic diterpenoid phytohormones that regulate many aspects of plant development, including seed germination, stem elongation, leaf expansion, pollen maturation, and the development of flowers, fruits and seeds. During the past decades, the primary objective of crop breeding programs has been to increase productivity or yields. 'Green Revolution' genes that can produce semidwarf, high-yielding crops were identified as GA synthesis or response genes, confirming the value of research on GAs in improving crop productivity. The manipulation of GA status either by genetic alteration or by exogenous application of GA or GA biosynthesis inhibitors is often used to optimize plant growth and yields. In this review, we summarize the roles of GAs in major aspects of crop growth and development and present the possible targets for the fine-tuning of GA metabolism and signaling as a promising strategy for crop improvement.

Keywords: Crop yield • Dormancy and germination • Gibberellins • Nitrogen use efficiency • Plant stature • Stress tolerance.

Introduction

The improvement of yield is a challenge for modern agriculture due to a finite amount of arable land and an increasing world population. Consequently, improving traits related to yield and stress tolerance are urgently required to meet future demand (Sakamoto and Matsuoka 2004, Takeda and Matsuoka 2008). During the past few decades, tremendous progress has been made in understanding the molecular mechanisms underlying important agronomic traits. Gibberellins (GAs), a class of tetracyclic diterpenoid phytohormones, play an important role in modulating diverse processes throughout plant growth and development, including seed germination, stem elongation, leaf expansion, pollen maturation, and the development of flowers, fruits and seeds (Chhun et al. 2007, Piskurewicz et al. 2008, Aya et al. 2009, Arnaud et al. 2010, Fuentes et al. 2012, Hauvermale et al. 2012, Sakata et al. 2014). Furthermore, the previous finding implies that GAs play a positive role in rice (*Oryza sativa*) heterosis at the seedling developmental stage (Ma et al. 2011). In addition, GAs regulate plant adaptation to biotic and abiotic stresses (Dreher and Callis 2007, Colebrook et al. 2014). As a consequence, manipulation of GA levels is often used in agricultural practice to optimize plant growth and yields.

GAs were initially identified in the pathogenic fungus *Gibberella fujikuroi*, the causal agent of the 'foolish-seedling' disease of rice, causing excessive stem elongation and falling over easily. Since its original discovery, at least 136 fully characterized GAs, named from GA_1 to GA_{136}, have been identified in plants, fungi and bacteria (MacMillan 2001, Tudzynski et al. 2016). Among the GAs produced in plants, only a few of the GAs, such as GA_1, GA_3, GA_4 and GA_7, have biological activity as regulators of plant growth and development (Yamaguchi 2008, Hedden and Thomas 2012). Additional forms of GAs that exist in plants are precursors of the bioactive forms or deactivated metabolites. GA_1 and GA_4 are the two major active GAs in most plant species, although GA_3 has also been identified in plants. The bioactivity of GA_4 is much higher than that of GA_1 in both *Arabidopsis* and rice, which is presumably attributed to their differences in binding affinity to the GA receptor (Cowling et al. 1998, Ueguchi-Tanaka et al. 2005, Magome et al. 2013, Nomura et al. 2013). Plants defective in GA biosynthesis or signaling show characteristic phenotypes, including dwarfism, small dark-green leaves, prolonged germination, root growth retardation, suppression of flowering, reduced seed production, and male sterility (Olszewski et al. 2002, Lo et al. 2008). Therefore, it is crucial for plants to tightly regulate the GA signaling pathway.

Different strategies have been employed for GA-mediated agronomic trait improvement: exogenous application of GAs or their inhibitors and genetic manipulation of their activities. These approaches have delivered promising results for improving agronomic performance in different crops. Due to the high cost of synthetic GA molecules and variability in the results, fine-tuning of the endogenous GA levels by genetic methods represents an efficient strategy for improving crop yield in a low-cost and predictable manner.

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GA Metabolism and Signaling

The power of molecular biology and genetics has dramatically advanced our understanding of GA synthesis and signaling (Sakamoto et al. 2004, Sun and Gubler 2004, Ueguchi-Tanaka et al. 2005, Chhun et al. 2007, Xu et al. 2014). Many genes encoding the components for GA biosynthesis and signaling pathways have been identified, and now more elaborate genetic screens are producing additional mutants that are providing new insights into this pathway (**Fig. 1**).

The signaling pathway from GA perception to transcriptional activation has been intensively studied over the past two decades, and its major components have been identified. The nuclear DELLA proteins, a subgroup of the GRAS transcription factors family, suppress GA signaling (Locascio et al. 2013). Arabidopsis has five DELLA proteins, whereas rice, barley (*Hordeum vulgare*) and wheat (*Triticum aestivum*) each have only one, called SLENDER RICE1 (SLR1), SLENDER1 (SLN1) and Reduced height (Rht), respectively (Peng et al. 1999, Ikeda et al. 2001, Chandler et al. 2002). The current model of GA action proposes that DELLA proteins restrain plant growth, whereas the GA promotes growth by overcoming DELLA-mediated growth restraint (Fu et al. 2002, Ueguchi-Tanaka and Matsuoka 2010, Davière and Achard 2016). In rice, GA binds to the soluble receptor protein GIBBERELLIN INSENSITIVE DWARF1 (GID1), which promotes the interaction between GID1 and the transcriptional repressor DELLA protein, SLR1 (Chhun et al. 2007, Ueguchi-Tanaka et al. 2007, Shimada et al. 2008, Yoshida et al. 2018). SLR1 protein is the hub repressor of GA signaling (Hirano et al. 2008, Hirano et al. 2012). Loss-of-function mutants of the rice *SLR1* gene have a slender phenotype with elongated leaf and stem (Ikeda et al. 2001, Itoh et al. 2002). F-box protein *GIBBERELLIN INSENSITIVE DWARF2* (*GID2*) is involved in the formation of the Skp–Cullin–F-box (SCF) E3 ubiquitin ligase complex that polyubiquitinates DELLA protein for its subsequent degradation by the proteasome (Sasaki et al. 2003, Gomi et al. 2004, Hirano et al. 2010).

GA biosynthesis and signaling are critical to plant growth and development, and of vital importance in agriculture. In this review, we summarize the physiological effects of GAs on different rice agronomic traits, including plant stature, response to nutrient availability, seed dormancy and germination, and stress tolerance (**Fig. 2**).

The Roles of GAs in Agronomic Traits

Plant stature

The development of semidwarf varieties was the most significant achievement in the 20th century of agricultural practices and was one of the cornerstones of so-called 'Green Revolution', which led to a massive increase in both wheat and rice yields (Peng et al. 1999, Silverstone and Sun 2000, Khush 2001, Ashikari et al. 2002, Boss and Thomas 2002, Sasaki et al. 2002, Spielmeyer et al. 2002, Evenson and Gollin 2003, Ordonio et al. 2014). The semidwarf habit is governed by GA biosynthetic gene *semidwarf1* (*sd1*) in rice and GA signaling gene *Rht* in wheat. The *sd1* gene was first identified in the Chinese variety Dee-geo-woo-gen (DGWG) and was crossed in the early 1960s with Peta (tall) to develop the semidwarf cultivar IR8, which produced record yields throughout Asia, and formed the basis for the development of new high-yielding, semidwarf plant types. Since the 1960s, *sd1* is extensively used in modern rice cultivars (Spielmeyer et al. 2002, Asano et al. 2007, Tu and Wang 2019). Recessive semidwarfism *sd1* gene in rice is the most important in a shortened culm with improved lodging and a greater harvest index, allowing for the increased use of nitrogen fertilizers (Jennings 1964). The *sd1* gene was isolated and characterized to encode a GA20-oxidase isoenzyme (GA20ox2) that catalyzes the conversion of GA_{53} to GA_{20}, leading to changes in GA content (Sasaki et al. 2002). GA_{53} is over-accumulated, and GA_{20} is scarce in *sd1* plants. Correspondingly, most mutants or knockdown lines of GA biosynthesis genes, including *CPS*, *KS*, *KAO*, *KO*, *GA20oxs*, and *GA3oxs*, also exhibit dwarfism phenotypes, which results in improved lodging resistance, a valuable trait for rice breeding under high inputs (Sakamoto et al. 2004, Qin et al. 2013). Meanwhile, overexpression of GA catabolism genes, *GA2oxs*, also leads to dwarfism (Lo et al. 2008, Shan et al. 2014). It was found that SPINDLY, participating in both BR and GA responses, regulates the elongation of lower internodes, which is correlated with levels of *SPINDLY* expression (Shimada et al. 2006).

In wheat, the introduction of mutant dwarfing alleles at *Rht-B1* and *Rht-D1* loci led to large increases in grain yields worldwide in the 1960s, owing to the improvement in both harvest index and lodging resistance. Since then, *Rht-1* dwarfism alleles are widely used in breeding modern wheat cultivars. The wheat Green Revolution genes *Rht-B1* and *Rht-D1* encode mutated DELLA proteins that have a reduced affinity for the GA receptor GID1 (Peng et al. 1999). DELLA proteins act as repressors of GA signaling and are destabilized by GA. The mutant DELLA protein confers semidominant GA-insensitive dwarfism. Even though wheat has a hexaploid genome, these dominant alleles still cause obvious dwarf phenotypes. Similarly, mutations in the DELLA proteins were also identified as Sln1 in barley (Peng et al. 1999, Chandler et al. 2002).

In maize, genes defective in GA biosynthesis and signaling, including *anther ear1*, *dwarf1* (*d1*), *d3*, *Dwarf8* (*D8*) and *D9*, show various levels of plant height reduction (Bensen et al. 1995, Winkler and Helentjaris 1995, Peng et al. 1999, Cassani et al. 2009, Teng et al. 2013). The expression domains of *GA2ox1* and *KN1* (a maize *KNOX* gene) overlap mainly at the base of the shoot apical meristem (Bolduc and Hake 2009), and the KN1 directly induces *GA2ox1* expression in reproductive meristems (Bolduc and Hake 2009). Meristem activity and maintenance processes are regulated via KNOX-mediated GA and cytokinin crosstalk (Wu et al. 2016).

Genetic and functional analyses of the semidwarf genes not only greatly improved our understanding of the biosynthesis and signaling of GAs but also provided a powerful strategy for manipulating the plant height of crops. Although widespread cultivation of GA-deficient semidwarf varieties was successful in breeding, developing new varieties for further increasing the yield of crops is once again faced with the challenge

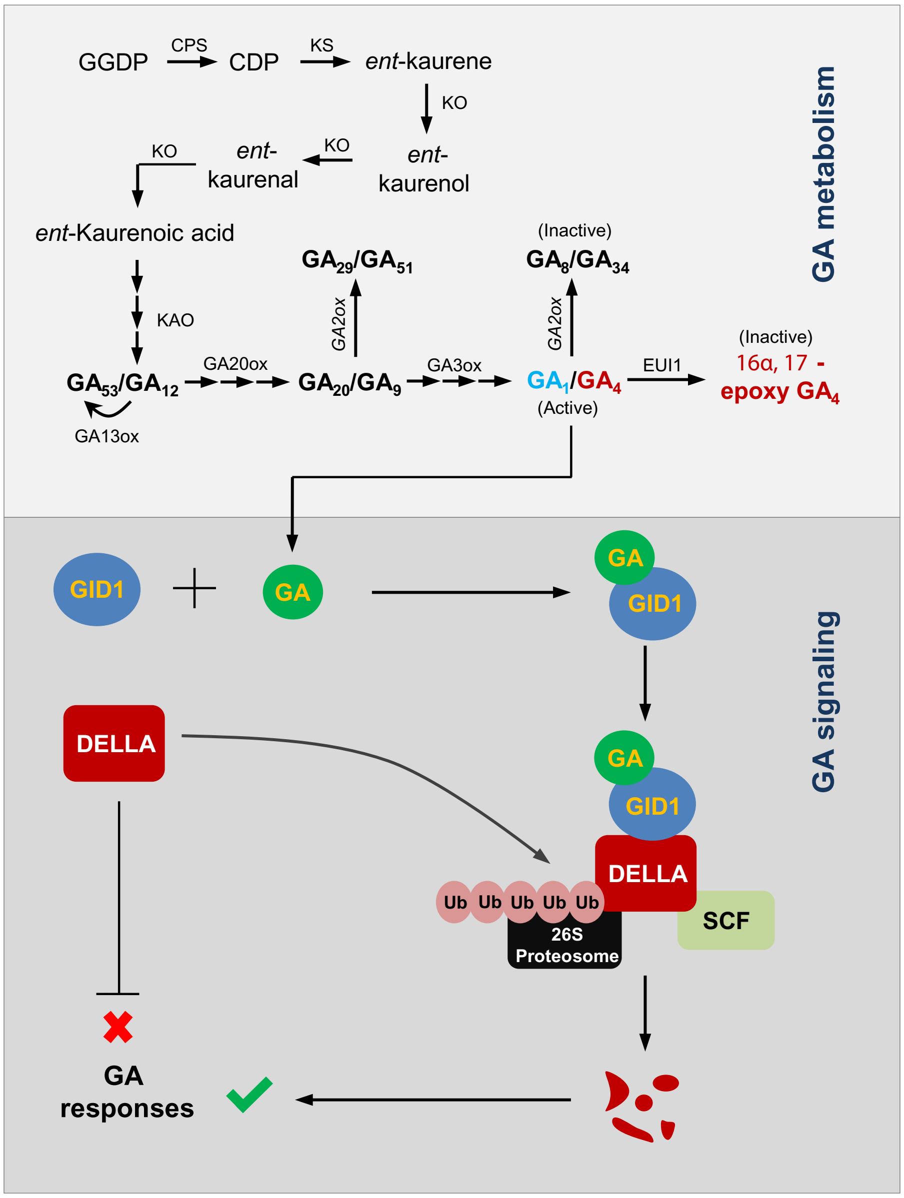

Fig. 1 A simplified illustration of GA metabolism and signaling pathways in rice. GA biosynthesis starts from GGDP in the plastid and a portion of it is catabolized to inactive forms. Bioactive GAs are perceived by the soluble GA receptor GID1. DELLA protein acts as a negative regulator of the GA responses. In the GA signaling pathway, GA causes the destruction of DELLAs via the 26S proteasome machinery, resulting in GA responses. CDP, *ent*-copalyl diphosphate; CPS, *ent*-copalyl diphosphate synthase; GA2ox, GA2 oxidase; GA3ox, GA3 oxidase; GA20ox, GA20 oxidase; GGDP, geranylgeranyl diphosphate; KAO, *ent*-kaurenoic acid oxidase; KO, *ent*-kaurene oxidase; KS, *ent*-kaurene synthase; Ub, ubiquitin.

(Hirano et al. 2017). It was found that higher lodging resistance could be achieved by improving the mechanical strength of the culm by identifying genes related to culm quality and introducing these genes into high-yielding rice cultivars (Li et al. 2003, Hirano et al. 2017).

In addition to semidwarf varieties, another contributor to rice yield increase is the application of heterosis. Interestingly, GA plays an indispensable role in hybrid rice seed production, since rice male sterile lines have a common defect in the elongation of the uppermost internode, leading to incomplete panicle exsertion, which blocks pollination (Luo et al. 2006, Zhu et al. 2006). Consequently, exogenous GA has to be used to amend the panicle enclosure. The rice *Elongated Uppermost Internode1* (*EUI1*) gene was found to encode a cytochrome P450 monooxygenase that inactivates 13-H GAs by epoxidation in anthers and might regulate the influx of GA_4 into the stems from panicles (Luo et al. 2006, Zhu et al. 2006, Gao et al. 2016, Gao and Chu 2018). Because of its prospective application to amend the panicle enclosure, the *EUI1* locus has been incorporated into many male sterile lines, and this recessive trait, along with the male sterile line, the maintainer line and the restorer line, is referred to as four genetic elements for hybrid rice seed production. Therefore, fully understanding the molecular mechanism through which EUI1 activity is regulated may greatly help breeders in improving hybrid rice seed production (Gao et al. 2016, Gao and Chu 2018, Xie et al. 2018). Consistent with the involvement of GAs in the control of plant

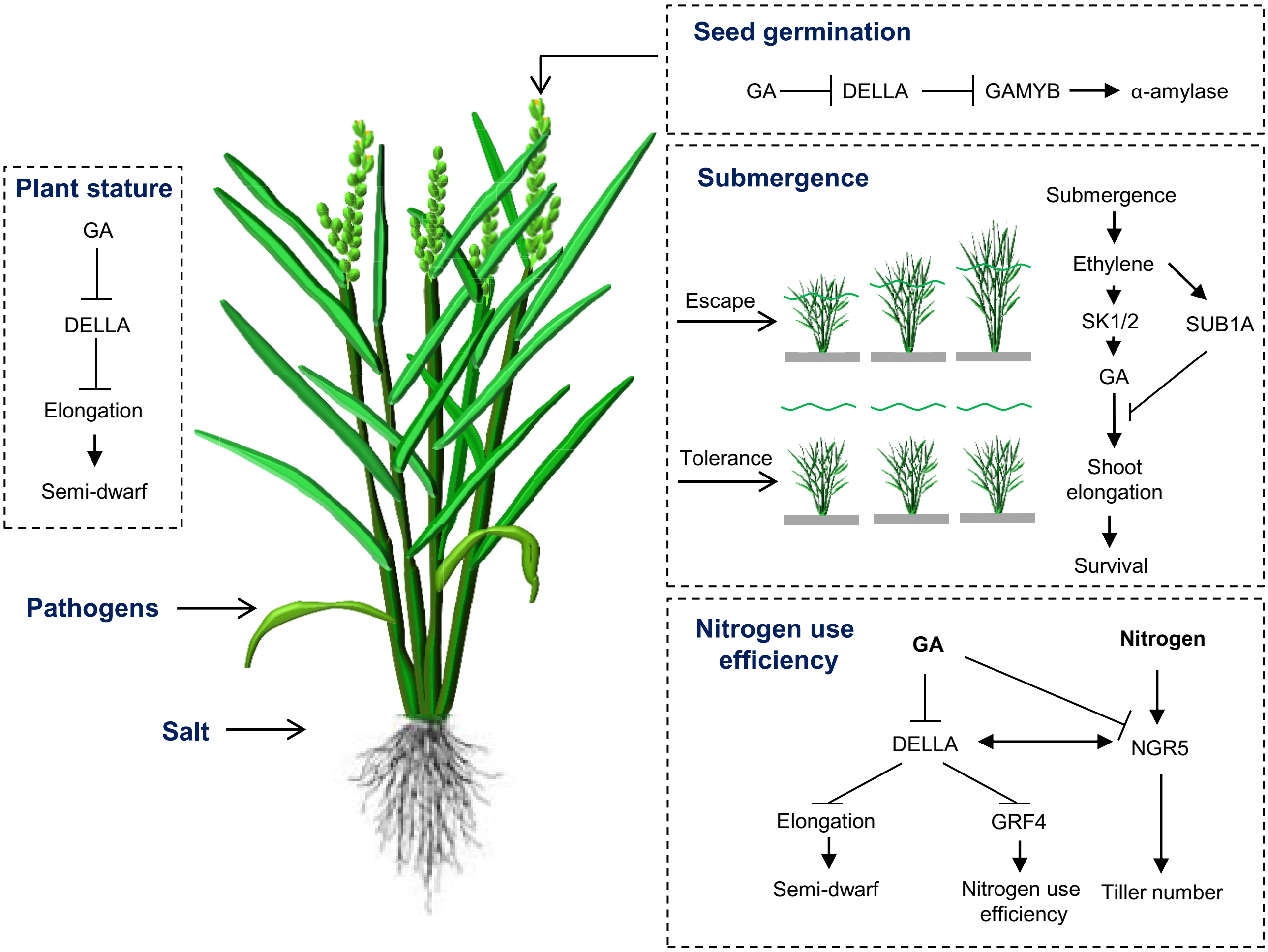

Fig. 2 GAs are crucial for agronomic traits and stress tolerance in crops. GAs act as growth-promoting phytohormones that play important roles throughout plant development, including plant stature, response to nutrient availability, seed germination, and stress tolerance.

architecture, GA biosynthesis inhibitors paclobutrazol and uniconazole are also often used to modulate plant growth responses (Ikeda et al. 2001, Gao et al. 2017).

It should be pointed out that the GA dwarf mutants tend to exhibit negative pleiotropic effects, which limit their breeding application (Lo et al. 2008). As changes in GA content cause a mix of positive and negative effects on traits of agronomic importance (e.g. reduced seed yield in rice), it is of utmost importance to determine how one GA effect could be uncoupled from another. When GA catabolism gene *OsGA2ox1* was expressed under the control of the constitutively expressed *Actin* promoter, the resulting plants were dwarf with reduced grain yields, because GA is required for flower development (Sakamoto et al. 2003). By expressing *OsGA2ox1* under the promoter of the GA biosynthesis gene *OsGA3ox2*, which expressed specifically in the upper internode, dwarf, high-yielding rice could be produced (Sakamoto et al. 2003). This result showed that tissue and cell-specific expression patterns of biosynthesis or deactivating enzymes can be used for the fine-tuning of plant growth. Thus, novel GA-related mutants with mild mutation effects and the breeding potential need to be further explored.

Response to nutrient availability

The Green Revolution represented by the breeding and wide application of semidwarf crops greatly promotes agricultural yield, but it also unfortunately led to the problem of reduced nitrogen use efficiency (NUE) of crops (Wu et al. 2020). Nitrogen is the most imperative element for the proper growth and development of plants. Crop yields are heavily dependent on sufficient nitrogen nutrition that is provided primarily through the application of inorganic fertilizers. Because Green Revolution varieties are relatively insensitive to nitrogen, which is adverse in efficient nitrogen utilization of crops, thus, these varieties require more nitrogen fertilizer input. How to reduce the input of nitrogen fertilizer in agricultural production and continuously increase the grain yield has become a major challenge, which needs to be addressed in sustainable agriculture.

Rice *GROWTH-REGULATING FACTOR 4* (*GRF4*) transcription factor was initially isolated as a major QTL in controlling grain size in three independent groups (Che et al. 2015, Duan et al. 2015, Hu et al. 2015). It has been shown to participate in brassinosteroid signaling and can interact with DELLA protein (Che et al. 2015). Later on, it has been further proved to play an important role in the GA signaling pathway (Li et al. 2018). *GRF4*^{ngr2} allele is semidominant for increasing NH_4^+ uptake. This allelic site was introduced into the current high-yield rice variety 9311 and the high-yielding wheat variety Kenong 199. The near-isogenic line 9311-*OsGRF4*^{ngr2} exhibited increased leaf and culm widths, enhanced NUE and grain yield, but plant height was not significantly changed. Similarly, *GRF4*^{ngr2} transgenic wheat plants also exhibited increased NUE and grain yield but no change in plant height (Li et al. 2018). Therefore, the high accumulation of GRF4 protein enables high yielding with increased NUE.

APETALA2-domain transcription factor *NITROGEN-MEDIATED TILLER GROWTH RESPONSE 5* (*NGR5*) is a key gene controlling tiller number changes under different nitrogen conditions (Wu et al. 2020). NGR5 is a target of GA receptor GID1-promoted proteasomal destruction. DELLA protein can competitively bind the GA receptor, GID1 protein, inhibits the GA-mediated degradation of NGR5 protein and then increases the stability of NGR5 protein (Wu et al. 2020). In addition to being negatively regulated by GA and its receptor GID1, *NGR5* is responsive to nitrogen and overexpression of *NGR5* in the semi-dwarf background significantly improves rice yields under low nitrogen conditions. NGR5 suppresses branching inhibitory genes, such as *D14* and *OsSPL14*, through nitrogen-dependent recruitment of polycomb repressive complex 2 that promotes histone H3 lysine 27 tri-methylation in the regions harboring the branching suppressors (Wu et al. 2020). The high-level accumulation of NGR5 does not change the semidwarf traits of the 'Green Revolution'. Instead, it can increase the tiller number of rice and promotes the uptake and utilization of nitrogen fertilizer (Wu et al. 2020). Thus, these studies uncover a new mechanism of GA signaling and enlighten novel breeding strategies for Green Revolution by breeding high-yield crops with enhanced NUE.

In addition, recent advances indicate that GAs substantially modulate the responses to other nutrient availabilities (Wild et al. 2016, Eggert and von Wiren 2017). In Arabidopsis, e.g. the spatial distribution of GA-regulated DELLA growth repressors in roots adapts the root system architecture and the iron-uptake machinery to the plant's iron demand (Wild et al. 2016). Phosphate starvation root architecture is modulated by the GA-DELLA signaling pathway (Jiang et al. 2007). In addition, DELLAs participate in potassium uptake under conditions of potassium scarcity (Oliferuk et al. 2017).

Seed dormancy and germination

Seed dormancy and germination are two distinct developmental steps in the life cycle of plants and important for agricultural production. Seed dormancy is a mechanism by which seeds can inhibit their germination to wait for more favorable conditions. A high level of dormancy in cereal seeds can cause slow and uneven postharvest germination of seeds. Therefore, for cultivated crops, domestication of low dormancy cultivars over a long period ensures a higher and uniform emergence rate after sowing. However, lack of adequate seed dormancy leads to preharvest sprouting, which severely reduces both grain yield and quality (Fang et al. 2008). Hence, the suitable dormancy extent allows uniformity of postharvest germination of seeds as it prevents the problems of sprouting and is generally regarded as a desirable trait (Fang et al. 2008, Tuan et al. 2018). Abscisic acid (ABA) and GAs act antagonistically in the control of seed dormancy and germination (Xie et al. 2006, Fang et al. 2008, Fang and Chu 2008, Penfield 2017, Du et al. 2018, Xu et al. 2019). ABA positively regulates the induction and maintenance of dormancy, while GAs are known as promoters of germination (Koornneef et al. 2002, Shu et al. 2016).

In barley, GA acts by promoting the activity of the *GAMYB* transcription factor, which induces the expression of genes, including α-amylase, β-glucanase, cathespin protease and β-glucosidase, promoting nutrient mobilization and cell wall loosening (Gubler et al. 1995, Gubler et al. 2002, Woodger et al. 2003). Inhibition of *SLN1* leads to derepression of α-amylase even in the absence of GA (Zentella et al. 2002), and the *sln1* mutant is characterized by nondormant seeds with high amylase activity in aleurone (Chandler 1988). The degradation of DELLA by GA activates *GAMYB*, which in turn induces the transcription of α-amylase in the aleurone of barley and rice seeds via binding to the GA-responsive elements present in its promoter (Gubler et al. 1995, Gubler et al. 1999, Sun and Gubler 2004). GAMYB can also interact synergistically with other transcription factors and regulate the expression of α-amylase in barley (Zou et al. 2008). A recent study suggests that GAMYB might regulate GATA-type zinc finger transcription factor *GATA12* that acts as a positive regulator of seed dormancy (Ravindran et al. 2017). Moreover, reactive oxygen species (ROS) have been reported to have effects on ABA and GA metabolism, which eventually influence seed dormancy in barley (Bahin et al. 2011).

Similarly, seed dormancy and germination in wheat are also reported to be associated with changes in seed sensitivity to GAs, which is influenced by the expression of genes encoding the GA signaling components (Penfield 2017, Guo et al. 2018). Inhibition of the germination of nondormant seeds of wheat is associated with increased expression of *Rht1*, suggesting the role of GA signaling or seed GA sensitivity in the induction of dormancy (Izydorczyk et al. 2018). Wheat allelic variations in the *Rht1* loci are able to produce different levels of seed dormancy (Izydorczyk et al. 2018). Dormancy decay in wheat seeds due to imbibition at lower than optimal temperature is related to enhanced expression of *TaGA3ox2* and increased levels of bioactive GA in the embryo. While inhibition of germination at suboptimal temperature is associated with decreased expression of *TaGA20oxs* and *TaGA3ox2* and reduced bioactive GA levels in both embryo and endosperm (Kashiwakura et al. 2016, Izydorczyk et al. 2018).

In rice, ABA can inhibit GA-inducible responses, such as the expression of α-amylase by regulating WRKY transcription factors (Xie et al. 2006). AP2 domain-containing transcription factor OsAP2-39 in rice directly promotes transcription of the ABA biosynthesis gene *OsNCED1* and expression of the GA deactivation gene *EUI1*, thus enhancing ABA biogenesis and impairing GA accumulation (Yaish et al. 2010, Shu et al. 2018). Overexpression of *OsAP2-39* leads to increased seed dormancy, indicating that OsAP2-39 plays a pivotal role in regulating the ABA/GA ratio. Likewise, the expression of the GA biosynthetic genes (*GA20ox* and *GA3ox2*) is induced while that of GA-inactivating gene (*GA2ox*) is repressed during the imbibition of nondormant rice seeds, and this has been shown to be associated with an increased level of bioactive GA (Ye et al. 2015, Magwa et al. 2016). *OsGA20ox2* and *OsGA2ox3* were identified as candidate genes for controlling seed germination, and loss-of-function mutation in *OsGA20ox2* leads to reduced seed GA level and enhanced dormancy (Ye et al. 2015, Magwa et al. 2016). However, further genetic analyses are required for a detailed understanding of the physiological roles of GA metabolic genes in the regulation of seed dormancy in cereals.

Abiotic stress tolerance

There is increasing evidence for the involvement of GA signaling in growth suppression or promotion, depending on the response to a particular abiotic stress (Colebrook et al. 2014, Illouz-Eliaz et al. 2019). By modifying GA levels and signaling, plants are able to regulate and coordinate both growth and stress tolerance to better survival under unfavorable conditions.

The involvement of GA in response to abiotic stress is supported by rice varieties adapted to escape or tolerate flooding. Unanticipated flooding challenges plant growth and fitness in natural and agricultural ecosystems. Rice varieties adapted to shallow, long-lived floods commonly employ an escape strategy, in which submergence triggers rapid internode elongation. Upon submergence, these varieties have evolved an ethylene-driven and GA-enhanced module that regulates the growth of submerged organs. Internode elongation is triggered by the upregulation of the ethylene response factors SNORKEL1 and SNORKEL2, which directly or indirectly leads to an increase in bioactive GA levels (Hattori et al. 2009). GA promotes rapid growth in dark-grown plant tissues and in deepwater rice during flooding. This response allows the shoot to outgrow the floodwaters. On the other hand, the rice *Sub1* locus controls the tolerate strategy of rice varieties that are adapted to short-lived, deep floods. Upon submergence, rice plants carrying the *Sub1A* gene will not activate an escape response. Instead, shoot elongation is restricted and carbohydrate resources are conserved for utilization in regrowth when the flood recedes. This restriction of elongation growth is associated with increased levels of the rice DELLA protein SLR1 and the negative regulator of GA signaling, SLR1-LIKE1 (Fukao et al. 2006, Xu et al. 2006). Breeding programs have introduced the submergence tolerance trait into high-yielding rice varieties, which are expected to produce enough grains to feed millions of people in flood-prone areas. More recently, a transcriptional gain-of-function allele of the *SD1* gene can trigger rapid stem elongation in deepwater rice, enabling it to survive under adverse flooding conditions (Kuroha et al. 2018). Interestingly, the *SD1* gene has been co-opted several times to permit rice cultivation in highly contrasting production systems via decreasing the enzymatic activity in one case and enhancing the transactivation in another case. The capacity of SD1 to function in such diverse roles in cultivated rice highlights the intrinsic complexity and molecular plasticity of plant adaptation strategies (Kuroha et al. 2018).

GAs also can respond to salt stress. Under high salinity, plants rapidly reduce the growth and developmental program to enhance the survival rate. Salt stabilizes DELLA proteins, and DELLA-deficient plants are less tolerant to salt stress (Achard et al. 2006, Achard et al. 2008). Analysis of growth parameters and salt tolerance in a range of DELLA mutants indicated a strong correlation between plant height, time to flowering transition, and susceptibility to severe salt stress, suggesting that DELLA proteins may restrain growth and enhance stress tolerance through a common mechanism. In rice, the ubiquitin-binding protein OsDSK2a interacts with EUI1 and promotes its degradation to maintain GA homeostasis under normal conditions, thereby contributing to vegetative growth. Under salt stress, OsDSK2a protein levels decrease, thereby releasing EUI1 protein and allowing it to decrease bioactive GA levels, leading to inhibited plant growth and increased survival rate (Wang et al. 2020).

Thus, it is important at times for a plant to have enough GA to promote developmental changes, and important for a plant to limit GA production or response to survival under unfavorable environments. Further characterization of the molecular mechanisms regulating GA synthesis, signaling and action will facilitate the modification in GA biosynthetic pathways to breed crops with enhanced abiotic stress tolerance.

Biotic stress tolerance

Pathogen attack is one of the major limiting factors to crop productivity and ultimately food security. GAs also play important roles in triggering the plant immune signaling network (De Bruyne et al. 2014). In rice, GAs enhance susceptibility against the pathogens *Xanthomonas oryzae* pv. *oyrzae* (*Xoo*, causing bacterial blight) and *Magnaporthe oryzae* (*Mo*, causing rice blast) (Yang et al. 2008). Mutants deficient in GA biosynthesis and signaling show resistance phenotypes when plants are treated with *Xoo* or *Mo* (Yang et al. 2008, Qin et al. 2013, De Vleesschauwer et al. 2016). Transgenic rice overexpressing *EUI1* accumulates low levels of GA and SA and displays enhanced resistance to *Mo* and *Xoo*, whereas loss-of-function mutations in *EUI1* are more vulnerable to these pathogens (Yang et al. 2008). The *OsGA20ox3* knockdown lines show enhanced resistance against rice pathogens *Mo* and *Xoo* and increased expression of defense-related genes. On the contrary, *OsGA20ox3* overexpressing plants are more susceptible to these pathogens compared with the wild-type plants. The susceptibility of plants to *Xoo* is increased by exogenous application of GA_3 (Qin et al. 2013).

It has also been shown that foliar spray of plants with a low concentration of GA enhanced nematode infection (Yimer et al. 2018). GAs antagonize jasmonate (JA)-induced defense against *Meloidogyne graminicola* in rice. GA signaling suppresses JA-mediated defense against *M. graminicola*, and likewise, the JA-induced defense against *M. graminicola* requires SLR1-mediated repression of the GA pathway (Yimer et al. 2018). GAs are positive players in resistance against the necrotrophic root pathogen *Pythium graminicola* (De Vleesschauwer et al. 2012). SLR1-overaccumulating mutants show increased susceptibility to the necrotroph *P. graminicola* but enhanced resistance to the (hemi)biotrophs *Xoo* and *Mo* (Tanaka et al. 2006, De Vleesschauwer et al. 2012). SLR1 serves as the main target of JA-mediated growth inhibition and immunity and is required for the expression of JA-inducible rice genes (Yang et al. 2012).

Conclusions and Perspectives

Over the past decades, significant progress has been made in elucidating the GAs' metabolism and signaling pathways in both model plants and crops. Accumulating results indicate that GAs are strongly involved in tuning a number of agronomically important traits, including plant stature, nutrient use efficiency, seed dormancy and germination, and tolerance to various abiotic and biotic stresses. These have continuously delivered the promising targets for seed yield and stress tolerance improvement of crops. Elucidation of the role of GA signaling in these responses would be an important step toward understanding and improving crop growth and stress responses under adverse environmental conditions. A recent report that natural variations in the maximal quantum yield of photosystem II also associate with the GA signaling pathway, indicating that GAs also participate in photosynthesis, adding to the list of potentially innovative applications in agriculture (Hamdani et al. 2019). GA is a mobile signal in plants, and developmental and adaptive growth processes require the mobility of GA to take place properly (Regnault et al. 2015, Regnault et al. 2016, Binenbaum et al. 2018). Hence, spatial control is an additional layer of regulation that plants exert over their GA signaling, which can be manipulated to improve plant growth and stress responses (Regnault et al. 2015, Binenbaum et al. 2018). The molecular basis of GA mobility and long-distance coordination are needed to be investigated further.

The relatively high cost of synthetic GA molecules and variability in the results have discouraged the use of exogenous GA in agriculture. By contrast, modulation of endogenous GA levels by genetic engineering represents an efficient strategy for improving crop yield in a uniform and predictable manner. New approaches, such as functional genomics and CRISPR/Cas (clustered regularly interspaced short palindromic repeat/CRISPR-associated protein) genome editing systems, promise even more rapid progress in unraveling the physiology and biochemistry of GA-regulated processes (Chen et al. 2019, Hu et al. 2019). Using CRISPR-based editing, de novo mutations could be generated, which facilitates the directed evolution of GA biosynthesis and signaling genes and accelerates the trait development of crops. In addition, the identified GA effectors can be engineered to boost crop productivity and food security, which is an important priority to cope with a constantly changing world. Therefore, combining with new technologies, such as genome-wide association study, genome editing and other genetic engineering techniques, for improved productivity in agronomically important crops will have great potential.

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Disclosures

The authors have no conflicts of interest to declare.

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