The Role of Dwarfing Traits in Historical and Modern Agriculture with a Focus on Rice

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Semidwarf stature is a valuable agronomic trait in grain crops that reduces lodging and increases harvest index. A fundamental advance during the 1960s Green Revolution was the introduction of semidwarf cultivars of rice and wheat. Essentially, all semidwarf varieties of rice under cultivation today owe their diminished stature to a specific null mutation in the gibberellic acid (GA) biosynthesis gene, *SD1*. However, it is now well-established that, in addition to GAs, brassinosteroids and strigolactones also control plant height. In this review, we describe the synthesis and signaling pathways of these three hormones as understood in rice and discuss the mutants and transgenics in these pathways that confer semidwarfism and other valuable architectural traits. We propose that such genes offer underexploited opportunities for broadening the genetic basis and germplasm in semidwarf rice breeding.

The term "Green Revolution" refers to increases in grain production starting in the 1960s resulting from the introduction of new varieties of wheat and rice, particularly dwarf varieties, for use in the developing world. This development was a significant factor in maintaining per capita food supplies worldwide in the late twentieth century despite a doubling in the world population during this time (Dalrymple 1986; Evenson and Gollin 2003).

Perhaps the first known reports of dwarf forms of rice date back to the first half of the 19th century by Japanese naturalist and samurai Iwasaki Tsunemasa (Fig. 1; Iwasaki 1915). Traditionally, two main groups of dwarf *japonica* rice have been described: the more common "*Daikoku*," which is named after Daikokuten, the Japanese deity of agriculture and rice, and the less common "*Bonsai*" (Nagai 1959). Within the "*Daikoku*" group, plants show erect, short, and rigid leaves with a deep green color. Panicles are short, erect, and compact, with small and round grains. On the other hand, "*Bonsai*" plants show increased tillering, with narrow and slender leaves. In the 1950s, segregation analysis suggested the division of the "*Daikoku*" and "*Bonsai*" types into different linkage subgroups (Nagao and Takahashi 1952).

Although this early genetic characterization of dwarfism was conducted in *japonica* rice, the most significant advances in breeding in the early twentieth century occurred mostly in *indica* varieties. The Taiwan Agricultural Experiment Station described varieties that were grown at that time, including a series of dwarf cultivars. One of them was "Dee-geo-woo-gen" (DGWG), which was recorded in 1906. Its origin is attributed to a spontaneous mutation in the "Woo-

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Figure 1. First known report of a dwarf rice variety in the 19th century by Iwasaki Tsunemasa. (From Iwasaki 1915; image in the public domain and not subject to copyright.)

gen" variety, brought to Taiwan from mainland China before the Japanese occupation. For half a century, DGWG was not part of breeding programs because the Japanese administration in Taiwan focused at the time on the breeding of *japonica* varieties (Chandler 1968). However, in 1956, Taiwanese scientists released the semidwarf "Taichung Native 1" ("TN1") from a 1949 cross between the DGWG dwarf variety from Taiwan, and "Tsai-yuan-chon" (Athwal 1971). TN1 was found to be fertilizer responsive, and farmers in India grew more than 800,000 ha of TN1 between 1968 and 1969 (Hargrove and Cabanilla 1979).

In 1962, a cross between DGWG, and "PETA," a tall variety from Indonesia resulting from the cross between a Chinese variety, "Cina" (also known as Tjina), and an Indian variety, "Latisail" (Hargrove et al. 1980), resulted in a high-yielding semidwarf variety that is considered to have started the Green Revolution in Asia, IR8. Originally branded as "miracle rice," IR8 was also the first variety to be released by the International Rice Research Institute (IRRI). IR8 produced 9.4 tons per ha, 10 times higher than the average yield in the Philippines at the time (Gnanamanickam 2009). This "miracle rice" was rapidly adopted by farmers, especially in irrigated areas of Asia (Dalrymple 1986). To put what IR8 meant at the time into perspective, U.S. forces during the Vietnam war used IR8 as a propaganda tool, releasing it in South Vietnam, while flooding North Vietnam with leaflets announcing the rice revolution that their neighbors were experiencing (Bourne 2015).

As many as 85% of the crosses made by rice breeders between 1974 and 1975 involved at least one semidwarf parent, usually IR8, and the original efforts made in crossing tall versus dwarf parents shifted to crosses between semidwarf parents (Hargrove and Cabanilla 1979). All cultivars released between 1974 and 1979 from IRRI, except "IR5," can be traced to DGWG (Hargrove et al. 1980).

It was not until 2002 that the mutation responsible for the dwarf phenotype of DGWG was identified, namely, a 383-bp deletion in *SD1*, a gibberellin 20-oxidase (Os01g0883800), which is a key enzyme in gibberellin synthesis (Monna et al. 2002; Sasaki et al. 2002; Spielmeyer et al. 2002). Before the identification of the responsible gene, it was simply known as the "Dee-geo-woo-gen" gene. Because varieties developed from this gene suffered from very narrow germplasm, breeders were encouraged to identify alternative sources of dwarfism (Chang and Vergara 1972; Hargrove et al. 1980). However, some of the varieties that were used as an alternative to DGWG, such as "Jikokku," and "Reimei," were later found to also contain the same causative mutation as in DGWG, namely, *sd1* (Tsunoda and Takahashi 1984).

In the second half of the twentieth century, IR8 started to be replaced by other semidwarf IRRI varieties. IR20, showing improved disease resistance, was released in 1969 (Pathak et al. 1973). IR26, released in 1973, had even higher insect and disease resistance and replaced IR20. In 1982, IR36 became the most popular variety

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in the world. IR36 maintained disease and insect resistance, achieving high yields in 111 days from seed to seed, compared with 130 days for IR8 (Khush 2005), and was cultivated in 11 million ha (Khush 1987). IR64, a semidwarf *indica* variety released in 1985, combines the desirable traits of IR36 with a superior grain quality (Khush 1987). IR64 can still be traced back to the original DGWG variety and the same *sd1* allele confers its semidwarf phenotype (Wei et al. 2016). In the last 10 years, the area of cultivation of IR64 has declined, being replaced by a new generation of high-yielding semidwarf varieties; yet, these also originate from crosses that include IR64 (Mackill and Khush 2018).

Two major challenges arise in breeding for semidwarf varieties in rice. The first challenge is that most breeding programs have focused on *indica* varieties, whereas the development of semidwarf *japonica* varieties has proved more challenging. Crosses between *indica* and *japonica* varieties are usually highly sterile (Chen et al. 2008). To overcome this, Korean researchers in collaboration with IRRI crossed the *indica* variety *TN1*, introducing the *sd1* allele, with the *japonica* variety "Yukara." To overcome spikelet sterility, the F1 was backcrossed with IR8. A resulting variety, "Tongil," was released in 1972 and provided a 30% increase in yield (Chung and Heu 1980; Kim et al. 2014). In general, original efforts made to introduce dwarfism in *japonica* varieties simply aimed to extend the strategy used in *indica* based on the DGWG gene.

The second challenge is that, despite efforts to identify alternative sources of dwarfism at the beginning of the Green Revolution (Reddy and Padma 1976; Singh et al. 1979), 90% of modern rice varieties still harbor the *sd1* allele (Kikuchi et al. 1985; Spielmeyer et al. 2002). Despite the many advantages of *sd1* as a source of dwarfism, its widespread use not only reduces genetic diversity but also imposes other associated negative effects. For instance, it has been found that dwarfism originating from DGWG also carries reduced spikelet fertility in response to cool temperatures (Murai et al. 1991). The drought sensitivity that is typically found in modern varieties (Vikram et al. 2015) has also been linked to the introduction of the *sd1* allele (Lafitte et al. 2006). Increasing genetic diversity in breeding programs would help to correct such secondary negative traits indirectly selected through breeding. Yet, more than 40 years since it was first suggested that scientists should identify and use alternative sources of dwarfism (Hargrove et al. 1980), the conservation in modern varieties of the *sd1* allele suggests that the introduction of alternative sources of dwarfism remains underexploited. In this review, we summarize the genes and genetic mechanisms known to result in dwarfism in rice, which could potentially contribute to this effort. We do so through a focus on the three major classes of hormones that control plant height: gibberellins, brassinosteroids (BRs), and strigolactones (SLs).

GIBBERELLINS

Gibberellic acids (GAs) are plant hormones that promote stem and internode elongation, leaf differentiation, pollen and flower development, and seed germination (Richards et al. 2001; Fleet and Sun 2005; Umehara et al. 2008; Sun 2011; Magome et al. 2013; Wiemann et al. 2013; Ayano et al. 2014). More than 100 GAs have been identified in plants, fungi, and bacteria but only a few GAs, particularly GA_1, GA_3, and GA_4, are bioactive in plants (Peng et al. 1999; Sakamoto et al. 2004; Yamaguchi 2008). GA-deficient and GA-insensitive rice mutants have shorter stature with darker green and rougher leaves than wild-type (Sakamoto et al. 2004; Hirano et al. 2010; Hedden and Thomas 2012; Liu et al. 2018).

GA Biosynthesis

GAs are diterpenoid compounds derived from four isoprenoid units that combine to form a four-ring structure with 19 to 20 carbons (Hedden and Thomas 2012). The synthesis of bioactive GA_1 and GA_4 starts with the conversion of geranylgeranyl diphosphate (GGDP) to the tetracyclic hydrocarbon intermediate ent-copalyl diphosphate and then to ent-kaurene, catalyzed by ent-copalyl diphosphate synthase (CPS) and ent-kaurene synthase (KS), respectively. Ent-

kaurene is then converted to ent-kaurenoic acid and then to GA_{12} by two successive P450 monooxygenase cytochromes (P450), ent-kaurene oxidase (KO) and ent-kaurenoic acid oxidase (KAO), which are localized in the endoplasmic reticulum (Hedden and Kamiya 1997; Sasaki et al. 2003). Subsequently, GA_{12} is converted into GA_9 by GA 20-oxidase (GA20ox) and then into bioactive GA_4 by GA3-oxidase (GA3ox) in the cytoplasm. GA_{12} is also converted into GA_{53} by GA13-oxidase (GA13ox) in the endoplasmic reticulum. GA_{53} is then converted into GA_{20} by GA 20-oxidase (GA20ox). GA_{20} is then converted into bioactive GA_1 by GA 3-oxidase (GA3ox) in the cytoplasm. GA_{20} is also converted into GA_5 and then to bioactive GA_3, with both reactions catalyzed by GA3ox (Fig. 2; Hedden and Phillips 2000).

In recent years, dwarfing genes involved in GA biosynthesis have been characterized in various plant species (Hedden and Phillips 2000; Luo et al. 2006; Zhu et al. 2006). Table 1 summarizes the genes involved in GA biosynthesis that are known to affect plant height in rice. In rice, two alleles of *CPS1*, three alleles of *KS1*, two alleles of *KO2*, and three alleles of *KAO* are all null mutants that confer deficiency in the production of bioactive GAs and cause severe dwarf phenotypes (Sakamoto et al. 2004; Toyomasu et al. 2009; Okuno et al. 2014). Interestingly, null mutants *cps1* and *ks1* do not develop flowers or seeds, whereas the null mutant *ko2*, also

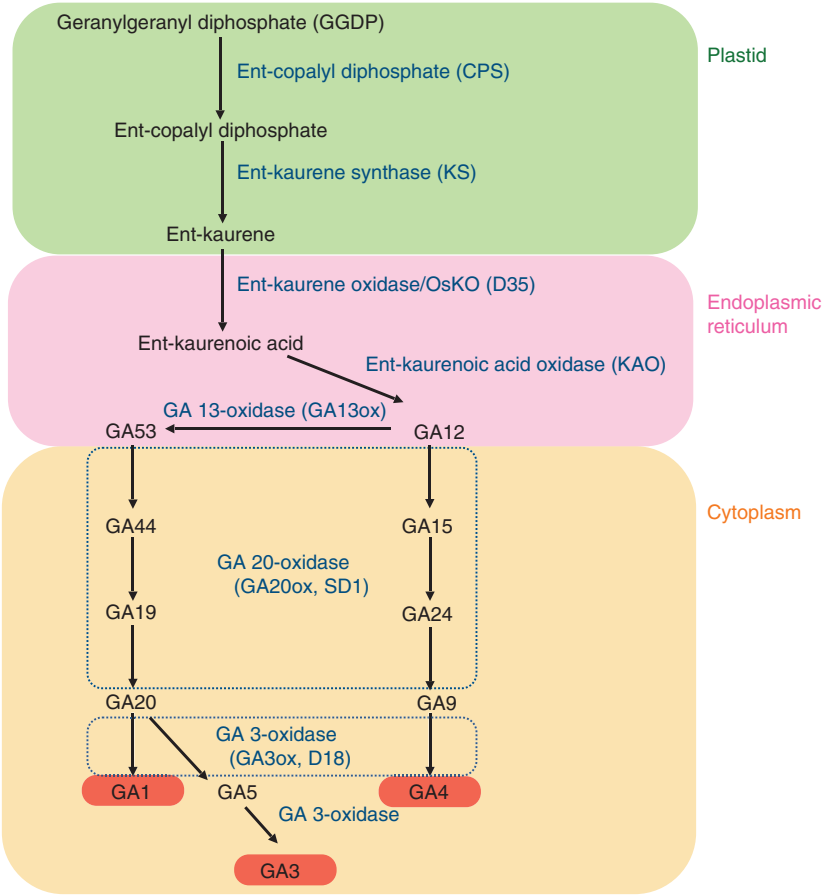

Figure 2. Gibberellic acid (GA) biosynthesis in rice. Gene and available mutant names are provided (see also Table 1). (Figure created from modified data in Sakamoto et al. 2004.)

Table 1. Genes and mutants in gibberellic acid (GA) synthesis and signaling

Pathway	Gene names	Gene encodes	Mutant names	Locus ID	Key references
GA biosynthesis	*CPS*	Ent-copalyl diphosphate	*cps1*	Os02g0278700	Sakamoto et al. 2004
	KS	Ent-kaurene synthase	*ks1*	Os04g0611800	Sakamoto et al. 2004
	KO	Ent-kaurene oxidase	*ko2/d35*	Os06g0570100	Sakamoto et al. 2004
	KAO	Ent-kaurenoic acid oxidase	*kao*	Os06g0110000	Sakamoto et al. 2004
	GA20ox	GA 20-oxidase	*sd1*	Os01g0883800	Ashikari et al. 2002; Spielmeyer et al. 2002
	GA3ox	GA 3-oxidase	*d18*	Os01g0177400	Itoh et al. 2004; Sakamoto et al. 2003
	EUI	P450 cytochrome monooxygenase	*eui1*	Os05g0482400	Luo et al. 2006; Zhu et al. 2006
	INO80	ATP-dependent chromatin-remodeling factor	*ino80*	Os03g0352450	Li et al. 2018
	PAD	Mild complementing activity 1	*pad*	Os03g0157300	Liu et al. 2015b
	SDSFL1	GA 20-oxidase 1	*sdsfl1*	Os03g0856700	Alamin et al. 2018
GA signaling	*GID1*	Nuclear protein receptor	*gid1*	Os05g0407500	Ueguchi-Tanaka et al. 2005; Hirano et al. 2010
	GID2	F-box subunit of SCF E3 complex	*gid2*	Os02g0580300	Sasaki et al. 2003
	SLR1	DELLA protein	*slr1*	Os03g0707600	Ikeda et al. 2001; Asano et al. 2009; Hirano et al. 2010
	Gα	α-Subunit of G protein	*d1*	Os05g0333200	Ashikari et al. 1999
	CIGR	Chitin-inducible gibberellin-responsive protein	*ph1*	Os07g0545800	Kovi et al. 2011
	DNL1	Cellulose synthase-like D4 protein	*dnl1*	Os12g0555600	Wei et al. 2013
	PP2C	Protein phosphatase 2C34	*pp2c34*	Os03g0761100	Hossain et al. 2018
	SPY	*O*-linked *N*-acetylglucosamine transferase	*spy*	Os08g0559300	Shimada et al. 2006

known as *d35*, develops flowers and produces seed. Application of exogenous bioactive GAs can restore wild-type phenotypes, confirming impairment in GA synthesis rather than sensing. These novel rice dwarf mutant lines could be used to introduce alternative sources of dwarfism (Sakamoto et al. 2004; Okuno et al. 2014).

The rice genome has four copies of the *GA20-oxidase* gene (*GA20ox1*, *GA20ox2*, *GA20ox3*, and *GA20ox4*), which are highly expressed in the stem (Kaneko et al. 2003; Oikawa et al. 2004; Zhu et al. 2006). Null mutation of *GA20ox2*, also known as the *sd1* mutation, is compensated for by expression of *GA20ox1* and *GA20ox4*, resulting in a semidwarf rather than a severe dwarf phenotype (Ashikari et al. 2002; Monna et al. 2002; Sasaki et al. 2002; Spielmeyer et al. 2002). As noted previously, during the Green Revolution, *sd1* alleles were utilized extensively in rice semidwarf breeding (Monna et al. 2002; Spielmeyer et al. 2002; Hedden 2003; Wang et al. 2005). A major advantage of the *sd1* null mutant is the internode elongation pattern in comparison to the $d35^{Tan\text{-}Ginbozu}$-null mutant, defective in *KO2*, and the *d18k*-null mutant, defective in *Ga3ox2*, respectively (Saka-

moto et al. 2003; Itoh et al. 2004). Generally, four to five internodes elongate during development from the vegetative to the reproductive stage. The *sd1*, *d18k*, and *d35*$^{Tan\text{-}Ginbozu}$ mutants all have shorter internodes than the wild-type, resulting in semidwarf stature. However, the internode elongation pattern between the three semidwarf null mutants is different. The *sd1* and *d18k* rice mutants have shorter lower internodes compared with the upper internodes (Sakamoto et al. 2004; Okuno et al. 2014). On the other hand, the *d35*$^{Tan\text{-}Ginbozu}$ mutant has shorter upper internodes compared with the lower internodes. As a result, the *sd1* and *d18k* rice mutants have a lower center of gravity, making them more resistant to lodging as compared to *d35*$^{Tan\text{-}Ginbozu}$ (Sakamoto et al. 2004; Okuno et al. 2014). Although *sd1* and *d18k* rice mutants have a similar pattern of relative internode length, the internodes of *d18k* are shorter than the equivalent internodes in the *sd1* mutant, making *d18k* shorter than the *sd1* mutant. This difference makes *sd1* mutant more desirable than the *d18k* mutant in semidwarf breeding (Itoh et al. 2004).

The rice mutant *semi-dwarf and short flag leaf 1* (*sdsfl1*), which harbors a single amino acid substitution in another *GA20-oxidase* gene, *GA20ox1*, shows shorter plant height and flag-leaf length with increased tiller number and decreased panicle length compared to wild-type (Alamin et al. 2018). Phytohormone profiling analyses revealed reduced levels of GA_3 and increased levels of ABA, IAA, and SA, suggesting a role in hormonal cross talk for plant height (Alamin et al. 2018).

Rice genes involved in GA catabolism have also been identified. There are four rice *GA2-oxidase* (*GA2ox*) genes that encode enzymes that reduce levels of bioactive GAs by hydroxylating bioactive GAs or their precursors (Hedden and Phillips 2000; Olszewski et al. 2002; Liu et al. 2018; Nagai et al. 2018). The two major classes of GA2ox are C19-GA2ox that hydroxylates the C-2 position of C19-GAs, such as GA_1 and GA_4, or C19-GA precursors, such as GA_9 and GA_{20}, and C20-GA2ox that only hydroxylates C20-GA precursors, such as GA_{12} and GA_{53} (Sakamoto et al. 2003; Lo et al. 2017). Knockout of *GA2ox* genes may have minimal impact owing to functional redundancy (Sakamoto et al. 2004). However, targeted overexpression of *GA2ox1* driven by a *GA3ox2* promoter results in semidwarf stature (Sakamoto et al. 2003). In addition, Huang et al. (2009) characterized a CaMV 35S enhancer-line rice mutant, which has a dominant dwarf phenotype. On analysis, a high expression level of *GA2ox6* and low levels of endogenous GA were observed, and application of exogenous bioactive GA could restore the wild-type phenotype. This suggests the potential of *GA2ox* manipulation in improving the semidwarf phenotype.

Table 1 describes some of the genes involved in GA homeostasis. The rice *ELONGATED UPPERMOST INTERNODE 1* (*EUI1*) gene is proposed to be involved in the negative feedback regulation of GA biosynthesis. It encodes a predicted P450 monooxygenase, CYP714D1, that catalyzes the 16α, 17-epoxidation of non-13-hydroxylated GAs, resulting in reduced activity of bioactive GA_1, GA_4, and GA_{12} (Zhang et al. 2011). Null mutants of *eui1* show high accumulation of bioactive GA_1 and GA_4 in the upper internode and a longer internode phenotype. Conversely, overexpression of this gene results in accumulation of SLENDER RICE 1, SLR1, a negative regulator of transcription factors that promote transcription of GA synthesis genes, resulting in significant reduction in GA levels accompanied by a dwarf phenotype. This suggests that *EUI* is a major component of negative feedback regulation of GA biosynthesis. In hybrid breeding, rice male sterile cultivars, which have a short uppermost internode owing to low levels of bioactive GAs, are crossed with *eui1* null mutants to enhance elongation of the uppermost internode, which improves panicle emergence and flower development (Zhu et al. 2006; Zhang et al. 2008; Chen et al. 2012).

The transcription factor *YABBY1* (*YAB1*) has a similar expression pattern as *GA3ox2* and *GA20ox2*. *YAB1* overexpression lines show a semidwarf phenotype with decreased expression of *GA3ox2* and low amounts of bioactive GA_1. Gel shift assays confirmed the binding of YAB1 to promoter regions of *GA3ox2*. GA suppression of *GA3ox2* expression is reduced in

YAB1 cosuppression lines, consistent with a role of YAB1 in negative feedback regulation of GA biosynthesis (Dai et al. 2007). The *DWARF RICE WITH OVEREXPRESSION OF GIBBERELLIN-INDUCED GENE* (*DOG*) gene encodes an A20/AN1 zinc-finger protein that confers a dwarf phenotype with incomplete panicle emergence on overexpression. These lines also show reduced expression of *GA3ox2*, resulting in a decreased concentration of bioactive GA_1. *DOG* is itself induced by GA, suggesting that it, like *YAB1*, plays a role in negative feedback regulation of GA homeostasis; however, the exact mechanism is unknown (Liu et al. 2011).

INO80, a conserved ATP-dependent chromatin-remodeling factor protein, appears important for expression of GA biosynthesis genes. Homozygous transfer DNA (T-DNA) insertion mutants could not be recovered, suggesting lethality, but *INO80* heterozygous T-DNA mutants, as well as RNA interference (RNAi) knockdown lines, show a dwarf phenotype and retarded reproductive development, accompanied by down-regulation of *CPS1* and *GA3ox2* and reduced GA levels. ChIP analyses show direct binding of INO80 to the 5′ untranslated region (UTR) of *CPS1* and 3′ UTR of *GA3ox2* loci (Li et al. 2018b).

The rice recessive mutant *plant architecture determinant* (*pad*), which confers a single amino acid change to MILD COMPLEMENTING ACTIVITY 1 (MCA1), a plasma membrane protein, shows a severe dwarf phenotype, shorter and stunted leaves, and fewer secondary branches. Quantitative real-time polymerase chain reaction (qPCR) analysis revealed up-regulation of genes related to GA-deactivation, such as *GA2ox1*, *GA2ox3*, and *EUI1*, and the bioactive GA_1 level was significantly decreased, especially in the third internode. This suggests a role of MCA1 in regulating GA catabolism, although the mechanism remains unknown (Liu et al. 2015b).

GA Signaling

In the past decade, major components involved in GA signaling have been discovered and characterized through genetic screening of rice dwarf mutant lines. These components include the nuclear-localized GA receptor, GIBBERELLIN INSENSITIVE DWARF 1 (GID1), DELLA proteins (specifically in rice, SLENDER RICE1 [SLR1]), and the F-box protein, GIBBERELLIN INSENSITIVE DWARF 2 (GID2; Ikeda et al. 2001; Sasaki et al. 2003; Achard and Genschik 2009). Table 1 summarizes rice genes involved in GA signaling that impact plant height. The current model of the GA signal transduction pathway suggests that, in the absence of bioactive GA, GID1 does not interact with SLR1 and SLR1 is thus available to interact with and repress diverse transcription factors in GA signaling, making SLR1 a negative regulator of rice growth. In the presence of bioactive GA, GID1 perceives GA through binding the C3-hydroxyl group of GA in the GID1-binding pocket. This triggers a conformational change in the amino-terminal end of the binding pocket to promote its closure. The upper surface of the lid then binds SLR1 to form the GA–GID1–SLR1 protein complex (Ueguchi-Tanaka et al. 2007; Hirano et al. 2008). On formation of the complex, GID2, an F-box protein subunit of the SKP–CULLIN–F-box (SCF) E3 ubiquitin ligase complex, binds to SLR1 and adds a polyubiquitin chain. The ubiquitinated SLR1 is then targeted for degradation by the 26S proteasome pathway (Fig. 3). The degradation of SLR1 triggers various GA responses in rice that modulate plant height, flower development, and seed formation.

Null mutants of *gid1* and *gid2* show a dwarf phenotype and are insensitive to the application of exogenous bioactive GAs (Ueguchi-Tanaka et al. 2005). Conversely, null mutants of *slr1* show longer internodes, pale green leaves, and lower fertility, similar to rice plants treated with exogenous bioactive GAs (Harberd 2003; Achard and Genschik 2009; Nagai et al. 2018).

In *Arabidopsis*, *O*-fucosylation of DELLA proteins by the *O*-fucosyltransferase encoded by the *SPINDLY* (*SPY*) gene promotes interaction between DELLA proteins and transcription factors, thereby negatively regulating GA signaling and plant growth (Zentella et al. 2017). Consistent with the mechanism deduced from *Arabidopsis*, in rice, *spy* RNAi transgenic lines show increased elongation of lower internodes,

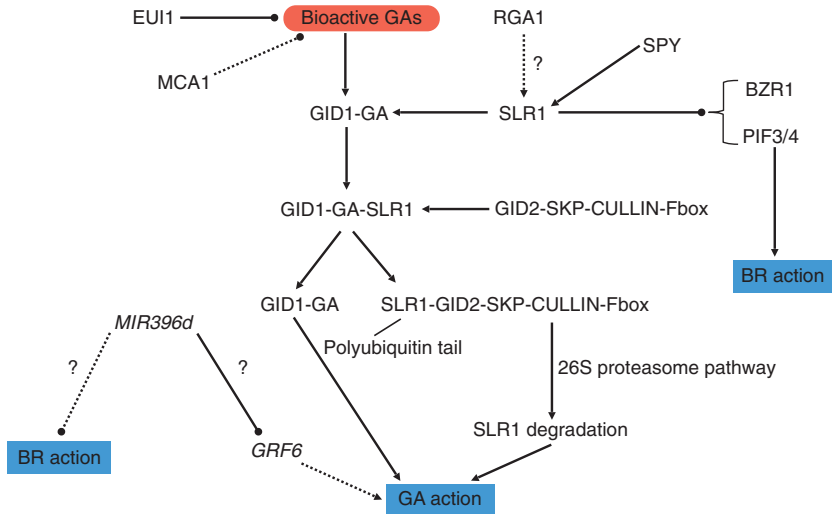

Figure 3. Gibberellic acid (GA) signaling in rice. Solid lines indicate direct regulation. Dotted lines with question marks indicate hypothesized relationships. Regular arrows indicate positive regulation/activation, whereas arrows terminating in a circle indicate negative regulation/inhibition. The mechanism of SPY regulation has not been elucidated in rice but is hypothesized to be analogous to that described for *Arabidopsis* (Zentella et al. 2017; see also Table 1).

similar to the phenotype of the *slr1* mutant, as expected if SPY functions in wild-type plants to promote SLR1 repression of GA response (Shimada et al. 2006).

Several other rice genes have been identified that regulate GA signaling, although mechanistic details await elucidation. The rice *CHITIN INDUCIBLE GIBBERELLIN-RESPONSIVE PROTEIN* (*CIGR*) gene shows increased expression upon application of exogenous bioactive GA. These results suggest that *CIGR* may be involved in GA response. Quantitative RT-PCR of *CIGR* reveals higher expression level in a taller rice variety, Pokkali, as compared with a shorter rice variety, Zhenshan 97, suggesting that *CIGR* plays a role in regulating plant height (Kovi et al. 2011). The rice *DWARF AND NARROW LEAF 1* (*DNL1*) gene encodes a cellulose synthase-like D4 protein predicted to be involved in GA signaling. The null-mutant *dnl1* shows a dwarf and narrow leaf phenotype, increased number of tillers with thinner culm, and decreased seed yield and grain weight as compared with wild-type (Ding et al. 2015). *dnl1* mutants show insensitivity to exogenous GA, and quantitative RT-PCR shows increased expression of *D1*, *EUI1*, *GA20ox2*, and *GA20ox3* genes and decreased expression of *SLR1*, *GID1*, *GID2*, *GA20ox1*, *GA20ox3*, and *GA3ox2* genes (Wei et al. 2013). RNAi lines of rice *Polycomb* (*PcG*) genes such as *EMF2b*, *FIE2*, and *CLF* also show dwarf stature with reduced cell expansion and cell division. The endogenous GA_3 concentration is reduced and the application of exogenous GA_3 fails to restore a wild-type phenotype. These results suggest a role of *PcG* genes in GA homeostasis and signaling, but the mechanism is still unknown (Zhong et al. 2018). The rice *Protein Phosphatase 2C34* (*PP2c34*) gene is suggested to be a positive regulator of both GA biosynthesis and GA signaling. *pp2c34* T-DNA insertional mutants show reduced plant height and shorter internode length, and GA application did not recover a wild-type phenotype. RT-PCR revealed reduced expression of the GA-biosynthesis gene, *GA3ox2*, and the GA-signaling gene, *GID1*. *pp2c34* mutants also show delayed expression of GA-induced α-amylase genes such as *RAmy3E* and *Amy* on treatment with GA (Hossain et al. 2018).

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BRASSINOSTEROIDS

BRs are steroidal hormones that are major regulators of plant development. In rice, BRs influence important architectural traits, including plant height, tiller angle, and grain size and shape. These traits are impacted by mutations that affect BR synthesis, BR catabolism, and BR signaling. In general, mutations that result in reduced BR levels or impaired BR signaling result in favorable agronomic traits of semidwarf to dwarf stature, increased chlorophyll content, and an acute laminar joint angle that promotes leaf erectness, allowing both improved light penetration to the lower canopy for increased photosynthesis and increased planting density. However, these same mutations also frequently lead to grain rounding and reduced grain size, with negative impacts on yield. BR levels are feedback inhibited and elevated BR levels reduce BR synthesis rates, and also repress synthesis of GAs. Thus, somewhat paradoxically, manipulations that result in supraoptimal levels of BRs can also result in dwarfing. In addition, BRs play complex roles in rice biotic and abiotic stress tolerance, with both positive and negative impacts observed depending on the particular environmental conditions (Hao et al. 2013; Zhang et al. 2014a; Tong and Chu 2018). For all of these reasons, usage of BR-related mutants for breeding of semidwarf plants is not straightforward. On the positive side, the complicated pathways of BR synthesis and response provide many entry points for manipulation, and non-null mutations, as well as knockouts of individual family members wherein several genes have partially redundant functions, provide opportunities for nuanced manipulation. Here, we focus on BR-related mutations that affect plant stature; additional BR-related mutations have been discussed elsewhere (Kim and Wang 2010; Tong and Chu 2018).

Brassinosteroid Synthesis

As lipid-based hormones, BRs are thought to be synthesized in membrane compartments, particularly the endoplasmic reticulum (Vukašinović and Russinova 2018). BR synthesis is complex because of the nonlinearity of the synthesis schema. Campesterol is the first committed steroid in the pathway, and castasterone (in rice) (Mori et al. 2002) or brassinolide (e.g., in *Arabidopsis*) is the final product, but a matrix of enzymes and synthesis routes links these two metabolites, and resultant intermediate products have varying degrees of bioactivity. A simplified schematic of BR synthesis is provided in Figure 4 (for additional and alternative pathways, see Sakamoto and Matsuoka 2006; Zhao and Li 2012). As is illustrated, a major "decision point" is whether the C-6 position is oxidized as one of the late steps in synthesis (from 6-deoxocastasterone to castasterone) or as one of the early steps in synthesis (from campestanol to 6-oxo-campestanol). The majority of the enzymes in BR synthesis are cytochrome P450s and determination of the substrate specificity of cytochrome P450s can be challenging. GC-MS assay of BR intermediates in mutant plants can provide clues as to function, but the implied enzymatic role from these measurements sometimes differs from that ascertained when the purified recombinant enzyme is assayed, presumably because of complex feedback regulation occurring *in planta* (Sakamoto et al. 2012).

Table 2 summarizes mutations in BR biosynthetic enzymes that affect plant stature (Bishop 2003; Sakamoto and Matsuoka 2006; Zhao and Li 2012). These mutations intervene at multiple points in the synthetic pathway. For example, *brd2* (Hong et al. 2005) and *lhdd10* (Liu et al. 2016) are mutations in a gene orthologous to *Arabidopsis DIMINUTO/DWARF1* (*AtDIM/DWF1*) (Klahre et al. 1998) that encodes a FAD-linked oxidoreductase that catalyzes the conversion of 24-methylene cholesterol to campesterol upstream of the committed BR pathway. Resultant plants are dark green semidwarfs with erect leaves and reduced fertility. Proceeding along the synthesis scheme, two enzymes, CYP90B1 and CYP724B1, function redundantly in C-22α hydroxylation according to in vitro assays with the recombinant proteins (Sakamoto et al. 2006). The *dwarf4* mutation in CYP90B1 mildly reduces plant stature and confers erectness; field trials suggest that its yield per hectare might exceed that of wild-type un-

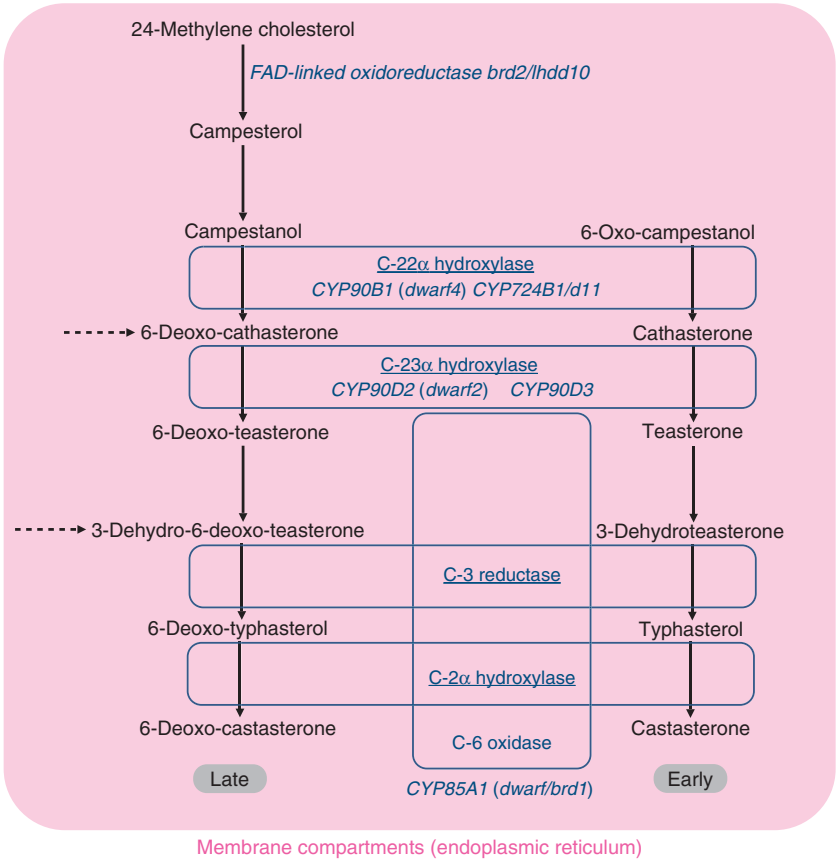

Figure 4. Brassinosteroid (BR) biosynthesis in rice. Black dotted arrows indicate that alternative routes of synthesis are available. When gene names differ from mutant names, the mutant names are provided in parentheses after the gene names. "Late" and "Early" refer to the relative timing of C6 oxidation (see also Table 2). (Created from modified data in Figure 1 of Sakamoto and Matsuoka 2006.)

der increased planting densities (Sakamoto et al. 2006). The *d11* mutation in CYP724B1 causes stronger phenotypes of semidwarfness and rounded seeds (Tanabe et al. 2005), suggesting that it is the major enzyme catalyzing this conversion. The double *dwarf4-1/d11-4* mutant is severely dwarfed (Sakamoto et al. 2006).

At the next step in BR synthesis, two enzymes, CYP90D2 and CYP90D3 have been ascribed C-23α hydroxylation activity based on in vitro assays on the recombinant proteins (Sakamoto et al. 2012). CYP90D2 was previously thought to catalyze C-3 dehydrogenation, based on the levels of BRs found in *ebisu dwarf* (*d2*) mutant plants harboring an introduced stop codon in CYP90D2 (Hong et al. 2003), showing the difficulty in ascribing enzymatic roles to cytochrome P450s. The *d2* mutation causes semidwarf erect tillers and rounded seeds (Hong et al. 2003). However, the *d2* mutation may not result in complete loss-of-function because T-DNA null mutations in *CYP90D2* cause much more severe dwarfism (Li et al. 2013). Two other genes, CYP90A3 and CYP90A4, were hypothesized early on to also perform C-23α hydroxylation based on their sequence identity to the corresponding *Arabidopsis* genes (Sakamoto and Matsuoka 2006), but neither activity has been confirmed at the biochemical level, and CPY90A3 *tos17* insertional mutants are not dwarfs (Sakamoto and Matsuoka 2006).

Table 2. Genes and mutants in brassinosteroid (BR) synthesis and signaling

Pathway	Gene names	Gene encodes	Mutant names	Locus ID	Key references
BR biosynthesis	*BRD2*	FAD-linked oxioreductase	*brd2* *lhdd10*	Os10g0397400	Hong et al. 2005; Liu et al. 2016
	CYP90B2	C-22α hydroxylation	*dwarf4*	Os03g0227700	Sakamoto et al. 2006
	CYP724B1	C-22α hydroxylation	*dwarf11/d11*[a]	Os04g0469800	Tanabe et al. 2005; Sakamoto et al. 2006
	CYP90D2	C-23α hydroxylation	*d2*[b]	Os01g0197100	Sakamoto et al. 2012
	CYP90D3[b]	C-23α hydroxylation	–	Os05g0200400	Sakamoto et al. 2012
	CYP90A3	C-23α hydroxylation	*cpd1*	Os11g0143200	Sakamoto and Matsuoka 2006
	CYP90A4	C-23α hydroxylation	*cpd2*	Os12g0139300	Sakamoto and Matsuoka 2006
	CYP85A1	C-6 oxidation (L)	*dwarf/brd1*	Os03g0602300	Hong et al. 2002; Mori et al. 2002
	SLENDER GRAIN	BAHD Acyltransferase-like protein	*slg*	Os08g0562500	Feng et al. 2016
	CYP734A2	Multifunctional multisubstrate oxidases	–	Os02g0204700	Sakamoto et al. 2011
	CYP734A4			Os06g0600400	
	CYP734A6			Os01g0388000	
BR signaling	*BRI1*	BR receptor kinase	*d61-1* (weak allele); *d61-2* (stronger allele); *d61-4* (null)	Os01g0718300	Yamamuro et al. 2000; Zhang et al. 2016
	BRL1	BR receptor kinase	–	Os09g0293500	Nakamura et al. 2006
	BRL3	BR receptor kinase	–	Os08g0342300	Nakamura et al. 2006
	BAK1	BR coreceptor	*sg2*	Os08g0174700	Li et al. 2009; Yuan et al. 2017
	BSK3	Kinase downstream from BR receptor	–	Os04g0684200	Zhang et al. 2016
	BSL1	Proposed by sequence homology with *Arabidopsis* BSU family members, to dephosphorylate and inactivate GSK2	–	Os05g0144400	Tong et al. 2012
	GSK2	GSK3-like kinase	–	Os05g0207500	Tong et al. 2012
	BZR1	Transcription factor	–	Os07g0580500	Bai et al. 2007
	RAVL1	Transcription factor	*ravl1*	Os04g0581400	Je et al. 2010
	OFP19	Ovate family transcription factor	–	Os05g0324600	Yang et al. 2018
	DLT	GRAS family transcription factor	*dlt/smos2*	Os06g0127800	Tong et al. 2009; Hirano et al. 2017
	RLA1/ SMOS1	AP2-type transcription factor	*rla1/smos1*	Os05g0389000	Aya et al. 2014; Hirano et al. 2017; Qiao et al. 2017
	RGA1	G protein α-subunit	*d1*	Os05g0333200	Ashikari et al. 1999
	TUD1	E3 ubiquitin ligase	*tud1*	Os03g0232600	Hu et al. 2013

Continued

Table 2. *Continued*

Pathway	Gene names	Gene encodes	Mutant names	Locus ID	Key references
	XIAO	LRR-RLK	*xiao*	Os04g0576900	Jiang et al. 2012
	SG1	Unknown protein involved in BR signaling	*sg1*	Os09g0459200	Nakagawa et al. 2012
	MKKK10	Mitogen-activated protein kinase kinase kinase 10	*smg2*	Os04g0559800	Xu et al. 2018
	MPKK4/ SMG1	Mitogen-activated protein kinase kinase 4	*smg1*	Os02g0787300	Duan et al. 2014; Xu et al. 2018
	MAPK6	Mitogen-activated protein kinase 6	*dsg1*	Os06g0154500	Liu et al. 2015a; Xu et al. 2018
	MKP1/GSN1	Mitogen-activated protein kinase phosphatase	*gsn1*	Os05g0115800	Guo et al. 2018

"–" signifies that mutants have not been identified, although in some cases relevant transgenics (e.g., overexpression or RNAi lines) have been generated (see text).

[a]Originally thought to function in C-3 reduction based on which exogenous BRs restored/failed to restore BR response and BR quantification in *d11* mutants (Tanabe et al. 2005).

[b]Alternatively thought to function in C-3 dehydration based on which exogenous BRs restored/failed to restore BR response in laminar joint bending assay (Hong et al. 2003), and enzyme activity from crude extracts of mutant versus wild-type plants (Li et al. 2013).

Late C-6 oxidation is catalyzed by CYP85A1, and deletion and loss-of-function mutations in this gene, known respectively as *dwarf* and *brd1*, cause reduced tillering and panicle production, sterility, and severe dwarfing with curled leaves only 1/10 the length of those of wild-type plants (Hong et al. 2002; Mori et al. 2002). These phenotypes suggest that the late C-6 pathway of BR synthesis may be the predominant pathway in rice. Finally, *SLG*, a gene with homology with BADH acyltransferases, alters BR synthesis and its RNAi knockdown results in semidwarf erect plants with rounded seeds; however, the substrates of SLG remain unknown (Feng et al. 2016).

In reviewing BR synthesis in rice, it is useful to note that enzymes and corresponding mutants have not been identified for all steps in the pathway (Fig. 4). Whether this reflects a lack of saturation in forward genetic screens or lethality on loss of the specific enzyme activity is an interesting question. Opportunities for targeted gene knockout offered by CRISPR systems seem one way forward to address this question.

Dwarfing can arise not only from blocking BR synthesis but also from promoting BR degradation. Overexpression of each of the cytochrome P450s CYP734A2, CYP734A4, and CYP734A6 results in dwarf phenotypes, ranging from moderate to severe, and failure to form floral organs (Sakamoto et al. 2011). Enzyme assays on recombinant proteins revealed that CYP734A2, CYP734A4, and to a lesser extent CYP734A6 are multifunctional enzymes that catalyze the oxidation of a number of C-22 hydroxylated BRs; CYP734A2 and CYP734A4 can also use the resultant oxidized products as substrates for further oxidation (Sakamoto et al. 2011).

Brassinosteroid Signaling

The BR signaling pathway in rice (Fig. 5) appears to essentially mirror that elucidated in *Arabidopsis* (Kim and Wang 2010), although the information available in rice is less complete. In both species, BRs are perceived at the plasma membrane by receptor-like kinases (RLKs)—

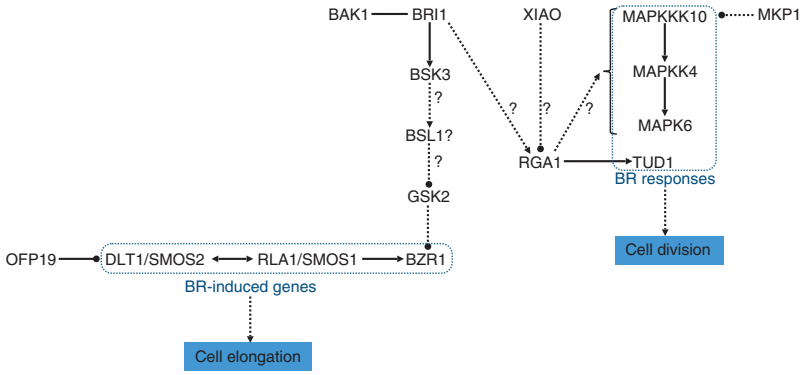

Figure 5. Brassinosteroid (BR) signaling elements discussed in this review. Dotted lines indicate multiple steps. Dotted lines with question marks indicate hypothesized relationships. Regular arrows indicate positive regulation/activation, whereas arrows terminating in a circle indicate negative regulation/inhibition (see also Table 2).

unlike nuclear perception of steroidal hormones in mammals—followed by a signaling cascade comprised of kinases and phosphatases that ultimately results in de-repression of transcription factors that activate expression of BR-induced genes (Tong and Chu 2018).

In rice, BRI1 is the major RLK mediating BR perception in above-ground organs. Two homologs, BRL1 and BRL3, are primarily expressed in roots (Nakamura et al. 2006). BRI1 mutations, named *d61*, were some of the earliest BR-related mutants to be identified in rice (Yamamuro et al. 2000). Phenotypes range from semidwarf erect plants for mutants with single amino acid substitutions such as *d61-1*, *d61-2*, *d61-7*, *d61-8*, *d61-9*, and *d61-10* (Yamamuro et al. 2000; Nakamura et al. 2006) to sterile severe dwarfs with curled leaves for two other amino acid substitutions, *d61-3* and *d61-5*, as well as for two mutations, *d61-4* and *d61-6*, that each introduce a stop codon (Nakamura et al. 2006). Although grain number is reduced in *d61-1*, *d61-2*, and *d61-8*, grain yield per area in the field of the mild mutant *d61-7* can match, although not exceed, that of wild-type at high planting densities (Morinaka et al. 2006). However, minimal cosuppression of *BRI1* results in plants that have no alterations in height, panicle morphology, or seed shape but have a more erect architecture (Morinaka et al. 2006). Accordingly, it has been hypothesized that these lines will yield better than wild-type under high-density conditions in the field (Morinaka et al. 2006). These observations on *BRI1* are important because they suggest that gene dosage can be manipulated to produce organ-specific effects on BR-related agricultural traits.

As in *Arabidopsis*, BRI1 in rice functions with a coreceptor RLK, BAK1; however, antisense *BAK1* lines (Li et al. 2009), the *sg2* single-site mutant of *BAK1* (Yuan et al. 2017), and *BAK1* CRISPR mutants with introduced stop codons (Yuan et al. 2017) show only mild dwarfism along with slightly rounded smaller seeds. In all of these variants, yield is somewhat reduced (Li et al. 2009; Yuan et al. 2017).

As in *Arabidopsis*, ligand activation of BR receptors results in their transphosphorylation of a downstream kinase, BSK3 in rice, with consequent BSK3 activation caused by the alleviation of autoinhibition (Zhang et al. 2016). Cosuppression of *BSK3* results in semidwarf erect phenotypes similar to those of weak mutants of *BRI1* (Zhang et al. 2016). In *Arabidopsis*, BSK3 activates a phosphatase, BSU1; by analogy, the BSU1 homolog, BSL1, may play a similar role in rice although this has not been shown. Phosphatases activity, in turn, is posited to inhibit GSK3-like kinases, particularly GSK2 in rice (BIN2 in *Arabidopsis*), thereby alleviating phosphorylation-based repression of a number of transcription factors. GSK2 is accordingly a negative regulator of BR signaling; its moderate overexpression results in semidwarf erect rice with

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rounded seeds, whereas strong overexpression results in severely dwarfed plants with curled leaves and sterile seeds (Tong et al. 2012).

In *Arabidopsis*, the transcription factors BZR1 and BES1 are among the major targets of BIN2 inhibition in the absence of BR. In rice, a number of transcription factors have been identified as targets of GSK2 repression. Here, we focus on those BR-regulated transcription factors with reported impacts on plant stature; a comprehensive discussion of GSK2 targets has been provided elsewhere (Tong and Chu 2018). In rice, there are four BZR1 homologs, with *BZR1* showing greatest homology with *Arabidopsis* BZR1 and BES1 (Bai et al. 2007). RNAi against *BZR1* results in semidwarf erect plants (Bai et al. 2007).

Like BZR1, the AP2-type transcription factor RLA1/SMOS1 is also destabilized by GSK2-mediated phosphorylation (Qiao et al. 2017). Protein–protein interaction tests show that RLA1/SMOS1 physically interacts with BZR1; moreover, RLA1/SMOS1 enhances the transcriptional activity of BZR1 in a yeast-based assay as well as in transient reporter assays in *Nicotiana benthamiana* (Qiao et al. 2017). Consistent with a significant positive role in BR signaling, the *smos1* truncation mutant (Aya et al. 2014) and the *rla1* insertional mutant (Qiao et al. 2017) are semidwarfs with small rounded seeds. Another target for GSK2 phosphorylation is the GRAS-type transcription factor, DLT/SMOS2 (Tong et al. 2012). The *dlt* T-DNA mutant (Tong et al. 2009) and the *smos2* deletion mutant (Hirano et al. 2017) are dark green erect semidwarfs with reduced tillering and seed fertility. DLT/SMOS2 interacts with RLA1/SMOS1, and the two transcription factors have mutual transactivation activity in a yeast reporter assay (Hirano et al. 2017), consistent with their similar mutant phenotypes.

Although it is not yet known whether it is regulated by GSK2, RAVL1 is another transcription factor that positively regulates genes involved in both BR signaling and BR synthesis (Je et al. 2010). *ravl1-1* and *ravl1-2* transposon-generated mutants show mild impairments in stature and leaf inclination. *ravl1-1* shows reduced expression of the BR receptor *BRI1* and the BR biosynthetic genes *D2*, *D11*, and *BRD1*; both gel shift and ChIP assays show direct binding of RAVL1 to the promoters of *BRI1* and BR biosynthesis genes (Je et al. 2010).

Although the above transcription factors are positive regulators of BR signaling, the OVATE family protein OFP19 complexes with DLT and antagonizes its transcriptional activity (Yang et al. 2018). Consistent with a negative role for OFP19 in BR signaling, OFP19 overexpression lines show dwarfism, erect leaves, and rounded seeds (Yang et al. 2018).

STRIGOLACTONES

SLs are a group of small tricyclic lactones joined to a butanolide moiety by an enol-ether bond (Cook et al. 1966; Waters et al. 2017). Like ABA, SLs are carotenoid-derived, and when plants are treated with inhibitors of carotenoid biosynthesis, SL biosynthesis is also reduced (Matusova et al. 2005). SLs are root-to-shoot phytohormones that regulate key agricultural traits associated with plant architecture and yield. A well-known correlation between plant height and tiller number exists in rice (Yan et al. 1998; Li et al. 2003), and rice mutants in SL synthesis and signaling typically display both reduced stature and increased tillering (Kinoshita and Shinbashi 1982; Kinoshita and Takahashi 1991). It is therefore not surprising that SL biosynthesis has been proposed as a target for breeding (Yoneyama et al. 2012; Saeed et al. 2017).

Strigolactone Biosynthesis

The biosynthesis of SL in rice (Fig. 6; Table 3) starts in the plastid with the conversion of all-*trans* β-carotene to 9-*cis* β-carotene, in a reaction catalyzed by the enzyme carotenoid cleavage dioxygenase 7, encoded by the gene *Dwarf17* (*D17*) (Zou et al. 2005). A second enzyme, all-*trans*-β-carotene isomerase, encoded by *Dwarf 27* (*D27*) (Ishikawa et al. 2005; Alder et al. 2012) catalyzes the structural rearrangement of 9-*cis* β-carotene into 9-*cis*-β-apo-10′-carotenal. A third enzyme, carotenoid cleavage dioxygenase 8, encoded by *Dwarf 10* (*D10*) (Ishikawa et al. 2005) catalyzes the conversion of carotenal into carlac-

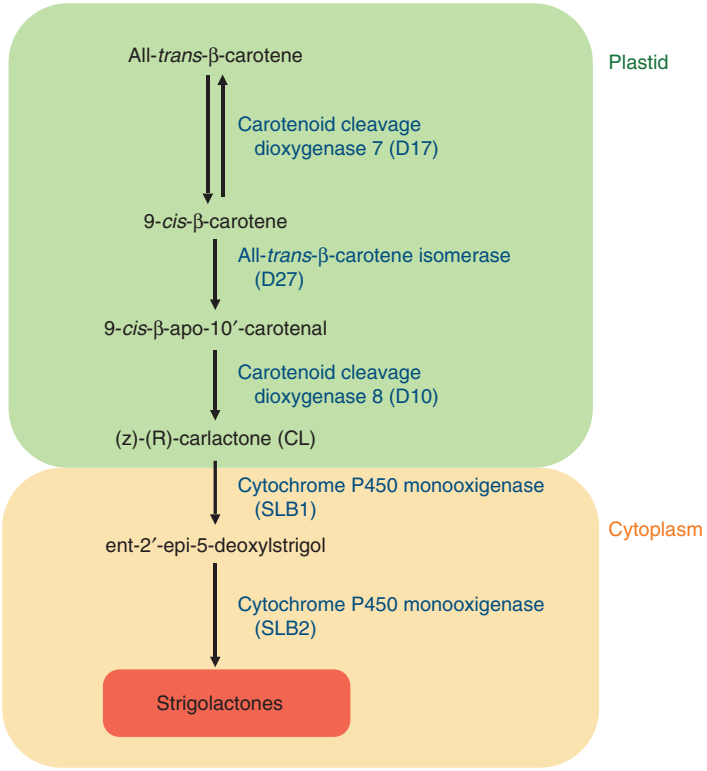

Figure 6. Strigolactone (SL) biosynthesis in rice (see also Table 3).

tone, a key intermediary of SL biosynthesis (Seto et al. 2014).

D17, *D27*, and *D10* mutants show a recessive dwarfing trait, increased tillering, and reduction in grain size (Ishikawa et al. 2005). For example, rice varieties homozygous for the *high tillering dwarf 1* (*htd1*) allele are semidwarf and high tillering as a result of a point mutation that causes a single amino acid change in D10 (Zou et al. 2005). *d10*, *d17*, and *d27* also exhibit delayed dark-induced leaf senescence, which is reversed by the application of exogenous SL (Yamada et al. 2014).

Following its synthesis in the plastid, carlactone is exported to the cytoplasm and oxidized for conversion into SLs. *SLB1*, the rice homolog of the *Arabidopsis MAX1* (Abe et al. 2014) gene, encodes a cytochrome P450 monooxygenase enzyme that converts carlactone to deoxylstrigol (Zhang et al. 2014b). A second cytochrome P450 monooxygenase, SLB2, then catalyzes the synthesis of SL from deoxylstrigol (Zhang et al. 2014b). Resulting SLs are classified in two different groups based on the orientation of their C-ring: those with an α-oriented C-ring such as orobanchol, and those with an β-oriented C-ring like strigol. In tobacco, both types are present, whereas, intriguingly, only SLs with an α-oriented C-ring are found in rice (Xie et al. 2013). Decreased SL biosynthesis was found to be associated with a naturally occurring deletion in the Bala cultivar of a chromosomal region that contains both *SLB1* and *SLB2* (Cardoso et al. 2014). Other cultivars carrying this deletion had lower SL root content and showed more tillering (Cardoso et al. 2014).

The potential of bioengineering the SL biosynthetic pathway for targeted improvement of crops also has been explored. Using CRISPR/Cas9 in a proof-of-concept approach, seven complete or partial knockout mutant *d17* alleles were generated. The mutant plants showed re-

Table 3. Genes and mutants involved in strigolactone (SL) biosynthesis and signaling

Pathway	Gene names	Gene encodes	Mutant names	Locus ID	Key references
SL biosynthesis	*D17*	Carotenoid cleavage dioxygenase 7	*dwarf 17*	Os04g0550600	Zou et al. 2005
	D27	β-Carotene isomerase, SL biosynthesis	*dwarf 27*	Os11g0587000	Ishikawa et al. 2005; Alder et al. 2012
	D10	Carotenoid cleavage dioxygenase 8	*dwarf 10, htd1*	Os01g0746400	Ishikawa et al. 2005
	SLB1	Cytochrome P450 monooxygenase	*strigolactone biosynthesis 1*	Os01g0700900	Zhang et al. 2014b
	SLB2	Cytochrome P450 monooxygenase	*strigolactone biosynthesis 2*	Os01g0701400	Zhang et al. 2014b
SL signaling	*Dwarf 14*	α/β-Hydrolase	*dwarf 14, amikawabunwai tillering dwarf, htd4*	Os03g0203200	Arite et al. 2009
	Dwarf 3	F-box/LRR- repeat MAX2 homolog	*dwarf 3, bunketsuwaito tillering dwarf*	Os06g0154200	Jiang et al. 2013
	Dwarf 53	Substrate of SCF-D3 ubiquitination complex	*dwarf 53, dwarf kyushu 3*	Os11g0104300	Jiang et al. 2013
	FC1	TCP family transcription factor	*fine culm 1*	Os03g0706500	Lu et al. 2013
	IPA1	Squamosa promoter–binding-like transcription activator	*ideal plant architecture 1*	Os08g0509600	Jiao et al. 2010; Miura et al. 2010
	MADS57	MADS-box transcription factor	*mads-box transcription factor 57*	Os02g0731200	Chen et al. 2018
	DEP1	G protein γ subunit	*dense and erect panicle 1*	Os09g0441900	Lu et al. 2013; Huang et al. 2009; Xu et al. 2016

duced SL biosynthesis, reduced plant height, and increased tillering (Butt et al. 2018), phenotypes that are advantageous from an agricultural standpoint.

Strigolactone Signaling

SL signaling in rice (Fig. 7; Table 3) starts with the binding of an SL molecule to the α/β hydrolase receptor, D14 (Dwarf 14; Arite et al. 2009). According to a proposed signaling model, this results in the hydrolysis of the SL molecule, and the formation of an intermediary molecule covalently linked to D14 (Yao et al. 2016, 2018). This noncanonical perception mechanism contrasts with the perception of other plant hormones, which typically involves reversible interactions between receptor and ligand. This model has been challenged recently by the observation that the active binding site appears too small to accommodate the SL hydrolysis product (Carlsson et al. 2018). Based on the observation in *Arabidopsis* that an enzymatically dead version of D14 can restore SL signaling to a *d14* null mutant, it has been proposed recently that signaling by D14 is instead initiated by intact SL binding (Seto et al. 2019). This alternative mechanism would be more typical of perception mechanisms described for plant hormones; it does incorporate D14-mediated SL hydrolysis, but as a subsequent step occurring after signal transmission (Seto et al. 2019). Given that SLs

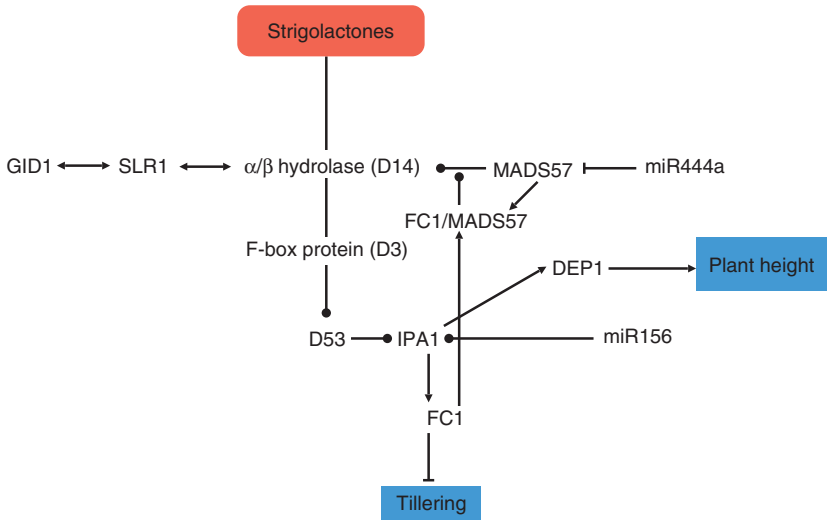

Figure 7. Strigolactone (SL) signaling elements discussed in this review. Regular arrows indicate positive regulation/activation, whereas arrows terminating in a circle indicate negative regulation/inhibition (see also Table 3).

are the newest group of plant hormones to be characterized, it is not surprising that, despite the significant advances in recent years and the well-characterized biosynthetic pathway, the signaling mechanism remains to some extent a topic of debate.

D14, also *kamikawabunwai tillering dwarf*, corresponds to the quantitative trait locus (QTL) for primary panicle branch number qPPB3 (Peng et al. 2014). The *d14* mutant shows a dwarf phenotype with increased tillering and reduced grain size (Ishikawa et al. 2005). *d14* and another dwarf, *d88*, later also identified as a *D14* mutant (Gao et al. 2009), show a reduced number and size of parenchyma cells, smaller vascular volume, and delayed vascular development, resulting in tiller diameters that are reduced by half (Gao et al. 2009). The dwarf phenotype arises from reduced elongation of parenchyma cells and shortening of each internode except for the fourth (Gao et al. 2009). Furthermore, both *d14* and *d88* mutants display a larger number of shorter tillers with smaller panicles and seeds (Gao et al. 2009). The spontaneous, mild phenotype mutant allele of *D14*, *htd4*, results from a nonsense mutation that causes a premature stop codon (Wang et al. 2017). *htd4* plants also display higher tiller number, dwarf stature, shorter internodes, and smaller panicles and leaves (Wang et al. 2017). Another *D14* mutant, *htd2*, also shows high tillering, reduced height, and reduction in blade length and width, culm diameter, and panicle size (Liu et al. 2009).

Following the conformational change in D14 as a result of SL perception, D14 interacts with the F-box protein D3 (Dwarf 3; Yao et al. 2016, 2018; Seto et al. 2019). Mutations in *D3*, also known as *bunketsuwaito tillering dwarf*, produce plants with short stature (Ishikawa et al. 2005), increased leaf longevity during dark-induced senescence (Yan et al. 2007), decreased production of adventitious roots (Xu et al. 2015), and a strong defect in colonization by arbuscular mycorrhizal fungi (Yoshida et al. 2012).

D14 interaction with D3 leads to the ubiquitination of the downstream protein, D53, a transcription factor that is a class I Clp ATPase protein. Ubiquitination targets D53 for degradation by the ubiquitin–proteasome system, and thus eliminates D53 repression of downstream target genes (Jiang et al. 2013; Zhou et al. 2013). The *d53* gain-of-function mutation named *dwarf kyushu 3* increases D53 repression of downstream SL target genes, resulting in an exaggerated number of tillers and a dwarf phenotype and plants that are insensitive to exogenous

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SL application (Jiang et al. 2013; Zhou et al. 2013). Conversely, *D53* RNAi knockdown lines display reduced numbers of tillers (Zhou et al. 2013).

In the absence of SLs, D53 is available and interacts physically with the transcription factor IDEAL PLANT ARCHITECTURE 1 (IPA1; also known as SQUAMOSA PROMOTER BINDING PROTEIN-LIKE 14, SPL14), thereby suppressing its transcriptional activation of downstream targets and promoting tillering (Song et al. 2017). In the presence of SLs, the degradation of D53 by the proteasome system releases the repression of IPA1-regulated gene expression and leads to SL response (Song et al. 2017). *IPA1* is negatively regulated at the transcript level by miR156 (Jiao et al. 2010; Miura et al. 2010). A point mutation in *IPA1* that disrupts its down-regulation by miR156 gives rise to plants with "ideal plant architecture," consisting of reduced tiller number, reduced height, increased lodging resistance, and increased yield (Jiao et al. 2010). Manipulation of *IPA1* has been thus proposed as a target of breeding programs to increase yield potential (Jiao et al. 2010).

Based on a chromatin immunoprecipitation assay, IPA1 binds to the promoter, of the Gγ heterotrimeric G-protein gene *DENSE AND ERECT PANICLE1*, *DEP1*, activating its expression (Lu et al. 2013). *DEP1* is an agronomically important gene (Huang et al. 2009; Xu et al. 2016) for which the loss-of-function truncated alleles, *Dn1-1* and *dep1*, cause semidwarfism and a dense erect panicle morphology (Huang et al. 2009; Taguchi-Shiobara et al. 2011).

Expression of *FINE CULM 1*, *FC1*, another important locus from a breeding perspective, is also positively regulated by IPA1 (Lu et al. 2013). *FC1* in rice is the ortholog of *TEOSINTE BRANCHED 1* (*TB1*) in maize, a key domestication gene that controls major differences in architecture between cultivated maize and its wild ancestor, teosinte (Doebley et al. 1997). FC1 is a negative regulator of tillering; thus, loss-of-function mutations in *FC1* produce plants with increased numbers of tillers (Takeda et al. 2003), whereas overexpression of FC1 results in plants with a reduced number of tillers (Choi et al. 2012). The resulting phenotype cannot be rescued by exogenous application of SL, indicating that FC1 is a downstream component in SL signaling (Minakuchi et al. 2010). This interpretation is supported by the observation that double mutants harboring *fc1* and *d17* loss-of-function alleles show the phenotype of the *d17* allele (Minakuchi et al. 2010).

MADS57 is a MADS-box transcription factor that physically interacts with FC1 to bind the promoter of the SL receptor gene *D14* (Guo et al. 2013; Chen et al. 2018). More precisely, the interaction of FC1 with MADS57 reduces the inhibition of *D14* by MADS57, thereby inhibiting tillering (Guo et al. 2013). Additionally, MADS57 is negatively regulated by miR444a (Guo et al. 2013). Accordingly, *MADS57* overexpression lines display increased tillers, whereas *MIR444a* overexpressing lines suppress *MADS57* expression, resulting in reduced tillering (Guo et al. 2013).

The study of SL signaling provides the opportunity to study the differential regulation of two essential agronomical traits: plant height and tillering. Many of the downstream components involved in the SL signaling pathway correspond to well-known architectural QTLs that have since been mapped to specific genes, such as *IPA*, *FC1*, and *DEP1*. Although the SL signaling pathway still awaits complete elucidation, our understanding is advancing rapidly and holds great promise for the incorporation of alternative sources of dwarfing traits.

HORMONE CROSS TALK IN REGULATION OF RICE ARCHITECTURAL TRAITS

Cross talk is a ubiquitous theme in hormonal regulation of plant physiology and development. Although the above sections have largely discussed GA, BR, and SL regulation of rice agronomic traits in isolation, in this section we discuss some of the key molecular and phenotypic interactions between these hormones.

GA–BR Cross Talk

Several genes in rice are a nexus of GA signaling interaction with other plant hormones. Based

on ChIP analysis, targets of the BR-activated transcription factor BZR1 include three GA biosynthesis genes, GA20ox-2, GA3ox-2, and GA2ox-3 (Tong et al. 2014), of which GA3ox-2 is of particular note as it encodes the enzyme catalyzing the conversion of GA20 to bioactive GA1. Consistent with the hypothesis that BR signaling induces GA production, the BR synthesis mutant *d11*, and the BR signaling mutant *dlt1*, have reduced GA levels (Tong et al. 2014). These observations indicate that BR stimulation of cell elongation and thus of plant stature is in part mediated by GA.

In addition, DELLA proteins (SLR1 in rice) interact with BZR1 in both *Arabidopsis* and rice. GA-induced DELLA degradation releases BZR1 from repression, which promotes BR signaling (Unterholzner et al. 2015, 2016; Tong and Chu 2016). In *Arabidopsis*, SPY-mediated *O*-fucosylation of the DELLA protein RGA results in its stronger binding to BZR1 (Zentella et al. 2017), which is among the transcription factors repressively targeted by DELLA proteins. Consistent with the hypothesis that a similar mechanism operates with the sole rice DELLA protein, SLR1, rice *spy* RNAi lines show an increase in lamina joint bending, a phenotype promoted by BRs (Shimada et al. 2006), and consistent with loss of repression of BZR1. These data indicate the involvement of SPY in regulating both GA and BR signaling pathways.

The rice microRNA miR396 targets the transcript of *Growth Regulating Factor 6* (*GRF6*), a transcription factor that participates in GA signaling. miR396 overexpression lines reveal impaired biosynthesis and signaling of GA, resulting in a semidwarf stature. Reduced lamina joint bending was also observed, consistent with a defect in BR synthesis or perception. These results suggest cross talk between GA and BR signaling in controlling plant height (Tang et al. 2018). There are additional complexities in BR–GA cross talk as well (Gao et al. 2018; Tang et al. 2018), including negative feedback by GA on BR synthesis (Tong et al. 2014).

Heterotrimeric G proteins composed of Gα subunits and interacting Gβγ dimers are GTP-/GDP-modulated molecular switches that relay signals from receptor molecules to effector proteins (Assmann 2002; Jones and Assmann 2004; Urano et al. 2013). The rice Gα subunit, RGA1, links BR and GA signaling via a pathway apparently separate from canonical BR signaling mediated by BRI1 and its downstream elements. The rice mutant *DWARF 1* (*d1*) was the first null rice mutant to be discovered by segregation analysis, long before modern tools for genetic analysis were available. *d1* plants show a dwarf stature, broad erect leaves, erect and compact panicles, and small rounded seeds (Ashikari et al. 1999). In 1999, the *d1* mutation was mapped to the *RGA1* gene (Ashikari et al. 1999). *d1* was initially classified as a GA-insensitive mutant based on the observation that GA application failed to result in α-amylase production in seeds and caused only partial elongation of the second leaf sheath (Mitsunaga et al. 1994). In addition, the double mutant of *d1* and *slr1*, a GA negative regulator, shows the "slender" phenotype with pale green and elongated leaf sheaths and leaf blades. This was interpreted as *SLR1* being epistatic to *RGA1* for these phenotypes, supporting that the Gα subunit of heterotrimeric G proteins is involved in GA signaling (Ueguchi-Tanaka et al. 2000). However, given that *slr1* is a semi-dominant mutation, epistasis may be difficult to ascertain. Detailed assays of GA-related phenotypes showed *d1* to be GA-hyposensitive rather than GA-insensitive. These assays revealed that supranormal GA levels can induce α-amylase production in *d1* seeds, reported reduced responsiveness to GA of gene induction in callus and of elongation of the second leaf sheath to GA, and showed that 100 times greater GA concentrations were required to induce internode elongation in *d1* as compared with wild-type (Ueguchi-Tanaka et al. 2000; Day et al. 2004). Despite their dwarf status, *d1* internodes were found to have elevated levels of GA20 and GA1. All these phenotypes are consistent with a defect in GA perception.

On the other hand, *d1* mutants (Ashikari et al. 1999) and *RGA1* antisense lines (Fujisawa et al. 1999) also show many of the phenotypes of BR-insensitive mutants, including semidwarf stature, dark green erect leaves, and small rounded seeds. Indeed, *d1* mutants show hypo-

sensitivity to applied BR in BR inhibition of root elongation, BR promotion of second leaf sheath elongation, and BR enhancement of lamina joint inclination (Oki et al. 2009a,b). However, *d1* mutation, unlike mutations in the canonical BRI1-based BR signaling pathway, does not impair feedback regulation of BR production. Interestingly, dwarfing in *d1* mutants is associated with a reduction in cell division (Iwasaki 2009; Oki et al. 2009a; Izawa et al. 2010), suggesting a phenotype that does not simply arise from hyposensitivity to GA- and BR-induced cell elongation.

Importantly, epistasis between the *d61-7* mutation in the BR receptor, BRI1, and the *T65d1* mutation in *RGA1* was not found for most traits: the double mutant showed increased dwarfism and increased erectness as compared with the single mutants, suggesting that these two genes function in parallel pathways (Oki et al. 2009a). However, epistasis was observed for seed shape and size (Oki et al. 2009a). At present, these results suggest that RGA1 may function in the canonical BR pathway in seed development but resides in a BRI1-independent BR pathway in vegetative tissues. It would be of interest to repeat this epistasis analysis using a complete null of *BRI1*, especially given recent observations in *Arabidopsis* that have shown that GPA1, the *Arabidopsis* ortholog of RGA1, physically interacts with and is phosphorylated by a number of RLKs, including the *Arabidopsis* canonical BR receptors BRI1 and BAK1 (Aranda-Sicilia et al. 2015; Chakravorty and Assmann 2018; Li et al. 2018a).

In rice, another RLK, the LRR-RLK XIAO, with 33% identity to BRI1, is also linked to BR signaling (Jiang et al. 2012). The *xiao* T-DNA mutant has slightly dwarfed erect leaves with small rounded seeds and reduced fertility. *xiao* plants show reduced cell division, consistent with a connection to the RGA1-based pathway of BR response. *xiao* mutants show reduced expression of *D11* and *DWARF4* BR biosynthesis genes, accompanied by reduced BR levels. This result suggests either that, with regard to BR synthesis, XIAO might be a positive regulator, or that the *xiao* mutant misperceives BR levels, with attendant lesions in BR feedback regulation. Despite phenocopying BR-insensitive mutants, *xiao* is not impaired in sensing exogenous BR and in fact shows enhanced sensitivity in some responses, indicating that the mutant is not defective in BR perception and consistent with the hypothesis that, with regard to BR signaling, XIAO might be a negative regulator.

TUD1 appears to be one definitive component of the alternative RGA1-based BR signaling pathway. Screening for mutants that phenocopy *d1* identified an allelic series of five *tud1* mutants that confer different degrees of dwarfing and impacts on seed size and shape (Hu et al. 2013). The *tud* mutations map to an E3 ubiquitin ligase. *tud1-1*, *tud1-3*, and *tud1-4* were biochemically shown to lack ubiquitin ligase activity present in the wild-type TUD1 protein, whereas *tud1-1*, *tud1-2*, and *tud1-5* conferred the strongest plant phenotypes. TUD1 and RGA1 physically interact. Analysis of double mutants indicates that *tud1-5* is epistatic to *d1* for internode elongation, panicle development, and seed size and shape, whereas *tud1-4* is additive with *d61-2* for plant height (seed phenotypes were not reported). Unlike *d1*, *tud1* shows normal responsiveness to GA in α-amylase activity and stimulation of seedling elongation, suggesting that, unlike RGA1, TUD1 does not participate in GA-BR cross talk (Hu et al. 2013). It will be of interest to determine how RGA1 regulates TUD1 and which specific TUD1 ubiquitination substrates are implicated in the agronomic phenotypes affected by *tud1* mutation.

One candidate protein downstream from RGA1 and/or TUD1 is the protein of unknown function, SG1. *sg1* dominant mutants and overexpression lines phenocopy *d1* mutants in gross morphology and show decreased sensitivity to exogenous BR in laminar joint bending (Nakagawa et al. 2012). Reminiscent of *d1* mutants (Izawa et al. 2010) but unlike BR synthesis and signaling mutants such as *brd1* and *d61*, dwarfing in *sg1* appears to be conferred by a reduction in cell division, consistent with SG1 and RGA1 functioning in the same pathway. Based on similar observations and reasoning, *SMG1*, encoding the mitogen-activated protein kinase kinase MPKK4 (Duan et al. 2014), the SMG1 down-

stream target MAPK6 (Liu et al. 2015a), and the SMG1 upstream kinase MKKK10 (Xu et al. 2018), and its negative regulator, the MKP1 phosphatase GSN1 (Guo et al. 2018) may also be components of the RGA1 pathway. Consistent with this hypothesis, MAPK6 protein level and possibly its activation by sphingolipid elicitor are impaired in the *d1* mutant (Lieberherr et al. 2005).

Independent of the dwarf phenotype, *d1* rice mutants also show improved drought tolerance (Ferrero-Serrano and Assmann 2016), decreased photoinhibition damage, and improved photoavoidance and photoprotection (Ferrero-Serrano et al. 2018). These findings suggest that the rice *d1* mutant, in addition to its beneficial architectural features, could also improve rice phenotypes related to abiotic stress tolerance.

SL Hormonal Cross Talk

SL signaling is also significantly affected by cross talk with other hormonal pathways (Cheng et al. 2013; Ito et al. 2018a). Notably, the SL receptor itself, D14, is involved in cross talk with the GA pathway. D14 hydrolyzes the enol ether of SLs producing D-OH and ABC-OH (Zhao et al. 2013). D-OH induces the physical interaction between D14 and SLR1 (Nakamura et al. 2013). SLR1 is the only DELLA protein in rice and is a negative regulator of GA signaling (Wu et al. 2018). The D14-interacting domain overlaps with the GID1-interacting domain in SLR1, suggesting a paradigm that involves competition for SLR1 binding (Nakamura et al. 2013). According to this, the D14–SLR1 interaction is competitive with the GA-bound GID1–SLR1 physical interaction (Nakamura et al. 2013). Both SL and GA repress the elongation of tillering buds, and exogenous application of both hormones reduces tillering (Ito et al. 2018b). Exogenous treatment with GA results in shoot elongation, whereas SL treatment does not (Nakamura et al. 2013). It may be plausible that the repression of tillering is D14–SLR1-dependent, whereas the dwarfism observed in SL biosynthesis mutants may be the result of a reduced D14–SLR1 interaction that increases the availability of SLR1 to interact with GID1, and therefore repress the GA pathway.

Interestingly, although dwarfism is most often a recessive trait, many *SLR1* mutants show a dominant dwarf phenotype with wide, dark-green leaf blades (Asano et al. 2009). Like *SLR1* loss-of-function mutants, *D53* mutants show a dominant dwarf phenotype, with high tillering, short stature, and increased SL production (Wei et al. 2006). Dominant dwarf mutants are rare, and mutant phenotypes of these two D14 interactors, D53 and SLR1, both render dwarf phenotypes. This may be because of the central role of these proteins in controlling the cross talk between GA and SL signaling.

An interplay between BRs and SLs may be assumed from the observation that mutants in synthesis and signaling components of each hormonal pathway result in dwarfing and increased tillering. The actual evidence of cross talk between the BR and SL signaling pathways comes from *Arabidopsis*. BES1 is the *Arabidopsis* BZR1 ortholog and a positive regulator of BR signaling. A gain-of-function mutant of *BES1* shows more rosette branches, enhanced transcript levels of *MAX3* (the *Arabidopsis D10* ortholog) and *MAX4* (the *Arabidopsis D17* ortholog), and is insensitive to exogenous SL application. Conversely, in a *BES1* RNAi line, transcript levels of *MAX3* and *MAX4* are significantly reduced, promoting SL signaling, and the plants displayed reduced shoot branching (Wang et al. 2013). The hypothesized cross-talk mechanism involves BES1 physically interacting with MAX2, the D3 ortholog in *Arabidopsis*, and BES1 negatively regulating SL signaling downstream from MAX2, thereby promoting shoot branching (Wang et al. 2013). Although this cross-talk mechanism between SLs and BRs has yet to be elucidated in rice, a recent study revealed that D3 can degrade a GSK2-phosphorylated U-type cyclin, CYC U2, to inhibit mesocotyl elongation. This mechanism is affected by genetic variation in GSK2, leading to natural phenotypic variation in mesocotyl length (Sun et al. 2018).

Cross talk between auxin and SL has been discussed for years in the context of bud outgrowth and tillering (Dun et al. 2009; Waters et al. 2017). SL biosynthesis is promoted by aux-

in, which was first deduced from the positive regulation of *D10* by auxin, whereas the expression of *D3* and *FC1* was not responsive to exogenous auxin (Arite et al. 2007). It was later confirmed that exogenous auxin application to leaves also increases the expression levels of biosynthetic chloroplastic SL enzymes *D17*, *D27*, and *D10* in tiller nodes (Xu et al. 2015).

CONCLUDING REMARKS

The introduction of dwarfism in breeding programs is one of the most significant scientific advances in human history. Dwarfism opposed lodging associated with increased nitrogen fertilization and led to an improved harvest index per plant. Higher density plantings were also possible, as a result of both the smaller size of dwarf varieties and the traits associated with dwarfism, such as erect leaf disposition (Sinclair and Sheehy 1999), allowing increased yield per unit area. All of these traits enabled the dramatic increase in grain yield during the Green Revolution (Evenson and Gollin 2003).

The Green Revolution also increased yields in wheat as a result of the introduction of dwarfism. Although dwarfism in cultivated rice originated from a loss-of-function recessive mutation in *SD1*, dwarfism in wheat had a different genetic basis. In wheat breeding, dwarfism originated from a semi-dominant mutation in the *Reduced height-1* gene, a DELLA protein, which therefore acts to repress GA-responsive growth. By analogy, would historically targeting SLR1, the sole DELLA protein in rice, as an alternative source for dwarfism have yielded more promising germplasm than the use of *sd1*?

Modern rice crops and the increases in yield production today have been possible thanks to the 1962 cross between DGWG, and PETA and the introduction of IR8, indeed a "miracle rice." Almost 60 years later, most of the modern rice varieties grown today can be traced back to that single cross. When IR8 was developed, knowledge of the genetic basis of dwarfism, and available technologies were rudimentary compared with what is available today in the postgenomic era. The dwarfing allele introduced by DGWG was not characterized, and early breeders were not aware of its biological function. The use of alternative sources of dwarfism was argued to be a necessity a decade after the initial introduction of *sd1*-based semidwarfism in the 1960s (Chang and Vergara 1972; Hargrove et al. 1980). However, 60 years later, we still have not tested whether the loss-of-function of *SD1* is indeed the best source of dwarfism in rice, given the large pool of genes controlling dwarfism, as described here.

The tools and advances in genetics and genomics since the beginning of the Green Revolution have been enormous. For example, we could speculate today that the ancient distinction between *Daikoku* versus *Bonsai* dwarfs (Nagao and Takahashi 1952) broadly reflect defects in GA-BR versus SL synthesis/signaling. The rapidly accumulating genetic characterization of thousands of varieties, with the recent release of genome sequences for more than 3000 rice varieties (Wang et al. 2018; Zhao et al. 2018), should further facilitate the identification of alternative sources of dwarfism that may complement modern varieties. Targeted genome editing using CRISPR systems also has the potential to accelerate development of dwarf cultivars by providing the means to modify genomes in a precise and predictable manner (Belhaj et al. 2015; Bortesi and Fischer 2015). Given the transcendence of the dwarfism trait, the tremendous benefits that its introduction provided, and the vast knowledge accumulated in the last half-century, we are now in an excellent position to widen its genetic basis.

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