Plant Cell Rep
DOI 10.1007/s00299-013-1438-x

REVIEW

Brassinosteroid signaling network: implications on yield and stress tolerance

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Received: 17 January 2013 / Revised: 19 March 2013 / Accepted: 25 March 2013

Abstract The steroidal hormone brassinosteroids (BRs) play important roles in plant growth and development. Genetic, genomic and proteomic studies in *Arabidopsis* have identified major BR signaling components and elucidated the signal transduction pathway from the cell surface receptor kinase BRI1 to the BES1/BZR1 family of transcription factors. BRs interact with other plant hormones in coordinating gene expression and plant growth and development. In this review, we provide an update on the latest progress in characterizing the BR signaling network and discuss its interactions with other hormone pathways in determining yield component traits and in regulating stress responses.

Keywords Brassinosteroid · Signaling · Homeostasis · Phytohormone · Yield component trait · Stress tolerance

Introduction

Brassinosteroids (BRs) are a class of plant steroidal hormones that are involved in the regulation of multiple developmental and physiological processes essential for plant vegetative and reproductive growth and development, including cell elongation and division, vascular differentiation, senescence, flowering time, male fertility, pollen development, seed size, photomorphogenesis, and resistance to biotic and abiotic stresses (Clouse et al. 1996; Li and Chory 1999; Ye et al. 2010; Clouse 2011). BR-deficient or -insensitive mutants generally display altered phenotypes, such as dwarfism, abnormal vascular development, dark-green leaves, delayed flowering and senescence, reduced male fertility and seed germination, and de-etiolation in the dark (Clouse et al. 1996; Li et al. 1996; Szekeres et al. 1996; Noguchi et al. 1999; Steber and McCourt 2001). During the last two decades, BR mutants have been identified in *Arabidopsis* (Clouse et al. 1996; Li et al. 1996; Li and Chory 1999; Clouse 2011) and various crop species, including rice (*Oryza sativa*) (Yamamuro et al. 2000; Hong et al. 2005), tomato (*Solanum lycopersicum*) (Koka et al. 2000; Montoya et al. 2002), barley (*Hordeum vulgare*) (Chono et al. 2003), pea (*Pisum sativum*) (Nomura et al. 2003), and maize (*Zea mays*) (Hartwig et al. 2011; Makarevitch et al. 2012). In rice, a model monocot and major crop, leaf angles increase in response to exogenously applied BRs. In BR-deficient rice, reduced leaf angle (i.e., more erect leaves) can greatly increase grain yield by allowing increased planting densities, less canopy shading, and higher light capture for improved photosynthetic capacity (Sakamoto et al. 2006). On the other hand, overexpression of a BR biosynthetic gene in rice led to increased BR levels and promoted grain yield by as much as 40 % which was attributed to increased seed size (Wu et al. 2008). Further characterization of BR signaling in rice and other crops, particularly cereals, will likely uncover novel mechanisms that could be used for crop improvement or provide insight into the evolution of BR signaling.

Communicated by A. Feher.

A contribution to the Special Issue: Plant Hormone Signaling.

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Published online: 09 April 2013

Extensive genetic and molecular studies have helped elucidate the BR signaling pathway and major signaling components in *Arabidopsis*. In summary, BRs directly bind to the receptor-like kinase BRASSINOSTEROID-INSENSITIVE 1 (BRI1) at the cell surface and activate a signal transduction cascade that leads to activation of two key transcription factors, BRASSINAZOLE-RESISTANT1 (BZR1) and BRI1-EMS-SUPPRESSOR 1 (BES1), also known as BZR2 (Wang et al. 2002). These two transcription factors directly regulate BR-responsive gene expression and plant growth and development (Fig. 1) (Kim and Wang 2010; Sun et al. 2010; Yu et al. 2011). Several important signaling components and the underlying mechanisms of BR perception and signal transduction, from receptor kinase activation to transcriptional networks, have been identified by proteomic and genetic approaches in *Arabidopsis* and rice (Clouse 2011; Tong and Chu 2012). In addition, proteomic analyses and genome-wide transcriptional analyses, such as chromatin immunoprecipitation-microarray (ChIP-chip), have made significant progresses in identifying and characterizing a large number of BES1 and BZR1-targeted genes. The transcriptional networks, either regulated by BRs alone or through interactions among BRs and other phytohormones in coordinating gene expression and plant developmental processes, are also well characterized in both *Arabidopsis* and rice (Deng et al. 2007; Tang et al. 2008a; Sun et al. 2010; Wang et al. 2010; Yang et al. 2011; Yu et al. 2011; Choudhary et al. 2012b; Tong and Chu 2012; Wang et al. 2012c). Furthermore, the BR biosynthetic pathway is well established, and several key BR biosynthetic regulators have been characterized in *Arabidopsis* and rice (Fujioka and Yokota 2003; Zhao and Li 2012).

Here, we provide an update on the latest progress in characterizing the BR signaling network as well as BR interactions with other hormones in coordinating gene expression and plant growth and development. In addition, we discuss the effects of BRs and interactions of BRs with other hormones in determining yield component traits in various crop species. Finally, regulation of stress responses by BRs alone or in coordination with other hormones is also reviewed.

BR signaling pathway

BR perception and receptor kinases

In plants, the BR signal is perceived by BRI1, which is a plasma membrane localized leucine-rich repeat (LRR) receptor-like kinase. It is composed of a large extracellular ligand-binding domain of 25 LRRs, a 70-amino acid island domain between LRR21 and LRR22, a single transmembrane domain, and a cytoplasmic domain with kinase activity (Li and Chory 1997; He et al. 2000; Wang et al. 2001; Kinoshita et al. 2005). Recent structural studies have confirmed the role of BRI1 as a plasma membrane receptor for BRs (Hothorn et al. 2011; She et al. 2011). In the absence of BRs, BRI1 is inactive as a homodimer, due to its binding with the negative regulator BRI1 KINASE INHIBITOR 1 (BKI1) through its cytoplasmic domain (Wang and Chory 2006). In the presence of BRs, BR binding activates BRI1 kinase activity, through association with its co-receptor kinase BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1)/SOMATIC EMBRYOGENESIS RECEPTOR KINASE3 (SERK3) (Li et al. 2002; Nam and Li 2002; Russinova et al. 2004) and phosphorylation of BKI1 on Tyr211, leading to the disassociation of BKI1 from the plasma membrane (Wang and Chory 2006; Jaillais et al. 2011). Phosphorylated BKI1 can also interact with the phosphopeptide-binding proteins 14–3–3s and relieve its inhibition of BES1 and BZR1 (Wang et al. 2011). A recent study showed that Ser270 and Ser274 in the C-terminal region of BKI1 are required for subsequent phosphorylation of Tyr211 and the subsequent dissociation of BKI1 (Wang et al. 2011). Phosphorylation sites at Ser/Thr and Tyr of both BRI1 and BAKI have been identified through phosphorylation site mapping and functional studies. A sequential transphorylation model has been proposed, in which BR binding to BRI1 activates its kinase activity through autophosphorylation and then phosphorylates and activates BAK1, which in turn phosphorylates BRI1 at the juxtamembrane and C-terminal domains to fully activate BRI1 kinase activity (Wang et al. 2005, 2008b; Clouse 2011). Besides BAK1/SERK3, SERK4 has been designated BAK1-LIKE 1 (BKK1) as it functions redundantly with BAK1 (Roux et al. 2011). Recent genetic and biochemical evidence also demonstrated that SERK1, SERK2 and SERK4 are all possible BAK1-redundant proteins that are required for BR signaling in *Arabidopsis* (Gou et al. 2012).

Inhibitors, kinases, and phosphatase

Activated BRI1 phosphorylates the receptor-like cytoplasmic kinases (RLCKs), BR SIGNALING KINASES (BSKs) and CONSTITUTIVE DIFFERENTIAL GROWTH 1 (CDG1), which then activate a phosphatase, BRI1-SUPPRESSOR 1 (BSU1) (Tang et al. 2008b; Kim et al. 2011). CDG1 was recently shown to function much like BSKs (Kim et al. 2011). BRI1 phosphorylates Ser230 of BSK1 and Ser234 of CDG1. Phosphorylated BSK1 and CDG1 then activate BSU1 (Kim et al. 2009, 2011). BSU1 in turn inactivates the negative regulator, a glycogen synthase kinase 3 (GSK3)/Shaggy-like kinase named BRASSINOSTEROID-INSENSITIVE 2 (BIN2) through dephosphorylation (Choe

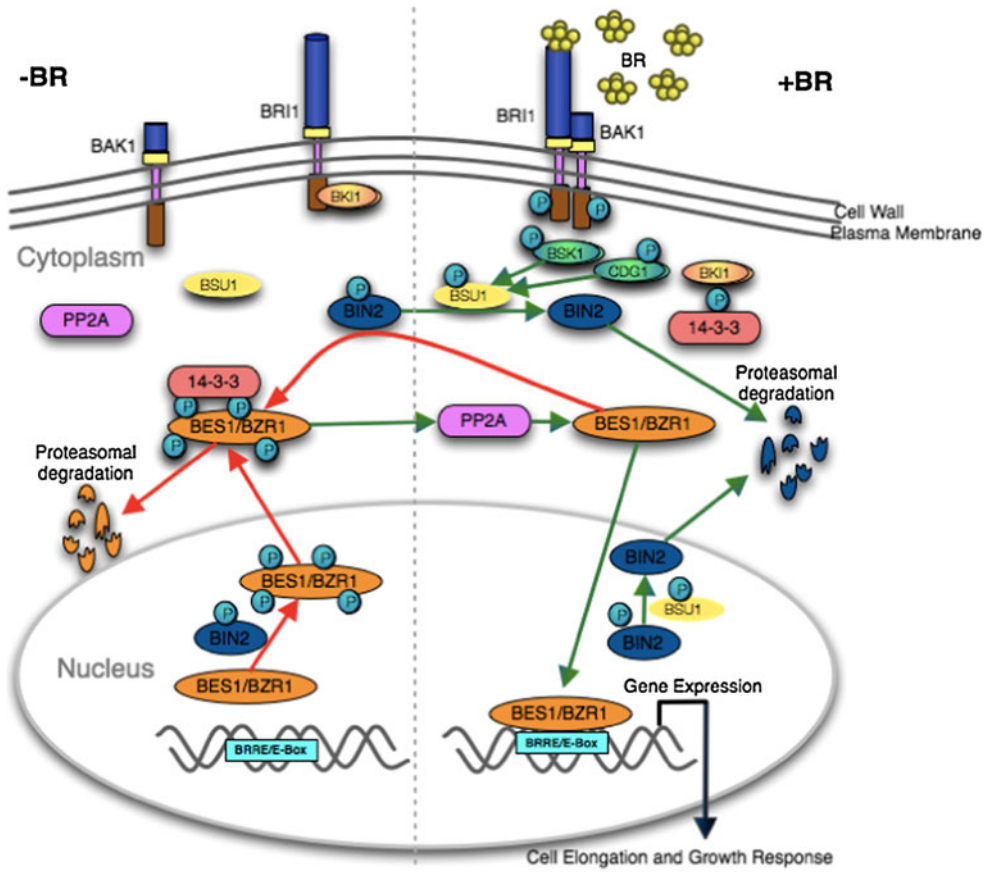

Fig. 1 Brassinosteroid signaling pathway in the absence (*left half*) or presence (*right half*) of BRs in *Arabidopsis*. In the absence of BRs, BRI1 is inactive due to its binding with the negative regulator BKI1. BIN2 phosphorylates and inactivates BES1 and BZR1, leading to export of BES1 and BZR1 from the nucleus, cytoplasmic retention by interaction with 14–3–3s, and proteasome-mediated protein degradation. In the presence of BRs, BRs binding to BRI1 activates BRI1 kinase activity, including the association with its co-receptor kinase BAK1 and also disassociation of BKI1. Activated BRI1 phosphorylates BSK1/CDG1, which then activates the phosphatase BSU1. Activated BSU1 in turn dephosphorylates and inactivates BIN2. Inhibition of BIN2 and the action of PP2A dephosphorylate and activate BES1 and BZR1. Activated BES1 and BZR1 subsequently translocate from cytoplasm into the nucleus where they regulate BR-responsive gene expression. *Circles* with P represent phosphate residues

et al. 2002; Li and Nam 2002; Kim et al. 2009; Yan et al. 2009). Genetic evidence suggests that BSU1 may directly dephosphorylate and inactivate BIN2 at Tyr200, which is the BIN2 autophosphorylation site necessary for BIN2 function (Kim et al. 2009).

Signal transduction to BES1 and BZR1 transcription factors

Inhibition of BIN2 and the action of the protein phosphatase 2A (PP2A) lead to the dephosphorylation and activation of two homologous transcription factors, BES1 and BZR1 (Wang et al. 2002; Zhao et al. 2002; He et al. 2002, 2005; Yin et al. 2002, 2005; Ryu et al. 2007; Tang et al. 2011). BES1 and BZR1 share 88 % identity in their amino acid sequences. They are predicted to have a basic HELIX–LOOP–HELIX (bHLH)-like DNA binding motif with functional redundancy but each has distinctive functions (He et al. 2005; Yin et al. 2005). PP2A was shown in a recent study to directly bind and dephosphorylate BZR1 (Tang et al. 2011). Dephosphorylated and activated BES1 and BZR1 subsequently translocate from cytoplasm into the nucleus where they regulate BR-responsive gene expression. In the absence of BRs, BIN2 phosphorylates BES1 and BZR1 at their phosphorylation domains containing more than 20 putative phosphorylation sites. BIN2 phosphorylation at different sites inhibits BES1 and BZR1 function through various mechanisms, including interference with DNA binding, cytoplasmic retention by interaction with 14-3-3s, and proteasome-mediated protein degradation (He et al. 2002; Bai et al. 2007; Gampala et al. 2007; de Vries 2007; Ryu et al. 2010; Ye et al. 2011).

BES1 and BZR1 regulated network

Genome-wide transcriptional analyses, including microarray and ChIP-chip, have identified large numbers of

BES1 and BZR1-targeted genes (Sun et al. 2010; Yu et al. 2011). Previous studies showed that BZR1 mainly binds to the BR-response element (BRRE) (CGTGT/CG) that is enriched in BR-repressed genes, repressing gene expression, and BES1 mainly binds to the E-Box element (CANNTG) that is mostly enriched in BR-induced genes, activating target gene expression (He et al. 2005; Yin et al. 2005). Recently, studies showed that both BES1 and BZR1 can bind to the BRRE and the E-box elements, functioning similarly either to activate or repress gene expression (Sun et al. 2010; Yu et al. 2011). Further investigations into BES1 and BZR1 binding elements and their interactions with other proteins to function as activators or repressors are needed. BES1 has been shown to interact with other transcription factors to promote gene expression, including the bHLH factor BES1-INTERACTING MYC-LIKE 1 (BIM1), two Jumonji domain-containing proteins, EARLY FLOWERING 6 (ELF6) and its homolog RELATIVE OF EARLY FLOWERING 6 (REF6), the MYB factor MYB30, and components involved in RNA polymerase II functioning, such as INTERACTING-WITH-SPT6–1 (IWS1) (Yin et al. 2005; Yu et al. 2008; Li et al. 2009b, 2010). A recent study showed that MYELOBLASTOSIS FAMILY FACTOR LIKE-2 (MYBL2) cooperates with BES1 to inhibit BR target-gene expression (Ye et al. 2012). Other recent studies also reported interactions between BES1/BZR1 and several other proteins, including DELLA proteins involved in negative regulation of gibberellin response and PHYTOCHROME-INTERACTING FACTOR (PIF), to regulate gene expression and plant growth, which will be discussed in the following sections (Bai et al. 2012b; Gallego-Bartolome et al. 2012; Oh et al. 2012a).

BR signaling in rice

BR biosynthesis and signaling are well understood in *Arabidopsis*. In rice, identification of a series of BR signaling components that are orthologous to those in *Arabidopsis* suggests that the BR signaling pathway is largely conserved among plants. OsBRI1 and OsBAK1, orthologous to the *Arabidopsis* BRI1 and BAK1, respectively, have been shown to be receptor kinases perceiving BR signals (Yamamuro et al. 2000; Li et al. 2009a). OsGSK1 in rice is an ortholog of BIN2 and functions as a negative regulator in BR signaling (Koh et al. 2007). OsBZR1, the closest ortholog of both BES1 and BZR1, functions as a positive regulator of BR response that interacts with 14-3-3s and translocates from the cytoplasm to the nucleus in response to BRs (Bai et al. 2007; Yu et al. 2011). The rice DWARF AND LOW-TILLERING (DLT), which belongs to the GRAS family of transcription factors, has also been proved to be a positive regulator involved in BR signaling. The *dlt* mutant displayed a typical BR loss-of-function dwarf phenotype, and overexpression of *DLT* conferred an enhanced BR-response phenotype with hypersensitivity to exogenous BRs in lamina-inclination experiments (Tong and Chu 2009, 2012). GSK2, a GSK3-like kinase in rice, has been shown to be an ortholog of BIN2 and functions as the rice counterpart of BIN2 in *Arabidopsis*. GSK2 phosphorylates DLT both in vitro and in vivo (Tong et al. 2012). These findings further confirm the conservation of BR signaling between *Arabidopsis* and rice, in which DLT or BES1 and BZR1 act as direct targets of the GSK3-like kinase (BIN2/GSK2) to mediate many of the BR responses.

BR homeostasis and signaling attenuation

As with other plant hormones, including abscisic acid (ABA), auxins, cytokinins, ethylene, and gibberellins (GA), in vivo regulation of BR homeostasis is critical to ensure normal plant growth and development under various environmental conditions. As shown from a study in pea, BRs were unable to be transported over long distances (Symons and Reid 2004). This suggests that plants need to precisely regulate BR biosynthesis and inactivation to maintain an appropriate internal active BR levels in various organs and tissues or at different developmental stages (Zhao and Li 2012).

The BR biosynthetic pathway has been well characterized in both *Arabidopsis* and rice. In *Arabidopsis*, a series of key BR biosynthetic genes has been identified, including *DEETIO-LATED2* (*DET2*), *CONSTITUTIVE PHOTOMORPHOGENIC DWARF* (*CPD*), *ROTUNDIFOLIA3* (*ROT3*), *DWARF4* (*DWF4*), and *BR-6-OXIDASE1* (*BR6ox1*) (Li et al. 1996; Szekeres et al. 1996; Choe et al. 1998; Shimada et al. 2001; Kim et al. 2005). Levels of endogenous BRs regulate the expression of these genes to maintain optimal concentrations through a feedback loop (Mathur et al. 1998; Mussig et al. 2002). Several biosynthetic genes in rice, such as *D2*, *D11*, and *BRD1*, have been identified (Hong et al. 2002; Hong et al. 2003; Tanabe et al. 2005). RAV-LIKE 1 (RAVL1), a transcription factor containing a B3 DNA binding domain that positively regulates the expression of *OsBRI1*, activates the expression of these biosynthetic genes (*D2*, *D11*, and *BRD1*) via binding to the E-box motif within their promoter regions (Je et al. 2010). BR biosynthetic mutants have also been reported recently in maize (Hartwig et al. 2011; Makarevitch et al. 2012).

The inactivation of BRs is mainly achieved through hydroxylation, glycosylation, and sulfonation (Hategan et al. 2011). The cytochrome P450 protein encoded by *PHYB ACTIVATION TAGGED SUPPRESSOR1 (BAS1)* has been shown to inactivate BRs (Neff et al. 1999; Turk et al. 2005). DWF4 and CPD are involved in rate-limiting

processes of steroid C-22α and C-23α hydroxylation to control endogenous BR homeostasis (Kim et al. 2006). Recent studies in *Arabidopsis* provided novel insights into the involvement of the BAHD acyltransferase family (benzyl-alcohol O-acetyltransferase, anthocyanin O-hydroxycinnamoyltransferase, anthranilate N-hydroxycinnamoyl/benzoyltransferase, and deacetylvindoline 4-O-acetyltransferase) (D'Auria 2006) in the regulation of endogenous BR homeostasis (Roh et al. 2012; Wang et al. 2012a). Two BAHD family acyltransferase-like genes, *BIA1* (Roh et al. 2012) and *ABS1* (Wang et al. 2012a), have also been shown to be involved in the inactivation of BRs, possibly through acylation.

In addition to negative regulations discussed before, several recent studies expanded our understanding of how BRI1-mediated regulation is involved in the attenuation of BR signaling. For instance, Wu et al. (2011) showed that methylation of PP2A can dephosphorylate BRI1, which results in BRI1 degradation and subsequent termination of BR signaling. Irani et al. (2012) developed a fluorescently labeled BR that enabled visualization of receptor-ligand complexes between BRI1 and BRs for the first time in plants. They demonstrated that endocytosis is a major factor that leads to BR signal attenuation and receptor degradation. Autophosphorylation of BRI1 at Ser891 in the kinase domain is also known to be one of the critical deactivation mechanisms that inhibit BRI1 activity and BR signaling (Oh et al. 2012c). Finally, *Arabidopsis* calmodulin was found to bind to BRI1 in a Ca^{2+}-dependent manner and may attenuate the kinase activity of BRI1 (Oh et al. 2012b).

Interaction of BRs and other phytohormones

BRs interact with many other plant hormones, such as ABA, GA, auxin, cytokinin, jasmonic acid (JA), salicylic acid (SA), and ethylene, to regulate numerous plant biological processes in a coordinated manner. Interactions of BRs and each of the other classes of phytohormones were the subject of a recent detailed review by Choudhary et al. (2012b). Thus, in our review, we intend only to emphasize the most recent progresses.

Auxin

BRs and auxins function synergistically to improve plant growth responses and transcriptional regulation (Nemhauser et al. 2004; Vert et al. 2008). Physiological studies showed that BRs can enhance auxin-induced growth responses, including root development, hypocotyl elongation, laminar inclination, and shoot gravitropism (Yokota et al. 1992; Bao et al. 2004; Li et al. 2005; Nakamura et al. 2006; Vandenbussche et al. 2012). Comprehensive, genome-wide microarray analyses in *Arabidopsis* have identified a large number of common genes that are induced by both BRs and auxins (Goda et al. 2004; Nemhauser et al. 2004). Identification of BES1 and BZR1 target genes also showed that many auxin-responsive genes are regulated by these BR-regulated transcription factors (Sun et al. 2010; Yu et al. 2011).

Auxins regulate target gene expression through two types of transcription regulators, AUXIN RESPONSE FACTOR (ARF) and AUXIN/INDOLE-3-ACETIC ACID (Aux/IAA). Auxin-induced degradation of Aux/IAAs releases ARFs, which activate target gene expression (Tiwari et al. 2001; Hagen and Guilfoyle 2002). BR-auxin crosstalk has been demonstrated in a study in which BRs continuously induced the expression of two ARF/Aux family members, *IAA19* and *IAA5* (Nakamura et al. 2003). Expression of a BR biosynthetic gene, *CPD*, is activated by an auxin-inducible transcription factor BREVIS RADIX (BRX) (Mouchel et al. 2006). And expression of another BR biosynthetic gene, *DWARF4*, is upregulated by auxin (Chung et al. 2011; Yoshimitsu et al. 2011). Direct molecular connections between BRs and auxin signaling were revealed via the direct interaction of BIN2 and ARF2. Phosphorylated BIN2 directly inactivates ARF2, which is a negative regulator of cell elongation (Vert et al. 2008). Another molecular link connecting BRs and auxins is that BZR1 directly binds to the promoter region of both *IAA19* and *ARF7*. BZR1 represses *IAA19* expression and induces *ARF7* expression, leading to ARF7 accumulation and downstream gene expression, which regulates *Arabidopsis* seedling morphogenesis in the dark (Zhou et al. 2012).

Additional evidence of BR-auxin interactions is through the receptor BRI1. Sakamoto et al. (2013) found that auxin stimulates BR perception by increasing the amount of rice BR receptor OsBRI1. Exogenous application of IAA (a bioactive auxin) induced a transient upregulation of *OsBRI1* expression. They determined (Sakamoto et al. 2013) that the promoter of *OsBRI1* contains an auxin response element (AuxRE) motif essential for ARF binding and, thus, for the increased expression of *OsBRI1* by IAA. The expression of a primary BR-responsive gene, *BR UNREGULATED 1 (BU1)*, was also increased by IAA treatment, indicating that auxin-induced *OsBRI1* expression affects BR signaling by upregulating downstream BR-responsive gene expression (Sakamoto et al. 2013).

In addition, the actin cytoskeleton was recently reported to play an essential role in integrating BR signaling and BR-mediated auxin response. *Arabidopsis ACTIN2* mutant *act2-5* produces an altered actin cytoskeleton phenotype with constitutive BR-mediated auxin responses. The upregulation of BR-responsive genes in the mutant corresponds to the accumulation of the dephosphorylated form of BZR1 (Lanza et al. 2012).

GA

Both BRs and GA are involved in regulation of plant photomorphgenesis and other developmental processes, including cell elongation, flowering, and seed germination. Recent studies established a direct connection between BRs and GA through a DELLA-BZR-PIF module, which regulates a broad spectrum of light-response components. DELLA, a family of five proteins in *Arabidopsis* that negatively controls plant growth, is a target of gibberellin receptor GIBBERELLIN INSENSITIVE DWARF1 (GID1) for degradation by proteasomes. Two recent studies (Bai et al. 2012b; Gallego-Bartolome et al. 2012) independently verified that a physical interaction occurred both in vitro and in vivo between DELLA proteins and the BZR1 transcription factor. They demonstrated that a DELLA protein GIBBERELLIC ACID-INSENSITIVE (GAI), which is a major negative regulator of the GA-signaling pathway, physically binds to BZR1 to prevent it from binding to target promoters, and the degradation of DELLA releases BZR1 to promote hypocotyl elongation. The dark- and heat-activated transcription factor PHYTOCHROME-INTERACTING FACTOR 4 (PIF4) has also been found to physically interact with BZR1 both in vitro and in vivo (Oh et al. 2012a). BZR1 and PIF4 can form a heterodimer that synergistically regulates the expression of thousands of common target genes, including HLH proteins of the PRE family that are positive regulators of cell elongation (Lee et al. 2006; Wang et al. 2009; Zhang et al. 2009; Bai et al. 2012a).

A model for BR and GA interaction in the regulation of light response has thus been established, based on the evidence presented above (Bai et al. 2012b; Gallego-Bartolome et al. 2012; Oh et al. 2012a). GA-mediated DELLA degradation inactivates both BZR1 and PIF4, preventing them from binding to their target genes. A genome-wide gene-expression analysis by RNA-sequencing (RNA-Seq) demonstrated that BZR1 and PIF4 can both independently and interdependently regulate GA-responsive gene expression. These findings together established the important role of the highly integrated module of DELLA-BZR1-PIFs in connecting the BR-GA interaction, and also in mediating plant growth and response to environmental signals (Bai et al. 2012b; Gallego-Bartolome et al. 2012; Oh et al. 2012a).

Other phytohormones

Interactions between BRs and other phytohormones, such as ABA, JA, cytokinins, and ethylene, have been described extensively in a recent review (Choudhary et al. 2012b). The latest research findings (not included in Choudhary et al. 2012b) have expanded our understanding of BRs in modulating plant growth by crosstalking with other phytohormones.

The crosstalk between BR and SA has been shown to be mainly involved in regulation of plant response to environmental stresses. Specifically, BR-induced *Arabidopsis* tolerance to salt and high temperature is mediated by a major SA regulatory protein NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1 (NPR1) (Divi et al. 2010). Recent studies showed that application of BRs and SA together can enhance plant salt tolerance in *Brassica* (Hayat et al. 2012).

An antagonistic relationship between BRs and JA in controlling plant growth was reported by Ren et al. (2009), where BRs negatively regulated JA-induced inhibition of root growth in *Arabidopsis*. Recently, BRs were shown to antagonize the JA-signaling pathway in a reciprocal manner in rice to suppress plant defense against root-knot nematodes (Nahar et al. 2013). Application of exogenous BRs suppressed the expression of two important genes in the rice JA-signaling pathway, *ALLENE OXIDE SYNTHASE* (*OsAOS2*) and *JA-INDUCIBLE RICE MYB* (*OsJAMYB*). In contrast, exogenous JA application suppressed BR-related gene expression. Notably, this mutual antagonism is accompanied by an enhanced susceptibility to root-knot nematode infection (Nahar et al. 2013). These findings also demonstrated the negative role of the BR-signaling pathway in innate immunity in rice.

The involvement of BRs in the regulation of cytokinin levels in wheat seedlings was reported recently (Yuldashev et al. 2012). Furthermore, BRs interact with ethylene and auxin to control shoot gravitropism in *Arabidopsis* (Vandenbussche et al. 2012). Interaction between BRs and ethylene in the regulation of ethylene-induced hyponastic growth was also observed in *Arabidopsis* (Polko et al. 2013). Finally, Trupkin et al. (2012) identified the cyclophilin gene *ROTAMASE CYCLOPHILIN 1* (*ROC1*) as a mediator of the crosstalk between phytochrome/cryptochrome signaling and BR response. Expression of *ROC1* was increased by activation of phytochrome/cryptochrome, which reduces BES1 activity and BES1 targeted gene expression, and therefore, reduces the sensitivity to BRs and seedling de-etiolation. On a related note, BR interactions with light signaling have been recently reviewed (Wang et al. 2012c) and will not be described herein.

BR signaling and yield

Increasing crop yield is the most important breeding goal all over the world, especially for major cereal crops such as rice, wheat, and maize. Crop yield is a complex polygenic trait involving various biological processes that interact with environmental signals. BRs are thought to be a class

of hormone with great potential to boost crop yield (Vriet et al. 2012). Although synthetic BR analogs have been applied to different species in attempts to boost yield, the underlying molecular mechanisms behind observed changes are largely unknown. To understand BRs' effect on yield, one can dissect yield into many component traits. In rice, for example, yield components are divided into plant density, panicle number per plant, grain number per panicle, and average grain weight (Vriet et al. 2012). All these component traits are closely related to BR-regulated phenotypes, such as dwarfism and leaf angle (which affect plant density), tiller number (which affects panicle number), and response to environmental cues (which can strongly affect grain number and quality). Following are the latest advances in our understanding of BR signaling-mediated contributions to increasing yield.

Leaf bending

Leaf bending in response to BRs has been used to increase crop yield, mainly through the modification of plant architecture (Sakamoto 2006; Sakamoto et al. 2006). For instance, BR-deficient rice plants display erect leaf angles, which allow increased plant density, resulting in higher yield (Wang et al. 2008a). A recent study has identified LEAF AND TILLER ANGLE INCREASED CONTROLLER (LIC) as a negative regulator that functions as an antagonistic transcription factor of OsBZR1 to repress the BR-signaling pathway in rice (Zhang et al. 2012). *LIC* gain-of-function mutants displayed erect leaves and reduced BR sensitivity. OsBZR1 shares similar functions with its closest ortholog of *Arabidopsis* BES1 and BZR1 (Bai et al. 2007). Like BZR1, LIC is phosphorylated by GSK1/BIN2. In rice, two antagonizing HLH/bHLH factors, INCREASED LEAF INCLINATION 1 (ILI1) and ILI1 BINDING bHLH (IBH1), have been shown to function downstream of OsBZR1 to regulate cell elongation and leaf bending. BZR1 mainly binds to *IBH1* to affect the balance of these two factors (Zhang et al. 2009). LIC strongly binds to *BZR1* and *ILI1* but weakly to *IBH1* and antagonizes BZR1 in controlling BR-mediated leaf bending in rice (Zhang et al. 2012).

Organ boundary formation

BRs regulating specific developmental processes, such as shoot regeneration and root meristem, have been reported in *Arabidopsis* (Cheon et al. 2010; Gonzalez-Garcia et al. 2011; Hacham et al. 2011). A recent study by Gendron et al. (2012) reported a novel role for BR signaling in plant architecture by spatial regulation during the formation of organ boundaries in *Arabidopsis*. In organ boundary cells, BR-activated BZR1 inhibits the expression of *CUP-SHAPED COTYLEDON (CUC)*, which is required for organ boundary formation, and results in organ-fusion phenotypes. In wild-type *Arabidopsis* plants, BZR1 accumulated at a relative low level in organ boundary cells to allow normal organ development. In addition, the *Arabidopsis* boundary cell-specific transcription factor LATERAL ORGAN BOUNDARIES (LOB) negatively regulates accumulation of BRs in organ boundaries through transcriptional activation of *BAS1* (Bell et al. 2012).

Stomatal development

Stomatal development and regulation are closely associated with gas exchange in plant cells, which affects photosynthetic and water-use efficiencies. BRs' regulation of stomatal development was discovered recently. Kim et al. (2012) reported that BRs negatively regulate stomatal development by suppressing BIN2-mediated regulation of YDA, a MAPK-kinase kinase (MAPKKK) involved in the specific MAP-kinase pathway that regulates stomatal development (Wang et al. 2007; Lampard et al. 2008). The YDA-initiated MAPK pathway negatively regulates stomatal development by phosphorylating and degrading the bHLH transcription factor SPEECHLESS (SPCH), which acts downstream of the ERECTA family and regulates stomatal lineage development (MacAlister et al. 2007). The ERECTA family in *Arabidopsis* is composed of three receptor-like kinases that control organ growth and floral development by promoting cell proliferation (van Zanten et al. 2009). BIN2 phosphorylates and inactivates YDA both in vitro and in vivo. Increased levels of BRs induce BR signaling through inactivation of BIN2 and therefore activate the MAPK pathway, reducing stomatal production. Interestingly, a conflicting study in *Arabidopsis* provided evidence that BRs promote stomatal development downstream of YDA in the ERECTA receptor kinase pathway through inhibition of BIN2-mediated phosphorylation and degradation of SPCH (Gudesblat et al. 2012b). Conflicts between these two studies regarding MAPK- and GSK3-mediated signaling pathways reflect complex regulations of plant development under different environmental or growth conditions by BRs (Gudesblat et al. 2012a).

Cell elongation and proliferation

BRs' role in regulating leaf cell elongation and proliferation has been well established in *Arabidopsis* (Gonzalez-Garcia et al. 2011; Hacham et al. 2011; van Esse et al. 2012; Zhiponova et al. 2013). A recent study showed that SHORT GRAIN1 (SG1) in rice affects both elongation of grains and of internodes in rachis branches (Nakagawa et al. 2012). Overexpression of *SG1* produced BR-deficient mutants, but with no reduction in cell size, suggesting that

SG1 might control organ elongation by decreasing cell proliferation via a mechanism that occurs downstream of the BR response. Wang et al. (2012b) provided evidence for the involvement of a microtubule regulatory protein, MICROTUBULE DESTABILIZING PROTEIN40 (MDP40), in BR-mediated hypocotyl cell elongation. BR-activated BZR1 directly targets and promotes the expression of the *MDP40* gene, whose gene product acts on destabilization of cortical microtubules and promotes hypocotyl cell elongation. In addition, BRs have been found to control ovule and seed number through the regulation of ovule-development-related genes by BZR1 in *Arabidopsis*. BR-deficient or -insensitive mutants showed lower seed number, smaller seed size, and abnormal seed morphogenesis, while BR-enhanced mutants produced more ovules and seeds (Huang et al. 2012).

BR signaling and stress tolerance

Exogenous application of BRs alone or coupled with other hormones has been widely used in attempts to improve crop yield and stress tolerance in various plant species (Divi and Krishna 2009; Peleg and Blumwald 2011). For instance, improved plant tolerance to biotic and abiotic stresses, including bacteria, viruses, low temperatures, drought, salt, Cu and peroxide, by the application of BRs has been reported in rice, tobacco (*Nicotiana tabacum*), cucumber (*Cucumis sativus*), *Brassica juncea*, and radish (*Raphanus sativus*) (Krishna 2003; Nakashita et al. 2003; Hu et al. 2005; Kagale et al. 2007; Divi and Krishna 2009; Xia et al. 2009; Hayat et al. 2012). Recently, Villiers et al. (2012) discovered connections for the first time between BR signaling and plant response to the heavy metal, cadmium (Cd), in *Arabidopsis*. Contrary to the well-established roles of BRs in improving plant tolerance, BR treatment in *Arabidopsis* reduces cadmium tolerance. This also contradicts the protective role of BRs against heavy metal toxicity in other species, including *Brassica juncea*, radish, tomato, and wheat (Hayat et al. 2007, 2010; Hasan et al. 2011; Yusuf et al. 2011; Choudhary et al. 2012a).

The molecular mechanisms of BR-induced plant stress tolerance remain poorly understood. Cui et al. (2012) reported that an endoplasmic reticulum (ER) localized *Arabidopsis* ubiquitin-conjugating enzyme UBC32 is an essential factor involved in both BR-mediated growth promotion and salt stress tolerance. In vivo data in *Arabidopsis* showed that UBC32 is a functional component of the ER-associated protein degradation (ERAD) pathway, which is an important ubiquitin–proteasome system regulating plant growth and development, known to contribute to plant salt tolerance (Liu et al. 2011). UBC32 affects the accumulation of BRI1 and connects the ERAD pathway to BR-mediated growth promotion and salt stress tolerance. A recent study in tomato revealed one possible mechanism of BR-induced abiotic stress tolerance, especially for oxidative and heat stress (Nie et al. 2012). BRs trigger apoplastic H_2O_2 accumulation generated by NADPH oxidase, which is encoded by the *RESPIRATORY BURST OXIDASE HOMOLOG 1*(*RBOH1*) gene. The RBOHs are involved in plant reactive oxygen species (ROS) production and plant response to various abiotic stresses (Marino et al. 2012). NADPH oxidase in turn activates MAPKs, which play critical roles in plant signal transduction during stress responses (Mittler et al. 2004; Pitzschke et al. 2009), giving rise to increased stress tolerance.

BRs have been shown to affect plant immunity response. Microbial-associated molecular patterns (MAMP) are molecules that elicit defense responses, known either as microbe- or pathogen-induced immunity (MTI or PTI). Flagellin 22 (flg 22), a MAMP, binds to the *Arabidopsis* LRR-RLKs FLAGELLIN-SENSING 2 (FLS2) to activate the innate immune response (Chinchilla et al. 2007; Heese et al. 2007; Schwessinger et al. 2011). BAK1, in addition to being a coreceptor for BRI1, is also a coreceptor for FLS2. In a pair of recently published reports (Albrecht et al. 2012; Belkhadir et al. 2012), different conclusions were drawn on the relationship between BR signaling and immunity response. Albrecht et al. (2012) showed a unidirectional inhibition of both the BAK1-dependent, FLS2-mediated immune response as well as a BAK1-independent immune response by BR perception through a yet unknown mechanism, suggesting that BAK1 is not rate-limiting in these pathways. In contrast, Belkhadir et al. (2012) showed that overexpression of BRI1 in *Arabidopsis* reduced BAK1-dependent, but not BAK1-independent immune responses, suggesting that BRI1 competes for BAK1 with other MAMP receptors. Their study, however, also showed a synergistic interaction between BR signaling and immune response that requires BAK1, suggesting a complex interplay between BR signaling and immunity responses involving BAK1.

In rice, De Vleesschauwer et al. (2012) reported that BRs also suppress rice root immunity to *Pythium graminicola*, a soil-born oomycete that has been identified as one of the factors causing rice yield decline in aerobic fields. The authors demonstrated that *P. graminicola* exploits endogenous BRs as virulence factors and disturbs host BR cellular homeostasis to cause disease. And this BR-induced susceptibility is driven, at least in part, by interfering with the effective SA- or GA-mediated resistance to *P. graminicola*.

Future perspectives

Considering the importance of BRs in both model plants and crop species, further investigations of key regulators in its

signaling pathway and the mechanisms underlying the whole regulatory system are needed. The complete elucidation of BR signaling and biosynthetic pathways in rice and other major crop species will contribute to a better understanding of the effects of BRs on important agronomic traits and their potential use in genetic engineering for crop improvement. More components that regulate BR biosynthesis and inactivation and contribute to BR homeostasis are likely to be identified. Considering the complex regulation of various BR signaling components, additional components and/or mechanisms are likely to be discovered, which may refine or modify current models of BR signaling. Genome-wide technologies should enable the dissection of the complex regulatory network of BRs and their interactions with other phytohormone and signaling pathways. The involvement of thousands of BR target genes in BR responses requires large-scale genomic studies and use of computational modeling to illustrate the complex BR-regulatory network. The BR-regulatory network and its underlying molecular mechanisms can help us design optimal strategies to increase crop yield and enhance performance under stress conditions.

Acknowledgments The research in the authors' lab is supported by The Consortium for Plant Biotechnology Research, Inc to S.F & Y.Y (GO12026-322) and NSF (IOS-1122166) to Y.Y. We thank Dr. Mark Widrelechner for his assistance in improving the manuscript.

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