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Trade-off between growth and immunity: role of brassinosteroids

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A balance between growth and immunity exists in plants. Recently, the growth-promoting hormones brassinosteroids (BR) have emerged as crucial regulators of the growth-immunity trade-off, although the molecular mechanisms underlying this role remained unclear. New evidence obtained from the model plant *Arabidopsis thaliana* points at an indirect crosstalk between BR signaling and immunity, mediated by the transcription factors BZR1 and HBI1, which suppress immunity upon BR perception. The core transcriptional cascade formed by BZR1 and HBI1 seems to act as a regulatory hub on which multiple signaling inputs impinge, ensuring effective fine-tuning of the trade-off between growth and immunity in a timely and cost-efficient manner.

The dilemma of plants: to grow or to defend

Plants need to effectively integrate multiple signaling inputs to ultimately guarantee perpetuation [1]. Because resources are limited, costs can arise from investment of resources to immunity and away from growth and development, which potentially creates an allocation dilemma [2–4]. Crosstalk between growth and immune signaling is a requisite for plants to resolve this dilemma, finely balancing resource allocation in an efficient and timely manner.

The first layer of plant immunity relies on the specific detection of conserved pathogen-associated molecular patterns (PAMPs) by plant pattern-recognition receptors (PRRs) at the cell surface [5]. Binding of the cognate PAMPs leads to activation of PRRs and, in turn, initiation of a signaling cascade that ultimately results in the onset of the so-called PRR-triggered immunity (PTI). An effective PTI serves to fend off most pathogens, therefore providing evident fitness benefits; however, immunity is costly in terms of cellular resources, compelling a rigorous control of PTI activation.

Plant growth and development are regulated by several plant hormones that interact in complex networks, most of which have been shown in recent years to also exert direct or indirect effects on plant immunity [6–8]. Among them, jasmonates (JA), gibberellins (GA), and more recently brassinosteroids (BR) and salicylic acid (SA), have been proposed to modulate the trade-off between growth and immunity [9–16]. This review will focus on the role of BR in regulating the crosstalk between these two processes, reinterpreting the biological implications of this function in light of recent reports.

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Similarities between signaling pathways in BR and PAMP perception

The steroid hormones BR are key regulators of plant growth and development, and play essential roles in nearly all stages of the plant life cycle, controlling processes such as seed germination, etiolation, vegetative growth, stomata development, flowering, and fertility [17,18]. The *Arabidopsis* (*Arabidopsis thaliana*) BR signaling pathway has been dissected in great detail, and is currently one of the best-understood signal transduction pathways in plants. The main BR receptor is the plasma membrane-localized leucine-rich repeat receptor kinase (LRR-RK) BRASSINOSTEROID INSENSITIVE 1 (BRI1) [19–22], which initiates a signaling cascade ultimately leading to BR-induced changes in gene expression (Figure 1). Upon BR binding, BRI1 heterodimerizes with its co-receptor BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1) [23,24] and dissociates from its inhibitor BRI1 KINASE INHIBITOR 1 (BKI1) [25,26], which leads to activation of BRI1 kinase activity and to sequential transphosphorylation between the kinase domains of BRI1 and BAK1 [27,28]. Phosphorylated BKI1 interacts with 14-3-3 proteins and promotes BR signaling [29] (Figure 1). Activation of BRI1 also results in phosphorylation and release of the receptor-like cytoplasmic kinase (RLCK) BOTRYTIS-INDUCED KINASE 1 (BIK1), which acts genetically as a negative regulator of BR signaling [30]. In addition, BRI1 phosphorylates two additional RLCKs, BRASSINOSTEROID-SIGNALING KINASE 1 (BSK1) and CONSTITUTIVE DIFFERENTIAL GROWTH 1 (CDG1) [31,32], which in turn bind to and phosphorylate the phosphatase BRI1-SUPPRESSOR 1 (BSU1), rendering it active [31,33,34]. BSU1 inactivates the GSK3-like kinase BRASSINOSTEROID INSENSITIVE 2 (BIN2) through dephosphorylation; inactive BIN2 is degraded by the proteasome [35]. In the steady-state situation, in the absence of BR, active BIN2 phosphorylates the two major transcription factors mediating BR-induced transcriptional changes, BRASSINAZOLE-RESISTANT 1 (BZR1) and BRI1-EMS-SUPPRESSOR 1 (BES1; also named BZR2) [36–39]. Phosphorylated BZR1 and BES1 display abolished DNA-binding activity and are retained in the cytoplasm by 14-3-3 proteins [40,41] (Figure 1). Following activation of the BR signaling pathway, BZR1 and BES1 are dephosphorylated by PROTEIN PHOSPHATASE 2A

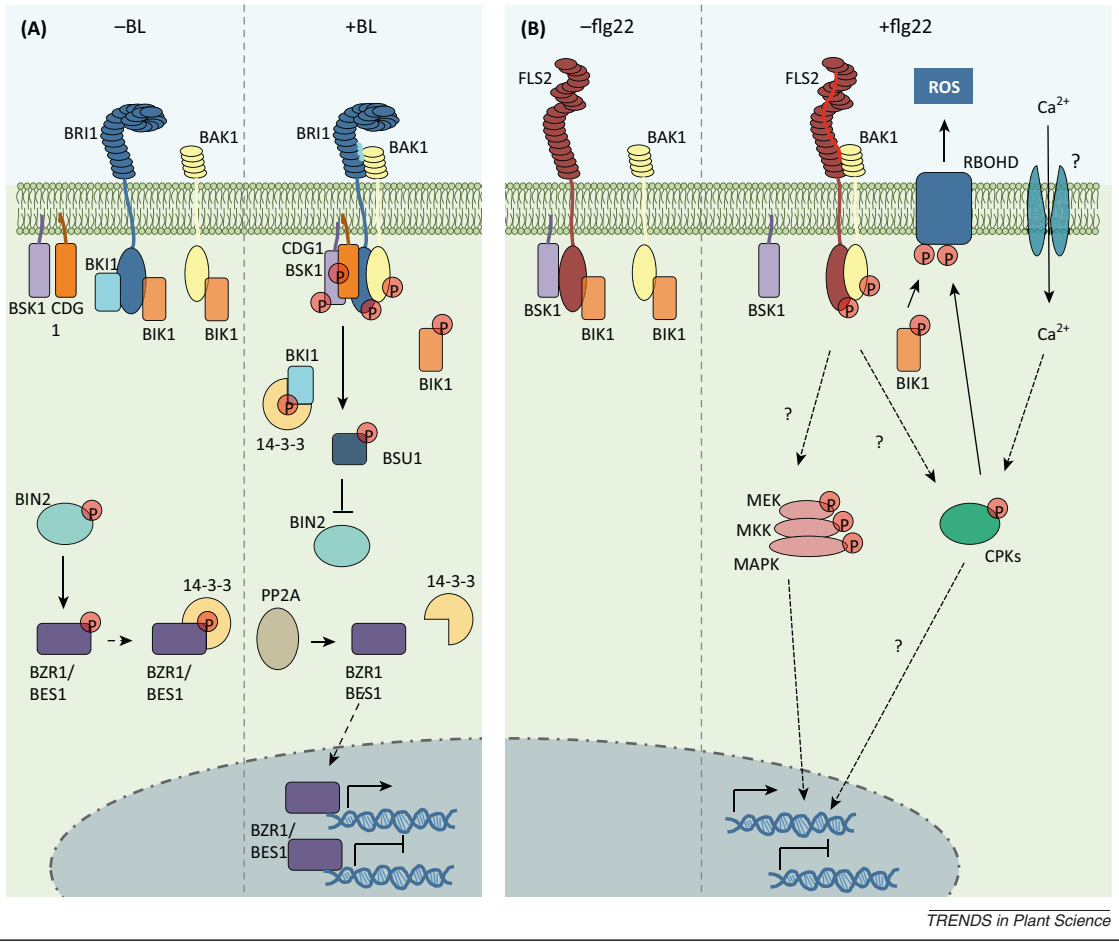

Figure 1. Simplified BRI1 and FLS2 signaling pathways in *Arabidopsis* (BL, brassinolide; flg22, bacterial flagellin active epitope flg22). **(A)** Simplified BRI1 signaling pathway in *Arabidopsis*. Upon BR binding, BRI1 heterodimerizes with its co-receptor BAK1 and dissociates from the inhibitor BKI1, leading to activation of the BRI1 kinase activity and transphosphorylation events. Both BKI1 and BIK1, which act as negative regulators of BRI1, are phosphorylated and released. In addition, BRI1 phosphorylates (P) BSK1 and CDG1, which then bind to and phosphorylate the phosphatase BSU1, rendering it active. BSU1 dephosphorylates and inactivates the kinase BIN2; inactive BIN2 is degraded by the proteasome. In the absence of brassinosteroids (BR), or when the concentration of the hormone is low, active BIN2 phosphorylates the two major transcription factors mediating BR-induced transcriptional changes, BZR1 and BES1. Phosphorylated BZR1 and BES1 do not bind DNA and are retained in the cytoplasm by 14-3-3 proteins. Following BR perception, BZR1 and BES1 are dephosphorylated by PP2A and released from the 14-3-3 proteins, moving to the nucleus and orchestrating the extensive BR-induced transcriptional reprogramming. BKI1 acts as a positive regulator at this level, by binding to and antagonizing 14-3-3s, enhancing BZR1 and BES1 nuclear accumulation. **(B)** Simplified FLS2 signaling pathway in *Arabidopsis*. Upon flg22 recognition, FLS2 heterodimerizes with its co-receptor BAK, leading to activation of their kinase domains and transphosphorylation events. As a result, the positive regulator BIK1 is phosphorylated and dissociates from the receptor complex to phosphorylate downstream targets for signal transduction. One such target is the NADPH oxidase RBOHD, which upon phosphorylation triggers a burst of reactive oxygen species (ROS). BSK1 also positively regulates flg22-triggered signaling and dissociates from FLS2 upon ligand perception. Activation of mitogen-associated protein kinases (MAPK) and calcium-dependent protein kinases, defining two independent branches of signaling, ultimately determine flg22-induced transcriptional changes.

(PP2A) [42] and released from the 14-3-3 proteins, moving to the nucleus and orchestrating the extensive BR-induced transcriptional reprogramming [43,44] (Figure 1).

Probably the best-studied plant PRR is the *Arabidopsis* LRR-RK FLAGELLIN SENSING 2 (FLS2), which recognizes bacterial flagellin (or its active epitope flg22) [45]. Upon flg22 recognition, FLS2 is activated, initiating a signaling cascade only partially dissected yet. As in the case of BRI1, flg22 perception triggers rapid heterodimerization between FLS2 and BAK1, activation of their kinase domains, and transphosphorylation [46–48]. These events lead to phosphorylation and dissociation of the RLCK BIK1 from FLS2 and BAK1 to phosphorylate downstream targets for signal transduction [30,49–52]. One such target is the membrane-associated NADPH oxidase RBOHD which, upon phosphorylation, triggers the production of reactive oxygen species (ROS) [49,53]. In addition, the RLCK BSK1 also positively regulates flg22-triggered signaling and dissociates from FLS2 upon ligand perception [54]. Activation of mitogen-associated protein kinases (MAPKs) and calcium-dependent protein kinases, which define two independent branches of signaling downstream of the receptor complex, ultimately determine flg22-induced transcriptional changes [55,56].

Evident parallels exist between the BRI1 and FLS2 signaling pathways. On one hand, the overall structure of the signaling cascade is very similar in both cases, initiating in protein complexes at the plasma membrane upon ligand binding, heavily relying on a phosphorelay, and ending in dramatic transcriptional reprogramming in the nucleus. On the other hand, several components, namely BAK1, BSK1, and BIK1, are shared between the two pathways, and this list may grow in the near future. These similarities, together with the supposedly opposing outcomes of BR and PAMP perception on plant growth, led to the longstanding hypothesis that crosstalk between these pathways may exist. Being the co-receptor for both ligands [57,58], BAK1 was considered a particularly strong