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Guarding the central regulator of extracellular perception in plants – A job for two

Julian R. Greenwood[1] **and Simon J. Williams**[1,*]
[1]Research School of Biology, The Australian National University, Canberra, ACT 2601, Australia
*Correspondence: simon.williams@anu.edu.au
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BAK1 is a central regulator of extracellular receptor proteins, essential in plant development and defense. In this issue of *Cell Host & Microbe*, dual reports (Schultze et al. and Yang et al.) describe how intracellular NLR immune receptors guard BAK1, with implications for extracellular perception and immune receptor engineering.

Plant immunity to pathogen attack involves the recognition of conserved and specialized molecules produced by microbes. The conserved molecules are described as PAMPs (pathogen-associated molecular patterns) and include peptides derived from bacteria flagellin (flg22) and polysaccharides that decorate fungal cell walls (chitin). They are generally "passive" molecules required for microbial survival, hence their conservation. Conversely, specialized molecules play an active role in infection and are generally described in the plant-microbe interaction field as "effectors." Secreted from the pathogen during infection, effectors (often proteins) function outside and within the plant cell to facilitate colonization and promote disease.

Recognition of PAMPs occurs at the cell surface facilitated by PAMP recognition receptors (PRRs). A major class of PRRs encode leucine-rich repeat (LRR)-receptor kinases (RKs), whereby the LRR domain is responsible for detection of the PAMP ligand, resulting in the activation of PAMP-triggered immunity (PTI). In plants, LRR receptor proteins (RPs) represent another important class of cell-surface immunity receptors. LRR-RPs differ from LRR-RKs as they lack an intracellular kinase domain. Recent reports, demonstrate that LRR-RPs can recognize both PAMPs and effectors and the immune pathway that they activate leads to cell death.[1,2] A unifying feature of many described RKs and RPs is the requirement of BAK1 (BRI1-associated receptor kinase), also an LRR-RK, for signal transduction following extracellular pathogen perception (Figures 1A and 1B).

BAK1 is also required for signaling function of non-immune receptors. BAK1 was first investigated for its role in plant hormone signaling where its interaction with the RK BRI1 is required for brassinosteroid signaling.[3] In addition to complex formation with a functionally diverse set of developmental and immune receptors, BAK1 also interacts with members of a family of small LRR-RKs, termed BAK1-interacting receptor-like kinases (BIR). BIR proteins modulate BAK1-mediated immunity by interaction with BAK1, reducing BAK1 association with ligand-binding receptors until ligand perception creates a high-affinity binding surface for BAK1.[4] Intriguingly, double *bak1 bir* mutants exhibit spontaneous cell death phenotypes. Similarly, loss-of-function of both *bak1* and the functionally redundant *bkk1* also leads to cell death.[5] Together, these results imply that disrupting BAK1-BKK complex stability results in phenotypes consistent with autoimmunity.

To supress plant immunity, pathogen derived effectors that function within the plant cell often target proteins involved in defense pathways, including BAK1[6] (Figure 1C). To combat this, effectors can be recognized by intracellular immune receptors known as nucleotide binding-LRR receptors (NLRs). NLRs recognize effectors directly or by guarding the targets (or decoy targets) of effectors. NLRs can function alone and as pairs. In paired systems, often the effector target has been integrated into the "sensor" NLR, which functions to detect the effector, while the paired "activator" NLR is responsible for immune signaling. NLRs active a hypersensitive response often leading to cell death, and the process is commonly referred to as effector-triggered immunity (ETI). The pathways and responses that distinguish the

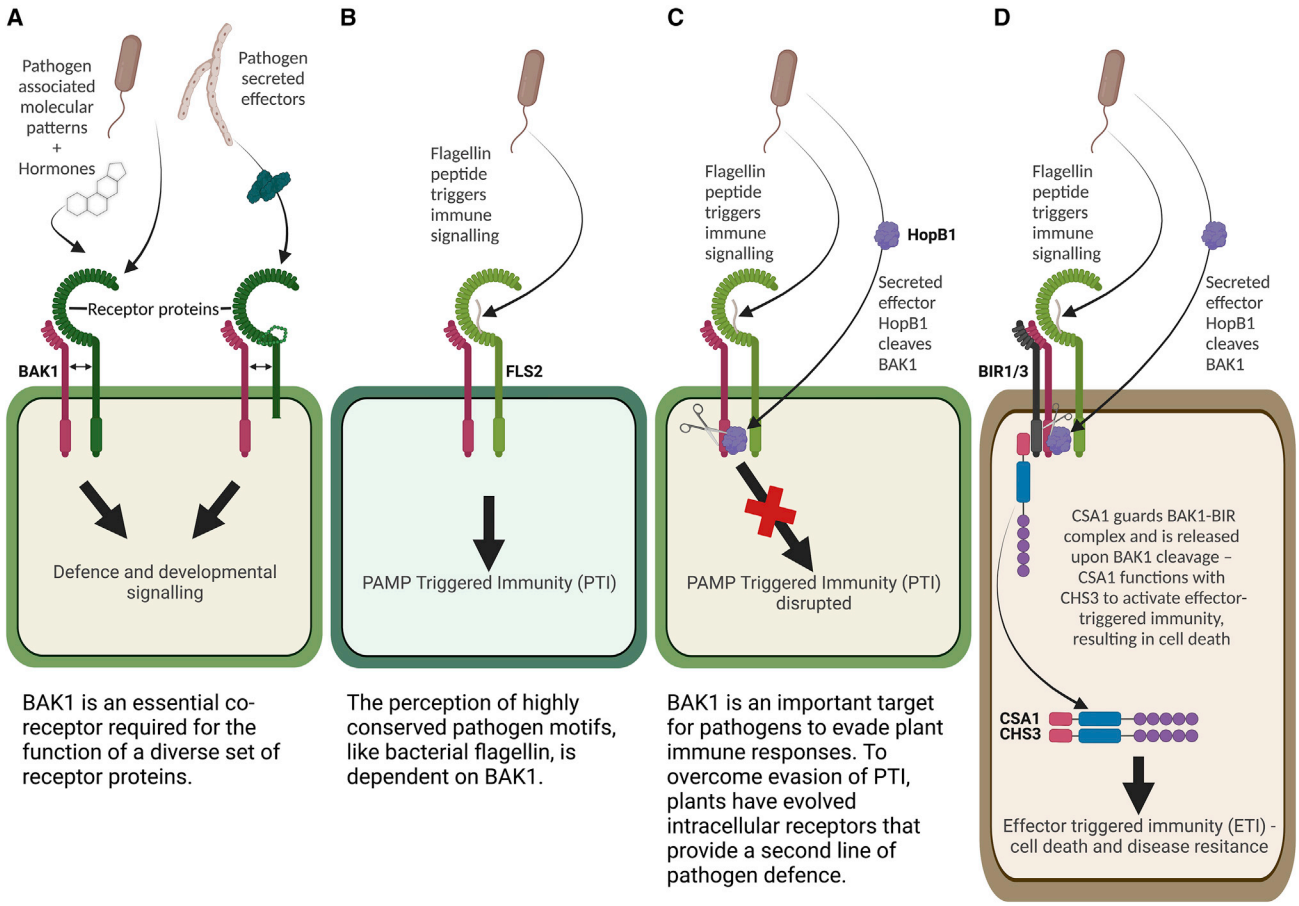

Figure 1. BAK1 is an essential co-receptor in plants, which is targeted by pathogens to suppress immune signaling

(A) BAK1 acts as a co-receptor for several extracellular proteins and is required for the perception of numerous extracellular signals.

(B) BAK1 is required for the perception of highly conserved pathogen-associated molecular patterns (PAMPs), like bacterial flagellin, resulting in PAMP-triggered immune responses and preventing disease establishment by most potential pathogens.

(C) Adapted pathogens secrete specialized effector proteins, which can suppress PAMP-triggered immunity (PTI). For example, the bacterial effector HopB1 specifically degrades immune-activated BAK1, thus preventing PTI.

(D) To overcome the suppression of PTI caused by degradation of BAK1, BAK1 is guarded by the NLR CSA1. Upon modification of BAK1, CSA1 is released and interacts with the NLR CHS3. CSA1-CHS3 interaction triggers a strong immune response known as effector-triggered-immunity (ETI) resulting in localized cell death and disease resistance.

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recognition of PAMPs and effectors are somewhat blurred. Despite some exceptions, the magnitude of the ETI response, typified by the induction of cell death, is often a distinguishing feature.

In this issue of *Cell Host & Microbe*, back-to-back reports demonstrate that BAK1 is guarded by a pair of NLRs.[7,8] These data are consistent with previous studies that show autoimmune phenotypes generated by the perturbation of BAK1 complexes are dependent on the same intracellular components required for ETI responses.[9,10] Here, Schultze and colleagues utilize the autoimmune bak1 bir3 mutant to show that the cell death phenotype occurs via the NLR protein CSA1, which forms a direct association with BIR proteins. They also demonstrate that cell death associated with effector (HopB1) targeting of BAK1 is dependent on CSA1. Yang and colleagues confirm a similar reliance on CSA1 for the autoimmune phenotypes arising from the loss-of-function of both *bak1* and its closest paralog *bak1-like 1* (*bkk1*). They also show that CSA1 functions as a paired NLR, in complex with CHS3. Collectively, these studies demonstrate that in the context of pathogen invasion, paired NLRs CSA1-CHS3 act as a guard of BAK1/BKK1-BIR complex stability allowing for a strong immune response to be initiated in response to manipulation of BAK1/BKK1 complexes by effector proteins (Figure 1D).

An additional interesting finding from the study of the NLR pairs is the presence of different clades (or functional pairs) of CSA1 and CHS3 within *Arabidopsis*. In one clade, CHS3 contains an integrated decoy domain that impacts both its function and capacity to interact with CSA1 from other clades. Collectively, the interrogation of different clade members by Yang and colleagues provides insights into the requirements for dual-NLR immunity and will likely influence the growing interest and developing field of NLR engineering.

It is important to note that while BAK1 and its homologues are essential for receptor function in other plant species, the conservation of receptor complex guarding by NLRs beyond *Arabidopsis* remains to be explored. Given that extracellular receptor complexes are an important first line of defense in plants, a common guarding of receptor complexes may be conserved, at least in certain lineages of plant species.

In the context of studying plant receptor complexes, an important outcome of the work described here is the potential for utilizing *csa1* mutants for the study of BAK1-dependent extracellular receptor signaling complexes, without the induction of cell death. By working in a *csa1* mutant background, the co-receptor function of *Bak1* and related genes can be studied without the confounding impacts of CSA1-dependent cell death induction that can arise when these genes are mutated.

Collectively, these works add to a growing number of recent seminal findings concerning plant immunity, bringing this field and those dedicated to it "BAK" into the spotlight.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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