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The apoplastic battlefield: Pathogen proteases target BAK1 to disarm plant immunity

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ABSTRACT

Pattern-triggered immunity (PTI) is activated when plant cell-surface pattern recognition receptors (PRRs) detect microbe- or damage-associated molecular patterns. The receptor-like kinase BAK1 functions as a shared co-receptor for many PRRs, integrating and relaying a broad spectrum of immune signals. Exploiting the central role of BAK1, pathogens have evolved multiple effectors that specifically target BAK1 to disrupt PTI signaling and enhance their infectivity. The apoplast, a critical interface for plant-pathogen interactions, witnesses intricate battles between host immunity and microbial virulence strategies. However, it is unclear whether pathogens secrete apoplastic effectors that directly target BAK1 to suppress plant immune signaling. A recent study published in *Nature Plants* revealed for the first time that *Phytophthora sojae* secretes a conserved trypsin-like serine protease, PsTry1, which directly cleaves the extracellular leucine-rich repeat (LRR) domain of BAK1 at Leu163, thereby disrupting immune-receptor complex assembly and attenuating PTI responses. This discovery fundamentally advances our understanding of apoplastic warfare by demonstrating how pathogen-secreted proteases directly disarm a core immune regulator. Notably, homologs of PsTry1 across diverse pathogenic oomycetes and fungi similarly cleave the extracellular domain of BAK1 and suppress immunity, revealing a conserved and sophisticated virulence strategy. These findings redefine the apoplast as a dynamic proteolytic battlefield where pathogen proteases act as precision weapons to disarm a central hub of plant immunity. Nevertheless, the battle between plants and pathogenic microorganisms has not come to an end yet. Future research should focus on this protease-receptor interaction, which offers promising avenues for the engineering of durable, broad-spectrum resistance in crops.

As the primary culprits behind yield loss and quality decline, plant pathogens pose a global threat to food security, making them a pressing concern worldwide. Deciphering the intricate interactions between plants and pathogenic microorganisms is therefore essential for safeguarding global food security. In addition to the physical barriers formed by the cuticle and cell wall, the apoplastic space between the plant cell wall and the plasma membrane serves as a pivotal battleground for plant-pathogen confrontations. Here, plasma-membrane-anchored pattern-recognition receptors (PRRs) act as vigilant sentinels that detect conserved microbe-associated molecular patterns (MAMPs) from invading pathogens and initiate the first layer of plant innate immunity, termed pattern-triggered immunity (PTI) (Buscaill and van der Hoorn, 2021). To colonize and proliferate within the apoplastic niche, pathogens must subvert PTI-mediated defenses. Through millennia of co-evolutionary arms races with plants, they have evolved a diverse arsenal of secreted effectors that function either in the apoplast (apoplastic effectors) or inside the host cell (cytoplasmic effectors). These effectors physically interact with or enzymatically modify key components of PTI signaling, thereby manipulating host physiology and promoting successful infection (Buscaill and van der Hoorn, 2021). Cytoplasmic effectors can, in turn, be directly or indirectly recognized by intracellular nucleotide-binding leucine-rich repeat receptors (NLRs), which activate effector-triggered immunity (ETI), the second layer of defense (Spoel and Dong, 2012; An and Zhang, 2024). Apoplastic effectors initiate the first line of attack within the apoplastic space (Doehlemann and Hemetsberger, 2013). However, for the vast

majority of these apoplastic effectors, key aspects—including biochemical properties, precise molecular targets, and specific roles in virulence—remain poorly understood. Recent breakthroughs have begun to fill this gap. Zhang et al. identified an apoplastic trypsin-like serine protease, PsTry1, secreted by *Phytophthora*, which directly targets the core immune co-receptor BAK1 and cleaves its extracellular domain at Leu163. This cleavage disrupts the formation of the PRR-BAK1 complex and thereby blocks PTI signal initiation (Zhang et al., 2025c). Here, we synthesize these new findings, outline emerging questions, and propose roadmaps that link a mechanistic understanding of apoplastic effectors to durable resistance breeding. Our goal is to provide a conceptual framework for engineering broad-spectrum, apoplast-focused immunity in next-generation disease-resistant crops.

BAK1 mediates the activation of plant immune responses

BAK1 (BRI1-associated receptor kinase 1) is a key member of the plant receptor-like kinase superfamily. It was initially identified as a co-receptor of BRI1, with which it forms a heterodimer upon brassinosteroid perception to regulate diverse aspects of plant growth and development (Li et al., 2002; Nam and Li, 2002). Subsequent studies have shown that BAK1 does not merely serve as an auxiliary regulator of growth signaling but also functions as a central signaling hub at which multiple pathways converge (Postel et al., 2010; He and Wu, 2016). In immune signaling, BAK1 forms complexes with diverse PRRs to detect pathogen- and damage-associated molecular patterns (PAMPs/DAMPs)

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(He and Wu, 2016). These PRRs include receptor-like kinases (RLKs) such as FLS2, EFR, PEPR1/2, and MIK2, as well as receptor-like proteins (RLPs) like RLP23, RXEG1, and REL. Together, they recognize a wide range of ligands, including bacterial flagellin, elongation factors, nlp20, XEG1, INF1, and endogenous DAMPs such as Peps and SCOOP peptides, thereby initiating the PTI response (Chinchilla et al., 2007; Heese et al., 2007; Roux et al., 2011; Albert et al., 2015; Wang et al., 2018; Chen et al., 2023; Krol et al., 2010; Hou et al., 2021). Notably, BAK1 is also indispensable for the transition from PTI to ETI, providing the molecular scaffolding for a multilayered, highly coordinated plant immune network (Wu et al., 2020).

BAK1: An ideal target for pathogen effectors

Given its central and multi-functional role in PTI signaling, BAK1 has emerged as a prime target for pathogen attack. By disabling this critical signaling node, microbes can efficiently disrupt multiple downstream PTI pathways simultaneously. For example, cytoplasmic effectors such as AvrPtoB and HopF2 (secreted by *Pseudomonas syringae*) (Mathieu et al., 2014; Zhou et al., 2014), as well as NIS1 (from *Colletotrichum orbiculare*) (Irieda et al., 2019), have been shown to specifically target BAK1. These effectors inhibit BAK1 kinase activity, thereby blocking multiple PRR-triggered immune signaling pathways. By contrast, HopB1, another cytoplasmic effector from *P. syringae* with serine protease activity, does not directly interact with BAK1 (Li et al., 2016). Instead, it binds specifically to the kinase domain of FLS2 and selectively cleaves immune-activated BAK1 and its closest paralogs, thus disrupting PTI signal transduction (Li et al., 2016). These findings demonstrate that the intracellular kinase domain of BAK1 is not only crucial for initiation of plant immune responses but also serves as a primary target for pathogen effectors. However, a key question remains: Do pathogens deploy apoplastic effectors that directly target BAK1 or other immune receptors in the extracellular space?

The canonical trypsin-like serine protease PsTry1 acts as an apoplastic effector to influence the PTI response

Phytophthora, an ancient genus of plant pathogens, harbors an extensive repertoire of apoplastic effector genes (Kronmiller et al., 2023), which pose a formidable threat to agriculture and food security. These effectors function as glycoside hydrolases, proteases, necrosis-inducing proteins (NLPs), protease inhibitors, lipases, and lipid-binding proteins, act at multiple levels to modulate plant immune responses and facilitate disease progression (Kronmiller et al., 2023). Accordingly, apoplastic immunity is a key determinant of successful pathogen infection, making it a critical focus of plant disease research.

Using secreted protein domain predictions and transcriptomic data, a recent study has, for the first time, systematically identified a cohort of apoplastic effectors that likely operate as key virulence factors during the early stages of *Phytophthora sojae* infection (Zhang et al., 2025c). Further investigation revealed that multiple trypsin-like serine proteases were significantly induced within the first hours of host contact, suggesting their involvement in the initial stages of *P. sojae* infection (Zhang et al., 2025c). To determine how these effectors suppress host immune responses in the apoplast, the authors screened for candidates capable of interfering with PAMP-triggered immune responses. PsTry1 was identified as a key effector that fully suppressed the cell-death phenotype triggered by the *Phytophthora* elicitor INF1. Meanwhile, exogenous application of PsTry1 significantly suppressed the production of reactive oxygen species and the expression of defense-related genes in plants, while simultaneously enhancing pathogen infectivity (Zhang et al., 2025c). These results establish PsTry1 as a frontline immunosuppressive weapon deployed in the apoplast (Fig. 1). As a canonical trypsin-like serine protease, PsTry1 suppresses PTI responses, raising the question of whether this activity depends on its protease function. To address this question, the authors performed site-directed



Fig. 1. PsTry1 undermines plant immunity through site-specific cleavage of the BAK1 ectodomain.

Phytophthora (represented here as Dragon King Ao Shun) secretes the trypsin-like serine protease PsTry1. This enzyme interacts with BAK1 (represented here as Nezha and the Red Armillary Scarf) and cleaves its extracellular domain, thereby inhibiting the activation of plant immune responses. To counteract this immune suppression, plants may produce inhibitors or proteases that target PsTry1 (represented here as a small-molecule compound), relieving its inhibitory effects on immunity. Therefore, artificially modifying BAK1 to create a variant that competitively binds PsTry1 (crafted by Taiyi Zhenren) offers promising strategies for developing disease-resistant crops.

mutagenesis to disrupt key catalytic residues required for PsTry1 proteolytic activity. They found that the catalytically inactive mutant failed to suppress PAMP-triggered immune responses, demonstrating that protease activity is indispensable for PsTry1-mediated immunosuppression (Zhang et al., 2025c).

PsTry1, a highly conserved apoplastic effector, targets and cleaves BAK1 to suppress plant immunity

To determine the mechanism by which PsTry1 mediates PTI inhibition, the authors used liquid chromatography-tandem mass spectrometry to identify PsTry1-interacting proteins. BAK1 emerged as a significantly enriched interactor in both soybean and *Nicotiana benthamiana* systems. Upon PsTry1 treatment, the interactions between BAK1 and immune receptors (FLS2 and RXEG1) were markedly attenuated, and BAK1 protein abundance was sharply reduced (Zhang et al., 2025c). These findings suggest that PsTry1 may act as molecular scissors that dismantle immune receptor complexes by cleaving BAK1 and thereby blocking PTI activation. To test this hypothesis, the authors confirmed BAK1 cleavage through co-expression of PsTry1 and BAK1 in both *in vivo* and *in vitro* systems. Notably, the immune-activated form of BAK1 was cleaved more efficiently than its resting state (Zhang et al., 2025c). However, unlike HopB1, which exclusively cleaves immune-activated BAK1 (Li et al., 2016), PsTry1 also shows cleavage activity toward resting-state BAK1. This observation suggests that PsTry1-mediated cleavage may not depend entirely on BAK1 kinase activity. Nevertheless, why immune-activated BAK1 is the preferred substrate remains unclear, and resolving this question will provide important insights into the pathogenic strategies of *P. sojae*.

To pinpoint the specific residue where PsTry1 cleaves BAK1, the authors performed an amino-acid-resolution screen and identified Leu163 of soybean GmBAK1 as the scissile site. Functional assays demonstrated that, although an L163A substitution did not disrupt the PsTry1-BAK1 interaction, it blocked assembly of the BAK1-PRR immune receptor complex and consequently silenced downstream

Table 1
Key residues that govern BAK1 function.

Key residues	Modification type	Functional impact	Reference
K367	SUMOylation	Specifically regulates BR signaling and modulates interaction intensity with BRI1	Xia et al., (2025)
T446, T449, T450, T455	Phosphorylation	Maintains kinase activity	Yan et al., (2012)
Y403	Phosphorylation	Specifically regulates immune signaling	Bender et al., (2021)
S602, T603, S604, S612	Phosphorylation	Specifically regulates immune signaling	Perraki et al., (2018)
L163	Mutation	Blocks protein hydrolysis, reducing disease resistance	Zhang et al., (2025c)
D287	Mutation	Blocks protein hydrolysis, reducing disease resistance	Zhou et al., (2019)
Arg297/Gly298	Mutation	Blocks protein hydrolysis, reducing disease resistance	Li et al., (2016)
C408	Mutation	Specific immune deficiency, impaired PAMP response to PAMPs	Schwessinger et al., (2011)

immune signaling (Zhang et al., 2025c). Structural analysis further revealed that Leu163 is located within the fourth leucine-rich repeat (LRR4) of the BAK1 extracellular domain, specifically on an α -helix that directly mediates ligand recognition (Fig. 1). Previous studies have shown that LRR4 of Arabidopsis BAK1 is essential for binding the FLS2 ectodomain (Sun et al., 2013b). Key residues within this region (e.g., Arg143, Phe144, Arg146) directly modulate the interactions of BAK1 with both FLS2 and BRI1 (Sun et al., 2013a, 2013b). Consequently, apoplastic effectors may strategically target these critical sites to disrupt plant immune signaling. However, whether pathogenic microorganisms harbor apoplastic effectors that specifically target these residues remains to be determined. Nevertheless, it is clear that trypsin-like effectors homologous to PsTry1 are widely distributed across oomycetes and fungal pathogens. Their mechanism of inhibiting PTI via BAK1 cleavage appears to be highly conserved, representing a stable virulence strategy that has evolved in microbes (Fig. 1).

Conclusions and perspectives

As a highly conserved plant receptor-like kinase, BAK1 functions as a central hub in the regulation of plant growth, development, and immune responses owing to its unique intracellular kinase domain and extracellular structure (Ma et al., 2016). Numerous studies have shown that BAK1 is targeted by various cytoplasmic effector proteins, which proteolytically cleave its intracellular domain or inhibit its kinase activity, thereby suppressing PTI. In response, certain NLR proteins can monitor perturbations of BAK1 and activate NLR-dependent ETI. However, it has been unclear whether pathogenic microorganisms can directly modify the extracellular domain of BAK1 to interfere with pathogen perception and suppress immune activation. Recently, Zhang et al. provided the first evidence that a pathogen-encoded, highly conserved apoplastic effector specifically targets and disables the extracellular domain of BAK1, thereby suppressing immune responses triggered by various MAMPs (Zhang et al., 2025c). This strategy appears to represent an evolutionary "Achilles' heel" in plant immunity, as it enables the pathogen to evade detection by NLR surveillance systems. In the ongoing evolutionary arms race between plants and pathogens, both sides continuously refine their molecular weaponry to survive. For example, XEG1, an effector secreted by *P. sojae*, exhibits xyloglucan hydrolase activity that degrades plant cell-wall components and thereby promotes infection (Ma et al., 2015). To counteract XEG1-mediated damage, plants have evolved a three-tiered defense system involving specific protein inhibitors (GmGIP1) (Ma et al., 2017), proteases (GmAP5) (Xia et al., 2020), and receptors (RXEG1) (Wang et al., 2023), which collectively confer resistance to *P. sojae*. However, the pathogen has also evolved countermeasures: its decoy protein XLP1 competes with XEG1 for GmGIP1 binding, releasing XEG1 to resume cell-wall degradation (Zhang et al., 2025a). In addition, unidentified *Phytophthora* proteins catalyze N-glycosylation of XEG1, preventing its cleavage by GmAP5 (Xia et al., 2020). Looking forward, using proteomic technologies to identify receptors of PsTry1, such as receptor-like proteins that associate with SOBIR1, BAK1, or both to perceive apoplastic effectors (Liebrand et al., 2014), as well as to identify

proteases or inhibitors that interact with PsTry1, will provide critical insights into the molecular mechanisms that underlie plant-pathogen interactions.

Zhang et al. performed a comprehensive Ala-substitution mutagenesis screen and identified Leu163 of GmBAK1 as a critical residue required for BAK1 kinase activity (Zhang et al., 2025c). Although PsTry1-mediated cleavage is not entirely dependent on BAK1 kinase activity, PsTry1, like HopB1, preferentially cleaves BAK1 that has been phosphorylated and activated after MAMP perception. At the level of signal transduction, BAK1's phosphorylation can stabilize the P-loop conformation and enhancing ATP-binding capacity to propagates downstream signals, for example T446, T449, T450 and T455 plays a crucial role in the functioning of BAK1 (Moffett and Shukla, 2020; Yan et al., 2012) (Table 1). Concurrently, interactions between BAK1 and other regulatory proteins allosterically modulate its P-loop dynamics, fine-tuning the balance between growth and immunity (Ma et al., 2017). Structurally, the HopB1 cleavage site (Arg297/Gly298) and the phosphorylated residue pT455 are both located on the same surface of phosphorylated BAK1. Thus, the specific cleavage of MAMP-activated BAK1 by HopB1 may be associated with direct exposure of the Arg297/Gly298 site (Li et al., 2016). Similarly, a phosphorylation-dependent conformational change likely explains why PsTry1 also favors immune-activated BAK1. Therefore, determining the structure of the PsTry1-BAK1 complex will be critical for clarifying this specificity and could enable *in silico* docking screens for small-molecule or protein inhibitors, providing a rational framework for the development of biopesticides against *Phytophthora* infection in crops (Han et al., 2024). Recently, two studies leveraging AlphaFold-based structure predictions proposed a modification strategy for FLS2 and demonstrated that numerous residues outside the FLS2-BAK1 interaction interface can enhance pathogen recognition (Zhang et al., 2025b; Li et al., 2025). Similarly, examining the evolutionary conservation of Leu163 in GmBAK1 across species and systematically testing the effect of artificial substitutions at this or other residues outside the BAK1-PRR interaction surface could provide valuable insights for breeding crops with enhanced disease resistance.

Author contributions

Juan Lang drafted the manuscript. Yujun Wu conceived and revised the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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