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An epic war between an oomycete pathogen and plants

Oomycetes, commonly known as water molds and phylogenetically belonging to stramenopiles, can infect a wide range of plants and animals, with some members eliciting the most destructive plant diseases and posing severe threats to global food security and natural ecosystems (Thines, 2018). For example, *Phytophthora infestans* causes potato late blight and triggered the Irish Famine in the 1840s, and *Phytophthora sojae* damages soybean production worldwide. Breeding resistant cultivars is the most efficient measure for managing the diseases instigated by oomycetes, but the success of the endeavor requires a sound and deep understanding of the molecular basis underlying pathogen–host interactions. Recently, Sun et al. (2022) elucidated the mechanism underlying the recognition of XEG1, a key virulent effector of *P. sojae*, by host immune receptor through combining genetic, molecular, and structural approaches, which represents a significant step forward in deeply understanding the infection biology and host immune responses in oomycete diseases.

Pathogen's arsenals: Diverse virulent effectors

As an adapted pathogen, *P. sojae* has evolved the ability to deliver diverse virulent effectors into the apoplastic and intracellular compartments of host plants to establish a successful infection (Ma et al., 2015; Wang and Wang, 2018). Some effectors act to dampen host immunity, while others subvert host physiology to aid pathogen growth. Of the dozens of virulent effectors relatively well characterized, XEG1, encoding an apoplastic xyloglucan-specific endoglucanase highly conserved in *Phytophthora* species and other plant-associated microbes, has been studied in more detail (Ma et al., 2015; Wang et al., 2018; Xia et al., 2020; Sun et al., 2022). XEG1 participates in cell-wall degradation and is required for full virulence of *P. sojae* in host plants. It is sensed by host as a pathogen-associated molecular pattern (PAMP), induces PAMP-triggered immunity (PTI), and results in cell death in both soybean and *Nicotiana benthamiana* (Ma et al., 2015). However, XEG1 and the PTI responses induced by it are actively suppressed by both host factors and additional pathogen effectors (e.g., RXLR effectors) in natural infections. Clearly, XEG1 represents an ideal entry point for disentangling the complex interplays between *Phytophthora* pathogens and host plants.

Hosts fighting back: Multiple types of defense strategies

Unlike PTI, which is usually activated by apoplastic effectors upon recognition by host pattern recognition receptors located on the plasma membrane, effector-triggered immunity (ETI) is typically initiated by host-encoded nucleotide-binding leucine-rich repeat (LRR) receptors (NLRs) recognizing pathogen avirulent proteins or the structures modified by avirulent proteins in the cytoplasm (Ngou et al., 2022). PTI offers partial resistance to an invading pathogen and is likely more durable and broad spectrum, whereas ETI is often pathogen-race specific and is more likely overcome by newly evolved pathogenic isolates. Race-specific resistance controlled by *Rps* genes has been used for breeding soybean cultivars' resistance to *P. sojae*, but resistance break down has already been reported (Scott et al., 2019). Although *Rps1-k* and *Rps11* have been cloned and found to encode NLRs (Wang et al., 2021), the molecular mechanism underlying the function of these NLRs remains elusive.

In contrast, at least three host defense strategies have been identified for combating XEG1 virulence. First, soybean plants produce glucanase inhibitor protein I (GIP1), which directly binds to XEG1 and inhibits the hydrolysis of cell-wall xyloglucans by XEG1 (Figure 1A), thus suppressing the virulence function of XEG1 (Ma et al., 2017). Second, upon *P. sojae* infection, soybean increases the secretion of GmAP5, an aspartic protease, into the apoplast, which binds with and degrades XEG1 to decrease its contribution to virulence (Xia et al., 2020). Lastly, using the model species *N. benthamiana*, a plasma-membrane-located receptor-like protein with an LRR ectodomain, RXEG1, has been found to recognize XEG1 to induce cell death (Wang et al., 2018). Furthermore, it is observed that RXEG1 constitutively associates with the LRR receptor-like kinase SOBIR1 and requires BAK1, a multifunctional LRR receptor-like kinase, to efficiently induce cell death upon recognition of XEG1 (Ma et al., 2015; Wang et al., 2018). Because XEG1 can also trigger cell death in soybean and several other species (Ma et al., 2015), it is of great interest to clarify how RXEG1 recognizes XEG1 and thereby triggers cell death in host plants.

To this end, Sun et al. (2022) analyzed the structural changes of RXEG1(LRR) before and after binding by XEG1 and the role of these changes in RXEG1's interaction with BAK1. The results show that both the N-terminal loop and the island domain of RXEG1(LRR) bind to XEG1, with XEG1 enzyme activity inhibited by the binding. Importantly, XEG1 binding causes conformational changes the N-terminal loop, the island domain, and the last four LRRs of RXEG1(LRR), thus facilitating BAK1's interaction with RXEG1 and the downstream immune signaling possibly involving transphosphorylation of SOBIR1 and BAK1 (Figure 1B). Consequently, recognition of XEG1 by RXEG1 brings a double-killing effect, inhibition of XEG1 enzyme activity and activation of immune signaling, which together contribute to host defense to the invading pathogen. Further to this exciting achievement (Sun et al., 2022), it is worthy to examine if an

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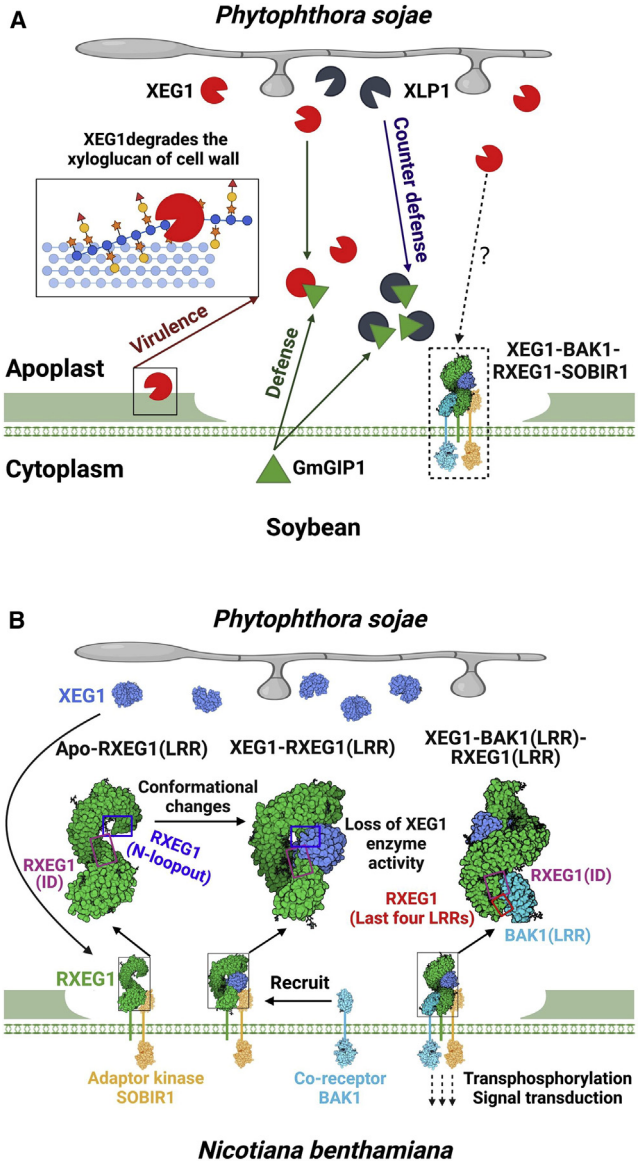

Figure 1. The apoplastic effector XEG1 of Phytophthora sojae and its recognition by the receptor-like protein RXEG1.

(A) Degradation of host cell-wall xyloglucan by XEG1 and the defense and counter-defense strategies revealed using XEG1. XEG1 plays a key role in soybean infection by *P. sojae* through degrading cell-wall xyloglucan. GmGIP1 contributes to soybean defense to *P. sojae* via directly binding to XEG1 and inhibiting its hydrolysis of xyloglucan. As a counter defense, XLP1, a mutated paralog of XEG1 from *P. sojae*, lessens the inhibition of XEG1 by GmGIP1 through competitively binding to GmGIP1. There also exists another layer of defense and counter defense involving GmAP5 and N-glycosylated XEG1 in the apoplast (Xia et al., 2020), which is not shown here for clarity.

(B) Structural basis of XEG1 recognition by RXEG1 and immune signaling activation. Comparative analysis of three atomically resolved structures, i.e., apo-RXEG1(LRR), XEG1–RXEG1(LRR), and XEG1–BAK1(LRR)–RXEG1(LRR), reveals that both the N-terminal loop and the island domain loop of RXEG1(LRR) bind to XEG1, with XEG1 enzyme activity inhibited by the binding. Concomitantly, XEG1 binding causes conformational changes of the N-terminal loop, the island domain, and the last four LRRs of RXEG1, thus facilitating the interaction of BAK1 with RXEG1. SOBIR1 constitutively associates with RXEG1, forming a bipartite LRR receptor-like kinase. Binding of XEG1 to RXEG1 renders the recruitment of BAK1. The resulting complex then functions in immune signal transduction in *Nicotiana benthamiana* probably involving transphosphorylation of SOBIR1 and BAK1. Whether there exists an analogous RXEG1 protein that functions similarly in soybean as RXEG1 does in *N. benthamiana* awaits further investigation (A).

This figure was created with the software BioRender (BioRender.com).

analogous RXEG1 protein may exist in soybean and functions similarly as RXEG1 does in *N. benthamiana*.

Pathogen's counter defense: Decoy and shielding

The battle between *P. sojae* and soybean becomes even more fascinating with the discovery of XLP1 and the N-glycosylated form of XEG1 (Ma et al., 2017; Xia et al., 2020). XLP1 is a paralog of XEG1; it lacks the xyloglucanase activity but gains the ability to bind GmGIP1 more strongly than XEG1, which lessens the inhibition of XEG1 by GmGIP1, thus benefiting XEG1's virulence function (Ma et al., 2017). Remarkably, N-glycosylation shields XEG1 from degradation by GmAP5, and the glycosylated XEG1 is less inhibited by GmGIP1, both of which may contribute to XEG1's virulence function (Xia et al., 2020). These findings demonstrate that *P. sojae* has evolved sophisticated counter defenses to protect its key virulence factor XEG1.

Future perspectives

The series of studies centered around XEG1 have illuminated the multilayered and complex battles between oomycetes and host plants. As an oomycete can deliver more than a dozen of effectors into the apoplastic and intracellular spaces of host cells during infection (Ma et al., 2017; Wang and Wang, 2018), future studies may reveal additional types of defense, counter defense, and even counter-counter defense strategies. Although genetic, molecular, and biochemical studies are effective in unraveling the various processes operating in oomycete–host interactions, structural biology research, such as the one highlighted here (Sun et al., 2022), is essential for precisely dissecting the molecular details involved in specific offensive-defensive actions.

From a practical viewpoint, developing durable and broad-spectrum resistance is highly desirable for controlling the damages of *P. sojae* to global soybean production. As race-specific resistance (e.g., *Rps*-conditioned ETI) to *P. sojae* tends to fail owing to rapid evolution of new pathogenic isolates, the deployment of partial resistance, which is controlled by quantitative trait loci (QTLs) and resembles PTI in being more durable, has been advocated (Scott et al., 2019). However, no QTL conferring partial resistance to *P. sojae* has hereto been cloned. Therefore, the substantial insights and resources gained from analyzing XEG1-augmented PTI may be harnessed for more effective control of *P. sojae* in the future.

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