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The role of effectors and host immunity in plant–necrotrophic fungal interactions

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Fungal diseases pose constant threats to the global economy and food safety. As the largest group of plant fungal pathogens, necrotrophic fungi cause heavy crop losses worldwide. The molecular mechanisms of the interaction between necrotrophic fungi and plants are complex and involve sophisticated recognition and signaling networks. Here, we review recent findings on the roles of phytotoxin and proteinaceous effectors, pathogen-associated molecular patterns (PAMPs), and small RNAs from necrotrophic fungi. We also consider the functions of damage-associated molecular patterns (DAMPs), the receptor-like protein kinase BIK1, and epigenetic regulation in plant immunity to necrotrophic fungi.

Introduction

Plant fungal diseases and biotrophic, hemibiotrophic, and necrotrophic pathogens

Plant fungal diseases represent a worldwide threat to food security and ecosystem health.[1] Based on their lifestyle, plant-pathogenic fungi have been classified as biotrophs, hemi-biotrophs, and necrotrophs. Biotrophic pathogens must obtain nutrients from living host cells and tissues and often secrete limited amounts of cell wall-degrading enzymes and effectors to suppress the host immune system.[2] In contrast, necrotrophic pathogens thrive on the dead host tissues that they kill before or during colonization; to induce cell necrosis, they often secrete phytotoxic secondary metabolites (SMs) and peptides, and produce reactive oxygen species (ROS).[3] Hemi-biotrophic pathogens display a biotrophic phase early during infection and display a necrotrophic phase only later; these pathogens produce toxins only at late stages in order to kill the host cells and complete their life cycle on dead tissues.[3]

Necrotrophs can be further divided into host-specific and broad host-range species. Host-specific necrotrophs produce host-specific toxins (HSTs) that are toxic only to host plants of the fungus. Host-specific necrotrophs include *Cochliobolus carbonum* (causal agent of northern corn leaf spot), *C. heterostrophus* (causal agent of southern corn leaf blight), *C. victoriae* (causal agent of Victoria blight of oats), *Parastagonospora nodorum* (previously *Stagonospora nodorum*,[4] causal agent of *Stagonospora nodorum* blotch of wheat), and *Pyrenophora tritici-repentis* (causal agent of tan spot of wheat). The archetypical broad host-range fungal necrotrophs are *Botrytis cinerea*, *Alternaria brassicicola*, *Plectosphaerella cucumerina*, and *Sclerotinia sclerotiorum*.

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Necrotrophic pathogens cause severe economic losses in agriculture

The economic impact of necrotrophic pathogens on agriculture was highlighted by a recent survey.[5] The report indicated that the losses in wheat and barley in Australia resulting from tan spot and *Stagonospora nodorum* blotch, both of which are caused by necrotrophic pathogens, significantly exceeded losses resulting from wheat rusts and mildews, which are caused by biotrophic pathogens. In addition, the necrotroph *B. cinerea* infects almost all vegetable and fruit crops and annually results in worldwide losses of $10 to $100 billion. It is clearly important to develop effective methods to control plant diseases caused by necrotrophic fungi. Knowledge on the mechanism of pathogen virulence and host immune responses is most relevant to future management of necrotrophic pathogens.

Plant innate immunity

Because they lack somatic adaptive immune systems, plants depend solely on innate immunity to cope with pathogens.[6-8] Regardless of the lifestyle of the attacking pathogen, the plant innate immune system has two layers: pathogen-associated molecular pattern (PAMP)-triggered immunity or PTI, and effector-triggered immunity or ETI. PTI is the first layer of innate immunity and is initiated in plants when PAMPs are recognized by pattern recognition receptors (PRRs); such recognition triggers a relatively weak but broad-spectrum immune response to pathogen infection. In contrast, ETI (the second layer of innate immunity) is induced by direct or indirect recognition of highly variable pathogen avirulence effectors by host disease-resistance (R) proteins; the recognition in this case leads to a rapid and robust response that is often referred to as a hypersensitive reaction (HR).

Plant immune responses to necrotrophs may be similar to or different from plant immune responses to biotrophs depending on the pathogen species and the primary determinant of virulence. In the case of necrotrophs, plant immune systems are very

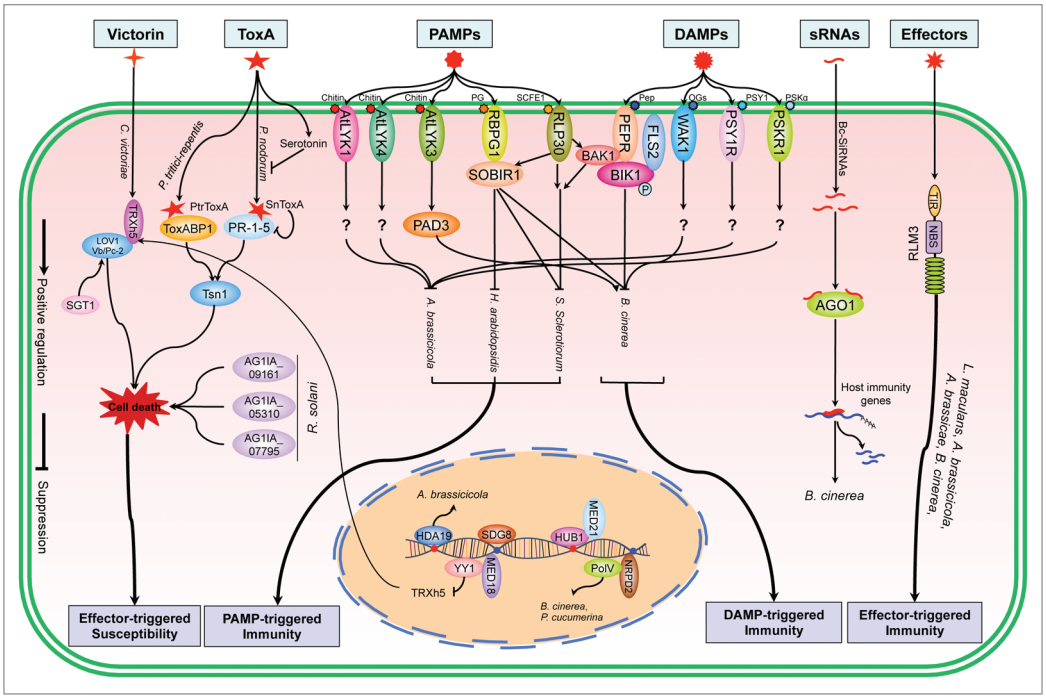

Figure 1. The major immune signaling pathways in the interaction between necrotrophic fungi and plants. The effector victorin binds to the host virulence target Trx-h5, which activates the NBS-LRR protein LOV1-mediated susceptibility to *Cochliobolus victoriae*. The transcription of *Trx-h5* is regulated by the transcription factor YY1 through the interaction with the mediator MED18. In addition, the chaperone SGT1 is required for victorin-mediated cell death by affecting the accumulation of LOV1.ToxA-triggered susceptibility to necrotrophic pathogens is governed by an R-like protein Tsn1. PtrToxA targets to a chloroplastic protein ToxABP1 and this interaction may trigger ToxA-mediated cell death. Moreover, a pathogenesis-related protein PR-1–5 is a potential target of SnToxA and the interaction between PR-1–5 and ToxA may mediate ToxA-induced necrosis in sensitive wheat. Three effectors, AG1IA_09161, AG1IA_05310 and AG1IA_07795, secreted by *Rhizoctonia solani* are delivered into rice cells and induce cell death in rice. Two major LysM-containing receptor-like kinases AtLYK1 and AtLYK4 perceive the PAMP chitin to induce a PTI response. AtLYK1 and AtLYK4 positively regulate *Arabidopsis* resistance to necrotrophic fungi. However, AtLYK3 as a negative regulator in *Arabidopsis* modulates the resistance to the necrotrophic fungi depending on PAD3. The PAMPs PG and SCFE1 are recognized by the *Arabidopsis* LRR-RLP RBPG1 and RLP30, respectively, to trigger an *Arabidopsis* PTI response. SOBIR1 is required for the activation of RBPG1- and RLP30-mediated immune response. SCFE1-triggered immune responses also require the LRR-RLK BAK1. The DAMPs OGs, PEP1, PSKα and PSY1 are perceived by the PRRs WAK1, PEPR1/PEPR2, PSKR1 and PSY1R, respectively. DAMP and PRR recognition can trigger immune responses and may overlap with PAMP-triggered immunity. In particular, the *Arabidopsis* peptide Pep1 triggers immunity through the receptor kinases PEPR1 and PEPR2. PEPR1 directly phosphorylates BIK1 and BAK1 to activate downstream signaling. Some small RNAs delivered by *Botryits cinerea* into host cells can bind to the *Arabidopsis* RNA interference machinery and suppress host immune responses. The TIR-NB RLM3 protein shows a gene-for-gene resistance relationship to the semibiotrophic fungus *Leptosphaeria maculans* and three necrotrophic fungi *B. cinerea*, *A. brassicicola*, and *A. brassicae* although the cognate effector needs to be determined.

complex and reflect the multiplicity of necrotroph virulence mechanisms targeting diverse host cellular processes. Plants have evolved effective immune responses to counter the "pro-death" virulence strategies of necrotrophic fungi. Recent research has increased our understanding of the recognition events and defense signaling processes in necrotroph–host interactions. In this review, we highlight the recent advances in elucidating the roles of immune-related molecules from both necrotrophic fungi and plants in various plant pathosystems (**Fig. 1**).

Effector-Triggered Immunity to Necrotrophic Fungi

Gene-for-gene resistance to necrotrophic fungi is rare in plants. The semibiotrophic fungus *Leptosphaeria maculans* displays a gene-for-gene relationship with both *Brassica napus* and *Arabidopsis*.[9] Using a microarray-based cloning strategy, researchers identified the *RLM3* locus on chromosome 4 of *Arabidopsis*.[10] *RLM3* encodes a putative Toll interleukin-1 receptor-nucleotide binding (TIR-NB) class protein. Interestingly, the *rlm3* mutant not only loses resistance to *L. maculans* but also exhibits enhanced susceptibility to the necrotrophic fungi *B. cinerea*, *A. brassicicola*, and *A. brassicae*. A 3:1 segregation of resistance against *A. brassicicola*, *A. brassiciae*, and *B. cinerea* was observed in the F_2 population, indicating that *RLM3* is a single dominant gene that governs resistance to these necrotrophic pathogens. The effector of RLM3 in the necrotrophic pathogens and the function of the *RLM3* gene in response to these pathogens are unknown.

Effector-Triggered Susceptibility to Necrotrophic Fungi

In a broad sense, effectors are defined as any pathogen proteins and small molecules that can alter the structure and function of host cells.[11] Effectors of necrotrophic pathogens include

Table 1. Overview of effectors of necrotrophic fungi

Pathogen	Effectors	Structure	Plant target	R gene	References
Parastagonospora nodorum	SnToxA	Protein	Chloroplasts, ToxABP1	*Tsn1*	12 and 13
P. nodorum	SnTox1	Protein	Probably chloroplasts	*Snn1*	14 and 15
P. nodorum	SnTox2	Protein	Probably chloroplasts	*Snn2*	16
P. nodorum	SnTox3	Protein	Unknown	*Snn3*	17
P. nodorum	SnTox4	Protein	Probably chloroplasts	*Snn4*	18
P. nodorum	SnTox5	Protein	Unknown	*Snn5*	19
Pyrenophora tritici-repentis	PtrToxA	Protein	Chloroplasts, ToxABP1	*Tsn1*	12, 13, 20, and 21
P. tritici-repentis	PtrToxB	Protein	Probably chloroplasts	*Tsc2*	22
Alternaria alternata	AM-toxin	Cyclic depsipeptide	Plasma membrane and chloroplasts	Unknown	23 and 24
A. alternata	AAL-toxin	Aminopentol ester	Asc	Unknown	25 and 26
A. alternata	AT-toxin	Unknown	Unknown	Unknown	27 and 28
A. alternata	AF-toxin	Epoxy-decatrienoic acid	Unknown	Unknown	29 and 30
A. alternata	AK-toxin	Epoxy-decatrienoic acid	Unknown	Unknown	27 and 31
A. alternata	ACT-toxin	Epoxy-decatrienoic acid	Unknown	Unknown	32
A. alternata	ACR-toxin	Polyketide	ACRS	Unknown	33–35
Cochliobolus heterostrophus	T-toxin	Linear polyketide	URF13	Unknown	36 and 37
C. carbonum	HC-toxin	Cyclic tetrapeptide	HDACs	Unknown	38
C. victoriae	victorin	Cyclic chlorinated pentapeptide	Unknown	*LOV1*	39 and 40
Rhynchosporium commune	NIP1	A phytotoxic protein	Plasma membrane H^+-ATPase	*Rrs1*	41–43
R. commune	NIP2	Protein	Unknown	Unknown	41
R. commune	NIP3	A glycoprotein	Plasma membrane H^+-ATPase	Unknown	41 and 42
Botrytis cinerea	NEP1-like	Protein	Cell membranes and nuclear envelope	Unknown	44
Mycosphaerella zeae-maydis	PM-toxin	Linear polyketide	URF13 13-KDa mitochondrial protein	Unknown	45
Periconia circinata	PC toxin	Unknown	Unknown	*PC*	46
Sclerotinia sclerotiorum	SSITL	Integrin protein	Unknown	Unknown	47
S. sclerotiorum	Ss-caf1	Protein with a putative $Ca2^+$-binding EF-hand motif	Unknown	Unknown	48
S. sclerotiorum	SSV263	A hypothetical secreted novel protein	Unknown	Unknown	49
S. sclerotiorum	Sspg1d	Endopolygalacturonases	IPG-1	Unknown	50 and 51
R. solani	AG1IA_09161	Protein with a glycosyltransferase GT family 2 domain	Unknown	Unknown	52
R. solani	AG1IA_05310	Protein with a cytochrome C oxidase assembly protein CtaG/cox11 domain	Unknown	Unknown	52
R. solani	AG1IA_07795	Protein with a peptidase inhibitor I9 domain	Unknown	Unknown	52

phytotoxins and traditional proteinaceous effectors (**Table 1**). Phytotoxins can be either non-HSTs that affect a broad range of plant species or HSTs that affect only a particular plant species or more often genotypes of that species.[53,54] Based on their chemical structure, phytotoxins are commonly classified as polyketides, nonribosomal peptides, alkaloids, terpenes, or metabolites of mixed biosynthetic origin.[55] So far, the protein effectors found in necrotrophs don't have a conserved domain like the RXLR motif in oomycetes.[56]

ETI is triggered by the recognition of pathogen effectors by plant R proteins, a recognition that leads to a HR and localized host cell death.[57] As a consequence, biotrophic pathogens, which require living host tissues, fail to survive and infect. Interestingly, HSTs secreted by necrotrophic fungi activate R protein-mediated ETI to cause HR cell death, which leads to effector-triggered susceptibility (ETS), as is the case for the cyclic peptide HST victorin that is produced and secreted by *C. victoriae.* Pathogenesis by *C. victoriae*, the causal agent of Victoria blight

Table 2. Overview of PAMPs/DAMPs of necrotrophic fungi and plant pattern recognition receptors (PRRs)

Molecule	PAMP/DAMP	Structure	PRR	PRR structure	Target	References
Chitin	PAMP	A polymer of N-acetyl-D-glucosamine	AtCERK1/ AtLYK4	LysM receptor kinase	?	79–81
PGs	PAMP	Enzyme	RBPG1	Leucine-rich repeat receptor-like protein	SOBIR1	82
SCFE1	PAMP	Peptide	RLP30	Receptor like protein	BAK1/ SOBIR1	83
Pep1/Pep2	DAMP	Peptide	PEPR1/ PEPR2	Leucine-rich repeat protein kinase	?	84 and 85
OGs	DAMP	A polymer of 1,4-linked α-D-galacturonic acid	WAK1	Wall-associated kinase1	?	86
PSKα and PSY1	DAMP	The tyrosine-sulfated peptides	PSKR1	Phytosulfokine (PSK) receptor	?	110 and 111

of oats, is determined by its production of victorin.[58,59] Victoria blight exclusively appeared on oat plants carrying the R gene *Pc2*, which is associated with disease resistance to the biotrophic fungus *Puccinia coronate*.[60] HST victorin sensitivity is dominated by the *Vb* R gene in oats. The results of many genetic and mutagenic efforts to separate *Pc2* and *Vb* suggest that *Pc2* and *Vb* are the same gene.[61-64] Susceptibility of *Arabidopsis* to *C. victoriae* is mediated by the NBS-LRR R protein LOCUS ORCHESTRATING VICTORIN EFFECTS1 (LOV1).[39]

TRX-h5, a defense-associated thioredoxin, is required for victorin sensitivity mediated by LOV1 in *Arabidopsis*, and the *trx-h5* mutant is insensitive to victorin.[65] In LOV1's absence, victorin inhibits TRX-h5, resulting in compromised defense but no disease symptoms after *C. victoriae* infection. In LOV1's presence, the binding of victorin to TRX-h5 activates LOV1 and elicits a HR-like response that confers susceptibility to *C. victoriae*. Recently, Lai et al.[66] confirmed that the transcription of the *TRX-h5* gene is repressed by the transcription factor YIN YANG1 through the interaction with mediator MED18. The chaperone SGT1 (SUPPRESSOR OF G2 ALLELE OF SKP1), which affects the accumulation of R proteins, is also involved in victorin-mediated cell death resulting from the reduced accumulation of LOV1 protein.[67] In addition, the silencing of six genes that encode different metabolic enzymes in *Nicotiana benthamiana* suppresses the *LOV1*-mediated, victorin-induced cell death. Simultaneously, cell death induced by a closely related *RPP8* R gene is also suppressed due to silencing of these six genes.[67]

The proteinaceous HST ToxA is produced by two fungal pathogens of wheat, *P. nodorum* and *P. tritici-repentis*.[12,20,68] The ToxA gene was originated in *P. nodorum* and was only recently transferred to *P. tritici-repentis* through interspecies hybridization[69,70] The dominant *Tsn1* allele in wheat confers susceptibility to ToxA.[12,71] In *P. tritici-repentis*, PtrToxA activates host responses that are typically observed in resistance responses to biotrophic pathogens, thereby providing additional evidence that necrotrophic pathogens such as *P. tritici-repentis* subvert host resistance mechanisms to cause disease.[72-74] Recently, Du et al.[75] demonstrate the induction of the monoamine serotonin in wheat after SnToxA infiltration. As a phytoalexin, serotonin can inhibit sporulation of *P. nodorum* by interfering with spore formation and maturation within pycnidial structures.[75] PtrToxA targets to the chloroplastic protein ToxABP1 and this interaction may induce alterations in photosystems I and II leading to a light-dependent accumulation of ROS in chloroplasts that disrupts their photosynthetic capacity and triggers PCD.[13,14,73] In addition, PR-1–5, a dimeric PR-1-type pathogenesis-related protein, is a potential target of ToxA, and the site-specific interaction between PR-1–5 and ToxA may mediate ToxA-induced necrosis in sensitive wheat.[76] How the ToxABP1 and PR-1–5 mediate ToxA-induced necrosis remain to be investigated.

PAMP-Triggered Immunity to Necrotrophic Fungi

PAMPs are conserved microbe-specific molecules or signatures that activate the plant defense response in a manner analogous to the way in which molecules trigger an immune response in animals.[77] PAMPs are often structural components of the pathogen cell wall or other conserved macromolecules.[78] As noted earlier, PAMPs are perceived by PRRs, which are currently divided into receptor-like kinase proteins (RLKs) and receptor-like proteins (RLPs). RLKs have a cytoplasmic kinase domain that participates in intracellular signal transduction and an extracellular domain that is potentially responsible for ligand perception. RLPs have structures similar to RLKs but lack the cytoplasmic kinase domain. Plant resistance against necrotrophic pathogens with a broad host range is considered to be complex early in the research. Recent studies showed that the plant resistance to necrotrophs also involves PRR perception of PAMPs (**Table 2**). The following examples demonstrate the relevance of PTI in resistance against necrotrophic fungi.

Chitin

Chitin perception and signaling has been well characterized in *Arabidopsis*. Chitin perception depends on the lysin motif (LysM)-containing receptor-like kinases such as LysM RLK1/ CHITIN ELICITOR RECEPTOR KINASE 1 (AtLYK1/ AtCERK1). *Arabidopsis* resistance against an incompatible fungus, *A. brassicicola*, was partly impaired in the *AtLYK1/AtCERK1* mutant.[79,80] The lysM domain directly binds to chitin, and the intracellular kinase domain is responsible for the activation of the downstream signaling.[79,80] The binding of chitin to the LysM motif induces the dimerization of AtCERK1, which is essential for the downstream response signaling.[87] In addition, AtLYK4 binds to chitin and is required for full induction of chitin signaling; the *lyk4* mutant confers enhanced susceptibility to the necrotrophic fungus *A. brassicicola*.[81]

There are five LYK genes (*AtLYK1/AtCERK1*, *AtLYK2*, *AtLYK3*, *AtLYK4*, and *AtLYK5*) in *Arabidopsis*. In contrast to the other members of the *Arabidopsis* LYK gene family, *AtLYK3* is transcriptionally repressed in response to *B. cinerea* infection and to treatments with different elicitors, including chitin.[88-90] The *atlyk3* mutant shows increased expression of basal levels of defense-related genes and enhanced resistance to *B. cinerea*. Furthermore, the enhanced resistance of *atlyk3* to *B. cinerea* depends on the increased expression of PHYTOALEXIN DEFICIENT 3 (*PAD3*), a defense-related gene that is regulated by fungal infection and elicitors independently of SA-, JA-, and ethylene-mediated pathways.[88] In addition, AtLYK3 is a positive regulator of ABA signaling, which is involved in the plant immune response to necrotrophic fungi.[91] These results demonstrate that AtLYK3 regulates the cross talk between immunity and ABA responses.[91]

Fungal endopolygalacturonases

Fungal endopolygalacturonases (PGs) act as PAMPs that are recognized by the *Arabidopsis* LRR-RLP RBPG1 (RESPONSIVENESS TO BOTRYTIS POLYGALACTURONASES1). Infiltration of *B. cinerea* PGs into the *Arabidopsis* accession Columbia induced necrotic cell death. Coimmunoprecipitation experiments demonstrated that RBPG1 and PG form a complex in *Nicotiana benthamiana*, which also involves the *Arabidopsis* leucine-rich repeat receptor-like protein SOBIR1 (for SUPPRESSOR OF BIR1).[82] PGs do not induce necrosis in *sobir1* mutant plants, and PG-induced resistance to *Hyaloperonospora arabidopsidis* is compromised in such plants.[82]

SCLEROTINIA CULTURE FILTRATE ELICITOR1 (SCFE1)

Recently, the novel proteinaceous elicitor SCFE1 was identified in the necrotrophic fungal pathogen *S. sclerotiorum*.[83] Its corresponding receptor in *Arabidopsis* is the RECEPTOR LIKE PROTEIN30 (RLP30). The *rlp30* mutant is more susceptible than the wild type to both *S. sclerotiorum* and *B. cinerea*. In addition, SCFE1-mediated immunity is dependent of the receptor-like kinase BRASSINOSTEROID (BR) INSENSITIVE1-ASSOCIATED RECEPTOR KINASE1, BAK1, and SOBIR1/EVR. Double mutants of *bak1* and *sobir1* are more susceptible to *S. sclerotiorum* and the related fungus *B. cinerea* than the wild type.[83]

Three new PAMP effectors identified from *Rhizoctonia solani*

The fungus *Rhizoctonia solani* is an important soil-borne, necrotrophic pathogen with a broad host range.[1] *R. solani* is the causal agent of the sheath blight of rice, a disease that causes severe yield losses in many rice-growing areas. There is little effective resistance against *R. solani* in rice or other crop plants. A large and diverse set of secreted proteins, enzymes of primary and secondary metabolism, carbohydrate-active enzymes, and transporters were identified from the draft sequence of the AG1 IA strain of *R. solani*.[52] Among the 25 candidate pathogen effectors, three secreted effectors, AG1IA_09161 (glycosyltransferase GT family 2 domain), AG1IA_05310 (cytochrome C oxidase assembly protein CtaG/cox11 domain), and AG1IA_07795 (peptidase inhibitor I9 domain) caused cell death phenotypes after inoculation in rice. In addition, these effectors show host-specific toxin characteristics for different hosts (rice, maize, and soybean). These results demonstrate that the three effectors are delivered into rice cells and might play a role in inducing cell death in rice during infection. How these effectors are delivered into rice cells and the identity of their host targets, however, remain unknown.

Damage-Associated Molecular Pattern (DAMP)-Triggered Immunity

DAMPs are endogenous molecules with elicitor activity and are released from host cellular components during pathogen attack or abiotic stress. Well-characterized DAMPs include oligogalacturonides (OGs), peptides, and cutin monomers (**Table 2**). The responses triggered by DAMPs largely overlap with those activated by PAMPs. For instance, transcript profiling of seedlings treated with OGs and flg22 revealed an extensive overlap of responses at least during the early stages after treatments.[89]

Oligogalacturonides

Researchers have speculated that OGs are derived from the degradation of a major component of pectin in plant cell walls by microbial polygalacturonases during infections or by the action of endogenous polygalacturonases that are induced by mechanical damage.[92,93] OGs elicit a wide range of defense responses, including an oxidative burst,[94] accumulation of phytoalexins,[95] an increase of glucanase, and chitinase activity,[96,97] deposition of callose,[98] increased hormone biosynthesis,[89] and enhanced resistance to *B. cinerea*.[88] Cell wall-associated receptor kinases have historically been considered potential receptors of OGs because of their ability to bind to OGs in vitro.[99] WAK1, a member of the wall-associated kinase family, acts as a receptor of OGs as revealed by a receptor domain-exchange approach.[86] The EF-Tu receptor (EFR) is a LRR receptor kinase for the bacterial PAMP elf18.[96] The chimeric receptor by fusing the extracellular domain of WAK1 with the kinase portion of EFR is able to activate the kinase domain in response to OGs.[86,100] On the other hand, after the treatment with the cognate ligand elf18, the EFR ectodomain activates the WAK1 kinase that triggers defense responses similar with those activated by OGs and effective against fungal and bacterial pathogens. In addition, *WAK1* overexpression in *Arabidopsis* increases resistance to *B. cinerea*.[86,101]

Peptides

In *Arabidopsis*, Peps, the small peptides derived from *PROPEP* genes, act as DAMPs. Six members of the *PROPEP* family are transcriptionally induced by pathogen infection and by PAMPs like elf18 and flg22.[102,103] By binding to the promoter of the W-boxes, WRKY-type transcription factors are the major regulators of PAMP-induced *PROPEP2* and *PROPEP3* expression.[104] Perception of Peps by the LRR receptor kinases PEPR1 and PEPR2 amplifies the immune response.[84,85] The importance of the Pep immune signaling pathway is indicated by the finding that PEPR can activate the PTI response.[105] The importance of the Pep immune signaling pathway has been further demonstrated that PEPR1 specifically interacts with BIK1 and

PBS1-like 1 (PBL1) to mediate Pep1-induced defenses and both PEPR1 and PEPR2 directly phosphorylate BIK1 in response to Pep1 treatment. In addition, PEPR1, and PEPR2 were found to interact with BAK1.[106] The pepr1/pepr2 double-mutant has a reduced sensitivity to ethylene (ET) and confers susceptibility to *B. cinerea*, demonstrating an important role of PEPRs in the ET-mediated defense response to necrotrophic pathogens.[107] In addition, a recent study indicated that PEPRs are required to connect local immunity to systemic immunity by reinforcing the separate defense signaling pathways.[108]

Phytosulfokine receptor

Phytosulfokines (PSKs) are secreted sulfated pentapeptides that have been purified from plant cell culture media.[109] PSKα, a bisulfated five-amino acid peptide, and PSY1, an 18-amino acid sulfated and glycosylated peptide, are perceived by LRR-RLK receptors PSKR1 (phytosulfokine receptor) and PSY1R, which are involved in plant growth and development.[110,111] The *Arabidopsis* pskr1 plants showed enhanced PTI against the bacterial pathogen *Pseudomonas syringae*, suggesting that PSKRs are involved in PAMP responses.[112] Similarly, Mosher et al.[111] determined that PSKα and PSY1 are involved in the PAMP-mediated defense. *pskr1* and *psyr1* mutants exhibit enhanced defense gene expression and heightened resistance to the biotrophic pathogen *P. syringae*. Conversely, *pskr1* mutants showed enhanced susceptibility to the necrotrophic fungus *A. brassicicola*. Molecular analysis revealed that the mutants accumulate elevated levels of salicylate, enhance the transcription of salicylic acid (SA) responsive or inducible pathogenesis-related genes, but repress the expression of jasmonic acid (JA)-responsive genes. These findings are consistent with the antagonistic effect of SA and JA on biotrophic and necrotrophic pathogen resistance. Integration of PSKα and PSY1 signaling in plant development and defense may involve the interactions between different phytohormones. Further investigation about hormone crosstalk in PSKα/PSY1 signaling is needed to determine the causal relationships in this complex network.[111]

Fungal Small RNAs as a Novel Type of Effector for Suppression of Plant Immunity

In most eukaryotic organisms, small RNAs regulate many biological processes, including development, stress responses, metabolism, and maintenance of genome integrity. Accumulating evidence has revealed that small RNAs play critical roles in plant–microbe interactions.[113,114] A recent, surprising finding is that pathogen small RNAs and the host RNA silencing machinery are important in the *B. cinerea*–plant interaction.[115] The authors found that some *B. cinerea* small RNAs (Bc-sRNAs) can bind to the *Arabidopsis* Argonaute 1 (AGO1), a component of the RNA interference machinery, and selectively silence host immunity genes.[115] The *ago1* mutant confers reduced susceptibility to *B. cinerea* while the *B. cinerea* mutant that could not produce these Bc-sRNAs had reduced pathogenicity on *Arabidopsis* and tomato. These results demonstrate that the necrotrophic pathogen *B. cinerea* can deliver "virulent" small RNAs into host cells and that such small RNAs function as effectors that suppress plant immunity.

The Functions of the Receptor-Like Kinase BIK1 in PTI to Necrotrophs

BIK1, a receptor-like cytoplasmic kinase in *Arabidopsis*, is induced early during infection by *B. cinerea* and plays an essential role in mediating plant resistance to necrotrophic pathogens.[116] BIK1 is also a positive regulator in plant immunity as a component of the FLS2-BAK1 immune receptor complex and is directly phosphorylated by BAK1.[117,118] The ligand-binding to FLS2 recruits BAK1, forming active receptor complexes.[117] The activation of these receptors results in a rapid phosphorylation of BIK1, which then dissociates from the receptor complexes to activate downstream signaling. BIK1 also associates with several RLKs including BRI1, elongation factor-Tu receptor (EFR), and the LysM-RK CERK1, DAMP peptide 1 receptor (AtPEPR1).[107,118] Lin et al.[119] show that BIK1 acts as a negative regulator in BR signaling because the bik1 mutant displays various BR hypersensitive phenotypes. A recent study shows that BIK1 directly interacts with and phosphorylates RBOHD upon PAMP perception, which is critical for the PAMP-induced ROS burst and antibacterial immunity.[120] These results indicate that BIK1 acts as a central regulator of defense signals in that it integrates PAMP, DAMP, ET, and BR signals from multiple surface-localized receptors. However, it is not known how signals from distinct receptors are integrated to activate an overlapping set of downstream defense responses.

A recent study indicates that BIK1 is a dual-specific kinase and that both tyrosine and serine/threonine kinase activity are essential for its function in *Arabidopsis* innate immunity.[121] The difference in BIK1 phosphorylation by BAK1 and BRI1 may account for the distinct functions of BIK1 in different signaling pathways. It will be interesting to determine whether tyrosine phosphorylation activity is required for BIK1 function in BR and ET signaling. In addition, more experiments are needed to determine whether the multiple functions of BIK1 are achieved through different phosphorylation sites mediated by different receptors or co-receptors.

Epigenetic Regulation of Plant Innate Immunity to Necrotrophic Fungi

A growing body of evidence shows that epigenetic mechanisms, including DNA methylation and histone modifications, play important roles in plant defense responses.[122-125] RNA-directed DNA methylation (RdDM) is a small interfering RNA-mediated epigenetic modification that induces de novo methylation of cytosines at the target genomic regions and leads to transcriptional gene silencing.[122,126] Lopez et al. identified NRPD2, which encodes the subunit of the plant-specific RNA

Polymerases IV and V (Pol IV and Pol V); these polymerases are important components of the RdDM pathway and have been implicated in immune responses.[123] The *nrpd2* mutants are more susceptible than the wild type to the necrotrophic pathogens *B. cinerea* and *P. cucumerina*. Studies on other defective mutants related to the RdDM pathway suggest that Pol V is required for plant immunity to necrotrophs.[123]

Histone modifications are also involved in the regulation of defense genes.[127] For example, HISTONE DEACETYLASE19 (HDA19) modulates the resistance to *A. brassicicola* by mediating the JA and ET signaling pathways.[124] Interestingly, some toxins produced by necrotrophic pathogens can inhibit histone deacetylases and thereby suppress immune responses and facilitate infection.[128-130] For example, the necrotrophic pathogen *C. carbonum* produces HC toxins that induce histone hyperacetylation in maize.[129] *A. brassicicola* produces the toxin depudecin, which can also inhibit histone deacetylase. In addition, the histone methyltransferase SET DOMAIN GROUP8 (SDG8)-mediated histone H3 lysine 36 methylation is required for basal and R protein-mediated resistance to necrotrophs and biotrophs.[126,131]

Furthermore, HISTONE MONOUBIQUITINATION1 (HUB1), a RING E3 ligase that ubiquitinates histone H2B, has been proved to regulate plant resistance to necrotrophic fungi.[125] HUB1 can interact with MED21, which is a subunit of the *Arabidopsis* mediator and an evolutionarily conserved transcriptional cofactor complex in all eukaryotes. MED21 is involved not only in immune responses to necrotrophs but also in embryo development.[125] Several mediator subunits in *Arabidopsis* (MED8, MED15, MED16, MED18, and MED25) are also implicated in resistance to necrotrophs and/or biotrophs.[66,132-134] It remains unclear, however, how these mediator components and chromatin modification regulate resistance.

Summary Points

1. Toxin effectors from necrotrophic fungi can target a host's central signal regulator to trigger R gene-mediated resistance and to thereby increase host susceptibility to attack by necrotrophic fungi.

2. Chitin, PGs, SCFE1, and other PAMP effectors secreted by necrotrophic fungi can be recognized by RLPs or RLKs, and such recognition triggers a series of PTI responses.

3. Although necrotrophic fungi can secrete enzymes that degrade the host cell wall, some of the degradation products, i.e., DAMPs, act as elicitors that trigger host immune responses.

4. By binding to the host RNAi machinery, small RNAs delivered by necrotrophic fungi into host cells can act as virulence effectors that suppress host immune responses.

5. Although PAMPs/DAMPs are initially recognized by distinct upstream PRRs, the immune signaling pathways triggered by those PRRs may converge on a central regulator like BIK1 and SOBIR1.

6. By regulating the expression of defense genes, epigenetic modifications, including DNA methylation and histone modifications, play important roles in plant immunity to necrotrophic fungi.

Future Issues

1. To date, RLM3, a TIR domain-encoding gene in *Arabidopsis*, is the only cloned R gene that is involved in broad-range immunity to necrotrophic fungal pathogens. Identifying additional R genes in host plants and their corresponding avirulence effector genes from necrotrophic fungi will provide new insights into plant immunity against this group of important fungal pathogens.

2. Although the mechanisms by which effectors are translocated into host cells during infection have been elucidated for biotrophic/hemibiotrophic plant pathogens, further research is required to determine how necrotrophic fungal effectors enter host cells.

3. Although a few PRRs targeted by effectors have been characterized, additional effector targets should be identified and their functions in plant innate immunity to necrotrophic fungi should be determined.

4. Small RNAs from *B. cinerea* have been identified as a new type of effector that suppresses the host innate immunity. As additional necrotrophic fungi are sequenced in the next few years, new small RNAs with similar effector functions will be identified.

5. BIK1 is a central regulator connecting plant development to immune responses through its function in ET signaling. It will be interesting to determine how diverse biological processes are integrated in a way that increases plant fitness in dynamic environments that provide only limited resources.

6. So far, only a few gene promoters that are targeted by epigenetic regulators have been described. Genome-level binding studies will be required to identify gene promoters that are targeted by epigenetic regulators during infection. Similarly, it will be important to determine the specific epigenetic modifications that occur after the recognition of PAMP or DAMP effectors and to establish the direct relationship to the plant immune response.

7. Although recent advances in the understanding of necrotrophic fungal and plant interactions have been substantial, few breakthroughs have been exploited for practical application. It is imperative that we begin to use this new understanding of pathogen effectors and R genes for the development of sustainable resistance to necrotrophic fungi.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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