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Review Article

Molecular plant immunity against biotrophic, hemibiotrophic, and necrotrophic fungi

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Pathogenic fungi use diverse infection strategies to obtain nutrients from plants. Biotrophic fungi feed only on living plant tissue, whereas necrotrophic fungi kill host cells to extract nutrients. To prevent disease, plants need to distinguish between pathogens with different life cycles, as a successful defense against a biotroph, which often involves programmed cell-death around the site of infection, is not an appropriate response to some necrotrophs. Plants utilize a vast collection of extracellular and intracellular receptors to detect the signatures of pathogen attack. In turn, pathogens are under strong selection to mask or avoid certain receptor responses while enhancing or manipulating other receptor responses to promote virulence. In this review, we focus on the plant receptors involved in resistance responses to fungal pathogens and highlight, with examples, how the infection strategy of fungal pathogens can determine if recognition responses are effective at preventing disease.

Introduction

Crop-infecting fungi are estimated to be responsible for an annual pre-harvest yield-loss of ∼20% worldwide [1]. The infection strategies used by fungi to obtain plant nutrients can be grouped into three broad categories, biotrophic, hemibiotrophic, and necrotrophic. Biotrophic pathogens extract nutrients from living cells, necrotrophic pathogens kill plant cells to access nutrients, and hemibiotrophs initially extract nutrients from living tissue before switching to a necrotrophic phase.

Plants rely on an innate immune system that is activated by receptor proteins at the cell surface and within the cell [2,3]. Extracellular pathogen recognition is controlled by plasma-membrane embedded receptors, while intracellular recognition often utilizes cytosolic nucleotide binding (NB) leucine-rich repeat (LRR) receptors (NLRs). Receptors are responsible for sensing molecules characteristic of pathogen infection, including microbe-associated molecular patterns (MAMPs), damage-associated molecular patterns (DAMPs), phytocytokines and pathogen-derived virulence molecules, known as effectors (Box 1). Effectors are secreted by adapted pathogens to promote virulence and are utilized by biotrophic, hemibiotrophic, and necrotrophic fungal pathogens to aid in colonization of host plants [4]. The responses activated by plant receptors can include the production of reactive oxygen species (ROS) and anti-microbial compounds, the influx of Ca^{2+} into the cytosol, immune signaling via mitogen-activated protein kinase (MAPK) cascades, transcriptional reprogramming, and a hypersensitive response (HR) leading to localized plant cell death [5,6].

In this review, we summarize recent findings concerning pathogen recognition via plant receptors, with a focus on their capacity to activate appropriate defense responses against biotrophic, hemibiotrophic, and necrotrophic pathogens.

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Box 1 Definitions for the types of molecules that are characteristic of infection and can be sensed by plant receptor proteins to activate defense responses

Term	Definition
MAMP	Microbe-associated molecular patterns are compounds derived from molecules required for microbial survival. MAMPs do not actively promote infection, examples include chitin oligomers from fungi and flagellin peptides from bacteria.
DAMP	Damage-associated molecular patterns are plant molecules that are released by cellular damage resulting from pathogen infection.
Phytocytokine	Plant peptides produced in the cytosol and secreted into the apoplast to stimulate plant immunity.
Effector	A secreted molecule, typically a small protein, that functions to promote infection.

Cell-surface recognition

Most cell-surface pathogen-recognition receptors are categorized as either receptor-like proteins (RLPs) or receptor-like kinases (RLKs), depending on the absence or presence of an intracellular kinase domain. Both receptor classes have a membrane-embedded domain and an extracellular ligand-binding domain. RLPs and RLKs can be further classified into subfamilies based on their extracellular domain (ECD). Identified ECDs on plant pathogen recognition receptors include lysin motif (LysM), leucine-rich repeat (LRR), lectin (lec), epidermal growth factor (EGF)-like, galacturonan-binding wall-associated-kinase (GubWAK) and WAK-associated C-terminal domain [7,8] (Figure 1). Cell-surface receptors are essential components to many cellular and developmental functions, and provide the first opportunity for detection of pathogen attack. They are therefore subject to manipulation by plant pathogens to facilitate infection and prevent appropriate resistance responses.

LysM receptors

LysM-RLP/RLKs are essential for microorganism perception and the activation of various plant responses facilitating defense and symbiosis. The ECDs of LysM receptors typically bind to polysaccharides, including chitin oligomers cleaved from the cell wall of invading fungi. Chitin elicitor receptor kinase1 (CERK1) is a LysM-RLK crucial for chitin-induced defense responses and is present in both monocot and dicot plants [9,10]. In rice, CERK1 is recruited by the chitin elicitor binding protein (CEBiP), a LysM-RLP, following homodimerization of CEBiP promoted by binding to long-chain chitin oligomers [11]. The CERK1 and CEBiP complex activates immune signaling pathways and ultimately promotes fungal disease resistance [11] (Figure 1 and Table 1). Rice CERK1 is also implicated in symbiosis with arbuscular mycorrhizal fungi [12,13] and can detect short-chain chitin oligomers produced by mycorrhizal fungi when in complex MYR1 (another LysM-RLK) [14,15]. A recent discovery demonstrated that MYR1/CERK1 complex formation reduces the chitin-induced immune response by inhibiting the recruitment of CERK1 by CEBiP [16], emphasising the complex nature of cell surface perception and signaling.

Arabidopsis thaliana has three LysM-RLP homologs of CEBiP, but none of these are required for general chitin-induced immune responses [17]. In *A. thaliana*, two LysM-RLKs with pseudo-kinase domains (LYK4 and LYK5), in addition to CERK1, are indispensable for the typical immune responses following chitin perception [9,18] (Figure 1 and Table 1). Like CEBiP, LYK4/LYK5 interact with CERK1 to form hetero-oligomers and mediate downstream immune signaling following chitin binding [10,18]. It is believed that the oligomerization of *At*LYK4/LYK5 and CEBiP with CERK1 facilitates CERK1 homodimerization and the subsequent phosphorylation of CERK1 that is required for effective downstream signaling [19–21]. The kinase domain of CERK1 potentiates immune signaling by phosphorylating target proteins, including various receptor-like cytoplasmic kinases (RLCKs) [22–27]. In addition to typical intracellular immune responses (ROS production, Ca^{2+} influx, MAPK signaling, transcriptional changes), recent work demonstrated that chitin perception dependent on CERK1 induces stomatal closure, likely inhibiting the entry of certain foliar pathogens [28,29]. For further details concerning CERK1 mediated defense and the methods fungi use to suppress chitin-triggered immunity, we refer readers to a recent review [19].

By recognizing highly conserved fungal cell wall components, LysM-RLPs/RLKs can inhibit the growth of a diverse range of pathogenic fungi, including biotrophs, hemibiotrophs, and necrotrophs. The fact that a single LysM-RLK can both promote the establishment of symbiotic fungi and restrict the growth of pathogenic fungi implies a complex signaling system which probably requires additional receptors and/or co-receptors to differentiate friend from foe.

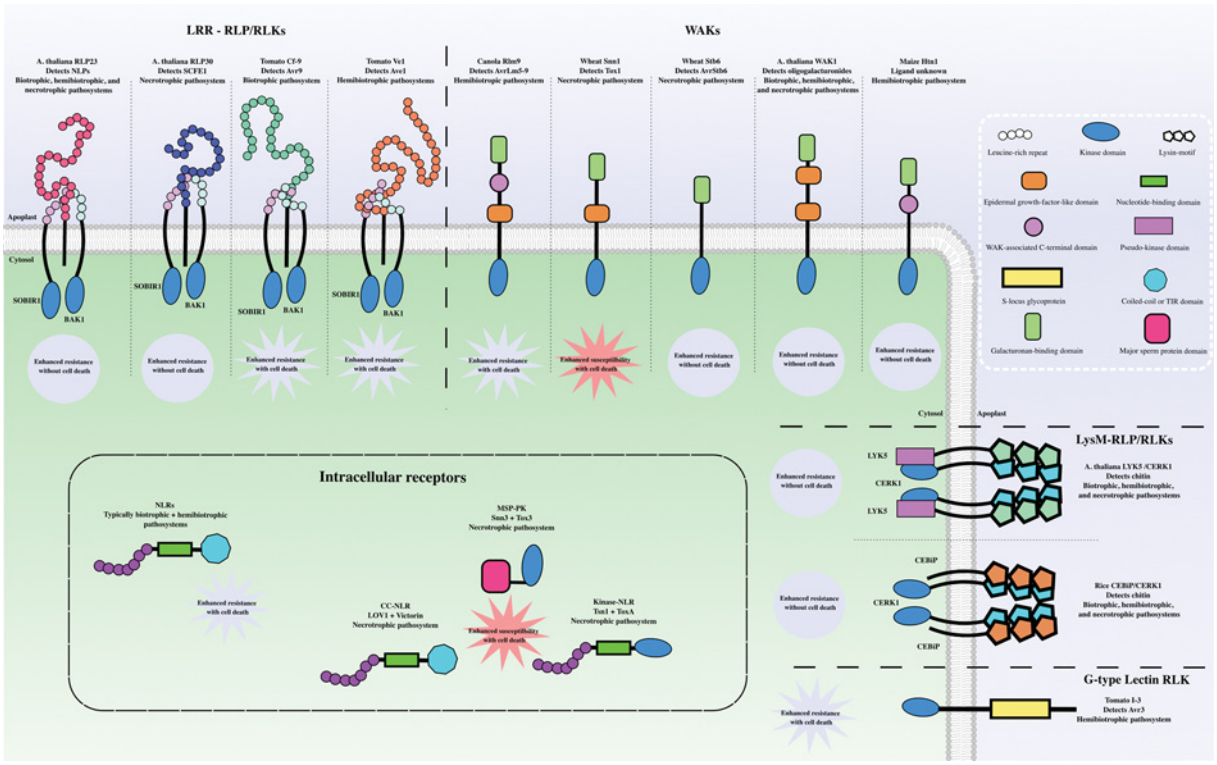

Figure 1. Extracellular and intracellular receptor proteins can promote disease resistance or susceptibility to fungal pathogens

Cell-surface receptors are embedded in the plasma-membrane while intracellular receptors are localized to the cytosol. The cell-surface receptors are grouped into subfamilies based on their extracellular domain/s. Lysin-motif receptor-like proteins and receptor-like kinases (LysM-RLP/RLKs) can detect chitin oligomers released from the fungal cell wall to activate defense responses that promote disease resistance against biotrophic, hemibiotrophic, and necrotrophic fungi without leading to plant cell death. Leucine-rich repeat (LRR) receptors can detect secreted proteins (effectors) from pathogenic fungi and mediate downstream immune signaling by forming receptor complexes with other LRR-RLKs (SOBIR1 and BAK1). Notably, the LRR-RLP/RLKs that detect effectors from necrotrophic fungi and promote disease resistance do not lead to plant cell death. Likewise, wall-associated kinase (WAK) receptor proteins activate responses that typically promote disease resistance. However, Snn1 from wheat detects a necrotrophic effector (Tox1) and triggers a cell-death response that supports the growth of the invading necrotroph. Inside the cell, intracellular receptors detect effectors and typically promote disease resistance by initiating a localized cell-death response that restricts the growth of biotrophic and hemibiotrophic fungi. However, multiple necrotrophic fungi use effectors to manipulate intracellular receptors into activating cell death, ultimately promoting disease susceptibility. Only the receptors discussed in this review are depicted in the figure.

LRR receptors

LRR ECDs commonly bind to peptides or proteins (although a well-studied exception is the detection of brassinosteroids (BRs) (reviewed in [30])). Like the LysM-RLP/RLK heteromeric receptor complexes, LRR-RLP/RLKs interact with each other to perceive ligands and potentiate intracellular signaling. To identify LRR-RLK receptor complexes, Smakowska-Luzan et al. used high-throughput assays investigating pair-wise interactions between 200 *A. thaliana* LRR-RLKs [31]. A key finding from the interaction network was that LRR-RLKs with small ECDs (<12 leucine rich repeats) typically interact with LRR-RLKs with large ECDs (>12 repeats) [31]. The concept that small LRR-RLKs are more likely to act as co-receptors for multiple receptor complexes is demonstrated by the well-characterized BAK1, a small LRR-RLK (4 repeats) that forms receptor complexes with multiple large LRR-RLKs, including those required for the perception of BRs (BRI1, 25 repeats) and peptides from bacterial flagellin (FLS2, 28 repeats) [32–36]. Immune signaling via BAK1 and FLS2 also requires the malectin-like receptor kinase FERONIA, which acts as a scaffold that can be regulated by plant RAPID ALKALINIZATION FACTOR propeptides to inhibit plant immune responses [37].

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Table 1 A summary of the receptors used by plants to detect invading fungi and the outcome of receptor activation as discussed in this review and depicted in Figure 1

Plant receptor and species	Identified co-receptor/s	Molecule detected	Infection strategy of associated pathogen/s	Plant cell death	Outcome (enhanced disease resistance or susceptibility)
		LysM-RLP/RLKs			
LYK5 – *A. thaliana*	CERK1	Chitin oligomers	All	No	Resistance
CEBiP – Rice	CERK1	Chitin oligomers	All	No	Resistance
		LRR-RLP/RLKs			
RLP30 – *A. thaliana*	SOBIR1/BAK1	A small secreted protein	Necrotroph	No	Resistance
RLP23 – *A. thaliana*	SOBIR1/BAK1	NLPs	All	No	Resistance
Ve1 - Tomato	SOBIR1/BAK1	Ave1	Hemibiotroph	Yes	Resistance
Cf-9 - Tomato	SOBIR1/BAK1	Avr9	Biotroph	Yes	Resistance
		WAKs			
Stb6 – Wheat	None	AvrStb6	Necrotroph	No	Resistance
Snn1 – Wheat	None	Tox1	Necrotroph	Yes	Susceptibility
Rlm-9 – Canola	None	AvrLm5-9	Hemibiotroph	Yes	Resistance
WAK1 - *A. thaliana*	None	Oligogalacturonides	All	No	Resistance
Htn1 - Maize	None	Unknown	Hemibiotroph	No	Resistance
		G-type lectin RLKs			
I-3 – Tomato	None	Avr3	Hemibiotroph	Yes	Resistance
		NLRs			
LOV1 – *A. thaliana*	None	Victorin	Necrotroph	Yes	Susceptibility
Tsn1 – Wheat	None	ToxA	Necrotroph	Yes	Susceptibility
		MSP-kinase			
Snn3 – Wheat	None	Tox3	Necrotroph	Yes	Susceptibility

This table is not an exhaustive list of all plant receptors that detect pathogenic fungi.

Most LRR-RLP/RLKs that perceive fungal-specific molecules detect effector proteins. *Fulvia fulva* (syn. *Cladosporium fulvum)* is a biotrophic pathogen responsible for leaf mold in tomato. The first effector-detecting LRR-RLP gene identified was Cf-9 (28 repeats) from tomato, that detects the *F. fulva* effector Avr9 [38]. Subsequent work identified more LRR-RLPs responsible for detecting *F. fulva* effectors, in all cases, the receptors lack intracellular kinase domains typically used for signal transduction [39–42]. It was therefore assumed that the effector-detecting receptors form complexes with RLKs to initiate immune signaling. SOBIR1, a small LRR-RLK (5 repeats), was the first Cf-9 interacting receptor identified [43]. Additional research determined that BAK1 and SERK1 (both small LRR-RLKs) are recruited to the SOBIR1/Cf receptor complex following ligand binding and are required for immune activation [44]. The Cf receptors trigger a local HR that restricts biotrophic pathogen growth [45] (Figure 1 and Table 1). HR activating LRR-RLPs are also effective at preventing the growth of certain hemibiotrophic pathogens. The Ave1 effector from *Verticillium, Fusarium* and *Colletotrichum spp.* is recognized by the LRR-RLP Ve1 (38 repeats) in tomato [46,47]. Like the Cf receptors, Ve1 requires SOBIR1 [43] and BAK1 [48] for complete immune activation (Figure 1 and Table 1). LRR-RLPs are also important for disease resistance against necrotrophic pathogens; however in this case the activation of plant immunity does not result in a HR (Figure 1). The LRR-RLP RLP30 (21 repeats) from *A. thaliana* detects a small (16–22 kDa) secreted protein from the necrotrophic pathogen *Sclerotinia sclerotiorum*, activating immune responses and decreasing fungal growth without inducing plant cell-death [49]. Likewise, RLP23 (27 repeats) detects a small peptide from Nep1-like proteins (NLPs) encoded by diverse microbes to activate plant immunity without a HR [50,51] (Figure 1 and Table 1). NLPs can also act as cytotoxic effectors that interact with plasma-membrane embedded sphingolipids and an extracellular plant LRR protein to cause plant cell death, this is believed to promote the virulence of certain necrotrophic and hemibiotrophic pathogens [52–55]. However, NLPs are also encoded by biotrophic pathogens and many are not cytotoxic, suggesting that they likely have another unknown function [55]. By detecting NLPs without inducing a HR, RLP23 increases disease resistance against various biotrophic, hemibiotrophic, and necrotrophic pathogens [50,51,56].

As illustrated in Figure 1, RLP23, RLP30, Ve1, and the Cf-9 receptors all rely on similar RLK co-receptors (SOBIR1 and BAK1) for immune signaling despite differences in the outcome of the immune response [49,51]. The signaling output from LRR-RLP/RLKs is often controlled by the intracellular domain (ICD) and can be uncoupled from the

ECD [57]. For example, Wu et al. recently reported that swapping the ECD of Cf-9 with the ECD of EFR (an LRR-RLK that does not activate a HR), leads to a HR when the chimeric protein is expressed in tobacco and exposed to the ligand detected by EFR [58]. The exact mechanism by which the ICDs of RLP/RLKs fine-tune immune signaling is currently unknown. Potentially the different responses may be achieved by the different receptor complexes influencing the phosphorylation of the ICD of BAK1 and/or SOBIR1 which in turn affects downstream signaling. Perraki et al. demonstrated that BAK1 has phosphosites that are required for immune responses activated by FLS2 but are not necessary for BRI1 signaling [59]. Future studies characterizing the phosphorylation of BAK1 and/or SOBIR1 in different receptor complexes may uncover how the receptors effective against biotrophs and hemibiotrophs signal for a HR, while the receptors detecting effectors from necrotrophs signal for immune activation without cell death.

The presented examples demonstrate that LRR receptor complexes have the capacity to increase disease resistance against a broad range of fungal pathogens by detecting effectors. Interestingly, the detection of biotrophic/hemibiotrophic effectors typically activates a localized HR preventing biotrophic growth whereas the detection of necrotrophic effectors stimulates the immune system without causing plant cell death that could promote necrotrophic infection [45,46,49,51].

Lectin domain receptors

Receptors with lectin (carbohydrate binding) domains (Lec-RLKs) are more commonly associated with developmental process rather than defense. Lec-RLKs can be divided into three classes: L-type, C-type and G-type. Only G-type Lec-RLKs are known to detect molecules of fungal origin, for a detailed overview of all types of Lec-RLKs and their potential ligands we refer readers to recent reviews [60,61]. The ECD of G-type Lec-RLKs includes a G-lectin domain, plasminogen-apple-nematode (PAN) motif, and a *S*-locus glycoprotein (SLG) domain. G-type Lec-RLKs are best known for their role in self-incompatibility (SI) systems [62–64]. To prevent self-fertilization, pollen and pistil cells recognize 'self' using a secreted small cysteine-rich protein (SCR) and extracellular SLG-domain containing receptor capable of binding to the SCR [65,66]. SCR-binding can trigger homodimerization of the receptor, likely causing transphosphorylation of the ICDs that initiates downstream signaling [66,67]. Studies in field poppy, reviewed in [68], have demonstrated that SI activation can result in ROS production, increased cytosolic [Ca^{2+}], irreversible oxidation of plant proteins, cytosolic acidification, and cell death [69–73].

The I-3 protein from tomato is currently the only G-type Lec-RLK known to recognize a fungal molecule [74]. I-3 detects the Avr3 effector from the hemibiotroph *Fusarium oxysporum f. sp. lycopersici* and inhibits pathogen growth (Table 1). Transient expression of Avr3 in I-3 containing tomato or co-expression of Avr3 and I-3 in *Nicotiana benthamiana* does not lead to a HR [74]. However, it was recently demonstrated that infiltration of purified recombinant Avr3 protein into I-3 tomato results in an I-3-dependent cell-death response [75]. Whether I-3 mediated immunity and plant cell death depends on the same signaling components as SI activation remains to be determined. Avr3 is a small cysteine-rich protein, analogous to the SCRs involved in SI, suggesting that Avr3 may bind directly to the I-3 SLG domain [76]. While not sufficient to rule out a direct interaction, previous yeast-two-hybrid experiments were unable to detect binding of Avr3 to the I-3 ectodomain [74]. Avr1, which is recognized by the LRR-RLP I [77], bears structural similarity to Avr3 [75] and is able to inhibit Avr3 resistance responses [78]. The mechanism of Avr3 mediated resistance suppression by Avr1 is unknown, but in-light of the structural similarity it is tempting to speculate that Avr1 interferes with Avr3 mediated recognition by binding to I-3 or a common 'guarded' host target. Given the ability of *S*-locus glycoproteins to detect small cysteine-rich proteins and activate plant cell death, it is likely that future research will identify more effector detecting G-type Lec-RLKs involved in promoting plant immunity against biotrophic and hemibiotrophic pathogens.

WAK receptors

Wall-associated kinases (WAKs) are characterized by a galacturonan-binding GubWAK ECD and often also have an extracellular EGF-like domain. There are 22 members of the WAK and WAK-like gene family in Arabidopsis [79], but these families have expanded in other plant species with 99 members in *Gossypium hirsutum* (cotton) [80], 91 members in barley [81], 125 in rice [82] and 555 in wheat [83]. The expansion of WAKs in both monocot and dicot species and the presence of unique structural families within species suggests that WAKs may have evolved following the divergence of monocots and dicots and during speciation. WAK1 from *A. thaliana* was first described to associate with the plant cell wall [84], specifically via pectin [85]. In addition, a recombinantly produced fragment of the WAK1 ectodomain was able to interact with cell wall extracted polygalacturonic acid, oligogalacturonides and pectin [86]. WAK1 was then shown to activate immunity by recognising plant-derived oligogalacturonides [87,88], and recent evidence demonstrates that WAKs can also detect fungal effectors [89–91]. Rlm9 from canola is a WAK immune receptor that perceives the AvrLm5-9 effector from the hemibiotrophic fungus *Leptosphaeria maculans*,

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the causal agent of blackleg disease [90]. Recognition of AvrLm5-9 by Rlm9 results in a HR and inhibits infection, however whether other immune responses are activated, how Rlm-9 potentiates immune signals, or if Rlm-9 requires co-receptors is unknown [90]. Rlm4 and Rlm7 are allelic variants of Rlm9 and detect the *L. maculans* effectors AvrLm4 and AvrLm4-7 to activate a HR and prevent further infection [91]. AvrLm4-7 and AvrLm5-9 are structurally similar [92], and AvrLm4-7 can inhibit AvrLm5-9 mediated resistance [93]. Like the Avr1 and Avr3 effectors mentioned previously, the mode of inhibition is unknown, but a common means of recognition evasion by pathogens could come from the selection of structurally similar effector proteins that are able to negate established forms of pathogen detection.

A WAK from wheat, Stb6, recognizes the AvrStb6 effector from the necrotrophic pathogen *Zymoseptoria tritici* [89]. Stb6 lacks an EGF-like domain, suggesting that this domain is not critical for the activation of immune responses by WAKs [89]. As opposed to Rlm9, Stb6 does not induce a HR following effector recognition [89]. The Tox1 effector from the necrotroph *Parastagonospora nodorum* is also recognized by a wheat WAK, Snn1 [94]. In contrast to all effector detecting receptors discussed above, the recognition of Tox1 by Snn1 promotes disease through a model known as effector-triggered susceptibility [94–96]. Snn1 activation results in typical immune responses, including the production of ROS, the expression of defense-related genes, and plant-cell death [95]. Both Rlm9 and Snn1 activation leads to plant cell death. However, due to different infection strategies, Snn1 enhances disease-susceptibility in the wheat-*P. nodorum* pathosystem, whereas Rlm9 promotes disease-resistance in the canola-*L. maculans* pathosystem (Figure 1 and Table 1). An exciting avenue for future research could be aiming to engineer Stb6, a WAK that enhances immunity against a necrotrophic pathogen without inducing a HR, to detect Tox1 by swapping ECDs with Snn1. Proof-of-concept domain-swapping experiments using WAK1 and the LRR-RLK EFR have demonstrated that WAK1 immune signaling by the ICD can be uncoupled from ligand-binding by the ECD [87].

Several other WAKs involved in fungal-disease resistance have been described, but their means of pathogen perception and ability to confer resistance require further investigation (Figure 1). Agriculturally important alleles of the maize WAK *ZmWAK-RLK1* are able to delay the progression of northern corn leaf blight (NCLB), but not completely halt the disease [97,98]. A resistance allele of *ZmWAK-RLK1* has been reported to modify the expression of genes involved in jasmonic acid (JA) and ethylene defense pathways, lignin synthesis, and cell wall maintenance, with most of these genes differentially expressed before infection occurs [99]. Unlike the previous WAK examples, alleles of ZmWAK-RLK1 may therefore function independently of the recognition of pathogen derived components to confer resistance.

WAKs are fast emerging as important receptor proteins capable of promoting disease resistance against biotrophic, hemibiotrophic, and necrotrophic pathogens (Figure 1 and Table 1). Similar to LRR receptors, the WAKs that detect effector proteins can activate pathways that lead to cell death or to enhanced immunity without cell death. Whether the response reduces or promotes infection depends on the lifestyle of the pathogen. The expansion of the WAK and WAK-like gene family in plants suggests that this family of genes is under strong selection for roles in defense responses, much like the expanded intracellular nucleotide-binding, LRR receptor (NLR) family (discussed below). Unlike NLRs however, WAKs seem to maintain diverse roles in cell maintenance and development [100], as well as in abiotic [101] and biotic stress responses.

Intracellular recognition

NLRs are cytosolic proteins that activate immune responses following the detection of an effector. Typically, NLRs are composed of a C-terminal LRR domain, central NB domain, and variable N-terminal domain. The two major classes of NLR are CC-NLRs that have a coiled-coil N-terminal domain and TIR-NLRs that have a toll/interleukin-1 receptor N-terminal domain. In general, the CC and TIR domains are responsible for signalling and the NB and LRR domains regulate NLR activation. The activation of an NLR by a fungal effector typically results in a HR that prevents the growth of biotrophic and hemibiotrophic pathogens [102]. They are the most crucial defense receptor against many adapted pathogens and have been studied and reviewed extensively. For a detailed understanding of how NLRs perceive effectors, and the subsequent immune signaling pathways see [103–106].

Interestingly, necrotrophic pathogens can co-opt NLR effector recognition to promote cell death and enhance disease. LOV1 is an *A. thaliana* CC-NLR that confers susceptibility to the necrotrophic fungus *Cochliobolus victoriae* (Table 1) [107]. LOV1 guards a plant thioredoxin TRX-h5 to detect ribosomally produced cyclic hexapeptides (victorin) secreted by *C. victoriae* during infection, leading to cell death and plant susceptibility [108,109]. Victorin binds directly to the active site of TRX-h5, and in the absence of LOV1 inhibits plant defense [108]. The high conservation of LOV1 across *A. thaliana* accessions suggests that it plays an important role in plant immunity, likely mediating resistance against a biotrophic or hemibiotrophic pathogen by detecting an effector that interferes with TRX-h5 [110].

Victorin-induced susceptibility to *C. victoriae* is also controlled by a CC-NLR in common bean and the gene responsible for susceptibility in oats co-segregates with a resistance gene to the biotrophic pathogen *Puccinia coronata* [111,112]. Collectively, the victorin research indicates that necrotrophic pathogens can promote infection by secreting effectors that mimic recognised effectors from biotrophic or hemibiotrophic pathosystems to activate a HR. An analogous example involves the protein effector ToxA from necrotrophic pathogens *Pyrenophora tritici-repentis*, *Parastagonospora nodorum*, and *Bipolaris sorokiniana.* ToxA is recognized by the intracellular wheat NLR receptor Tsn1, a non-canonical NLR with a kinase domain at the N-terminus (Table 1) [113]. The ToxA protein, in the absence of the pathogen causes plant cell-death in wheat lines carrying Tsn1 [114]. In the context of these necrotrophic pathogens, ToxA is a major determinant in promoting disease in wheat that possess Tsn1 [115–118]. Snn3 is another wheat disease susceptibility gene that encodes an intracellular protein with a kinase domain [119]. The *P. nodorum* effector Tox3 is detected by Snn3, which results in the upregulation of defense-related transcripts, indicating that Snn3 likely functions in plant defense but is being manipulated by Tox3 to promote infection [120]. Unlike previously characterized pathogen-detecting receptors, Snn3 has a C-terminal major sperm protein (MSP) domain [119]. It is predicted that the MSP domain is responsible for effector perception and the kinase domain then activates defense responses, including the plant cell-death that promotes the necrotrophic growth of *P. nodorum*. Genes with MSP and protein kinase domains are specific to monocot plants and significant diversity exists in the sequences of the MSP domains, including the presence of uncharacterized integrated domains [119]. It is tempting to speculate that future research efforts will identify more receptors in monocot plants that use an MSP domain to detect effector proteins and activate defense responses. For further discussion on the various receptors hijacked by necrotrophic pathogens see [121].

To defend against biotrophic and hemibiotrophic pathogens intracellular effector-detecting plant receptors often activate immune signaling that culminates in a HR, restricting the growth of pathogens that require living plant tissue. However, the examples presented here demonstrate how necrotrophic pathogens can manipulate intracellular receptors to promote plant-cell death and enable nutrient acquisition.

Receptor cross-talk

We have divided this review into sections based on the structure of the immune receptors. However, regardless of structure, most receptors activate similar, overlapping pathways and recent advances have demonstrated that diverse receptors work co-operatively to promote plant immunity. BAK1, the common LRR-RLP/RLK co-receptor, phosphorylates CERK1 following activation, which promotes rapid activation of CERK1 following chitin perception [122]. A cotton WAK positively regulates resistance to wilt-diseases by promoting the heterodimerization of the LysM-RLKs LYK5 and CERK1 [123]. Likewise, WAK1 from tomato acts to promote apoplastic immunity activated by an LRR-RLK [124].

Extracellular receptors can also enhance the immune responses activated by intracellular receptors, and vice-versa. The Cf-4 LRR receptor complex requires a downstream CC-NLR to activate a HR and restrict the growth of the biotrophic invader [125,126]. Furthermore, two recent publications demonstrated that NLR activation results in the up-regulation of extracellular receptor signaling components, and the HR activated by NLRs requires the activation of extracellular receptors [127,128]. For an in-depth discussion on the cross-over between immunity activated by intracellular and extracellular receptors, we refer readers to recent reviews [129–131].

Summary

- Pathogenic fungi use biotrophic, hemibiotrophic, and necrotrophic infection strategies to infect plants and reduce crop productivity.
- Plants produce a variety of receptor proteins that can detect danger from the cell-surface or inside the cell, leading to defense responses against diverse fungal pathogens.
- Recent evidence suggests that pathogenic fungi can interfere with receptor activation via the release of effectors with structural similarity to the recognized effectors.
- The success of an immune response can depend on the infection strategy of the invader. A hypersensitive cell-death response is often effective at preventing biotrophic growth but can be manipulated by necrotrophs to promote infection.

Competing Interests

The authors declare that there are no competing interests associated with this manuscript.

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Author Contribution

C.L.M. and J.R.G. drafted the manuscript. P.S.S. and S.J.W. conceptualized the manuscript. All authors revised and edited the manuscript.

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Abbreviations

DAMP, damage-associated molecular pattern; HR, hypersensitive response; LRR, leucine-rich repeat; MAMP, microbe-associated molecular pattern; MAPK, mitogen-activated protein kinase; NB, nucleotide binding; NLR, nucleotide binding leucine-rich repeat receptor; PAN, plasminogen-apple-nematode; ROS, reactive oxygen species; SLG, *S*-locus glycoprotein; WAK, Wall-associated kinase.

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