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PERSPECTIVE

Of PAMPs and Effectors: The Blurred PTI-ETI Dichotomy [OA]

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Typically, pathogen-associated molecular patterns (PAMPs) are considered to be conserved throughout classes of microbes and to contribute to general microbial fitness, whereas effectors are species, race, or strain specific and contribute to pathogen virulence. Both types of molecule can trigger plant immunity, designated PAMP-triggered and effector-triggered immunity (PTI and ETI, respectively). However, not all microbial defense activators conform to the common distinction between PAMPs and effectors. For example, some effectors display wide distribution, while some PAMPs are rather narrowly conserved or contribute to pathogen virulence. As effectors may elicit defense responses and PAMPs may be required for virulence, single components cannot exclusively be referred to by one of the two terms. Therefore, we put forward that the distinction between PAMPs and effectors, between PAMP receptors and resistance proteins, and, therefore, also between PTI and ETI, cannot strictly be maintained. Rather, as illustrated by examples provided here, there is a continuum between PTI and ETI. We argue that plant resistance is determined by immune receptors that recognize appropriate ligands to activate defense, the amplitude of which is likely determined by the level required for effective immunity.

INTRODUCTION: A CONTEMPORARY VIEW OF PLANT IMMUNITY

Early in the 20th century, by performing genetic experiments, Harold Flor showed that inheritance of plant immunity to pathogens, as well as the ability of the pathogen to cause disease, is controlled by corresponding gene pairs (Flor, 1942). The plant genetic factor was referred to as the resistance (*R*) gene, while the pathogen genetic factor that determined the inability to cause disease was referred to as the avirulence (*Avr*) gene. A plant producing an R protein is resistant toward a pathogen strain that produces the corresponding Avr protein, and it was originally believed that gene-for-gene resistance was conferred by a direct interaction between the R and Avr proteins (Keen, 1990). However, experiments designed to show such direct ligand–receptor interactions often produced negative results, which led to the formulation of the guard hypothesis, stating that R proteins monitor the state of host components that are targeted by pathogen molecules (Van der Biezen and Jones, 1998). This model recognizes that pathogen molecules have intrinsic functions to promote pathogen virulence, which requires the modulation of host components that have thus become virulence targets. Rather than the presence of the pathogen molecules themselves, it is the manipulation of their host targets that is sensed by the R proteins (Chisholm et al., 2006; Jones and Dangl, 2006). Thus, the pathogen molecules that were originally referred to as avirulence factors genuinely are virulence factors. Presently, the term "effector" is commonly used for this type of molecule (Bent and Mackey, 2007; Boller and Felix, 2009).

In parallel to research on gene-for-gene resistance, the existence of inducers of plant defense responses that were not determinants of race or cultivar specificity became evident (Ebel and Cosio, 1994). These non-race-specific inducers of defense were termed elicitors and harbored a wide range of different types of molecules (Boller, 1995). However, for a long time it was debated whether elicitor-induced defense responses were physiologically relevant to plant immunity and what the relationship between gene-for-gene resistance and elicitor-induced defense would be. With the identification of the first elicitor receptor (FLS2; Gómez-Gómez and Boller, 2000), subsequent proof for its role in plant immunity (Zipfel et al., 2004), and identification of microbial effectors that suppress this type of immunity (Hauck et al., 2003), proof that both types of defense contribute to plant immunity was eventually provided.

A simple but elegant view of innate immunity in plant pathogen interactions is depicted by the so-called zigzag model introduced by Jones and Dangl (2006). This model proposes that the first line of active plant defense is formed by pattern recognition receptors (PRRs). These are cell surface receptors that recognize pathogen-associated molecular patterns (PAMPs). PAMPs were originally defined as highly conserved molecules within a class of microbes that have an essential function in microbial

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PERSPECTIVE

fitness or survival (Medzhitov and Janeway, 1997; Nürnberger and Brunner, 2002). As they may also occur in nonpathogenic microorganisms, the alternative term microbe-associated molecular pattern also is used (Boller and Felix, 2009). PRRs activate an innate immune response upon detection of PAMPs, so-called PAMP-triggered immunity (PTI). Successful pathogens are able to overcome PTI by means of secreted effectors that suppress PTI responses, resulting in effector-triggered susceptibility. Pathogenic bacteria typically inject such effectors directly into the host cytoplasm by means of their type III secretion machinery, and during evolution, plants have responded to these effectors through the development of cytoplasmic R proteins that recognize (the presence or activity of) single effectors. The majority of these R proteins are intracellular receptor proteins of the nucleotide binding–leucine-rich repeat (NB-LRR) type that activate so-called effector-triggered immunity (ETI). Typically, the propensity to trigger ETI is pathogen strain or race specific and is associated with programmed cell death, a response which is referred to as the hypersensitive response (HR), and systemic acquired resistance (SAR) in the host. As a result of selection pressure, pathogen isolates evolved that have either lost or altered the effector that is recognized or that have gained novel effectors to suppress the ETI response. In turn, new plant receptors evolved that either recognize the obvious effectors or the newly acquired effectors, resulting again in ETI. This coevolution proceeds, with continuous selection for novel pathogen isolates that overcome ETI and new plant genotypes that resurrect ETI.

In accordance with the zigzag model, plant pathologists discriminate two phases of plant immunity: PTI triggered by PAMPs and ETI triggered by effectors, with the paradigm that activated immune responses in ETI occur quicker and are more prolonged and more robust than those in PTI (Tao et al., 2003; Jones and Dangl, 2006; Tsuda and Katagiri, 2010). As a consequence, the molecules that were historically termed elicitors or avirulence factors have more recently been renamed PAMPs and effectors, respectively (Chisholm et al., 2006; Jones and Dangl, 2006; Bent and Mackey, 2007). However, accumulating evidence indicates that the separation between PAMPs and effectors, and between PRRs and R proteins, and thus also between PTI and ETI, cannot strictly be maintained. Rather, as illustrated by examples provided here, there is a continuum between PTI and ETI.

THE AMBIGUOUS PAMP-EFFECTOR DICHOTOMY

Classical examples of PAMPs are structural molecules, such as bacterial flagellin, peptidoglycan, and lipopolysaccharides, oomycete glucans, and fungal chitin (Ayers et al., 1976; Felix et al., 1993, 1999; Dow et al., 2000; Gust et al., 2007; Erbs et al., 2008). While PAMPs are widely conserved across genera, effectors are specific to single or a few related species (Chisholm et al., 2006; Jones and Dangl, 2006; Bent and Mackey, 2007). However, based on their widespread occurrence, several groups of effector proteins qualify to be designated as PAMPs.

Fungal LysM Effectors Suppress Chitin-Triggered Immunity

Chitin, a β-(1,4)-linked homopolymer of *N*-acetylglucosamine, is an essential component of the cell walls of all fungi that is not found in plants and vertebrates. Chitin fragments have long been known to act as elicitors of defense responses in plants (Felix et al., 1993). Taking the widespread, conserved, and intrinsic structural nature of this polysaccharide into account, chitin is an undisputed fungal PAMP. Presently, a number of plant immune receptors for chitin have been characterized. A high-affinity chitin binding protein, the Chitin Oligosaccharide Elicitor Binding Protein (CEBiP) receptor, was isolated from the plasma membranes of rice (*Oryza sativa*) cells (Kaku et al., 2006). Knockdown of *CEBiP* expression resulted in suppression of chitin-induced defense responses, showing that CEBiP plays a key role in perception of chitin oligosaccharides. CEBiP is a receptor-like protein (RLP) that contains extracellular LysM domains but lacks an obvious intracellular signaling domain, suggesting that additional components are required for subsequent initiation of defense signaling. A potential coreceptor of CEBiP is the recently identified LysM-containing Chitin Elicitor Receptor Kinase-1 (Os-CERK1) that, similar to CEBiP, is required for chitin signaling in rice cells (Shimizu et al., 2010). In addition, a similar LysM-containing plasma membrane receptor required for chitin-triggered immunity was identified in *Arabidopsis thaliana* (Miya et al., 2007; Wan et al., 2008), and recent evidence suggests that it directly binds chitin fragments (Petutschnig et al., 2010; Iizasa et al., 2010).

Based on the zigzag model, it must be anticipated that successful fungal pathogens have developed effectors to interfere with chitin-triggered immunity (Figure 1). From the fungal tomato pathogen *Cladosporium fulvum*, the abundantly secreted protein Ecp6 (for extracellular protein 6) was identified that, like the plant chitin receptors CEBiP and CERK1, also contains LysM domains (Bolton et al., 2008). Ecp6 was found to bind chitin fragments to suppress chitin-triggered immune responses and, moreover, to compete with the plant LysM-containing CEBiP receptor for the binding of chitin oligomers (de Jonge et al., 2010). Thus, the Ecp6 protein prevents activation of host immunity by sequestering chitin fragments that are released during host colonization (de Jonge et al., 2010). Interestingly, the *Ecp6* gene is found in all strains of *C. fulvum* that have been analyzed thus far, and only little sequence variation is observed (Bolton et al., 2008). Moreover, conserved Ecp6 orthologs, termed LysM effectors, widely occur in the fungal kingdom (Bolton et al., 2008; de Jonge and Thomma, 2009), suggesting that scavenging of chitin oligosaccharides is fundamental to the lifestyle of fungal pathogens upon colonization of their hosts (de Jonge et al., 2010). Indeed, several LysM effectors from other pathogenic fungi may contribute to virulence through suppression of chitin-triggered host immunity (B.P.H.J. Thomma, unpublished data). Although these orthologs have been named LysM effectors (de Jonge and Thomma, 2009), their widespread functional conservation in the fungal kingdom is reminiscent of typical PAMPs.

PERSPECTIVE

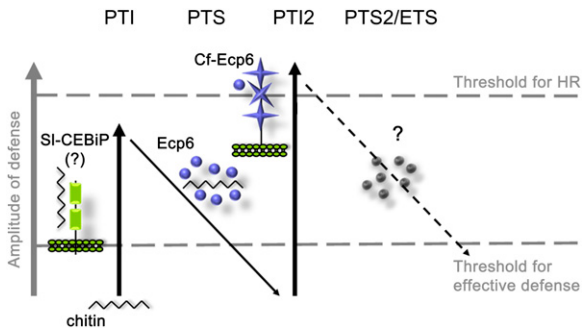

Figure 1. A Variation on the Zigzag Model to Describe the Evolution of Chitin Signaling in the Interaction between *C. fulvum* and Tomato.

The *C. fulvum* PAMP chitin activates PTI in tomato plants, presumably upon perception by the tomato homolog of the rice cell surface receptor CEBiP. Thus far, a chitin-triggered HR has not been observed in tomato. To overcome PTI, *C. fulvum* employs the abundantly secreted LysM effector Ecp6 that binds chitin, thereby preventing activation of Sl-CEBiP. Since LysM effectors are widely conserved in the fungal kingdom, they qualify as PAMPs, and Ecp6-mediated PTI suppression therefore should be referred to as PAMP-triggered susceptibility (PTS). Tomato genotypes that have evolved to recognize Ecp6 develop an HR upon Ecp6 infiltration and presumably carry a cell surface receptor for this molecule, tentatively called *C. fulvum* resistance to Ecp6 (Cf-Ecp6), again resulting in PTI (PTI2). The question mark indicates that subsequent susceptibility can again be provoked by *C. fulvum*, either through mutation of the Ecp6 protein such that it still sequesters chitin fragments but is no longer recognized by Cf-Ecp6 or by producing an effector that suppresses Sl-CEBiP signaling in an alternative manner. (*Adapted by permission from Macmillan Publishers Ltd.: Nature; Jones and Dangl [2006].*)

This aspect is further substantiated by the recent identification of tomato (*Solanum lycopersicum*) genotypes that specifically recognize *C. fulvum* Ecp6 (B.P.H.J. Thomma, unpublished data; Figure 1).

The LysM effectors are not the only group of effectors that qualify to be designated as PAMPs based on their widespread occurrence. This similarly applies to, for instance, necrosis- and ethylene-inducing peptide 1 (Nep1)-like proteins that are conserved among bacteria, fungi, and oomycetes (Gijzen and Nürnberger, 2006; Kamoun, 2006), crinklers that are produced by oomycete species (Torto et al., 2003; Haas et al., 2009), and harpins that are produced by Gram-negative bacteria (Tampakaki et al., 2010).

PAMPs with Narrow Distribution

In contrast with the groups of widely conserved effectors mentioned above, several studies have shown that some PAMPs are only narrowly conserved (Brunner et al., 2002; Lee et al., 2009).

The rice *Xa21* gene, which encodes a receptor-like kinase, confers immunity to most strains of the bacterium *Xanthomonas oryzae* pv *oryzae* (Xoo; Song et al., 1995). Resistance is activated by avrXa21 (avirulence protein corresponding to XA21), a protein recently renamed Ax21 (activator of Xa21-mediated immunity; Lee et al., 2009). Several bacterial genes that are required for Ax21 activity were identified that either encode components of a bacterial type I secretion system or are involved in sulfation (da Silva et al., 2004). A sulfated, 17–amino acid synthetic peptide (axYS22) derived from the N-terminal region of Ax21 was found to be sufficient for biological activity and to bind to Xa21, whereas peptides lacking sulfation were inactive (Lee et al., 2009). Interestingly, axYS22 is fully conserved in strains of *Xanthomonas campestris* pv *campestris*, *Xanthomonas axonopodis* pv *glycinea*, *X. axonopodis* pv *vesicatoria*, and *X. oryzae* pv *oryzicola*.

Another PAMP with a similarly narrow distribution spectrum is Pep-13, a surface-exposed fragment of a calcium-dependent cell wall transglutaminase (TGase) that is conserved among *Phytophthora* species and that activates defense in various plants (Nürnberger et al., 1994; Brunner et al., 2002). Thus, in contrast with the current paradigm that PAMPs are broadly conserved, at least some PAMPs have a rather narrow distribution. In addition to this, despite being widespread, some PAMPs are only recognized by a narrow range of plant hosts as recognition of the ubiquitous bacterial PAMPs EF-Tu and cold-shock protein is restricted to the *Brassicaceae* and *Solanaceae*, respectively, which again is an effector-like characteristic (Felix and Boller, 2003; Zipfel et al., 2006).

PAMPs and Virulence

Apart from their distribution, the intrinsic function for the pathogen has been a parameter to distinguish PAMPs from effectors. Whereas PAMPs are essential for microbial fitness and survival, effectors specifically contribute to virulence by targeting host (defense) physiology. Nevertheless, several examples indicate that the distinction between requirement for fitness and survival on the one hand and for virulence on the other hand is difficult to maintain. For example, one of the most widely studied PAMPs, flagellin, also plays a role in virulence. It has been shown that specific *Pseudomonas syringae* pv *tabaci* flagellin mutants affected in elicitor activity also display reduced virulence in planta due to reduced motility (Taguchi et al., 2006, 2010; Naito et al., 2008). The importance of flagellar motility in bacterial virulence has also been reported for other *P. syringae* pathovars (Panopoulos and Schroth, 1974; Haefele and Lindow, 1987; Hattermann and Ries, 1989) and other bacterial species, including *Erwinia carotovora* (Hossain et al., 2005) and *Ralstonia solanacearum* (Tans-Kersten et al., 2004). Interfering with biological activity through changes in composition of the lipopolysaccharide (LPS) or peptidoglycan envelope may similarly affect bacterial virulence (Newman et al., 2007). For example, while bacterial LPS generally acts as an inducer of defenses (Zeidler et al., 2004), LPS of the symbiont *Sinorhizobium meliloti* suppresses defense responses in the host plant *Medicago truncatula* (Tellström et al., 2007). Furthermore, other bacterial

PERSPECTIVE

exopolysaccharides also can suppress immune responses (Aslam et al., 2008).

There are other examples indicating that a strict discrimination between PAMPs and effectors cannot be maintained. CBEL is a cell wall glycoprotein PAMP that was identified in *Phytophthora parasitica* var *nicotianae*, the causal agent of tobacco Black Shank disease, which occurs widely in the genus *Phytophthora* (Mateos et al., 1997; Khatib et al., 2004). CBEL induces HR-like lesions and defense responses in tobacco (*Nicotiana tabacum*), but also in nonhost plants including *Arabidopsis* (Khatib et al., 2004). Compromised CBEL expression in *P. parasitica* var *nicotianae* demonstrates a role in cell wall polysaccharide deposition and adhesion to cellulose, although knockdown transformants do not display significantly reduced virulence (Gaulin et al., 2002). The *Trichoderma viride* ethylene-inducing xylanase (EIX) is a PAMP that likely contributes to the ability of the fungus to enter the host. In this case, the epitope that is recognized by plants consists of five surface-exposed amino acids that are not involved in enzyme activity. The finding that in the presumed PAMP Pep-13 the same amino acid residues that are required for eliciting plant defenses are also required for TGase activity (Nürnberger et al., 1994; Brunner et al., 2002) suggests that TGase activity also may contribute to virulence. In addition, Ax21 is characterized as a secreted peptide that is produced in a cell density–dependent manner and may play a role in quorum sensing and thereby virulence of the bacterium (Lee et al., 2006). The harpin HrpZ of the bacterial pathogen *P. syringae* represents another example, as it is a PAMP that appears to play a role in virulence by affecting host membrane integrity (Lee et al., 2001; Kvitko et al., 2007, 2009; Engelhardt et al., 2009).

Final examples of PAMPs that play a role in virulence are the PWL proteins of the fungus *Magnaporthe oryzae*, causal agent of rice blast that infects a large range of grass (*Poaceae*) species. Interestingly, the fungus secretes proteins that limit its host range, as strains that carry the *PWL1* or *-2* gene are avirulent on weeping lovegrass (Kang et al., 1995; Sweigard et al., 1995). The *PWL* gene family is large and ubiquitously represented throughout the *M. oryzae* population, and the encoded PWL proteins share significant homology. Interestingly, it was recently shown that PWLs are translocated to the cytoplasm of the invaded host cell and are likely to be involved in virulence. The proteins were found to be highly mobile in the symplast of the host tissue, as they moved to uninvaded neighboring cells where they may act to prime cells for fungal invasion, for instance through suppression of host defense responses (Khang et al., 2010; Valent and Khang, 2010).

THE AMBIGUOUS PRR-R PROTEIN DICHOTOMY

In accord with the current paradigm, PRRs are cell surface receptors that recognize PAMPs and are required for the first layer of active defense against invading pathogens. They are evolutionarily ancient receptors that may be conserved between species, exemplified by the homologous chitin receptors in rice and *Arabidopsis* (Kaku et al., 2006; Miya et al., 2007) and by the widespread occurrence of homologs of the FLS2 receptor for bacterial flagellin (Gómez-Gómez and Boller, 2000; Hann and Rathjen, 2007; Robatzek et al., 2007; Takai et al., 2008; Boller and Felix, 2009). By contrast, most R proteins typically are intracellular receptor proteins of the NB-LRR type that recognize effectors in the cytoplasm. R proteins are evolutionarily relatively young, and novel members continuously arise in the coevolutionary interaction between pathogens and their hosts. However, on the one hand, some of the currently recognized R proteins display the typical properties of PRR receptors, whereas on the other hand, PRRs may be relatively young as some PAMPs are only recognized by a narrow range of plant hosts (Felix and Boller, 2003; Zipfel et al., 2006). Furthermore, despite recognizing the same PAMP, different plant species may recognize different epitopes. For instance, distinct β-glucan cell wall fragments of fungi and oomycetes are recognized by different plant species (Côté et al., 2000; Klarzynski et al., 2000; Yamaguchi et al., 2000). Furthermore, flg15, a shortened version of the flagellin derived 22-amino acid peptide flg22 carrying the epitope, does not act as an elicitor in *Arabidopsis* or *Nicotiana benthamiana*, while it is fully active in tomato (Robatzek et al., 2007).

Typically, PAMPs are perceived by extracellular domains of plasma membrane receptors, and no intracellular PAMP receptors have yet been reported. Cell surface receptors that act as genuine PAMP receptors typically perceive pathogen molecules in a receptor-ligand fashion in which they physically interact with pathogen molecules (Chinchilla et al., 2006; Kaku et al., 2006; Zipfel et al., 2006). However, not all effectors are perceived inside host cells, and not all extracellular pathogen receptors perceive pathogen molecules through direct physical interactions. For example, the race-specific Cf-2 receptor from tomato monitors the presence of *C. fulvum* strains that produce the Avr2 effector by guarding the Rcr3 protease, which is targeted by Avr2 (Rooney et al., 2005; Shabab et al., 2008; van Esse et al., 2008). Similarly, direct as well as indirect recognition of pathogen effectors by intracellular pathogen receptors occurs (Dodds and Rathjen, 2010).

Cf-4–Mediated Recognition of *C. fulvum* Avr4 Homologs from Other Pathogenic Fungi

Prior to the discovery of Ecp6, the secreted race-specific chitin binding *C. fulvum* effector Avr4 was identified (Joosten et al., 1994). Three of the four disulfide bonds of Avr4 were found to encompass an invertebrate chitin binding domain, allowing it to specifically bind to chitin of fungal cell walls in planta (van den Burg et al., 2003, 2004, 2006). In this way, Avr4 contributes to fungal virulence by protecting the fungal hyphae against hydrolysis by host chitinases that are secreted into the tomato apoplast during infection (Joosten et al., 1995; van den Burg et al., 2006; van Esse et al., 2007).

PERSPECTIVE

Typical for a race-specific effector, initially no clear Avr4 homologs were reported in any other species. However, a query of the recently released publicly available genome sequence of *Mycosphaerella fijiensis*, phylogenetically related to *C. fulvum* and causal agent of the Black Sigatoka disease of banana, revealed the Avr4 homolog Mf-Avr4 (Stergiopoulos et al., 2010). The positioning and spacing of the six Cys residues that constitute the chitin binding domain of *C. fulvum* Avr4 is conserved, and Mf-Avr4 binds chitin and protects fungal hyphae against hydrolysis by plant chitinases in vitro. Additional Avr4 homologs were identified in several *Cercospora* species that also belong to the *Mycosphaerellaceae* family and that share the positioning and spacing of the six Cys residues required for chitin binding of *C. fulvum* Avr4 (Stergiopoulos et al., 2010).

Tomato genotypes that produce the *C. fulvum* (Cf)-4 resistance protein respond to Avr4 with an HR and are resistant to *C. fulvum* strains that secrete Avr4. Intriguingly, the Avr4 homolog of the banana pathogen *M. fijiensis* is recognized by the tomato Cf-4 resistance protein and triggers the activation of an HR in Cf-4 tomato plants. Mediated by various Cf-4–like proteins, recognition of *C. fulvum* Avr4 also occurs in the wild *Solanum* species *S. peruvianum*, *S. chmielewskii*, and *S. parviflorum* (Laugé et al., 2000; Kruijt et al., 2004). When coexpressed with Mf-*Avr4* in *N. benthamiana*, these Cf-4–like proteins all trigger HR, confirming the occurrence of wide recognitional specificity for Avr4-like proteins within the *Solanum* genus (Stergiopoulos et al., 2010). Based on these findings Avr4 and its homologs can be classified as PAMPs, and based on this classification, Cf-4 qualifies as a PRR.

Interestingly, the *Cercospora* Avr4 homologs are neither recognized by Cf-4 nor by any of the Cf-4–like proteins. Although in these *Cercospora* homologs the Cys spacing is conserved, other amino acids that are essential for chitin binding are not (van den Burg et al., 2004; Stergiopoulos et al., 2010); therefore, it can be anticipated that the *Cercospora* Avr4s do not bind to chitin. This suggests that there is a strict correlation between the capacity of the various Avr4 homologs to bind chitin and their recognition by Cf-4 and that as a result of coevolution there is only recognition by tomato of Avr4 homologs that protect the pathogen against chitinases. In this case, as typically occurs with PAMPs, direct binding to the immune receptor is expected.

Recognition of *C. fulvum* Ecp2 Homologs

In addition to Ecp6, all *C. fulvum* strains produce the conserved extracellular protein 2 (Ecp2) (Stergiopoulos et al., 2007). Gene disruption revealed that Ecp2 is required for virulence as the *C. fulvum* mutants trigged a fast induction of pathogenesis-related proteins, caused leaf desiccation and senescence, accumulated much less biomass in susceptible plants, and produced very few conidia (Laugé et al., 1997). Interestingly, several tomato genotypes and lines of the wild currant tomato species *Solanum pimpinellifolium* were identified that recognize Ecp2 and thus presumably carry *Cf-Ecp2* resistance genes (Laugé et al., 1998, 2000; Haanstra et al., 1999). Strikingly, specific HR-associated recognition of Ecp2 also occurs in several *Nicotiana* species that are nonhost to *C. fulvum*, such as *N. tabacum*, *N. paniculata*, *N. undulata*, and *N. sylvestris* (de Kock et al., 2004). Population analysis revealed quite some sequence variation in the *Ecp2* gene. However, only four open reading frame mutations were identified and these do not affect recognition by the presumed Cf-Ecp2 resistance protein (Stergiopoulos et al., 2007).

Three genes encoding proteins that are highly homologous to *C. fulvum* Ecp2 were recently identified in the *M. fijiensis* genome, of which the most homologous was designated Mf-*Ecp2* (Stergiopoulos et al., 2010). Interestingly, Mf-Ecp2 is also recognized by tomato plants that respond to *C. fulvum* Ecp2, as inoculation with recombinant potato virus X (PVX) expressing Mf-*Ecp2* results in a systemic necrosis (Stergiopoulos et al., 2010). By contrast, the other two proteins Mf-Ecp2-1 and -2 do not trigger an HR in these tomato plants. Further data mining revealed that the *M. graminicola* genome also encodes three Ecp2 homologs (Stergiopoulos et al., 2010). In contrast with *Avr4*, *Ecp2* homologs are not restricted to the *Mycosphaerellaceae* family, as they also occur in several fungal species outside this family, including plant pathogenic (*Fusarium graminearum* and *Verticillium dahliae*), animal pathogenic (*Trichophyton equinum*), and nonpathogenic (*Aspergillus nidulans*, *Neurospora crassa*, and *Podospora anserina*) species. Thus, like Ecp6 and Avr4, Ecp2 also qualifies as PAMP. As a consequence, the host proteins that mediate recognition of Ecp2 qualify as PRRs.

Tomato Ve1 as PRR

Tomato Cf proteins that provide resistance to *C. fulvum* strains that express the corresponding elicitors belong to the eLRR-RLP class of resistance proteins, which are cell surface receptors with extracellular LRRs that lack an obvious cytoplasmic signaling domain (Thomma et al., 2005; Wang et al., 2008, 2010). Tomato Eix2 is an RLP–type PRR that confers recognition of the PAMP EIX of the biocontrol fungus *T. viride* (Ron and Avni, 2004). The tomato RLP-encoding gene *Ve1* has been characterized as a resistance gene that mediates race-specific resistance to race 1 strains of vascular fungal pathogens of the *Verticillium* genus (Fradin et al., 2009). Interestingly, race 1 resistance affects two distinct fungal species: *V. dahliae* and *V. albo-atrum*. This suggests that the yet unidentified elicitor of Ve1-mediated resistance is conserved between fungal species and is potentially a PAMP, which would in turn imply that that Ve1 is a PRR.

Three additional observations support the hypothesis that Ve1 is a PRR rather than an R protein, namely, the physiology of Ve1-mediated *Verticillium* resistance, the involvement of BAK1/SERK3 in Ve1 signaling, and the observation that functional Ve1 can be transferred across families. In resistant as well as susceptible plants, *Verticillium* enters root xylem vessels and sporulates, which results in colonization of stem vessels (Gold and Robb, 1995; Heinz et al., 1998; Chen et al., 2004). After a week, fungal elimination as a consequence of plant defense occurs. Whereas the pathogen is able to overcome this elimination in

susceptible plants and extensive host colonization occurs, the fungus is not able to overcome elimination in resistant plants and remains present in the host at a low level (Gold and Robb, 1995; Heinz et al., 1998; Chen et al., 2004; van Esse et al., 2009). In accord with the paradigm that ETI quickly and strongly provides a robust type of resistance and PTI is a weak variant of ETI, Ve1-mediated resistance is reminiscent of PTI.

In several independent studies, the receptor-like kinase BAK1/SERK3 was identified as crucial factor in various PTI responses. In *Arabidopsis* and *N. benthamiana*, BAK1/SERK3 was found to interact with the flagellin receptor FLS2 (Chinchilla et al., 2007; Heese et al., 2007). In addition, BAK1 controls spreading necrosis after infection with bacterial and fungal pathogens in a brassinosteroid-independent manner, while silencing of *BAK1* in *N. benthamiana* results in enhanced cell death upon infection with the oomycete pathogen *Hyaloperonospora arabidopsidis* (Heese et al., 2007; Kemmerling et al., 2007). Furthermore, silencing of *BAK1* in *N. benthamiana* attenuates the response to the cold-shock protein and *Phytophthora infestans* INF1 (Heese et al., 2007). Recently, it was demonstrated that BAK1 is involved in Ve1-mediated *Verticillium* resistance of tomato (Fradin et al., 2009).

The transfer of race-specific *R* genes across species boundaries has been successful as long as recipient species are phylogenetically closely related. For example, transfer of the gene *Rx* that provides resistance to PVX, from potato to *N. benthamiana*, which both belong to the Solanaceae family, successfully provided PVX resistance (Bendahmane et al., 1999). However, interfamily transfer of race-specific *R* genes has met little success (Gust et al., 2010). By contrast, interfamily transfer of PAMP receptors appears to be more successful, as exemplified by the transfer of the PRRs EFR for bacterial EF-Tu and FLS2 for bacterial flagellin from *Arabidopsis* to *N. benthamiana* and tomato (Chinchilla et al., 2006; Zipfel et al., 2006; Lacombe et al., 2010). Intriguingly, preliminary results suggest that the tomato gene *Ve1* might be transferred across family boundaries while remaining fully functional, as transgenic *Arabidopsis* expressing *Ve1* appear to be resistant toward race 1 strains of *V. dahliae* and *V. albo-atrum* (E.F. Fradin and B.P.H.J. Thomma, unpublished data).

Kinases that carry an Arg (R) preceding the catalytic Asp (D) have been termed RD kinases, whereas non-RD kinases lack this Arg but carry a Cys or Gly instead (Johnson et al., 1996). The non-RD domain has been suggested to be a hallmark of kinases involved in innate immunity signaling (Dardick and Ronald, 2006). Despite the presence of relatively few non-RD kinases in the kinase families of yeast, fly, worm, human, *Arabidopsis*, and rice, 12 of 15 kinases known or predicted to function in PRR signaling fall into the non-RD class, including FLS2, EFR, and XA21 (Dardick and Ronald, 2006). It was hypothesized that the non-RD kinase motif has been recruited by plants and animals to mediate the activation of innate immune responses, which discriminates PRRs from other receptors (Dardick and Ronald, 2006; Ronald and Beutler, 2010). Nevertheless, in this respect, it is interesting to note that the receptor-like kinase BAK1/SERK3 that acts as a coreceptor in various PTI responses and has been implicated in Ve1 signaling does not belong to the class of non-RD kinases. Furthermore, the CERK1 receptors for chitin from *Arabidopsis* (Miya et al., 2007) and rice (Shimizu et al., 2010) also do not belong to this class (Dardick and Ronald, 2006).

Evasion of Host Recognition through PAMP Plasticity

Likely as a result of coevolution, *C. fulvum* strains have evolved that evade Cf-4–mediated recognition by producing Avr4 isoforms in which one disulfide bond is lost (Joosten et al., 1994). This results in a less compact overall structure of the Avr4 protein and prompt degradation by host proteases upon secretion into the apoplast (Joosten et al., 1997). However, once bound to fungal cell wall chitin, these instable Avr4 isoforms are stabilized and can still exert their intrinsic function for the pathogen (van den Burg et al., 2003). In this way, Cf-4–mediated recognition of mutant Avr4 isoforms is evaded without loss of intrinsic function, suggesting that both native and mutant Avr4 forms contribute to *C. fulvum* fitness (van den Burg et al., 2003; van Esse et al., 2007).

PAMPs are usually considered as invariant or highly constrained structures that are extremely difficult for microbes to alter because of fitness penalties. Nevertheless, PAMP plasticity has been observed, and pathogens apparently evolve to avoid recognition of their PAMPs. In mammalian pathogens, examples of LPS variants that perturb host recognition have been reported (Reife et al., 2006; Coats et al., 2007). Also, altered acylation compromises recognition of LPS by the corresponding TLR4 receptor (Montminy et al., 2006; Rebeil et al., 2006). A similar situation seems to occur in plants (Silipo et al., 2008). Furthermore, bacterial pathogens can suppress flagellin expression when colonizing their hosts (Akerley et al., 1995, Wolfgang et al., 2004; Shen and Higgins, 2006), and some bacteria, such as *Agrobacterium* spp, *Rhizobium* spp, and *R. solanacearum*, do not elicit flagellin-triggered immunity due to mutations in the epitope (Felix et al., 1999; Pfund et al., 2004). Similarly, a specific strain of *X. campestris* pv *campestris* does not cause disease symptoms due to a single amino acid difference in the flagellin sequence (Sun et al., 2006). Furthermore, a nonglycosylated flagellin mutant protein from *P. syringae* pv *tabaci* displays reduced HR-inducing capacity in tobacco and soybean (*Glycine max*) plants (Taguchi et al., 2003, 2006) and induces a weaker defense response in the nonhost plant *Arabidopsis* (Ishiga et al., 2005). Finally, as discussed above, whereas the sulfated 17–amino acid synthetic peptide (axYS22) derived from the N-terminal region of Xoo Ax21 displays elicitor activity, variants lacking sulfation were inactive (da Silva et al., 2004; Lee et al., 2009). Thus, although PAMPs are often thought to be invariant, it is evident that sequence variation and posttranslational modifications can modulate PAMP recognition.

THE AMBIGUOUS PTI-ETI DICHOTOMY

Although it is generally known that PTI and ETI share many signaling components, it has been proposed that immune

PERSPECTIVE

responses in ETI occur more quickly, are more prolonged, and are more robust than those in PTI, suggesting that PTI is a weak variant of ETI (Tao et al., 2003; Jones and Dangl, 2006; Tsuda et al., 2009; Tsuda and Katagiri, 2010). Typically, ETI is associated with an HR and SAR, while PTI is not. However, the PAMPs CBEL, EIX, and harpins all induce HR in plants (Bailey et al., 1990; Wei et al., 1992; Khatib et al., 2004; Ron and Avni, 2004). Furthermore, it has been demonstrated that flg22 induces an HR in *Arabidopsis* (Naito et al., 2007, 2008), whereas flagellins from *Pseudomonas avenae* and distinct *P. syringae* pathovars activate HR in the nonhost plants rice and tobacco (Che et al., 2000; Taguchi et al., 2003; Hann and Rathjen, 2007). These data demonstrate that the occurrence of HR is not restricted to ETI but can also occur in PTI responses. Furthermore, it has been demonstrated that PAMP perception also results in SAR in *Arabidopsis* (Mishina and Zeier, 2007). Inoculation with nonhost strains of *P. syringae*, as well as application of flagellin and LPS, resulted in the activation of systemic resistance in *Arabidopsis* in the absence of necrosis. The activation of SAR was accompanied by the typical hallmarks of elevated SA levels, pathogenesis-related gene expression, and SAR marker gene expression and was impaired in typical SAR mutants.

Beside atypical examples of strong PTI responses, examples of weak ETI responses have been presented as well. In addition to the example of tomato *Ve1*-mediated *Verticillium* resistance mentioned above, resistance mediated by RPS4 that recognizes the *P. syringae* type III effector AvrRps4 is rather weak (Wirthmueller et al., 2007). Furthermore, it is well documented that the spectra of responses triggered by AvrRpm1 and AvrRpt2 in plants that carry the CC-NB-LRR–type R proteins RPM1 and RPS2, respectively, are very similar although the AvrRpm1-triggered responses are substantially faster (Ritter and Dangl, 1996; Tao et al., 2003). This illustrates that effector-triggered responses differ in speed and strength. Intriguingly, RPS4-mediated HR triggered by *P. syringae* AvrRps4 was recently found to depend on autophagy, whereas RPS2-mediated HR triggered by AvrRpt2 was not (Hofius et al., 2009). This demonstrates the existence of different mechanisms that culminate in HR in ETI triggered by different effectors.

In conclusion, it is questionable whether PTI and ETI are always distinct defense responses with PTI being a weak variant of ETI. Rather, it appears that ETI and PTI both can be robust or weak, depending on the specific interaction; different molecules activate different defense signaling pathways, depending on the trigger, the receptor, and possibly also environmental conditions.

CONCLUSION

Numerous examples, some of which are discussed in this review, illustrate that classifying a particular molecule as PAMP or effector, or as PRR or R protein, has become a nebulous exercise. Importantly, it should be realized that models are typically generalizations of real life situations based on single or few specific examples, and the field of PAMP signaling has mainly been driven by hallmark discoveries made for the *Arabidopsis* FLS2 (recognizing bacterial flagellin), EFR (recognizing bacterial EF-Tu), and CERK1 (recognizing fungal chitin receptors). Obviously, such models are important conceptual tools, yet they may lead to oversimplification of real life situations in nature. Cell surface pathogen receptors as well as cytoplasmic pathogen receptors both fall into the subclass of R proteins as originally described by Flor (1942). Whereas PRRs typically recognize conserved microbial signatures, NB-LRRs do not, which is the conceptual basis for the PTI-ETI dichotomy. This concept needs to be refined by accepting that some pathogens deploy evolutionarily ancient effectors that are instrumental for pathogenicity; thus, it became important for plants to evolve recognition of these molecules. Essentially, these effectors now act as PAMPs and thereby blur the PAMP-effector dichotomy. A further refinement is that PTI and ETI both can be robust or weak, depending on the specific interaction and that conserved microbial signature molecules can be modified to avoid recognition.

In addition to this, it is increasingly being recognized that activation of innate immunity in multicellular eukaryotic systems essentially boils down to recognition of danger signals (Matzinger, 2007; Boller and Felix, 2009). These danger signals are either molecules that are directly derived from the microbe (PAMPs and effectors) or represent microbial invasion-derived, damaged, or modified eukaryotic host structures that are not present or not released in noninfected organisms (Matzinger, 2002, 2007; Lotze et al., 2007; Boller and Felix, 2009).

Ultimately, plants sense the presence of microbial invaders by means of receptors that detect microbial structures or by receptors that directly or indirectly detect plant-manipulating activities of microbial effectors. In other words, microbe sensing and plant immune activation is determined by any type of plant receptor that recognizes appropriate ligands to activate defense. From the plant immunity point of view, the nature and intrinsic function of the ligand is not relevant as long as it timely and accurately betrays the potential microbial invader to the plant surveillance system. As a result of continuous coevolution between plant and pathogen, a wealth of plant perception systems for microbe-derived molecules has been shaped that reliably fulfills roles in mediating the establishment of plant immunity.

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PERSPECTIVE

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REFERENCES

Akerley, B.J., Cotter, P.A., and Miller, J.F. (1995). Ectopic expression of the flagellar regulon alters development of the Bordetella-host interaction. Cell **80:** 611–620.

Aslam, S.N., et al. (2008). Bacterial polysaccharides suppress induced innate immunity by calcium chelation. Curr. Biol. **18:** 1078–1083.

Ayers, A.R., Ebel, J., Finelli, F., Berger, N., and Albersheim, P. (1976). Host-pathogen interactions: IX. Quantitative assays of elicitor activity and characterization of the elicitor present in the extracellular medium of cultures of *Phytophthora megasperma* var. *sojae.* Plant Physiol. **57:** 751–759.

Bailey, B.A., Dean, J.F., and Anderson, J.D. (1990). An ethylene biosynthesis-inducing endoxylanase elicits electrolyte leakage and necrosis in *Nicotiana tabacum* cv *xanthi* leaves. Plant Physiol. **94:** 1849–1854.

Bendahmane, A., Kanyuka, K., and Baulcombe, D.C. (1999). The Rx gene from potato controls separate virus resistance and cell death responses. Plant Cell **11:** 781–792.

Bent, A.F., and Mackey, D. (2007). Elicitors, effectors, and R genes: The new paradigm and a lifetime supply of questions. Annu. Rev. Phytopathol. **45:** 399–436.

Boller, T. (1995). Chemoperception of microbial signals in plant cells. Annu. Rev. Plant Physiol. Plant Mol. Biol. **46:** 189–214.

Boller, T., and Felix, G. (2009). A renaissance of elicitors: Perception of microbe-associated molecular patterns and danger signals by pattern-recognition receptors. Annu. Rev. Plant Biol. **60:** 379–406.

Bolton, M.D., et al. (2008). The novel *Cladosporium fulvum* lysin motif effector Ecp6 is a virulence factor with orthologues in other fungal species. Mol. Microbiol. **69:** 119–136.

Brunner, F., Rosahl, S., Lee, J., Rudd, J.J., Geiler, C., Kauppinen, S., Rasmussen, G., Scheel, D., and Nürnberger, T. (2002). Pep-13, a plant defense-inducing pathogen-associated pattern from *Phytophthora transglutaminases*. EMBO J. **21:** 6681–6688.

Che, F.S., Nakajima, Y., Tanaka, N., Iwano, M., Yoshida, T., Takayama, S., Kadota, I., and Isogai, A. (2000). Flagellin from an incompatible strain of *Pseudomonas avenae* induces a resistance response in cultured rice cells. J. Biol. Chem. **275:** 32347–32356.

Chen, P., Lee, B., and Robb, J. (2004). Tolerance to a non-host isolate of *Verticillium dahliae* in tomato. Physiol. Mol. Plant Pathol. **64:** 283–291.

Chinchilla, D., Bauer, Z., Regenass, M., Boller, T., and Felix, G. (2006). The *Arabidopsis* receptor kinase FLS2 binds flg22 and determines the specificity of flagellin perception. Plant Cell **18:** 465–476.

Chinchilla, D., Zipfel, C., Robatzek, S., Kemmerling, B., Nürnberger, T., Jones, J.D.G., Felix, G., and Boller, T. (2007). A flagellin-induced complex of the receptor FLS2 and BAK1 initiates plant defence. Nature **448:** 497–500.

Chisholm, S.T., Coaker, G., Day, B., and Staskawicz, B.J. (2006). Host-microbe interactions: Shaping the evolution of the plant immune response. Cell **124:** 803–814.

Coats, S.R., Do, C.T., Karimi-Naser, L.M., Braham, P.H., and Darveau, R.P. (2007). Antagonistic lipopolysaccharides block *E. coli* lipopolysaccharide function at human TLR4 via interaction with the human MD-2 lipopolysaccharide binding site. Cell. Microbiol. **9:** 1191–1202.

Côté, F., Roberts, K.A., and Hahn, M.G. (2000). Identification of high-affinity binding sites for the hepta-beta-glucoside elicitor in membranes of the model legumes *Medicago truncatula* and *Lotus japonicus.* Planta **211:** 596–605.

Dardick, C., and Ronald, P. (2006). Plant and animal pathogen recognition receptors signal through non-RD kinases. PLoS Pathog. **2:** e2.

da Silva, F.G., Shen, Y., Dardick, C., Burdman, S., Yadav, R.C., de Leon, A.L., and Ronald, P.C. (2004). Bacterial genes involved in type I secretion and sulfation are required to elicit the rice Xa21-mediated innate immune response. Mol. Plant Microbe Interact. **17:** 593–601.

de Jonge, R., and Thomma, B.P.H.J. (2009). Fungal LysM effectors: extinguishers of host immunity? Trends Microbiol. **17:** 151–157.

de Jonge, R., van Esse, H.P., Kombrink, A., Shinya, T., Desaki, Y., Bours, R., van der Krol, S., Shibuya, N., Joosten, M.H., and Thomma, B.P. (2010). Conserved fungal LysM effector Ecp6 prevents chitin-triggered immunity in plants. Science **329:** 953–955.

de Kock, M.J.D., Iskandar, H.M., Brandwagt, B.F., Laugé, R., de Wit, P.J.G.M., and Lindhout, P. (2004). Recognition of *Cladosporium fulvum* Ecp2 elicitor by non-host *Nicotiana* spp. is mediated by a single dominant gene that is not homologous to known *Cf*-genes. Mol. Plant Pathol. **5:** 397–408.

Dodds, P.N., and Rathjen, J.P. (2010). Plant immunity: Towards an integrated view of plant-pathogen interactions. Nat. Rev. Genet. **11:** 539–548.

Dow, M., Newman, M.-A., and von Roepenack, E. (2000). The induction and modulation of plant defense responses by bacterial lipopolysaccharides. Annu. Rev. Phytopathol. **38:** 241–261.

Ebel, J., and Cosio, E.G. (1994). Elicitors of plant defense responses. Int. Rev. Cytol. **148:** 1–36.

Erbs, G., Silipo, A., Aslam, S., De Castro, C., Liparoti, V., Flagiello, A., Pucci, P., Lanzetta, R., Parrilli, M., Molinaro, A., Newman, M.A., and Cooper, R.M. (2008). Peptidoglycan and muropeptides from pathogens *Agrobacterium* and *Xanthomonas* elicit plant innate immunity: Structure and activity. Chem. Biol. **15:** 438–448.

Engelhardt, S., Lee, J., Gäbler, Y., Kemmerling, B., Haapalainen, M.L., Li, C.M., Wei, Z., Keller, H., Joosten, M., Taira, S., Nürnberger, T. (2009). Separable roles of the *Pseudomonas syringae* pv. *phaseolicola* accessory protein HrpZ1 in ion-conducting pore formation and activation of plant immunity. Plant J. **57:** 706–717.

Felix, G., and Boller, T. (2003). Molecular sensing of bacteria in plants. The highly conserved RNA-binding motif RNP-1 of bacterial cold shock proteins is recognized as an elicitor signal in tobacco. J. Biol. Chem. **278:** 6201–6208.

Felix, G., Duran, J.D., Volko, S., and Boller, T. (1999). Plants have a sensitive perception system for the most conserved domain of bacterial flagellin. Plant J. **18:** 265–276.

Felix, G., Regenass, M., and Boller, T. (1993). Specific perception of subnanomolar concentrations of chitin fragments by tomato cells: Induction of extracellular alkalinization, changes in protein phosphorylation, and establishment of a refractory state. Plant J. **4:** 307–316.

Flor, H.H. (1942). Inheritance of pathogenicity in *Melampsora lini.* Phytopathology **32:** 653–669.

Fradin, E.F., Zhang, Z., Juarez Ayala, J.C., Castroverde, C.D., Nazar, R.N., Robb, J., Liu, C.-M., and Thomma, B.P.H.J. (2009). Genetic dissection of *Verticillium* wilt resistance mediated by tomato Ve1. Plant Physiol. **150:** 320–332.

Gaulin, E., Jauneau, A., Villalba, F., Rickauer, M., Esquerré-Tugayé, M.T., and Bottin, A. (2002). The CBEL glycoprotein of *Phytophthora*

PERSPECTIVE

parasitica var-*nicotianae* is involved in cell wall deposition and adhesion to cellulosic substrates. J. Cell Sci. **115:** 4565–4575.

Gijzen, M., and Nürnberger, T. (2006). Nep1-like proteins from plant pathogens: Recruitment and diversification of the NPP1 domain across taxa. Phytochemistry **67:** 1800–1807.

Gold, J., and Robb, J. (1995). The role of the coating response in Craigella tomatoes infected with *Verticillium dahliae*, races 1 and 2. Physiol. Mol. Plant Pathol. **47:** 141–157.

Gómez-Gómez, L., and Boller, T. (2000). FLS2: An LRR receptor-like kinase involved in the perception of the bacterial elicitor flagellin in Arabidopsis. Mol. Cell **5:** 1003–1011.

Gust, A.A., Biswas, R., Lenz, H.D., Rauhut, T., Ranf, S., Kemmerling, B., Götz, F., Glawischnig, E., Lee, J., Felix, G., and Nürnberger, T. (2007). Bacteria-derived peptidoglycans constitute pathogen-associated molecular patterns triggering innate immunity in Arabidopsis. J. Biol. Chem. **282:** 32338–32348.

Gust, A.A., Brunner, F., and Nürnberger, T. (2010). Biotechnological concepts for improving plant innate immunity. Curr. Opin. Biotechnol. **21:** 204–210.

Haanstra, J.P.W., Laugé, R., Meijer-Dekens, F., Bonnema, G., de Wit, P.J.G.M., and Lindhout, P. (1999). The *Cf-ECP2* gene is linked to, but not part of, the *Cf-4/Cf-9* cluster on the short arm of chromosome 1 in tomato. Mol. Gen. Genet. **262:** 839–845.

Haas, B.J., et al. (2009). Genome sequence and comparative analysis of the Irish potato famine pathogen *Phytophthora infestans*. Nature **461:** 393–398.

Haefele, D.M., and Lindow, S.E. (1987). Flagellar motility confers epiphytic fitness advantages upon *Pseudomonas syringae.* Appl. Environ. Microbiol. **53:** 2528–2533.

Hann, D.R., and Rathjen, J.P. (2007). Early events in the pathogenicity of *Pseudomonas syringae* on *Nicotiana benthamiana.* Plant J. **49:** 607–618.

Hattermann, D.R., and Ries, S.M. (1989). Motility of *Pseudomonas syringae* pv. *glycinea* and its role in infection. Phytopathology **79:** 284–289.

Hauck, P., Thilmony, R., and He, S.Y. (2003). A *Pseudomonas syringae* type III effector suppresses cell wall-based extracellular defense in susceptible Arabidopsis plants. Proc. Natl. Acad. Sci. USA **100:** 8577–8582.

Heese, A., Hann, D.R., Gimenez-Ibanez, S., Jones, A.M., He, K., Li, J., Schroeder, J.I., Peck, S.C., and Rathjen, J.P. (2007). The receptor-like kinase SERK3/BAK1 is a central regulator of innate immunity in plants. Proc. Natl. Acad. Sci. USA **104:** 12217–12222.

Heinz, R., Lee, S.W., Saparno, A., Nazar, R.N., and Robb, J. (1998). Cyclical systemic colonization in Verticillium-infected tomato. Physiol. Mol. Plant Pathol. **52:** 385–396.

Hofius, D., Schultz-Larsen, T., Joensen, J., Tsitsigiannis, D.I., Petersen, N.H., Mattsson, O., Jørgensen, L.B., Jones, J.D., Mundy, J., and Petersen, M. (2009). Autophagic components contribute to hypersensitive cell death in Arabidopsis. Cell **137:** 773–783.

Hossain, M.M., Shibata, S., Aizawa, S.-I., and Tsuyumu, S. (2005). Motility is an important determinant for pathogenesis of *Erwinia carotovora* subsp. *carotovora.* Physiol. Mol. Plant Pathol. **66:** 134–143.

Iizasa, E., Mitsutomi, M., and Nagano, Y. (2010). Direct binding of a plant LysM receptor-like kinase, LysM RLK1/CERK1, to chitin *in vitro.* J. Biol. Chem. **285:** 2996–3004.

Ishiga, Y., Takeuchi, K., Taguchi, F., Inagaki, Y., Toyota, K., Shiraishi, T., and Ichinose, Y. (2005). Defense responses of *Arabidopsis thaliana* inoculated with *Pseudomonas syringae* pv. *tabaci* wild type and defective mutants for flagellin (ΔfliC) and flagellin-glycosylation (Δorf1). J. Gen. Plant Pathol. **71:** 302–307.

Johnson, L.N., Noble, M.E., and Owen, D.J. (1996). Active and inactive protein kinases: Structural basis for regulation. Cell **85:** 149–158.

Jones, J.D.G., and Dangl, J.L. (2006). The plant immune system. Nature **444:** 323–329.

Joosten, M.H.A.J., Cozijnsen, T.J., and De Wit, P.J.G.M. (1994). Host resistance to a fungal tomato pathogen lost by a single base-pair change in an avirulence gene. Nature **367:** 384–386.

Joosten, M.H.A.J., Verbakel, H.M., Nettekoven, M.E., Van Leeuwen, J., Van der Vossen, R.T.M., and De Wit, P.J.G.M. (1995). The phytopathogenic fungus *Cladosporium fulvum* is not sensitive to the chitinase and β-1,3-glucanase defence proteins of its host, tomato. Physiol. Mol. Plant Pathol. **46:** 45–59.

Joosten, M.H.A.J., Vogelsang, R., Cozijnsen, T.J., Verberne, M.C., and De Wit, P.J.G.M. (1997). The biotrophic fungus *Cladosporium fulvum* circumvents Cf-4-mediated resistance by producing unstable AVR4 elicitors. Plant Cell **9:** 367–379.

Kaku, H., Nishizawa, Y., Ishii-Minami, N., Akimoto-Tomiyama, C., Dohmae, N., Takio, K., Minami, E., and Shibuya, N. (2006). Plant cells recognize chitin fragments for defense signaling through a plasma membrane receptor. Proc. Natl. Acad. Sci. USA **103:** 11086–11091.

Kamoun, S. (2006). A catalogue of the effector secretome of plant pathogenic oomycetes. Annu. Rev. Phytopathol. **44:** 41–60.

Kang, S., Sweigard, J.A., and Valent, B. (1995). The PWL host specificity gene family in the blast fungus *Magnaporthe grisea.* Mol. Plant Microbe Interact. **8:** 939–948.

Keen, N.T. (1990). Gene-for-gene complementarity in plant-pathogen interactions. Annu. Rev. Genet. **24:** 447–463.

Kemmerling, B., et al. (2007). The BRI1-associated kinase 1, BAK1, has a brassinolide-independent role in plant cell-death control. Curr. Biol. **17:** 1116–1122.

Khang, C.H., Berruyer, R., Giraldo, M.C., Kankanala, P., Park, S.Y., Czymmek, K., Kang, S., and Valent, B. (2010). Translocation of *Magnaporthe oryzae* effectors into rice cells and their subsequent cell-to-cell movement. Plant Cell **22:** 1388–1403.

Khatib, M., Lafitte, C., Esquerré-Tugayé, M.-T., Bottin, A., and Rickauer, M. (2004). The CBEL elicitor of *Phytophthora parasitica* var. *nicotianae* activates defence in *Arabidopsis thaliana* via three different signalling pathways. New Phytol. **162:** 501–510.

Klarzynski, O., Plesse, B., Joubert, J.M., Yvin, J.C., Kopp, M., Kloareg, B., and Fritig, B. (2000). Linear beta-1,3 glucans are elicitors of defense responses in tobacco. Plant Physiol. **124:** 1027–1038.

Kruijt, M., Brandwagt, B.F., and de Wit, P.J.G.M. (2004). Rearrangements in the *Cf-9* disease resistance gene cluster of wild tomato have resulted in three genes that mediate Avr9 responsiveness. Genetics **168:** 1655–1663.

Kvitko, B.H., Park, D.H., Velásquez, A.C., Wei, C.F., Russell, A.B., Martin, G.B., Schneider, D.J., and Collmer, A. (2009). Deletions in the repertoire of *Pseudomonas syringae* pv. tomato DC3000 type III secretion effector genes reveal functional overlap among effectors. PLoS Pathog. **5:** e1000388.

Kvitko, B.H., Ramos, A.R., Morello, J.E., Oh, H.S., and Collmer, A. (2007). Identification of harpins in *Pseudomonas syringae* pv. *tomato* DC3000, which are functionally similar to HrpK1 in promoting translocation of type III secretion system effectors. J. Bacteriol. **189:** 8059–8072.

PERSPECTIVE

Lacombe, S., Rougon-Cardoso, A., Sherwood, E., Peeters, N., Dahlbeck, D., van Esse, H.P., Smoker, M., Rallapalli, G., Thomma, B.P.H.J., Staskawicz, B., Jones, J.D., and Zipfel, C. (2010). Inter-family transfer of a plant pattern-recognition receptor confers broad-spectrum bacterial resistance. Nat. Biotechnol. **28:** 365–369.

Laugé, R., Goodwin, P.H., de Wit, P.J.G.M., and Joosten, M.H.A.J. (2000). Specific HR-associated recognition of secreted proteins from *Cladosporium fulvum* occurs in both host and non-host plants. Plant J. **23:** 735–745.

Laugé, R., Joosten, M.H.A.J., Haanstra, J.P., Goodwin, P.H., Lindhout, P., and De Wit, P.J.G.M. (1998). Successful search for a resistance gene in tomato targeted against a virulence factor of a fungal pathogen. Proc. Natl. Acad. Sci. USA **95:** 9014–9018.

Laugé, R., Joosten, M.H.A.J., Van den Ackerveken, G.F.J.M., Van den Broek, H.W.J., and De Wit, P.J.G.M. (1997). The *in planta*-produced extracellular proteins ECP1 and ECP2 of *Cladosporium fulvum* are virulence factors. Mol. Plant Microbe Interact. **10:** 725–734.

Lee, J., Klusener, B., Tsiamis, G., Stevens, C., Neyt, C., Tampakaki, A.P., Panopoulos, N.J., Nöller, J., Weiler, E.W., Cornelis, G.R., Mansfield, J.W., and Nürnberger, T. (2001). HrpZ$_{(Psph)}$ from the plant pathogen *Pseudomonas syringae* pv. *phaseolicola* binds to lipid bilayers and forms an ion-conducting pore *in vitro.* Proc. Natl. Acad. Sci. USA **98:** 289–294.

Lee, S.W., Han, S.W., Bartley, L.E., and Ronald, P.C. (2006). From the Academy: Colloquium review. Unique characteristics of *Xanthomonas oryzae* pv. oryzae AvrXa21 and implications for plant innate immunity. Proc. Natl. Acad. Sci. USA **103:** 18395–18400.

Lee, S.W., Han, S.W., Sririyanum, M., Park, C.J., Seo, Y.S., and Ronald, P.C. (2009). A type I-secreted, sulfated peptide triggers XA21-mediated innate immunity. Science **326:** 850–853.

Lotze, M.T., Zeh, H.J., Rubartelli, A., Sparvero, L.J., Amoscato, A.A., Washburn, N.R., Devera, M.E., Liang, X., Tör, M., and Billiar, T. (2007). The grateful dead: Damage-associated molecular pattern molecules and reduction/oxidation regulate immunity. Immunol. Rev. **220:** 60–81.

Mateos, F.V., Rickauer, M., and Esquerré-Tugayé, M.-T. (1997). Cloning and characterization of a cDNA encoding an elicitor of *Phytophthora parasitica* var. *nicotianae* that shows cellulose-binding and lectin-like activities. Mol. Plant Microbe Interact. **10:** 1045–1053.

Matzinger, P. (2002). The danger model: A renewed sense of self. Science **296:** 301–305.

Matzinger, P. (2007). Friendly and dangerous signals: Is the tissue in control? Nat. Immunol. **8:** 11–13.

Medzhitov, R., and Janeway, C.A., Jr. (1997). Innate immunity: The virtues of a nonclonal system of recognition. Cell **91:** 295–298.

Mishina, T.E., and Zeier, J. (2007). Pathogen-associated molecular pattern recognition rather than development of tissue necrosis contributes to bacterial induction of systemic acquired resistance in Arabidopsis. Plant J. **50:** 500–513.

Miya, A., Albert, P., Shinya, T., Desaki, Y., Ichimura, K., Shirasu, K., Narusaka, Y., Kawakami, N., Kaku, H., and Shibuya, N. (2007). CERK1, a LysM receptor kinase, is essential for chitin elicitor signaling in *Arabidopsis.* Proc. Natl. Acad. Sci. USA **104:** 19613–19618.

Montminy, S.W., et al. (2006). Virulence factors of *Yersinia pestis* are overcome by a strong lipopolysaccharide response. Nat. Immunol. **7:** 1066–1073.

Naito, K., Ishiga, Y., Toyoda, K., Shiraishi, T., and Ichinose, Y. (2007). N-terminal domain including conserved flg22 is required for flagellin-induced hypersensitive cell death in *Arabidopsis thaliana.* J. Gen. Plant Pathol. **73:** 281–285.

Naito, K., Taguchi, F., Suzuki, T., Inagaki, Y., Toyoda, K., Shiraishi, T., and Ichinose, Y. (2008). Amino acid sequence of bacterial microbe-associated molecular pattern flg22 is required for virulence. Mol. Plant Microbe Interact. **21:** 1165–1174.

Newman, M.A., Dow, J.M., Molinaro, A., and Parrilli, M. (2007). Priming, induction and modulation of plant defence responses by bacterial lipopolysaccharides. J. Endotoxin Res. **13:** 69–84.

Nürnberger, T., and Brunner, F. (2002). Innate immunity in plants and animals: emerging parallels between the recognition of general elicitors and pathogen-associated molecular patterns. Curr. Opin. Plant Biol. **5:** 318–324.

Nürnberger, T., Nennstiel, D., Jabs, T., Sacks, W.R., Hahlbrock, K., and Scheel, D. (1994). High affinity binding of a fungal oligopeptide elicitor to parsley plasma membranes triggers multiple defense responses. Cell **78:** 449–460.

Panopoulos, N.J., and Schroth, M.N. (1974). Role of flagellar motility in the invasion of bean leaves by *Pseudomonas phaseolicola.* Phytopathology **64:** 1389–1397.

Petutschnig, E.K., Jones, A.M., Serazetdinova, L., Lipka, U., and Lipka, V. (2010). The lysin motif receptor-like kinase (LysM-RLK) CERK1 is a major chitin-binding protein in *Arabidopsis thaliana* and subject to chitin-induced phosphorylation. J. Biol. Chem. **285:** 28902–28911.

Pfund, C., Tans-Kersten, J., Dunning, F.M., Alonso, J.M., Ecker, J.R., Allen, C., and Bent, A.F. (2004). Flagellin is not a major defense elicitor in *Ralstonia solanacearum* cells or extracts applied to *Arabidopsis thaliana.* Mol. Plant Microbe Interact. **17:** 696–706.

Rebeil, R., Ernst, R.K., Jarrett, C.O., Adams, K.N., Miller, S.I., and Hinnebusch, B.J. (2006). Characterization of late acyltransferase genes of *Yersinia pestis* and their role in temperature-dependent lipid A variation. J. Bacteriol. **188:** 1381–1388.

Reife, R.A., Coats, S.R., Al-Qutub, M., Dixon, D.M., Braham, P.A., Billharz, R.J., Howald, W.N., and Darveau, R.P. (2006). *Porphyromonas gingivalis* lipopolysaccharide lipid A heterogeneity: Differential activities of tetra- and penta-acylated lipid A structures on E-selectin expression and TLR4 recognition. Cell. Microbiol. **8:** 857–868.

Ritter, C., and Dangl, J.L. (1996). Interference between two specific pathogen recognition events mediated by distinct plant disease resistance genes. Plant Cell **8:** 251–257.

Robatzek, S., Bittel, P., Chinchilla, D., Köchner, P., Felix, G., Shiu, S.H., and Boller, T. (2007). Molecular identification and characterization of the tomato flagellin receptor LeFLS2, an orthologue of Arabidopsis FLS2 exhibiting characteristically different perception specificities. Plant Mol. Biol. **64:** 539–547.

Ron, M., and Avni, A. (2004). The receptor for the fungal elicitor ethylene-inducing xylanase is a member of a resistance-like gene family in tomato. Plant Cell **16:** 1604–1615.

Ronald, P.C., and Beutler, B. (2010). Plant and animal sensors of conserved microbial signatures. Science **330:** 1061–1064.

Rooney, H.C., Van't Klooster, J.W., van der Hoorn, R.A.L., Joosten, M.H.A.J., Jones, J.D.G., and de Wit, P.J.G.M. (2005). Cladosporium Avr2 inhibits tomato Rcr3 protease required for Cf-2-dependent disease resistance. Science **308:** 1783–1786.

Shabab, M., Shindo, T., Gu, C., Kaschani, F., Pansuriya, T., Chintha, R., Harzen, A., Colby, T., Kamoun, S., and van der Hoorn, R.A. (2008). Fungal effector protein AVR2 targets diversifying defense-related cys proteases of tomato. Plant Cell **20:** 1169–1183.

PERSPECTIVE

Shen, A., and Higgins, D.E. (2006). The MogR transcriptional repressor regulates nonhierarchal expression of flagellar motility genes and virulence in *Listeria monocytogenes.* PLoS Pathog. **2:** e30.

Shimizu, T., Nakano, T., Takamizawa, D., Desaki, Y., Ishii-Minami, N., Nishizawa, Y., Minami, E., Okada, K., Yamane, H., Kaku, H., and Shibuya, N. (2010). Two LysM receptor molecules, CEBiP and OsCERK1, cooperatively regulate chitin elicitor signaling in rice. Plant J. **64:** 204–214.

Silipo, A., Sturiale, L., Garozzo, D., Erbs, G., Jensen, T.T., Lanzetta, R., Dow, J.M., Parrilli, M., Newman, M.A., and Molinaro, A. (2008). The acylation and phosphorylation pattern of lipid A from *Xanthomonas campestris* strongly influence its ability to trigger the innate immune response in Arabidopsis. ChemBioChem **9:** 896–904.

Song, W.Y., Wang, G.L., Chen, L.L., Kim, H.S., Pi, L.Y., Holsten, T., Gardner, J., Wang, B., Zhai, W.X., Zhu, L.H., Fauquet, C., and Ronald, P. (1995). A receptor kinase-like protein encoded by the rice disease resistance gene, *Xa21.* Science **270:** 1804–1806.

Stergiopoulos, I., De Kock, M.J., Lindhout, P., and De Wit, P.J.G.M. (2007). Allelic variation in the effector genes of the tomato pathogen *Cladosporium fulvum* reveals different modes of adaptive evolution. Mol. Plant Microbe Interact. **20:** 1271–1283.

Stergiopoulos, I., van den Burg, H.A., Okmen, B., Beenen, H.G., van Liere, S., Kema, G.H., and de Wit, P.J.G.M. (2010). Tomato Cf resistance proteins mediate recognition of cognate homologous effectors from fungi pathogenic on dicots and monocots. Proc. Natl. Acad. Sci. USA **107:** 7610–7615.

Sun, W., Dunning, F.M., Pfund, C., Weingarten, R., and Bent, A.F. (2006). Within-species flagellin polymorphism in *Xanthomonas campestris* pv *campestris* and its impact on elicitation of Arabidopsis FLAGELLIN SENSING2-dependent defenses. Plant Cell **18:** 764–779.

Sweigard, J.A., Carroll, A.M., Kang, S., Farrall, L., Chumley, F.G., and Valent, B. (1995). Identification, cloning, and characterization of *PWL2*, a gene for host species specificity in the rice blast fungus. Plant Cell **7:** 1221–1233.

Taguchi, F., Shimizu, R., Inagaki, Y., Toyoda, K., Shiraishi, T., and Ichinose, Y. (2003). Post-translational modification of flagellin determines the specificity of HR induction. Plant Cell Physiol. **44:** 342–349.

Taguchi, F., et al. (2006). Identification of glycosylation genes and glycosylated amino acids of flagellin in *Pseudomonas syringae* pv. *tabaci.* Cell. Microbiol. **8:** 923–938.

Taguchi, F., Yamamoto, M., Ohnishi-Kameyama, M., Iwaki, M., Yoshida, M., Ishii, T., Konishi, T., and Ichinose, Y. (2010). Defects in flagellin glycosylation affect the virulence of *Pseudomonas syringae* pv. *tabaci* 6605. Microbiology **156:** 72–80.

Takai, R., Isogai, A., Takayama, S., and Che, F.-S. (2008). Analysis of flagellin perception mediated by flg22 receptor OsFLS2 in rice. Mol. Plant Microbe Interact. **21:** 1635–1642.

Tampakaki, A.P., Skandalis, N., Gazi, A.D., Bastaki, M.N., Sarris, P.F., Charova, S.N., Kokkinidis, M., and Panopoulos, N.J. (2010). Playing the "Harp": Evolution of our understanding of hrp/hrc genes. Annu. Rev. Phytopathol. **48:** 347–370.

Tans-Kersten, J., Brown, D., and Allen, C. (2004). Swimming motility, a virulence trait of *Ralstonia solanacearum*, is regulated by FlhDC and the plant host environment. Mol. Plant Microbe Interact. **17:** 686–695.

Tao, Y., Xie, Z., Chen, W., Glazebrook, J., Chang, H.S., Han, B., Zhu, T., Zou, G., and Katagiri, F. (2003). Quantitative nature of Arabidopsis responses during compatible and incompatible interactions with the bacterial pathogen *Pseudomonas syringae.* Plant Cell **15:** 317–330.

Tellström, V., Usadel, B., Thimm, O., Stitt, M., Küster, H., and Niehaus, K. (2007). The lipopolysaccharide of *Sinorhizobium meliloti* suppresses defense-associated gene expression in cell cultures of the host plant *Medicago truncatula.* Plant Physiol. **143:** 825–837.

Thomma, B.P.H.J., VAN Esse, H.P., Crous, P.W., and DE Wit, P.J. (2005). *Cladosporium fulvum* (syn. *Passalora fulva*), a highly specialized plant pathogen as a model for functional studies on plant pathogenic Mycosphaerellaceae. Mol. Plant Pathol. **6:** 379–393.

Torto, T.A., Li, S., Styer, A., Huitema, E., Testa, A., Gow, N.A.R., van West, P., and Kamoun, S. (2003). EST mining and functional expression assays identify extracellular effector proteins from the plant pathogen *Phytophthora.* Genome Res. **13:** 1675–1685.

Tsuda, K., and Katagiri, F. (2010). Comparing signaling mechanisms engaged in pattern-triggered and effector-triggered immunity. Curr. Opin. Plant Biol. **13:** 459–465.

Tsuda, K., Sato, M., Stoddard, T., Glazebrook, J., and Katagiri, F. (2009). Network properties of robust immunity in plants. PLoS Genet. **5:** e1000772.

Valent, B., and Khang, C.H. (2010). Recent advances in rice blast effector research. Curr. Opin. Plant Biol. **13:** 434–441.

van den Burg, H.A., Harrison, S.J., Joosten, M.H.A.J., Vervoort, J., and de Wit, P.J.G.M. (2006). *Cladosporium fulvum* Avr4 protects fungal cell walls against hydrolysis by plant chitinases accumulating during infection. Mol. Plant Microbe Interact. **19:** 1420–1430.

van den Burg, H.A., Spronk, C.A., Boeren, S., Kennedy, M.A., Vissers, J.P., Vuister, G.W., de Wit, P.J.G.M., and Vervoort, J. (2004). Binding of the AVR4 elicitor of *Cladosporium fulvum* to chitotriose units is facilitated by positive allosteric protein-protein interactions: The chitin-binding site of AVR4 represents a novel binding site on the folding scaffold shared between the invertebrate and the plant chitin-binding domain. J. Biol. Chem. **279:** 16786–16796.

van den Burg, H.A., Westerink, N., Francoijs, K.J., Roth, R., Woestenenk, E., Boeren, S., de Wit, P.J.G.M., Joosten, M.H.A.J., and Vervoort, J. (2003). Natural disulfide bond-disrupted mutants of AVR4 of the tomato pathogen *Cladosporium fulvum* are sensitive to proteolysis, circumvent *Cf-4*-mediated resistance, but retain their chitin binding ability. J. Biol. Chem. **278:** 27340–27346.

Van der Biezen, E.A., and Jones, J.D. (1998). Plant disease-resistance proteins and the gene-for-gene concept. Trends Biochem. Sci. **23:** 454–456.

van Esse, H.P., Bolton, M.D., Stergiopoulos, I., de Wit, P.J.G.M., and Thomma, B.P.H.J. (2007). The chitin-binding *Cladosporium fulvum* effector protein Avr4 is a virulence factor. Mol. Plant Microbe Interact. **20:** 1092–1101.

van Esse, H.P., Fradin, E.F., de Groot, P.J., de Wit, P.J.G.M., and Thomma, B.P.H.J. (2009). Tomato transcriptional responses to a foliar and a vascular fungal pathogen are distinct. Mol. Plant Microbe Interact. **22:** 245–258.

van Esse, H.P., Van't Klooster, J.W., Bolton, M.D., Yadeta, K.A., van Baarlen, P., Boeren, S., Vervoort, J., de Wit, P.J.G.M., and Thomma, B.P.H.J. (2008). The *Cladosporium fulvum* virulence protein Avr2 inhibits host proteases required for basal defense. Plant Cell **20:** 1948–1963.

Wan, J., Zhang, X.-C., Neece, D., Ramonell, K.M., Clough, S., Kim, S.-Y., Stacey, M.G., and Stacey, G. (2008). A LysM receptor-like kinase plays a critical role in chitin signaling and fungal resistance in *Arabidopsis.* Plant Cell **20:** 471–481.

Wang, G., et al. (2008). A genome-wide functional investigation into the

roles of receptor-like proteins in Arabidopsis. Plant Physiol. **147:** 503–517.

Wang, G., Fiers, M., Ellendorff, U., Wang, Z., De Wit, P.J.G.M., Angenent, G., and Thomma, B.P.H.J. (2010). The diverse roles of extracellular leucine-rich repeat-containing receptor-like proteins in plants. Crit. Rev. Plant Sci. **29:** 285–299.

Wei, Z.M., Laby, R.J., Zumoff, C.H., Bauer, D.W., He, S.Y., Collmer, A., and Beer, S.V. (1992). Harpin, elicitor of the hypersensitive response produced by the plant pathogen *Erwinia amylovora.* Science **257:** 85–88.

Wirthmueller, L., Zhang, Y., Jones, J.D., and Parker, J.E. (2007). Nuclear accumulation of the Arabidopsis immune receptor RPS4 is necessary for triggering EDS1-dependent defense. Curr. Biol. **17:** 2023–2029.

Wolfgang, M.C., Jyot, J., Goodman, A.L., Ramphal, R., and Lory, S. (2004). *Pseudomonas aeruginosa* regulates flagellin expression as part of a global response to airway fluid from cystic fibrosis patients. Proc. Natl. Acad. Sci. USA **101:** 6664–6668.

Yamaguchi, T., Yamada, A., Hong, N., Ogawa, T., Ishii, T., and Shibuya, N. (2000). Differences in the recognition of glucan elicitor signals between rice and soybean: Beta-glucan fragments from the rice blast disease fungus *Pyricularia oryzae* that elicit phytoalexin biosynthesis in suspension-cultured rice cells. Plant Cell **12:** 817–826.

Zeidler, D., Zähringer, U., Gerber, I., Dubery, I., Hartung, T., Bors, W., Hutzler, P., and Durner, J. (2004). Innate immunity in *Arabidopsis thaliana*: Lipopolysaccharides activate nitric oxide synthase (NOS) and induce defense genes. Proc. Natl. Acad. Sci. USA **101:** 15811–15816.

Zipfel, C., Kunze, G., Chinchilla, D., Caniard, A., Jones, J.D., Boller, T., and Felix, G. (2006). Perception of the bacterial PAMP EF-Tu by the receptor EFR restricts Agrobacterium-mediated transformation. Cell **125:** 749–760.

Zipfel, C., Robatzek, S., Navarro, L., Oakeley, E.J., Jones, J.D., Felix, G., and Boller, T. (2004). Bacterial disease resistance in Arabidopsis through flagellin perception. Nature **428:** 764–767.