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# Of PAMPs and Effectors: The Blurred PTI-ETI Dichotomy

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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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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

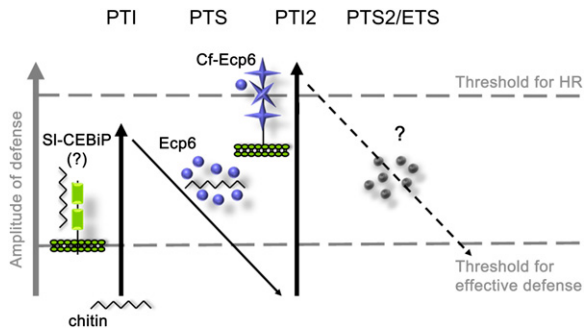
Classical examples of PAMPs are structural molecules, such as bacterial flagellin, peptidoglycan, and lipopolysaccharides, oomycete glucans, and fungal chitin (Ayers et al., 1976; Felix et al., 1993, 1999; Dow et al., 2000; Gust et al., 2007; Erbs et al., 2008). While PAMPs are widely conserved across 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  $\beta$ -(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.

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**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 SI-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 SI-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

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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 (Nürnberg 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  $\beta$ -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).

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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 recognition 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 triggered 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 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

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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

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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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