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Plant Immunity: The MTI-ETI Model and Beyond

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Abstract
In plant-microbe interactions, a pathogenic microbe initially has to overcome preformed and subsequently induced plant defenses. One of the initial host-induced defense responses is microbe-associated molecular pattern (MAMP)-triggered immunity (MTI). Successful pathogens attenuate MTI by delivering various effectors that result in effector-triggered susceptibility and disease. However, some host plants developed mechanisms to detect effectors and can trigger effector-triggered immunity (ETI), thereby abrogating pathogen infection and propagation. Despite the wide acceptance of the above concepts, more and more accumulating evidence suggests that the distinction between MAMPs and effectors and MTI and ETI is often not given. This review discusses the complexity of MTI and ETI signaling networks and elaborates the current state of the art of defining MAMPs versus effectors and MTI versus ETI, but also discusses new findings that challenge the current dichotomy of these concepts.

Introduction
Plants are constantly exposed to a wide variety of adverse environmental conditions that can be broadly classified as biotic (bacteria, viruses, fungi, parasites, etc.) or abiotic stresses (drought, extreme temperature, chemicals, salinity, etc.). Attacks by pathogenic organisms constitute one of the most challenging situations during the life of a plant. Unlike animals, plants do not possess specialized mobile immune cells, but have nonetheless developed a rapid and effective immune system to survive and resist various pathogens. In addition, plants make use of preformed physical barriers, namely the cuticle and the cell wall, and constitutively produce antimicrobial compounds. The cuticle is a hydrophobic layer present on the external surface of the aerial epidermis of all land plants and is mainly composed of cutin and waxes (Yeats and Rose, 2013). Not only does it play a role in defense but it also acts as a barrier to transpirational water loss and as a protection against UV radiation. Although the cuticle is a good barrier against a number of pathogens, many fungal pathogens can penetrate the cuticle by mechanical rupture and secretion of cutinases that hydrolyze the cutin polyester (Longhi and Cambillau, 1999; Mendgen et al., 1996). In addition to the cuticle, the plant cell wall, which mainly consists of high molecular weight polysaccharides such as cellulose, hemicelluloses and pectin, glycosylated proteins and in certain cases lignin (Somerville et al., 2004), also protects plants against biotic aggressors. While fungal pathogens are equipped with cuticle and cell wall degrading enzymes to penetrate the epidermis, bacterial pathogens on the other hand do not typically enter plant tissues by directly penetrating the cuticle and cell wall. As a result they evolved strategies to enter the plant through a number of natural surface openings, such as stomata and through surface wounds caused by various environmental factors (Melotto et al., 2008).

Many plants produce two types of antimicrobial compounds, (i) preformed compounds also termed phytoanticipins that become toxic upon pathogen perception and (ii) induced compounds, such as camalexin produced following a pathogen attack (Arbona and Gomez-Cadenas, 2015; Osbourn, 1996). The induced compounds also include various proteins and small metabolites, such as phenolics, unsaturated lactones, saponins, cyanogenic glycosides and glucosinolates, that inhibit pathogen growth (Osbourn, 1996).

The two strategies, a preformed defense system and an inducible defense system, allow plants to withstand against a majority of plant pathogens, a phenomenon that is called non-host resistance. The inducible plant defense system has two layers, called microbe-associated molecular pattern (MAMP)-triggered immunity (MTI) and effector-triggered immunity (ETI). This review first discusses the signaling mechanisms occurring during MTI and ETI, and then discusses the current MTI-ETI dichotomy.

Signaling in MTI

The complex network of signaling events that occur during MTI has been exhaustively reviewed recently, with a specific emphasis on mitogen-activated protein kinases (MAPKs) (Bigeard et al., 2015). In the present review, we thus only briefly recapitulate the signaling in MTI.

MAMPs and PRRs

In MTI, the defense system is triggered by the detection and recognition of MAMPs, which are synthesized by pathogens and non-pathogens. Plants are also able to detect damage-associated molecular patterns (DAMPs) which are plant degradation products resulting from the action of invading pathogens, or endogenous peptides, constitutively present or newly synthesized, that are released by plants following a pathogen attack (Boller and Felix, 2009). Recognition of DAMPs also triggers responses similar to MTI responses. The most well characterized MAMP is flg22, a 22-amino-acid long epitope in the N-terminus of bacterial flagellin that is evolutionarily conserved and induces different defense responses (Zipfel, 2009; Zipfel et al., 2004). Other well-known examples of MAMPs that activate similar cellular responses are elf18 or elf26 (a conserved N-terminal portion of the bacterial elongation factor Tu), peptidoglycans (a component of bacterial cell walls), and chitin (a component of fungal cell walls) (Boller and Felix, 2009; Chisholm et al., 2006; Gomez-Gomez and Boller, 2002; Zipfel et al., 2006). MAMPs are recognized by Pattern-Recognition Receptors (PRRs) which are usually plasma membrane receptor-like kinases (RLKs) or receptor-like proteins (RLPs) with extracellular domains (Bohm et al., 2014a; Macho and Zipfel, 2014; Schwessinger and Ronald, 2012; Segonzac and Zipfel, 2011). Some of the best-known examples of PRRs are FLS2 (flagellin-sensitive 2), a leucine-rich receptor kinase, which recognizes flg22 (Gomez-Gomez and Boller, 2000) EF-Tu receptor (EFR) that perceives EF-Tu with the help of its minimal 18 amino acid epitope elf18 (Zipfel et al., 2006) and PEPR1, the receptor of the DAMP AtPep1 (Yamaguchi et al., 2006).

For MAMP perception and signal transduction, a number of PRRs have to associate with co-receptor RLKs (Monaghan and Zipfel, 2012), as shown for BAK1 (BRI1 associated receptor kinase 1), which can associate with a number of PRRs including FLS2, (Roux et al., 2011; Segonzac and Zipfel, 2011). FLS2 also associates with the RLK BIK1 (Botrytis-induced kinase 1) and related PBL (PBS1-like) proteins, which are rapidly released from FLS2 upon flg22 binding (Liu et al., 2013; Lu et al., 2010; Zhang et al., 2010). MAMP perception induces very rapid auto- and trans-phosphorylation reactions of these interacting proteins (Lu et al., 2010; Schulze et al., 2010), followed by a complex sequence of choreographed events (Figure 1).

Early events in MTI signaling

Among the earliest responses to MAMP/DAMP perception is an influx of extracellular Ca^{2+} ions into the cytosol (Jeworutzki et al., 2010; Nomura et al., 2012; Ranf et al., 2011), inducing the opening of other membrane channels (influx of H^+, efflux of K^+, Cl^- and nitrate) which lead to an extracellular alkalinization and a depolarization of the plasma membrane (Jeworutzki et al., 2010). In addition to Ca^{2+} ion fluxes, a very early event following MAMP/DAMP recognition is the production of reactive oxygen species (ROS) (Chinchilla et al., 2007); (Nuhse et al., 2000); (Ranf et al., 2011) mainly by the plasma membrane-localized NADPH oxidase RBOHD (respiratory burst oxidase homolog D) (Nuhse et al., 2007; Ranf et al., 2011). Upon MAMP perception, RBOHD is phosphorylated by Ca^{2+}-induced CDPKs (calcium-dependent protein kinases) and BIK1 on different residues, which are all required for activation of the NADPH oxidase (Boudsocq et al., 2010; Dubiella et al., 2013; Kadota et al., 2014). Ca^{2+} itself also regulates RBOHD through direct binding to the N-terminal EF-hand

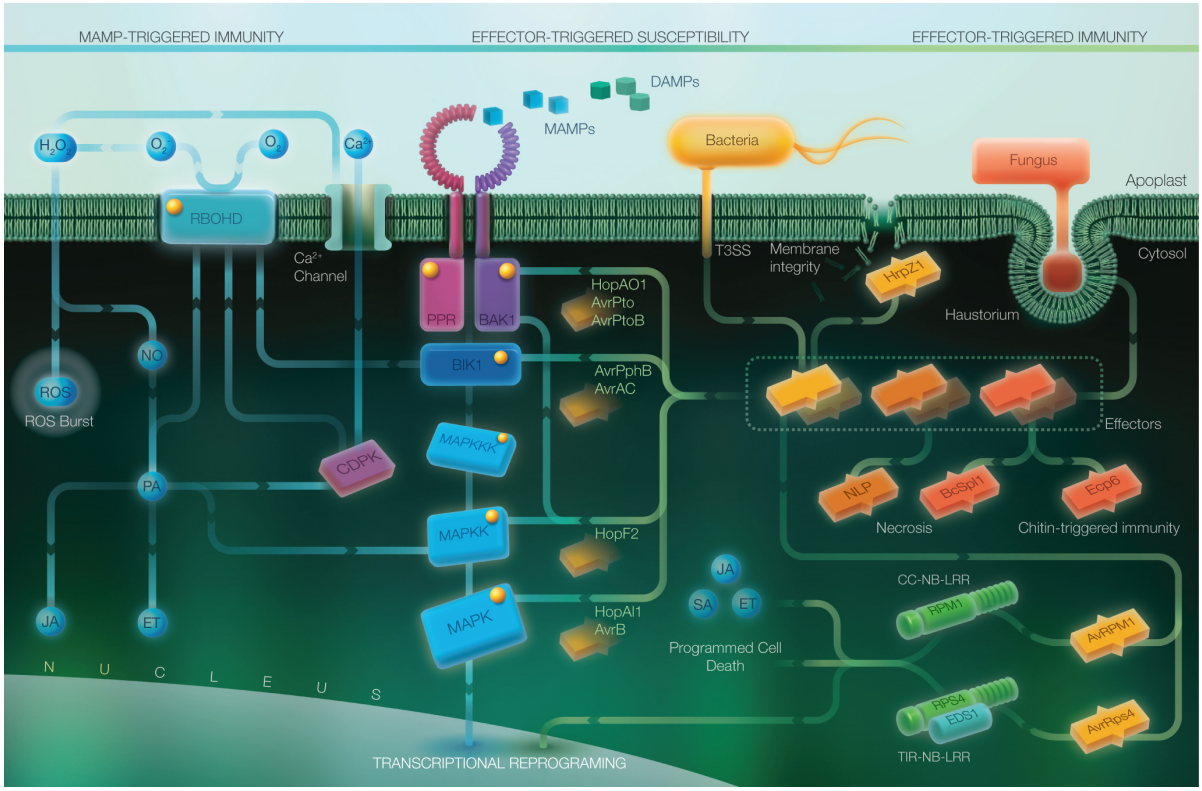

Figure 1. Inducible defense systems in plants. PRRs perceive the MAMPs and recruit BAK1 and BIK1 to induce MTI involving notably MAPK modules. Plants also detect DAMPs that are degradation products and trigger responses similar to the MTI responses. This is accompanied by a ROS burst via the NADPH oxidase RBOHD which in turn is phosphorylated by Ca^{2+}-induced CDPKs. RNS, such as NO, are required for generation of PA via both PLD and PLC/DGK pathways. PA can interact and modulate the activity of CDPKs, MAPKs and RBOHD/F (Zhang et al., 2009) and can regulate production of JA and ET. Bacterial and fungal pathogens may deliver effectors via the T3SS and haustoria, respectively, that block MTI. Plants evolved CNLs or TNLs to nullify the effect of the effectors leading to a stronger immune response termed ETI that involves transcriptional reprogramming, programmed cell death and increased levels of the hormones SA, JA and ET. The effector HopAO1 dephosphorylates the PRR and suppresses subsequent immune response. The effectors AvrPto and AvrPtoB suppress immunity by acting directly on the MAMP receptors via inhibiting BAK1 kinase activity while the effectors AvrPphB and AvrAC inhibit the response by cleaving or uridylylating BIK1. The effectors AvrB, HopAI1 and HopF2 directly target different components of the MAPK cascades. The TIR-NB-LRR, RPS4 recognizes the effector AvrRPS4 and redistributes the EDS1-RPS4 complex between the nucleus and cytoplasm to induce defense responses. An example of CC-NB-LRR is RPM1 that recognizes AvrRpm1. Some MAMPs, such as flg22, bacterial LPS and harpin (HrpZ1) act as effectors too. Similarly, certain effector proteins such as NLPs, BcSpl1 and LysM domain containing proteins such as Ecp6 have a more widespread occurrence and function as MAMPs too.

motifs of the protein (Ogasawara et al., 2008). RBOHD produces membrane-impermeable superoxide ($O_2^{\cdot-}$) in the apoplast, which is converted into hydrogen peroxide (H_2O_2) by superoxide dismutases. In contrast to other ROS, H_2O_2 is relatively stable and membrane-permeable and can enter the cytosol and different organelles of plant cells. However, NADPH oxidases are not the only source for ROS, but multiple ROS sources seem to be involved in a complex temporal and spatial coordination (Baxter et al., 2014; Gross et al., 2013).

Other than Ca^{2+} and ROS, reactive nitrogen species (RNS), such as nitric oxide, were shown to be involved at different steps of MAMP/DAMP signaling, e.g. via inhibition of RBOHD or regulation of NPR1 (non-expresser of PR genes 1), a master regulator of defense gene expression, which both become nitrosylated on cysteine residues (Tada et al., 2008; Yun et al., 2011). Some lipid derivatives, such as phosphatidic acid (PA) and ceramides, were also proposed to function as signaling molecules upon pathogen infection (Okazaki and Saito, 2014). MAMP/DAMP-induced NO production is partly also required for PA generation via both the

phospholipase D (PLD) and phospholipase C/ diacylglycerol kinase (PLC/DGK) pathways (Raho et al., 2011). PA can interact and modulate the activity of CDPKs (Farmer and Choi, 1999; Szczegielniak et al., 2005) MAPKs (Testerink et al., 2007), RBOHD/F (Zhang et al., 2009) and can regulate production of jasmonic acid (JA) and ethylene (ET) (Nakano et al., 2013; Testerink et al., 2008; Testerink et al., 2007; Wang et al., 2000).

Activation of protein kinases

Besides the very rapid auto- and trans-phosphorylation reactions at the level of the receptor complexes, other protein kinases get activated in a matter of minutes and most of these belong to the CDPK and MAPK protein kinases and are key elements in regulating defense at the level of the transcriptional and metabolic responses (Boudsocq et al., 2010; Frei dit Frey et al., 2014; Lassowskat et al., 2014).

Among the CDPKs, CPK4, 5, 6 and 11 are rapidly activated upon flg22 signaling (Boudsocq et al., 2010) and were shown to regulate ROS production via phosphorylation of NADPH oxidase RBOHD, transcriptional reprogramming and resistance to the bacterial pathogen *Pseudomonas syringae* pv tomato DC3000 (*Pst* DC3000) (Boudsocq et al., 2010; Romeis and Herde, 2014). CDPK substrates include the important regulators RBOHD and ACS2 (Boudsocq and Sheen, 2013; Dubiella et al., 2013; Kamiyoshihara et al., 2010; Schulz et al., 2013). Another important CDPK seems to be CPK28, as loss of function *cpk28* mutant accumulates high levels of the plasma membrane associated cytoplasmic kinase BIK1 and exhibits strong MAMP-triggered responses (Monaghan et al., 2014). CPK28 is genetically upstream of the MAMP-triggered Ca^{2+} burst and negatively regulates BIK1 by phosphorylation that marks it for ubiquitination and subsequent degradation (Monaghan et al., 2015).

MAMP/DAMP perception activates a number of MAPKs, including the following members of the gene family of 20 MAPKs MPK1, 3, 4, 6, 11 and 13 (Bethke et al., 2012; Nitta et al., 2014; Nuhse et al., 2000; Zipfel et al., 2006). MAPK kinase kinases (MAPKKKs), MAPK kinases (MAPKKs) and MAPKs constitute functional signaling modules. Two signaling modules have been defined to date upon MAMP perception, namely MKK4/MKK5-MPK3/ MPK6 (Asai et al., 2002; Ren et al., 2002) and MEKK1-MKK1/MKK2-MPK4 (Berriri et al., 2012; Gao et al., 2008; Hadiarto et al., 2006; Huang et al., 2000; Ichimura et al., 2006; Ichimura et al., 1998; Matsuoka et al., 2002; Mizoguchi et al., 1998; Nakagami et al., 2006; Petersen et al., 2000; Qiu et al., 2008; Suarez-Rodriguez et al., 2007; Teige et al., 2004). In the current model, both modules positively regulate defense responses (Berriri et al., 2012; Kong et al., 2012; Pitzschke et al., 2009; Rasmussen et al., 2012; Su et al., 2013; Zhang et al., 2012; Zhao et al., 2014). However, the molecular link between the PRRs and these MAPK pathways remains to be elucidated. Regarding MPK1, MPK11 and MPK13, their upstream MAPKKs and MAPKKKs have not been identified yet. Besides, *mpk1*, *mpk11* and *mpk13* mutants do not show altered resistance to a bacterial pathogen suggesting a functional redundancy among the MAPKs and does not preclude yet the identification of their roles in plant immunity (Nitta et al., 2014). MPK3, MPK4 and MPK6 phosphorylate specific and redundant substrates to control many cellular responses. For example, the ET-related ERF104 is specifically targeted by MPK6 (Bethke et al., 2009), while ACS2 and ACS6 are phosphorylated by both MPK3 and MPK6 (Han et al., 2010; Liu and Zhang, 2004). The number of identified substrates is constantly growing, highlighting the importance of MAPKs during MTI. Additionally, MAPKs also play important roles in abiotic stresses and development (Colcombet and Hirt, 2008; Rodriguez et al., 2010).

Role of hormones in MTI signaling

In response to infection by biotrophic and hemibiotrophic pathogens, salicylic acid (SA) plays a pivotal role in plant defense by regulating its downstream components. Elevated levels of SA cause nuclear accumulation of NPR1 (SA receptor), which is subsequently degraded to mediate systemic acquired resistance (SAR) (Vlot et al., 2009; Wu et al., 2012). SA is also associated with the accumulation of antimicrobial pathogenesis-related (PR) proteins (Moore et al., 2011). MPK3 and to a lesser extent MPK6 have been proposed to play an important role in SA-mediated priming and enhancing defense gene activation and resistance (Beckers et al., 2009). On the other hand, the MPK4 cascade negatively regulates SA signaling and mutants of this cascade exhibit SA accumulation, constitutive pathogenesis-related gene expression and SAR (Petersen et al., 2000). In the case of necrotrophic pathogen infections, JA and ET are induced. The two tobacco orthologs of MAPKs, WIPK and SIPK, regulate the levels of JA in wounded tobacco plants (Seo et al., 2007). Both MAPKs are required but not sufficient to induce JA production (Kim et al., 2003). MKK3 and MPK6

negatively regulate *AtMYC2* in both JA-dependent gene expression and inhibition of root growth, which indicates a possible role for the MKK3-MPK6 cascade in JA signal transduction (Takahashi et al., 2007). Moreover, it has been found that *mpk4* mutant plants are defective in inducing JA and ET defense marker genes such as *PDF1.2* in response to JA. MPK4 positively regulates JA/ET-inducible gene responses through the defense regulators EDS1 and PAD4 independently of its negative regulation of SA biosynthesis (Kong et al., 2012; Petersen et al., 2000). Thus, MPK4 is proposed to be required for the balance between SA and JA/ET related defense (Brodersen et al., 2006).

Reprogramming of gene expression

MAMPs/DAMPs trigger a massive and dynamic reprogramming of plant genome expression. Several thousand genes are affected by flg22 perception (Denoux et al., 2008). Transcriptional reprogramming of defense hormone signaling as well as the synthesis of antimicrobial compounds becomes apparent after 1 hour (Tsuda et al., 2009). Later, genes mainly involved in SA-mediated secretory processes and senescence are prominently affected (Denoux et al., 2008). The chloroplast resident calcium-sensing receptor (CAS) acts upstream of SA accumulation and is involved in MAMP-induced expression of defense genes while also suppressing chloroplast gene expression thus allowing chloroplast mediated transcriptional reprogramming in cytoplasmic-nuclear plant immune responses (Nomura et al., 2012). Numerous transcription factors are thus involved in plant immunity (Alves et al., 2013; Ambawat et al., 2013; An and Mou, 2013; Eulgem and Somssich, 2007; Gatz, 2013; Gutterson and Reuber, 2004; Nuruzzaman et al., 2013; Pandey and Somssich, 2009; Puranik et al., 2012). In addition, it is becoming more and more clear that chromatin remodelers and modifiers also contribute strongly to transcriptional regulation of defense (Berr et al., 2012; Dowen et al., 2012; Ma et al., 2011; Yu et al., 2013).

Signaling in ETI

Effectors and R proteins

Effectors are molecules produced by plant pathogens and function as virulence factors to mediate infection of specific plant species or varieties. These molecules can be proteins, nucleic acids, carbohydrates or metabolites. Effectors can have different effects such as inhibiting MTI or ETI and can be secreted either into the extracellular matrix or directly delivered into the plant cell (Hogenhout et al., 2009). Many effectors are proteins that are injected into plant host cells through bacterial type III secretion systems (T3SS) (Feng and Zhou, 2012; Hann et al., 2010; Lohou et al., 2013). The genomes of plant pathogens may contain a considerable number of effectors, as evidenced from analysis of the model bacterial pathogen *P. syringae* that contains between 30 - 50 genes coding for effector proteins (Buell et al., 2003). A significant number of effectors target components of PRR immune complexes or the downstream signaling cascades (Feng and Zhou, 2012; Mukhtar et al., 2011). For instance, the *P. syringae* effector HopAI1, a phosphothreonine lyase, directly targets and inactivates MPK3, MPK4 and MPK6 by dephosphorylating these kinases (Zhang et al., 2007). The HopF2 effector inactivates MKK5 and probably other MKKs to inhibit MAPK signaling to suppress downstream defense responses (Wang et al., 2010). Another effector, HopAO1, a protein tyrosine phosphatase targets the phosphorylation on a specific tyrosine residue on the PRR EFR (Y836) (and also probably FLS2) to inhibit ligand-induced activation of the PRR and suppresses the subsequent immune response (Espinosa et al., 2003) (Macho et al., 2014). The effector AvrB was also reported to regulate hormone signaling by inducing MPK4 phosphorylation thus enhancing plant susceptibility (Cui et al., 2010). An alternative way to suppress immunity is by targeting components upstream of MAPKs by pathogen effectors such as the MAMP receptors FLS2, EFR, and CERK1 by AvrPto and AvrPtoB, by inhibiting BAK1 kinase activity via interaction with AvrPtoB, or by cleaving and uridylylating BIK1 by AvrPphB and AvrAC to inhibit MTI signaling (Meng and Zhang, 2013). The *Agrobacterium* T-DNA associated virulence protein VirE2 together with the host cell transcription factor VIP1 binds to the nuclear import machinery to transfer the T-DNA to the nucleus. For this process to occur, VIP1 needs to be phosphorylated by MPK3 to translocate from the cytoplasm to the nucleus. The bacterial VirF effector contains an F-box motif and targets VirE2 and VIP1 for proteosomal degradation (Djamei et al., 2007; Tzfira et al., 2004). Plant pathogens not only produce protein effectors, but also small molecules, such as the polyketide coronatine, which structurally and functionally mimics the active plant hormone conjugate JA-isoleucine (JA-Ile). Coronatine is secreted by several pathovars of *P. syringae* and contributes to virulence by antagonizing SA-mediated host responses (Weiler et al., 1994; Xin and He, 2013). However, yet another strategy is the production of small RNAs to hijack the plant RNA

interference (RNAi) machinery, as recently shown for *Botrytis cinerea* via the host protein AGO1, which in turn silences host immunity genes (Weiberg et al., 2013).

Plant R proteins are intracellular receptors that detect the presence of pathogen effectors in the host cell. Most of them are nucleotide-binding domain and leucine-rich repeat (NB-LRR or NLR) proteins (Jacob et al., 2013; Maekawa et al., 2011; Qi and Innes, 2013). Briefly, NLR proteins are divided into two groups depending on their N-terminal structures: CNL (CC-NB-LRR) with an N-terminal coiled-coil domain and TNL (TIR-NB-LRR) with an N-terminal Toll/interleukin-1 receptor domain (TIR). Some NLRs contain domains termed integrated decoys that recognize effectors from pathogens. These were found in multiple plant families indicating their functional significance and conservation. Across plant lineages, domains already known to be implicated in pathogen defense such as in the case of RIN4, NPR1 and Zinc Finger BED type protein (ZBED) have been integrated into NLR proteins (Kroj et al., 2016; Sarris et al., 2016). They can have different sub-cellular localizations (plasma membrane-associated, cytosolic, nuclear, etc.) and intracellular shuttling is important for some NLR proteins to fulfill their functions (Dowen et al., 2009; Garcia et al., 2010; Wirthmueller et al., 2007). An accumulation of plant NLRs leads to autoimmunity and so NLR homeostasis is tightly regulated at multiple levels (Huang et al., 2016; Kadota et al., 2010; Shirasu, 2009; Takken and Goverse, 2012). R proteins detect pathogen effectors in three possible ways, either through direct physical interaction (Dodds and Rathjen, 2010) or by sensing effector-induced modification of other plant proteins termed as the guardee/decoy model (Dangl and Jones, 2001; van der Hoorn and Kamoun, 2008) or via a third method termed the integrated decoy model where in the R proteins have incorporated a decoy domain into their structure (Cesari et al., 2014). They are thought to be auto-inhibited and activated upon ligand binding. LRR domains mostly seem to be responsible for effector recognition, while the TIR or CC domains function in signal transduction (Qi and Innes, 2013) (Figure1).

Signaling mechanisms by some NLRs

The mechanism of effector recognition is now known for a number of NB-LRR-effector pairs. The *P. syringae* type III effector AvrRps4 is recognized by the TIR-NB-LRR receptor RPS4 (Gassmann et al., 1999). RPS4 distributes between endomembranes and nuclei both in healthy and AvrRps4-triggered tissues (Wirthmueller et al., 2007). Like all TIR-type NB-LRRs, RPS4 requires interaction with the basal defense regulator enhanced disease susceptibility 1 (EDS1), a lipase-like protein, to activate ETI, and a coordinated nucleo-cytoplasmic partitioning of EDS1-RPS4 complex is necessary to trigger the full set of immune responses (Bhattacharjee et al., 2011; Heidrich et al., 2011). In fact, forced nuclear localization of the AvrRps4 effector is sufficient to induce RPS4-mediated bacterial growth inhibition but hinders RPS4-mediated HR, while forced cytoplasmic localization of AvrRps4 decreases RPS4-mediated bacterial growth inhibition but only moderately reduces RPS4-mediated HR (Heidrich et al., 2011). These results suggest that a single NLR may activate distinct signaling pathways in the cytoplasm and nucleus and that cell death and the restriction of pathogen growth are two separate phenotypes. Recognition of the bacterial effector proteins AvrB and AvrRpm1 occurs via RPM1, a CC-NB-LRR (Grant et al., 1995). RPM1 is plasma membrane-localized in both the inactive and active forms (Boyes et al., 1998; Gao et al., 2011) and in this case nuclear re-localization is not required for RPM1-mediated defense responses or the induction of HR (Gao et al., 2011), suggesting that ETI signaling can function by different mechanisms.

RPS2 and RPM1 are two plasma membrane-associated CC-NB-LRRs. In their case, the signaling mechanisms are well documented. Using inhibitors, RPS2- and RPM1-mediated signaling was shown to depend on the sequential production of PA by PLC/DGK and the influx of extracellular Ca^{2+} followed by production of ROS and PA via PLD (Andersson et al., 2006). The influx of extracellular and release of internal Ca^{2+} then results in a complex system of CDPK activations (Gao et al., 2013). The immune response is orchestrated by defense gene expression via phosphorylation of the WRKY8/28/48 transcription factors by CPK4/5/6/11, the induction of ROS production through phosphorylation of the NADPH oxidases RBOHD and F by CPK1/2/4/11. ETI mediated by RPS2 and RPM1 was also shown to be reduced in a calcium-sensing receptor (CAS) mutant, as revealed by reduced ROS and NO production and a delayed and suppressed HR cell death and demonstrating the role of chloroplast signaling in these NLR-triggered responses (Nomura et al., 2012). The contribution of the SA, JA and ET hormone pathways in ETI was estimated by measuring the relative growth of *Pst* DC3000 strains expressing

either of the effectors AvrRpt2, AvrRpm1 or AvrPphB, which are recognized by the CC-NB-LRRs RPS2, RPM1 and RPS5, respectively (Tsuda et al., 2009). While the absence of individual phytohormone signaling pathways had no dramatic effect on the ETI response, the defense responses decreased by up to 80% in the combined absence of the SA, JA and ET signaling pathways. These results demonstrate the overlapping contributions of SA, JA and ET signaling pathways in NLR-mediated immune responses but also the variability in phytohormone-dependency of different NLRs to trigger defenses. (Tao et al., 2003).

Besides the signaling mechanisms described above, other signaling routes are observed in the case of several TIR-NB-LRRs. Indeed, some TIR-NB-LRR-interacting proteins such as EDS1, suppressor of rps4-RLD1 (SRFR1) and Topless-related 1 (TPR1) probably represent signaling complexes that act as transcriptional regulators (Bhattacharjee et al., 2013; Bhattacharjee et al., 2011; Kim et al., 2014b; Zhu et al., 2010). Interestingly, chromatin regulation also seems to contribute to transcription regulation in ETI as seen for example by the histone deacetylase 19 (HDA19) that forms a complex with TPR1 (Ma et al., 2011; Zhu et al., 2010). Some CC-NB-LRRs also interact with transcription factors, such as the activated barley (*Hordeum vulgare*) MLA10 which induces MYB6-dependent gene regulation and the rice Pb1 which interacts with WRKY45 to prevent its ubiquitin-proteasome degradation (Bhattacharjee et al., 2013; Chang et al., 2013; Inoue et al., 2013). It thus seems that direct R gene-mediated transcriptional regulation might in some cases also be at the heart of ETI.

Signaling mechanisms by RPW8.2

Resistance to powdery mildew (*Golovinomyces orontii*) requires the atypical R gene RPW8.2 (resistance to powdery mildew 8.2). Although RPW8.2 shows no similarity to other NLRs, RPW8.2 also requires EDS1 to induce HR and as well as SA, PAD4, EDS5 and NPR1 (Xiao et al., 2005). Upon infection by *Golovinomyces orontii*, the transcription of *RPW8.2* is strongly induced and RPW8.2 protein is carried on VAMP721/722 vesicles to the extrahaustorial membrane (EHM) independently of SA signaling (Kim et al., 2014a; Wang et al., 2009). RPW8.2 activates an EDS1 and SA signaling-dependent defense process that concomitantly enhances callose deposition and accumulation of H_2O_2 at the haustorial interface (Wang et al., 2009). In addition, RPW8.2 interacts with the 14-3-3 isoform lambda protein which may positively regulate RPW8.2 (Yang et al., 2009). 14-3-3 proteins were also shown to be involved in ETI in other systems (Oh and Martin, 2011; Oh et al., 2010; Teper et al., 2014).

Observations going beyond the MTI-ETI model

The strict separation of MTI and ETI results in the assumption that MAMPs are very conserved molecules that are widely detected while effectors are variable and only sensed by specific hosts. However, accumulating evidences suggest that the story of MAMPs and effectors is more complicated. The disappearing boundaries differentiating MTI-ETI and the concept of invasion model of plant immune system were put forth by Thomma and co-workers (Cook et al., 2015; Thomma et al., 2011).

Effectors and R proteins with broader scopes

Recently, it has become apparent that many effector proteins have a more widespread occurrence, which would equally qualify them as MAMPs. A good example is the necrosis and ET-inducing peptide 1 (Nep1) that was originally identified from *Fusarium oxysporum* (Bailey, 1995). Moreover, various Nep1-like proteins (NLPs) are encoded by bacteria, fungi and oomycetes and positively contribute to virulence of these pathogens (Gijzen and Nurnberger, 2006; Ottmann et al., 2009). Interestingly, a conserved amino acid motif was recently identified in NLPs that serves as a potent MAMP (Bohm et al., 2014b; Oome et al., 2014), thereby NLPs fulfill all the criteria for being effectors and MAMPs. Another example is BcSpl1, an effector protein required for full virulence of the necrotrophic fungus *Botrytis cinerea* (Frias et al., 2014; Frias et al., 2011). Two conserved peptide stretches of BcSpl1 can induce host defense and cell death. Since the two conserved regions are present in all BcSpl1 family members and belong to a highly conserved protein effector family in fungi, BcSpl1 can be classified as an effector and also as a MAMP (Frias et al., 2014). The *Pseudomonas syringae pv. phaseolicola* protein HrpZ1 has the ability to form ion-conducting pores and these pores have been proposed to facilitate delivery of effectors into the plant, thus functioning as a virulence factor that affects host membrane integrity. HrpZ1, especially the C-terminal fragment, is a MAMP that triggers MTI-like responses in a variety of plants, thus exhibiting a dual role in plant immunity during infection (Engelhardt et al., 2009). Yet another example of a fungal effector that also behaves as a MAMP is the well characterized LysM effector Ecp6 (extra cellular protein 6). Ecp6 interferes with chitin-triggered activation of host

immune responses by sequestering chitin fragments thereby qualifying as an effector. Interestingly, Ecp6 also competes with the plant LysM domain-containing chitin receptor CEBiP for binding chitin fragments. Ecp6 is found in all strains of *Cladosporium fulvum* with very little sequence variation. The widespread occurrence and functional conservation of LysM effectors is reminiscent of MAMPs and qualifies them to be designated as MAMPs (de Jonge and Thomma, 2009; de Jonge et al., 2010; Thomma et al., 2011).

Along the same line, R genes have been mostly thought of being receptors with specificity to a particular pathosystem. However, the NLR Rxo1 of maize not only confers resistance to *Burkholderia andropogonis*, the causal agent of maize stripe disease, but also to the unrelated bacterial rice pathogen *Xanthomonas oryzae* pv. oryzicola, which triggers ETI upon recognition of the type III effector protein AvrRxo (Zhao et al., 2004). Similarly, the physically linked NLR pair RRS1 and RPS4 confers resistance to Brassicaceae to the fungal pathogen *Colletotrichum higginsianum*, the broad-host range bacterial wilt pathogen *Ralstonia solanacearum*, and the bacterial pathogen *P. syringae* (Narusaka et al., 2009). In another example, the NLR immune receptor of tomato Mi-1.2 confers resistance to phloem-feeding insects as well as root-knot nematodes (Rossi et al., 1998; Vos et al., 1998). In a screen of 171 predicted bacterial effectors from *Pseudomonas, Ralstonia*, and *Xanthomonas* expressed in 59 plants from four plant families, it was found that each plant responded to an average of 19 effectors. Interestingly, the necrotic response to an effector was generally not taxonomically defined (Wroblewski et al., 2009). Taken together, these examples demonstrate that resistance conferred by NLR immune receptors is not necessarily restricted to a single pathosystem. Although some NLRs may directly perceive effectors, broadly detected effectors are likely perceived indirectly because they induce DAMPs or modify host targets that are guarded by R proteins (the guard model) (Van der Biezen and Jones, 1998). Nevertheless, broad detection of effectors by NLRs is conceptually similar to MAMP recognition by PRRs.

MAMPs and PRRs with reduced scopes

Conversely for MAMPs and PRRs, purified flagella and flg22 can induce immune responses in many different plant species, but with different efficiencies (Felix et al., 1999). The naturally occurring variation in the flagellin amino acid sequences of the bacterial pathogen *Xanthomonas campestris* pv. *campestris* (Xcc) correlates with its pathovar-dependent potential of defense response induction (Sun et al., 2006). Similarly, *R. solanacearum* strain K60 and *Pseudomonas cannabina* pv. *alisalensis* (*Pcal*) strain ES4326 show convincing correlations between their respective flg22 epitope sequence variations and the induced immune responses (Clarke et al., 2013; Pfund et al., 2004). Additional evidence comes from the analysis of the evolution of the flagellin sequences in natural populations of *P. syringae* pathovars. Here, the variation of the flg22 epitope sequences clearly indicated the evolution of the pathogenic potential to escape MAMP detection. Moreover, a second, 28-amino acid immunogenic region of flagellin, termed flgII-28, induced defense responses in tomato, and both the flg22 and flgII-28 peptides contribute to the ROS burst (Cai et al., 2011). Interestingly, the flgII-28 epitope induced immune responses in various solanaceous species but not in a variety of plants from five other families, suggesting that the perception system for the flgII-28 epitope is a rather recent specific achievement of solanaceae (Clarke et al., 2013). The recent characterization of the orthologous grape flagellin receptor VvFLS2 indicates that the flagellin encoded by a grape-adapted, plant growth-promoting rhizobacterium (PGPR), *Burkholderia phytofirmans*, elicits a weaker immune response on grape compared with flg22, which is specifically conditioned by the VvFLS2 receptor (Trda et al., 2014).

Correlatively, variation for flagellin perception is also conditioned by variation in the plant receptor FLS2 (Gomez-Gomez and Boller, 2000). The *Arabidopsis thaliana* accession Ws-0 does not respond to flg22 nor does it contain a functional FLS2 allele as it carries a point mutation that results in a stop codon in the kinase domain of FLS2 (Bauer et al., 2001; Zipfel et al., 2004), and genotypes in closely related *Arabidopsis lyrata*, *Cardamine hirsuta*, and additional Brassicaceae species do not bind the flg22 epitope (Vetter et al., 2012). The tomato and *Nicotiana benthamiana* orthologs of AtFLS2 display species-specific, receptor-dependent variation for flagellin perception (Robatzek et al., 2007).

Protease activated immune signaling

The bacterial pathogen *Pseudomonas aeruginosa* strain P14 secretes a PvdS-regulated lysyl class serine protease (protease IV) that elicits a strong immune response comparable to the response elicited by flg22 in terms of the activation of MPK3 and MPK6 but not MPK4, oxidative burst,

expression of defense related genes and protects Arabidopsis plants from *Pst* DC3000 infection. The activation of MAPKs in response to protease IV requires the Gα, Gβ and Gγ subunits of the heterotrimeric G-protein complexes. The receptor activated C kinase 1 (RACK1) acts as a scaffold and connects G-protein signaling to the downstream MAPK cascade. This module, involving the protease-G-protein-RACK1-MAPK cascades, forms a novel protease mediated immune signaling pathway distinct from the ones previously described (Cheng et al., 2015).

Signaling similarities in MTI and ETI

While MTI employs a core set of signaling events, ETI does not seem to be mediated by such a core set of signaling components. Rather, and dependent on the activated R protein, different subsets of signaling elements are solicited which nonetheless finally result in an efficient immune response. In addition to sharing a number of similar events between MTI and ETI, such as the production of ROS via the NADPH oxidase RBOHD, a calcium burst, the synthesis of PA and NO, MTI and ETI also employ common signaling pathways, as exemplified by the MAPK and CDPK cascades.

Before R protein-mediated signaling can occur in ETI, first the R proteins need to detect the presence of the effector. Several reports indicate that effectors injected by *P. syringae* are detected in plant cells (*Arabidopsis*, tobacco, tomato) 2 to 3 h post-inoculation (Mudgett and Staskawicz, 1999; Schechter et al., 2004). These results are consistent with another pathosystem, *Xanthomonas campestris pv. vesicatoria*/pepper plants (Casper-Lindley et al., 2002). These results as well as the comparison of ROS burst in *Arabidopsis* leaves with live *Pseudomonas* and flg22 elicitation (Smith and Heese, 2014) indicate that ETI may be initiated rapidly during the infection process and that MTI and ETI probably occur very close in time.

However, in contrast to the transient MAPK activation in MTI, induction of the expression of effectors by estradiol-inducible promoters resulted in the activation of MPK3 and MPK6 for several hours (Tsuda et al., 2013). Interestingly, Qi et al. showed that FLS2 can form a complex with the R proteins RPS2, RPM1 and RPS5 which are all plasma membrane-localized CC-NB-LRRs (Qi et al., 2011). The biological significance of this MTI-ETI receptor R protein complex is however currently not known but the existence of such a complex due to the possibility of several shared components between MTI and ETI is not far fetched.

Signaling by the three phytohormones SA, JA and ET has shown to be activated in some cases of both MTI as well as ETI (Tsuda and Katagiri, 2010; Tsuda et al., 2009). A positive role for the three hormones in flg22-triggered immunity (MTI) and AvrRpt2-triggered immunity (ETI) was demonstrated using an *Arabidopsis* dde2/ein2/pad4/sid2 quadruple mutant, which is a loss of function mutant of essential components involved in JA, ET and SA signaling. This again reinforces the fact that MTI and ETI share common signaling networks but use them in specific circumstances.

The transcriptional reprogramming integrates a large part of the upstream signaling inputs mediated mainly by the protein kinases and allows the implementation of induced defense mechanisms. It is dynamically regulated and it involves numerous transcription factors and chromatin regulators (Moore et al., 2011). Importantly, the differentially expressed genes during MTI and ETI are identical, but differ in quantity and kinetics (Tao et al., 2003). The stronger response in ETI suggests that ETI employs some of the same signaling components as MTI but results in higher expression of its target genes. Considering the hypothesis of MTI having evolved before ETI, these observations imply that ETI acquired R proteins during the course of evolution while adopting several signaling components of the MTI pathway (Tsuda and Katagiri, 2010).

Conclusions

Plant defense against pathogens is based on both preformed and induced defenses. Preformed defenses hinder pathogen entry and are among the main contributors to non-host resistance. Induced defenses are activated after perception of invading pathogens via two classically separate routes, MTI and ETI. Pathogen perception that leads to MTI is mediated by recognition of MAMPs by PRRs, whereby ETI recognizes effectors by intracellular R proteins. Although the MTI-ETI model constitutes an important and useful concept, the separation between MAMPs and effectors, and between PRRs and R proteins is not always so clear, and thus the dichotomy of MTI-ETI cannot be maintained but is rather a continuum between MTI and ETI.

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