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Endless Hide-and-Seek: Dynamic Co-evolution in Plant-Bacterium Warfare

Libo Shan*, Ping He and Jen Sheen

(*Department of Molecular Biology*, *Massachusetts General Hospital and Department of Genetics*, *Harvard Medical School*, Boston, Massachusetts 02114, USA)

Abstract

Plants possess innate immune systems to prevent most potential infections. The ancient and conserved innate immune responses are triggered by microbe-associated molecular patterns (MAMPs) and play important roles in broad-spectrum defenses. However, successful bacterial pathogens evolved type III virulence effectors to suppress MAMP-mediated immunity. To survive, plants further developed highly specific resistance (*R*) genes to trigger gene-for-gene-mediated immunity and turn the virulent pathogens into avirulent ones. We summarize here the very recent advances in this dynamic coevolution of plant-bacterium interaction.

Key words: MAMP; type III effector; gene-for-gene resistance.

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Plants rely on innate immune systems to distinguish self and non-self based on the detection of microbe-associated molecules and launch the first line of inducible defense against infectious disease. The microbe-associated molecules, such as bacterial flagellin, lipopolysaccharide (LPS) and fungal chitin, are generally termed PAMPs (pathogen-associated molecular patterns) and are only produced by potentially infectious agents - not host cells (Nurnberger et al. 2004; Chisholm et al. 2006). However, since nonpathogenic microbes also produce these molecules that effectively activate innate immune responses, we use the term MAMPs (microbe-associated molecular patterns) (Ausubel 2005; Li et al. 2005; de Torres et al. 2006; He et al. 2006; Torres et al. 2006). The recognition of different MAMPs presumably by specific plant pattern-recognition receptors (PRR) activates the common signaling pathways including MAP kinase (MAPK) cascade and defense gene transcription (Figure 1A) (Asai et al. 2002; Nurnberger et al. 2004; Navarro et al. 2004; He et al. 2006; Kaku et al. 2006; Zipfel et al. 2006). New evidence supports an essential role of MAMP-mediated innate immunity in plant nonhost immunity, a phenomenon known as resistance of most plant species to most potential pathogens (Mysore and Ryu 2004; Li et al. 2005; He et al. 2006). To be pathogenic, many gram-negative bacteria inject an array of virulent effector proteins into host cells through type III secretion system (TTSS) to effectively suppress MAMP-mediated immune responses (Figure 1B) (Kim et al. 2005; Li et al. 2005; Abramovitch et al. 2006; Chisholm et al. 2006; He et al. 2006). It appears that different effectors suppress plant immunity through distinct molecular actions. However, plants have coevolved specific resistance (R) proteins to recognize effector proteins and induce potent gene-for-gene resistance (Figure 1C) (Abramovitch et al. 2006; Chisholm et al. 2006). Interestingly, many type III effectors can also suppress gene-for-gene-based defense responses (Alfano and Collmer 2004; Mudgett et al. 2005; Nomura et al. 2005; Abramovitch et al. 2006).

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*Author for correspondence. Tel: +1 617 643 3314; E-mail: <shan@molbio.mgh.harvard.edu>.

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MAMP Signaling in Plant Innate Immunity

MAMP-mediated immunity is probably the first active response

of plants to microbe infection (Abramovitch et al. 2006; Chisholm et al. 2006). Recent studies discovered the common features of innate immunity in plants and animals including receptor perception, conserved MAPK cascades and the production of antimicrobial compounds (Ausubel 2005; Nurnberger et al. 2004). Unlike animals, plants lack the adaptive immune system, but they have elaborated and greatly expanded the innate immune system through the evolution of a large set of PRRs (Meyers et al. 2003). It seems that most plant cells have the ability to respond to MAMPs and activate convergent defense responses (Nurnberger et al. 2004; Abramovitch et al. 2006; Chisholm et al. 2006; Robatzek et al. 2006).

Distinct MAMP perception

Plants have evolved a variety of PRRs to perceive diverse microbial patterns (Meyers et al. 2003). Much effort has been made to isolate and characterize the MAMP receptors by using biochemical and genetic approaches. A 75-kDa soybean plasma membrane protein was purified as the binding protein for hepta-β-glucan, the cell wall component of oomycetes (Umemoto et al. 1997). Two proteins with extracellular leucine-rich repeat domain (LRR) were genetically identified as receptors for the fungal elicitor ethylene-inducing xylanase. It is interesting that although both proteins could bind to xylanase, only one protein could transmit downstream signaling (Ron and Avni 2004). The understanding of MAMP perception was greatly advanced with the isolation of the putative bacterial flagellin receptor FLS2 in *Arabidopsis*. FLS2 is a transmembrane receptor-like kinase (RLK) with extracellular LRR domain (Gomez-Gomez and Boller 2000). The discovery of LRR-RLK as a putative MAMP receptor in plants is significant because it shares certain similarity with Toll or Toll-like MAMP receptors in animals (Gomez-Gomez and Boller 2000; Nurnberger et al. 2004; Ausubel 2005). Recently, the specific and physical interaction between FLS2 and flg22, a conserved 22 amino acid peptide from flagellin, has been demonstrated by chemical cross-linking and immunoprecipitation (Chinchilla et al. 2006). There are a larger number of RLKs in plants, with more than 600 in *Arabidopsis* (Shiu and Bleecker 2003). It is not a surprise that additional MAMPs are also perceived by RLKs. Indeed, a targeted reverse-genetic approach has successfully identified another LRR-RLK as the receptor of bacterial elongation factor EF-Tu (Zipfel et al. 2006).

Recently, a chitin oligosaccharide elicitor binding protein (CEBiP) was identified in rice suspension-cultured cells. Molecular cloning of CEBiP reveals a signal peptide, two extracellular LysM motifs and a single transmembrane domain without any intracellular domain. RNA interference experiments in the rice cell line support the role of CEBiP in chitin signaling and transcriptional regulation (Kaku et al. 2006). The LysM motif is found among both prokaryotes and eukaryotes, and was proposed to function as a peptidoglycan- and chitin-binding site (Radutoiu et al. 2003). It is intriguing that two LysM-type receptor-like kinases are the putative receptors of Nod-factor, a lipochitin-oligosaccharide produced by rhizobial bacteria to establish a symbiosis with legume plants (Radutoiu et al. 2003). It is possible that the same type of receptors could perceive both MAMP signal for defense and rhizobial signal for symbiosis, although the downstream signaling and the outcome of plant-microbe interactions appear to be different in defense and symbiotic responses.

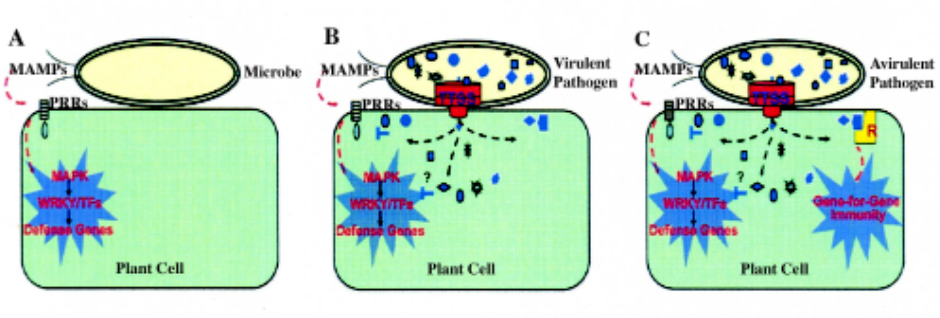

Figure 1. Dynamic co-evolution in plant-bacterium interactions.

(A) Plants detect microbe-associated molecular patterns (MAMPs) through pattern recognition receptors (PRRs) and activate defense responses including activation of MAPK cascade, WRKY and other transcription factors (TFs) and downstream defense genes. The MAMP-mediated defense contributes to plant immunity to most potential pathogens.

(B) Successful bacterial pathogens secrete a set of effector proteins through type III secretion system (TTSS) into plant cells to interfere with MAMP-mediated immunity at different steps. Thus, the bacteria are virulent to the plants, and the plants are diseased.

(C) Some plant species further evolved resistance (R) proteins to recognize the specific type III effectors and trigger gene-for-gene resistance. The bacteria are avirulent to the plants, and the plants are resistant.

Convergent MAMP signaling

Extensive studies have shown that direct exposure of purified MAMPs leads to change in cytoplasmic Ca^{2+} levels, production of reactive oxygen species (ROS) and nitric oxide (NO), activation of MAPK cascade and induction of defense genes in many plant species including *Arabidopsis*, parsley, tobacco and rice (Ligterink et al. 1997; Lee et al. 2001; Asai et al. 2002; Fellbrich et al. 2002; Navarro et al. 2004; Zeidler et al. 2004; Ramonell et al. 2005; Kaku et al. 2006). Although different MAMPs are probably perceived by distinct receptors, emerging evidence suggests that multiple MAMPs activate the convergent defense signaling. For example, the same set of MAPKs and defense genes are activated by bacterial elicitors flg22, HrpZ and EF-Tu, and the oomycete elicitor NPP1 (Lee et al. 2001; Asai et al. 2002; Fellbrich et al. 2002; He et al. 2006; Zipfel et al. 2006). Our recent study reveals that a large set of overlapping genes are induced or repressed by different MAMPs based on the global gene expression profiles in response to purified flg22, HrpZ, NPP1, Chitin and LPS (LS, PH and JS, unpublished data). The clear correlation was also observed in the genes induced or repressed by EF-Tu and flagellin (Zipfel et al. 2006). Thus, multiple MAMP signaling pathways appear to converge at a step upstream of MAPK cascade and transcriptional regulation.

As plants respond to more than one MAMP, it is possible that activation of multiple MAMP signaling pathways can enhance the amplitude of immune responses (Chisholm et al. 2006). The combined treatment with both EF-Tu and flagellin did not cause a synergistic effect on the extracellular alkalinization, MAPK activation and defense gene expression at the saturated dosage of both MAMPs (Zipfel et al. 2006). The results further support the convergent regulatory system activated by distinct MAMPs. This convergent signaling may ensure the efficient detection of pathogens by plants because the pathogens have evolved strategies to avoid host recognition of some specific MAMPs. However, the additive effect of EF-Tu and flagellin was observed when both MAMPs were applied at a low and unsaturated concentration (Zipfel et al. 2006). During natural infection, individual MAMPs detected by plants from nonpathogenic or pathogenic microbes may act together to reach the maximal defense capacity.

MAMP-meditated resistance

It has been shown in various animal systems that the immune responses activated by MAMPs could prevent disease progression. It is difficult to genetically dissect the importance of MAMP signaling in plant disease resistance, mainly because of the robustness of host immune responses activated by multiple MAMPs and functional redundancy of signaling components (Nurnberger et al. 2004). The causal link between MAMP-mediated immunity and plant disease resistance has been recently demonstrated by different approaches. Using a modified bacterial infection assay, it has been shown that the *fls2* mutant plants are more susceptible than wild-type plants to infection by a virulent pathogen *Pseudomonas syringae* pv. *tomato* DC3000. The treatment of wild-type but not the *fls2* mutant *Arabidopsis* plants with flg22 enhances resistance to *P. s. tomato* DC3000 (Zipfel et al. 2004). Moreover, activation of MAPK cascade and WRKY transcription factors in flg22 signaling confers resistance to both bacterial and fungal infections (Asai et al. 2002). Furthermore, the mutations in certain chitin responsive genes enhance plant susceptibility to the fungal pathogen, powdery mildew (Ramonell et al. 2005). All these studies provide the direct evidence of MAMP perception and signaling in plant innate immunity to virulent pathogens.

Most plants are nonhost to most potential pathogens. Nonhost immunity is the most prevalent form of plant defense against a broad spectrum of potential infections (Mysore and Ryu 2004). It has been unclear whether plant nonhost immunity relies on MAMP-mediated defense (Nurnberger et al. 2004). Recent studies show that the flagellin mutant of a *P. s. tabaci*, a naturally nonpathogenic bacterium to *Arabidopsis*, no longer activates the flagellin-inducible gene and it causes disease symptoms in *Arabidopsis* (Li et al. 2005). In transgenic *Arabidopsis*, suppression of MAMP signaling by a bacterial type III effector, AvrPto, enables the growth of two bacteria, *P. s. tabaci* and *P. s. phaseolicola*, to which *Arabidopsis* is a nonhost plant (He et al. 2006). Similarly, another bacterial effector AvrPtoB can also suppress MAMP signaling (He et al. 2006). Expression of AvrPtoB is sufficient to convert a nonpathogenic *P. s. phaseolicola* strain to a pathogenic one that causes disease in *Arabidopsis* plants (de Torres et al. 2006). All these data strongly suggest a direct molecular link between MAMP-mediated nonhost immunity and bacterial pathogenicity. It is likely that the robustness of species resistance or nonhost resistance is the result of multiple layers of preformed and inducible defense. New molecular mechanisms underlying nonhost resistance remain to be discovered.

Bacterial Virulence Effectors as Suppressors of Plant Innate Immunity

It has been observed that virulent bacteria can suppress plant defense responses, including the expression of defense genes, the biosynthesis of antimicrobial phytoalexins, the thickening of plant cell wall and the exudation of root-derived antimicrobial metabolites, in a TTSS dependent manner (Jakobek et al. 1993; Bais et al. 2005; Mudgett 2005; Nomura et al. 2005). The observations suggest that, reminiscent of animal pathogens, the key function of type III effectors in plant pathogens is to block host immunity. However, unlike animal bacterial

pathogens that secrete only a few type III effectors into host cells, the plant pathogens, such as *Pseudomonas*, secrete more than 40 effectors (Petnicki-Ocwieja et al. 2002; Chang et al. 2005). Thus, a major challenge following the identification of numerous type III effectors in plant pathogenic bacteria is to elucidate their molecular functions in plants. It has been shown that many type III effectors possess different enzymatic activities, which may be required for modifying plant proteins to promote pathogenicity (Mudgett 2005; Chisholm et al. 2006).

Suppressors of MAMP-mediated immunity

It is likely that many successful pathogens evolved effectors to suppress plant innate immunity (Abramovitch et al. 2006; Chisholm et al. 2006). The best characterized effectors as potential MAMP suppressors have been uncovered from the studies with bacterial pathogens. For example, transgenic expression of a bacterial effector AvrPto suppresses a cell wall-based defense marked by callose deposition and supports the multiplication of a TTSS deficient mutant in *Arabidopsis* (Hauck et al. 2003). The study of two *P. syringae* type III effectors, AvrRpt2 and AvrRpm1, has revealed their distinct ability to inhibit flg22-induced GST6 expression and callose deposition (Kim et al. 2005). Transient expression of HopAI1 and eight other effectors from a pathogenic bacterium in *Arabidopsis* cells suppresses flagellin-induced *NHO1* expression. *NHO1* encodes a glycerol kinase and is important for *Arabidopsis* nonhost immunity to some bacterial strains (Li et al. 2005). However, it remains unclear whether any of these effectors have the potential to suppress nonhost immunity. Heterologous expression of AvrPto, AvrE, HopPtoM, HopPtoF and HopPtoG in a nonpathogen *P. fluorescens* suppresses the reduced vascular staining, a defense response induced by flagellin, nonpathogenic and TTSS-deficient bacteria (Oh and Collmer 2005). Type III effectors of *Xanthomonas* can also suppress plant defense and LPS responses (Keshavarzi et al. 2004; Metz et al. 2005).

Applying a cell-based genetic screen, two specific type III effectors, AvrPto and AvrPtoB, have been identified as similar potent suppressors of early immune responses triggered by diverse MAMPs, including flg22, HrpZ and NPP1. This finding is surprising because AvrPto and AvrPtoB have previously been shown to mediate distinct virulence activities, for example, AvrPto suppresses cell wall-based defense while AvrPtoB inhibits defense-associated cell death (Abramovitch et al. 2003; Hauck et al. 2003). Mutagenesis and functional analysis of AvrPtoB uncovers two domains with separable virulence functions. Its C-terminal domain carries an E3 ubiquitin ligase activity required for inhibition of defense-associated cell death and the N-terminal region shares the MAMP suppressor function with AvrPto (He et al. 2006; Janjusevic et al. 2006). Epistasis study suggests that AvrPto and AvrPtoB suppress multiple MAMP signaling upstream of MAPK cascade at the plasma membrane linked to the receptors (He et al. 2006). The effect of AvrPto and AvrPtoB in early MAMP signaling immediately after signal perception is unique and has not been observed for many other effectors examined. Thus, different mechanisms are used by individual effectors to block plant innate immunity mediated by MAMPs. Using a nonpathogenic bacterium *P. s. phaseolicola* RW60 as a delivery vehicle, AvrPtoB, but not other AvrPtoB homologues, has also been identified as a suppressor of *Arabidopsis* basal defense presumably mediated by MAMPs. Surprisingly, AvrPto was not identified in this screen (de Torres et al. 2006). It is probably caused by the restricted bacteria-host interaction specificity for these two effectors. For example, both AvrPto and AvrPtoB recognize tomato Pto when they are delivered by *P. s. tomato* strain PT11, but AvrPtoB is not functional in *P. s. tomato* strain T1 (Kim et al. 2002). It is interesting that strong AvrPtoB virulence on *Arabidopsis* was co-segregated with the absence of the *FLS2* gene, which encodes the flagellin receptor. However, AvrPtoB also possesses weak virulence effect in *Arabidopsis* accession Col and Ler, both of which have a functional *FLS2* gene (de Torres et al. 2006). This suggests that FLS2 may function quantitatively differently in different *Arabidopsis* genetic backgrounds.

Virulence targets in plants

With the identification of type III virulence effectors as suppressors of host immunity, the field is quickly moving forward to the isolation of their plant targets. Two recent studies show that different effectors interact with specific plant targets to enhance plant susceptibility to bacterial pathogens. A conserved *P. syringae* effector HopM1 targets and destabilizes host protein AtMIN7 to promote disease symptoms. Significantly, the increased susceptibility of *min7* knockout *Arabidopsis* plants is specific to the *P. syringae* DCEL mutant without the *hopM1* gene, but not to the pathogenic bacterium *P. s. tomato* DC3000 or the TTSS mutant (Nomura et al. 2006). It appears that multiple host components are targeted by HopM1 for parasitism because transgenic plants with HopM1 expression are more susceptible than *min7* knockout plants to the infection by *P. syringae* DCEL mutant. Using global gene expression profiling, the rice *Os8N3* gene has been isolated based on its induction by a virulent bacterial pathogen linked to a type III effector gene *pthXo1* (Yang et al. 2006). Rice plants with silenced *Os8N3* gene expression are resistant to the infection by the bacterium carrying *pthXo1*. It is interesting that *Os8N3* gene is *xa13,* a rice recessive resistance gene to *Xanthomonas oryzae* pv. *oryzae* (Chu et al. 2006). Thus, the identification of virulence targets or host susceptibility genes provides the molecular basis for the action of recessive resistance genes.

Turning Pathogens from Virulence to Avirulence

Abundant evidence now supports the primary function of type III effectors as suppressors of host immunity. However, in the case of plant bacterial pathogens, many type III effectors were originally identified as so-called avirulence factors that turn virulent strains into avirulent ones. During coevolution with pathogens, individual plants developed highly specific resistance gene products to recognize specific type III effectors and trigger potent gene-for-gene resistance that leads to the hypersensitive response (HR), a localized programmed cell death (Abramovitch et al. 2006; Chisholm et al. 2006). For example, the virulent pathogen *P. s. tomato* DC3000 evolved or acquired type III effectors including AvrPto and AvrPtoB to suppress MAMP-meditated immune responses. To survive, tomato but not *Arabidopsis* evolved the unique *Pto* and/or *Prf* gene products to recognize AvrPto and AvrPtoB and trigger specific gene-for-gene resistance (Abramovitch et al. 2006; He et al. 2006). Several excellent reviews on the mechanisms of gene-for-gene-mediated resistance have been recently published (Abramovitch et al. 2006; Chisholm et al. 2006; Takken et al. 2006).

However, the disarmed pathogens did not stop evolving new strategies to evade plant defense or creative weapons to attack plants. The gene-for-gene-based defense is usually not durable because of the emergence of new virulent pathogen strains that are no longer recognized by plant *R* genes (Crute and Pink 1996). In an interesting experiment, an avirulent bacterial strain becomes a virulent one after being repeatedly recovered from the plant tissue undergoing the gene-for-gene response and cycled for five passages (Pitman et al. 2005). The loss of avirulence in bacteria is caused by the deletion of a genomic island that contains an avirulence gene *avrPphB*, which is recognized by plant resistance gene *R3*. In another scenario, the mutation of type III effectors can avoid the detection by plant R proteins, while still keep the virulence function. For instance, the virulence and avirulence activities of some type III effectors, such as AvrPto, are separable in structure (Shan et al. 2000). Moreover, a large number of type III effectors can suppress gene-for-gene-mediated responses, especially HR, in plants (Abramovitch et al. 2003; Jamir et al. 2004, also reviewed by Alfano and Collmer 2004; Mudgett et al. 2005; Nomura et al. 2005; Abramovitch et al. 2006; Chisholm et al. 2006). Not surprisingly, plants need to develop new resistance genes or other strategies to win this endless warfare between plants and pathogens.

Conclusions and Future Directions

During co-evolution with pathogens, plants evolved two types of innate immunity, the MAMP-mediated immunity and the gene-for-gene-mediated immunity. Their molecular overlaps and distinctions remain to be resolved. In the future, the identification of other MAMP receptors and the discovery of early MAMP signaling upstream or independent of MAPK cascades will shed new light on the molecular mechanisms of convergent MAMP signaling in plant innate immunity. Although extensive genetic studies have revealed the molecular identity of more than 40 plant *R* genes, better understanding of gene-for-gene resistance requires new approaches to dissect the signaling pathways acting downstream of R proteins. Type III effectors have been successfully used by pathogenic bacteria to suppress multiple plant defense responses at different steps. It appears that different type III effectors use specific mechanisms for parasitism. The identification of their plant targets will help to elucidate detailed molecular actions of individual effectors in promoting pathogenicity. Finally, knowledge about the molecular mechanisms of plant immunity and bacterial pathogenicity will eventually help the incorporation of effective and durable resistance in crop plants by enhancing the active defense responses or intervening the disease processes.

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