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SI PLANT BIOTIC INTERACTIONS

Constant vigilance: plant functions guarded by resistance proteins

Jianbin Su[1], Benjamin J. Spears[1], Sang Hee Kim[2] and Walter Gassmann[1,*]

[1]*Division of Plant Sciences, C.S. Bond Life Sciences Center and Interdisciplinary Plant Group, University of Missouri, Columbia, MO 65211, USA, and*

[2]*Division of Applied Life Science (BK 21 Plus Program), Plant Molecular Biology and Biotechnology Research Center, Division of Life Science, Gyeongsang National University, Jinju 52828, Korea*

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*For correspondence (e-mail gassmannw@missouri.edu).

SUMMARY

Unlike animals, plants do not have an adaptive immune system and have instead evolved sophisticated and multi-layered innate immune mechanisms. To overcome plant immunity, pathogens secrete a diverse array of effectors into the apoplast and virtually all cellular compartments to dampen immune signaling and interfere with plant functions. Here we describe the scope of the arms race throughout the cell and summarize various strategies used by both plants and pathogens. Through studying the ongoing evolutionary battle between plants and key pathogens, we may yet uncover potential ways to achieve the ultimate goal of engineering broad-spectrum resistant crops without affecting food quality or productivity.

Keywords: effector-triggered immunity, effectors, plant immunity, plant pathogens, resistance genes.

INTRODUCTION

Plants are exposed to a wide variety of potential biotic stresses, but only a limited number of pathogens and pests can successfully invade host plants. Plants have developed versatile strategies in the form of an innate immune system to effectively protect themselves against pathogens (Chisholm *et al.*, 2006; Dangl *et al.*, 2013; Cao *et al.*, 2017). Because this review will mostly focus on how the study of pathogens has informed our understanding of plant cellular functions, we will limit our discussion to biotrophs, which manipulate and require a living cell (Glazebrook, 2005; Prusky *et al.*, 2013; Niks *et al.*, 2015). The plant immune system that has evolved to combat biotrophs consists of two layers (Jones and Dangl, 2006), PAMP/MAMP (pathogen/microbe-associated molecular pattern)-triggered immunity (PTI/MTI) and effector-triggered immunity (ETI). In the first layer, cell surface localized pattern recognition immune receptors (PRRs) respond to the presence of PAMPs/MAMPs, which represent conserved pathogen-derived non-self molecules such as bacterial flagellin or chitin from fungal cell walls. Upon sensing of PAMPs/MAMPs, these PRRs initiate a hierarchical series of immune responses, including MAPK activation, production of reactive oxygen species, transcriptional reprogramming, and antimicrobial compound biosynthesis, which function cooperatively to limit pathogen growth (Monaghan and Zipfel, 2012; Schwessinger and Ronald, 2012; Zipfel and Oldroyd, 2017).

As a result of the evolutionary arms race between plants and pathogens, successful invaders have found ways to hinder the plant immune tactics by deploying effectors. These effectors are delivered either to the extracellular space to halt the recognition of PAMPs/MAMPs, or they are injected into host cells where they target components of the host immune system to suppress immunity or components of host physiology in general to promote virulence (Block and Alfano, 2011; Deslandes and Rivas, 2012; Feng and Zhou, 2012). The resulting improved pathogen persistence and growth to the detriment of the host is described as effector-triggered susceptibility (ETS) (Jones and Dangl, 2006).

To suppress ETS, plants evolved mechanisms to recognize pathogen effectors and initiate immune response, called ETI (Jones and Dangl, 2006; Cui *et al.*, 2010). ETI has formerly been described by the gene-for-gene hypothesis

formulated by Flor, according to which immune responses are genetically determined by the presence or absence of plant resistance (*R*) genes and cognate pathogen avirulence (*Avr*) genes (Flor, 1971). The largest class of *R* genes encode intracellular proteins which harbor a NB-ARC (Nucleotide Binding site and ARC subdomain originating in Apaf-1, R proteins, and CED-4) domain and leucine-rich repeats (LRRs). Therefore, plant R proteins and their animal analogs containing these structural features were named NLRs (Ting *et al.*, 2008; Jones *et al.*, 2016). Usually, plant NLRs can be grouped into two families based on their N-terminal domains, the CC (coiled-coil)-NBS-LRR (CNL) family and the TIR (Toll/interleukin-1 receptor)-NBS-LRR (TNL) family, the N-termini of which show structural homology to the cytoplasmic domain of animal Toll-like receptors (McHale *et al.*, 2006). It is worth noting that not all NLRs contain an N-terminal CC or TIR domain. For example, the tomato NLR protein Prf has a distinct N-terminal domain (Salmeron *et al.*, 1996). R proteins can detect effectors directly or indirectly to initiate a strong immune response, which is often associated with a rapid form of programmed cell death called the hypersensitive response (HR). In direct recognition, R proteins bind their cognate effectors as a receptor would bind a ligand, whereas in indirect recognition the R protein responds to the alteration or manipulation of a host protein by an effector. Indirect recognition of effectors by NLRs was first proposed as a guard hypothesis describing the functional interaction in tomato between the kinase Pto, a target of the bacterial effectors AvrPto and AvrPtoB, and the NLR Prf (van der Biezen and Jones, 1998).

These aspects of the plant immune system have been covered by several excellent reviews (Jones and Dangl, 2006; Cui *et al.*, 2010; Tsuda and Katagiri, 2010; Schwessinger and Ronald, 2012; Spoel and Dong, 2012; Bigeard *et al.*, 2015; Li *et al.*, 2016). Because a wealth of research has shown that pathogen effectors target a diversity of biological processes (Xin and He, 2013), R proteins can be considered to be signposts directing our attention to important and sometimes previously unknown plant functions. In this review, we will therefore focus on examples how effectors interfere with and manipulate various host biological processes throughout the cell that are important for plant health, and how these plant functions are guarded by R proteins.

THE CELL UNDER SIEGE: BATTLE IN THE APOPLAST

Plant biotrophic pathogens, whether they are bacteria, oomycetes, fungi, nematodes or insects, remain in the apoplast where they absorb nutrients and proliferate. The apoplastic space represents the first battlefield for plant–pathogen interactions (Doehlemann and Hemetsberger, 2013; Giraldo and Valent, 2013; Rovenich *et al.*, 2014; Lo Presti *et al.*, 2015). Normal plant physiology renders the apoplast inhospitable for microbial invaders. In addition, plants secrete several defense compounds, such as papain-like cysteine proteases (PLCPs), which play essential roles in plant immunity (van Esse *et al.*, 2008; Shabab *et al.*, 2008; Misas-Villamil *et al.*, 2016). In the absence of invaders, these PLCPs exist in an inactive state through association with cystatins to form a relatively stable complex (Benchabane *et al.*, 2010). Upon detection of microbial invaders, these PLCPs are activated to degrade pathogens or play a role in the intracellular response (Misas-Villamil *et al.*, 2016). Simultaneously, detection of invaders by plants also triggers a burst of reactive oxygen species and accumulation of phytoalexins in the apoplast (Monaghan and Zipfel, 2012; Doehlemann and Hemetsberger, 2013; Zipfel and Oldroyd, 2017). Successful pathogens have developed sophisticated mechanisms to antagonize host threats, including the secretion of an array of effectors into the host apoplast (Doehlemann and Hemetsberger, 2013; Giraldo and Valent, 2013; Rovenich *et al.*, 2014; Lo Presti *et al.*, 2015). For example, Avr2, an effector secreted by *Cladosporium fulvum*, can inhibit multiple extracellular PLCPs, including the major PLCP PIP1 in tomato (Figure 1a; Shabab *et al.*, 2008; van Esse *et al.*, 2008). In an evolutionary counter-measure, plants developed a 'decoy' strategy to recognize Avr2 and induce an immune response. The mechanism involves RCR3, a paralog of PIP1 expressed at low levels, which functions as a decoy to trap Avr2. Inhibition of RCR3 protease activity by Avr2 triggers Cf-2-dependent disease resistance (Dixon *et al.*, 1996; Kruger *et al.*, 2002; Rooney *et al.*, 2005; van Esse *et al.*, 2008; Shabab *et al.*, 2008).

It is now clear that both hosts and pathogens have adopted the decoy strategy into their repertoire. A fascinating example of such a co-evolutionary arms race is the interference of GmGIP1-mediated soybean resistance by *Phytophthora sojae* (Ma *et al.*, 2015, 2017). As is shown in Figure 1(b) the apoplastic soybean protein GmGIP1 contributes to resistance by directly binding to and inhibiting the activity of PsXEG1, a xyloglucan-specific endoglucanase secreted by *Phytophthora sojae* that degrades the plant cell wall during infection. However, *P. sojae* also secretes a paralog of PsXEG1, named PsXLP1, which exhibits reduced endoglucanase activity but higher binding affinity towards GmGIP1. Consequently, binding of PsXLP1 to GmGIP1 protects the activity of PsXEG1 and thus promotes virulence. Another interesting pathogen strategy to suppress host immunity is the case of *C. fulvum* effector Ecp6. Ecp6, an apoplastic effector with three lysine motif (LysM) domains, can bind chitin oligomers, a potent PAMP derived from fungal cell walls, and thus helps the pathogen escape detection by host PRRs (de Jonge *et al.*, 2010).

Due to technical limitations, our knowledge of the apoplast-localized secretome of both hosts and pathogens is still very limited (Gupta *et al.*, 2015). Interestingly, a recent

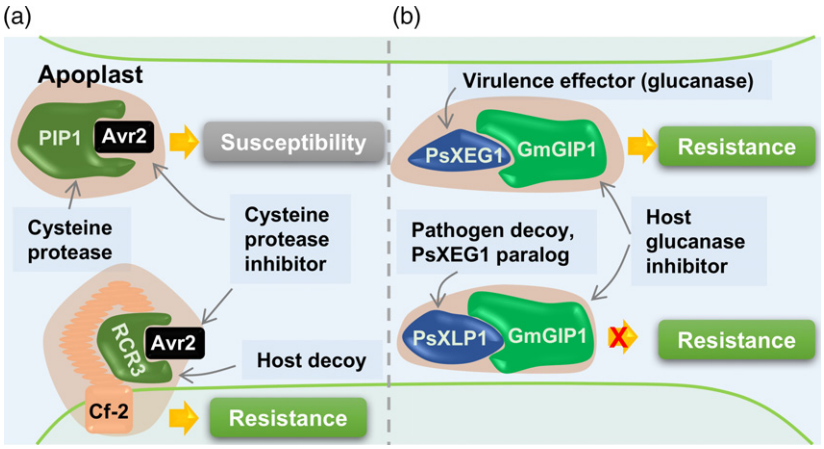

Figure 1. Guarding the apoplast, site of an enzyme-inhibitor arms race.
(a) Model for recognition of *Cladosporium fulvum* effector Avr2 by Cf2 and RCR3 in tomato. PIP1 is the major protease in the apoplast degrading proteins of invading pathogens. Avr2 functions as a protease inhibitor, targeting PIP1 to promote susceptibility. RCR3, a paralog of PIP1 expressed as low levels, can also be targeted by Avr2. Inhibition of RCR3 protease activity by Avr2 triggers Cf-2-dependent resistance.
(b) Suppression of soybean defenses by *Phytophthora sojae* effector PsXLP1. GmGIP1 contributes to resistance by directly binding to and inhibiting the activity of *Phytophthora sojae* effector PsXEG1, a cell wall degrading enzyme. PsXLP1, a paralog of PsXEG1 exhibiting reduced endoglucanase activity but higher binding affinity towards GmGIP1, protects the activity of PsXEG1 by competitively binding to GmGIP1.

study has shown that extracellular vesicles carrying stress-related proteins are induced upon pathogen infection, indicating an important role for these vesicles in plant immunity (Rutter and Innes, 2017). Developing new tools for secretome analysis during host-pathogen interaction would be highly useful in characterizing the battle between hosts and pathogens in the apoplast.

R PROTEINS GUARD PLASMA MEMBRANE PATTERN RECOGNITION RECEPTORS

In addition to defense compounds in the apoplast, plasma membrane-localized PRRs recognize common PAMPs/MAMPs to induce an immune response. PRRs are a family of highly conserved transmembrane proteins consisting of an extracellular domain, usually a LysM or LRR domain, and an intracellular kinase domain. The LysM containing PRRs OsCEiBP1 in rice and AtLYK4/LYK5 in Arabidopsis mediate the recognition of fungal chitin (Kaku *et al.*, 2006; Cao *et al.*, 2014). OsCEBiP1 and AtLYK4/LYK5 lack the intracellular kinase domain. Data showed that perception of chitin induces their interaction with CERK1, a LysM containing protein with an intracellular kinase domain, to transduce signals into the cytoplasm (Miya *et al.*, 2007; Wan *et al.*, 2008; Shimizu *et al.*, 2010; Cao *et al.*, 2014; Hayafune *et al.*, 2014). The LRR containing PRRs FLS2 and EFR recognize bacterial flagellin and elongation factor EF-Tu, respectively (Gomez-Gomez *et al.*, 1999; Gomez-Gomez and Boller, 2000; Zipfel *et al.*, 2006). Upon perception of their corresponding PAMPs, FLS2 and EFR form a receptor complex with BAK1 (Chinchilla *et al.*, 2007; Heese *et al.*, 2007), a LRR receptor-like kinase originally identified as a co-receptor of the brassinosteroid receptor BRI1 (Li and Chory, 1997). The activation of the FLS2-BAK1 or EFR-BAK1 complex leads to the phosphorylation and activation of BIK1 (BOTRYTIS-INDUCED KINASE 1) (Veronese *et al.*, 2006), a receptor-like cytoplasmic kinase (RLCK). BIKI functions downstream of several PRR complexes that play a central role in PTI (Lu *et al.*, 2010; Zhang *et al.*, 2010; Liu *et al.*, 2013). Protein turnover and its kinase activity are finely regulated by protein phosphorylation and dephosphorylation, which are mediated by CIPK28 and PP2C38, respectively (Monaghan *et al.*, 2014; Couto *et al.*, 2016). Perhaps due to the importance of BIK1 in PTI, it has also been identified as a common target of several unrelated pathogen effectors.

The AvrPphB effector is secreted by *Pseudomonas syringae* and has cysteine protease activity (Shao *et al.*, 2003; Zhu *et al.*, 2004). BIK1 and its close homolog PBS1 were shown to be cleaved by AvrPphB (Zhang *et al.*, 2010). Cleavage of PBS1-like (PBL) kinases results in inhibition of PTI (Figure 2a). To counteract this immune suppression, the Arabidopsis NLR protein RPS5 indirectly recognizes the cleavage of PBS1 by AvrPphB1 (Shao *et al.*, 2003; Ade *et al.*, 2007; Zhang *et al.*, 2010; Qi *et al.*, 2014). Recognition of the cleavage of PBS1 leads to R protein activation and a strong immune response. Interestingly, PBS1 does not have any detectable function in PTI and therefore represents one of the clearest examples of a decoy in the plant immune system, in this case to detect cleavage of BIK1-related kinases by unrelated effectors (Zhang *et al.*, 2010). This feature of PBS1 was recently exploited to engineer new RPS5 recognition specificities targeting a range of effectors exhibiting protease activity (Kim *et al.*, 2016).

Another effective decoy strategy to protect BIK1 is ZAR1-mediated detection of uridylylation of PBL2, another homolog of BIK1 (Figure 2b). AvrAC, an effector from

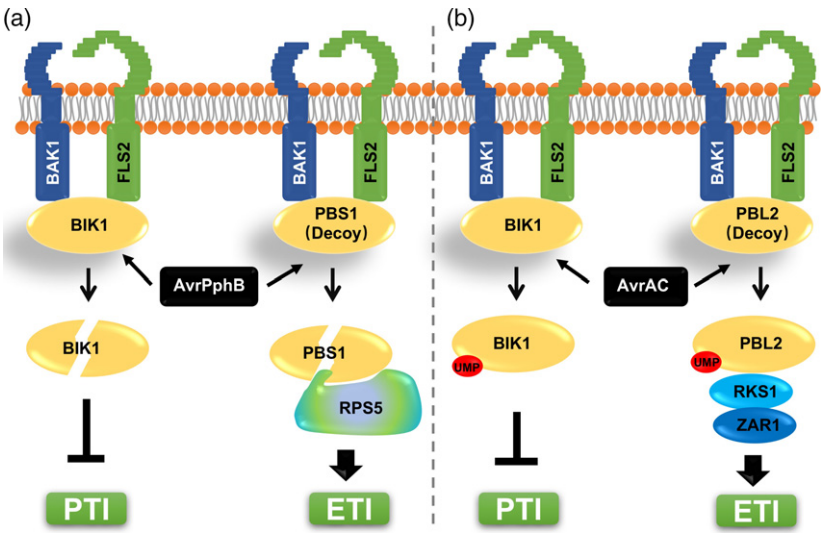

Figure 2. Guarding initial PTI signaling events via decoys of the central immune regulator BIK1.
(a) *Pseudomonas syringae* type III effector AvrPphB exhibits cysteine protease activity. Cleavage of BIK1 by AvrPphB leads to suppression of PTI, while cleavage of its close homolog PBS1 causes RPS5-dependent ETI. PBS1 has no detectable function in PTI, and is thought to protect BIK1 as a host decoy.
(b) *Xanthomonas campestris* type III effector AvrAC uridylylates BIK1 and suppresses BIK1-induced PTI. The uridylylation of PBL2, a homolog of BIK1 and host decoy, can be recognized by a protein complex formed by the pseudokinase RKS1 and the R protein ZAR1, resulting in an ETI response.

Xanthomonas campestris, uridylylates BIK1 and suppresses BIK1-induced basal defense responses (Feng *et al.*, 2012; Guy *et al.*, 2013). AvrAC-mediated PBL2 uridylylation is detected by a protein complex formed by RKS1, a pseudokinase of the ZRK family, and the NLR ZAR1 (Wang *et al.*, 2015b). ZAR1 was originally identified to recognize the type III effector HopZ1a, which shows acetyltransferase activity (Lewis *et al.*, 2010). ZAR1-mediated HopZ1a recognition requires the pseudokinase ZED1, which belongs to the RLCK XII-2 subfamily (Lewis *et al.*, 2013). Because acetylation of ZED1 by HopZ1a causes ZAR1 activation, it is reasonable to speculate that the pseudokinase ZED1 functions as a decoy to protect its close homologs from acetylation by HopZ1a. Due to the importance of BIK1 and possibly other RCLKs in PTI, it is not surprising that different homologs of BIK1 in the RLCK family have evolved as decoys to detect specific effector strategies attacking the immune function of BIK1.

R PROTEINS GUARD RIN4 AT THE INTERIOR SIDE OF THE PLASMA MEMBRANE

RIN4 (RPM1-INTERACTING PROTEIN 4), a negative regulator of innate immune responses, is targeted by several unrelated pathogen effectors and is guarded by R proteins (Mackey *et al.*, 2002; Belkhadir *et al.*, 2004; Kim *et al.*, 2005). AvrRpm1 and AvrB induce phosphorylation of RIN4, leading to activation of the R protein RPM1 (RESISTANCE TO PSEUDOMONAS SYRINGAE PV. MACULICOLA 1) (Mackey *et al.*, 2002). AvrRpt2, a type III effector exhibiting cysteine protease activity, cleaves RIN4 and triggers the activation of the R protein RPS2 (RESISTANT TO PSEUDOMONAS SYRINGAE 2) (Axtell and Staskawicz, 2003; Mackey *et al.*, 2003). RIN4 was demonstrated to function as a phosphoswitch in the transition of PTI, ETS and ETI (Figure 3) (Chung *et al.*, 2014). While basal phosphorylation of RIN4 at Ser^{141} and Thr^{166} keeps it at resting state, hyperphosphorylation of RIN4 at Ser^{141} induced by flg22 contributes to derepression of PTI, whereas AvrB- or AvrRpm1-induced hyperphosphorylation at Thr^{166} promotes ETS. The accumulation of Thr^{166}-phosphorylated RIN4, in turn, activates RPM1 to trigger ETI.

The RIN4 model nicely exemplifies both the detection of a novel immune regulator by identifying effector targets, and the evolutionary strategies of plants to protect themselves against pathogens by deploying NLRs. Precise sensing of effector-induced RIN4 modification also offers an answer to the riddle of how a limited number of NLRs may be able to detect a large number of structurally unrelated effectors, allowing the plant to respond efficiently and specifically to pathogen threats. Elucidating how the different phosphorylation states of RIN4 modulate PTI and ETS on a molecular level should provide additional insights into the regulation of the plant immune system.

SUMM2 GUARDS THE MEKK1–MKK1/MKK2–MPK4 CASCADE

BIK1 activation leads to a ROS burst and MAPK activation. Direct phosphorylation of the plasma membrane-localized NADPH oxidase RBOHD by BIK1 (Kadota *et al.*, 2014; Li *et al.*, 2014b), and in a parallel pathway by CPK5 (Dubiella *et al.*, 2013), induces an apoplastic ROS burst. Moreover, BIK1 activation also causes downstream activation of two distinct MAPK cascades, the MEKK1–MKK1/MKK2–MPK4 cascade and the MKK4/MKK5–MPK3/MPK6 cascade, each with different downstream products and responses. MAPK cascades are conserved among eukaryotes, playing a central role in both plant and animal innate immunity (Meng and Zhang, 2013; Gur-Arie and Rosenshine, 2015).

Unrelated effectors from different human pathogens with distinct activities, including phosphatases, methyl-

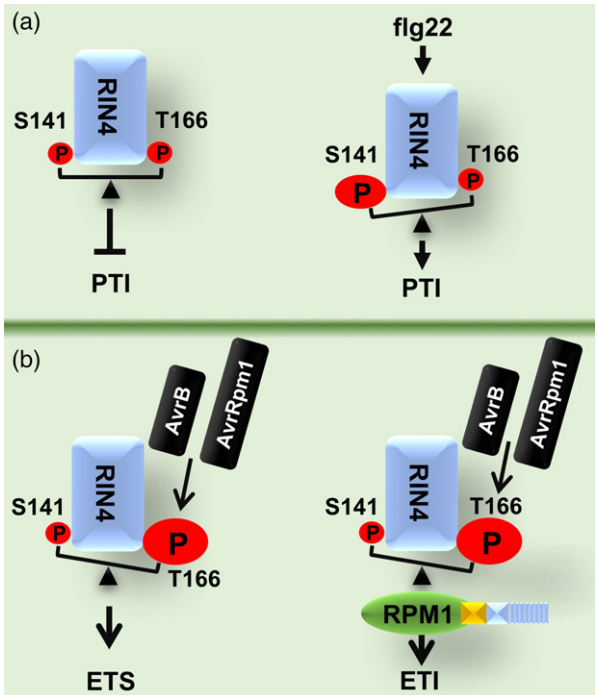

Figure 3. RPM1 guards the plant phosphoswitch RIN4.
(a) Basal level phosphorylation of RIN4 at S141 and T166 suppress PTI. The PAMP flg22 induces hyperphosphorylation of RIN4 at S141 and leads to derepression of PTI.
(b) AvrB and AvrRpm1 cause enhanced RIN4 phosphorylation at T166, which triggers ETS. In contrast, detection of T166 hyperphosphorylation of RIN4 by RPM1 activates ETI.

transferases, acetyltransferases, and proteases were found to disturb MAPK cascades (Gur-Arie and Rosenshine, 2015). Targeting MAPK signaling cascades by pathogen effectors seems to be a common strategy to suppress innate immunity. The *P. syringae* type III effector HopF2 was found to block MKK5 activation through its ADP-ribosyltransferase activity (Wang *et al.*, 2010). Another *P. syringae* effector, HopAI1, was shown to interact and inactivate both MPK4 and MPK3/MPK6 cascades through its phosphatase activity (Zhang *et al.*, 2007, 2012). Inhibition of MPK4 activity by HopAI1 triggers R protein SUMM2-dependent ETI (Zhang *et al.*, 2012). Further studies have suggested that SUMM2 may guard the MPK4 branch by monitoring the phosphorylation status of MPK4 substrates, such as MEKK2, the mRNA decapping protein PAT1, and CRCK3 (CALMODULIN BINDING RECEPTOR-LIKE CYTOPLASMIC KINASE 3) (Figure 4) (Kong *et al.*, 2012; Su *et al.*, 2013; Roux *et al.*, 2015; Zhang *et al.*, 2017).

It is interesting to note that mutants of the MEKK1–MKK1/MKK2–MPK4 cascade such as *mekk1*, *mkk1 mkk2*, and *mpk4*, all show autoimmune phenotypes and enhanced resistance against *Pseudomonas* (Suarez-Rodriguez *et al.*, 2007; Gao *et al.*, 2008; Qiu *et al.*, 2008), while mutants of the MKK4/MKK5–MPK3/MPK6 pathway (*mkk4 mkk5* and *mpk3 mpk6*) show compromised resistance (Su *et al.*, 2017). Constitutive activation of MPK3/MPK6 leads to HR-like cell death and accumulation of defensive phytoalexins (Ren *et al.*, 2002, 2008); however, constitutive MPK4 activation compromises both PTI and ETI mediated by the TNL proteins RPS4 and RPP4 (Berriri *et al.*, 2012). Based on these observations, the MPK4 and MPK3/MPK6 branches were proposed to function oppositely in innate immunity, in which the MPK4 branch negatively and the MPK3/MPK6 branch positively regulate plant immunity (Berriri *et al.*, 2012). However, the notion of MPK4 as a negative regulator in plant immunity was challenged upon the identification of SUMM2. In a guard model, MPK4 activity was proposed to be guarded by the R protein SUMM2, with inhibition of MPK4 activity leading to SUMM2 activation, i.e. the autoimmune phenotype of *mekk1*, *mkk1 mkk2*, and *mpk4* would be caused by SUMM2 activation. The MPK4–SUMM2 functional interaction illustrates that care must be taken when mutant autoimmune phenotypes are interpreted as evidence for a function as a negative regulator of the affected gene (Malinovsky *et al.*, 2010; Palma *et al.*, 2010; Rodriguez *et al.*, 2016). Because the activation loops of MPK4 and MPK3/MPK6 are highly conserved and are both targeted by a common effector, HopAI1, it is possible that SUMM2 also guards the MPK3/MPK6 branch through monitoring MPK4 activity (Figure 4).

A SPY IN THE RANKS: AN INTEGRATED DECOY STRATEGY TO PROTECT WRKY TRANSCRIPTION FACTORS IN THE NUCLEUS

The decoy model of indirect effector recognition by NLRs initially described decoy proteins that interact with NLRs. An evolutionary elaboration on this model with an increasing number of examples are paired NLRs, in which one NLR possesses a fusion to a decoy domain ('integrated decoy') for sensing the presence of effectors, and the other NLR having the canonical domains of an NLR as an executor. The genes encoding the TNL class resistance proteins RPS4 (RESISTANCE TO *PSEUDOMONAS SYRINGAE* 4) and RRS1 (RESISTANCE TO *RALSTONIA SOLANACEARUM* 1) are closely positioned next to each other in a head-to-head configuration and function together to recognize the bacterial effectors AvrRps4 from *P. syringae* and PopP2 from *Ralstonia solanacearum* and an uncharacterized effector from the fungus *Colletotrichum higginsianum* (Gassmann *et al.*, 1999; Deslandes *et al.*, 2002; Birker *et al.*, 2009; Narusaka *et al.*, 2009). RRS1 contains a WRKY DNA-binding domain at its C-terminus (Deslandes *et al.*, 2002). The WRKY domain of RRS1 is required for AvrRps4 and PopP2 recognition (Williams *et al.*, 2014). PopP2 was shown to acetylate lysine residues in the WRKY domain of several defense-related WRKY transcription factors and to suppress basal immune responses by interfering with DNA-binding activity (Le Roux *et al.*, 2015; Sarris *et al.*,

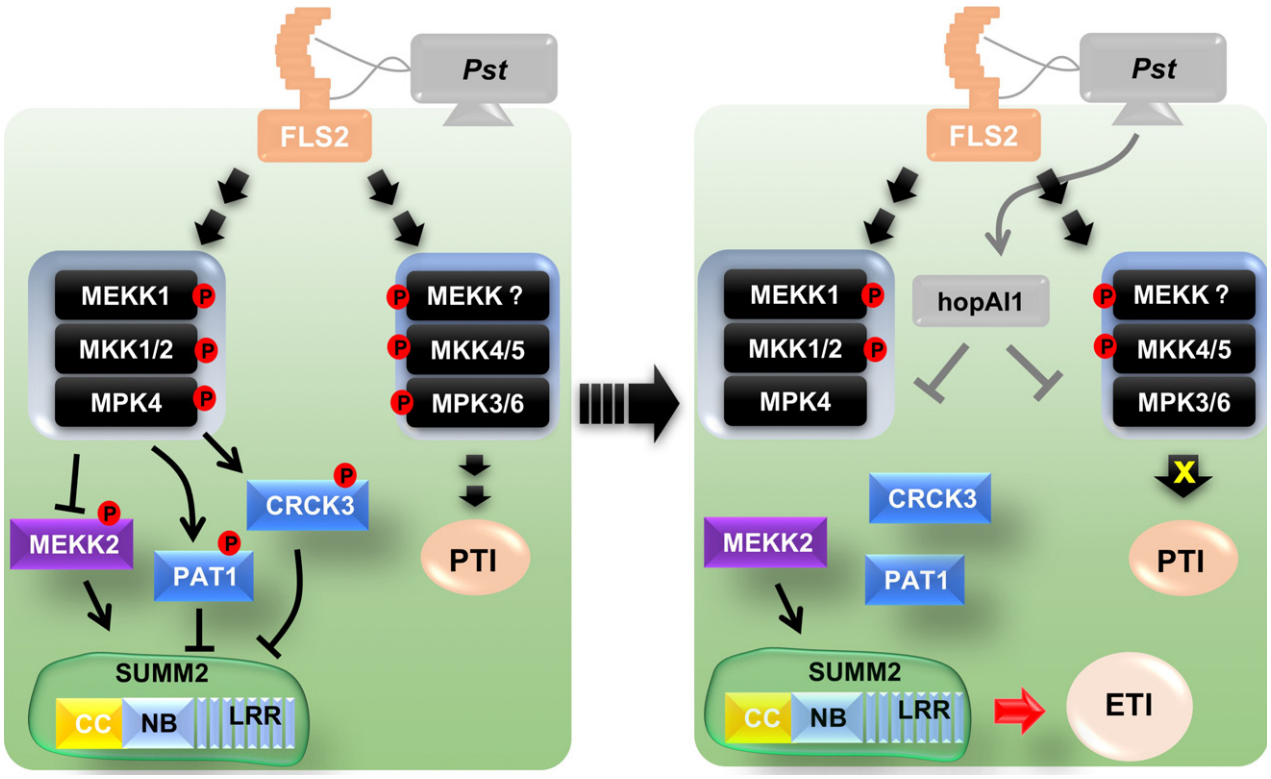

Figure 4. Guarding of the MAPK signal transduction pathway by SUMM2.
Perception of PAMPs/MAMPs by cell surface localized PRRs activates two branches of MAPK cascades in plants, the MEKK1–MKK1/MKK2–MPK4 and the MEKK?–MKK4/MKK5–MPK3/MPK6 cascade. The MKK4/MKK5–MPK3/MPK6 branch contributes to PTI, while the MEKK1–MKK1/MKK2–MPK4 branch is guarded by SUMM2 through monitoring of MPK4 substrates. *Pseudomonas syringae* type III effector HopAI1 inactivates MPK3/4/6 through dephosphorylation of the activation loop. Inhibition of MPK3/MPK6 causes impaired PTI, while inhibition of MPK4 induces SUMM2 activation and ETI. Just as BIK1 homologs act as decoys for effector activity at the plasma membrane, so may the MAPK4 cascade function as a decoy for MPK3/MPK6.

2015). Acetylation of the equivalent residues in the WRKY domain of RRS1 is thought to lead to a conformational change in the RPS4-RRS1 pair, which in turn activates ETI (Figure 5) (Le Roux *et al.*, 2015; Sarris *et al.*, 2015). Interestingly, RRS1 at resting state is required to hold RPS4 in an off state (Narusaka *et al.*, 2016). Even though AvrRps4 interacts with the WRKY domain of RRS1 as well, a thorough mechanism explaining how AvrRps4 might modify the integrated decoy domain and whether this interaction is direct are both currently not understood.

A founding member of the integrated decoy or sensor strategy of effector recognition has also been described in rice, in which the RGA4 and RGA5/Pik-1 CNL pair evolved recognition specificity for the *Magnaporthe oryzae* effectors AVRPia and AVRPik (Cesari *et al.*, 2013). These unrelated effectors interact directly with the RATX1/HMA domain of RGA5/Pik-1. Interestingly, while it is impossible to predict which R protein recognizes a given effector, the identification of non-NLR domains in R proteins allows one to propose novel cellular targets in a variety of cellular compartments and plant species of as yet uncharacterized effectors (Kroj *et al.*, 2016; Sarris *et al.*, 2016).

MULTIPLE STRATEGIES TO COMBAT TAL EFFECTORS THAT TARGET HOST DNA

Pathogen effectors utilize multiple strategies to dampen plant immunity and promote susceptibility. Unlike *Pseudomonas* spp. effectors that based on current knowledge largely target host proteins, pathogens in the bacterial genus *Xanthomonas* rely to a significant degree on injecting a family of transcription activator-like effectors (TALEs) into the host cell to induce the expression of susceptibility genes by directly targeting specific DNA sequences termed effector binding elements (EBEs). TALEs have a conserved modular structure composed of a type III signal peptide at the N-terminus, a nuclear localization signal and an acidic transcription activation domain at the C-terminus, and a central region with varying numbers of 33–35 amino acid repeats. While most of the amino acids at each position are conserved between repeats, the amino acids at positions 12 and 13 exhibit polymorphisms and are called repeat variable di-residues (RVDs). These RVD polymorphisms determine the sequence specificity of DNA binding by a given TALE (Mak *et al.*, 2013; Schornack *et al.*, 2013).

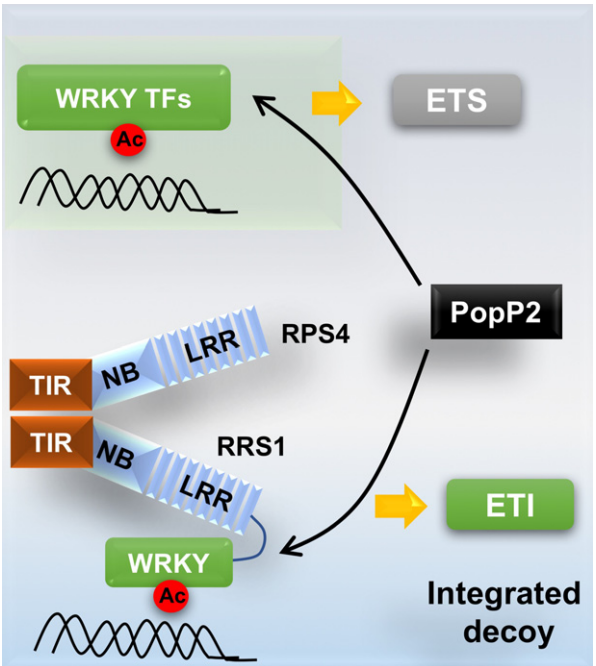

Figure 5. Guarding of WRKY transcription factors by an R protein pair.
WRKY transcription factors play key roles in plant immunity, and the *Ralstonia solanacearum* effector PopP2 acetylates a subset of WRKY TFs to induce ETS. The R protein RRS1 contains a WRKY domain that has been demonstrated to interact with the W-box motif, although *in planta* targets have yet to be identified. The WRKY domain of RRS1 is acetylated by PopP2, disrupting interactions with DNA and triggering ETI through interactions with its partner R protein RPS4. The current model posits that the targeting of the WRKY domain of RRS1 by PopP2 for acetylation may induce a conformational change in the RRS1–RPS4 pair, and characterizes RRS1 and its WRKY domain as an integrated decoy protein.

Two *X. oryzae* pv. *oryzae* (*Xoo*) effectors, AvrXa7 and PthXo3, were shown to target the same EBE in the promoter of the rice gene *OsSWEET14* (Yang *et al.*, 2006; Antony *et al.*, 2010). The induction of *OsSWEET14* leads to the efflux of sucrose or glucose to the apoplast, promoting *Xoo* virulence and implicating sugar efflux as a component of disease susceptibility. The importance of TALEs for the infection strategy by *Xanthomonas* spp. is confirmed by the observation that *Xoo* strains relying on AvrXa7 or PthXo3 lose virulence towards rice cultivars containing mutations in $EBE_{AvrXa7/PthXo3}$ (Yang *et al.*, 2006; Antony *et al.*, 2010) (Figure 6a), and similar examples have been accumulating for other *Xanthomonas* TALEs (Boch *et al.*, 2014). To counter the virulence function of TALEs, plants developed a promoter-trap strategy to confer disease resistance. As is shown in Figure 6(b), binding of AvrXa27 to $EBE_{AvrXa27}$ induces the expression of *Xa27* that encodes the small executor R protein Xa27 localized apoplastically where it functions to elicit HR (Gu *et al.*, 2005). Recently, two other executor R proteins, Xa10 and Xa23, were identified also in rice (Tian *et al.*, 2014; Wang *et al.*, 2015a). Similarly, the promoter regions of *Xa10* and *Xa23* contain corresponding EBEs for AvrXa10 and AvrXa23, respectively.

During the evolutionary arms race between *Xanthomonas* spp. and their hosts, TALEs likely became recognized by host NLRs such as rice Xa1, a classical NB-LRR R protein (Yoshimura *et al.*, 1998). As is shown in Figure 6(c), Xa1 recognizes multiple TALEs of *Xanthomonas* to confer resistance (Ji *et al.*, 2016). To block Xa1-mediated resistance, some *Xanthomonas* isolates secrete truncated versions of TALEs lacking the transcription activation domain. These truncated TALEs are targeted to the nucleus where they may competitively interfere with the recognition of full-length TALEs by Xa1 (Ji *et al.*, 2016). The truncated TALEs, known as interfering TALEs (iTALEs), seem to function as pathogen decoy proteins to block the function of host R proteins. This concept is also supported by a similar study, in which the authors showed that the truncated TALE Tal2 h from *Xoc* strain BLS256 can block Xo1-mediated resistance (Read *et al.*, 2016).

GUARDING OF EDS1 BY RPS4 AND RPS6 IN THE NUCLEUS AND AT MICROSOMAL MEMBRANES

Arabidopsis ENHANCED DISEASE SUSCEPTIBILITY 1 (EDS1) is a positive regulator of both basal immunity and ETI mediated by TIR-NB-LRR R proteins (Aarts *et al.*, 1998; Feys *et al.*, 2005; Wiermer *et al.*, 2005; Wirthmueller *et al.*, 2007). Previous studies have demonstrated that a balanced cytoplasmic and nuclear distribution of EDS1 is essential for complete innate immunity (Garcia *et al.*, 2010). In line with its role as a critical signaling hub, EDS1 was observed to be targeted by AvrRps4 in the cytoplasm and nucleus (Bhattacharjee *et al.*, 2011; Heidrich *et al.*, 2011). Because the interaction between EDS1 and the two unrelated pathogen effectors AvrRps4 and HopA1 also occurred *in vitro*, it was concluded that EDS1 is a direct target of these effectors (Bhattacharjee *et al.*, 2011). Although previously disputed by work from a separate group (Sohn *et al.*, 2012), recently published data confirm the interaction between AvrRps4 and EDS1 by co-immunoprecipitation and bimolecular fluorescence complementation analyses (Huh *et al.*, 2017).

While guarding of EDS1 by R proteins has gained some acceptance, how the targeting of EDS1 is integrated into RPS4 activation remains to be elucidated. Bhattacharjee *et al.* showed that AvrRps4 or HopA1 disrupt RPS4–EDS1 or RPS6–EDS1 interactions, and proposed that the disassociation of RPS4 and RPS6 from EDS1 leads to activation (Figure 7a) (Bhattacharjee *et al.*, 2011). This model may be an oversimplification, as it was shown that AvrRps4 does not disrupt the RPS4–EDS1 interaction in the presence of RRS1, indicating that RPS4 activation may be mediated by AvrRps4-induced RPS4-RRS1 conformational changes (Figure 7b; Huh *et al.*, 2017). However, the observation that

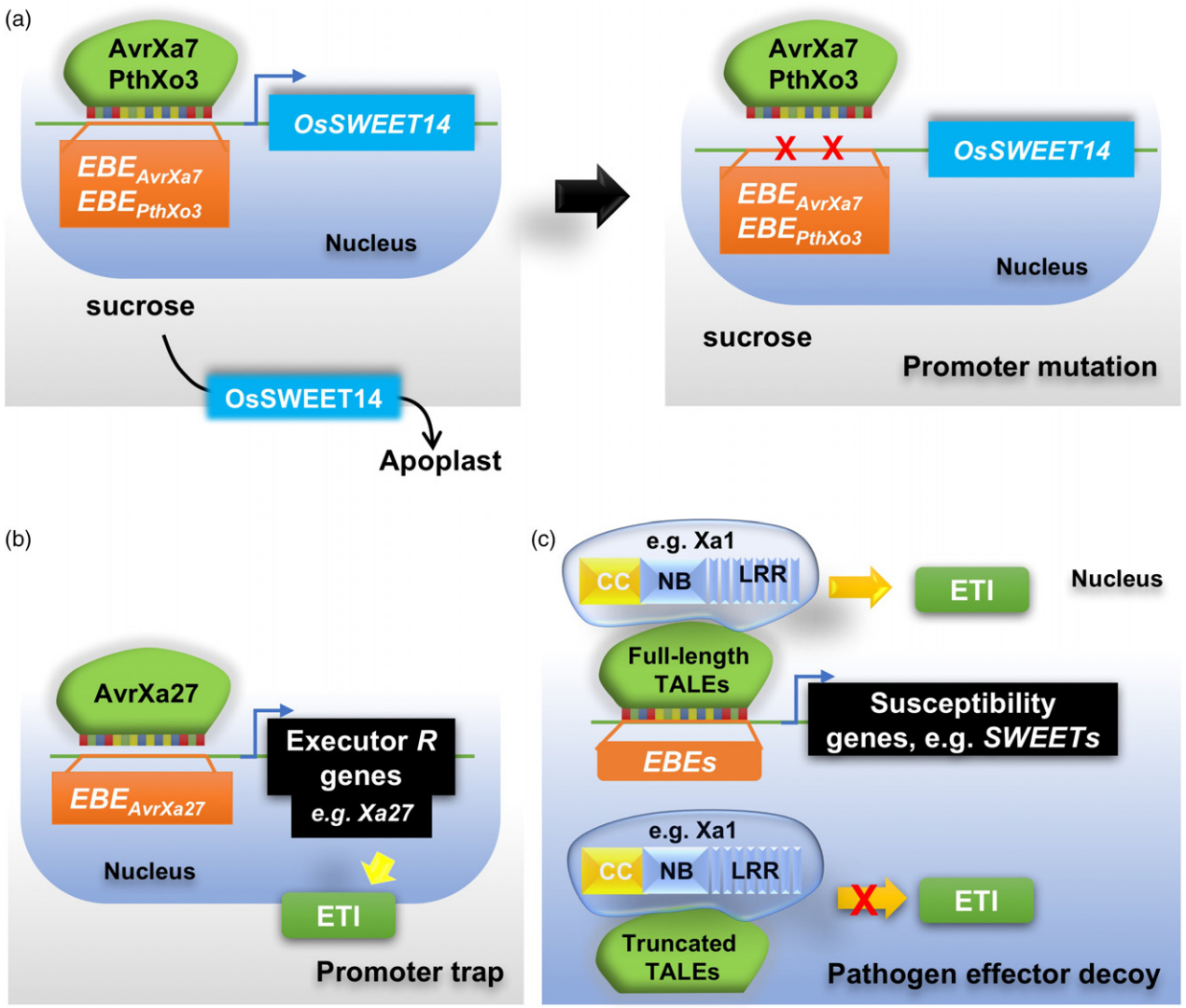

Figure 6. Guarding against pathogen-induced susceptibility genes at the DNA level.
(a) *Xanthomonas* transcription activator-like effectors (TALEs), such as AvrXa7 and PthXo3, promote susceptibility by directly binding to effector binding elements (EBEs) in the promoter region of susceptibility genes such as *OsSWEET14*, activating their expression. The virulence function of AvrXa7 and PthXo3 is lost in rice cultivars with mutations in the promoter region of *OsSWEET14*.
(b) Integration of EBEs with executor *R* genes provides an effective strategy to confer resistance. Targeting $EBE_{AvrXa27}$ by *Xanthomonas* TALE AvrXa27 induces the expression of *Xa27* and elicitation of HR.
(c) The rice R protein Xa1 can recognize a large number of TALEs and induce ETI. Some *Xanthomonas* isolates secrete truncated TALEs that interfere with the recognition of full-length TALEs by Xa1. These truncated TALEs, which lack DNA-binding domains, were proposed to function as pathogen decoys to protect the virulence functions of full-length TALEs.

RPS4 overexpression, when the amount of RPS4 protein exceeds that of RRS1, induces auto-immunity and HR (Huh *et al.*, 2017) is more consistent with the dissociation model. In addition, co-expression of RRS1 can abolish the RPS4 overexpression-induced phenotype (Huh *et al.*, 2017), indicating that RRS1 is required to lock RPS4 in an inactive state under normal conditions and that higher RPS4 protein amounts compared with RRS1 could activate this system (Figure 7c). *RPS4* is induced by AvrRps4 (Zhang and Gassmann, 2007), and protein complexes containing RPS4 are also modulated by additional proteins such as SRFR1 and SGT1 (Kwon *et al.*, 2009; Kim *et al.*, 2010; Li *et al.*, 2010), which are not usually included in transient expression studies. Therefore, to elucidate AvrRps4-induced RPS4 activation, genomic promoter-driven epitope-tagged RPS4 transgenic lines with comparable protein levels to wild-type RPS4 in an *rps4* mutant background will be necessary.

An additional level of complexity in the RPS4/RRS1 system that nevertheless may help in reconciling contrasting models of RPS4/RRS1 activation is the fact that AvrRps4 is processed *in planta* (Sohn *et al.*, 2009). It is therefore

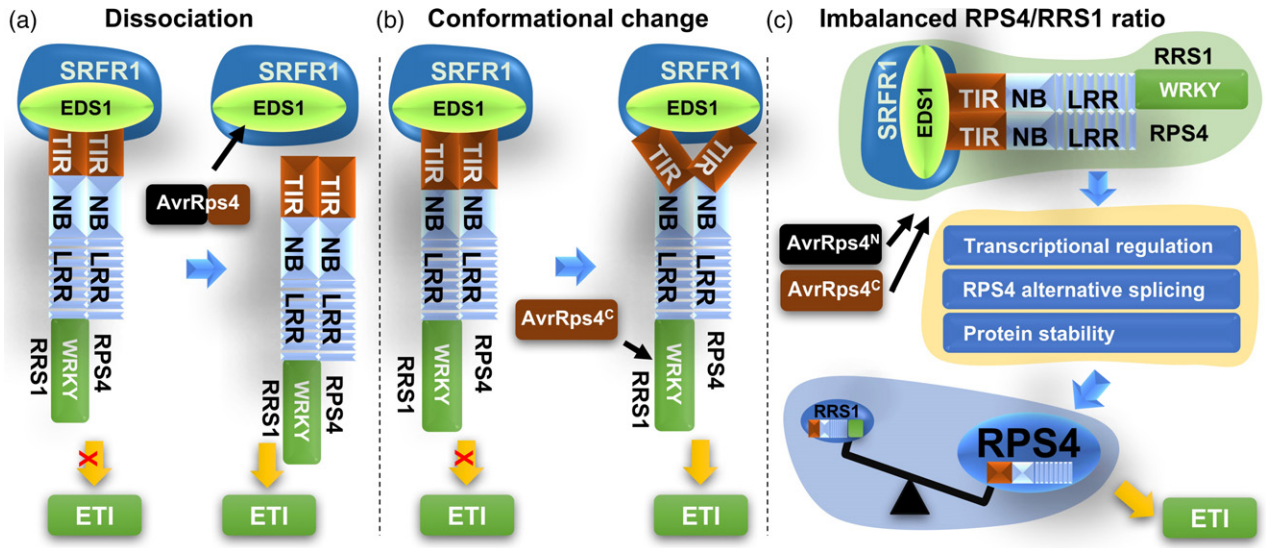

Figure 7. Possible mechanisms for AvrRps4-induced RPS4/RRS1 activation via EDS1 targeting.
(a) *Pseudomonas syringae* type III effector AvrRps4 targets EDS1 and induces the disassociation of the RPS4–RRS1 protein pair from EDS1, which causes subsequent RPS4 activation.
(b) The AvrRps4 C-terminal fragment (AvrRps4^{C}) directly or indirectly targets the WRKY domain of RRS1 and induces a conformational change of the RPS4–RRS1 protein pair, thus activating RPS4.
(c) AvrRps4^{N} and AvrRps4^{C} target the EDS1–SRFR1–RPS4–RRS1 complex and induce multi-layered changes. In this model, RRS1 suppresses RPS4 activity. If the RPS4/RRS1 ratio is ≤ 1, RPS4 activation is blocked by RRS1. If the RPS4/RRS1 ratio is > 1, unpaired RPS4 activates ETI.

conceivable that the 88 amino acid (aa) C-terminus of processed AvrRps4 interacts directly or indirectly with the WRKY domain of RRS1 (Sarris *et al.*, 2015), while the 133 aa N-terminus has other targets such as EDS1 (Bhattacharjee *et al.*, 2011) (Figure 7). An equally important gap in our understanding of the RPS4/RRS1 system is the unknown molecular function of EDS1. Given the nuclear localization of a sub-pool of all components in this system, the targeting of WRKY transcription factors by effectors that trigger RPS4/RRS1, and the emerging role of SRFR1 as a counterbalancing transcriptional repressor (Kim *et al.*, 2014), it is tempting to speculate that effectors are guiding us towards identifying a key role of EDS1 in defense gene regulation that is protected by R proteins.

ADDITIONAL PLANT FUNCTIONS ARE LIKELY PROTECTED BY R PROTEINS

Pathogens usually secrete a diverse array of functionally distinct and redundant effectors. For example, *Pseudomonas syringae* pv. tomato DC3000, a model pathogen, secretes about 30 effectors into host cells to target most organelles and at least as many important biological processes (Xin and He, 2013). HopI1, a chloroplast localized J-domain virulence factor, hijacks the host HSP70 chaperone machinery to remodel thylakoid structure and suppress SA accumulation (Jelenska *et al.*, 2007, 2010). Similarly, localization to the chloroplast has been demonstrated for the highly identical processed N-termini of AvrRps4 and HopK1 through their transit peptides, although a mechanism for virulence has not been established (Li *et al.*, 2014a). As a critical production center for a variety of defense hormones and antimicrobial molecules, the chloroplast would appear to be an attractive target for effector activity. The *Pseudomonas syringae* effector HopG1 was shown to localize to mitochondria, where it suppresses respiration and promotes disease susceptibility (Block *et al.*, 2010). HopM1 suppresses the apoplastic ROS burst and vesicle trafficking (Nomura *et al.*, 2011; Gangadharan *et al.*, 2013; Lozano-Duran *et al.*, 2014), and HopW1 disrupts the actin cytoskeleton (Kang *et al.*, 2014).

At this time, the R proteins recognizing these virulence factors mentioned above are yet to be determined, as most of these studies used Arabidopsis accessions as a host in which DC3000 is virulent. In the field of plant immunity, only a very limited number of *Arabidopsis* accessions are frequently used, artificially limiting the scope of our search for signaling components critical to innate immunity. With the numerous resources generated by the Arabidopsis 1001 project (Kawakatsu *et al.*, 2016, The 1001 Genome Consortium, 2016) and recent identification of Arabidopsis accessions fully or partly resistant to DC3000 (Velasquez *et al.*, 2017), detailed analysis of these lines will likely facilitate the identification of additional cognate R proteins, furthering efforts to characterize the plant innate immune system. In addition, equally important insights are being gained from the study of other plant hosts, such as tomato, rice, soybean and others (Liu *et al.*, 2014; Vleeshouwers and Oliver, 2015; de Wit, 2016).

Most of the discussion of guarded plant functions in the literature focuses on NLRs that indirectly detect their cognate effectors. Conceptually, NLRs that directly interact with effectors also bear lessons what these NLRs are protecting. In the case of the flax rust fungus *Melampsora lini*, a suite of effectors that are small cysteine-rich proteins with a compact structure have been characterized (Catanzariti *et al.*, 2006). Some of these effectors bear sequence and structural features that are consistent with protease inhibitor functions, but the virulence targets in the host are not known. Identifying these targets is likely to identify additional plant functions that the immune system is protecting.

FUTURE DIRECTIONS

With the accumulated knowledge on plant–pathogen interactions, engineering crops with broad-spectrum resistance is promising. For instance, PBS1 has been successfully engineered to function as a decoy to multiple pathogen effectors to expand specificity of RPS5 (Kim *et al.*, 2016). This observation opens the door to scientists to engineer plant immunity against any pathogen that employs proteases in its effector repertoire, as shown in many economically important pathogens.

While recognition of a single effector is sufficient to trigger ETI and defeat a pathogen, reliance on a single recognition event often has proven to be unstable in agricultural applications. A few exceptions exist when R proteins target conserved effectors with measurable virulence functions (Tai *et al.*, 1999; Vera Cruz *et al.*, 2000). But even in these cases, pathogens can evolve effectors with intermediate virulence and avirulence functions (Gassmann *et al.*, 2000). Deeper insights into the layers of plant functions that are targets of pathogens should allow the design of engineered resistance specificities protecting different cellular compartments and biochemical or physiological functions. Such a distributed network of resistance will be much harder for a pathogen to overcome, as it would entail the simultaneous evolution of several evasion strategies (Michelmore *et al.*, 2017). In addition, such engineering approaches will likely have to include a better understanding of regulatory mechanisms that keep the plant immune system in check to prevent yield penalties. In the end, constant vigilance will be necessary not only by plants, but also by plant pathologists.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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