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REVIEW

Effectors of *Phytophthora* pathogens are powerful weapons for manipulating host immunity

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Abstract

Main conclusion **This article provides an overview of the interactions between *Phytophthora* effectors and plant immune system components, which form a cross-linked complex network that regulates plant pathogen resistance.**

Abstract Pathogens secrete numerous effector proteins into plants to promote infections. Several *Phytophthora* species (e.g., *P. infestans*, *P. ramorum*, *P. sojae*, *P. capsici*, *P. cinnamomi*, and *P. parasitica*) are notorious pathogens that are extremely damaging to susceptible plants. Analyses of genomic data revealed that *Phytophthora* species produce a large group of effector proteins, which are critical for pathogenesis. And, the targets and functions of many identified *Phytophthora* effectors have been investigated. *Phytophthora* effectors can affect various aspects of plant immune systems, including plant cell proteases, phytohormones, RNAs, the MAPK pathway, catalase, the ubiquitin proteasome pathway, the endoplasmic reticulum, NB-LRR proteins, and the cell membrane. Clarifying the effector–plant interactions is important for unravelling the functions of *Phytophthora* effectors during pathogenesis. In this article, we review the effectors identified in recent decades and provide an overview of the effector-directed regulatory network in plants following infections by *Phytophthora* species.

Keywords *Phytophthora* · Effectors · Plant immune system components · Interaction · Network

Introduction

Plants are constantly attacked by pathogens during their growth and development. Unlike animals, plants are sessile organisms unable to physically escape from pathogens. Consequently, they have evolved an advanced and sophisticated immune system to perceive pathogens and prevent infections. The plant immune system consists of two related layers: microbe- and pathogen-associated molecular pattern (MAMP and PAMP)-triggered immunity (PTI) and effector-triggered immunity (ETI) (Jones and Dangl 2006; Dodds and Rathjen 2010).

In the first layer of immunity, the pattern-recognition receptors (PRRs) on the plant cell membrane perceive PAMPs/MAMPs and activate PTI, which can temporarily prevent further pathogen infections (Jones and Dangl 2006; Couto and Zipfel 2016a, b). A number of PAMPs/MAMPs with conserved structures, which are common in microbes but not in host plants, have been identified in bacterial, fungal, and oomycete pathogens, including a bacterial flagellum peptide comprising 22 conserved amino acids (flg22) (Felix et al. 1999; Taguchi et al. 2003; Chinchilla et al. 2006), bacterial elongation factor Tu (EF-Tu) (Zipfel et al. 2006), Nep1-like proteins (NLPs) (Fellbrich et al. 2002; Qutob et al. 2006), cellulose-binding elicitor lectins (CBELs) (Gaulin et al. 2006), INF1 (Heese et al. 2007; Kamoun et al. 1997, 1998), and the glycoside hydrolase protein PsXEG1 (Ma et al. 2017).

In the second layer of immunity, pathogens that have penetrated plant cells secrete effector molecules that interfere with or inhibit PTI to enhance infections (Jones and Dangl 2006; Win et al. 2012). Bacteria use the type III secretion system (T3SS) to directly inject effectors into plant cells, whereas fungi and oomycetes introduce effectors into plant

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cells through appressoria or haustoria (Galan et al. 2014; Panstruga and Dodds 2009; Wang et al. 2017, 2018). Effectors can be categorized as apoplastic or cytoplasmic depending on their location in plants (Whisson et al. 2007). Apoplastic effectors accumulate in the intercellular spaces and interact with extracellular defense-related factors, whereas cytoplasmic effectors are transported into the cytoplasm via known and unknown mechanisms and are localized in various plant subcellular regions (Sharpee and Dean 2016).

To decrease their susceptibility to pathogens, plants have evolved resistance proteins (R proteins) that directly or indirectly interact with effectors and usually induce a hypersensitive response (HR) (Boller and He 2009). The HR, which is a form of programmed cell death (PCD), is often associated with the resistance of plants to pathogens at the infection site, and prevents pathogenic microorganisms from further infecting the plant (Jones and Dangl 2006; Dangl et al. 2013). The main R proteins are nucleotide-binding leucine-rich repeat (NB-LRR) proteins (Lee and Yeom 2015).

Large family of *Phytophthora* effectors

Phytophthora is a genus in the class Oomycota (Stramenopila) (Beakes et al. 2012). Because of similarities in morphological structures, such as mycelia and spores, oomycetes were considered to be fungi. However, a phylogenetic analysis revealed oomycetes are more closely related to diatoms and brown algae (Thines et al. 2014). Approximately 60% of oomycetes are plant pathogens, including the species in the genus *Phytophthora* (Thines et al. 2014). A previous study confirmed there are more than 100 *Phytophthora* species, several of which are notorious pathogens that can severely damage crops, including vegetables, and forests (Érsek and Ribeiro 2010). For example, *Phytophthora infestans* is responsible for late blight in potato and tomato, which annually cause tremendous yield losses worldwide (Zadoks 2008). Additionally, *Phytophthora ramorum* is the causative agent of sudden oak death (SOD), which kills oak trees and other tree species, resulting in considerable economic losses in North America and Europe (Grünwald et al. 2008). *Phytophthora sojae*, *Phytophthora parasitica*, and *Phytophthora capsici* cause major losses to soybean, tobacco, and pepper production, respectively, and consequently substantial economic losses (Tyler 2007; Meng et al. 2014; Hausbeck and Lamour 2004). *Phytophthora* species exhibit a hemibiotrophic lifestyle, initially existing as biotrophs before becoming necrotrophs (Fawke et al. 2015). The jasmonate (JA) and salicylate (SA) signaling pathways in plants mediate a universal defense response. Specifically, the SA and JA pathways generally initiate the resistance to biotrophic and necrotrophic pathogens, respectively (Zhang et al. 2017). An earlier investigation determined that SA contributes to the resistance of plants to *P. sojae* (Liu et al. 2014).

The genomes of *P. infestans*, *P. sojae*, *P. ramorum*, *P. parasitica*, and *P. capsici* have been fully sequenced (Haas et al. 2009; Tyler et al. 2006; Liu et al. 2016; Lamour et al. 2012) (Table 1). The generated genomic data suggest that *Phytophthora* species produce many effectors (Table 1), which have been divided into two main types, namely, RxLR and CRN effectors (Haas et al. 2009). The N terminus of RxLR effectors contains a conserved arginine–any amino acid–leucine–arginine (R–x–L–R) motif. This motif is usually followed by a small, conserved glutamic acid–glutamic acid–arginine (EER) domain. The conserved RxLR-dEER domain is closely related to the transport of effectors into cells (Jiang et al. 2008; Win and Kamoun 2007). The CRN effectors (crinkling- and necrosis-inducing proteins), which were originally identified in *P. infestans*, have a highly conserved N-terminal LFLAK domain (Haas et al. 2009). The C-terminal regions of RxLR and CRN effectors are relatively diverse.

The considerable abundance of effectors produced by *Phytophthora* species is important for overcoming plant immune systems. In recent decades, many *Phytophthora* effectors have been identified, and their targets and functions in plant cells have been analyzed. Researchers have confirmed that *Phytophthora* effectors influence various aspects of plant immune systems (Dou and Zhou 2012; Whisson et al. 2016; Wang et al. 2019). The effectors and plant immune system components form a complex network

Table 1 Genome size and the number of encoded effector proteins of *Phytophthora* species whose genome sequences are available

Organisms	Genome size	Number of genes	Number of RXLR effectors	Number of CRN effectors	References
P. infestans	240 Mb	17.797	563	196	Haas et al. (2009)
P. sojae	95 Mb	16,988	335	100	Tyler et al. (2006)
P. ramorum	65 Mb	14,451	309	19	Tyler et al. (2006)
P. capsici	63.8 Mb	19.805	400	80	Lamour et al. (2012)
P. nicotianae race 0	80 Mb	17,797	308	32	Liu et al. (2016)
P. nicotianae race 1	69 Mb	14,542	199	26	Liu et al. (2016)

that modulates plant resistance. We herein review the *Phytophthora* effector proteins identified in recent decades regarding their current known plant targets and the relationships among these targets. Thus, we provide an overview of the plant–pathogen interaction network involving multiple plant immune system components. This review is relevant for characterizing the mechanisms underlying pathogenicity and plant resistance.

Manipulating cell protease-mediated immunity

Proteases, which can catalyze the hydrolysis of their target proteins, have been detected in almost all plants, animals, and microorganisms (Mosolov and Valueva 2005). Many resistance-related proteases are present in plant apoplasts and are important components of plant immune systems (Habib and Majid 2007). For example, P69B is a tomato subtilisin-like apoplastic serine protease, whereas *Phytophthora*-inhibited protease 1 (PIP1), Rcr^{3pim}, and C14 are papain-like extracellular apoplastic cysteine proteases (Tornero et al. 1997; Jorda et al. 1999; Kruger et al. 2002). All of these proteases are important for plant resistance responses, and both SA and BTH (i.e., SA analog) can induce *P69B* expression.

To promote infections, *Phytophthora* pathogens secrete effectors that inhibit protease activities. The *P. infestans* effectors EPI1 (Tian et al. 2004), EPI10 (Tian et al. 2005), EPIC2B (Tian et al. 2007; Song et al. 2009; Kaschani et al. 2010; Kaschani and Van Der Hoorn 2011), EPIC1 (Kaschani et al. 2010; Kaschani and Van Der Hoorn 2011), and AVRblb2 (Bozkurt et al. 2011) function as protease inhibitors. Additionally, EPI1 and EPI10 interact with tomato P69B to inhibit its function (Tian et al. 2004, 2005). Moreover, EPI1 and EPI10, which have two and three Kazal-like domains, respectively, are structurally diverse, but they both target the same plant protease, P69B, implying that P69B is an important target of *P. infestans* (Tian et al. 2004, 2005). In contrast, AVRblb2, which mainly accumulates around haustoria, targets C14 and specifically prevents its secretion into the apoplast (Bozkurt et al. 2011), whereas $Rcr3^{pim}$ helps plants defend against *P. infestans* strains producing EPIC1 and EPIC2B (Tian et al. 2007; Song et al. 2009; Kaschani et al. 2010; Kaschani and Van Der Hoorn 2011). Interestingly, EPIC2B can interact with and inhibit three proteases (i.e., PIP1, Rcr^{3pim}, and C14), suggesting it considerably promotes *P. infestans* infections. The *P. sojae* effector glucanase inhibitor protein 1 (GIP1) can inhibit the release of glucan elicitors from the *P. sojae* cell wall by forming a complex with endoglucanases (Rose et al. 2002). The above-mentioned examples indicate that various effectors from the same pathogen can target the same plant immune system components. For example, the *P. infestans* effectors EPI1 and EPI10 both affect P69B, whereas EPIC1 and EPIC2B both target Rcr3, and EPIC2B and AVRb1b2 both target C14. However, the same effectors can also target different components. For instance, EPIC2B can target three immune system components, namely PIP1, Rcr3, and C14, which suggests there is a link between PIP1 and Rcr3. The relationships among these effectors are presented in Fig. 1a.

Manipulating phytohormone-mediated immunity

Phytohormone signaling pathways play important roles in plant disease resistance (Robert-Seilaniantz et al. 2011). Specifically, SA, jasmonic acid (JA), ethylene (ET), and auxin form a complex signaling network that regulates plant resistance to pathogenic microbes (Pieterse et al. 2012; Thaler et al. 2012). The *P. sojae* effector PsIsc1 can hydrolyze host isochorismate and modulate SA metabolism, thereby decreasing SA levels in hosts and suppressing immunity (Liu et al. 2014). The *P. infestans* effector PexRD24 (also known as Pi04314) interacts with three protein phosphatase 1 catalytic (PP1c) isoforms required for disease development and induces their re-localization from the nucleolus to the nucleoplasm, which decreases JA and SA accumulation and suppresses host immunity (Boevink et al. 2016). Regarding *P. parasitica*, penetration-specific effector 1 (PSE1), whose transcript is transiently accumulated during the penetration of host roots, can modulate auxin contents at the penetration points and facilitate infections (Evangelisti et al. 2013). In *Arabidopsis thaliana*, PSE1 also has regulatory functions and is associated with the low auxin concentrations at the root apex (Evangelisti et al. 2013). The relationships among these effectors are presented in Fig. 1a.

A physical interaction network has been constructed for *A. thaliana* proteins and effector proteins from pathogens, including the Gram-negative bacterium *Pseudomonas syringae* and the obligate biotrophic oomycete *Hyaloperonospora arabidopsidis* (Mukhtar et al. 2011). According to this network, the effectors of these two pathogens strongly interact with JAZ proteins, which are important JA signaling components (Mukhtar et al. 2011). Like *Phytophthora* species, *H. arabidopsidis* is an oomycete. Accordingly, *Phytophthora* effector proteins may also influence the JA pathway.

Manipulating MAPK-mediated immunity

Mitogen-activated protein kinase (MAPK) cascades, which form a highly conserved signaling pathway in all eukaryotes, can transfer extracellular signals into cells via the protein phosphorylation and dephosphorylation catalyzed by

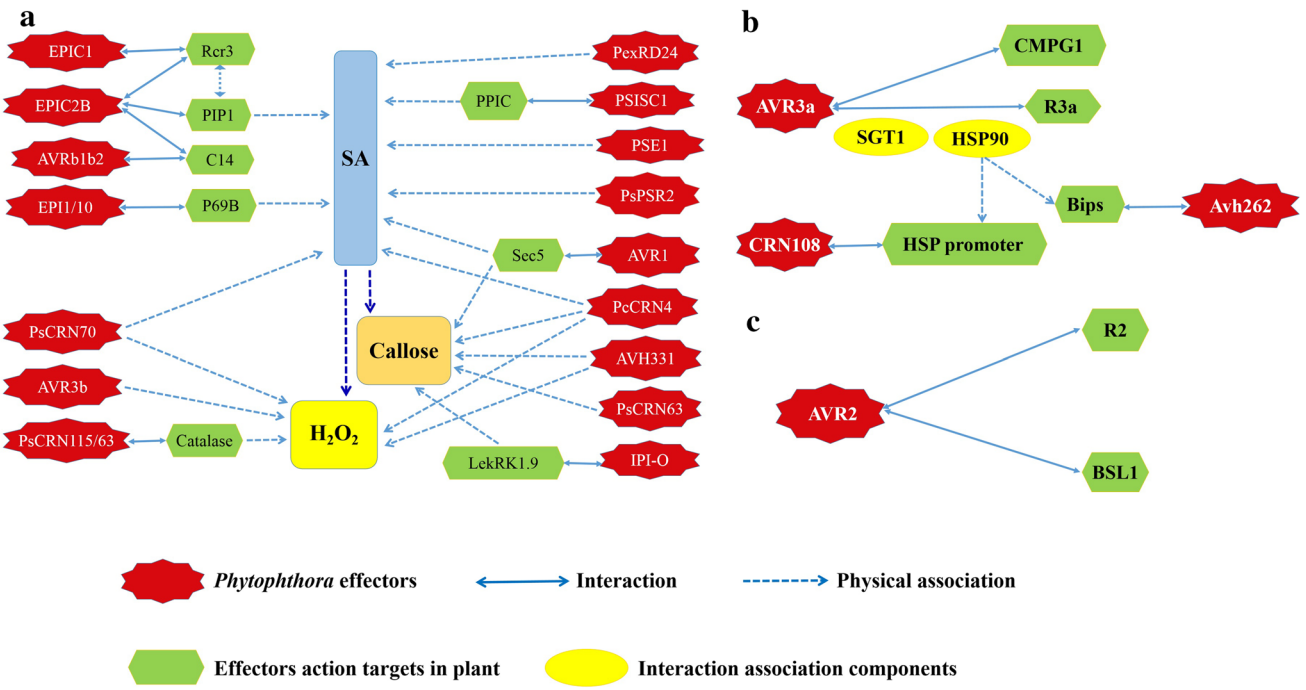

Fig. 1 *Phytophthora* effectors target plant immune system components. **a** Targeting of plant components by *Phytophthora* effectors leading to modifications in SA, H_2O_2, and callose contents. Interaction indicates a direct interaction between effectors and the targets. Physical association indicates a close correlation, but no direct interaction observed between the effectors and the plant targets. **b** Interaction network of AVR3a, PsAvh262 and PsCRN108 with their targets, which involves SGT1, HSP90, BiPs, and the HSP promoters. **c** Diagram of the interactions between AVR2 and BSL1 as well as R2

MAPK kinases (MAPKKs) and MAPKK kinases (MAPKKKs) (Rodriguez et al. 2010; Melech-Bonfil and Sessa 2010). The MAPKs are crucial for regulating plant defensive responses to pathogens (Meng and Zhang 2013; Pitzschke et al. 2009). The flg22 bacterial flagellin peptide is a typical MAMP directly recognized by the plant protein FLAGELLIN SENSITIVE2 (FLS2), and this recognition activates the MAPK immunity pathway to induce the expression of numerous defense-related genes, including *FRK1* (Chinchilla et al. 2006; Taguchi et al. 2003).

The *P. infestans* RXLR effector, PexRD2, interacts with the MAPKKKe kinase domain to suppress activity (King et al. 2014). The overexpression of *PexRD2* or the silencing of *MAPKKKe* in *Nicotiana benthamiana* promotes infection. Eight suppressors of the early flg22-induced immune response (SFIs), which were identified as RXLR effectors in *P. infestans*, can alter various steps of the MAPK signaling pathway to suppress early-induced immunity (Zheng et al. 2014). A *P. sojae* RXLR effector, Avh331, manipulates the MAPK signaling pathway to promote the infection of *A. thaliana* and *N. benthamiana*. This process is accompanied by significantly decreased H_2O_2 accumulation and callose deposition (Cheng et al. 2012). The PsCRN63 of *P. sojae* functions downstream of MAPK cascades to suppress flg22-induced defense responses, such as *FRK1* expression, and callose deposition (Li et al. 2016). The relationships among these effectors are presented in Fig. 1a.

Manipulating cell membrane-mediated immunity

The plasma membrane–cell wall continuum in plants is important for defense responses, and disrupted plasma membrane–cell wall adhesions may increase the susceptibility of plants to pathogens (Zhu et al. 1993; Mellersh and Heath 2001). The *P. infestans in planta* induced-O (IPI-O), which is an RXLR-dEER effector, can disrupt the plasma membrane–cell wall adhesions in *A. thaliana* through its RGD motif (arginine–glycine–aspartic acid) (Senchou et al. 2004; Gouget et al. 2006; Bouwmeester et al. 2011). However, when the IPI-O RGD motif is mutated to RGE or RGA, the adhesions remain intact. An 80-kDa RGD plasma membrane protein of *A. thaliana* and the legume-like lectin receptor kinase LecRK-I.9 can interact with IPI-O through the RGD motif. Additionally, LecRK-I.9 can directly or indirectly trigger increases in callose deposition (Fig. 1a). A *P. sojae* RxLR effector, Avh241, which localizes to the membrane and triggers cell death in multiple plant species (Yu et al. 2012), is essential for the full virulence of *P. sojae* and functions as a

susceptibility inducer when produced in plant cells. However, it does not need to induce cell death to promote susceptibility, suggesting Avh241 interacts with the plant immune system in at least two different ways (Yu et al. 2012).

Manipulating RNA-mediated immunity

In eukaryotic organisms, RNA silencing is a universal gene regulatory mechanism that controls many biological processes (Baulcombe 2004; Sarkies and Miska 2014). Small RNAs comprising 20–30 nucleotides play a central role in this process. Plants produce two types of small RNAs, microRNAs (miRNAs) and small interfering RNAs (siRNAs), which help mediate the plant disease resistance system (Vance and Vaucheret 2001; Huang et al. 2016). Specifically, miRNAs are transcribed from endogenous MIR family genes, whereas siRNAs are derived from invading nucleic acids, such as viruses and transgenes, and from endogenous loci, such as repeats, transposable elements, and genes (Voinnet 2009).

Three *Phytophthora* effectors that regulate RNA silencing have been identified (PSR1, PSR2, and PiPSR2) (Qiao et al. 2013, 2015; Xiong et al. 2014). The PSR1 and PSR2 effectors of *P. sojae* suppress RNA silencing in plants by inhibiting the biogenesis of small RNAs (Qiao et al. 2013). Similarly, PiPSR2, which is a PSR2-like effector produced by *P. infestans*, also suppresses RNA silencing by inhibiting the biogenesis of small RNAs (Xiong et al. 2014). Additionally, PSR1 interacts with PSR1-interacting protein 1 (PINP1), which regulates the accumulation of both miRNAs and endogenous siRNAs in *A. thaliana* (Qiao et al. 2015). The PsAvr3c effector from *P. sojae* interacts with and stabilizes the soybean serine/lysine/arginine-rich proteins GmSKRPs, which contain plant spliceosome components and modulate host pre-mRNA splicing to regulate plant immunity (Huang et al. 2017). In *P. infestans*, Pi14054 is a novel candidate suppressor affecting the RNA silencing of plant hosts (Vetukuri et al. 2017). Moreover, the *P. infestans* RXLR effector Pi04089 interacts with StKRBP1, which is a predicted K-homology (KH) class putative RNA-binding protein in *Solanum tuberosum*, and this interaction occurs in the plant nucleus (Wang et al. 2015). Interestingly, *PR1* expression is completely abolished in *PsPSR2*-expressing plants, which suggests that PsPSR2 interferes with the SA-dependent defense pathway during an infection by *Phytophthora* species (Xiong et al. 2014) (Fig. 1a).

Manipulating E3 ubiquitin ligase-mediated immunity

The ubiquitin proteasome pathway is the most important protein degradation pathway in eukaryotic organisms, and in plants, it regulates growth, development, and responses to abiotic and biotic stresses (Zhou and Zeng 2017). Ubiquitination involves a series of reactions catalyzed by the E1 ubiquitin-activating enzyme, E2 ubiquitin-binding enzyme, and E3 ubiquitin ligase (Callis 2014). The *P. infestans* effector AVR3a interacts with the U-box E3 ligase CMPG1 and inhibits its activity, thereby controlling the normal protein degradation system of plants (Bos et al. 2010). Two *Avr3a* alleles encode distinct 147-amino acid sequences, $AVR3a^{KI}$ and $AVR3a^{EM}$, which differ in only three amino acids. Moreover, $AVR3a^{KI}$ strongly interacts with and stabilizes CMPG1, whereas $AVR3a^{EM}$ only weakly interacts with CMPG1 (Bos et al. 2010). According to previous reports, AVR3a also interacts with R3a, an intracellular NBS-LRR domain-containing protein. This interaction is dependent on the ubiquitin ligase-associated protein SGT1 and heat-shock protein 90 (HSP90), which can trigger R3a-dependent HR and suppress the cell death induced by the *P. infestans* elicitin INF1 (Armstrong et al. 2005; Bos et al. 2006) (Fig. 1b).

Manipulating catalase-mediated immunity

Hydrogen peroxide (H_2O_2), which is a reactive oxygen species (ROS), plays an important role in plant defense responses (Yoshioka et al. 2009; Petrov and Van Breusegem 2012). Catalases in cells convert H_2O_2 into water and oxygen (Li et al. 2013). The *P. sojae* effectors PsCRN63/115 manipulate plant PCD by interfering with catalases and perturbing H_2O_2 homeostasis (Zhang et al. 2015). Additionally, PsCRN63 also suppresses the flg22-induced expression of PTI marker genes and callose deposition (Liu et al. 2011; Li et al. 2016). The PsCRN70 effector of *P. sojae*, which localizes to the plant cell nucleus and functions as a universal suppressor of the cell death induced by many elicitors, may promote *Phytophthora* infections by suppressing H_2O_2 accumulation and the production of defense proteins, including the pathogenesis-related (PR) proteins PR1a and PR2b (markers for SA-dependent defense), ethylene response factor 1 (ERF1), and lipoxygenase (LOX; involved in JA synthesis) (Rajput et al. 2014). The relationships among these effectors are presented in Fig. 1a.

Manipulating endoplasmic reticulum-mediated immunity

The endoplasmic reticulum (ER) is an important site for the modification and folding of eukaryotic secretory and membrane proteins (Kim et al. 2008; Hetz 2012). Only correctly folded and modified proteins can be transported to the cytoplasm, nucleus, mitochondria, and other organelles to exert their biological functions (Hetz 2012). Protein folding in the ER is mainly mediated by molecular

chaperones and cofactors (Saijo 2010). Binding immunoglobulin protein (BiP), which is a member of the large HSP70 family of molecular chaperones, is a high molecular weight chaperone in the ER (Bertolotti et al. 2000). The accumulation of unfolded or incorrectly folded proteins in the ER due to environmental stresses causes the cell to initiate an unfolded protein response (UPR) by regulating a series of downstream genes, such as those encoding molecular chaperones, to promote the correct folding of proteins and the degradation of improperly folded proteins (Saijo 2010). Four important UPR signaling pathways are present in *A. thaliana*, of which two are mediated by the bZIP family membrane-binding transcription factors bZIP28 and bZIP60, whereas the other two are mediated by the NAC (NAM/ATAF/CUC) family membrane-binding transcription factors NAC062 and NAC089 (Saijo 2010; Yang et al. 2014a, b). Previous research revealed that ER stress responses regulate plant immunity in several ways. For example, the *A. thaliana* HSP AtBiP2 is involved in the secretion of PR proteins (Wang et al. 2015), and the processing of the pattern-recognition receptor EFR requires BiP (Nekrasov et al. 2009). The fungus *Piriformospora indica* induces cell death by inhibiting the UPR-related pro-survival machinery and then activating the ER stress-mediated cell death machinery (Qiang et al. 2012). The UPR is crucial for inducing systemic acquired resistance (SAR) against bacterial pathogens as well as abiotic stress tolerance (Moreno et al. 2012).

Two NAC transcription factors, NTP1 and NTP2, are localized in the ER membrane and contribute to the resistance of tobacco against *P. infestans*. The *P. infestans* effector Pi03192 interacts with NTP1 and NTP2 and prevents their transmission from the ER into the nucleus, thereby decreasing the pathogenicity of *P. infestans* towards potato and *N. benthamiana* (McLellan et al. 2013). Additionally, PsAvh262 from *P. sojae* can stabilize BiPs and facilitate *Phytophthora* infections (Jing et al. 2016). The *P. sojae* CRN effector PsCRN108, which contains a helix–hairpin–helix (HhH) motif, targets *HSP* promoters in an HSE- and HhH-dependent manner and inhibits *HSP* expression in response to stress (Song et al. 2015). Moreover, PcAvr3a12 of *P. capsici* can directly target the ER-localized plant peptidyl-prolyl *cis–trans* isomerase (PPIase) and facilitate infections (Fan et al. 2018).

The PsCRN108 effector targets *HSP* promoters and inhibits *HSP* expression in response to stress, whereas Avh262 affects the ER of plants and interacts with BiPs. Furthermore, AVR3a interacts with R3a, while simultaneously associating with HSP90, which is one of the molecular chaperones of BiPs, and SGT1 (as described in a previous section). These observations imply there are some obvious correlations among AVR3a, PsCRN108, and Avh262 functions in plants (Fig. 1b).

Manipulating NB-LRR protein-mediated immunity

Hundreds of resistance (*R*) genes, which mainly encode NB-LRR proteins, are important components of plant immune systems (Eitas and Dangl 2010). On the basis of the encoded N-terminal domain, NB-LRR genes can be classified into two groups: toll/interleukin-1 receptor (TIR)–NB-LRRs (TNLs) and coiled-coil (CC)–NB-LRRs (CNLs). Additionally, the N-terminal TIR and CC domains are required for plant defense responses (Lee and Yeom 2015). The *RB* gene (also known as *Rpi-blb1*) from the wild potato species *Solanum bulbocastanum* encodes a CNL protein and mediates broad spectrum resistance to most pathogen strains by detecting IPI-O family effectors (Champouret et al. 2009). Moreover, IPI-O4 can interact with the CC domain of CNLs to suppress the immunity induced by RB (Chen et al. 2012). The *P. infestans* RXLR effector AVR2 is recognized by the NB-LRR protein R2, which requires the host phosphatase protein BSU-like protein 1 (BSL1) (Saunders et al. 2012) (Fig. 1c).

Manipulating other plant component-mediated immunity

The *P. sojae* effector Avr3b and the *P. infestans* effector CRN8 are the only effectors known to be enzymatically active in plant cells (Dong et al. 2011; van Damme et al. 2012). Specifically, Avr3b, an ADP-ribose/NADH pyrophosphorylase identified in soybean varieties containing the disease resistance gene *Rps3b*, functions as a Nudix hydrolase that impairs host immunity when delivered into the host cells. Moreover, the deletion of the Nudix motif abolishes the enzyme activity (Dong et al. 2011). The accumulation of ROS is significantly decreased when Avr3b is transiently produced in *N. benthamiana* (Dong et al. 2011) (Fig. 1a). The C-terminal of CRN8 is similar to a serine/threonine RD kinase domain, and its autophosphorylation is dependent on an intact catalytic site (van Damme et al. 2012). The functions of Avr3b and CRN8 indicate that plant pathogens can translocate biochemically active kinase effectors inside host cells.

The plant exocyst influences defense responses, and Sec5 is an exocyst subunit (Cole et al. 2005; Hála et al. 2008). The *P. infestans* RXLR effector AVR1 can interact with Sec5 and regulate callose deposition and *PR1* expression (Du et al. 2015) (Fig. 1a). The PcCRN4 effector of *P. capsici* may inhibit host immunity by suppressing *PR1b* expression, ROS accumulation, and callose deposition in plants (Mafurah et al. 2015) (Fig. 1a).

Table 2 Functions of the *Phytophthora* effectors described in this review in plants

Effectors	Origins	Functions	References
EPI1	*P. infestans*	Interacting with tomato P69B and inhibiting its function	Tian et al. (2004)
EPI10	*P. infestans*		Tian et al. (2005)
EPIC2B	*P. infestans*	Interacting with PIP1, C^{14}, $Rcr3^{pim}$ and inhibiting theirs function	Tian et al. (2007), Song et al. (2009), Kaschani et al. (2010) and Kaschani and Van Der Hoorn (2011)
EPIC1	*P. infestans*	Interacting with C^{14}, $Rcr3^{pim}$ and inhibiting theirs function	Kaschani et al. (2010) and Kaschani and Van Der Hoorn (2011)
AVRblb2	*P. infestans*	Preventing C^{14} into the apoplast	Bozkurt et al. (2011)
GIP1	*P. sojae*	Inhibiting glucan elicitor release from *P. sojae* cell walls	Rose et al. (2002)
PexRD2	*P. infestans*	Interacting with the kinase domain of MAPKKKe and suppress MAPKKKe activity	King et al. (2014)
SFIs	*P. infestans*	Acting at different MAPK signaling pathway	Zheng et al. (2014)
PsCRN63	*P. sojae*	Suppressing flg22-induced expression of defense-related genes and the accumulation of callose and H_2O_2	Liu et al. (2011), Li et al. (2016) and Zhang et al. (2015)
Avh331	*P. sojae*	Manipulating the plant MAPK signaling pathway and causing accumulation reduction of the callose and H_2O_2	Cheng et al. (2012)
PSR1	*P. sojae*	Inhibiting the biogenesis of small RNAs	Qiao et al. (2013, 2015)
PSR2	*P. sojae*	Inhibiting the biogenesis of small RNAs accompanied by the reduction of SA accumulation	Qiao et al. (2013) and Xiong et al. (2014)
PiPSR2	*P. infestans*	Suppressing RNA silencing in plants and promoting Phytophthora infection	Xiong et al. (2014)
PsAvr3c	*P. sojae*	Binding to and stabilizing soybean serine/lysine/arginine-rich proteins GmSKRPs, negative regulators of plant immunity	Huang et al. (2017)
Pi14054	*P. infestans*	Suppressor of the host RNA silencing	Vetukuri et al. (2017)
Pi04089	*P. infestans*	Interacting with StKRBP1 to regulate mRNA processing	Wang et al. (2015)
PsCRN115	*P. sojae*	Interfering with catalase and perturbing H_2O_2 homeostasis	Zhang et al. (2015)
PsCRN70	*P. sojae*	Suppressing the host H_2O_2 accumulation and the expression of defense-related genes, such as PR1a, PR2b, ERF1, LOX	Rajput et al. (2014)
Pi03192	*P. infestans*	Preventing re-localisation of StNTP1 and StNTP2 from the ER into the nucleus	McLellan et al. (2013)
PsAvh262	P. sojae	Stabilizing BiPs and facilitates Phytophthora infection	Jing et al. (2016)
PsCRN108	*P. sojae*	Inhibiting the HSP gene expression in response to stress	Song et al. (2015)
Pslsc1	*P. sojae*	Hydrolyzing host isochorismate and modulating the SA metabolism pathway	Liu et al. (2014)
PexRD24	*P. infestans*	Causing PP1c isoforms re-localization from the nucleolus to the nucleoplasm thereby reducing JA and SA accumulation	Boevink et al. (2016)
PSE1	*P. parasitica*	Modulating auxin content at the penetration points of *P. parasitica* and facilitate infection	Evangelisti et al. (2013)
IPI-O	*P. infestans*	Disrupting the cell wall and plasma membrane adhesions	Senchou et al. (2004), Gouget et al. (2006) and Bouwmeester et al. (2011)
Avh241	*P. sojae*	Localizing to the membrane and triggers cell death in multiple plant species	Yu et al. (2012)
IPI-O4	*P. infestans*	Suppressing the immunity induced by Rpi-blb1	Chen et al. (2012)
AvR2	*P. infestans*	Interacting with both the NB-LRR protein R2 and phosphatase protein BSU-like protein 1 (BSL1)	Saunders et al. (2012)
Avr3a	*P. infestans*	Inhibiting the activity of E3 ubiquitin ligase and controlling the normal protein degradation system of plants; triggering R3a-dependent HR and suppressing the cell death induced by the elicitin INF1 of *P. infestans*	Bos et al. (2006, 2010) and Armstrong et al. (2005)
AVR1	*P. infestans*	Stabilizing Sec5 and manipulating the host vesicle-trafficking machinery	Du et al. (2015)

Table 2 (continued)

Effectors	Origins	Functions	References
Avr3b	*P. sojae*	Acting as an ADP-ribose/NADH pyrophosphorylase to impair host immunity	Dong et al. (2011)
CRN8	*P. infestans*	Similar to a serine/threonine RD kinase	van Damme et al. (2012)
PexRD54	*P. infestans*	Interacting with ATG8CL by outcompeting a plant autophagy cargo receptor to make plant more susceptible	Dagdas et al. (2016)
PcCRN4	*P. capsici*	Suppressing the host accumulation of SA, callose and H_2O_2	Mafurah et al. (2015)
Avh238	*P. sojae*	Contributing to the virulence of *P.sojae* and also triggering plant innate immunity	Yang et al. (2017)
PcAvr3a12	*P. capsici*	Target the ER-localized FKBP15-2 protein (a PPIase) directly and facilitate infection	Fan et al. (2018)

Autophagy is a conserved catabolic pathway that sequesters unwanted cytosolic components in newly formed double membrane vesicles (autophagosomes) to direct them to the cell lytic compartment (He et al. 2009). Autophagy has vital roles in plant defense responses. The *P. infestans* effector PexRD54 can interact with ATG8CL by outcompeting a plant autophagy cargo receptor that would otherwise bind to ATG8CL (Dagdas et al. 2016). By preventing the cargo receptor from interacting with ATG8CL, PexRD54 increases the susceptibility of the plant to an infection by *P. infestans*. Specifically, autophagy is implicated in the accumulation of defense hormones.

The *P. sojae* effector Avh238 is a virulence factor that also triggers plant innate immunity, but its target and activity in plants remain unknown (Yang et al. 2017).

Conclusions

Thousands of effectors represent powerful weapons used by *Phytophthora* pathogens to promote infections. We herein reviewed the *Phytophthora* effectors identified in recent decades and described their known targets and modes of action in plants (Table 2, Fig. 2). Although some effectors affect different plant parts, they are ultimately accompanied by changes to SA, callose, and H_2O_2 contents (Fig. 1). For example, the effects of EPIC2, AVR1, EPI1, EPI10, and PsPSR2 on plants include changes to SA contents, while PsIsc1, PexRD24, and PSE1 directly affect plant hormones, including SA and auxin. Moreover, PsCRN63 and CRN4 influence the accumulation of SA, callose, and H_2O_2, and PsCRN70 affects the accumulation of SA and H_2O_2. Additionally, PsCRN115 regulates H_2O_2 homeostasis, whereas IPI-O affects the accumulation of callose. These results indicate that SA, callose, and H_2O_2 are important stress-resistance substances in plants, which is consistent with the results of previous studies (Luna et al. 2011; Jwa and Hwang 2017). Furthermore, SA can regulate the metabolism of callose and H_2O_2 (Nishimura et al. 2003; Dong et al. 2008; Chen et al. 1993), and a correlation between callose metabolism and H_2O_2 metabolism has been confirmed (Luna et al. 2011).

However, these physiological phenomena are insufficient to reveal the regulatory roles of effectors related to plant immunity because the functions of effectors in plants are extremely complex. For instance, the *P. infestans* effector AVR3a interacts with the E3 ligase CMPG1 to manipulate plant immunity, whereas the *P. syringae* T3SS AvrPtoB exhibits E3 ubiquitin ligase activity, which is required to suppress plant innate immunity (Abramovitch et al. 2006; Rosebrock et al. 2007). In addition, the XopL effector of *Xanthomonas campestris* pv. *vesicatoria* can suppress plant defenses in an E3 ubiquitin ligase activity-dependent manner (Singer et al. 2013). Therefore, E3 ubiquitin ligase is a ubiquitous component of plant immune systems, and the effectors of bacteria, fungi and oomycetes affect the E3 ubiquitin ligase-mediated system to promote infections. The MAPK pathway-mediated immune system is influenced by the *P. syringae* effectors HopAI1 and HopF2 and the *Phytophthora* effectors PexRD2, Avh331, and PsCRN63 (Zhang et al. 2007; Wang et al. 2010), implying that the effectors of bacteria and oomycetes act on the same plant immune system.

Plants contain distinct conserved immune systems, with certain associations existing among the immune system components. Numerous interactions between the effectors and immune system components form a complex cross-linked network that regulates plant stress resistance, but the network has only been preliminarily characterized. The gradual elucidation of the entire network is an important objective for future studies and will greatly aid investigations regarding pathogenesis and plant disease resistance.

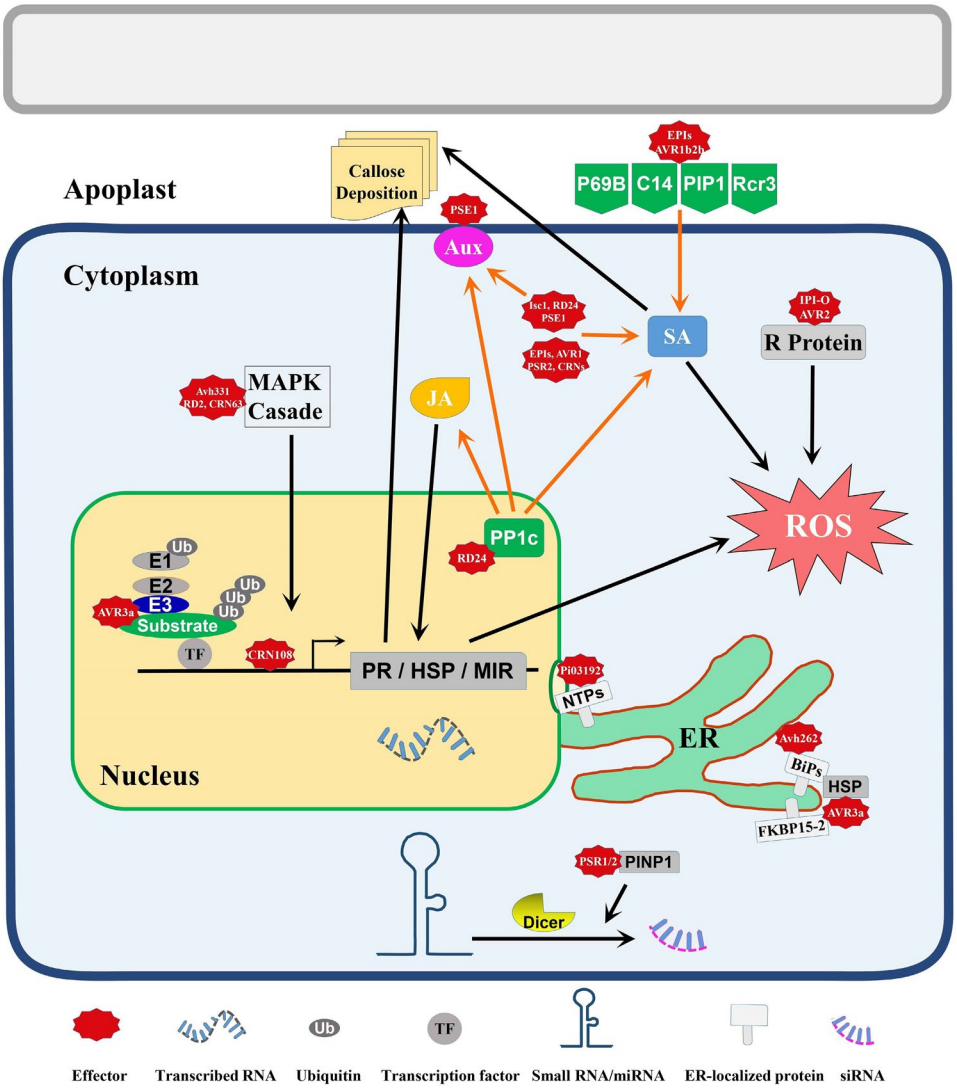

Fig. 2 Proposed model of *Phytophthora* effectors acting on various plant immune system components. *Phytophthora* species secrete a large number of effectors acting on various plant immune system components during the infection processes. The effectors may manipulate the phytohormone (e.g., Aux, JA, SA) level or the apoplastic proteases (e.g., P69B, C14, PIP1 and Rcr3), nucleus protein phosphatase (e.g., PP1c), etc. (as indicated with orange arrows). They could also affect the cell signaling through manipulation of the MAPK cascade or the R protein-mediated responses. And, the endoplasmic reticulum (ER) and ER-localized proteins are also the targets of effectors, which may disturb the protein interacting network (e.g., BiPs) or the movement of ER-localized proteins (e.g., NTPs). Furthermore, the effectors could regulate the transcription factors that control the pathogen responses by manipulating the correlated proteasome pathway ligase (e.g., E3) or direct binding their target promoters, and interact with components (e.g., PINP1) that mediate the processing of small RNA or miRNA to affect the production of pathogen responsive siRNAs

Author contribution statement WW designed the outline of the article, composed the manuscript, and prepared the figures and tables. FJ compiled and reviewed the literature and edited the manuscript.

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