Go in for the kill
How plants deploy effector-triggered immunity to combat pathogens

Liang Wu[†], Huan Chen[†], Chad Curtis, and Zheng Qing Fu*

Department of Biological Sciences; University of South Carolina; Columbia, SC USA

[†]These authors contributed equally to this work.

Plant resistance (R) proteins perceive specific pathogen effectors from diverse plant pathogens to initiate defense responses, designated effector-triggered immunity (ETI). Plant R proteins are mostly nucleotide binding-leucine rich repeat (NB-LRR) proteins, which recognize pathogen effectors directly or indirectly through sophisticated mechanisms. Upon activation by effector proteins, R proteins elicit robust defense responses, including a rapid burst of reactive oxygen species (ROS), induced biosynthesis and accumulation of salicylic acid (SA), a rapid programmed cell death (PCD) called hypersensitive response (HR) at the infection sites, and increased expression of *pathogenesis-related* (*PR*) genes. Initiation of ETI is correlated with a complex network of defense signaling pathways, resulting in defensive cellular responses and large-scale transcriptional reprogramming events. In this review, we highlight important recent advances on the recognition of effectors, regulation and activation of plant R proteins, dynamic intracellular trafficking of R proteins, induction of cell death, and transcriptional reprogramming associated with ETI. Current knowledge gaps and future research directions are also discussed in this review.

Introduction

All organisms constantly interact with other organisms and the surrounding environment. Because of their sessile nature, plants cannot escape harsh environments or detrimental organisms. However, partially due to their rigid cell wall, plants are competent in dealing with a wide variety of abiotic and biotic stresses.[1,2] One of the major challenges that plants face is defending against many pathogens that cause diseases in plants.[3] Unlike animals, which have developed a circulatory system and specialized immune cells, plants rely on both conserved and unique defense mechanisms to defend themselves against pathogen infection.

The first layer of plant defense is a conserved defense mechanism shared by plants and animals. Plants and animals both have developed the ability to detect conserved small molecules associated with microbes called MAMPs, or microbe-associated molecular patterns. This first layer of immunity is called MAMP-triggered immunity (MTI). Two major MAMPs associated with plant bacterial pathogens, flagellin and EF-Tu, are recognized by the pattern recognition receptors (PRRs), FLS2 kinase and EFR kinase, respectively. Chitin is believed to be the major MAMP from plant fungal pathogens and the receptor for chitin has been shown to be a LysM domain receptor-like kinase, CERK1[4] or RLK1,[5] in *Arabidopsis*. The consequence of this recognition includes activation of a Mitogen-activated protein kinase (MAPK) pathway, oxidative burst, callose deposition, and restriction of pathogen growth, etc.[6] In order to cause diseases, plant pathogens such as fungi, oomycetes, and bacteria deliver effectors into plant cells. These effectors collectively suppress MTI; therefore, the pathogens carrying these effectors cause diseases on their host plants. During plant–pathogen coevolution, plants have developed resistance (R) proteins to recognize at least some of the effectors and activate plant defense. Effectors that are recognized by corresponding R proteins are called avirulence (Avr) proteins.[7] A pathogen that carries an Avr protein, which triggers plant resistance, is called an avirulent pathogen. Unlike virulent pathogens, which cause diseases, avirulent pathogens trigger plant defense. Infection by an avirulent pathogen will produce rapid programmed cell death (PCD), called the hypersensitive response (HR), in the local tissue.[8] Meanwhile, plants undergo transcriptional reprogramming and the expression of plant defense genes is activated.[9,10] This second layer defense is called effector-triggered immunity (ETI). Recognition of avirulent pathogens will also generate immune signal plant hormone salicylic acid (SA) and activate systemic acquired resistance (SAR) in the whole plant.[11,12] SAR is a broad-spectrum, long-lasting resistance in the whole plant after local exposure to an avirulent or virulent pathogen.

This review will be focused on ETI. In the last decade, tremendous progress has been made toward a better understanding of the molecular mechanism of ETI. Here we describe in detail the recent exciting developments on how plants deploy ETI to

combat pathogens. The current knowledge gaps and future directions will be discussed as well.

R Proteins

The majority of R proteins are intracellular nucleotide binding-leucine rich repeat (NB-LRR) proteins (**Fig. 1A**), which are subclassified based on their variable N-terminal domain into coiled-coil (CC)-NB-LRR or toll/interleukin 1 receptor-like (TIR)-NB-LRR protein families. Some R proteins have a C-terminal extension. For example, *Arabidopsis* RRS1-R (resistance to *Ralstonia solanacearum*-resistant allele), includes a WRKY transcription factor domain following the LRR at the C-terminal (**Fig. 1A**). Inactive R protein binds ADP, with intramolecular interactions between its different domains.[13] Upon induction, R proteins undergo conformational change, which releases the hidden nucleotide-binding site from intramolecular interactions in the presence of effector ligands, leading to ADP/ATP nucleotide exchange and hydrolysis in the central NBS domain.[13,14] It is generally believed that ENHANCED DISEASE SUSCEPTIBILITY1 (EDS1) is required for the disease resistance mediated by the TIR-NB-LRR class R proteins, while NON-RACE-SPECIFIC DISEASE RESISTANCE1 (NDR1) plays an essential role in the activation of resistance signaling mediated by the CC-NB-LRR class of resistance proteins.[15]

In response to pathogen infections, R proteins induce dramatic local physiological responses, including oxidative burst, production and accumulation of SA and nitric oxide (NO), and expression of *pathogenesis-related* (*PR*) genes and PCD, at the cost of altering normal physiological processes. Therefore, the activity of R proteins needs to be tightly controlled under uninfected conditions.

Regulation of R Genes

Some *R* genes only express in response to Avr effectors.[16-18] Rice (*Oryza sativa*) *R* gene *Xa27* is induced when challenged by *Xanthomonas oryzae* pv *oryaze* (*Xoo*) carrying *avrXa27* effector gene.[19] AvrXa27 belongs to the AvrBs3/PthA TAL effector family, the members of which contain repeats of 34 amino-acids with DNA-binding activity and a conserved C-terminal region with nuclear localization signal (NLS) motifs and transcription activation domains.[20] AvrXa27 differs from other members in the same family based on the number and arrangement of the repeats, which contribute to target binding specificity.[19] The expression of Xa27 is only detectable upon inoculation of the *Xoo* strain that delivers AvrXa27, while undetectable when challenged with PXO99^AME1 strain, which has an insertion mutation in the *avrXa27* gene.[19]

RNA silencing is a central regulator that controls gene expression at the transcriptional level via DNA methylation (TGS, transcriptional gene silencing) and posttranscriptional level via direct mRNA interference mediated by small RNAs (PTGS, posttranscriptional gene silencing).[21] Recently, RNA silencing has appeared as a key regulatory mechanism in negatively regulating expression of a cluster of *R* genes.[22] It was first determined that several *RPP5* locus *R* genes, including *RPP4* and *SNC1*, are regulated by siRNA-mediated PTGS. Upregulation of *SNC1* transcription is found in mutants, *dcl4* and *ago1*, which abrogate RNA silencing. In addition, microRNA miR482 was shown to target many *R* genes in different species and subsequently cause the cleavage of *R* gene mRNA and production of secondary siRNAs.[23] More recently, it has been demonstrated that *RNA-DEPENDENT RNA POLYMERASE 6* (*RDR6*) and *miR472* play important roles in ETI and basal defenses through PTGS of a subset of *R* genes.[24] Mutants of *rdr6* and *miR472m* displayed enhanced RPS5-mediated resistance with high accumulation of *RPS5* transcripts, suggesting that both *RDR6* and *miR472* act as negative regulators of ETI through post-transcriptional control of disease resistance genes.

Regulation of R Protein Level and Stability

Many *R* genes are expressed constitutively under uninfected conditions. Regulation of R protein level and stability is another mechanism for plants to control R protein signaling, avoiding unnecessary activation of defense responses and autoimmunity. A chaperone protein complex containing HSP90, SGT1, and RAR1 contributes to the stability and proper folding of R proteins during activation,[25] leading to downstream signaling. In addition to its positive regulatory role as a chaperone for R proteins, SGT1b was also demonstrated to negatively regulate the accumulation of RPS5 and SNC1.[26,27] An effort to screen for mutants with constitutive defense responses in *npr1–1* background identified a tetratricopeptide repeat-domain containing protein-encoding gene, *SUPPRESSOR OF rps4-RLD,* known as *SRFR1*. SRFR1 functions together with SGT1 to negatively regulate the accumulation of SNC1, RPS2, and RPS4 to prevent auto-activation of plant immunity.[27] Further study showed that F-box protein CPR1/CPR30 targets SNC1 and RPS2 for degradation through the SKP1-Cullin1-F-box (SCF) E3 ubiquitin ligase complex.[28,29] Light has been demonstrated to regulate plant R protein-mediated resistance and photoreceptors are involved in this regulation.[30-34] In-depth study showed that blue light receptors, CRY2 and PHOT2, stabilize R protein HRT against Turnip Crinkle Virus (TCV) infection by suppressing COP1 E3 ubiquitin ligase-mediated degradation of HRT.[34] R proteins stay inactive and are tightly controlled under non-pathogenic conditions even though they are required for plants to initiate robust defense responses to fight back pathogen attacks.

The Recognition between R Proteins and Pathogen Effectors

The first step for plants to activate an effective ETI upon infection from pathogens carrying avirulence genes is to recognize those Avr effectors that have been delivered into plant cells. Effector proteins usually interfere with plant basal resistance, or
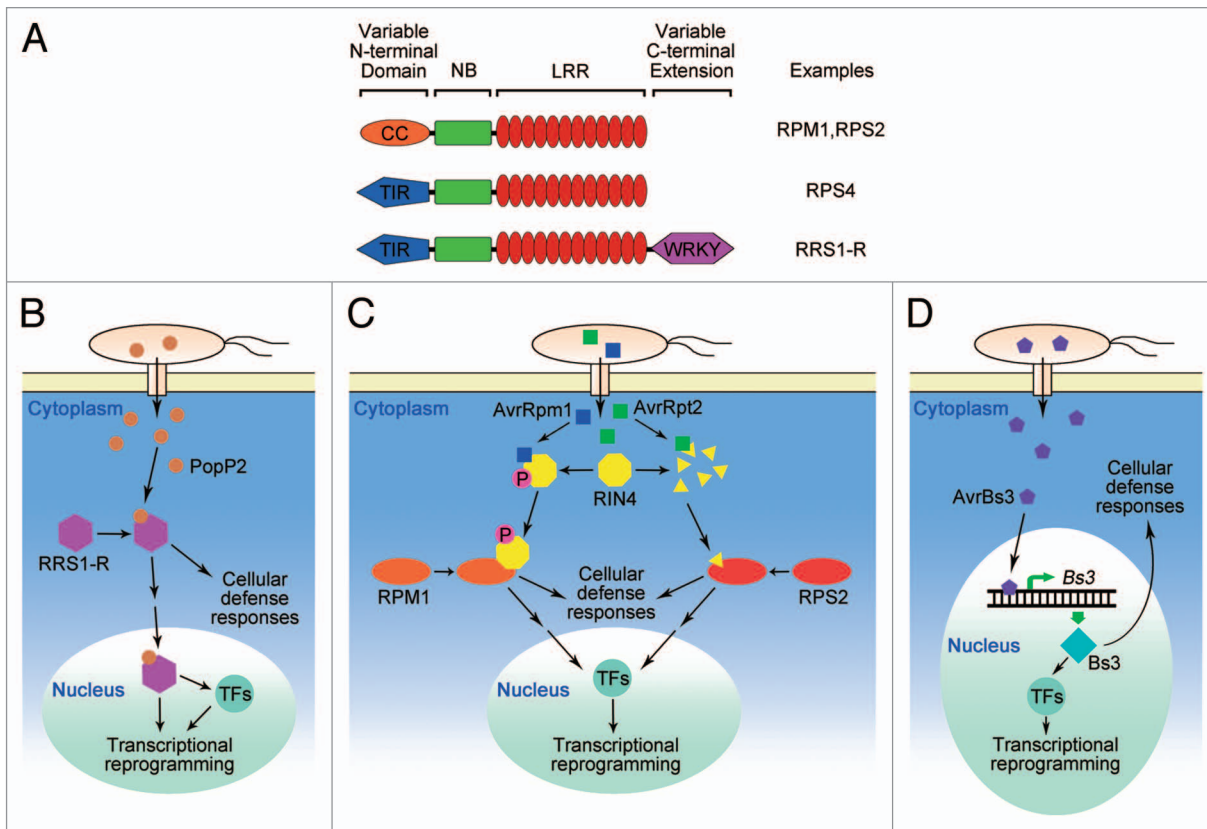
Figure 1. Recognition of pathogen effectors by plant resistance (R) proteins. (**A**) Structures of R proteins. The majority of R proteins are NB (nucleotide binding)-LRR (leucine-rich repeat) proteins, which are grouped into CC (coiled-coil)-NB-LRRs and TIR (toll/interleukin 1 receptor like)-NB-LRRs based on their distinct N-terminal domains. Some R proteins have a C-terminal extension required for their biological function, such as RRS1-R, which has a WRKY domain. (**B–D**) Simplified model showing examples of recognition between plant R proteins and pathogen effectors. (**B**) RRS1-R recognizes effector PopP2 through direct interaction, and relocated into nucleus to promote defense-related gene expression through its C-terminal WRKY transcription activator domain. (**C**) RIN4 is targeted by type III effectors AvrRpm1 and AvrRpt2, and surveilled by resistance proteins RPM1 and RPS2, respectively. RPM1 recognizes AvrRpm1-meidtaed phosphorylation of RIN4, while RPS2 detects the degradation of RIN4 by cysteine protease activity of AvrRpt2. (**D**) TAL (Transcription activator-like) effector AvrBs3 from xanthomonads (*Xanthomonas* spp.) induces the expression of R protein Bs3 after its nuclear localization to activate ETI (effector-triggered immunity). Recognition of effectors by plant R proteins triggers robust cellular defense responses, and transcriptional reprogramming of defense genes. TFs, transcription factors.

MTI, to help pathogens overcome plant resistance. Plants have evolved distinct mechanisms to recognize effectors. The direct interaction between a plant R protein and an Avr effector protein can be demonstrated by a recent example in *Arabidopsis*, where R protein RRS1-R recognizes effector protein PopP2 from a causal agent of bacterial wilt, *R. solanacearum* (**Fig. 1B**). Molecular evidence was provided to show the direct protein-protein interactions between RRS1-R and PopP2 in *Arabidopsis*-resistant Nd-1 ecotype,[35] and RRS1-R was shown to translocate into nucleus after PopP2 binding to regulate downstream gene expression (**Fig. 1B**). Direct recognition was also shown by the recognition of fungal effector AvrPita from *Magnaporthe grisea* by the rice R protein Pi-ta to trigger a signal transduction cascade that led to resistance.[36] AvrPita is predicated to encode a neutral zinc metalloprotease.[37] A variant of AvrPita, AvrPita[176], which lacks the N-terminal secretory signal and pro-protein sequences of AvrPita, elicited Pi-ta-dependent resistance responses when transiently expressed inside rice cells. Yeast two-hybrid and in vitro

binding assays showed direct interaction between AvrPita[176] and the Pi-ta leucine-rich repeat domain.[36] A recent study showed direct recognition of multiple effectors by the same R protein, which usually happens through indirect recognition. Evidence was provided to show that two distinct effectors, Avr1-CO39 and AvrPia, from rice blast fungal pathogen *M. oryzae* interacted directly with rice R protein RGA5, which worked in pair with RGA4 to induce resistance.[38] However, only a few cases of direct recognition between an R protein and an Avr effector have been demonstrated, even though direct recognition possibly contributes to gene-specific evolution diversity of both *R* and *Avr* genes, while indirect recognition imposes selection against the biological function of Avr effectors.[39]

The guard model has been developed to explain indirect recognition between R proteins and Avr effectors in plant, in which a target host protein is manipulated by pathogen effectors and the perturbation of the target protein is monitored by plant R proteins. Plant RPM1-INTERACTING PROTEIN 4 (RIN4) has

been shown to play a crucial role in the recognition of AvrRpm1 and AvrRpt2 by the corresponding plant R proteins, RPM1 and RPS2, respectively[40,41] (**Fig. 1C**). RPM1 perceives the phosphorylation of RIN4, while RPS2 senses the disappearance of RIN4 protein.[40,41] Recent studies showed that a receptor-like cytoplasmic kinase, RIPK (RPM1-induced protein kinase), physically interacts with RIN4 and phosphorylates RIN4 at multiple amino acid residues in response to bacterial effectors AvrRpm1 and AvrB.[42,43] AvrRpt2 induces RIN4 degradation with its cysteine protease activity[44-46] (**Fig. 1C**). RIN4 is a regulator of plant MTI. RIN4 controls stomatal apertures through associated plasma membrane H(+)-ATPases, AHA1 and AHA2, to resist pathogen invasion.[47,48] Independently evolved virulence effectors targeting hub proteins, such as RIN4, in plant immune system networks enable the plant to respond to infections by monitoring these hub proteins with a relatively limited number of R proteins.[49,50] Another example of a guarded hub protein is EDS1, which was assumed to constitute a common downstream signaling component of several TIR-NBS-LRR proteins based on genetic studies.[51] EDS1 was recently shown to be a target for AvrRps4 and HopA1 effectors, and was guarded by RPS4, RPS6, and SNC1 resistance proteins.[52,53]

Some of the plant target proteins evolved into decoys, which were no longer biologically functional, but remained to be the targets for pathogen effectors and guardees for plant R proteins. ZED1 in *Arabidopsis* is a nonfunctional kinase that interacts with and is acetylated by HopZ1a, a type III effector from *Pseudomonas syringae* that triggers ZAR1-mediated defense responses. HopZ1a is an acetyltransferase that is hypothesized to target kinases to promote pathogen virulence. Conserved domain analysis of the protein sequence indicated that ZED1 is a kinase, however, showed no kinase activity in phosphorylation assays. ZED1 interacts with both HopZ1a and ZAR1, and is required for the recognition of HopZ1a by the ZAR1 to induce a robust immune response to limit bacteria growth. Thus, ZED1 very likely evolved as a decoy to trap HopZ1a and lure it to the ZAR1 resistance-complex.[54] Even though the decoy model is supported by multiple cases, it is arguable that discrimination between the decoy model and the guard model remains challenging and requires further experimental evidences.[55] An interesting case involves tomato (*Solanum lycopersicum*) protein kinase Pto, which is targeted by the corresponding Avr effector, AvrPto, from *P. syringae* pv *tomato*. It was first described as an example for direct recognition supported by evidence from the yeast two-hybrid, protein mutagenesis and infection assays that strongly indicated direct physical interaction between Pto and AvrPto.[56-59] Further study showed the involvement of NBS-LRR protein Prf in AvrPto-Pto triggered immune response, leading to Pto kinase being considered as a guardee monitored by Prf resistance protein.[60] More recent work proposed that Pto acts as a decoy in competition with FLS2 for AvrPto binding.[61,62] FLS2 is a receptor kinase which recognizes bacterial MAMP flagellin to trigger MTI and is believed to be the real target of AvrPto.[63]

The knowledge of a unique way of recognition between a plant R protein and a pathogen Avr effector came from studies on transcription activator-like (TAL) effectors from *Xanthomonas* pathovars. These effectors enter the nucleus and bind to promoters to alter the expression of target genes in order to promote virulence. AvrBs3 from *X. campestris* pv *vesicatoria* targets the promoter of *UPA20*, which is a master regulator gene of cell enlargement in pepper, to help bacterial proliferation.[64] AvrBs3 is recognized by Bs3, a protein product of the *R* gene *Bs3*, which shares a similar promoter sequence to AvrBs3 target genes,[65,66] and thus can be induced by AvrBs3 (**Fig. 1D**). No *Bs3* expression was detected in the absence of AvrBs3 in different plant tissues, indicating that Bs3 is not functional for normal cellular activities,[65,66] and likely a decoy to trap AvrBs3 to initiate Bs3-mediated resistance.[67]

Nuclear Function of R Proteins

Nuclear localization of several R proteins is essential for ETI, which leads to transcriptional activation of defense signaling. Deslandes et al. identified TIR-NB-LRR-WRKY protein RRS1-R to be the first R protein that has been shown to localize in the nucleus.[68] The presence of a C-terminal WRKY domain suggested a biological function for RRS1-R in the nucleus. Sequence analysis further showed that RRS1-R has an NLS signal.[68] Indeed, it has been shown that RRS1-R localized into the nucleus and its nuclear localization is dependent on the type III effector PopP2, which is recognized by the R protein RRS1-R.[35] RRS1-R was found to physically interact with its cognate effector PopP2 and to co-localize with PopP2 in the plant nucleus.[35] More clearly through quantitative fluorescence lifetime imaging, it is illustrated that barley (*Hordeum vulgare*) mildew R protein A10 (MLA10), recognizing effector AvrA10, traffics from the cytoplasm into the nucleus where its CC domain interacts with transcription factors HvWRKY1/2 and MYB6 in the nucleus to activate downstream transcriptional reprogramming.[69] *P. syringae* type III effector AvrRps4 is recognized by resistance protein RPS4 and triggers ETI. The cell has cytoplasmic and nucleoplasmic pools of EDS1, which must accumulate in the nucleus for RPS4 to trigger proper immunity processes.[52,70] After injection into plant cells, AvrRps4 is cleaved to trigger RPS4-mediated signaling, which results in nuclear localization of RPS4 to interact with RRS1-R, a resistance receptor with a C-terminal WRKY transcription factor DNA-binding domain, to promote immunity.[71,72] RPS4 is believed to be a receptor that intercepts targeting of EDS1 by effectors.[52] This interception and subsequent nuclear localization of RPS4-AvrRps4 triggers EDS1 to activate EDS1-dependent resistance genes, mounting an ETI response.

Trafficking of R Proteins between the Nucleus and Cytoplasm

Intracellular movement of different proteins between the cytoplasm and nucleus is an important feature in plant immunity.[73,74] Recent studies revealed that nucleo-cytoplasmic

trafficking though nuclear pore complexes plays an important role for R protein nuclear localization and the proper function of R proteins. In an effort to discover key components involved in R protein function, several *mos* (*modifier of SNC1*) mutants were identified in a suppressor screen in gain of function *snc1* (*Arabidopsis suppressor of npr1–1, constitutive 1*) mutant, which showed a phenotype of constitutively activated plant defense due to a mutation in the TIR-NB-LRR *R* gene *SNC1*.[75] Among them, three MOS proteins that are important for nuclear pore function were required for the functions of R proteins. MOS3 is required for basal resistance and proper SNC1 function. *mos3–1* mutant suppressed the constitutive activation of resistance phenotype in *snc1* plants. Green fluorescent protein (GFP) tagging of MOS3 showed localization of MOS3-GFP to the nuclear envelope. Due to similarities in sequence between MOS3 and nucleoporin 96, it is likely that *MOS3* encodes a nucleoporin that plays a central role in the nuclear transport of SNC1.[76] *MOS6* encodes importin α3, which is instrumental in transport across the nuclear envelope. When MOS6 protein was tagged with GFP on the C-terminus, the GFP fluorescence signal was concentrated in the nucleus, supporting the nuclear localization pattern necessary for an importin protein. The *mos6* mutant partially suppresses the constitutive defense phenotype in *snc1* mutant plants, and *mos6* mutant plants were more susceptible to a virulent oomycete pathogen.[77] MOS7 is homologous to nuclear pore complex component Nup88 in humans and *Drosophila*. MOS7 C-terminus GFP fusion protein showed accumulation at the nuclear rim. SNC1 has a nuclear localization sequence; however, in *mos7–1* mutant, nuclear accumulation of SNC1 resistance protein is diminished.[78] NPR1 and EDS1 plant basal resistance proteins also have reduced localization to the nucleus in *mos7* mutants.[78] Thus, MOS3, MOS6, and MOS7 have a central role in R protein nuclear localization.[78]

Plant Defense Responses Associated with ETI

Localized programmed cell death

The striking characteristic of ETI is the hypersensitive response, which exhibits a rapid induction of programmed cell death at the local infection site (localized PCD). The primary purpose of this cell death is to kill biotrophic pathogens, which have to obtain nutrients from living cells. PCD has been classified into two different types, autolytic-PCD and nonautolytic-PCD,[79] with distinct characteristics. Autolytic-PCD involves the release of hydrolases from vacuoles, leading to a rapid cytoplasm clearance and localized cell death. Nonautolytic-PCD, however, does not release hydrolases that clear the cytoplasm even when the permeability of tonoplasts is persistently increased.[79] The cell death upon the activation of R protein signaling was described as a process of releasing vacuolar antibacterial proteins into the apoplast, resulting from the fusion of the central vacuole membrane and plasma membrane,[80] and thus is likely nonautolytic-PCD.[81]

Regulation of localized PCD by salicylic acid concentration gradient and NPR proteins

PCD in *Arabidopsis* is under regulation by SA, NPR1, and SA receptors NPR3 and NPR4. Low level of SA suppresses cell death, while over-accumulation of SA induces cell death. When infected by an avirulent pathogen, the plants undergo PCD at the local infection sites. In an area up to 3.5 mm away from the center of cell death zone on *Nicotiana tabacum* L. leaves, the level of SA is 8-fold higher than in the zone 3.5–6.5 mm from the center 120 h post tobacco mosaic virus (TMV) infection, and 27-fold higher than in the zone 6.5–10 mm from the center.[82] NPR1 is a suppressor of cell death. NPR3 and NPR4, as BTB/POZ domain proteins, interact with both NPR1 and Cullin 3 E3 ligase and function as adaptor proteins to facilitate the poly-ubiquitination and subsequent degradation of NPR1 protein by the 26S proteasome.[83] NPR4 has a high affinity for SA while NPR3 has a low affinity for SA. High SA level at the center of cell death zone disrupts the interaction between NPR1 and NPR4, but favors the interaction between NPR1 and NPR3. NPR3 then promotes degradation of NPR1 to a level that is not sufficient to suppress cell death. In neighboring cells, the intermediate level of SA disrupts NPR1–NPR4 interaction, but is not high enough to promote NPR1–NPR3 interaction, so neither NPR3 nor NPR4 can mediate the degradation of NPR1. As a result, the high level of NPR1 in these neighboring cells suppresses the spreading of cell death and interacts with transcription factors to activate plant defense responses.[83]

ROS and cell death

It is generally believed that the onset of HR is due to elevated level of reactive oxygen species (ROS). One major way of generating ROS during plant–pathogen interactions is through NADPH oxidases, which are called respiratory burst oxidase homologs (RBOHs) in plants. Cell death is greatly reduced in *Arabidopsis atrbohD* mutant and *atrbohD/F* double mutant plants compared with that in wild type plants following infection by an avirulent bacterial pathogen,[84] indicating that RBOHs and ROS are required for cell death induced by avirulent pathogens (**Fig. 2**). However, the relationship between ROS production and cell death is far more complicated than originally thought. For example, when infected with an avirulent oomycete pathogen, *Arabidopsis atrbohD/F* double mutant plants exhibited more cell death even though the ROS was eliminated.[84] When challenged by bacterial AvrRpm1, *Arabidopsis nca1* (no catalase activity 1) and *cat2* (*catalase 2*) mutants, which were supposed to have elevated ROS, surprisingly showed reduced cell death.[85] This result suggests the presence of additional pathways downstream of catalase other than through ROS in regulating cell death. The biological connection between ROS and PCD thus remains to be further studied.

Autophagy and cell death

One important discovery related to ETI is the finding that PCD is regulated by autophagy (**Fig. 2**). Liu et al. showed that downregulation of autophagy genes *ATG6* and *ATG7* in *Nicotiana benthamiana* caused extended cell death when these plants were infected by TMV.[86] Later, the same group showed AvrRpm1-induced HR in *ATG6* antisense plants also spread to uninfected tissue.[87] Both studies support a function for
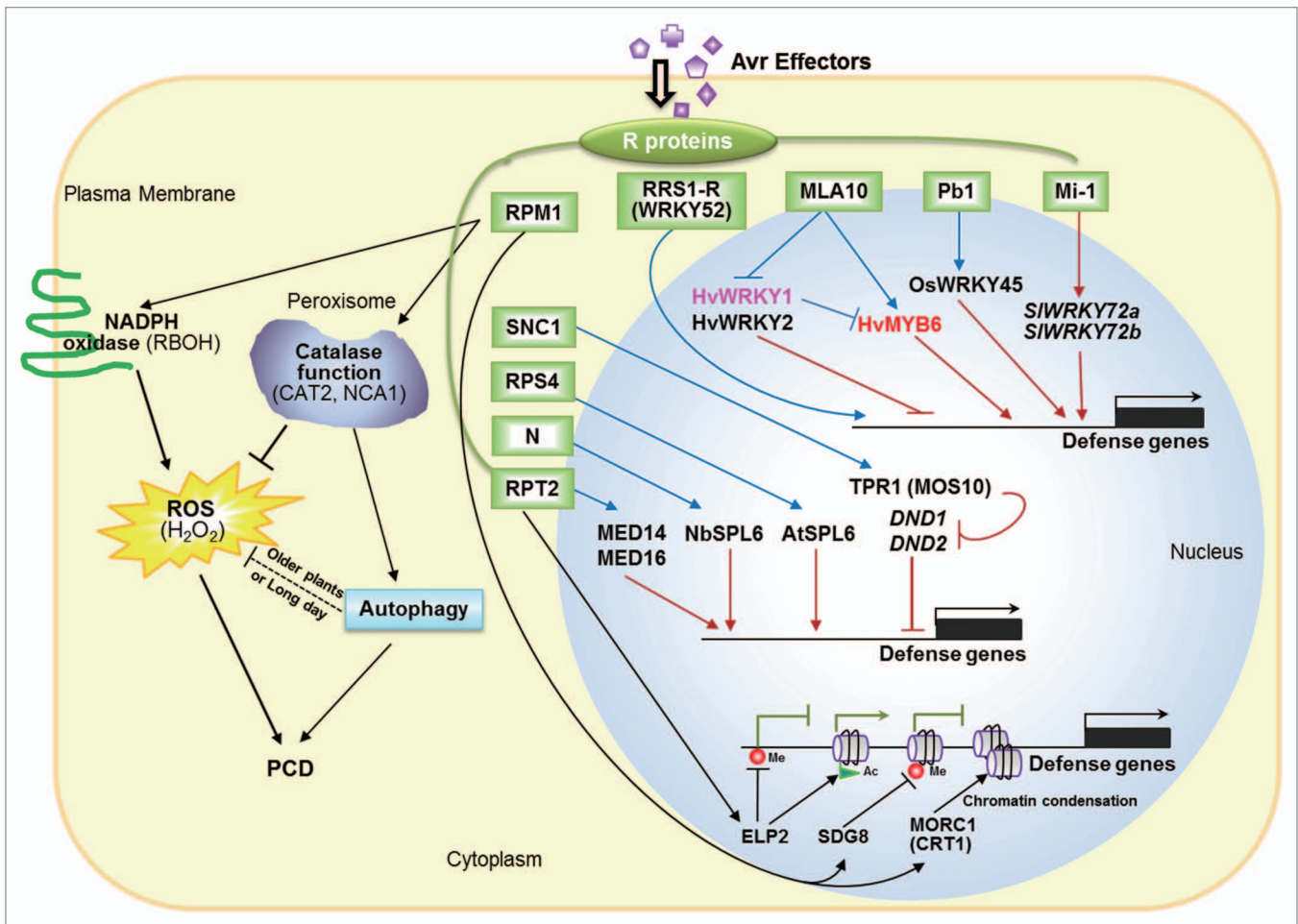
Figure 2. For figure legend, see page 716.

autophagy genes to restrict PCD to infection sites and negatively regulate PCD. However, a different study showed that *ATG7* and *ATG9* knockout plants exhibited suppressed initiation of TIR-NB-LRR type R proteins-mediated EDS1-dependent cell death, while CC-NB-LRR type R proteins-mediated NDR1-dependent cell death is autophagy-independent. Therefore, autophagic cell death regulated by ATG7 and ATG9 contributes to PCD mediated by certain type R proteins.[88] This dual role of autophagy in PCD is partially explained by studies from a third group, which showed that the positive or negative role of autophagy in PCD is dependent on the age of the plant leaves and photoperiod conditions used in the assays. Only older leaves of *atg5* mutant plants showed spread RPM1-mediated cell death, which is believed to be a result of excessive ROS production and over-accumulation of SA.[89] In addition, the role of autophagy in PCD is dependent on the photoperiod conditions (**Fig. 2**), as *atg2* mutant plants showed reduced cell death under short-day conditions, and exaggerated cell death when short-day-grown plants were moved to long-day conditions.[89] Furthermore, autophage-dependent cell death has been demonstrated to be regulated by ROS and catalase[85] (**Fig. 2**). It will be of interest to the field of plant-microbe interactions to uncover the molecular mechanism underlying the regulatory role for autophage in PCD.

Transcriptional Reprogramming of Defense-Responsive Genes

WRKY transcription factors

ETI is a strong plant immune response associated with extensive transcriptional reprogramming that involves numerous transcriptional regulators[9,10,90,91] (**Fig. 2**). Dynamic recruitment of transcriptional regulators into R protein-mediated signaling pathways has emerged as an important signaling event after the recognition of Avr effectors during ETI.[92,93] Many WRKY transcription factors have been shown to play pivotal roles in regulating defense responses.[94,95] TIR type R protein RRS1-R/WRKY52, which contains a C-terminal WRKY domain, interacts with the *R. solanacearum* type III effector PopP2 in the nucleus.[35,68,96,97] RRS1-R/WRKY52 is identical to SENSITIVE TO LOW HUMIDITY 1 (SLH1), which, when inactive, functions as a transcription repressor of many downstream defense genes including *PR1*, *PR2*, *PR5*, *EDS1*, and *PHYTOALEXIN-DEFICIENT4* (*PAD4*).[98] Upon recognition of PopP2, RRS1-R/WRKY52 induces resistance signaling, possibly by suppressing the negative function of its WRKY DNA-binding domain, or through activation of other positive transcription regulators[96] (**Fig. 2**). Future research on identification of the RRS1-R/

WRKY52/SLH1 interacting components and target genes will facilitate better understanding of the regulatory role of RRS1-R in plant defense signaling.

In barley, HvWRKY1/2 TFs interact with R protein MLA10 upon activation by avirulence A10 effector[69] (**Fig. 2**). Silencing and overexpression experiments have shown that these WRKY TFs act as transcriptional repressors of basal defense during compatible and incompatible interaction with pathogens, indicating that repression of these WRKY TFs-mediated negative regulation of MAMP-induced genes could be a way to trigger the MLA-mediated defense responses.[69] Likewise, the homologs of HvWRKY1/2 in *Arabidopsis*, known as AtWRKY18/40, have been identified in repressing basal defense responses to virulent hemibiotrophic *P. syringae* and virulent powdery mildew pathogen *Golovinomyces orontii*. AtWRKY18 and AtWRKY40 repress the expression of positive regulators of defense by direct binding to the W-box *cis*-elements in the promoters of these regulator genes such as *EDS1*, APETALA2/Ethylene Responsive Factor (AP2/ERF)-type TF gene *RRTF1* and *JASMONATE-ZIM-DOMAIN PROTEIN 8* (*JAZ8*).[69,99] Indeed, MLA10 interacts with two antagonistically acting TFs, HvWRKY1 transcription repressor and HvMYB6 transcription activator. The activated MLA10 can release the positive regulator HvMYB6 from HvWRKY1 repression to initiate downstream transcriptional reprogramming during innate immune responses[100] (**Fig. 2**). Additional defense genes directly modulated by WRKY1-MYB6 will need to be defined. These findings demonstrated that MLA10 activates

defense gene transcription by interfering with WRKY repressors through direct interaction and releasing transcription activators from WRKY repression.

Differing from the majority of WRKY TFs, OsWRKY45 is a transcriptional activator and positively regulates rice resistance to panicle blast (**Fig. 2**). A CC-NB-LRR family R protein Pb1 stabilizes OsWRKY45 to avoid its degradation in a ubiquitin proteasome system.[101] It is possible that the stabilization of OsWRKY45 enhances its transcriptional activity and upregulates expression level of its encoding gene *OsWRKY45*, and also *OsWRKY46* and *RDX* genes in blast resistance.[101,102] In tomato, two SlWRKY72 type TFs were also shown to positively regulate basal resistance and resistance mediated by R protein Motelle (Mi-1)[103] (**Fig. 2**).

SPL6 transcription factor and TPR1 corepressor

Similar to the function of WRKY TFs in R protein Pb1 and Mi-1-mediated resistance, SQUAMOSA PROMOTER BINDING PROTEIN (SBP) domain-containing transcription factor SPL6 and corepressor TPR1 have been shown to play positive roles in TIR-NB-LRR R proteins, N and SNC1, -mediated plant defense responses, respectively (**Fig. 2**). SPL6 has been shown to directly bind to N protein and is required for N-mediated resistance to TMV. *Arabidopsis* SPL6 homolog, AtSPL6, activates expression of a subset of defense genes. It is required for TIR-NB-LRR type R protein RPS4-mediated resistance, but not required for the signaling of CC-NB-LRR type R proteins RPM1 and RPS2, suggesting that the regulatory role of SPL6 in ETI might be specific.[104] The transcription corepressor Topless-related1

(TPR1; previously identified as *modifier of snc1, 10* [MOS10]), which interacts with SNC1 in vivo and in vitro, has been shown to be a positive regulator to activate SNC1-mediated resistance.[105] Two negative regulators of plant defense, *Defense no Death 1* (*DND1*) and *Defense no Death 2* (*DND2*), were among dozens of genes that are suppressed by TPR1 in defense responses.[105] Thus, the repression of negative regulators is implicated in SNC1-mediated downstream transcriptional reprogramming in ETI.

The Mediator complex

The Mediator (MED) complex is a conserved transcription regulator in eukaryotes, which acts as an adaptor between TFs and the RNA polymerase II (RNAPII) to regulate transcriptional reprogramming.[106] The core of mediator consists of more than 20 subunits, which are organized into three modules, namely head, middle and tail. To date, many characterized Mediator subunits (MED8, MED14, MED15, MED16, MED19a, MED21, and MED25) in *Arabidopsis* have been functionally characterized in plant immunity.[91,107,108] Two tail module subunits, MED14 and MED16, function as positive regulators in ETI[91,109] (**Fig. 2**). Both the *med14* and *med16* mutants were deficient in transcriptional reprogramming induced by avirulent bacterial pathogen *P. syringae* pv *tomato* (*Pst*) DC3000 (*avrRpt2*), and conferred susceptibility to both *Pst* DC3000 (*avrRpt2*) and *Pst* DC3000. Interestingly, the number of affected genes was smaller in *med14* mutant plants than in *med16* mutant post *Pst* DC3000 (*avrRpt2*) infection.[109] These data imply that MED14 and MED16 might regulate plant defense gene expression using different mechanisms during ETI.

Chromatin modifications

Rapid transcriptional changes in ETI can be extensively influenced by modulation of chromatin configuration utilizing different mechanisms, such as methylation of cytosine residues located in DNA, posttranslational modifications of histones and ATP-dependent chromatin remodeling. The *Arabidopsis* Elongator complex subunit2 (ELP2) was recently postulated as a genomic DNA demethylase, which is typically required for the demethylation and induction of *NPR1* and *PAD4* genes in response to avirulent DC3000 (*avrRpt2*) infection[107] (**Fig. 2**). Also, ELP2 possesses histone acetyltransferase activity, which is essential for the expression of several defense genes (i.e., *NPR1*, *PR2*, *PR5*, *EDS1*, and *PAD4*)[107] (**Fig. 2**). In fact, ELP2 has been confirmed as a major positive regulator of ETI, which promotes RPS2 and RPS4-mediated resistance to pathogens and kinetically induces defense genes, likely through histone modification.[110] Being a histone methyltranserase, *Arabidopsis* ATX1, a Trithorax (TRX) family protein, mediates the methylation of lysine 4 in histone H3 protein through its SET (named after three *Drosophila* proteins SUPPRESSOR OF VARIEGATION 3–9 (SU[VAR] 3–9), ENHANCER OF ZESTE (E[Z]) and TRX-containing domain, and is responsible for the upregulation of defense genes (i.e., *WRKY70*, *PR1*, and *R* genes).[111] Infection assays showed that *atx1* mutant was resistant to *Pst* DC3000 *hrcC* mutant strain rather than virulent DC3000, indicating that ATX1 is a positive regulator of basal resistance.[111] However, the potential role of ATX1 in ETI remains to be further determined, considering the altered expression of TIR-NB-LRR *R* genes and other defense-related genes in *atx1* mutant. Remarkably, another histone methyltransferase, SET DOMAIN GROUP 8 (SDG8), which epigenetically upregulates expression of a TIR-NB-LRR (*RPS4*-like) gene in a gene-specific manner, was shown to be required for RPM1-mediated resistance in *Arabidopsis*[112] (**Fig. 2**).

A conserved tetratricopeptide repeat (TPR) domain-containing protein known as SRFR1, similar to transcription repressors in other organisms, negatively regulates multiple NB-LRR R proteins and might work to suppress target genes by directing the preacetylation of nucleosomes.[113] Another conserved transcription cofactor, AtTIP49a, was shown to interact with the N-terminal half of RPM1 (CC-NB-LRR) and RPP5 (TIR-NB-LRR), and may act as a negative regulator of two RPP (for Resistance to *Peronospora parasitica*) proteins-dependent disease resistance.[114] TIP49a was initially found to be associated with the TATA binding protein (TBP) complex. TBP complex negatively regulates the transcription of oncogene *c-myc*, which contributes to cancer genesis and is induced by hepatitis C-virus infection,[115] through modification of chromatin involved in the recruitment of histone deacetylases.[116] Thus, it will be interesting to study other examples of the recruitment of SRFR1 or TIP49a, as well as chromatin-remodeling complexes, to specific target genes in plants.

Chromatin superstructure

Mutation of Microrchidia (MORC) family ATPase genes, *AtMORC1* and *AtMORC6*, results in the induction of DNA-methylated genes and transposable elements without affecting the DNA and histone methylation status. Based on data from Hi-C analysis, a method to study three-dimensional architecture of genomes,[117] the *atmorc1* and *atmorc6* mutants both showed decondensation of pericentromeric DNA regions.[118] *AtMORC1* is the same gene as *CRT1*, which was found to be required for disease resistance to TCV mediated by HRT.[119] In addition, CRT1 physically interacts with several R proteins including RPS2, Rx, and RPP8, and also R protein chaperone HSP90.[120] Silencing of CRT1 homolog in *N. benthamiana* caused reduced cell death triggered by Pto and RPM1, and *crt1* mutant plants showed compromised *R* gene-mediated defense responses[120] (**Fig. 2**). Taken together, these studies suggest that regulation of chromosome superstructure plays an important role in proper function of ETI.

Future Perspectives

There is no doubt that many recent discoveries have helped the community to gain a much better understanding of ETI. Tremendous progress has been made in unraveling the molecular mechanisms of ETI, especially in the recognition of Avr effectors, activation of R proteins and transcriptional reprogramming of plant defense genes. New models, including guard hypothesis and decoy model, have been developed to explain the recognition mechanism of Avr effectors by R proteins, along with the discovery and characterization of new effectors and their corresponding R proteins. However, details of these recognition events at the molecular level remain to be further studied. The resolution of molecular structures of Avr and R proteins will increase our understanding of the interactions between Avr and R proteins,

and their biological roles. For example, a structural study of the molecular basis for plant immunity activated by AvrPto confirmed the inhibition of Pto kinase activity by AvrPto.[121] This study challenged a widely held hypothesis that AvrPto activates Pto kinase activity and helped with a better understanding of Pto-mediated defense signaling. Structural studies of Avr and R proteins will also make it more accurate to predict potential interactions between Avr and R proteins. R proteins undergo conformational changes upon activation. Alteration of intramolecular interaction between its different domains results in the binding of ADP to inactive R proteins and the binding of ATP to active R proteins. The model for the activation of R protein by an ATP/ADP molecular switch is largely based on their similarities to animal nucleotide-binding oligomerisation domain (NOD) proteins.[122-124] More data from structural studies of plant R proteins are needed to support the legitimacy of this model. Furthermore, structural studies of purified R protein complexes before and after pathogen infection could be the key to understanding the dynamics of R protein functions. Knowledge of the crystal structure of R proteins with their corresponding partners in their inactive and active status will greatly benefit the understanding of the ETI initiation.

Activation of R proteins leads to extensive transcriptional reprogramming of plant defense genes. Plant transcriptional regulators related to ETI comprise not only canonical DNA-binding TFs that act as transcription activators or repressors, but also cofactors including coactivators and corepressors that associate with DNA-binding and transcription regulatory components to fine-tune host transcription during ETI. Characterized transcription regulators have been shown to play crucial roles in manipulating transcriptional reprogramming of many defense-responsive genes through dynamic interaction with cognate R proteins and recruitment of factors to modify chromatin structure. However, novel transcription regulators and their specific regulatory roles in plant defense signaling remain to be discovered. Further decryption of interplay between different transcriptional and posttranscriptional modifications (e.g., methylation, acetylation, S-nitrosylation, phosphorylation, and ubiquitinylation) will shed light on the regulatory network of plant immunity. It is also noteworthy that extensive transcriptional changes during ETI may require alteration of chromatin configuration through orchestrating transcription associated factors, histone modification, and chromatin remodelers. Thus, to better understand the precise role of epigenetic regulation of R protein-mediated resistance, a study utilizing both classic genetic analysis and cutting-edge systemic approaches will be extremely helpful and necessary.

To better control plant disease in the field, one potential application of the knowledge we gained so far is to construct transgenic crop plants expressing exogenous *R* genes to reduce the risk of infection of the host plants by certain pathogens. However, overexpression of *R* genes in transgenic plants carries a tremendous fitness cost. One possible strategy to bypass this problem is to introduce *R* genes into crop plants under the control of pathogen inducible promoters. Furthermore, introducing an exogenous *R* gene could potentially expose plants to new diseases caused by nectrotrophic pathogens. Lorang et al. recently reported that victorin effector from necrotrophic pathogen *Cochliobolus victoriae*, which kills plants to obtain nutrients, binds to the target protein TRX-h5 to activate R protein LOV1-mediated cell death in order to cause diseases in *Arabidopsis*.[125] This provided an excellent example of a necrotrophic pathogen taking advantage of cell death caused by ETI. This area of research is a new emerging theme in plant-pathogen interaction research. Another study showed that effector ToxA, from necrotrophic fungal pathogen *Stagonospora nodorum,* promotes the susceptibility of host plants by inducing *Tsn1*-dependent cell death.[126] *Tsn1* encodes a protein similar to R protein with a serine/threonine protein kinase (S/TPK) domain and NBS-LRR domains.[126] It is likely that more examples of this kind of interaction between a pathogen and host plant will be discovered soon. As discussed by Lorang et al., while scientists explore the possibility of utilizing R proteins to control plant diseases, it is also possible that the newly introduced R proteins will be targeted by effectors from necrotrophic pathogens, and benefit necrotrophic pathogen infections.[125]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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