

Effector-Triggered Immunity in Plants

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Plants rely on multiple immune systems to protect themselves from pathogens. When pattern-triggered immunity (PTI)—the first layer of the immune response—is no longer effective as a result of pathogenic effectors, effector-triggered immunity (ETI) often provides resistance. In ETI, host plants directly or indirectly perceive pathogen effectors via resistance proteins and launch a more robust and rapid defense response. Resistance proteins are typically found in the form of nucleotide-binding and leucine-rich-repeat-containing receptors (NLRs). Upon effector recognition, an NLR undergoes structural change and associates with other NLRs. The dimerization or oligomerization of NLRs signals to downstream components, activates “helper” NLRs, and culminates in the ETI response. Originally, PTI was thought to contribute little to ETI. However, most recent studies revealed crosstalk and cooperation between ETI and PTI.

pathogen

effector

PTI

ETI

NLR

plant immunity

1. Introduction

Plants and pathogens continually compete for supremacy as they coevolve. In nature, many plants are resistant to most pathogens, but some pathogenic microbes are capable of causing severe diseases. The primary barrier of plants against pathogenic invasion is the preformed defense layer, including the plant cell wall and pre-produced metabolites ^{[1][2][3][4]}. To successfully respond to and defend against pathogenic microbes, plants developed multilayered protective and surveillance networks ^[5]. The first layer of the plant immune system is pattern-triggered immunity (PTI), which is activated by pathogen-associated molecular patterns (PAMPs), the conserved molecular structures of pathogens such as fungal chitin or bacterial flagellin, or damage-associated molecular patterns, which are molecules resulting from plant–pathogen interactions such as peptides and oligosaccharides ([Figure 1](#)). These inducers can be recognized by pattern recognition receptors (PRRs), plasma membrane-localized plant immune receptors, which are mainly found in the forms of receptor-like protein kinases and receptor-like proteins ^{[6][7][8]}. Activation of these receptors provokes an array of plant defense responses to halt pathogen spread and colonization ^{[9][10]}. PTI activates multiple signaling pathways in the host cells ([Figure 1](#)). One of the rapid responses is an influx of extracellular Ca^{2+} into the cytosol ^{[11][12][13]}, followed by the activation of mitogen-activated protein kinases ^{[14][15]}, reactive oxygen species (ROS) signaling ^{[12][16]}, and other signaling molecules, such as reactive nitrogen species, lipids, callose, salicylic acid, n-hydroxypipericolic acid, jasmonic acid, ethylene, and cytokinin ^{[17][18][19][20][21][22][23][24][25][26][27][28][29]}. However, to defeat PTI responses, many pathogens deploy a variety of effector proteins ([Figure 1](#)). When they are recognized by specialized receptors in the plant called resistance (R) proteins, the second layer of plant immune responses is activated, which is effector-triggered immunity (ETI) ^{[30][31]}.

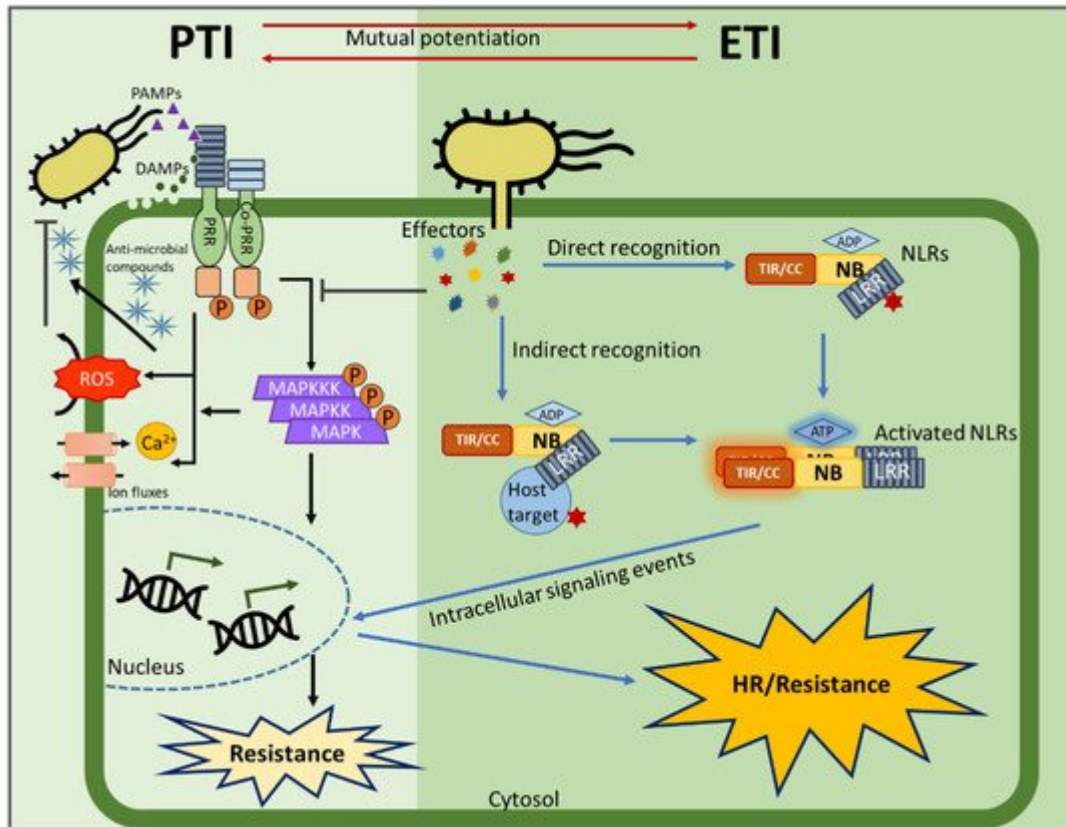


Figure 1. Schematic view of pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) in plants. The first layer of induced immunity, called PTI (indicated by black arrows), is activated by the recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs). Several PTI signaling events occur, such as activation of the mitogen-activated protein kinases (MAPK) kinase cascades, an influx of Ca²⁺ into the cytosol, and production of reactive oxygen species (ROS). Antimicrobial compounds are produced and the defense genes are activated. However, to suppress PTI, the pathogens deploy effectors. When they are recognized by nucleotide-binding (NB) and leucine-rich-repeat (LRR)-containing receptors (NLRs), the second immune layer, called ETI (indicated by blue arrows), takes place. NLRs directly or indirectly perceive pathogenic effectors, leading to a conformational change, which together with several intracellular signaling events, ultimately trigger the hypersensitive response (HR) or other defense responses. Surprisingly, the most recent studies reported that PTI and ETI are mutually linked and together potentiate the immune response (indicated by red arrows).

Structural and functional analysis in current studies of many R proteins reveals that there are two conserved features, nucleotide-binding (NB) and leucine-rich repeat (LRR) domains, known as NLRs. The structure of other NLR domains depends on whether a Toll-interleukin 1-like receptor (TIR) or a coiled-coil (CC) is attached at the N terminus ([Figure 1](#)) ^{[32][33]}. Host plants employ a diverse family of NLRs to detect effectors rapidly during pathogen invasion. NLRs selectively recognize the effectors, either directly or indirectly, and such recognition often leads to a hypersensitive response, a form of rapid localized programmed cell death ([Figure 1](#)) ^{[28][34][35]}. The immune responses elicited by PRRs and NLRs are similar, although the duration and amplitude of ETI responses are often vastly larger than those of PTI responses ([Figure 1](#)) ^[30]. However, it was reported that there is a hefty overlap in

the transcriptional regulation during PTI and ETI [36][37]. Surprisingly, the most recent studies reported that there is even a substantial linkage between NLR-mediated ETI and PRR-mediated PTI (Figure 1) [38][39].

2. The Evolution of Pathogen Perception by NLRs

As explained by the gene-for-gene hypothesis in which a resistance gene in the host plants corresponds to an avirulence (*avr*) gene in pathogens [40]; an NLR can recognize the presence of a pathogenic effector and trigger plant immunity. Effector recognition is described by diverse models explaining suggested direct or indirect detection [5][41]. In the earliest studies, cloning of *R* genes revealed the physical interaction of effectors with NLRs and the receptor–ligand model was proposed [5]. Direct effector recognition of NLRs depends on their LRR domains (Figure 2A).

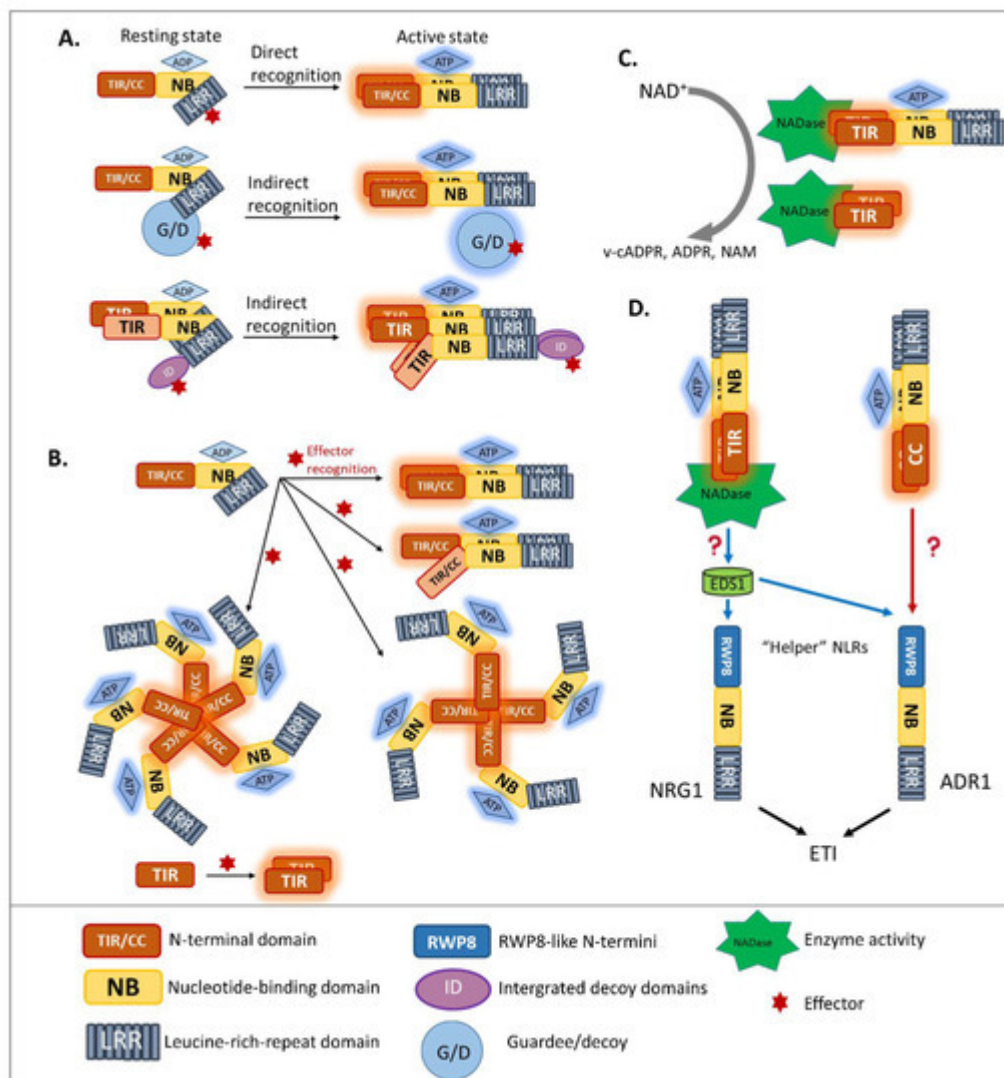


Figure 2. Diverse roles of nucleotide-binding and leucine-rich-repeat-containing receptors (NLRs) in immune signaling. (A) The evolution of NLR effector recognition systems. A common NLR consists of a diverse N-terminal domain, a central nucleotide-binding (NB) domain, and a C-terminal leucine-rich repeat (LRR) domain. NLRs are classified into two groups, depending on the N-terminus—toll interleukin-1-receptor (TIR) NLR (TNL) and coiled-

coil (CC) NLR (CNL). NLRs recognize pathogen effectors directly through the LRR domain or indirectly through a host guardee/decoy protein. During coevolution, some NLRs acquired unusual integrated decoy (ID) domains for pathogen recognition. **(B)** The molecular switch of NLRs during effector recognition leads to NLR homo/hetero/oligomerization (the NLR “resistosome”). In response to pathogen effectors, the open-lid form of NLRs is formed. ADP–ATP exchange occurs, leading to NLR activation. The associations of NLRs, such as homodimerization, heterodimerization, and oligomerization, are important for downstream signaling. **(C)** After the formation of an NLR resistosome, the enzymatic activity of plant TIR produces nicotinamide adenine dinucleotide (NAD) derivatives. **(D)** Downstream components, ENHANCED DISEASE SUSCEPTIBILITY 1 (EDS1) and “helper NLRs” (N REQUIREMENT GENE 1 (NRG1) and ACTIVATED DISEASE RESISTANCE PROTEIN 1 (ADR1)), are required for NLR signaling. While CNLs depend on helper ADR1 to function (indicated by red arrow), TNLs activate NADase and require EDS1 (indicated by blue arrows) and both helpers (ADR1 and NRG1) for signal transduction. NRG1 and ADR1 mediate effector-triggered immunity (ETI) (indicated by black arrows). Question marks indicate the unknown mechanisms in NLR-triggered immunity.

Pathogen effectors evolutionarily adapted to avoid direct binding to NLRs, [\[42\]](#) while plant coevolution to restore direct effector detection seems to be slower. However, plants evolved indirect effector recognition systems ([Figure 2A](#)). To date, cases in which plants indirectly recognize effectors are more diverse and numerous than those illustrating direct recognition. In one indirect effector detection system—the guard model—NLRs perceive modifications of a host target protein, called the guardee [\[5\]](#). One of the most famous examples of the guard model is the Arabidopsis RESISTANCE TO PSEUDOMONAS SYRINGAE PV. MACULICOLA 1 (RPM1)-INTERACTING PROTEIN4 (RIN4). RIN4—a negative regulator of immune responses—plays an important role in normal plant growth as a mutation of *RIN4* constitutively activates RESISTANT TO PSEUDOMONAS SYRINGAE 2 (RPS2) and is lethal [\[43\]\[44\]](#). When RIN4 is targeted by the *Pseudomonas syringae* effector proteins AvrRpm1 or AvrRpt2, it leads to the activation of the NLR RPM1 or RPS2, respectively [\[5\]\[45\]\[46\]](#). In addition, the cleavage of RIN4 by AvrRpt2 leads to the activation of the NLR Malus x Robusta 5 in apples [\[47\]](#).

It is not easy for plant hosts to modify functional guardee proteins to further increase pathogen detection since pathogen effectors evolutionarily reduce the targeting of guardee proteins [\[42\]](#). Plants, however, evolved an adapted recognition system that detects modified decoys. In the decoy model, plant R proteins recognize effector-mediated modifications of a plant decoy protein that has a very similar structure to the actual host target protein, thereby confining the pathogen effectors to the host recognition system [\[42\]](#). For instance, the plant decoy protein, AVIRULENCE PROTEIN PSEUDOMONAS PHASEOLICOLA B (AVRPPHB)-SUSCEPTIBLE 1 (PBS1), is structurally similar to BOTRYTIS-INDUCED KINASE 1 (BIK1), a component of PTI that can be targeted and cleaved by effector AvrPphB to compromise resistance [\[48\]\[49\]](#). Cleavage of PBS1 by AvrPphB instead, triggers RPS5-mediated cell death [\[50\]\[51\]\[52\]\[53\]](#).

By utilizing the indirect recognition systems, plants can likely expand the pathogen-recognition spectrum with a limited number of NLR proteins. For example, a pair of NLR, RESISTANCE TO RALSTONIA SOLANACEARUM 1 (RRS1)/RPS4, can recognize the presence of the *Ralstonia Solanacearum* effector *Pseudomonas*-out-protein P2 (PopP2), *Pseudomonas syringae* effector AvrRps4 and an unknown *Colletotrichum* effector [\[54\]\[55\]](#). In these

recognition events, the decoy domain, containing the conserved amino acid sequence WRKYGQK found in WRKY transcription factors, became integrated into the NLR RRS1 during plant evolution. The WRKY decoy domain plays a critical role as a target of those effectors and triggers RRS1/RPS4-mediated immunity [56][57]. This integrated decoy model provides self-monitoring activity for NLRs in effector recognition (Figure 2A) [42]. It appears to be an effective tool for plants in detecting pathogen effectors, as shown by an examination of the canonical RRS1 and R-GENE ANALOG 5 (RGA5) homologs in other plant species. A wide range of integrated decoy types was found along with an abundance of NLRs with one or multiple integrated decoys [42][58]. Thus, the integrated decoy model highlights the structural evolution of plant NLRs in the context of pathogen evolution.

3. NLR Activation and Signaling Events Following Pathogen Recognition

3.1. Multi-Domain NLRs Act as Molecular Switches

A common NLR consists of a diverse N-terminal domain, an NB domain, and an LRR domain [42][48][59]. NLRs are normally classified into two groups (Figure 2A), depending on the N-terminus [48]. They are Toll interleukin-1-receptor NLRs (TNLs) and coiled-coil NLRs (CNLs). Other functional NLR-like proteins contain only a TIR or TIR-NB [42]. Each domain of the NLR has a function. The LRR domain is responsible for effector recognition and acts as an auto-inhibitory domain that prevents the auto-enabling downstream signaling [42][60]. The NB domain is specific to the ATP/ADP exchange and serves as a switch to turn NLRs on or off [42][59]. The phosphate-binding loop and methionine–histidine–aspartate region within the NB domain are two highly conserved motifs that essentially regulate the activity of NLRs [61]. While mutation of the phosphate-binding loop leads to NLR loss-of-function, the methionine–histidine–aspartate-motif mutation causes a gain-of-function [60][61]. The CC and TIR domains were originally thought to function as protein–protein interactions involved in NLR signaling [42].

3.2. Homo/Hetero-Complex Formation Is Necessary for NLR Signaling

Previous studies reported that disruption of the Mildew A 10 (MLA10) CC dimerization abolished the activation of immunity [42][62][63], suggesting that CNLs require dimerization of the CC domain for signal transduction. Moreover, pentameric oligomerization of the CNL Hrp-dependent outer protein (Hop) Z-Activated Resistance 1, termed the “HopZ-Activated Resistance 1 resistosome”, is important for the formation of putative membrane pores and the immune response [64]. Similarly, several well-studied plant NLRs containing TIR domains, such as RECOGNITION OF PERONOSPORA PARASITICA 1 (RPP1), the flax resistance protein L6, RRS1, and RPS4, were found to require oligomerization by two distinct interfaces, for both self-association and defense signaling [65][66][67][68][69]. Similar to the case of MLA10, disrupting the homo-dimerization of L6 TIRs interferes with downstream signaling (Figure 2B). To effectively recognize the effector *Xanthomonas* outer protein Q (XopQ), the TNL Recognition of XopQ 1 resistosome requires tetramerization [70]. In addition, two asymmetric TIR homodimers that form an RPP1 tetrameric resistosome activate downstream signaling, in response to effector *Arabidopsis thaliana* Recognized 1 (Figure 2B) [66].

Hetero-associations in addition to homo-dimerization were proven to be an indispensable aspect in NLR-mediated signaling. Indeed, genetically-linked paired NLRs were characterized as functioning together in conferring pathogen resistance [42]. RGA4/RGA5 is one of the functionally paired CNLs for *Magnaporthe oryzae* AVR-Pia/AVR-Pik-mediated resistance [41]. In addition, genetically-linked, paired TNLs, such as RPP2A/RPP2B, were found to provide resistance against *Hpa race Cala 2* [71], along with previously discussed RRS1/RPS4 recognize AvrRps4 and PopP2 [55][72]. In the paired cases listed above, one NLR, the “sensor NLR”, usually contains an evolutionarily incorporated integrated domain, and acts as an effector receptor, while the second NLR, the “executor NLR”, induces downstream signaling [41].

3.3. Intramolecular Regulation of Guardee/Decoy Contributes to NLR-Mediated Resistance

It is now clear that R proteins can guard plant functions by monitoring different post-translational modifications of effector targets (guardee/decoy), and that different modifications can compete with or support each other. RIN4 was proposed to act as a phosphoswitch to detect the effector AvrRpm1. Targeting of RIN4 by AvrRpm1 causes the phosphorylation of threonine 166 within its C-terminal nitrate-induced domain; which leads to RPM1 activation and resistance [73]. A recent study revealed that the ADP-ribosylation of RIN4 at aspartate 153 by AvrRpm1, leads to threonine 166 phosphorylation and promotes RPM1 activation [74]. The addition of ADP-ribose supports the complete phosphorylation of threonine 166 in RIN4 [74]. Taken together, these reports indicate that several additive modifications can occur in a single guardee protein.

On the other hand, a post-translational modification of one effector target can antagonize another. The newest report of RRS1/RPS4-mediated immunity revealed that phosphorylation regulates the activation of paired RRS1/RPS4 [68]. In the absence of effector AvrRps4 or PopP2, phosphorylation at threonine 1214 in the integrated decoy WRKY domain keeps RRS1 from the resistant ecotype Wassilewskija, in a resting state. Dephosphorylation at that residue leads to the autoactivation of RRS1. Interestingly, PopP2 induces O-acetylation in the WRKY domain of RRS1, which competes with its phosphorylation and results in the dephosphorylated activated RRS1-mediated resistance to *Ralstonia Solanacearum* [68]. Other phosphorylation sites at the C terminus of RRS1 are required for PopP2 recognition, which enhances the interaction of the TIR domain with the WRKY domain. This study also proved that wild-type Columbia RRS1 lacks the C-terminal 83 amino acids that include the target phosphorylation sites, fails to recognize PopP2, and is thus susceptible to *Ralstonia Solanacearum*.

However, RRS1-mediated resistance to the *Pseudomonas syringae* effector AvrRps4 is determined by the association of the RRS1 C-terminus with its TIR, not by its phosphorylation status [68]. The C terminus and TIR of RRS1 interact with each other only in the presence of AvrRps4 [68]. During recognition of AvrRps4 or PopP2, the interaction of the RRS1 TIR domain with its C terminus is enhanced. This enhanced interaction releases the RPS4 TIR from the inhibition by the RRS1 TIR. Thus, the RPS4 TIR is activated, resulting in resistance to *Pseudomonas syringae*. The regulation of guardee/decoy monitoring is likely much more complex than is presently known.

3.4. News-Breaking: Enzyme Activity of Plant TIR in ETI Signaling

In animal immunity, an important function of Toll-like receptors is specifically recognizing their cognate pathogen-associated molecular patterns or synthetic compounds. Most animal Toll-like receptors contain two domains, one of which—the LRR domain—is necessary for PAMP recognition, while the other—the TIR domain—functions in signaling scaffolds. Some studies of animal-TIR domain crystallization showed that animal TIR associates during PAMP recognition. Animal TIR oligomerization is required for immune signaling, leading to the inflammatory cytokine response [75][76][77]. Unlike most Toll-like receptors, Sterile Alpha and TIR Motif Containing 1 (SARM1) was shown to have a surprisingly novel function [78][79]. Specifically, the nicotinamide adenine dinucleotide (NAD) hydrolase activity of its TIR domain contributes to axon degradation. This unique function raised the hypothesis that SARM1 probably arose from other domains in the animal system, through an evolutionary transfer event [80].

In plants, after NLR activation, the subsequent signal transduction cascade leading to the hypersensitive response and expression of plant immunity is at present unresolved. Although the signaling pathway of CNLs remains unclear, a piece of TNL downstream signaling was discovered [77][81]. As TIR domains are found in both plant intracellular TNLs and the animal cell surface Toll-like receptors, researchers compared the characteristics of plant TIR and animal TIR. Wan et al. and Horsefield et al. demonstrated that the TIR domains of plant TNLs are structurally similar to the TIR domain of mammalian SARM1 and that their enzymatic activity could degrade oxidized nicotinamide adenine dinucleotide (NAD⁺) (Figure 2C) [77][81]. Cell death activation and NAD⁺ catalytic activity of plant TIRs are self-association interface-dependent, placing the TIR enzyme activity downstream of TIR oligomerization. A conserved glutamic acid was found in plant TIR NAD⁺-cleaving enzymes and the human SARM1 NADase [81]. Although the putative catalytic glutamic acid does not affect the TIR association, it is the key residue for TIR-NADase activation. The accumulation of enzymatic products, such as variant-cyclic ADP-Ribose (v-cADPR), ADP-Ribose, and nicotinamide, which are necessary for immune signaling, are proposed to be downstream of TIR-enzyme activation. The NADase activity of the plant TIR domain is solely required for plant immunity, since the fusion of plant TIR (not animal or bacterial TIR) to the mammalian NLR Family CARD Domain Containing 4 activates immune signaling in plants [82]. Interestingly, in both *enhanced disease susceptibility 1* (*eds1*) and *n requirement gene 1* (*nrg1*) mutants, the activation of RBA1 accumulates v-cADPR but fails to induce a cell-death response [81], indicating that the accumulation of enzymatic products happens upstream of EDS1-NRG1. However, from catalytic product accumulation to EDS1-NRG1 downstream signaling, an undefined gap remains.

4. Helper NLR Cooperation beyond Genetically Linked Pairs

The concept of NLR cooperation broadened since more distinct NLRs were reported to be required for ETI, forming an NLR signaling network [42]. Some “sensor” NLRs, which recognize effectors, genetically interact with a limited number of “helper” NLRs that are required for cell death. These “helper” NLRs are required, not only for NLR-mediated effector recognition but also for signaling and programmed cell death (Figure 2D) [83][84]. In tomato and tobacco, CNL-type-NLRs required for cell death are crucial for NLR-triggered immunity [84].

Helper ACTIVATED DISEASE RESISTANCE PROTEIN 1 (ADR1)s and NRG1s were separated from CNLs into a new clade called Resistance to Powdery Mildew 8 (RPW8)-NLR (Figure 2D) [42]. The N-terminus of RPW8-NLR,

with an atypical conserved R protein RPW8 that confers powdery mildew resistance [85], is crucial for the activation of downstream signaling. ADR1, ADR1-L1, and ADR1-L2 are three homologous RPW8-NLRs required for signaling of several NLRs, in resistance to bacterial or oomycete effectors [86][87]. The *adr1* triple mutant was shown to suppress the dwarf phenotype of autoimmune mutant *chilling sensitive 2, suppressor of npr1-1, constitutive1* (*snc1*), and *sensitive to low humidity 1*, which attenuate salicylic acid levels, and impair AvrRpt2- and AvrRps4-mediated immunity [86][87]. Although NRG1s are close homologs of ADR1s, they function independently [88]. NRG1 was first found to play a role downstream of the tobacco NLR protein N, which confers resistance to tobacco mosaic virus [89]. NRG1 also associates with EDS1 to recognize *Xanthomonas* effector XopQ in XopQ-mediated resistance in tobacco [90]. Interestingly, NRG1s cannot be found in plants lacking TNL, suggesting that they might function in TNL-mediated immunity [88]. Arabidopsis full-length NRG1A and NRG1B, but not truncated NRG1C, have a redundant function in *chilling sensitive 3*-triggered autoimmunity [88]. In detail, the *nrg1s* null mutant can convert the dwarfism of autoimmune *chilling sensitive 3* to a normal phenotype.

Downstream of NLR-triggered immunity, ADR1s and NRG1s, function synergistically in Arabidopsis [88]. For instance, CNL RPS2, TNL RPP2, RPP4, and paired NLR RRS1/RPS4 were reported to signal via helper ADR1s [86]. A further study demonstrated that entire RPP2-, RPP4-, and RRS1/RPS4-mediated immune responses require helper NRG1s [91]. Therefore, these TNLs transduce the signal via ADR1s, as well as NRG1s. However, no study showed physical interactions of ADR1s with other “sensor” NLRs or downstream proteins. Arabidopsis NRG1s also do not interact with themselves or other functional known proteins, downstream of TNLs [88]. Therefore, the process through which NRG1s and ADR1s trigger NLR-mediated immune response is still an unresolved question.

5. PTI/ETI Unity Produces Full Plant Immunity

It was always clear that PTI functions as the first tier in an induced defense against pathogens. However, ETI apparently functioned only after an effector had suppressed PTI. This led to the interpretation that PTI had little effect on the immune response during ETI. However, increasing evidence indicates that PTI and ETI signaling interact (Figure 3). Transcriptional profiling of PTI and ETI largely overlap [36][92]. In addition, Hatsugai et al. showed that PTI suppresses an ETI signaling sector, suggesting that PTI controls the immune signal pathways to fine-tune plant defenses and limit useless fitness costs [93].

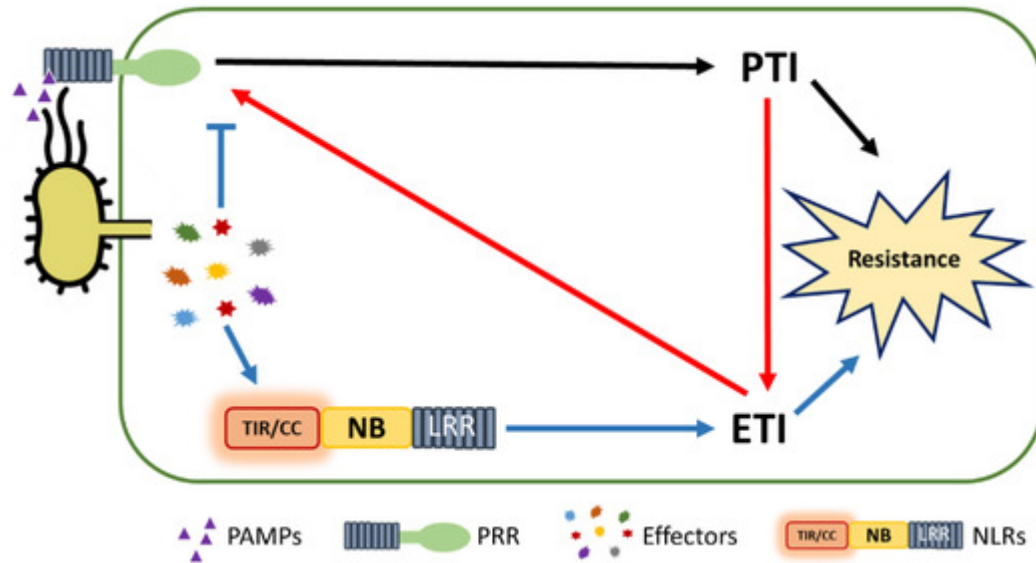


Figure 3. The integration of pattern-triggered immunity (PTI) and effector-triggered immunity (ETI) in plant immunity. In response to pathogens, an induced defense response is turned on by pattern recognition receptors (PRRs)-mediated PTI (indicated by black arrows) and nucleotide-binding and leucine-rich-repeat-containing receptors (NLRs)-mediated ETI (indicated by blue arrows). Recent reports indicate that there is substantial crosstalk between PTI and ETI (indicated by red arrows). ETI functions through PTI components and potentiates PTI signaling. Synergistically, PTI also enhances the ETI response. The cooperation of PTI and ETI mutually contributes to plant innate immunity.

Recently, two independent research groups presented evidence suggesting that NLR-mediated plant immune responses require PRRs to function [38][39]. Specifically, two PTI-related mutants, *bbc* and *fec*, were compromised in effector AvrRpt2-mediated resistance, while in Col-0, AvrRpt2-triggered immunity was increased, in response to PAMP flagellin peptide flg22 [39]. This suggested that PTI signaling through PRR/co-receptors induces ROS accumulation during an ETI response. The research group also found that the enhancement of ROS in ETI was due to β -nicotinamide adenine dinucleotide phosphate oxidase activity. Indeed, *RESPIRATORY BURST OXIDASE HOMOLOGUE D (RBOHD)*, a canonical pathogen-triggered ROS gene, regulates ROS produced by ETI. Furthermore, the well-known PTI-defective mutant, *rbohD*, exhibited a susceptible phenotype in response to *Pseudomonas syringae* DC3000 expressing *avrRpt2*. This data suggested that RBOHD acts as a central hub that links PTI and ETI. In detail, RBOHD only produces ROS when it is phosphorylated by BIK1, emphasizing the importance of the PTI protein kinase BIK1 in an ETI response. Additionally, Ngou et al. found considerable accumulation of PTI-responsive gene transcripts, as well as PTI-related proteins, by conditionally expressing effector AvrRps4 in Arabidopsis [38]. With bacterial treatment, Yuan et al. obtained similar results in which PTI components such as BRASSINOSTEROID INSENSITIVE 1-associated receptor kinase 1, BIK1, mitogen-activated protein kinase 3, and mitogen-activated protein kinase 6, were boosted by AvrRpt2-triggered immunity [39]. Taken together, these results indicate that ETI signals through PTI and increases the PTI response (Figure 3). Concurrently, PTI also enhances ETI and is functionally essential for the ETI response (Figure 3). The synergistic cooperation of PTI and ETI provides a robust immunity to confront pathogenic invasion. In particular, PTI combats

pathogenic microbes by reinforcing cell walls, increasing callose deposition, and producing anti-microbial compounds. Meanwhile, ETI sharpens PTI function by upregulating the PTI components. These findings revealed the mutual relationships of immune extra- and intracellular receptors, providing insight into the whole picture of plant immunity. However, the mechanism of how ETI potentiates PTI remains a question to explore. The biochemical function of NLR downstream components, such as helper NLRs, EDS1, and NON-RACE-SPECIFIC DISEASE RESISTANCE 1, is also still unclear, preventing the determination of component positions in PTI–ETI crosstalk.

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