

## REVIEW

# Thirty years of resistance: Zig-zag through the plant immune system

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**Short title:** The plant immune system

**One-sentence summary:** A review of major research advances in plant immunity during the last three decades and individual characterized immune receptors, their immune signaling pathways, and interactions between immune systems.

### Abstract

Understanding the plant immune system is crucial for using genetics to protect crops from diseases. Plants resist pathogens via a two-tiered innate immune detection-and-response system. The first plant *Resistance (R)* gene was cloned in 1992 (Johal and Briggs, 1992). Since then, many cell-surface pattern recognition receptors (PRRs) have been identified, and *R* genes that encode intracellular nucleotide-binding leucine-rich repeat receptors (NLRs) have been cloned. Here, we provide a list of characterized PRRs and NLRs. In addition to immune receptors, many components of immune signaling networks were discovered over the last 30 years. We review the signaling pathways, physiological responses, and molecular regulation of both PRR- and NLR-mediated immunity. Recent studies have reinforced the importance of interactions between the two immune systems. We provide an overview of interactions between PRR- and NLR-mediated immunity, highlighting challenges and perspectives for future research.

### 1 The plant immune system

2 Plants are constantly challenged by diverse organisms, including viruses, bacteria, fungi,  
3 oomycetes, herbivores, and parasitic plants. Disease ensues when a plant is susceptible to any  
4 of these organisms. Plants carry powerful defense mechanisms. To cause disease, pathogens  
5 usually need to evade detection by the host and/or to suppress these immune responses. Cell-  
6 surface pattern-recognition receptors (PRRs) in plants recognize conserved pathogen-/damage-  
7 /microbe-/herbivore-associated molecular patterns (PAMP/DAMP/MAMP/HAMPs) and  
8 activate pattern-triggered immunity (PTI), which restricts pathogenicity. PRRs are plasma  
9 membrane-associated and are usually either Receptor-Like Kinases (RLKs) or Receptor-Like  
10 Proteins (RLPs) that lack a protein kinase domain. Pathogens have evolved to evade or suppress

11 PTI through secreted effector molecules, which results in effector-triggered susceptibility  
12 (ETS). Plants, in turn, have evolved intracellular nucleotide-binding leucine-rich repeat  
13 receptors (NLRs) to detect effectors, which are often encoded by *Resistance (R)* genes, and  
14 activate effector-triggered immunity (ETI) upon effector perception. Pathogens might then  
15 evolve or diversify or lose effectors to suppress or evade ETI. The interaction between PTI,  
16 ETS and ETI was incorporated into the widely cited ‘zig-zag-zig’ intellectual framework  
17 (Jones and Dangl, 2006).

### 18 **The alphabet soup digested: nomenclatures applied to the plant immune system**

19 PTI was originally an abbreviation for ‘PAMP-triggered immunity’, mediated by PRRs such  
20 as *Arabidopsis thaliana* Flagellin-Sensing 2 (FLS2). ETI is an acronym for ‘effector-triggered  
21 immunity’, which is mostly mediated by NLRs (Jones and Dangl, 2006), but can also involve  
22 RLP-mediated detection of apoplastic effectors (Jones et al 1994). While the terms PTI and  
23 ETI are frequently used in the literature, there are limitations to their use in describing specific  
24 immune responses (Thomma et al., 2011). For example, the apoplastic effector Avr4 from the  
25 tomato (*Solanum lycopersicum*) leaf mold pathogen *Cladosporium fulvum* binds to fungal  
26 chitin to retard cell wall degradation by host chitinases and thus the release of N-acetyl  
27 glucosamine oligomers that activate defense (Joosten et al., 1994; van den Burg et al., 2006).  
28 Avr4 is recognized by the tomato cell-surface receptor-like protein (RLP) Cf-4 (Thomas et al.,  
29 1997). Thus, while immunity activated by some PRRs can be classified as PTI, others can be  
30 classified as ETI, since cell-surface receptors can recognize both PAMPs and apoplastic  
31 effectors (Thomma et al., 2011). Other terms have been introduced to classify immune  
32 responses based on receptors, such as PRR-mediated immunity (PMI) and NLR-mediated  
33 immunity (NMI) (Lacaze and Joly, 2020). Immune responses are best defined by the location  
34 of recognition by the initiating protein, such as extracellularly triggered immunity (ExTI) and  
35 intracellularly triggered immunity (InTI) (van der Burgh and Joosten, 2019), or surface-  
36 receptor-mediated immunity (SRMI) and intracellular-receptor-mediated immunity (IRMI)  
37 (van der Burgh and Joosten, 2019; Ding et al., 2020). Each of these terms has its own  
38 advantages and should be used with caution (Figure 1A). In this review, we try to minimize the  
39 overuse of these acronyms and emphasize immune responses triggered by the corresponding  
40 receptors.

### 41 **The protein structural and evolutionary views of PRRs**

42 Plant PRR proteins are either receptor-like proteins (RLPs) or receptor-like kinases (RLKs).  
43 RLKs consist of an extracellular domain, a transmembrane domain, and cytoplasmic kinase

44 domain. RLPs lack a cytoplasmic kinase domain, and both require co-receptors to transduce  
45 immune signals. PRRs are localized to the plasma membrane via a transmembrane  $\alpha$ -helix or  
46 a glycosylphosphatidylinositol (GPI)-anchor (Boutrot and Zipfel, 2017). Both RLPs and RLKs  
47 perceive ligands via a range of extracellular domains. These include leucine-rich repeat (LRR),  
48 lectin, malectin, lysin motif (LysM), and epidermal growth factor (EGF)-like domains (Boutrot  
49 and Zipfel, 2017).

50 RLKs are found in *Plasmodium*, plants, and animals but not fungi (Shiu and Bleecker, 2003).  
51 Conceivably, RLKs were present in the common ancestors of these organisms but were later  
52 lost in the fungi. Plant RLKs underwent remarkable expansion and constitute 60% of the  
53 kinases in the *Arabidopsis* genome (Shiu and Bleecker, 2003). *Arabidopsis* RLKs can be  
54 classified into 44 subfamilies based on their kinase domains (Shiu and Bleecker, 2003). The  
55 LRR-RLKs represent the largest subfamily of RLKs and are the best characterized RLKs in  
56 plants. A phylogenetic study of 33 plant species concluded that the average number of LRR-  
57 RLKs in angiosperms is approximately 250 per species (Dufayard et al., 2017) (Figure 1B).  
58 LRR-RLKs are further classified into 20 subgroups, with subgroup XII constituting genes  
59 involved in pathogen recognition, such as *FLS2*, *EFR*, and *Xa21* (Dufayard et al., 2017).  
60 Interestingly, the gene number in the LRR-RLK subgroup XII is highly variable across plant  
61 species, indicating that these genes underwent either expansion or contraction in particular  
62 lineages (Dufayard et al., 2017; Ngou et al., 2022). Similarly, the LRR-RLPs represent the  
63 largest subfamily of RLPs in plants, and the size of this gene family is also highly variable  
64 across plant species (Ngou et al., 2022) (Figure 1B).

### 65 **Structural and evolutionary overview of NLR proteins**

66 NLRs are grouped into three classes according to their N-terminal domains: coiled-coil (CC)  
67 NLRs (CNLs), Toll/Interleukin-1 receptor/Resistance protein (TIR) NLRs (TNLs), and RPW8-  
68 like coiled-coil domain (RPW8) NLRs (RNLs). Both CNLs and RNLs contain N-terminal CC-  
69 domains. Plant NLRs carry a nucleotide-binding (NB) domain shared by APAF-1, various  
70 plant *R* proteins and CED-4 (together, the NB-ARC domain), and LRR domains at their C-  
71 termini. These domains vary between NLRs, and additional non-canonical domains can be  
72 integrated into some NLRs (also known as NLR-Integrated Domains, or NLR-IDs) (Sarris et  
73 al., 2016). The functions of these domains also vary among NLRs. The LRR domain is involved  
74 in direct or indirect recognition of effectors (Krasileva et al., 2010; Ma et al., 2020a; Martin et  
75 al., 2020). The NB-ARC domain exhibits ATP binding activity and acts as a switch for NLR  
76 activation (Wang et al., 2019b). The CC, TIR and RPW8 domains function as signaling

77 domains to downstream responses upon NLR activation (Adachi et al., 2019a; Bi et al., 2021;  
78 Duxbury et al., 2021; Jacob et al., 2021). Some CC-domains are involved in effector  
79 recognition and interact directly with effectors (Avr-Pik) as well as a ‘guardee’ protein (such  
80 as RIN4), which is a target of pathogen effectors (Lukasik and Takken, 2009; Kanzaki et al.,  
81 2012). The  $\alpha$ -helices in both the CC and RPW8 domains were recently shown to form cation  
82 channels required for defense signaling (Bi et al., 2021; Jacob et al., 2021). TIR domains can  
83 also self-associate or associate with the TIR domains from paired TNLs, which is crucial for  
84 their activation (Williams et al., 2014; Duxbury et al., 2020). TIR domains, upon  
85 oligomerization, exhibit NADase activity, which leads to the production of variant-cyclic-  
86 ADP-ribose (v-cADPR) (Horsefield et al., 2019; Wan et al., 2019a). TIR domains also exhibit  
87 2’,3’-cAMP/cGMP synthetase activity (Yu et al., 2021). These small molecules produced by  
88 TIR domains likely function in signaling. The ID domain in NLR-IDs functions as a decoy,  
89 which enables the NLR to detect effectors targeting proteins with homology to the ID (van der  
90 Hoorn and Kamoun, 2008; Sarris et al., 2016; Baggs et al., 2017).

91 NLR genes are present in the genomes of all land plants (Gao et al., 2018). CNLs, TNLs, and  
92 RNLs are present in basal angiosperm species such as *Amborella* and *Nymphaea* (Baggs et al.,  
93 2020; Liu et al., 2021). However, TNLs are absent from most monocot genomes, indicating  
94 that gene loss likely occurred before monocots diverged from dicots (Tarr and Alexander,  
95 2009). The loss of TNLs was also accompanied by the loss of TNL-signaling components, such  
96 as ENHANCED DISEASE SUSCEPTIBILITY 1 (EDS1), PHYTOALEXIN DEFICIENT 4  
97 (PAD4), and SENESCENCE-ASSOCIATED GENE 101 (SAG101) (Baggs et al., 2020; Liu  
98 et al., 2021). The loss of these signaling components may have driven the contraction of TNLs  
99 in some angiosperm lineages, or vice versa (Liu et al., 2021). Similar to the LRR-RLK-XII and  
100 LRR-RLP, the number of NLRs (or NB-ARC containing proteins) is also highly variable across  
101 the angiosperms (Baggs et al., 2020; Liu et al., 2021). Furthermore, the LRR-RLK-XII, LRR-  
102 RLP, and NLR gene families have undergone lineage-specific co-expansion or co-contraction  
103 (Ngou et al., 2022) (Figure 1B). The cause of these concerted expansions and/or contractions  
104 is currently unclear but has been proposed to be linked to pathogen pressure and ecological  
105 specialization (Plomion et al., 2018; Baggs et al., 2020; Liu et al., 2021; Ngou et al., 2022).

### 106 **PRRs involved in pathogen recognition**

107 PRRs recognize PAMPs/MAMPs/HAMPs from bacteria, fungi, oomycetes, parasitic plants,  
108 and herbivores. Some PRRs also recognize self-molecules, such as DAMPs and other plant  
109 endogenous peptides (phyto cytokines) (Hou et al., 2021). Some PRRs are not involved in direct

110 ligand recognition but function as PRR co-receptors and negative regulators of immune  
 111 signaling. There are more than 60 characterized immunity-related PRRs with known elicitors,  
 112 and we attempt here to list those PRRs with known elicitors that are involved in pathogen  
 113 recognition (Figure 2). Due to space limitations, some PRR gene names are abbreviated: the  
 114 full gene names can be found in Supplemental Data Set S1.

#### 115 *PRRs involved in bacterial recognition*

116 Plants perceive a range of PAMPs from bacteria, including peptides, lipids, peptidoglycans  
 117 (PGs), and polysaccharides. *Arabidopsis* perceives the bacteria-derived peptides flg22, elf18,  
 118 and xup25 via the LRR-RLKs *AtFLS2*, *AtEFR*, and *AtXPS1* and the proteinaceous eMAX and  
 119 translation initiation factor 1 (IF1) via the LRR-RLPs *AtRLP1* and *AtRLP32*, respectively  
 120 (Chinchilla et al., 2006; Zipfel et al., 2006; Jehle et al., 2013; Mott et al., 2016; Fan et al.,  
 121 2021). Other bacterial peptides such as RaxX21, flgII-28, and csp22 are perceived by rice  
 122 (*Oryza sativa*) *OsXa21*, tomato *SIFLS3*, and *SICORE/NbCSPR* (from tomato and *Nicotiana*  
 123 *benthamiana*), respectively (Pruitt et al., 2015; Hind et al., 2016; Saur et al., 2016; Wang et al.,  
 124 2016; Luu et al., 2019). The bacterial lipid 3-hydroxydecanoic acid (3-OH) is perceived  
 125 through the lectin receptor kinase *AtLORE* (Kutschera et al., 2019). PGs from bacterial cell  
 126 walls are perceived by the LysM-containing RLP *AtLYM1/3* and rice *OsLYP4/6* (Willmann et  
 127 al., 2011; Liu et al., 2012). Bacterial exopolysaccharides (EPS) are perceived by the LysM-  
 128 containing RLK *LjEPR3* from *Lotus japonicus* to control rhizobium infections (Kawaharada et  
 129 al., 2015) (Figure 2A).

#### 130 *PRRs involved in fungal recognition*

131 The fungal cell wall comprises chitin and oligo-galacturonides (OGs), which are perceived by  
 132 multiple PRRs. Chitin is perceived by LysM-containing RLKs such as *AtLYM2/4/5*,  
 133 *OsLYP4/6*, *Medicago truncatula* *MtLYK4/9*, grapevine (*Vitis vinifera*) *VvLYK1-1/2*, *Lotus*  
 134 *japonicus* *LjLYS6*, and pea (*Pisum sativum*) *PsLYK9* (Wan et al., 2008, 2012; Liu et al., 2012;  
 135 Faulkner et al., 2013; Cao et al., 2014; Bozsoki et al., 2017; Leppyanen et al., 2017; Brulé et  
 136 al., 2019). OGs are perceived by the cell wall-associated kinases *AtWAK1/2* (Brutus et al.,  
 137 2010). *AtWAK1/2* also perceive pectin from the plant cell wall (Kohorn and Kohorn, 2012).  
 138 The common wheat (*Triticum aestivum*) wall-associated kinase *TaWAK* perceives the protein  
 139 SnTox1 from the necrotrophic fungal pathogen *Parastagonospora nodorum* and induces cell  
 140 death (Shi et al., 2016). In addition to the fungal cell wall, apoplastic effectors from fungal  
 141 pathogens are recognized by multiple LRR-RLPs. These include *SICf-2*, *SICf-4*, *SICf-5*, *SICf-*  
 142 *9*, *SIEIX2*, *SIVe1*, *SIHrc9-4E*, *SII*, *SII-3* and *Brassica napus* *BnRLM2* (Jones et al., 1994; Dixon

143 et al., 1996, 1998; Thomas et al., 1997; Krüger et al., 2002; Westerink et al., 2004; Rep et al.,  
144 2004; Ron and Avni, 2004; Houterman et al., 2008; de Jonge et al., 2012; Larkan et al., 2013;  
145 Catanzariti et al., 2015). A proteinaceous elicitor from the fungal pathogen *Sclerotinia*  
146 *sclerotiorum*, sclerotinia culture filtrate elicitor 1 (SCFE1), is perceived by *AtRLP30*, and  
147 fungal endopolygalacturonases (endo-PGs) are perceived by the LRR-RLP *AtRLP42* (Zhang  
148 et al., 2013; Zhang et al., 2014) (Figure 2B).

#### 149 *PRRs involved in the recognition of oomycetes*

150 The oomycete cell wall is also composed of chitin, endo-PGs, and OGs. Thus, plants also  
151 perceive oomycetes via PRRs described in the previous section. In addition, some PRRs  
152 recognize specific PAMPs from oomycetes. For example, the glycoside hydrolase XEG1 from  
153 *Phytophthora sojae* is recognized by the LRR-RLP *NbRXEG1* (Wang et al., 2018d). INF1  
154 elicitor from *Phytophthora infestans* is recognized by the LRR-RLP *SmELR* from *Solanum*  
155 *microdontum* (Kamoun et al., 1997; Domazakis et al., 2020). *Arabidopsis AtRLP23* recognizes  
156 a conserved peptide (nlp20) in necrosis and ethylene-inducing peptide 1-like protein (NLP)  
157 from multiple pathogens, including *Phytophthora parasitica* (Böhm et al., 2014; Albert et al.,  
158 2015). The *Arabidopsis* lectin-receptor kinase *AtRDA2* was recently shown to recognize 9-  
159 methyl sphingoid base, a PAMP derived from oomycete ceramide (Kato et al., 2021) (Figure  
160 2C).

#### 161 *PRRs involved in self-recognition*

162 Plants perceive DAMPs and phytochemicals from damaged or infected tissues to amplify and  
163 modulate immune responses against pathogens. Damage-induced cytosolic calcium influx  
164 activates metacaspases, which cleave the DAMP precursor PROPEPs into PEPs (Hander et al.,  
165 2019). PEPs are then secreted and perceived by the LRR-RLKs *AtPEPR1/2* (Yamaguchi et al.,  
166 2006, 2010). Multiple phytochemicals are upregulated during immunity (Hou et al., 2021). The  
167 stress-induced plant signaling peptides CTNIPs are upregulated during PTI and are perceived  
168 by the *Arabidopsis* LRR-RLK *AtHSL3* (Rhodes et al., 2021a). Another defense-induced  
169 secreted peptide, PIP1, is recognized by *AtRLK7* (Hou et al., 2014). The *Arabidopsis* LRR-  
170 RLK *AtMIK2* perceives the phytochemical SCOOP peptides and SCOOP-like peptides from  
171 *Fusarium* spp. (Coleman et al., 2021; Rhodes et al., 2021b). Thus, *AtMIK2* is involved in both  
172 self- and fungal recognition during immunity. Plant PRRs also perceive a range of extracellular  
173 (e) self-molecules, such as eH<sub>2</sub>O<sub>2</sub>, eATP and eNAD. These molecules are perceived by  
174 *AtHPCA1* (also known as *AtCARD1*), *AtDORN1*, and *AtLecRK-1.8*, respectively (Chen et al.,  
175 2017a; Wang et al., 2017; Wu et al., 2020a). In tomato, the hormone peptide systemin is

176 perceived by *SISYR1/2* to enhance resistance against herbivores (Wang et al., 2018b) (Figure  
177 2D).

#### 178 *PRRs involved in the recognition of parasitic plants*

179 In addition to eH<sub>2</sub>O<sub>2</sub>, *AtCARD1* has also been shown to perceive the self-derived quinone  
180 compound 2,6-dimethoxy-1,4-benzoquinone (DMBQ) (Laohavisit et al., 2020). Perception of  
181 DMBQ induces *AtCARD1*-dependent immune responses. On the other hand, the parasitic plant  
182 *Phtheirospermum japonicum* perceives DMBQ via *AtCARD1* homologues *PjCADL1/2/3*,  
183 which leads to development of haustoria for parasitic infection (Laohavisit et al., 2020). Thus,  
184 *CARD1* is involved in both immunity (for non-parasitic plants) and parasitic plant infection.  
185 Plants also perceive PAMPs from parasitic plants to restrict infection. The tomato LRR-RLP  
186 *SlCuRe1* perceives the peptide Crip21 from the parasitic plant *Cuscuta* spp. (Hegenauer et al.,  
187 2020). Crip21 is derived from a *Cuscuta* glycine-rich cell wall protein (GRP). Activation of  
188 *SlCuRe1* by Crip21 elicits cell death and defense responses in tomato (Hegenauer et al., 2020)  
189 (Figure 2E).

#### 190 *PRRs involved in viral recognition*

191 While some PRRs, such as *AtNIK1*, have been shown to be required for viral resistance, no  
192 PRR has been reported to directly perceive viral particles (Zorzatto et al., 2015). However, the  
193 *Arabidopsis* PRR co-receptor *bak1* loss-of-function mutant exhibits enhanced susceptibility to  
194 multiple viruses (Kørner et al., 2013). In addition, exogenous application of double-stranded  
195 RNAs and viral coat protein elicits PTI responses in plants (Allan et al., 2001; Niehl et al.,  
196 2016). Conceivably, some uncharacterized PRR(s) are involved in the recognition of viral  
197 PAMPs (Figure 2F).

#### 198 *PRRs involved in the recognition of herbivores*

199 In addition to eNAD<sup>+</sup>, *AtLecRK-1.8* and *AtLecRK-1.1* are involved in the perception of *Pieris*  
200 *brassicae* (cabbage moth) eggs (Gouhier-Darimont et al., 2019; Groux et al., 2021). The ligand  
201 from *Pieris brassicae* eggs that activates *AtLecRK-1.8* remains to be identified and  
202 characterized. The *Arabidopsis* LRR-RLK *AtNILR1* is involved in the perception of  
203 *Heterodera schachtii* (sugarbeet nematode) extracts, and *nilr1* mutants are hypersusceptible to  
204 nematode infection (Mendy et al., 2017). The cowpea (*Vigna unguiculata*) LRR-RLP *VuINR*  
205 was shown to perceive inceptin, a proteolytic fragment of chloroplastic ATP synthase from the  
206 oral secretions of *Lepidopteran* herbivores (a HAMP) (Steinbrenner et al., 2019). Whether  
207 PRRs can perceive ligands directly from herbivores remains to be determined (Figure 2G).

## 208 *PRR co-receptors*

209 Most, if not all, PRRs function with co-receptors to activate downstream immune responses.  
 210 Multiple LRR-RLKs, such as FLS2, EFR, and PEPRs function with the co-receptors *AtBAK1*  
 211 and *AtBKK1* (Chinchilla et al., 2007; Roux et al., 2011). LRR-RLPs function with the co-  
 212 receptors *SOBIR1* and *BAK1*, and the LysM-RLK *LYKs* and LysM-RLP *LYMs* function with  
 213 the co-receptor *CERK1* (Miya et al., 2007; Willmann et al., 2011; Liebrand et al., 2013; Cao  
 214 et al., 2014). These co-receptors are highly conserved in land plants and are crucial for PRR-  
 215 mediated immunity (Figure 2H).

216

## 217 **NLRs involved in pathogen recognition**

218 Sensor NLRs are involved in the recognition of effectors from viruses, bacteria, fungi,  
 219 oomycetes, parasitic plants, and herbivores. Some NLRs act as helpers or co-receptors to  
 220 transduce immune signals from sensor NLRs following effector recognition (Wu et al., 2018).  
 221 Currently, there are more than 140 characterized NLRs with known recognized effectors  
 222 (Kourelis and Kamoun, 2020). Here, we summarize a list of NLRs involved in effector  
 223 recognition (Figure 3; Supplemental Data Set S2).

### 224 *NLRs involved in bacterial recognition usually act by guarding host components*

225 Bacterial effectors have been selected that target PRR signaling components and suppress host  
 226 immunity. Plants have evolved multiple NLRs to guard host immune components, which  
 227 indirectly detect bacteria and induce ETI. For example, the *Pseudomonas syringae* effector  
 228 *AvrPto* suppresses PTI by inhibiting host kinase activity (Li et al., 2005; He et al., 2006; Xing  
 229 et al., 2007; Xiang et al., 2008; Wu et al., 2017b). The tomato decoy kinase *Pto* is guarded by  
 230 the CNL *Prf*, which detects the perturbation of *Pto* kinase activity by *AvrPto* and activates ETI  
 231 (Wu et al., 2004; Mucyn et al., 2006; Ntoukakis et al., 2013). Since plants have evolved  
 232 multiple NLRs to guard central immune signaling pathways, some effectors from  
 233 *Pseudomonas syringae* are recognized by multiple NLRs from different plant species (Jones  
 234 and Dangl, 2006). Examples include the following: *AvrB* is recognized by *AtTAO1*, *AtRPM1*,  
 235 and *Glycine max GmRPG1b* (Grant et al., 1995; Ashfield et al., 2004; Eitas et al., 2008).  
 236 *AvrRpm1* from *P. syringae* pv. *maculicola* (*Pma*) is recognized by *AtRPM1*, *AtRPS2* and  
 237 *GmRPG1r* (Ashfield et al., 1995; Grant et al., 1995; Kim et al., 2009a). *AvrPphB* is recognized  
 238 by *AtRPS5*, *Hordeum vulgare HvPbr1.b* and *HvPbr1.c* (DeYoung et al., 2012; Carter et al.,  
 239 2019; Laflamme et al., 2020). *AvrRpt2* from *Pseudomonas syringae* and *RipBN* from



240 *Ralstonia pseudosolanacearum* are recognized by the CNL Ptr1 from multiple Solanaceous  
 241 species (Mazo-Molina et al., 2020). In addition, AvrRpt2 is recognized by the CNL *AtRPS2*,  
 242 and AvrRpt2\_EA from *Erwinia amylovora* is recognized by FB\_MR5 from *Malus × robusta*  
 243 5 (Axtell and Staskawicz, 2003; Mackey et al., 2003; Peil et al., 2019). HopA1 is recognized  
 244 by *AtRPS6*, and HopA11 is recognized by both *AtSUMM2* and *AtRPS6* (Kim et al., 2009b;  
 245 Zhang et al., 2012; Takagi et al., 2019).

246 On the other hand, central hubs of the immune system are targeted by multiple effectors.  
 247 Correspondingly, NLRs, which guard central immune signaling components, can recognize  
 248 multiple effectors (Khan et al., 2016). For example, the CNL *AtZAR1* functions with the  
 249 pseudokinase RKS1 to guard the receptor-like cytoplasmic kinase (RLCK) PBL2 (Wang et al.,  
 250 2015). By guarding RLCKs or decoy pseudokinases, *AtZAR1* indirectly recognizes HopZ1a,  
 251 HopF2, HopBA1, HopO1, HopX1 and AvrAC from *P. syringae* or *Xanthomonas campestris*,  
 252 and potentially more effectors that target RLCKs (Wang et al., 2015; Laflamme et al., 2020).  
 253 *NbZAR1* is also required to recognize XopJ4 from *Xanthomonas perforans* via the  
 254 pseudokinase JIM2 (Schultink et al., 2019). Other examples include the following: AvrRpm1<sub>Psa</sub>  
 255 and AvrRpm1<sub>Psy</sub> from *P. syringae* pv. *actinidiae* biovar 3 (*Psa*) and *P. syringae*  
 256 pv. *syringae* strain B728a (*Psy*) are recognized by *Nicotiana tabacum* *NitabRPA1* (Yoon and  
 257 Rikkerink, 2020). AvrE and HopAA are both recognized by *Arabidopsis* *CAR1* (Laflamme et  
 258 al., 2020). AvrRps4 from *P. syringae* pv. *pisi* and PopP2 from *Ralstonia solanacearum* are  
 259 recognized by the paired-TNLs *AtRRS1-R* and *AtRPS4* (Narusaka et al., 2009; Sarris et al.,  
 260 2015). In addition, AvrRps4 can also be recognized by the paired-TNLs *AtRRS1B* and  
 261 *AtRPS4B* (Saucet et al., 2015). The TNL *NbRoq1* recognizes HopQ1-1, XopQ and RipB from  
 262 *P. syringae*, *Xanthomonas*, and *Ralstonia solanacearum*, respectively (Schultink et al., 2017;  
 263 Thomas et al., 2020). Multiple TRANSCRIPTION ACTIVATOR-LIKE (TAL) effectors from  
 264 *Xanthomonas oryzae* are recognized by the CNLs *OsXo1* and *OsXa1* (Yoshimura et al., 1998;  
 265 Triplett et al., 2016; Read et al., 2020a, 2020b). The tomato TNL *S/BS4* also recognizes multiple  
 266 *Xanthomonas* effectors (Schornack et al., 2004, 2005). AvrRxo1-ORF1 from *Xanthomonas*  
 267 *oryzae* and *Burkholderia andropogonis* are recognized by the CNL *ZmRxo1* from maize (*Zea*  
 268 *mays*) (Zhao et al., 2004) (Figure 3A).

### 269 *NLRs involved in fungal recognition*

270 Plant NLRs recognize multiple effectors and molecules from fungal pathogens. Victorin, a  
 271 secondary metabolite from *Cochliobolus victoriae*, is recognized by LOV1 from *Arabidopsis*  
 272 and *Phaseolus vulgaris* (Sweat et al., 2008; Lorang et al., 2018). AvrFom2 from *Fusarium*

273 *oxysporum* is recognized by the CNL *CmFom-2* from *Cucumis melo* (Schmidt et al., 2016).  
274 *Hordeum vulgare* RESISTANCE LOCUS A (*HvMLA*) NLRs recognize a range of effectors  
275 from *Blumeria graminis* (Ridout et al., 2006; Lu et al., 2016; Saur et al., 2019) and can even  
276 recognize races of wheat stripe rust (Bettgenhaeuser et al., 2021). Multiple TNLs from *Linum*  
277 *usitatissimum* recognize effectors from *Melampsora lini* (Dodds et al., 2004; Dodds and Thrall,  
278 2009; Catanzariti et al., 2010; Anderson et al., 2016). Effectors from the rice blast fungus  
279 *Magnaporthe oryzae* are recognized by multiple CNLs from *Oryza sativa* (Jia et al., 2000;  
280 Ashikawa et al., 2008, 2012; Li et al., 2009, 2019; Zeng et al., 2011; Rai et al., 2011; Sone et  
281 al., 2013; Zhai et al., 2014; Devanna et al., 2014; Zhang et al., 2015; Wu et al., 2015; Vo et al.,  
282 2019). Effectors from *Blumeria graminis*, *Parastagonospora nodorum*, *Pyrenophora tritici-*  
283 *repentis* and *Puccinia graminis* are recognized by multiple CNLs from *Triticum* species  
284 (Srichumpa et al., 2005; Liu et al., 2006; Salcedo et al., 2017; Bourras et al., 2019; Navathe et  
285 al., 2020; Manser et al., 2021). *AvrSr50* from *Puccinia graminis* is recognized by *ScSr50* from  
286 *Secale cereale* (Chen et al., 2017b). *Avr2* from *Fusarium oxysporum* is recognized by the CNL  
287 *SII2*, and *Pc-toxin* from *Periconia circinata* is recognized by the CNL *SbPc* from *Sorghum*  
288 *bicolor* (Nagy et al., 2007; Nagy and Bennetzen, 2008; Houterman et al., 2009) (Figure 3B).

#### 289 *NLRs involved in the recognition of oomycetes*

290 Multiple effectors from *Hyaloperonospora arabidopsidis* (*Hpa*) are recognized by *Arabidopsis*  
291 NLRs. *ATR1*, *ATR4*, *ATR5*, *ATR13* and *ATR39* are recognized by *AtRPP1*, *AtRPP4*, *AtRPP5*,  
292 *AtRPP13* and *AtRPP39*, respectively (Rentel et al., 2008; Krasileva et al., 2010; Bailey et al.,  
293 2011; Goritschnig et al., 2012; Asai et al., 2018). *CX2CX5G* effector-like proteins (CCG  
294 effectors) from *Albugo candida* are recognized by *AtWRR4A* and *AtWRR4B* (Redkar et al.,  
295 2021).

296 The oomycete genus *Phytophthora* carries multiple phytopathogenic species that cause  
297 enormous crop losses worldwide. Identification of NLRs that recognize *Phytophthora* effectors  
298 provides resources for crop resistance. The *Phytophthora sojae* effectors *Avr1k* and *Avr1b-1*  
299 are recognized by *GmRps1-k* (Song et al., 2013). Effectors from *P. infestans* are also  
300 recognized by NLRs from multiple *Solanaceae* species. For example, the effectors *Avramr1*  
301 and *Avramr3*, with homologs in many *Phytophthora* species, are recognized by *Rpi-amr1* (from  
302 *S. americanum*) and *Rpi-amr3*, respectively (Lin et al., 2020, 2021; Witek et al., 2021). *Avrblb1*  
303 is recognized by *Rpi-blb1* (from *S. bulbocastanum*), *Rpi-pta1* and *Rpi-sto1* (from *S.*  
304 *stoloniferum*) (Vleeshouwers et al., 2008; Oh et al., 2009). *Avrblb2* is recognized by *Rpi-blb2*  
305 and *R9a* (from *S. bulbocastanum* and *S. demissum*, respectively) (Oh et al., 2009; Jo, 2013).

306 PexRD12 is recognized by Rpi-*chc1* (from *S. chacoense*) (Petre et al., 2021). Avr1, Avr3b and  
 307 Avr8 are recognized by R1, R3b and R8, respectively (Ballvora et al., 2002; Li et al., 2011; Jo,  
 308 2013; Du et al., 2015; Vossen et al., 2016). *PiAvr2* is recognized by multiple NLRs from  
 309 *Solanaceae* (Park et al., 2005; Lokossou et al., 2009; Champouret, 2010; Aguilera-Galvez et  
 310 al., 2018). Avr3a is recognized by Rpi-*sto2* and R3a (from *S. tuberosum*) (Bos et al., 2010;  
 311 Champouret, 2010; Vleeshouwers et al., 2011; Chapman et al., 2014). Avrnt1 is recognized  
 312 by Rpi-*vnt1* from *S. venturi* (Foster et al., 2009; Pel, 2010) (Figure 3C).

### 313 *Apparent absence of NLRs involved in self-recognition in plants*

314 In mammals, DAMPs can be indirectly recognized the intracellular NOD-, LRR- and pyrin  
 315 domain-containing protein 3 (NLRP3)-inflammasome in macrophages (Swanson et al., 2019).  
 316 However, no plant NLRs have been reported to detect self-molecules so far (Figure 3D).

### 317 *NLRs involved in the recognition of parasitic plants*

318 Virus-induced silencing of the CNL *VuRSG3-301* from *Vigna unguiculata* leads to enhanced  
 319 susceptibility to the parasitic plant *Striga gesnerioides* race 3 (SG3) (Li and Timko, 2009). The  
 320 effector recognized by *VuRSG3-301* has not yet been identified (Figure 3E).

### 321 *NLRs involved in viral recognition*

322 The coat proteins (CPs) from different viruses are recognized by pepper (*Capsicum annuum*)  
 323 *CaL*<sup>1</sup>, *CaL*<sup>1a</sup>, *Capsicum baccatum CbL*<sup>2b</sup>, *Capsicum chacoense CchaL*<sup>4</sup>, *Capsicum chinense*  
 324 *CchiL*<sup>1c</sup>, *CchiL*<sup>3</sup>, *Capsicum frutescens Cfl*<sup>2</sup>, *Nicotiana glauca NgN*<sup>1</sup>, *Solanum acaule Rx2*,  
 325 *Solanum stoloniferum Ry<sub>sto</sub>* and potato (*Solanum tuberosum*) *Rx* (Saito et al., 1987;  
 326 Bendahmane et al., 1995; Berzal-Herranz et al., 1995; Gilardi et al., 2004; Tameling and  
 327 Baulcombe, 2007; Matsumoto et al., 2008; Tomita et al., 2011; Mizumoto et al., 2012; Grech-  
 328 Baran et al., 2021). Viral movement proteins (MPs) are recognized by *Tm2*, *STm2*<sup>2</sup> and  
 329 *SSw5-b* (Pelham, 1966; Hall, 1980; Weber and Pfitzner, 1998; Peiró et al., 2014). The RNA-  
 330 Dependent RNA Polymerase (N1b) of potyviruses is recognized by the *Ca Pvr4* (Kim et al.,  
 331 2015). The RNA silencing suppressor protein NSs from tomato spotted wilt virus (TSWV) is  
 332 recognized by *CchiTsw* (de Ronde et al., 2013). P3 cistrons from soybean mosaic virus (SMV)  
 333 are recognized by *Gm3gG2* (Wen et al., 2013). The helicase domain of the tobacco mosaic  
 334 virus (TMV) replicase (p50) is recognized by *Nicotiana glutinosa N* (Whitham et al., 1994;  
 335 Erickson et al., 1999). Cucumber mosaic virus (CMV) 2a protein is recognized by *Phaseolus*  
 336 *vulgaris PvRT4-4* (Seo et al., 2006). To summarize, multiple components involved in the  
 337 process of viral infection are recognized by NLRs. (Figure 3F).

### 338 *NLRs involved in the recognition of herbivores*

339 Multiple NLRs were shown to be involved in resistance against herbivores. NLRs involved in  
 340 nematode resistance include the TIR-NB-LRR pair *AtDSC1* and *AtWRKY19*, *Aegilops*  
 341 *tauschii* *AtaCD3.1*, *CaMi*, *Prunus cerasifera* *PcMa*, *SlHero*, *StGpa-2*, and *StGro1-4* (Lagudah  
 342 et al., 1997; van der Voort et al., 1997; Milligan et al., 1998; Paal et al., 2004; Sobczak et al.,  
 343 2005; Chen et al., 2007; Claverie et al., 2011; Warmerdam et al., 2020). In addition, the tomato  
 344 *Mi* gene confers resistance to multiple herbivores, such as nematodes, aphids and whiteflies  
 345 (Kaloshian et al., 1995; Milligan et al., 1998; Rossi et al., 1998; Neiva et al., 2019). Other  
 346 NLRs have been shown to confer resistance against the arthropod *Nilaparvata lugens* (brown  
 347 planthopper). These include the rice *OsBph1/9* and *OsBph14* (Du et al., 2009; Zhao et al.,  
 348 2016). While multiple NLRs are involved in herbivore resistance, more work is needed to  
 349 identify the recognized effectors (Figure 3G).

### 350 *Helper NLRs*

351 While some sensor NLRs do not require helper NLRs, many NLRs function with helper NLRs  
 352 to transduce immune signals. In *Arabidopsis*, some CNLs and/or most TNLs require the RNLs  
 353 ACTIVATED DISEASE RESISTANCE 1 (collectively known as ADR1s, which includes  
 354 *AtADR1*, *AtADR1-L1* and *AtADR1-L2*) and/or N REQUIREMENT GENE 1 (collectively  
 355 known as NRG1s, which includes *AtNRG1A* and *AtNRG1B*) (Bonardi et al., 2011; Castel et  
 356 al., 2019a; Wu et al., 2019; Saile et al., 2020). In *Arabidopsis* accession Col-0, the four RPW8  
 357 homologs, *AtHR1*, *AtHR2*, *AtHR3* and *AtHR4*, also contribute to resistance against bacterial  
 358 and fungal pathogens (Barragan et al., 2019; Castel et al., 2019b). In Solanaceous plants, the  
 359 CNLs NB-LRR REQUIRED FOR HR-ASSOCIATED CELL DEATH-2 (NRC2), NRC3, and  
 360 NRC4 function as helper NLRs for multiple sensor NLRs (Wu et al., 2017a) (Figure 3H). The  
 361 contribution of the NRC network to the functions of sensor NLRs has been extensively  
 362 discussed (Wu et al., 2018; Ngou et al., 2021c).

363

### 364 **The PRR signaling pathway**

365 The extracellular domains of plant PRRs perceive diverse ligands (Boutrot and Zipfel, 2017).  
 366 Binding of ligands leads to heterodimeric receptor complex formation between PRRs and their  
 367 co-receptors, such as BAK1 and CERK1 (Miya et al., 2007; Ma et al., 2016; Hohmann et al.,  
 368 2017). On the other hand, RLPs constitutively interact with SOBIR1 and recruit BAK1 upon  
 369 ligand recognition (Liebrand et al., 2013; Albert et al., 2015). In *Arabidopsis*, the bacterial

370 flagellin peptide flg22 is perceived by the LRR-RLK FLS2 (Felix et al., 1999; Chinchilla et  
371 al., 2006). Flg22 acts as a ‘molecular glue’ and interacts with and brings together the  
372 extracellular LRR domains of FLS2 and BAK1 (Sun et al., 2013; Hohmann et al., 2017).  
373 Heterodimeric complex formation between the LRR domains of FLS2 and BAK1 brings their  
374 cytoplasmic kinase domains into close proximity, which leads to a series of auto- and trans-  
375 phosphorylation events (Schwessinger et al., 2011; Cao et al., 2013; Sun et al., 2013). This  
376 activated receptor complex then phosphorylates RECEPTOR-LIKE CYTOPLASMIC  
377 KINASEs (RLCKs) (Lin et al., 2013; Liang and Zhou, 2018). RLCK subfamily VII members  
378 (collectively known as RLCK-VIIs) were first shown to be important for surface receptor-  
379 mediated immunity in tomato and tobacco and to be required for *Cf-4* and *Cf-9* to confer fungal  
380 resistance (Rowland et al., 2005). In *Arabidopsis*, RLCKs play particularly important roles  
381 during PRR-mediated immunity (Lu et al., 2010; Lin et al., 2014; Liang and Zhou, 2018; Rao  
382 et al., 2018). BAK1 associates with and phosphorylates the RLCK-VII BIK1 at the Try243 and  
383 Try250 residues (Lu et al., 2010; Lin et al., 2014).

384 The activation of RLCK-VIIs promotes the phosphorylation of multiple signaling components,  
385 including the calcium channels CNGC2/4 and OSCA1.3, the NADPH oxidase respiratory burst  
386 oxidase protein D (RbohD), and the mitogen-activated protein kinase kinase kinase  
387 MAPKKK5 (Kadota et al., 2014; Li et al., 2014; Bi et al., 2018; Tian et al., 2019; Thor et al.,  
388 2020). The activation of multiple calcium channels by BIK1 leads to cytosolic calcium influx,  
389 which activates calcium-dependent protein kinases (CDPKs/CPKs). In *Arabidopsis*,  
390 CPK4/5/6/11, together with BIK1, phosphorylate and activate RbohD, which leads to reactive  
391 oxygen species (ROS) production (Kadota et al., 2014, 2015; Li et al., 2014). The  
392 phosphorylation of multiple ion channels by RLCKs also leads to stomatal closure in response  
393 to PAMPs (Liu et al., 2019; Thor et al., 2020). In parallel, MAPKKK3 and MAPKKK5  
394 phosphorylate the MAPKKs MKK4 and MKK5, which then phosphorylate the MAPKs MPK3  
395 and MPK6 in *Arabidopsis*. In parallel, MKK1/MKK2 also phosphorylate MPK4 (Asai et al.,  
396 2002; Rasmussen et al., 2012). RLCK-VIIs, CPKs and MPKs phosphorylate and activate  
397 multiple defense-related transcription factors, such as WRKY transcription factors, resulting  
398 in the upregulation of defense-related genes (Boudsocq et al., 2010; Gao et al., 2013; Lal et al.,  
399 2018). PTI-induced transcriptional reprogramming leads to the biosynthesis of antimicrobial  
400 compounds and defense-related hormones, such as ethylene (ET) and salicylic acid (SA)  
401 (Macho et al., 2014; Bigeard et al., 2015; Guan et al., 2015; Bjornson et al., 2021). Hydrogen  
402 peroxide (a type of ROS) promotes protein and phenolic cross-linking, which result in callose

403 deposition and restricts fungal and oomycete infection (Luna et al., 2011; Voigt, 2014) (Figure  
404 4A).

#### 405 **Signaling pathway of singleton NLRs**

406 NLR-mediated immunity is triggered by the detection of effectors through intracellular NLRs.  
407 NLRs detect effectors either *via* direct interactions with effectors, guarding effector targets, or  
408 guarding decoy proteins (Van der Biezen and Jones, 1998; Dangl and Jones, 2001; van der  
409 Hoorn and Kamoun, 2008). In *Arabidopsis*, CNLs and TNLs act as sensor NLRs that recognize  
410 effectors, while RNLs act as helper NLRs to transduce immune signals (Feehan et al., 2020).  
411 While the majority of sensor NLRs in *Arabidopsis* require helper NLRs to mediate immunity,  
412 some CNLs mediate immune responses alone. These are known as singleton NLRs, such as  
413 ZAR1 and RPM1 (Adachi et al., 2019b). ZAR1 recognizes a range of effectors by monitoring  
414 pseudokinases such as RKS1 and PBL2, which mimic authentic RLCK targets of effectors  
415 (Wang et al., 2019a). The bacterial effector AvrAC from *Xanthomonas campestris* uridylylates  
416 the RLCK PBL2. The ZAR1/RKS1 heterodimer associates with uridylylated PBL2 (PBL2<sup>UMP</sup>),  
417 which leads to conformational changes in the heterodimer. ADP in the NB-ARC domain in  
418 ZAR1 is ejected and replaced by ATP (Wang et al., 2019b). This results in the oligomerization  
419 of ZAR1/RKS1/PBL2<sup>UMP</sup> oligomers into pentameric resistosomes (Wang et al., 2019a) that  
420 localize to the plasma membrane to trigger downstream immune responses (Wang et al., 2019a;  
421 Bi et al., 2021).

422 ZAR1 resistosomes were recently shown to exhibit cation channel activity (Bi et al., 2021).  
423 The N-terminal alpha-helices in ZAR1 form a funnel-shaped structure with a negatively  
424 charged carboxylate ring, which allows cations to pass through into the cytosol. Co-expression  
425 of ZAR1 with RKS1, PBL2 and AvrAC in plant protoplasts results in cytosolic calcium influx,  
426 ROS accumulation, and the perturbation of chloroplasts and vacuoles (Bi et al., 2021). Robust  
427 ROS accumulation during ZAR1 activation is likely caused by the activation of multiple  
428 downstream signaling components, such as the NADPH oxidases, since the CPKs are activated  
429 by cytosolic calcium influx (Gao et al., 2013). In addition, multiple CPKs and RbohD have  
430 been shown to be phosphorylated during RPS2 activation (Gao et al., 2013; Kadota et al.,  
431 2019). Defense-related transcription factors are also likely activated by cytosolic calcium  
432 influx (Boudsocq et al., 2010; Gao et al., 2013). The perturbation of chloroplasts and vacuoles  
433 is quickly followed by the loss of plasma membrane integrity and cellular rupture (Bi et al.,  
434 2021) (Figure 4B). How these processes are regulated by immune signaling components and  
435 their relationships to transcriptional reprogramming are currently unclear.

### 436 **The signaling pathway of helper-NLR-dependent sensor NLRs**

437 The majority of sensor NLRs require helper NLRs to mediate immunity. In solanaceous plants,  
438 the NB-LRR REQUIRED FOR HR-ASSOCIATED CELL DEATH proteins (collectively  
439 known as NRCs) are required for immunity and the hypersensitive cell death response (HR)  
440 mediated by multiple sensor NLRs (Wu et al., 2017a). Interestingly, the N-terminal CC domain  
441 in ZAR1 contains a ‘MADA motif’ that is also present in NRCs (Adachi et al., 2019a). This  
442 suggests that perhaps NRCs also form cation channels with alpha-helices following activation.  
443 In *Arabidopsis*, ADR1s and NRG1s are required for resistance and HR mediated by some  
444 CNLs and many TNLs (Bonardi et al., 2011; Castel et al., 2019a; Wu et al., 2019; Saile et al.,  
445 2020). Following effector recognition, TNLs also oligomerize into resistosomes to mediate  
446 resistance (Ma et al., 2020a; Martin et al., 2020). The *Arabidopsis* RPP1 recognizes the *Hpa*  
447 effector ATR1, and *N. benthamiana* ROQ1 recognizes the *Xanthomonas* effector XopQ. These  
448 effectors are recognized by the LRR and post-LRR (PL) domain, which likely leads to  
449 conformational changes and oligomerization of these TNLs into tetrameric resistosomes (Ma  
450 et al., 2020a; Martin et al., 2020).

451 The TIR domains of TNLs are brought into close proximity following oligomerization,  
452 activating NADase activity and producing variant-cyclic-ADP-ribose (v-cADPR) (Horsefield  
453 et al., 2019; Wan et al., 2019a; Duxbury et al., 2020; Ma et al., 2020a; Martin et al., 2020). TIR  
454 domains also exhibit 2',3'-cAMP/cGMP synthetase activity by hydrolyzing RNA or DNA (Yu  
455 et al., 2021). V-cADPR and 2',3'-cAMP/cGMP are proposed to be signaling molecules that  
456 activate downstream signaling components (Horsefield et al., 2019; Wan et al., 2019a; Yu et  
457 al., 2021). Following the activation of TNLs, the EP-domain containing proteins (EP-proteins)  
458 SAG101 and EDS1 associate with NRG1 (Sun et al., 2021). Similarly, the activation of TNLs  
459 also leads to the association of the EP-proteins PAD4 and EDS1 with ADR1 (Wu et al., 2021b).  
460 These associations lead to the activation of these signaling components, which in turn activate  
461 downstream immune responses, such as defense-related gene expression and the HR (Lapin et  
462 al., 2019; Sun et al., 2021). The RNLs ADR1 and NRG1 were also recently shown to function  
463 as calcium channels to activate immunity (Jacob et al., 2021). It is conceivable that the  
464 association and activation of helper RNLs and EP-proteins induces calcium influx and triggers  
465 downstream immune responses (Figure 4C).

466

### 467 **Physiological responses induced by RLKs**

468 Following ligand perception, the PRR co-receptor BAK1 and the RLCK BIK1 are  
469 phosphorylated (Lin et al., 2014; Perraki et al., 2018). This leads to the phosphorylation and  
470 activation of multiple signaling components (Macho and Zipfel, 2014). The activation of  
471 multiple calcium channels and NADPH oxidases leads to calcium influx, stomatal closure,  
472 ROS production, and callose deposition (Luna et al., 2011; Kadota et al., 2014; Li et al., 2014;  
473 Thor et al., 2020). The activation of CPKs and MAPKs leads to transcriptional reprogramming  
474 and the biosynthesis of defense-related hormones (Boudsocq et al., 2010). In *Arabidopsis*,  
475 MPK3/MPK6 activate 1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACID SYNTHASE  
476 (ACS) isoforms ACS2 and ACS6, which are involved in ET biosynthesis (Liu and Zhang,  
477 2004; Han et al., 2010). The transcription factors SYSTEMIC ACQUIRED RESISTANCE  
478 DEFICIENT 1 (SARD1) and CALMODULIN-BINDING PROTEIN 60 G (CBP60g) are  
479 required for PTI-induced upregulation of SA biosynthesis genes, such as *ISOCHORISMATE*  
480 *SYNTHASE 1 (ICS1)*, *ENHANCED DISEASE SUSCEPTIBILITY 5 (EDS5)*, and *AVRPPHB*  
481 *SUSCEPTIBLE 3 (PBS3)* (Zhang et al., 2010b; Sun et al., 2015). SARD1 and CBP60g are also  
482 required for the upregulation of pipecolic acid (N-hydroxyl-pipecolic acid, NHP) biosynthesis  
483 genes, such as *FLAVIN-CONTAINING MONOOXYGENASE 1 (FMO1)* (Sun et al., 2015; Liu  
484 et al., 2020) (Figure 5).

#### 485 **Physiological responses induced by RLPs**

486 Similar to RLKs, RLPs also require PRR co-receptors, RLCKs, CPKs, and MAPKs to  
487 transduce immune signals (Piedras et al., 1998; Romeis et al., 1999, 2000; Rowland et al.,  
488 2005; González-Lamothe et al., 2006; Yang et al., 2006; van den Burg et al., 2008). In  
489 *Arabidopsis*, nlp20-induced immune responses mediated by RLP23 require the co-receptors  
490 BAK1, SOBIR1, and multiple RLCKs such as PBL19/20/30/31/32 (Albert et al., 2015; Pruitt  
491 et al., 2020; Tian et al., 2020). The activation of RLP23 leads to changes in plasma membrane  
492 potential, an ROS burst, the phosphorylation of BIK1 and MAPKs, callose deposition, and SA  
493 and ET production, similar to the activation of FLS2 (Wan et al., 2019b). In addition, flg22 and  
494 nlp20 induce highly overlapping transcriptional reprogramming in *Arabidopsis* (Wan et al.,  
495 2019b; Bjornson et al., 2021). Thus, RLKs and RLPs induce overlapping responses due to the  
496 activation of similar downstream signaling components. However, the individual activation of  
497 multiple RLPs, such as *SfCf-4*, *SfCf-9*, and *AtRLP23*, leads to the HR, perhaps due to the  
498 prolonged activation of downstream signaling components (Jones et al., 1994; Thomas et al.,  
499 1997; Rowland et al., 2005; Albert et al., 2015). PAD4, EDS1 and ADR1 are required for both  
500 RLK- and RLP-mediated immunity (Pruitt et al., 2021; Tian et al., 2021). Thus, EP-proteins



501 and helper NLRs might also be activated during some PTI signaling, although it remains to be  
502 established whether EP proteins play a primary or secondary role in defense signaling (Figure  
503 5).

#### 504 **Physiological responses induced by CNLs alone**

505 Activation of the *Arabidopsis* CNL RPS2 in the absence of PTI leads to the phosphorylation  
506 of RbohD (in Ser343/347), CPKs, and MAPKs (Gao et al., 2013; Tsuda et al., 2013; Kadota et  
507 al., 2019; Ngou et al., 2021a; Yuan et al., 2021). RPS2-induced RbohD phosphorylation and  
508 ROS production are dependent on BAK1/BKK1 and BIK1 (Yuan et al., 2021). However, it is  
509 currently unclear whether BAK1/BKK1 and BIK1 are directly or indirectly activated by CNLs.  
510 While the ZAR1 resistosome directly triggers calcium influx, other calcium channels may also  
511 be activated by CNLs (Bi et al., 2021). The activation of RPM1, RPS2, and RPS5 leads to  
512 MAPK activation and the HR (Ngou et al., 2021a). In addition, the activation of many CNLs  
513 leads to the upregulation of SA- and NHP-biosynthesis genes (Jacob et al., 2018; Ngou et al.,  
514 2021a). Thus, ET, SA, and NHP are likely to be produced during CNL activation (Figure 5).

#### 515 **Physiological responses induced by TNLs alone**

516 Activation of the *Arabidopsis* TNL RRS1/RPS4 does not lead to the phosphorylation of BIK1,  
517 RbohD (in Ser39/343/347), MAPKs, calcium influx, ROS accumulation, or the HR (Ngou et  
518 al., 2020, 2021a). Thus, RLCKs, NADPH oxidases, calcium channels, or CPKs are unlikely to  
519 be activated by RRS1/RPS4 alone. Activation of RRS1/RPS4 induces weak callose deposition,  
520 perhaps via SA accumulation (Tateda et al., 2014; Ngou et al., 2021a). Activation of TNLs  
521 leads to the association of EP-proteins with helper NLRs, which induces transcriptional  
522 reprogramming (Saile et al., 2020; Sun et al., 2021; Wu et al., 2021b). Similar to CNLs, the  
523 activation of TNLs leads to the upregulation of SA- and NHP-biosynthesis genes (Ding et al.,  
524 2020; Ngou et al., 2021a). Thus, SA and NHP are likely to be produced during TNL activation  
525 (Figure 5).

#### 526 **Physiological responses induced by the co-activation of PRRs and NLRs**

527 Co-activation of PRRs and NLRs ('PTI + ETI') leads to the robust activation of BIK1, RbohD,  
528 and MPK3 (Tsuda et al., 2013; Su et al., 2018; Ngou et al., 2021a; Yuan et al., 2021). This  
529 results in stronger calcium influx, ROS accumulation, and callose deposition compared to PTI  
530 or ETI alone (Ngou et al., 2021a; Yuan et al., 2021). In addition, 'PTI + ETI' leads to stronger  
531 accumulation of SA and NHP compared to PTI alone, which is likely due to the stronger

532 expression of SA- and NHP-biosynthesis genes during ETI (Wang et al., 2018c; Castel et al.,  
533 2019a; Ding et al., 2020; Liu et al., 2020) (Figure 5).

534

### 535 **Regulation of PRR-mediated immunity**

536 The PRR-signaling pathway is tightly regulated, as the excessive activation of PRRs leads to  
537 autoimmunity and growth inhibition (Navarro et al., 2006; Albrecht et al., 2012; Huot et al.,  
538 2014).

#### 539 *Regulation of PRRs*

540 Both the transcript and protein levels of PRRs are regulated by multiple mechanisms. For  
541 example, the expression of *FLS2* is regulated by the microRNA miR172b (Zou et al., 2018).  
542 The expression of *FLS2* is also upregulated by ET (Boutrot et al., 2010). U-BOX DOMAIN-  
543 CONTAINING PROTEIN 12 (PUB12) and PUB13 mediate the polyubiquitination of *FLS2*,  
544 which leads to the endocytosis and degradation of this protein (Lu et al., 2011). Cf-4 also  
545 undergoes endocytosis upon Avr4 recognition (Postma et al., 2016). The activation of PRRs  
546 and their co-receptors must also be regulated. BAK1-INTERACTING RECEPTOR-LIKE  
547 KINASE 1 (BIR1) is an RLK that associates with and sequesters BAK1 to prevent the auto-  
548 activation of BAK1-associated PRRs (Gao et al., 2009; Ma et al., 2017; Hohmann et al., 2018).  
549 Following PAMP perception, the peptide RAPID ALKALINIZATION FACTOR 23  
550 (RALF23) is perceived by a PRR complex composed of the *CtRLK1L FERONIA* (FER) and  
551 the LORELEI-LIKE-GPI ANCHORED PROTEIN 1 (LLG1). The perception of RALF23 by  
552 FER negatively regulates the formation of the *FLS2*-BAK1 complex (Stegmann et al., 2017;  
553 Xiao et al., 2019). FER regulates plasma membrane nanodomain organization to modulate PRR  
554 signaling (Gronnier et al., 2020). In addition, the phosphorylation status of PRRs is regulated  
555 by multiple protein phosphatases. In *Arabidopsis*, POLTERGEIST-LIKE 4 (PLL4) and PLL5  
556 associate with EFR and negatively regulate elf18-induced responses (Holton et al., 2015).  
557 PROTEIN PHOSPHATASE 2A (PP2A) negatively regulates the phosphorylation status of  
558 BAK1 (Segonzac et al., 2014) (Figure 6).

#### 559 *Regulation of PRR-signaling components*

560 In addition to PRRs, downstream signaling components are also regulated to prevent prolonged  
561 activation. As a central signaling component in the PRR-signaling pathway, the *Arabidopsis*  
562 RLCK BIK1 is regulated by multiple mechanisms. EXTRA-LARGE G PROTEIN 2 (XLG2)  
563 functions with other heterotrimeric G proteins to attenuate proteasome-mediated degradation

564 of BIK1 (Liang et al., 2016). The turnover of BIK1 is regulated by CPK28, PUB4/25/26, and  
 565 the E3 ubiquitin ligases RING-H2 FINGER A3A/B (RHA3A/B) (Monaghan et al., 2014; Wang  
 566 et al., 2018a; Derkacheva et al., 2020; Ma et al., 2020b). The phosphorylation status of BIK1  
 567 is also negatively regulated by the protein phosphatase PP2C38 (Couto et al., 2016). In addition  
 568 to RLCKs, other PRR-signaling components must also be regulated. RbohD is ubiquitinated  
 569 by the E3 ubiquitin ligase PIRE, which leads to proteasome-mediated degradation (Lee et al.,  
 570 2020). PHAGOCYTOSIS OXIDASE/ BEM1P (PB1) DOMAIN-CONTAINING PROTEIN  
 571 (PB1CP) negatively regulates ROS production by controlling the localization of RbohD (Goto  
 572 et al., 2020). The PP2C phosphatases PP2C5 and AP2C1 negatively regulate the  
 573 phosphorylation of MPK3 and MPK6 (Brock et al., 2010) (Figure 6).

#### 574 **Regulation of NLR-mediated immunity**

575 Similar to PRRs, the prolonged activation of NLRs also leads to autoimmunity. Thus, the  
 576 regulation of both NLRs and downstream signaling components is important to prevent  
 577 autoimmunity.

#### 578 *Regulation of NLRs*

579 The expression of NLRs is regulated at multiple levels (van Wersch et al., 2020). The  
 580 transcription of *NLRs* is regulated by chromatin-remodeling proteins such as DECREASE IN  
 581 DNA METHYLATION 1 (DDM1), SWI/SNF CHROMATIN REMODELER SYD  
 582 (SPLAYED), and multiple WRKY transcription factors (Li et al., 2010b; Johnson et al., 2015;  
 583 Lai and Eulgem, 2018). *NLR* transcript stability is also regulated by microRNAs (miRNAs)  
 584 and NONSENSE-MEDIATED mRNA DECAY factors, such as UP-FRAMESHIFT1/2/3  
 585 (UPF1/2/3) (Shivaprasad et al., 2012; Jung et al., 2020). *NLR* transcripts also undergo  
 586 alternative splicing, which is regulated by some MODIFIER OF SNC1 (MOS) proteins such  
 587 as MOS4/12/14 (Zhang and Gassmann, 2007; Xu et al., 2011, 2012).

588 REQUIRED FOR MLA12 RESISTANCE 1 (RAR1), SUPPRESSOR OF THE G2 ALLELE  
 589 OF SKP1 (SGT1), and HEAT SHOCK PROTEIN 90 (HSP90) function together as protein  
 590 chaperones to regulate the folding, localization, and turnover of NLRs (Azevedo et al., 2002;  
 591 Peart et al., 2002; Takahashi et al., 2003; Shirasu, 2009). In addition, NLR protein turnover is  
 592 regulated by the SGT1-interacting protein SUPPRESSORS OF RPS4-RLD (SRFR1), multiple  
 593 MUTANT SNC1-ENHANCING proteins (MUSEs), and the E3 ligases SNIPER1 and  
 594 SNIPER2 (Li et al., 2010a; Huang et al., 2016; Dong et al., 2018; Wu et al., 2020c).

595 The localization of the ZAR1 resistosome to the plasma membrane is required for ZAR1-  
596 mediated resistance (Wang et al., 2019a; Bi et al., 2021). In addition, the *Arabidopsis* importin-  
597  $\alpha$  nuclear transport receptor protein IMP- $\alpha$ 3/MOS6 is required for SUPPRESSOR OF NPR1-  
598 1- (SNC1)-mediated immunity (Lüdke et al., 2021). Thus, the localization of NLRs is important  
599 and is likely regulated by proteins involved in trafficking (Figure 6).

#### 600 *Regulation of NLR-signaling components*

601 The correct localization of helper NLRs is likely important for signaling. For example, the  
602 helper NLR NRC4 accumulates at the extra-haustorial membrane following *P. infestans*  
603 infection (Duggan et al., 2021). In addition, the balanced activity of both cytosolic- and  
604 nuclear-EDS1 is required for full immunity (García et al., 2010). Thus, the localization of  
605 helper NLRs and NLR-signaling components is important for defense. The activity of NLR  
606 signaling components is also negatively regulated. The *Arabidopsis* RNL NRG1C functions as  
607 a negative regulator in NLR-mediated immunity; overexpressing *NRG1C* compromised TNL-  
608 mediated HR and resistance (Wu et al., 2021a). In addition, an atypical member of the NRC  
609 family, NRCX, negatively regulates other NRC members to modulate immunity (Adachi et al.,  
610 2021). Post-translational modifications (PTMs) are important for the functions of both PRRs  
611 and NLRs. For example, the phosphorylation of the C-terminus of the TNL RRS1-R is crucial  
612 for its recognition of the effector PopP2 (Guo et al., 2020). It is currently unclear whether PTMs  
613 are important for the activation and/or stability of NLR-signaling components. Perhaps EP-  
614 proteins and helper NLRs must also undergo PTMs in order to function properly. The  
615 additional regulation of NLR-signaling components pre- and post-NLR activation remains to  
616 be investigated (Figure 6).

#### 617 **Suppression of immunity by effectors**

618 Multiple effectors have been shown to target both the PRR- and NLR-signaling pathways.  
619 Here, we summarize our knowledge of effectors reported to target PTI or ETI. Unless specified,  
620 the effectors mentioned in this section are from various *P. syringae* strains. AvrPtoB is an E3  
621 ubiquitin ligase that induces the degradation of FLS2 (Göhre et al., 2008; Lu et al., 2011).  
622 HopB1 specifically degrades activated BAK1 (Li et al., 2016). AvrPto targets SOBIR1 and the  
623 FLS2-BAK1 complex by inhibiting their kinase activities (Xing et al., 2007; Shan et al., 2008;  
624 Xiang et al., 2008; Meng and Zhang, 2013; Wu et al., 2017b). Similarly, the conserved  
625 *Colletotrichum* effector NIS1 also targets receptor kinase complexes (Irieda et al., 2019). The  
626 tyrosine phosphatase HopAO1 directly dephosphorylates EFR (Macho et al., 2014). As RLCKs  
627 are central immune regulators, they are targeted by multiple effectors. AvrAC from

628 *Xanthomonas campestris* uridylylates BIK1 and PBL2 (Feng et al., 2012; Wang et al., 2015).  
629 HopZ1a acetylates RLCKs, and AvrPphB is a cysteine protease that degrades RLCKs such as  
630 BIK1, PBS1, and PBL1 (Zhang et al., 2010a; Bastedo et al., 2019). Other downstream PRR  
631 signaling components are also targeted by effectors. The ADP-ribosyltransferase HopF2  
632 targets both BAK1 and MKK5 to suppress PTI signaling (Wang et al., 2010; Zhou et al., 2014).  
633 HopAI1 inactivates MPK3, MPK4, and MPK6 via its phosphothreonine lyase activity (Zhang  
634 et al., 2007). AvrRpt2 suppresses MPK4/11 activation (Eschen-Lippold et al., 2016).  
635 Interestingly, many parallel mechanisms are employed to suppress the same PRR-signaling  
636 node in different hosts by different pathogens (Figure 6).

637 Phosphorylation of SGT1 by MAPKs is required for NLR activation, implying that NLRs are  
638 regulated by SGT1 following PTI-induced MAPK activation (Hoser et al., 2013; Yu et al.,  
639 2020). The *Ralstonia solanacearum* effector RipAC prevents MAPK-mediated  
640 phosphorylation of SGT1, which suppresses NLR-mediated immunity (Yu et al., 2020). Two  
641 effectors were recently shown to suppress NRC-mediated HR. The *P. infestans* effector  
642 AVRcap1b and the cyst nematode effector SPRYSEC15 can suppress autoimmunity induced  
643 by autoactive alleles of NRC2 and NRC3 (Derevnina et al., 2021). Suppression of NRC2 and  
644 NRC3 by AVRcap1b is dependent on the membrane trafficking-associated protein TARGET  
645 OF MYB 1-LIKE PROTEIN 9A (*NbTOL9a*) (Derevnina et al., 2021). AVRcap1b suppresses  
646 NRC2 and NRC3 by directly interacting with their NB-ARC domains (Derevnina et al., 2021).  
647 Another *Phytophthora* effector (from *P. capsici*), PcAvh103, suppresses immunity by  
648 promoting the disassociation of the EDS1–PAD4 complex (Li et al., 2020). More studies are  
649 needed to identify pathogen effectors that target the NLR signaling pathway.

650 In *Arabidopsis*, the transcription factors CALMODULIN-BINDING TRANSCRIPTION  
651 ACTIVATOR 1/2/3 (CAMTA1/2/3) and CBP60a negatively regulate defense-induced  
652 transcriptional reprogramming (Truman et al., 2013; Kim et al., 2020; Sun et al., 2020).  
653 Pathogens also target defense-related transcription factors to suppress immunity. For example,  
654 the *Ralstonia solanacearum* effector PopP2 acetylates and inhibits WRKY transcription factors  
655 to suppress immunity (Le Roux et al., 2015; Sarris et al., 2015; Zhang et al., 2017b). In addition,  
656 the *Verticillium dahliae* effector VdSCP41 inhibits SARD1 and CBP60g to facilitate its  
657 proliferation (Qin et al., 2018) (Figure 6).

658

## 659 **The interactions between PTI and ETI**

660 While PRR- and NLR-mediated immunity have been extensively studied for the last 20 years,  
661 it has not been clear how or if these defense mechanisms interact. NLR-mediated immunity is  
662 mostly activated in the presence of microbes or PAMPs. Most studies on NLR-mediated  
663 immunity have involved transient expression-based comparisons between PTI and ‘PTI + ETI’.  
664 The activation of NLRs in the absence of PTI has not been extensively studied until recently.  
665 There have been multiple reports on the different interactions between these two immune  
666 systems. Here, we describe three situations in which PTI and ETI interact with each other.

#### 667 *NLRs guard the PRR-signaling pathway*

668 Many effectors target the PRR-signaling pathway. Plants have evolved multiple NLRs to detect  
669 these effectors *via* the guarding of PRR-signaling components or decoys. As a result, many  
670 PRRs and PRR-signaling loss-of-function mutants, such as the Arabidopsis mutants *bak1-4*  
671 *bkk1-1*, *bik1*, *cgnc2/4*, *rbohdf*, *mekk1*, *mkk1/2*, *mpk4* and *camta3*, exhibit autoimmune  
672 phenotypes (Torres et al., 2002; Roux et al., 2011; Zhang et al., 2012; Chen et al., 2016; Liu et  
673 al., 2017; Lolle et al., 2017; Kadota et al., 2019; Tian et al., 2019). The autoimmunity observed  
674 in some of these mutants is caused by the activation of multiple NLRs. The TNL  
675 CONSTITUTIVE SHADE-AVOIDANCE 1 (CSA1) guards both BAK1-INTERACTING  
676 RECEPTOR 3 (BIR3) and BAK1 (Schulze et al., 2021). In addition, *bak1-3 bkk1-1*-  
677 autoimmunity and HopB1-triggered immunity are dependent on ADR1s (Wu et al., 2020b).  
678 RLCKs are targeted by multiple effectors. The CNL ZAR1 together with the RLCK RKS1  
679 monitor PBL2, and the CNL RPS5 monitors PBS1, to reverse ETS (Shao et al., 2003; Zhang  
680 et al., 2010a; Wang et al., 2015). The CNL SUMM2 guards and senses the disruption of the  
681 MEKK1-MKK1/2-MPK4 kinase cascade via CALMODULIN-BINDING RECEPTOR-LIKE  
682 CYTOPLASMIC KINASE 3 (CRCK3), a substrate protein of MPK4 (Zhang et al., 2012,  
683 2017a). SUMM2 also detects the *P. syringae* effector HopAI1, which inhibits MPK4 kinase  
684 activity (Zhang et al., 2012). The TNL RPS6 also contributes to HopAI1-triggered immunity  
685 (Takagi et al., 2019). Whether the autoimmunity in *bik1*, *cgnc2/4* and *rbohdf* is dependent on  
686 NLRs remains unclear. Other NLRs that guard the PRR-signaling pathway remain to be  
687 identified (Figure 7A).

#### 688 *Interdependency of signaling components between PRRs and NLRs*

689 PRR co-receptors, RLCKs, NADPH oxidases, calcium channels, CPKs, and MAPKs are  
690 considered to be canonical PRR-signaling components, while EP proteins and helper NLRs are  
691 considered to be canonical NLR-signaling components. However, recent studies indicated that  
692 PRR-mediated resistance is dependent on canonical NLR-signaling components and *vice versa*

693 (Ngou et al., 2021a; Pruitt et al., 2021; Tian et al., 2021; Yuan et al., 2021) (Figure 7B). As  
694 mentioned, flg22- and nlp20-induced resistance is partially dependent on EDS1, PAD4,  
695 SAG101, ADR1s, and NRG1s (Pruitt et al., 2021; Tian et al., 2021). Pruitt et al. (2021)  
696 proposed that EP-proteins and helper NLRs are activated by RLPs through interactions  
697 between RLP co-receptors (SOBIR1), EP-proteins, and helper NLRs, although it remains to be  
698 determined whether EP-proteins play a primary or secondary role in RLP defense signaling.  
699 Another report, however, suggested that the activation of PRRs leads to increased expression  
700 of multiple NLRs and other TIR-domain containing proteins, promoting downstream signaling  
701 (Tian et al., 2021). These two hypotheses are not mutually exclusive, and the exact mechanisms  
702 by which PRR-mediated immunity involves NLR-signaling components remain to be  
703 determined.

704 NLR-mediated immunity is also dependent on PRRs and multiple PRR-signaling components.  
705 In *Arabidopsis*, RPS2-, RPS5- and RRS1/RPS4- mediated resistance is dependent on BAK1  
706 and BKK1 (Ngou et al., 2021a; Yuan et al., 2021). RPS2-mediated resistance is also be  
707 dependent on BIK1 and RbohD (Kadota et al., 2019; Yuan et al., 2021). Both RPM1- and  
708 RPS2-mediated resistance and the HR are dependent on CPK1/2/5/6 (Gao et al., 2013). The  
709 activation of MPK3 and MPK6 is also required for the HR and resistance mediated by multiple  
710 NLRs including RPM1, RPS2, RPS5 and RRS1/RPS4 (Su et al., 2018). One of the proposed  
711 key mechanisms by which ETI halts pathogen infection is to potentiate and restore PTI from  
712 turnover and the action of pathogen effectors (Ngou et al., 2021a; Yuan et al., 2021). As a  
713 result, PRRs and PRR-signaling components are required for NLR-mediated resistance. The  
714 molecular mechanisms by which ETI potentiates PTI will be discussed in the next section.

#### 715 *Mutual potentiation between PRR- and NLR-mediated immunity*

716 Activation of the TNLs RRS1/RPS4 and RPP4 using an estradiol-inducible recognized effector  
717 (ETI without PTI) did not trigger the HR. The presence of PAMPs/MAMPs restored the HR  
718 induced by these TNLs (Ngou et al., 2020, 2021a). Similarly, the HR induced by the CNLs  
719 RPM1, RPS2 and RPS5 was also potentiated by the activation of PRRs (Ngou et al., 2021a).  
720 In addition, the HR and resistance induced by RPS2 are compromised in PRR mutants (Ma et  
721 al., 2012; Yuan et al., 2021). There are a few possible mechanisms by which PRRs potentiate  
722 NLR-induced immunity. Firstly, the activation of PRRs could induce the expression of NLRs  
723 and NLR-signaling components (Navarro et al., 2004; Bonardi et al., 2011; Brendolise et al.,  
724 2018; Jung et al., 2020). A recent transcriptomics study suggested that the activation of  
725 different PRRs induces highly overlapping transcriptional changes (Bjornson et al., 2021).

726 Indeed, the activation of six distinct PRRs led to the upregulation of genes encoding most  
727 TNLs, CNLs, EP-proteins, and helper NLRs in *Arabidopsis* (Bjornson et al., 2021) (Figure 7C;  
728 Supplemental Data Set S3). The increased abundance of these proteins might therefore ‘prime’  
729 the activation of NLRs upon effector recognition. Secondly, the activation of PRRs might  
730 prime NLR-mediated immunity *via* PTMs. Upon PAMP perception, SGT1 is phosphorylated  
731 by MAPKs, which is important for the stability of NLRs (Yu et al., 2020). In addition,  
732 nonsense-mediated decay of *NLR* transcripts is inhibited upon PAMP recognition (Jung et al.,  
733 2020). Thus, the stability of NLRs can be affected by both transcriptional and post-  
734 transcriptional modifications activated by PTI. Conceivably, EP-proteins and helper NLRs  
735 might also be primed *via* PTMs induced by PTI. Flg22 treatment led to reduced  
736 polyubiquitination levels of EDS1 (Grubb et al., 2021; Ma et al., 2021). Whether and how PTI  
737 primes NLR-signaling components remain to be investigated.

738 The activation of NLRs potentiates PAMP-induced cellular responses, such as ROS  
739 production, callose deposition, and defense-related gene expression (Ngou et al., 2021a). The  
740 activation of multiple PRR signaling components, such as BIK1, RbohD and MPK3, is also  
741 potentiated by ETI (Ngou et al., 2021a; Yuan et al., 2021). ETI induces the transcript and  
742 protein accumulation of SOBIR1, BAK1, BIK1, RbohD and MPK3 (Ngou et al., 2021a).  
743 Transcriptomic analysis confirmed that multiple PRR signaling components are also  
744 upregulated upon the activation of RRS1/RPS4. These include CPK1/2/5/6, XLG2 and the  
745 calcium channels OSCA1.3, CNGC19/20, GLR2.7/2.8/2.9 (Ngou et al., 2021a) (Figure 7C;  
746 Supplemental Data Set S4). Interestingly, the transcript levels of *BIK1*, *MPK3* and *RbohD* are  
747 only transiently upregulated during ETI. However, the protein levels of these genes remain  
748 upregulated for an extensive period of time (Ngou et al., 2021a). This implies that PTMs or  
749 other post-transcriptional mechanisms might also influence the stability of PRR-signaling  
750 components during ETI. The protein abundance of PRR signaling components, such as BAK1,  
751 BIK1, and RbohD, is tightly regulated by multiple processes (Figure 6). How ETI regulates or  
752 affects these processes remains unclear. In addition, calcium influx induced by NLRs might  
753 contribute to the potentiation of PTI through CPKs (Bi et al., 2021; Jacob et al., 2021; Ngou et  
754 al., 2021b). To summarize, PTI and ETI mutually potentiate each other through multiple  
755 mechanisms to induce robust immunity against pathogens (Figure 7C).

756



## 757 **Historic overview of research in PTI and future challenges**

758 Researchers identified the first PRR-encoding gene, *Cf-9*, back in 1994 (Jones et al., 1994).  
759 Multiple PRR genes, such as *Xa21*, *Cf-2*, *Cf-4*, *FLS2*, *EFR* and *RLP23*, were subsequently  
760 identified and used as models to study PTI. (Song et al., 1995; Dixon et al., 1996; Thomas et  
761 al., 1997; Gómez-Gómez and Boller, 2000; Zipfel et al., 2006). Researchers then explored  
762 PRR-induced physiological responses and identified multiple signaling components. The  
763 activation of MAPKs by cell-surface receptors were reported back in 1997 (Ligterink et al.,  
764 1997) and was verified for *Cf*- genes two years later (Romeis et al., 1999). In tobacco  
765 (*Nicotiana tabacum*), the perception of PAMPs leads to the activation of wounding-induced  
766 protein kinase (WIPK) and salicylic acid-induced protein kinase (SIPK) (Zhang and Klessig,  
767 1998; Yang et al., 2001). WIPKs and SIPKs are orthologs of the subsequently identified  
768 *Arabidopsis* MPK3 and MPK6, respectively (Asai et al., 2002). Accumulation of ROS and  
769 callose deposition during infection were also reported in 1997 (Thordal-Christensen et al.,  
770 1997), and for *Cf*- initiated responses (Piedras et al., 1998). Researchers identified the human  
771 RESPIRATORY BURST NADPH OXIDASE HOMOLOGS (Rboh) in *Arabidopsis* and  
772 showed that two of these (RbohD and RbohF) are required for ROS production during infection  
773 (Torres et al., 1998, 2002). It was unclear how these signaling components were activated by  
774 PRRs until the identification of the PRR co-receptors and RLCKs. BAK1 was identified as a  
775 co-receptor essential for *FLS2*-mediated resistance in 2007 (Chinchilla et al., 2007). In the  
776 same year, CERK1 was also shown to be essential for chitin-mediated immunity (Miya et al.,  
777 2007). In 2013, SOBIR1 was identified as a co-receptor of RLPs, and the structure of the  
778 *FLS2*/BAK1 receptor complex was also defined (Liebrand et al., 2013; Sun et al., 2013). In  
779 2018, a genome-wide analysis of *Arabidopsis* LRR-RLKs interactions was reported, further  
780 supporting the theory that PRRs interact with each other to modulate and transduce signals  
781 (Smakowska-Luzan et al., 2018). Tomato ACIK1 was the first RLCK shown to be an essential  
782 signaling component in PRR-mediated immunity (Rowland et al., 2005). The *Arabidopsis*  
783 ortholog BIK1 was subsequently shown to be a central PRR-signaling component (Lu et al.,  
784 2010; Zhang et al., 2010a). RbohD, MAPKKKs, and multiple calcium channels were shown to  
785 be phosphorylated by RLCKs, which leads to downstream immune responses (Boudsocq et al.,  
786 2010; Kadota et al., 2014; Li et al., 2014; Yamada et al., 2016; Bi et al., 2018; Tian et al., 2019;  
787 Thor et al., 2020) (Figure 8A).

788 More than 60 immunity-related PRRs with known ligands have now been identified.  
789 *Arabidopsis* *EFR* has been introduced into multiple plant species, such as tomato, rice, orange,

790 and apple, providing broad-spectrum resistance to many bacteria (Lacombe et al., 2010;  
791 Schwessinger et al., 2015; Mitre et al., 2021; Piazza et al., 2021). Therefore, the identification  
792 of novel PRRs that recognize PAMPs or other elicitors would provide resources to engineer  
793 disease-resistant crops. Other challenges in PRR biology include trying to understand how  
794 PRRs activate downstream signaling components and physiological responses, how these  
795 processes are regulated and suppressed by effectors, and how resistance against pathogens is  
796 achieved (Figure 8B).

### 797 **Historic overview of research in ETI and future challenges**

798 *Arabidopsis RPS2* and the tobacco *N* gene were the first reported NLR genes (Bent et al., 1994;  
799 Mindrinos et al., 1994; Whitham et al., 1994). Multiple NLRs, including RPM1 and L6, were  
800 subsequently identified (Grant et al., 1995; Lawrence et al., 1995). Understanding how NLRs  
801 detect effectors has led to multiple models. The guard hypothesis was proposed to explain how  
802 the protein kinase Pto confers Prf-dependent recognition of AvrPto (Van der Biezen and Jones,  
803 1998). Many other examples have emerged that are consistent with this hypothesis, such as the  
804 requirement of the protease Rcr3 for Cf-2-mediated resistance (Van der Biezen and Jones,  
805 1998; Dangl and Jones, 2001; Krüger et al., 2002). The decoy model was then proposed, which  
806 is further supported by the discovery of integrated decoy domains in NLRs (van der Hoorn and  
807 Kamoun, 2008; Cesari et al., 2014; Le Roux et al., 2015; Sarris et al., 2015, 2016). The  
808 discovery of NRCs led to the concept of NLR networks (Gabriëls et al., 2007; Wu et al., 2017a,  
809 2018). Following the identification of multiple NLRs, researchers identified multiple genetic  
810 components required for NLR-mediated immunity. These include EDS1, NDR1, PAD4,  
811 RPW8, SGT1, RAR1, HSP90, SAG101, NRG1s and ADR1s (Parker et al., 1996; Century et  
812 al., 1997; Zhou et al., 1998; Falk et al., 1999; Xiao et al., 2001; Azevedo et al., 2002; Takahashi  
813 et al., 2003; Feys et al., 2005; Peart et al., 2005; Bonardi et al., 2011). EDS1 was later shown  
814 to co-function with SAG101 and PAD4 to mediate HR and resistance during ETI (Feys et al.,  
815 2001, 2005; Wagner et al., 2013; Sun et al., 2021; Wu et al., 2021b). Similarly, ADR1 and  
816 NRG1 have been shown to function downstream of multiple sensor NLRs to mediate the HR  
817 and resistance (Castel et al., 2019a; Wu et al., 2019; Saile et al., 2020). How sensor NLRs  
818 activate these signaling components is currently under investigation. v-cADPR produced by  
819 TIR domains might contribute to the activation of EP-proteins and helper NLRs (Horsefield et  
820 al., 2019; Wan et al., 2019). NLRs were shown to oligomerize and trigger cytosolic calcium  
821 influx following effector recognition (Grant et al., 2000; Mestre and Baulcombe, 2006). The  
822 discovery of the structures of multiple NLR resistosomes proved that the oligomerization of

823 NLRs is required for resistance, likely through the formation of cation channels (Wang et al.,  
824 2019a; Ma et al., 2020a; Martin et al., 2020; Bi et al., 2021; Jacob et al., 2021). However,  
825 oligomerization of TIR domains imposed by an NLRC4 scaffold is sufficient to activate  
826 defense (Duxbury et al., 2020) (Figure 8A).

827 More than 140 NLRs with known recognized effectors have been identified (Kourelis and  
828 Kamoun, 2020). Cross-species transfer of NLR ‘stacks’ provides durable resistance against  
829 pathogens (Jones et al., 2003; Mukhtar, 2013; Ghislain et al., 2019; Luo et al., 2021; Witek et  
830 al., 2021). Identification of novel NLRs will provide resources to engineer crop resistance  
831 against multiple pathogens. Current challenges in NLR biology include understanding how  
832 NLRs activate downstream signaling components, how these signaling components then  
833 trigger immune responses, how these processes are regulated and suppressed by effectors, and  
834 how NLRs and PRRs co-function to achieve resistance against pathogens (Figure 8B).

### 835 **Conclusion and perspectives**

836 Plants respond to pathogens using a two-tier innate immune system activated by both cell-  
837 surface and intracellular immune receptors. The perception of  
838 PAMPs/MAMPs/DAMPs/HAMPs on the cell surface leads to PRR-mediated immunity, and  
839 the recognition of effectors leads to intracellular NLR-mediated immunity. Many immune  
840 receptors have been identified since 1994, when the first PRR and NLRs were identified.  
841 Tremendous efforts have been made to understand the PRR- and NLR-signaling pathways.  
842 PRRs and NLRs utilize some overlapping but also unique signaling components to activate  
843 each of their downstream physiological responses, which thwart pathogen proliferation. Both  
844 signaling pathways are tightly regulated to prevent autoimmunity, while being suppressed by  
845 pathogen effectors. Recent studies have shown that PRR- and NLR-mediated immunity can be  
846 mutually potentiated and are dependent on each other. Great opportunities for novel discoveries  
847 remain in addressing the following challenges in the research of plant immunity: (1) identifying  
848 novel immune receptors; (2) understanding the signaling pathways and physiological responses  
849 triggered by both cell-surface and intracellular immune receptors; (3) understanding how  
850 immunity is intrinsically regulated and manipulated by external biotic and/or abiotic factors;  
851 (4) understanding the vastly diverse mechanisms by which plants resist pathogen infections,  
852 and (5) understanding how different immune systems function synergistically during  
853 infections. These challenges overlap with some of the ‘top 10 unanswered questions in  
854 molecular plant-microbe interactions’ (Harris et al., 2020) and will shape our understanding of  
855 plant immunity in the coming decades (Figure 8B).

856

## 857 **Supplemental Data**

858 **Supplemental Data Set S1.** PRRs involved in plant immunity.

859 **Supplemental Data Set S2.** NLRs involved in plant immunity.

860 **Supplemental Data Set S3.** Expression of ETI-related genes during PTI.

861 **Supplemental Data Set S4.** Expression of PTI-related genes during ETI.

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## 865 **Author contributions**

866 B.P.M.N., P.D. and J.D.G.J. conceptualized the review outline; B.P.M.N. curated information,  
867 prepared the figures, and wrote the original draft; and B.P.M.N., P.D. and J.D.G.J. reviewed  
868 and edited the manuscript.

## 869 **Competing interests**

870 The authors declare no competing interests.

871

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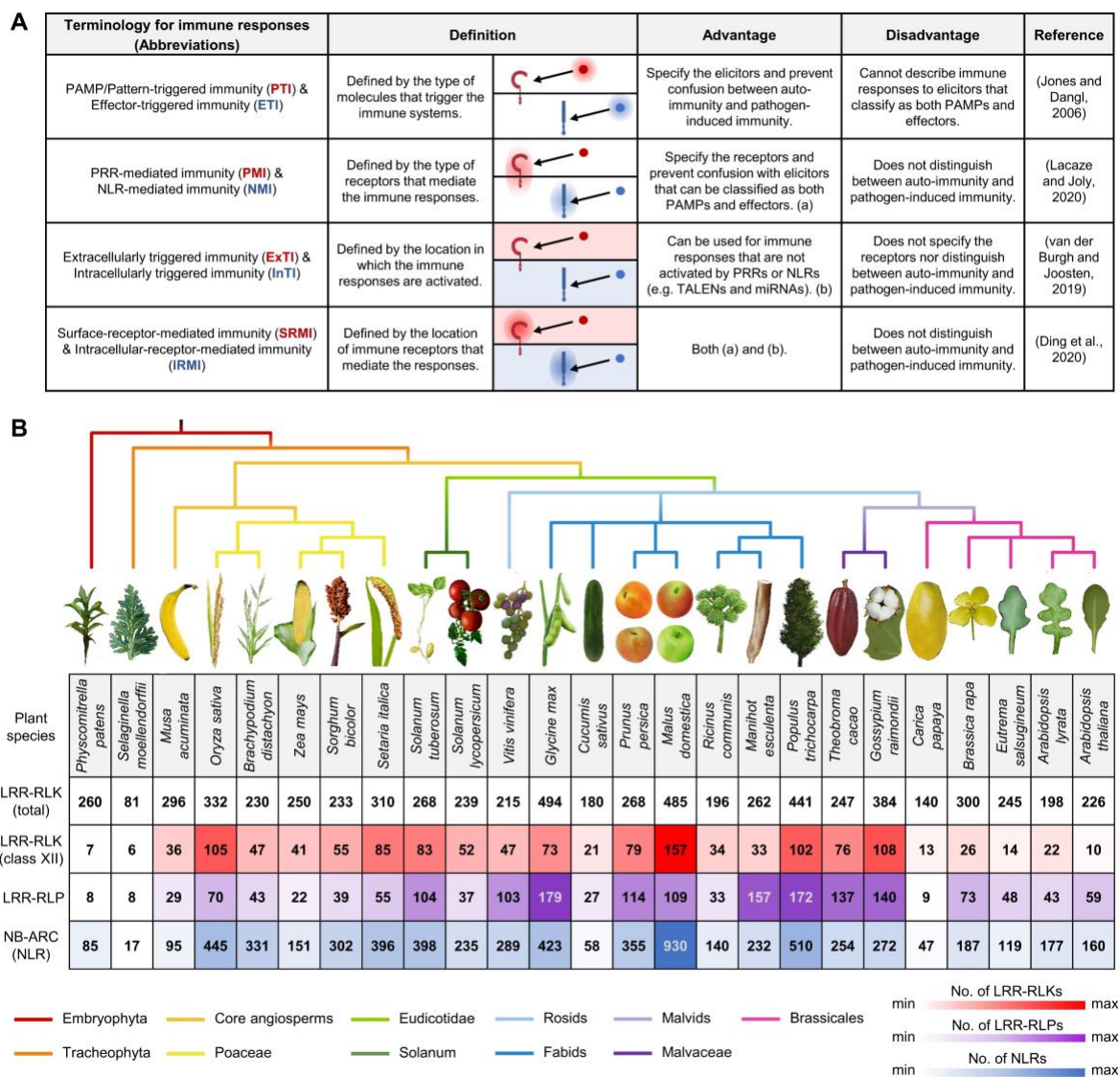
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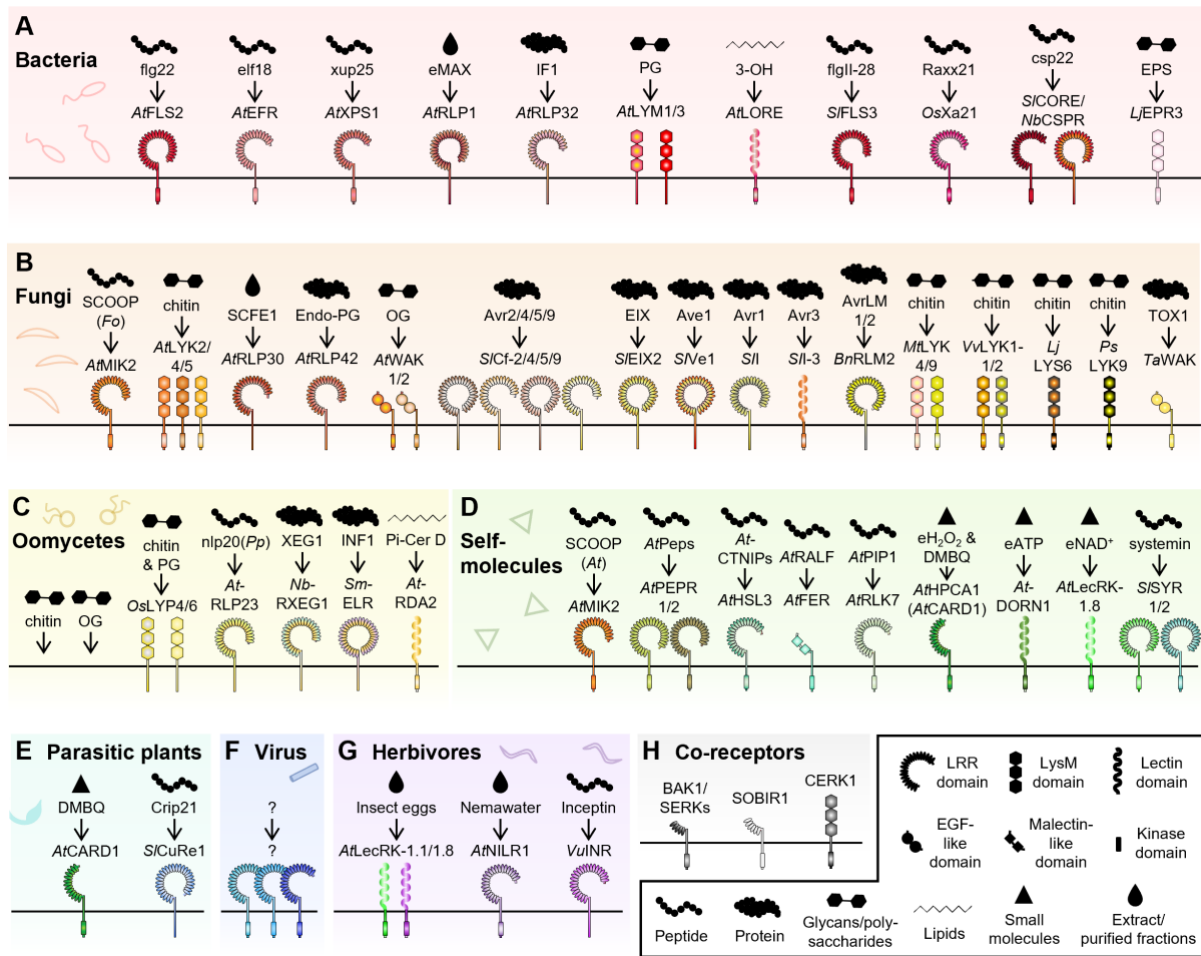
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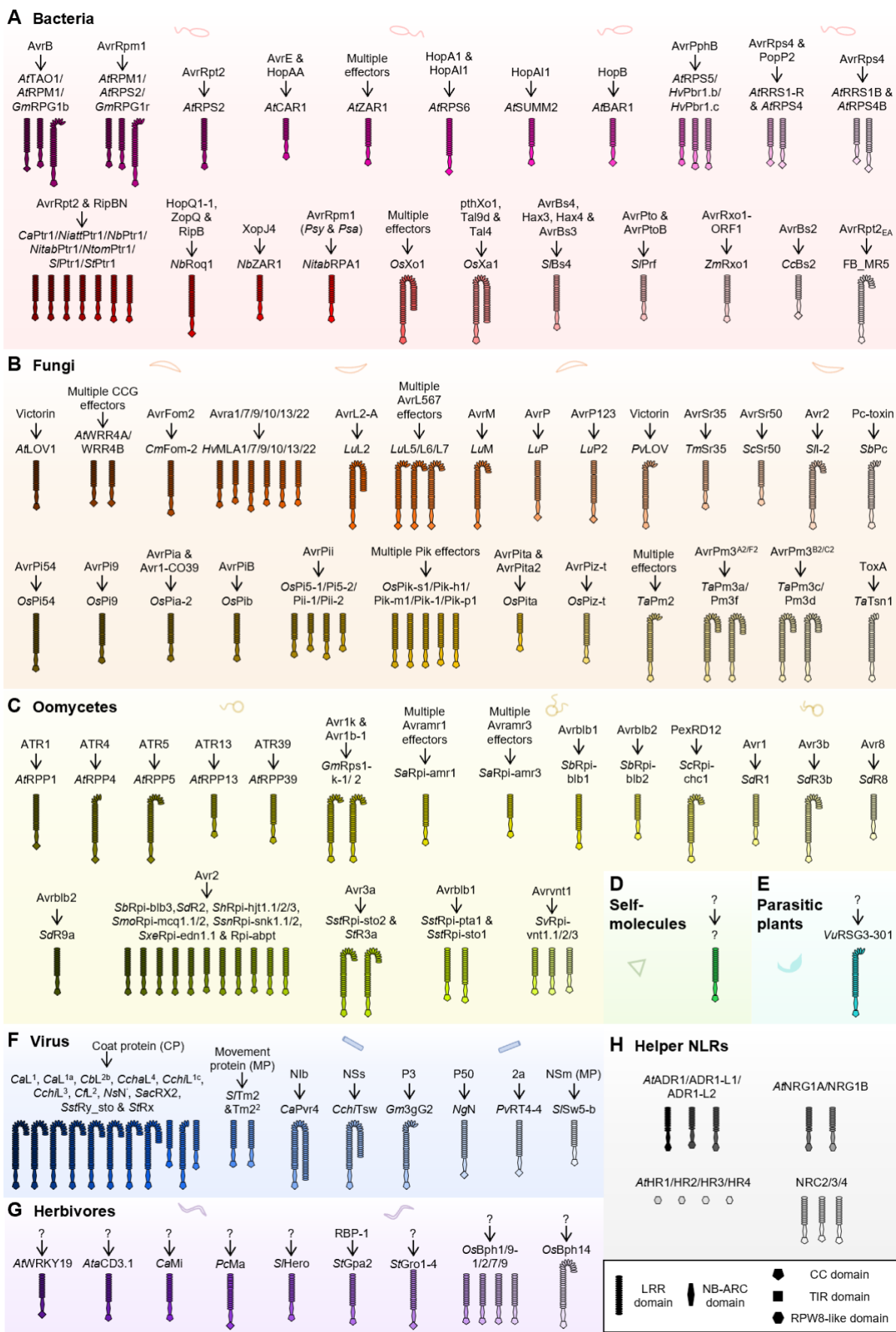


**Figure 1. Nomenclatures in plant immunity and the evolution of plant immune receptors. (A)** Terminology for plant immune responses. Tabular summary of the different terms used to describe plant immune responses. Definitions, advantages, and disadvantages for each of these are included. **(B)** Number of LRR-RLKs, LRR-RLPs and NLRs in different plant species. Phylogenetic tree illustrating different plant species with the corresponding numbers of LRR-RLKs, LRR-RLK XII (class or subgroup XII), LRR-RLPs and NLRs. Red heatmap indicates the number of LRR-RLK XIIs, purple heatmap indicates the number of LRR-RLPs, and blue heatmap indicates the number of NLRs. The phylogenetic tree was generated using phyloT (<https://phylot.biobyte.de/>) based on the NCBI taxonomy database and visualized by iTOL (<https://itol.embl.de/>). LRR-RLK data were obtained from Dufayard et al., 2017, LRR-RLP data were obtained from Ngou et al., 2022, and NLR data were obtained from Baggs et al., 2020.

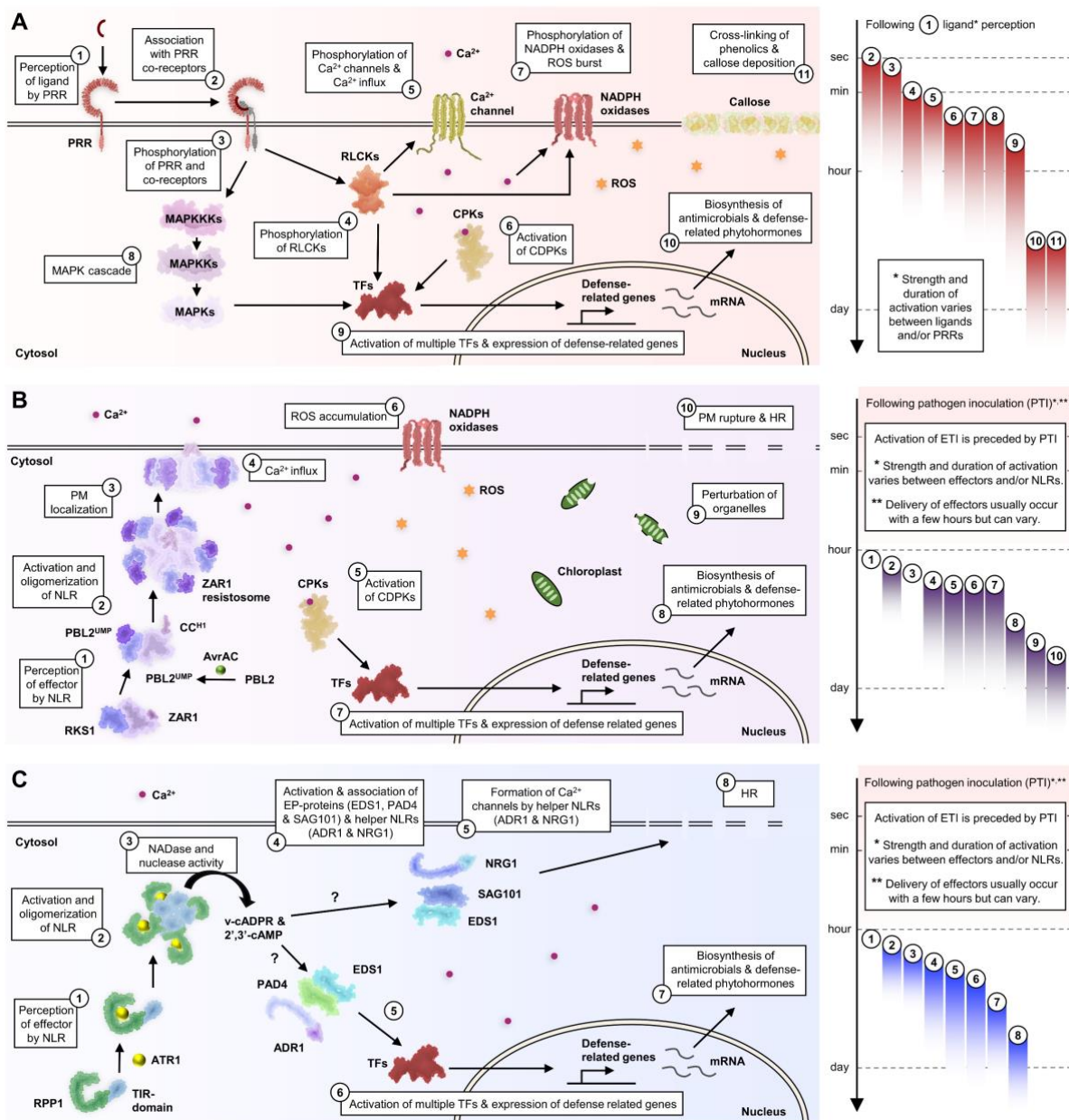


**Figure 2. PRRs involved in plant immunity.** Characterized PRRs with known elicitors from **(A)** bacteria, **(B)** fungi, **(C)** oomycetes, **(D)** self-molecules, **(E)** parasitic plants, **(F)** viruses, **(G)** herbivores. **(H)** PRR co-receptors. Abbreviations for plant species: *Arabidopsis thaliana*, *At*; *Solanum lycopersicum*, *Sl*; *Oryza sativa*, *Os*; *Nicotiana benthamiana*, *Nb*; *Lotus japonicus*, *Lj*; *Brassica napus*, *Bn*; *Medicago truncatula*, *Mt*; *Vitis vinifera*, *Vv*; *Lotus japonicus*, *Lj*; *Pisum sativum*, *Ps*; *Triticum aestivum*, *Ta*; *Solanum microdontum*, *Sm*; *Phtheiospermum japonicum*, *Pj*; *Vigna unguiculata*, *Vu*. Abbreviation for pathogens: *Fusarium oxysporum*, *Fo*; *Phytophthora parasitica*, *Pp*. Number of LRR repeats in the LRR-RLKs and LRR-RLPs were predicted by phytoLRR (Chen, 2021). The full name of these PRR genes can be found in Supplemental Data Set S1.





**Figure 3. NLRs involved in plant immunity.** Characterized NLRs with known effectors from **(A)** bacteria, **(B)** fungi, **(C)** oomycetes, **(D)** self-molecules, **(E)** parasitic plants, **(F)** viruses, **(G)** herbivores. **(H)** Helper NLRs. Abbreviations for plant species: *Arabidopsis thaliana*, At; *Glycine max*, Gm; *Hordeum vulgare*, Hv; *Capsicum annuum*, Ca; *Nicotiana attenuate*, Niatt; *Nicotiana benthamiana*, Nb; *Nicotiana tabacum*, Nitab; *Nicotiana tomentosiformis*, Ntom; *Solanum lycopersicum*, Sl; *Solanum tuberosum*, St; *Oryza sativa*, Os; *Zea mays*, Zm; *Capsicum chacoense*, Cch; *Cucumis melo*, Cm; *Linum usitatissimum*, Lu; *Phaseolus vulgaris*, Pv; *Triticum monococcum*, Tm; *Secale cereale*, Sc; *Sorghum bicolor*, Sb; *Triticum aestivum*, Ta; *Solanum americanum*, Sa; *Solanum bulbocastanum*, Sbu; *Solanum chacoense*, Sch; *Solanum demissum*, Sd; *Solanum hjertingii*, Sh; *Solanum mochicense*, Smo; *Solanum nigrescens*, Ssn; *Solanum x edinense*, Sxe; *Solanum stoloniferum*, Sst; *Solanum venturi*, Sv; *Capsicum baccatum*, Cb; *Capsicum chinense*, Cchi; *Capsicum frutescens*, Cf; *Nicotiana sylvestris*, Ns; *Solanum acaule*, Sac; *Nicotiana glutinosa*, Ng; *Aegilops tauschii*, Ata; *Prunus cerasifera*, Pc. Number of LRR repeats in the NLRs were predicted by LRRpredictor (Martin et al., 2020a). The full list of NLRs can be found in Supplemental Data Set S2.

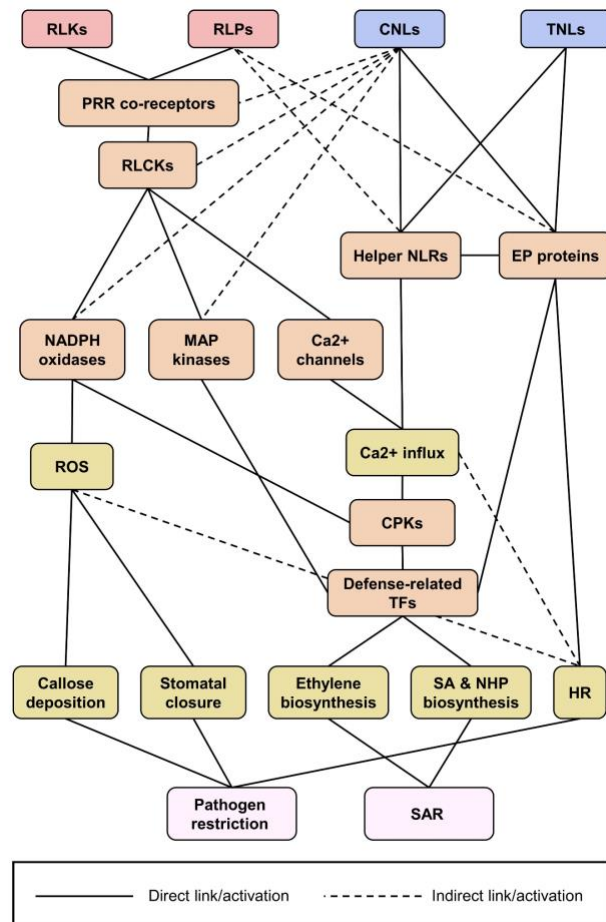


**Figure 4. Plant immune signaling pathways. (A)** PRR signaling pathway. Ligand perception by PRRs activates multiple kinases, which leads to calcium influx to the cytosol, ROS production, transcriptional reprogramming, and callose deposition. **(B)** Singleton NLR signaling pathway. The ZAR1/RKS1 heterodimer detects the effector AvrAC *via* association with uridylylated PBL2 by AvrAC. This leads to the activation and oligomerization of ZAR1. The ZAR1 resistosome localizes to the plasma membrane (PM) and triggers calcium influx, which leads to the hypersensitive response (HR) and cell rupture. **(C)** Helper-NLR-dependent sensor NLR signaling pathway. Recognition of ATR1 by the TNL RPP1 leads to oligomerization and the induced proximity of TIR domains. The TIR domain exhibits NADase activity and produces v-cADPR, which might activate EP-proteins and the helper NLRs (RNLs). Following TNL activation, EP-proteins and RNLs associate with each other and activate downstream immune responses, likely *via* cation channel activity from the helper NLRs. Timeline on the right indicates the order and duration of each signaling event following ligand/effector perception. Numbers indicate the corresponding signaling events in the figure on the left. Note that the activation of ETI is usually preceded by PTI activation, and the strength and duration of each event vary and are dependent on the PRRs/NLRs that are activated.

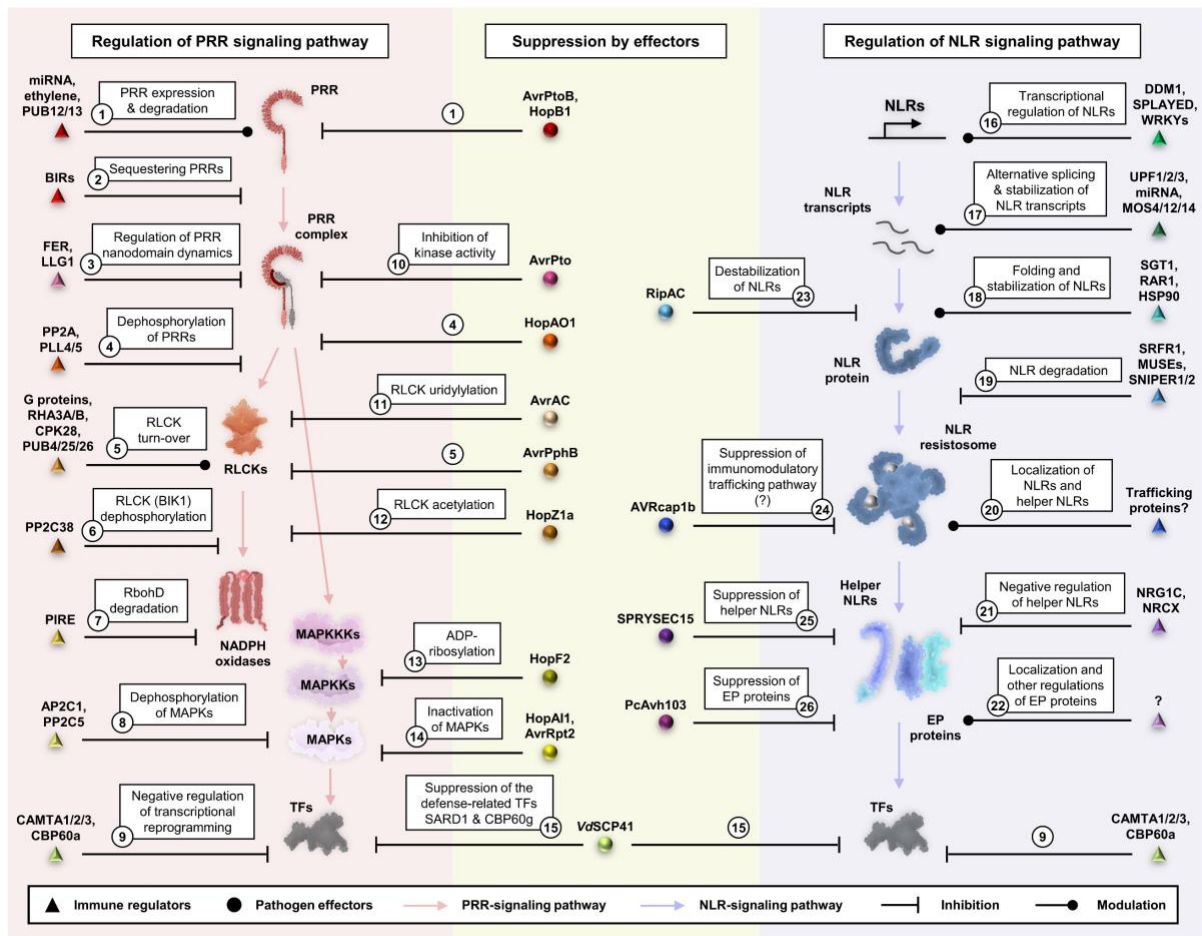
Immune response	PRR activation (PTI)		NLR activation (ETI)		Both (PTI+ETI)	
Immune receptor	RLKs	RLPs	CNLs	TNLs	Coact (Mix)	
Activation of signaling components	PRR co-receptor	Weak activation (confirmed)	Weak activation (confirmed)	Unclear (not predictable)	No activation (confirmed)	No activation (confirmed)
	RLCKs	Weak activation (confirmed)	Weak activation (confirmed)	Unclear (not predictable)	No activation (confirmed)	Strong activation (confirmed)
	NADPH oxidases	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	Strong activation (confirmed)
	Calcium channels	Weak activation (confirmed)	Weak activation (confirmed)	Unclear (not predictable)	No activation (confirmed)	No activation (confirmed)
	CPKs	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	No activation (confirmed)
	MAPKs	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	Strong activation (confirmed)
	Helper NLRs	No activation (confirmed)	No activation (confirmed)	★	Weak activation (confirmed)	Weak activation (confirmed)
	EP proteins	No activation (confirmed)	No activation (confirmed)	★	Weak activation (confirmed)	Weak activation (confirmed)
	Defense-related TFs	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)
Physiological responses	Calcium influx	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	Strong activation (confirmed)
	ROS accumulation	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	Strong activation (confirmed)
	Stomatal closure	Weak activation (confirmed)	No activation (confirmed)	Unclear (not predictable)	Unclear (not predictable)	Unclear (not predictable)
	Callose deposition	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	Weak activation (confirmed)	Strong activation (confirmed)
	Ethylene biosynthesis	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	No activation (confirmed)	No activation (confirmed)
	SA biosynthesis	Weak activation (confirmed)	Weak activation (confirmed)	No activation (confirmed)	No activation (confirmed)	Strong activation (confirmed)
	NHP biosynthesis	Weak activation (confirmed)	*	No activation (confirmed)	No activation (confirmed)	No activation (confirmed)
	HR	No activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	Weak activation (confirmed)	Strong activation (confirmed)

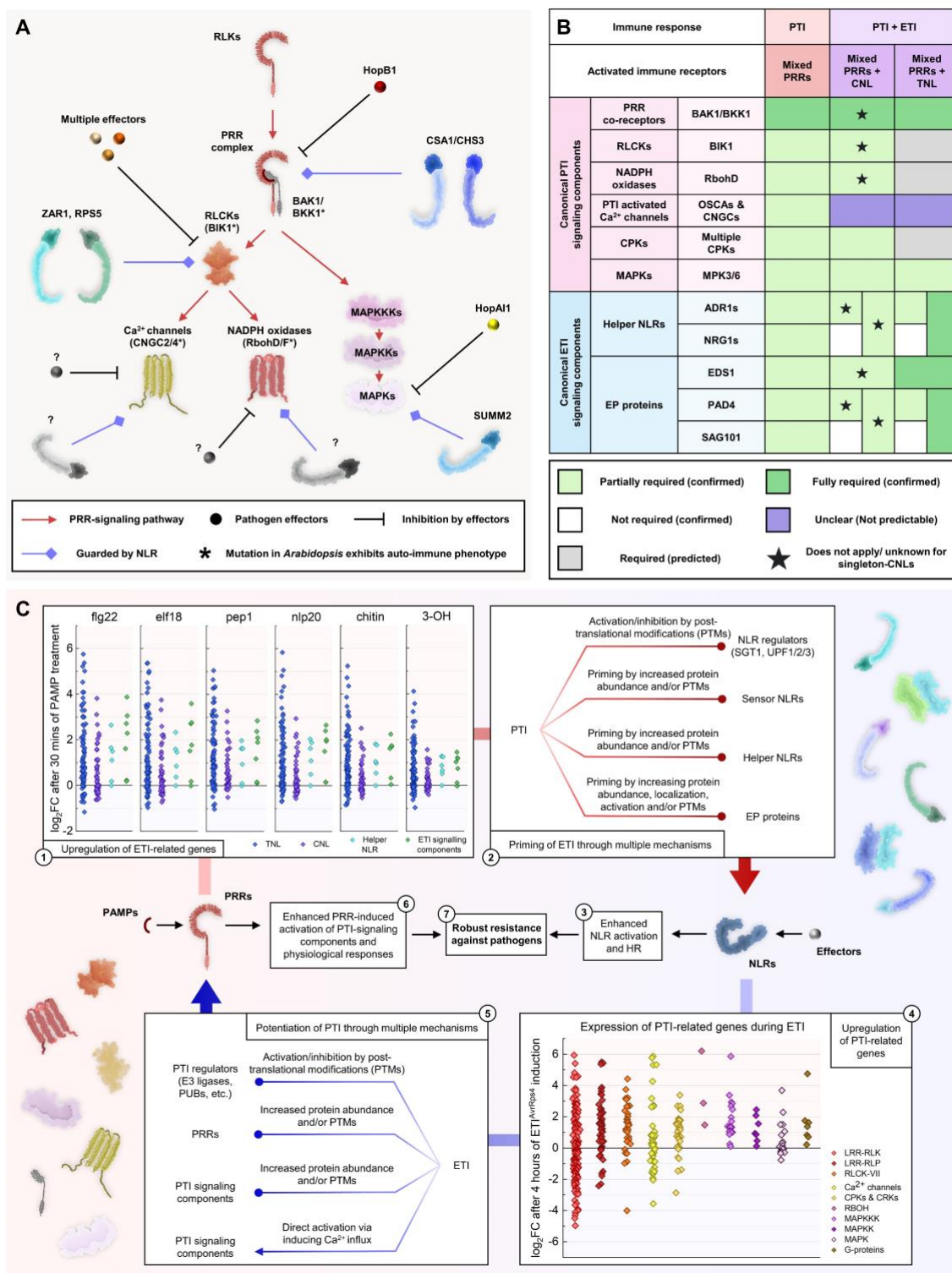
<span style="display:inline-block; width:15px; height:15px; background-color:#d9ead3;"></span> Weak activation (confirmed)	<span style="display:inline-block; width:15px; height:15px; background-color:#5cb85c;"></span> Strong activation (confirmed)
<span style="display:inline-block; width:15px; height:15px; background-color:#fff2cc;"></span> No activation (confirmed)	<span style="display:inline-block; width:15px; height:15px; background-color:#cccccc;"></span> Unclear (not predictable)
<span style="display:inline-block; width:15px; height:15px; background-color:#f2f2f2;"></span> No activation (predicted)	<span style="display:inline-block; width:15px; height:15px; background-color:#d9ead3;"></span> Activation (predicted)
★ Does not apply for singleton-CNLs	



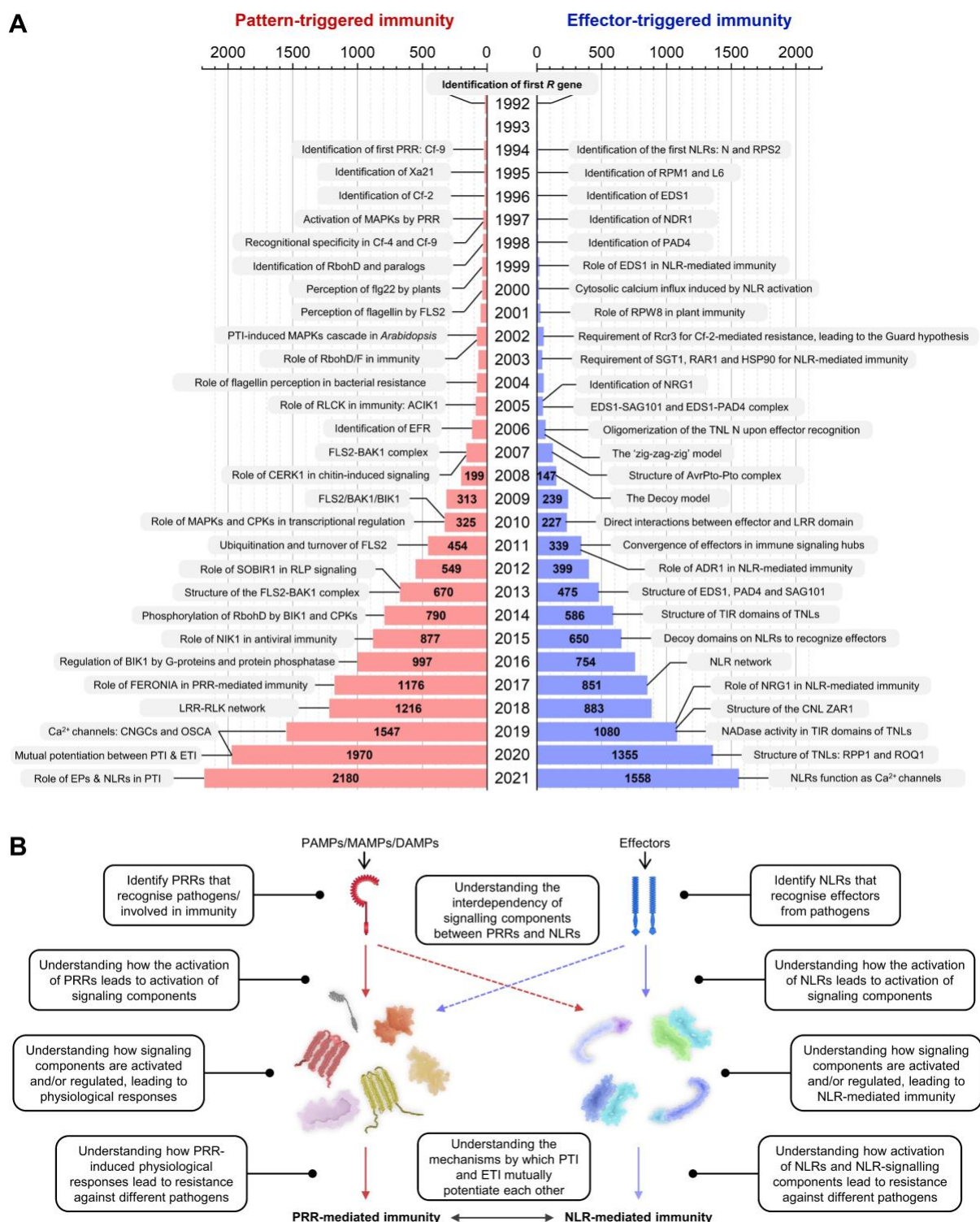
**Figure 5. Signaling components and physiological responses activated by different modes of action of immune receptors. (Left)** Tabular summary of signaling components and physiological responses activated by RLKs, RLPs, CNLs, TNLs and coactivation of PRRs and NLRs. Green (weak or strong activation) and white (no activation) shading represent confirmed responses from publications. Gray shading indicates predicted responses. Purple shading represents unclear responses that cannot be predicted. \*Inoculation with the bacterial pathogen *Pseudomonas syringae* pv. *maculicola* (*Psm*) leads to NHP accumulation (Wang et al., 2018c; Liu et al., 2020). **(Right)** PRR and NLR signaling network. Activation of PRRs (red) and NLRs (blue) lead to the activation of downstream signaling components (orange) and physiological responses (yellow), which result in resistance against pathogens (pink). Note that the activation of physiological responses can vary between immune receptors and are dependent on specific PRRs/NLRs.



**Figure 6. Regulation and suppression of immunity by plant proteins and pathogen-derived effectors. (Left; red shading)** Regulation of the PRR signaling pathway by host proteins. Protein abundance and post-translational modifications (PTMs) of PRRs and PRR signaling components are tightly regulated. **(Middle; yellow shading)** Suppression of immunity by pathogen effectors. Many identified effectors suppress PTI *via* multiple mechanisms. Very few effectors that target the NLR signaling pathway have been identified so far. **(Right; blue shading)** Regulation of the NLR signaling pathway by host proteins. Both the transcript and protein level of NLRs are tightly regulated by multiple processes. The regulation of signaling events post-NLR activation has not been well characterized. Numbers indicate the corresponding mechanisms of immune regulation.



**Figure 7. Interactions between PRR- and NLR-mediated immunity.** (A) NLRs guarding the PRR-signaling pathway. Multiple PRR-signaling components are suppressed by effectors. NLRs guard these signaling components and reverse susceptibility triggered by these effectors. Question marks (?) indicate unidentified effectors or NLRs. (B) Tabular summary of signaling components required for PRR- and NLR-mediated immunity. Green shading represents confirmed requirement from publications. Gray shading indicates predicted requirement. Purple shading represents unclear requirement that cannot be predicted. (C) Mechanisms involved in the mutual potentiation between PRR- and NLR-mediated immunity. Transcriptomic data were obtained from previously published data (Bjornson et al., 2021; Ngou et al., 2021a). Numbers indicate the corresponding mechanisms to potentiate PRR- or NLR-mediated immunity to achieve robust resistance against pathogens.



**Figure 8. Historic overview of PTI and ETI and future challenges. (A)** Discoveries in PTI (left) and ETI (right) in the past thirty years. Bar charts represent the number of ‘plant biology’ publications that mentioned ‘pattern-trigger immunity’ (red) and ‘effector-triggered immunity’ (blue). Data obtained from Dimensions (<https://www.dimensions.ai/>). **(B)** Future challenges and outlook in plant immunity research.