



Review

Post-Translational Modifications of Proteins Have Versatile Roles in Regulating Plant Immune Responses

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Abstract: To protect themselves from pathogens, plants have developed an effective innate immune system. Plants recognize pathogens and then rapidly alter signaling pathways within individual cells in order to achieve an appropriate immune response, including the generation of reactive oxygen species, callose deposition, and transcriptional reprogramming. Post-translational modifications (PTMs) are versatile regulatory changes critical for plant immune response processes. Significantly, PTMs are involved in the crosstalk that serves as a fine-tuning mechanism to adjust cellular responses to pathogen infection. Here, we provide an overview of PTMs that mediate defense signaling perception, signal transduction in host cells, and downstream signal activation.

Keywords: plant immunity; post-translational modifications; signal transduction

1. Introduction

Plants are exposed to diverse types of pathogen during their lifetimes. To protect themselves from pathogen threats, plants have evolved effective immune systems that mediate microbe interactions. Several molecules are involved in plant immune systems. Pathogen-associated molecular patterns (PAMPs) are members of a large group of microbial molecules that include lipooligosaccharides of gram-negative bacteria, bacterial flagellin, elongation factor thermo unstable, glucans and glycoproteins from oomycetes, chitin from the fungal cell wall, and RaxX from *Xanthomonas oryzae* pv. *oryzae* (Xoo) [1,2]. Once PAMPs are recognized by plant cells, PAMP-triggered immunity (PTI), which is the first layer in plant innate immunity, is activated.

PAMPs are detected by pattern-recognition receptors (PRRs), which are normally surface-localized receptor kinases or receptor proteins [3,4]. However, only a handful receptor-like kinases (RLKs) and receptor-like proteins (RLPs) have been identified as being PRRs that perceive ligands in plants. A typical RLK should contain an extracellular domain (ECD) to bind the extracellular molecules, a transmembrane domain, and an intracellular kinase domain to activate signal transduction in cells [5]. In contrast, the intracellular domains of RLPs are very short and lack kinase activity [6,7]. The ECDs have various structures, including leucine-rich repeat (LRR) domains, lysin motifs, lectins, and epidermal growth factor-like domains. RLKs and RLPs can be divided into multiple subfamilies on the basis of ECDs [8]. As soon as the molecules are recognized by PRRs, the generation of reactive oxygen species (ROS), transcriptional reprogramming, and downstream gene activation occur subsequently [9–11].

Some evolved pathogens secrete effectors into the apoplast or directly into the cytoplasm of host cells, which can suppress PTI [12,13]. Conversely, plant cultivars have developed a

family of polymorphic intracellular nucleotide-binding/leucine-rich-repeat (NLR) receptors that recognize particular effectors directly or indirectly, and induce the second major immune layer, called effector-triggered immunity (ETI), in order to stop pathogen growth [14,15]. The immune response elicited by ETI is very strong, typically accompanied with the programmed cell death of plant cells at the infection site, representing a hypersensitive response (HR) [16,17]. NLR receptors are structurally similar, containing an N-terminal coiled-coil or Toll-interleukin receptor domain, a central nucleotide-binding and a C-terminal LRR domain. The effectors recognized by NLR receptors are highly variable microbial molecules [18,19]. Therefore, the resistance mediated by ETI is predicted to be less durable and more specific than that of PTI.

Post-translational modifications (PTMs) of proteins are universal events in cell signaling networks, regulating protein stability, localization, activity levels, and interactions that help substrate proteins enter different pathways in order to activate signaling transduction [20]. At present, various types of PTMs have been identified. For, example, phosphorylation is a famous PTM that prefers to target the hydroxyl groups of hydroxyl amino acids, such as threonine (Thr), serine (Ser) and tyrosine (Tyr), but can also target unusual residues, such as hydroxy-proline [21]. It is a reversible process that regulates signal transduction in eukaryotic cells. Ubiquitination is a PTM that modulates protein stability or activity and plays important roles in various aspects of plant growth and development, including embryogenesis, floral development, plant senescence and disease resistance [22,23]. A group of small Ub-like modifiers (SUMOs) can target lysine residues of proteins to initiate SUMOylation [24]. SUMOylation significantly influences the transcriptional and epigenetic landscape in order to enhance stress tolerance and development [25]. In addition, cysteine proteases mediated by PTMs can cleave the peptide bonds of substrates, leading to the target's rapid degradation [26]. Protein *N*-glycosylation may be a PTM that can remove glucose and some specific mannose residues in the endoplasmic reticulum [27]. Moreover, these PTMs are not independent and participate in crosstalk. In most cases, the initiation of a PTM is dependent on other PTMs interacting with the same protein. Here, we present recent progress in understanding PTMs in plant immune-related networks, which play important roles in mediating signal exchanges between microbes and hosts that eventually control associations.

2. Many Protein Effectors Function through PTMs of Host Proteins in Plant Cells

Effectors are typically secreted from pathogens and then translocate into host tissues and cells to mediate their interactions with hosts [28]. Recent advances suggest that effectors can be divided into non-protein and protein effectors. Non-protein effectors consist of chemical and sRNA effectors [29]. During the infection process, pathogens can secrete a large array of chemical effectors, such as some toxins and hormones, to affect protein biosynthesis, fate and delivery [30–34]. Pathogen-derived sRNA effectors have important roles in host–microbe interactions. sRNA effectors can regulate the expression of multiple host genes involved in plant immunity through either transcriptional or posttranscriptional gene silencing [35–37]. However, the detailed molecular mechanisms of non-protein effectors remain elusive. Based on a working model, protein effectors are generally classified into two distinct groups: apoplastic protein effectors and cytoplasmic effectors. Apoplastic protein effectors work in the extracellular spaces of host tissues and are involved in immune evasion, host cell wall degradation and host proteolytic activity inhibition. Cytoplasmic effectors disrupt the activity of host proteins involved in various cellular signal regulatory processes [38]. In recent years, studies have been conducted to elucidate the functions of PTMs triggered by effectors.

The host proteins' stability may be destroyed by effectors. The effector AvrPtoB is secreted from *Pseudomonas syringae* (*P. syringae*) pv. *tomato* DC3000 and contains a plant U-box (PUB) type E3 ubiquitin ligase domain in its carboxyl terminus. AvrPtoB interacts with diverse host proteins through its N-terminal region and ubiquitinates them, including some receptor kinases such as Pto, Fen, Flagelin Sensing 2 (FLS2), Chitin Elicitor Receptor Kinase 1 (CERK1), BRI1-associated receptor kinase1 (BAK1) and Bti9 [39–43], transcriptional coactivators, such as nonexpressor of pathogenesis-related (PR) genes 1 (NPR1) [44], and mitogen-activated protein kinase (MAPK) kinase (MAPKK), such as MKK2 [45].

AvrPtoB manipulates the host's ubiquitin system and induces the degradation of its targets in order to suppress plant immunity, providing a typical model of effector-triggered host protein degradation. Several other effectors, like XopL, XopK and XopAE from different *Xanthomonas* strains, also have the E3 ubiquitin ligase activity that is required for ETI and full virulence [46,47]. XopD, another type III effector from *Xanthomonas euvesicatoria*, carries a C-terminal SUMO protease domain that can process the precursor of the small ubiquitin-related modifier SUMO or remove SUMO from its target proteins. Tomato ethylene response factor (ERF) SIERF4 is a substrate of XopD. XopD directly targets SIERF4 in the subnuclear foci to deSUMOylate, causing SIERF4 destabilization and ethylene production inhibition, which is required for ethylene-mediated immunity and symptom development [48]. In addition to SUMO protease activity, XopD has nonspecific DNA-binding activity within its helix-loop-helix domain and transcriptional repression ability within its two conserved ERF-associated amphiphilic motifs [49]. Some studies suggested that XopD can target some transcription factors, such as myeloblastosis 30 (MYB30), in order to inhibit transcriptional activity through its helix-loop-helix domain [50].

In addition to ubiquitinating host proteins for degradation, some effectors belong to a family of cysteine proteases that proteolytically cleave their targets, leading to the targets' rapid degradation. AvRpt2 was one of the first cytoplasmic effectors that was demonstrated to act as a cysteine protease [51]. After being secreted from bacteria and delivered into host cells, AvRpt2 is auto-cleaved and enters an active state. The activated AvRpt2 interacts with, and directly cleaves RPM1-interacting protein 4 (RIN4), generating two cleavage products that are suppressors of PTI [52,53]. Several putative AvRpt2 homologs in sequenced bacterial genomes may have similar functions on their targets [54]. Cytoplasmic receptor-like protein kinases (RLCKs) belong to a subgroup of RLKs that possess cytoplasmic kinase domains but lack extracellular ligand-binding domains. Studies of RLCK-associated components and targets indicate that RLCKs regulate various downstream signaling nodes to set a complex array of defense responses against microbial pathogens [55]. Some effectors suppress plant immunity by blocking the functions of RLCKs. The *P. syringae* effector AvrPphB was identified as a cysteine protease protein, which cleaves PBL1-like protein kinases belonging to the subfamily of RLCK VII and inhibits PTI signaling [56].

Phosphorylation is an important process in the activation of immune responses upon ligand binding. Effector XopAU is a catalytically active protein kinase conserved in various *Xanthomonas* species. XopAU can directly associate and phosphorylate MAPKK/MEKK2, contributing to the development of disease symptoms in pepper plants [57]. Unlike XopAU, effector proteins HopAI1 and HopAO have been identified as phosphatases that reduce the phosphorylation of their substrates. HopAI1 is another widely conserved *P. syringae* effector in both plant and animal bacterial pathogens that can inactivate MAPKs by removing the phosphate group through its unique phosphor-threonine lyase activity, resulting in enhanced disease susceptibility in plants [58]. Tyrosine phosphatase, HopAO1 can directly interact with FLS2 and EF-TU receptor (EFR). Consistent with these interactions, HopAO1 leads to a reduction in the phosphorylation of FLS2 and EFR upon ligand treatment [59].

During the process of plant-pathogen co-evolution, plants have evolved multiple receptors to recognize different effectors and activate plant defense responses. The effectors detected by 'matching' resistance proteins (named R protein) may also be avirulence (AVR) proteins [60]. AvrPto is a bacterial avirulence protein that confers disease resistance to tomato carrying the *PtoR* gene. Upon delivered into plant cells, AvrPto can localize at the plasma membrane and recruit two LRR-RLKs, FLS2 and EFR. Binding of AvrPto to FLS2 and EFR can inhibit their kinase activities, blocking downstream phosphorylation signal transduction [61]. *Xanthomonas campestris* pv. *campestris* type III effector AvrAC is an uridylyltransferase that adds uridine 5'-monophosphate to, and conceals, conserved phosphorylation sites in PBL2's activation loop [62]. Uridylylated PBL2 (PBL2UMP) acts as a ligand to initiate an ETI response [63]. However, under natural selection, avirulence genes seem to change rapidly, allowing pathogens to diversify their effectors and escape recognition by the plant R genes. Therefore, studying the molecular mechanisms of Avr proteins and R proteins is a challenge.

3. PTMs of Receptor Complexes Initiate Plant Immune Signaling

Pathogen recognition by PRRs results in the activation of signaling pathways that induce defense reactions. Most known PRRs can recruit other LRR-RLKs to form a receptor complex. The binding of PAMPs to the extracellular domains of the PRRs leads to the dimerization or oligomerization of receptors and co-receptors, causing phosphorylation dynamics in host cells [20].

One of the best characterized PRRs is the *Arabidopsis* LRR-RLK FLS2, which can recognize the bacterial PAMP flagellin (flg22 epitope) [9]. After flg22 perception, FLS2 forms a receptor complex with another LRR-RLK BAK1 and enters an activated state [64] (Figure 1). BAK1 is required for the immune responses mediated by multiple PRRs other than FLS2 [65]. The ligand-induced PRR-BAK1 complex formation can initiate phosphorylation/dephosphorylation between BAK1 and its interacting partners. Different phospho-patterns of BAK1 are associated with different RLKs, suggesting a phospho-code-based dichotomy of BAK1 functions in plant development and PRR-mediated immunity [66,67]. The activated PRR-BAK1 complex's formation could initiate trans-phosphorylation between the receptor complex and receptor-like cytoplasmic kinases (RLCKs), such as Botrytis-induced kinase1 (BIK1). BIK1 can phosphorylate many PRRs and BAK1, and BIK1 is phosphorylated by BAK1 [46,68]. Phosphorylated BIK1 then directly interacts and phosphorylates NADPH oxidase, respiratory burst oxidase homolog protein D (RBOHD) and the phosphorylation of serine residues 39, 339, and 343 (S39, S339, S343) on RBOHD can modulate the ROS level [69,70]. BIK1 is not the only RLCKs involved in PRR-mediated immune signaling. Like BIK1, PTI-compromised receptor-like cytoplasmic kinase (PCRK) 1 and PCRK2 can interact with FLS2, and the flg22 treatment triggers PCRK2 phosphorylation to activate immune responses [71].

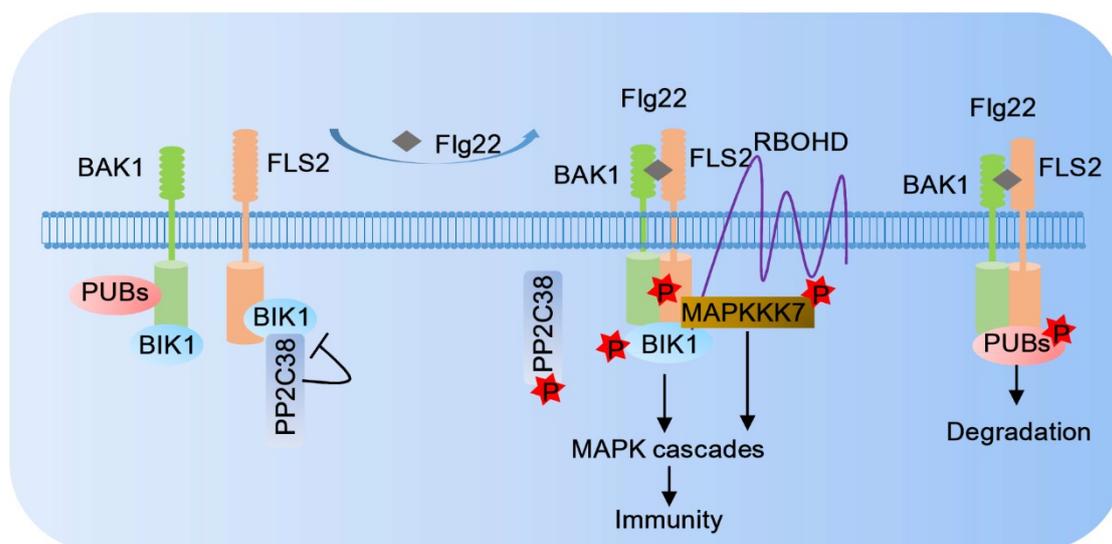


Figure 1. Ligand perception activates FLS2-mediated plant immunity. In the absence of flg22, BIK1 associates separately with FLS2 and BAK1 in an inactive state. Ligand perception induces rapid FLS2–BAK1 receptor complex formation and probably transphosphorylation, which further activates downstream intracellular immunity signaling.

CERK1 is a Lys-RLK containing three extracellular LysM motifs and an intracellular Ser/Thr kinase domain, which is required for chitin- and peptidoglycan (PGN)-induced defense signaling [72]. In *Arabidopsis*, CERK1 works together with lysin motif receptor kinase 5 (LYK5), forming a receptor kinase complex to perceive chitin, and mutations in LYK5 result in a significant reduction in the chitin response [73]. Autophosphorylation of CERK1 triggered by chitin perception is essential for the activation of downstream responses. Like FLS2, some RLCKs, such as PBL27, are substrates of CERK1 that are required to transduce phosphorylation signals in plant immunity [74]. Unlike CERK1 in *Arabidopsis*, CERK1 in rice (*Oryza sativa*) cannot bind chitin molecules directly, despite the presence

of extracellular LysM motif. Chitin elicitor-binding protein (CEBiP) is another LysM protein in the rice chitin receptor complex that can bind chitin with a high affinity [75]. Several RLCK VII members are immediate downstream signaling components of OsCERK1, including OsRLCK57, OsRLCK185, OSRLCK107, OsRLCK118 and OsRLCK176. OsRLCK118, OsRLCK176, and OsRLCK185 also emerged as substrates of other PRRs, including lysin motif-containing protein (LYP4), LYP6, and SPL11 cell-death suppressor2 [55,76], suggesting that the phosphorylation signaling triggered by PAMPs is transduced from PRRs located on the cell surface to cell cytoplasmic proteins dependent on these RLCKs.

Interactions between E3 ligase proteins and the kinase domains of RLKs appear to be a common feature of the regulation of various plant processes, including plant immunity. For example, two E3 ligases, PUB12 and PUB13, interact with the FLS2–BAK1 receptor complex, and the interaction between PUB12/13 and FLS2 is induced by flg22. PUB12 and PUB13 are substrates of BAK1, and the phosphorylation of PUB12/13 mediated by BAK1 is essential for the ubiquitination of FLS2 by PUB12/13. PUB12 and PUB13 ubiquitinate FLS2 for degradation, and flg22-triggered immunity responses are potentiated in the *pub12* and *pub13* mutants [77]. PUB12 and PUB13 ubiquitinate the brassinosteroid (BR) hormone receptor BRI1, which is important for the endocytosis and degradation of BRI1, a scenario that has been suggested for FLS2 [47]. In addition, PUB13 also ubiquitinates another chitin receptor LYK5. In the *pub13* mutant, the protein levels of LYK5 are constitutively enhanced [78]. XA21 is a rice RLK protein that confers resistance to *Xoo*. A RING-type E3 ubiquitin ligase, XA21-Binding Protein3 (XB3), binds to the kinase domain of XA21 through an ankyrin repeat domain. XB3 is also a substrate for XA21 Ser and Thr kinase. Reducing the expression of *Xb3* increases resistance to *Xoo* and decreases the XA21 protein level, indicating that *Xb3* is necessary for the full accumulation of the XA21 protein and for Xa21-mediated resistance [79]. Like PRR activation, the ubiquitin-mediated regulation of PRRs is crucial for preventing the excessive or prolonged activation of immune responses.

Protein *N*-glycosylation is another major PTM in eukaryotic cells. Most PRRs are transmembrane glycoproteins that need to be transported by the secretory pathway to maturity and form their correct destination targets on the plasma membrane. Endoplasmic reticulum quality control (ERQC) is a pivotal process that assists these proteins to fold properly and avoid aggregation after they translocate into the ER. The *N*-glycosylation/ERQC pathway is necessary for the biogenesis and functions of several RLKs [80,81]. EFR is a typical example. EFR is specifically impaired in ERQC deficient mutants, including *stt3a*, *crt3*, *uggt*, *erd2b*, and *sdf2* [82–84]. Moreover, a single mutation at the conserved *N*-glycosylation site (N143Q) in the EFR ectodomain results in the loss of its ability to bind its ligand and to mediate elf18-elicited oxidative bursts [81]. However, the FLS2-mediated PTI response is not impaired in these ERQC mutants, suggesting that the folding of some PRRs is more complicated.

4. PTMs of RLCK–MAPK Are Required for Immune Signal Transduction

MAPK cascades represent signaling modules important for diverse intracellular immune responses in both PTI and ETI in plants [85]. A classic MAPK cascade has a set of three sequentially acting protein kinases, a MAPK, a MAPK kinase (MAPKK, MKK or MEK) and a MAPK kinase kinase (MAPKKK or MEKK), within which phosphorylation signals are transduced linearly from MAPKKK to MAPK [86]. Two MAPK cascades are activated by PRRs (Figure 2). One cascade is composed of the MAPKKK MEKK1, the two MAPKKs MKK1 and MKK2, and the MAPK MPK4. The other cascade consists of MAPKKK3 and MAPKKK5, the two MAPKKs MKK4 and MKK5, and the two MAPKs MPK3 and MPK6.

The first MAPK cascade, MEKK1-MKK1/2-MPK4 negatively regulates plant cell death and immunity. In *mekk1*, *mkk1/2* and *mpk4* mutants, programmed cell death and defense responses are constitutively activated [87–90]. MAPKKs, MKK1 and MKK2 can directly interact with both MEKK1 and MPK4 to form a special MAPK cascade. MPK4 is the substrate of MKK1/2 *in vitro* and *in vivo*, and MEKK1 and MKK1/2 are essential for the flg22-mediated activation of MAPK4 [88,90]. Interestingly, kinase inactivated MEKK1 (MEKK K361 M) rescues the autoimmune phenotype of *mekk1* and restores the flg22-induced activation of MPK4, suggesting that the MEKK1-activated MEKK1-MKK1/2-MPK4

pathway is independent of its kinase activity [90]. *Arabidopsis* SH4-Related3 functions as a transcriptional repressor and may be a substrate of MEKK1-MKK1/2-MPK4. It negatively regulates a large subset of flg22-induced genes through its ERF-associated amphiphilic repression motifs [91]. Another MAPK cascade, MAPKKK3/5-MKK4/5-MPK3/6 may be activated by the PRRs. It plays a far more important role in plant immunity by regulating defense hormones and phytoalexin synthesis and signaling, defense-related gene expression, ROS bursts and stomatal immunity [85]. Unlike the MEKK1-MKK1/2-MPK4 cascade, increasing evidence indicates that the MAPKKK3/5-MKK4/5-MPK3/6 cascade acts as positive regulator of defense responses. The MPK3/6 activation triggered by multiple patterns are greatly inhibited in *mapkkk3 mapkkk5* double mutants but slightly reduced in *mapkkk3* and *mapkkk5* single mutants [74,92,93]. Recently, other MAPK cascades have been found to play important roles in plant immunity. MKKK7 is a FLS2-interacting kinase and is rapidly phosphorylated on two different serine residues upon flg22 treatment. The *mpkkk7* mutant exhibits enhanced MPK6 activity, increased expression of defense genes, and increased ROS production [94]. The cascades mediated by MAPKKK7 remain elusive.

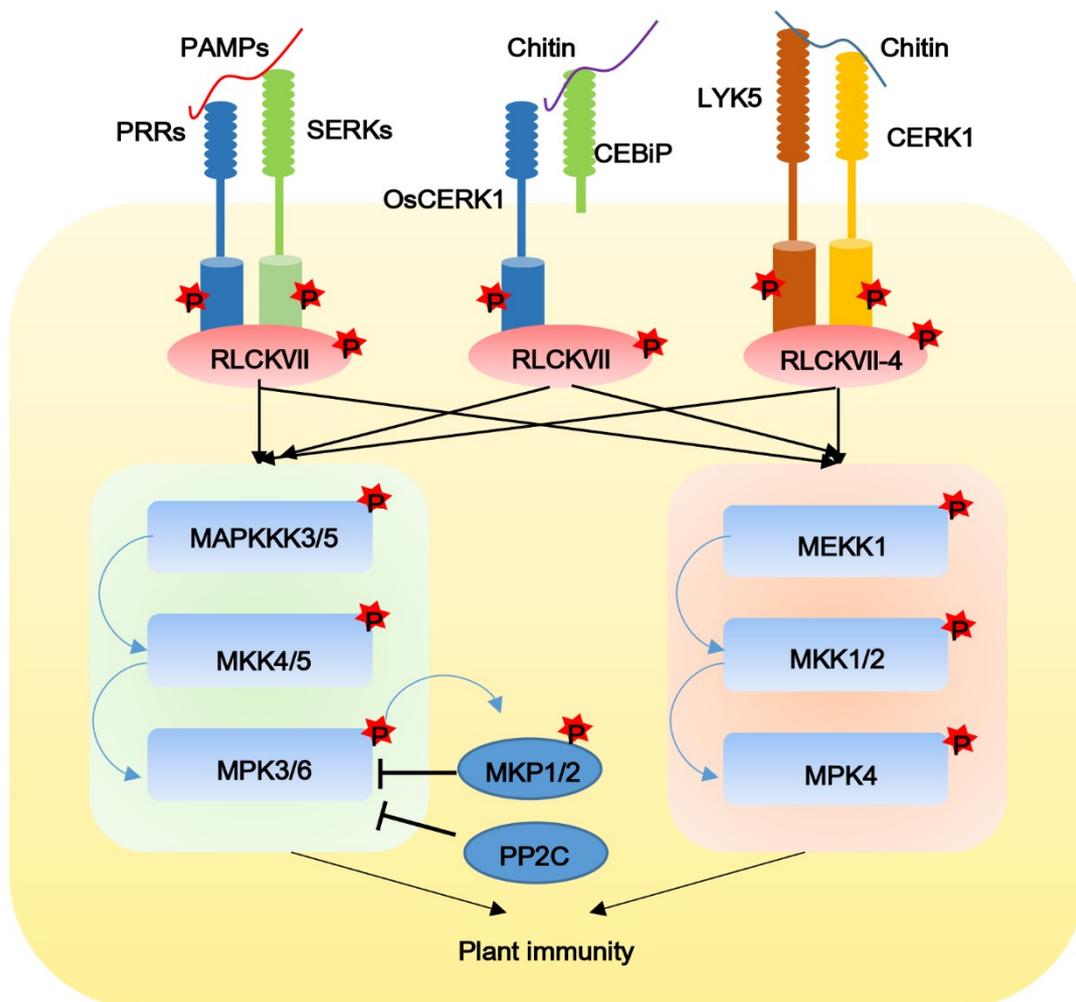


Figure 2. RLCKs and MAPK cascades function downstream of diverse PRRs to activate plant immune signals. Ligand perception induces rapid immune receptor complex formation and transphosphorylation. Several RLCK VII members rapidly become phosphorylated, which further activates evolutionarily conserved mitogen-activated protein kinase (MAPK) signaling modules, thereby activating pathway-specific transcription factors to activate plant immunity.

In addition to the PTMs of MAPK cascades mediated by effectors, several phosphatases that negatively regulate these MAPK cascades have been reported. Dual-specificity MAP kinase phosphatases (MKPs), such as MKP1 and MKP2, dephosphorylate both conserved Thr and Tyr residues of the MAPK activation loop, leading to the full inactivation of the MAPKs [95–97]. Furthermore, it is suggested that an efficient negative feedback loop exists between MKPs and MAPKs during PAMP responses and bacterial resistance [96]. Members of the protein phosphatase 2C (PP2C) family, AP2C1 and AP2C5, are classified as phosphor-Ser/Thr phosphatases that target a specific phosphor-Thr in the MAPK activation loop and negatively regulate PTI responses [98]. Loss of AP2C1 function results in an increased activation of MPK3, -4 and -6 in response to flg22 and elf18 treatments as well as enhanced callose deposition and bacterial resistance.

Upon PAMP recognition by RLK receptors, the receptor complex is activated, and immune signals are transduced into the nucleus by MAPK phosphorylation cascades, resulting in transcriptional reprogramming for defense. As we just mentioned, RLCKs associate with, and rapidly become phosphorylated, by immune receptor complexes upon PAMP perception. RLCKs may fill the gap between the immune receptor kinase complex and the MAPK cascades [86,99]. In *Arabidopsis*, PBL27 associates with both CERK1 and MAPKKK5 on the plasma membrane. Chitin perception induces the CERK1-mediated phosphorylation of PBL27, which in turn phosphorylates MAPKKK5, leading to the activation of MPK3/6 through MKK4 and MKK5. The *mapkkk5* mutant displays compromised chitin-induced activation and disease resistance to *Alternaria brassicicola* [73,74,100,101]. Furthermore, Bi et al. found that MAPKKK3/5-MAPK3/6 MAPK kinase cascades can be activated by multiple PRRs and confer resistance to bacterial and fungal pathogens in *Arabidopsis* [102]. Chitin induces the phosphorylation of MAPKKK5, and MEKK1 is largely disrupted in the *rlck vii-4* sextuple mutant. The RLCKVII-4 member, PBL9, can phosphorylate MAPKKK5 at Ser-599, which is required for MAPK activation and disease resistance [102]. The chitin-induced MAPK signaling pathway is conserved in rice and *Arabidopsis*. In rice, upon chitin perception, OsCERK1 phosphorylates OsRLCK185, an ortholog of PBL27 in *Arabidopsis*. Multiple MAPKKKs have been identified as substrates of OsRLCK185, including OsMAPKKK11, OsMAPKKK18 and OsMAPKKKε [103,104].

5. PTM Modulates TF Activities in Plant Immunity

Transcriptional reprogramming in response to a pathogen challenge is regulated by a broad variety of transcription factors (TFs) and cofactors in the nucleus. The study of TF regulatory mechanisms mediated by PTMs has increased our knowledge regarding the action of plant immunity. Among the 58 identified TF families in higher plants, six appear to be involved in defense signaling (Table 1) [105].

Table 1. The major transcription factor (TF) families involved in plant defenses.

TF Families	Descriptions
AP2/ERF	The proteins in this family contain an AP2/ERF DNA-binding domain that consists of three β -sheet strands followed by an α -helix motif [106].
bHLH	This family is characterized by a basic-helix-loop-helix domain containing an N-terminal basic DNA-binding region and a C-terminal protein-interaction domain [107].
MYB	This family is characterized by the presence of four repeat sequences, each containing three α -helices [108].
NAC	NAC TFs each contain a conserved DNA-binding domain on their N-termini and an activation domain on their C-termini [109].
WRKY	The WRKY TFs contain WRKY domains having the typical WRKYGQK sequence followed by a zinc finger motif [110].
bZIP	The bZIP proteins contain a basic region for DNA binding and a leucine zipper region for protein dimerization [111].

The ubiquitin proteasome system is responsible for controlling the stability and transcriptional activity levels of TFs involved in plant immunity. For example, MYB30 is a R2R3 MYB TF involved in pathogen-induced HR and cell death. Plants with a reduced *AtMYB30* expression level have a

strongly compromised resistance to different bacterial strains [112]. A RING type E3 ubiquitin ligase, MYB30-interacting E3 ligase1 (MIEL1), interacts with and ubiquitinates MYB30, leading to MYB30 proteasomal degradation and the downregulation of its transcriptional activity. The *miel1* mutant plants show stronger HR cell death symptoms than Col-0 wild-type plants at 64 h post-infection with low dose of *P. syringae* pv. *tomato* DC3000 expressing the avirulence gene *AvrRpm1*. This is similar to MYB30 overexpression plants [113,114]. In the AP2/ERF subgroup, another RING domain containing E3 ligase mediates AtERF53 for proteolytic degradation [115]. Similarly, the protein levels of many WRKY TFs are controlled by the ubiquitin proteasome system, including WRKY53 in *Arabidopsis*, and OsWRKY6, OsWRKY11, and OsWRKY45 in rice [116–120].

In response to pathogen attack, WRKYs are activated by MAPK cascades. WRKY33 is a substrate of MPK3/MPK6. A mutation of MPK3/MPK6 phosphorylation sites in WRKY33 compromises its ability to complement camalexin induction in the *wrky33* mutant [121]. In another MAPK cascade, MAPK4 substrate 1 (MKS1) acts downstream of MPK4 in a salicylic acid (SA)-dependent pathway. MKS1 interacts with WRKY 25 and WRKY33, and it regulates gene expression by releasing these TFs into the nucleus upon activation [122,123]. In tobacco, WRKY1 is a substrate of SA-induced protein kinase (SIPK). SIPK works as a MAPK to phosphorylate WRKY1, which results in enhanced the DNA-binding activity of WRKY1 to its cognate binding site, a W box sequence from the tobacco chitinase gene *CHN50* [124]. Phosphorylation may also be important for balancing rice yield and resistance. The *ideal plant architecture 1* (*IPA1*) gene encodes a kind of plant specific SQUAMOSA promoter-binding protein-like (SPL) TF, also known as *OsSPL14*, which activates yield-related genes [125]. Upon pathogen attack, IPA1 becomes phosphorylated at S163, which alters its DNA-binding specificity. IPA1(S163D) preferentially binds the WRKY45 promoter and activates WRKY45 expression, leading to enhanced resistance in *Magnaporthe oryzae*. However, IPA1 returns to the nonphosphorylated state within 48 h post-infection in order to active genes related to growth and high yield. Furthermore, the protein kinase regulating this process remains to be determined.

In addition to TFs, transcription cofactors play important roles in plant immunity. For example, NPR1 is hypothesized to be a transcription cofactor, contributing to the establishment of systemic acquired resistance (SAR), a mechanism of induced defense that is activated throughout a plant after exposure to various elicitors. NPR1 may also repress ETI by promoting programmed cell death (PCD) [126]. NPR1 is present as a homo-oligomer in a resting state that is dependent on its intermolecular disulfide bonds between cysteine residues. As the SA concentration increases in plant cells, NPR1 dissociates into mono molecules and is released into nuclei. NPR1 monomers in the nuclei prefer to interact with TFs and confer immunity through transcriptional cascades, resulting in the activation of *PR* genes and SA tolerance [127–129]. However, the expression of the *PR1* gene can be further upregulated in response to SAR induction in NPR1 cysteine mutants, such as *npr1C82A-GFP* and *npr1C216A-GFP*, suggesting that PTMs are involved in regulating the activity of NPR1 [129]. The proteasome-mediated degradation of NPR1 is required for its role in modulating the transcription of its targets. NPR1, containing a conserved broad-complex, tramtrack, and bric-à-brac/poxvirus, zinc finger (BTB/POZ) domain, is a substrate of CUL3-based ubiquitin ligase. In the absence of pathogen infection, the NPR4–CUL3-mediated degradation of NPR1 monomers is necessary to prevent the excessive activation of SAR and maintain plant development [130,131]. Recently, studies indicated that immune-induced transcriptome reprogramming mediated by NPR1 requires the sequential actions of multiple E3 and E4 ligases [131]. In addition to ubiquitination, SUMOylation mediated by SUMO3 is also a regulatory step involved in the proteasome-mediated degradation of NPR1 [132]. Moreover, SUMOylation and phosphorylation work together to provide another regulatory layer that fine-tunes NPR1's transcriptional activity. There are four putative phosphorylation serine residues on NPR1, Ser11, Ser15, Ser55 and Ser59. Under normal conditions, Ser55 and Ser59 of NPR1 are phosphorylated, which completely destroys the interaction between NPR1 and SUMO3. Non-SUMOylated NPR1 prefers to target WRKY70 to repress the expression of the *PR1* gene [132–134]. Upon pathogen challenge, Ser55 and Ser59 of NPR1 are rapidly dephosphorylated, allowing NPR1 to become SUMOylated.

SUMOylated NPR1 can interact with TGA to promote the transcriptional activity of the *PR1* gene [132]. Furthermore, SUMOylation is required for SA-induced phosphorylation of Ser11 and Ser15 in NPR1, which accelerates the degradation of NPR1 facilitated by the NPR3–CUL3 E3 complex [132]. Interplay between phosphorylation and SUMOylation represents a perfect working model for NPR1's regulation of plant immunity.

6. Conclusions

PTMs are essential tools in plant defense signaling that allow plants to fight against pathogen invasions. Here, we have provided an overview of PTMs that modify components involved in plant defense signaling. PTMs establish communication between pathogens and plants to alter cell signaling at multiple nodes for the rapid reprogramming of the plant for defense responses (Figure 3). Within the developed proteomic technologies, PTMs that occur at a low stoichiometry are easier to detect. Their detection will accelerate our understanding of the regulatory mechanism of plant immunity mediated by PTMs.

Plant growth is usually inhibited by an active immune response, resulting in yield penalties for fighting pathogens. Plants with inactive immune responses may grow faster, but they will be more susceptible to various diseases [135]. Balancing development and resistance is a major challenge in crop breeding programs. PTMs, such as phosphorylation, may be involved in controlling the trade-off between plant development and resistance [66,67,136]. Gaining an in-depth understanding of how phosphorylation facilitates the balance between development and resistance, and whether other PTMs, such as ubiquitination and *N*-glycosylation, regulate these processes will provide new strategies for efficiently increasing plant resistance without fitness costs.

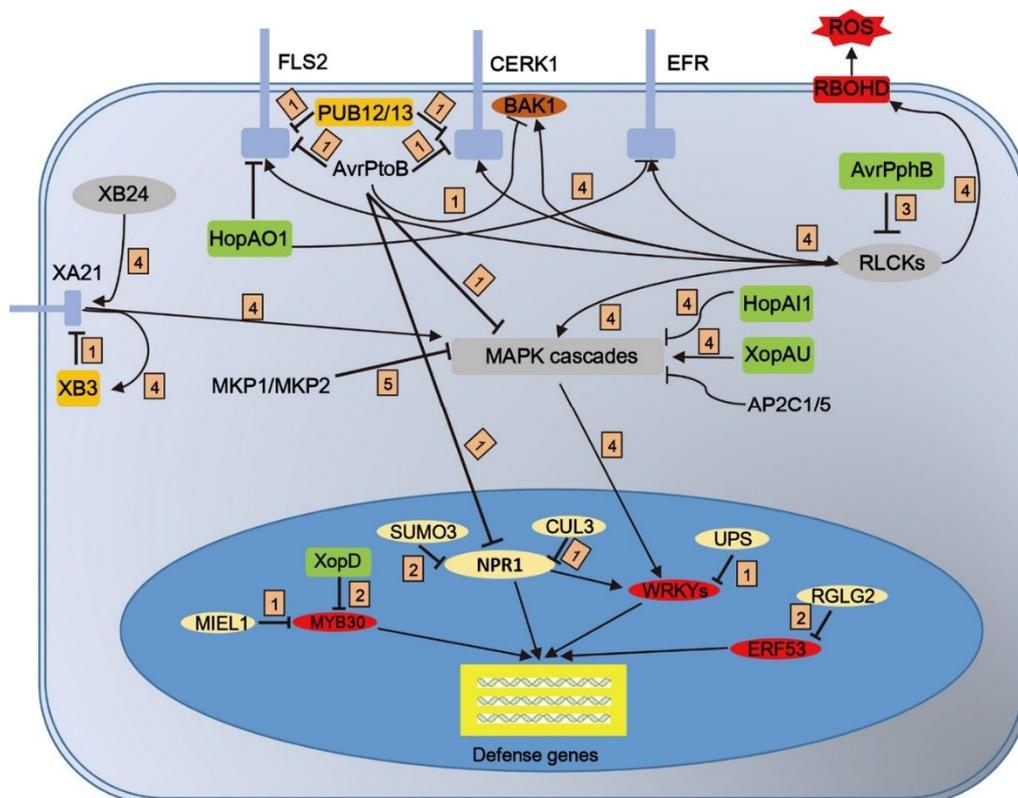


Figure 3. Schematic main PTMs in innate immunity of plants. Direct or indirect PTM activities plant immune response. PTM processes indicated are: 1, Ubiquitination/De-ubiquitination; 2, SUMOylation/De-SUMOylation; 3, cysteine protease; 4, Phosphorylation/De-phosphorylation.

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Abbreviations

AP2C1	<i>Arabidopsis</i> PP2C-type phosphatase
AVR	avirulence
BAK1	BRI1-associated receptor kinase1
BIK1	botrytis-induced kinase1
BR	brassinosteroid
BTB/POZ	broad-complex, tramtrack, and bric-à-brac/poxvirus, zinc finger
bZIP	basic leucine zipper
CEBiP	chitin elicitor-binding protein
CERK1	chitin elicitor receptor kinase 1
ECD	extracellular domain
EFR	EF-TU receptor
ETI	effector-triggered immunity
ERF	ET responsive TF
ER-QC	endoplasmic reticulum-quality control
FLS2	Flagellin Sensing2
HR	hypersensitive response
<i>IPA1</i>	<i>ideal plant architecture 1</i>
LRR	leucine-rich repeat
LYK5	lysine motif receptor kinase 5
LYP4	lysin motif-containing protein 4
MAMPs	microbe associated molecular patterns
MAPK	mitogen-activated protein kinase
MAPKK/MKK/MEK	MAPK kinase
MAPKKK/MEKK	MAPK kinase kinase
MIEL1	MYB30-interacting E3 ligase1
MKS1	MAPK4 substrate 1
MYB	myeloblastosis
NAC	no apical meristem, <i>Arabidopsis</i> transcription activation factor, cup-shaped cotyledon
NLRs	NOD-like receptors
NOD-like receptors	nucleotide-binding oligomerization domain-like receptors
<i>P. syringae</i>	<i>Pseudomonas syringae</i>
PAMPs	pathogen associated molecular patterns
PBL2	PBS1-like protein 2
PCD	programmed cell death
PCRK1	PTI compromised receptor-like cytoplasmic kinase1
PGN	eptidoglycan
PP2C	protein phosphatase 2C
PRRs	PAMPs are detected by pattern-recognition receptors
PTI	PAMP-/MAMP-triggered immunity
PTMs	post-translational modifications
PUB	plant U-box
RBOHD	respiratory burst oxidase homolog protein D
R protein	resistance protein
RLCKs	receptor-like cytoplasmic kinases
RIN4	RPM1-interacting protein 4

RLKs	receptor-like kinases
RLPs	receptor-like proteins
ROS	reactive oxygen species
RKS1	resistance-related kinase 1
SAR	systemic acquired resistance
Ser	serine
SERKs	somatic embryogenesis receptor kinases
SDS2	SPL11 cell-death suppressor 2
SIPK	SA-induced protein kinase
SPL	SQUAMOSA promoter-binding protein-like
SUMO	small Ub-like modifier
Thr	threonine
Tyr	tyrosine
XB3	XA21-Binding Protein3
Xoo	<i>Xanthomonas oryzae</i> pv. <i>Oryzae</i>
ZAR1	HOPZ-activated resistance 1

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