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Transcriptional Coactivators: Driving Force of Plant Immunity

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Salicylic acid (SA) is a plant defense signal that mediates local and systemic immune responses against pathogen invasion. However, the underlying mechanism of SA-mediated defense is very complex due to the involvement of various positive and negative regulators to fine-tune its signaling in diverse pathosystems. Upon pathogen infections, elevated level of SA promotes massive transcriptional reprogramming in which Non-expresser of PR genes 1 (NPR1) acts as a central hub and transcriptional coactivator in defense responses. Recent findings show that Enhanced Disease Susceptibility 1 (EDS1) also functions as a transcriptional coactivator and stimulates the expression of *PR1* in the presence of NPR1 and SA. Furthermore, EDS1 stabilizes NPR1 protein level, while NPR1 sustains *EDS1* expression during pathogenic infection. The interaction of NPR1 and EDS1 coactivators initiates transcriptional reprogramming by recruiting cyclin-dependent kinase 8 in the Mediator complex to control immune responses. In this review, we highlight the recent breakthroughs that considerably advance our understanding on how transcriptional coactivators interact with their functional partners to trigger distinct pathways to facilitate immune responses, and how SA accumulation induces dynamic changes in NPR1 structure for transcriptional reprogramming. In addition, the functions of different Mediator subunits in SA-mediated plant immunity are also discussed in light of recent discoveries. Taken together, the available evidence suggests that transcriptional coactivators are essential and potent regulators of plant defense pathways and play crucial roles in coordinating plant immune responses during plant–pathogen interactions.

Keywords: salicylic acid, NPR1, EDS1, mediator, CDK8, transcriptional coactivators, plant immunity

INTRODUCTION

Plants are constantly exposed to a wide range of destructive pathogens that cause dreadful diseases and considerably reduce crop yield by 10–40% (Yadav and Srivastava, 2017; Savary et al., 2019). To cope with these challenges, plants have developed a multilayered immune system that is highly eficient in the prevention of pathogen infections. Plant defense is an extremely complex and tightly regulated process that involves regulations at the transcriptional

level (Yuan et al., 2021). These signaling cascades are activated after the recognition of pathogenic microbes. The pathogen-associated molecular patterns (PAMPs) are recognized by plasma membrane-localized leucine-rich repeat (LRR) receptor kinases or receptor-like proteins to trigger a multifaceted basal immune response, known as PAMP-triggered immunity (PTI; Chen et al., 2021b). To enhance pathogenicity for successful establishment of growth, plant pathogens secrete effectors to compromise PTI. To combat this, plants have evolved sophisticated mechanisms for the recognition of pathogen effectors or their actions on host targets and induce a more effective and robust resistance response known as effector-triggered immunity (ETI; Martel et al., 2021).

Effector-triggered immunity activates strong defense responses that lead to programmed cell death (PCD; including swelling of mitochondria, ROS generation, enlargement of central cell vacuole, rupturing of the plasma membrane, and shrinkage of protoplast), which completely inhibits pathogen colonization at the infection site and is known as the hypersensitive response (HR; Betsuyaku et al., 2018; Peng et al., 2018; Liu et al., 2020a). ETI is mainly regulated by intracellular immune receptors known as nucleotide-binding (NB) LRR receptors (NLRs). According to the presence of coiled-coil (CC), Toll/interleukin-1 receptor (TIR), or Resistance to Powdery Mildew 8 (RPW8) domains at the N-terminus, plant NLRs are divided into three subgroups: CNLs (CC-NLRs), TNLs (TIR-NLRs), and RNLs (RPW8-NLRs; Chen et al., 2021c). CNLs and RNLs are considered as "sensor NLRs" and could directly or indirectly detect the presence of pathogen effectors and activate immune responses (Jones et al., 2016). Several lines of evidence suggest that NLRs are responsible for the recognition of pathogen effectors, and this recognition is the first step of immunity activation, whereas the actual process of stimulation of ETI needs other signaling components (Saleem et al., 2021). The coordinated action of ETI stimulates mitogen-activated protein kinase signaling, oxidative stress, the expression of *pathogenesis-related* (*PR*) genes, and the production of salicylic acid (SA). High level of SA will then induce the generation of mobile signals to trigger systemic acquired resistance (SAR) at the distal parts of the plants (Fu and Dong, 2013; Saleem et al., 2021).

Under biotrophic and hemibiotrophic pathogens attacks, SA accumulation and signaling cascade are primarily regulated by Enhanced Disease Susceptibility 1 (EDS1) and Non-expresser of PR genes 1 (NPR1), which act as transcriptional coactivators, to activate defense-related pathways to establish plant immunity (Li et al., 2019a). Transcriptional coactivator works together with other partners to positively regulate the transcription of certain genes (Jin et al., 2018). Multiple transcriptional coactivators are essential for transcriptomic reprogramming in SA-dependent plant immunity. Despite the growing body of evidence demonstrating their dynamic participation in defense responses, underlying processes related to their activation, regulation, pre/post-transcriptional and translational modifications, and interactions are still largely unknown (Jin et al., 2018; Yu et al., 2021). Over the past few decades, considerable advancement has been made in elucidating SA-mediated immune signaling at both molecular and cellular levels. Here, we summarize recent literature revealing the details of an emerging role of transcription coactivators, such as NPR1, EDS1, and Mediators, in the context of plant immunity. In addition, we also discuss recent breakthroughs in the field that could provide a mechanistic understanding of functional interactions between plant immunity and regulators of SA signaling at different levels.

SALICYLIC ACID BIOSYNTHESIS AND ITS FUNCTIONS IN PLANT IMMUNITY

The plant hormone SA is a phenolic compound that plays a critical role in regulating immune responses. Studies have shown that pathogen infection increases SA level; SA is essential for SAR establishment and acts as a vital modulator of plant immunity (Chen et al., 2020). In *Arabidopsis thaliana*, approximately 90% of pathogen-induced SA is synthesized by the isochorismate pathway; two *isochorismate synthase* (*ICS*) genes *ICS1* and *ICS2* are found in the *Arabidopsis* genome, although only *ICS1* is rapidly induced by pathogens (Wildermuth et al., 2001). Pathogen-induced SA accumulation and SAR were abolished when *ICS1* was knocked out. ICS1 converts chorismate to isochorismate in the plastid, and Enhanced Disease Susceptibility 5 (EDS5) transports isochorismate into the cytoplasm, where it is further metabolized to produce SA *via* the action of PBS3 and EPS1 (**Figure 1**; Wildermuth et al., 2001; Torrens-Spence et al., 2019). PBS3, as a GH3 acyl adenylase-family enzyme, catalyzes the conjugation of L-glutamate to isochorismate in the cytosol to generate isochorismate-9-glutamate, which is then used to produce SA through spontaneous decay. EPS1 functions as a BAHD acyltransferase-family protein, which could break down N-pyruvoyl-L-glutamate to generate SA.

Apart from playing a critical role in the regulation of SAR signaling, SA also amplifies PTI signaling. It was revealed in a recent study that after pathogen attack, the transcription of the early PAMP marker genes was significantly reduced in the SA receptor mutant *npr1-2* (Chen et al., 2017). SA contributes to activation of the genes that function both upstream and downstream of PAMP receptors (Ding et al., 2018). SA serves dual functions in ETI. According to an early finding, the *A. thaliana* SA-deficient *NahG* transgenic lines are more vulnerable to the avirulent bacterial pathogen *Pseudomonas syringae* pv. *tomato* carrying *avrRpt2* (Delaney et al., 1994), suggesting that initiation of ETI requires SA signaling. Consistently, when ETI is activated in *Arabidopsis* by the *Pseudomonas* effector AvrRpm1 or AvrRpt2, local SA content is remarkably elevated, with the elevated SA concentration associated with HR or PCD (Nawrath and Metraux, 1999). Additionally, artificial enhancement of SA signaling has been shown to negatively affect cell death during ETI. Devadas and Raina (2002) demonstrated that the *P. syringae* pv. *maculicola* ES4326 strain harboring *avrRpm1* failed to elicit HR in the *Arabidopsis* Col-0 plants pre-treated with SA. Rate and Greenberg (2001) reported that the NPR1-overexpressing *Arabidopsis* plants exhibited a reduced HR response, while the *npr1* mutants displayed a more severe HR, in the infection assays conducted with *P. syringae* carrying the *avrRpm1*

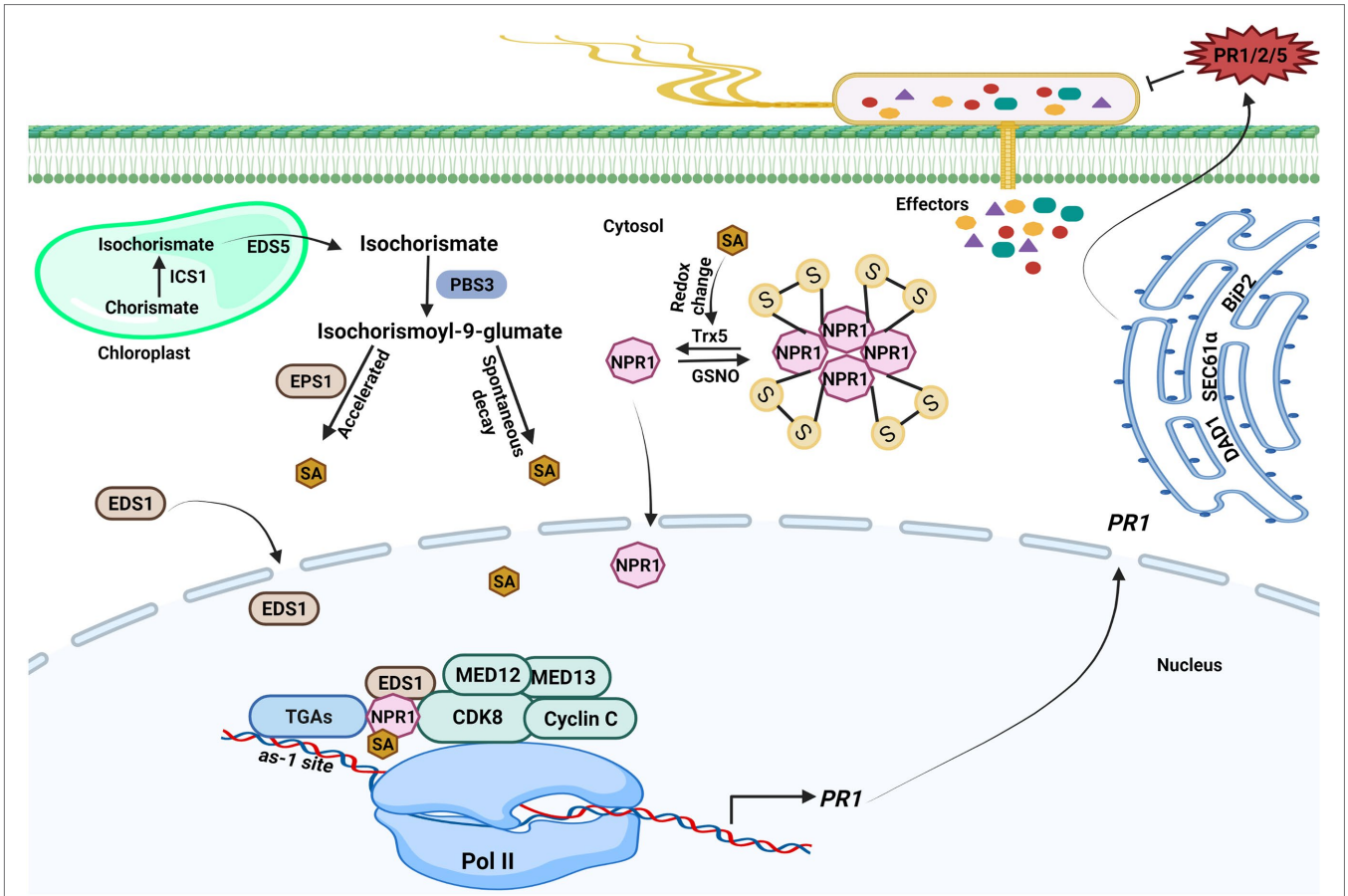

FIGURE 1 | Transcriptional regulations of salicylic acid-mediated plant immunity. Upon pathogen infection, salicylic acid (SA) generation is initiated in the chloroplast. ICS1 catalyzes the conversion of chorismate to isochorismate, and then, isochorismate is exported to the cytosol by Enhanced Disease Susceptibility (EDS5) 5. PBS3 catalyzes the conjugation of L-glutamate to isochorismate in the cytosol, resulting in isochorismate-9-glutamate. SA is produced from isochorismate-9-glutamate through spontaneous decay. The EPS1 acts as an isochorismate-9-glutamate pyruvoyl-glutamate lyase that could also break down N-pyruvoyl-L-glutamate to create SA. The *NPR1* gene expression is aided by SA because it encourages the interaction between the WRKY transcription factors and NPR1, which brings cyclin-dependent kinase 8 (CDK8) to the *NPR1* promoter's W-box and enables gene expression. The CDK8 kinase module mediators are also implicated in *PR1* gene expression. SA also promotes redox changes, which reduces NPR1 oligomers to monomers. The monomeric NPR1 molecule travels from the cytosol to the nucleus and activates downstream NPR1-dependent genes. NPR1 physically interacts with other coactivators, such as Enhanced Disease Susceptibility (EDS1) 1 and CDK8, to positively regulate the expression of *PR* genes expression in an SA-dependent environment. The *PR1* mRNA is further exported from the nucleus to the cytosol to produce PR1 protein. ER-resident genes (*SEC61α*, *DAD1*, and *BiP2*) govern the secretion of PR proteins into the apoplast to counter pathogen. The figure was created with BioRender.com.

gene. These studies suggest that SA is a multifaceted phytohormone involved in various signal transduction systems in plant immune responses (Li et al., 2019a).

ROLES OF MEDIATOR IN THE TRANSCRIPTIONAL REGULATIONS OF PLANT IMMUNITY

The Functional and Modular Organization of Mediator

Plants have evolved a substantial number of transcription factors (TFs) to coordinate and to fine-tune complex transcriptional programs (Malik et al., 2020). For example, the *Arabidopsis* genome has about 1,500 transcription factors, which may form diverse protein complexes to orchestrate different gene expression patterns in various signaling cascades (Sinha and Kumar, 2021). As a multi-protein complex, Mediator connects DNA-binding TFs with RNA polymerase II (Pol II) and serve as a central hub to regulate diverse aspects of transcription (Malik and Roeder, 2010). The initiation, elongation, and termination steps of mRNA synthesis are catalyzed by RNA Pol II, which is modulated by specific transcription factors and the Mediator complex.

According to structural studies, the overall structure of the Mediator complex may be categorized into three major modules (Head, Middle, and Tail). The head and middle modules interact with Pol II, while the tail module interacts with various transcription factors (Larivière et al., 2012; Verger et al., 2019; Malik et al., 2020). According to previous studies, *Arabidopsis*

consists of four (MED34, MED35, MED36, and MED37) plant-specific subunits of Mediator (**Figure 2**). However, Guo et al. (2021) carried out the afinity purification and mass spectrometry analysis of these four Mediator subunits and found that these could not be co-purified with other Mediator subunits, so they believe that MED34, MED35, MED36, and MED37 should not be regarded as Mediator subunits of *Arabidopsis*.

Mediator Middle Module

In transcriptional regulation, the various Mediator subunits can function as coactivator or co-repressor. Gene expression can be altered due to the involvement of certain Mediator subunits in the epigenetic and architectural modifications of chromatin (Lai et al., 2013). MED19 is a Mediator subunit located in the middle module. It assists the defense mechanism of plants *via* regulating the gene expression in SA, jasmonic acid (JA), and ethylene (ET) signaling pathways (**Figure 2**). Caillaud et al. (2013) reported the interaction between the HaRxL44 effector protein from the oomycete pathogen *Hyaloperonospora arabidopsidis* and host Mediator component MED19a. This effector destabilizes MED19 at the protein level and consequently results in the downregulation of SA marker genes (*PR1*, *PR2*, *PR5*, and *WRKY70*). Furthermore, *med19a* mutants show reduced SA-triggered immune responses, whereas overexpression of MED19a promotes SA-mediated plant defense. The presence of the HaRxL44 effector or the lack of MED19a in plants was linked to lower *PR1* expression. SA-induced *PR1* expression was similarly shown to be decreased in *med19a* mutants but increased in *MED19a* overexpressing lines. In *HaRxL44* overexpression lines and *med19a* mutants, JA/ET marker genes, such as *PDF1.2*, *JAZ1*, and *JAR1,* were activated. As a result of HaRxL44-mediated MED19a degradation, SA-dependent transcription was altered, and the balance between the JA/ET and SA pathways was disrupted. These findings imply that MED19a is a positive regulator of SA-triggered immunity against biotrophic pathogens and is engaged in SA/JA crosstalk (Caillaud et al., 2013).

Mediator Tail Module

MED14 is a component of the Mediator tail module and has been found to regulate various plant development and

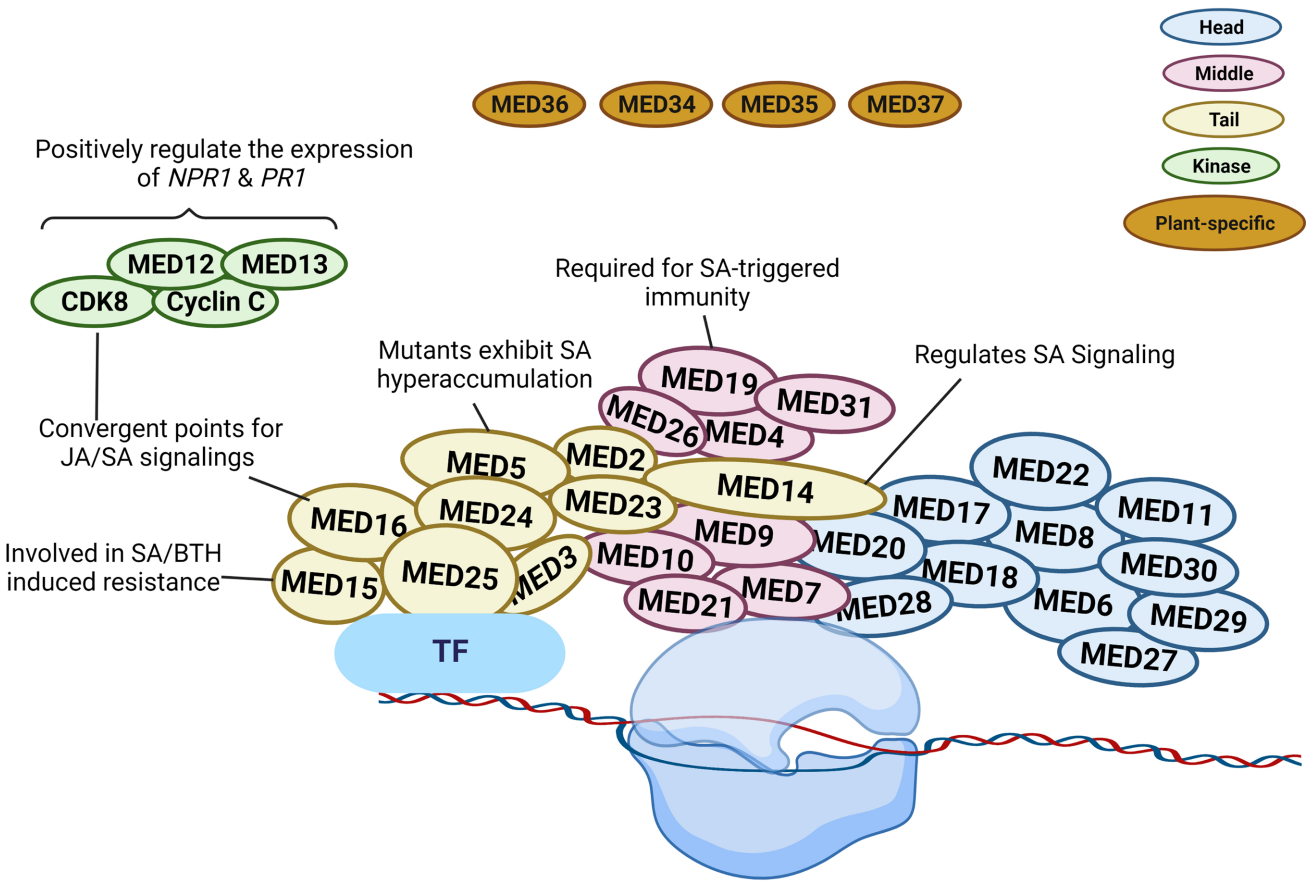

FIGURE 2 | Schematic illustration of plant Mediator structure and function. The Mediator complex in *Arabidopsis* is categorized into the following modules: Head (blue), Middle (pink), Tail (yellow), kinase (green), and plant-specific subunit (brown). The localization of the individual subunit within each module is arbitrary. The head and middle Mediator modules are attached to RNA polymerase II (Pol II), whereas the tail submodule interacts with certain transcription factors (TFs). Mediators connect DNA-binding TFs with the Pol II and serve as a bridge to regulate diverse aspects of transcription. Some Mediators with known functions in SA signaling are represented in the diagram. The figure was created with BioRender.com.

pathogen defense processes. In rice, the knockdown of *OsMED14* showed pleiotropic effects (fewer panicles, reduced plant height, lower pollen fertility, and narrow leaves, etc.; Malik et al., 2020). In addition, MED14 controls immune responses to pathogen infection *via* regulating SA signaling in plants. Zhang et al. (2013) evaluated the T-DNA insertion mutant of *MED14* and found that *med14* mutants were susceptible to the avirulent pathogen *Pst* DC3000 carrying *avrRpt2*. The mutation of *med14* resulted in the inhibition of the NAD^+-mediated *PR1* gene expression. In complementation lines, NAD^+ driven *PR1* gene expression was restored, supporting the significance of MED14 in extracellular NAD^+-mediated signaling (Zhang et al., 2013). After pathogen infection, the *med14-1* mutants showed reduced resistance to *Pst* DC3000 carrying *avrRpt2,* and several genes were differentially regulated between wild-type and *med14* mutant plants. Importantly, the master regulator of SA signaling, *NPR1,* was significantly downregulated in *med14* mutants. It is also worth noting that activation of the SA biosynthesis genes *ICS1*, *EDS5*, and *PBS3* requires functional MED14 (Zhang et al., 2013). Furthermore, compared to *med16* mutants, the transcriptional alterations in response to *Pst* DC3000 carrying *avrRpt2* in *med14-1* mutant plants demonstrated differential expression in numerous genes associated with SAR and NPR1, showing that MED14 and MED16 use distinct mechanisms to regulate the SA signaling and SAR pathways (**Figure 2**; Zhang et al., 2013).

Another Mediator tail module subunit in *Arabidopsis*, MED15, was first discovered as NRB4 (non-recognition-of-BTH4) during mutant screening (Canet et al., 2012). The *med15* mutant showed unresponsiveness toward an analog of SA, benzothiadiazole (BTH), similarly to the *npr1-1* mutant exhibiting insensitivity to SA. When exposed to SA or BTH, the wild-type plants but not the *med15* or *npr1* mutants developed increased resistance to *Pst* DC3000. In addition to that, the *Pst* DC3000 or BTH treatment did not affect the PR1 protein level in *med15* or *npr1* mutants. However, yeast two-hybrid analysis showed no interaction between NPR1 and MED15, even in the presence of SA. Moreover, the overexpression lines of *MED15* displayed an enhanced response to SA (**Figure 2**). Canet et al. (2012) showed that MED15 may act downstream of NPR1 to control SA-mediated responses.

MED16 is also a subunit in the tail module of Mediator complex and was first identified during a screen for mutants vulnerable to acclimatization under cold stress conditions. Thus, this gene was named SENSITIVE TO FREEZING 6 (Warren et al., 1996). Wathugala et al. (2012) reported that mutation of *MED16* led to susceptibility to *P. syringae* and lower *PR1*, *PR2*, and *PR5* mRNA levels compared to Col-0, indicating that MED16 is required for the regulation of SA-induced *PR* genes expression. Another research group suggested a crucial role of MED16 in basal resistance against the necrotrophic fungus *Sclerotinia sclerotiorum,* as the *med16* mutant displayed compromised resistance response (Wang et al., 2015). Further analysis uncovered that the *med16* plants not only showed reduced *NPR1* expression but also exhibited lower expression of JA/ET-responsive genes (**Figure 2**).

A further tail module component of Mediator is MED5/MED33. The *med5a*/*med5b* mutant hyper-accumulates phenylpropanoids, indicating that MED5 plays a key role in phenylpropanoid homeostasis (Bonawitz et al., 2012). In contrast, a single amino acid alteration in MED5b (i.e., mutant ref4-3) could turn MED5b into a repressor of the pathway, leading to a lower accumulation of phenylpropanoids, dwarfism, and reduced lignin contents (Bonawitz et al., 2012). In *ref4-3*, the expression of defense genes, such as *ICS1*, *PR1*, *PR2*, and *PR5,* was elevated. Furthermore, there was an increased accumulation of free SA and SA conjugates in *ref4-3* (Mao et al., 2019). However, the upregulation of SA signaling genes in *ref4-3* was changed in the *ref4-3*/*cdk8-1* double mutant, resulting in suppressed expression of SA-responsive defense genes and reduced SA accumulation. Consequently, the cyclin-dependent kinase 8 (CDK8) kinase activity was required for SA hyperaccumulation in the *ref4-3* mutant (**Figure 2**). CDK8 does not physically interact with MED5 according to the structural analysis of the yeast Mediator complex. Hence, future research is required for achieving a better understanding of the functional association between the MED5 and CDK8 subunits in regulating SA signaling.

CDK8 Kinase Module

The CDK8 kinase module participates actively in transcriptomic reprogramming during plant response to pathogen infection (Mao et al., 2019; Liu et al., 2020b). CDK8 has positive transcriptional regulatory activities in SA-mediated immunity *via* phosphorylating RNA Pol II at the CTD site (Wang and Chen, 2004; Chen et al., 2019). Zhu et al. (2014) discovered that CDK8 promotes *Arabidopsis* resistance to *Alternaria brassicicola* by directly regulating the transcription of *AGMATINE COUMAROYLTRANSFERASE* (*AACT1*). AACT1 participates in the production of a family of secondary metabolites known as hydroxycinnamic acid amides, which have been implicated in fungal resistance (Zhu et al., 2014). As a result, *Arabidopsis* plants are unable to elicit essential defensive responses in the absence of CDK8. MED12 and MED13, two subunits of the CDK8 module, share the same structural and functional roles as CDK8. In *Arabidopsis*, MED12 and MED13 are involved in positive gene regulation under specific circumstances and promote the initial stages of gene transcription (Liu et al., 2020b). Huang et al. (2019) demonstrated that *cdk8* mutants grown under normal conditions showed reduced expression of *ICS1* and *EDS5*, indicating that CDK8 is involved in the transcriptional control of these SA production and transport genes (**Figure 2**). Similarly, *med12* mutants exhibited lowered SA levels and hampered SAR. The mutation in *MED12* resulted in similar defects, such as lower SA level and weakened SAR (Huang et al., 2019).

The subsequent study by Chen et al. (2019) demonstrated that NPR1 interacts with CDK8 and WRKY transcription factors, such as WRKY18, to promote the expression of *PR* genes in *Arabidopsis*, thereby promoting defense responses. The *cdk8* mutant had lower levels of *NPR1* and *NPR1*-dependent defense gene expression as compared to WT control. CDK8 regulates *NPR1* expression by interacting with WRKY6 and WRKY18

at *NPR1*'s promoter. TGA5 and TGA7 are transcription factors associated with the *PR1* promoter and work together with CDK8 to regulate *PR1* gene expression. This study also discovered that CDK8 recruits RNA Pol II to *NPR1* and *PR1* promoters and coding regions to increase the expression of those genes (Chen et al., 2019). Thus, the contribution of CDK8 to SA-mediated plant immunity was further established as CDK8 promotes functional interactions among NPR1, TGA, TFs, and RNA Pol II under the influence of SA to facilitate *PR1* gene expression.

HAC1 AND HAC5: LOOSENING UP CHROMATIN

Histones are alkaline proteins in the nuclei of eukaryotic cells that function to package DNA into structural components known as nucleosomes (Yang et al., 2020). The addition or removal of acetyl and methyl groups to the histone tails, which protrude from the nucleosome core, might alter the physical accessibility of DNA to cell's transcriptional machinery. Histone acetylation reduces positive charges from histone proteins by adding an acetyl group to the lysine residues, lowering histone-DNA binding, leading to chromatin de-condensation and gene activation (Kumar et al., 2021). The combined actions of several histone acetyltransferases (HATs or HACs) and histone deacetylases constantly regulate the level of histone acetylation (Yang et al., 2020). HATs are divided into four groups based on sequence similarity and domain organization; GNAT (General Control Non-depressible 5-related Acetyltransferase), MYST (MOZ-YBF2/SAS3-SAS2/TIP60), CBP (cAMP-Responsive Element Binding Protein), and TAFII250 (TATA-binding protein Associated Factor; Hu et al., 2019). The abbreviations HAG, HAM, HAC, and HAF are used to represent these families (Pandey et al., 2002).

Histone acetyltransferases may alter plant immunity in both NPR1-dependent and NPR1-independent ways (Jin et al., 2018). Under normal conditions, a small fraction of monomeric NPR1 is present inside the nucleus and interacts with TGA and HAC to form a ternary HAC–NPR1–TGA complex (Jin et al., 2018). However, some TGAs that are not part of this complex binds to *PR* promoters and inhibit *PR* transcription. Thus, HAC–NPR1–TGA complex is not recruited to *PR* chromatin in this situation. During pathogen attack, SA upsurges and binds to NPR1 in the nucleus. HAC1, HAC5, and NPR1 create a coactivator complex and bind to *PR* chromatin *via* TGAs, forming HAC–NPR1–TGA complex to promote *PR* transcription through histone acetylation-mediated epigenetic reprogramming (Jin et al., 2018). Mutation of *hac1/5* leads to reduced pathogen-induced expression of various SA biosynthesis or accretion-related genes like *EDS5*, *PAD4*, and *ICS1*, whereas *npr1* mutation did not affect the induction of these genes in *hac1/5* mutants (Jin et al., 2018). This indicates that HACs also regulate SA biosynthesis or accumulation-related genes in an NPR1-independent manner (Jin et al., 2018).

Even though HAC1/5 may not be essential for NPR1 to interact with free TGAs, they are likely required for NPR1 to bind to TGAs eficiently in the chromatin. One possibility is that acetylation of histones by HAC, which was recruited *via* NPR1 to *PR* gene chromatin, can alter the local conformation of chromatin so that the HAC–NPR1–TGA complex is more stable in connection with chromatin (Jin et al., 2018). Conversely, HAC could serve as an adapter, creating multivalent associations with transcription factors, thereby maintaining NPR1's engagement with *PR* chromatin (Jin et al., 2018). Another possibility is that SA-binding to NPR1 may modify the HAC-NPR1 complex or the ternary HAC–NPR1–TGA complex, allowing for more eficient DNA binding of TGAs on *PR* promoters (Jin et al., 2018). Hence, HAC may help enhance or stabilize the formation of the HAC–NPR1–TGA complex on *PR* chromatin and facilitate the transcription of *PR* genes during plant defense responses.

NPR1: A SALICYLIC ACID RECEPTOR AND A MASTER REGULATOR

Dynamic structural changes determine the transcriptional regulation efficiency of NPR1

Several studies have identified SA-regulated downstream signaling components. Among them, NPR1 is considered to be a vital SA receptor and a leading redox controller of SA-regulated defense signaling by modulating the expression of a series of disease-resistant genes. Of the approximate 2,800 SA-responsive genes, the great majority (more than 98%) are NPR1-dependent. Structurally, NPR1 contains several characterized functional elements, including a BTB/POZ domain in the N-terminus, ankyrin repeat and transactivation domains in the C-terminus, and a nuclear localization sequence, with the BTB/POZ sequence showing resemblance to E3 ligase adaptor motif (Dong, 2004; Dieterle et al., 2005; Rochon et al., 2006). Interestingly, the paralogs of NPR1, NPR3, and NPR4, have been verified to possess an E3 ligase adaptor domain and were identified as Cullin 3 RING E3 ligase adaptors, which promoted the degradation of NPR1 in the nucleus (Spoel et al., 2009; Fu et al., 2012). The studies on *npr1* mutant plants demonstrated that malfunction of NPR1 completely abolishes plant defense against pathogens due to interruption in SA-regulated downstream signaling and transcription.

During pathogen infection, SA directly binds to NPR1 to regulate its activity and stability, which is essential for its downstream activation of effector proteins/genes. Upon activation, NPR1 undergoes several post-translation modifications. In the normal state, NPR1 is resting in the form of high-molecular-weight oligomers in the cytoplasm (Withers and Dong, 2016). Under pathogenic attacks, the presence of a higher concentration of SA disturbs redox balance in the cytoplasm, changing NPR1 from oligomers to monomers *via* thioredoxin (TRX-h3 and TRX-h5)-mediated reduction of a cysteine residue (Cys156) in NPR1 (Waszczak et al., 2015; Withers and Dong, 2016). In normal conditions, NPR1 is associated with transcription repressor and is phosphorylated at serine residues 55 and 59, thus blocking its promotion of the expression of SA-responsive genes (Waszczak et al., 2015; Withers and Dong, 2016). Upon

pathogenic infection, increasing cellular concentration of SA leads to the dephosphorylation of Ser55/Ser59 and SUMOylation at the SUMO-interacting motif 3, which triggers the phosphorylation of Ser11/Ser15, in NPR1 (Saleh et al., 2015). The recent findings of Zavaliev et al. (2020) demonstrated that dephosphorylation Ser55/Ser59 and phosphorylation of Ser11/Ser15 facilitate NPR1 to enter the nucleus or assemble cell death regulators and stress response proteins to form punctate structures known as SA-induced NPR1 condensates (SINCs). The authors further demonstrated that SA also promotes NPR1's interaction with Cullin3 (CUL3) E3 ligase by phosphorylating NPR1 at Ser11/Ser15 to stimulate NPR1 turnover (Zavaliev et al., 2020).

NPR1 ubiquitination by CUL3 and degradation by the 26 proteasome in the nucleus also influence SINC formation in the cytoplasm, as demonstrated in the SUMOylation-deficient mutant of NPR1 (Zavaliev et al., 2020). In SNICs, NPR1 enables SA-responsive ubiquitination of target proteins to boost cell survival; therefore, SINCs serve as a site for recruitment and ubiquitination (with the help of CUL3 E3 ligases) of key members of the stress response machinery, such as EDS1 and WRKY54/70, to promote cell survival. This is because, under pathogen infection, SA level increases, which inhibits the $CUL3^{NPR4}$ but promotes $CUL3^{NPR3}$-mediated degradation of NPR1, leading to ETI. However, in adjacent cells, a lower concentration of SA is not sufficient to promote the interaction of NPR3 with NPR1, which enables the accumulation of NPR1 to suppress cell death. NPR1-mediated SINC formation may be essential for robust transcriptional reprogramming to redirect energy for defense instead of growth upon pathogenic infection (Peng et al., 2021; Chen et al., 2021b). However, the mechanism through which SA triggers the dynamic formation of SINCs requires future elucidation.

NPR1-Mediated Transcriptional Regulation of Plant Immunity

The NPR1 protein does not contain a canonical DNA-binding domain; instead, after monomerization and re-localization to the nucleus, NPR1 promotes transcriptional activation by interacting with appropriate transcription factors to mediate the expression of more than 2,000 genes (Liu et al., 2018).

In *Arabidopsis*, NPR1 interacts with seven out of a total of 10 TGA TFs. TGA1 and TGA4 interact with NPR1 in a redox-dependent manner, while TGA2, TGA3, TGA5, and TGA6 are prerequisites for SA-regulated gene expression (Lindermayr et al., 2010; Spoel and Loake, 2011; Herrera-Vásquez et al., 2015). It has been established that SA induces reduction of the disulfide bridges in TGA proteins, which enable them to interact with NPR1. In turn, TGA and NPR1 interaction activate the expression of *PR1* (Fan and Dong, 2002; Rochon et al., 2006).

Besides TGAs, TCP and WRKY TFs have also been implicated in SA-mediated SAR responses. A recent study demonstrated that TCP8, TCP14, and TCP15 physically interacted with NPR1, and TCP15 binds to the promoter of *PR5* under the influence of NPR1 (Li et al., 2018). However, the precise molecular mechanism of NPR1-assisted TCP binding to the promoter of *PR5* is obscure, which warrants further investigation (Li et al., 2018). The presence of several WRKY TF binding sites (W-box elements) in the promoter region of *NPR1* implies that NPR1 may be cross-regulated by WRKY TFs (Pajerowska-Mukhtar et al., 2013). A growing body of evidence suggests that the interaction of WRKY TFs with NPR1 stimulates the expression of SA-responsive genes (Pajerowska-Mukhtar et al., 2013), and the expression of these genes is associated with the strengthening of *R* gene-dependent resistance (Meena and Swapnil, 2019). However, despite the finding of three WRKY TF binding sites, that is, W-box (TTGAC) elements in *NPR1* promoter, the precise molecular mechanism underlying the regulation of NPR1 expression and function by WRKY TFs remains to be clarified. One useful clue for further research is that NPR1 could promote its own expression by binding to self-promoter through interacting with WRKY18 (Chen et al., 2019).

EDS1: A MULTITALENTED DEFENDER

EDS1 and Its Interacting Partners Trigger Distinct Pathways

One important mechanism underpinning SA's involvement in plant immunity (PTI, ETI, and SAR) is transcriptional reprogramming of SA biosynthesis genes (Wildermuth et al., 2001). The downstream responses of SA-mediated immunity are modulated by the nucleocytoplasmic regulator NPR1, which is a transcriptional coactivator of SA-dependent local and systemic immunity (Fu and Dong, 2013; Saleem et al., 2021). On the other hand, EDS1 is a necessary component in both basal and R protein-mediated resistance (TIR-NBS-LRR class) against virulent and avirulent pathogens (Peart et al., 2002; Li et al., 2019a). In flowering plants, EDS1 forms functional heterodimers with SAG101 or PAD4, with EDS1–SAG101 and EDS1–PAD4 heterodimers having diverse functions in plant immunity (Wiermer et al., 2005; Wagner et al., 2013). The interaction of these regulatory nodes distinctly reprograms transcriptional activities in infected cells and initiates the production of SA and other stress signals to limit the growth of invading pathogens. EDS1 and PAD4 are crucial for regulating plant basal immunity. The heterodimer complex of EDS1 and PAD4 stimulates SA accumulation, which in turn induces the expression of *EDS1* and *PAD4*. As a result, they are forming a positive feedback loop to enhance SA-activated immune system (Jirage et al., 1999; Feys et al., 2001; Vlot et al., 2009). Usually, EDS1 and PAD4 work together, but they can also function independently. For example, EDS1 interacts with SAG101–NRG1 module in TNL-triggered ETI to induce host cell death and transcriptional reprogramming without needing PAD4 (Lapin et al., 2019).

EDS1–PAD4 interacts with ADR1 type of RNLs to regulate basal immunity by transcriptionally modifying SA signaling pathway to induce local and systemic defense under TNL/CNL-triggered ETI (Bonardi et al., 2011; Cui et al., 2017; Lapin et al., 2019; Saile et al., 2020). Recently, Sun et al. (2021) showed that EDS1–PAD4–ADR1 and EDS1–SAG101–NRG1

constitute two separate immunity signaling nodes downstream of NLR activation to boost basal immunity against pathogens.

Nucleocytoplasmic Distribution of EDS1 During Plant Innate Immune Responses

The shuttling of EDS1 and PAD4 in the cytoplasm and the nucleus is important for defense activation processes (Cheng et al., 2009; García et al., 2010). Most of the regulatory proteins are present in the cytoplasm; however, EDS1–SAG101 heterodimer exists mainly in the nucleus. The EDS1-PAD4 heterodimer is present in both the cytoplasm and the nucleus, whereas the complex of EDS1, PAD4, and SAG101 is predominantly nuclear-localized. Less is known about the mechanism that maintains a delicate balance of these regulatory proteins in the cytosolic and nuclear compartments. Interestingly, recent molecular studies highlighted the roles of EIJ1 and RIN13 in regulating the subcellular distributions of EDS1 or PAD4 in infected cells. EIJ1, a DnaJ type of chaperone, rapidly relocalizes from the chloroplast to the cytoplasm, where it interacts with EDS1, during the early stage of pathogen infection in *Arabidopsis* (Liu et al., 2021). This interaction prevents EDS1 trafficking to the nucleus and prohibits the elicitation of unnecessary immune responses to short-term pathogenic stimulation. However, when plants are under prolonged attack of pathogens, EIJ1–EDS1 complex degrades cytoplasmic EDS1, and the accumulation of EDS1 increases in the nucleus to reinforce long-term resistance in the plants (Liu et al., 2021). Similarly, RIN13 could drive PAD4 into the nucleus (Liu et al., 2021). The shuttling of EDS1 and PAD4 proteins from the cytoplasm to the nucleus is necessary to activate defense gene expression and for the accumulation of stress signaling molecules, such as SA. These findings point out the vital roles of EIJ1 and RIN13 during pathogen invasion and provide new information about how the subcellular localization of EDS1/PAD4 is regulated to confer resistance in pathogen-challenged plants (Liu et al., 2021).

EDS1-Mediated SA-Dependent/Independent Signaling

Enhanced Disease Susceptibility 1 initiates SA-dependent and SA-independent pathways to transcriptionally reprogram infected cells for immunity and localized cell death (Bartsch et al., 2006; Cui et al., 2017). The existence of multiple pathways warrants robust activation of defense responses. If one pathway is blocked due to manipulation by pathogen effector or other unknown reasons, the alternate pathway would still ensure defense (Cui et al., 2017). Overexpression analysis of EDS1 and PAD4 validates the expression of both SA-dependent and SA-independent genes. Both SA-dependent and SA-independent functions of EDS1/PAD4 mediate plant basal immunity and ETI (Cui et al., 2017). The SA-dependent pathway is associated with pathogen-induced SA accumulation to boost resistance, while the other one is independent of SA synthesis *via* ICS1 by recruiting other functional partners (ALD1/FMO1-dependent) to amplify resistance (Bartsch et al., 2006; Cui et al., 2017). In the SA-dependent pathway, EDS1 heterodimer promotes SA biosynthesis *via* ICS1 and transcriptionally induces defense responses. In the absence of EDS1, heterodimer partners like PAD4 and SGS101 are ineffective in promoting plant defense due to improper accumulation of SA and *PR1* expression (Rietz et al., 2011).

Enhanced Disease Susceptibility 1 regulates the SA-independent signaling cascade by triggering the transcriptional activation of FMO1, irrespective of local SA production/accumulation (Bartsch et al., 2006; Cui et al., 2017). The SA-independent branch of EDS1 with PAD4 module activates FMO1 and induces *PR1* gene expression due to enhanced accumulation of free and conjugated SA, but this increase in SA was not associated with ICS1 activity under pathogenic attack. Analysis of *eds1-2* and *pad4-1* single and double mutants revealed that pathogen effector-induced *FMO1* expression was significantly reduced, which clearly suggests that the activation of FMO1 and SA accumulation is due to functions of the EDS1–PAD4 complex (Joglekar et al., 2018). Additionally, it was observed that EDS1-induced SA-independent immunity was effective against the infections by *Pst* DC3000 and the oomycete pathogen *H. arabidopsidis* in *Arabidopsis*, illustrating that the mobilization of SA-independent defense pathways by EDS1/PAD4 signaling is an effective immune response in controlling pathogenic diseases in plants (Mishina and Zeier, 2006; Joglekar et al., 2018). Likewise, when *Arabidopsis* plants were infected with the *Pst* carrying *avrRpt2*, EDS1-meditated SA-independent contribution to defense responses appeared stronger with sustained MAPK activation (Hartmann et al., 2018; Wang et al., 2018). Lastly, EDS1-PAD4 also controls the receptor-like kinase BAK1-mediated cell death signaling in an SA-independent manner because cell death of *bak1-3 bkk1-1 sid2-3* in *eds1* or *pad4* background was suppressed, which suggests that EDS1 contributes to BAK1-mediated cell death pathway *via* SA-independent signaling pathway (Gao et al., 2017). Clearly, the SA-independent branch of EDS1 signaling is active in the stimulation of local immunity in infected plants (Hartmann et al., 2018; Wang et al., 2018).

EDS1 Crosstalking With Other Regulatory Hubs

EDS1 suppresses the function of JA regulators to reinforce SA-mediated plant defense. JA signaling under pathogenic infection works antagonistically to SA signaling (Vlot et al., 2009; Yang et al., 2012). *Pst* DC3000 toxin coronatine (COR), a bacterial JA mimicker, could disable SA signaling *via* modulation of JA signaling pathways (Brooks et al., 2005; Kazan and Lyons, 2014; Yang et al., 2017). Upon the inoculation of *Pst* DC3000 carrying *avrRps4*, EDS1/PAD4 complexes mobilize a major portion of the TNL (RRS1-S/RPS4) immune response to counter bacterial COR-mediated MYC2 transcriptional reprogramming of JA responsive genes (*VSP1* and *JAZ10*). Molecular analysis shows that EDS1 antagonizes MYC2 function in the nucleus rather than its entry into the nucleus *via* suppressing MYC2 binding to a responsive promoter (*pANAC019*) and improving the SA defense sector independent of EDS1-triggered SA synthesis (Cui et al., 2018). Similarly, gibberellic acid repressors, DELLA proteins, act as modulators

between growth and resistance responses under pathogenic infection. When plants are infected, EDS1 rapidly induces and promotes SA-induced defense responses. At the same time, defense signaling activates EDS1-dependent DELLA stabilization to suppress plant growth. Later, the stabilized DELLAs interact with EDS1 to slow down SA production and repress resistance response to maintain the balance between growth and defense under long-term pathogen attack. This suggests that regulatory feedback exists between EDS1-DELLA and SA under pathogenic infections (Li et al., 2019b). Recently, it was also found that EDS1 interacts with BRASSINAZOLE RESISTANT 1 (BZR1), a major regulator of BR-induced transcriptional changes, to regulate immune responses in infected *Arabidopsis* plants (Qi et al., 2021). During compatible pathogen infection, EDS1 negatively regulates BZR1 signaling by binding to BZR1, which suppresses the expression of BR-responsive genes (e.g., *EXP8* and *SAUR15*) and BR-promoted growth with concomitant onset of eficient PTI. On the other hand, presence of suficient BZR1 in the cytoplasm is required for effective induction of RPS4-mediated ETI *via* facilitating the dissociation of EDS1 and RPS4 dimers in the cytoplasm, which is a crucial step in the ETI controlled by RPS4 (Qi et al., 2021). Thus, it seems that extensive crosstalking exists among EDS1 and diverse regulatory hubs (e.g., EDS1, BZR1, MYC2, and DELLA), which contributes to the mounting of effective and yet balanced disease resistance in different pathogen–host interactions.

NPR1 AND EDS1: TWO INTERDEPENDENT AND SYNERGISTIC COACTIVATORS

Both EDS1 and NPR1 function as central hubs in plant immunity, and they are both targeted by pathogen effectors (Chen et al., 2021a). Through yeast two-hybrid screening, EDS1 was identified as a NPR1-interacting protein. Importantly, Chen et al. (2021a) demonstrated that EDS1 has transcriptional activation activity. Through analyzing EDS1 deletions and truncations, Chen et al. (2021a) found that two regions in EDS1 are necessary and suficient for EDS1's transcriptional activation activity. Amino acid sequence analysis revealed that acidic and hydrophobic amino acids are enriched in these two regions, which are presumably involved in the ionic and hydrophobic interactions with their target molecules. Therefore, EDS1 harbors two acidic transcriptional activation domains, similar to those identified in the TFs, such as P53, GCN4, GAL4, and VP16 (Chen et al., 2021a). This realization provides new insight into EDS1's function in the regulation of downstream defense genes upon SA accumulation under pathogenic attack (Chen et al., 2021a).

Further examination revealed that EDS1 and NPR1 bind to similar regions in the *PR1* promoter, which are TGA-binding *as-1* and WRKY-binding W-box elements (Chen et al., 2021a). EDS1 and NPR1 synergistically promote the expression of *PR* genes. Another transcriptional coactivator, CDK8, physically interacts with NPR1 and EDS1 and acts as a bridge between transcription factors and RNA polymerase II to promote the expression of plant defense genes (Chen et al., 2019). NPR1 facilitates SA-induced EDS1 chromatin binding and *PR1* activation by effectively recruiting EDS1 to the *PR1* promoter (Chen et al., 2021a; **Figure 1**). Thus, physical interaction between EDS1 and NPR1 plays an intrinsic role in the interaction of EDS1 with *PR1* promoter, while the two transcriptional coactivators, EDS1 and NPR1, may directly recruit the Mediator complex in the transcription machinery to reinforce the expression of SA-responsive genes and thus SA-mediated defense responses (Chen et al., 2021a).

Genetic experiment revealed that NPR1 transcriptionally upregulates *EDS1* expression *via* TGA2-NPR1 interaction, and *in planta* analysis discovered that EDS1 stabilizes NPR1 protein level by preventing its degradation to sustain immune responses under pathogenic infection (Chen et al., 2021a). These results support the idea that the functions of EDS1 and NPR1 in SA-mediated immunity are interdependent.

CONCLUSION AND FUTURE PROSPECTS

In the past two decades, tremendous progress has been made toward understanding SA signaling and regulation under pathogenic attack in plants. However, many questions still need to be answered. As transcriptional coactivators, plant Mediator subunits play vital roles in the transcriptional regulations of plant immunity, but this driving force in SA-mediated plant defense has yet to be fully understood. For instance, the functions of MED11, MED22, MED26, and other subunits in SA signaling still need to be explored. The MED12 and MED13 subunits of the CDK8 module are involved in the transcriptional regulation of *NPR1* and its target genes, but the transcriptional factors that interact with these two subunits are still unknown. Similarly, the TFs that interact with MED5/14/15/16/19, which are involved in SA signaling, remain to be identified.

The precise biochemical roles of EDS1, NPR1, and related components in signaling PTI and ETI need further elucidation (Bjornson and Zipfel, 2021; Yuan et al., 2021). For instance, how are Ca^{2+} signatures and Ca^{2+} channels integrated with activation of the transcriptional coactivators, such as NPR1 and EDS1, to orchestrate different defense responses in both PTI and ETI immune systems? What genes do EDS1 and NPR1 control during these processes? More detailed genetic and biochemical investigations of the spatial and temporal regulation of defense genes regulated by EDS1 and NPR1 will help to better understand how EDS1 and NPR1 control plant immunity.

As a transcriptional coactivator without a DNA-binding domain, EDS1 has to interact with appropriate TFs, such as TGAs and WRKYs, to facilitate transcription. Therefore, it is necessary to identify the TFs that interact with EDS1 in different pathosystems. Similarly, further studies of additional transcriptional regulators, including the HACs, HDAs, and

other epigenetic regulators that directly or indirectly interact with EDS1-NPR1-CDK8 complex, are needed to facilitate an in-depth understanding of coactivator-mediated plant immunity. Previous studies have revealed the crystal structure of truncated NPR4, EDS1/PAD4, and EDS1/SAG101 heterodimers, but the crystal structure of EDS1-NPR1-CDK8 complex remains undetermined. In view of the crucial importance of EDS1-NPR1-CDK8 in SA-mediated immunity (Chen et al., 2021a), it now becomes necessary to determine the crystal structure of this complex, the insight from which will guide further and deeper functional and mechanistic studies of transcriptional coactivators in controlling plant immunity.

AUTHOR CONTRIBUTIONS

MK drew the figures. All authors contributed to writing the article and approved the submitted version.

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