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REVIEW PAPER

The plant Mediator complex and its role in jasmonate signaling

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Abstract

The Mediator complex is an essential, multisubunit transcriptional coactivator that is highly conserved in eukaryotes. Mediator interacts with gene-specific transcription factors, the RNA polymerase II transcriptional machinery, as well as several other factors involved in transcription, and acts as an integral hub to regulate various aspects of transcription. Recent studies of the plant Mediator complex have established that it functions in diverse aspects of plant development and fitness. Jasmonate (JA) is an oxylipin-derived plant hormone that regulates plant immunity and development. The basic helix–loop–helix transcription factor MYC2, which is a master regulator of JA signaling, orchestrates genome-wide transcriptional reprogramming of plant cells to coordinate defense- and growth-related processes. Here, we review the function of the plant Mediator complex in regulating JA signaling. We focus on the multifunctional Mediator subunit MED25, which emerges as an integrative hub for the transcriptional regulation of jasmonate signaling.

Keywords: Jasmonate signaling, MED25, Mediator, MYC2, transcriptional regulation.

Introduction

Dynamic changes in eukaryotic gene expression in response to intracellular or environmental stimuli are largely regulated by DNA-binding transcription factors (TFs). Mediator is a multiprotein complex that functions as a signal integrator transmitting information from the DNA-binding TFs to the RNA polymerase II (Pol II) transcriptional machinery (Malik and Roeder, 2010). Kornberg and colleagues first identified Mediator in yeast in 1990 (Kelleher *et al.*, 1990). The addition of a crude protein fraction from yeast to a reconstituted Pol II transcriptional system relieved competition between activators for a common target that was present in a limited amount. The activity in this crude protein fraction was named Mediator. Subsequently, similar activities were reported in mammals, both *in vitro* (Kretzschmar *et al.*, 1993; Merino *et al.*, 1993) and *in vivo* (Keaveney *et al.*, 1993). In 1994, Kornberg and colleagues purified the yeast Mediator as a large complex containing 20 subunits (Kim *et al.*, 1994). The first mammalian Mediator-like complex was isolated from human HeLa cells by Roeder and colleagues (Fondell *et al.*, 1996). Several laboratories used conventional chromatography to purify Mediator-like complexes from mouse, rat, and other species (reviewed in Conaway *et al.*, 2005). The current evidence indicates that Mediator is an evolutionarily conserved multisubunit protein complex comprising 25 subunits in yeast and up to 30 subunits in human (Fig. 1; Soutourina, 2018).

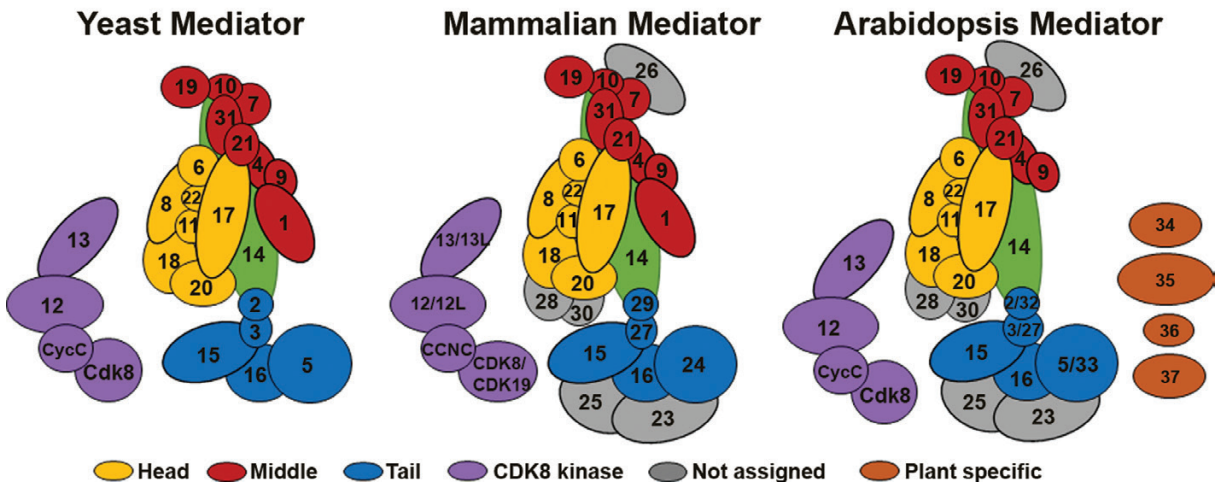

Fig. 1. Subunit composition of the Mediator complex. The illustrations represent the modular organization of the Mediator complex in yeast (A), mammals (B), and Arabidopsis (C) based on a recently revised structure derived from electron microscopy data in yeast and human complexes. Mediator comprises four distinct modules: Head (yellow), Middle (red), Tail (blue), and CDK8 (purple). Mediator subunit 14 (MED14), which links the three main modules (Head, Middle, and Tail), is indicated in green. The exact module localization of five metazoan and plant conserved subunits (MED23, MED25, MED26, MED28, and MED30) remains to be assigned (subunits indicated in gray). Four plant-specific subunits are indicated in orange.

Structural studies reveal that Mediator subunits form stable subcomplexes, and the structure of the whole complex can be divided into three main modules (Head, Middle, and Tail) plus a transiently associated cyclin-dependent kinase 8 (CDK8) module (Asturias *et al.*, 1999; Dotson *et al.*, 2000; Bourbon, 2008; Tsai *et al.*, 2014; Wang *et al.*, 2014). The modular organization of Mediator may reflect the different functions of Mediator components. Structural and biochemical studies in yeast and human indicate that the subunits comprising the Head and Middle modules are tightly associated with each other and constitute a stable core (Cevher *et al.*, 2014; Plaschka *et al.*, 2015). The Head module binds to Pol II and stabilizes the transcription initiation complex. The Middle module extends to the Pol II foot and may influence polymerase conformation (Cevher *et al.*, 2014; Plaschka *et al.*, 2015). Different from the Head and Middle modules, the individual subunits of the Tail module are relatively loosely associated, and are considered to be targeted by specific TFs (Blazek *et al.*, 2005). Mediator subunit14 (MED14) contacts all three main modules (Head, Middle, and Tail) and has a critical role in Mediator organization (Cevher *et al.*, 2014; Plaschka *et al.*, 2015). The CDK8 module reversibly associates with the main modules and broadly tends to have a regulatory function (Knuesel *et al.*, 2009; Tsai *et al.*, 2013). The Mediator structure can shift dramatically on binding to other proteins or protein complexes (Allen and Taatjes, 2015). These structural rearrangements are essential for Pol II holoenzyme formation, and could explain the capacity of Mediator to integrate multiple regulatory signals (Tsai *et al.*, 2017).

The most well-studied function of Mediator is its ability to regulate the formation of the transcriptional pre-initiation complex (PIC). Mediator is recruited to the target promoter and enhancer regions via direct interactions with specific TFs, while also directly interacting with Pol II and other PIC components. Thus, Mediator acts as a molecular bridge that communicates regulatory signals from DNA-binding TFs to the Pol II enzyme (Holstege *et al.*, 1998; Asturias *et al.*, 1999; Myers *et al.*, 1999; Davis *et al.*, 2002; Bernecky *et al.*, 2011). After PIC formation, Mediator is required for phosphorylation of the carboxy-terminal domain of Pol II, which in turn disrupts the Mediator–Pol II interaction and results in the escape of Pol II from the promoter (Nair *et al.*, 2005; Boeing *et al.*, 2010; Wong *et al.*, 2014). Structural and biochemical data also implicate Mediator in regulating the functions of Pol II subunit M (POLR2M) and the TFIIF TF during Pol II pausing and elongation (Cheng *et al.*, 2012; Jishage *et al.*, 2012; Wu *et al.*, 2012). The metazoan-specific MED26 subunit of Mediator is reported to interact with the super-elongation complex to facilitate Pol II elongation. CDK8 is reported to positively regulate Pol II elongation during serum and hypoxia responses (Donner *et al.*, 2010; Galbraith *et al.*, 2013). Newly emerging functions are continuously ascribed to yeast and metazoan Mediator in regulating almost every step of Pol II-dependent gene transcription, including chromatin remodeling and modification, non-coding RNA activation, mRNA processing, chromatin loop formation, and super-enhancer-dependent transcriptional regulation (Malik and Roeder, 2010; Poss *et al.*, 2013; Hnisz and Young, 2017; Jeronimo and Robert, 2017; Soutourina, 2018). Here, we review the function of Mediator complex in plants, especially its role in jasmonate (JA) signaling.

Mediator complex in plants

The first plant Mediator complex was isolated from Arabidopsis in 2007 (Bäckström *et al.*, 2007). Björklund and colleagues performed biochemical purification of the complex and identified 21 conserved and six plant-specific Mediator subunits. Although the CDK8 module was not identified in that study, Arabidopsis has homologs to *MED12*, *MED13*, *CDK8*, and *CycC* genes encoding subunits of the CDK8 module (Bäckström *et al.*, 2007). Bourbon performed

a bioinformatics analysis to identify an Arabidopsis homolog of metazoan-specific MED30, a subunit that was not purified from the Arabidopsis complex. That study also identified that the plant-specific MED32 and MED33 subunits were homologs of the yeast/metazoan MED2/29 and MED5/24 subunits, respectively (Bourbon, 2008). Recent evidence suggests that the metazoan-specific MED26 subunit may have a homolog in land plant species (Mathur *et al.*, 2011). By contrast, the conserved yeast and metazoan MED1 subunit was not biochemically purified or identified by bioinformatics analysis in Arabidopsis. Therefore, the Arabidopsis Mediator complex currently comprises 29 conserved and four plant-specific subunits (Fig. 1).

Comparative genomics analyses indicate that homologs of the Arabidopsis Mediator subunits are expressed in diverse plants, such as *Oryza sativa* and *Physcomitrella patens* (Mathur *et al.*, 2011). The subunit sequences displayed high similarity in different plants, suggesting that the function of the corresponding subunits is conserved in different plant species (Yang *et al.*, 2016). Several Mediator subunits were studied genetically before biochemical purification of the Arabidopsis Mediator complex, including PHYTOCHROME and FLOWERING TIME1 (PFT1)/MED25 and STRUWWELPETER (SWP)/MED14 (Autran *et al.*, 2002; Cerdán and Chory, 2003). A growing body of evidence suggests that plant Mediator subunits participate in multiple biological processes including flowering, defense, abiotic stress, non-coding RNA production, genomic stability, metabolism homeostasis, and growth and development (Kidd *et al.*, 2011; Kim and Chen, 2011; An and Mou, 2013; Samanta and Thakur, 2015; Yang *et al.*, 2016; Dolan and Chapple, 2017).

MYC-orchestrated transcriptional regulation is a central theme of JA signaling

Plant oxylipins such as JAs are a major class of immunity hormone that functions in diverse aspects of plant immunity and development (Creelman and Mullet, 1997; Turner *et al.*, 2002; Howe and Jander, 2008; Browse, 2009; Sun *et al.*, 2011; Kazan and Manners, 2013; Wasternack and Hause, 2013; Zhai *et al.*, 2017b). Extensive studies in Arabidopsis have revealed a core JA signaling module consisting of the F-box protein CORONATINE INSENSITIVE 1 (COI1) that forms a functional SCF E3 ubiquitin ligase complex (Devoto *et al.*, 2002; Xu *et al.*, 2002), a group of Jasmonate ZIM-domain (JAZ) proteins that function as transcriptional repressors (Chini *et al.*, 2007; Thines *et al.*, 2007; Yan *et al.*, 2007), and a battery of TFs that differentially regulate diverse aspects of JA responses (Gimenez-Ibanez *et al.*, 2015; Zhai *et al.*, 2017b). Among these TFs, the basic helix–loop–helix TF MYC2 is the most important and well-studied and differentially regulates two branches of JA-responsive genes (Boter *et al.*, 2004; Lorenzo *et al.*, 2004; Dombrecht *et al.*, 2007; Kazan and Manners, 2013; Zhai *et al.*, 2013). A breakthrough in the mechanistic understanding of JA signal transduction was the discovery that jasmonoyl-isoleucine (JA-Ile) is the receptor-active form of the hormone and that JA-Ile perception involves the formation of a SCF^{COI1}–JAZ co-receptor complex (Fonseca *et al.*, 2009; Yan *et al.*, 2009; Pauwels *et al.*, 2010; Sheard *et al.*, 2010). In the absence of the hormone, JAZ proteins interact with and prevent MYC2 from activating JA-responsive gene expression. In response to stimuli that trigger JA-Ile synthesis, JA-Ile promotes direct binding of JAZ repressors to the F-box protein COI1. SCF^{COI1}-dependent degradation of JAZ repressors via the ubiquitin–proteasome system leads to de-repression of MYC2-directed transcription of JA-responsive genes. In addition to MYC2, other members of the bHLH TFs including MYC3, MYC4, and MYC5 work redundantly to regulate the expression of JA-responsive genes (Cheng *et al.*, 2011; Fernández-Calvo *et al.*, 2011; Niu *et al.*, 2011; Figueroa and Browse, 2015; Qi *et al.*, 2015). These data indicate that MYC-orchestrated transcriptional reprogramming is a central theme of JA signaling (Kazan and Manners, 2013; Wasternack and Hause, 2013; Zhai *et al.*, 2017b).

Tomato is another plant model system that has been extensively studied to identify the mechanisms underlying JA-triggered plant immunity (Ryan, 2000; Schilmiller and Howe, 2005; Howe and Jander, 2008; Sun *et al.*, 2011; Rosli and Martin, 2015). The major molecular components that constitute the core JA signaling pathway in tomato (i.e. COI1, JAZs, and MYC2) are largely conserved with those in Arabidopsis (Boter *et al.*, 2004; Li *et al.*, 2004; Sun *et al.*, 2011). However, the action modes of specific molecular components differ in the two species. For example, in both tomato and Arabidopsis, the active hormone JA-Ile promotes COI1-dependent degradation of JAZ repressors and thereby de-represses the master TF, MYC2. In Arabidopsis, MYC2 positively regulates wounding-responsive genes and negatively regulates pathogen-responsive genes (Lorenzo *et al.*, 2004; Dombrecht *et al.*, 2007). By contrast, in tomato, MYC2 positively regulates both wounding- and pathogen-responsive genes. Tomato MYC2 directly regulates the transcription of its downstream intermediate TFs, which in turn regulate the expression of late wounding- or pathogen-responsive genes. MYC2 and its downstream intermediate TFs form a hierarchical transcriptional cascade that initiates and amplifies JA-mediated transcriptional output in tomato (Du *et al.*, 2017). The functional divergence of the two MYC2 TFs might be due to recruitment of different cofactors while regulating the transcription of pathogen-responsive genes (Du *et al.*, 2017). Nevertheless, MYC-mediated transcriptional regulation is a central theme of JA signaling in both Arabidopsis and tomato.

MED25 is an integrator of JA-mediated transcriptional activation

The COI1-dependent degradation of JAZ repressors leads to the 'de-repression' of MYC TFs (Chini *et al.*, 2007; Thines *et al.*, 2007; Yan *et al.*, 2007; Fonseca *et al.*, 2009; Sheard *et al.*, 2010). In turn, free MYC TFs form a transcriptional activation complex with the MED25 subunit of the plant Mediator to activate the expression of JA-responsive genes (Çevik *et al.*, 2012; Chen *et al.*, 2012; Zhang *et al.*, 2015; An *et al.*, 2017; Zhai *et al.*,

2017a). First, MED25 functionally interacts with both MYC2 and Pol II, thereby promoting PIC assembly during MYC2-dependent transcription of JA-responsive genes (Chen *et al.*, 2012). Second, MED25 physically recruits COI1 to MYC2 target promoters in the resting state, and facilitates COI1-dependent degradation of JAZ repressors in the presence of JA-Ile (An *et al.*, 2017). Third, MED25 physically and functionally interacts with HISTONE ACETYLTRANSFERASE OF THE CBP FAMILY1 (HAC1), which selectively regulates hormone-induced acetylation of lysine 9 (K9) in histone H3 (H3K9ac) at MYC2 target promoters (An *et al.*, 2017). These combined results indicate that MED25 acts as an integrative hub to coordinate the actions of multiple regulators during hormone-triggered MYC2 activation.

MED25 promotes PIC assembly on MYC2 target promoters

The MED25 subunit has not been identified in yeast, and the location of MED25 within the Mediator complex is unknown (Soutourina, 2018). However, human MED25 interacts extensively with different Tail subunits and gene-specific TFs, suggesting that MED25 is most likely associated with the Tail module of the Mediator complex (Fig. 1; Tsai *et al.*, 2014; Soutourina, 2018). Consistently, Arabidopsis MED25 also interacts with the Tail module MED16 subunit and several TFs (Elfving *et al.*, 2011; Ou *et al.*, 2011; Çevik *et al.*, 2012; Chen *et al.*, 2012; Yang *et al.*, 2014; Ito *et al.*, 2016). Arabidopsis MED25 contains a von Willebrand factor type A (vWF-A) domain ($MED25^{1–242}$), a non-conserved middle domain (MD, $MED25^{243–540}$), an activator-interacting domain (ACID, $MED25^{541–680}$), and a glutamine-rich domain (GD, $MED25^{681–836}$) (Fig. 2). The amino-terminal vWF-A domain, which is conserved in mammalian and plant MED25, is required for MED25 binding with the Mediator complex (Mittler *et al.*, 2003; Yang *et al.*, 2014). The MED25 ACID is essential for its interaction with different TFs and coactivators, such as MYC TFs (Çevik *et al.*, 2012; Chen *et al.*, 2012; Zhang *et al.*, 2015), APETALA2 (AP2)/ETHYLENE RESPONSE FACTOR (ERF) TFs (Ou *et al.*, 2011), and histone acetyltransferase HAC1 (An *et al.*, 2017). The C-terminal GD is necessary for MED25 interaction with the JA receptor COI1 and JAZ repressors (An *et al.*, 2017; Zhai *et al.*, 2017a).

MED25 was originally identified in Arabidopsis (previously designated as PFT1) as a factor of the phytochrome B (phyB) signaling pathway, which promotes flowering in response to shade (Cerdán and Chory, 2003). Biochemical purification of the Arabidopsis Mediator revealed that PFT1 was homologous to the MED25 subunit of the metazoan Mediator complex (Bäckström *et al.*, 2007). Early evidence that plant MED25 participates in JA signaling came from a study in Kazan's lab. They found that an Arabidopsis *pft1/med25* mutant exhibited reduced expression of JA-responsive genes and attenuated resistance in response to necrotrophic pathogen infection, suggesting that MED25 positively regulates JA-mediated plant defense (Kidd *et al.*, 2009). In addition, they found that a wheat homolog of MED25 could complement the defense and the developmental defects of the Arabidopsis *pft1/med25* mutant, suggesting that the function of MED25 in regulating JA signaling is conserved in higher plants (Kidd *et al.*, 2009). Further evidence for the role of MED25 in JA signaling came from our genetic analysis of the *bestatin resistant 6* (*ber6*) mutant, which exhibits attenuated sensitivity to JA-mediated root growth inhibition (Zheng *et al.*, 2006) and reduced expression of the two branches of JA-responsive genes (Chen *et al.*, 2012). Map-based cloning combined with complementation analysis revealed that the defective JA response phenotype of *ber6* resulted from a mutation in *MED25* (Chen *et al.*, 2012). Very recently, tomato MED25 has been implicated in the regulation of JA-mediated wounding and pathogen responses (Liu *et al.*, 2019), further confirming the conserved function of MED25 in higher plants.

The fundamental role of MED25 in JA signaling is to promote PIC assembly on MYC2 target promoters. In both Arabidopsis and tomato, MED25 physically interacts with MYC2 (Çevik *et al.*, 2012; Chen *et al.*, 2012; Liu *et al.*, 2019). The MED25 ACID and the MED25-interacting domain (MID) of MYC2 are necessary for MED25–MYC2 interactions (Chen *et al.*, 2012; Liu *et al.*, 2019). The MID is located on the transcriptional activation domain of MYC2 (Chen *et al.*, 2012; Liu *et al.*, 2019). MYC2 recruits MED25 to its target promoters in a JA-dependent manner, and in turn, MED25 recruits Pol II to the promoter of MYC2 targets (Chen *et al.*, 2012). Thus, during hormone-triggered transcription of JA-responsive genes, MED25 directly bridges communication between the gene-specific MYC2 TF and the Pol II general transcription machinery for PIC assembly (Chen *et al.*, 2012).

MED25 facilitates COI1-dependent de-repression of JA signaling

In addition to interacting with the master TF, MYC2, MED25 also interacts with the hormone receptor protein COI1 and a subset of JAZ repressors. The MED25 GD is necessary for its interaction with both COI1 and JAZ proteins (An *et al.*, 2017; Zhai *et al.*, 2017a). In the absence of active hormone, MYC2 forms a ternary complex together

Fig. 2. Schematic representation of the MED25 protein structure. ACID, activator-interacting domain; GD, glutamine-rich domain; MD, non-conserved middle domain; vWF-A, von Willebrand factor type A domain.

with MED25 and JAZ proteins (An *et al.*, 2017); JAZ repressors compete with MED25 for interaction with MYC TFs (Zhang *et al.*, 2015). The MYC2–JAZ interaction is relatively strong and the MYC2–MED25 interaction is relatively weak. MED25 has a relatively strong interaction with COI1 and brings COI1 to MYC2 target promoters. In the presence of active hormone, JA-Ile acts as molecular glue to promote the formation of the COI1–JAZ co-receptor complex, which leads to proteasome-dependent degradation of JAZ repressors. During this stage, MED25 contributes to JA-Ile-mediated promotion of the COI1–JAZ interaction and subsequent JAZ degradation (An *et al.*, 2017). Upon JAZ degradation, the MED25–COI1 interaction is weakened, whereas the MED25–MYC2 interaction is enhanced, which favors MYC2-mediated transcription of JA-responsive genes (An *et al.*, 2017). These results indicate that MED25 has an important role in the dynamic changes of JA signaling from the repression stage to the de-repression stage (Fig. 3).

The action mode of plant MED25 in regulating JA signaling exhibits a striking analogy to that of metazoan MED25, which participates in ligand-dependent interactions with several nuclear receptors (NRs) (Malik and Roeder, 2010; Fondell, 2013; Poss *et al.*, 2013; Allen and Taatjes, 2015). Mammalian NRs are ligand-activated TFs that contain a conserved DNA-binding domain and a ligand-binding domain. After binding to hormone, NRs undergo significant conformational changes that create hydrophobic binding surfaces suitable for the interaction with MED25 (Malik and Roeder, 2010; Fondell, 2013; Poss *et al.*, 2013; Allen and Taatjes, 2015). The COI1–JAZ–MYC2 module in JA signaling resembles the metazoan NR system with respect to its interactions with MED25. JA-Ile-triggered COI1-dependent degradation of JAZ proteins releases the interaction surface of MYC2 with MED25, which resembles the hormone-triggered conformational changes in NRs (An *et al.*, 2017; Zhai *et al.*, 2017a). These studies reveal that plants and animals have evolved distinct, but largely similar, mechanisms for NR activation at the level of transcriptional regulation.

MED25 cooperates with HAC1 to activate MYC2-mediated transcription

During the activation stage, MED25 directly interacts with and recruits HISTONE ACETYLTRANSFERASE1 (HAC1), an evolutionarily conserved histone modification enzyme, to MYC2 target promoters (An *et al.*, 2017). MED25 interacts with HAC1 via its ACID, which also is required for the MED25–MYC2 interaction (Chen *et al.*, 2012; An *et al.*, 2017), suggesting that the ACID is important for the MED25 activation function (Fig. 2). HAC1 selectively regulates H3K9ac at MYC2 target promoters, which favors gene activation (An *et al.*, 2017). This action mode of MED25 also is conserved between Arabidopsis and human. Human MED25 cooperates with CREB-binding protein, which is the human ortholog of the Arabidopsis HAC1, in the activation of retinoic acid receptor-mediated gene expression (Lee *et al.*, 2007).

These combined results reveal that MED25 is involved in the assembly of a MYC2–MED25 functional transcription complex, which acts as an integrative hub that coordinates the actions of multiple regulators during hormone-triggered MYC2 activation (Fig. 3).

The MYC2–MED25 functional complex regulates the termination of JA signaling

Our recent study identified an additional and unexpected function of the MYC2–MED25 complex in regulating the

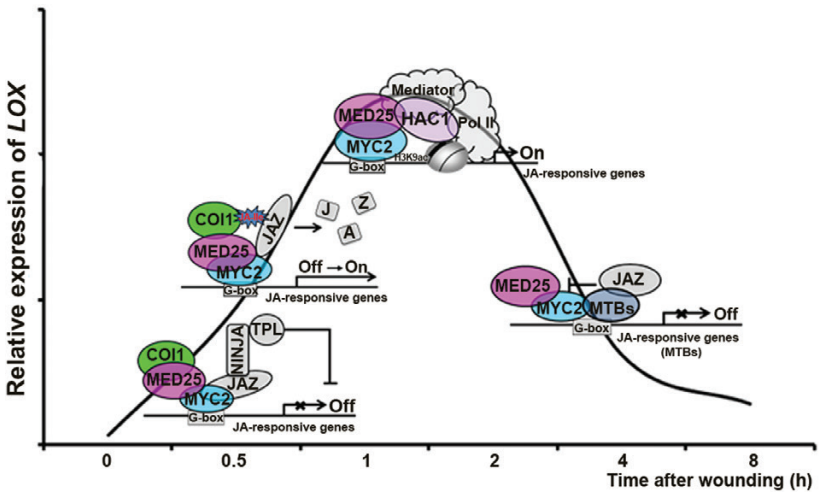

Fig. 3. A model of MED25 regulation of different stages of JA signaling. In response to wounding or other stimulus, MED25 coordinates the actions of multiple components of JA signaling to regulate the expression of JA-responsive genes such as *LOX*. In the absence of stimulus, MED25 interacts with COI1 at the *LOX* promoter, whereas JAZ proteins interact with MYC2 and repress MYC2 activity. The expression level of *LOX* is low. In response to stimulus, MED25 promotes JA-triggered interaction of COI1 and JAZ proteins and subsequent degradation of JAZ repressors, which released the activity of MYC2. Then, MED25 interacts with MYC2 and recruits the coactivator HAC1 to activate *LOX* expression. The MYC2–MED25 functional complex activates the expression of *MTB*s, which form an autoregulatory negative feedback circuit to terminate JA signaling and thus reduce the *LOX* expression level. COI1, CORONATINE INSENSITIVE 1; JA, jasmonate; JA-Ile, jasmonoyl-isoleucine; JAZ, jasmonate-ZIM domain; *LOX*, *LIPOXYGENASE*; MED25, Mediator subunit 25; MTB, MYC2-TARGETED BHLH; NINJA, novel interactor of JAZ; TPL, TOPLESS.

termination of JA signaling in tomato (Liu *et al.*, 2019). MYC2 and MED25 activate the expression of three bHLH TFs, MYC2-TARGETED BHLH 1 (MTB1), MTB2, and MTB3. MTB proteins negatively regulate JA signaling via their antagonistic effects on the functionality of the MYC2–MED25 transcriptional activation complex. MTB proteins impair the formation of the MYC2–MED25 complex and compete with MYC2 in binding to its target gene promoters. Therefore, MYC2–MED25 and MTB proteins form an autoregulatory negative feedback circuit to terminate JA signaling in a highly organized manner (Liu *et al.*, 2019). Considering that the MYC2–MED25 functional complex has a central role in the initiation and amplification of JA-mediated transcriptional responses (Chen *et al.*, 2012; An *et al.*, 2017; Du *et al.*, 2017), the formation of the MYC2–MTB feedback loop is already preprogrammed during the induction phase of JA signaling. Thus, in addition to controlling the initiation and amplification of JA-mediated transcriptional responses, the MYC2–MED25 functional complex also executes intrinsic termination of JA-mediated defense responses.

Phylogenetic analysis revealed that MTB proteins are homologs of the Arabidopsis JASMONATE-ASSOCIATED MYC2-LIKE (JAM) proteins (Nakata *et al.*, 2013; Sasaki-Sekimoto *et al.*, 2013; Song *et al.*, 2013; Fonseca *et al.*, 2014; Goossens *et al.*, 2017; Liu *et al.*, 2019). Similarly, JAM proteins play a negative role in JA-mediated defense responses by competing with the DNA-binding capacity of Arabidopsis MYC2 (Nakata *et al.*, 2013; Sasaki-Sekimoto *et al.*, 2013; Song *et al.*, 2013; Fonseca *et al.*, 2014). However, in tomato, MTB1 physically interacts with MYC2 and competitively inhibits the interaction of MYC2 and MED25; because the MYC2–MED25 complex is essential for MYC2-dependent PIC formation, the interference of MTB1 determines the transcriptional output of the MYC2–MED25 transcriptional activation complex (Chen *et al.*, 2012; An *et al.*, 2017; Du *et al.*, 2017; Liu *et al.*, 2019). In this regard, the action mechanism of MTB proteins is different from the Arabidopsis JAM proteins, which did not show physical interaction with AtMYC2 in yeast two-hybrid and coimmunoprecipitation assays (Song *et al.*, 2013; Fonseca *et al.*, 2014).

MED25 interacts with intermediate TFs of JA signaling

MYC2 is a master regulator of JA signaling and targets groups of intermediate TFs, which directly regulate the JA-induced transcription of late defense genes (Bu *et al.*, 2008; Zheng *et al.*, 2012; Zhai *et al.*, 2013; Du *et al.*, 2017). MED25 also interacts with these intermediate TFs, such as the AP2/ERF TFs OCTADECANOID-RESPONSIVE ARABIDOPSIS AP2/ERF59 (ORA59) and ERF1 (Ou *et al.*, 2011; Çevik *et al.*, 2012). The MED25 ACID and the transcription activation domain (TAD) of these ERFs are necessary for their interactions (Çevik *et al.*, 2012). Transcriptional activation experiments indicate that ORA59- and ERF1-dependent activation of pathogen defense genes such as *PLANT DEFENSIN1.2* (*PDF1.2*) requires a functional MED25. These studies implicate an extensive function of MED25 in regulating JA-mediated transcription. First, MYC2 recruits MED25 to activate the expression of the intermediate TFs; further, the intermediate TFs also recruit MED25 to activate the expression of downstream plant defense genes. MED25 acts as a major player in the hierarchical transcriptional cascade that initiates and amplifies transcriptional output. MED25 uses its ACID to interact with the MID (or TAD) of these different TFs, suggesting that interacting with MED25 is an important part of TF-mediated transcriptional activation in JA signaling.

Other Mediator subunits in JA signaling

Several other Mediator subunits have been reported to participate in JA-mediated plant immunity, including MED8, MED16, MED18, and CDK8 (Kidd *et al.*, 2009; Wathugala *et al.*, 2012; Zhang *et al.*, 2012; Lai *et al.*, 2014; Zhu *et al.*, 2014; Li *et al.*, 2018).

A mutation in the Arabidopsis *MED8* gene results in susceptibility to *Alternaria brassicicola* but resistance to *Fusarium oxysporum*, suggesting a role for MED8 in JA-dependent plant immunity (Kidd *et al.*, 2009). The *med8 med25* double mutant exhibits an additive effect in the phenotypic deficiency relative to the single mutants, suggesting that MED8 and MED25 probably affect JA-mediated plant immunity via independent and additive mechanisms (Kidd *et al.*, 2009). A recent study reported that MED8 regulates plant immunity to *Botrytis cinerea* by interacting with the FAMA TF, which was previously shown to control the final proliferation/differentiation switch during stomatal development (Li *et al.*, 2018). The *fama* mutant exhibits increased susceptibility to *B. cinerea* infection and reduced defense-responsive gene expression. Genetic analyses of MED8 and FAMA suggest that FAMA-regulated plant defense against *B. cinerea* depends on MED8 function. FAMA recruits MED8 to the *ORA59* promoter and activates *ORA59* expression, which in turn regulates the expression of downstream plant defense genes (Li *et al.*, 2018).

The role of Arabidopsis MED16 in regulating JA/ethylene (ET)-mediated plant immunity has been reported recently (Wathugala *et al.*, 2012; Zhang *et al.*, 2012; Wang *et al.*, 2015). Mutants of *MED16* are more susceptible to *Sclerotinia sclerotiorum* than mutants of 13 other Mediator subunits, and *med16* is also more susceptible to *S. sclerotiorum* than *coi1-1*, which is the most susceptible mutant reported so far (Wang *et al.*, 2015). Hence, MED16 is an important regulator of basal resistance against *S. sclerotiorum*. Furthermore, ET-induced suppression of JA-activated wound responses is compromised in *med16*, suggesting a role for MED16 in JA–ET cross talk (Wang *et al.*, 2015). MED16 also physically associated with TF WRKY33 to regulate the transcription of *PDF1.2* and *ORA59*, indicating that MED16 regulates resistance to *S. sclerotiorum* by governing both JA/ET-mediated and WRKY33-activated defense signaling in Arabidopsis (Wang *et al.*, 2015). MED16 not only positively regulates the expression of JA-responsive genes but also positively regulates the expression of salicylic acid (SA)-responsive genes (Wathugala *et al.*, 2012; Zhang *et al.*, 2012). It is generally believed that the JA and SA signaling pathways antagonize each other (Kunkel and Brooks, 2002). Recently, it has been found that MED16 and the other two-tail module subunits, MED14 and MED15, are required for both SA- and ET-promoted inhibition of JA-mediated wound signaling. These results indicate that MED16 and some other Mediator subunits not only relay

defense signaling from the SA and JA/ET pathways to the Pol II transcription machinery, but also fine-tune defense-related transcriptional changes (Wang *et al.*, 2016). Another interesting point is that MED25 could interact with MED16 via its vWF-A domain (Çevik *et al.*, 2012). Thus, it will be crucial to elucidate the functional relevance of these two subunits in regulating JA signaling or other signal transduction pathways.

Arabidopsis MED18 is another subunit that contributes to plant immunity against necrotrophic pathogens (Lai *et al.*, 2014). Mutants of *MED18* exhibit enhanced susceptibility to *B. cinerea*, suggesting that MED18 positively regulates *B. cinerea*-induced plant immunity. However, the expression of *PDF1.2* induced by *B. cinerea* or MeJA was increased rather than decreased in the *med18* mutant, indicating that MED18 might function in a JA-independent manner (Lai *et al.*, 2014). MED18 interacts with the YIN YANG1 (YY1) TF, which acts as a transcriptional repressor. MED18 positively regulates the function of YY1 to suppress the transcription of thioredoxin (*TRX-h5*, *LIV1*) and glutaredoxin (*GRXS13*, *GRX480*). Genetic data indicate that elevated expression of *GRX* and *TRX* contributes to the enhanced susceptibility of *med18* and *yy1* mutants to fungal infection (Lai *et al.*, 2014). Another study reported that MED18 and MED20 form a subdomain within Mediator that controls the balance of JA and SA signaling pathways (Fallath *et al.*, 2017). In that study, MED18 and MED20 conferred susceptibility to *F. oxysporum*. In *F. oxysporum*-infected *med18* and *med20*, the expression of JA-responsive genes was significantly reduced, whereas the expression of SA-associated genes and several genes associated with reactive oxygen species (ROS) production was upregulated. It is possible that both JA and SA signaling is channeled through the Mediator complex via MED18 and MED20; alternatively, misregulation of the JA pathway in *med18* and *med20* mutants may lead to defects in ROS production and tolerance (Fallath *et al.*, 2017). Consistent with the role of MED18 in regulating the balance of JA and SA signaling pathways, MED18 is recruited by the histone acetyltransferase HOOKLESS1 to the *WRKY33* promoter, thereby increasing *WRKY33* expression (Liao *et al.*, 2016). It is believed that WRKY33 has an important role in regulating JA–SA crosstalk and redox homeostasis (Birkenbihl *et al.*, 2012). These studies indicate that MED18 regulates plant immunity in both JA-independent and JA-dependent manners.

The CDK8 module is involved in JA-mediated plant immunity (Zhu *et al.*, 2014). The *cdk8* mutant exhibits enhanced resistance to *B. cinerea* infection but susceptibility to *A. brassicicola* infection. However, both *B. cinerea*- and *A. brassicicola*-induced *PDF1.2* expression is reduced in the *cdk8* mutant, which is similar to the MeJA-induced expression levels of *PDF1.2* in the *cdk8* mutant. CDK8 interacts with MED25 and is required for ERF1- and ORA59-dependent activation of *PDF1.2* expression, indicating that CDK8 regulates plant immunity through a JA-dependent pathway (Zhu *et al.*, 2014). CDK8 regulates resistance to *A. brassicicola* through direct transcriptional regulation of *AGMATINE COUMAROYLTRANSFERASE* (*AACT1*), which is critical for the biosynthesis of hydroxycinnamic acid amides, secondary metabolites that function in fungal resistance (Zhu *et al.*, 2014). CDK8 negatively regulates *B. cinerea*-induced plant immunity by interacting with WAX INDUCER1 (WIN1), an ERF family protein that regulates cuticular wax biosynthesis. Genetic evidence supports the notion that the resistance to *B. cinerea* in the *cdk8* mutant is due to the altered cuticle profile linked to the loss of CDK8 functions (Zhu *et al.*, 2014). The kinase activity is necessary for CDK8 regulation of *A. brassicicola*-induced plant immunity, but not for regulation of *B. cinerea*-induced plant immunity (Zhu *et al.*, 2014). Two other kinase module mutants, *med12* and *med13*, exhibit disease responses and increased cuticle permeability similar to that of the *cdk8* mutant, revealing the common functions and structural conservation of the kinase module (Zhu *et al.*, 2014).

Conclusions and perspectives

Multiple Mediator subunits are important for JA-dependent plant immunity. MED25 is the most well-studied Mediator subunit; it has critical roles in different stages of JA signaling. MED25 acts as a master coordinator to integrate the actions of the hormone receptor COI1, the master TF, MYC2, and its coactivator, HAC1, into a concerted transcriptional program. Future structural studies will help to fully identify the mechanism by which MED25 dynamically changes its interaction with different regulators to spatiotemporally regulate the transcriptional output. In addition to JA, the main receptors for several other plant hormones are localized in the nucleus and directly linked to hormone-regulated gene transcription. An important future direction will be to determine whether the action mode of MED25 in regulating JA signaling can be extended to other hormones whose receptors are localized in the nucleus. If so, it will be crucial to identify the mechanisms that regulate the general and context-specific functions of Mediator, and especially to determine how a single multiprotein complex can perform so many diverse tasks.

Several other Mediator subunits, including MED8, MED16, MED18, and CDK8, have been identified as important players in JA-dependent plant immunity. However, compared with MED25, the mechanisms of these subunits in regulating JA signaling remain elusive. Considering that MED8, MED16, and CDK8 physically interact with MED25, it is possible that these Mediator subunits execute their functions in JA signaling by cooperating with MED25. Alternatively, these Mediator subunits could regulate JA-mediated plant immunity by cooperating with new players in JA signaling.

Plant Mediator is a large complex that currently comprises more than 33 subunits. A more comprehensive screen could identify additional Mediator subunits that function in the JA signaling pathway. Future studies of the intact plant Mediator complex will shed new light on our understanding of plant Mediator and its role in regulating the JA signaling pathway.

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