Chapter 1
Role of Plant Mediator Complex in Stress Response

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Abstract Class II gene loci of eukaryotes are transcribed by RNA Polymerase II, which functions in coordination with several other proteins like transcription factors, general transcription factors, and cofactors. Recently, Mediator complex, a multi-subunit, megadalton size protein complex has gained lots of attention as an important component of RNA pol II transcriptional machinery because of its essentiality in the regulation of most of the class II genes. Like yeast and other metazoans, plants also possess the Mediator complex across the kingdom, and its isolation and subunit analyses have been reported from the model plant, *Arabidopsis*. Recent times have experienced a flurry of scientific papers containing the functional information of individual Mediator subunits in plants, although many were reported earlier without consideration of their association with the Mediator complex. Among its diverse functional aspects, several reports have established the Mediator complex as an important integrative hub of different biotic and abiotic stress signaling pathways, which have been discussed in this chapter from the functional genomics perspectives. Although reports are emerging in support of its inclusion as a component of the basic transcriptional machinery, the gene selective roles of the individual Mediator subunits are proven and indisputably accepted.

Keywords Transcription • RNA Polymerase II • Mediator complex • Mediator subunit • Biotic stress • Abiotic stress • Defense signaling • *Arabidopsis* • Rice

Abbreviations

BR	Brassinosteriod
ChIP	Chromatin immunoprecipitation
JA	Jasmonic acid
LC-MS/MS	Liquid chromatography-mass spectrometry
MED	Mediator
MudPIT	Multidimensional protein identification technology

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RNAP II	RNA Polymerase II
SA	Salicylic acid
TAP	Tandem affinity purification

1.1 Introduction

The process of transcription in eukaryotic organism is a highly orchestrated and immensely complex phenomenon and mediated by a plethora of proteins with the prime role played by RNA Polymerase II (RNAP II) (Lee and Young 2000). RNAP II with the basal transcription factors forms the heart of the transcription machinery. Over the time, several cofactors have been discovered, which offer the basic transcriptional machinery diverse regulatory avenues in terms of controlling gene expression (Woychik and Hampsey 2002). Among these cofactors, Mediator, a multi-subunit protein complex, has been proved to be quintessential in RNAP II-mediated gene expression (Myers and Kornberg 2000; Conaway et al. 2005; Kornberg 2005; Malik and Roeder 2005). Mediator complex, an ensemble of around 25–30 Mediator subunits, could be imagined as a bridge connecting the basic transcription machinery with the *cis*-element bound transcription factors (Fig. 1.1). However, Mediator does not act simply as a scaffold protein, rather as a subtle and complex modulator of gene expression during transcription. Although far from a clear and detailed understanding, the binding of transactivator or repressor with the Mediator complex might bring about certain conformational changes, which are transmitted to the RNAP II resulting into the desired changes in the level of gene expression. Apart from transcription factors (transactivator and repressor), Mediator complex also acts as docking site for several other proteins, which elicit their regulatory roles through Mediator-induced structural changes on RNAP II machinery (Meyer et al. 2010; Taatjes 2010). Since the discovery of plant Mediator in 2007, its subunits have been implicated in several biological processes. Recently, role of Mediator in growth and development was reviewed (Kidd et al. 2011). Here, in this chapter, we discuss the current status of Mediator research in plants from functional genomics perspectives with special emphasis on its role in biotic and abiotic stresses.

1.2 Discovery of Mediator Complex

Until now, Mediator complex has only been reported in eukaryotes. The complex was first isolated from the yeast as a factor required for enhanced transcription in a cell-free, in vitro transcriptional system, composed of RNAP II and general transcription factors in *Saccharomyces cerevisiae* (Kim et al. 1994; Myers et al. 1998) as well as in *Saccharomyces pombe* (Spahr et al. 2000). Later, the complex was isolated from almost all the eukaryotic organisms ranging from human (Fondell et al. 1996; Ito et al. 1999), *Drosophila* (Park et al. 2001), *Caenorhabditis* (Park et al. 2001) to even plant (Backstrom et al. 2007). The yeast Mediator complex was

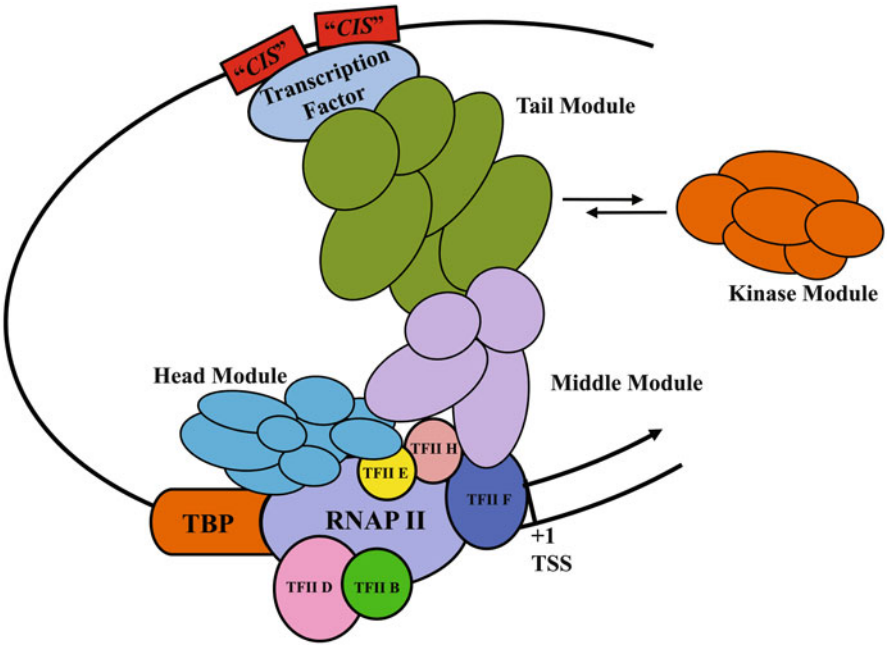

Fig. 1.1 Modular structure of Mediator complex and its interaction with transcriptional machinery. Head, Middle, and Tail modules form the Mediator complex along with a separable kinase module. Generally, the tail module interacts with the *cis*-element bound transcription factors, whereas the Head and Middle modules bind to the components of the basic transcriptional machinery of class II genes. In response to different signals, the Mediator complex helps the transcription factors transmit the messages encrypted in the regulatory DNA elements and engages the transcription apparatus to the promoter of the transcribing genes. **RNAP II**: RNA Polymerase II, **TBP**: TATA-box binding protein, **TFII**: transcription factor II, **TSS**: transcription start site

isolated using the principles of traditional biochemistry, i.e., fractionation of total protein through a series of chromatography based on different principles, and then immunoprecipitating the Mediator complex from the Mediator enriched chromatographic fractions. Using similar techniques, the first biochemical purification of Mediator complex among plants was reported from *Arabidopsis* (Backstrom et al. 2007). After protein fractionation by two different chromatographic techniques, the final step was performed by immunoprecipitation with antibody raised against a Mediator subunit, AtMED6. Apart from *Arabidopsis*, the bioinformatics analyses encompassing 16 plant species across the entire plant kingdom revealed the ubiquitous presence of this important regulatory complex in every plant groups included in the study (Bourbon 2008; Mathur et al. 2011). The presence of almost all the fungal/metazoan Mediator subunits in one or other plant species using HMM (Hidden Markov Model) profile of Mediator subunits was predicted (Bourbon 2008; Mathur et al. 2011). However, some plant-specific Mediator subunits are also reported. Thus, it seems that Mediator subunits have emerged at the very early stages of eukaryotic evolution and some extra subunit might have been added or lost in different lineages in course of evolution (Conaway and Conaway 2011).

1.3 Functions of Mediator Complex

RNAP II along with the components of preinitiation complex (PIC) is the minimum requirement to start any successful transcription event at the initiator region of a gene. In order to achieve increased or activated level of transcription, the requirement of Mediator complex has been proved quintessential almost for every gene of eukaryotes (Myers and Kornberg 2000). In fact, Mediator complex was first discovered as an entity required for enhanced transcription of an in vitro transcription system, which included RNAP II and other accessory factors (Kim et al. 1994). Very recently, critical role of Mediator was explained in the function of super-enhancers in increased level of gene expression to establish and maintain cell identity (Loven et al. 2013; Whyte et al. 2013). However, the inhibitory role of Mediator complex in the repression of gene functions has also been reported and is discussed in a later section. But, the controversial aspect of Mediator function as a cofactor or a basal transcription factor is still debatable (Taatjes 2010). There are evidences, which support the dual role of Mediator function, i.e., as a part of the basal transcriptional machinery as well as a selective regulator of gene function. The Mediator complex can support basal level of transcription as evidenced by its significant roles in the assembly of PIC and in the initiation of transcription (Mittler et al. 2001; Baek et al. 2002). On the other hand, Mediator complex enhances the RNAP II recruitment to the protein coding genes and provides stability to the transcription machinery assembled at the promoter region (Cantin et al. 2003; Baek et al. 2006). The repression of almost all the protein coding genes in yeast conditional mutant *MED17* corroborates the essentiality of Mediator complex in RNAP II-mediated transcription (Thompson and Young 1995; Ansari et al. 2009). In plants, the essentiality of Mediator complex in RNAP II-mediated gene expression became evident when 84 % of downregulated genes in *nrpb2–3* (second largest subunit of RNAP II) and *MED20A* mutant *Arabidopsis* plants were found to be common (Kim et al. 2011). Thus, literature evidences suggest that the Mediator complex is as important as the RNAP II and could be regarded as an integral component of the basal transcriptional machinery in eukaryotes. Nevertheless, reports of severe specific functional abnormalities, be it in growth and development or in the response to biotic and abiotic stresses, when a particular Mediator subunit gene is deleted, are proving that Mediator subunits do possess specific functions (Kidd et al. 2011). Although initial emphasis was laid in the crucial role of Mediator in the assembly of transcription initiation complex (Cantin et al. 2003; Johnson and Carey 2003; Wang et al. 2005), the more recent reports suggest its function in almost every steps of transcription such as promoter escape (Malik et al. 2007; Cheng et al. 2012; Jishage et al. 2012), elongation (Takahashi et al. 2011; Conaway and Conaway 2013; Galbraith et al. 2013), termination (Mukundan and Ansari 2011, 2013), and other related RNA-processing events (Kim et al. 2011; Huang et al. 2012; Oya et al. 2013). In last few years, Mediator has also been implicated in epigenetic modification of chromatin leading to changes in gene expression (Ding et al. 2008; Kagey et al. 2010; Zhu et al. 2011; Fukasawa et al. 2012; Liu and Myers 2012; Tsutsui et al. 2013; Zhang et al. 2013a; Lai et al. 2013).

1.4 Modular Organization and Composition of Mediator Complex in Plants

Mediator is a multi-protein complex, which is composed of several subunits. The number of subunits varies according to the species. The yeast Mediator complex is composed of 25 subunits whereas the metazoans possess 25–30 Mediator subunits (Boube et al. 2002; Bourbon 2008). On an average, the plants contain around 30–35 Mediator subunits (Backstrom et al. 2007; Mathur et al. 2011; Pasrija and Thakur 2012). However, expansion of some subunits has also been observed in plants. Apart from the orthologs of the yeast Mediator subunits, the plants also contain a unique set of Mediator subunits, which are not present either in yeast or in metazoans. Plants are sessile organisms and the Mediator complex assisted gene regulation seems to be more complicated in plants. This could be corroborated by the fact that plants possess increased number of transcription factors (Riechmann et al. 2000; Riechmann and Ratcliffe 2000). As the Mediator complex elicits its gene regulatory action by forging a bridge between the *cis*-element bound transcription factors and the RNAP II, the increased number of Mediator subunits might have evolved to interact with increased number of transcription factors in plants. Another important discovery is the presence of increased number of paralogs of some Mediator subunits in plants. Certain species of yeast like *Candida glabrata* and the metazoans do possess paralogs of MED15 and kinase module genes, respectively. But the possession of nine paralogs of MED15 in *Populus trichocarpa* and quite a few in other plant species is a distinguishing feature for the plant Mediator complex in general (Mathur et al. 2011; Pasrija and Thakur 2012). At present, the presence of all the paralogs of a particular Mediator subunit at the same time has not been validated. However, from the functional perspective, the spatial and temporal regulation of the expression level of different paralogs of a particular Mediator subunit has been reported (Mathur et al. 2011; Thakur et al. 2013). The rice *OsMED31_1* exhibits pronounced expression level in the leaves whereas *OsMED31_2* exhibits higher expression level only during early stages of panicle development. In *Arabidopsis*, there is only one *AtMED31* gene and it shows higher expression in reproductive organs including flower and seed. In rice, *OsMED15_1* showed seed preferential expression whereas *OsMED15_2* is expressed at similar level in vegetative and reproductive tissues (Thakur et al. 2013). Thus, the presence of multiple paralogs and the spatiotemporal regulation of Mediator subunits make the Mediator structure more dynamic depending upon the external milieu and the growth and developmental phases of the plants. Mediator subunits have been grouped into four modules according to the biochemical and structural evidences obtained from the 3D structure of the yeast Mediator complex (Asturias et al. 1999; Dotson et al. 2000; Chadick and Asturias 2005) assembled from the EM structure of the purified yeast Mediator complex. The following is a brief account of the Mediator complex subunits according to their arrangement in specific modules.

1.4.1 Head Module

The head module consists of MED6, MED8, MED11, MED17, MED18, MED19, MED20, MED22, MED28, and MED30. The head module subunits can establish direct contacts with RNAP II and with other components of the basic transcriptional machinery and, alone could stimulate transcription rate over the basal rate, but it does not support activator-dependent transcription (Takagi et al. 2006; Cai et al. 2010). Disruption of the head module leads to the dissociation of the Mediator complex from the promoter of the transcribing genes (Lariviere et al. 2006). Apart from the direct interaction of head module with the RNAP II (Soutourina et al. 2011), it also interacts with the components of the basic transcriptional machinery. The interaction between head module and TFIIH is probably mediated by an interface created by MED11/MED22 heterodimer of the head module, whereas the interaction with TBP is mainly through MED8 (Kim et al. 1994; Lariviere et al. 2006; Imasaki et al. 2011; Seizl et al. 2011). In yeast, MED17 performs the task of maintaining a link with the middle module through its interaction with the MED21 from the middle module. Similarly, MED17 also interacts with the reversible kinase module via its interaction with CDK8 (Guglielmi et al. 2004). MED17 is the most important Mediator subunit of the head module, as mutation in this gene in yeast affects the expression of most of the protein coding genes just like the deleterious effects caused by mutations in RPB1 subunit of RNAP II (Thompson and Young 1995). Given the fact that head module subunits establish direct contacts with the components of the RNAP II machinery and form the core of the Mediator complex, the head module subunits are thought to be the most conserved Mediator subunits of the complex. In general, structural analysis of the Mediator complex has been impeded by the low expressibility of the Mediator subunit proteins and by the inherent difficulties in the in vitro assembly of the Mediator complex. However, assembly of the head module has become feasible with the recent advances in heterologous protein expression technology, and a low resolution, EM structure of the head module has already been reported (Cai et al. 2010). More recently, a seven subunit partial backbone structure of the head module has been resolved with the help of X-ray crystallography (Imasaki et al. 2011). Only a limited number of head module Mediator subunits have been addressed functionally in plants. Among the significant ones, AtMED8 has been implicated in flowering and root hair biogenesis (Kidd et al. 2009; Sundaravelpandian et al. 2013) whereas AtMED17, 18, and 20 were found to be involved in siRNA and non-coding RNA production (Kim et al. 2011).

1.4.2 Middle Module

The Mediator subunits, MED4, MED7, MED9, MED10, MED21, and MED31 form the middle module. Although MED1 is an important middle module constituent in yeast and metazoans as it regulates many important genes by binding to their respective transcription factors, so far bioinformatics analyses from different

studies in different organisms have never been able to find its orthologs in plants except in a distantly related red algae (Ito and Roeder 2001; Bourbon 2008; Mathur et al. 2011). The apparent absence of plant MED1 suggests that either MED1 has been lost in course of evolution or its function might have been acquired by some other Mediator subunit. Middle module subunits, MED1 and MED10, interact with the tail module subunit, MED14, which happens to be at the interface of middle and the tail modules (Li et al. 1995; Lee et al. 1999; Guglielmi et al. 2004). The interaction between MED21 and MED3 also strengthens the connection between middle and tail module (Guglielmi et al. 2004). A combination of biomolecular techniques including small angle X-ray scattering revealed that a high degree of intrinsic flexibility and the elongated shape are the characteristic features of the middle module (Koschubs et al. 2010). MED4 and MED7 are probably the most important middle module subunits as they form three heterodimeric subcomplexes, Med7N/21, Med7C/31, and Med4/9 (Koschubs et al. 2010). Large-scale structural changes in the Mediator subunits are effected by a flexible hinge formed by MED7 and MED21 in the middle module (Baumli et al. 2005). The Med7C/31 is characterized by a novel conserved fold and is essential for activator-dependent transcription (Koschubs et al. 2009). Most of the middle module subunits are conserved in plants too, except a "poly Pro" region in AtMED31C, followed by a nuclear localization signal, which is absent in yeast and human (Mathur et al. 2011). Except AtMED21 whose involvement in pathogenesis is discussed in latter section, function of no other plant Mediator subunits from the middle module has been characterized.

1.4.3 Tail Module

The tail module is arguably the least conserved and functionally most significant Mediator module. The subunits from the tail module maintain direct contacts with the *cis*-element bound transcription factors and accordingly recruit the DNA bound Mediator complex to the RNAP II machinery. The module includes MED2/29/32, MED3/27, MED5/24/33, MED14, MED15, MED16, and MED23. Structural analysis revealed that MED14 occurs at the interface of middle and tail module. In yeast, heterodimer of MED2 and MED3 interacts with MED15 to form a triad (Zhang et al. 2004). Similarity analyses among the tail module subunits revealed that MED2 and MED3 of plants, are more similar to human as compared to yeasts (Mathur et al. 2011). Size of MED15 in plants is bigger than that of fungi and animals, though its amino terminal KIX domain is conserved in them (Thakur et al. 2013). Functionally, the KIX domain seems to be very important domain of MED15 proteins and so, structurally the most well-investigated one (Thakur et al. 2008, 2009, 2013, 2014, Lariviere et al. 2012). A myriad of transcription factors have been reported to interact with MED15 via KIX domain regulating diverse pathways in different organisms (Malik and Roeder 2005; Thakur et al. 2014). Despite poor structural similarity except in the N-terminal transcription factor interacting KIX domain among the MED15 proteins, the crucial amino acid residues of the KIX domain are surprisingly conserved among human, yeast, and *Arabidopsis*, three

important model organisms from three different kingdoms (Mathur et al. 2011). The importance of the tail module subunits in the transcriptional regulation could be well imagined by the fact that the maximum numbers of subunits, whose functions are elucidated, belong to this module. Although no interaction has been reported among them, an intriguing hypothesis regarding the formation of a triad consisting of MED15, MED16, and MED14 in plant defense signaling has been recently put forward (Zhang et al. 2013b). Apart from its gene-specific role, the tail module has recently been implicated in many different aspects of transcriptional regulations as a separate entity. The TATA-box containing and SAGA-regulated genes are much more dependent on the tail module for their transcription as compared to the TFIID-dependent gene expression (Ansari et al. 2012; Ansari and Morse 2012). Interestingly, a role of Mediator tail module in the maintenance of heterochromatin region of chromosome telomere has also been reported (Peng and Zhou 2012).

1.4.4 Kinase or CDK8 Module

The stimulatory role of Mediator complex in gene regulation has become complicated with the discovery of kinase module, which can reversibly associate with the core part of the Mediator complex. The kinase module is composed of MED12, MED13, Cyclin-Dependent Protein Kinase 8 (CDK8), and Cyclin C (CycC). All the kinase module subunits were discovered in yeasts in a screen for suppressor of RNAP II CTD mutation (Liao et al. 1995). Basically, the association of kinase module with the core complex inhibits its interaction with the RNAP II machinery (Akoulitchev et al. 2000; Knuesel et al. 2009a). Also, initial genetic studies revealed negative effect of this module on a subset of genes (Holstege et al. 1998; Samuelsen et al. 2003). However, recent reports contradicted these observations and showed the positive regulation of some genes by the Mediator complex, which had the kinase module associated with it (Donner et al. 2007, 2010; Belakavadi and Fondell 2010). Thus, the CDK8 kinase module can modulate the transcription factor activity in both positive and negative way (Taatjes 2010). Among the regulators of CDK8 kinase activity, MED12 has been established as the most significant one as CDK8 requires MED12 for its kinase activity (Knuesel et al. 2009a). Moreover, MED12 might directly interact with transcription factors for recruiting CDK8 to the chromosomal loci. MED13 helps in association and recruitment of kinase module to the Mediator complex via its interaction with the tail module (Knuesel et al. 2009a). Mediator also regulates kinase activity of CDK8 on chromatin by restricting its association with it (Knuesel et al. 2009b). The bioinformatics analyses have revealed the presence of kinase module in almost all the plant groups analyzed. Like in mammals and other metazoans, paralogs of the kinase module subunits have also been discovered in plants, which raise the possibility of combinatorial control of Mediator function in plants too. Since the kinase module bound Mediator complex accounts for only a small fraction of the total Mediator, the absence of kinase module

subunits in the first-ever Mediator complex purified from *Arabidopsis* is not so surprising (Backstrom et al. 2007). Among the four members of the kinase module, CDK8, Cyclin C, and MED12 have not been found to interact with any other subunit of the Mediator complex (Guglielmi et al. 2004). However, a comprehensive analysis in different organisms needs to be done before making any conclusion.

1.4.5 Plant-Specific and Module-Unassigned Mediator Subunits

Positions of MED25 and MED26 have not been understood yet. Similarly, the plant-specific Mediator subunits, MED34, MED35, MED36, and MED37, have not been assigned any module (Backstrom et al. 2007). Other two plant-specific Mediator subunits, MED32 and MED33, identified during biochemical purification of Mediator complex from *Arabidopsis*, have reported to be apparent homologs of MED2 and MED5, respectively (Mathur et al. 2011). MED26, which remained unreported for a long time from any plant species, has been reported from all the plant species using a rigorous HMM search except algal group (Mathur et al. 2011). Most of these MED26 proteins have been described as transcriptional elongation factors especially in rice and *Arabidopsis* databases, probably because of the presence of TFIIS helical bundle in them (Mathur et al. 2011). This helical bundle is a characteristic feature of RNAP II elongation factors, TFIIS and Elongin A. Thus, MED26 of the Mediator complex contributes to the elongation step of RNAP II-mediated transcriptional event, which is unusual as compared to the canonical role of the Mediator complex in the assembly of initiation complex (Takahashi et al. 2011; Conaway and Conaway 2013). As of now, in plants, MED25 is the most well-characterized Mediator subunit, which has been described to function in different biotic and abiotic stresses and in diverse developmental processes like root development, flowering, and fruit development. As the plants are sessile organisms, perhaps the gene regulatory mechanisms in plants are more diverse and complicated. Several transcription factors function as the master regulator of the cellular and physiological processes, and so their complex network can contribute immensely to the complexity of gene regulation. The genome analysis of plants revealed that plants contain more number of transcription factors as compared to animals (Riechmann et al. 2000; Riechmann and Ratcliffe 2000). As Mediator functions by interacting with the transcription factors, the increased number Mediator subunits in plants might have evolved to cover more number of transcription factors. Also, plant-specific Mediator subunits might be targeted by plant-specific transcription factors conferring the plants better transcript alteration ability in response to diverse internal and external cues. On the other hand; as the basic, overall structure of the Mediator complex is same in all the organisms, most of the plant-specific subunits, if not all, will predictably occupy the tail module of the Mediator complex, bestowing the plants with seemingly unlimited gene regulatory potential.

1.5 Transcriptomics of Mediator Genes

Most of the total protein-coding genes in eukaryotes require the contribution of Mediator complex even to sustain basal level of transcription proves unequivocally that Mediator constitutes the part of the basal transcriptional machinery (Ansari et al. 2009; Kim et al. 2011; Lacombe et al. 2013). At the same time, the increasing numbers of reports describing the effects of mutation in specific subunit on the transcription of specific set of genes strongly suggest that Mediator could also act as selective gene regulator (Taatjes 2010; Kidd et al. 2011). This raises the possibility of regulation of specific *MED* genes in response to specific signals. In order to address this, expression analyses of *MED* genes were performed by different research groups in animals and plants. In human endothelial progenitor cells, expression of *MED12* and *MED30* increased and decreased, respectively, after L-arginine treatment (Rienzo et al. 2010). Additionally, Mediator subunit genes were also found to undergo alternative splicing in tissue-specific manner (Rienzo et al. 2012). In plants too, alternatively spliced isoforms of *MED* transcripts are predicted. In rice, *MED* genes are more pronouncedly expressed in seeds of different stages as compared to shoot and root (Mathur et al. 2011). This is in accordance with the enrichment of seed storage-specific promoter elements on certain *MED* genes indicating the important regulatory role of MED subunits during seed development and maturation. A genome level transcriptome analysis of *MED* transcripts in response to different stresses like drought, cold, and salinity did not reveal much perturbations except that in *OsMed37_6*, which exhibited around twofold changes in transcript abundance in response to different stresses (Mathur et al. 2011). In *Arabidopsis*, some hormones such as brassinosteroid (BR) and ABA affect the stoichiometric concentrations of a set of MED subunits by regulating their transcript abundance (Pasrija and Thakur 2012). However, other hormones like auxin, jasmonic acid (JA) affect very few *MED* genes. *AtMED37*, which has been discovered as a plant-specific Mediator subunit, is highly up-regulated in response to BR treatment. A significant transcriptomic reprogramming of the Mediator subunit genes in *Arabidopsis* happens in response to stresses like salinity, cold, high light and continuous dark and is summarized in Table 1.1 (Pasrija and Thakur 2012). Additionally, in *Arabidopsis*, tissue- and organ-specific analyses revealed changes in transcriptome profile of several *MED* genes during development and maturation of tissues and organs (Pasrija and Thakur 2013). On the basis of their studies, apart from spatiotemporal regulations of individual Mediator subunits, enrichment of specific structural arrangement composed of specific Mediator subunits during certain developmental stages can be predicted. In the following section, we describe the change in the transcript abundance of individual Mediator subunits according to their module occupancy, at different developmental stages and in response to different environmental cues.

Table 1.1 Transcript perturbation of Mediator subunit genes of *Arabidopsis* in response to different abiotic cues

Mediator genes	Salt	Cold	High light	Dark
Head module				
MED6	+	nc	nc	−
MED8	+	nc	+	−
MED11	nc	nc	nc	−
MED17	+	nc	+	−
MED18	+	−	nc	−
MED19	+	nc	nc	nc
MED20	+	−	nc	−
MED22	+	−	nc	−
MED28	nc	nc	nc	−
Middle module				
MED4	+	nc	+	−
MED7	nc	nc	nc	nc
MED9	+	nc	nc	−
MED10	+	nc	nc	−
MED21	nc	nc	nc	−
MED31	+	nc	+	−
Tail module				
MED2	nc	nc	nc	−
MED3	−	nc	nc	−
MED5	+	nc	+	nc
MED14	+	nc	+	nc
MED15	nc	nc	+	+
MED16	+	nc	nc	nc
MED23	+	−	+	−
Kinase module				
MED12	+	nc	+	nc
MED13	nc	nc	+	nc
CDK8	+	nc	+	−
Cyclin C	nc	−	nc	−
Module-unassigned subunits				
MED25	nc	nc	+	−
MED34	−	nc	nc	nc
MED35	nc	nc	+	−
MED36	nc	nc	−	−
MED37	+	+	+	+

"+" : up-regulation, "−" : downregulation; "*nc*" : no change

1.5.1 MED Genes Coding for Head Module Subunits

Among the core Mediator subunits, in rice, *OsMED8_1* showed increased transcript abundance (around threefold) in the early panicle stages. Other important core Mediator subunits, *OsMED6*, *17*, *20*, *22*, *28*, and *30* maintain a steady-state level

irrespective of any developmental stages indicative of its basal role in transcription (Mathur et al. 2011). However, *OsMED11_1* showed more than twofold up-regulation in early stages of seed development. In *Arabidopsis*, more than 2.5-fold up-regulation of *AtMED6* and *AtMED17* is the notable changes among the head module Mediator subunits in response to BR treatment (Pasrija and Thakur 2012). Among the other significant expression changes of the head module subunits in response to phytohormone treatments, more than twofold buildup in the transcript level of *AtMED18* in response to JA deserves special mention. AtMED18 has been reported to be involved not only in flowering but also in regulation of organ number and shape (Zheng et al. 2013). It would be interesting to find out whether AtMED18 regulates these processes through JA-regulated pathways or not. More than twofold up-regulation of *AtMED17* in response to high light is an indication of its important gene regulatory role in light-dependent plant processes (Kim et al. 2011; Pasrija and Thakur 2012). The downregulation of *AtMED18* and the up-regulation of *AtMED20* in response to cold and salinity stresses (Table 1.1), respectively, may connect the Mediator functions to the growth and development of the plant under harsh environmental conditions.

1.5.2 MED Genes Coding for Middle Module Subunits

The study of expression pattern of *MED9* revealed its up-regulation during seed development in *Arabidopsis* while it declined in rice in the equivalent stages (Mathur et al. 2011). Similar to *AtMED9*, *AtMED10* also showed increased transcripts during the advanced stages of seed development. More than 2.5-fold increase in the *AtMED9* transcript level in response to BR treatment may hint at its important role during seed development. Another, middle module Mediator subunit, *AtMED21_1* showed approximately twofold upsurge in the advanced stages of seed development, which conforms to the already reported role of AtMED21 in embryo development and cotyledon expansion whereas OsMED21 might be involved more in the early stages of panicle development (Mathur et al. 2011). Among the other notable changes, *OsMED31_1* showed around threefold induction in leaf as compared to root. A slight increase in the transcript level of *AtMED4* and *AtMED31* in response to auxin treatment was noted. Among the physical stresses, NaCl increases the transcript level of *MED4* quite significantly, more than twofold.

1.5.3 MED Genes Coding for Tail Module Subunits

Among the tail module Mediator subunits, *MED3*, *5*, *14*, and *15* showed differential expression during different stages of reproductive developments, both in rice and *Arabidopsis* (Mathur et al. 2011). Mediator subunit *MED14*, also known as *STRUWWELPETER* (*SWP*), is characterized by its stronger expression level in the

leaf and has been implicated in the control of cell cycle duration and root elongation (Autran et al. 2002; Krichevsky et al. 2009). Between the two rice *OsMED14* paralogs, *OsMED14_1* showed more than 11-fold upsurge just after pollination and then gradually dropped down. However, the expression enhancement of *AtMED14_1* was specifically confined to advanced stages of seed development. *OsMED5_2* shows downregulation during reproductive developments. Significant up-regulation of *OsMED15_1* during different stages of seed development supports its probable role in seed development (Thakur et al. 2013). In *Arabidopsis*, *AtMED15_1* shows very high expression in mature leaves as compared to the young ones (Pasrija and Thakur 2013). Surprisingly, its transcript level goes down with the maturation of the flower. It will be interesting to dissect the function of AtMED15_1 in leaf and flower. In earlier reports, AtMED16 has been implicated to be involved in freezing tolerance (Warren et al. 1996; Knight et al. 1999). But the expression analyses of both *AtMED16* and *OsMED16* do not show any alteration in their transcript abundance across different stages, and also under the cold stress condition. Function of MED16 has been predicted to be at the post-translational stage of C-Box binding transcription factors (CBFs) involved in cold stress signaling pathways (Knight et al. 2009). Like its role in cold signaling, more than twofold increase of *MED16* transcript in response to salinity stress may imply its role as a converging point of both salt and cold signaling pathways. On the other hand, we noted significant downregulation (>40 %) of tail module subunit genes like *AtMED15*, *AtMED14*, and *AtMED5* in response to auxin treatment (Pasrija and Thakur 2012). Although auxin and BR are known for their synergistic effects on plant growth and development, the same study reported the up-regulations of a set of Mediator genes, including the tail module subunit, *AtMED15* in response to BR treatment. However, overall, there is an overlap in the *MED* gene transcriptomic changes barring its antagonistic nature in response to these hormones. The increase in the transcript level of *AtMED15* under both dark and light conditions needs to be studied further (Table 1.1).

1.5.4 MED Genes Coding for Kinase Module Subunits

Kinase module Mediator subunits, MED12 and MED13, also known as GRAND CENTRAL (GCT) and CENTER CITY (CCT), respectively, have been reported to take part in the pattern formation of *Arabidopsis* embryos, and determine the central and peripheral identity of the same (Gillmor et al. 2010; Ito et al. 2011). Moreover, AtMED12 has been shown to be a positive regulator of flowering process (Imura et al. 2012). In compliance of the reported functions, the expression level of *MED12* increased significantly at globular embryo stage in both *Arabidopsis* and rice. On the other hand, the reported 2.5-fold increase of *AtMED12* in response to BR treatment might also shed some light on its role in embryo development (Pasrija and Thakur 2012). The important regulatory role of AtMED12 in light and salt signaling pathways could also not be ruled out because of its twofold up-regulation in response to high light and salt conditions. However, the Mediator subunit *OsMED13* did not

show any change in the expression level in both, *Arabidopsis* and Rice. *OsMED13_1* expresses usually more in the leaf as compared to the root (Mathur et al. 2011). Around 40 % reduction in the expression level of *AtMED13* was observed in response to auxin treatment, which, perhaps, plays a significant role in its tissue-specific function (Pasrija and Thakur 2012). Though AtCDK8 or HEN3 has been reported to be involved in stamen and carpel development in *Arabidopsis*, the expression analyses of *Cyclin C* and *CDK8* genes revealed no significant alteration in their expression pattern during different stages of reproductive development (Wang and Chen 2004). In rice, *OsCDK8* expresses more in the leaf when compared with its expression in root. Also, more than twofold downregulation of *AtCycC* of the kinase module during cold stress may be worth mentioning here.

1.5.5 MED Genes Coding for Plant-Specific and Module-Unassigned Subunits

Several plant-specific Mediator subunits like *MED34*, *35*, *36*, and *37*, which have not been assigned any module yet, are expressed more in reproductive stages as compared to vegetative parts implying its tissue-specific functions. Another module-unassigned Mediator subunit is MED25, which has extensively been characterized to be involved in both biotic and abiotic stress responses (Kidd et al. 2009; Elfving et al. 2011). In *Arabidopsis*, the positive regulatory role of AtMED25 in flower development has been documented by several research groups (Cerdan and Chory 2003; Kidd et al. 2009; Inigo et al. 2012a, b). In rice, its expression remains constant during panicle initiation, increases nearly twofolds during seed maturation stages (Mathur et al. 2011). The induction of *AtMED37* in response to BR and low light suggests a probable link between shade and brassinosteroid signaling, and the process may be mediated by Endoplasmic Reticulum-Associated Degradation (ERAD) (Hong et al. 2008). The up-regulation of *AtMED37* in response to cold and salinity stresses (Table 1.1) provokes an intriguing hypothesis that AtMED37 may act as an integrative hub of many different signaling pathways, which is supported by the near ubiquitous, high expression level of *AtMED37* in all the organs tested so far (Pasrija and Thakur 2013). Another Mediator subunit, *MED36* expresses highly in the root of *Arabidopsis* and is anticipated to be involved in root-specific gene regulatory functions (Pasrija and Thakur 2013). In rice, *OsMED26* is expressed more in root as compared to leaves.

1.6 Role of Mediator in Biotic Stress

Plants in its natural environments are being constantly challenged by myriad of insects, pests, and other pathogens, which together constitute the biotic stresses. A survivor plant must activate its defense arsenal quickly and efficiently in order to

triumph over the invading and inflicting biotic agents. Any orchestrated and rapid response is achieved by the timely expression of defense genes, which is usually implemented and coordinated by the combined action of RNAP II machinery and Mediator complex. Emerging reports have started establishing Mediator complex as an essential component of defense gene regulatory pathway (An and Mou 2013). In comparison to other responses where few subunits are involved, maximum number of subunits are reported to be involved in defense signaling (Table 1.2). The first one reported to be involved in defense response was AtMED25 (Kidd et al. 2009). AtMED25 bears similarity with human MED25, where it also plays the role in defense response (Leal et al. 2009). In *Arabidopsis*, it directly affects the jasmonate-dependent expression of *PDF1.2*, *HEL*, *CHIB*, and *ESP* genes and provides resistance against the leaf infecting necrotrophic fungi, *Alternaria brassicicola* and *Botrytis cinerea* (Kidd et al. 2009). The complementation of *Atmed25* by its homologs from wheat strengthened the view that functions of some of the Mediator subunits may be conserved in higher plants (Kidd et al. 2009). AtMED25 takes part in ERF1- and ORA59-dependent activation of the *PDF1.2* gene as well as MYC2-dependent activation of the *VSP1* gene, which are some important target genes of JA signaling pathway (Çevik et al. 2012). In fact, MED25 physically associates with the basic helix-loop-helix transcription factor, MYC2 in promoter regions of MYC2 target genes to elicit its positive effect on their transcription (Chen et al. 2012). A group of 12 transcription factors (TFs) including AP2/ERF, bHLH, MYB, WRKY, and bZIP have been shown to interact with AtMED25. Among these transcription factors, many have previously been demonstrated to be involved in JA signaling pathway (Çevik et al. 2012). Thus, it is tempting to speculate that defense signaling evoked by different pathogens might be integrated at MED25 level for their proper channeling into the transcription apparatus via Mediator complex.

AtMED8 is one of the Mediator subunits, which has been reported to be involved not only in plant development, but also in its defense response. The plants carrying mutation in *AtMED8* behave quite similar to *Atmed25* but show more pronounced susceptibility towards *A. brassicicola*. Intriguingly, there is no genetic interaction between these genes, leading to the speculation that these Mediator subunits, AtMED25 and AtMED8, might be acting in two independent pathways controlling the same phenotype (Kidd et al. 2009).

Embryonic lethality of homozygous *Arabidopsis* lines carrying T-DNA insertion in *AtMED21* suggests the essentiality of MED21 in plant's life (Dhawan et al. 2009). The RNA interference lines of *MED21* are highly susceptible to *A. Brassicicola* and *B. Cinerea*. The detailed study revealed that MED21 interacts with RING E3 ligase, Histone Monoubiquitination 1 (HUB1), which mediates the H2B ubiquitination, and thus establishes a link between Mediator and the chromatin remodeling (Dhawan et al. 2009). The induced expression of both *MED21* and *HUB1* in response to chitin treatment, an important constituent of fungal cell wall that function as pathogen-associated molecular pattern (PAMP), suggests their probable role in defense signaling. Just like *Atmed21* mutants, loss of function mutation in *HUB1* makes the plant susceptible to *B. cinerea* and *A. brassicicola*. It

Table 1.2 Role of Mediator subunits in biotic and abiotic stresses in plants

Stress type	Gene name	Functions	References
Biotic	*AtMED25/PFT1*	Regulates the gene expression of jasmonate pathway genes and provides resistance against *Alternaria brassicicola* and *Botrytis cinerea*. It interacts with several transcription factors including MYC2, AP2/ERF, bHLH, MYB, WRKY, and bZIP.	Kidd et al. (2009), Cevik et al. (2012), Chen et al. (2012)
	AtMED8	Same like AtMED25. The mutant shows more disease susceptibility as compared to AtMED25 towards *A. Brassicicola*.	Kidd et al. (2009)
	AtMED16/SFR16	Involved in SA and JA pathways of disease signaling. Regulates expression of *PR1*, *PR2*, *PR5*, *GST11*, *EDR11*, and *SAG21* genes. Also regulates expression of the jasmonate pathway genes. The mutants are susceptible to *Pseudomonas syringae* and necrotrophic fungi like *A. brassicicola* and *B. cinerea*.	Wathugala et al. (2012), Zhang et al. (2012)
	AtMED21	*MED21* gets induced in response to fungal elicitors and provides resistance against *A. brassicicola* and *B. cinerea*. It interacts with Ring E3 ligase, HUB1, and regulates H2B ubiquitination.	Dhawan et al. (2009)
	AtMED15/NRB4	Involved in SA response pathway of disease signaling.	Canet et al. (2012)
	AtMED14/SWP	Regulates expression of *NPR1*, *EDS1*, *PAD4*, *ICS1*, *EDS5*, *NIMIN2*, *WRKY38*, and *WRKY62* genes of SA pathway and confers resistance against *Pseudomonas syringae pv. tomato* (*Pst* DC3000). Also regulates the expression of SAR genes, *PR1*, *PR2*, *PR5*, *GST11*, *EDR11*, and *SAG21*.	Zhang et al. (2013b)
Abiotic	*AtMED25*	AtMED25 regulates responses to salinity stress and drought stress, antagonistically. It interacts with different transcription factors like DREB2A, ZFHD1, and MYB, which are also known to be involved in salt and drought tolerance.	Elfving et al. (2011)
	AtMED16/SFR16	Regulates partly the expression of *LTI78*, *COR15A*, and *KIN1/2* genes in response to cold stress.	Knight et al. (1999, 2008, 2009)

seems that MED21 integrates signals from transcription regulators and HUB1-mediated chromatin modification to regulate transcriptional machinery.

Prior to its identification as a part of the Mediator complex, AtMED16 was initially discovered as SFR6 (sensitive to freezing). Mutation in *SFR6* compromised the ability of the plant to withstand lower temperature (Warren et al. 1996). Subsequently, an array of papers has documented its important roles not only in cold and drought responses (Knight et al. 1999, 2009; Wathugala et al. 2011) but also in the regulation of flowering and circadian clock in plants (Knight et al. 2008). Detailed analyses of mutants carrying defective *MED16* revealed compromised regulation of defense genes controlled by salicylic acid and jasmonic acid pathways (Wathugala et al. 2012). The *sfr6* mutant plants are more susceptible to *Pseudomonomas syringae* attack and exhibit lower expression level of defense-related genes coding for proteins like PR proteins and defensins. In another study, the expression levels of the important SAR (systemic acquired resistance) markers like *PR1*, *PR2*, *PR5*, *GST11*, *EDR11*, and *SAG21* were severely reduced in *Atmed16* mutant (Zhang et al. 2012). Hence, MED16 acts as a positive regulator of SA-induced gene expression. From the detailed studies of MED16-GFP recombinant protein, it was reasoned that the non-accumulation of NPR1, which resides at the nodal point of SA-induced gene expression pathway, might be responsible for the improper regulation of SAR genes in *Atmed16* mutant during pathogen attack (Zhang et al. 2012). Similarly, the *MED16* mutation also blocks the induction of the JA/ethylene (ET)-induced gene expression making the plants vulnerable to necrotrophic fungi like *Alternaria brassicicola* and *Botrytis cinerea*. Hence, MED16 might act as a converging point for both salicylic acid and jasmonate signaling pathways.

Another tail module Mediator subunit, AtMED15, also dubbed as NRB4 (Nonrecognition of BTH4, a salicylic acid analog), has recently been shown to be involved in SA-dependent defense signaling (Canet et al. 2012). The plants carrying mutation in *MED15* do not show any noticeable phenotype change except its attenuated response to salicylic acid (SA), reminiscent of the effects of *npr1* mutation in plant's defense signaling. NPR1 (non-expresser of *PR* genes) plays a pivotal role and takes the center stage in the SA signaling pathway (Dong 2004). However, neither a genetic interaction nor a biochemical interaction has been reported between MED15 and NPR1. That *nrb4-1*/*npr1-70* plants show additive phenotypes indicates that they might work independently in SA acid signaling pathway. Moreover, *nrb4* affects neither localization of NPR1 nor its stability. Thus, mechanistically, MED15/NRB4 functions downstream of NPR1 in the regulation of SA response pathway. But, how MED15/NRB4 mediates the SA-responsive gene expression in plants warrants still more detailed investigations.

The latest member to join the growing number of Mediator subunits playing important roles in defense response in plants is AtMED14/SWP (Zhang et al. 2013b), which has earlier been shown to be involved in meristem pattern formation and control of cell cycle duration (Autran et al. 2002). A mutation in *AtMED14* subunit gene suppresses the salicylic acid-induced expression of defense genes. AtMED14 does not interfere with the binding of NPR1, the master regulator of defense gene regulation, to the promoter of defense gene, *PR1*. However, it prevents

the expression of *PR1* leading to the speculation that AtMED14 might be responsible for the recruitment of RNAP II to the promoter of *PR1* gene. Further investigation is needed to delineate the exact mechanism involved in this process.

Thus, the tail module as a whole plays significant role in the regulation of defense genes during pathogen attack. But the mechanisms employed by these three different Mediator subunits (MED14, MED15, and MED16) differ considerably in controlling the pathogenesis-related genes. The *MED16* mutation differentially affects the expression of different positive and negative regulators of SAR whereas *MED14* mutation inhibits both the positive and negative regulators of the SAR. Moreover, defense-related transcriptomic change in case of *Atmed14* is much smaller as compared to that of *Atmed16*.

1.7 Role of Mediator in Abiotic Stress

Being sessile organisms, plants cannot run away to safer places during inclement weather. On the other hand, growth and development of a plant is profoundly influenced by the environment. In order to survive, a plant must translate the vagaries of the surrounding environments into proper molecular cascades relaying the signals to the transcriptional machinery ensuring the adaptability of the plants to the changed milieu. Of late, Mediator has emerged as an integrative hub for the different signaling pathways leading to the transcriptional regulation by RNAP II. So, it is quite obvious that the Mediator plays crucial roles in the integration of signals evolved in response to stresses like drought, cold, salinity etc. So far two Mediator subunits, which too play important roles in biotic stresses, have been reported to be involved in abiotic stresses (Table 1.2). The importance of MED25 in salt signaling is conserved across the plant species (Elfving et al. 2011). In a yeast two-hybrid screen, utilizing the activator interacting domain (ACID) domain (551–680 a.a.) of AtMED25, Bjorklund's group identified three transcription factors, DREB2A, ZFHD1, and MYB like proteins as the probable interacting partners of AtMED25 (Elfving et al. 2011). Mutations in the genes of these transcription factors make the plants more sensitive to salt. Mechanistically, these transcription factors, in response to salt stress, might be recruiting Mediator and the RNAP II machinery to their respective target promoter affecting the salt-responsive transcriptomic changes in plants. On the other hand, surprisingly, AtMED25 negatively regulates drought tolerance in plants (Elfving et al. 2011). Plants with mutation in *AtMED25* display huge increase in the expression level of drought-responsive marker genes like *RD29A*, *RD29B*, and *DREB2A*. In wild type plants, AtMED25 was projected as a co-repressor interacting with the repressor domain of DREB2A making the plants vulnerable to drought stress. Thus, it is a unique example, where the same Mediator subunit, AtMED25 controls similar kind of stresses in antagonistic manner.

MED16, originally discovered as SFR6 before being identified as a part of Mediator complex, has been reported as an important regulatory component of cold response in *Arabidopsis* (Knight et al. 1999, 2008; Wathugala et al. 2011). The

mutant plants fail to embrace freezing temperature following its exposure to subzero temperature. At the molecular level, the plants are incapable of switching on the COR (cold on regulation) regulation including the expression of *LTI78*, *COR15A*, and *KIN1/2*. Microarray analysis of *sfr6* mutant plant revealed that a group of cold regulatory genes, which are regulated by CRT/DRE motifs are misregulated (Knight et al. 1999). The CRT/DRE motif containing genes involved in freezing tolerance are under the control of CBF transcription factors (Boyce et al. 2003). However, neither expression of *CBF* genes nor the localization of their proteins is affected in *sfr6* mutant plants. Thus, it provokes the intriguing speculation that MED16/SFR6 might modulate the activity of CBFs post-translationally (Knight et al. 2009).

Conclusion and Future Perspective

Mediator research in plants is relatively new as compared to its study in fungi and metazoans. In spite of that, significant developments have been made in plant Mediator research in last couple of years. Isolation of Mediator complex from *Arabidopsis* has been reported and proven the usefulness of bioinformatics predictions. Many Mediator subunits were characterized in mutant screening even before their identification as a bona fide component of Mediator complex. In recent times, many Mediator subunits have been reported to be involved in biotic and abiotic stresses. As a matter of fact, the Mediator complex has emerged as an integrative hub for different biotic and abiotic signaling pathways. In most of the cases, phenotypes of a particular Mediator subunit mutation have been described but its association with transcription factors and the set of genes under its control are yet to be achieved. What is lacking more is the understanding of how the Mediator components interact with components of the basic transcriptional machinery resulting in the activated transcription. Recently, many of the hitherto unknown but interesting aspects of Mediator functions have been unveiled in other organisms broadening the horizon of understanding of Mediator functions. Mediator not only takes part in the recruitment of RNAP II on the promoters of the active genes but also in transcript elongation, termination of transcription, chromatin remodeling, regulation of chromatin architecture, alternative splicing, miRNA biogenesis, and non-coding RNA production. Although there is an overall structural conservation among the Mediator complexes isolated from different organisms, there will be lots of minute and subtle differences, which may bring differential functioning of the Mediator complex in different organisms. That necessitates the isolation of Mediator complex from economically important crop species and to study the mechanistic and functional details of the Mediator complex as a whole as well as its individual subunits. As far as the structure is concerned, no plant Mediator structure has been resolved till date. There are multiple paralogs of many Mediator subunits, and the number is more in case of plants. Another level of complicacy may arise due to selection of a particular paralog for complex formation, which most probably is controlled in a temporal and

spatial manner. The presence of more than one paralog at a time in the Mediator complex has not been reported by any group. The more interesting question, which is just being started to be answered is how stable is the Mediator structure in terms of the amount of subunits present at a given point. Researchers are now very much certain that Mediator structure changes depending on the stoichiometric concentration of Mediator subunits, which again is controlled by different biotic and abiotic stimuli. So, complex isolation and its structural comparison from different stages of growth and development hold the key to the question of how the structural changes in the Mediator are translated into transcriptomic changes of a species in response to different developmental and environmental cues. Armed with the tools of modern molecular biology like tandem affinity purification (TAP), multidimensional protein identification technology (MudPIT), liquid chromatography-mass spectrometry (LC-MS/MS), high-throughput ChIP sequencing (HT-ChIP), the aforementioned questions are anticipated to be answered in accelerated speed in the near future.

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