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Origins and Activity of the Mediator Complex

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Abstract

The Mediator is a large, multisubunit RNA polymerase II transcriptional regulator that was first identified in *Saccharomyces cerevisiae* as a factor required for responsiveness of Pol II and the general initiation factors to DNA binding transactivators. Since its discovery in yeast, Mediator has been shown to be an integral and highly evolutionarily conserved component of the Pol II transcriptional machinery with critical roles in multiple stages of transcription, from regulation of assembly of the Pol II initiation complex to regulation of Pol II elongation. Here we provide a brief overview of the evolutionary origins of Mediator, its subunit composition, and its remarkably diverse collection of activities in Pol II transcription.

1. Introduction

1.1 Mediator in RNA polymerase II transcription

The synthesis of messenger RNA (mRNA) is a major site for the regulation of gene expression. In eukaryotes, mRNA is synthesized by RNA polymerase II (Pol II), whose activity is controlled both positively and negatively by a seemingly endless number of transcriptional regulatory proteins. Among these proteins are a small set of evolutionarily conserved “general transcription factors” that constitute a critical core transcriptional machinery that together with Pol II are essential for transcription of most or all protein-coding genes. These general transcription factors include the five general initiation factors, TFIIB, TFIID, TFIIE, TFIIIF, and TFIIH, which are the minimum set of proteins needed for initiation of transcription by Pol II from its promoters. In addition to the initiation factors, the class of general Pol II transcription factors includes the multisubunit Mediator complex, which is the subject of this review and which has key roles in regulating multiple stages of Pol II transcription.

1.2 Isolation and activities of the Mediator complex

The Mediator complex was identified and purified to near homogeneity by Kornberg and coworkers from *Saccharomyces cerevisiae* as an activity required to reconstitute activation of Pol II transcription by DNA binding transactivators, in an enzyme system composed of purified *S. cerevisiae* Pol II and the general initiation factors [1]. Subsequent studies showed that Mediator is present in species from yeast to man [reviewed in 2, 3]. Although initially identified by its ability to support activator-dependent transcription, Mediator can also

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stimulate basal Pol II transcription carried out in the presence of just the general initiation factors, in the absence of DNA binding transactivators [1, 4].

Investigations of the mechanism of Mediator action in Pol II transcription have revealed an important role for Mediator in facilitating assembly of the preinitiation complex. This activity of Mediator is thought to depend in part on its ability to recruit Pol II to promoters by functioning as an adaptor that binds directly both to Pol II to form the so-called “oloenzyme” and to the transcriptional activation domains of DNA binding transactivators [1, 5, 6]. In addition, Mediator can bind to the general initiation factor TFIID [7, 8] and stabilize its binding to promoters [9, 10]. Mediator can also bind directly to TFIIE and TFIIH and, through this interaction, help to recruit both TFIIE and TFIIH into the preinitiation complex [11].

Mediator also regulates Pol II transcription at steps after initiation. A variety of evidence suggests that Mediator can promote efficient Pol II transcript elongation by recruiting elongation factors [12, 13]. In addition, Mediator was found to potently stimulate TFIIH kinase-dependent phosphorylation of the Pol II CTD [1, 14, 15], a Pol II post-translational modification implicated in a variety of steps in mRNA maturation, including efficient elongation and capping of transcripts [16]. Thus, the Mediator possesses an array of activities that function at multiple stages of transcription, from promoting recruitment of Pol II to promoters and assembly of the preinitiation complex to facilitating efficient elongation and processing of transcripts to produce mature mRNAs.

2. The *S. cerevisiae* Mediator complex

2.1 Subunit composition

The *S. cerevisiae* Mediator complex is composed of more than 20 distinct proteins with a combined molecular mass of more than 1.5 megadaltons. Peptide sequencing and/or molecular cloning of its subunits revealed that it included a collection of proteins that had been implicated previously in Pol II transcription and other processes, as well as seven previously uncharacterized proteins, which were designated MED1, MED2, MED4, MED6, MED7, MED8 and MED11 [17–19].

2.2 Genetics

Among the *S. cerevisiae* Mediator subunits are proteins encoded by the *GAL11*, *SIN4*, *RGR1*, *NUT1*, *NUT2*, *ROX3*, and multiple *SRB* genes, all of which were initially identified in screens for genes involved in regulation of Pol II transcription [1, 19–21]. Nonet and Young [22] identified the *SRB* genes in a screen for extragenic suppressors of a Pol II mutant lacking a portion of the CTD of its largest subunit. Remarkably, *SRB2*, *SRB4*, *SRB5*, *SRB6*, *SRB7*, *SRB8*, *SRB9*, *SRB10*, and *SRB11* [5, 23–25], which represent a large fraction of the genes identified in this screen, all turned out to encode Mediator subunits. In the now commonly used Mediator nomenclature [26], these *Srb* proteins are referred to as MED20, MED17, MED18, MED22, MED21, MED12, MED13, CDK8, and Cyclin C, respectively.

The *GAL11* gene, which encodes MED15, was initially identified by its requirement for activation of Pol II transcription by the DNA binding transactivator Gal4 [27]. *GAL11* was also isolated in screens for genes that affect transcriptional start site selection [28] and derepression of *SUC2* gene transcription [29]. The *RGR1* gene, which encodes MED14, was isolated by its requirement for glucose-dependent repression of the *SUC2* gene [30, 31].

The *SIN4* gene, which encodes MED16, was initially isolated as a negative regulator of Pol II transcription of the *GAL1* and *HO* genes; however, additional genetic experiments suggested MED16 can also act as a positive regulator of Pol II transcription [32, 33].

Biochemical support for this idea came from the observation that *S. cerevisiae* transcription extracts prepared from a strain lacking the *SIN4* gene are defective in Mediator-dependent activation of Pol II transcription [34].

The *ROX3* gene encodes MED19. *ROX3* was isolated in a search for mutants with elevated expression of the heme-regulated *CYC7* gene [35]. Subsequently, genetic studies implicated the *ROX3* gene in proper expression of genes controlled by diverse regulatory pathways, consistent with the idea that it has a general role in transcriptional regulation [36, 37]. In human cells, MED19 is also known as LCMR1 (Lung Cancer Metastasis Related Protein 1) because of its overexpression in some lung cancers [38].

Mutations of the genes encoding the *S. cerevisiae* Nut1 and Nut2 proteins (now referred to as MED5 and MED10, respectively) were originally found to relieve the requirement for the DNA binding transactivator Swi4 in Pol II transcription of a Swi4-dependent reporter [39]. Interestingly, mutations in *SIN4* (*MED16*), *ROX3* (*MED19*), *SRB8* (*MED12*), *SRB9* (*MED13*), *SRB10* (*CDK8*), and *SRB11* (*Cyclin C*) were found to give rise to similar phenotypes [39].

Genes encoding several subunits of *S. cerevisiae* Mediator were identified in genetic screens for mutations that affect genome stability. For example, *CSE2*, which encodes MED9, was originally isolated in a screen for genes required for proper mitotic chromosome segregation [40]. The *SOH1* and *HRS1* (*PGD1*) genes, encoding MED31 and MED3, respectively, were isolated as extragenic suppressors of the hyperrecombination phenotype of strains lacking the Hpr1p subunit of the THO complex [41, 42]. Hpr1p and other THO complex subunits are required for co-transcriptional packaging of nascent transcripts into messenger ribonucleoprotein particles (mRNPs), and it has been proposed that the hyperrecombination phenotypes associated with *HPR1* mutations are due to cotranscriptional accumulation of RNA-DNA hybrids behind transcribing Pol II [43, 44]. Why mutation of Mediator subunits suppresses hyperrecombination is not clear; however, it has been reported that a reduction in the rate of Pol II initiation can suppress the hyperrecombination phenotypes arising from defects in function of the THO complex [45]. Notably, defects in other components of the Pol II transcription machinery, such as Pol II itself and the general initiation factor TFIIB, can give rise to a similar hyperrecombination phenotype [46].

3. Conservation of Mediator from yeast to man

3.1 Evolutionary relationships

Evidence for the existence of Mediator in higher eukaryotes came with the isolation of Mediator-like complexes in various laboratories using different purification strategies; these included Mediator-like complexes from mouse [14], *Drosophila* [47, 48], and rat [49], as well as human complexes referred to as Thyroid hormone Receptor-Associated Proteins/SRB-Med containing cofactor (TRAP/SMCC) [50–52], Positive Cofactor 2 (PC2) [53, 54], vitamin D receptor-interacting proteins (DRIP) [55], activator-recruited factor-large (ARC-L) [56], and Cofactor Required for Sp1 activation (CRSP) [57, 58]. At first, it was unclear whether these Mediator-like complexes were homologous to *S. cerevisiae* Mediator, because they initially appeared to be composed of distinct but overlapping sets of subunits. In addition, there was some controversy surrounding the evolutionary relationship between *S. cerevisiae* Mediator and higher eukaryotic Mediator-like complexes because only a handful of the *S. cerevisiae* Mediator subunits had obvious orthologs in higher eukaryotes.

Input from two technological developments led to the discovery that Mediator is quite highly evolutionarily conserved. First, use of improved mass spectrometry approaches such as MudPIT (Multidimensional Protein Identification Technology) allowed definition of a

complete set of mammalian Mediator subunits and suggested that the various human Mediator-like complexes were indeed closely related to one another [59]. Second, the availability of a complete list of mammalian Mediator subunits, together with the sequencing of genomes from an increasing number of species, made it possible to discern the evolutionary relationships between subunits of *S. cerevisiae* and higher eukaryotic Mediator despite the fact that, in many cases, only short and rather divergent blocks of sequence exhibit significant conservation throughout evolution [2, 3]. To date, orthologs of least 22 out of 25 *S. cerevisiae* subunits have been identified in higher eukaryotes, and, as discussed below, Mediator complexes from all organisms appear to have a similar, evolutionarily ancient, modular organization [3].

Finally, it is perhaps not surprising that, despite the striking evolutionary conservation of Mediator from yeast to man, higher eukaryotic Mediator was found to possess a small cadre of additional, apparently metazoan-specific subunits. Among these, at least 5, and as many as 8, appear to be completely distinct from those found in *S. cerevisiae* and thus could endow metazoan Mediator with additional activities required by multicellular organisms.

3.2 Modular organization

Evidence from biochemical and structural studies argue that Mediator is organized into at least four modules [17, 60–63]. These modules, which have been referred to as the head, middle, tail, and kinase are likely to have different but overlapping functions. The head, middle, and tail modules assemble together to form a core complex that can be isolated from cells alone or stably associated with either Pol II or the kinase module. Evidence suggests that binding of Pol II and the kinase module to the Mediator core complex is mutually exclusive [64, 65].

The *S. cerevisiae* head module includes MED6, MED8, MED11, MED17, MED18, MED19, MED 20, and MED22. The head module can bind Pol II and general initiation factors and can stimulate basal transcription even in the absence of the remaining Mediator subunits; however, the head module alone does not support activator-dependent transcription [7, 66, 67].

The Middle module includes Mediator subunits MED1, MED4, MED7, MED9, MED10, MED21, MED31. In its C-terminal half, mammalian MED1 includes LXXLL motifs, which bind to multiple nuclear receptors in a ligand-dependent fashion; this interaction is thought to be sufficient to recruit Mediator to many nuclear receptor-regulated genes [68]. MED14 appears to be at the interface of the middle and tail modules and may contribute to the overall organization of Mediator [69]. In addition to this apparent structural role, human MED14 has been shown to interact directly with ligand-independent transcriptional activation domains in the glucocorticoid receptor and PPAR γ and, in so doing, to contribute to the activation of transcription by these transcription factors [70, 71].

In *S. cerevisiae*, the tail module includes Mediator subunits MED2, MED3, MED5, MED15, and MED16, which all appear to function in recruitment of Mediator to genes through direct interactions with various DNA binding transactivators [34, 72–78]. Tail module subunits MED15 and MED16 have obvious higher eukaryotic orthologs, which also interact with activators [79–82]. MED2, MED3, and MED5 are less highly conserved and, as discussed below, it is not yet completely clear whether they have orthologs in higher eukaryotes. Intriguingly, the DNA binding activator Gcn4 can recruit a tail module subassembly containing MED2, MED3, and MED15 independent of the rest of Mediator to the *S. cerevisiae* *ARG1* promoter, where it can support transcriptional activation [74].

The final Mediator module, the kinase module, is a four subunit complex that is associated with only a fraction of Mediator complexes that can be isolated from cells. Kinase module is composed of the cyclin-dependent kinase CDK8-Cyclin C as well as MED12 and MED13 [83]. Interestingly, genes encoding all of the kinase module subunits were identified in the *SRB* screen as suppressors of a Pol II CTD mutant [5, 24]. In mammals and some other vertebrates there are paralogs of the kinase module subunits CDK8, MED12, and MED13, which have been designated CDK19, MED12L, and MED13L, respectively [3, 59]. The evolution of paralogs of human kinase module subunits raises the possibility this module assembles combinatorially and possesses an expanded array of functions in higher eukaryotes.

The role of the kinase module in Mediator function remains enigmatic. For some time the kinase module was thought to be primarily a negative regulator of Mediator activity. Initial genetic studies indicated that the kinase module negatively regulates a subset of genes in yeast [84, 85]. In addition, the binding of kinase module to Mediator was found to prevent it from binding to Pol II and activating transcription *in vitro* [65, 86, 87]. Despite these early studies, it is now clear that kinase module also has important roles in gene activation, functioning at least in part by mechanisms that contribute to recruitment of the transcription elongation factor P-TEFb and the release of promoter-proximally paused Pol II into productive elongation [12, 88, 89].

4. Mediator subunits specific to higher eukaryotes

It was initially thought that MED23-30 were specific to higher eukaryotic Mediator [2, 26, 59]. More recently, MED24, MED27, and MED29 have been proposed to be very distantly related orthologs of *S. cerevisiae* Mediator subunits MED5, MED3, and MED2, respectively [3]. As discussed in more detail below, of the remaining five apparently non-conserved Mediator subunits, all except MED30 have had one or more functions ascribed to them.

4.1 Subunits of the tail module

The Mediator tail is perhaps the most evolutionarily divergent module of the entire complex. This might not be surprising in light of its important role in interacting physically with DNA binding transactivators, which vary considerably in structure and function from yeast to man. In addition to the conserved subunits MED15 and MED16, Mediator tail subunits from higher eukaryotes include three additional subunits, MED23, MED24, and MED25. MED23 and MED25 are unique to higher eukaryotes; however, as noted above MED24 may be a highly divergent ortholog of *S. cerevisiae* MED5 [3]. Deletion of either *MED23* or *MED24* is lethal in mice; however, cells lacking one or the other of these genes are viable [90, 91]. Loss of either MED23 or MED24 leads to disruption of the tail module and loss of at least MED16, MED23, and MED24 from the Mediator complex [90, 91].

MED23 and MED25 provide essential binding surfaces for a variety of DNA binding transactivators. In mammalian cells, MED23 has been shown to bind directly to and play an important role in activation of transcription by the Ets domain transcription factors Elk1 and Elf3 [73, 90, 90], CCAAT/enhancer binding protein family member C/EBP β [92], and the Adenovirus E1A oncogene [90].

In *Arabidopsis*, MED25 has been shown to interact with and to be required for gene regulation by multiple transactivators, including Drought Response Element Protein B (DREB2A), several MYB-like transcription factors, and the zinc finger homeodomain protein ZFHD1 [93, 94]. These transactivators affect responses to light, salt, drought, and other stresses. Accordingly, *Arabidopsis* MED25 has been proposed to serve as a hub that integrates the response to various signaling pathways [94]. In mammalian cells, MED25

binds directly to and supports activation of transcription by several nuclear receptors including the retinoic acid receptor RAR α [95] and the orphan receptor HNF4 α [96]. Human MED25 binds to and links the Mediator to the Herpesvirus transactivator VP16 [97, 98]. Recently, high resolution structural models of the VP16 binding site on MED25 were obtained by NMR in several laboratories [99–101]. In these models, the VP16 binding domain in MED25 adopts an unusual structure comprising a 7 stranded β -barrel flanked by 3 α helices. Two different helices of the VP16 activation domain interact with an extended surface of MED25, making contacts with opposite faces of the binding domain. These MED25 structures provide the first detailed insights into molecular mechanisms underlying the targeting of Mediator by activators.

It has also been suggested that MED27 and MED29 may be components of the Mediator tail module based on their proposed similarities to the *S. cerevisiae* tail subunits MED3 and MED2 [3]. There is not yet direct experimental evidence for this proposal, and MED27 and MED29 have both been shown to be capable of binding to known Mediator head module subunits [102, 103]. That said, it is intriguing that the *Drosophila* MED29 protein binds directly to the DNA binding transactivator Doublesex and is required for Doublesex-dependent transcription activation [104]. Thus, like the tail module subunits MED23 and MED25, MED29 appears to play an important role as a link between transactivators and the Mediator complex.

4.2 MED28

MED28, also known as either magicin or EG-1, was initially identified as a protein that interacts with the cytoskeletal neurofibromatosis 2 tumor suppressor protein merlin and that is differentially expressed in endothelial cells [105, 106]. MED28 has been reported to be overexpressed in some human cancers [107], and forced MED28 overexpression drives cell proliferation in several human cell lines [108]. Notably, MED28 was found to act in concert with several other Mediator subunits as a negative regulator of smooth muscle cell differentiation [109].

4.3 MED26

MED26 has identifiable orthologs in species from insects to mammals; however, even among these species it includes only two regions of similarity: a C-terminal region that is required for its assembly into Mediator, and an N-terminal domain that resembles the N-terminal domains of Pol II transcription elongation factors TFIIS (SII) and Elongin A [2, 3, 13]. MED26 has a unique role in Mediator function in higher eukaryotes; it is found in only a subset of Mediator complexes isolated from cells. MED26 is highly enriched in the Mediator-Pol II holoenzyme, but is present in very small amounts in Mediator complexes that include the kinase module.

Several observations suggest that MED26 plays an important role in activation of Pol II transcription. Biochemical experiments have shown that Mediator containing MED26 is capable of supporting activation of Pol II transcription *in vitro* by DNA binding transactivators, whereas Mediator lacking MED26 but containing the kinase module is not [54, 58]. In cells, a transcriptionally active form of the transactivator C/EBP β was found to recruit Mediator containing MED26 to promoters during Pol II transcription activation, whereas a repressive form of C/EBP β recruited Mediator containing the kinase module [92].

Insight into one mechanism by which MED26 contributes to transcriptional activation has come from evidence that its TFIIS-like N-terminal domain serves as a docking site for the recently identified Super Elongation Complex (SEC) [13], which is composed of Pol II elongation factors P-TEFb and ELL/EAF, as well as several MLL translocation partners

found in leukemias [110–112]. Thus, MED26-containing Mediator may support activation of Pol II transcription by facilitating not only initiation, but also post-initiation steps including transcript elongation and perhaps mRNA maturation, since P-TEFb-dependent phosphorylation of the Pol II CTD is needed to recruit multiple RNA processing enzymes to the nascent transcript [16].

5. Conclusion

Mediator is a eukaryote-specific regulator of gene expression. Its enormous size and subunit complexity have made Mediator a daunting problem for biochemists and geneticists. Nevertheless, salient features of Mediator function in regulation of Pol II transcription are emerging from work carried out in many laboratories. These studies argue that Mediator is a fundamental component of the Pol II transcription machinery, required for regulation of transcription of most protein-coding genes. In addition, these studies have revealed that a critical aspect of Mediator action is ability to interact physically with diverse DNA binding transactivators and to communicate transcription signals from these transactivators to Pol II and general initiation factors to turn transcription on or off. Finally, one of the most intriguing and tantalizing new insights into Mediator action is that it has important functions not only in Pol II transcription initiation, but also in post-initiation steps, such as recruiting and coordinating the activities of Pol II elongation factors. It is likely that, in the future, efforts to elucidate the range of Mediator functions will lead to even more surprises.

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Highlights

- Mediator is composed of head, middle, and tail modules and a separable kinase module.
- Mediator complexes from yeast to man share at least 22 conserved subunits.
- Mediator provides a physical link between transcription regulators and Pol II.
- Mediator regulates Pol II activity in both transcription initiation and elongation.