Seminars in Cell & Developmental Biology 22 (2011) 735–740

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Control of gene transcription by Mediator in chromatin

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ARTICLE INFO

Article history:
Available online 12 August 2011

Keywords:
Kinase
Transcription
Chromatin
PC2
Regulation

ABSTRACT

The Mediator complex serves as an adaptor for regulatory factors, recruits and controls RNA polymerase II promotes preinitiation complex formation and functions post initiation. There is increasing evidence for further coordinating roles of the Mediator complex in chromatin. Here we summarize interactions with regulatory, general and accessory factors that function in transcription and chromatin.

Contents

1. Introduction

The name *Mediator* originates from a biochemical study in bakers yeast, where it was initially given to activities that released squelching of *in vitro* transcription by the Herpes simplex activator VP16 [1]. Independent of it genetic screens identified the first Mediator genes as suppressor of truncations of the carboxyterminal domain (CTD) of the largest subunit of RNA polymerase B (which is RNA polymerase II, so called SRB proteins [2]). A Mediator activity was then described in yeast extracts [3]. In parallel, related activities showed up in biochemical screens of reconstitution of activator function *in vitro* [4]; reviewed in [5]. The Mediator protein complex containing SRB and other MED proteins was first purified from yeast extracts [6]. Following the initial discovery of human subunits that bound to the thyroid hormone receptor activation domain by Roeder and colleagues [7] altogether 30 subunits of a human Mediator were identified using biochemical approaches as well as mass spectrometry ([8–14]; reviewed in). Mediator–activator interactions proved relevant for many activators in distinct signaling pathways. Table 1 provides an update of Mediator–activator interactions for those pathways that have been characterized at the molecular level in mammals.

2. Structurally and functionally distinct Mediator complexes in mammals

Mediator complexes come in several variants. The large Mediators contain the core complex – consisting of head, middle and tail domains – and the CDK8 module. The latter consists of the Cdk8/CDK11-cyclin C pair that forms an active module with MED12 (230 kDa) and MED13 (240 kDa) subunits. The large complexes reach an estimated mass of approximately 1.8 MDa. The small Mediators (called PC2 or CRSP) lack the 600 kDa CDK8 module, they associate with MED26, a metazoan-specific subunit and may display further differences to large Mediators [8,15–17]. Additional gene-specific Mediator variants can arise through substoichiometric association of core complexes with *metazoa*-specific

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doi:10.1016/j.semcdb.2011.08.004

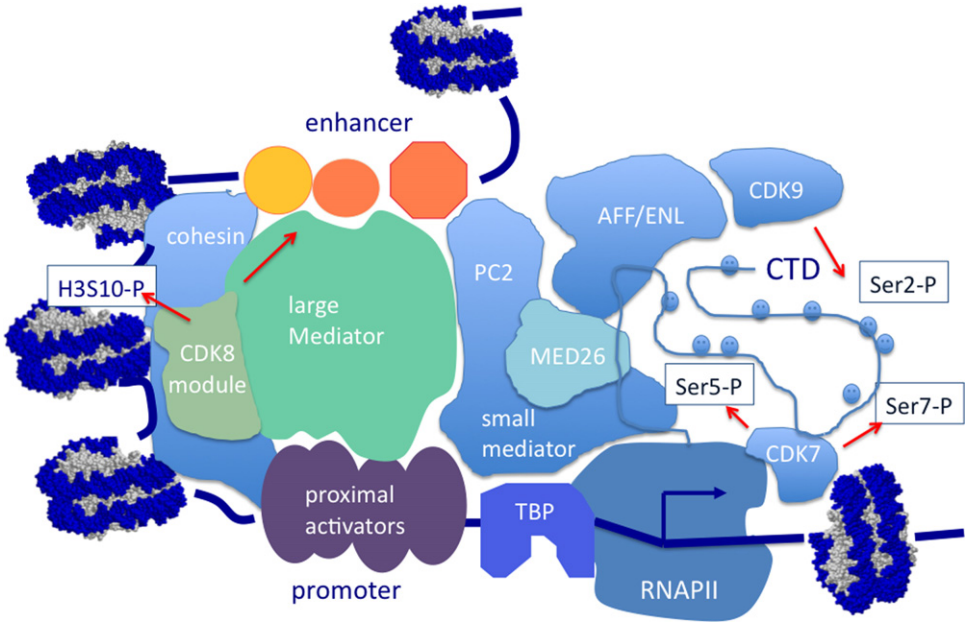

Fig. 1. Hypothetical model for combined action of large and small (PC2) Mediator complexes in gene transcription: The model integrates both the large Mediator (green) with the CDK8 module (khaki), and the small mediator variant PC2 (blue), with its characteristic MED26 subunit (light blue). Both variants are in contact with enhancers (yellow and orange) and proximal activators (violet), but differ in functions mediated either through CDK8 module or RNAPII-binding and MED26. Part of the Mediator function is an adapter that brings together regulatory and basal elements. Large Mediators have been shown to colocalize with cohesin [60]. CDK8 is further involved in chromatin control via phosphorylation of H3S10 (enzymatic activities are depicted with red arrows). PC2 recruits AFF/ENL and thereby CDK9 and ELL/EAF via interaction with MED26. Phosphorylating kinases CDK7 (Ser5 and ser7) and CDK9 (Ser2) and their targets at the CTD repeat YSPTSPS are indicated.

components such as MED1 and MED25 [12,18]. To date, we have only begun to understand the role of the different Mediator complexes. Both large and small Mediators carry subunits interact with activators. Preliminary functional distinctions stem from *in vitro* transcription experiments where the small Mediators (PC2/CRSP) strongly influenced basal RNAPII-transcription and activator-dependent transcription [15,16,19]. A recent genetic and biochemical study of MED26 further reasoned for the functional relevance of the small Mediator PC2 [17]. On certain model promoters CDK8 complexes decrease during gene activation, on others CDK8 levels seem to remain constant [20,21]. It is uncertain, however, whether large and small Mediators can be freely converted into each other. In fact, direct evidence for an exchange of CDK8 with RNAPII and association of MED26 is missing. Alternatively, it is also possible that large and small Mediators operate independently of each other on genes to affect distinct processes. Consistent with such a scenario, a number of distinct functions have been assigned to CDK8 in the recent years suggesting that the kinase module must play an important role in gene expression (discussed below). Fig. 1 summarizes some of the general functions presently attributed to large and small Mediators.

3. Mediator binds and functions through RNA polymerase II

Mediator occurrence is closely connected to the development of the carboxyterminal repetitive domain (CTD) of the largest subunit RPB1 of RNA polymerase II (RNAPII). Mediator is absent in bacteria including *Archea* whose RNA polymerase structurally most closely resembles the eukaryotic RNAPII – but lacks a CTD. The other two RNA polymerases I and III – that do relate to RNAPII in their core structure and also lack a structure like the CTD – do not interact with Mediator. Early EM structures suggested that the complex contacts RNAPII with the head and the middle module while the tail points upstream and engages in regulatory interactions [22,23]. More recently structural and genetic investigations suggested that Mediator–RNAPII contacts involve RPB3 and MED17, MED18 and MED22 [24,25]. Mediator–RNAPII interactions seem to also require the CTD [26]. Curiously, however, specific robust interaction domains for the CTD repeat YSPTSPS (like the CTD interaction domain (CID) that is found in downstream effectors) have not been uncovered in Mediator subunits. Furthermore, direct CTD contacts of Mediator with the CTD repeat so far remain invisible in structures.

4. Mediator–general factor interactions

Purified RNAPII assembles with general factors TBP, TFIIB, TFIIE, TFIIF and TFIIH, it initiates transcription and transcribes genes well *in vitro*, in the absence of Mediator. However, formation of preinitiation complexes as well as their activation is entirely dependent on Mediator in more physiological systems like nuclear extracts [16,19]. The underlying mechanisms remain poorly understood. Further consistent with such a general function of Mediator yeast cells require RNAPII–Mediator contacts for transcription of virtually all genes [24]. So how does Mediator facilitate PIC formation and activation of RNAPII? Early studies suggested that Mediator interacts with TFIIH through its subunits MED4 and MED15 [27,28]. Later, direct interactions between Mediator head module component MED11 and Rad3, a subunit of TFIIH, was reported [29].

Other reports point to a functional interplay and interactions of Mediator with TFIID. The TFIID complex consists of TATA box-binding protein TBP and associated factors (TAFs). TBP interacts with MED8, a component of the head module [30,31]. More recently, the PC2-subunit MED26 was shown to interact with TFIID [17]. In this study Conaway and collaborators could demonstrate that MED26 controls RNAPII at c-myc and heat shock genes. Consistent with a role in elongation factor recruitment (Figure 1) the knockdown of MED26 leads to reduction of binding of AFF/ENL complexes throughout the genes. It is notable, however, that deletion of the TFIID-interaction domain in MED26 had only moderate impact on TBP binding to the c-myc and the hsp70 gene promoters [17]. Also Med8–TBP interactions remain to be validated *in vivo*.

Table 1
Activation pathways with direct contacts to Mediator.

Factor	Mediator subunit	References
ERα and ERβ	MED1	Zhu et al. [61], Burakov et al. [62], Warnmark et al. [63], Kang et al. [64]
AR	MED1	Wang et al. [65]
GR	MED1, MED14	Hittelman et al. [66]
TRα	MED1, MED21	Yuan et al. [67], Zhu et al. [68], Nevado et al. [69]
TRβ	MED1	Yuan et al. [67], Zhu et al. [68]
VDR	MED1	Rachez et al. [70]
RARα	MED1	Zhu et al. [68], Shao et al. [71]
RXRα	MED1	Zhu et al. [68], Yuan et al. [67]
PPARα	MED1	Zhu et al. [68], Yuan et al. [67]
PPARγ	MED1	Zhu et al. [68], Ge et al. [72]
HNF-4	MED1, MED14	Malik et al. [73]
FXR	MED1	Pineda Torra et al. [74]
RORα	MED1	Atkins et al. [75]
STAT2	MED14, MED17	Lau et al. [76]
Elk-1	MED23	Stevens et al. [77]
Esx/Elf-3	MED23	Asada et al. [78], Shimogawa et al. [79]
C/EBPβ	MED23	Mo et al. [80]
SMAD2, SMAD3, SMAD4	MED15	Kato et al. [81]
DSX^F	MED29	Sato et al. [82], Garrett-Engele et al. [83]
SOX9	MED12	Zhou et al. [84]
Dif (dmNF-κB like)	MED17, MED16, MED23, MED25	Park et al. [85], Kim et al. [86]
E1A-13S	MED23	Stevens et al. [77], Wang und Berk [87]
RTA	MED12	Gwack et al. [88]
VP16	MED25, MED17	Mittler et al. [18], Ito et al. [89], Yang et al. [90]
Myc	Cdk8	Eberhardy and Farnham [91]
p53	MED1, MED17	Drane et al. [92], Frade et al. [93], Ito et al. [89]
BRCA1	MED1	Wada et al. [94]
HSF	MED17, MED23, MED25	Park et al. [95], Kim et al. [86]
Aryl HC receptor	MED1	Wang et al. [96]
SREBP-1a	MED14	Toth et al. [97]
GATA-1	MED1	Stumpf et al. [98]
GABPA	MED1	Udayakumar et al. [99]
GATA-2	MED1	Gordon et al. [100]
MYC	MED1	Liu et al. [101]
POU1F1	MED1	Gordon et al. [100]
14-3-3	MED1	Zilliacus et al. [102]
CTNNB1	MED12	Kim et al. [103]
REST	MED12	Ding et al. [59]
G9a	MED12	Ding et al. [59]
Gli3	MED12	Zhou et al. [104]
Nanog	MED12	Tutter et al. [105]
GRB2	MED28	Wiederhold et al. [106]
PPARGC1A	MED1	Wallberg et al. [107]

There are, however, indirect functional links between Mediator function and TFIID binding. Prebinding of TFIID to the E4 promoter reduces the function of Mediator *in vitro* [32,33]. Collectively, influence of Mediator on TFIID may ultimately depend on both the regulatory and the core promoter of the specific genes involved. As one example, the strong Adenovirus major late core promoter allows TFIID to bind fully independent of Mediator [34].

An interesting unresolved issue is how Mediator–RNAPII interactions enable the RNAPII enzyme to more efficiently stimulate

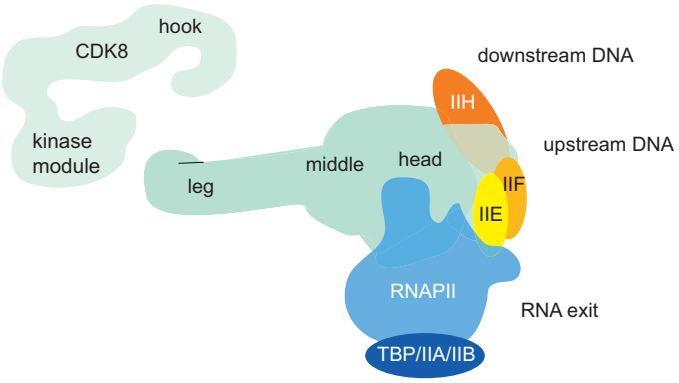

Fig. 2. Mediator in the preinitiation complex. Shown is a side-view of the small Mediator (green), with the docked RNAPII (light blue) and the GTFs TFIIA, TFIIB, TBP (dark blue), TFIIE (yellow), TFIIF and TFIIH (orange). The kinase module (khaki) is positioned near the Mediator leg, where it normally binds via the hook to the leg region. RNA exit, and approximate positions of upstream and downstream DNA are indicated. The model is largely based on investigations by E. Nogales, D. Taajes and colleagues [35,38].

preinitiation complex formation as the free enzyme. As a first step towards solving this molecular scenario the general factor TFIIF was recently shown to stabilize a distinct conformation of RNAPII [35]. Thus, one may speculate that such a chaperone-like function of Mediator contributes to the initial inactivation of RNAPII in physiological systems and that TFIIF than eventually converts the enzyme into an efficient binder of general factors like TFIIB.

5. Mediator–CDK interactions

5.1. Mediator binds CDK8 in a manner that excludes binding of RNAPII

The intact CDK8 module phosphorylates serine 5 in the CTD repeat (YSPTSPS) of RNAPII. Also phosphorylation of a number of accessory and regulatory targets requires the large subunits MED12 and MED13 in addition to the catalytic subunit CDK8 and its cyclin C (summarized in [13]). There is a second highly related kinase in mammals (termed CDK19, summarized in [11,36]) that likely has related catalytic activity and may either function redundantly or in a cell-type-specific manner. A number of specific functions have been attributed to CDK8. Phosphorylation of the RNAPII-CTD at serine 5 prior to binding to promoters in solution prevented association with the preinitiation complex [37]. Negative functions also result of mutually exclusive binding of CDK8 and RNAPII binding to Mediator [38]. This is observed although CDK8 binds to the leg region of Mediator – far away from the head module of Mediator where RNAPII binds. The apparent paradox was recently solved in cryo-EM studies. These suggested that binding of RNAPII alters the conformation of the leg region such that a hook-like structure formed by the CDK8 module can no longer associate with it (Figure 2; [35]). Importantly, CDK8 seems to also act positively in defined regulatory pathways (namely the p53-, serum response- and Wnt/β-catenin signaling pathways). The latter require the kinase function [13,36,39,40]. There are also reports reasoning for general positive functions of CDK8 [41].

5.2. Mediator controls phosphorylation of the CTD at serine 5 and serine 7 by CDK7

Already in the first description of the Mediator complex it was proposed that the cofactor complex enhances the activity of the kinase KIN28 (which is the yeast homologue of mammalian CDK7 [6]). At human promoters CDK7 hypophosphorylates the CTD of

RNAPII after the formation of a stable preinitiation complex. Phosphorylation of serine 5 in the CTD repeat YSPTSPS correlates well with the transition from initiation to early elongation. ChIPseq analyses showed that serine 5 phosphate levels increase together with elongating RNAPII within the first few hundred base pairs to then decline towards the 3′ end of genes [42]. Recent evidence suggests that CDK7 phosphorylates the RNAPII CTD at both serine 5 and serine 7 residues [43]. Notably, also the phosphorylation of serine 7- by CDK7 is controlled by Mediator [34]. Following hypophosphorylation the CTD is further hyperphosphorylated, likely by other kinases (such as DNA-PK) that do not require Mediator [34].

KIN28 is an essential gene in yeast whose deletion leads to loss of all mRNAs ([37] and references therein). This reasoned for an essential role of CTD phosphorylation by CDK7 in transcription. Ansari and colleagues challenged this view recently by using specific chemically modified substrates of KIN28. Their results suggest that CDK7 is not required for mRNA synthesis but instead may play a role in mRNA splicing [44]. Other predicted functions of CTD phosphorylation are the binding of factors following initiation of transcription. For example, serine 5-phosphate helps to recruit factors involved in downstream processes such as capping of the transcripts [45,46] and binding of histone modifiers such as H3K4 methyltransferases [47,48]. Remarkably, in mammals CDK7 also represents the major CDK-activating kinase. It functions in both G1/S- and in G2/M transitions indicating that transcription and cell cycle control are interconnected [49].

6. Postrecruitment functions of Mediator

Early indications for postrecruitment functions originate from investigation of the immediate early Egr-1 gene [21]. Functional evidence for a role in elongation stems from a recent investigation of the MED26 subunit found in small Mediator (PC2) complexes. MED26 binds directly to AFF/ENL complexes (Figure 1), which in turn recruits CDK9 and the functional elongation factors ELL-EAF [17,50]. MED26 carries an N-terminal domain that resembles TFIIS, a protein involved in release of pausing. In mammals there are three genes in encoding TFIIS-like activities all of which cleave protruding 5′ RNA-ends after arrest and backtracking of RNAPII. In yeast, AFF/ENL complexes as well as ELL/EAF proteins seem to be absent. Of note, however, yeast Mediator binds to and recruits TFIIS [51]. Curiously, also the CDK8 module and large Mediators carrying the CDK8 module have been implied in control of transcription elongation. Mass spec data suggest that CDK8 Mediator interacts specifically with ENL/AFF factors [52]. Furthermore, it has been hypothesized that CDK8 controls elongation via pTEFb [36].

7. Mediator–chromatin interactions

An early holoenzyme concept implicated Mediator in a complex with RNAPII, general factors and chromatin modifiers [53]. It is still not clear whether this supercomplex exists as a stable entity inside cells. However, clearly several components were later found to associate with Mediator. For example, Mediator binds and perhaps in part functions through the histone acetyltransferases CBP/p300 [54,55]. In yeast GCN4 first recruits Mediator and subsequently the remodeling factor Swi/Snf. This is dependent on SAGA, another cofactor that carries the histone acetyltransferase GCN5 [56,57]. In mammals, the transcriptionally inactive CDK8-form of Mediator was found to associate with TRAPP and GCN5L (termed T/G-Mediator) leading to the hypothesis that an elongating Mediator may act in chromatin [58]. CDK8 directly phosphorylates H3S10, which in turn activates acetylation of H3K14 residues by the GCN5L enzyme [13,38]. In other studies CDK8 was shown to bind the histone methyltransferase G9A, which leads to gene-specific H3K9 methylation [59]. Notably, CDK8 complexes also associate with the Swi/Snf subunit Ini1/SMARCB1 [52]. Mass spec analyses further identified the cohesin complex as a target of human Mediator. 3C studies and colocalization of Mediator with cohesin at distal enhancers and proximal promoter regions supported the notion that Mediator also serves as looping device in chromatin ([60], see also Figure 1). In mammals only MED1 and MED12 have been characterized genome-wide manner in mouse ES cells [60]. Predictably, with increasing sensitivity of ChIPseq analyses further functions of defined Mediator forms and novel downstream activities in transcription and chromatin control will be uncovered.

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