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Review

The Mediator complex in thyroid hormone receptor action ☆

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ABSTRACT

Background: Mediator is an evolutionarily conserved multisubunit complex that plays an essential regulatory role in eukaryotic transcription of protein-encoding genes. The human complex was first isolated as a transcriptional coactivator bound to the thyroid hormone receptor (TR) and has since been shown to play a key coregulatory role for a broad range of nuclear hormone receptors (NRs) as well as other signal-activated transcription factors.
Scope of review: We provide a general overview of Mediator structure and function, summarize the mechanisms by which Mediator is targeted to NRs, and outline recent evidence revealing Mediator as a regulatory axis for other distinct coregulatory factors, chromatin modifying enzymes and cellular signal transduction pathways.
Major conclusions: Besides serving as a functional interface with the RNA polymerase II basal transcription machinery, Mediator plays a more versatile role in regulating transcription including the ability to: a) facilitate gene-specific chromatin looping events; b) coordinate chromatin modification events with preinitiation complex assembly; and c) regulate critical steps that occur during transcriptional elongation. The variably associated MED1 subunit continues to emerge as a pivotal player in Mediator function, not only as the primary interaction site for NRs, but also as a crucial interaction hub for other coregulatory factors, and as an important regulatory target for signal-activated kinases.
General significance: Mediator plays an integral coregulatory role at NR target genes by functionally interacting with the basal transcription apparatus and by coordinating the action of chromatin modifying enzymes and transcription elongation factors. This article is part of a Special Issue entitled Thyroid hormone signalling.

1. Introduction

The biological action of thyroid hormone (3,5,3′-triiodothyronine or T3) is mediated primarily through thyroid hormone receptors (TRs), members of the nuclear hormone receptor (NR) family of ligand-activated transcription factors [1,2]. Mammals express two different yet highly homologous TR subtypes, TRα and TRβ, each encoded from separate genes [1]. TRs regulate transcription from target genes bearing T3 response elements (TREs) and typically bind TREs as heterodimers with retinoid X receptors (RXRs) [1,2]. On positively regulated target genes, TRs possess the dual ability to activate transcription upon ligand binding and to repress basal transcription in the absence of ligand. TRs repress basal transcription in the absence of T3 through interactions with corepressors such as the nuclear receptor corepressor (NCoR) and the silencing Mediator for retinoid and thyroid hormone receptors (SMRT) [reviewed in Refs. 3–6]. The N-terminal domains of both NCoR and SMRT recruit a variety of histone deacetylase (HDAC) complexes resulting in hypoacetylation of local histones and a chromatin structure resistant to transcription [3,6].

Upon binding to T3, a conserved helical motif (α-helix 12) located within the TR carboxy-terminal activation domain (AF2) undergoes a significant conformational shift [7]. The realigned AF2 domain creates a hydrophobic binding surface specific for the recruitment of transcriptional coactivators containing canonical LxxLL motifs [7,8]. For most NRs, three distinct types of coactivators are essential for transcriptional activation, a) ATP-dependent chromatin-remodeling complexes that facilitate promoter accessibility for other transcription factors, b) histone acetyltransferases and histone methyltransferases (HATs and HMTs, respectively) that generate covalent activation marks in chromatin, and c) the Mediator complex that functionally interfaces with the basal transcription machinery [for reviews see Refs. 9–12]. The p160/SRC family of NR-interacting proteins contains multiple LxxLL motifs that are crucial for T3-dependent TR binding and act as docking surfaces for the recruitment of HATs such as p300/CBP, HMTs such as CARM1 and PRMT1, and ATP-dependent chromatin-remodeling complexes such as the SWI/SNF complex [10–12]. In addition, the initial recruitment of p160/SRC–p300/CBP complexes to TR-bound target genes can facilitate the subsequent recruitment of the SWI/SNF complex [13].

The Mediator coactivator complex, contrary to the action of the chromatin modifying coactivators, functionally bridges DNA-bound NRs and other signal-activated transcription factors with the basal transcription apparatus thereby facilitating the assembly and activation of RNA polymerase II (Pol II) and its associated general factors at target core promoters [9,14–17]. In mammalian cells, the complex was first

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purified as a coactivator complex bound to TRα [18] and was later shown to be an essential ligand-dependent coactivator for a broad range of NRs as well as other signal-activated transcription factors [9,14,16,17]. The mammalian Mediator complex is comprised of at least 30 subunits [19] most of which are conserved amongst all eukaryotes [14,16]. Akin to the way p160/SRC associated protein complexes bind to NRs, the MED1 subunit of the mammalian Mediator complex contains two signature LxxLL motifs and serves to target Mediator to the AF2 domain of TR and other NRs in a ligand-dependent manner [9,14].

While Mediator is firmly established as a regulator of Pol II transcriptional initiation, emerging evidence surprisingly reveals a far greater functional role for Mediator in transcriptional regulation including the ability to control steps that occur during transcriptional elongation. Furthermore, recent studies demonstrate that Mediator and distinct chromatin modifying complexes can directly and functionally cooperate with one another leading to a unified transcriptional response. In this review, we discuss new mechanistic insights into the specific functional role of Mediator complex in thyroid hormone signaling pathways and more generally, summarize recent discoveries in how the complex facilitates NR target gene transcription.

2. The Mediator complex: an overview

2.1. Evolutionary conservation from yeast to human

The Mediator complex was first discovered in yeast and shown to be essential for Pol II transcription and yeast viability [15]. The yeast complex is composed of 25 subunits that functionally associate as a group with the C-terminal domain (CTD) of the largest subunit of yeast Pol II. In mammals, a number of highly related complexes sharing conserved subunit homology with yeast Mediator were subsequently identified. The first such complex was TRAP (i.e., TR-associated protein complex) isolated by virtue of its ability to interact with TR in the presence of T3 [18]. This was followed by the isolation of similar if not identical complexes variously termed ARC, DRIP, and NAT, as well as two smaller derivative complexes termed CRSP and PC2 [20–25]. Stringent proteomic analyses suggest that human Mediator complexes share at least 30 common subunits [19] (Fig. 1) including orthologs for most if not all of the yeast Mediator subunits [26]. Conserved Mediator subunits have also been biochemically and genetically identified in fruit flies, nematodes, plants, fungi and algae [26], and in many cases, further demonstrated to play critical roles in metazoan growth and development [14,16,27,28]. The existence of conserved Mediator polypeptides and complexes from such a diverse range of eukaryotic species has led to a unified nomenclature for Mediator subunits [29].

2.2. Structure and submodules

Structural, biochemical, and genetic analyses reveal that both yeast and human Mediator subunits are organized in a similar core structure comprised of a head, middle and tail module (Fig. 1) [16,26,30,31]. The middle and head modules appear to functionally interface with the Pol II basal transcription machinery [32,33], whereas subunits in the tail and middle modules are predominantly targeted by gene-specific activators (Fig. 1). Electron microscopy studies show that human Mediator adopts different conformations upon binding distinct types of activators [34,35] thus suggesting that the complex is a dynamic entity and structurally flexible. In addition to the head, middle and tail modules, the conserved Mediator subunits MED12, MED13, cyclin C and cyclin-dependent kinase 8 (CDK8) comprise a fourth distinct module simply termed the CDK8 module (Fig. 1). The CDK8 module is reversibly associated with the core complex in both yeast and humans, and can be purified as a separate entity [36,37].

2.3. Interactions with the Pol II basal transcription apparatus

Evidence supports the idea that Mediator functions, at least in part, by directly binding to Pol II and facilitating its recruitment to target gene promoters [14–17,32,33]. Moreover, Mediator functionally interacts with multiple components of the basal transcription apparatus including TFIIB, TFIID, TFIIE, and TFIIH, consistent with a regulatory role in Pol II preinitiation complex (PIC) assembly [16,17]. Indeed, Mediator might be regarded as a component of the PIC, comparable in importance to the basal transcription factors and to Pol II itself. Mediator also appears to be required for transcription initiation steps subsequent to the recruitment and assembly of the PIC [38,39]. One way Mediator might facilitate this action is suggested from yeast studies in which the complex was shown to stimulate the Pol II CTD-kinase activity of TFIIH [40], an activity associated with Pol II escape from the PIC. Other studies suggest that specific activator-induced structural shifts within Mediator may be

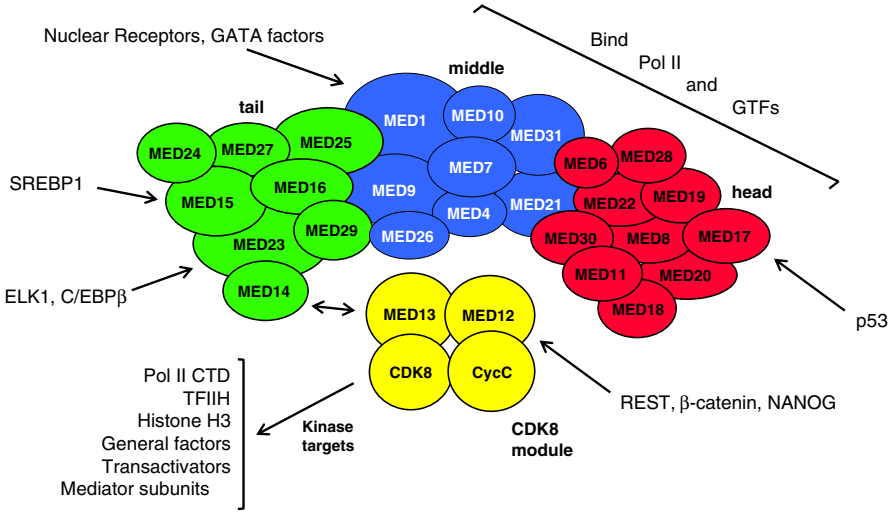

Fig. 1. The human Mediator complex: subunits, submodules, regulatory targets, and interactions with gene-specific transcription factors. Structural organization of the human Mediator complex comprised of the head (red), middle (blue), tail (green), and reversibly associated CDK8 (yellow) submodules. The relative placement of distinct subunits into specific submodules is based upon preliminary structural, biochemical, and binary binding analyses. The precise structural location of some subunits remains poorly characterized. The unified nomenclature for Mediator subunits has been used [29]. Arrows pointing toward the complex indicate specific Mediator binding targets for known gene-specific transcriptional activators. Also indicated are specific phosphorylation substrates of the CDK8 subunit.