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Review

Mediator-dependent nuclear receptor function

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ABSTRACT

As gene-specific transcription factors, nuclear receptors are broadly involved in many important biological processes. Their function on target genes requires the stepwise assembly of different coactivator complexes that facilitate chromatin remodeling and subsequent preinitiation complex (PIC) formation and function. Mediator has proved to be a crucial, and general, nuclear receptor-interacting coactivator, with demonstrated functions in transcription steps ranging from chromatin remodeling to subsequent PIC formation and function. Here we discuss our current understanding of (i) pathways involved in Mediator recruitment and function through nuclear receptor target gene enhancers and promoters, (ii) conditional requirements for the strong nuclear receptor–Mediator interactions mediated by NR AF2 domains and the MED1 LXXLL motifs, (iii) Mediator functions, through different nuclear receptor-interacting subunits, in different metabolic pathways, (iv) emerging functions of Mediator as a corepressor in addition to its major role as a coactivator and (v) mechanisms by which Mediator acts to transmit signals from enhancer-bound nuclear receptors to the general transcription machinery at core promoters to effect PIC formation and function. As a nuclear receptor coregulator with increasingly diverse functions, Mediator may thus modulate nuclear receptor signaling through several different mechanisms.

Contents

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1. Introduction

Nuclear receptors (NRs) comprise a large family of transcription factors that regulate expression of specific genes during development, cell differentiation, reproduction and homeostasis [1–3]. A typical NR consists of structural domains that include a relatively less conserved N-terminal activation domain (AF1), a highly conserved central DNA-binding domain, a hinge region and a conserved C-terminal ligand binding domain (LBD) that contains a second and very strong activation domain (AF2) [3,4]. Many NRs regulate target gene expression in a ligand-dependent manner and typical ligands include steroids (e.g., ER and GR ligands), non-steroids (e.g., TR and VDR ligands) and products of lipid metabolism (e.g., PPAR ligands) [3,4]. The NR superfamily also includes many orphan NRs, such as HNF4α and ERRs, whose ligands are not yet identified [5]. NRs function as homo- or hetero-dimers bound to specific DNA sequences on target gene enhancers and promoters and generally regulate gene expression in a ligand-dependent manner through concerted and stepwise recruitment of various transcription coregulators (including both coactivators and corepressors).

The NR coactivators include (i) factors that effect chromatin modifications, such as the ATP-dependent chromatin remodelers and various factors (e.g., histone acetyl- and methyl-transferases) that directly modify histone tails through their intrinsic enzymatic activities, (ii) steroid receptor coactivator (SRC) and peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) family members that serve as scaffolds to recruit histone-modifying (and potentially other) factors, and (iii) factors, such as the Mediator, that act more directly on the general transcription machinery and RNA polymerase II (for reviews see [3,4,6–12]).

The NR corepressors, which actively repress target gene expression, include the related NR corepressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) proteins. These factors associate with NRs in unliganded states and recruit histone deacetylase (HDAC) complexes to NR target gene promoters to repress transcription [4,12,13]. Other NR corepressors, notably receptor interacting protein 140 (RIP140), interact with NRs and repress their target gene expression in a ligand-dependent manner. The underlying repression mechanisms for RIP140 are thought to involve direct interactions with C-terminal binding proteins (CtBPs), which in turn recruit HDACs [14], as well as competitive interactions with coactivators with overlapping binding sites on liganded NRs [12,13].

The Mediator, mentioned above, is a large multisubunit complex that was originally identified as an activity in yeast [15] and mammalian [16] cell extracts that effected activator-dependent transcription in systems reconstituted with RNA polymerase II and cognate initiation factors. Mediator was first purified, and shown to interact with RNA polymerase II, in yeast [17,18]. The mammalian complex was first purified through an intracellular ligand-dependent association with TRα (and thus called the TRAP complex) and simultaneously shown to be a TRα coactivator [19]. Similar or identical complexes were subsequently reported as the VDR-interacting DRIP complex [20], the SREBP-interacting ARC complex [21], SRB/Med-containing cofactor complex (SMCC) [22], the E1A-interacting human Mediator complex [23], the CRSP complex [24], positive cofactor 2 (PC2) [25], mammalian mediator [26] and negative regulator of activated transcription (NAT) [27]. The yeast and metazoan complexes share many conserved subunits and now are commonly referred to as Mediator [28]. Combined biochemical, genetic and structural studies have revealed that Mediator is organized into discrete head, middle and tail modules, with some subunits (MED1 and MED26) located at the junction of the middle and tail modules [29].

Initial functional studies established that Mediator functions as a coactivator for a variety of DNA-binding activators (reviewed in [29,30]). Subsequent analyses revealed that mammalian Mediator functions not only to effect activator-dependent transcription, but also to stimulate activator-independent basal transcription [31,32] and to suppress transcription through the dissociable CDK8-kinase submodule [4,29]. It is noteworthy that several isolates of Mediator were co-purified with NRs and that Mediator has been found to be a crucial, and general, coactivator for ligand-dependent NR functions. In this review, we will discuss functions of Mediator as an integration center for NR signaling pathways in response to a variety of signal inputs and how Mediator processes these signals to transcription outputs. We discuss, first, how NRs anchor the Mediator complex to target gene promoters; second, types of cell signals that affect this process; and, finally, models of how Mediator transmits the signals from NRs to the general transcription machinery to effect PIC formation and function.

2. MED1 acts as a key component to mediate strong ligand-dependent interactions between Mediator and NRs

Since the cloning of its cognate cDNA, the MED1 subunit of Mediator has been demonstrated to interact strongly with most tested NRs in a ligand-dependent manner and, consequently, to facilitate strong NR–Mediator interactions. These strong, well-characterized interactions between MED1/Mediator and NRs depend upon the MED1 LXXLL motifs and the NR AF2 domain and, importantly, are necessary for maximal NR-dependent transcription in reconstituted cell free systems. Remarkably, however, they were found to be unnecessary for most normal physiological functions, including the adipogenic differentiation pathway that was first shown to require MED1 [33,34]. These results have suggested a conditional requirement for these strong NR–Mediator interactions and functions, perhaps under conditions of dietary stress, as well as the existence of alternative, potentially redundant, pathways for Mediator recruitment. In this regard, there are recent reports of NR/cofactor interactions with the conserved MED1 N-terminal domain that is essential for adipogenesis. These issues and their implications are discussed below.

2.1. MED1 LXXLL motif- and NR AF2-dependent interactions between Mediator and NRs

Along with associated functional studies, the isolation of human Mediator through an intracellular T_3-dependent interaction with TRα [19] and through an *in vitro* $1,25(OH)_2D_3$-dependent interaction with VDR [20] revealed an important new function for NR AF2 domains and greatly enhanced our understanding of how NRs regulate target gene expression in response to cognate ligands. Subsequent studies revealed that TRα and VDR [35,36], as well as many other NRs that include TRβ, ERα/β, PPARα/γ, GR, AR, RARα and RXRα [35,37–43], interact with MED1 in a ligand-dependent manner. Corresponding functional studies have shown MED1-dependent activation of NRs both in cell-based assays [35,37,39–41,44] and, especially, in cell-free systems reconstituted with MED1-deficient Mediator [33,45].

Besides the *in vitro* studies, *in vivo* functional studies with mouse models and derived mouse embryonic fibroblasts (MEFs) with deletions or mutations in the endogenous *Med1* gene also have demonstrated the importance of MED1 in NR-mediated biological processes. The deletion of *Med1* in mice results in embryonic lethality at E11.5 days [44,46], demonstrating an important role of MED1 in transcription during development but not for cell viability per se. Further analysis of MEFs derived from $Med1^{-/-}$ mouse embryos revealed that MED1 is essential for some NR pathways