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Review

Mediator complex proteins are required for diverse developmental processes

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ABSTRACT

The Mediator complex serves a crucial function in gene regulation, forming a link between gene-specific transcription factors and RNA polymerase II. Most protein-coding genes therefore require Mediator complex activity for transcriptional regulation. Given the essential functions performed by Mediator complex proteins in gene regulation, it is not surprising that mutations in Mediator complex genes disrupt animal and plant development. What is more intriguing is that the phenotypes of individual Mediator complex mutants are distinct from each other, demonstrating that certain developmental processes have a greater requirement for specific Mediator complex genes. Additionally, the range of developmental processes that are altered in Mediator complex mutants is broad, affecting a variety of cell types and physiological systems. Gene expression defects in Mediator complex mutants reveal distinct roles for individual Mediator proteins in transcriptional regulation, suggesting that the deletion of one Mediator complex protein does not interfere with transcription in general, but instead alters the expression of specific target genes. Mediator complex proteins may have diverse roles in different organisms as well, as mutants in the same Mediator gene in different species can display dissimilar phenotypes.

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1. Introduction

Organismal development is a complex and highly regulated process relying on the differential expression of various genes required for the generation of diverse cell types. These developmental determinants promote cell fate decisions, which enable the formation of organs with the correct cell content and morphology to allow adult function. Therefore, the regulation of gene expression during development is critical for engineering the correct transition from embryo to adult. The coordinated action of a variety of transcription factors sets into motion the differentiation process whereby specific cell lineages are established. While gene-specific transcription factors are critical for development, confirmed through numerous studies on mutants with developmental defects, specific developmental functions for components of the transcriptional machinery such as co-activators of the TAF complex has also been confirmed through analysis of mutant phenotypes in several organisms [1–4]. In addition, multiple components of the transcriptional Mediator complex are required during development. Perhaps surprisingly, the analysis of Mediator complex mutants in plants and animals has revealed that rather than being generally required for transcription, certain proteins of the Mediator complex regulate the transcription

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Table 1

Mediator gene	Organism	Mutant phenotype	Reference
Med1	Mouse	Cardiac hypoplaysia, placental insufficiency, liver haemorrhage and necrosis, growth delay; Erythropoiesis defects	[14,18,31–33]
Med6	*Drosophila*	Third-instar larval lethality, absence of imaginal discs	[30]
Med12	*C. elegans*	Ectopic vulva cells; Defects in asymmetric cell division	[41,43]
Med12	*Drosophila*	Aberrant photoreceptor differentiation; Disrupted wing disc cell affinity; Deficient expression of *Wg* target genes; Impaired crystal cell development	[35–38,40]
Med12	Zebrafish	Defects in brain, neural crest, and kidney development; Deficits in differentiation in neuronal subtypes and cardiovascular defects; Abnormal cranial neural crest, cartilage, and ear development; Endodermal differentiation defects; Reduced hindbrain cell proliferation and aberrant rhombomere boundaries	[17,46–49]
Med12	Mouse	Dysregulation of *Nanog* target genes in ES cells; Abnormal neural tube closure, axis elongation, somitiogenesis, and cardiac development	[51–53]
Med12	*Arabidopsis*	Delayed expression of embryonic patterning genes, uncoupled cell division, pattern formation and morphogenesis	[45]
Med13	*C. elegans*	Embryonic lethality, vulva defects	[42]
Med13	*Drosophila*	Aberrant photoreceptor differentiation; Disrupted wing disc cell affinity; Deficient expression of *Wg* target genes; Impaired crystal cell development	[35–39]
Med13	*Arabidopsis*	Delayed expression of embryonic patterning genes, uncoupled cell division, pattern formation and morphogenesis	[45]
Med14	Zebrafish	Slight reduction in retinal amacrine cell number, rod cell formation unaffected	[56]
Med15	*Drosophila*	Loss of wing veins, reduction in wing size	[58]
Med21	Mouse	Arrest at blastocyst stage	[27]
Med23	*C. elegans*	Larval lethality, vulva and gonad defects	[65]
Med23	Mouse	Systemic circulatory failure	[66]
Med24	Zebrafish	Lacks retinal dopanergic amacrine cells, decreased rhodopsin expressing cells; Reduction in enteric nervous system neurons	[55,56]
Med24	Mouse	Cardiac hypoplasia, poor vascular development, thin neural tube, intrinsic cell growth defects	[54]
Med25	Zebrafish, Mouse	Palatal malformations	[50]
Med27	Zebrafish	Reduction in retinal amacrine cell layer, increase in rhodopsin expressing cells	[56]
Med28	NIH3T3 cells, C2C12 cells	Smooth muscle gene expression defects	[64]
Med31	*Drosophila*	Cell fate and A/P axis defects	[23]
Med31	Mouse	Cell proliferation defect and developmental delay	[24]

of only a subset of target genes, affecting specific developmental processes (Table 1).

2. The Mediator complex

The Mediator complex is a key transcriptional co-factor, serving as a link between gene-specific transcription factors and RNA polymerase II (pol II). It contains up to 30 proteins [5–7], and shows conservation from yeast to man [8,9]. Structural analysis, co-immunoprecipitation, and protein–protein interaction experiments have revealed that the Mediator complex is composed of four domains: the head, middle, and tail regions which are continually associated with the complex, and the Cdk8 module, whose flexible association with the complex may provide an additional source of regulation of complex activity [10]. Although proteins of the Mediator complex do not directly interact with DNA elements [9], they do bind both general transcription factors and gene-specific transcription factors. For example, mammalian Mediator complex proteins interact with thyroid hormone receptors, serving as a bridge between the receptors and RNA polymerase II [11]. Interactions between individual Mediator proteins and other nuclear hormone receptors, as well as other transcription factors, have been identified [9,12–19]. Due to its key role in bridging interactions between transcription factors and pol II [8], the Mediator complex may perhaps be required for the transcription of all protein-coding genes.

Many of the initial studies revealing a role for the Mediator complex in gene transcription were performed in yeast [20]. While these studies were crucial to determine the function of Mediator complex proteins in recruitment of pol II to active promoters, questions remained as to the conservation of Mediator complex function in plant and animal species. Given the fundamental role of the Mediator complex in transcription of protein-coding genes, it is not unreasonable to propose that loss of function of individual Mediator complex genes would lead to global gene expression defects and reduced cell viability, and that severe developmental abnormalities would be observed in organisms lacking Mediator gene activity. However, recent experimental studies in a variety of organisms have revealed that loss of function mutants in individual Mediator complex genes have very specific developmental defects. The phenotypes resulting from the mutation of different Mediator complex genes in the same organism do not resemble each other. Additionally, mutations in the same gene in different species generate distinct phenotypes [21–24], suggesting that certain Mediator complex genes have functions that are not entirely conserved throughout evolution. A greater understanding of the requirements for individual Mediator complex proteins during development has been gained through the study of mutant phenotypes in plants and animals. This article will present an overview of the Mediator complex genes linked to developmental abnormalities in various organisms, and the developmental processes that rely on Mediator complex function.

3. Mediator complex mutant phenotypes

The developmental defects resulting from mutations in Mediator complex genes reveal that Mediator complex genes are critical regulators of developmental gene expression.

3.1. Cell viability defects: Med21 mutant mice

The Med21 (Srb7) gene was initially identified from a genetic screen in yeast to identify components of the transcriptional machinery [25]. Critically, the Srb proteins as well as Mediator proteins were found to associate with a subcomplex that promoted transcription in response to activators [26]. Due to the