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Review

Mediator and human disease

Jason M. Spaeth, Nam Hee Kim, Thomas G. Boyer*

Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78245, USA

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ABSTRACT

Since the identification of a metazoan counterpart to yeast Mediator nearly 15 years ago, a convergent body of biochemical and molecular genetic studies have confirmed their structural and functional relationship as an integrative hub through which regulatory information conveyed by signal activated transcription factors is transduced to RNA polymerase II. Nonetheless, metazoan Mediator complexes have been shaped during evolution by substantive diversification and expansion in both the number and sequence of their constituent subunits, with important implications for the development of multicellular organisms. The appearance of unique interaction surfaces within metazoan Mediator complexes for transcription factors of diverse species-specific origins extended the role of Mediator to include an essential function in coupling developmentally coded signals with precise gene expression output sufficient to specify cell fate and function. The biological significance of Mediator in human development, suggested by genetic studies in lower metazoans, is emphatically illustrated by an expanding list of human pathologies linked to genetic variation or aberrant expression of its individual subunits. Here, we review our current body of knowledge concerning associations between individual Mediator subunits and specific pathological disorders. When established, molecular etiologies underlying genotype–phenotype correlations are addressed, and we anticipate that future progress in this critical area will help identify therapeutic targets across a range of human pathologies.

Contents

* Corresponding author. Tel.: +1 210 567 7258; fax: +1 210 567 7247.
E-mail address: boyer@uthscsa.edu (T.G. Boyer).

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1. Introduction

The specification and maintenance of cell fate in multicellular organisms is critically dependent upon the precise spatiotemporal control of RNA polymerase II transcription in response to a determinative set of cell-intrinsic and -extrinsic signals. Accordingly, genetic or environmental factors that perturb physiologic transcription controls can alter cell fate decisions leading to a variety of pathologic conditions including developmental defects and cancer. Because of its central importance in organismal biology, metazoans have evolved an elaborate protein machinery to ensure proper transcription control. Work over the last decade and a half has identified Mediator as a critical component of this regulatory apparatus. Mediator is a conserved multiprotein interface between gene-specific transcription factors and RNA polymerase II [1]. In this capacity, Mediator serves to channel regulatory signals from activator and repressor proteins to affect changes in gene expression programs that control diverse physiological processes, including cell growth and homeostasis, development, and differentiation [2,3]. Originally discovered in the budding yeast *Saccharomyces cerevisiae*, Mediator has since been identified as an essential component of the RNA polymerase II transcriptional apparatus in metazoans ranging from worms to humans [4]. Nonetheless, consistent with the enhanced complexity of multicellular organisms, metazoan Mediator complexes are generally larger than their yeast counterparts and include both orthologous as well as metazoan-specific subunits. Among metazoans, mammalian Mediator exhibits the greatest degree of compositional and structural complexity, comprising 33 subunits, 23 of which correspond to clear orthologs in *S. cerevisiae* Mediator.

Because of its role as an integrator and processor of regulatory information conveyed by signal-activated transcription factors, Mediator represents an endpoint in a variety of fundamentally important developmental signaling pathways [2,3,5]. Consistent with such a role, genetic studies in mice have broadly implicated Mediator in mammalian development. Genetic inactivation of core Mediator subunits responsible for direct communication with RNA polymerase II result in very early embryonic lethality, indicating that Mediator *per se* is likely required for cell viability [6]. However, targeted inactivation or mutation of peripheral Mediator subunits, while invariably lethal, nonetheless confers broad yet distinctive defects in organogenesis and altered programs of gene expression that generally phenocopy mutations in essential developmental transcription factors [7–18]. These observations support the idea borne from biochemical and cell-based studies that Mediator transduces regulatory information conveyed by signal-controlled transcription factors that interface with distinct Mediator subunits. Thus, individual Mediator subunits can manifest activator- and/or repressor-selective functions in the regulation of developmental gene programs. It is therefore not unexpected, and emerging studies have indeed confirmed, that individual Mediator subunits are associated with wide range of human diseases spanning congenital malformations to cancer. In this review, we highlight examples in which overt mutation or altered expression of human Mediator subunits have been linked with specific pathological disorders (summarized in Table 1).

2. Mediator and disorders of development

2.1. Neurodevelopmental disorders

2.1.1. MED25 and Charcot–Marie–Tooth disease

Charcot–Marie–Tooth (CMT) disease or hereditary motor and sensory neuropathy (HMSN) comprises a large group of clinically and genetically heterogeneous peripheral nervous system disorders. CMT is the most commonly inherited peripheral neuropathy worldwide, and all mendelian modes of inheritance have been described [19]. Two major CMT forms are distinguishable based on electrophysiological and pathological criteria: the demyelinating CMT type I (CMT1) and the axonal CMT type II (CMT2) [20]. Among all forms of CMT, the autosomal recessive axonal forms (ARCMT2) are comparatively rare and severe [20]. To date, genes for three distinct and specific ARCMT2 loci have been identified on chromosomes 8q (Lamin A/C; *LMNA*), 1q (ganglioside-induced differentiation-associated protein 1; *GDAP1*), and 19q (Mediator subunit 25; *MED25*) [20].

The association of *MED25* on chromosome 19q13.3 with ARCMT2 was initially established through investigation of an extended consanguineous Costa Rican family of Spanish and Amerindian ancestry [21]. Affected patients in this family presented with relatively late-onset chronic symmetric sensory–motor polyneuropathy and axon degeneration. Refined genetic mapping within the 19q13.3 region identified a critical interval of 1 Mb; sequence analysis of this region identified 53 genes, 3 of which exhibited variations that cosegregated with the recessive neuropathy in this family. Among these, a p.A335V missense mutation in *MED25* was identified as the likely disease causing variation.

The molecular basis by which a homozygous A335V missense mutation in MED25 triggers ARCMT2 is unclear. Amino acid 335 lies between two established structural and functional domains in MED25: an N-terminal 'von Willebrand factor type A' domain (aa 17–226) through which MED25 associates with core Mediator, and a C-terminal seven-stranded β-barrel activator interaction domain (aa 402–590) targeted by the viral transactivator VP16 [22,23]. Possibly, the A335V mutation could compromise the structural integrity and/or crosstalk between these two established functional domains, although evidence to support this conjecture is currently lacking. Amino acid 335 is located in a MED25 proline-rich domain with high affinity for SH3 domains of the Abelson type; molecular and biochemical analyses have further revealed that the A335V mutation relaxes the binding specificity of this region, expanding the range of SH3-type domains with which it interacts [21]. However, the functional relevance of the SH3-binding domain for MED25-dependent transcriptional regulation remains to be established, and the significance of these findings is presently unclear. While the direct molecular consequence(s) of the A335V mutation on MED25 structure and/or protein interaction preference thus remains to be established, a likely biological outcome is disruption of MED25 as a critical Mediator interface for an unidentified transcriptional regulator of genes required for peripheral nervous system function.

2.1.2. MED17 and infantile cerebral and cerebellar atrophy

Postnatal-onset microcephaly (POM), in which a normal head circumference at birth declines to >2SD below the mean after the