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Review

Involvement of Mediator complex in malignancy

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ABSTRACT

Mediator complex (MED) is an evolutionarily conserved multiprotein, fundamental for growth and survival of all cells. In eukaryotes, the mRNA transcription is dependent on RNA polymerase II that is associated to various molecules like general transcription factors, MED subunits and chromatin regulators. To date, transcriptional machinery dysfunction has been shown to elicit broad effects on cell proliferation, development, differentiation, and pathologic disease induction, including cancer. Indeed, in malignant cells, the improper activation of specific genes is usually ascribed to aberrant transcription machinery. Here, we focus our attention on the correlation of MED subunits with carcinogenesis. To date, many subunits are mutated or display altered expression in human cancers. Particularly, the role of MED1, MED28, MED12, CDK8 and Cyclin C in cancer is well documented, although several studies have recently reported a possible association of other subunits with malignancy. Definitely, a major comprehension of the involvement of the whole complex in cancer may lead to the identification of MED subunits as novel diagnostic/prognostic tumour markers to be used in combination with imaging technique in clinical oncology, and to develop novel anti-cancer targets for molecular-targeted therapy.

Contents

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1. Introduction

Transcriptional regulation is one of the most important steps in the control of cell identity, growth, differentiation and development. Many signalling pathways, which control these processes, ultimately target the core transcription machinery. For protein coding genes, this apparatus consists of RNA polymerase II (Pol II) and the general transcription factors (TFs) TFIIA, TFIIB, TFIID, TFIIE, TFIIF and TFIIH that contact Mediator complex (MED). MED is the essential coactivator/activator complex acting as a bridge between transcription factors bound at the upstream regulatory elements and the transcription machinery. Crucially, the pre-initiation complex (PIC) consists of MED, Pol II and TFs [1], with MED as a central scaffold within the PIC and regulator of Pol II activity [2–4]. It strongly interacts with Pol II, changes its conformation and influences the transcription initiation process as well as other transcription steps, although the whole involved molecular mechanisms have not yet fully elucidated [5,6]. At present, mammalian MED is composed of at least 31 subunits that are arranged in four structurally distinct modules, head, middle and tail modules representing the main complex core, and kinase module (CDK module), variably associated with the core (Fig. 1) [1,3,7–10]. Structural and biochemical studies have recently revealed the existence of further sub-modules [8,11]. The head and middle modules, containing CDK19 kinase, are known to interact directly with Pol II, whereas the tail module interacts with gene-specific regulatory proteins [2,4,7,8]. In particular, the head module interacts with the Pol II subunit Rpb3 through the MED17 subunit [12,13] whereas MED11 and MED22, other two important head subunits, interact with the TFIIH subunit Rad3 [14]. Finally, crystal structure