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Characterization of subunits of the general transcription factor TFIID

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Background

Initiation of transcription is a key regulatory step affecting gene expression in response to a variety of extra- and intracellular signals, during developmental processes and for tissue specificity. The rate of transcription initiation is determined by enhancer elements that are bound by gene-specific transcription factors; these are modular in their nature, typically consisting of a DNA binding domain and one or more activation (or repression) domains. The transcription initiation site is determined by core promoter elements that direct the assembly of general transcription factors (GTFs) and RNA polymerase II to form the preinitiation complex (PIC).

The general transcription factor TFIID plays an essential role in transcription initiation as it recognizes and binds the core promoter and nucleates the assembly of the PIC (Figure 1). In addition, TFIID plays an important role in mediating transcription activation signals by gene specific activators (Fig. 1).

TFIID is a multisubunit complex that consists of the TATA box-binding protein TBP and a number of TBP associated factors (TAFs) that are present in all cells (Fig. 2). Some of these TAFs have been shown to directly bind activation domains of activators. This interaction is essential for activator-dependent transcription in vitro. At present, little is known about the physiological relevance of these findings as well as the specific functions of TAFs in biological processes involving transcription regulatory programs.

Scientific Activities

The research in our lab focused on deciphering the molecular mechanism of TAFs activities and on the role of TAFs in biological pathways. As a model we are characterizing the function of TAFII105, a subunit that has several unique properties. Unlike the other core TAFs that are expressed in all cells, TAFII105 expression is regulated in a cell type-specific manner. It is more enriched in B and T lymphocytes compared to other cell types. In addition, TAFII105 exists in sub-stoichiometric amounts relative to the core TAFs (Fig. 2a). TAFII105 shares regions of high homology with the core TFIID subunits TAFII130 from human and TAFII110 from *Drosophila* (Fig. 2b). The highly conserved C-terminus of these TAFs mediates interaction with other TAFs and therefore is required for assembly into the TFIID complex. The diverged N-terminus of TAFII105 directs interaction with activation domains of activators.

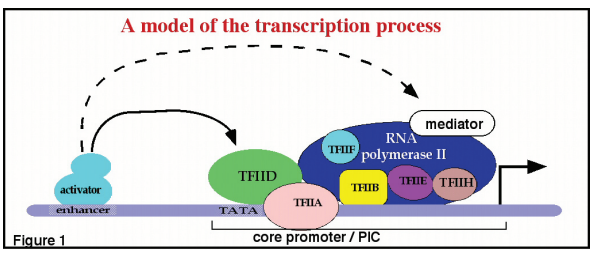

Fig. 1 *A model of the transcription transcription process. Activators bind to enhancer elements and communicate with the general transcription apparatus that is bound to core promoter element.*

Our functional analysis of TAFII105 revealed several transcription factors that selectively interact with the coactivator domain of TAFII105. Among these are members of NF-kappaB family and OCA-B, both play crucial role in lymphocytes gene expression. The transcription factor NF-kappaB is important for specific gene expression in the immune system. In addition, NF-kappaB activates anti-apoptotic genes that protect cells from apoptosis induced by stress and cytokines. Our studies revealed TAFII105 mediates transcription activation of subset of NF-kappaB regulated genes in vitro as well as in cell culture and in an animal model. This function of TAFII105 involves its direct interaction with NF-kappaB and is crucial for lymphocytes survival and differentiation.

TAFII105 also interacts with OCA-B and mediates octamer-dependent transcription in B cells. OCA-B is a B cell specific cofactor of OCT1 and OCT2 transcription factors that are required for transcription of many B cell specific genes.

All these findings provide evidence supporting a notion, that has been speculative so far, that a cell type specific component within the general transcription apparatus is involved in regulation of cell type specific genes.

We are currently using TAFII105-NF-kappaB association to investigate the molecular mechanism of TAFII105 function and the importance of its interaction with activators to the process of transcription activation. Our studies reveal a novel mode of TAF function as TAFII105-NF-kappaB complex was found to be important for transcription steps that are post pre-initiation complex formation such as transcription elongation and transcription re-initiation. Furthermore, our studies also provided a mechanistic explanation for rapid transcriptional induction of genes in response to extracellular signals.

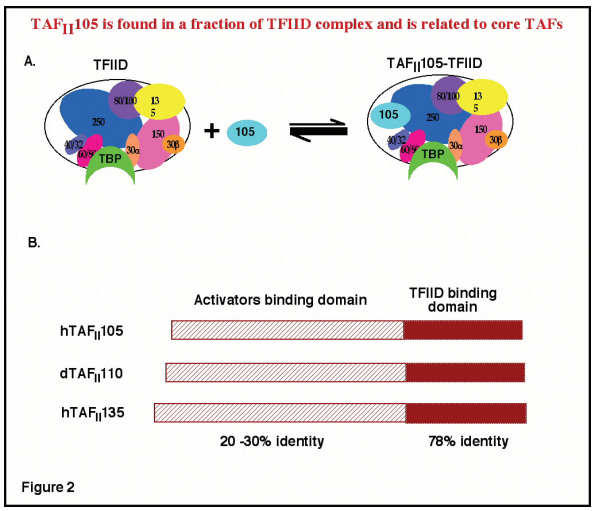

Fig. 2 *A. TFIID is composed of the TATA-binding protein TBP and 14 TBP-associated factors (TAFs). TAFII105 is a cell type specific TFIID component that is found only in a fraction of TFIID complex. B. Schematic structure of related TAFs.*

Our future goals are directed to the investigation of the exact mechanism of TAFs actions, the relationship between activators, TAFs and specific core promoter elements, and the mechanism of regulation of transcription in vivo.

Selected Publications

Yamit-Hezi, A. and Dikstein, R. (1998). TAFII105 mediates activation of anti-apoptotic genes by NF-kappaB. EMBO J. 17, 5161-5169.

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Revach, M., Ainbinder, E., Wolstein, O., Moshonov, S., Dikstein, R. The molecular mechanism of rapid transcriptional induction of NF-kB target genes. (submitted).

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