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Molecular Mechanisms of transcription regulation by TBP-Associated Factor (TAFs) and NF-κB

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Transcription of protein encoding genes in eukaryotes is an intricate and highly regulated process involving a large number of proteins and an elaborate network of interactions. This complexity produces a remarkable diversity in gene expression patterns. Elucidation of the mechanisms that generate such diversity is an important challenge and the primary goal of the research in my lab.

To initiate transcription, RNA polymerase II and basal transcription factors have to assemble into a pre-initiation complex (PIC) on the promoter (Fig 1). The basal factor TFIID is central to this process as it recognizes the core promoter and sets the platform for PIC assembly. The highly conserved TFIID is comprised of the TATA-binding protein (TBP) and 14 associated factors (TAFs). TAFs are important for core promoter recognition and act as coactivators, transducing signals from enhancer-bound activators to the basal transcription machinery (Fig 1).

The focus of our research is to decipher the mechanism underlying TAF-mediated transcription regulation. Although most of the TAFs from various species had been identified and cloned, our knowledge about the molecular function of individual TAFs in transcription is still limited. Our working hypothesis is that TAFs regulate transcription at multiple levels and possess both general and gene specific functions. One of the TAFs extensively characterized in our lab in recent years is **TAFII105** (recently renamed **TAF4b**), which unlike the other TAFs, is both sub-stoichiometric and tissue specific. This raised the possibility that TFIID has gene specific functions, in addition to its general role in transcription. We have used **TAF4b** (TAFII105) to study gene specific aspects of TFIID function and also as a model to investigate the mechanism underlying TAF-mediated transcription regulation *in vivo*. The results of our studies support the notion that a TFIID that contains a cell type-specific TAF has gene-specific functions. Thus, TFIID contributes to the diversity of gene expression that creates the cell specialization in metazoans. We provided evidence for the coactivator role of TAFs *in vivo,* showing that this function requires direct contact with activators. Biological pathways and genes, whose transcription is dependent on the interaction between **TAF4b** and the activator **NFκB** were identified and these were used to analyze the role of TAFs in transcription. Induction of the **TAF4b-NF-κB** target genes by NF-κB is remarkably fast. We investigated the molecular mechanism responsible for rapid transcriptional induction of **NF-κB** target genes and found that rapid transcriptional induction is primarily regulated at the post-initiation level, re-initiation and elongation.

Currently we extend the functional analysis of several TAFs by characterizing their biochemical properties, their core promoter functions, their role in different stages of the transcription cycle and their relations with other transcription regulators. We also define in greater detail the mechanism by which NF-κB target genes are rapidly induced.

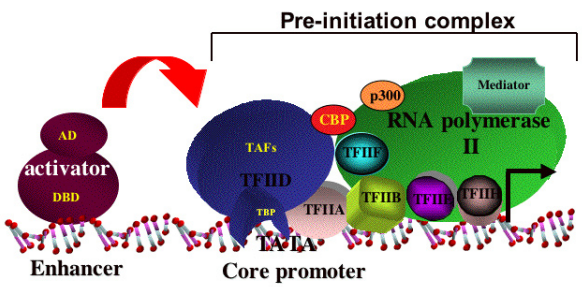

Fig. 1

Selected Publications

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