Molecular Mechanisms of Transcription Regulation

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Transcription of protein encoding genes is an intricate and highly regulated process that produces a remarkable diversity of gene expression patterns. Elucidation of the mechanisms that generate such diversity is an important challenge and the primary goal of the research in our lab. We are investigating the mechanism underlying both basal and regulated transcription.

Basal transcription

1. Characterization of the mammalian core promoter

The core promoter comprises the transcription start site and flanking sequences that anchor general transcription factors (GTFs) and RNA pol II. Until recently the core promoter was thought to be a general element common to most genes. However sequence analysis has revealed unexpected diversity among core promoters. Many promoters do not contain any known core promoter elements and the best known element, the TATA box is found in only ~20% of human promoters. To investigate the mammalian core promoter we are combining bioinformatic tools with molecular analysis. Considering that the core promoter is the ultimate target of all factors that control transcription, diversity in core promoter sequences may play an important regulatory role. Our findings of the past few years revealed revealed important new features of the mammalian core promoter and provide insights into its evolution. Furthermore we found unexpected links between core promoter elements (initiation) to other properties, including transcription elongation (Amir-Zilberstein et al 2007), gene size (Moshonov et al., 2008) and protein translation (Elfakess and Dikstein, submitted).

We are planning to extend this study with a particular emphasis on the biochemical and molecular features of newly identified core promoter elements.

2. TFIID

Among the general transcription factors TFIID is the major core promoter binding factor. TFIID is comprised of the TATA-binding protein (TBP) and 14 TBP-associated factors (TAFs). TAFs control transcription at multiple levels and possess gene-specific as well as general functions. Although our understanding of TFIID is continuously expanding, to date our knowledge on the specific function of individual TAFs is still very limited. We are investigating the function of the TAFs by characterizing their biochemical properties, their core promoter functions, their relations with other transcription regulators and their physiological functions.

Regulated transcription - NF-κB

An activated transcription regulatory pathway that we are studying involves the transcription factor NF-κB. NF-κB regulates the expression of genes involved in immune responses, viral infections, cytokine signaling and stress. While the NF-κB signaling pathways have been studied in great detail, much less is known about the nuclear events that lead to activation of genes by NF-κB. Our goal is to decipher the molecular means by which NF-κB activates the transcription of its native target genes. We have previously determined how, in principle, NF-κB-regulated anti-apoptotic genes are rapidly activated in response to extra-cellular signals. Most recently we discovered that these genes are differentially controlled at the elongation step by positive and negative elongation factors. Our current research is directed towards further elucidating the mechanism by which NF-κB target genes are induced so rapidly and what role is played by transcription elongation factors in this regulation. In addition we are examining the interplay between NF-κB and other transcription factors which contribute to differential activation of NF-κB target genes. Since NF-κB is directly involved in several diseases, including chronic inflammation and cancer it has become an important target for drug development. Understanding the molecular basis of transcription regulation by NF-κB may help in identifying more specific targets for drugs, which will selectively manipulate expression of NF-κB-regulated genes under disease conditions.

MicroRNA transcription

MicroRNAs are non-coding small RNA that silence the expression of target genes. Beside the fact that microRNAs are transcribed by Pol II very little is known about the transcription regulation of the microRNA genes. Our goal is to determine the properties of microRNA transcription by combining bioinformatics and molecular tools.

Selected publications

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