

RNA polymerase II transcription control

RNA polymerase II transcription touches almost everything in eukaryotic biology. It underlies development and differentiation. It is an endpoint of signal transduction pathways. It continually reshapes the cell in response to metabolic needs and environmental information. The purpose of this Special Issue is to convey the current excitement in biochemical studies of polymerase II transcription, and in particular, to relate two recent developments. First, a complete molecular description of the transcription machinery is at hand. A crucial missing link in the pathway of communication between gene regulatory proteins and polymerase II has been found. Second, connections with human disease are coming to light.

Principles of polymerase II transcription

While the focus here upon these two aspects of transcription research might appear narrow, the underlying principles are broad, deriving from a generation of work by many investigators in diverse experimental systems. A simple picture of RNA polymerase II transcription has emerged, whose key features, reviewed in this issue by Roeder, include the following:

(1) Polymerase II promoters are composed of core and regulatory (enhancer, silencer) regions. The core comprises a TATA box and transcription start site, located about 30 basepairs (bp) apart, in almost all promoters, in almost all organisms. By contrast, the regulatory elements are highly varied and gene-specific. They contain one or more sequences for interaction with DNA-binding regulatory proteins. They are located near or at a great distance upstream or downstream from the core promoter.

(2) A universal set of proteins, termed the basal apparatus, recognizes a core promoter and initiates transcription. This basal apparatus comprises polymerase II and the general transcription factors (GTFs) TATA-binding protein (TBP), TFIIB, TFIIE, TFIIF and TFIIH. Virtually every core promoter employs the same basal apparatus, and all the subunits are conserved between yeast

and man. Functions of some GTFs are known (see Fig. 1): TBP binds the TATA box in the first step of forming a transcription initiation complex; TFIIB bridges to the polymerase, determining the 30 bp distance to the transcription start site; TFIIH contains both a helicase, thought to be involved in separation of DNA strands around the transcription start site, and a protein kinase responsible for extensive phosphorylation of the carboxy-terminal domain (CTD) of polymerase II at every round of transcription initiation.

(3) Cell type-specific and gene-specific activator proteins bind enhancer sequences. Additional proteins bind to the activators or to flanking DNA sequences, modulating activator function. These proteins and protein complexes form the interface for input of regulatory information to the transcription apparatus.

Missing link in the activation pathway

The discovery of the bipartite nature of promoters and of the proteins that associate with them raised the question of interaction between the parts. How are the regulatory influences conveyed from enhancers (or silencers) to core promoters? What is the mechanism of communication between activator (or repressor) proteins and the basal apparatus?

Early work, showing activator binding to components of the basal apparatus, suggested direct communication. Functional studies, however, led to a different conclusion. Transcription in a crude, cell-free system was stimulated by activators, but upon fractionation of the system, the stimulatory effect was lost. The effect could be restored by the addition of a novel protein factor(s), presumed to play an intermediary role between activators and the basal apparatus.

The isolation of the intermediary factor, or 'missing link' in the activation pathway, has been pursued in yeast, *Drosophila* and human cells. The outcome is described in three papers in this issue. Björklund and Kim recount the isolation from yeast of a complex termed 'mediator', which enables a response to

activators in a fully defined transcription system. Mediator interacts with the CTD of RNA polymerase II, forming a larger complex, referred to as a holoenzyme. Remarkably, most subunits of mediator were previously identified in genetic screens for mutations affecting the transcription of various yeast promoters. The genetic findings show that mediator is involved in transcriptional activation *in vivo* as well as *in vitro*, that mediator is important for repression as well as for activation, and that mediator interacts with the CTD *in vivo*. The CTD can be viewed as an antenna for regulatory information and the mediator as a signal-processing device, integrating positive and negative inputs, transducing them back to the polymerase for control of transcription.

Pursuit of the intermediary factor in *Drosophila* has given an altogether different result. Verrijzer and Tjian review the discovery and characterization of TBP-associated factors (TAFs), which form a complex with TBP termed TFIID. The presence of TAFs enables a response to activators in a *Drosophila* transcription system. Activators bind to specific TAFs and require the same TAFs in recombinant form, reconstituted with TBP, for the stimulation of transcription. This striking correlation leads to the idea that activators exert their effects by recruiting TFIID to promoters, accelerating the first step in initiation complex formation. Apart from their role in transcriptional activation, certain TAFs directly contact promoter DNA and are suggested to contribute to the specificity of TFIID-promoter interaction. In support of the physiological relevance of TAFs, Verrijzer and Tjian cite two examples of alterations of TAF genes or their expression affecting transcription of specific promoters *in vivo*.

There is no significant overlap between mediator and TAFs. The response to activator proteins in the yeast system is effected by mediator-polymerase complex in the absence of TAFs, while the response in the *Drosophila* system is brought about by TAF-TBP complex in the apparent absence of mediator. The results from yeast and *Drosophila* systems therefore reflect altogether different pathways. These pathways need not, however, be mutually exclusive. Studies in the human system raise the possibility that mediator and TAFs function in concert. As described by Kaiser and Meisterernst, activation in the human system requires both TAFs and positive co-factors, one of which might

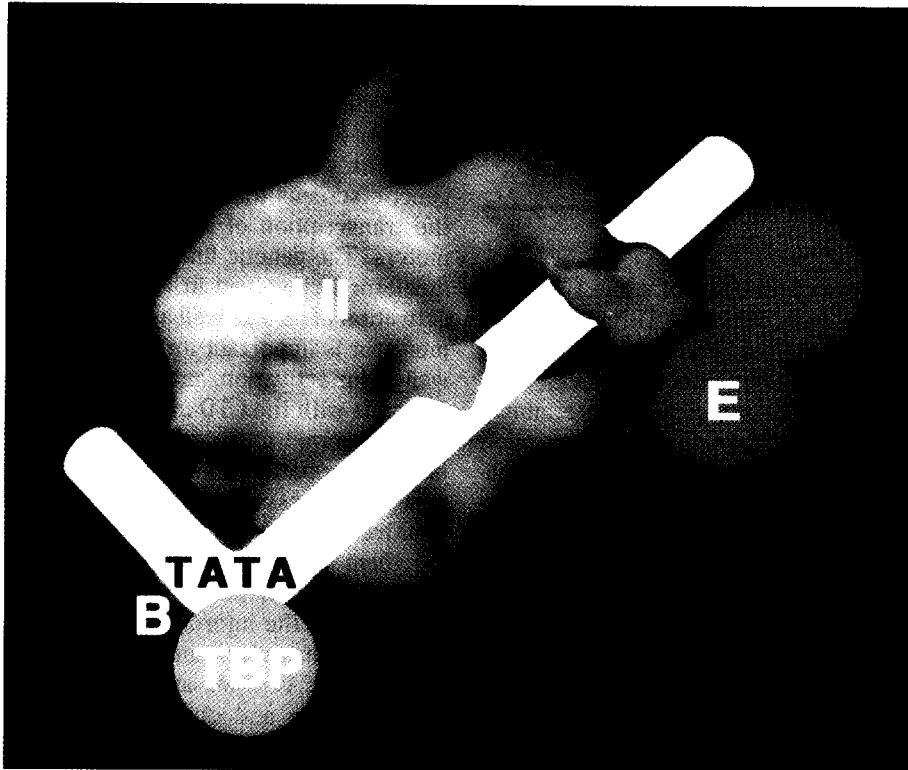


Figure 1

Structure of pre-initiation complex reveals the basis of transcription start-site determination by the TATA-binding protein (TBP) and TFIIB (B). Structure of RNA polymerase II (pol II) is from electron crystallography. TBP, TFIIB and TFIIE (E) are drawn symbolically, to scale, in locations indicated by X-ray and electron crystallography. Transcription initiation occurs at a point on DNA (yellow cylinder) lying within the circle of polymerase protein density abutted by TFIIE.

prove to be the mediator-polymerase complex. Positive co-factor activity is not limited to a single protein or complex, but rather appears to reside in multiple chromatographic fractions, one of which has been resolved to homogeneity as a polypeptide designated PC4. In some instances, the role of positive co-factors might be to relieve inhibition of transcription by negative co-factors, several of which have been identified as well.

At least three solutions have thus been found to the problem of communication between activators and the basal transcription apparatus. Mediator, TAFs

and positive co-factors allow communication *in vitro* and, in some cases, also *in vivo*. An important objective of future studies will be to determine which of these modes of communication predominates *in vivo*.

Disease connections

The TFIIE story, told in these pages by Svejstrup, Vichi and Egly, has two components. First, as mentioned above, TFIIE supplies DNA helicase and protein kinase activities required for the initiation of transcription. Second, TFIIE plays an extraordinary dual role,

participating both in transcription and in the seemingly unrelated process of DNA damage repair. Mutations in TFIIE subunits cause the repair disease xeroderma pigmentosum, as well as other disorders most likely due to defects in transcription.

Although neglected by comparison with initiation, transcription elongation is a source of no less dramatic disease relationships, attesting to its regulatory importance. Reines, Conaway and Conaway describe five protein factors affecting elongation *in vitro*, two of which have been implicated in human carcinogenesis. Further such evidence connecting biochemical studies of transcription with human disease is anticipated.

Back to the future

The biochemical studies of transcription summarized here have all employed naked DNA templates, in part because the natural chromosome template is inert in most transcription assays. Coiling of DNA in the nucleosome, the basal unit of chromosome structure, represses transcription *in vitro* and also *in vivo*. The cellular machinery for overcoming this repression, first exemplified by the yeast SWI-SNF complex, has only recently become accessible to investigation. As derepression is a necessary first step, preceding all RNA polymerase transactions, it is doubtless a major locus of regulation. Future studies will include stepping back along the pathway of gene expression to elucidate such primary events and their contributions to transcription control.

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