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Multiple TATA-Binding Factors Come Back Into Style

Minireview

Stephen Buratowski
Department of Biological Chemistry and
Molecular Pharmacology
Harvard Medical School
Boston, Massachusetts 02115

Clothing fashions come and go in cycles: hemlines go up and down, ties get wider or narrower. Who would have guessed that even bell-bottoms and platform heels would come back into style? In contrast, most of us like to think of science as a linear progression of discoveries, with new and improved theories replacing older, dated models. However, some recent discoveries in eukaryotic transcription provide an opportunity to reach back into the closet and dust off some ideas that had been put in storage. Studies of the RNA polymerase II transcription factor TFIID have updated the idea that there are multiple factors that bind to the TATA sequence and other elements of basal promoters. These results have also revived the notion that the interaction between basal factors and basal promoter sequences influence how the transcription complex responds to regulatory proteins.

First Appearances

In the early to mid-1980's, before any of the basal transcription factors had been cloned or even well characterized, gene expression studies mostly consisted of what is now often dismissed as "promoter bashing." However, these early studies led to several key concepts. In particular, they dissected promoters into two components: basal elements required for accurate start site selection and modular regulatory elements that could be moved about freely. These experiments contributed to the reductionist view that gene regulation was accomplished by taking a generic basal promoter (minimally a TATA box) and simply tacking on binding sites for regulatory transcription factors that responded to various stimuli (e.g., heat shock factor, hormone receptors, etc.). Even though it now appears that regulatory elements in natural promoters have been fine-tuned to a fairly precise architecture (Thanos and Maniatis, 1995), the concept of the generic basal promoter is still largely in fashion.

This simple model wasn't always favored: detailed promoter studies suggested a subtler interplay between regulatory and basal promoter elements. In particular, several labs found that small changes in the TATA element, sometimes even single base mutations, could cause a promoter to lose responsiveness to certain regulatory factors (Wu et al., 1987; Homa et al., 1988; Simon et al., 1988; Harbury and Struhl, 1989). These results were explained in one of two ways: either the DNA sequence was affecting the activity of a single TATA binding factor or perhaps there were actually multiple TATA binding factors in the cell with different functional properties.

Back into the Closet

The idea of multiple TATA binding factors was never widely favored, but it was certainly a viable hypothesis. The existence of multiple sigma factors in bacteria provided the paradigm. Several lines of research eventually made the idea less appealing in eukaryotes. First, as work focused on various inducible and cell type–specific activators, attention was drawn away from the basal promoter sequences. Natural promoters were usually replaced with work horses like the adenovirus major late promoter or the yeast CYC1 promoter without apparent differences in regulatory factor behavior. Next, the cloning of the TATA-binding protein (TBP) genes from yeast and many other organisms seemed to indicate that a single TBP was generally the rule. The recombinant TBPs could recognize many different versions of the TATA element, and so it seemed unnecessary to invoke multiple TBPs. Furthermore, TBP was found to be evolutionarily ancient, supporting transcription by all three eukaryotic polymerases and even appearing in the archaeal transcription machinery (reviewed in Hernandez, 1993).

Even exceptions to the single TBP rule were not considered worrisome. Two TBP genes were cloned from Arabidopsis (Gasch et al., 1990), but doubled genes are not uncommon in this organism and may reflect the history of its genome. A second TBP-related factor (TRF) was also found in Drosophila. TRF exhibits neural-specific expression, and mutations in the factor cause phenotypes related to improper neuron function. Surprisingly (or reassuringly), this protein apparently could not substitute for TBP in an in vitro transcription reaction, despite the fact that it could bind TATA elements (Crowley et al., 1993). It was postulated that TRF was a TBP descendent that had evolved into a more typical, neural-specific regulatory transcription factor.

Updating and Revitalizing

Recently, the idea of multiple TATA-binding factors has made a strong resurgence. The finding that the TATA-binding protein is only one subunit of the multisubunit factor TFIID immediately raised the possibility of multiple TBP-containing complexes with different promoter specificities or functional properties. The discovery of novel TBP-containing complexes functioning in snRNA expression as well as RNA polymerase I and III transcription provided striking proof that different TBP-associated factors (TAFs) could dramatically alter the behavior of TBP (reviewed in Hernandez, 1993). But what about within the family of RNA polymerase II–transcribed genes? Rather than a single monolithic TFIID complex used by all promoters, could there be multiple species of "TFIID" functioning at different points in the cell cycle or in different cell types?

Several papers persuasively argue that this is indeed the case. TFIID isolated from B cells contains a TAF that appears to be a cell type–specific homolog of one of the more ubiquitious TAFs (Dikstein et al., 1996). Human $TAF_{II}30$ appears in only a subset of TFIID molecules, and there appears to be differential responses to estrogen receptor depending on whether or not the TAF is present (Jacq et al., 1994). Thimmers and Sharp (1991) identified a TBP-containing complex that supported basal but not activated transcription. These are likely to be only the

first wave of reports describing variants of TFIID. The major challenge is to demonstrate that these new complexes are biologically relevant. First, it needs to be shown that they are not merely breakdown products or in vitro reassortments of what we currently refer to as TFIID. A key second question is whether the different complexes are simply redundant or whether they possess differential transcription properties that contribute to interesting biological phenomenon. A paper in this issue of *Cell* (Hansen et al., 1997) and a pair of papers in an earlier issue (Shen and Green, 1997; Walker et al., 1997) begin to address the question of whether interactions between specific TFIID subunits and the basal promoter elements affect the transcriptional regulation of genes.

Prompted by the newly discovered variants of TFIID, Hansen et al. (1997) decided to re-examine the properties of the TBP-like TRF. In contrast to the earlier results (Crowley et al., 1993), they found that TRF actually could support transcription in place of TBP, and that it was also complexed in vivo with its own set of associated factors. These TRF-associated proteins (designated nTAFs) are apparently distinct from the TBP-associated factors and are predicted to confer unique functional properties on the TRF–nTAF complex. What these functions are is not clear, but immunomicroscopy of Drosophila polytene chromosomes localizes TRF to a small number of specific loci. The abundance of TRF in the nervous system, as well as its mutant phenotype, makes a clear prediction that the TRF–nTAF complex supports transcription from a subset of neuron-specific genes. There is evidence that a TFIID-like activity derived from brain differs from TFIID derived from HeLa cells in its recognition of core promoter sequences in vitro (Tamura et al., 1990), and it would be interesting to see if this different activity is actually due to the TRF–nTAF complex. Brain cells also contain the "ubiquitous" TFIID complex, raising the question of how the different complexes act with or against each other. Are there even more "alternative" TBPs to be discovered? And could there be alternative versions of other basal factors? It seems very likely.

One Size Does Not Fit All

What are the implications of multiple TFIIDs? It introduces even more complexity to the RNA polymerase II transcription apparatus, which already is thought to contain upwards of 50 proteins. The stock answer to the question of "Why so many proteins?" is that it provides multiple points of regulation and a combinatorial diversity that is necessary for the complicated genetic program involved in metazoan development and adaptation. That may be part of the explanation, and a few gene knockout experiments in mice will undoubtedly address that hypothesis. However, the yeast transcription machinery is very similar to and nearly as complicated as the mammalian or fly (although there is only one TBP in yeast), and it suggests that some of these TAFs have basic functions other than simply acting as targets for activator proteins.

The Green and Struhl labs made the somewhat unsettling discovery that the loss of many TAFs in yeast did not result in a general loss of transcription (Moqtaderi et al., 1996; Walker et al., 1996). Upon closer examination, it has become clear that there is a small subset of genes that show a strong dependence on yTAF$_{II}$145 (Shen and Green, 1997; Walker et al., 1997). Interestingly, the TAF-requiring genes identified so far appear to fall in families, specifically G1- and B-type cyclins and the ribosomal protein genes. Strikingly, the dependence on TAFs is not conferred by the regulatory factors bound upstream in the promoter, but rather by sequence elements in the basal promoter. Also, it is interesting to note that loss of yTAF$_{II}$145 causes some genes to increase their level of expression (Shen and Green, 1997). Therefore, it is probably too simple to think of TAFs as one entity: each TFIID subunit may have different effects on different promoters. In some contexts, a single TAF might act as a coactivator for a specific regulatory protein. In others, it may function primarily as a basal transcription factor, exhibiting enzymatic activity or recognizing specific promoter sequences. In yet another promoter context, the same TAF might act as a transcriptional repressor.

The observation that the requirement for a specific TAF can be dependent upon basal promoter sequences echoes back to the earlier analyses suggesting that all TATA elements are not equivalent. Along similar lines, studies of the factor requirements for different basal promoters have demonstrated that some promoters are less dependent upon the RNA polymerase II C-terminal domain (Thompson et al., 1989) or TFIIE and/or TFIIH (Parvin et al., 1992). Therefore, the concept that basal promoters are generic and interchangeable is clearly an oversimplification. It will be extremely interesting to discover the molecular basis for TAF selectivity and to determine whether individual TAFs are required for unique sets of promoters. The recent advances in genomics should make this type of analysis feasible. Taken to its extreme, this line of thinking leads to the questions of whether every promoter makes a unique set of contacts with TFIID and the other basal transcription factors and whether these specific interactions contribute to the unique expression patterns of individual genes.

Selected Reading

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Author's Note

I apologize for being unable to cite all of the papers that are relevant to this topic. I would like to thank many of the participants of the recent Cold Spring Harbor meeting on "Mechanisms of Eukaryotic Transcription" for interesting discussions that contributed to the ideas presented here.