REVIEW

Regulation of gene expression by TBP-associated proteins

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Transcription of rRNA, mRNA, and small RNAs in eukaryotes is accomplished by RNA polymerases I, II, and III. Much of the control of transcription occurs at the promoters, where transcriptional regulators can affect the recruitment of polymerases and their accessory factors, the rate at which the polymerases leave the promoter and the rate of transcriptional elongation. At least three levels of control must operate to ensure that regulation of the entire genome is efficiently coordinated in response to the extracellular environment and the cell cycle. There must be mechanisms that permit cells to rapidly increase or reduce the transcription of specific protein-coding genes. There must be an ability to modulate global transcription to adjust for changing levels of nutrients or growth factors, and to accommodate the demands of the cell cycle. Finally, there must be a system to coordinate the relative amounts of rRNA, mRNA, and small RNAs.

One factor that is present at promoters used by all three RNA polymerases, and is thus a likely target for all three types of control, is TATA-binding protein (TBP). TBP is associated with a variety of factors that play important roles in both general and gene-specific regulation of gene expression. Early biochemical studies in mammalian, fly, and yeast systems identified three distinct complexes containing TBP, each of which directs transcription at class I, II, or III promoters. The TBP-associated factors that bind to class I, II, and III promoters are called TAF_Is, TAF_{II}s, and TAF_{III}s, respectively. There is now evidence that at least five additional factors interact with TBP. Among the eight factors that interact with TBP, four (TAF_I, TAF_{II}s, TAF_{III}s, and PTF/SNAPc) function in promoter selection (Fig. 1). The other four (SAGA, Mot1, NC2, and Nots) function together with TAF_{II}s to regulate expression of protein-coding genes (Fig. 2). All but one of these factors (PTF/SNAPc) is highly conserved among eukaryotes. The factors that interact with TBP in yeast are summarized in Table 1.

Here we review our current understanding of the eukaryotic TBP-associated proteins and their roles in regulation of gene expression. We describe evidence that rela-

tively small pools of each of the TBP-associated proteins interact with and regulate a large cellular pool of TBP in yeast, and discuss its implications for genome-wide regulation. The conservation of the TBP-associated proteins suggests that the regulatory mechanisms described here apply to eukaryotes in general. Among the concepts that emerge in this discussion, we note that the TBP-associated regulatory apparatus is more complex than is typically modeled for protein-coding genes, that the means by which TBP is recruited to promoters is not yet well understood, and that there are a surprising number and variety of regulatory factors devoted to repressing TBP function.

TAF_Is

TAF_Is function as promoter selectivity factors for rRNA genes (for review, see Geiduschek and Kassavetis 1995). Three TAF_Is are associated with TBP in a complex called SL1 (human), TIF-IB (mouse), or CF (yeast) (Learned et al. 1985; Clos et al. 1986; Schnapp et al. 1990; Comai et al. 1992; Radebaugh et al. 1994; Zomerdijs et al. 1994; Lalo et al. 1996; Lin et al. 1996). TBP-TAF_I complexes contact conserved sequences in the core promoter element of the rDNA promoter and are essential for in vitro transcription by RNA polymerase I (Learned et al. 1985; Clos et al. 1986; Bell et al. 1988; Eberhard et al. 1993; Rudloff et al. 1994; Beckmann et al. 1995; Gong et al. 1995; Lalo et al. 1996; Lin et al. 1996; Radebaugh et al. 1997). TAF_Is also interact with an upstream binding factor that stabilizes SL1/TIF-IB/CF binding and stimulates transcription (Beckmann et al. 1995; Steffan et al. 1996). Mutations in yeast TAF_I genes result in defects in 35S rRNA transcription and led to the cloning of the three yeast TAF_Is, all of which are essential (Keys et al. 1994; Lalo et al. 1996; Lin et al. 1996).

TAF_{II}s

TAF_{II}s bind TBP in a complex called TFIID and have been proposed to be promoter selectivity factors and transcriptional coactivators for protein-coding genes (for review, see Goodrich and Tjian 1994; Burley and Roeder 1996; Verrijzer and Tjian 1996). TFIID complexes have been purified from mammalian, *Drosophila*, and yeast

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Figure 1. Four complexes function as class-specific promoter selectivity factors. The association of TBP with TAF_{II}S, TAF_{II}S, TAF_{III}S, and PTF/SNAPc directs TBP to different promoter classes. The distribution of TBP among these factors contributes to the global regulation of gene expression.

cells, and 9–12 TAF_{II}S are found associated with TBP in these complexes. Almost all of the yeast TAF_{II}S are essential for viability (Henry et al. 1994; Reese et al. 1994; Verrijzer et al. 1994; Poon et al. 1995; Klebanow et al. 1996, 1997; Moqtaderi et al. 1996b; Walker et al. 1996). Several lines of evidence indicate that TAF_{II}S are promoter selectivity factors. TAF_{II}S are required to recognize sequence elements at promoters that lack the consensus sequence for TBP binding. Specific TAF_{II}S bind two such sites, the initiator (Inr) and downstream core promoter element (DPE), which are found at several mammalian and *Drosophila* TATA-less promoters (Verrijzer et al. 1994, 1995; Burke and Kadonaga 1996). Several Inr-directed *in vitro* transcription systems require TFIID and cannot utilize TBP (Smale et al. 1990; Pugh and Tjian 1991; Martinez et al. 1994; Purnell et al. 1994). Promoter hybrid experiments with conditional TAF_{II} mutants in yeast indicate that the requirement for TAF_{II} function maps to core promoter elements (Shen and Green 1997).

TAF_{II}S were originally described as transcriptional co-activators, but there is conflicting evidence for this function. In reconstituted *Drosophila* and human *in vitro* systems, activated transcription does not occur with TBP alone but can be obtained with TFIID (Pugh and Tjian 1990; Dynlacht et al. 1991; Tanese et al. 1991).

These results and evidence that various activators can interact directly with specific TAF_{II}S led to the model that TAF_{II}S mediate recruitment of TBP by activators (Chen et al. 1994; Jacq et al. 1994; Chiang and Roeder 1995; for review, see Verrijzer and Tjian 1996). However, yeast do not show global defects in class II transcription activation when TAF_{II} function is lost *in vivo* (Apone et al. 1996; Moqtaderi et al. 1996a; Walker et al. 1996). Instead, yeast TAF_{II}S appear to be essential for transcription of a subset of protein-coding genes, and TAF_{II} function at these promoters is associated with core promoter elements rather than elements bound by activators (Apone et al. 1996; Moqtaderi et al. 1996a; Shen and Green 1997; Walker et al. 1997). Consistent with the *in vivo* observations in yeast, recent evidence indicates that activation of transcription in crude HeLa extracts can occur independent of TAF_{II}S (Oelgeschlager et al. 1998). As in yeast, TAF_{II} mutations in higher eukaryotic cells affect specific subsets of genes (Wang and Tjian 1994; Sauer et al. 1996; Suzuki-Yagawa et al. 1997; Wang et al. 1997). Metazoan TAF_{II} function at one promoter is apparently associated with both core promoter and enhancer elements (Wang et al. 1997). A better understanding of TAF_{II} function in core promoter recognition and activation awaits more comprehensive *in vivo* analysis.

Figure 2. TBP function in class II transcription is regulated by diverse multisubunit complexes. TAF_{II}S, SAGA, Mot1, NC2, and Nots regulate the expression of protein-coding genes through diverse mechanisms.

Table 1. TBP-associated regulators in *S. cerevisiae*

Factor	Gene	Subunit (kD)	Essential? ^a	Features	References
TAF _I s	<i>RRN6</i>	102	Y		Keys et al. (1994)
	<i>RRN7</i>	60	Y		Keys et al. (1994)
	<i>RRN11</i>	59	Y		Lalo et al. (1996); Lin et al. (1996)
TAF _{II} s	<i>TAF150/TSM1</i>	161	Y	required for cell cycle progression	Verrijzer et al. (1994); Poon et al. (1995)
	<i>TAF145/TAF130</i>	121	Y	histone acetyltransferase	Reese et al. (1994); Poon et al. (1995); Mizzen et al. (1996)
	<i>TAF90</i>	89	Y	required for cell cycle progression	Reese et al. (1994); Poon et al. (1995)
	<i>TAF67</i>	67	Y		Moqtaderi et al. (1996b)
	<i>TAF61/TAF68</i>	61	Y	similar to histone H2B	Moqtaderi et al. (1996b); Walker et al. (1996)
	<i>TAF60</i>	58	Y	similar to histone H4	Poon et al. (1995)
	<i>TAF47</i>	40	Y		Walker et al. (1997)
	<i>TAF40</i>	41	Y		Moqtaderi et al. (1996b); Klebanow et al. (1997)
	<i>TAF30/ANC1/TFG3/SWP29</i>	27	N	component of TFIIF	Henry et al. (1994)
	<i>TAF25/TAF23</i>	23	Y		Klebanow et al. (1996); Moqtaderi et al. (1996b)
	<i>TAF19/FUN81</i>	19	Y		Moqtaderi et al. (1996b)
	<i>TAF17/TAF20</i>	17	Y	similar to histone H3	Moqtaderi et al. (1996b)
	<i>BRF1/TDS4/PCF4</i>	67	Y	homologous to TFIIB	Buratowski and Zhou (1992); Colbert and Hahn (1992); Lopez-de-Leon et al. (1992)
	<i>TFC5/TFC7</i>	68	Y	contains SANT domain	Kassavetis et al. (1995); Ruth et al. (1996)
SAGA	<i>SPT3</i>	38	N		Eisenmann et al. (1992)
	<i>SPT7</i>	153	N		Gansheroff et al. (1995)
	<i>SPT8</i>	66	N		Eisenmann et al. (1994)
	<i>SPT20/ADA5</i>	68	N		Marcus et al. (1996); Roberts et al. (1996)
	<i>ADA2/SWI8</i>	51	N		Berger et al. (1992)
	<i>ADA3/NGG1</i>	79	N		Brandl et al. (1993); Pina et al. (1993)
	<i>GCN5/ADA4/SWI9</i>	51	N	histone acetyltransferase	Georgakopoulos and Thireos (1992); Brownell et al. (1996); Grant et al. (1997)
Mot1	<i>MOT1/BUR3/ADI</i>	210	Y	member of SNF2 family of ATPases	Davis et al. (1992); Piatti et al. (1992); Auble et al. (1994)
NC2	<i>NCB1/BUR6</i>	16	Y	histone fold motif	Goppelt and Meisterernst (1996); Gadbois et al. (1997); Prelich (1997)
	<i>NCB2/YDR1</i>	17	Y	histone fold motif	Goppelt and Meisterernst (1996); Gadbois et al. (1997); Kim et al. (1997)
Nots	<i>NOT1/CDC39</i>	240	Y		Reed et al. (1980); Collart and Struhl (1993)
	<i>NOT2/CDC36</i>	22	N		Reed et al. (1980); Collart and Struhl (1994)
	<i>NOT3</i>	94	N		Collart and Struhl (1994)
	<i>NOT4/MOT2/SIG1</i>	65	N	zinc finger protein	Cade et al. (1994); Collart and Struhl (1994); Irie et al. (1994); Leberer et al. (1994)
	<i>NOT5</i>	66	U	regions of homology with <i>NOT3</i>	Oberholzer and Collart (1998)

^a (U) Unknown.

The largest of the cloned *Drosophila* TAF_{II}s has been reported to have two enzymatic activities. Two kinase domains, located at the termini of dTAF_{II}250, are capable of phosphorylating subunits of general transcription fac-

tors, principally TFIIF (Dikstein et al. 1996). dTAF_{II}250 also contains a highly conserved histone acetyltransferase domain that can acetylate multiple core histone subunits (Mizzen et al. 1996). The enzymatic activities of

this TAF_{II} may have roles in modifying the initiation apparatus or chromatin at promoters, but further study is necessary to determine how these activities are involved in transcriptional regulation *in vivo*.

TAF_{III}s

TAF_{III}s serve as promoter specificity factors for most genes transcribed by RNA polymerase III (for review, see Willis 1993; Kassavetis et al. 1994; White 1994; Geiduschek and Kassavetis 1995). In yeast, two TAF_{III}s are typically associated with TBP in a complex called TFIIB, and this complex can associate with class III promoters containing TBP binding sites (Margottin et al. 1991; Joazeiro et al. 1994). At promoters lacking strong TBP binding sites, TAF_{III}s interact with general factor TFIIC that binds other class III-specific sequence elements and directs TFIIB placement on the promoter (Kassavetis et al. 1990; Joazeiro et al. 1994; Khoo et al. 1994; Chaussivert et al. 1995; Gerlach et al. 1995). TAF_{III}s interact with specific subunits of RNA polymerase III (Werner et al. 1993; Wang and Roeder 1997). The interactions that have been observed between TAF_{III}s, TBP, and TFIIC have been confirmed by genetic analysis and both yeast TAF_{III}s are essential (Buratowski and Zhou 1992; Colbert and Hahn 1992; Lopez-De-Leon et al. 1992; Cormack and Struhl 1993; Werner et al. 1993; Lefebvre et al. 1994; Rameau et al. 1994; Kassavetis et al. 1995; Ruth et al. 1996; Vilalta et al. 1997).

PTF/SNAPc

PTF/SNAPc is a mammalian promoter specificity factor for snRNA promoters, subsets of which are transcribed by either RNA polymerase II or RNA polymerase III (Murphy et al. 1992; Sadowski et al. 1993; Henry et al. 1995; Yoon et al. 1995; for review, see Geiduschek and Kassavetis 1995). Purified PTF/SNAPc consists of four subunits that bind a core promoter element present at both class II and class III snRNA promoters. PTF/SNAPc is required for transcription from snRNA promoters *in vitro* (Henry et al. 1995; Yoon et al. 1995). Multiple subunits of PTF/SNAPc interact with TBP and TBP can be coimmunopurified with antibodies to PTF/SNAPc subunits (Henry et al. 1995, 1996; Bai et al. 1996; Sadowski et al. 1996; Yoon and Roeder 1996). PTF/SNAPc interacts with the nonconserved amino-terminal domain of TBP and stabilizes binding of TBP at snRNA promoters (Mittal and Hernandez 1997). PTF/SNAPc may also serve as the target for DNA-bound activators, which further stabilize the complex on DNA (Yoon et al. 1995; Mittal et al. 1996; Ford and Hernandez 1997; Wong et al. 1998). No obvious PTF/SNAPc homologs are encoded in the yeast genome. Consequently, PTF/SNAPc is the only TBP-associated regulator described here with no genetic evidence for a functional role *in vivo*.

SAGA histone acetylation complex

The SAGA complex regulates class II transcription at a subset of genes through its action on chromatin. Yeast

SAGA is composed of Spt, Ada, and Gcn5 subunits and is capable of nucleosome acetylation (Berger et al. 1992; Eisenmann et al. 1992, 1994; Georgakopoulos and Thireos 1992; Brandl et al. 1993; Pina et al. 1993; Gansheroff et al. 1995; Brownell et al. 1996; Marcus et al. 1996; Roberts and Winston 1996; Grant et al. 1997). Although SAGA does not copurify with TBP (Grant et al. 1997), multiple components of SAGA (Spt3, Ada2, Ada5/Spt20) associate with TBP and genetic evidence is consistent with such an interaction (Eisenmann et al. 1992; Barlev et al. 1995; Roberts and Winston 1996, 1997; Saleh et al. 1997). If SAGA functions through an interaction with TBP, this interaction could facilitate disruption of nucleosomes near promoters to enable efficient transcription initiation or elongation. The components of the SAGA complex are not essential but have positive roles in the regulation of a subset of class II genes including amino acid synthesis, mating pheromone response, mating-type switching, and carbon source metabolism genes (Winston et al. 1984; Hirschhorn and Winston 1988; Berger et al. 1992; Horiuchi et al. 1995; Marcus et al. 1996; Pollard and Peterson 1997; Roberts and Winston 1997). Although the homologous complex has yet to be purified from mammalian cells, homologs of two SAGA components are encoded in the human genome (Candau et al. 1996; Inoue et al. 1996; Wang et al. 1997).

TAF_I, TAF_{II}s, TAF_{III}s, PTF/SNAPc, and Mot1 can be purified in association with TBP. In contrast, SAGA, NC2, and Nots have not been observed to copurify with TBP. However, the lack of copurification of these regulators and TBP does not provide evidence against such an interaction. Indeed, TAF_I, TAF_{II}s, PTF/SNAPc, and Mot1 can be purified independent of TBP (Keys et al. 1994; Reese et al. 1994; Yoon et al. 1995; Bai et al. 1996; Sadowski et al. 1996; Wade and Jaehning 1996; Yoon and Roeder 1996; Auble et al. 1997). The combination of genetic evidence for a functional interaction and biochemical evidence for physical binding makes it likely that SAGA, NC2, and Nots have a functional interaction with TBP.

Mot1

Mot1 represses transcription at a subset of class II genes by inhibiting TBP binding. The 210-kD yeast Mot1 protein binds TBP-DNA complexes and causes the dissociation of TBP from the DNA in an ATP-dependent manner (Auble and Hahn 1993; Auble et al. 1994, 1997; Wade and Jaehning 1996). TBP-Mot1 complexes have been purified from yeast and mammalian sources (Timmers and Sharp 1991; Auble and Hahn 1993; Meyers and Sharp 1993; Auble et al. 1994; Poon et al. 1994; Van Der Knaap et al. 1997). Genetic studies in yeast have linked Mot1 to TBP function *in vivo* (Auble et al. 1994) and have suggested that Mot1 may act with other factors to influence promoter selection by TBP (Collart 1996; Madison and Winston 1997). Yeast Mot1 is essential and affects expression from a subset of genes, including mating pheromone response, DNA synthesis, and amino acid synthe-

sis genes (Davis et al. 1992; Piatti et al. 1992; Auble et al. 1994; Madison and Winston 1997).

NC2

NC2 (Dr1/DRAP1) is a general negative regulator of class II and class III gene expression (Meisterernst and Roeder 1991; Inostroza et al. 1992; Goppelt and Meisterernst 1996; Mermelstein et al. 1996; Gadbois et al. 1997; Kim et al. 1997; Prelich 1997). It has been shown to repress transcription from a wide variety of yeast, mammalian, and viral promoters (Meisterernst and Roeder 1991; Yeung et al. 1994; Kim et al. 1995, 1996; Goppelt and Meisterernst 1996; Goppelt et al. 1996; Mermelstein et al. 1996; Gadbois et al. 1997). NC2 binds to the basic repeat domain of TBP on promoter DNA and can prevent the RNA polymerase II holoenzyme, or its TFIIB subunit, from assembling into an initiation complex (Meisterernst and Roeder 1991; Inostroza et al. 1992; Kim et al. 1995; Goppelt et al. 1996; Mermelstein et al. 1996; Gadbois et al. 1997). We have observed that yeast NC2 can bind to TBP in the absence of DNA (C. Wilson, V. Myer, and R. Young, unpubl.). This leads us to consider whether NC2 might function to regulate the association of TBP with the RNA polymerase II holoenzyme prior to promoter recruitment, thereby preventing its stable association with promoter DNA.

NC2 is composed of two subunits, NC2 α (Dr1) and NC2 β (DRAP1), which dimerize through histone-fold structural motifs (Arents and Moudrianakis 1995). Purified NC2 appears to be a heterotetramer composed of two NC2 α /NC2 β dimers (Goppelt and Meisterernst 1996; Kim et al. 1996). Both subunits have been reported to be essential for yeast cell viability (Gadbois et al. 1997; Kim et al. 1997), although one study suggests that yeast cells can survive and grow extremely slowly without NC2 (Prelich 1997).

Nots

NOT genes have been identified in a screen for suppressors of a defect in the GCN4 transcriptional activator and in five additional yeast genetic screens as negative regulators of cell cycle, pheromone response, and filamentous growth genes (Reed 1980; Collart and Struhl 1993, 1994; Cade and Errede 1994; Irie et al. 1994; Leberer et al. 1994; Mosch and Fink 1997; Oberholzer and Collart 1998). We recently identified a subset of *NOT* genes as suppressors of mutations in the general transcription apparatus, suggesting that they function as general negative regulators (T.I. Lee, J.J. Wyrick, S.S. Koh, E. Jennings, E.L. Gadbois, and R.A. Young, in prep.). The protein products of these five genes form one or more complexes (Collart and Struhl 1994; Liu et al. 1998) and biochemical and genetic evidence has linked them physically and functionally to TBP (Collart and Struhl 1993, 1994; T.I. Lee, J.J. Wyrick, S.S. Koh, E. Jennings, E.L. Gadbois, and R.A. Young, in prep.), but their mechanism of action is not yet understood. *NOT1* is essential and mutations in the other *NOT* genes cause slow

growth phenotypes. A survey of sequence databases reveals that *NOT* genes are also encoded in metazoan genomes.

A large pool of TBP interacts with diverse regulatory proteins in vivo

The biochemical and genetic evidence suggests that at least seven factors, TAF_Is, TAF_{II}s, TAF_{III}s, SAGA, Mot1, NC2, and Nots, form complexes with yeast TBP. Is the level of TBP in yeast cells sufficient to permit independent interactions with each of these TBP-binding factors? We investigated this by preparing crude cell extracts from yeast cells and carrying out Western blot analysis with serial dilutions of extract and known amounts of purified or recombinant proteins. The results indicate that there are 30,000–50,000 molecules of TBP/cell (Table 2). In contrast, there appear to be only 3000–6000 molecules of TAF_{II}s, SAGA, Mot1, NC2, and Nots per cell. At an estimated 3000–6000 molecules per cell, there are sufficient amounts of each of these regulatory factors to regulate a significant fraction of the predicted 6275 class II genes in yeast (Goffeau et al. 1996). Previous results indicate that there are ~200–400 molecules of TAF_Is (Keys et al. 1994, 1996), 3000–6000 molecules of TAF_{II}s (Moqtaderi et al. 1996a; Walker et al. 1996), and

Table 2. Number of selected protein molecules in yeast cells

Yeast protein	Molecules/cell
<i>Transcriptional components</i>	
SRBs/RNA polymerase II holoenzyme	2–4,000 ^a
RNA polymerase II	10–20,000 ^a
TFIIF	30–50,000
TFIIB	30–50,000
TBP	30–50,000
TFIIA	30–50,000
TAF _I s	200–400 ^b
TAF _{II} s	3–6,000 ^{c,d}
TAF _{III} s	8–10,000 ^e
SAGA	3–6,000
Mot1	3–6,000
NC2	3–6,000
Nots	3–6,000
<i>Nontranscriptional components</i>	
Ribosomes	1,500,000 ^f
Tubulin	150,000 ^g
ORC	600 ^h

Whole cell extract was prepared from haploid, S288C wild-type yeast grown to mid-log phase in YPD at 30°C. Serial dilutions of extract were compared to known amounts of recombinant standards by Western blot analysis.

^a Koleske and Young (1994).

^b Keys et al. (1994).

^c Moqtaderi et al. (1996a).

^d Walker et al. (1996).

^e I. Sethy, A. Lopez-de-Leon, R. Moir, and I. Willis (pers. comm.).

^f Nomura et al. (1974).

^g Davis et al. (1993).

^h Rowley et al. (1995).

~10,000 molecules of TAF_{III}s per cell (I. Sethy, A. Lopez-de-Leon, R. Moir and I. Willis, pers. comm.). Quantitative Western analysis with epitope-tagged TBP, TAF_Is, TAF_{II}s, TAF_{III}s, or Mot1 has generated similar estimates for these factors (P.A. Weil, Y. Bai, and A.M. Campbell, unpubl.). Thus, there is a large global pool of TBP in yeast that can interact with smaller pools of these diverse regulatory proteins *in vivo*.

In higher eukaryotes, it would not be surprising to find that TAF_Is, TAF_{II}s, TAF_{III}s, PTF/SNAPc, SAGA, Mot1, NC2, and Nots also interact with and regulate a large global pool of TBP. Indeed, human TAF_I, TAF_{II}s, TAF_{III}s, and MOT1 can all be purified from cells in association with approximately stoichiometric amounts of TBP, suggesting that each of these factors interacts with a subset of cellular TBP.

Implications for gene regulation

Among the eight TBP-associated regulators discussed here, four have roles as class-specific promoter specificity factors (TAF_Is, TAF_{II}s, TAF_{III}s, and PTF/SNAPc), two are histone acetylases with roles at class II genes (TAF_{II}s and SAGA), two are negative regulators of class II genes (Mot1 and Nots), and one is a general negative regulator of class II and class III genes (NC2). There are substantial levels of TBP in yeast cells, more than is necessary to associate with the promoters of all genes at one time. [Yeast have an estimated 140 rRNA genes, 6275 protein-coding genes, and 315 genes for small stable RNAs (Goffeau et al. 1996).] The picture that emerges from this data is that TBP is parceled out among these regulators, and this view has a number of implications for the molecular mechanisms involved in regulation of gene expression.

One critical implication of the information reviewed here is that the role of TBP in transcription of protein-coding genes cannot be described in terms of TAF_{II}s alone. Most models for regulated transcription initiation at protein coding genes describe a process in which TBP, tightly associated with TAF_{II}s, is recruited to promoters. However, five factors have been identified that bind to TBP and that are clearly involved in expression of class II genes *in vivo*: TAF_{II}s, SAGA, Mot1, NC2, and Nots (Fig. 2). The levels of TBP in yeast are approximately tenfold greater than the levels of TAF_{II}s, SAGA, Mot1, NC2, and Nots. Taken together, these data argue that TBP function in class II transcription is regulated by diverse multisubunit complexes including, but not limited to, TAF_{II}s.

Recent genetic evidence in yeast and metazoans indicates that individual TAF_{II}s have essential roles at the promoters of specific subsets of genes but not, apparently, at promoters of all protein coding genes (Wang and Tjian 1994; Apone et al. 1996; Moqtaderi et al. 1996a; Sauer et al. 1996; Shen and Green 1997; Suzuki-Yagawa et al. 1997; Walker et al. 1997). Does this mean that TFIID is not part of the transcription initiation complex at the promoters of all protein coding genes? In our opin-

ion, the available evidence does not yet permit a definitive answer to this question.

If the TAF_{II}s are promoter-specificity factors and do not have essential roles as targets of gene-specific activators, how is TBP recruited to promoters? TBP may be recruited to promoters through direct interactions with activators (Stringer et al. 1990; Horikoshi et al. 1991; Lee et al. 1991; Lieberman and Berk 1991; Liu et al. 1993; Truant et al. 1993; Emili et al. 1994; Kashanchi et al. 1994; Klein and Struhl 1994; Melcher and Johnston 1995; Wu et al. 1996; for review, see Triezenberg 1995). It is also possible that it is brought to promoters in association with RNA polymerase II holoenzyme (Ossipow et al. 1995; Pan et al. 1997). Considerable genetic and biochemical evidence indicate that activators recruit the RNA polymerase II holoenzyme to promoters through interactions with the Srb/mediator complex (Kim et al. 1994; Koleske and Young 1994; Hengartner et al. 1995; Koh et al. 1998; Myers et al. 1998). Association with the holoenzyme may thus provide another pathway to recruit TBP to promoters.

Another implication that emerges from an examination of these TBP regulators is that negative regulation of TBP is so important that three different negative regulators are critical to maintain cell viability. Transcription initiation occurs only rarely for at least half of genes in yeast cells and for an even larger fraction in human cells (Velculescu et al. 1997). Genome packing and consequent steric hindrance may account for some general repression of gene expression, but perhaps is not adequate to completely prevent inappropriate gene expression. In this regard, Mot1, NC2, and Nots, which regulate the availability of TBP and its ability to function at specific promoters, are likely to contribute significantly to the repression of gene expression. The importance of this negative regulation is underscored by the observation that all three factors are essential for yeast cell viability.

Perhaps the most important implication of the observation that TBP function is controlled by a large number of regulatory factors is that much more study is needed to understand how global gene expression is regulated through TBP. The TAF_Is, TAF_{II}s, TAF_{III}s, and PTF/SNAPc clearly provide a means to apportion TBP among the various classes of genes. However, despite knowledge that TAF_{II}s, SAGA, Mot1, NC2, and Nots have important functions at class II promoters, our understanding of the roles of TBP-associated regulators is incomplete. It is not yet clear whether each of these regulators interacts independently with TBP as suggested in Figure 2. Crystallographic studies show that only small surfaces of TBP are required for protein-protein contact, so simultaneous interactions with multiple regulatory factors are possible (Nikolov et al. 1995; Geiger et al. 1996). Although the regulators in Figure 2 are shown functioning at promoters, it is not certain that the action of these factors occurs exclusively on DNA. For example, global regulation of gene expression by NC2 or Nots could involve the sequestering of functional TBP off promoter DNA. It will be important to understand which factors

act generally at class II promoters and which act on a subset, and genome-wide expression monitoring technology (Lashkari et al. 1997; Wodicka et al. 1997) should provide the means to do this. And, of course, it will be interesting to learn how these regulators are regulated.

Acknowledgments

We thank S. Buratowski, M. Green, K. Struhl, P.A. Weil, F. Winston, and members of the Young laboratory for comments on this manuscript. We thank P.A. Weil and I. Willis for sharing unpublished data. This work was supported by National Institutes of Health grants to R.A.Y.

References

- Apone, L.M., C.M. Virbasius, J.C. Reese, and M.R. Green. 1996. Yeast TAF(II)90 is required for cell-cycle progression through G2/M but not for general transcription activation. *Genes & Dev.* **10**: 2368–2380.
- Arents, G. and E.N. Moudrianakis. 1995. The histone fold: A ubiquitous architectural motif utilized in DNA compaction and protein dimerization. *Proc. Natl. Acad. Sci.* **92**: 11170–11174.
- Auble, D.T. and S. Hahn. 1993. An ATP-dependent inhibitor of TBP binding to DNA. *Genes & Dev.* **7**: 844–856.
- Auble, D.T., K.E. Hansen, C.G. Mueller, W.S. Lane, J. Thorner, and S. Hahn. 1994. Mot1, a global repressor of RNA polymerase II transcription, inhibits TBP binding to DNA by an ATP-dependent mechanism. *Genes & Dev.* **8**: 1920–1934.
- Auble, D.T., D. Wang, K.W. Post, and S. Hahn. 1997. Molecular analysis of the SNF2/SWI2 protein family member MOT1, an ATP-driven enzyme that dissociates TATA-binding protein from DNA. *Mol. Cell. Biol.* **17**: 4842–4851.
- Bai, L., Z. Wang, J.B. Yoon, and R.G. Roeder. 1996. Cloning and characterization of the beta subunit of human proximal sequence element-binding transcription factor and its involvement in transcription of small nuclear RNA genes by RNA polymerases II and III. *Mol. Cell. Biol.* **16**: 5419–5426.
- Barlev, N.A., R. Candau, L. Wang, P. Darpino, N. Silverman, and S.L. Berger. 1995. Characterization of physical interactions of the putative transcriptional adaptor, ADA2, with acidic activation domains and TATA-binding protein. *J. Biol. Chem.* **270**: 19337–19344.
- Beckmann, H., J.L. Chen, T. O'Brien, and R. Tjian. 1995. Coactivator and promoter-selective properties of RNA polymerase I TAFs. *Science* **270**: 1506–1509.
- Bell, S.P., R.M. Learned, H.M. Jantzen, and R. Tjian. 1988. Functional cooperativity between transcription factors UBF1 and SL1 mediates human ribosomal RNA synthesis. *Science* **241**: 1192–1197.
- Berger, S.L., B. Pina, N. Silverman, G.A. Marcus, J. Agapite, J.L. Regier, S.J. Triezenberg, and L. Guarente. 1992. Genetic isolation of ADA2: A potential transcriptional adaptor required for function of certain acidic activation domains. *Cell* **70**: 251–265.
- Brandl, C.J., A.M. Furlanetto, J.A. Martens, and K.S. Hamilton. 1993. Characterization of NGG1, a novel yeast gene required for glucose repression of GAL4p-regulated transcription. *EMBO J.* **12**: 5255–5265.
- Brownell, J.E., J. Zhou, T. Ranalli, R. Kobayashi, D.G. Edmondson, S.Y. Roth, and C.D. Allis. 1996. *Tetrahymena* histone acetyltransferase A: A homolog to yeast Gcn5p linking histone acetylation to gene activation. *Cell* **84**: 843–851.
- Buratowski, S. and H. Zhou. 1992. A suppressor of TBP mutations encodes an RNA polymerase III transcription factor with homology to TFIIB. *Cell* **71**: 221–230.
- Burke, T.W. and J.T. Kadonaga. 1996. *Drosophila* TFIID binds to a conserved downstream basal promoter element that is present in many TATA-box-deficient promoters. *Genes & Dev.* **10**: 711–724.
- Burley, S.K. and R.G. Roeder. 1996. Biochemistry and structural biology of transcription factor IID (TFIID). *Annu. Rev. Biochem.* **65**: 769–799.
- Cade, R.M. and B. Errede. 1994. MOT2 encodes a negative regulator of gene expression that affects basal expression of pheromone-responsive genes in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **14**: 3139–3149.
- Candau, R., P.A. Moore, L. Wang, N. Barlev, C.Y. Ying, C.A. Rosen, and S.L. Berger. 1996. Identification of human proteins functionally conserved with the yeast putative adaptors ADA2 and GCN5. *Mol. Cell. Biol.* **16**: 593–602.
- Chaussivert, N., C. Conesa, S. Shaaban, and A. Sentenac. 1995. Complex interactions between yeast TFIIB and TFIIC. *J. Biol. Chem.* **270**: 15353–15358.
- Chen, J.L., L.D. Attardi, C.P. Verrijzer, K. Yokomori, and R. Tjian. 1994. Assembly of recombinant TFIID reveals differential coactivator requirements for distinct transcriptional activators. *Cell* **79**: 93–105.
- Chiang, C.M. and R.G. Roeder. 1995. Cloning of an intrinsic human TFIID subunit that interacts with multiple transcriptional activators. *Science* **267**: 531–536.
- Clos, J., D. Buttgereit, and I. Grummt. 1986. A purified transcription factor (TIF-IB) binds to essential sequences of the mouse rDNA promoter. *Proc. Natl. Acad. Sci.* **83**: 604–608.
- Colbert, T. and S. Hahn. 1992. A yeast TFIIB-related factor involved in RNA polymerase III transcription. *Genes & Dev.* **6**: 1940–1949.
- Collart, M.A. 1996. The NOT, SPT3, and MOT1 genes functionally interact to regulate transcription at core promoters. *Mol. Cell. Biol.* **16**: 6668–6676.
- Collart, M.A. and K. Struhl. 1993. CDC39, an essential nuclear protein that negatively regulates transcription and differentially affects the constitutive and inducible HIS3 promoters. *EMBO J.* **12**: 177–186.
- . 1994. NOT1(CDC39), NOT2(CDC36), NOT3, and NOT4 encode a global-negative regulator of transcription that differentially affects TATA-element utilization. *Genes & Dev.* **8**: 525–537.
- Comai, L., N. Tanese, and R. Tjian. 1992. The TATA-binding protein and associated factors are integral components of the RNA polymerase I transcription factor, SL1. *Cell* **68**: 965–976.
- Cormack, B.P. and K. Struhl. 1993. Regional codon randomization: Defining a TATA-binding protein surface required for RNA polymerase III transcription. *Science* **262**: 244–248.
- Davis, A., G.R. Sage, L. Wilson, and K.W. Farrell. 1993. Purification and biochemical characterization of tubulin from the budding yeast *Saccharomyces cerevisiae*. *Biochemistry* **32**: 8823–8835.
- Davis, J.L., R. Kunisawa, and J. Thorner. 1992. A presumptive helicase (MOT1 gene product) affects gene expression and is required for viability in the yeast *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **12**: 1879–1892.
- Dikstein, R., S. Ruppert, and R. Tjian. 1996. TAFII250 is a bipartite protein kinase that phosphorylates the basal transcription factor RAP74. *Cell* **84**: 781–790.
- Dynlacht, B.D., T. Hoey, and R. Tjian. 1991. Isolation of coactivators associated with the TATA-binding protein that mediate transcriptional activation. *Cell* **66**: 563–576.
- Eberhard, D., L. Tora, J.M. Egly, and I. Grummt. 1993. A TBP-containing multiprotein complex (TIF-IB) mediates tran-

- scription specificity of murine RNA polymerase I. *Nucleic Acids Res.* **21**: 4180–4186.
- Eisenmann, D.M., K.M. Arndt, S.L. Ricupero, J.W. Rooney, and F. Winston. 1992. SPT3 interacts with TFIID to allow normal transcription in *Saccharomyces cerevisiae*. *Genes & Dev.* **6**: 1319–1331.
- Eisenmann, D.M., C. Chapon, S.M. Roberts, C. Dollard, and F. Winston. 1994. The *Saccharomyces cerevisiae* SPT8 gene encodes a very acidic protein that is functionally related to SPT3 and TATA-binding protein. *Genetics* **137**: 647–657.
- Emili, A., J. Greenblatt, and C.J. Ingles. 1994. Species-specific interaction of the glutamine-rich activation domains of Sp1 with the TATA box-binding protein. *Mol. Cell. Biol.* **14**: 1582–1593.
- Ford, E. and N. Hernandez. 1997. Characterization of a trimeric complex containing Oct-1, SNAPc, and DNA. *J. Biol. Chem.* **272**: 16048–16055.
- Gadbois, E.L., D.M. Chao, J.C. Reese, M.R. Green, and R.A. Young. 1997. Functional antagonism between RNA polymerase II holoenzyme and global negative regulator NC2 *in vivo*. *Proc. Natl. Acad. Sci.* **94**: 3145–3150.
- Gansheroff, L.J., C. Dollard, P. Tan, and F. Winston. 1995. The *Saccharomyces cerevisiae* SPT7 gene encodes a very acidic protein important for transcription *in vivo*. *Genetics* **139**: 523–536.
- Geiduschek, E.P. and G.A. Kassavetis. 1995. Comparing transcriptional initiation by RNA polymerases I and III. *Curr. Opin. Cell Biol.* **7**: 344–351.
- Geiger, J.H., S. Hahn, S. Lee, and P.B. Sigler. 1996. Crystal structure of the yeast TFIIA/TBP/DNA complex. *Science* **272**: 830–836.
- Georgakopoulos, T. and G. Thireos. 1992. Two distinct yeast transcriptional activators require the function of the GCN5 protein to promote normal levels of transcription. *EMBO J.* **11**: 4145–4152.
- Gerlach, V.L., S.K. Whitehall, E.P. Geiduschek, and D.A. Brow. 1995. TFIIB placement on a yeast U6 RNA gene *in vivo* is directed primarily by TFIIC rather than by sequence-specific DNA contacts. *Mol. Cell. Biol.* **15**: 1455–1466.
- Goffeau, A., B.G. Barrell, H. Bussey, R.W. Davis, B. Dujon, H. Feldmann, F. Galibert, J.D. Hoheisel, C. Jacq et al. 1996. Life with 6000 genes. *Science* **274**: 546, 563–567.
- Gong, X., C.A. Radebaugh, G.K. Geiss, M.N. Simon, and M.R. Paule. 1995. Site-directed photo-cross-linking of rRNA transcription initiation complexes. *Mol. Cell. Biol.* **15**: 4956–4963.
- Goodrich, J.A. and R. Tjian. 1994. TBP-TAF complexes: Selectivity factors for eukaryotic transcription. *Curr. Opin. Cell Biol.* **6**: 403–409.
- Goppelt, A. and M. Meisterernst. 1996. Characterization of the basal inhibitor of class II transcription NC2 from *Saccharomyces cerevisiae*. *Nucleic Acids Res.* **24**: 4450–4455.
- Goppelt, A., G. Stelzer, F. Lottspeich, and M. Meisterernst. 1996. A mechanism for repression of class II gene transcription through specific binding of NC2 to TBP-promoter complexes via heterodimeric histone fold domains. *EMBO J.* **15**: 3105–3116.
- Grant, P.A., L. Duggan, J. Cote, S.M. Roberts, J.E. Brownell, R. Candau, R. Ohba, T. Owen-Hughes, C.D. Allis et al. 1997. Yeast Gcn5 functions in two multisubunit complexes to acetylate nucleosomal histones: Characterization of an Ada complex and the SAGA (Spt/Ada) complex. *Genes & Dev.* **11**: 1640–1650.
- Hengartner, C.J., C.M. Thompson, J. Zhang, D.M. Chao, S.M. Liao, A.M. Koleske, S. Okamura, and R.A. Young. 1995. Association of an activator with an RNA polymerase II holoenzyme. *Genes & Dev.* **9**: 897–910.
- Henry, N.L., A.M. Campbell, W.J. Feaver, D. Poon, P.A. Weil, and R.D. Kornberg. 1994. TFIIF-TAF-RNA polymerase II connection. *Genes & Dev.* **8**: 2868–2878.
- Henry, R.W., B. Ma, C.L. Sadowski, R. Kobayashi, and N. Hernandez. 1996. Cloning and characterization of SNAP50, a subunit of the snRNA-activating protein complex SNAPc. *EMBO J.* **15**: 7129–7136.
- Henry, R.W., C.L. Sadowski, R. Kobayashi, and N. Hernandez. 1995. A TBP-TAF complex required for transcription of human snRNA genes by RNA polymerase II and III. *Nature* **374**: 653–656.
- Hirschhorn, J.N. and F. Winston. 1988. SPT3 is required for normal levels of a-factor and alpha-factor expression in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **8**: 822–827.
- Horikoshi, N., K. Maguire, A. Kralli, E. Maldonado, D. Reinberg, and R. Weinmann. 1991. Direct interaction between adenovirus E1A protein and the TATA box binding transcription factor IID. *Proc. Natl. Acad. Sci.* **88**: 5124–5128.
- Horiuchi, J., N. Silverman, G.A. Marcus, and L. Guarente. 1995. ADA3, a putative transcriptional adaptor, consists of two separable domains and interacts with ADA2 and GCN5 in a trimeric complex. *Mol. Cell. Biol.* **15**: 1203–1209.
- Inostroza, J.A., F.H. Mermelstein, I. Ha, W.S. Lane, and D. Reinberg. 1992. Dr1, a TATA-binding protein-associated phosphoprotein and inhibitor of class II gene transcription. *Cell* **70**: 477–489.
- Inoue, M., M. Isomura, S. Ikegawa, T. Fujiwara, S. Shin, H. Moriya, and Y. Nakamura. 1996. Isolation and characterization of a human cDNA clone (GCN5L1) homologous to GCN5, a yeast transcription activator. *Cytogenet. Cell Genet.* **73**: 134–136.
- Irie, K., K. Yamaguchi, K. Kawase, and K. Matsumoto. 1994. The yeast MOT2 gene encodes a putative zinc finger protein that serves as a global negative regulator affecting expression of several categories of genes, including mating-pheromone-responsive genes. *Mol. Cell. Biol.* **14**: 3150–3157.
- Jacq, X., C. Brou, Y. Lutz, I. Davidson, P. Chambon, and L. Tora. 1994. Human TAFII30 is present in a distinct TFIID complex and is required for transcriptional activation by the estrogen receptor. *Cell* **79**: 107–117.
- Joazeiro, C.A., G.A. Kassavetis, and E.P. Geiduschek. 1994. Identical components of yeast transcription factor IIIB are required and sufficient for transcription of TATA box-containing and TATA-less genes. *Mol. Cell. Biol.* **14**: 2798–2808.
- Kashanchi, F., G. Piras, M.F. Radonovich, J.F. Duvall, A. Fattaey, C.M. Chiang, R.G. Roeder, and J.N. Brady. 1994. Direct interaction of human TFIID with the HIV-1 transactivator tat. *Nature* **367**: 295–299.
- Kassavetis, G.A., C. Bardeleben, B. Bartholomew, B.R. Braun, C.A.P. Joazeiro, M. Pisano, and E.P. Geiduschek. 1994. Transcription by RNA polymerase III. In *Transcription, mechanisms and regulation* (ed. R.C. Conaway and J.W. Conaway), pp. 107–126. Raven Press, New York, NY.
- Kassavetis, G.A., B.R. Braun, L.H. Nguyen, and E.P. Geiduschek. 1990. *S. cerevisiae* TFIIB is the transcription initiation factor proper of RNA polymerase III, while TFIIA and TFIIC are assembly factors. *Cell* **60**: 235–245.
- Kassavetis, G.A., S.T. Nguyen, R. Kobayashi, A. Kumar, E.P. Geiduschek, and M. Pisano. 1995. Cloning, expression, and function of TFC5, the gene encoding the B' component of the *Saccharomyces cerevisiae* RNA polymerase III transcription factor TFIIB. *Proc. Natl. Acad. Sci.* **92**: 9786–9790.
- Keys, D.A., B.S. Lee, J.A. Dodd, T.T. Nguyen, L. Vu, E. Fantino, L.M. Burson, Y. Nogi, and M. Nomura. 1996. Multiprotein transcription factor UAF interacts with the upstream ele-

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- ment of the yeast RNA polymerase I promoter and forms a stable preinitiation complex. *Genes & Dev.* **10**: 887–903.
- Keys, D.A., L. Vu, J.S. Steffan, J.A. Dodd, R.T. Yamamoto, Y. Nogi, and M. Nomura. 1994. *RRN6* and *RRN7* encode subunits of a multiprotein complex essential for the initiation of rDNA transcription by RNA polymerase I in *Saccharomyces cerevisiae*. *Genes & Dev.* **8**: 2349–2362.
- Khoo, B., B. Brophy, and S.P. Jackson. 1994. Conserved functional domains of the RNA polymerase III general transcription factor BRF. *Genes & Dev.* **8**: 2879–2890.
- Kim, J., J.D. Parvin, B.M. Shykind, and P.A. Sharp. 1996. A negative cofactor containing Dr1/p19 modulates transcription with TFIIA in a promoter-specific fashion. *J. Biol. Chem.* **271**: 18405–18412.
- Kim, S., J.G. Na, M. Hampsey, and D. Reinberg. 1997. The Dr1/DRAP1 heterodimer is a global repressor of transcription *in vivo*. *Proc. Natl. Acad. Sci.* **94**: 820–825.
- Kim, T.K., Y. Zhao, H. Ge, R. Bernstein, and R.G. Roeder. 1995. TATA-binding protein residues implicated in a functional interplay between negative cofactor NC2 (Dr1) and general factors TFIIA and TFIIB. *J. Biol. Chem.* **270**: 10976–10981.
- Kim, Y.J., S. Bjorklund, Y. Li, M.H. Sayre, and R.D. Kornberg. 1994. A multiprotein mediator of transcriptional activation and its interaction with the C-terminal repeat domain of RNA polymerase II. *Cell* **77**: 599–608.
- Klebanow, E.R., D. Poon, S. Zhou, and P.A. Weil. 1996. Isolation and characterization of *TAF25*, an essential yeast gene that encodes an RNA polymerase II-specific TATA-binding protein-associated factor. *J. Biol. Chem.* **271**: 13706–13715.
- Klebanow, E.R., D. Poon, S. Zhou, and P.A. Weil. 1997. Cloning and characterization of an essential *Saccharomyces cerevisiae* gene, *TAF40*, which encodes yTAF_{II}40, an RNA polymerase II-specific TATA-binding protein-associated factor. *J. Biol. Chem.* **272**: 9436–9442.
- Klein, C. and K. Struhl. 1994. Increased recruitment of TATA-binding protein to the promoter by transcriptional activation domains *in vivo*. *Science* **266**: 280–282.
- Koh, S.S., A.Z. Ansari, M. Ptashne, and R.A. Young. 1998. An activator target in the RNA polymerase II holoenzyme. *Mol. Cell* **1**: (in press).
- Koleske, A.J. and R.A. Young. 1994. An RNA polymerase II holoenzyme responsive to activators. *Nature* **368**: 466–469.
- Lalo, D., J.S. Steffan, J.A. Dodd, and M. Nomura. 1996. *RRN11* encodes the third subunit of the complex containing Rrn6p and Rrn7p that is essential for the initiation of rDNA transcription by yeast RNA polymerase I. *J. Biol. Chem.* **271**: 21062–21067.
- Lashkari, D.A., J.L. DeRisi, J.H. McCusker, A.F. Namath, C. Gentile, S.Y. Hwang, P.O. Brown, and R.W. Davis. 1997. Yeast microarrays for genome wide parallel genetic and gene expression analysis. *Proc. Natl. Acad. Sci.* **94**: 13057–13062.
- Learned, R.M., S. Cordes, and R. Tjian. 1985. Purification and characterization of a transcription factor that confers promoter specificity to human RNA polymerase I. *Mol. Cell. Biol.* **5**: 1358–1369.
- Leberer, E., D. Dignard, D. Harcus, M. Whiteway, and D.Y. Thomas. 1994. Molecular characterization of *SIG1*, a *Saccharomyces cerevisiae* gene involved in negative regulation of G-protein-mediated signal transduction. *EMBO J.* **13**: 3050–3064.
- Lee, W.S., C.C. Kao, G.O. Bryant, X. Liu, and A.J. Berk. 1991. Adenovirus E1A activation domain binds the basic repeat in the TATA box transcription factor. *Cell* **67**: 365–376.
- Lefebvre, O., J. Ruth, and A. Sentenac. 1994. A mutation in the largest subunit of yeast TFIIC affects tRNA and 5 S RNA synthesis. Identification of two classes of suppressors. *J. Biol. Chem.* **269**: 23374–23381.
- Lieberman, P.M. and A.J. Berk. 1991. The Zta trans-activator protein stabilizes TFIID association with promoter DNA by direct protein–protein interaction. *Genes & Dev.* **5**: 2441–2454.
- Lin, C.W., B. Moorefield, J. Payne, P. Aprikan, K. Mitomo, and R.H. Reeder. 1996. A novel 66-kilodalton protein complexes with Rrn6, Rrn7, and TATA-binding protein to promote polymerase I transcription initiation in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **16**: 6436–6443.
- Liu, H.Y., V. Badarinarayana, D.C. Audino, J. Rappsilber, M. Mann, and C.L. Denis. 1998. The NOT proteins are part of the CCR4 transcriptional complex and affect gene expression both positively and negatively. *EMBO J.* **17**: 1096–1106.
- Liu, X., C.W. Miller, P.H. Koeffler, and A.J. Berk. 1993. The p53 activation domain binds the TATA box-binding polypeptide in Holo-TFIID, and a neighboring p53 domain inhibits transcription. *Mol. Cell. Biol.* **13**: 3291–3300.
- Lopez-De-Leon, A., M. Librizzi, K. Puglia, and I.M. Willis. 1992. *PCF4* encodes an RNA polymerase III transcription factor with homology to TFIIB. *Cell* **71**: 211–220.
- Madison, J.M. and F. Winston. 1997. Evidence that Spt3 functionally interacts with Mot1, TFIIA, and TATA-binding protein to confer promoter-specific transcriptional control in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **17**: 287–295.
- Marcus, G.A., J. Horiuchi, N. Silverman, and L. Guarente. 1996. *ADA5/SPT20* links the *ADA* and *SPT* genes, which are involved in yeast transcription. *Mol. Cell. Biol.* **16**: 3197–3205.
- Margottin, F., G. Dujardin, M. Gerard, J.M. Egly, J. Huet, and A. Sentenac. 1991. Participation of the TATA factor in transcription of the yeast U6 gene by RNA polymerase C. *Science* **251**: 424–426.
- Martinez, E., C.M. Chiang, H. Ge, and R.G. Roeder. 1994. TATA-binding protein-associated factor(s) in TFIID function through the initiator to direct basal transcription from a TATA-less class II promoter. *EMBO J.* **13**: 3115–3126.
- Meisterernst, M. and R.G. Roeder. 1991. Family of proteins that interact with TFIID and regulate promoter activity. *Cell* **67**: 557–567.
- Melcher, K. and S.A. Johnston. 1995. GAL4 interacts with TATA-binding protein and coactivators. *Mol. Cell. Biol.* **15**: 2839–2848.
- Mermelstein, F., K. Yeung, J. Cao, J.A. Inostroza, H. Erdjument-Bromage, K. Egelson, D. Landsman, P. Levitt, P. Tempst et al. 1996. Requirement of a corepressor for Dr1-mediated repression of transcription. *Genes & Dev.* **10**: 1033–1048.
- Meyers, R.E. and P.A. Sharp. 1993. TATA-binding protein and associated factors in polymerase II and polymerase III transcription. *Mol. Cell. Biol.* **13**: 7953–7960.
- Mittal, V. and N. Hernandez. 1997. Role for the amino-terminal region of human TBP in U6 snRNA transcription. *Science* **275**: 1136–1140.
- Mittal, V., M.A. Cleary, W. Herr, and N. Hernandez. 1996. The Oct-1 POU-specific domain can stimulate small nuclear RNA gene transcription by stabilizing the basal transcription complex SNAPc. *Mol. Cell. Biol.* **16**: 1955–1965.
- Mizzen, C.A., X.J. Yang, T. Kokubo, J.E. Brownell, A.J. Bannister, T. Owen-Hughes, J. Workman, L. Wang, S.L. Berger, T. Kouzanides et al. 1996. The TAF(II)250 subunit of TFIID has histone acetyltransferase activity. *Cell* **87**: 1261–1270.
- Moqtaderi, Z., Y. Bai, D. Poon, P.A. Weil, and K. Struhl. 1996a. TBP-associated factors are not generally required for transcriptional activation in yeast. *Nature* **383**: 188–191.
- Moqtaderi, Z., J.D. Yale, K. Struhl, and S. Buratowski. 1996b. Yeast homologs of higher eukaryotic TFIID subunits. *Proc. Natl. Acad. Sci.* **93**: 14654–14658.
- Mosch, H.U. and G.R. Fink. 1997. Dissection of filamentous

- growth by transposon mutagenesis in *Saccharomyces cerevisiae*. *Genetics* **145**: 671–684.
- Murphy, S., J.B. Yoon, T. Gerster, and R.G. Roeder. 1992. Oct-1 and Oct-2 potentiate functional interactions of a transcription factor with the proximal sequence element of small nuclear RNA genes. *Mol. Cell. Biol.* **12**: 3247–3261.
- Myers, L.C., C.M. Gustafsson, D.A. Bushnell, M. Lui, H. Erdjument-Bromage, P. Tempst, and R.D. Kornberg. 1998. The Med proteins of yeast and their function through the RNA polymerase II carboxy-terminal domain. *Genes & Dev.* **12**: 45–54.
- Nikolov, D.B., H. Chen, E.D. Halay, A.A. Usheva, K. Hisatake, D.K. Lee, R.G. Roeder, and S.K. Burley. 1995. Crystal structure of a TFIIB-TBP-TATA-element ternary complex. *Nature* **377**: 119–128.
- Nomura, M., A. Tissiers, and P. Lengyel, eds. 1974. Ribosomes. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.
- Oberholzer, U. and M.A. Collart. 1998. Characterization of *NOT5* that encodes a new component of the NOT protein complex. *Gene* **207**: 61–69.
- Oelgeschlager, T., Y. Tao, Y.-K. Kang, and R.G. Roeder. 1998. Transcription activation via enhanced preinitiation complex assembly in a human cell-free system lacking TAF_{II}s. *Mol. Cell* (in press).
- Ossipow, V., J.-P. Tassan, E.A. Nigg, and U. Schibler. 1995. A mammalian RNA polymerase II holoenzyme containing all components required for promoter-specific transcription initiation. *Cell* **83**: 137–146.
- Pan, G., T. Aso, and J. Greenblatt. 1997. Interaction of elongation factors TFIIS and eIF4A with a human RNA polymerase II holoenzyme capable of promoter-specific initiation and responsive to transcriptional activators. *J. Biol. Chem.* **272**: 24563–24571.
- Piatti, S., R. Tazzi, A. Pizzagalli, P. Plevani, and G. Lucchini. 1992. Control of DNA synthesis genes in budding yeast: Involvement of the transcriptional modulator MOT1 in the expression of the DNA polymerase alpha gene. *Chromosoma* **102**: S107–113.
- Pina, B., S. Berger, G.A. Marcus, N. Silverman, J. Agapite, and L. Guarente. 1993. *ADA3*: a gene, identified by resistance to GAL4-VP16, with properties similar to and different from those of *ADA2*. *Mol. Cell. Biol.* **13**: 5981–5989.
- Pollard, K.J. and C.L. Peterson. 1997. Role for *ADA/GCN5* products in antagonizing chromatin mediated transcriptional repression. *Mol. Cell. Biol.* **17**: 6212–6222.
- Poon, D., Y. Bai, A.M. Campbell, S. Bjorklund, Y.J. Kim, S. Zhou, R.D. Kornberg, and P.A. Weil. 1995. Identification and characterization of a TFIID-like multiprotein complex from *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci.* **92**: 8224–8228.
- Poon, D., A.M. Campbell, Y. Bai, and P.A. Weil. 1994. Yeast TAF₁₇₀ is encoded by MOT1 and exists in a TATA box-binding protein (TBP)-TBP-associated factor complex distinct from transcription factor IID. *J. Biol. Chem.* **269**: 23135–23140.
- Prelich, G. 1997. *Saccharomyces cerevisiae BUR6* encodes a DRAP1/NC2alpha homolog that has both positive and negative roles in transcription *in vivo*. *Mol. Cell. Biol.* **17**: 2057–2065.
- Pugh, B.F. and R. Tjian. 1990. Mechanism of transcriptional activation by Sp1: Evidence for coactivators. *Cell* **61**: 1187–1197.
- . 1991. Transcription from a TATA-less promoter requires a multisubunit TFIID complex. *Genes & Dev.* **5**: 1935–1945.
- Purnell, B.A., P.A. Emanuel, and D.S. Gilmour. 1994. TFIID sequence recognition of the initiator and sequences farther downstream in *Drosophila* class II genes. *Genes & Dev.* **8**: 830–842.
- Radebaugh, C.A., X. Gong, B. Bartholomew, and M.R. Paule. 1997. Identification of previously unrecognized common elements in eukaryotic promoters. A ribosomal RNA gene initiator element for RNA polymerase I. *J. Biol. Chem.* **272**: 3141–3144.
- Radebaugh, C.A., J.L. Matthews, G.K. Geiss, F. Liu, J.M. Wong, E. Bateman, S. Camier, A. Sentenac, and M.R. Paule. 1994. TATA box-binding protein (TBP) is a constituent of the polymerase I-specific transcription initiation factor TIF-IB (SL1) bound to the rRNA promoter and shows differential sensitivity to TBP-directed reagents in polymerase I, II, and III transcription factors. *Mol. Cell. Biol.* **14**: 597–605.
- Rameau, G., K. Puglia, A. Crowe, I. Sethy, and I. Willis. 1994. A mutation in the second largest subunit of TFIIC increases a rate-limiting step in transcription by RNA polymerase III. *Mol. Cell. Biol.* **14**: 822–830.
- Reed, S.I. 1980. The selection of *S. cerevisiae* mutants defective in the start event of cell division. *Genetics* **95**: 561–577.
- Reese, J.C., L. Apone, S.S. Walker, L.A. Griffin, and M.R. Green. 1994. Yeast TAF_{II}s in a multisubunit complex required for activated transcription. *Nature* **371**: 523–527.
- Roberts, S.M. and F. Winston. 1996. *SPT20/ADA5* encodes a novel protein functionally related to the TATA-binding protein and important for transcription in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* **16**: 3206–3213.
- . 1997. Essential functional interactions of SAGA, a *Saccharomyces cerevisiae* complex of Spt, Ada, and Gcn5 proteins, with the Snf/Swi and Srb/mediator complexes. *Genetics* **147**: 451–465.
- Rowley, A., J.H. Cocker, J. Harwood, and J.F. Diffley. 1995. Initiation complex assembly at budding yeast replication origins begins with the recognition of a bipartite sequence by limiting amounts of the initiator, ORC. *EMBO J.* **14**: 2631–2641.
- Rudloff, U., D. Eberhard, L. Tora, H. Stunnenberg, and I. Grummt. 1994. TBP-associated factors interact with DNA and govern species specificity of RNA polymerase I transcription. *EMBO J.* **13**: 2611–2616.
- Ruth, J., C. Conesa, G. Dieci, O. Lefebvre, A. Dusterhoft, S. Ottonello, and A. Sentenac. 1996. A suppressor of mutations in the class III transcription system encodes a component of yeast TFIIB. *EMBO J.* **15**: 1941–1949.
- Sadowski, C.L., R.W. Henry, R. Kobayashi, and N. Hernandez. 1996. The SNAP45 subunit of the small nuclear RNA (snRNA) activating protein complex is required for RNA polymerase II and III snRNA gene transcription and interacts with the TATA box binding protein. *Proc. Natl. Acad. Sci.* **93**: 4289–4293.
- Sadowski, C.L., R.W. Henry, S.M. Lobo, and N. Hernandez. 1993. Targeting TBP to a non-TATA box *cis*-regulatory element: A TBP-containing complex activates transcription from snRNA promoters through the PSE. *Genes & Dev.* **7**: 1535–1548.
- Saleh, A., V. Lang, R. Cook, and C.J. Brandl. 1997. Identification of native complexes containing the yeast coactivator/repressor proteins NGG1/ADA3 and ADA2. *J. Biol. Chem.* **272**: 5571–5578.
- Sauer, F., D.A. Wassarman, G.M. Rubin, and R. Tjian. 1996. TAF_{II}s mediate activation of transcription in the *Drosophila* embryo. *Cell* **87**: 1271–1284.
- Schnapp, A., J. Clos, W. Hadel, R. Schreck, A. Cvekl, and I. Grummt. 1990. Isolation and functional characterization of TIF-IB, a factor that confers promoter specificity to mouse RNA polymerase I. *Nucleic Acids Res.* **18**: 1385–1393.
- Shen, W.C. and M.R. Green. 1997. Yeast TAF_{II}145 functions as a core promoter selectivity factor, not a general coactivator.

- Cell* **90**: 615–624.
- Smale, S.T., M.C. Schmidt, A.J. Berk, and D. Baltimore. 1990. Transcriptional activation by Sp1 as directed through TATA or initiator: Specific requirement for mammalian transcription factor IID. *Proc. Natl. Acad. Sci.* **87**: 4509–4513.
- Steffan, J.S., D.A. Keys, J.A. Dodd, and M. Nomura. 1996. The role of TBP in rDNA transcription by RNA polymerase I in *Saccharomyces cerevisiae*: TBP is required for upstream activation factor-dependent recruitment of core factor. *Genes & Dev.* **10**: 2551–2563.
- Stringer, K.F., C.J. Ingles, and J. Greenblatt. 1990. Direct and selective binding of an acidic transcriptional activation domain to the TATA-box factor TFIID. *Nature* **345**: 783–786.
- Suzuki-Yagawa, Y., M. Guermah, and R.G. Roeder. 1997. The ts13 mutation in the TAF(II)250 subunit (CCG1) of TFIID directly affects transcription of D-type cyclin genes in cells arrested in G1 at the nonpermissive temperature. *Mol. Cell. Biol.* **17**: 3284–3294.
- Tanese, N., B.F. Pugh, and R. Tjian. 1991. Coactivators for a proline-rich activator purified from the multisubunit human TFIID complex. *Genes & Dev.* **5**: 2212–2224.
- Timmers, H.T. and P.A. Sharp. 1991. The mammalian TFIID protein is present in two functionally distinct complexes. *Genes & Dev.* **5**: 1946–1956.
- Triezenberg, S.J. 1995. Structure and function of transcriptional activation domains. *Curr. Opin. Genet. Dev.* **5**: 190–196.
- Truant, R., H. Xiao, C.J. Ingles, and J. Greenblatt. 1993. Direct interaction between the transcriptional activation domain of human p53 and the TATA box-binding protein. *J. Biol. Chem.* **268**: 2284–2287.
- Van Der Knaap, J.A., J.W. Borst, P.C. Van Der Vliet, R. Gentz, and H.T.M. Timmers. 1997. Cloning of the cDNA for the TATA-binding protein-associated factor(II)170 subunit of transcription factor B-TFIID reveals homology to global transcription regulators in yeast and *Drosophila*. *Proc. Natl. Acad. Sci.* **94**: 11827–11832.
- Velculescu, V.E., L. Zhang, W. Zhou, J. Vogelstein, M.A. Basrai, D. Bassett, Jr., P. Hieter, B. Vogelstein, and K.W. Kinzler. 1997. Characterization of the yeast transcriptome. *Cell* **88**: 243–251.
- Verrijzer, C.P. and R. Tjian. 1996. TAFs mediate transcriptional activation and promoter selectivity. *Trends Biochem. Sci.* **21**: 338–342.
- Verrijzer, C.P., K. Yokomori, J.L. Chen, and R. Tjian. 1994. *Drosophila* TAFII150: Similarity to yeast gene *TSM-1* and specific binding to core promoter DNA. *Science* **264**: 933–941.
- Verrijzer, C.P., J.L. Chen, K. Yokomori, and R. Tjian. 1995. Binding of TAFs to core elements directs promoter selectivity by RNA polymerase II. *Cell* **81**: 1115–1125.
- Vilalta, A., A. Trivedi, Z. Wang, R.G. Roeder, and D.L. Johnson. 1997. An RNA polymerase III-defective mutation in TATA-binding protein disrupts its interaction with a transcription factor IIIB subunit in *Drosophila* cells. *J. Biol. Chem.* **272**: 18087–18092.
- Wade, P.A. and J.A. Jaehning. 1996. Transcriptional corepression *in vitro*: A Mot1p-associated form of TATA-binding protein is required for repression by Leu3p. *Mol. Cell. Biol.* **16**: 1641–1648.
- Walker, S.S., J.C. Reese, L.M. Apone, and M.R. Green. 1996. Transcription activation in cells lacking TAFIIS. *Nature* **383**: 185–188.
- Walker, S.S., W.C. Shen, J.C. Reese, L.M. Apone, and M.R. Green. 1997. Yeast TAF(II)145 required for transcription of G1/S cyclin genes and regulated by the cellular growth state. *Cell* **90**: 607–614.
- Wang, E.H. and R. Tjian. 1994. Promoter-selective transcriptional defect in cell cycle mutant ts13 rescued by hTAFII250. *Science* **263**: 811–814.
- Wang, E.H., S. Zou, and R. Tjian. 1997. TAFII250-dependent transcription of cyclin A is directed by ATF activator proteins. *Genes & Dev.* **11**: 2658–2669.
- Wang, L., C. Mizzen, C. Ying, R. Candau, N. Barlev, J. Brownell, C.D. Allis, and S.L. Berger. 1997. Histone acetyltransferase activity is conserved between yeast and human GCN5 and is required for complementation of growth and transcriptional activation. *Mol. Cell. Biol.* **17**: 519–527.
- Wang, Z. and R.G. Roeder. 1997. Three human RNA polymerase III-specific subunits form a subcomplex with a selective function in specific transcription initiation. *Genes & Dev.* **11**: 1315–1326.
- Werner, M., N. Chaussivert, I.M. Willis, and A. Sentenac. 1993. Interaction between a complex of RNA polymerase III subunits and the 70-kDa component of transcription factor IIIB. *J. Biol. Chem.* **268**: 20721–20724.
- White, R.J. 1994. *RNA polymerase III transcription*. R.G. Landes Co., Austin, TX.
- Willis, I.M. 1993. RNA polymerase III. Genes, factors and transcriptional specificity. *Eur. J. Biochem.* **212**: 1–11.
- Winston, F., K.J. Durbin, and G.R. Fink. 1984. The *SPT3* gene is required for normal transcription of Ty elements in *S. cerevisiae*. *Cell* **39**: 675–682.
- Wodicka, L., H. Dong, M. Mittmann, M.H. Ho, and D.J. Lockhart. 1997. Genome-wide expression monitoring in *Saccharomyces cerevisiae*. *Nature Biotechnol.* **15**: 1359–1367.
- Wong, M.W., R.W. Henry, B. Ma, R. Kobayashi, N. Klages, P. Matthias, M. Strubin, and N. Hernandez. 1998. The large subunit of basal transcription factor SNAPc is a Myb domain protein that interacts with Oct-1. *Mol. Cell. Biol.* **18**: 368–377.
- Wu, Y., R.J. Reece, and M. Ptashne. 1996. Quantitation of putative activator-target affinities predicts transcriptional activating potentials. *EMBO J.* **15**: 3951–3963.
- Yeung, K.C., J.A. Inostroza, F.H. Mermelstein, C. Kannabiran, and D. Reinberg. 1994. Structure-function analysis of the TBP-binding protein Dr1 reveals a mechanism for repression of class II gene transcription. *Genes & Dev.* **8**: 2097–2109.
- Yoon, J.B. and R.G. Roeder. 1996. Cloning of two proximal sequence element-binding transcription factor subunits (gamma and delta) that are required for transcription of small nuclear RNA genes by RNA polymerases II and III and interact with the TATA-binding protein. *Mol. Cell. Biol.* **16**: 1–9.
- Yoon, J.B., S. Murphy, L. Bai, Z. Wang, and R.G. Roeder. 1995. Proximal sequence element-binding transcription factor (PTF) is a multisubunit complex required for transcription of both RNA polymerase II- and RNA polymerase III-dependent small nuclear RNA genes. *Mol. Cell. Biol.* **15**: 2019–2027.
- Zomerdijs, J.C., H. Beckmann, L. Comai, and R. Tjian. 1994. Assembly of transcriptionally active RNA polymerase I initiation factor SL1 from recombinant subunits. *Science* **266**: 2015–2018.

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Genes Dev. 1998, **12**:

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