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Review

TAFs revisited: more data reveal new twists and confirm old ideas

Shane R. Albright, Robert Tjian *

Howard Hughes Medical Institute, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720-3204, USA

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Abstract

Synthesis of messenger RNA by RNA polymerase II requires the combined activities of more than 70 polypeptides. Coordinating the interaction of these proteins is the basal transcription factor TFIID, which recognizes the core promoter and supplies a scaffolding upon which the rest of the transcriptional machinery can assemble. A multisubunit complex, TFIID consists of the TATA-binding protein (TBP) and several TBP-associated factors (TAFs), whose primary sequences are well-conserved from yeast to humans. Data from reconstituted cell-free transcription systems and binary interaction assays suggest that the TAF subunits can function as promoter-recognition factors, as coactivators capable of transducing signals from enhancer-bound activators to the basal machinery, and even as enzymatic modifiers of other proteins. Whether TAFs function similarly in vivo, however, has been an open question. Initial characterization of yeast bearing mutations in particular TAFs seemingly indicated that, unlike the situation in vitro, TAFs played only a minor role in transcriptional regulation in vivo. However, reconsideration of this data in light of more recent results from yeast and other organisms reveals considerable convergence between the models derived from in vitro experiments and those derived from in vivo studies. In particular, there is an emerging consensus that TAFs represent one of several classes of coactivators that participate in transcriptional activation in vivo.

Keywords: Coactivator; Gene profiling; RNA polymerase II; TBP-associated factors; TFIID; Transcription

1. Introduction

The initiation of RNA polymerase II-directed transcription is a multistep process requiring the coordinated interactions of many proteins. Basal factors assembled proximal to the transcription start site, activators bound to more distal enhancer sequences, and coactivators that function to bridge these two groups all make important contributions to transcriptional regulation (reviewed in Hampsey, 1998). The general transcription factor TFIID participates in this process by recognizing and binding the core promoter through interactions with the TATA box, the initiator sequence, and a downstream promoter element (Hoey et al., 1990; Verrijzer et al., 1995; Burke and Kadonaga, 1997).

Because early experiments demonstrated that binding of TFIID to the TATA box helps to nucleate the assembly of the general transcription factors (Buratowski et al., 1989), activator-mediated recruitment of the TFIID complex has been viewed as a likely mechanism of transcriptional regulation. Recent work emphasizing the role of the Pol II holoenzyme, holoenzyme-associated factors, or chromatin remodeling complexes as targets of activation signals has stimulated considerable debate about the importance of TFIID in mediating activated transcription (Barberis and Gaudreau, 1998; Natarajan et al., 1998; Gu et al., 1999; Ranish et al., 1999). Nevertheless, a substantial body of evidence supports the conclusion that a number of regulatory signals funnel primarily through TFIID components. This review summarizes these data, drawing both from early in vitro biochemical studies and from

Abbreviations: DPE, downstream promoter element; EST, expressed sequence tag; *e(y) 1*, *enhancer of yellow 1* gene; GAL1p, promoter from *gal1* gene; GTF, general transcription factor; HAT, histone acetyltransferase; PIC, pre-initiation complex; Pol II, RNA polymerase II; TAF,TBP-associated factor; TBP, TATA-binding protein; TFTC, 'TBP-free' TAF_{II} complex; TRF, TBP-related factor; TSRE, temperature-shift response element; yTAF, yeast TAF.

* Corresponding author. Tel.: +1-510-642-0884; fax: +1-510-643-9547.
E-mail address: jmlim@uclink4.berkeley.edu (R. Tjian)

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more recent in vivo experiments that help clarify the multiple functions of TFIID in the regulation of transcription.

2. Historical background

The earliest in vitro transcription experiments conducted in the late 1970s and early 1980s demonstrated the inability of purified RNA polymerase II to recognize promoter sequences and initiate RNA synthesis accurately. These results suggested that additional components were necessary to direct accurate transcription initiation, and subsequently, several such accessory factors (TFIIA, B, D, E, F, and H) were described (Matsui et al., 1980; Samuels et al., 1982). Termed general transcription factors (GTFs), these proteins were thought to assemble on eukaryotic promoters through a defined, hierarchical pathway and to recruit Pol II to the transcriptional start site in an activator-dependent fashion (reviewed in Zawel and Reinberg, 1992). In vitro assays suggested that binding of TFIID to the TATA box represented an early step in this pathway, forming a platform upon which the rest of the pre-initiation complex (PIC) was built (Nakajima et al., 1988; Buratowski et al., 1989). Consistent with this model, TFIID was (at the time) the only basal transcription factor to display unambiguous sequence-specific DNA-binding properties (Sawadogo and Roeder, 1985). A number of laboratories pursued the purification and biochemical characterization of TFIID, but were hampered by the relative scarcity and complexity of this essential transcription factor.

In 1989, several groups reported the purification and cloning of a yeast TATA-binding protein (TBP) (Cavallini et al., 1989; Eisenmann et al., 1989; Hahn et al., 1989; Horikoshi et al., 1989; Schmidt et al., 1989), and the cloning of *Drosophila* and human homologs was reported the following year (Hoey et al., 1990; Hoffman et al., 1990; Kao et al., 1990; Muhich et al., 1990; Peterson et al., 1990). A single polypeptide in all three species, TBP, could replace TFIID as the nucleating factor for the assembly of the PIC (Peterson et al., 1990). Speculation that TBP and TFIID were identical, however, was quickly cut short by subsequent experiments. While TFIID could direct activation by multiple transcription factors in vitro, it was found that TBP failed to support such activator-dependent transcription (Kambadur et al., 1990; Meisterernst et al., 1990; Pugh and Tjian, 1990; Dynlacht et al., 1991; Tanese et al., 1991). Apparently, TBP could participate in PIC assembly, but was unable to respond to upstream regulatory signals in the same manner as TFIID. To explain this result, Pugh and Tjian (1990) proposed that TFIID contained a new class of additional factors, termed coactivators, that served as potential targets for these signals.

Biochemical fractionation of TFIID revealed that at least some of these coactivators were tightly associated with TBP to form a large, stable multi-subunit complex. Using antibodies against TBP, Dynlacht et al. (1991) purified such a complex from *Drosophila* extracts and demonstrated that it, unlike TBP, could replace a crude TFIID fraction in supporting activated transcription (reviewed in Goodrich and Tjian, 1994). TBP-containing complexes capable of recapitulating TFIID function were subsequently identified in humans (Tanese et al., 1991; Takada et al., 1992; Zhou et al., 1992) and later in yeast (Poon et al., 1995; Moqtaderi et al., 1996b) using similar methodologies. Accordingly, it became clear that TFIID comprises not only TBP, but also 8–12 TBP-associated factors (TAFs) ranging in size from 250 kDa to less than 20 kDa.

Cloning of the TAFs from *Drosophila*, humans, and yeast (Goodrich et al., 1993; Hoey et al., 1993; Ruppert et al., 1993; Weinzierl et al., 1993a,b; Yokomori et al., 1993; Jacq et al., 1994; Kokubo et al., 1994; Verrijzer et al., 1994; Chiang and Roeder, 1995; Hisatake et al., 1995; Klemm et al., 1995; Mengus et al., 1995; Poon et al., 1995; Hoffmann and Roeder, 1996; Moqtaderi et al., 1996b; Tanese et al., 1996; Mengus et al., 1997) has revealed a striking evolutionary conservation in the architecture of this complex. This is evidenced particularly by various sequence motifs shared among homologs from all three species, such as WD40 repeats ($yTAF_{II}90/dTAF_{II}80/hTAF_{II}100$), as well as limited sequence homology to histones H3 ($yTAF_{II}17/dTAF_{II}40/hTAF_{II}31$), H4 ($yTAF_{II}60/dTAF_{II}60/hTAF_{II}70$), and H2B ($yTAF_{II}61/dTAF_{II}30\alpha/hTAF_{II}20$). Interestingly, human $TAF_{II}130$ and *Drosophila* $TAF_{II}110$ lack an obvious yeast homolog (Moqtaderi et al., 1996b), suggesting that the yeast and metazoan TFIID complexes, despite their many similarities, may nevertheless differ in functionally important respects.

3. Structural studies of TFIID

The large size of the TFIID complex, its complicated subunit composition, and its relative scarcity present significant obstacles to conventional X-ray crystallographic or NMR-based characterization. Nevertheless, some headway has been made by groups focusing on individual TFIID components. For example, TBP (without the TAFs) has been crystallized in several forms: alone (Nikolov et al., 1992; Nikolov and Burley, 1994), bound to DNA (Kim et al., 1993a,b; Kim and Burley, 1994), and in a ternary complex with DNA and either TFIIA (Geiger et al., 1996; Tan et al., 1996) or TFIIB (Nikolov et al., 1995). According to these studies, TBP is a pseudo-symmetric, crescent-shaped molecule whose concave surface forms most of the interface with the DNA, presumably leaving the upper, convex surface

available for interaction with the TAFs (Nikolov et al., 1995; Geiger et al., 1996; Tan et al., 1996).

Individual TAF pairs have also been amenable to limited structural analysis. Crystallization of a truncated $dTAF_{II}40$:$dTAF_{II}60$ complex, for example, has revealed a heterotetramer with homology to the histone H3:H4 nucleosomal core (Xie et al., 1996). Interestingly, $hTAF_{II}18$ and $hTAF_{II}28$ also interact through a histone fold, suggesting that this structural motif may be common to several of the components of TFIID (Birck et al., 1998). Further supporting this idea are the observations that portions of the primary sequence of $dTAF_{II}30\alpha$ are homologous to histone H2B and that the human histone fold-containing TAFs can bind histones in vitro (Hoffmann et al., 1996). A few groups have even proposed that the promoter DNA wraps around TFIID in a manner resembling a nucleosome (Oelgeschlager et al., 1996; Hoffmann et al., 1997), though no direct evidence for this type of architecture exists. Indeed, the high-resolution structure of the nucleosome core particle (Luger et al., 1997) reveals that the histones bind DNA predominantly through several arginine side chains, none of which are conserved in the TAFs. Thus, the use of the histone fold in the TAFs may simply reflect the ability of this structural motif to facilitate compact and tight protein–protein interactions (Birck et al., 1998) and does not necessarily imply that TAFs assemble into nucleosome-like particles.

The debate over how to interpret the presence of histone folds among the TAFs also illuminates a larger issue. Because none of the pieces of TFIID that have been subjected to crystallography are known to form independent complexes in vivo, the relevance of these structural studies may be limited. For example, the $dTAF_{II}40$:$dTAF_{II}60$ experiments, which initially fueled much of the speculation regarding a histone-like role for TAFs, utilized only short polypeptides encompassing the histone homology domains of both proteins (Xie et al., 1996). Thus, data from these experiments cannot necessarily be extrapolated to draw conclusions about the conformation of the full-length TAFs in the context of TFIID. Even in instances where full-length proteins are examined, it is possible that TAF–TAF interactions under crystallization conditions do not accurately reflect TAF behavior in TFIID. In fact, both *Drosophila* TFIID and an alternative TAF-containing complex (Mengus et al., 1995) appear to contain only one member of a structurally characterized TAF pair, indicating that even such well-studied interactions may not always be utilized by TAFs in vivo. A detailed understanding of TFIID's overall architecture would provide welcome context for the structural studies of TBP and the TAFs.

Unfortunately, information on the arrangement of the TAFs in TFIID is sparse. Although most models have assumed that each TFIID complex consists of TBP and a single molecule of each of the TAFs, data supporting this stoichiometry are simply not available. Rather, a more complex arrangement of subunits is perhaps suggested by isolated observations, such as the ability of TFIID to dimerize through TBP's DNA-binding domain (Coleman et al., 1995; Jackson-Fisher et al., 1999), the independent interaction of two domains of $TAF_{II}250$ with TBP (Ruppert et al., 1993; S.R. Albright, unpublished results), and the formation of $dTAF_{II}40$:$dTAF_{II}60$ heterotetramers under crystallization conditions (Xie et al., 1996). Resolution of this issue awaits the application of techniques appropriate to characterizing the structure of intact TFIID, such as single-particle cryo-electron microscopy (Nogales et al., 1999) or atomic force microscopy (Mou et al., 1996).

4. In vitro functional studies

The hallmark of TFIID is its ability to support activated transcription in reconstituted in vitro systems. Because TBP alone is incapable of such function (Hoey et al., 1990), it has been postulated that some of the TAFs can serve as coactivators targeted by DNA-binding transcription factors (Dynlacht et al., 1991; Tanese et al., 1991; Hoey et al., 1993). Consistent with this model, individual TAFs interact directly with several activation domains (reviewed in Sauer and Tjian, 1997). As expected, mutations in activation domains that compromise the binding of TAFs also fail to activate transcription, providing a good correlation between activator:TAF interactions and transcription (Gill et al., 1994). Studies utilizing in vitro assembled TFIID have further demonstrated that many of these activation domains no longer function in the absence of their partner TAF, suggesting that the TAF–activator interactions are indeed critical for transcriptional activation by at least some activators (Chen et al., 1994; Thut et al., 1995). Importantly, these experiments revealed different TAF requirements even though they utilized identical core promoters, inconsistent with the notion that TAFs function solely as promoter selectivity factors, as has been suggested (Hampsey and Reinberg, 1997; Shen and Green, 1997).

Although the available evidence favors a model in which TAFs bridge activators to the basal machinery, the mechanistic consequences of this linkage remain unclear. Activator-mediated recruitment of TFIID is certainly important, but there are other attractive possibilities beyond this simple scenario. For example, a portion of $TAF_{II}250$ has been shown to associate with TBP's DNA binding domain and inhibit TBP:DNA interactions (Liu et al., 1998). Conceivably, relief of this inhibition by activator-induced conformational changes in $TAF_{II}250$ could mediate transcriptional activation. It is equally likely that TAF–activator contact could lead

to other structural alterations that enhance the rate of formation of the PIC or its stability on particular promoters. Indeed, the presence of multiple, potentially interchangeable, histone folds among the TAFs raises the possibility that TFIID possesses an inherently plastic structure that can be re-organized in response to activator-derived signals.

Other mechanisms of TAF-dependent activation are also possible. For instance, $TAF_{II}250$ catalyzes both phosphorylation and acetylation reactions in vitro (Dikstein et al., 1996a; Mizzen et al., 1996; O'Brien and Tjian, 1998), suggesting a possible role for enzymatic modification of downstream targets upon TFIID recruitment. The $TAF_{II}250$ acetylase was initially characterized as a histone acetyltransferase (HAT) similar to those found in the yeast adaptor Gcn5 and the mammalian co-factor CBP (Mizzen et al., 1996). Thus, histone acetylation by $TAF_{II}250$ could increase access to the core promoter, ostensibly aiding the binding of TFIID or other basal factors. Recently, potential non-histone substrates for the $TAF_{II}250$ acetylase have also been identified, including TFIIE and TFIIF (Imhof et al., 1997). The RAP74 subunit of TFIIF is also a potential target of the $TAF_{II}250$ kinase (Dikstein et al., 1996a; O'Brien and Tjian, 1998). Consequently the HAT and kinase activities of $TAF_{II}250$ may function in tandem to transduce activation signals directly to other basal factors.

It is likely that TAFs also act to orient and stabilize the basal machinery on the core promoter. While binding of TBP to the TATA box frequently drives the assembly of the transcriptional apparatus, other DNA–protein interactions also appear to contribute to the productive initiation of transcription. Various studies have described a regulatory role for the binding of factors to a loosely conserved initiator element (consensus $PyPyA^{+1}NT/APyPy$) that overlaps the transcription start site in some promoters (Kaufmann and Smale, 1994; Purnell et al., 1994; Verrijzer et al., 1995). Basal promoter strength in the case of TATA-less promoters is critically dependent on the presence of this initiator element, as well as on an additional downstream promoter element (DPE) (Burke and Kadonaga, 1996). Even on some TATA-containing promoters, TBP alone binds the TATA box weakly and with little preference for orientation (Cox et al., 1997), suggesting a role for auxiliary contacts on this class of promoters as well. Several pieces of evidence implicate specific TAFs as recognizing both the initiator and the DPE. First, it has been shown that purified, recombinant $dTAF_{II}150$ binds the initiator directly in both DNase I footprinting and electrophoretic mobility shift assays (Verrijzer et al., 1994). Second, CIF150, the human homolog of $dTAF_{II}150$, was identified as an essential cofactor for TFIID-dependent transcription from promoters containing initiator elements (Kaufmann et al., 1998). Third, UV-crosslinking experiments reveal that TFIID recruitment places $dTAF_{II}150$, $dTAF_{II}250$, and $dTAF_{II}60$ in close proximity to the DNA (Sypes and Gilmour, 1994; Verrijzer et al., 1995; Burke and Kadonaga, 1997). This last observation, together with similar results obtained using human TFIID (Oelgeschlager et al., 1996), suggests that specific TAF:DNA contacts do occur within the context of the assembled TFIID complex. Consequently, it is likely that efficient promoter recognition is significantly enhanced by the cooperative efforts of several subunits of TFIID.

While early studies demonstrated the inability of several activators to stimulate transcription in the absence of TFIID, more recent experiments suggest that not all activators are strictly TFIID-dependent. For example, TBP alone is able to support activated transcription by GAL4-VP16 and GAL4-CTF1 in crude nuclear extracts immunodepleted of TFIID using multiple anti-TAF antibodies (Oelgeschlager et al., 1998), implying the existence of alternative or redundant coactivators for these chimeric transcription factors. Moreover, in a transcription system reconstituted with largely purified factors but lacking TAFs, thyroid hormone receptor (TR)-mediated activation appears unaffected (Fondell et al., 1999). Instead, TR activity is highly dependent on a set of TR-associated proteins (TRAPs) (Fondell et al., 1996), nearly all of which are also present in a complex (DRIP) bound to liganded vitamin D receptor (VDR) (Rachez et al., 1998). Interestingly, several of these proteins are also components of the putative mammalian mediator SMCC (Gu et al., 1999; Ito et al., 1999), the Sp1 cofactor CRSP (Ryu et al., 1999), and the multisubunit complex ARC, which has been shown to bind a wide variety of activators in vitro (Naar et al., 1999). These related complexes may therefore define a class of coactivators distinct from the TAFs, and it is tempting to speculate that these mediator-like factors and TFIID may possess overlapping functions. Difficult to establish, however, is whether SMCC/TRAP can fully replace TFIID, since crude fractions 'depleted' of TFIID may still possess sufficient quantities of other TAF-containing complexes or modified TFIID complexes to support activated transcription. Moreover, an assay of SMCC function in a fully reconstituted system devoid of TFIID revealed that it repressed, rather than enhanced, transcriptional activation under these conditions (Gu et al., 1999); similarly, the SMCC-related factor NAT also appears to be a transcriptional repressor (Sun et al., 1998). Thus, the issue of whether other coactivator complexes such as SMCC, TRAP, ARC, and so on can substitute for TFIID remains an open question. Indeed, it is equally likely that these two classes of coactivators are cooperative, rather than competitive, as evidenced by recent experiments demonstrating that TFIID and ARC can

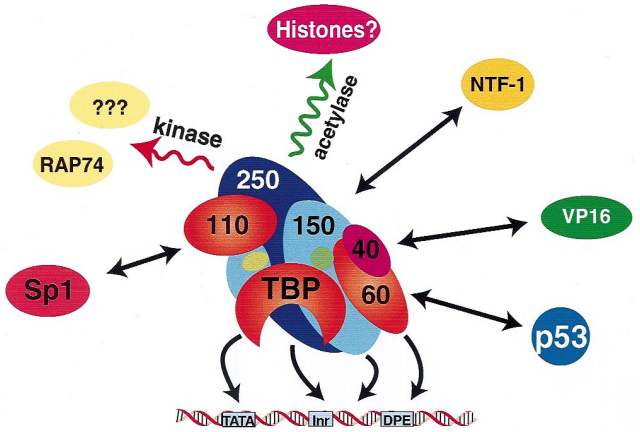

Fig. 1. Functions of TAFs. TAFs can serve as core promoter recognition factors by binding to the Inr and DPE sequences and, in conjunction with TBP:TATA box interactions, can orient TFIID on the DNA (single-sided arrows). Certain TAFs are also activator targets that are capable of binding to activation domains in vitro (double-sided arrows). Additionally, $TAF_{II}250$ has two enzymatic activities, a kinase and an acetylase, that can modify proteins (squiggly arrows). The subunit composition shown is that of *Drosophila* TFIID.

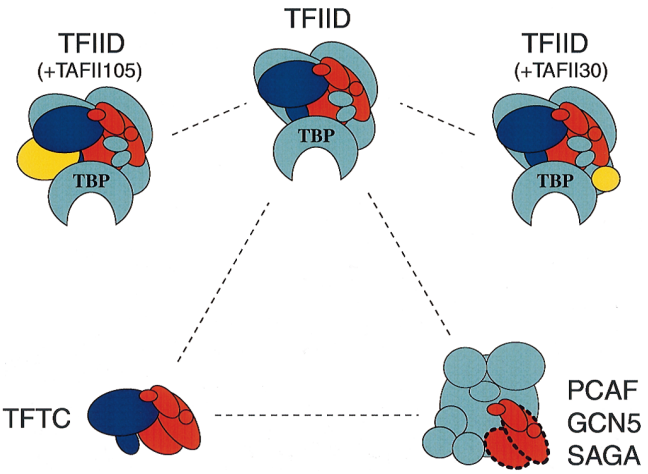

Fig. 2. Interrelationship between TAF-containing complexes. The closely related subunit compositions of TFIID, $TAF_{II}105$-containing TFIID, $TAF_{II}30$-containing TFIID, TFTC, and yeast SAGA (human PCAF/GCN5 complex) are diagrammed. The five TAFs common to all five complexes ($yTAF_{II}17$, $yTAF_{II}60$, $yTAF_{II}68$, $yTAF_{II}25$ and $yTAF_{II}90$, and their human homologs) are indicated in red; TAFs that are present only in TFIID and TFTC, but not SAGA, are colored dark blue. Note that while both $yTAF_{II}90$ and $yTAF_{II}60$ are components of SAGA, the equivalent subunits of PCAF/GCN5 are not TAFs, but close relatives of $hTAF_{II}100$ and $hTAF_{II}70$; this substitution is signified by dotted borders. Also indicated are $TAF_{II}30$ and $TAF_{II}105$ (both orange) and subunits that either TFIID-specific or SAGA-specific (light blue).

act synergistically on composite promoters (Naar et al., 1999).

In summary, a wide variety of in vitro data suggests that TAFs contribute to transcriptional regulation on multiple levels: (1) as coactivators that couple activator-mediated signals to the basal machinery; (2) as promoter selectivity factors that stabilize TFIID on core promoters, augmenting or replacing TBP:TATA box interactions; and (3) in the case of $TAF_{II}250$, as an enzyme capable of modifying neighboring proteins and potentially modulating their activities (Fig. 1). The importance of these contributions, however, appears to vary from promoter to promoter, possibly reflecting redundant or compensatory coactivator activities present in nuclear extracts.

5. Alternative TAF-containing complexes and TBP-related factors

Recently, a subset of the TAFs was identified as components of the yeast SAGA and human PCAF histone acetylase complexes (Fig. 2) (Grant et al., 1998; Ogryzko et al., 1998). In particular, SAGA, which is thought to serve as a coactivator in yeast, includes each of the histone fold-containing TAFs ($yTAF_{II}17$, $yTAF_{II}60$, $yTAF_{II}61/68$), along with $yTAF_{II}25/23$, $yTAF_{II}90$, and previously identified Ada and Spt proteins (Grant et al., 1998). PCAF, on the other hand, contains Ada and Spt family members, two human histone fold-containing TAFs ($hTAF_{II}31$ and $hTAF_{II}20/15$), $hTAF_{II}30$, a $hTAF_{II}80$ homolog (PAF65α), and a $hTAF_{II}100$ homolog (PAF65β) (Ogryzko et al., 1998). By sequence comparison, PAF65α and PAF65β retain the structural features (histone folds and WD40 repeats, respectively) shared by their human TFIID and yeast SAGA counterparts. Since both SAGA and PCAF are thought to regulate gene expression by modifying chromatin structure, the discovery of TAFs and TAF-like proteins in these complexes indicate a potential transcriptional role for TAFs outside of TFIID.

An additional TAF-containing complex distinct from TFIID has also been described recently (Wieczorek et al., 1998). Possibly related to the PCAF complex, this 'TBP-free' TAF_{II} complex (TFTC) contains a subset of the human TAFs, but apparently lacks TBP and $hTAF_{II}250$. In vitro, TFTC has been reported to substitute for TFIID in supporting transcriptional activation on both TATA-containing and TATA-less promoters. Although it is unclear whether TFTC exists as a functional unit in vivo, this result raises the possibility that the coactivator function of TAFs is independent of their association with TBP. In addition, the existence of multiple TAF-containing complexes like TFTC and PCAF/SAGA may partly explain the differential requirement for various TAFs in yeast and other organisms.

In addition to these various assemblages of TAFs and TAF-like molecules is the long-standing observation that TBP itself has a tissue-specific homolog (Crowley et al., 1993). The TBP-related factor (TRF1) is a *Drosophila* protein found primarily in neural tissues and

developing reproductive organs, and it appears to function through association with factors that are distinct from TAFs (Hansen et al., 1997). Preliminary data indicate that TRF1 is part of a high molecular weight complex (S. Takada, personal communication), but the identity and nature of these so-called nTAFs (neuronal-specific TRF-associated factors) remains unclear. Adding to this complexity, another TBP-related protein (TRF2, or TLF) has also been described (Wieczorek et al., 1998; Rabenstein et al., 1999). In contrast to the highly localized expression of TRF1, human TRF2 appears to be widely expressed (Rabenstein et al., 1999). Notably, TRF2 has been identified in multiple species, including *Caenorhabditis elegans*, *Drosophila*, and mammals, through computerized screens of expressed sequence tags (ESTs), while similar searches have revealed no discernable TRF homolog outside of *Drosophila*. A potential explanation is that TRF is simply underrepresented in the EST databases as a result of its highly restricted expression. However, the possibility that TRF represents an evolutionary anomaly specific to flies cannot be excluded.

By suggesting that the scope of TAF and TBP functionality in Pol II-mediated transcription may extend beyond a single, monolithic TFIID molecule, the existence of multiple TAF- and TBP-containing complexes supports a model in which gene specificity is encoded by both enhancer-binding factors and the basal transcriptional machinery. Consistent with this model, a distinct, $hTAF_{II}30$-containing subpopulation of TFIID has been isolated from HeLa cells and shown to be required for estrogen receptor-mediated activation in vitro (Jacq et al., 1994). Also consistent with this model is the recent discovery of a cell type-regulated component of TFIID, $TAF_{II}105$ (Dikstein et al., 1996b). Present at exceedingly low levels in most human cell lines, $TAF_{II}105$ nonetheless appears to be preferentially associated with TFIID derived from B lymphocyte lines. However, even in B cells, $TAF_{II}105$ is substoichiometric relative to the other TAFs, suggesting that its presence, like that of $TAF_{II}30$, defines a distinct TFIID subset. Intriguingly, $TAF_{II}105$ is homologous to $hTAF_{II}130$ and $dTAF_{II}110$, which have both been described as coactivators for various transcription factors (Hoey et al., 1993; Saluja et al., 1998), raising the possibility that $TAF_{II}105$ may function similarly. In fact, a recent report (Yamit-Hezi and Dikstein, 1998) provides evidence supporting a coactivation role for $TAF_{II}105$ in NF-κB-mediated anti-apoptotic responses. The full functional significance of $TAF_{II}105$-containing TFIID remains unclear, however.

6. In vivo studies

Taken together, the biochemical characterization of TFIID and other TAF-containing complexes has identified numerous protein–protein or protein–DNA interactions that are thought to influence Pol II transcription, from which potential functions for individual TAFs have been deduced (reviewed in Sauer and Tjian, 1997; Björklund et al., 1999). However, the cell-free assays through which much of this understanding has been gained cannot easily distinguish between essential contacts and those that are incidental. Thus, in the last few years there has been active inquiry into the role of yeast, *Drosophila*, and mammalian TAFs in vivo. These in vivo studies have at times engendered confusion, because of apparent discrepancies with the presumed role of TAFs as deduced from in vitro experiments. However, recent data and more careful analysis reveals considerable convergence between the models derived from in vitro experiments and those obtained from in vivo studies.

6.1. Yeast

Thus far, the majority of studies on the physiologic functions of TAFs have been performed in the yeast *Saccharomyces cerevisiae*. Nearly all of the yTAF mutations are lethal (Reese et al., 1994; Poon et al., 1995), and of these, $yTAF_{II}145$, TSM1, and $yTAF_{II}90$ mutants each undergo cell-cycle arrest (Apone et al., 1996; Walker et al., 1996). Though such evidence suggests a critical role for TAFs in the cell, initial work examining TAF mutants was interpreted to indicate that all of the yTAFs tested (i.e., $yTAF_{II}145$, $yTAF_{II}90$, $yTAF_{II}68/61$, $yTAF_{II}60$, $yTAF_{II}47$, $yTAF_{II}30$, $yTAF_{II}19$, and TSM1) were dispensable for transcriptional activation in vivo (Apone et al., 1996; Moqtaderi et al., 1996a; Walker et al., 1996). In these experiments, several approaches were used to generate strains depleted of individual yTAFs, including (1) yTAF temperature-sensitive strains assayed under nonpermissive conditions (Apone et al., 1996; Walker et al., 1996), (2) strains harboring GAL1p-yTAF fusions assayed under glucose repression (Apone et al., 1996; Walker et al., 1996), and (3) strains with conditional yTAF alleles assayed following copper-induced transcriptional repression and ubiquitin-mediated protein degradation (Moqtaderi et al., 1996a). Taken together, these various methodologies revealed that RNA expression from 12 of the 14 genes examined was unaffected by the absence of TAFs. However, depletion of $yTAF_{II}145$ and $yTAF_{II}19$ repressed two genes, TRP3 and HIS3+1, whose promoters exhibited non-canonical TATA sequences (Moqtaderi et al., 1996a). Similar transcriptional defects were later obtained in both $yTAF_{II}67$- and $yTAF_{II}40$-depletion strains (Moqtaderi et al., 1998). Thus, while supporting the limited conclusion that yTAFs are dispensable for activation of 12 specific genes, these data also suggest that transcription from certain promoters is compromised in the absence of particular yTAFs.

Extending this notion of promoter-specific effects, subsequent work by Walker et al. (1997) and others (Shen and Green, 1997; Holstege et al., 1998) has uncovered additional genes that are downregulated in yTAF$_{II}$145 mutants. Consistent with the G1 arrest exhibited by these cells, repressed genes include the G1/S cyclins CLN1, CLN2, PCL1, and PCL2, as well as the B-type cyclins necessary for S phase progression (Walker et al., 1997; Holstege et al., 1998). More recent DNA microarray studies indicate that up to 16% of all yeast genes require yTAF$_{II}$145 to achieve wild-type levels of expression (Holstege et al., 1998). Although this downregulation may represent a combination of both direct and secondary effects, the authors minimized the contribution of the latter category by scoring only those mRNAs depleted with rapid kinetics upon inactivation of yTAF$_{II}$145. Interestingly, promoter-swapping experiments have suggested that yTAF$_{II}$145-dependence is, in part, an inherent property of some core promoters, and not necessarily the upstream regulatory regions (Shen and Green, 1997; Walker et al., 1997). In light of the dTAF$_{II}$250 crosslinking experiments and template commitment assays reported previously (Verrijzer et al., 1995), these in vivo results support the idea that yTAF$_{II}$145 and its metazoan homolog TAF$_{II}$250 can participate in promoter selectivity (Verrijzer and Tjian, 1996). Whether this function alone is sufficient to explain why nearly one out of every six yeast promoters is dependent on yTAF$_{II}$145 remains unclear.

Contrasting with the early studies of yeast TAFs, recent in vivo studies on several histone fold-containing TAFs (yTAF$_{II}$17, yTAF$_{II}$60, yTAF$_{II}$68/61) suggest a central role for these factors in transcriptional activation (Apone et al., 1998; Michel et al., 1998; Moqtaderi et al., 1998; Natarajan et al., 1998). In addition, yTAF$_{II}$25, which lacks any histone homologies, has also been shown to be essential for Pol II-mediated transcription in vivo (Sanders et al., 1999). Of these proteins, yTAF$_{II}$17 has produced the most incontrovertible data: three different laboratories using three different methodologies — thermosensitive alleles (Apone et al., 1998; Michel et al., 1998), glucose-mediated repression (Apone et al., 1998), and copper-inducible repression and degradation (Moqtaderi et al., 1998) — reached the identical conclusion that this yTAF is broadly required for transcription in yeast. Concurring with these results, DNA microarray studies placed the number of dependent genes at 67% of the identifiable yeast ORFs (Holstege et al., 1998). Curiously, yTAF$_{II}$68/61 and yTAF$_{II}$60 — whose histone folds may mediate interactions with yTAF$_{II}$17 — were previously reported to be dispensable for transcription (Moqtaderi et al., 1996a; Walker et al., 1996). Subsequent work, however, identified temperature-sensitive alleles of both yTAFs that clearly abolished transcription of most genes at the non-permissive temperature (Michel et al., 1998; Natarajan et al., 1998), raising the possibility that the early experiments suffered from incomplete inactivation of these factors and an overzealous interpretation of the data (discussed in Michel et al., 1998).

Identification of yTAF$_{II}$17, yTAF$_{II}$60, and yTAF$_{II}$68/61 as components of SAGA (Grant et al., 1998) potentially explains why these proteins are more generally required than other yTAFs for transcriptional activation. This rationale, however, ascribes to SAGA a central role in transcriptional regulation that is not substantiated by the bulk of experimental data. For example, mutations in other SAGA components are not lethal, indicating that the non-viability of yeast TAF mutants most likely reflects essential contributions made by TAFs in TFIID to cell viability. Further emphasizing the importance of TFIID, inactivation of TAFs found in TFIID but not in SAGA reveals that the transcription of over half the genes in the genome is dependent on at least one of these proteins (R. Young, personal communication). This effect is over 10-fold greater than that induced by mutations in the SAGA component Gcn5 (Holstege et al., 1998). How mere participation in SAGA could lead to a broad requirement for the histone fold-containing TAFs remains unclear. One possibility is that TAF-containing complexes other than TFIID and SAGA exist and that much of the data derived from TAF mutations reflect the unseen contribution of these critical, though as yet undiscovered, factors.

An intriguing alternative is that the yeast results, rather than indicating which TAFs are broadly shared with other complexes, reflect instead the relative importance of individual TAFs to the stability of TFIID. It is reasonable to speculate that certain TAFs play key structural roles and are therefore indispensable for organizing an active TFIID complex. An assumption that yTAF$_{II}$145 falls into this category runs through many of the early yeast experiments and often formed the logical basis for arguments that TAFs in general were not required for activation in vivo. Contrary to this assumption, however, recent work demonstrates that disruption of the yTBP:yTAF$_{II}$145 interaction does not lead to complete dissolution of the TFIID complex (Ranallo et al., 1999), a result consistent with the non-global transcriptional effects of yTAF$_{II}$145 inactivation. Mutations in histone fold-containing TAFs, on the other hand, may be more likely to destabilize TFIID, thereby leading to more severe effects. Surprisingly little is known about the biochemistry of the yTAFs, and as a result, testing the above hypothesis will require a more careful analysis of TAF-containing complexes and subcomplexes in yeast bearing TAF mutations. It is somewhat ironic that the wealth of in vivo data on the yeast TAFs may, in the end, turn out to be less interpretable in the absence of complementary in vitro biochemical studies to place the data in a mechanistic context.

6.2. Drosophila

Investigation into the in vivo functions of the *Drosophila* TAFs has been greatly aided by the serendipitous isolation of two separate nonsense mutations in $dTAF_{II}110$ and one insertional mutation in $dTAF_{II}60$ that affect the ability of these molecules to assemble into a functional TFIID complex (Sauer et al., 1996). The genetic screen that identified the mutations was designed to isolate suppressors of an eye phenotype caused by an activated ras introduced in *trans* (Karim et al., 1996). Presumably, the TAF alleles suppressed the eye phenotype because of their effects on the expression of the mutant ras. Although all of the mutations are homozygous lethal, there are sufficient gene-dosage and/or dominant negative effects in heterozygous embryos to enable an analysis of the role played by TAFs in activated transcription.

After an initial false start due to technical problems with mutant embryo staining experiments (Sauer et al., 1998), a number of studies utilizing *Drosophila* mutants have provided compelling evidence for an important role of TAFs in mediating transcriptional activation in vivo. For example, both Zhou et al. (1998) and Pham et al. (1999) examined the activation of the *Drosophila* embryonic genes *snail* and *twist* in flies heterozygous for the TAF mutations. Both genes are regulated by the Rel domain transcription factor Dorsal in a concentration-dependent manner, and perturbations in this regulation lead to altered patterns of *snail* and *twist* expression, which can be detected by in situ hybridization. Interestingly, the presence of a single mutant allele of either TAF was sufficient to affect the expression pattern of either gene, whereas an unrelated developmental mutation had little or no effect. The data suggest that the TAF mutation acts not by reducing the levels of Dorsal, but instead by affecting the ability of Dorsal to transactivate its target genes. Accordingly, the authors propose that $dTAF_{II}60$ and $dTAF_{II}110$ function as coactivators for Dorsal. Consistent with this model, Dorsal binds to both $dTAF_{II}110$ and $dTAF_{II}60$ in vitro, and the mutant forms of these TAFs act as dominant negatives to repress Dorsal-mediated activation in cell-free transcription assays.

In addition to $dTAF_{II}60$ and $dTAF_{II}110$, mutations in two other *Drosophila* TAFs have recently been isolated. First, Soldatov et al. (1999) discovered that the *e(y)1* gene, previously identified as a genetic modulator of both *yellow* and *white* gene expression (Georgiev and Gerasimova, 1989; Georgiev, 1994), encodes $dTAF_{II}40$. Not surprisingly, mutations that strongly repressed $dTAF_{II}40$ expression led to embryonic lethality, indicating that $dTAF_{II}40$ is an essential gene. Milder alleles of *e(y)1/TAF$_{II}$40*, on the other hand, had no adverse affects on viability, though one allele that reduced $TAF_{II}40$ mRNA levels 4- to 9-fold resulted in female sterility secondary to dramatic underdevelopment of the ovaries. This mild allele, termed $e(y)1^{ul}$, also affected expression of the *white* gene, particularly in the context of enhancerless mini-*white* constructs introduced on P elements into mutant flies. It is possible that the TATA-less nature of the *white* promoter renders its transcription more dependent on $TAF_{II}40$- and $TAF_{II}60$-mediated interactions with the DPE.

Second, the *cannonball* gene, identified previously as important for progression through the G2/M transition of meiosis I in males (Lin et al., 1996), appears to encode a tissue-specific $dTAF_{II}80$-related protein (M. Fuller, personal communication). Male flies bearing mutations at the *cannonball* locus are sterile as a result of defective spermatid development characterized by cell-cycle arrest at the primary spermatocyte stage. Interestingly, the yeast homolog of $dTAF_{II}80$, $yTAF_{II}90$, also plays an essential role in traversing the G2/M boundary, suggesting that rough parallels may exist between the functions of individual TAFs in diverse species.

6.3. Mammals

In mammals, mutations in $hTAF_{II}250$ and in CIF150 lead to cell-cycle arrest phenotypes that closely parallel those observed in yeast strains deleted for their homologs ($TAF_{II}145$ and TSM1, respectively). Both CIF150 and TSM1 appear critical for the G2/M transition (Martin et al., 1999), while a hamster cell line (ts13) bearing a temperature-sensitive point mutation in $TAF_{II}250$, like the $yTAF_{II}145$ mutants, exhibits G1 arrest at nonpermissive temperatures (Nishimoto and Basilico, 1978; Wang and Tjian, 1994). Using ts13 cells, several groups have identified genes that are down-regulated following upon temperature shift — including the genes encoding cyclin A, the D-type cyclins, and MHC class I — but transcriptional activation is not globally compromised under these conditions (Wang and Tjian, 1994; Suzuki-Yagawa et al., 1997; Wang et al., 1997). Current microarray experiments on the ts13 cell line suggests that as many as 18% of expressed genes may be misregulated at the nonpermissive temperature (T. O'Brien, personal communication).

Detailed analysis of the both the cyclin A and cyclin D1 promoters suggests that upstream enhancer regions and core promoter sequences, acting together, are necessary for the temperature-responsive transcriptional regulation of these genes in ts13 cells (Suzuki-Yagawa et al., 1997; Wang et al., 1997). In the case of the cyclin A promoter, the upstream region that contributes to $TAF_{II}250$ dependence, termed TSRE (temperature-shift response element), overlaps with binding sites for the ATF/CREB family of transcription factors (Wang et al., 1997). In vitro transcriptional activation by a mixture of these transcription factors, purified by TSRE-affinity

chromatography, was shown to be temperature-sensitive in ts13 nuclear extracts.

Recently, $TAF_{II}250$ was also shown to be involved in the repression of MHC class I expression by the HIV protein Tat. Using a two-hybrid screen, Weissman et al. (1998) identified a portion of mouse $TAF_{II}250$ that interacted with the C-terminus of Tat, the region both necessary and sufficient for Tat-mediated repression. This group accumulated several pieces of evidence that this interaction is likely relevant to Tat function. First, the effect of Tat on MHC class I expression can be titrated by the addition of increasing amounts of a Tat-binding $TAF_{II}250$ fragment. Second, the Tat:$TAF_{II}250$ interaction inhibits $TAF_{II}250$'s acetylation activity, presumably because Tat binding occludes the HAT domain. Third, promoters susceptible to Tat repression also lose activity in tsBN462 cells (a $TAF_{II}250$-mutant cell line related to ts13 cells; Noguchi et al., 1994) at the nonpermissive temperature. Thus, it is likely that Tat represses transcription at the MHC class I promoter by interfering with $TAF_{II}250$ function.

To date, $TAF_{II}250$ and CIF150 remain the only mammalian TAFs that have been amenable to in vivo evaluations of their function. As models for investigating TFIID's contribution to activated transcription, such studies have provided considerable insight. Several shortcomings, however, are worth noting. First, the temperature-sensitive $TAF_{II}250$ defects in ts13 and tsBN462 stem from the alteration of a single amino acid, which is not necessarily a null mutation. This concern is particularly warranted in light of observations from yeast laboratories that some temperature-sensitive yTAF mutations, but not others, lead to widespread alterations in gene regulation. Second, studies on $TAF_{II}250$ or CIF150 alone may present an overly complex picture on the role of the TAFs, since available evidence indicates that both molecules are likely involved in multiple processes such as promoter recognition by TFIID, activator-mediated recruitment of the complex, and, in the case of $TAF_{II}250$, perhaps even enzymatic modification of other regulatory factors. Third, the widespread reliance on a handful of mutant cell lines to deduce the in vivo functions of TAFs may fail to capture the full breadth of TAF functionality throughout a complex organism.

An attractive solution to these problems is to generate mice harboring null alleles of other TAFs through embryonic stem cell manipulation. However, nearly all mutations described in TAFs are lethal, and the prospect of a similar phenotype in mice potentially limits the usefulness of TAF knockouts. Instead, it may be necessary to generate conditional alleles of TAFs or to focus knockout efforts on TFIID components likely not to be essential for viability, such as the tissue-specific $TAF_{II}105$. Current evidence suggests a possible role for $TAF_{II}105$ as a transcriptional regulator in B lymphocytes, which are dispensable for murine survival; therefore, it is conceivable that mice would tolerate homozygous null alleles at the $TAF_{II}105$ locus. In addition, $TAF_{II}105$ is closely related in sequence to $hTAF_{II}130$ and $dTAF_{II}110$ — both of which have been implicated as coactivators (Chen et al., 1994; Gill et al., 1994; Sauer et al., 1995; Saluja et al., 1998; Zhou et al., 1998) — and it is possible that this family of TAFs, for which no apparent yeast homologs exist (Moqtaderi et al., 1996b), evolved to accommodate the increased

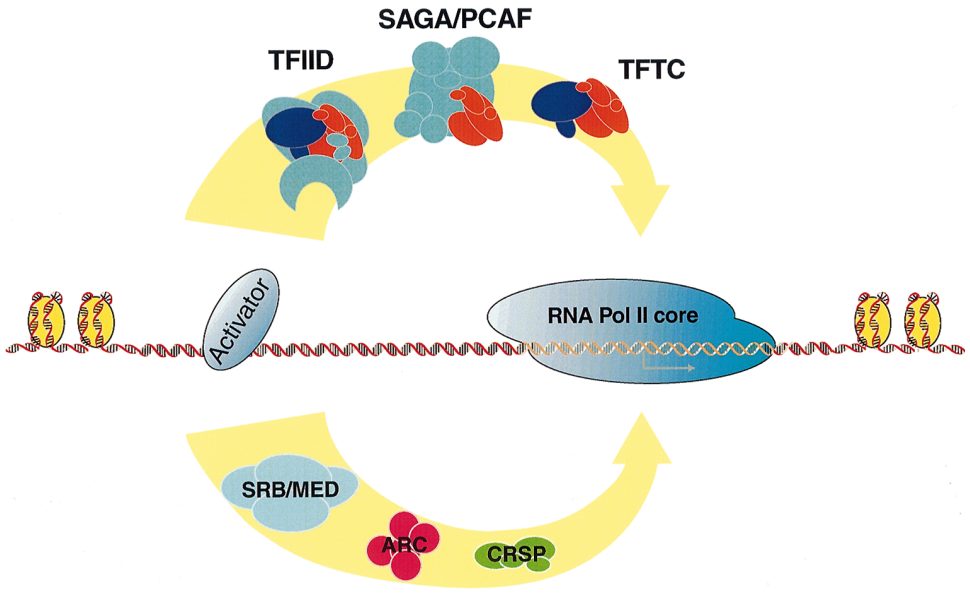

Fig. 3. Multiple pathway model for transcriptional activation. Activation signals from DNA-bound activators can be transduced to PolII through multiple coactivator complexes, including TAF-containing complexes (upper yellow arrow) and mediator-like complexes (lower yellow arrow). The relative contribution of each pathway to transcriptional regulation is likely to be activator- and/or promoter-dependent.

complexity of metazoan gene regulation. It is tempting to speculate, then, that a $TAF_{II}105$ knockout may reveal activator-specific effects and thereby provide an accessible in vivo system to examine the mechanism of TAF-mediated coactivation.

What types of phenotypes might we expect from a $TAF_{II}105$ knockout? Certainly, defects in B-cell development or function are likely to be present, though gene targeting of B-cell-specific transcriptional regulators has often led to surprisingly subtle phenotypes. Data from *Drosophila* and yeast further suggest that TAF deficiencies generally lead to phenotypes such as aberrant cell-cycle control and reproductive defects, perhaps reflecting the inherent sensitivity of these processes to inappropriate transcriptional programs. This observation, viewed in light of the significant expression of $TAF_{II}105$ in the testis, ovary, and early embryo, may suggest a reproductive function for this protein as well.

7. Conclusion

Just 3 years ago, the results of in vivo studies on TAF function in yeast were reported to be irreconcilable with models suggested by in vitro biochemical experiments. However, it is now clear that these in vivo studies, rather than requiring wholesale reconsideration of the importance of TAFs, actually strengthen the contention that TAFs are key players in transcriptional initiation. Indeed, most of the discrepancies currently separating the in vitro and in vivo data merely result from the inability of in vitro techniques to capture the full breadth of transcriptional regulation found in vivo. As a result of this limitation, cell-free assays using only partially purified components frequently fail to reveal additional requirements for achieving high-levels of activated transcription. For example, while specific TAFs and holoenzyme/mediator components are both clearly essential at most promoters in vivo, reconstituted transcription systems ostensibly lacking either one have been successfully developed (Chen et al., 1994; Fondell et al., 1999). Intriguingly, two recent studies dissecting activator-dependent transcriptional activation (Naar et al., 1999; Ryu et al., 1999) reveal separate, equally essential roles for TFIID and mediator-like complexes (Fig. 3). Consequently, future studies may bring an even greater convergence between in vitro and in vivo models of TAF function, although they are also likely to reveal greater complexity.

Note added in proof

While this manuscript was in press, two groups published nearly identical three-dimensional structures for TFIID, both obtained through electron microscopy and single-particle image analysis (Brand et al., 1999; Andel et al., 1999). Taken together, these data reveal a horseshoe-like structure for TFIID and suggest that the complex may exhibit some conformational flexibility. In addition, Andel et al. localized TBP near the midpoint of the complex, directly adjoining a 4 nm central cavity that most likely accommodates the TATA box during promoter recognition by TFIID. Intriguingly, the three-dimensional structure of TFTC, as described by Brand et al., exhibits similarities to TFIID in all the regions flanking the central cavity, supporting the notion that the TAFs shared among TFIID and TFTC form the structural core of these complexes.

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