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A multiplicity of mediators: alternative forms of transcription complexes communicate with transcriptional regulators

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ABSTRACT

The already complex process of transcription by RNA polymerase II has become even more complicated in the last few years with the identification of auxiliary factors in addition to the essential general initiation factors. In many cases these factors, which have been termed mediators or co-activators, are only required for activated or repressed transcription. In some cases the effects are specific for certain activators and repressors. Recently some of these auxiliary factors have been found in large complexes with either TBP, as TBP-associated factors (TAFs) in the general factor TFIID, or with pol II and a subset of the general factors, referred to as the 'holoenzyme'. Although the exact composition of these huge assemblies is still a matter of some debate, it is becoming clear that the complexes themselves come in more than one form. In particular, at least four forms of TFIID have been described, including one that contains a tissue-specific TAF and another with a cell type-specific form of TBP. In addition, in yeast there are at least two forms of the 'holoenzyme' distinguished by their mediator composition and by the spectrum of transcripts whose expression they affect. Genetic and biochemical analyses have begun to identify the interactions between the components of these complexes and the ever increasing family of DNA binding regulatory factors. These studies are complicated by the fact that individual regulatory factors often appear to have redundant interactions with multiple mediators. The existence of these different forms of transcription complexes defines a new target for regulation of subsets of eukaryotic genes.

INTRODUCTION

The initial phase of characterization of protein factors required for accurate transcription by RNA polymerase II (pol II) utilized relatively simple model templates for *in vitro* reconstitution experiments. This work resulted in the description of the factors necessary and sufficient for initiation, including TBP, TFIIB, TFIIF, TFIIE and TFIIH (reviewed in 1,2). When this collection of factors was used to recapitulate the effects of enhancer binding transcriptional regulatory factors it became clear that TBP and the TFII general transcription factors (GTFs) were not sufficient to communicate the full spectrum of activating and repressing signals to pol II. Biochemical searches for the missing components have identified a large and growing family of proteins capable of communicating signals from DNA binding regulatory factors to the transcription apparatus. In some cases the mediators and co-activators identified *in vitro* have turned out to be encoded by genes already known to play a role in transcriptional regulation.

Although there are clearly many different ways for regulatory factors to transmit signals, including direct contacts with the GTFs and alterations of chromatin structure, this review will focus on mediators and co-activators demonstrated to exist in stable complexes with pol II and the GTFs. Even within this narrow focus significant complexity has been found. Multiple forms of the co-activators associated with TBP as factor TFIID have been described in yeast and mammalian cells and at least two forms of the pol II holoenzyme have been shown to exist in yeast. In some cases there is functional redundancy between different mediators and co-activators. Transcriptional activators and repressors have apparently taken advantage of this redundancy by establishing contacts with many of these auxiliary factors.

The multiple contacts made are also important for the synergistic effects observed in complex promoters. Understanding how regulatory factors function will therefore involve defining the full range of contacts they make with this large family of transcriptional cofactors.

TBP, TAF_{II}s AND MULTIPLE TFIID COMPLEXES

It is now well established that the TATA box binding protein TBP is essential for transcription by all three nuclear RNA polymerases (reviewed in 3–5). TBP associates with different accessory factors, TAFs, for its various roles in transcription of all classes of genes. The TAF_{II}s were originally identified as cofactors required for activated transcription in reconstituted reactions (reviewed in 4). Their discovery and characterization explained the different properties of the large complex form of TBP initially identified from mammalian cells and the single polypeptide found in fractionated transcription extracts from yeast. It is now clear that all eukaryotic cells tested

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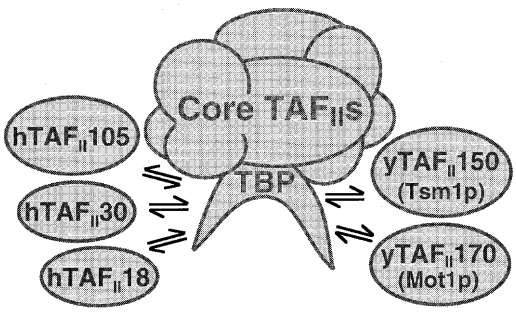

Figure 1. The presence of alternative TAF$_{II}$s defines different functional forms of TFIID.

so far contain a similar complex form of TBP, referred to as TFIID. In some cases (mammalian cells) the TFIID complex is very stable and resistant to dissociation, while in other cases (yeast) the TAF$_{II}$s are readily separated from TBP during biochemical fractionation. The TAF$_{II}$s in the TFIID complex have been highly conserved from yeast to humans, although there appear to be significant differences in TAF$_{II}$ composition between species (reviewed in 5). The TFIID complex has been reassembled from purified components and distinct protein–protein interactions have been identified between a variety of transcriptional activators and individual TAFs (reviewed in 6). Although there is currently a great deal of debate about the *in vivo* role of TAF$_{II}$s (see below), it is clear that they are critical for expression of important subsets of genes (7,8).

As more and more activators and repressors have been used in *in vitro* reconstituted transcription systems it has become apparent that there is not just a single form of TFIID, but instead multiple forms with different functions. The first report of multiple forms of TFIID was from Timmers and Sharp, who identified two large TBP-containing complexes: both were capable of supporting basal transcription, but only one was capable of responding to acidic and glutamine-rich activators (9). These investigators found that the two complexes had different protein components as well as different transcriptional properties (10).

Brou *et al.* (11,12) and Jacq *et al.* (13) also identified multiple TFIID complexes capable of responding to different classes of activators. In particular, these investigators identified hTAF$_{II}$30 as a factor associated with only a subset of TFIID complexes but required for activation by the estrogen receptor (13). Mengus *et al.* subsequently found that hTAF$_{II}$18 is uniquely present in the subform of TFIID that lacks hTAF$_{II}$30 (14). As diagrammed in Figure 1, different forms of TFIID appear to share a core of hTAF$_{II}$s, with co-existing subpopulations that contain or lack hTAF$_{II}$30 and hTAF$_{II}$18. Based on the observation that the hTAF$_{II}$30-containing form of TFIID is required for activation by the estrogen receptor, it is probable that these different forms of TFIID interact with or respond to different subsets of transcriptional regulators.

Different forms of TFIID have also been identified during the cell cycle. Segil *et al.* (15) found that phosphorylation of some of the hTAF$_{II}$s correlated with the appearance of two populations of TFIID during mitosis. The phosphorylated form was not responsive to activators, consistent with a role in the down-regulation of pol II transcription during mitosis.

The studies described above found multiple forms of TFIID in a single cell type. In contrast, Dikstein *et al.* (16) found that hTAF$_{II}$105 is uniquely present in differentiated B lymphocytes while, as schematized in Figure 1, the core TAF$_{II}$s were the same as in other cell types. Overexpression of hTAF$_{II}$105 in B cells led to changes in transcription from some but not all promoters tested (16). In recent work from the Tjian laboratory an entirely new TFIID-like complex has been identified in *Drosophila* (17). The complex is composed of a cell type-specific form of TBP called TRF and a unique collection of TAFs. This complex and cell type-specific hTAF$_{II}$105 are both probably involved in determining the pattern of transcripts during development and in differentiated tissues.

Different forms of TFIID also play a role in repression of transcription. Wade and Jaehning (18) identified a subpopulation of yeast TFIID required for repression by Leu3p. The repression-competent form of TFIID contained several of the core TAF$_{II}$s but lacked yTAF$_{II}$150, encoded by the essential *TSM1* gene. Instead, this subpopulation of TFIID was associated with the product of the essential *MOT1* gene. Mot1p has been shown to be a substoichiometric yeast TAF$_{II}$ (19) and it plays a critical role in expression of a subset of yeast genes (20,21). Mot1p may exert its effects on transcription via its ability to redistribute TBP from some TATA boxes to other promoters (20,21). Thus Tsm1p and Mot1p, like hTAF$_{II}$105, hTAF$_{II}$30 and hTAF$_{II}$18, are associated with different subpopulations of TFIID (Fig. 1), where they may direct the interactions of TBP with different promoters or regulatory factors.

Recent work from Timmers and co-workers (22) has established that a human Mot1p homolog is responsible for the unique properties of the second form of TFIID described above that is competent for basal transcription but unresponsive to activators (9,10). This observation, plus the fact that a newly identified *Drosophila* homolog of Mot1p (23) affects expression of developmentally regulated genes (24), is strong support for the idea that a Mot1p-containing form of TFIID is used in many if not all eukaryotes to differentially regulate expression of subsets of genes.

THE POL II 'HOLOENZYME(S)'

As described for the discovery of the TAF$_{II}$s in TFIID, the complex form of pol II referred to as the holoenzyme was identified in a search for factors that would mimic the *in vivo* effects of activators *in vitro*. Kornberg and co-workers found a complex of proteins, dubbed the 'mediator', essential for high levels of transcriptional activation in a highly purified system from yeast (25,26). Subsequently the mediator complex was found to co-purify with pol II, specifically interacting with the C-terminal domain (CTD) of the largest subunit of the enzyme (27). Young and co-workers identified a similar complex form of pol II containing the products of the *SRB* genes (28,29). The *SRB* genes were found as genetic suppressors of deletions of the pol II CTD (reviewed in 30). When the Srbps were followed through an extensive purification they were found to be tightly associated with a subpopulation of pol II. Both purification strategies result in holoenzymes containing TFIIF, Srb2,4,5+6p, and a dissociable subcomplex of Gal11p, Rgr1p and Sin4p (27,28,31). The presence of other Srbps, some of the GTFs (TBP, TFIIB, TFIIH) and components of the chromatin remodeling apparatus is still controversial (29,32–34). A schematic of the consensus elements of the holoenzyme including two recently described components, Rox3p (35) and Med6p (36), is shown on the left in Figure 2.

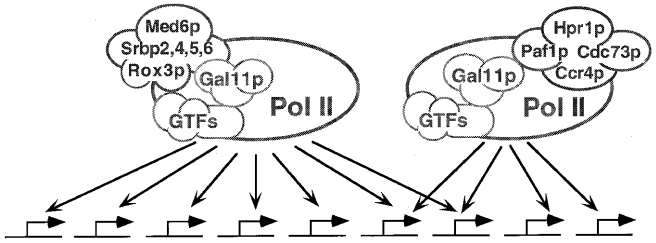

Figure 2. Two biochemically distinct forms of the pol II holoenzyme co-exist in yeast.

With the addition of the missing GTFs the holoenzyme is competent for communication with a model transcriptional activator, GAL4–VP16, *in vitro* (27,37). In addition, some of the Srbps (35), Gal11p (38,39), Sin4p, Rgr1p (31) and Rox3p (40) were initially identified as gene regulatory factors. Furthermore, tethering Gal11p or Srb5p to DNA via a DNA binding domain is sufficient for activation *in vivo* (29,41). It is therefore clear that this large pol II complex includes both critical GTFs and important mediators for communication with activators and repressors.

A very different purification strategy has led to the identification of a distinct form of the holoenzyme. In this case Wade *et al.* (42) used an immobilized form of an antibody directed against the pol II CTD for affinity isolation of proteins tightly bound to a transcriptionally active form of pol II. The proteins included some of those found in the holoenzyme (TFIIB, TFIIF and Gal11p) but lacked the Srbps. In addition, proteins not found in the holoenzyme were identified, including Paf1p and Cdc73p (42). Isolation of tagged forms of Paf1p and Cdc73p confirmed the existence of a distinct pol II complex lacking the Srbps (43). The two forms of holoenzyme have been shown to co-exist in yeast cells (43). Although the *PAF1* and *CDC73* genes are not essential, mutations cause temperature sensitivity and alterations in transcription of a subset of yeast genes (43,44). Recently two additional proteins, Ccr4p and Hpr1p, have been found in the Paf1p/Cdc73p-containing complex (Chang and Jaehning, unpublished observations). Both Ccr4p and Hpr1p affect transcription of subsets of yeast genes and neither is found in the Srbp-containing holoenzyme (45,46). The composition of this second biochemically distinct form of the pol II holoenzyme is shown on the right side of Figure 2.

The two holoenzyme complexes are portrayed transcribing overlapping major and minor subsets of genes. This model is based on the fact that some of the *SRB*s are essential genes shown to affect transcription of most yeast genes (47), while *PAF1*, *CDC73*, *CCR4* and *HPR1*, in addition to the shared components *GAL11*, *SIN4* and *RGR1*, are all non-essential and appear to affect only a subset of transcripts (31,39,43,45,46). The overlapping nature of the effects of the two complexes is based on the fact that expression of some genes is affected by mutations in either complex. In addition, many combinations of mutations in these factors are lethal (for example *srb5*, *paf1* and *srb5*, *ccr4*; Chang and Jaehning, unpublished observations).

Holoenzyme complexes and homologs of some of the Srbps have recently been identified in mammalian cells. In contrast to the complexes identified in yeast, these mammalian complexes contain some or all of the GTFs in addition to several known co-activators (48–50). Without the addition of exogenous factors, one of these complexes is capable of activator-responsive transcription *in vitro* (48). Perhaps, as in the case of TFIID, the stability of the pol II–GTF complexes in yeast is less than that in mammalian cells. Substoichiometric amounts of TBP and TFIIH have been reported in some preparations of the yeast holoenzyme in support of this idea (28,29).

In addition to the GTFs, mammalian pol II holoenzyme complexes have been described containing DNA repair proteins (49), splicing and polyadenylation factors (51) and the breast cancer tumor suppressor BRCA1 (52). It is not yet clear whether these different reports are each describing one huge complex or, if as found for yeast, mixtures of different holoenzyme forms are present. As different laboratories use multiple techniques to isolate and characterize these large complexes this question should be resolved.

FUNCTIONAL REDUNDANCY IN TFIID AND HOLOENZYME COMPONENTS

Both the TFIID TAF_{II}s and the mediators of the holoenzyme are capable of communicating signals from activators to pol II. Some activators can clearly use either pathway; activating signals from the hybrid activator Gal4p–VP16 are mediated by either yeast TFIID (53) or the holoenzyme (27,29) *in vitro*. The ability to interact with both complexes can also lead to synergistic effects on activation of transcription *in vivo* (54). Although it will take many more experiments to determine all of the possible interactions between regulatory factors and mediators, there are undoubtedly some factors with a restricted set of connections such that a single pathway is critical for function. However, with the relatively strong activators that have been studied in some detail redundancy appears to be the rule rather than the exception. The 'model' activator VP16 for example has been reported to make specific protein–protein contacts with TFIIB (55), TFIIH (56), $TAF_{II}40$ (57), $TAF_{II}32$ (58), TBP (59) and the holoenzyme (37). The contribution of each of these interactions to the full level of activation by VP16 has not been determined, but abolishing the contacts for *in vitro* interaction with TBP has little effect on activation *in vivo* (60).

This redundancy in interaction is consistent with the fact that most regulatory factors have redundant activation or repression domains. VP16 is one of many examples of this phenomenon, demonstrating many closely spaced activation subdomains (61,62). The yeast Gcn4p activator has as many as seven redundant clusters of amino acids that contribute to activation (63). The yeast Gal4p activator has been extensively studied in terms of its activation functions and its requirements for communication with pol II. Both types of analyses have revealed extensive redundancy. The major Gal4p activation domain is complex, with many elements contributing to full function (64,65). As shown in Figure 3, Gal4p also depends on many known mediators for full activity. These include the Gal11 (38), Srb2,10+11 (32), Paf1 (44), Med6 (36), Rox3 (35) and Hpr1 (46) proteins, all found in the holoenzymes, plus many other factors implicated as mediators. It is clear that connections to many parts of the transcription apparatus are an important feature of a 'strong' activator like VP16 or Gal4p. As additional weaker activators and repressors are analyzed in detail it will be

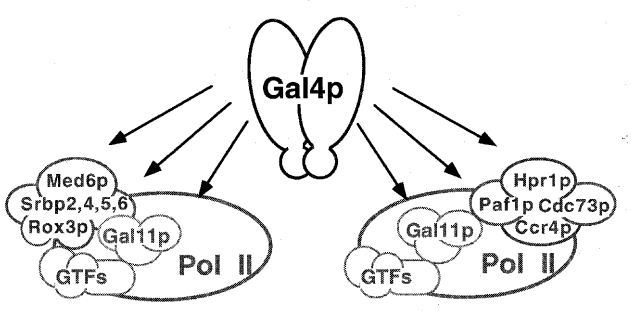

Figure 3. The Gal4p transcriptional activator requires many of the holoenzyme-associated mediators for complete function.

interesting to learn if some display less functional redundancy or if their properties are simply due to weaker interactions.

SEEING PATTERNS IN A SEA OF REDUNDANCY

How can we determine which of these many mediator interactions is most important for a particular activator or repressor? Part of the current problem is the lack of a complete story for any one regulatory factor. For example, extensive biochemical experiments with VP16 have identified interactions which may or may not be relevant *in vivo*. Conversely, the Gal4p–mediator connections shown in Figure 3 have been determined genetically, but are as yet unsupported by biochemical experiments to determine if they reflect direct protein–protein interactions or failure to assemble required complexes. It is interesting to note that mutations in many of the non-essential genes encoding the mediators shown in Figure 3 lead to only partial diminution of activation by Gal4p. In most cases activation is diminished from 3- to 10-fold (38,44,46,48). This indicates that each mediator connection is contributing to an overall level of activation. When possible, making similar measurements in double mutant strains may help to confirm this interpretation.

Some of the mediators are clearly important for expression of a broader spectrum or a more critical class of genes than others. For example, the yeast *TAF*-encoding genes (66), including *MOT1* (67), and holoenzyme factors, including some of the *SRB*s (30), *ROX3* (40) and *MED6* (36), are essential genes in yeast, while other *SRB*s and mediators shown in Figures 2 and 3 are non-essential. Combinations of mutations in some of the non-essential mediators do, however, lead to severe phenotypes or death (44; Chang and Jaehning unpublished observations), indicating that these factors have overlapping functions in essential cellular processes. Although defects in the essential *SRB*s have been shown to affect expression of many yeast genes (47), the role of the TAF_{II}s is not as clear. Transcription of the majority of genes appears to go on more or less as usual in the absence of the TAF_{II}s (68,69). However, $yTAF_{II}145$ and $hTAF_{II}250$ are critical for expression of some cyclin genes in yeast and mammalian cells (70,71), consistent with the fact that $yTAF_{II}$s are essential for progression through the cell cycle (7). Individual TAF_{II}s have also been shown to be important for expression of bicoid-dependent genes in flies (8) and for potentiating signals from the HTLV Tax transactivator (72) and the retinoic acid and thyroid hormone receptors (73,74) in mammalian cells.

How can the complete role for each of these complex factors be determined? Fortunately, technology is catching up with the problem. The ability to analyze expression of every transcription unit in a genome is almost a reality with the development of solid state arrays of entire genomes (75,76). In addition, powerful PCR-based techniques like differential display (77) and SAGE (78) are currently being used to identify many coordinately regulated transcription units at once. The application of differential display to strains mutant in the non-essential mediators has already begun to create a more detailed picture of the overlapping roles these complex factors play *in vivo* (44). In the future the genome-wide analysis of expression patterns will certainly resolve many of the issues raised in this review.

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