Analysis

Genes Encoding *Drosophila melanogaster* RNA Polymerase II General Transcription Factors: Diversity in TFIIA and TFIID Components Contributes to Gene-specific Transcriptional Regulation

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How have the factors required for transcription initiation (TFIIA, TFIIB, TFIID, TFIIE, TFIIF, TFIIH, and RNA polymerase II [pol II]) evolved to accommodate the elaborate transcriptional programs required for growth, differentiation, and development of multicellular organisms? Here we present analysis of the recently completed *Drosophila melanogaster* genome sequence, as well as those of *Caenorhabditis elegans*, *Saccharomyces cerevisiae*, and humans, that sheds light on this well studied question in eukaryotic biology. All four organisms encode single isoforms of RNA pol II, TFIIB, TFIIE, TFIIF, and TFIIH components, but multiple, sequence-related isoforms of TFIID components (Fig. 1; Albright and Tjian, 2000). In addition, *Drosophila* and humans encode multiple isoforms of TFIIA components (Upadhyaya et al., 1999; Ozer et al., 2000). Current evidence indicates that tissue- and cell type–specific transcription is directed by differentially expressed TFIID and possibly TFIIA isoforms (Zeidler et al., 1996; Upadhyaya et al., 1999; Albright and Tjian, 2000; Ozer et al., 2000). Thus, in accord with experimental data, this analysis points to TFIIA and TFIID as the factors that help generate the broad transcriptional repertoire of multicellular organisms. The identification of the complete set of TFIIA and TFIID components in a genetically and biochemically tractable organism like *Drosophila* is an important step toward understanding the mechanisms governing developmentally regulated transcription not only in *Drosophila* but also in humans.

The Biology of Transcription Initiation

Biochemical fractionation of *Drosophila* embryos, human cells, and yeast cells has defined a set of multiprotein complexes termed general transcription factors (GTFs; TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH)[1] required for mRNA transcription initiation in vitro (Orphanides et al., 1996; Hampsey, 1998). Transcription is initiated by recognition of core promoter elements by TFIID and sequential or concerted assembly of the other GTFs and RNA pol II to form the preinitiation complex (PIC). Although GTFs play essential roles during transcription initiation, it is the factors that regulate the ability of the GTFs to assemble and stably bind a core promoter that are probably major determinants of gene-specific transcription levels. For example, activators and coactivators are thought to stimulate transcription by recruiting GTFs to a promoter, thereby accelerating PIC assembly.

The GTF TFIID is composed of TATA-binding protein (TBP) and coactivator subunits termed TBP-associated factors (TAF_{II}s; Burley and Roeder, 1996; Green, 2000; Albright and Tjian, 2000). TAF_{II}s not only function as "conventional" coactivators by serving as physical links between DNA-binding activator proteins and the PIC but also possess enzymatic or promoter recognition activities that presumably enhance the efficiency of PIC assembly. TFIIA has also been described as a coactivator and displays a number of TAF_{II}-like properties: it binds to TBP and TAF_{II}s; it interacts with specific transcriptional activators; it is generally required for activated transcription in vitro; and it contributes to promoter selectivity (Orphanides et al., 1996; Hampsey, 1998).

TAF_{II}, TBP, and TFIIA Components Mediate Gene-specific Transcription

Inactivation of individual TAF_{II}s in *Drosophila*, mammalian, and yeast cells has demonstrated that TAF_{II}s are not required for the transcription of all RNA pol II genes, and in fact there is great variation in regard to the identity and number of gene targets for individual TAF_{II}s (Green, 2000; Albright and Tjian, 2000). Furthermore, different domains within a single TAF_{II} can play gene-specific roles in transcription (O'Brien and Tjian, 2000). The isolation of a

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[1]*Abbreviations used in this paper:* GTF, general transcription factor; PIC, preinitiation complex; TAF_{II}, TBP-associated factor; TBP, TATA-binding protein.

A

Complex	*Drosophila*	*C. elegans*	Human	Yeast
RNA Pol II	RpII215 CG1554	ama-1/RPB1 F36A4.7	RPB1	RPB1/RPO21
	RpII140 CG3180	RPB2 C26E6.4	RPB2	RPB2
	RpII33 CG7885	C36B1.3	RPB3	RPB3
	RPB4 CG7150	F43E2.1	RPB4	RPB4
	RPB7 CG6572	Y54E10BR.c	RPB7	RPB7
	RpII15 CG3284	Y97E10AR.a	RPB9	RPB9
	RPB11 CG6840	W01G7.3	RPB11	RPB11
	RPB5 CG11979	H27M09.2	RPB5	RPB5
	RpII18 CG1163	RPB6 C06A1.5	RPB6	RPB6/RPO26
	RPB8 CG11246	RPB8 F26F4.11	RPB8	RPB8
	RPB10 CG13628	C01B7.1	RPB10	RPB10
	RPB12 ND	F23B2.13	RPB12	RPB12/RPC10
TFIIB	TFIIB CG5193	W03F9.5	TFIIB	TFIIB/SUA7
TFIIE	TFIIEα CG10415	TFIIEα ZK550.4	TFIIEα	TFA1
	TFIIEβ CG1276	TFIIEβ F54D5.11	TFIIEβ	TFA2
TFIIF	TFIIFα CG10281	C01F1.1	RAP74	TFG1
	TFIIFβ CG6538	Y39B6A.i	RAP30	TFG2
	ENL/AF-9 CG4913	Y105E8B.f	ENL, AF-9	TAF30/ANC1
TFIIH	TFB1 CG8151	R02D3.3	p62	TFB1
	TFB2 CG7764	Y73F8A.24	p52	TFB2
	Mat1 CG7614	F53G2.7	Mat1	TFB3
	TFB4 CG5041	ZK1128.4	p34	TFB4
	SSL1 CG11115	T16H12.4	SSL1/p44	SSL1
	haywire CG8019	H06O01.2	XPB/ERCC3	SSL2/RAD52
	XPD/ERCC2 CG9433	Y50D7A.i	XPD/ERCC2	RAD3
	CycH CG7405	H14E04.5	CycH	CCL1
	CDK7 CG3319	cdk-7 Y39G10AL.a	CDK7	KIN28

Figure 1. RNA pol II and GTF-encoding subunit genes from *D. melanogaster*, *C. elegans*, humans, and *yeast* are grouped by protein complex. Additional information about these genes can be accessed using the indicated gene name or identification number at web sites for the *Drosophila* (http://www.fruitfly.org/annot/), *C. elegans* (http://www.wormbase.org/), yeast (http://www.proteome.com/databases/index.html), or human genomes (http://www.ncbi.nlm.nih.gov/). No Gadfly identification has been assigned for Rpb12 because it was not identified by gene prediction programs and no expressed sequence tags have been isolated. However, searches using the human and yeast Rpb12 homologues match translated genomic sequence from EMBL/GenBank/DDBJ accession No. AC017903, and further analysis of sequences surrounding this match reveal additional amino acid similarity that spans 3 exons (our unpublished observation). Each row contains homologous genes from each of the four organisms. An asterisk indicates that the gene is alternatively spliced. ND indicates information that has not been determined. The following identification numbers correlate to predicted mRNAs that in addition to encoding the indicated protein may also encode another protein, presumably due to a gene prediction error: *Drosophila* CG7150, CG6572, and *C. elegans* C36B1.3, F43E2.1, Y97E10AR.a, F39H11.2, and Y37E11AL.c. (A) Genes encoding components of RNA pol II, TFIIB, TFIIE, TFIIF, and TFIIH. (B) Genes encoding components of TFIIA and TFIID. Genes in bold typeface have been demonstrated experimentally to be a component of the indicated complex. Genes in normal typeface that are bordered in a black box may be a component of the indicated complex and await experimental evidence. Genes that are not bordered in a black box are components of other complexes. Genes that are expressed in a tissue- or cell type–specific manner are shaded orange, genes that encode components of HAT complexes are shaded pink, and genes that encode sequence similarity to the histone fold motif are shaded blue. A search program that identifies protein motifs (http://www.isrec.isb-sib.ch/software/PFSCAN_form.html) and visual comparison of sequences was used to find the histone fold motifs in TAF_{II}s and the transcription factors indicated in the text. Yeast BDF1, $TAF_{II}48$, and $TAF_{II}65$ are recently described components of TFIID (Sanders and Weil, 2000; Matangkasombut et al., 2000; Reese et al., 2000). Yeast $TAF_{II}145$ and BDF1 display functional and sequence similarity to the NH_2 and COOH termini, respectively, of human $TAF_{II}250$ and therefore are placed in the same box (Matangkasombut et al., 2000). Bdf1 and Bdf2 display sequence similarity but only Bdf1 has been demonstrated to associate with TFIID. $TAF_{II}30$/ANC1 is also a component of NuA3, TFIIF, and SWI/SNF complexes (John et al., 2000).

B

Complex	*Drosophila*			*C. elegans*		Human		Yeast		Histone-fold
TFIIA	**TFIIA-L* CG5930**			K11D12.2		**TFIIA-L***	**ALF***	**TOA1**		
	TFIIA-S CG5163	TFIIA-S-2 CG11639		B0336.5		**TFIIA-S**		**TOA2**		
TFIID	**TBP** CG9874	TRF1 CG7562	TRF2 CG18009	TBP T20B12.2	TLP F39H11.2	**TBP**	TLP/TRF2	**TBP/SPT15**		
	TAF250/230 CG17603			Y71A12B.a		**TAF250/CCG1**		**TAF145/130**		
								BDF1	BDF2	
	TAF150 CG6711			Y37E11B.4		**CIF150**		**TSM1**		
	TAF110 CG5444	no hitter CG15259		R119.6		**TAF130/135**	**TAF105**	**TAF48/MPT1**		H2A
	TAF80 CG7704	cannonball CG6577		F30F8.8		**TAF100**	PAF65β	**TAF90**		
	TAF60/62 CG9348	TAF60-2 CG10390		W09B6.2	Y37E11AL.c	**TAF70/80**	PAF65α	**TAF60**		H4
	TAF55 CG2670			111B2D.d	F54F7.1	**TAF55**		**TAF67**		
	TAF40/42/e(y)1 CG6474			T12D8.7		**TAF31/32**		**TAF17**		H3
	TAF30α/28* CG17358	TAF30α-2 CG15632		Y56A3A.4		**TAF20***		**TAF61**		H2B
	TAF30β CG4079			F48D6.1	K10D3.3	**TAF28**		**TAF40**		H3
	TAF18 CG10756	SPT3 CG3169		C14A4.10		**TAF18**	SPT3	**TAF19/FUN81**	SPT3	H4
	TAF16 CG3069	**TAF24** CG2859		K03B4.3		**TAF30**		**TAF25/23**		
	cabeza CG3606			C27H5.3		**TAF68**		none		
	ENL/AF-9 CG4913	CG9207		Y105E8B.f	M04B2.3	ENL	AF-9	**TAF30/ANC1**	YAF9	
	none			none		ND		**TAF65**		
	none			none		ND		**TAF47**		

human B cell–specific isoform of $TAF_{II}130$ ($TAF_{II}105$) raised the possibility that substoichiometric subunits of TFIID mediate tissue- or cell type–specific transcription and that additional components of TFIID may have escaped detection because of their low abundance (Dikstein et al., 1996, Yamit-Hezi et al., 2000). These possibilities have been born out in *Drosophila* where isoforms of $TAF_{II}110$ and $TAF_{II}80$ (No hitter [Nht] and Cannonball [Can], respectively) are expressed exclusively in testis and regulate transcription of a subset of genes required for spermatogenesis, and isoforms of TBP (TBP-related factors [TRF1 and TRF2]) are expressed in a tissue-specific manner and bind different genes in salivary gland cells (Hansen et al., 1997; Rabenstein et al., 1999; Hiller, M., T.-Y. Lin, and M. Fuller, personal communication). Similarly, analysis of the human TFIIA-L isoform ALF (TFIIAα/β-like factor) reveals that its expression is restricted to the testis; however, it remains to be determined if it is used for the transcription of testis-specific genes (Upadhyaya et al., 1999; Ozer et al., 2000). In *Drosophila*, TFIIA-S is expressed in a dynamic pattern during eye development and is transiently upregulated in photoreceptor precursor cells before their fate is determined (Zeidler et al., 1996). Therefore, the role of TFIIA and TFIID in transcription initiation is governed by the expression patterns and activities of their varied components.

Finally, it is critical to note that analysis of the function of TAF_{II}s is complicated by the fact that they are components of at least two other complexes that lack TBP, p300/CBP-associated factor (PCAF) and TBP-free TAF_{II}-containing complex (TFTC) (Struhl and Moqtaderi, 1998; Bell and Tora, 1999). The human PCAF histone acetyltransferase (HAT) complex contains three TAF_{II}s that are shared with TFIID ($TAF_{II}31/32$, $TAF_{II}20/15$, and $TAF_{II}30$) and three TAF_{II} isoforms (PCAF-associated factor 65β [PAF65β], PAF65α, and SPT3) related to $TAF_{II}100$, $TAF_{II}70/80$, and $TAF_{II}18$, respectively (Birck et al., 1998; Ogryzko et al., 1998). Yeast possess an analogous complex, Spr-Ada-Gcn5-acetyltransferase (SAGA), containing TFIID TAF_{II}s and the Gcn5 HAT, and *Drosophila* may also, as it contains a Gcn5/PCAF homologue that interacts with $TAF_{II}24$ (Smith et al., 1998; Brown et al., 2000; Georgieva et al., 2000).

The Genomics of Transcription Initiation

Searches of the completed *Drosophila*, *C. elegans*, and yeast genomes and the partial human genome for sequence homologues of biochemically identified components of the general transcription machinery have led to the following conclusions. First, all of the components of RNA pol II, TFIIB, TFIIE, TFIIF, and TFIIH are encoded by single copy genes in *Drosophila*, *C. elegans*, and yeast (Fig. 1 A). Second, multiple isoforms of TFIID components are encoded in *Drosophila*, *C. elegans*, humans, and yeast, and multiple isoforms of TFIIA components are encoded in *Drosophila* and humans (Fig. 1 B). Third, each organism encodes isoforms of different sets of TFIIA and TFIID components, some which are unique to a particular organism.

Sequence comparisons uncovered *Drosophila* homologues of TAF_{II}s previously identified in yeast or humans by biochemical means but which had not been described in *Drosophila* (yeast $TAF_{II}67$/human $TAF_{II}55$, yeast $TAF_{II}30$/human ENL/AF-9, and yeast $TAF_{II}19$/human $TAF_{II}18$; Green, 2000). Thus, all TAF_{II}s present in both yeast and humans are present in *Drosophila*, as well as *C. elegans*. In contrast, yeast $TAF_{II}47$ and $TAF_{II}65$ are absent from *Drosophila*, *C. elegans*, and apparently from humans, suggesting that these TAF_{II}s perform a yeast-specific role, such as serving as coactivators for DNA-binding activators that are not present in metazoans. Finally, there are TAF_{II}s present in *Drosophila*, *C. elegans*, and humans that are absent from yeast (human $TAF_{II}68$/*Drosophila* Cabeza and multiple TAF_{II} isoforms). In addition to Can and Nht, there are alternatively spliced forms of $TAF_{II}30\alpha$, two genes ($TAF_{II}24$ and $TAF_{II}16$) that encode *Drosophila* homologues of human $TAF_{II}30$, and $TAF_{II}60$ and $TAF30\alpha$ isoforms ($TAF_{II}60$-2 and $TAF30\alpha$-2, respectively) (Kokubo et al., 1994; Georgieva et al., 2000). TFIIA-S and TFIIA-L are the only other GTF components in *Drosophila* and humans, respectively, that are expressed in multiple isoforms (Upadhyaya et al., 1999; Ozer et al., 2000). The fact that these proteins are unique to multicellular organisms suggests that they play cell-specific roles.

A number of TAF_{II}s contain a common structural motif called the histone fold that was originally shown to drive folding and association of each of the core histones (H2A, H2B, H3, and H4) and subsequently shown to play a similar role in association of TAF_{II}s (Xie et al., 1996; Wolffe, 1998). TAF_{II} pairs, such as *Drosophila* $TAF_{II}40$ and $TAF_{II}60$, form heterotetramers, analogous to H3 and H4, and numerous other TAF_{II}–TAF_{II} and TAF_{II}–nonTAF_{II} interactions have been shown to involve histone fold motifs (Gangloff et al., 2000). The demonstrated histone fold interaction of human $TAF_{II}135$ and $TAF_{II}20$, predicts that *Drosophila* isoforms of these proteins, Nht and $TAF_{II}30\alpha$-2, respectively, may heterodimerize and hints at the existence of a human $TAF_{II}20$ isoform that would heterodimerize with the $TAF_{II}135$ isoform, $TAF_{II}105$. B cell–specific expression of the hypothetical $TAF_{II}20$ isoform may explain why $TAF_{II}105$ associates with TFIID in B cells but not in other cell types (Dikstein et al., 1996).

In addition to the TAF_{II}s indicated in Fig. 1 B, other *Drosophila* transcription factors contain histone fold motifs: Prodos (*Drosophila* genome project Gadfly accession number CG7128), NF-YB-like (CG10477), NF-YC-like (CG3075, CG11301), CHRAC-14 (CG13399), CHRAC-16 (CG15736), Dr1 (CG4185), NC2α (CG10318), and BIP2 (CG2009). It is interesting to speculate that these factors may be unidentified TAF_{II} components of TFIID or binding partners for known TAF_{II}s in complexes that lack TBP.

Putting It All Together

Analysis of eukaryotic genomes has defined sets of proteins that are similar in sequence to known components of TFIIA and TFIID. Since known components of TFIIA and TFIID have been shown to play key roles in developmentally regulated transcription, it is exciting to speculate that the newly identified genes will play similar roles and that TFIIA and TFIID components have evolved to support tissue- or cell type–specific transcriptional requirements of individual eukaryotic organisms.

The challenge now is to determine if TAF_{II}s that have been identified on the basis of their sequence are components of TBP-containing complexes or other TAF_{II}-containing complexes, whether TAF_{II}s and TFIIA isoforms are differentially expressed during development, and how differentially expressed TBP, TAF_{II}, and TFIIA isoforms function in concert with the ubiquitously expressed form of TFIID and TFIIA to regulate gene expression. The subunit composition of human PCAF complex leads to the prediction that *Drosophila* TAF_{II}60-2 and Can and *C. elegans* Y37E11AL.c are components of PCAF/SAGA and not TFIID. On the other hand, protein isoforms that are unique to a particular organism, such as *Drosophila* TAF_{II}30α-2 and *C. elegans* F54F7.1 and K10D3.3, may be tissue- or cell type–specific components of TFIID and not PCAF/SAGA.

Drosophila may be the most appropriate organism for these studies since the biochemical activities of these factors can be determined using established TFIIA and TFIID purification schemes and in vitro transcription systems, and developmental requirements for these factors can be determined using existing mutants or mutants generated by traditional mutagenesis schemes, P-element insertion, RNA interference (RNAi), or homologous recombination (Kennerdell and Carthew, 1998; Rörth et al., 1998; Spradling et al., 1999; Rong and Golic, 2000).

In terms of the RNA pol II transcriptional machinery, this review has covered only the tip of the iceberg. Detailed analysis of *Drosophila* genes encoding DNA-binding transcription factors, coactivators, corepressors, chromatin remodeling factors, and other trans-acting regulators of transcription remains to be tackled. However, completion of the *Drosophila* genome sequence has set the stage for biochemical, molecular, and genetic studies in *Drosophila* that should lead to advances in our understanding of developmentally regulated RNA pol II transcription.

In addition to being able to identify new components of the transcription machinery, the *Drosophila* genome project has provided several valuable tools for studying RNA pol II transcription. First, it has led to the identification of fly stocks containing P-element insertions that disrupt GTF genes, providing the opportunity to investigate developmental and possibly mechanistic roles for the encoded factors (Rörth et al., 1998; Spradling et al., 1999). Second, sequencing of full-length expressed sequence tags (i.e., cDNAs) has helped define RNA pol II transcription start sites that may lead to the identification of novel core promoter elements or provide insight into how different combinations of core promoter elements contribute to transcription initiation. The recent description of a TC-rich sequence (TC-box) that is specifically bound by *Drosophila* TRF1 and the identification of isoforms (i.e., TAF_{II}60-2) of known TAF_{II}s (i.e., TAF_{II}60) that recognize core promoter elements hints at the existence of additional core promoter elements (Burke et al., 1998; Holmes and Tjian, 2000). Finally, the description of the ~13,600 *Drosophila* genes allows for construction of DNA microarrays (i.e., gene chips) that can be used to identify gene targets for individual components of the transcription machinery (Adams et al., 2000).

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