Cell PRESS

Conservation between the RNA Polymerase I, II, and III Transcription Initiation Machineries

Alessandro Vannini[1,2,*] and Patrick Cramer[1,*]
[1]Gene Center and Department of Biochemistry, Center for Integrated Protein Science Munich, Ludwig-Maximilians-Universität München, Feodor-Lynen-Strasse 25, 81377 Munich, Germany
[2]Present address: Section of Structural Biology, Institute of Cancer Research, Chester Beatty Laboratories, 237 Fulham Road, London SW3 6JB, UK
*Correspondence: alessandro.vannini@icr.ac.uk (A.V.), cramer@genzentrum.lmu.de (P.C.)
DOI 10.1016/j.molcel.2012.01.023

Recent studies of the three eukaryotic transcription machineries revealed that all initiation complexes share a conserved core. This core consists of the RNA polymerase (I, II, or III), the TATA box-binding protein (TBP), and transcription factors TFIIB, TFIIE, and TFIIF (for Pol II) or proteins structurally and functionally related to parts of these factors (for Pol I and Pol III). The conserved core initiation complex stabilizes the open DNA promoter complex and directs initial RNA synthesis. The periphery of the core initiation complex is decorated by additional polymerase-specific factors that account for functional differences in promoter recognition and opening, and gene class-specific regulation. This review outlines the similarities and differences between these important molecular machines.

Introduction

Three multisubunit RNA polymerase (Pol) enzymes, Pol I, II, and III, transcribe the eukaryotic genome. The three polymerases were first described after their chromatographic separation over four decades ago (Roeder and Rutter, 1969, 1970). Subsequent exploitation of the differential sensitivity of the enzymes to the toxin α-amanitin revealed that the polymerases synthesize different classes of cellular RNA (Seifart and Sekeris, 1969; Kedinger et al., 1970; Lindell et al., 1970; Zylber and Penman, 1971; Weinmann and Roeder, 1974). Pol I, II, and III synthesize the 25S rRNA precursor, messenger RNAs (mRNAs), and short untranslated RNAs such as transfer RNAs (tRNAs) and 5S ribosomal RNA (rRNA), respectively. The development of assays for promoter-specific in vitro transcription (Bikoff et al., 1975; Bikoff and Gefter, 1975; Weil et al., 1979; Manley et al., 1980) then led to the fundamental finding that transcription initiation from promoters requires, in addition to the polymerases, several general transcription factors (reviewed in Roeder, 1996; Orphanides et al., 1996; Conaway and Conaway, 1997). The isolation of a transcriptionally active form of Pol II from yeast (Lue and Kornberg, 1987) represented a starting point for detailed structure-function studies of eukaryotic RNA polymerases (reviewed in Kornberg, 2007; Cramer et al., 2008).

Transcription starts with assembly of initiation complexes on gene promoters. During initiation, the general transcription factors recognize promoter elements, recruit and orient the polymerase, and assist the polymerase in DNA opening and initial RNA synthesis. All polymerases require TBP (Cormack and Struhl, 1992), which binds upstream of the transcription start site at all promoters (Rhee and Pugh, 2012) and can induce a 90° bend in the DNA (Nikolov et al., 1995). Pol II initiation further requires TFIIB, which forms a bridge to TBP (Kostrewa et al., 2009; Liu et al., 2010), as well as TFIIE, TFIIF, and TFIIH. Since Pol I and Pol III use a distinct set of general factors, they were thought to use different molecular mechanisms to initiate transcription. Recent results, which will be discussed later in this review, have however revealed that the Pol I and Pol III machineries contain a core that is structurally and functionally conserved in the Pol II initiation complex. In this review, we set out the similarities between RNA polymerase initiation machineries, and discuss differences that lead to gene class-specific functions.

Pol I, II, and III contain 14, 12, and 17 subunits, respectively (Table 1). All three polymerases contain a ten-subunit catalytic core. In Pol I and Pol III, one subunit of this core is related not only to the Pol II subunit Rpb9 but also to the Pol II-associated factor TFIIS (Ruan et al., 2011). Pol I, II, and III further contain the related heterodimeric subcomplexes A14/43, Rpb4/7, and C17/25, respectively, which form the polymerase stalk (Hu et al., 2002; Peyroche et al., 2002; Armache et al., 2005; Jasiak et al., 2006; Kuhn et al., 2007). In addition, Pol I contains the subcomplex A49/34.5 (Kuhn et al., 2007), and Pol III contains subcomplexes C37/53 (Kassavetis et al., 2010; Landrieux et al., 2006) and C82/34/31 (Wang and Roeder, 1997).

Pol I and Pol III Contain a TFIIF-like Subcomplex

The general Pol II transcription factor TFIIF stabilizes the initiation complex, participates in open complex formation and transcription start site selection, enhances early RNA elongation, and stimulates polymerase escape from the promoter (Yan et al., 1999; Chen et al., 2007; Čabart et al., 2011; Fishburn and Hahn, 2012). TFIIF contains a dimerization module that holds together its subunits α (Tfg1) and β (Tfg2) (Gaiser et al., 2000) (Figure 1). A similar dimerization module was discovered in the Pol I subcomplex A49/34.5 (Kuhn et al., 2007; Geiger et al., 2010). Crosslinking experiments demonstrated that the dimerization modules of both A49/34.5 and TFIIF bind the lobe domain on one side of the active center cleft of the polymerase (P.C., unpublished data) (Chen et al., 2010; Eichner et al., 2010) (Figure 2). The Pol III subcomplex C37/53 apparently also contains a TFIIF-like dimerization module (Kuhn et al., 2007;

Table 1. Yeast RNA Polymerase Subunits and Initiation Factor Homologies

Pol II	Pol I	Pol III	Function
Polymerase Core			
Rpb1	A190	C160	Active center
Rpb2	A135	C128	Active center
Rpb3	AC40	AC40	
Rpb11	AC19	AC19	
Rpb9	A12.2 N ribbon	C11 N ribbon	RNA cleavage
TFIIS C-ribbon[a]	A12.2 C ribbon	C11 C ribbon	RNA cleavage
Rpb5	Rpb5	Rpb5	
Rpb6	Rpb6	Rpb6	
Rpb8	Rpb8	Rpb8	
Rpb10	Rpb10	Rpb10	
Rpb12	Rpb12	Rpb12	
Polymerase Stalk			
Rpb4	A14	C17	Initiation complex formation
Rpb7	A43	C25	Initiation complex formation
General Transcription Factors and Their Counterparts			
Tfg1 (TFIIFα)	A49 (N-terminal domain)	C37	Initiation complex stabilization, start site selection
Tfg2 (TFIIFβ)	A34.5	C53	Initiation complex stabilization, start site selection
Tfa1 (TFIIEα)[b]		C82[b]	Open complex stabilization
Tfa2 (TFIIEβ)[c]	A49 (C-terminal domain)[c]	C34[c]	Open complex stabilization
		C31	Open complex stabilization
TBP[d]	TBP[f]	TBP[g]	DNA binding
TAFs[d,e]			
TFIIB	Rrn7[f]	Brf1[g]	TBP/polymerase binding, DNA opening, start site selection
Specific Factors			
		B[g]	
	Rrn6[f]		
	Rrn11[f]		
SAGA			
TFIIH			
Mediator[h]	Rrn3[h]		
	UAF		
		TFIIIC	
		SNAPc	

[a] TFIIS is a dissociable factor that is not part of the polymerase core. Its C-terminal ribbon domain (C ribbon) is however structurally and functionally related to the corresponding domains of A12.2 and C11.
[b] These proteins share “extended” WH domains but their evolutionary relationship remains at present tentative.
[c] These proteins share two subsequent WH domains but their evolutionary relationship remains at present tentative.
[d] TBP and the TAF proteins form transcription factor IID, TFIID.
[e] TAF, TBP-associated factor.
[f] TBP Rrn7, Rrn6, and Rrn11 form the core factor.
[g] TBP, Brf1, and B″ form the transcription factor IIIB, TFIIIB.
[h] Only a topological similarity has been noticed (Blattner et al., 2011).

Cramer et al., 2008; Carter and Drouin, 2010), and also binds the polymerase lobe (Wu et al., 2011; Vannini et al., 2010; Fernández-Tornero et al., 2010). Thus, A49/34.5, TFIIF, and C37/53 are related protein complexes with a structurally conserved dimerization module that binds the polymerase lobe.

In line with the function of TFIIF in stabilizing the Pol II initiation complex, subcomplex A49/34.5 was implicated in Pol I initiation complex stabilization (Beckouet et al., 2008) and is required for a high rate of Pol I loading onto genes (Albert et al., 2011). A49/34.5 also enhances RNA elongation and cleavage (Geiger et al., 2010; Kuhn et al., 2007). The Pol III subcomplex C37/53 facilitates formation of an open promoter complex and extends near the active center (Kassavetis et al., 2010; Wu et al., 2011), also similarly to TFIIF (Eichner et al., 2010). C37/53 is further

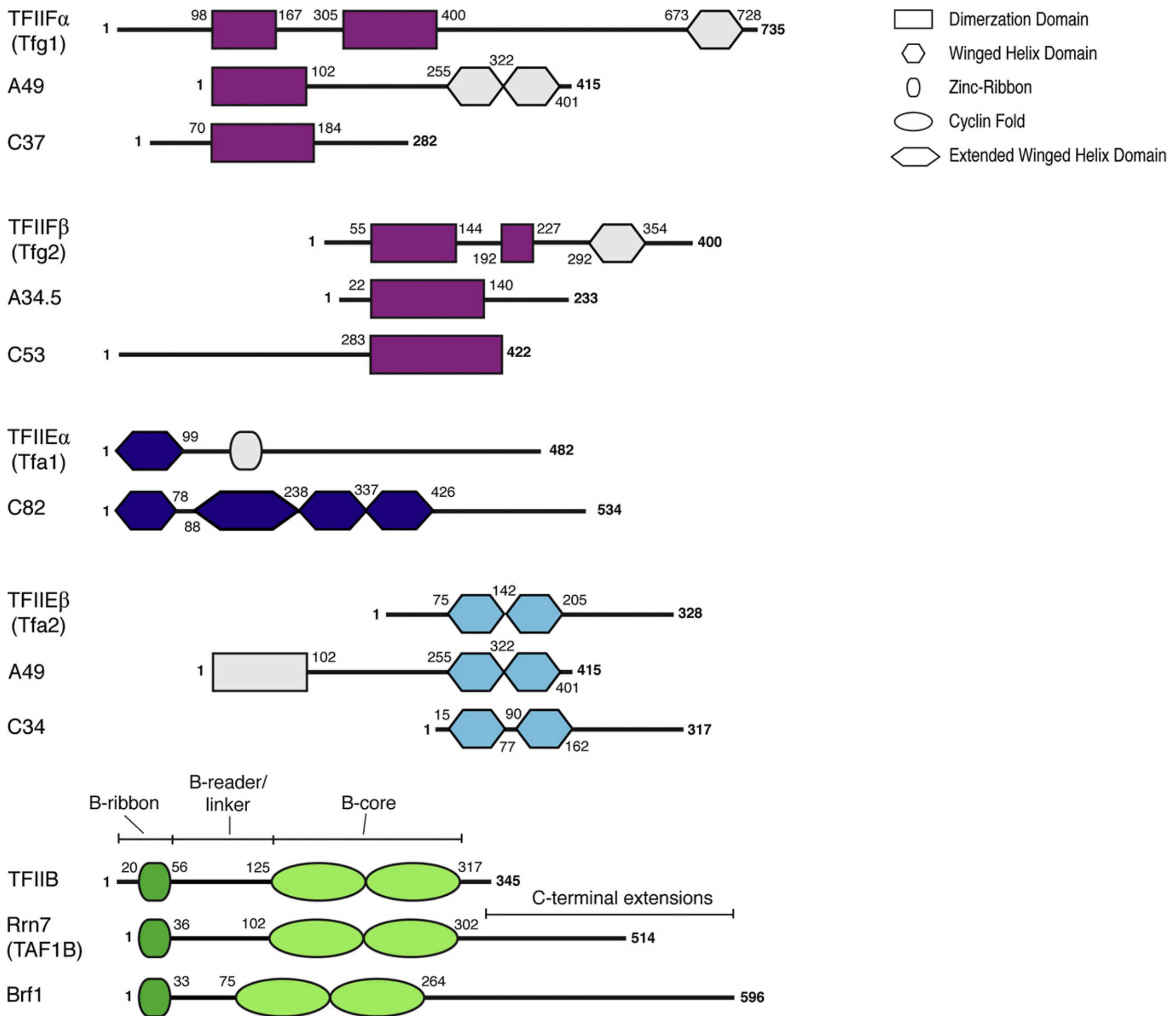

Figure 1. Related Domains in TFIIB-, TFIIE-, and TFIIF-like Initiation Factors
Schematic representation of domains in TFIIB, TFIIE, and TFIIF, and in related factors in the Pol I and Pol III systems. For each class, additional domains that are not related to the cognate Pol II transcription factor are depicted in gray. TFIIF-related dimerization modules are depicted in purple, TFIIE-related winged helix (WH) domains are in cyan. TFIIB-like factors contain a B ribbon (green), B reader, B linker, and a B core domain with two cyclin folds (light green). Rrn7 and Brf1 contain an unrelated C-terminal extension. All residue numbers in all proteins refer to the yeast proteins, except for subunit C82, where the human homolgue is depicted.

involved in Pol III termination and reinitiation (Landrieux et al., 2006). Thus A49/34.5, TFIIF, and C37/53 share not only structural but also functional similarities.

Pol I and Pol III Contain TFIIE-Related Domains

Another general Pol II transcription factor, TFIIE, recruits TFIIH to Pol II promoters (Li et al., 1994; Maxon et al., 1994; Ohkuma et al., 1995) and stimulates its ATPase activity to initiate transcription (Ohkuma and Roeder, 1994). TFIIE comprises two subunits that both contain winged helix (WH) domains (Figure 1). The small TFIIE subunit β (Tfa2) contains a pair of WH domains that resembles the tandem WH domain that was recently observed in the C-terminal region of the Pol I subunit A49 (Geiger et al., 2010). Thus, in addition to its N-terminal region, which is structurally homologous to TFIIF, A49 may be homologous to parts of TFIIE in its C-terminal region (Geiger et al., 2010). The Pol III subcomplex C82/34/31 also contains WH domains. Two adjacent WH domains exist in the N-terminal region of C34 (Geiger et al., 2010). Four WH domains were found in the human homolog of C82 (Lefèvre et al., 2011) and resemble the "extended" WH domain present in the large TFIIE subunit α (Tfa1) and its archaeal homolog TFE (Meinhart et al., 2003).

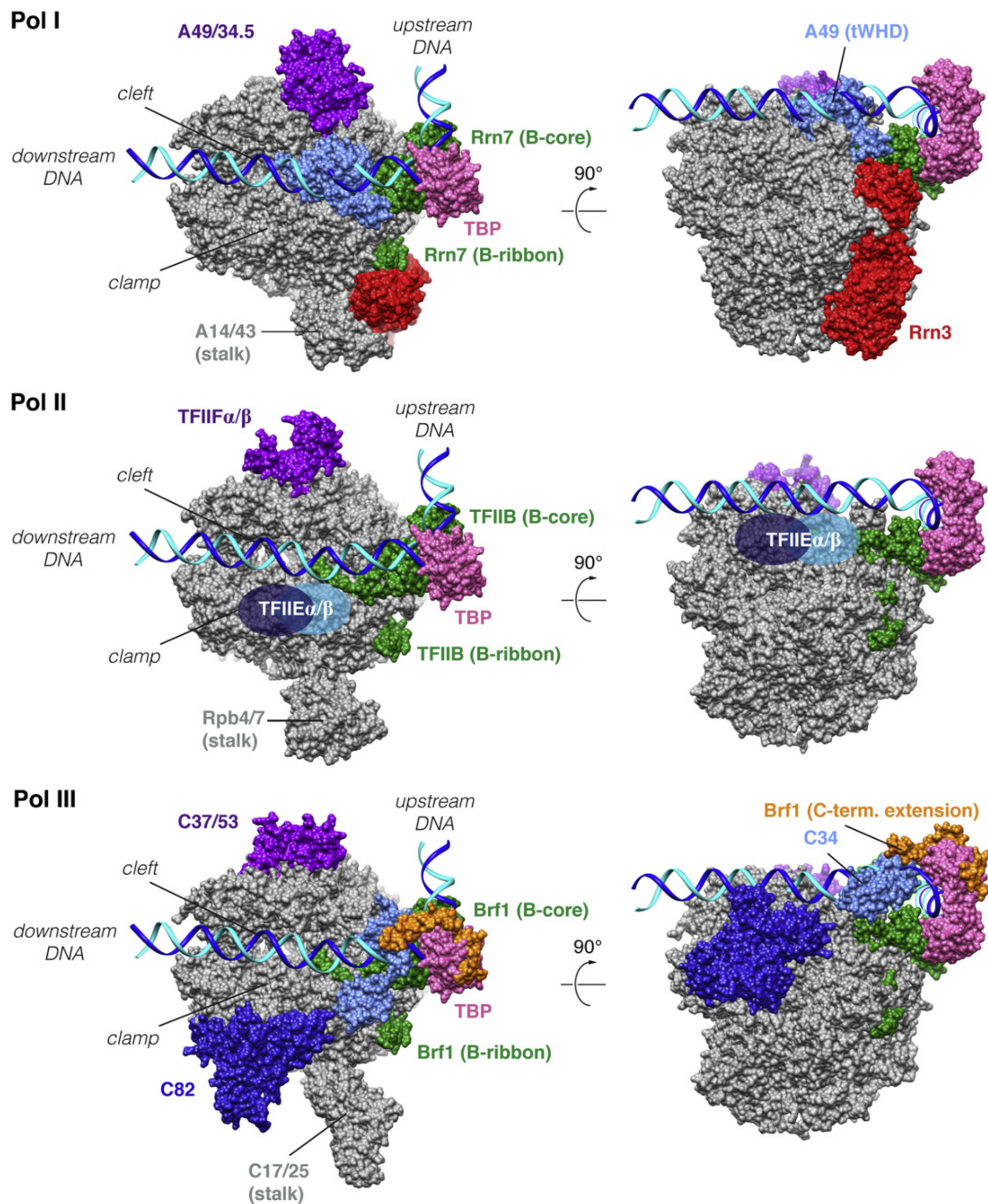

Figure 2. Conserved Core Topology of Transcription Initiation Complexes

Initiation complex models are based on a minimal Pol II initiation complex model containing closed promoter DNA, Pol II, TBP, and TFIIB (Kostrewa et al., 2009). The X-ray structure of the complete Pol II (Armache et al., 2005) and the Pol II-based homology models for the Pol I and Pol III core (Kuhn et al., 2007; Jasiak et al., 2006) are represented as gray molecular surfaces. TBP and Rrn3 (Blattner et al., 2011) are shown as pink and red molecular surfaces, respectively. TFIIB, TFIIE, TFIIF, and related factors are depicted as molecular surfaces, color-coded as in Figure 1 (Chen et al., 2010; Vannini et al., 2010; Blattner et al., 2011) (P.C., unpublished data). The presumed location of TFIIE, based on crosslinking data, is indicated with semitransparent filled circles (Chen et al., 2007). The locations of C82 and C34 were determined by electron microscopy (Vannini et al., 2010), and the location of the A49 tandem WH domain was inferred by crosslinking (P.C., unpublished data). For each of the three models, two orthogonal views are shown.

TFIIE and TFE both bind the polymerase clamp domain (Chen et al., 2007; Grohmann et al., 2011), and the WH domains in A49 and C34 are also located on the clamp over the cleft (Vannini et al., 2010) (P.C., unpublished data). Thus, Pol I and Pol III contain subcomplexes that are partially related to the Pol II initiation factor TFIIE and topologically adopt similar positions at the polymerase clamp over the cleft (Figure 2).

TFIIE and its related proteins may share an ancient functional role in binding and stabilizing the DNA bubble region above the active center cleft in an open promoter complex. TFIIE may

Cell PRESS

facilitate promoter opening, as suggested from transcription of supercoiled DNA templates (Holstege et al., 1995). Archaeal TFE was shown to stabilize the open promoter complex (Naji et al., 2007). TFIIE, archaeal TFE, and the A49 tandem WH domain all bind single-stranded DNA (Grünberg et al., 2007; Okuda et al., 2000; Geiger et al., 2010), indicating that they may stabilize the initial DNA transcription bubble. C34 has a function in DNA opening (Brun et al., 1997). TFIIE-like proteins may also contribute to maintenance of the transcription bubble during RNA elongation, based on in vitro studies in an archaeal transcription system and in vivo studies of a yeast strain lacking part of the A49 tandem WH domain (Grünberg et al., 2007; Beckouet et al., 2008). Thus TFIIE and TFIIE-related factors contain WH domains and help to form and/or stabilize the open promoter complex.

Pol I and Pol III Use TFIIB-like Factors

TFIIB is required for polymerase recruitment to the promoter, forming a bridge between the promoter and Pol II. It was long known that Pol III initiation requires a structural and functional homolog of TFIIB, the TFIIB-related factor 1 (Brf1), which together with TBP and a protein called B″forms the transcription factor TFIIIB (López-De-León et al., 1992; Colbert and Hahn, 1992; Wang and Roeder, 1995; Kassavetis et al., 1991; Kassavetis et al., 1992). However, in the Pol I system, a putative TFIIB homolog was only recently discovered by sequence homology searches (Knutson and Hahn, 2011; Naidu et al., 2011; Blattner et al., 2011) (Table 1). Functional data established yeast Rrn7, and its human ortholog TAF1B, as the TFIIB-related factor in the Pol I system (Knutson and Hahn, 2011; Naidu et al., 2011). Rrn7 associates with Rrn6 and Rrn11 to form the core factor, which is required for Pol I transcription (Lalo et al., 1996; Lin et al., 1996; Steffan et al., 1996). Rrn7 and TAF1B share the modular domain architecture of TFIIB and Brf1, including the N-terminal B ribbon domain, the C-terminal B core domain, and the interconnecting region containing the B reader and B linker, which are less conserved (Knutson and Hahn, 2011; Naidu et al., 2011; Blattner et al., 2011) (Figure 1). Thus, a factor that is structurally related to TFIIB exists in the Pol I and Pol III transcription initiation machineries.

TFIIB-like factors share several functions. TFIIB, Brf1, and Rrn7/TAF1B are required for polymerase recruitment to the promoter (Knutson and Hahn, 2011; Naidu et al., 2011). TFIIB-like factors contact the polymerase dock domain via their B ribbon, and may all bind TBP and DNA via their B core domains (Chen and Hahn, 2004; Chen et al., 2007; Kostrewa et al., 2009; Liu et al., 2010; Knutson and Hahn, 2011) (Figure 2). TFIIB-like factors have additional functions after polymerase recruitment. The B linker is positioned close to the site where DNA opening commences, and contributes to DNA melting in an archaeal system (Kostrewa et al., 2009). The B reader contributes to selection of the transcription start site (Hampsey, 1998; Chen and Hampsey, 2004) and may interact with the DNA template strand in the open promoter complex (Kostrewa et al., 2009). Structural and functional interactions of TFIIB-like proteins are at least partially conserved, because B ribbon domain mutations that reduce or eliminate transcription in a minimal Pol II system can be compensated for by TFIIF (Thompson et al., 2009), and, similarly, removal of the B-ribbon of Brf1 that eliminates transcription can be compensated for by the TFIIF-like Pol III subcomplex C37/53 (Kassavetis et al., 2010). The B ribbon domains of Rrn7 and Brf1 are functionally exchangeable, and the B linker can be swapped between all three members of the TFIIB-like protein family, whereas the B reader has a polymerase-specific function (Knutson and Hahn, 2011). Thus all three polymerases use structurally and functionally related TFIIB-like factors for transcription initiation.

Open Complex Formation

As described above, recent studies reveal a conserved core transcription initiation complex in eukaryotes that consists of promoter DNA, polymerase, TBP, a TFIIB-like factor, a TFIIF-like protein, and TFIIE or proteins with TFIIE-related domains. Except for the TFIIF-like proteins, the core initiation complex is related to the archaeal initiation complex in structure, topology, and function (Grohmann et al., 2011; Kostrewa et al., 2009). The core initiation complex is generally responsible for stable open complex formation and initial RNA synthesis. Cellular RNA polymerases generally open DNA together with their initiation factors with the use of binding energy. For example, bacterial RNA polymerase binds the σ70 initiation factor, which traps the DNA nontemplate strand during promoter opening (Feklistov and Darst, 2011). The archaeal polymerase, Pol I, and Pol III likely use similar strategies to open DNA, as they do not require additional energy in the form of ATP hydrolysis. In contrast, Pol II requires the additional general factor TFIIH for DNA opening (Egly and Coin, 2011; Lin et al., 2005; Kim et al., 2000; Dvir et al., 1997; Holstege et al., 1997; Kumar et al., 1998). TFIIH contains the subunit XPB, which harbors an ATPase activity that is needed for promoter opening, and a helicase activity that is required for promoter escape (Lin et al., 2005). The ability of the Pol II core initiation complex to open DNA may have been lost due to alterations in the TFIIB reader/linker region and loss of C-terminal extensions, compared to TFIIB-like factors in Pol I and Pol III. The C-terminal extension of Brf1 binds TBP (Juo et al., 2003), and C34, which is involved in DNA opening (Khoo et al., 1994; Andrau et al., 1999; Brun et al., 1997; Kassavetis et al., 2003; Vannini et al., 2010). The Pol II core initiation complex is however able to stabilize the open complex with the use of TFIIF (Fishburn and Hahn, 2012) and TFIIE (Cabart and Luse, 2012). Thus, although initiation complexes share a conserved core and overall function, they exhibit functional differences during open promoter complex formation.

Distinct Initiation Complex Peripheries

Outside of the conserved core, the topology and function of initiation complexes differ strongly. Although TBP is part of the core initiation complex and likely interacts with DNA at all promoters, it is also a subunit of different higher-order complexes (Table 1) and engages in different interactions. In Pol II initiation complexes, TBP is part of the 14 subunit TFIID complex (Näär et al., 2001; Müller et al., 2010), but also of the SAGA coactivator complex (Weake and Workman, 2011), which is important for transcription of a subset of genes. TBP also binds the 25 subunit Mediator coactivator complex (Larivière et al., 2006), which is required for initiation (Takagi and Kornberg, 2006). In the Pol I

initiation complex, TBP associates with the core factor subunits Rrn6 and Rrn7 (Steffan et al., 1996) and with the upstream activating sequence-binding factor (Aprikian et al., 2000; Siddiqi et al., 2001). Pol I also requires Rrn3, a factor that can modulate rRNA production according to nutrient availability (Bodem et al., 2000; Moorefield et al., 2000; Yamamoto et al., 1996). Rrn3 binds Pol I in a position resembling the location of a Mediator module on Pol II (Blattner et al., 2011; Takagi et al., 2006; Soutourina et al., 2011), suggesting a topological conservation of the interaction sites. In the Pol III initiation complex, TBP resides within the TFIIIB complex and interacts with the Pol III-specific transcription factors TFIIIC (Deprez et al., 1999) and SNAPc (Henry et al., 1995). TFIIIC and SNAPc are required for recruitment of the polymerase and TFIIIB at promoters containing gene-internal and gene-external binding sites, respectively (Schramm and Hernandez, 2002). Taken together, TBP has a conserved role in binding TFIIB-like factors, but it is also part of gene-class specific complexes that bind specific promoter elements or other gene-class specific factors.

Concluding Remarks

After the three eukaryotic RNA polymerases were discovered over four decades ago, subsequent work revealed that these enzymes transcribe different classes of genes and use different factors to initiate transcription. This apparent diversity of the transcription initiation machineries raised the question how the three transcription systems are evolutionarily related, and whether there are any underlying principles for transcription initiation, especially since archaea contain a single Pol II-like transcription initiation machinery. This question was answered over the last years. It was realized that Pol I and Pol III contain additional subunits that are not present in Pol II but are related to parts of the Pol II general initiation factors TFIIE and TFIIF. It was also found that the initiation complexes of Pol I and Pol III contain a factor related to the Pol II factor TFIIB. These findings indicate that the core of all transcription initiation complexes is structurally and functionally conserved, whereas distinct peripheral factors are used to achieve gene-class specific functions such as promoter recognition and regulation. In the future, the core Pol II initiation complex should be structurally resolved, ideally at atomic detail and trapped in different functional states, to unravel the mechanisms and the dynamics of the machinery. Detailed structural insights into the alternative RNA polymerases, Pol I and Pol III, must be obtained, to investigate the differences in core initiation complex structure and function. Many questions remain on the structure and function of gene class-specific peripheral factors, and it is likely that currently unexpected topological or mechanistic similarities between these factors wait to be unveiled.

REFERENCES

Albert, B., Léger-Silvestre, I., Normand, C., Ostermaier, M.K., Pérez-Fernández, J., Panov, K.I., Zomerdijk, J.C.B.M., Schultz, P., and Gadal, O. (2011). RNA polymerase I-specific subunits promote polymerase clustering to enhance the rRNA gene transcription cycle. J. Cell Biol. *192*, 277–293.

Andrau, J.C., Sentenac, A., and Werner, M. (1999). Mutagenesis of yeast TFIIIB70 reveals C-terminal residues critical for interaction with TBP and C34. J. Mol. Biol. *288*, 511–520.

Aprikian, P., Moorefield, B., and Reeder, R.H. (2000). TATA binding protein can stimulate core-directed transcription by yeast RNA polymerase I. Mol. Cell. Biol. *20*, 5269–5275.

Armache, K.J., Mitterweger, S., Meinhart, A., and Cramer, P. (2005). Structures of complete RNA polymerase II and its subcomplex, Rpb4/7. J. Biol. Chem. *280*, 7131–7134.

Beckouet, F., Labarre-Mariotte, S., Albert, B., Imazawa, Y., Werner, M., Gadal, O., Nogi, Y., and Thuriaux, P. (2008). Two RNA polymerase I subunits control the binding and release of Rrn3 during transcription. Mol. Cell. Biol. *28*, 1596–1605.

Bikoff, E.K., and Gefter, M.L. (1975). In vitro synthesis of transfer RNA. I. Purification of required components. J. Biol. Chem. *250*, 6240–6247.

Bikoff, E.K., LaRue, B.F., and Gefter, M.L. (1975). In vitro synthesis of transfer RNA. II. Identification of required enzymatic activities. J. Biol. Chem. *250*, 6248–6255.

Blattner, C., Jennebach, S., Herzog, F., Mayer, A., Cheung, A.C.M., Witte, G., Lorenzen, K., Hopfner, K.-P., Heck, A.J.R., Aebersold, R., and Cramer, P. (2011). Molecular basis of Rrn3-regulated RNA polymerase I initiation and cell growth. Genes Dev. *25*, 2093–2105.

Bodem, J., Dobreva, G., Hoffmann-Rohrer, U., Iben, S., Zentgraf, H., Delius, H., Vingron, M., and Grummt, I. (2000). TIF-IA, the factor mediating growth-dependent control of ribosomal RNA synthesis, is the mammalian homolog of yeast Rrn3p. EMBO Rep. *1*, 171–175.

Brun, I., Sentenac, A., and Werner, M. (1997). Dual role of the C34 subunit of RNA polymerase III in transcription initiation. EMBO J. *16*, 5730–5741.

Cabart, P., and Luse, D.S. (2012). Inactivated RNA polymerase II open complexes can be reactivated with TFIIE. J. Biol. Chem. *287*, 961–967.

Čabart, P., Újvári, A., Pal, M., and Luse, D.S. (2011). Transcription factor TFIIF is not required for initiation by RNA polymerase II, but it is essential to stabilize transcription factor TFIIB in early elongation complexes. Proc. Natl. Acad. Sci. USA *108*, 15786–15791.

Carter, R., and Drouin, G. (2010). The increase in the number of subunits in eukaryotic RNA polymerase III relative to RNA polymerase II is due to the permanent recruitment of general transcription factors. Mol. Biol. Evol. *27*, 1035–1043.

Chen, H.-T., and Hahn, S. (2004). Mapping the location of TFIIB within the RNA polymerase II transcription preinitiation complex: a model for the structure of the PIC. Cell *119*, 169–180.

Chen, B.-S., and Hampsey, M. (2004). Functional interaction between TFIIB and the Rpb2 subunit of RNA polymerase II: implications for the mechanism of transcription initiation. Mol. Cell. Biol. *24*, 3983–3991.

Chen, H.-T., Warfield, L., and Hahn, S. (2007). The positions of TFIIF and TFIIE in the RNA polymerase II transcription preinitiation complex. Nat. Struct. Mol. Biol. *14*, 696–703.

Chen, Z.A., Jawhari, A., Fischer, L., Buchen, C., Tahir, S., Kamenski, T., Rasmussen, M., Lariviere, L., Bukowski-Wills, J.-C., Nilges, M., et al. (2010). Architecture of the RNA polymerase II-TFIIF complex revealed by cross-linking and mass spectrometry. EMBO J. *29*, 717–726.

Colbert, T., and Hahn, S. (1992). A yeast TFIIB-related factor involved in RNA polymerase III transcription. Genes Dev. *6*, 1940–1949.

Conaway, R.C., and Conaway, J.W. (1997). General transcription factors for RNA polymerase II. Prog. Nucleic Acid Res. Mol. Biol. *56*, 327–346.

Cormack, B.P., and Struhl, K. (1992). The TATA-binding protein is required for transcription by all three nuclear RNA polymerases in yeast cells. Cell *69*, 685–696.

Cramer, P., Armache, K.J., Baumli, S., Benkert, S., Brueckner, F., Buchen, C., Damsma, G.E., Dengl, S., Geiger, S.R., Jasiak, A.J., et al. (2008). Structure of eukaryotic RNA polymerases. Annu. Rev. Biophys. *37*, 337–352.

Deprez, E., Arrebola, R., Conesa, C., and Sentenac, A. (1999). A subunit of yeast TFIIIC participates in the recruitment of TATA-binding protein. Mol. Cell. Biol. *19*, 8042–8051.

Cell PRESS

Dvir, A., Tan, S., Conaway, J.W., and Conaway, R.C. (1997). Promoter escape by RNA polymerase II. Formation of an escape-competent transcriptional intermediate is a prerequisite for exit of polymerase from the promoter. J. Biol. Chem. *272*, 28175–28178.

Egly, J.M., and Coin, F. (2011). A history of TFIIH: two decades of molecular biology on a pivotal transcription/repair factor. DNA Repair (Amst.) *10*, 714–721.

Eichner, J., Chen, H.-T., Warfield, L., and Hahn, S. (2010). Position of the general transcription factor TFIIF within the RNA polymerase II transcription preinitiation complex. EMBO J. *29*, 706–716.

Feklistov, A., and Darst, S.A. (2011). Structural basis for promoter-10 element recognition by the bacterial RNA polymerase σ subunit. Cell *147*, 1257–1269.

Fernández-Tornero, C., Böttcher, B., Rashid, U.J., Steuerwald, U., Flörchinger, B., Devos, D.P., Lindner, D., and Müller, C.W. (2010). Conformational flexibility of RNA polymerase III during transcriptional elongation. EMBO J. *29*, 3762–3772.

Fishburn, J., and Hahn, S. (2012). Architecture of the yeast RNA polymerase II open complex and regulation of activity by TFIIF. Mol. Cell. Biol. *32*, 12–25.

Gaiser, F., Tan, S., and Richmond, T.J. (2000). Novel dimerization fold of RAP30/RAP74 in human TFIIF at 1.7 A resolution. J. Mol. Biol. *302*, 1119–1127.

Geiger, S.R., Lorenzen, K., Schreieck, A., Hanecker, P., Kostrewa, D., Heck, A.J.R., and Cramer, P. (2010). RNA polymerase I contains a TFIIF-related DNA-binding subcomplex. Mol. Cell *39*, 583–594.

Grohmann, D., Nagy, J., Chakraborty, A., Klose, D., Fielden, D., Ebright, R.H., Michaelis, J., and Werner, F. (2011). The initiation factor TFE and the elongation factor Spt4/5 compete for the RNAP clamp during transcription initiation and elongation. Mol. Cell *43*, 263–274.

Grünberg, S., Bartlett, M.S., Naji, S., and Thomm, M. (2007). Transcription factor E is a part of transcription elongation complexes. J. Biol. Chem. *282*, 35482–35490.

Hampsey, M. (1998). Molecular genetics of the RNA polymerase II general transcriptional machinery. Microbiol. Mol. Biol. Rev. *62*, 465–503.

Henry, R.W., Sadowski, C.L., Kobayashi, R., and Hernandez, N. (1995). A TBP-TAF complex required for transcription of human snRNA genes by RNA polymerase II and III. Nature *374*, 653–656.

Holstege, F.C., Tantin, D., Carey, M., van der Vliet, P.C., and Timmers, H.T. (1995). The requirement for the basal transcription factor IIE is determined by the helical stability of promoter DNA. EMBO J. *14*, 810–819.

Holstege, F.C., Fiedler, U., and Timmers, H.T. (1997). Three transitions in the RNA polymerase II transcription complex during initiation. EMBO J. *16*, 7468–7480.

Hu, P., Wu, S., Sun, Y., Yuan, C.-C., Kobayashi, R., Myers, M.P., and Hernandez, N. (2002). Characterization of human RNA polymerase III identifies orthologues for Saccharomyces cerevisiae RNA polymerase III subunits. Mol. Cell. Biol. *22*, 8044–8055.

Jasiak, A.J., Armache, K.-J., Martens, B., Jansen, R.-P., and Cramer, P. (2006). Structural biology of RNA polymerase III: subcomplex C17/25 X-ray structure and 11 subunit enzyme model. Mol. Cell *23*, 71–81.

Juo, Z.S., Kassavetis, G.A., Wang, J., Geiduschek, E.P., and Sigler, P.B. (2003). Crystal structure of a transcription factor IIIB core interface ternary complex. Nature *422*, 534–539.

Kassavetis, G.A., Bartholomew, B., Blanco, J.A., Johnson, T.E., and Geiduschek, E.P. (1991). Two essential components of the Saccharomyces cerevisiae transcription factor TFIIIB: transcription and DNA-binding properties. Proc. Natl. Acad. Sci. USA *88*, 7308–7312.

Kassavetis, G.A., Joazeiro, C.A., Pisano, M., Geiduschek, E.P., Colbert, T., Hahn, S., and Blanco, J.A. (1992). The role of the TATA-binding protein in the assembly and function of the multisubunit yeast RNA polymerase III transcription factor, TFIIIB. Cell *71*, 1055–1064.

Kassavetis, G.A., Han, S., Naji, S., and Geiduschek, E.P. (2003). The role of transcription initiation factor IIIB subunits in promoter opening probed by photochemical cross-linking. J. Biol. Chem. *278*, 17912–17917.

Kassavetis, G.A., Prakash, P., and Shim, E. (2010). The C53/C37 subcomplex of RNA polymerase III lies near the active site and participates in promoter opening. J. Biol. Chem. *285*, 2695–2706.

Kedinger, C., Gniazdowski, M., Mandel, J.L., Jr., Gissinger, F., and Chambon, P. (1970). Alpha-amanitin: a specific inhibitor of one of two DNA-pendent RNA polymerase activities from calf thymus. Biochem. Biophys. Res. Commun. *38*, 165–171.

Khoo, B., Brophy, B., and Jackson, S.P. (1994). Conserved functional domains of the RNA polymerase III general transcription factor BRF. Genes Dev. *8*, 2879–2890.

Kim, T.K., Ebright, R.H., and Reinberg, D. (2000). Mechanism of ATP-dependent promoter melting by transcription factor IIH. Science *288*, 1418–1422.

Knutson, B.A., and Hahn, S. (2011). Yeast Rrn7 and human TAF1B are TFIIB-related RNA polymerase I general transcription factors. Science *333*, 1637–1640.

Kornberg, R.D. (2007). The molecular basis of eukaryotic transcription. Proc. Natl. Acad. Sci. USA *104*, 12955–12961.

Kostrewa, D., Zeller, M.E., Armache, K.-J., Seizl, M., Leike, K., Thomm, M., and Cramer, P. (2009). RNA polymerase II-TFIIB structure and mechanism of transcription initiation. Nature *462*, 323–330.

Kuhn, C.-D., Geiger, S.R., Baumli, S., Gartmann, M., Gerber, J., Jennebach, S., Mielke, T., Tschochner, H., Beckmann, R., and Cramer, P. (2007). Functional architecture of RNA polymerase I. Cell *131*, 1260–1272.

Kumar, K.P., Akoulitchev, S., and Reinberg, D. (1998). Promoter-proximal stalling results from the inability to recruit transcription factor IIH to the transcription complex and is a regulated event. Proc. Natl. Acad. Sci. USA *95*, 9767–9772.

Lalo, D., Steffan, J.S., Dodd, J.A., and Nomura, M. (1996). RRN11 encodes the third subunit of the complex containing Rrn6p and Rrn7p that is essential for the initiation of rDNA transcription by yeast RNA polymerase I. J. Biol. Chem. *271*, 21062–21067.

Landrieux, E., Alic, N., Ducrot, C., Acker, J., Riva, M., and Carles, C. (2006). A subcomplex of RNA polymerase III subunits involved in transcription termination and reinitiation. EMBO J. *25*, 118–128.

Larivière, L., Geiger, S., Hoeppner, S., Röther, S., Strässer, K., and Cramer, P. (2006). Structure and TBP binding of the Mediator head subcomplex Med8-Med18-Med20. Nat. Struct. Mol. Biol. *13*, 895–901.

Lefèvre, S., Dumay-Odelot, H., El-Ayoubi, L., Budd, A., Legrand, P., Pinaud, N., Teichmann, M., and Fribourg, S. (2011). Structure-function analysis of hRPC62 provides insights into RNA polymerase III transcription initiation. Nat. Struct. Mol. Biol. *18*, 352–358.

Li, Y., Flanagan, P.M., Tschochner, H., and Kornberg, R.D. (1994). RNA polymerase II initiation factor interactions and transcription start site selection. Science *263*, 805–807.

Lin, C.W., Moorefield, B., Payne, J., Aprikian, P., Mitomo, K., and Reeder, R.H. (1996). A novel 66-kilodalton protein complexes with Rrn6, Rrn7, and TATA-binding protein to promote polymerase I transcription initiation in Saccharomyces cerevisiae. Mol. Cell. Biol. *16*, 6436–6443.

Lin, Y.C., Choi, W.S., and Gralla, J.D. (2005). TFIIH XPB mutants suggest a unified bacterial-like mechanism for promoter opening but not escape. Nat. Struct. Mol. Biol. *12*, 603–607.

Lindell, T.J., Weinberg, F., Morris, P.W., Roeder, R.G., and Rutter, W.J. (1970). Specific inhibition of nuclear RNA polymerase II by alpha-amanitin. Science *170*, 447–449.

Liu, X., Bushnell, D.A., Wang, D., Calero, G., and Kornberg, R.D. (2010). Structure of an RNA polymerase II-TFIIB complex and the transcription initiation mechanism. Science *327*, 206–209.

López-De-León, A., Librizzi, M., Puglia, K., and Willis, I.M. (1992). PCF4 encodes an RNA polymerase III transcription factor with homology to TFIIB. Cell *71*, 211–220.

Lue, N.F., and Kornberg, R.D. (1987). Accurate initiation at RNA polymerase II promoters in extracts from Saccharomyces cerevisiae. Proc. Natl. Acad. Sci. USA *84*, 8839–8843.

Manley, J.L., Fire, A., Cano, A., Sharp, P.A., and Gefter, M.L. (1980). DNA-dependent transcription of adenovirus genes in a soluble whole-cell extract. Proc. Natl. Acad. Sci. USA *77*, 3855–3859.

Maxon, M.E., Goodrich, J.A., and Tjian, R. (1994). Transcription factor IIE binds preferentially to RNA polymerase IIa and recruits TFIIH: a model for promoter clearance. Genes Dev. *8*, 515–524.

Meinhart, A., Blobel, J., and Cramer, P. (2003). An extended winged helix domain in general transcription factor E/IIE alpha. J. Biol. Chem. *278*, 48267–48274.

Moorefield, B., Greene, E.A., and Reeder, R.H. (2000). RNA polymerase I transcription factor Rrn3 is functionally conserved between yeast and human. Proc. Natl. Acad. Sci. USA *97*, 4724–4729.

Müller, F., Zaucker, A., and Tora, L. (2010). Developmental regulation of transcription initiation: more than just changing the actors. Curr. Opin. Genet. Dev. *20*, 533–540.

Näär, A.M., Lemon, B.D., and Tjian, R. (2001). Transcriptional coactivator complexes. Annu. Rev. Biochem. *70*, 475–501.

Naidu, S., Friedrich, J.K., Russell, J., and Zomerdijk, J.C.B.M. (2011). TAF1B is a TFIIB-like component of the basal transcription machinery for RNA polymerase I. Science *333*, 1640–1642.

Naji, S., Grünberg, S., and Thomm, M. (2007). The RPB7 orthologue E' is required for transcriptional activity of a reconstituted archaeal core enzyme at low temperatures and stimulates open complex formation. J. Biol. Chem. *282*, 11047–11057.

Nikolov, D.B., Chen, H., Halay, E.D., Usheva, A.A., Hisatake, K., Lee, D.K., Roeder, R.G., and Burley, S.K. (1995). Crystal structure of a TFIIB-TBP-TATA-element ternary complex. Nature *377*, 119–128.

Ohkuma, Y., and Roeder, R.G. (1994). Regulation of TFIIH ATPase and kinase activities by TFIIE during active initiation complex formation. Nature *368*, 160–163.

Ohkuma, Y., Hashimoto, S., Wang, C.K., Horikoshi, M., and Roeder, R.G. (1995). Analysis of the role of TFIIE in basal transcription and TFIIH-mediated carboxy-terminal domain phosphorylation through structure-function studies of TFIIE-alpha. Mol. Cell. Biol. *15*, 4856–4866.

Okuda, M., Watanabe, Y., Okamura, H., Hanaoka, F., Ohkuma, Y., and Nishimura, Y. (2000). Structure of the central core domain of TFIIEbeta with a novel double-stranded DNA-binding surface. EMBO J. *19*, 1346–1356.

Orphanides, G., Lagrange, T., and Reinberg, D. (1996). The general transcription factors of RNA polymerase II. Genes Dev. *10*, 2657–2683.

Peyroche, G., Levillain, E., Siaut, M., Callebaut, I., Schultz, P., Sentenac, A., Riva, M., and Carles, C. (2002). The A14-A43 heterodimer subunit in yeast RNA pol I and their relationship to Rpb4-Rpb7 pol II subunits. Proc. Natl. Acad. Sci. USA *99*, 14670–14675.

Rhee, H.S., and Pugh, B.F. (2012). Genome-wide structure and organization of eukaryotic pre-initiation complexes. Nature, in press. Published online January 18, 2012.

Roeder, R.G. (1996). The role of general initiation factors in transcription by RNA polymerase II. Trends Biochem. Sci. *21*, 327–335.

Roeder, R.G., and Rutter, W.J. (1969). Multiple forms of DNA-dependent RNA polymerase in eukaryotic organisms. Nature *224*, 234–237.

Roeder, R.G., and Rutter, W.J. (1970). Specific nucleolar and nucleoplasmic RNA polymerases. Proc. Natl. Acad. Sci. USA *65*, 675–682.

Ruan, W., Lehmann, E., Thomm, M., Kostrewa, D., and Cramer, P. (2011). Evolution of two modes of intrinsic RNA polymerase transcript cleavage. J. Biol. Chem. *286*, 18701–18707.

Schramm, L., and Hernandez, N. (2002). Recruitment of RNA polymerase III to its target promoters. Genes Dev. *16*, 2593–2620.

Seifart, K.H., and Sekeris, C.E. (1969). Alpha-amanitin, a specific inhibitor of transcription by mammalian RNA-polymerase. Z. Naturforsch. B *24*, 1538–1544.

Siddiqi, I., Keener, J., Vu, L., and Nomura, M. (2001). Role of TATA binding protein (TBP) in yeast ribosomal dna transcription by RNA polymerase I: defects in the dual functions of transcription factor UAF cannot be suppressed by TBP. Mol. Cell. Biol. *21*, 2292–2297.

Soutourina, J., Wydau, S., Ambroise, Y., Boschiero, C., and Werner, M. (2011). Direct interaction of RNA polymerase II and mediator required for transcription in vivo. Science *331*, 1451–1454.

Steffan, J.S., Keys, D.A., Dodd, J.A., and Nomura, M. (1996). The role of TBP in rDNA transcription by RNA polymerase I in Saccharomyces cerevisiae: TBP is required for upstream activation factor-dependent recruitment of core factor. Genes Dev. *10*, 2551–2563.

Takagi, Y., and Kornberg, R.D. (2006). Mediator as a general transcription factor. J. Biol. Chem. *281*, 80–89.

Takagi, Y., Calero, G., Komori, H., Brown, J.A., Ehrensberger, A.H., Hudmon, A., Asturias, F., and Kornberg, R.D. (2006). Head module control of mediator interactions. Mol. Cell *23*, 355–364.

Thompson, N.E., Glaser, B.T., Foley, K.M., Burton, Z.F., and Burgess, R.R. (2009). Minimal promoter systems reveal the importance of conserved residues in the B-finger of human transcription factor IIB. J. Biol. Chem. *284*, 24754–24766.

Vannini, A., Ringel, R., Kusser, A.G., Berninghausen, O., Kassavetis, G.A., and Cramer, P. (2010). Molecular basis of RNA polymerase III transcription repression by Maf1. Cell *143*, 59–70.

Wang, Z., and Roeder, R.G. (1995). Structure and function of a human transcription factor TFIIIB subunit that is evolutionarily conserved and contains both TFIIB- and high-mobility-group protein 2-related domains. Proc. Natl. Acad. Sci. USA *92*, 7026–7030.

Wang, Z., and Roeder, R.G. (1997). Three human RNA polymerase III-specific subunits form a subcomplex with a selective function in specific transcription initiation. Genes Dev. *11*, 1315–1326.

Weake, V.M., and Workman, J.L. (2011). SAGA function in tissue-specific gene expression. Trends Cell Biol., in press. Published online December 21, 2011.

Weil, P.A., Luse, D.S., Segall, J., and Roeder, R.G. (1979). Selective and accurate initiation of transcription at the Ad2 major late promotor in a soluble system dependent on purified RNA polymerase II and DNA. Cell *18*, 469–484.

Weinmann, R., and Roeder, R.G. (1974). Role of DNA-dependent RNA polymerase 3 in the transcription of the tRNA and 5S RNA genes. Proc. Natl. Acad. Sci. USA *71*, 1790–1794.

Wu, C.-C., Lin, Y.-C., and Chen, H.-T. (2011). The TFIIF-like Rpc37/53 dimer lies at the center of a protein network to connect TFIIIC, Bdp1, and the RNA polymerase III active center. Mol. Cell. Biol. *31*, 2715–2728.

Yamamoto, R.T., Nogi, Y., Dodd, J.A., and Nomura, M. (1996). RRN3 gene of Saccharomyces cerevisiae encodes an essential RNA polymerase I transcription factor which interacts with the polymerase independently of DNA template. EMBO J. *15*, 3964–3973.

Yan, Q., Moreland, R.J., Conaway, J.W., and Conaway, R.C. (1999). Dual roles for transcription factor IIF in promoter escape by RNA polymerase II. J. Biol. Chem. *274*, 35668–35675.

Zylber, E.A., and Penman, S. (1971). Products of RNA polymerases in HeLa cell nuclei. Proc. Natl. Acad. Sci. USA *68*, 2861–2865.