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Transcription factors that influence RNA polymerases I and II: To what extent is mechanism of action conserved?

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Abstract

In eukaryotic cells, nuclear RNA synthesis is accomplished by at least three unique, multisubunit RNA polymerases. The roles of these enzymes are generally partitioned into the synthesis of the three major classes of RNA: rRNA, mRNA, and tRNA for RNA polymerases I, II, and III respectively. Consistent with their unique cellular roles, each enzyme has a complement of specialized transcription factors and enzymatic properties. However, not all transcription factors have evolved to affect only one eukaryotic RNA polymerase. In fact, many factors have been shown to influence the activities of multiple nuclear RNA polymerases. This review focuses on a subset of these factors, specifically addressing the mechanisms by which these proteins influence RNA polymerases I and II.

Keywords

transcription; transcription initiation; transcription elongation; RNA polymerase II; RNA polymerase I

Introduction

Since the seminal discovery of three eukaryotic nuclear RNA polymerases by Roeder and Rutter, substantial effort has been invested in defining the unique characteristics of RNA polymerases I, II, and III [1]. Soon after their discovery, it was appreciated that the eukaryotic RNA polymerases evolved specialized roles: RNA polymerase I (Pol I) synthesizes the three largest ribosomal RNAs (rRNA), Pol II transcribes protein-coding genes and most regulatory, non-coding RNAs, and Pol III synthesizes primarily transfer RNA and the 5S rRNA. Biochemical, genetic, and structural analyses have demonstrated that these RNA polymerase systems employ largely unique sets of transcription initiation factors, though these factors are functionally conserved [2]. Indeed, with divergent roles and

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different cohorts of essential regulatory factors, there are substantial differences among the nuclear RNA polymerases. However, there is a growing list of factors that have been shown to affect more than one RNA polymerase. Here, we focus on a subset of those transcription factors, with a specific focus on proteins that influence both Pools I and II.

Unlike Pool III, Pools I and II must transcribe long genes, encountering diverse template/chromatin barriers, and both enzymes employ promoter structures with sequence elements primarily positioned upstream of the transcription start site. Thus, it is reasonable to expect that cells may have evolved “dual use” proteins that can influence both of these processive enzymes. Indeed, many labs have discovered roles for several factors in transcription by both Pool I and Pool II; however, the mechanisms by which these factors influence transcription can vary between polymerase systems.

Pool I and Pool II are multi-subunit RNA polymerases, with 14 and 12 core subunits respectively. These enzymes share five subunits, but the other subunits, including the two largest subunits that comprise the catalytic center, are not shared [3]. The overall structures of Pools I and II are similar; however, differences have been observed in and around the active center [4–6]. Furthermore, genetic and biochemical studies focused on the trigger loop domain identified surprising differences between Pools I and II [7]. It is these similarities and differences between the enzymes, as well as differences in the polymerase density on transcribed genes, that likely account for the range of effects observed for transacting transcription factors. Here, we describe the identified roles for several transcription factors that have been shown to influence both Pools I and II. This list is in no way complete. As shown in table 1, there are reports of many additional proteins that influence both mRNA and rRNA synthesis, directly or indirectly. The transcription factors discussed below demonstrate a range of functions in both transcription initiation and elongation. In each section, we evaluate the discovery of the protein factor, as well as its described roles in the two polymerase systems. Understanding the extent to which the effect of these factors is conserved is fundamentally important to defining the specialized roles of the multiple nuclear RNA polymerases.

Tata binding protein (TBP)

Of all the factors discussed in this review, TBP is the only factor that plays essential roles in transcription by all three eukaryotic nuclear RNA polymerases [8, 9]. By interacting with specific TBP-associated factors (TAFs), TBP selectively affects transcription by different RNA polymerases [10]. Recruitment of TBP to promoters is universally important for gene expression, indicating its unique role in global gene transcription [11]. Below, we focus on TBP's function in Pool I and Pool II transcription.

TBP, as its name suggests, binds the TATA element, a cis-regulatory element found in promoters for Pool II. TBP, along with other TAFs, forms a general transcription factor, TFIID, which is a key factor in Pool II transcription initiation. Roles for TBP distinct from TFIID were not identified until it was purified from budding yeast and shown to bind the TATA box and substitute for mammalian TFIID in a reconstituted mammalian Pool II system [12, 13]. TFIID was subsequently discovered to be a multi-subunit complex containing TBP

and its associated TAFs, which are important for TFIID in the absence of a TATA-box [14, 15]. It was later shown that TFIID recruits TBP to TATA-less promoters, whereas the SAGA (Spt-Ada-Gcn5 acetyltransferase) complex is preferentially utilized to recruit TBP to TATA-containing promoters [16]. SAGA is a multi-functional complex and is conserved between yeast and human. Of its various functions, SAGA can recruit TBP to mediate formation of PIC and transcriptional activation [17]. Interestingly, TFIID and SAGA can functionally compensate for each other indicating potentially overlapping roles at many gene promoters [18]. Recently, the structure of promoter-bound TFIID was solved [19]. The structure suggests that TFIID positions TBP on the promoter, such that TBP can properly position Pol II relative to the transcription start site. This study presented the model that the TAF subunits of TFIID serve as a molecular ruler for proper TBP positioning, which, in turn, allows for proper Pol II positioning for transcription initiation.

TBP has been implicated in several steps in preinitiation by Pol II. It is thought that TBP binding to the promoter limits the rate of transcription initiation, and slow binding of TBP may prevent unregulated gene expression [20, 21]. TBP binding to the minor groove of DNA introduces a dramatic bend in the DNA to assist promoter melting [22, 23]. The binding of TBP introduces a negative twist in the DNA, a topological change that chromatin remodelers require to manipulate and influence changes in nucleosome positioning [22, 24]. Consistent with this idea, TBP-induced DNA bending has been shown to promote nucleosome sliding, in conjunction with the chromatin remodeler SWI/SNF [25]. Furthermore, TBP binds to the transcription factor TFIIB and Pol II CTD [26, 27], which aids recruitment of Pol II and TFIIF to the promoter [28]. Altogether, TBP is a critical, well-defined member of the Pol II preinitiation complex.

TBP is essential for transcription by all three nuclear RNA polymerases [29–31]. TBP interacts with two Pol I transcription initiation factors: upstream associated factor (UAF) and core factor (CF) in yeast [32]. CF interacts with TBP and co-localizes with TBP on the rDNA. Because TBP also binds directly to the Rrn9 subunit of UAF, Nomura and colleagues proposed the model that TBP serves as a bridge between these two key transcription factors [32].

In mammalian cells and amoebae, TBP is considered a subunit of SL1, an essential Pol I transcription initiation factor and orthologue of CF [29, 33]. TBP binds to upstream binding factor (UBF; a key regulator of Pol I, discussed below), and this binding is critical for UBF-mediated recruitment of SL1 to the core promoter of rDNA [34]. TBP association with the acidic tail of UBF is sensitive to the phosphorylation state of the tail [35], implicating TBP-binding as one mechanism by which Pol I transcription initiation is regulated.

For both Pol II and Pol I, TBP plays a critical role in preinitiation complex formation. The identities of proteins contacted by TBP certainly vary at these different classes of promoter, but the overall effects of these proteins on preinitiation complex formation are well conserved [8, 9, 11, 36].

Hmo1

Hmo1 is a member of the chromatin-associated “high mobility group” (HMG) family of proteins in *S. cerevisiae*. Hmo1 is likely the fungal homologue of the vertebrate UBF protein, discussed below. HMG proteins are abundant in eukaryotic cells, comprising a significant portion of the non-histone components of the chromatin [37]. Hmo1 is not a general transcription factor but is specific for rDNA and a subset of Pol II-transcribed genes, mainly ribosomal protein genes.

Deletion of *HMO1* causes a two-fold reduction in cell growth compared to WT. Isotopic labeling indicated that deletion of *HMO1* reduces rRNA content in the cell [38]. Consistent with above findings, genetic data indicate that the *hmo1* mutant is synthetic lethal with at least three mutations in Pol I subunits: *rpa49*, *rpa12*, and *rpa43–24*, suggesting that Hmo1 contributes to Pol I-dependent rRNA synthesis [38]. These three subunits have distinct roles in Pol I activity. Rpa49 is an intrinsic transcription elongation factor for Pol I [39], Rpa12 is thought to play a role in Pol I fidelity much like Rpb9 in Pol II [40, 41], whereas Rpa43 associates with Pol I initiation factor Rrn3 to aid preinitiation complex formation on the rDNA promoter [42, 43]. Overexpression of Hmo1 not only suppresses the cold-sensitive *rpa49* phenotype, but also significantly enhances rRNA synthesis in the *rpa49* mutant indicating that Hmo1 functions synergistically with Rpa49 in Pol I transcription [38]. More recent results suggest that actively transcribed rDNA is mostly devoid of histones, but it is instead occupied by Hmo1, apparently providing a chromatin-like structure [44]. All of these data support the model that Hmo1 activates rDNA transcription in yeast.

Hmo1 also affects Pol II pre-initiation complex formation and transcription start site selection. Hmo1 genetically and physically interacts with Pol II factors TBP/TFIID. Deletion of *HMO1* rescues the phenotypes associated with TFIIB mutants and a TAF1 N-terminal domain (TAND) mutant, indicating that Hmo1 may compete with TFIIB for TBP binding. Additionally, deletion of *HMO1* causes a shift in the transcription start site at several ribosomal protein genes, the promoters of which are Hmo1-enriched [45].

Together, these data suggest that Hmo1 affects pre-initiation complex stability through interaction with TBP at protein-coding gene promoters [45]. On the contrary, Hmo1 associates with the entire rDNA locus, and deletion of *HMO1* reduces rRNA synthesis and causes rRNA processing defects, suggesting a role in transcription initiation and potentially elongation [46]. Thus, Hmo1 promotes transcription by both Pools I and II, but the mechanisms of these effects are quite different. Interestingly, given its apparent roles in ribosomal protein gene expression and rRNA synthesis, Hmo1 may help coordinate Pools I and II activity for ribosome biogenesis in response to nutrient conditions [47].

Upstream binding factor (UBF)

UBF (also called UBTF) was discovered based on its ability to “bind upstream” of the mammalian rDNA promoter [48, 49]. Similar to Hmo1, UBF contains multiple nucleic acid-binding, HMG boxes [50, 51], which can bend and wrap DNA [52–54]. Work from the Moss lab showed that UBF can generate 360° loops in rDNA that resemble standard nucleosomes

and have been termed ribosomal enhancesomes [55]. Given the observation that Hmo1 may displace nucleosomes in the yeast rDNA [44], it is tempting to conclude that UBF and Hmo1 are functionally equivalent. Indeed, genetic studies from the Gadal lab support this assertion [56]; however, mechanistic comparisons have not yet been described.

In mammalian cells, two isoforms arise as splice variants of UBF and are called UBF1 and UBF2 [57]. UBF1 induces changes in rDNA chromatin state [58, 59], whereas UBF2 is a transcriptional enhancer of the β -catenin pathway [60]. UBF2 is 37 amino acid shorter in HMGB-box2 than UBF1, and is incapable of bending DNA [61]. Distinct functions of these isoforms are discussed further below.

UBF plays multiple different roles in Pol I transcription, affecting pre-initiation complex formation, initiation, promoter escape, and elongation [62–65]. UBF not only associates with the rDNA core promoter, but also binds the transcribed rDNA region and the intergenic spacer region in vertebrates [66, 67]. UBF was identified for its ability to bind upstream of the rDNA promoter and cooperate with SL1 to activate transcription initiation [48, 49, 68]. Consistent with a role in preinitiation complex formation, deletion of *UBF* not only completely eliminated rRNA synthesis but also prevented the formation of pre-initiation complexes and eliminated SL1 from the DNA. Depletion of UBF has no effect on 47S rRNA processing or levels of other Pol I-associated proteins (RPA194, Rrn3/TIFIA, TBP, TAFIB and 1C, TTF1, or fibrillarin) [69]. These and other data demonstrate a role for UBF in maintenance of the pre-initiation complex and activation of transcription initiation by Pol I.

Since UBF associates with the entire rDNA repeat, its function may not be limited to pre-initiation complex (PIC) formation. Using a reconstituted *in vitro* transcription system on immobilized DNA templates, the Zomerdijs lab found that UBF did not stimulate PIC formation, but rather it activated Pol I transcription after PIC assembly and incorporation of the first few nucleotides [65]. If UBF were only required for promoter escape and not recruitment, then one would expect an accumulation of Pol I at the promoter after depletion of UBF. Such an accumulation was not observed [69]. Thus, although UBF may assist Pol I in promoter escape, it is also essential for proper recruitment *in vivo*.

UBF has also been shown to affect transcription elongation by Pol I. The Moss lab used a series of biochemical assays and molecular biology approaches in cells to show that UBF inhibits Pol I transcription elongation through rDNA. This barrier function was overcome by ERK-dependent phosphorylation of UBF at two amino acids within its HMG boxes [70, 71]. These findings demonstrated that the elongation step in Pol I transcription is an important regulatory target and that UBF plays a pivotal role in that step. Thus, UBF is a multi-functional factor in rDNA transcription and regulates Pol I transcription in response to environmental stimuli.

Recent genome-wide analyses have found that UBF1/2 localizes to multiple loci throughout the genome [72, 73]. Consistent with its occupancy on non-ribosomal DNA loci, UBF1/2 affects Pol II transcription [73]. Depletion of UBF1/2 reduced phosphorylation of Pol II-CTD on both Serine 2 and Serine 5, indicating direct or indirect roles for UBF1/2 in transcription initiation, promoter escape and elongation by Pol II. ChIP-seq data indicate

that UBF1/2 binds actively transcribed Pol II genes with a preference for transcription start sites but not termination sites. Genes important for nucleosome organization and assembly and chromatin assembly are enriched for UBF1/2 occupancy. Consistent with this observation, depletion of UBF1/2 reduced histone mRNA abundance, potentially due to altered accessibility of the histone gene promoters to Pol II. Surprisingly, UBF1 is not required for histone mRNA expression. UBF2 alone is sufficient to control the expression of histone genes. Thus these two isoforms of UBF may coordinate transcription by Pools I and II [73].

Despite its initial identification as a transcription factor for Pol I, a role for UBF, at least the UBF2 isoform, in Pol II transcription is increasingly clear. For both Pools I and II it appears that UBF plays a direct role in transcription initiation; however, the protein contacts made by UBF and the precise effect on promoter accessibility may differ substantially between the rDNA promoter and Pol II-transcribed genes. Furthermore, it is not yet clear whether UBF may also affect promoter escape or transcription elongation by Pol II on select genes.

TFIIH

TFIIH was originally named transcription factor delta when purified from rat liver cells [74], transcription factor b from yeast [75], and BTF2 from human [76]. This factor was ultimately renamed TFIIH [77]. Of the 10 subunits of TFIIH, 3 have enzymatic activities: the ATP-dependent DNA helicases XPB and XPD, and the kinase Kin28/Cdk7 [78, 79]. The helicase activity of Rad25 (the yeast homolog of XPB) is required for Pol II transcription [80]. A temperature-sensitive allele of *RAD25* induced a significant decrease in mRNA synthesis at the non-permissive temperature. The *rad25^{ts}* mutation also reduced promoter melting in constitutively expressed genes at the non-permissive temperature [81]. TFIIH-mediated promoter melting is ATP-dependent [82], and the ATP-dependent helicase activity is specifically required for promoter escape [78]. It was later shown that TFIIH interacts with DNA downstream of the promoter region to influence promoter escape by Pol II [83]. Interestingly, a recent study found that TFIIH with a Rad3 mutation lost helicase activity, but maintained wild-type levels of transcription by Pol II *in vitro*. TFIIH instead acts as a translocase to track along the non-template DNA strand in the open complex formation [84]. Another recent study found that TFIIH is dispensable for promoter DNA opening [85]. These findings have led to the model that TFIIH translocates ahead of Pol II along the promoter DNA, rotates downstream DNA and inserts DNA template into the Pol II active site cleft [84, 85].

Other studies found that depletion of the kinase Kin28 impairs promoter escape by Pol II [86]. Depletion of Kin28 resulted in a dramatic accumulation of the mediator complex, a transcription coactivator, at the core promoter. This observation led to the model that Kin28 stimulates promoter escape by promoting the dissociation of the mediator complex from the pre-initiation complex. Thus, TFIIH may use multiple mechanisms to control promoter escape by Pol II.

In addition to transcription initiation and promoter clearance, TFIIH has a role in preventing premature arrest prior to the transition to stable elongation. Pol II is known to be susceptible

to arrest after synthesis of the first 9–13 nucleotides [87]. TFIIF can mediate ATP-dependent suppression of such arrests. Furthermore, it is not crucial that TFIIF is assembled into the PIC to mediate this stable transition into elongation [88]. The helicase XPB has been implicated in the suppression of this early transcription arrest [78].

TFIIF was originally thought to be uniquely required for Pol II transcription. In 2002, a study conducted by the Grummt lab demonstrated that TFIIF also affects rRNA synthesis by Pol I [89]. Using a GFP-tagged XPB, they showed that TFIIF localizes to the nucleolus, the site of rDNA transcription. They also determined that TFIIF associates with transcriptionally active Pol I, and depletion of TFIIF impaired transcription by Pol I. ChIP analysis showed that TFIIF with mutations in XPB and XPD did not bind the rDNA as well as WT. The most direct evidence that TFIIF affects Pol I activity came from *in vitro* transcription assays. These assays detected reduced transcription by Pol I in extracts depleted of TFIIF, and the addition of WT TFIIF restored activity, even in the presence of the Pol II inhibitor alpha amanitin. Later studies demonstrated that TFIIF does not affect transcription initiation or promoter escape by Pol I but rather has a post-initiation role in transcription elongation [90]. Thus, unlike for Pol II, TFIIF seems to function as an elongation factor for Pol I.

Spt4/5

The *SPT4* and *SPT5* genes were first isolated as a part of a screen for mutants that suppress transcription defects caused by insertions of the retrotransposons Ty1 and Ty2 in yeast [91]. Spt4/5 was also isolated from mammalian cell nuclear extracts as a factor that influences pausing by Pol II in the presence of the transcription inhibitor 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole (DRB) [92]. As a consequence, Spt4/5 is also referred to as DSIF (DRB sensitivity-inducing factor) in the literature. The Spt4/5 complex has been referred to as the only universally conserved transcription factor, due to the homology between eukaryotic and archaeal Spt5 proteins and prokaryotic NusG [93]. NusG carries an N-terminal NusG (NGN) domain, and a C-terminal nucleic acid binding, KOW domain [94]. Archaeal and eukaryotic Spt5 protein structure is more complex; they contain a single NGN domain, and several KOW domains [95]. *SPT4* does not have a homolog in bacteria, and is not essential for viability in yeast [96]. However, genetic similarities between *spt4* and partial loss-of-function mutations in *SPT5* suggest that in eukaryotes, Spt4 is critical for normal Spt5 function within the Spt4/5 complex [97–99]. Spt4 and Spt5 indeed form a heterodimeric complex that has diverse effects on transcription by Pols I and II [97].

The Winston lab showed that *SPT4* and *SPT5* genetically interact with mutations that affect Pol II [97]. Mutations in the two largest subunits of Pol II, Rpb1 and Rpb2, rescued cold sensitive phenotypes observed in a mutant *spt5* strain. Based on a series of genetics analyses, a role for Spt5 in Pol II processivity was identified [97]. Several studies have supported the model that Spt4/5 promotes processive elongation by archaeal RNA polymerase or eukaryotic Pol II [100, 101]. Addition of Spt4/5 to archaeal *in vitro* transcription assays stimulated processive elongation by RNA polymerase. Very recent work from the Reese lab characterized the interactions of Spt4/5 with the Pol II elongation complex, and showed that Spt4/5 enhances processivity of eukaryotic Pol II [102]. Consistent with these functional

data, structural studies found that the archaeal Spt4/5 complex encloses the DNA in a manner similar to DNA polymerase clamps and ring helicases [103]. Furthermore, Spt4/5 is capable of closing the polymerase active center cleft to enclose nucleic acid and maintain the stability of the transcription bubble supporting a role of Spt4/5 in processive transcription elongation [101].

Besides its positive role in transcription elongation, in *Drosophila*, Spt4/5 also promotes promoter proximal pausing by Pol II on the heat shock activated promoter for the gene *hsp70* [104]. After heat shock, Spt4/5 dissociates from the *hsp70* promoter enabling elongation through the gene. Consistent with this promoter-proximal role for Spt4/5 in flies, work in yeast suggests a role for Spt4/5 in ensuring proper recruitment of the mRNA capping machinery prior to processive elongation [105]. Together, these and many other studies identify complex but crucial roles for Spt4/5 in Pol II transcription.

In 2003, proteomic studies aimed at defining the multifaceted roles of Spt4/5 also identified a physical association between Spt5 and Pol I subunits. [106]. Later, the Nomura lab confirmed this association and showed that Spt4/5 is localized to the rDNA and deletion of *SPT4* resulted in reduced rDNA copy number, altered Pol I occupancy of the rDNA, and impaired rRNA processing. Interestingly, EM analysis of Miller chromatin spreads showed that processivity of Pol I was not impaired [107]. To further test the effect of Spt4/5 on Pol I transcription, temperature-sensitive alleles of *SPT5* were isolated and characterized [108]. Point mutations in *SPT5* as well as deletion of *SPT4* were shown to suppress growth defects induced by deletion of the gene that encodes a TFIIIF-like subunit of Pol I, *RPA49*. This observation suggested an inhibitory role for Spt4/5 in Pol I transcription. However, mutation of *SPT5* resulted in different phenotypes than *spt4* [107]. Though the *spt5* (*C292R*) allele induced a 4-fold decrease in rRNA synthesis, this mutation has no effect on rDNA copy number or polymerase density per gene. Thus, this study identified a direct or indirect positive role for Spt4/5 in transcription elongation by Pol I [108]. The current model suggests that Spt4/5 can both positively and negatively influence Pol I transcription.

It is clear that the conserved Spt4/5 complex can influence transcription by both Pools I and II. Characterization of the interaction between Spt5 and Pools I and II showed that the contacts between Pol I and Spt5 were similar to the contacts made with Pol II [109]. Structural insights suggest a potential mechanism by which Spt4/5 can influence Pol II processivity. Interestingly, there is no evidence supporting a role for Spt4/5 in processivity by Pol I. Furthermore, the mechanism(s) by which Spt4/5 affects pausing or elongation rate by either enzyme remains unclear. Thus, despite a large body of work on this key transcription factor, many questions remain.

Paf1 Complex (Paf1C)

The Paf1 complex (RNA Polymerase II associated factor 1 complex) consists of five subunits in yeast and was initially identified biochemically [110–114]. Paf1C is conserved among eukaryotes [115–117], with human Paf1C carrying a sixth subunit Ski8 [118]. Paf1C has been shown to influence almost every step in transcription, including transcription

activation, transcription initiation, elongation and termination, RNA processing and histone modification [119–121]. Here we focus on its roles in transcription initiation and elongation.

Several studies have implicated Paf1C in transcription initiation. First, Paf1C and the general initiation factors TFIIB and TFIIF can form a complex with Pol II that may be primed for transcription initiation [122, 123]. Genetics studies found that truncation of Rtf1 subunit of Paf1C could rescue mutations that impair TBP function, further suggesting an effect on transcription initiation [123]. In addition, parafibromin, the homologue of yeast Paf1C subunit Cdc73p, was shown to bind the unphosphorylated, transcription initiation-competent form of Rpb1 [116]. Paf1C also represses cryptic transcription initiation independent of the Set2 pathway [124]. Together, all of these studies suggest a role for Paf1C in Pol II recruitment and transcription initiation.

Paf1C is also well characterized for its role in transcription elongation by Pol II. Several *in vivo* studies showed that mutations in genes that encode Paf1C subunits induced sensitivity to inhibitors of transcription elongation and resulted in defective mRNA synthesis [111, 125–127]. Paf1C occupies promoter regions and gene bodies, suggesting that Paf1C could have an effect on later steps in the transcription cycle [112, 128, 129]. Finally both genetic and physical interactions between Paf1C and several other Pol II transcription elongation factors such as Spt4/5, Spt16-Pob3, and TFIIS [111, 130] support a role for Paf1C in Pol II transcription elongation.

Biochemical studies show that the effect of Paf1C on transcription elongation is direct. Using cell extracts made from *paf1* and *cdc73* mutant cells, Aguilera and colleagues found that Paf1C contributes to Pol II transcription elongation efficiency [131]. Later, Roeder and co-workers purified both native and fully recombinant human Paf1C. They showed that Paf1C can either function alone or in cooperation with TFIIS to stimulate Pol II transcription elongation *in vitro* [130]. Furthermore, Paf1C was shown to cooperate with Spt4/5 to facilitate efficient transcription elongation [132]. Together, these biochemical findings assert a direct, positive role for Paf1C in transcription elongation by Pol II.

Recently, a role for Paf1C in metazoan promoter-proximal pausing by Pol II was described [133]. Unlike in yeast, higher eukaryotes demonstrate accumulation of Pol II at the 5' end of most genes as an additional regulatory step in the transcription cycle [134, 135]. Depletion of Paf1 caused promoter-proximally paused Pol II to elongate into gene bodies. As a consequence, more RNA transcripts are produced after depletion of Paf1C. It turns out that depletion of Paf1C recruits SEC (Ser2P kinase super elongation complex) to the Pol II CTD, increases phosphorylation of serine 2, and releases Pol II into coding regions. Thus, Paf1C could regulate Pol II promoter-proximal pausing to govern gene expression [133].

Besides its well established role in Pol II transcription, Paf1C also directly affects transcription elongation by Pol I. Mutations in genes that encode Paf1C subunits were synthetic lethal in combination with mutations that perturb Pol I transcription elongation. Furthermore, Paf1C physically localizes to the rDNA promoter and coding regions, and deletion of *PAF1*, *CDC73*, or *CTR9* reduced rRNA synthesis without affecting Pol I occupancy of the rDNA [136]. In the same study, EM of Miller chromatin spreads identified

enhanced pausing by Pol I in a *ctr9* strain (reflected by increased frequency of detecting large gaps between transcribing polymerases [136]). As in Pol II studies, purified Paf1C also directly increased the rate of transcription elongation by Pol I *in vitro* [137]. Thus, Paf1C directly affects rRNA synthesis, perhaps by preventing pausing and increasing the net elongation rate. Although there is no apparent effect of Paf1C on transcription initiation by Pol I, there appears to be shared mechanistic roles for Paf1C in elongation by both Pals I and II.

Ccr4-Not

Ccr4-Not is a multi-subunit complex that was initially identified by genetic screens for mutants that cause cell cycle arrest or affect mating type and filamentous growth in *S. cerevisiae* [138–140]. Over the years, it has become clear that Ccr4-Not affects most steps in protein expression such as chromatin modification, transcription, mRNA modification, mRNA export, and translation [141–143]. The complex is conserved among eukaryotes and has been described as a master regulator of gene expression. Among all of these roles for Ccr4-Not, it has become apparent that the complex affects transcription initiation and elongation by Pals I and II.

Ccr4-Not plays an important role in Pol II transcription initiation by affecting the basal transcription machinery and chromatin structure. The Ccr4-Not complex physically and genetically interacts with factors that are involved in transcription initiation including TBP, TFIID, Ada/Gcn5 histone acetyltransferase, and SRB/mediators [144–150]. Ccr4 is tethered to the promoters of some genes to either activate or repress transcription [144, 151]. A genomic mapping analysis of Ccr4-Not binding sites found that Ccr4-Not subunit Pop2 associates with gene promoters, further indicating that Ccr4-Not is involved in transcription initiation [152]. Though Ccr4-Not resides at the promoter and controls the transcription initiation, the exact mechanism by which Ccr4-Not controls Pol II initiation is not clear and may vary among target genes.

In addition to its roles at Pol II promoters, biochemical and genetic assays have identified a role for Ccr4-Not in transcription elongation. Mutations in genes that encode Ccr4-Not subunits cause enhanced sensitivity to inhibitors of transcription elongation such as 6-azauracil and mycophenolic acid [153, 154]. Additionally, Ccr4-Not physically or genetically interacts with other known transcription elongation factors such as Paf1C, TFIIS, Spt16, and Bur1/2 kinase [122, 153, 155]. Consistent with genetic observations, a series of biochemical assays confirmed that Ccr4-Not directly promotes Pol II transcription elongation. *In vitro* transcription assays on tailed DNA templates showed that Ccr4-Not directly interacts with elongating Pol II and increases Pol II transcription [156]. The mechanism by which Ccr4-Not promotes Pol II elongation is by rescuing stalled Pol II, not by affecting elongation rate [156]. Interestingly, Ccr4-Not does not activate the intrinsic cleavage activity of Pol II to escape from arrests, rather, the effect of Ccr4-Not is independent of cleavage of the 3'-end of the nascent RNA. More recently, it was shown that Ccr4-Not physically interacts with TFIIS, suggesting a collaboration between Ccr4-Not and TFIIS in preventing transcriptional arrest by Pol II *in vivo* [157]. Further study is needed to elucidate the mechanisms by which Ccr4-Not promotes Pol II elongation.

In addition to all of its roles in mRNA metabolism, Ccr4-Not was also shown to influence Pol I activity. In yeast cells, deletion of the *CCR4* gene resulted in enhanced occupancy of the rDNA by Pol I and CF, increased abundance of pre-rRNA species, and increased abundance of the Pol I transcription factor Rrn3 [158]. Together, all of these observations provide support for a role for Ccr4-Not in transcription initiation by Pol I. Although the direct or indirect mechanism by which this effect is induced is unclear, given the many roles of Ccr4-Not in gene expression, it is clear that Ccr4 has a repressive effect on transcription by Pol I under the conditions tested. This repressive effect is likely mediated at least partially through interactions with Rrn3 because deletion of *CCR4* causes enhanced Rrn3 expression and initiation-competent Rrn3-Pol I complexes [158].

In the same study, the authors assessed the effect of a deletion of the gene that encodes the A12 subunit of Pol I on the effect of Ccr4-Not. A12 is a paralogue of TFIIS and is thought to influence transcription elongation and termination [158, 159]. They found that Pol I occupancy of the rDNA and rRNA synthesis are decreased in double mutant of *ccr4 rpa12* compared to either single mutant or WT. Furthermore, in the presence of 6-AU in rich medium in the *ccr4 rpa12* cells, Pol I remains on rDNA. This observation led to the conclusion that the absence of Ccr4-Not caused slowed transcription elongation by Pol I [158]. More investigation is required to identify a potential mechanism by which this effect could be mediated.

Ccr4-Not plays many roles in gene expression, including affecting both Pol I and Pol II transcription. The influence of Ccr4-Not on Pol I activity was only recently described, thus mechanistic comparison is difficult. There is no paralogue to Rrn3 in Pol II transcription, thus a direct analogy is unlikely. However, a functional interaction between A12 and Ccr4-Not at the rDNA might be similar to the published relationship between TFIIS and Ccr4-Not. Many questions remain regarding the mechanisms by which Ccr4-Not affects global gene expression.

Spt6

The *SPT6* gene was first isolated as a part of the screen for suppressors of transcription defects caused by Ty1 or Ty2 insertions (the same screen that identified *SPT4* and *SPT5*, described above [91]). Like other “Spt” factors, Spt6 has many roles in RNA synthesis. The best characterized roles for Spt6 are in chromatin remodeling and transcription elongation.

Spt6 is a histone chaperone that mediates nucleosome reassembly co-transcriptionally, and modulates histone modifications to alter chromatin structure [160–164]. Through its effects on chromatin reassembly after transcription by Pol II, Spt6 influences gene activation. One excellent example of this effect was observed at the *PHO5* gene. *PHO5* is repressed under phosphate rich conditions, and Spt6 was shown to associate with the *PHO5* promoter under repressive conditions and with the gene body upon activation, where it is thought to mediate nucleosome reassembly behind Pol II. Impaired Spt6 function results in derepression of *PHO5*, even in the presence of phosphate [165]. Spt6 is also required for faithful recruitment of the Set2 lysine methyltransferase to the chromatin during transcription elongation. Inactivation of Spt6 results in loss of histone H3 lysine 36 mono-, di-, and tri-methylation

[162, 163]. Loss of this modification in transcribed regions of the genome is thought to promote cryptic and antisense transcription by Pol II [166, 167]. Clearly, Spt6 plays an important role in controlling chromatin structure, and as a consequence of reorganizing histones or modifications thereof, transcription initiation by Pol II is affected.

Several studies have also shown that Spt6 can influence Pol II transcription elongation [97, 162, 168, 169]. An early study showed that *spt6* mutants resulted in conditional lethality when combined with *ppr2*, a mutation that results in loss of function of the Pol II elongation factor TFIIS. That study provided evidence for a potential effect on transcription elongation [97]. Later, it was shown that human Spt6 stimulated transcription elongation by Pol II in a reconstituted *in vitro* transcription system [169]. Furthermore, this effect was enhanced by the addition of Spt4/5. Of note, this template was nucleosome-free, showing that Spt6 can promote transcription by a mechanism independent of nucleosomes. Chromatin IP and fluorescence recovery after photobleaching assays were used to show that Spt6 enhances Pol II transcription elongation rate in *Drosophila* S2 cells [168]. The molecular mechanism by which Spt6 controls Pol II transcription elongation remains unclear, but a nucleosome-independent, direct effect is well supported.

Spt6 also plays an important role in Pol I transcription of the rDNA. The first hint of a possible role for Spt6 at the rDNA was provided by a yeast two-hybrid analysis examining proteins that interact with the A43 subunit of Pol I. Thuriaux and colleagues revealed a physical interaction between Pol I and Spt6 [170]. Later, it was shown that Spt6 associates with actively transcribed rDNA repeats and inactivation of the *spt6-1004* allele resulted in nearly complete loss of rRNA synthesis [171]. Consistent with the loss of rRNA synthesis, Pol I occupancy of the rDNA was essentially eliminated, and this effect did not depend on nucleosome remodeling or histone H3 lysine 36 methylation. To account for the repression of Pol I transcription, it was found that the Pol I initiation factor Rrn3 abundance, as well as Rrn3 association to Pol I, was greatly reduced in *spt6-1004* at the non-permissive temperature [171]. Rrn3 associates with Pol I, and this complex is then recruited to the rDNA promoter [172]. The formation of this complex is essential for Pol I transcription initiation, and these results suggest that Spt6 is involved in this step. Overexpression of Rrn3 rescued the formation of the Pol I-Rrn3 complex in *spt6-1004* at non-permissive conditions, but did not rescue the loss of rRNA synthesis or Pol I occupancy of the rDNA. Therefore, although Spt6 is not required for the formation of the Pol I-Rrn3 complex, it is required for recruitment of the Pol I-Rrn3 complex to the rDNA or for retaining this complex on the rDNA for efficient transcription initiation.

Spt6 is an essential transcription factor that influences mRNA and rRNA synthesis; however, the mechanisms by which Spt6 affects Pol II and Pol I seem opposed. Although Spt6 affects transcription initiation by Pol II, its effects appear to be mediated by chromatin, and inactivation of Spt6 generally increased transcription (cryptic and natural). On the other hand, inactivation of Spt6 results in nearly complete loss of Pol I from the rDNA. The nature of this difference between Pools I and II is unclear, but unique properties of the genomic loci or enzymatic activities for Pools I and II may contribute.

Are the mechanisms of effect for these factors conserved?

In this review, the roles for eight well-characterized transcription factors in mRNA and rRNA synthesis are highlighted and summarized in Table 2. Given the vast amount of work that has been invested in the characterization of these and other factors, only a small subset of supporting studies are described. However, it is hopefully clear that factors with defined roles in transcription by one nuclear RNA polymerase also have additional, crucial roles in other transcription systems. Indeed it should not be surprising that these complex, evolutionarily and structurally related RNA polymerases can share transcription factors. In some cases (e.g. TBP, Spt4/5, or Paf1C), the functional roles for trans-acting factors appear well conserved among polymerase systems. This conservation of function is likely attributable to the universal conservation of certain features of the transcription cycle and the multi-subunit RNA polymerases in all domains of life. For TBP, it accomplishes its primary role via direct contacts with different TAFs that are unique for the different RNA polymerases, but its role to enhance recruitment of the RNA polymerase to the promoter is well preserved. Spt4/5 and Paf1C both influence transcription elongation by both Pols I and II *in vivo* and *in vitro*. Since the basic steps in transcription and the overall architecture of the enzymes is conserved it is easy to imagine how trans-acting factors like these can have similar effects on rRNA and mRNA synthesis.

What may be more difficult to explain, both for several cases described here and elsewhere in the literature, is that many of these trans-acting factors appear to exert distinct or opposing effects on Pols I and II (e.g. HmoI, TFIIF, or Spt6). How can these differences be explained, given the similarities between the enzymes? With the available literature, one cannot conclude definitively how the mechanisms of effect of these transcription factors on Pol I and Pol II differ; however, there are at least three critical differences to consider. First, the ribosomal DNA is an actively transcribed and open DNA locus that is thought to carry a high polymerase density. All of these features create a set of DNA topological constraints that may be quite unique compared to “average” mRNA encoding genes. If Pols I and II are subject to different states of crowding or topological constraints in the templates, then barriers to efficient transcription may be quite different. Thus, each enzyme will only be sensitive to transcription factors that control step(s) limiting that enzyme or transcription unit.

Another explanation for observed mechanistic differences among these factors builds on the fact that Pols I and II are not structurally or functionally identical. Genetic and biochemical studies from the Schneider and Kaplan labs showed that Pols I and II adopt divergent phenotypes in response to identical mutations. These data suggested potential differences in the biochemical properties of these closely related enzymes [7]. Another study clearly documented that Pol I possesses an intrinsic, robust 3'-nucleolytic activity that is absent in Pol II [173]. These studies reveal functional differences between Pols I and II that may render the enzymes differentially sensitive to the influence of transcription factors.

Finally, the compositions and the detailed structures of Pol I versus Pol II are different. As stated above, five subunits are shared between Pols I and II, but all of the others are not. The largest subunit for Pol II carries the C-terminal heptapeptide repeat domain that plays crucial

roles in orchestrating co-transcriptional events [174]; however, there is no such domain in Pols I or III. Cryo-EM studies identified smaller, but likely significant structural differences in the active sites of Pols I and II. For example, the bridge helix adopts a partially unwound conformation in Pol I that is not observed in Pol II structures [4, 175]. The structural and compositional differences between polymerases present different targets for transcription factors, potentially explaining some differences in effects noted above.

Clearly, eukaryotic cells have evolved sophisticated, partially overlapping control mechanisms that orchestrate all aspects of RNA synthesis. Mechanistic understanding of the similarities and differences between the effects of individual factors requires substantially more work; however, the observation of these differences may reflect the selective pressures applied to RNA polymerases to suit their specialized cellular roles over evolutionary time.

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Highlights

- Many transcription factors affect both RNA polymerases I and II.
- The effects of factors may be similar or divergent between polymerases.
- Understanding divergent effects sheds light on unique properties of the nuclear RNA polymerases.

Table 1

Additional transcription factors with defined effects on Pols I and II.

	Pol II	Pol I
CSB/Rad26	CSB plays a role in maintaining and remodeling chromatin [177]. CSB/Rad26 is involved in transcription-coupled nucleotide excision repair, and interacts with stalled Pol II [178–180]. CSB is also important in recruitment of Pol II and its basal TFs to the promoters of housekeeping genes [181].	CSB promotes efficient rRNA synthesis and recruits the histone methyltransferase G9a to rDNA repeats to activate Pol I transcription [182, 183].
c-Myc	c-myc regulates Pol II transcription elongation [184]. Association of c-myc with P-TEFb contributes to transcriptional pause release of Pol II [185].	c-Myc can directly activate Pol I transcription, and the effect of c-myc on Pol I transcription is evolutionarily conserved [186–188].
Actin and Myosin	Actin is part of the Pol II pre-initiation complex and stimulates Pol II transcription [189, 190]. Myosin co-localizes with Pol II and affect Pol II transcription as well [191].	Actin and Myosin positively influence Pol I transcription [192–194].
Reb1/TTF1	Reb1/TTF1 Reb1 can mediate Pol II transcription termination [195].	Reb1 mediates Pol I transcription termination [196, 197].
THO	THO complex is required for efficient Pol II elongation through genes containing GC-rich or tandemly repeating DNA sequences [198]. THO is critical for Pol II transcription elongation and associated recombination <i>in vivo</i> and <i>in vitro</i> [199–202].	THO complex positively influences Pol I initiation and elongation [203].
SWI/SNF	The SWI/SNF complex can positively and negatively regulate Pol II transcription via chromatin remodeling [204–207].	SWI/SNF positively influences the elongation step of Pol I transcription [208].
Spt16	Spt16 facilitates Pol II transcription through nucleosomes [209].	Spt16 mediates nucleosome assembly to promote Pol I transcription [210].

Table 2

Transcription factors cited herein

	Pol II	Pol I
TBP	Interacts with other Pol II initiation factors to facilitate promoter melting and transcription start site selection	Recruited to Pol I promoter during transcription initiation, and thought to be crucial for Pol I recruitment to rDNA
Hmo1	Interacts with Pol II promoters, stabilizes pre-initiation complex and mediates proper start site selection	Interacts with the entire rDNA locus, has a potentially activating role in transcription initiation and elongation
UBF	Binds preferentially to Pol II promoters at transcription start site, may have a role in transcription initiation, promoter escape and elongation by Pol II	Binds to rDNA and can generate nucleosome-like structures at the rDNA called ribosomal enhancosomes, has critical roles in pre-initiation complex formation, promoter escape and elongation by Pol I
TFIIH	Essential for transcription initiation and promoter escape by Pol II, also has a role in preventing premature arrest prior to the transition to stable elongation	Important for transcription by Pol I, seems to function as an elongation factor.
Spt4/5	Promotes processive elongation by Pol II by maintaining the stability of the transcription bubble, can also promote promoter proximal pausing	Localizes to rDNA, plays a positive and negative role in transcription elongation by Pol I
Paf1	Influences transcription activation, initiation, elongation and termination, promotes promoter proximal pausing by Pol II	Directly promotes Pol I transcription, possibly by preventing pausing and increasing elongation rate
Ccr4-Not	Important for initiation and elongation, is tethered to promoters of some Pol II genes to activate or repress transcription, can rescue stalled Pol II via interaction with TFIIIS	Functions downstream of mTOR signaling pathway to control Pol I transcription
Spt6	Facilitates Pol II transcription through nucleosomes, can stimulate Pol II elongation independent of nucleosomes	Required for the recruitment and retention of Pol I to the rDNA promoter