Comparative overview of RNA polymerase II and III transcription cycles, with focus on RNA polymerase III termination and reinitiation

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Abbreviations: TAF, TFIID-associated factors; MTE, Motif 10 element; DPE, downstream promoter element; BREu, upstream B recognition element; BREd, downstream B recognition element; Inr, initiator element; term, terminator

In eukaryotes, RNA polymerase (RNAP) III transcribes hundreds of genes for tRNAs and 5S rRNA, among others, which share similar promoters and stable transcription initiation complexes (TIC), which support rapid RNAP III recycling. In contrast, RNAP II transcribes a large number of genes with highly variable promoters and interacting factors, which exert fine regulatory control over TIC lability and modifications of RNAP II at different transitional points in the transcription cycle. We review data that illustrate a relatively smooth continuity of RNAP III initiation-elongation-termination and reinitiation toward its function to produce high levels of tRNAs and other RNAs that support growth and development.

Introduction

Eukaryotes use three different RNA polymerases to carry out transcription (RNAP I, II and III). All three are multisubunit protein complexes that share structural and mechanistic homology.¹ RNAP II is responsible for transcription of most of the genes in eukaryotes, RNAP I transcribes multiple copies of the single gene for the large rRNA, and RNAP III transcribes short non-coding RNAs such as tRNAs, 5S rRNA, U6 snRNA and a limited number of others. Both RNAP I and RNAP III transcripts are required in high quantities as building blocks of ribosomes and adapters used by the translation machinery in growing cells.² By contrast, transcript levels of RNAP II-transcribed genes vary very widely (several orders of magnitude) depending on gene type and environmental cues.

While initiation, elongation and termination mechanisms of the three RNAP follow similar principles, each of them has specific features. As reflected by the quantitative and qualitative complexity of the RNAP II transcriptome, the initiation mechanism of RNAP II is the most intricately regulated of the three.

This contrast is reflected in part by promoter architecture. All RNAP III-transcribed genes are classified into three promoter types. Type 1 promoter is present in 5S rRNA genes, and requires transcription factors TFIIA, TFIIB and TFIIC. The most abundant RNAP III gene class is represented by the tRNAs, which have a Type 2 promoter that requires TFIIB and TFIIC. Lastly, the metazoan U6 promoter (Type 3) requires SNAPc and TFIIB (recently reviewed in 3). RNAP II control in metazoan is so variable that the prototypical promoters with a TATA box constitute only ~20% of all RNAP II-transcribed genes. About 30% of mammalian genes have no recognizable promoter elements, suggesting more complexity than currently known.⁴

In this review, we will focus more on concepts rather than on mechanistic details, many of which have been very well reviewed previously.⁵⁻⁷ Specifically, we will concentrate on how RNAP III can achieve very high levels of rapid repetitive cycles of initiation, termination and reinitiation. RNAP III is responsible for more transcription initiations in a eukaryotic cell than RNAP I or II (approximately 2–4 transcripts per gene per second; recently reviewed in 8). RNAP III transcription initiation complexes (TICs) are extremely stable, indicating that more than 99% of RNAP III-transcripts produced per cell doubling result from reinitiation (274 tRNA genes producing ~6 x 10⁶ transcripts, see below). Differently from RNAP II, RNAP III followed an evolutionary course that included a reduction in the number of dissociable transcription factors that would otherwise have to be pre-assembled at the promoter, accompanied by a corollary increase in the number of stably integrated RNAP III subunits that function in initiation. Other strategies appear to be a decisive mechanism of termination that supports rapid reinitiation and efficient reuse of RNAP III, and stable TICs with no apparent need for posttranslational modifications at different transitional stages of the transcription cycle (as occurs on the RNAP II CTD).

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We highlight recent advances describing functional TATA boxes located upstream of a majority of human tRNA genes,⁹ a double hinge model for TFIIC on tRNA genes observed in vivo,¹⁰ new homology models for TFIIC and TFIIF,¹¹ and nutrition-dependent phosphoregulation of the RNAP III integral subunit and TFIIF homolog, Rpc53.¹² We also critically review a newly proposed model of RNAP III termination.¹³

Stable and Simple Recruitment Factor for RNAP III Reinitiation: TFIIB

The functions of transcription initiation factors (TIFs) can be divided in two groups: those that occur before the recruitment of the polymerase and those that occur after recruitment of the polymerase. RNAP II interacts with a variety of TIFs. Some of them have either pre- or post-recruitment functions, but others have both functions. Pre-recruitment factors recognize promoter elements and contribute to recruiting the polymerase. The binding of the multisubunit TFIID to promoter DNA is an early step in TIC formation. The TATA-binding protein, TBP, a subunit of TFIID, anchors the complex; TFIIA stabilizes it.^{14,15} Some TFIID subunits bind to other core promoter elements such as initiator and downstream promoter elements.⁴ A central TF that has homologs in archaeal and in the three eukaryotic RNAPs is TFIIB: it binds to promoter DNA on both sides of TBP and to TBP itself, and acts as a link between TFIID and RNAP II during recruitment.¹⁶⁻¹⁸ Apart from its pre-recruitment function, TFIIB also functions later, in promoter opening, although RNAP II also requires TFIIE, TFIIF and TFIH for this, as well as initial transcription and promoter escape (all post-recruitment functions).

De novo initiation of tRNA transcription by RNAP III is preceded by binding of TFIIC to the internal A and B box promoter elements,³ followed by positioning of TFIIB upstream of the start site. Despite the differences between RNAP II and III TICs, some similarities regarding general architecture can be appreciated in the multipoint contacts between promoter elements and TFs around the transcription start sites (TSS). **Figure 1** shows a highly schematized representation of the core promoters and bound TIFs of a composite RNAP II promoter that bears some of the common elements and the RNAP III promoter type used by tRNA genes. It should be noted that there are no universal elements found in all RNAP II promoters and that great diversity comes from combinatorial use of a large number of different promoter elements.⁴ A theme of this review is the significant differences in RNAP II and RNAP III TICs concerning their post-recruitment stability and receptivity for a single recruitment (RNAP II) vs. multiple reinitiation (RNAP III). We acknowledge that while some RNAP II TICs, e.g., on heavily transcribed genes, are receptive to sequential RNAP II recruitments, others are apparently programmed to be labile and must be reassembled, at least in part, prior to the next recruitment.¹⁹

TFIIB is the initiation factor proper for RNAP III

The transcription factor required by all RNAP III promoters is TFIIB, a three-subunit complex comprised of TBP, a TFIIB-related factor (Brf1 or Brf2) and Bdp1.²⁰ Once a TFIIB-DNA

complex is formed, it is sufficient to recruit RNAP III and direct transcription, suggesting that TFIIB is the transcription initiation factor proper for RNAP III while the others function as pre-recruitment assembly factors, as was demonstrated in vitro and in vivo.^{21,22} Interactions between Brf1 and the integral RNAP III subunits C34 and C17 are important for RNAP III recruitment.²³⁻²⁶ Similar to the role of TFIIB during RNAP II initiation, Brf1 plays a major role in promoter opening during initiation by RNAP III. Bdp1 has no apparent homolog in the RNAP II or I transcription systems and, along with Brf1, serves in post-recruitment functions such as promoter opening.⁷

TFIIB-DNA complex: a paradigm for recycling DNA bound transcription factors

De novo assembly of preinitiation complexes (PIC) can be a slow step in initiation. To achieve higher transcription rates, some steps of the PIC assembly pathway may be circumvented at subsequent transcription cycles by retaining some of the transcription factors at the promoter^{19,27} (**Fig. 2**).

As alluded to above, RNAP II transcription complexes can vary widely in their propensity for reinitiation.¹⁹ A notable feature of RNAP II PICs is their lability. In the absence of activators, some RNAP II PICs fall apart after each round of transcription, requiring de novo assembly preceding each transcription cycle.²⁷ Thus, activators can increase the stability of a PIC.¹⁹ Studies of the adenovirus major late promoter have shown that TFIID, but not several of the other TFs, remains bound to the template after transcription initiation.²⁸ On the *D. melanogaster* heat shock promoter, when the heat shock factor (HSF) was present, both TFIID and TFIIA were retained on the promoter after the first round of transcription.²⁹ When the Gal4-VP16 fusion activator was used on an immobilized template, TFIID, TFIIA, TFIH, TFIIE and the mediator complex remained associated with the promoter while TFIIB and TFIIF dissociated after promoter escape.³⁰ In contrast, the fusion activator protein Gal4-AH did not retain any of these factors, suggesting that activator mechanisms can vary in this aspect of transcription. In accordance with TF retention, the reinitiation rate for Gal4-VP16 was 3-fold higher than for Gal4-AH.³⁰ Thus, it can be suggested that RNAP II transcription factor-DNA complexes are intrinsically labile and different regulatory proteins can manipulate the stability of PICs to achieve variable levels of transcription.

When compared with RNAP II, the RNAP III machinery appears to have been streamlined for highly efficient transcription reinitiation. It is well documented that RNAP III genes efficiently recycle/reuse their stably associated PICs.^{21,31,32} More explicitly, once the RNAP III TIC is assembled it can be recycled in its stable form for many rounds of transcription. As noted above, TFIIB forms very stable complexes with DNA, which is resistant to high ionic strength and polyanions such as heparin.^{21,33} The high relative stability of RNAP III PICs is partially reflected by the observation that although TBP is required for transcription by all three RNAPs, yeast RNAP III transcribed genes show the highest TBP enrichment, suggesting high stability of TFIIB complexes, compared to the more dynamic nature of RNAP II PICs.³⁴ High stability has also been demonstrated in vivo. While ChIP assays for RNAP II factors require prior crosslinking of

Figure 1. Schematic comparison of the promoter elements and transcription factor recruitment systems for RNAP II and III. **(A)** RNAP II. Some of the core promoter elements are shown as part of a composite promoter for RNAP II (see text). It should be noted that more elements are known than are shown here, and that the promoters of different genes contain variable combinations of the different elements; the consensus sequences are for metazoans.⁴ TBP and other TAFs constitute TFIID. Different TAFs interact with different core promoter elements, as indicated by the double-sided arrows. It should also be noted that TFIID is not required by all genes, at least in yeast, in which another TBP containing complex, SAGA, can take the place of TFIID. RNAP II is recruited largely via interaction with TFIIB, as indicated by the thick double-sided arrow. **(B)** RNAP III. Schematic of the tRNA gene, type 2 RNAP III promoter. While there are hundreds of tRNA genes of variable sequence, they all share the A and B box promoter elements, the consensus sequences of which were highly conserved through eukaryotic evolution, and the terminator element. Different subunits of TFIIB and TFIIC interact with the elements, as indicated by the double-sided arrows. The proximal TFIIC subunits (Tfc1, Tfc4) comprise the τ A module of TFIIC, which binds to the A box promoter element, whereas the distal subunits (Tfc3, Tfc6) comprise τ B binds with high affinity to the B box.^{47,49} A major function of TFIIC τ A is to place TFIIB upstream of the initiation site, where a TATA box is rarely present in *S. cerevisiae* tRNA genes, but is much more frequently found in *S. pombe* and human tRNA genes (in the latter, it has recently been shown to be flanked by BREu and BREd elements).^{9,36}

DNA-protein complexes, crosslinking is not necessary for RNAP III TICs, as native IPs show genome-wide high levels of TFIIB and TFIIC occupancy on tRNA gene promoters.¹⁰

While the mechanism for TFIIB placement upstream of tRNA genes in *S. cerevisiae* clearly does not require a TATA box element,³⁵ RNAP III-transcribed genes from other species have a -30 positioned TATA box for TBP binding. In the fission yeast *S. pombe*, all tRNA genes contain a TATA element at -30, and in vitro and in vivo data show that it is required for transcription.³⁶ Some plants also use an upstream TATA for tRNA

transcription (36 and references therein). A recent study found that a -30 TATA element was detected for 386 (of 506 total predicted) human tRNA genes that were found to crosslink TBP.⁹ Moreover, sequence-specific TFIIB binding sites (BREu and BREd) could also be discerned.⁹ In previous attempts to identify TATA elements upstream of human tRNA genes, only small enrichment was found in the 625 tRNA genes examined³⁶; moreover, that gene set has since been refined by elimination of a large number of pseudogenes. New findings suggest that, within the predicted human tRNA genes, the 386 human tRNA genes with

a crosslinked TBP, TATA, BREu and BRED elements may represent the most stably expressed.

TFIIIC: an RNAP III PIC assembly factor

In contrast to TFIIIB, both in vitro and in vivo experiments suggest that the intragenic promoter bound TFIIIC is displaced by RNAP III during active transcription. In vitro binding of RNAP III to the TFIIIC-TFIIIB-DNA complex to form the PIC abolished the TFIIIC-A box interaction, as evidenced by the loss of its footprint.³⁷ In vitro transcription assays to analyze the fate of TFs show that RNAP III could easily disrupt the TFIIIC-DNA interaction during elongation.³⁸ As expected, this should not affect transcription output because reinitiation on tRNA genes does not require TFIIIC.³⁹ These biochemical studies were substantiated by in vivo quantitative ChIP assays in *S. cerevisiae* that show that TFIIIC signal was low (5–25%) compared with that of TFIIIB on actively transcribing tRNA genes.⁴⁰ The data indicate that the stably bound, three-subunit TFIIIB is sufficient to support efficient reinitiation.

In addition to initiation requirements for multiple TFs, RNAP II itself undergoes a series of transitions, mediated by phosphorylation and dephosphorylation on different residues of its C-terminal domain (CTD) that activate it, for example, for promoter escape. Additional CTD modifications promote elongation and, later in the transcription cycle, in preparation for termination.⁴¹ Apparently, these modifications must then be cleared to reset RNAP II for reinitiation. Moreover, RNAP II does not efficiently terminate transcription but appears instead to linger and accumulate on the downstream regions of many genes.⁴² Thus, reinitiation in the RNAP II system would appear to be limited by PIC instability and by an intricacy of CTD modifications of the polymerase itself.

In summary, comparison of the RNAP II and III systems suggests that TFIIIB functions as a minimal RNA polymerase recruitment system, in which TFIIIB-related factor, Brf1, is directly anchored to the DNA in addition to being bound by TBP and, together with Bdp1, serves both pre- and post-recruitment functions. The stability of the TFIIIB-DNA complex as well as its ability to direct many rounds of transcription, even in the absence of other assembly factors, support the high efficiency of RNAP III reinitiation. Again, by comparison, stable RNAP II TF-promoter complexes appear to occur only with strong activators, implying that the 'basal' RNAP III TF machinery also serves activator function, a conformation designed to achieve high levels of transcription efficiency.

TFIIIC Dynamics: A tRNA Gene Guardian?

RNAP III gene complexes are dynamic during the different transcriptional states in vivo. Several stimuli lead to the repression of RNAP III transcription. The central regulator of RNAP III is the conserved Maf1 protein, which inhibits RNAP III recruitment to the TFIIIB-promoter complex.⁴³ In *S. cerevisiae*, Maf1-mediated repression is rapid, being achieved within 15 min of the stimulus.^{34,44} Chromatin immunoprecipitation studies show a robust reduction in RNAP III occupancy levels following repression.^{34,45} In contrast to RNAP III, TFIIIC levels

increase upon repression, consistent with in vitro observations that TFIIIC stably associates with DNA in the absence of RNAP III but is displaced during transcription.³⁸ TFIIIB levels show very little, if any, reduction upon Maf1-mediated repression.^{34,45} Thus, even upon repression, RNAP III genes still retain their TFs, preserving readiness without requiring reassembly.

As noted above, TFIIIC helps preserve tRNA transcription complexes even under periods of transcriptional repression. Also as noted, while retention of TFIIIB would presumably be sufficient for RNAP III recruitment upon reversal of repression, we suggest that TFIIIC occupies the body of the tRNA gene to stave off otherwise encroaching nucleosomes. It is known that RNAP III-transcribed genes are free of nucleosomes during repression.⁴⁶ The much longer RNAP II-transcribed genes have developed intricate ways to regulate the activity of nucleosomes that occupy their lengths. The TFIIIB/C-tRNA gene complexes occupy a DNA length similar to nucleosomes, although perhaps more stably so.¹⁰ Thus, in addition to its assembly factor function, TFIIIC occupies tRNA and other genes during transitions in RNAP III activity.

TFIIIC Has Adjustable Hinges and Flexibly Encompasses tRNA Gene Terminators

A remarkable feature of the TFIIIC complex is its flexibility, which can accommodate a range of tRNA gene lengths, encompassing their beginnings and ends. In *S. cerevisiae*, TFIIIC is a 6 subunit protein complex with two domains (τ A and τ B).^{47–49} τ B binds with high affinity to the B box promoter element, while τ A binds to the A box promoter (Fig. 1B).^{47,49} The A and B box sequences are transcribed to become the dihydrouridine loop and T ψ C loop of the tRNA. The distance between the A and B box elements can vary by 40 bp or more, depending on whether the tRNA gene has an intron and the length of the variable arm in the tRNA.

In vitro footprinting, as well as DNA-protein crosslinking on a tRNA gene and on the *S. cerevisiae* U6 snRNA gene (in which the A-B box distance is 200 bp), show that TFIIIC is able to bind the A and B boxes simultaneously.^{47,50–52} An electron microscopic examination of tRNA gene variants with altered distances between A and B boxes showed that, with increasing distance, the structure of TFIIIC varied from compact globular to a more stretched dumbbell shape, without significant looping of DNA,⁴⁹ indicating proximal flexibility between τ A and τ B (hinge 1; see below).

Photocrosslinking studies used to analyze the interaction between TFs and the promoters of a 5S rRNA gene and a tRNA gene have shown that the Tfc4 subunit of TFIIIC associates with the region around the transcription start site (TSS), which is consistent with proximal flexibility,²⁰ while the 90 kDa subunit of TFIIIC, TFC6, associates with the terminator element.⁴⁷ Nagarajavel et al.¹⁰ analyzed genome-wide 'bootprints' of TFIIIC and TFIIIB in vivo, with single nucleotide resolution, using ChIP-seq. This revealed that TFIIIC is more flexible than previously thought, having a distal hinge as well as a proximal hinge. They grouped all *S. cerevisiae* tRNA genes based on

Figure 2. RNAP III is equipped for streamlined initiation and reinitiation of stable complexes. **(A and B)** Comparison of RNAP II and III promoter complexes. **(A)** Schematic showing RNAP II and its dissociable initiation factors, TFIIS A, B, D, E, F and H. During elongation, RNAP II initiation factors dissociate from the promoter complex (see text). **(B)** Schematic of RNAP III and initiation factors. RNAP III contains its integral subunits C53/C37 (TFIIIF like), C31/C34/C82 (TFIIE like) and C11 (TFIIS like). C53/C37 and C11 also function during reinitiation, elongation and termination as well. After initiation, TFIIB remains bound to the promoter. In the case of RNAP II, the interaction between RNAP II and TFIIB plays major role in recruitment of RNAP II, while for RNAP III, it is the interaction between Brf1 and the TFIIE-like subunit C34. **(C and D)** RNAP II and III maintained similar peripheral architecture while diverging functionally during evolution. **(C)** A schematic based on electron microscopic structure of RNAP III (EMDB accession no: EMD-1802).^{1,71} Electron densities corresponding to the RNAP III specific subunits C53/C37 and C34/C83/C31 are shown in pink and blue, respectively, while RNAP III core is gray and the stalk is green. The N-terminal domain of C11 is shown in yellow. **(D)** Schematic of 12 subunit RNAP II based on crystal structure (PDB ID:1Y1Y). RNAP II core is shown in gray, RPB9 subunit in yellow and stalk in green. TFIIIF dimerization domain is shown in pink (based on crystal structure of human TFIIIF; PDB ID:1F3U) and TFIIE complex in blue.

separate variations of A-B box length and B box-terminator length. Although an expandable hinge per se has not been visualized, it would appear that the proximal one accommodates variable lengths in between the A and B boxes, and another hinge

(hinge 2) accommodates variable lengths between the B box and the terminator of tRNA genes.

Another finding was that oligo(dT) terminator elements delimit the 3' boundaries of the TFIIC complex on tRNA

genes, genome-wide. This observation not only corroborates previous *in vitro* observations of TFC6 crosslinking to the terminator of a single tRNA gene,^{47,53} but also indicates that this is a global characteristic of TFIIC-tDNA *in vivo*. This structure was observed both *in vivo* (on most tRNA genes) and *in vitro*, suggesting functional significance.^{10,47} The data suggest that even within the τ B domain, there is flexibility between Tfc3, the B box-binding subunit, and Tfc6, a subunit for which a distinct activity is unknown, to accommodate variable distances. Though the terminator did not have apparent interaction with TFIIC on long genes, such as SCR1 or RPR1, it is possible that T stretches downstream of their B boxes serve as contact points for TFIIC. The observations suggest that the Tfc3-Tfc6 flexible hinge may exist to accommodate the significant range of lengths among tRNA genes in their B box-terminator elements. It is possible that this may be relevant to termination and reinitiation by RNAP III and also possibly at extra-TFIIC (ETC) sites, which bind TFIIC but not TFIIB, and do not recruit RNAP III.¹⁰

Transcription Initiation Factor (TIF) Homologs Are Integral RNAP III Subunits

As mentioned above, efficient multi-round transcription requires not only a stable and receptive promoter complex but also a reinitiation-competent polymerase. Among the nuclear RNA polymerases, RNAP II has the least number of stably-associated (i.e., integral) subunits, a total of 12, while RNAP III has the most, 17 (See 1 for review). Five subunits of RNAP II are shared with RNAP I and III, while the other RNAP II subunits have homologous subunits in the two other polymerases. This suggests that the RNAP II complex can be considered as an architectural core of eukaryotic RNA polymerases¹ (Fig. 2).

Two homologs of each of two multisubunit RNAP II TIFs, TFIIE and TFIIF, are found in the 17-subunit RNAP III complex. In addition, a homolog of the single subunit elongation and RNA 3' cleavage factor for RNAP II, TFIIS, is another integral RNAP III subunit, C11 (Fig. 2A and B).

TFIIE and the RNAP III initiation subcomplex: similar design, different function

Three of the five subunits that are unique to RNAP III are C31, C34 and C82, and constitute a peripheral subcomplex. This subcomplex, termed the initiation subcomplex, is attached to the clamp domain of RNAP III, is essential for RNAP III recruitment and transcription initiation in yeasts as well.^{23,54,55} Bioinformatics suggested that two of these, C34 and C82, show structural homology to RNAP II TIF, TFIIE, a two-subunit factor that has essential post-recruitment functions.⁵⁶ C34 and C82 interact via their winged helix domains, homologous to the dimerization domains of the TFIIE subunits. Consistently, the positioning of C34 and C82 on RNAP III is very similar to that of TFIIE on RNAP II, as revealed by crosslinking (schematicized in Fig. 2C and D).^{57,58} While TFIIE and the RNAP III initiation subcomplex are required for initiation and share structural homology within their PICs, their functions differ, presumably contributing specificities to their core systems.

In the RNAP II system, major roles of TFIIE are recruitment and activation of TFIIF, and contributions to promoter opening.⁵⁹⁻⁶¹ TFIIF is a multi-subunit complex that has several catalytic activities, such as kinase, ATPase and helicase. Its ATPase and helicase activities are required for activation and promoter opening by RNAP II, which is a major deviation from other multisubunit RNAPs, which do not require such activity. Similarly, the kinase activity of TFIIF phosphorylates the multi-repeat, CTD of RNAP II, a feature that other RNA polymerases lack, suggesting that TFIIF has no functional homolog in the RNAP III system (Fig. 2A and B).^{62,63}

It would appear that the C31/34/82 initiation subcomplex has adapted RNAP III specific function. The C34 subunit of this subcomplex is the major interaction partner for the Brf1 subunit of TFIIB, suggesting the major role of C34 is in recruitment of RNAP III to the promoter.^{23,24} This further suggests that while RNAP II and III diverged, the former acquired TFIIE as a means to recruit the multifunctional complex factor, TFIIF, for polymerase-specific post-recruitment functions, whereas the structurally-homologous initiation subcomplex of RNAP III was adapted for efficient recruitment of RNAP III.

C53/C37 functions in (re)initiation, elongation and termination

Structural similarity to TFIIF exists not only for TFIIC¹¹ but also for the two RNAP III subunits of the C53/37 heterodimer, which also shares some functional resemblance.^{56,64} TFIIF associates with RNAP II before recruitment, increases its affinity for and stabilizes the PIC, promotes initial transcription and, upon promoter escape, dissociates from RNAP II but rejoins during elongation.⁶⁵ The C53/37 heterodimer mediates promoter opening and is required for efficient reinitiation by RNAP III, along with the RNA 3' cleavage activity of the C11 subunit⁶⁶ (below).

The C53/C37 heterodimer was initially described as a termination subcomplex, because a mutant RNAP III that lacks these two subunits, as well as C11, failed to terminate efficiently.⁶⁶ A basic activity of the C53/C37 subcomplex is to reduce the elongation rate of RNAP III.⁶⁶ Elongation rate and termination efficiency of RNA polymerases are inversely related, and the increased elongation rate of RNAP III lacking C53/C37 and C11 (pol III Δ) was suggested as the underlying mechanism of terminator read through by RNAP III Δ .⁶⁶ Apart from its elongation-termination function, C53/C37 also plays a role in promoter opening; however, this function may not be essential, as RNAP III lacking these subunits can be engaged for promoter-mediated transcription initiation *in vitro*.^{64,66}

Both C53/C37 and the TFIIF subunits dimerize using the triple barrel motif present in these subunits.⁵⁶ This triple barrel motif serves not only as a dimerization interface but also as a dock for the subcomplex to the RNAP III surface. Both TFIIF and C53/C37 associate with their respective polymerases on the lobe domain of the second largest subunit (Rpb2 and Rpc2, respectively) suggesting similar architectures (Fig. 2C, D).⁶⁷ Structural homology of the C53/C37 subcomplex to TFIIF is limited to their dimerization domains suggesting that, similar to TFIIE, this subcomplex also diverged during evolution to incorporate RNAP III-specific functions while maintaining similar architecture.

During various stress conditions, including nutrient deprivation, Maf1 represses RNAP III transcription by preventing recruitment of RNAP III to TFIIB-promoters.^{68,69} Repression signals also lead to phosphorylation of the C53 subunit by LAMMER/Clk and GSK-3 family kinases, and this phosphorylation is required for efficient repression of RNAP III transcription.¹² Though the mechanism of action of these phosphorylations during repression is not known, they genetically interact with mutations in C11.¹² These phosphorylation sites were mapped to a region outside the dimerization domains and were shown to crosslink to the largest subunit of RNAP III.^{12,67} Since C53/C37 and C11 play major roles in termination and reinitiation,⁶⁶ it is possible that these mutations help in repression by affecting the reinitiation properties of RNAP III.

Two subunits of the τ A subcomplex of *S. pombe* TFIIC, Sfc1 and Sfc7, associate using dimerization domains similar to the TFIIF subunits.¹¹ Whether the structural similarity of TFIIF and TFIIC subunits is more functional than providing an interaction mechanism is unknown. In addition, Sfc1 possesses a winged helix domain similar to that of the TFIIF subunit, Rap30. This winged helix of Sfc1 binds to both single stranded and double-stranded DNA.¹¹

C11, the RNA cleavage homolog of elongation factor TFIIS, is integral to RNAP III

The efficient association of C53/C37 with the RNAP III core complex depends on the presence of C11, an 11 kDa protein that has two zinc ribbon domains separated by a linker.⁷⁰ The N-terminal domain of C11 is homologous to the RNAP II subunit RPB9 and appears to dock on the RNAP III lobe, analogous to the RPB9-RPB2 interaction in RNAP II.^{71,72} The C53/C37 binding site on RPC2 is adjacent to the C11 site and mutations that affect assembly of C11 lead to dissociation of C53/C37.^{66,67}

The C-terminal domain of C11 is homologous to the C-terminal domain of the RNAP II elongation factor TFIIS⁷⁰, providing another example of acquisition of an otherwise soluble TF as an integral subunit of RNAP III. C11 is also homologous to Rpa12, the RNA 3' cleavage subunit of RNAP I.⁷³ TFIIS stimulates an activity intrinsic to RNAP II, the 3' end hydrolysis of the growing nascent RNA and this promotes elongation under conditions in which elongation by RNAP II is compromised.⁷⁴ RNA 3' end hydrolysis stimulatory activities, as mediated by TFIIS homologs, are observed in all multisubunit RNA polymerases, but in others (RNAP II, bacterial and archaeal RNAP) the S-like factors are soluble and function to promote elongation by transiently associating with their polymerase.^{70,75}

Other functions of these S-like RNA cleavage factors include removal of misincorporated nucleotides and rescue of RNA polymerases that are inactivated by stalling or backtracking.⁷⁶ RNA polymerases tend to backtrack when faced with transcription roadblocks or when the RNA-DNA hybrid that forms in the transcription bubble is of very weak thermo stability, such as when formed of oligo(rU:dA).⁷⁷ During backtracking, the 3' end of the nascent RNA in the RNA:DNA hybrid is unzipped and its 3' end can fray and protrude from a conserved tunnel feature known as the secondary channel that connects the catalytic center to outside of the polymerase. This process renders the 3'

end of the RNA out of register with the catalytic center, trapping and inactivating the polymerase. Cleavage of the RNA by the catalytic center creates a new 3' end in register with the catalytic site.^{75,78-81} By having the 3' RNA cleavage factor, C11, as an integral subunit, RNAP III would appear to be equipped to handle all obstacles, without having to call in a soluble factor. As will be reviewed in the next section, C11 appears to also contribute to a much more seamless transcription cycle than is observed for RNAP II.

With regard to elongation, RNAP II and RNAP III differ most obviously in the lengths of the genes they transcribe. A very large number of RNAP II-transcribed genes span tens-of thousands to millions of base pairs in humans. As such, elongation control is a major feature of RNAP II transcription, as evidenced by the multitude and intricacy of factors involved.^{82,83} It is very important for RNAP II to remain on the template rather than disengage (terminate) at pause sites or obstructions, in part because doing so half way through a million base pair (bp) gene would be wasteful. Moreover, control of elongation is a major regulatory feature of RNAP II transcription.⁸⁴ The great majority of RNAP III-transcribed genes are less than 150 bp long, with some exceptions (which are not much longer). Elongation control per se may be less of an issue for RNAP III and it would appear that it is used more during termination than as a general means of transcription regulation (see below).

In summary, the RNAP III system appears to be streamlined for efficient transcription reinitiation, in part by a stable TFIIB-promoter complex that is receptive to reinitiation. Moreover, the incorporation into RNAP III of what are soluble promoter assembly TIFs in the RNAP II system, namely the C34/82 homologs of TFIIE and the C53/37 homologs of TFIIF, further contributes to facile reinitiation. In addition, RNAP III itself appears to efficiently transition from termination to reinitiation without apparent need (in non-repressive state) to be reset, for example, by complex RNAP II CTD modifications.

Simple Termination Signal for RNAP III: Decisive, Precise and Efficient

Termination by RNA polymerases is a complex process by which an exceptionally stable elongation complex has to be dismantled to release the template and the nascent RNA.⁷⁶ For RNAP I and RNAP II, as well as for bacterial and archaeal RNAPs (all of which synthesize relatively long transcripts), the stability of elongation complexes (ECs) should be very important because of the risk of wasteful production of truncated functionless RNAs (or worse, dominant negative transcripts). Accordingly, the programmed dismantling of these elongation complexes at termination may be expected to be multipartite and intricate. Indeed, even the simplest of these, bacterial RNAP, requires a bipartite termination signal in the DNA and a two-component mechanism by the polymerase for intrinsic (factor-independent) termination.⁷⁶ As part of the adaptation by RNAP III for short gene transcripts, the benefit of a facile termination mechanism may offset the relatively low risk of premature truncation.

The bipartite signal for bacterial RNAP is a T-rich tract in the non-template DNA very closely preceded by a G+C-rich inverted repeat that forms a hairpin in the nascent transcript. The close juxtaposition of these two definitive elements comprise a highly specific composite termination signal. Each of these elements contributes distinct destabilizing effects on the EC, as part of a two-component mechanism that results in termination.⁷⁶ Factor-mediated termination by RNAP uses the Rho-helicase, an RNA-binding protein that associates with the nascent transcript as it remains attached to the elongating polymerase and tracks along to trigger termination, presumably by allosteric effects, at least in part. This too would appear to require a two-component mechanism, interactions between Rho and the RNAP and dismantling of the active center with release of the transcript. Not too dissimilarly, RNAP I and RNAP II would appear to use two-component mechanisms, involving RNA-binding factors that track down the polymerase as described by the torpedo model.⁸⁵ Termination by RNAP II involves a multitude of ancillary factors. Moreover, its actual termination sites, i.e., where it releases from the template, are spread over several hundred base pairs as they accumulate on the downstream regions of genes.⁸⁵

By comparison, RNAP III has a more simple termination mechanism that is decisive, precise and efficient. The termination control element for RNAP III is monopartite, a stretch of five or more T residues, oligo(T), on the non-template strand, oligo(dA) on the template, which leads to formation of an oligo(rU:dA) RNA-DNA hybrid in the active center.⁷⁶ RNA synthesis indeed terminates within the oligo(dT) tract, such that the nascent transcripts that are produced end with oligo(U)-3'OH. RNAP III-transcribed genes appear to exhibit relative ease of dismantling of their ECs at the terminator and this may contribute to their efficiency for reinitiation. The apparent efficiency of termination may reflect the relative ease with which RNAP III can be made ready for reinitiation.

Efficient Termination and Reinitiation by RNAP III Are Mediated by Integral Subunits

Termination by RNAP III consists of two phases: pausing in the oligo(dT) tract and release of the RNA.⁸⁶ Recent analyses confirmed these two phases and distinguished two mechanistic aspects of RNAP III termination, a holoenzyme mechanism manifested by the full 17-subunit RNAP III, and a distinct core mechanism manifested by a 14-subunit core RNAP III.⁸⁷ The latter reflects an apparent sensitivity of the RNAP III core (lacking C11 and C53/C37, a.k.a., RNAP III Δ) to a weak RNA:DNA hybrid, the oligo(rU:dA). The holoenzyme mechanism complements the core activity by minimizing the otherwise significant propensity for transcription arrest, including backtracking at a weak hybrid which is known to occur with other RNA polymerases.⁸⁷ It should be noted that transcript release activity by the RNAP III core was found to occur at a significant level, albeit less efficiently than by the holoenzyme.⁸⁷ Interestingly, C11-mediated RNA 3' cleavage activity is required to efficiently prevent arrest at the terminator.⁸⁷

Genetic and biochemical analyses of *S. pombe* C11 indicate that its two domains serve distinct functions during termination.^{88,89} Its C-terminal domain, which is very highly homologous to the RNA cleavage domain of TFIIS, is responsible for transcript cleavage. Point mutations that affect this activity cause increased length of the 3' terminal oligo(rU) tract on the nascent RNAs.⁸⁹ This increases their affinity for the oligo(U)3'-OH binding protein, La, which promotes efficient maturation of nascent pre-tRNAs.⁸⁹ Studies of C11 provided evidence that a TFIIS-like RNA 3' end cleavage activity is involved in nascent RNA 3' trimming,⁸⁹ later proposed for the Rpa12 RNA cleavage subunit of RNAP I during termination of rRNA synthesis.⁹⁰ C11 is active for RNA 3' end cleavage in the context of a functional RNAP III termination complex.⁸⁹ Notably, the same mutations did not interfere with terminator pausing as they had no effect on terminator read-through in vitro or in vivo,^{88,89} consistent with recent data.⁸⁷ In contrast, mutations in the N-terminal domain of C11, which localizes adjacent to the dimerization domains of C53/37 on the peripheral upper jaw of RNAP III, had a different phenotype, terminator read-through.⁸⁸ Thus, the C11 N-terminal domain is involved in pausing or terminator recognition, while its C-terminal domain mediates termination-associated RNA 3' cleavage.

A Newly Proposed 'Hairpin' Model of RNAP III Termination

A recent study by Nielsen et al. suggests that hairpin formation by the nascent RNA in addition to an oligo(dT) tract, is a conserved requirement for termination by RNAP III and archaeal RNAP,¹³ somewhat similar to bacterial RNAP. According to this model, RNAP III pauses upon encountering the oligo(dT) and then goes backward (backtracks) on the template, without RNA 3' end cleavage/retraction, until it finds an RNA hairpin or as proposed, another type of RNA duplex in the transcript. A difference between this model for RNAP III¹³ and bacterial RNAP is that a recognizable G+C-rich hairpin is associated closely upstream of the T-rich tracts of intrinsic terminators for the latter.⁹¹

The authors compared 9 bp hairpins to stretches of ≥ 10 bp DNA with no hairpin, and duplexes with no duplex. While a hairpin is found within 5 nt upstream of the oligo(T) tract in some RNAP III-transcribed genes, in many others it is not.¹³ For genes with no recognizable hairpin closely upstream of the oligo(T), such as tRNAs whose Ψ stem typically begins ≥ 10 nt upstream of the oligo(U) tract, a more complex RNA duplex would be required. In these cases, including for some tRNAs, the duplex would be provided by long-distance base pairing between the 5' and 3' end regions of the transcript, e.g., assembling the aminoacyl stem in tRNAs.

It should be emphasized that the RNAP III 'hairpin' model acknowledges that RNA synthesis indeed terminates within the oligo(T) tract, producing oligo(U)3'-OH in the nascent RNA products, but poses that release requires RNAP III to backtrack to a 'hairpin.' Thus, by the criterion of termination of RNA

synthesis, the signal for RNAP III is monopartite, oligo(A) in the template.

Nielsen et al. reported transcript release by *S. cerevisiae* RNAP III within one minute when a hairpin is present but no release even at ten minutes in the absence of a hairpin.¹³ Backtracking was indeed demonstrated in the absence of a hairpin, supporting their model.¹³ However, prior studies indicate that oligo(dT) alone, in the absence of an upstream hairpin, is sufficient for efficient RNAP III termination.^{92,93} A more recent study of *S. cerevisiae* RNAP III that used a very similar approach demonstrated efficient release in ten minutes in the absence of a predicted hairpin.⁸⁷ One difference between these investigations was that the polymerase used by Nielsen et al. unexpectedly exhibited low termination efficiency, $\geq 50\%$ read-through of T-tracts of 12 consecutive T residues when a hairpin was present,¹³ whereas RNAP III in the other study terminated with higher efficiency, $\sim 80\%$ at a 9 bp oligo(dT) track terminator.⁸⁷

Nielsen et al. analyzed effects of distance between the oligo(T) tract and the upstream hairpin. A hairpin located 12 nucleotides upstream of the oligo(T) could cause efficient transcript release with no transcripts arrested at the terminator. With a hairpin located 15 nt upstream of the terminator, about 50% of the transcripts were arrested at the terminator and about 50% were released. With a hairpin located 18 nt upstream the vast majority of the transcripts were arrested at the terminator with very little if any release.¹³

Nielsen et al. cataloged the distances from oligo(T) to the upstream hairpin or the more complex, long-range duplex structures for all RNAP III-transcribed genes in yeast. On the genes with a hairpin ≥ 5 nt upstream of the T-tract, RNAP III would have to back up as part of termination but, as shown by the new data, without RNA 3' end retraction.¹³ The elongation rate for RNAP III on yeast 5S rRNA genes has been calculated to be 60–75 nt/s with an occupancy of 2–3 RNAP III molecules per 5S gene and a reinitiation interval of 1.2 s.⁹⁴ Calculations based on tRNA levels in yeast estimate the rate of RNA production, i.e., termination, at 2–4 transcripts/gene/s⁹⁵ (or a time between two successive terminating RNAP III molecules equal to 250–500 ms). To put it another way, an RNAP III molecule involved in tRNA production in fast growing yeast cells has only 0.25–0.5 s to terminate as it approaches the terminator. The rate of RNAP II backtracking in the absence of RNA 3' end retraction is about one nucleotide per 0.3 s, about 20-fold slower than forward polymerization.⁹⁶ Assuming a similar rate for RNAP III, for the $\sim 20\%$ of tRNA genes that have a predicted structure 4–5 nts upstream of the T tract, the required backtracking would represent a relatively slow step. For the dozens of genes with hairpins farther upstream, 6–12 nts,¹³ the required backtracking would be more time consuming. A backtracking RNAP III might also interfere with an approaching polymerase. As noted, yeast 5S rRNA genes of 132 bp contains 2–3 elongating RNAP III molecules.⁹⁴ Many tRNA genes contain introns and are as long as this, and dimeric tRNA genes are significantly longer, apparently loaded with successive RNAP III.

Nielsen et al. propose that the oligo(U) tract causes catalytic inactivation of RNAP III, with switching off of its C11-mediated

RNA 3' hydrolytic activity, followed by backtracking.¹³ However, previous work had shown that RNA 3' hydrolysis was active during RNAP III termination in vivo and in vitro.^{89,97,98} Other work suggests that cleavage-active C11 facilitates termination by preventing arrest.⁸⁷ Additional work should reconcile these differences.

Understanding mechanisms that promote high efficiency RNAP III transcription is important because RNAP III activation occurs in cancer, accompanied by elevated levels of tRNA and 5S rRNA to support growth and proliferation.^{68,69,99,100} The model proposed by Nielsen et al. consists of catalytic inactivation followed by backtracking and duplex-mediated destruction of the complex.¹³ Concurrent models of RNAP III termination envision it as a process that maintains the polymerase for facile reinitiation (below).

Mechanisms of Reinitiation by RNAP III

Although it was noted that the C53/37 heterodimer confers function not only in termination but also in promoter opening and reinitiation, it is appropriate to also elaborate on its associated subunit, C11. The data suggest a cleavage-independent but C53/37-dependent function for C11 in RNAP III reinitiation,⁶⁶ and that the N-terminal domain of C11 appears to be involved in both terminator recognition and reinitiation.^{87,88} Thus, C11 would appear to contribute to the seamlessness of termination and reinitiation.

A high rate of transcript production requires multiple RNAP III molecules per gene and that every phase of the transcription cycle is fast. The vast majority of the transcripts produced in vivo occur by RNAP III reinitiation onto stable transcription initiation complexes (TICs). In yeast, 274 tRNA genes plus another 30–50 5S genes and a few single copy genes are transcribed by a total of what appears to be about 2×10^3 molecules of RNAP III (based on global analyses of the proteome);¹⁰¹ together, these produce $3\text{--}6 \times 10^6$ tRNAs per cell.⁸ Although it would be helpful to know the actual number of active RNAP III molecules in a cell (below), observations nonetheless suggest that the tRNA TICs and RNAP III are recycled for $\sim 10^4$ and $10^2\text{--}10^3$ reinitiations per doubling, respectively.

The molecular details of how this high rate of RNAP III reinitiation is achieved in vivo are currently unknown. An open question is if reinitiating RNAP III is transferred from the terminator to the transcription start site of the same gene, according to a model of facilitated recycling,¹⁰² or whether it is loaded onto the TIC in competition with free soluble RNAP III molecules. Measurements in *S. cerevisiae* and *S. pombe* of the number of molecules of the largest RNAP III subunits estimate $2\text{--}3 \times 10^3$, a significant excess relative to TICs, consistent with observations and estimations of transcription rates requiring multiple molecules of RNAP III on its transcribed genes.^{94,101,103} Electron microscopic examination indicate up to three RNAP III molecules on a 5S rRNA gene (132 bp).⁹⁴ The most numerous RNAP III-transcribed genes, the tRNAs, have an average length of about 90 bp, and would expectedly accommodate two RNAP III molecules. Accordingly, the entire RNAP III gene class would account for $\leq 10^3$ molecules of RNAP III engaged on genes. The

Figure 3. Schematic models of reinitiation in conditions of limiting (in vitro reactions monitoring facilitated reinitiation) or excess RNAP III (presumed in vivo conditions, see text). Under limiting RNAP III concentrations (upper panel), RNAP III recruitment to the TFIIB-DNA complex is slower (as compared with when RNAP III is available in excess). Under limiting conditions, the terminating RNAP III is the only source of enzyme for reinitiation. In this case, proximity may drive the chance to reconnect with the initiation complex, which may be augmented by C53/C37-mediated pausing at the terminator. Lack of such a pause may explain the observed effect of C11 and C53/C37 on reinitiation in vitro. When RNAP III is present in excess (lower panel), multiple polymerases occupy the gene simultaneously. In addition, free polymerases in solution may compete with the terminating RNAP III for the initiation complexes.

cumulative observations suggest a significant excess of RNAP III relative to that engaged on active transcription units, presumably free in solution.

The model of facilitated recycling is based on several observations: i) reinitiating RNAP III is relatively resistant to heparin (see **Figure 2** of 102) and non-specific DNA¹⁰⁴; ii) 3 to 7-fold preferential reinitiation on the same gene relative to a pre-assembled PIC on a different gene in the same reaction tube or in the same plasmid^{102,104} and; iii) kinetics of reinitiation several fold faster than initiating the first round of transcription, determined under conditions of limiting RNAP III.¹⁰² While effects of different TFIIIs and characteristics of facilitated recycling have been examined, some of the molecular aspects remain unclear. Longer genes are less efficient substrates for facilitated recycling and rely on TFIIC.³⁹ However, as noted in an earlier section, TFIIC is not efficiently associated with the genes during active growth.^{34,40} Although physical connectivity between the terminating RNAP III and the reinitiating PIC (e.g., by looping) is a feature of this model, there is no direct evidence supporting direct transfer. The pathway by which a terminating RNAP III finds its way to its next reinitiation site in vivo remains uncertain.

A component of the model of facilitated recycling is normal termination, consistent with the short size of tRNA genes³⁹ (**Fig. 3**). However, this aspect of the model is not readily reconciled by RNAP III mutants with pervasive terminator read-through phenotypes that showed no deficiency of transcript production in vivo.⁹⁸ For these, after RNAP III has read through the natural terminator, the next terminator of the reporter tRNA gene was 100 bp downstream, increasing the distance from the TSS by nearly 2-fold.

Maf1 is incapable of repressing reinitiating RNAP III while it could efficiently repress free RNAP III.¹⁰⁴ Yet, Maf1 is known to cause rapid repression of RNAP III transcription in vivo in response to global environmental signals.¹⁰⁵ As noted,¹⁰⁴ if RNAP III was in a closed circuit of facilitated recycling, refractory to Maf1, transcription output should not be repressed by Maf1; yet, it is.

Another model is that reinitiating polymerase may be drawn from a soluble pool of excess unengaged RNAP III (**Fig. 3**). Increasing amounts of excess (more than saturating) RNAP III in vitro, relative to a fixed number of pre-initiated TICs, increases reinitiation rate many folds.^{39,106} Thus, it would seem that any increase in the pool of soluble RNAP III would be in competition

with the terminator-mediated, facilitated reinitiating-RNAP III (Fig. 3). We note that physical clustering of tRNA genes¹⁰⁷ would tend to increase the local concentration of RNAP III. New approaches that address these important issues and their relevance to the production of tRNAs and 5S rRNA in vivo are needed.

Conclusions

RNAP III-transcribed genes experience a very high rate of reinitiation in eukaryotic cells, producing high levels of tRNAs and other short RNAs. Their highly efficient reinitiation mechanism results from stable TF-initiation complexes that are almost limitlessly reused, and a polymerase that carries several

specialized integral subunits that facilitate termination with apparent smooth and rapid reinitiation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

- Vannini A, Cramer P. Conservation between the RNA polymerase I, II, and III transcription initiation machineries. *Mol Cell* 2012; 45:439-46; PMID:22365827; <http://dx.doi.org/10.1016/j.molcel.2012.01.023>
- Warner JR. The economics of ribosome biosynthesis in yeast. *Trends Biochem Sci* 1999; 24:437-40; PMID:10542411; [http://dx.doi.org/10.1016/S0968-0004\(99\)01460-7](http://dx.doi.org/10.1016/S0968-0004(99)01460-7)
- Orioli A, Pascali C, Pagano A, Teichmann M, Dieci G. RNA polymerase III transcription control elements: themes and variations. *Gene* 2012; 493:185-94; PMID:21712079; <http://dx.doi.org/10.1016/j.gene.2011.06.015>
- Kadonaga JT. Perspectives on the RNA polymerase II core promoter. *Wiley Interdiscip Rev Dev Biol* 2012; 1:40-51; PMID:23801666; <http://dx.doi.org/10.1002/wdev.21>
- Schramm L, Hernandez N. Recruitment of RNA polymerase III to its target promoters. *Genes Dev* 2002; 16:2593-620; PMID:12381659; <http://dx.doi.org/10.1101/gad.1018902>
- Geiduschek EP, Kassavetis GA. The RNA polymerase III transcription apparatus. *J Mol Biol* 2001; 310:1-26; PMID:11419933; <http://dx.doi.org/10.1006/jmbi.2001.4732>
- Kassavetis GA, Geiduschek EP. Transcription factor TFIIB and transcription by RNA polymerase III. *Biochem Soc Trans* 2006; 34:1082-7; PMID:17073756; <http://dx.doi.org/10.1042/BST0341082>
- Moir RD, Willis IM. Regulation of pol III transcription by nutrient and stress signaling pathways. *Biochim Biophys Acta* 2013; 1829:361-75; PMID:23165150; <http://dx.doi.org/10.1016/j.bbarm.2012.11.001>
- Venters BJ, Pugh BF. Genomic organization of human transcription initiation complexes. *Nature* 2013; 502:53-8; PMID:24048476
- Nagarajavel V, Iben JR, Howard BH, Maraia RJ, Clark DJ. Global 'bootprinting' reveals the elastic architecture of the yeast TFIIB-TFIIC transcription complex in vivo. *Nucleic Acids Res* 2013; 41:8135-43; PMID:23856458; <http://dx.doi.org/10.1093/nar/gkt611>
- Taylor NM, Baudin F, von Scheven G, Müller CW. RNA polymerase III-specific general transcription factor IIIC contains a heterodimer resembling TFIIF Rap30/Rap74. *Nucleic Acids Res* 2013; 41:9183-96; PMID:23921640; <http://dx.doi.org/10.1093/nar/gkt664>
- Lee J, Moir RD, McIntosh KB, Willis IM. TOR signaling regulates ribosome and tRNA synthesis via LAMMER/Clk and GSK-3 family kinases. *Mol Cell* 2012; 45:836-43; PMID:22364741; <http://dx.doi.org/10.1016/j.molcel.2012.01.018>
- Nielsen S, Yuzenkova Y, Zenkin N. Mechanism of eukaryotic RNA polymerase III transcription termination. *Science* 2013; 340:1577-80; PMID:23812715; <http://dx.doi.org/10.1126/science.1237934>
- Nikolov DB, Burley SK. RNA polymerase II transcription initiation: a structural view. *Proc Natl Acad Sci U S A* 1997; 94:15-22; PMID:8990153; <http://dx.doi.org/10.1073/pnas.94.1.15>
- Ranish JA, Yudkovsky N, Hahn S. Intermediates in formation and activity of the RNA polymerase II preinitiation complex: holoenzyme recruitment and a postrecruitment role for the TATA box and TFIIB. *Genes Dev* 1999; 13:49-63; PMID:9887099; <http://dx.doi.org/10.1101/gad.13.1.49>
- Ha I, Roberts S, Maldonado E, Sun X, Kim LU, Green M, Reinberg D. Multiple functional domains of human transcription factor IIB: distinct interactions with two general transcription factors and RNA polymerase II. *Genes Dev* 1993; 7:1021-32; PMID:8504927; <http://dx.doi.org/10.1101/gad.7.6.1021>
- Buratowski S, Hahn S, Guarente L, Sharp PA. Five intermediate complexes in transcription initiation by RNA polymerase II. *Cell* 1989; 56:549-61; PMID:2917366; [http://dx.doi.org/10.1016/0092-8674\(89\)90578-3](http://dx.doi.org/10.1016/0092-8674(89)90578-3)
- Buratowski S, Zhou H. Functional domains of transcription factor TFIIB. *Proc Natl Acad Sci U S A* 1993; 90:5633-7; PMID:8516312; <http://dx.doi.org/10.1073/pnas.90.12.5633>
- Hahn S. Activation and the role of reinitiation in the control of transcription by RNA polymerase II. *Cold Spring Harb Symp Quant Biol* 1998; 63:181-8; PMID:10384282; <http://dx.doi.org/10.1101/sqb.1998.63.181>
- Kassavetis GA, Driscoll R, Geiduschek EP. Mapping the principal interaction site of the Brf1 and Bdp1 subunits of *Saccharomyces cerevisiae* TFIIB. *J Biol Chem* 2006; 281:14321-9; PMID:16551611; <http://dx.doi.org/10.1074/jbc.M601702200>
- Kassavetis GA, Braun BR, Nguyen LH, Geiduschek EP. *S. cerevisiae* TFIIB is the transcription initiation factor proper of RNA polymerase III, while TFIIB and TFIIC are assembly factors. *Cell* 1990; 60:235-45; PMID:2404611; [http://dx.doi.org/10.1016/0092-8674\(90\)90739-2](http://dx.doi.org/10.1016/0092-8674(90)90739-2)
- Marsolier MC, Chaussivert N, Lefebvre O, Conesa C, Werner M, Sentenac A. Directing transcription of an RNA polymerase III gene via GAL4 sites. *Proc Natl Acad Sci U S A* 1994; 91:11938-42; PMID:7991561; <http://dx.doi.org/10.1073/pnas.91.25.11938>
- Werner M, Chaussivert N, Willis IM, Sentenac A. Interaction between a complex of RNA polymerase III subunits and the 70-kDa component of transcription factor IIB. *J Biol Chem* 1993; 268:20721-4; PMID:8407894
- Brun I, Sentenac A, Werner M. Dual role of the C34 subunit of RNA polymerase III in transcription initiation. *EMBO J* 1997; 16:5730-41; PMID:9312031; <http://dx.doi.org/10.1093/emboj/16.18.5730>
- Andrau JC, Sentenac A, Werner M. Mutagenesis of yeast TFIIB70 reveals C-terminal residues critical for interaction with TBP and C34. *J Mol Biol* 1999; 288:511-20; PMID:10329159; <http://dx.doi.org/10.1006/jmbi.1999.2724>
- Ferri M-L, Peyroche G, Saut M, Lefebvre O, Carles C, Conesa C, Sentenac A. A novel subunit of yeast RNA polymerase III interacts with the TFIIB-related domain of TFIIB70. *Mol Cell Biol* 2000; 20:488-95; PMID:10611227; <http://dx.doi.org/10.1128/MCB.20.2.488-495.2000>
- Dieci G, Sentenac A. Detours and shortcuts to transcription reinitiation. *Trends Biochem Sci* 2003; 28:202-9; PMID:12713904; [http://dx.doi.org/10.1016/S0968-0004\(03\)00054-9](http://dx.doi.org/10.1016/S0968-0004(03)00054-9)
- Zawel L, Kumar KP, Reinberg D. Recycling of the general transcription factors during RNA polymerase II transcription. *Genes Dev* 1995; 9:1479-90; PMID:7601352; <http://dx.doi.org/10.1101/gad.9.12.1479>
- Sandaltzopoulos R, Becker PB. Heat shock factor increases the reinitiation rate from potentiated chromatin templates. *Mol Cell Biol* 1998; 18:361-7; PMID:9418883
- Yudkovsky N, Ranish JA, Hahn S. A transcription reinitiation intermediate that is stabilized by activator. *Nature* 2000; 408:225-9; PMID:11089979; <http://dx.doi.org/10.1038/35041603>
- Maraia RJ, Kenan DJ, Keene JD. Eukaryotic transcription termination factor La mediates transcript release and facilitates reinitiation by RNA polymerase III. *Mol Cell Biol* 1994; 14:2147-58; PMID:8114745
- Wang Z, Roeder RG. DNA topoisomerase I and PC4 can interact with human TFIIC to promote both accurate termination and transcription reinitiation by RNA polymerase III. *Mol Cell* 1998; 1:749-57; PMID:9660958; [http://dx.doi.org/10.1016/S1097-2765\(00\)80074-X](http://dx.doi.org/10.1016/S1097-2765(00)80074-X)
- Kassavetis GA, Riggs DL, Negri R, Nguyen LH, Geiduschek EP. Transcription factor IIB generates extended DNA interactions in RNA polymerase III transcription complexes on tRNA genes. *Mol Cell Biol* 1989; 9:2551-66; PMID:2668737
- Roberts DN, Stewart AJ, Huff JT, Cairns BR. The RNA polymerase III transcriptome revealed by genome-wide localization and activity-occupancy relationships. *Proc Natl Acad Sci U S A* 2003; 100:14695-700; PMID:14634212; <http://dx.doi.org/10.1073/pnas.2435566100>
- Joazeiro CA, Kassavetis GA, Geiduschek EP. Alternative outcomes in assembly of promoter complexes: the roles of TBP and a flexible linker in placing TFIIB on tRNA genes. *Genes Dev* 1996; 10:725-39; PMID:8598299; <http://dx.doi.org/10.1101/gad.10.6.725>

36. Hamada M, Huang Y, Lowe TM, Maraia RJ. Widespread use of TATA elements in the core promoters for RNA polymerases III, II, and I in fission yeast. *Mol Cell Biol* 2001; 21:6870-81; PMID:11564871; <http://dx.doi.org/10.1128/MCB.21.20.6870-6881.2001>
37. Braun BR, Bartholomew B, Kassavetis GA, Geiduschek EP. Topography of transcription factor complexes on the *Saccharomyces cerevisiae* 5 S RNA gene. *J Mol Biol* 1992; 228:1063-77; PMID:1474578; [http://dx.doi.org/10.1016/0022-2836\(92\)90315-B](http://dx.doi.org/10.1016/0022-2836(92)90315-B)
38. Bardeleben C, Kassavetis GA, Geiduschek EP. Encounters of *Saccharomyces cerevisiae* RNA polymerase III with its transcription factors during RNA chain elongation. *J Mol Biol* 1994; 235:1193-205; PMID:8308884; <http://dx.doi.org/10.1006/jmbi.1994.1073>
39. Ferrari R, Rivetti C, Acker J, Dieci G. Distinct roles of transcription factors TFIIB and TFIIC in RNA polymerase III transcription reinitiation. *Proc Natl Acad Sci U S A* 2004; 101:13442-7; PMID:15347814; <http://dx.doi.org/10.1073/pnas.0403851101>
40. Soragni E, Kassavetis GA. Absolute gene occupancies by RNA polymerase III, TFIIB, and TFIIC in *Saccharomyces cerevisiae*. *J Biol Chem* 2008; 283:26568-76; PMID:18667429; <http://dx.doi.org/10.1074/jbc.M803769200>
41. Mayer A, Heidemann M, Lidschreiber M, Schreieck A, Sun M, Hintermair C, Kremmer E, Eick D, Cramer P. CTD tyrosine phosphorylation impairs termination factor recruitment to RNA polymerase II. *Science* 2012; 336:1723-5; PMID:22745433; <http://dx.doi.org/10.1126/science.1219651>
42. Le Martelot G, Canella D, Symul L, Migliavacca E, Gilardi F, Liechti R, Martin O, Harshman K, Delorenzi M, Desvergne B, et al.; CyclIX Consortium. Genome-wide RNA polymerase II profiles and RNA accumulation reveal kinetics of transcription and associated epigenetic changes during diurnal cycles. *PLoS Biol* 2012; 10:e1001442; PMID:23209382; <http://dx.doi.org/10.1371/journal.pbio.1001442>
43. Boguta M, Maf1, a general negative regulator of RNA polymerase III in yeast. *Biochim Biophys Acta* 2013; 1829:376-84; PMID:23201230; <http://dx.doi.org/10.1016/j.bbagr.2012.11.004>
44. Upadhyay R, Lee J, Willis IM. Maf1 is an essential mediator of diverse signals that repress RNA polymerase III transcription. *Mol Cell* 2002; 10:1489-94; PMID:12504022; [http://dx.doi.org/10.1016/S1097-2765\(02\)00787-6](http://dx.doi.org/10.1016/S1097-2765(02)00787-6)
45. Harismendy O, Gendrel CG, Soularue P, Gidrol X, Sentenac A, Werner M, Lefebvre O. Genome-wide location of yeast RNA polymerase III transcription machinery. *EMBO J* 2003; 22:4738-47; PMID:12970186; <http://dx.doi.org/10.1093/emboj/cdg466>
46. Kumar Y, Bhargava P. A unique nucleosome arrangement, maintained actively by chromatin remodelers facilitates transcription of yeast tRNA genes. *BMC Genomics* 2013; 14:402; PMID:23767421; <http://dx.doi.org/10.1186/1471-2164-14-402>
47. Braun BR, Bartholomew B, Kassavetis GA, Geiduschek EP. Topography of transcription factor complexes on the *Saccharomyces cerevisiae* 5 S RNA gene. *J Mol Biol* 1992; 228:1063-77; PMID:1474578; [http://dx.doi.org/10.1016/0022-2836\(92\)90315-B](http://dx.doi.org/10.1016/0022-2836(92)90315-B)
48. Bartholomew B, Kassavetis GA, Braun BR, Geiduschek EP. The subunit structure of *Saccharomyces cerevisiae* transcription factor IIIC probed with a novel photocrosslinking reagent. *EMBO J* 1990; 9:2197-205; PMID:2100996
49. Schultz P, Marzouki N, Marck C, Ruet A, Oudet P, Sentenac A. The two DNA-binding domains of yeast transcription factor tau as observed by scanning transmission electron microscopy. *EMBO J* 1989; 8:3815-24; PMID:2684647
50. Eschenlauer JB, Kaiser MW, Gerlach VL, Brow DA. Architecture of a yeast U6 RNA gene promoter. *Mol Cell Biol* 1993; 13:3015-26; PMID:8474459
51. Bartholomew B, Braun BR, Kassavetis GA, Geiduschek EP. Probing close DNA contacts of RNA polymerase III transcription complexes with the photoactive nucleoside 4-thiothymidine. *J Biol Chem* 1994; 269:18090-5; PMID:8027070
52. Burnol AF, Margottin F, Schultz P, Marsolier MC, Oudet P, Sentenac A. Basal promoter and enhancer element of yeast U6 snRNA gene. *J Mol Biol* 1993; 233:644-58; PMID:8411171; <http://dx.doi.org/10.1006/jmbi.1993.1542>
53. Braun BR, Riggs DL, Kassavetis GA, Geiduschek EP. Multiple states of protein-DNA interaction in the assembly of transcription complexes on *Saccharomyces cerevisiae* 5S ribosomal RNA genes. *Proc Natl Acad Sci U S A* 1989; 86:2530-4; PMID:2649882; <http://dx.doi.org/10.1073/pnas.86.8.2530>
54. Thuillier V, Stettler S, Sentenac A, Thuriaux P, Werner M. A mutation in the C31 subunit of *Saccharomyces cerevisiae* RNA polymerase III affects transcription initiation. *EMBO J* 1995; 14:351-9; PMID:7835345
55. Wang Z, Roeder RG. Three human RNA polymerase III-specific subunits form a subcomplex with a selective function in specific transcription initiation. *Genes Dev* 1997; 11:1315-26; PMID:9171375; <http://dx.doi.org/10.1101/gad.11.10.1315>
56. Carter R, Drouin G. 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* 2010; 27:1035-43; PMID:20026480; <http://dx.doi.org/10.1093/molbev/msp316>
57. Grünberg S, Warfield L, Hahn S. Architecture of the RNA polymerase II preinitiation complex and mechanism of ATP-dependent promoter opening. *Nat Struct Mol Biol* 2012; 19:788-96; PMID:22751016; <http://dx.doi.org/10.1038/nsmb.2334>
58. Wu CC, Herzog F, Jennebach S, Lin YC, Pai CY, Aebersold R, Cramer P, Chen HT. RNA polymerase III subunit architecture and implications for open promoter complex formation. *Proc Natl Acad Sci U S A* 2012; 109:19232-7; PMID:23132938; <http://dx.doi.org/10.1073/pnas.1211665109>
59. Maxon ME, Goodrich JA, Tjian R. Transcription factor IIE binds preferentially to RNA polymerase IIa and recruits TFIIF: a model for promoter clearance. *Genes Dev* 1994; 8:515-24; PMID:7926747; <http://dx.doi.org/10.1101/gad.8.5.515>
60. Ohkuma Y, Roeder RG. Regulation of TFIIF ATPase and kinase activities by TFIIE during active initiation complex formation. *Nature* 1994; 368:160-3; PMID:8166891; <http://dx.doi.org/10.1038/368160a0>
61. Ohkuma Y, Hashimoto S, Wang CK, Horikoshi M, Roeder RG. Analysis of the role of TFIIE in basal transcription and TFIIF-mediated carboxy-terminal domain phosphorylation through structure-function studies of TFIIE- α . *Mol Cell Biol* 1995; 15:4856-66; PMID:7651404
62. Egly JM, Coin F. A history of TFIIF: two decades of molecular biology on a pivotal transcription/repair factor. *DNA Repair (Amst)* 2011; 10:714-21; PMID:21592869; <http://dx.doi.org/10.1016/j.dnarep.2011.04.021>
63. Compe E, Egly J-M. TFIIF: when transcription met DNA repair. *Nat Rev Mol Cell Biol* 2012; 13:343-54; PMID:22572993; <http://dx.doi.org/10.1038/nrm3350>
64. Kassavetis GA, Prakash P, Shim E. The C53/C37 subcomplex of RNA polymerase III lies near the active site and participates in promoter opening. *J Biol Chem* 2010; 285:2695-706; PMID:19940126; <http://dx.doi.org/10.1074/jbc.M109.074013>
65. Vannini A. A Structural Perspective on RNA Polymerase I and RNA Polymerase III Transcription Machinery. *Biochim Biophys Acta* 2012; PMID:23031840
66. Landrieux E, Alic N, Ducrot C, Acker J, Riva M, Carles C. A subcomplex of RNA polymerase III subunits involved in transcription termination and reinitiation. *EMBO J* 2006; 25:118-28; PMID:16362040; <http://dx.doi.org/10.1038/sj.emboj.7600915>
67. Wu CC, Lin YC, Chen HT. The TFIIF-like Rpc37/53 dimer lies at the center of a protein network to connect TFIIC, Bdp1, and the RNA polymerase III active center. *Mol Cell Biol* 2011; 31:2715-28; PMID:21536656; <http://dx.doi.org/10.1128/MCB.05151-11>
68. Geiduschek EP, Kassavetis GA. Transcription: adjusting to adversity by regulating RNA polymerase. *Curr Biol* 2006; 16:R849-51; PMID:17027482; <http://dx.doi.org/10.1016/j.cub.2006.08.071>
69. Willis IM, Moir RD. Integration of nutritional and stress signaling pathways by Maf1. *Trends Biochem Sci* 2007; 32:51-3; PMID:17174096; <http://dx.doi.org/10.1016/j.tibs.2006.12.001>
70. Chédin S, Riva M, Schultz P, Sentenac A, Carles C. The RNA cleavage activity of RNA polymerase III is mediated by an essential TFIIS-like subunit and is important for transcription termination. *Genes Dev* 1998; 12:3857-71; PMID:9869639; <http://dx.doi.org/10.1101/gad.12.24.3857>
71. Fernández-Tornero C, Böttcher B, Rashid UJ, Steuerwald U, Flörchinger B, Devos DP, Lindner D, Müller CW. Conformational flexibility of RNA polymerase III during transcriptional elongation. *EMBO J* 2010; 29:3762-72; PMID:20967027; <http://dx.doi.org/10.1038/emboj.2010.266>
72. Yee NS, Gong W, Huang Y, Lorent K, Dolan AC, Maraia RJ, Pack M. Mutation of RNA Pol III subunit rpc2/polr3b Leads to Deficiency of Subunit Rpl1 and disrupts zebrafish digestive development. *PLoS Biol* 2007; 5:e312; PMID:18044988; <http://dx.doi.org/10.1371/journal.pbio.0050312>
73. Van Mullem V, Landrieux E, Vandenhaute J, Thuriaux P, Rpa12p, a conserved RNA polymerase I subunit with two functional domains. *Mol Microbiol* 2002; 43:1105-13; PMID:11918799; <http://dx.doi.org/10.1046/j.1365-2958.2002.02824.x>
74. Izban MG, Luse DS. The RNA polymerase II ternary complex cleaves the nascent transcript in a 3'→5' direction in the presence of elongation factor SII. *Genes Dev* 1992; 6:1342-56; PMID:1378419; <http://dx.doi.org/10.1101/gad.6.7.1342>
75. Wind M, Reines D. Transcription elongation factor SII. *Bioessays* 2000; 22:327-36; PMID:10723030; [http://dx.doi.org/10.1002/\(SICI\)1521-1878\(200004\)22:4<327::AID-BIES3>3.0.CO;2-4](http://dx.doi.org/10.1002/(SICI)1521-1878(200004)22:4<327::AID-BIES3>3.0.CO;2-4)
76. Arimbasseri AG, Rijal K, Maraia RJ. Transcription termination by the eukaryotic RNA polymerase III. *Biochim Biophys Acta* 2013; 1829:318-30; PMID:23099421; <http://dx.doi.org/10.1016/j.bbagr.2012.10.006>
77. Nudler E. RNA polymerase backtracking in gene regulation and genome instability. *Cell* 2012; 149:1438-45; PMID:22726433; <http://dx.doi.org/10.1016/j.cell.2012.06.003>
78. Borukhov S, Sagitov V, Goldfarb A. Transcript cleavage factors from *E. coli*. *Cell* 1993; 72:459-66; PMID:8431948; [http://dx.doi.org/10.1016/0092-8674\(93\)90121-6](http://dx.doi.org/10.1016/0092-8674(93)90121-6)
79. Cheung AC, Cramer P. Structural basis of RNA polymerase II backtracking, arrest and reactivation. *Nature* 2011; 471:249-53; PMID:21346759; <http://dx.doi.org/10.1038/nature09785>
80. Komissarova N, Kashlev M. Transcriptional arrest: *Escherichia coli* RNA polymerase translocates backward, leaving the 3' end of the RNA intact and extruded. *Proc Natl Acad Sci U S A* 1997; 94:1755-60; PMID:9050851; <http://dx.doi.org/10.1073/pnas.94.5.1755>
81. Nudler E, Mustaev A, Lukhtanov E, Goldfarb A. The RNA-DNA hybrid maintains the register of transcription by preventing backtracking of RNA polymerase. *Cell* 1997; 89:33-41; PMID:9094712; [http://dx.doi.org/10.1016/S0092-8674\(00\)80180-4](http://dx.doi.org/10.1016/S0092-8674(00)80180-4)

82. Conaway JW, Shilatifard A, Dvir A, Conaway RC. Control of elongation by RNA polymerase II. *Trends Biochem Sci* 2000; 25:375-80; PMID:10916156; [http://dx.doi.org/10.1016/S0968-0004\(00\)01615-7](http://dx.doi.org/10.1016/S0968-0004(00)01615-7)
83. Sims RJ 3rd, Belotserkovskaya R, Reinberg D. Elongation by RNA polymerase II: the short and long of it. *Genes Dev* 2004; 18:2437-68; PMID:15489290; <http://dx.doi.org/10.1101/gad.1235904>
84. Zhou Q, Li T, Price DH. RNA polymerase II elongation control. *Annu Rev Biochem* 2012; 81:119-43; PMID:22404626; <http://dx.doi.org/10.1146/annurev-biochem-052610-095910>
85. Richard P, Manley JL. Transcription termination by nuclear RNA polymerases. *Genes Dev* 2009; 23:1247-69; PMID:19487567; <http://dx.doi.org/10.1101/gad.1792809>
86. Campbell FE Jr., Setzer DR. Transcription termination by RNA polymerase III: uncoupling of polymerase release from termination signal recognition. *Mol Cell Biol* 1992; 12:2260-72; PMID:1314952
87. Arimbasseri AG, Maraia RJ. Distinguishing core and holoenzyme mechanisms of transcription termination by RNA polymerase III. *Mol Cell Biol* 2013; 33:1571-81; PMID:23401852; <http://dx.doi.org/10.1128/MCB.01733-12>
88. Iben JR, Mazeika JK, Hasson S, Rijal K, Arimbasseri AG, Russo AN, Maraia RJ. Point mutations in the Rpb9-homologous domain of Rpc11 that impair transcription termination by RNA polymerase III. *Nucleic Acids Res* 2011; 39:6100-13; PMID:21450810; <http://dx.doi.org/10.1093/nar/gkr182>
89. Huang Y, Intine RV, Mozlin A, Hasson S, Maraia RJ. Mutations in the RNA polymerase III subunit Rpc11p that decrease RNA 3' cleavage activity increase 3'-terminal oligo(U) length and La-dependent tRNA processing. *Mol Cell Biol* 2005; 25:621-36; PMID:15632064; <http://dx.doi.org/10.1128/MCB.25.2.621-636.2005>
90. Kuhn CD, Geiger SR, Baumli S, Gartmann M, Gerber J, Jennebach S, Mielke T, Tschochner H, Beckmann R, Cramer P. Functional architecture of RNA polymerase I. *Cell* 2007; 131:1260-72; PMID:18160037; <http://dx.doi.org/10.1016/j.cell.2007.10.051>
91. Peters JM, Vangeloff AD, Landick R. Bacterial transcription terminators: the RNA 3'-end chronicles. *J Mol Biol* 2011; 412:793-813; PMID:21439297; <http://dx.doi.org/10.1016/j.jmb.2011.03.036>
92. Spitalny P, Thomm M. A polymerase III-like reinitiation mechanism is operating in regulation of histone expression in archaea. *Mol Microbiol* 2008; 67:958-70; PMID:18182021; <http://dx.doi.org/10.1111/j.1365-2958.2007.06084.x>
93. Wang X, Folk WR. Termination of transcription by RNA polymerase III from wheat germ. *J Biol Chem* 1994; 269:4993-5004; PMID:8106475
94. French SL, Osheim YN, Schneider DA, Sikes ML, Fernandez CF, Copela LA, Misra VA, Nomura M, Wolin SL, Beyer AL. Visual analysis of the yeast 5S rRNA gene transcriptome: regulation and role of La protein. *Mol Cell Biol* 2008; 28:4576-87; PMID:18474615; <http://dx.doi.org/10.1128/MCB.00127-08>
95. Moir RD, Willis IM. Regulation of pol III transcription by nutrient and stress signaling pathways. *Biochim Biophys Acta* 2012; PMID:23165150
96. Zamft B, Bintu L, Ishibashi T, Bustamante C. Nascent RNA structure modulates the transcriptional dynamics of RNA polymerases. *Proc Natl Acad Sci U S A* 2012; 109:8948-53; PMID:22615360; <http://dx.doi.org/10.1073/pnas.1205063109>
97. Bobkova EV, Habib N, Alexander G, Hall BD. Mutational analysis of the hydrolytic activity of yeast RNA polymerase III. *J Biol Chem* 1999; 274:21342-8; PMID:10409694; <http://dx.doi.org/10.1074/jbc.274.30.21342>
98. Rijal K, Maraia RJ. RNA polymerase III mutants in TFIIIF-like C37 that cause terminator readthrough with no decrease in transcription output. *Nucleic Acids Res* 2013; 41:139-55; PMID:23093604; <http://dx.doi.org/10.1093/nar/gks985>
99. White RJ. RNA polymerases I and III, growth control and cancer. *Nat Rev Mol Cell Biol* 2005; 6:69-78; PMID:15688068; <http://dx.doi.org/10.1038/nrm1551>
100. Marshall L, Goodfellow SJ, White RJ. Diminished activity of RNA polymerase III selectively disrupts tissues with the most actively dividing cells. *PLoS Biol* 2007; 5:e286; PMID:20076650; <http://dx.doi.org/10.1371/journal.pbio.0050286>
101. Ghaemmaghami S, Huh W-K, Bower K, Howson RW, Belle A, Dephoure N, O'Shea EK, Weissman JS. Global analysis of protein expression in yeast. *Nature* 2003; 425:737-41; PMID:14562106; <http://dx.doi.org/10.1038/nature02046>
102. Dieci G, Sentenac A. Facilitated recycling pathway for RNA polymerase III. *Cell* 1996; 84:245-52; PMID:8565070; [http://dx.doi.org/10.1016/S0092-8674\(00\)80979-4](http://dx.doi.org/10.1016/S0092-8674(00)80979-4)
103. Marguerat S, Schmidt A, Codlin S, Chen W, Aebersold R, Bähler J. Quantitative analysis of fission yeast transcriptomes and proteomes in proliferating and quiescent cells. *Cell* 2012; 151:671-83; PMID:23101633; <http://dx.doi.org/10.1016/j.cell.2012.09.019>
104. Cabart P, Lee J, Willis IM. Facilitated recycling protects human RNA polymerase III from repression by Maf1 in vitro. *J Biol Chem* 2008; 283:36108-17; PMID:18974046; <http://dx.doi.org/10.1074/jbc.M807538200>
105. Desai N, Lee J, Upadhyay R, Chu Y, Moir RD, Willis IM. Two steps in Maf1-dependent repression of transcription by RNA polymerase III. *J Biol Chem* 2005; 280:6455-62; PMID:15590667; <http://dx.doi.org/10.1074/jbc.M412375200>
106. Maraia RJ. Transcription termination factor La is also an initiation factor for RNA polymerase III. *Proc Natl Acad Sci U S A* 1996; 93:3383-7; PMID:8622944; <http://dx.doi.org/10.1073/pnas.93.8.3383>
107. Hopper AK, Pai DA, Engelke DR. Cellular dynamics of tRNAs and their genes. *FEBS Lett* 2010; 584:310-7; PMID:19931532; <http://dx.doi.org/10.1016/j.febslet.2009.11.053>