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Review

The eukaryotic transcriptional machinery regulates mRNA translation and decay in the cytoplasm ☆

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ABSTRACT

In eukaryotes, nuclear mRNA synthesis is physically separated from its cytoplasmic translation and degradation. Recent unexpected findings have revealed that, despite this separation, the transcriptional machinery can remotely control the cytoplasmic stages. Key to this coupling is the capacity of the transcriptional machinery to "imprint" the transcript with factors that escort it to the cytoplasm and regulate its localization, translation and decay. Some of these factors are known transcriptional regulators that also function in mRNA decay and are hence named "synthegradases". Imprinting can be carried out and/or regulated by RNA polymerase II or by promoter *cis*- and *trans*-acting elements. This article is part of a Special Issue entitled: RNA polymerase II Transcript Elongation.

1. Introduction

The eukaryotic transcription apparatus, which utilizes *cis*-acting DNA elements and *trans*-acting factors, functions in the nucleus. Up until recently, it was believed that this machinery has no direct effect on the fate of the RNA in the cytoplasm. This common view is currently being challenged, at least in the case of RNAs that are synthesized by RNA polymerase II (Pol II). Pol II is responsible for the transcription of all mRNAs, many non-coding RNAs, all snoRNAs (except for snRN52), most of the snRNAs and the telomerase RNA. The ten-subunit structure of Pol II is capable of transcription *in vitro* and is considered to be the "core Pol II" [1–5]. Two other subunits, Rpb4p and Rpb7p, form a distinct substructure. These two subunits strongly interact with each other, forming the Rpb4/7 heterodimer [6]. The Rpb7p "tip" interacts with a small "pocket" in the Pol II core, composed mainly of a small region of Rpb1p, Rpb2p and Rpb6 [2,7]. The interface between Rpb7p and the core Pol II is small enough such that the two substructures readily dissociate *in vitro*. Indeed a single mutation in either Rpb1p or Rpb6p can destabilize and substantially weaken the interaction between the two substructures [2,7–9]. Rpb4p and Rpb7p are present in excess over the core subunits [10], raising the possibility that they also function outside the context of the polymerase [6]. Indeed, it was found that both subunits play roles in mRNA export [11], translation [12] and degradation [13–15]. Here we discuss the various roles of Rpb4/7, emphasizing its post-transcriptional functions. Remarkably, Pol II regulates these post-transcriptional stages by providing the correct context for Rpb4/7 to interact with the transcript, as it emerges from Pol II. In addition to Pol II, other elements of the transcription apparatus can control the fate of their transcripts; among them are promoter elements and *trans*-factors that bind these elements. The latter have the capacity to regulate both mRNA synthesis and decay. In this review we summarize the recent findings that assign additional roles to the transcription machinery in regulating the fate of its transcripts in the cytoplasm.

2. Structural and biochemical data indicate that Rpb4/7 binds the emerging transcript

X-ray crystallographic studies of Pol II have revealed structural elements with functional implications [3,4]. In a transcribing Pol II, nascent RNA moves from the active center to the exterior through an RNA exit tunnel [16–18]. Until recently, it was not clear which path the exiting RNA follows beyond the exit tunnel. Based on their positively charged surfaces, two prominent grooves on either side of the dock domain were proposed to further accommodate the exiting RNA [17–20]. Groove 1 winds along the base of the clamp towards the Rpb4/7 subcomplex, which can bind RNA via its ribonucleoprotein fold and/or oligonucleotide binding domain [5,7,21,22]. Groove 2 leads along Rpb11p towards Rpb8p, which also has a single-stranded nucleic acid-binding domain [23,24]. Two studies have provided evidence that exiting RNA follows the path along groove 1. The first study used cross-linkable nucleotides (located 3 nt from the RNA 5′ end) to characterize the interaction between nascent RNA and components of the transcription complex. They demonstrated that the 5′ end of the nascent RNA could be cross-linked to Rpb7p as soon as the RNA exited from the core Pol II, once the cross-linkable nucleotide was 23 nt from the 3′ end. When Pol II continued to transcribe and the cross-linkable nucleotide was 39 nt from the 3′ end, it could still crosslink, albeit less efficiently; no cross-linking could be detected when the Pol II moved

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further away from this position [25]. This indicates that, *in vitro*, Rpb7 serves as a tunnel through which the RNA exits the 12 subunit Pol II. The second study employed fluorescence resonance energy transfer (FRET) analysis to map the path of nascent RNA on Pol II. They demonstrated that the growing RNA leads towards Rpb4/7 and, once it extends to 26 nt, its 5′ end forms contacts with the ribonucleoprotein-binding domain of Rpb7 [26]. The emerging transcript can take an alternative route *in vitro* by binding to the dock domain without contacting either of the grooves on the Pol II surface [16].The choice as to which route to take may be dependent on the conditions of the *in vitro* studies [26]. *In vivo* analysis supports binding of the emerging transcript with Rpb4/7, because Rpb4/7 binds Pol II transcripts co-transcriptionally [13]. It is possible that in the absence of Rpb4/7 the RNA exits invariably from groove 2. The picture that emerges from these studies is that Rpb4/7 serves as the initial contact for the newly emerging RNA just beyond the mouth of exit groove 1. The Rpb4/7 heterodimer contacts the main body of Pol II adjacent to the C-terminal domain (CTD) of Rpb1p [2,7]. The CTD is known to have a role in recruitment of factors involved in transcription regulation, RNA capping, splicing, polyadenylation and termination [27–29]. Thus, Rpb4/7 may play a significant role in directing the transcript to the appropriate processing factors recruited to the CTD.

3. Rpb4/7 regulates transcription initiation, elongation and polyadenylation

Rpb4/7 is considered to be a canonical Pol II subunit with a role in transcription. *In vitro* studies demonstrated that Pol II requires Rpb4/7 for promoter-dependent transcription initiation [5,30], and for elongation [10]. In archaea, the Rpb4/7 homologue, F/E, facilitates DNA melting in conjunction with the basal transcription factor, TFE, during initiation [31,32]. In yeast cells, Rbp4p and Rpb7p do not contribute equally to the function of the heterodimer. Rpb7p is an essential protein, whereas Rpb4p is dispensable under optimal growth conditions at moderate temperatures. However, as soon as the environmental conditions deviate from the optimum, most notably temperature extreme, starvation, and ethanol, Rpb4p becomes important [33–37]. We suspect that Rpb7p is the core subunit that binds both Pol II and the transcript whereas Rpb4p mediates some of the many interactions between Rpb4/7 and regulatory factors [6].

Analysis of the genome-wide occupancy of Rpb4p using chromatin immunoprecipitation revealed that Rpb4p is recruited to coding regions of most transcriptionally active genes, similar to the core Pol II subunit, Rpb3p, although to a lesser degree [38,39]. Interestingly, the extent of Rpb4p recruitment increases with increasing gene length, and Pol II lacking Rpb4p is defective in transcribing long, GC-rich transcription units, as it is sensitive to 6 aza-uracil [39]. Moreover, Rpb4 was found to be important for Pol II processivity [40]. Consistently, *in vitro* studies demonstrated that Rpb4/7 enhances Pol II elongation activity [10] and that F/E has a profound effect on the transcription elongation properties of Pol II by enhancing processivity [41]. Importantly, this function is attributed to the ability of F/E to interact with the RNA transcript [41]. Thus, the capacity of Rpb4/7 or its archaeal homolog to enhance transcription elongation might be related to its binding of the emerging transcript. It would be interesting to examine whether this binding has some effect on the capacity of Pol II to backtrack, thereby affecting processivity.

4. Rpb4/7 is recruited onto mRNAs co-transcriptionally and is directly involved in all major post-transcriptional stages of the mRNA lifecycle

Consistent with its interaction with the emerging transcript *in vitro* (see previous section), Rpb4/7 has been shown to interact with Pol II transcripts *in vivo* [12,13], probably at the 3′-untranslated region (Guterman and Choder, unpublished result). This interaction occurs only in the context of Pol II. Surprisingly, at some stage of the transcription process, Rpb4/7 dissociates from Pol II together with the transcript and remains bound to the transcript throughout its life. This “mRNA imprinting” has bearing on each and every stage of the mRNA lifecycle.

Several studies have described the diverse roles of Rpb4/7 in post-transcriptional stages, linking its role in the nucleus to the cytoplasmic stages of gene expression. One such study demonstrated that Rpb4p is required for mRNA export under stress conditions. The roles of Rpb4p in transcription and in mRNA export can be uncoupled genetically by specific mutations in Rpb4p. Both activities are essential for survival under stress conditions [11].

Another study revealed a role for Rpb4/7 in translation [12]. This study demonstrated that the Rpb4/7 heterodimer interacts physically and functionally with components of the translation initiation factor 3 (eIF3), and is required for efficient translation initiation. This function is more apparent during starvation, suggesting that the role of Rpb4/7 in translation permits appropriate responses to environmental cues.

Two major mRNA decay pathways operate in the yeast cytoplasm. They both initiate by a shortening of the mRNA poly(A) tail; one culminates in exonucleolytic degradation of the mRNA from 5′ to 3′ by the Xrn1 exonuclease, and the other in 3′ to 5′ degradation by the exosome [42]. Rpb4/7 functions directly in shortening of the poly(A) tail and in these two degradation pathways [14,15]. Unlike Rpb7p whose role in mRNA decay is not specific [15], Rpb4p is involved in the degradation of a specific class of mRNAs encoding protein biosynthetic factors, including ribosomal proteins, translation initiation factors, aminoacyl tRNA synthetases and ribosomal biosynthetic proteins [14]. Overexpression of Rpb7p could not restore proper mRNA decay in *rpb4*Δ cells, suggesting that Rpb4p has a distinct role in the decay of these mRNAs. Both Rpb4p and Rpb7p interact with the basal decay factor Pat1p/Lsm1-7p via direct interactions with Pat1p and Lsm2p [14,15]. This interaction might be important for recruiting the Pat1/Lsm1-7 complex to the mRNP, or for stimulating Pat1/Lsm1-7 decapping activity. Consistent with their role in the major decay pathway, Rpb4p and Rpb7p are constituents of P bodies [14,15], where decapping and 5′ to 3′ degradation can occur [43].

Thus, by assuming various subcellular localizations and switching interacting partners, Rpb4/7 exerts its effect on different processes temporarily. Consistently, the Rpb4/7 heterodimer shuttles between the nucleus and the cytoplasm. Shuttling occurs via two distinct shuttling mechanisms (one dependent on transcription and the other not), depending on the environmental conditions [44].

5. mRNA imprinting

Several lines of evidence have started to reveal that nascent mRNAs emerge from the nucleus with “imprinted” information that serves to regulate post-transcriptional stages of gene expression [45]. As detailed above, Rpb4/7 represents a classic example of mRNA imprinting, whereby its co-transcriptional association with the nascent transcript affects all the major post-transcriptional stages that the mRNA undergoes [see Fig. 1].

In addition to Rpb4/7, She2p and Dbf2p have been shown to be loaded onto specific mRNAs during transcription, affecting their fate in the cytoplasm. She2p affects localization and translation of specific mRNAs [46,47] and Dbf2p binds *SWI5* and *CLB2* mRNAs and specifically affects their decay during mitosis [48]. Several other factors have been proposed to bind RNA in the nucleus and affect its fate in the cytoplasm: Exon-Junction Complex (EJC) components regulate localization and translation of *oskar* mRNA in *Drosophila* oocytes in a splicing-dependent manner [49]; Ssd1p affects mRNA localization [50]; ZBP1 affects localization and translatability of several different RNAs [51,52]; the TREX complex and Mex67p mediate mRNA export [53]; CPEB affects alternative splicing, cytoplasmic polyadenylation and translation [54]; Npl3p [55] and Sro9p [56] affect mRNA export

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and translation; Cth1/2 [57] and Sus1p [58] regulate mRNA stability; finally, the kinase Ctk1p, which phosphorylates the Pol II C-terminal domain, also phosphorylates the ribosomal protein Rps2p thereby regulating translation, and has the potential capacity (which remains to be determined) to phosphorylate some RNP proteins temporarily thereby regulating the mRNP fate [59]. Besides the cases of Rpb4/7, She2p, Dbf2p, and EJC components, it remains to be determined whether the post-transcriptional functions of the other above-mentioned factors are directly dependent on their co-transcriptional association with the mRNA.

6. Pol II and promoters regulate cytoplasmic post-transcriptional stages

Although a number of proteins have been reported to bind mRNA co-transcriptionally and later regulate diverse cytoplasmic processes, only a small number of studies have elucidated the precise mechanism by which such imprinting is achieved. It is plausible that the transcriptional machinery itself plays a direct regulatory role by recruiting the imprinting factor to the emerging transcript. Indeed, Shen et al. [47] demonstrated that She2p binds to *ASH1* mRNA cotranscriptionally in a Pol II-dependent manner. She2p is recruited to Pol II via its association with the transcription elongation factor, Spt4p–Spt5p. Mutating *SPT4* or *SPT5* disrupts the co-transcriptional recruitment of She2p to *ASH1* mRNA and affects subsequent localization of *ASH1* mRNA to bud tips [47]. Goler-Baron et al. [13] demonstrated that Rpb4/7 imprinting is directly dependent on Pol II. They made use of two Pol II mutant forms that poorly recruit Rpb4/7 due to mutations in either Rpb1 or Rpb6. Significantly, interaction of Rpb4/7 with the transcripts of these Pol II mutants is compromised, despite the presence of Rpb4/7 in excess over Pol II molecules in the nucleus. Furthermore, these mutant cells do not support efficient poly(A) shortening and mRNA decay [13] as well as translation [12]. Overexpression of both Rpb4p and Rpb7p, which increases the portion of mutant Pol II that manages to recruit Rpb4/7, partially restores mRNA decay in the mutant cells. Thus, the authors propose that the interaction of Rpb4/7 with the mRNA occurs only in the context of Pol II, and is required for Rpb4/7's capacity to stimulate translation and mRNA decay [12,13]. Interestingly, cells harboring a Pol II mutant whose *in vitro* elongation rate is abnormally slow also degrade mRNAs more slowly [60]. The underlying mechanism is still unknown and it would be interesting to examine the mRNA imprinting status in this mutant strain.

Two recent works in yeast demonstrated that the promoter itself can regulate mRNA stability, as suggested earlier in mammalian cells [61],

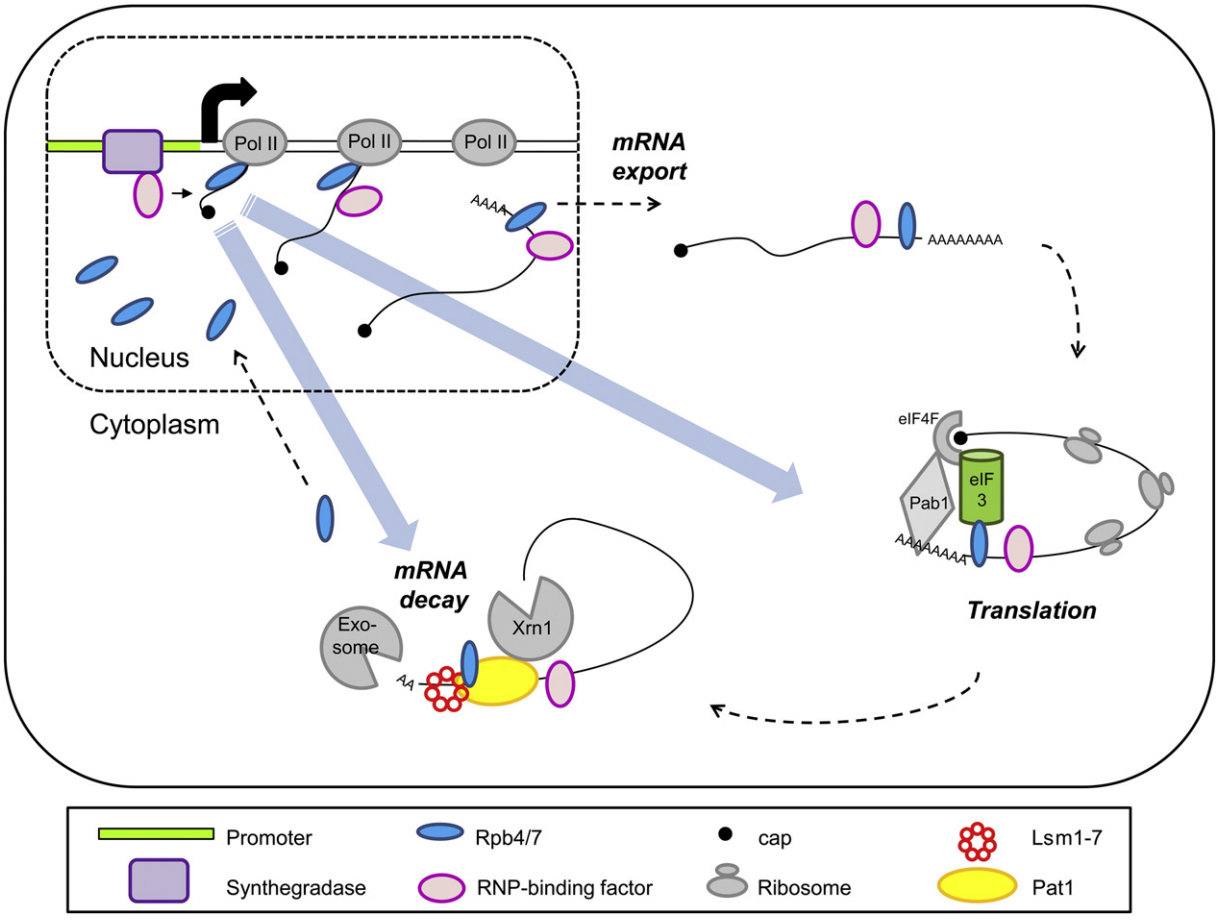

Fig. 1. RNA polymerase II and promoters remotely regulate cytoplasmic stages of gene expression. Pol II-associated Rpb4/7 is involved in transcription initiation, elongation and polyadenylation [6]. During transcription, Rpb4/7 interacts with the emerging transcript. This interaction is dependent on its proper association with Pol II [13]. Thus, despite being present in excess over Pol II complexes in the nucleus [10], the interaction of Rpb4/7 with the transcript occurs only in the context of Pol II. A representative promoter-bound synthegradase (such as Rap1) is also shown. It recruits a putative RNP-binding factor to the vicinity of the transcription apparatus, allowing binding of the factor to the emerging Pol II transcript (indicated by a small black arrow). In this example, Pol II and the promoter allow the mRNA transcript to be imprinted with Rpb4/7 and an RNP-binding factor. Such imprinting can later regulate translation and mRNA decay in the cytoplasm (light blue arrows). Specifically, following transcription, Rpb4/7 and the RNP-binding factor accompany the transcript during its export to the cytoplasm. They remain associated with the transcript throughout its lifecycle, affecting post-transcriptional stages. Rpb4/7 stimulates: (i) mRNA export (during stress) [11]; (ii) translation initiation, via its interaction with eIF3 [12]; and (iii) poly(A) tail shortening followed by mRNA degradation via the two major mRNA decay pathways [14,15]. Following decay, Rpb4/7 returns to the nucleus for an additional round [44]. Transcript-bound Rpb4/7 seems to be located at the 3′-UTR (Guterman and Choder, unpublished results) where it associates with the decay factor complex, Pat1/Lsm1-7 [14,15]. This location is strategic as it is not in conflict with translation [77]. Thus, this location would permit the continuous association of Rpb4/7 (and other putative RNP-binding factors) with the mRNA transcript throughout its lifecycle in the cytoplasm.

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possibly via an imprinting mechanism [48,62]. Bregman et al. [62] showed that Rap1p-binding sites in the upstream activating sequence (UAS) of the *RPL30* gene enhance transcript decay and are sufficient to confer transcript instability when inserted into the *ACT1* UAS. Consistently, depletion of Rap1p stabilizes reporter transcripts whose promoters contain Rap1p-binding sites, as well as endogenous mRNAs whose synthesis is driven by Rap1p. They propose that Rap1p is involved in co-transcriptional imprinting of the transcript, whereby binding of Rap1p to the promoter affects the composition of the exported mRNP, which in turn affects its cytoplasmic degradation. Trcek et al. [48] developed an RNA-fluorescence *in situ* hybridization technique to study mRNA stability at a single-molecule level. They found that the transcripts of *SWI5* and *CLB2*, genes that are responsible for mitotic progression, are rapidly degraded during mitosis. Exchanging their promoters with that of *ACT1* converts them from being unstable, cell-cycle-regulated transcripts into stable, constitutively expressed transcripts. Thus, the promoters of *SWI5* and *CLB2* are directly involved in regulating transcript stability in a cell-cycle dependent manner. They further demonstrated that Dbf2p binds to the mRNAs co-transcriptionally, and that its depletion destabilizes these mRNAs and delays mitotic progression. They propose that Dbf2p-imprinted RNA is protected from degradation until signals are received during mitosis.

These collective studies assign new roles to the transcription apparatus in regulating cytoplasmic stages of the mRNA lifecycle. The model shown in Fig. 1 depicts how translation and decay in the cytoplasm can be regulated remotely from the nucleus by Pol II and promoters. It also highlights the roles of Rpb4/7 in all the major post-transcriptional stages (splicing has not been examined, as only 15% of the yeast mRNAs contain introns).

7. Synthegradases, factors that stimulate both transcription and decay, couple these two processes

Previous works have described factors that function in both mRNA synthesis and mRNA decay. Rpb4/7, described earlier, stimulates both transcription [6] and mRNA decay [14,15]. The yeast Ccr4–NOT complex has been identified as a transcription activator and later was found to also function in deadenylation in the cytoplasm (recently reviewed in [63]). It remains to be determined whether co-transcriptional association of the Ccr4–NOT complex with mRNAs is required for its post-transcriptional functions, like the case of Rpb4/7. Recently, Rap1p, a known transcription activator of genes encoding ribosomal proteins, was found to also stimulate the degradation of their transcripts [62]. Due to their dual role, we name this kind of factors "synthegradases" [62]. Unlike Rpb4/7 and Ccr4p, Rap1p is a synthegradase of a specific family of genes.

It was recently shown that coupling between transcription and decay plays an important role in the normal response to the environment. Many environmentally induced genes are subject to induction of mRNA synthesis that is accompanied by an increase in its decay [64–69]. This counterintuitive "counter-action" characterizes mRNAs whose levels are shaped by a sharp "peaked" behavior [68,69]. Pol II is capable of regulating this pattern not only because it is responsible for transcription, but also by regulating mRNA decay [14,70]. Shalem et al. [70] have proposed that imprinting of some mRNAs with Rpb4/7 is regulated by environmental signals (see also [71]). They demonstrated that cells harboring the Rpb6p mutant form, whose Pol II poorly recruits Rpb4/7, exhibit abnormal transcriptome profiles in response to oxidative stress (0.3 mM hydrogen peroxide). Both the magnitude of the response and its kinetics were affected by the Rpb6 mutation. Thus, the coupling between mRNA synthesis and decay shapes the temporal kinetic response of mRNA abundance to changing external conditions.

Synthegradases might serve as a mechanistic basis for the characteristic "peaked" behavior of many genes whose expression responds to environmental changes in a manner that stimulates (or represses) both mRNA synthesis and decay. We suspect that the two-armed mechanism of synthegradases is more responsive to regulatory signals. Specifically, signaling pathways can modulate either the synthetic or the decay function of the synthegradases, thereby affecting the balance between mRNA synthesis and decay and fine-tuning the desired steady-state levels, as well as the kinetics with which they are achieved.

A recent comparison between mRNA degradation kinetics in two related yeast species revealed a significant difference in 11% of the orthologous mRNAs. In about half of these cases, the difference in decay was linked to a difference in transcription. Thus, coupling almost always involves stimulation of both mRNA synthesis and decay or, conversely, repression of both processes [72]. Moreover, some yeast factors seem to have evolved in a manner that either stimulates both mRNA synthesis and decay or represses both processes simultaneously. Among the most notable factors are Rpb4p and Ccr4p. At least 5% of the 3000 yeast genes examined in this study is likely to be regulated by synthegradases during optimal proliferation conditions [72]. This number is likely to increase upon shifts from optimal proliferation to stress conditions. The double roles of promoters and synthegradases might have evolutionary implications; a single mutation in either a promoter or a synthegradase can affect both transcription and mRNA degradation, which otherwise would require at least two independent mutations (see also [73]).

8. Concluding remarks

Coupling between transcription and translation is one of the known hallmarks of prokaryotic organisms. This coupling involves physical interaction between the two machineries, which is vital for both proper transcription and translation [74–76]. When the first eukaryotes evolved, this kind of physical interaction was interrupted by the nuclear envelope that separated transcription in the nucleus from the post-transcriptional stages in the cytoplasm. Here we have discussed works showing that the coupling has been preserved, but the mechanism has changed. Conservation of coupling raises the possibility that the cross talk between transcription and mRNA translation and decay is vital for any organism.

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References

[1] R.A. Young, RNA polymerase II, Annu. Rev. Biochem. 60 (1991) 689–715.
[2] K.J. Armache, S. Mitterweger, A. Meinhart, P. Cramer, Structures of complete RNA polymerase II and its subcomplex, Rpb4/7, J. Biol. Chem. 280 (2005) 7131–7134.
[3] P. Cramer, RNA polymerase II structure: from core to functional complexes, Curr. Opin. Genet. Dev. 14 (2004) 218–226.
[4] R.D. Kornberg, The molecular basis of eukaryotic transcription, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 12955–12961.
[5] S.M. Orlicky, P.T. Tran, M.H. Sayre, A.M. Edwards, Dissociable Rpb4–Rpb7 subassembly of RNA polymerase II binds to single-strand nucleic acid and mediates a post-recruitment step in transcription initiation, J. Biol. Chem. 276 (2001) 10097–10102.
[6] M. Choder, Rpb4 and Rpb7: subunits of RNA polymerase II and beyond, Trends Biochem. Sci. 29 (2004) 674–681.
[7] D.A. Bushnell, R.D. Kornberg, Complete, 12-subunit RNA polymerase II at 4.1-A resolution: implications for the initiation of transcription, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 6969–6973.
[8] I.M. Donaldson, J.D. Friesen, Zinc stoichiometry of yeast RNA polymerase II and characterization of mutations in the zinc-binding domain of the largest subunit, J. Biol. Chem. 275 (2000) 13780–13788.
[9] Q. Tan, M.H. Prysak, N.A. Woychik, Loss of the Rpb4/Rpb7 subcomplex in a mutant form of the Rpb6 subunit shared by RNA polymerases I, II, and III, Mol. Cell. Biol. 23 (2003) 3329–3338.
[10] S. Rosenheck, M. Choder, Rpb4, a subunit of RNA polymerase II, enables the enzyme to transcribe at temperature extremes *in vitro*, J. Bacteriol. 180 (1998) 6187–6192.
[11] M. Farago, T. Nahari, C. Hammel, C.N. Cole, M. Choder, Rpb4p, a subunit of RNA polymerase II, mediates mRNA export during stress, Mol. Biol. Cell. 14 (2003) 2744–2755.

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[12] L. Harel-Sharvit, N. Eldad, G. Haimovich, O. Barkai, L. Duek, M. Choder, RNA polymerase II subunits link transcription and mRNA decay to translation, Cell 143 (2010) 552–563.
[13] V. Goler-Baron, M. Selitrennik, O. Barkai, G. Haimovich, R. Lotan, M. Choder, Transcription in the nucleus and mRNA decay in the cytoplasm are coupled processes, Genes Dev. 22 (2008) 2022–2027.
[14] R. Lotan, V.G. Bar-On, L. Harel-Sharvit, L. Duek, D. Melamed, M. Choder, The RNA polymerase II subunit Rpb4p mediates decay of a specific class of mRNAs, Genes Dev. 19 (2005) 3004–3016.
[15] R. Lotan, V. Goler-Baron, L. Duek, G. Haimovich, M. Choder, The Rpb7p subunit of yeast RNA polymerase II plays roles in the two major cytoplasmic mRNA decay mechanisms, J. Cell Biol. 178 (2007) 1133–1143.
[16] J. Andrecka, R. Lewis, F. Bruckner, E. Lehmann, P. Cramer, J. Michaelis, Single-molecule tracking of mRNA exiting from RNA polymerase II, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 135–140.
[17] A.L. Gnatt, P. Cramer, J. Fu, D.A. Bushnell, R.D. Kornberg, Structural basis of transcription: an RNA polymerase II elongation complex at 3.3 A resolution, Science 292 (2001) 1876–1882.
[18] K.D. Westover, D.A. Bushnell, R.D. Kornberg, Structural basis of transcription: separation of RNA from DNA by RNA polymerase II, Science 303 (2004) 1014–1016.
[19] P. Cramer, D.A. Bushnell, J. Fu, A.L. Gnatt, B. Maier-Davis, N.E. Thompson, R.R. Burgess, A.M. Edwards, P.R. David, R.D. Kornberg, Architecture of RNA polymerase II and implications for the transcription mechanism, Science 288 (2000) 640–649.
[20] P. Cramer, D.A. Bushnell, R.D. Kornberg, Structural basis of transcription: RNA polymerase II at 2.8 Angstrom resolution, Science 292 (2001) 1863–1876.
[21] J.L. Craighead, W.H. Chang, F.J. Asturias, Structure of yeast RNA polymerase II in solution: implications for enzyme regulation and interaction with promoter DNA, Structure 10 (2002) 1117–1125.
[22] F. Todone, P. Brick, F. Werner, R.O. Weinzierl, S. Onesti, Structure of an archaeal homolog of the eukaryotic RNA polymerase II RPB4/RPB7 complex, Mol. Cell 8 (2001) 1137–1143.
[23] X. Kang, Y. Hu, Y. Li, X. Guo, X. Jiang, L. Lai, B. Xia, C. Jin, Structural, biochemical, and dynamic characterizations of the hRPB8 subunit of human RNA polymerases, J. Biol. Chem. 281 (2006) 18216–18226.
[24] S. Krapp, G. Kelly, J. Reischl, R.O. Weinzierl, S. Matthews, Eukaryotic RNA polymerase subunit RPB8 is a new relative of the OB family, Nat. Struct. Biol. 5 (1998) 110–114.
[25] A. Ujvari, D.S. Luse, RNA emerging from the active site of RNA polymerase II interacts with the Rpb7 subunit, Nat. Struct. Mol. Biol. 13 (2006) 49–54.
[26] C.Y. Chen, C.C. Chang, C.F. Yen, M.T. Chiu, W.H. Chang, Mapping RNA exit channel on transcribing RNA polymerase II by FRET analysis, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 127–132.
[27] D.L. Bentley, Rules of engagement: co-transcriptional recruitment of pre-mRNA processing factors, Curr. Opin. Cell Biol. 17 (2005) 251–256.
[28] M.J. Moore, N.J. Proudfoot, Pre-mRNA processing reaches back to transcription and ahead to translation, Cell 136 (2009) 688–700.
[29] N.J. Proudfoot, A. Furger, M.J. Dye, Integrating mRNA processing with transcription, Cell 108 (2002) 501–512.
[30] A.M. Edwards, C.M. Kane, R.A. Young, R.D. Kornberg, Two dissociable subunits of yeast RNA polymerase II stimulate the initiation of transcription at a promoter *in vitro*, J. Biol. Chem. 266 (1991) 71–75.
[31] S. Naji, S. Grunberg, M. Thomm, The RPB7 orthologue E' is required for transcriptional activity of a reconstituted archaeal core enzyme at low temperatures and stimulates open complex formation, J. Biol. Chem. 282 (2007) 11047–11057.
[32] M. Ouhammouch, F. Werner, R.O. Weinzierl, E.P. Geiduschek, A fully recombinant system for activator-dependent archaeal transcription, J. Biol. Chem. 279 (2004) 51719–51721.
[33] M. Choder, R.A. Young, A portion of RNA polymerase II molecules has a component essential for stress responses and stress survival, Mol. Cell. Biol. 13 (1993) 6984–6991.
[34] I. Maillet, J.M. Buhler, A. Sentenac, J. Labarre, Rpb4p is necessary for RNA polymerase II activity at high temperature, J. Biol. Chem. 274 (1999) 22586–22590.
[35] T. Miyao, J.D. Barnett, N.A. Woychik, Deletion of the RNA polymerase subunit RPB4 acts as a global, not stress-specific, shut-off switch for RNA polymerase II transcription at high temperatures, J. Biol. Chem. 276 (2001) 46408–46413.
[36] B. Pillai, V. Sampath, N. Sharma, P. Sadhale, Rpb4, a non-essential subunit of core RNA polymerase II of *Saccharomyces cerevisiae* is important for activated transcription of a subset of genes, J. Biol. Chem. 276 (2001) 30641–30647.
[37] A. Sheffer, M. Varon, M. Choder, Rpb7 can interact with RNA polymerase II and support transcription during some stresses independently of Rpb4, Mol. Cell. Biol. 19 (1999) 2672–2680.
[38] A.J. Jasiak, H. Hartmann, E. Karakasili, M. Kalocsay, A. Flatley, E. Kremmer, K. Strasser, D.E. Martin, J. Soding, P. Cramer, Genome-associated RNA polymerase II includes the dissociable Rpb4/7 subcomplex, J. Biol. Chem. 283 (2008) 26423–26427.
[39] J. Verma-Gaur, S.N. Rao, T. Taya, P. Sadhale, Genomewide recruitment analysis of Rpb4, a subunit of polymerase II in *Saccharomyces cerevisiae*, reveals its involvement in transcription elongation, Eukaryot. Cell 7 (2008) 1009–1018.
[40] V.M. Runner, V. Podolny, S. Buratowski, The Rpb4 subunit of RNA polymerase II contributes to cotranscriptional recruitment of 3′ processing factors, Mol. Cell. Biol. 28 (2008) 1883–1891.
[41] A. Hirtreiter, D. Grohmann, F. Werner, Molecular mechanisms of RNA polymerase —the F/E (RPB4/7) complex is required for high processivity *in vitro*, Nucleic Acids Res. 38 (2010) 585–596.
[42] N.L. Garneau, J. Wilusz, C.J. Wilusz, The highways and byways of mRNA decay. Nature reviews, Mol. Cell Biol. 8 (2007) 113–126.
[43] R. Parker, U. Sheth, P bodies and the control of mRNA translation and degradation, Mol. Cell 25 (2007) 635–646.
[44] M. Selitrennik, L. Duek, R. Lotan, M. Choder, Nucleocytoplasmic shuttling of the Rpb4p and Rpb7p subunits of *Saccharomyces cerevisiae* RNA polymerase II by two pathways, Eukaryot. Cell 5 (2006) 2092–2103.
[45] M. Choder, mRNA imprinting: additional level in the regulation of gene expression, Cell. Logist. 1 (2011) 37–40.
[46] Z. Shen, N. Paquin, A. Forget, P. Chartrand, Nuclear shuttling of She2p couples ASH1 mRNA localization to its translational repression by recruiting Loc1p and Puf6p, Mol. Biol. Cell. 20 (2009) 2265–2275.
[47] Z. Shen, A. St-Denis, P. Chartrand, Cotranscriptional recruitment of She2p by RNA pol II elongation factor Spt4-Spt5/DSIF promotes mRNA localization to the yeast bud, Genes Dev. 24 (2010) 1914–1926.
[48] T. Trcek, D.R. Larson, A. Moldon, C.C. Query, R.H. Singer, Single-molecule mRNA decay measurements reveal promoter-regulated mRNA stability in yeast, Cell 147 (2011) 1484–1497.
[49] O. Hachet, A. Ephrussi, Splicing of oskar RNA in the nucleus is coupled to its cytoplasmic localization, Nature 428 (2004) 959–963.
[50] C. Kurischko, V.K. Kuravi, C.J. Herbert, F.C. Luca, Nucleocytoplasmic shuttling of Ssd1 defines the destiny of its bound mRNAs, Mol. Microbiol. 81 (2011) 831–849.
[51] Y. Oleynikov, R.H. Singer, Real-time visualization of ZBP1 association with beta-actin mRNA during transcription and localization, Curr. Biol. 13 (2003) 199–207.
[52] J.K. Yisraeli, VICKZ proteins: a multi-talented family of regulatory RNA-binding proteins, Biol. Cell 97 (2005) 87–96.
[53] A. Kohler, E. Hurt, Exporting RNA from the nucleus to the cytoplasm. Nature reviews, Mol. Cell Biol. 8 (2007) 761–773.
[54] C.L. Lin, V. Evans, S. Shen, Y. Xing, J.D. Richter, The nuclear experience of CPEB: implications for RNA processing and translational control, RNA 16 (2010) 338–348.
[55] M. Windgassen, D. Sturm, I.J. Cajigas, C.I. Gonzalez, M. Seedorf, H. Bastians, H. Krebber, Yeast shuttling SR proteins Npl3p, Gbp2p, and Hrb1p are part of the translating mRNPs, and Npl3p can function as a translational repressor, Mol. Cell. Biol. 24 (2004) 10479–10491.
[56] S.G. Sobel, S.L. Wolin, Two yeast La motif-containing proteins are RNA-binding proteins that associate with polyribosomes, Mol. Biol. Cell. 10 (1999) 3849–3862.
[57] S.V. Vergara, S. Puig, D.J. Thiele, Early recruitment of AU-rich element-containing mRNAs determines their cytosolic fate during iron deficiency, Mol. Cell. Biol. 31 (2011) 417–429.
[58] B. Cuenca-Bono, V. Garcia-Molinero, P. Pascual-Garcia, E. Garcia-Oliver, A. Llopis, S. Rodriguez-Navarro, A novel link between Sus1 and the cytoplasmic mRNA decay machinery suggests a broad role in mRNA metabolism, BMC Cell Biol. 11 (2010) 19.
[59] S. Rother, K. Strasser, The RNA polymerase II CTD kinase Ctk1 functions in translation elongation, Genes Dev. 21 (2007) 1409–1421.
[60] M. Sun, B. Schwalb, D. Schulz, N. Pirkl, S. Etzold, L. Lariviere, K.C. Maier, M. Seizl, A. Tresch, P. Cramer, Comparative dynamic transcriptome analysis (cDTA) reveals mutual feedback between mRNA synthesis and degradation, Genome Res. 22 (2012) 1350–1359.
[61] J. Enssle, W. Kugler, M.W. Hentze, A.E. Kulozik, Determination of mRNA fate by different RNA polymerase II promoters, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 10091–10095.
[62] A. Bregman, M. Avraham-Kelbert, O. Barkai, L. Duek, A. Guterman, M. Choder, Promoter elements regulate cytoplasmic mRNA decay, Cell 147 (2011) 1473–1483.
[63] M.A. Collart, O.O. Panasenko, The Ccr4—not complex, Gene 492 (2012) 42–53.
[64] R. Elkon, E. Zlotorynski, K.I. Zeller, R. Agami, Major role for mRNA stability in shaping the kinetics of gene induction, BMC Genomics 11 (2010) 259.
[65] J. Garcia-Martinez, A. Aranda, J.E. Perez-Ortin, Genomic run-on evaluates transcription rates for all yeast genes and identifies gene regulatory mechanisms, Mol. Cell 15 (2004) 303–313.
[66] C. Molin, A. Jauhiainen, J. Warringer, O. Nerman, P. Sunnerhagen, mRNA stability changes precede changes in steady-state mRNA amounts during hyperosmotic stress, RNA 15 (2009) 600–614.
[67] J.E. Perez-Ortin, P.M. Alepuz, J. Moreno, Genomics and gene transcription kinetics in yeast, Trends Genet. 23 (2007) 250–257.
[68] M. Rabani, J.Z. Levin, L. Fan, X. Adiconis, R. Raychowdhury, M. Garber, A. Gnirke, C. Nusbaum, N. Hacohen, N. Friedman, I. Amit, A. Regev, Metabolic labeling of RNA uncovers principles of RNA production and degradation dynamics in mammalian cells, Nat. Biotechnol. 29 (2011) 436–442.
[69] O. Shalem, O. Dahan, M. Levo, M.R. Martinez, I. Furman, E. Segal, Y. Pilpel, Transient transcriptional responses to stress are generated by opposing effects of mRNA production and degradation, Mol. Syst. Biol. 4 (2008) 223.
[70] O. Shalem, B. Groisman, M. Choder, O. Dahan, Y. Pilpel, Transcriptome kinetics is governed by a genome-wide coupling of mRNA production and degradation: a role for RNA Pol II, PLoS Genet. 7 (2011) e1002273.
[71] P. Preker, T.H. Jensen, Translation by remote control, Cell 143 (2010) 501–502.
[72] M. Dori-Bachash, E. Shema, I. Tirosh, Coupled evolution of transcription and mRNA degradation, PLoS Biol. 9 (2011) e1001106.
[73] O. Dahan, H. Gingold, Y. Pilpel, Regulatory mechanisms and networks couple the different phases of gene expression, Trends Genet. 27 (2011) 316–322.
[74] B.M. Burmann, K. Schweimer, X. Luo, M.C. Wahl, B.L. Stitt, M.E. Gottesman, P. Rosch, A NusE:NusG complex links transcription and translation, Science 328 (2010) 501–504.
[75] S. Proshkin, A.R. Rahmouni, A. Mironov, E. Nudler, Cooperation between translating ribosomes and RNA polymerase in transcription elongation, Science 328 (2010) 504–508.
[76] C. Yanofsky, Attenuation in the control of expression of bacterial operons, Nature 289 (1981) 751–758.
[77] N. Eldad, Y. Yosefzon, Y. Arava, Identification and characterization of extensive intra-molecular associations between 3′-UTRs and their ORFs, Nucleic Acids Res. 36 (2008) 6728–6738.

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