Cell

Translation by Remote Control

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DOI 10.1016/j.cell.2010.10.039

Efficient and accurate gene expression requires the coordination of multiple steps along the pathway of mRNA and protein synthesis. Now, Harel-Sharvit et al. (2010) show that transcriptional imprinting of mRNAs with two subunits of RNA polymerase II, Rbp4p and Rpb7p, guides transcripts to the translation apparatus.

A defining feature of eukaryotic cells is compartmentalization. Whereas transcription of DNA into mRNA takes place in the nucleus, translation of the mRNA is physically separate and occurs in the cytoplasm, where ultimately the transcript is also degraded. In prokaryotes, transcription and translation are coupled in the protoplasm so that the translation machinery can directly engage the nascent mRNA. In this issue of *Cell*, Harel-Sharvit et al. (2010) provide surprising evidence that transcription and translation can also be coupled in eukaryotes—at least in the unicellular yeast *Saccharomyces cerevisiae*. The authors refer to this process as the ‘‘remote controlling’’ of translation by the transcription apparatus. Key to this coupling is a heterodimer composed of the Rpb4p and Rpb7p proteins (for review see, Choder, 2004; Sampath and Sadhale, 2005), a fraction of which forms a stalk-like and highly conserved protrusion of the decameric core of RNA polymerase II (RNAPII), the enzyme responsible for the production of mRNAs and many noncoding RNAs (Figure 1, inset). This places the two proteins at a strategic position near the exit channel of the nascent RNA (Brueckner et al., 2009), and the heterodimer has been found to associate both in vivo and in vitro with mRNA in a transcription-dependent manner (Goler-Baron et al., 2008; Ujvári and Luse, 2006).

Rpb4/7p is only loosely associated with the RNAPII core, and the degree of its association varies with physiological conditions in yeast (Choder, 2004; Sampath and Sadhale, 2005). In addition, the two proteins are in vast excess over other RNAPII subunits and continuously shuttle between the nucleus and the cytoplasm (Figure 1). Indeed, prior work has revealed a cytoplasmic function for Rpb4/7p in mRNA decay (for example, Goler-Baron et al., 2008). Presumably, the proteins influence the reversible transition of mRNA between the active translation machinery in the form of polysomes and the so-called processing (P) bodies, which are believed to be storage sites for RNAs and their degradation factors. The present study now demonstrates that Rpb4/7p also functions in translation, thus making it a ‘‘coordinator’’ of all major stages of gene expression.

Using a variety of methods, Harel-Sharvit et al. first show that Rpb4/7p interacts, independent of RNA, with two subunits (Nip1p and Hcr1p) of the hexameric translation initiation factor eIF3, which serves as a platform for the assembly of the translation-initiation complex (Sonenberg and Hinnebusch, 2009). Importantly, eIF3 does not interact with other RNAPII subunits, implying that it contacts the soluble pool of Rpb4/7p. Prompted by these observations, the authors go on to show that Rpb4/7p is required for efficient translation initiation by analyzing a deletion mutant of the nonessential *RPB4* gene (*rpb4Δ*) and a conditional mutant allele of the essential *RPB7* gene (*rpb7-26*). Importantly, the latter mutation does not markedly affect transcription or mRNA degradation rates (Goler-Baron et al., 2008), thus minimizing the possibility of indirect effects.

They find that the *RPB4* and *RPB7* mutant strains are hypersensitive to translation inhibitors and observe genetic interactions with regulators of translation. In addition, the two mutants exhibit reduced protein synthesis accompanied by a reduction in polysome content, as well as loss of *MFA2* and *HYP2* mRNA from polysomes. They also elicit decreased disassembly of P bodies and slower movement of *MFA2* mRNA from P bodies into polysomes. This last finding is important because mRNAs can also leave P bodies and (re)associate with polysomes (Figure 1; Parker and Sheth, 2007). Thus, in addition to directly docking mRNAs to the translation apparatus through eIF3, Rpb4/7p might facilitate translation initiation indirectly by stimulating P body disassembly and/or the release of mRNA from P bodies, thereby increasing the pool of translatable mRNA.

Perhaps the most significant result of this work is the finding that mutations in two RNAPII subunits (Rpb1p and Rpb6p) at the interface with Rpb7p, which have been previously shown to compromise the recruitment of the Rpb4/7p subcomplex to the catalytic core, phenocopy the defects displayed by the *RPB4* and *RPB7* mutant strains. Similar results are obtained using a mutation of Rpb4p that fails to enter the nucleus. Taken together, these findings suggest a model whereby nucleocytoplasmic shuttling and recruitment of Rpb4/7p to the nascent transcript by the core RNAPII is required for Rpb4/7p's cytoplasmic functions (Figure 1).

The physical separation of transcription and translation has allowed the spread of intervening sequences (introns) in the eukaryotic lineage, which in turn is thought to have fueled genomic evolution by aiding in the creation of new protein domains (Schmidt and Davies, 2007). It now appears that eukaryotes, despite this segregation of the two main activities of the central dogma in molecular biology, have maintained a mechanism that allows transcription and translation to

communicate through direct physical interactions. Apart from simply making translation more streamlined and efficient, what could be the functional implication(s) of such a coupling? Earlier findings suggested that, in yeast only, ~20% of RNAPII molecules contain Rpb4/7p under optimal growth conditions, whereas, during stationary phase, all subunits are stoichiometric (Choder, 2004). Even though genome-wide analysis of Rpb7p occupancy has contradicted these results (Jasiak et al., 2008), it would appear that any difference in the stoichiometry of Rpb4/7p could have bearing on the translational efficiency of certain mRNAs under different environmental conditions. This effect could be further fine-tuned by the impact of Rpb4/7p on degradation (Figure 1; Goler-Baron et al., 2008). The identification of the subsets of genes associated with Rpb4/7p under various conditions and an understanding of the mechanistic details that regulate the RNAPII-Rpb4/7p interaction would be required to foster this attractive hypothesis. Transcription-coupled imprinting of mRNAs with the Rpb4/7p subcomplex of RNAPII in the nucleus could potentially also serve as a form of quality control, possibly by ensuring that only mRNAs that have been properly terminated and loaded with Rpb4/7p are translated.

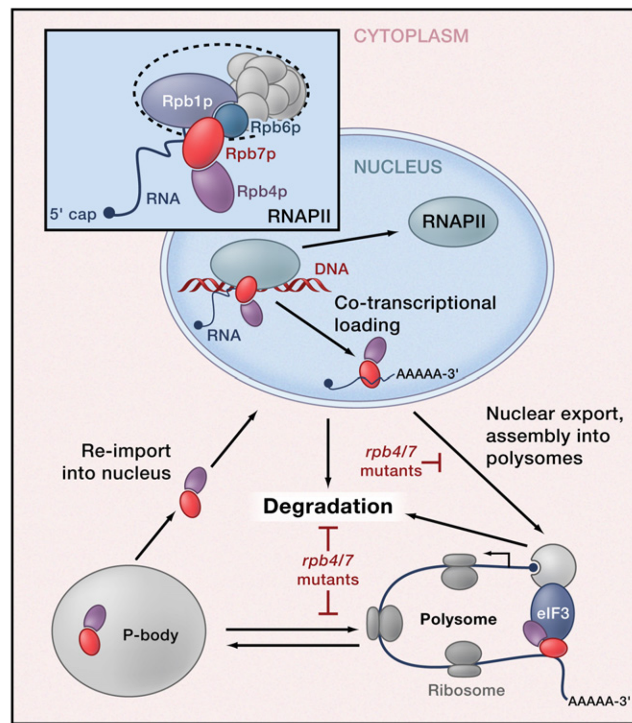

Figure 1. Rpb4/Rpb7p in Transcription, Translation, and Degradation

The inset (bottom left) represents the relevant interactions of RNA polymerase II (RNAPII) subunits: Rpb7p forms a heterodimer with Rpb4p and interacts with the catalytic core through Rpb1p and Rpb6p. The remaining eight subunits (gray) are placed arbitrarily. In the nucleus, Rpb4/7p is loaded cotranscriptionally onto the nascent RNA. The mature mRNA carrying a 5′ cap and a 3′ poly(A) tail is exported into the cytoplasm in complex with Rpb4/7p, which targets the mRNA to the general translation initiation factor eIF3. The latter provides a scaffold for the assembly of other initiation factors, which together recruit ribosomes. Translation initiation is further facilitated by interaction between the initiation complex and the poly(A) tail (not shown). Rpb4/7p and mRNA can also associate with processing (P) bodies or can return to polysomes. Mutations in the *RPB4* and *RPB7* genes both adversely affect the assembly of mRNA into polysomes and its transition between P bodies and polysomes. In addition, the mRNA can also be destined for degradation at various stages. Re-import into the nucleus completes the "shuttling" of Rpb4/7p.

Paralogs of Rpb4/7p can also be found in the RNA polymerases I and III, raising the possibility that they might utilize analogous mechanisms to control RNA metabolism.

Finally, the extent to which coupling of transcription and translation by Rpb4/7p is conserved in higher eukaryotes remains to be seen. The high degree of conservation of the heterodimer and its interaction partners make it plausible that whatever the precise mechanism, it may have coevolved—all the way to humans.

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