Transcription and mRNA Stability: Parental Guidance Suggested

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The level of an mRNA within a cell depends on both its rate of synthesis and rate of decay. Now, independent studies by Bregman et al. and Trcek et al. provide evidence that these two processes are integrated. They show that transcription factors and DNA promoters can directly influence the relative stability of transcripts that they produce.

Transcription is closely networked with mRNA processing events in the nucleus. However, popular models for the regulation of mRNA stability focus largely on connections with translation in the cytoplasm and with the assembly of RNA-binding proteins posttranscriptionally. Wouldn't the cell benefit if these two major determinants of mRNA levels—that is, transcription and RNA stability—could directly communicate with each other? In fact, tantalizing links between transcription and mRNA decay rates have been reported previously (Enssle et al., 1993; Lotan et al., 2005, 2007; Harel-Sharvit et al., 2010).

Now in this issue of *Cell*, studies by the Choder and Singer labs provide a bevy of observations clearly showing that promoters can contribute to the regulation of mRNA stability in yeast. Bregman et al. (2011) demonstrate that the transcription factor Rap1p influences the stability of its transcripts through its interaction with the upstream activating sequence (UAS) of the *RPL30* gene. Independently, Trcek et al. (2011) use powerful single-molecule techniques to show that the promoters of SWI5 and CLB2 influence their transcripts' stability in a cell cycle-dependent fashion. This might involve the polo kinase Cbc5p and phosphorylation of the transcription factor complex Mcm1p-Fkh2p-Ndd1p, which are both known to control the promoter of the cell cycle-regulated CLB2 gene cluster (Darieva et al., 2006).

The coordination of transcription and mRNA decay is an attractive idea in many ways. First, communication between synthesis and decay rates of a transcript would enhance efficiency in the usage of enzymes and substrates involved in the regulation of gene expression in the cell. Second, coordination of the two processes would enable more precise regulation of the kinetics of RNA accumulation in response to a variety of cellular signals. This point is nicely highlighted by the sharp transition of gene expression that Trcek et al. observe for SWI5 and CLB2 mRNAs at mitosis. Such precision results directly from the coordinate shutdown of transcription and increase in mRNA decay. Finally, this coordination has major mechanistic implications for posttranscriptional regulon models of gene expression, which now need addressing. Interestingly, recent analysis of two closely related species of *Saccharomyces* suggests a connection between transcriptional regulation and mRNA decay rates, which may have contributed to the evolution of gene regulation (Dori-Bachash et al., 2011).

How do transcription factors that influence mRNA decay rates leave their imprint on the transcript? Trcek et al. provide strong data suggesting that members of the highly conserved nuclear Dbf2-related (NDR) protein-kinase family (Hergovich et al., 2006) —specifically, Dbf2 and Dbf20—play a role in the cell-cycle imprint on SWI5 and CLB2 mRNAs. Interestingly, this imprinting role is independent of these proteins' kinase function.

Building on this important clue, a number of possible mechanisms need to be considered. First, the mark may be loaded onto the mRNA near its 5′ end early in transcription (Figure 1A). This mark could be a protein, such as Dbf2, or an RNA modification, such as methylation near the 5′ cap. In addition, the 5′ untranslated region (UTR) of the mRNA should also be considered. For example, the mRNA for Rpl30 and many other ribosomal proteins contain pyrimidine tracts at their 5′UTR. Could these tracts contribute to the regulation of mRNA decay by the Rap1p transcription factor?

Second, the mark could be loaded onto the transcription machinery itself, perhaps involving the C-terminal domain of the Rpb1 subunit of RNA polymerase II. The mark could then be deposited anywhere along the mRNA in coordination with splicing or polyadenylation events that are networked with transcription (Figure 1B). Enssle et al. (1993) previously observed that promoters influence rates of nonsense-mediated decay rates, which lends support for such a model.

Finally, transcription may regulate mRNA decay rates by influencing the length of the poly(A) tail or other properties of the mRNA's 3′ end (Figure 1C). This model is quite attractive because shortening of the poly(A) tail initiates major pathways of mRNA decay, and promoters have been shown to influence 3′ end processing of several types of RNA transcripts (Nagaike et al., 2011). However, Bregman et al. find no difference in gross length of the poly(A) tail for transcripts derived from the promoters that they tested. In addition to identifying the imprint mechanism, it will also be exciting to

discover the range of transcription factors that can dictate mRNA decay, whether posttranslational modifications of transcription factors might influence the process, and whether the context of chromatin and DNA plays a role in determining the efficiency or type of imprint.

The next key question is how the RNA decay machinery decodes the transcriptional imprint. Most mRNAs are degraded by first shortening their poly(A) tails (e.g., deadenylation), followed by one of two exonucleolytic pathways: (1) decapping the 5′ end and 5′-to-3′ decay using the enzyme Xrn1p or (2) 3′-to-5′ decay by the exosome. Two observations suggest that the major deadenylation-dependent exonuclease pathways are likely involved. By trapping decay intermediates, Bregman and colleagues present data suggesting that promoter-regulated decay involves, at least in part, the major 5′-3′ decay pathway. In addition, an independently performed yeast interactome analysis revealed an association between Dbf2 and the CCR4-NOT deadenylation complex. However, it is still unknown whether the imprint is directly altering deadenylation or decapping or whether it is recruiting an endonuclease that initiates promoter-regulated decay. Alternatively, the promoter imprint may have a more general effect on the assembly of the ribonucleoprotein complex (mRNP) on the transcript, rather than directly recruiting the RNA decay machinery. Finally, the imprint could affect RNA localization and/or translational competence, which contribute to mRNA half-life. Clearly, insight into how the promoter imprint functions could have major implications for our understanding of the networking of steps that govern communication in the process of gene expression.

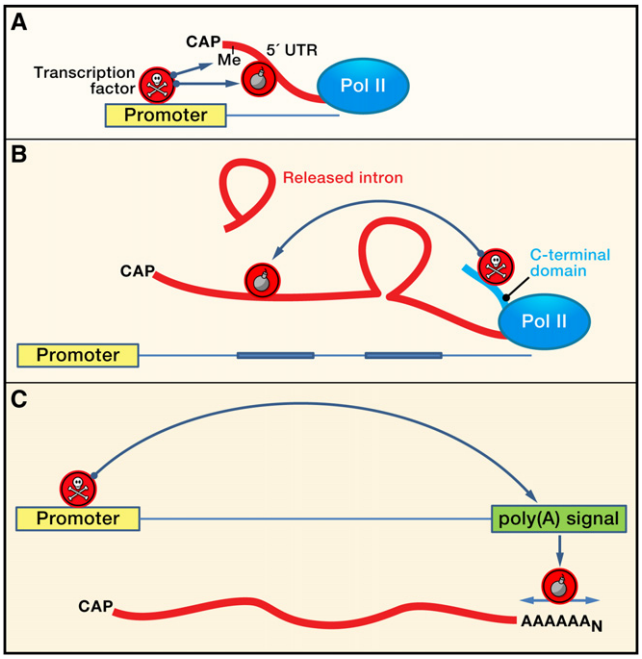

Figure 1. Possible Mechanisms for How a Promoter Can Imprint an mRNA and Influence Its Stability

(A) Early in transcription, the nascent transcript emerges from RNA polymerase II and is capped at its 5′ end. During this time, a nearby transcription factor could direct the methylation of 5′ nucleotides or the deposition of a protein on the 5′UTR, which would mark the transcript for decay.

(B) The promoter could cause a factor to associate with the carboxy-terminal domain (CTD) of the large subunit of RNA polymerase II. This factor would deposit an imprint that regulates mRNA stability on the growing transcript, perhaps in coordination with a cotranscriptional RNA-processing event.

(C) The promoter could also influence the process of polyadenylation. This process regulates the length of the poly(A) tail, and alterations can influence the composition of the ribonucleoprotein (mRNP) complexes at the 3′ end of the RNA. Both of these factors influence the stability of the transcript at a downstream step.

Finally, these studies raise two technical but important insights that should be taken into consideration when determining the half-lives of mRNA. First, the experimental approach of assessing biologically relevant mRNA half-lives by using "standard" promoters will likely need to be revisited and validated with cognate promoters in an endogenous context. Second, Trcek and colleagues clearly demonstrate that mRNA half-lives may differ throughout the cell cycle. Thus, mRNA half-lives determined from unsynchronized cell populations will need to be interpreted with this important caveat.

Although these two papers focus on mRNA stability regulation in yeast, it is likely that similar promoter-mediated regulation of mRNA stability may occur in a variety of eukaryotic species. In particular, it will interesting to determine whether this mechanism is present in trypanosomes and *C. elegans*, which relegate the synthesis of mRNA to relatively few promoters that drive long arrays of protein coding sequences. Finally, bacterial mRNA decay, at least in principle, parallels many of the pathways observed in eukaryotic cells; thus, it will be interesting to see how far back this phenomenon reaches on the evolutionary tree. Clearly, the time is upon us to revisit the question of "nature versus nurture" in the life span of an mRNA.

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