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Review

The fate of the messenger is pre-determined: A new model for regulation of gene expression ☆

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ABSTRACT

Recent years have seen a rise in publications demonstrating coupling between transcription and mRNA decay. This coupling most often accompanies cellular processes that involve transitions in gene expression patterns, for example during mitotic division and cellular differentiation and in response to cellular stress. Transcription can affect the mRNA fate by multiple mechanisms. The most novel finding is the process of co-transcriptional imprinting of mRNAs with proteins, which in turn regulate cytoplasmic mRNA stability. Transcription therefore is not only a catalyst of mRNA synthesis but also provides a platform that enables imprinting, which coordinates between transcription and mRNA decay. Here we present an overview of the literature, which provides the evidence of coupling between transcription and decay, review the mechanisms and regulators by which the two processes are coupled, discuss why such coupling is beneficial and present a new model for regulation of gene expression. This article is part of a Special Issue entitled: RNA Decay mechanisms.

1. Introduction

In many ways, transcription can be regarded as the most important part in the mRNA life cycle. It is not only responsible for the synthesis of a transcript itself, but via 5′ capping, splicing and 3′ end formation it also converts a pre-mRNA into an export, translation and decay competent mRNA. These three processes occur co-transcriptionally while a pre-mRNA is still associated with a transcribing RNA polymerase II (RNAPII). As transcription proceeds, an RNAPII recruits pre-mRNA processing regulators thus temporally dictating the conversion of each pre-mRNA into mature mRNA (reviewed in [1]). Transcription also controls the length of 5′ and 3′ untranslated regions (UTRs) through alternative transcription start site (TSS) choice [2] and alternative polyadenylation (APA) [3]. Since longer UTRs normally contain more *cis* regulatory sequences, which can be targeted by RNA-binding proteins (RBPs) or microRNAs (miRNAs), alternative TSS and polyadenylation thus affect mRNA stability and/or translatability. RNAPII and associated transcription factors can also recruit various post-transcriptional regulators that are co-transcriptionally deposited or imprinted onto a nascent mRNA (reviewed in [4,5], Table 1). By modulating this recruitment process a cell could vary the way a single mRNA species is regulated in the cytoplasm. Such RNAPII-dependent post-transcriptional mRNA regulation could play an important role during growth, differentiation, development and in response to environmental signals.

An essential and well-controlled component of the gene expression system is the cytoplasmic mRNA decay pathway, considered to represent the end-point of the mRNA life. Following shortening of the mRNA poly(A) tail by deadenylases, the eukaryotic mRNA can then be degraded via two pathways: from 3′ to 5′ by the cytoplasmic exosome or from 5′ to 3′ by the Xrn1p exonuclease. The latter pathway involves prior removal of the 5′-cap by the decapping complex. In yeast, it is composed of two proteins: Dcp2p, the decapping enzyme and Dcp1p, a regulatory subunit. In *Drosophila* and mammals a third protein, Ge-1/Hedls, is also a part of this complex. In mammalian cells there are multiple decapping enzymes, compared to a single enzyme in yeast. The decapping process is assisted and regulated by a multitude of proteins including Pat1p, Dhh1p, Edc3p and the Lsm1-7 heptamer (see reviews in this issue).

Commitment of an organism to a new physiological state involves transitions from one gene expression pattern to another. These transitions entail altered transcriptional profiles, which are often

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accompanied by changes in mRNA stability thus allowing an organism to quickly respond to cellular and environmental changes. For example, in budding yeast quiescence causes stabilization of newly transcribed G0 mRNAs [6] while cell cycle-dependent changes in transcriptional activity can be coupled with changes in mRNA stability [7–9]. Similarly, fission yeast control meiotic gene expression via global coordination between transcriptional control and mRNA decay [10]. Furthermore, environmental stimuli, such as temperature and osmotic shock, oxidative stress, amino acid starvation and nitrogen source depletion all cause changes in transcriptional program often accompanied by changes in mRNA stability [11–19]. These gene expression transitions involve groups of transcripts (RNA regulons), which can be post-transcriptionally regulated by one or more RBPs. Such co-regulation in turn facilitates synchronous cellular response to a particular stimulus [20]. For example, the Rpb4/7p heterodimer, an RNAPII subunit and a regulator of cytoplasmic mRNA stability, co-transcriptionally binds its target mRNAs [21,22]. These transcripts (and genes) thus comprise an Rpb4/7p-regulon. Coupling between transcription and decay via Rpb4/7p complex ensures two consequences: Rpb4/7p controls the cellular mRNA abundance by reducing the rate of decay thus preventing unnecessary mRNA synthesis (see Sections 2.1.1, 3.2), while precise titration of transcript levels involved in protein synthesis regulates cellular growth rate by globally fine-tuning the rate of translation in response to the environment and nutrient availability.

Coupling is also an evolutionary conserved phenomenon and is a strategy adopted by a variety of budding and fission yeast genes [23]. Mechanistically, the coupling is achieved via specific *cis* sequences or *trans* regulators and mutations in either of the two affect transcription and decay concurrently. Dori-Bachash et al. demonstrated that for most genes identified, the coupling occurs via Rpb4/7p and CCR4-NOT, two complexes involved in the regulation of both mRNA synthesis and mRNA decay, although several other regulators have also been identified (see Section 2.1). Interestingly, coupling can also involve specific promoters as well as transcription factors [23], raising a possibility that a promoter and a transcription factor recruit decay regulators, which are then imprinted onto an mRNA thus directly coupling transcription with decay. In support of this possibility are three publications that demonstrate promoter-regulated mRNA turnover in mammalian cells and in yeast [9,24,25]. Coupling transcription and decay via a promoter is a unique regulatory mechanism because the specificity of mRNA turnover is encoded entirely in the promoter sequence itself. mRNAs that share their promoter elements will therefore share not only their transcription patterns but also their decay patterns without the need for common, yet specific sequence motives. These groups of mRNAs constitute promoter-specified mRNA regulons.

Transcription and decay are not only mechanistically coupled through shared *cis* and *trans* regulatory sequences or factors, but can influence each other kinetically. In budding yeast and in higher eukaryotes, attenuated rate of transcription decreases the rate of mRNA turnover while an increase in the rate of transcription also increases the rate of mRNA decay. Such mutual feedback maintains the steady-state mRNA levels and either globally affects the cellular mRNA abundance [26,27] or acts in a gene-specific manner (see Section 3.3) [8]. These findings also imply that a single mRNA can exhibit several stabilities in its lifetime simply by responding to changes in transcription rates, presumably independently of specific *cis* mRNA sequences or *trans* regulators.

This review highlights the recent findings of coupling between transcription and decay. In many cases, it is this communication and mutual dependence between the two processes that finally shapes a gene expression response. Here, we propose a new model for gene expression regulation: coupling between transcription and decay lies at the core of eukaryotic gene expression regulation, a mechanism likely employed by the majority of genes and in a variety of organisms.

2. Mechanisms for coupling transcription and decay

The mechanism by which transcription affects mRNA decay in the cytoplasm is currently under intense investigation (summarized in Table 1, Fig. 1). Already, several findings suggest one possible mechanism, which involves direct imprinting of the mRNA with *trans* activating factors. These factors are recruited onto the mRNA during transcription, and affect post-transcriptional events, including decay. *cis*-Acting elements appear to be required for some imprinting mechanisms. In other cases, *cis*-acting elements directly regulate the stability of the mRNA, either by attracting cytoplasmic RNA binding factors that regulate decay, or by interacting with the decay factors themselves.

2.1. trans-Acting proteins: mRNA coordinators and mRNA imprinting

2.1.1. Rpb4/7p — the mRNA coordinator prototype

The best characterized imprinting process, and most direct evidence for coupling transcription and decay, is that of the yeast RNAPII subunits Rpb4p and Rpb7p. Rpb4p and Rpb7p were first identified as the fourth (Rpb4) and seventh (Rpb7) largest subunits of RNAPII and normally associate with the core polymerase as a heterodimer. Nevertheless, Rpb7p is an essential protein, whereas Rpb4p is dispensable under optimal environmental conditions but essential under some adverse conditions (reviewed in [4]). An early observation that singled Rpb4/7p out as unusual among RNAPII subunits was its sub-stoichiometric association with the RNAPII complex [28] (though free Rpb4p is found in excess of RNPII in yeast cells [29]) and its propensity to dissociate from the core polymerase [30].

The ability of Rpb4/7p to dissociate from RNAPII in a reversible manner has been exploited to demonstrate that this complex is required for promoter-directed initiation of transcription in vitro [30,31]. It is further required for recruitment of 3′-end processing factors and proper usage of polyadenylation sites [32] (see also Section 2.2.3). Recently, a mechanism for Rpb4/7p-induced dissociation was suggested, in which ubiquitylation of Rpb1p, phosphorylated at serine 5 on the C-terminal domain, excludes Rpb4/7p from RNAPII [33]. However, since this event occurs during early elongation, and renders RNAPII inactive (at least in vitro), this is likely a quality control mechanism, unrelated to the imprinting mechanism.

Two studies have provided evidence that during elongation, the extended RNA that exits the polymerase encounters Rpb7p and forms contacts with it [34,35]. It is probably through this strategy that Rpb4/7p becomes imprinted onto the mRNA. Although it is yet unknown exactly when during transcription Rpb4/7p leaves RNAPII and binds to the mRNA, evidence demonstrates that association of Rpb4/7p with the mRNA depends on the association with the core polymerase, presumably during transcription [21].

Finally, post-transcriptional roles for Rpb4/7p in regulating mRNA export, translation and mRNA decay have been described and depend on prior association of the complex with RNAPII [21,22,36–38]. Rpb4/7p shuttles between the nucleus and the cytoplasm, in a transcription dependent manner [39] and the nuclear localization signal required for import of Rpb4p to the nucleus was identified to be important for post-transcriptional regulatory functions of Rpb4/7p [37]. Importantly, Rpb4/7p must associate with RNAPII in order for it to exert its post-transcriptional roles [21,37]. Rpb4/7p was therefore proposed to function as an “mRNA coordinator”, since it seems to coordinate all four major stages of gene expression (see Ref. [37] for further discussion).

It is unknown how exactly Rpb4/7p regulates mRNA decay. However, some findings suggest possible mechanisms. Rpb4/7p can interact directly with the mRNA decay sub-complex of Pat1–Lsm1–7 [22,38]. It is therefore possible that Rpb4/7p recruits Pat1p to the mRNA. Pat1p seems to be a hub for the decay complex, since it interacts with multiple decay factors and it is required for recruiting

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