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Review / Revue

Translational regulation during oogenesis and early development: The cap-poly(A) tail relationship

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Abstract

Metazoans rely on the regulated translation of select maternal mRNAs to control oocyte maturation and the initial stages of embryogenesis. These transcripts usually remain silent until their translation is temporally and spatially required during early development. Different translational regulatory mechanisms, varying from cytoplasmic polyadenylation to localization of maternal mRNAs, have evolved to assure coordinated initiation of development. A common feature of these mechanisms is that they share a few key trans-acting factors. Increasing evidence suggest that ubiquitous conserved mRNA-binding factors, including the eukaryotic translation initiation factor 4E (eIF4E) and the cytoplasmic polyadenylation element binding protein (CPEB), interact with cell-specific molecules to accomplish the correct level of translational activity necessary for normal development. Here we review how capping and polyadenylation of mRNAs modulate interaction with multiple regulatory factors, thus controlling translation during oogenesis and early development. ***To cite this article: F. Piccioni et al., C. R. Biologies 328 (2005).***

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1. Introduction

Translational control is critical for the proper regulation of cell cycle, tissue induction and growth, normal embryogenesis, and germ-line development [1–5]. Translational regulation of an eukaryotic mRNA is achieved through the orchestrated action of *cis*-acting elements and *trans*-acting factors. Cap-dependent translation in eukaryotes requires the ordered assembly of a complex of evolutionarily conserved proteins, which starts with the binding of the translation initiation factor 4E (eIF4E) to the 7-methyl-guanosine

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(m^7GpppN) cap structure at the 5′ of the mRNA. Next, the eIF4G factor is recruited allowing additional factors (PABP, eIF4A, eIF4B, eIF1, eIF1A, eIF2, eIF3, among others, and the ribosomal subunits) [6] to form a complex that, after mRNA circularization, initiates translation [7–10]. The circularization might become possible once an adequate poly(A) tail is present at the 3′-UTR [11].

eIF4E is the rate-limiting component for cap-dependent translation initiation and therefore represents a major target for translational control [12,13]. eIF4E function can be regulated at different levels by a variety of molecular processes. First, eIF4E transcription inside a cell can be increased by growth factor stimuli [14,15]; second, the availability of eIF4E can be modulated by the binding to a set of proteins that compete with eIF4G, a scaffold protein that aggregates the mRNA and the ribosome [16], for eIF4E-binding, therefore inhibiting translation initiation [17]; third, elevated eIF4E activity depends upon its phosphorylation in response to extracellular stimuli, including hormones, growth factors, and mitogens, and correlates to an increase in translation rate [16,18]. The function of phosphorylated eIF4E was indeed shown to be necessary for proper growth and development of *Drosophila* [19].

During oogenesis in many species, cytoplasmic polyadenylation of a set of maternal mRNAs regulates their translation. A general scheme implies that elongation of a short poly(A) tail at the 3′-UTR during development is able to stimulate translation. The cytoplasmic polyadenylation element binding protein (CPEB) is a sequence-specific RNA interacting factor that is necessary to achieve adequate poly(A) addition within the cytoplasm. The rationale for the existence of a long poly(A) tail is, probably, to allow an mRNA to acquire a circular structure prior to translation initiation. Increasing evidence indeed suggest that the structure of an mRNA is essential for proper activity, including translation efficiency.

The past few years have witnessed considerable advancements in the field of translational control during development. In particular, recent studies have revealed the existence of various translational regulatory mechanisms and identified in the cap-poly(A) tail interaction the primary target for multiple regulatory factors. Moreover, novel repressive and stimulatory complexes involved in translational regulation of specific mRNAs have been described and analyzed.

In this review, we will focus on the molecules that by binding and/or modulating the modifications occurring at the end of mRNAs, the cap structure at the 5′ and the poly(A) tail at the 3′ end, are the targets of regulatory events that govern translation of select mRNAs playing crucial roles in specific developmental processes.

2. Structure of eukaryotic mRNAs and translational control

In the nucleus, eukaryotic mRNAs are first transcribed as precursor mRNAs (pre-mRNAs) and subsequently modified by capping, polyadenylation, and splicing. Mature mRNAs are ultimately exported into the cytoplasm where they can be translated into proteins.

Capping of eukaryotic mRNAs involves the addition of a 7-methyl-guanosine residue at the 5′ end to protect this end from nuclease degradation. The cap structure in eukaryotes can be of three types m^7GpppNp, m^7GpppN^{m}p, m^7GpppN^{m}pN^{m}p (m indicates a methyl group attached to the respective nucleotide), and is used as a docking point for the cap-binding protein complex that mediates the recruitment of the small ribosomal subunit to the 5′ end of the mRNA.

Polyadenylation occurs after cleavage of the pre-mRNA at the 3′ end and consists of the addition of up to 250 adenosine residues by the poly(A) polymerase (PAP) enzyme. Finally, the mechanism of splicing removes all intervening sequences from the pre-mRNA, thus producing a mature mRNA that is competent to be transported to the cytoplasm.

Once within the cytoplasm, only mRNAs that are properly capped and polyadenylated are efficiently translated. This has been demonstrated during oogenesis and early embryogenesis, where regulated cytoplasmic polyadenylation of mRNAs modulate their translation. During translation initiation, the cap structure is directly bound by eIF4E, and the poly(A) tail by the poly(A) binding protein (PABP) in a manner that induces a synergistic enhancement of translation. Translation that is both cap- and poly(A)-dependent requires moreover the activity of the eukaryotic ini-