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Review

Control of maternal mRNA stability in germ cells and early embryos☆

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ABSTRACT

mRNA regulation is essential in germ cells and early embryos. In particular, late oogenesis and early embryogenesis occur in the absence of transcription and rely on maternal mRNAs stored in oocytes. These maternal mRNAs subsequently undergo a general decay in embryos during the maternal-to-zygotic transition in which the control of development switches from the maternal to the zygotic genome. Regulation of mRNA stability thus plays a key role during these early stages of development and is tightly interconnected with translational regulation and mRNA localization. A common mechanism in these three types of regulation implicates variations in mRNA poly(A) tail length. Recent advances in the control of mRNA stability include the widespread and essential role of regulated deadenylation in early developmental processes, as well as the mechanisms regulating mRNA stability which involve RNA binding proteins, microRNAs and interplay between the two. Also emerging are the roles that other classes of small non-coding RNAs, endo-siRNAs and piRNAs play in the control of mRNA decay, including connections between the regulation of transposable elements and cellular mRNA regulation through the piRNA pathway. This article is part of a Special Issue entitled: RNA Decay mechanisms.

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1. Introduction

Oocytes and early embryos are transcriptionally silent, thus developmental processes at these stages rely exclusively on maternal mRNAs. Depending on the species, these maternal mRNAs are either produced by immature oocytes before transcription ceases or by specialized germ cells, the nurse cells. The regulation of maternal mRNAs that drives development during these early stages is mostly cytoplasmic and involves the control of mRNA stability, translation and localization, three highly interconnected processes.

mRNAs are capped (by addition of a 7-methylguanosine) at their 5′ end, and cleaved and polyadenylated (by addition of a poly(A) tail) at their 3′ end during nuclear co-transcriptional reactions. Both structures, 5′ cap and 3′ poly(A) tail, are essential for mRNA translation and stability. Once in the cytoplasm, the 5′ cap and 3′ poly(A) tail interact through protein-protein interactions to form a closed loop, required to stimulate initiation of translation [1,2]. The modulation of mRNA poly(A) tail lengths is therefore an important mechanism of translational control, whereby poly(A) tail elongation leads to translational activation and poly(A) tail shortening (deadenylation) results in translational repression. Deadenylation is also the first and rate-limiting step of the two major mRNA decay pathways (for review see [3]). In the 3′-to-5′ mRNA decay pathway, the deadenylation is followed by degradation of the mRNA from the 3′ end by the exosome, whereas in the 5′-to-3′ mRNA decay pathway, it is followed by decapping and subsequent degradation from the 5′ end by the exoribonuclease Xrn1. Deadenylation is therefore the major step in controlling mRNA decay and as such is highly regulated.

Three enzymes with deadenylase activity are present in most species, the CCR4-NOT complex, the PAN2-PAN3 complex and PARN (although only the two former complexes exist in *Drosophila* and yeast) [4–7]. The PAN2-PAN3 and CCR4-NOT complexes act sequentially on the same mRNAs [6,7] and deadenylation by these complexes can occur unspecifically on all mRNAs. Specificity is achieved through their recruitment to elements or motifs on mRNAs bound by specific RNA binding proteins or microRNAs (miRNAs). Recruitment of the CCR4-NOT complex to specific mRNAs is the most common mechanism of regulating mRNA deadenylation and degradation described so far in developmental processes.

This review reports recent data on the molecular mechanisms underlying the regulation of mRNA degradation or stabilization in germ cells and early embryos and how this regulation controls gene expression to drive developmental processes during these early stages.

2. mRNA deadenylation, stabilization and decay in oocytes

In *Drosophila*, the importance of mRNA regulation by poly(A) tail length during early development has long been controversial [8,9], although such a regulation had been recognized early to control *hunchback* mRNA, which encodes an essential determinant of embryonic antero-posterior patterning [10]. However, studies in the last decade have

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established that changes in poly(A) tail length is a common mechanism of regulation for many developmental processes in germ cells and early embryos. While CCR4-NOT complex-catalyzed deadenylation is not essential for viability in *Drosophila* [5], it is essential for oogenesis and embryonic patterning [11,12]. This shows that deadenylation can be achieved by redundant activities in somatic cells, as is the case in yeast [6], but that specific mechanisms of regulated deadenylation during early stages of development are not redundant. The *Drosophila* CCR4-NOT complex is composed of two potential deadenylases, CCR4 and CAF1, and five other proteins, NOT1-4 and CAF40. NOT4 is loosely associated with the complex [5,13]. Mutations in CCR4, which is encoded by the *twin* gene, cause defects in germ cells from early oogenesis, including apoptosis and cell cycle defects [11,12], consistent with reduced deadenylation of several mRNAs encoding Cyclins.

To date, only Bicaudal-C (Bic-C) has been described as a regulator of the CCR4-NOT complex in *Drosophila* oogenesis. Bic-C is a KH-domain RNA binding protein that binds to and regulates many mRNAs involved in cytoskeletal organization and oogenesis, including its own mRNA. Bic-C recruits the CCR4-NOT complex through direct interaction with the NOT3 protein to deadenylate mRNAs during early to mid-stages of oogenesis (germarium to stage 8 of 14 stages) [14] (Fig. 1A). Importantly, in contrast to the situation in embryos, deadenylation does not normally induce mRNA decay in oocytes. The deadenylated mRNAs are instead re-activated by poly(A) tail elongation during later stages of oogenesis [14,15] (Fig. 1A).

Similarly, immature vertebrate oocytes that are arrested at prophase of meiosis I produce mRNAs representing up to half of the genome before transcription stops [16,17]. These mRNAs are stored as dormant mRNAs in a deadenylated state before their activation to drive meiosis and early embryogenesis. This type of regulation has been thoroughly studied in *Xenopus* where translational activation depends on cytoplasmic poly(A) tail elongation of these mRNAs. The timing of activation for each mRNA depends on a combinatorial code of motifs present in the 3′ UTR (untranslated region), able to recruit different sets of RNA binding proteins [18]. These motifs include cytoplasmic polyadenylation elements (CPEs, UUUUAU or UUUUAAU) which are bound by CPE binding proteins (CPEBs) [16]. CPEBs have a dual function in deadenylation and polyadenylation. In stage I-IV oocytes, CPEB1 is in complex with several translational repressors including eIF4E-T [19], the homolog of *Drosophila* Cup which has been shown recently to mediate deadenylation through the recruitment of the CCR4-NOT complex [20]. Thus, by analogy, deadenylation in these early oocytes has been proposed to depend on CCR4-NOT, although this requires experimental confirmation [21] (Fig. 1B). In stage VI oocytes, CPEB1 bound to CPEs interacts with both the deadenylase PARN and the polyadenylation machinery, including Cleavage and Polyadenylation Specificity Factor (CPSF) and GLD-2 poly(A) polymerase [22]. PARN antagonizes GLD-2 to keep the mRNAs deadenylated. Upon meiotic maturation, the phosphorylation of CPEB1 increases its affinity for CPSF, while decreasing its interaction with PARN, thus switching its function to cytoplasmic polyadenylation and translational activation [22–24] (Fig. 1B). Another wave of deadenylation occurs after metaphase I and is driven by C3H-4, an AU-rich element (ARE) binding protein homolog of tristetraprolin (TTP), which recruits the CCR4-NOT complex to ARE-containing mRNAs [25]. C3H-4 synthesis is triggered by the early phase of cytoplasmic polyadenylation occuring during meiotic maturation. C3H-4 allows the deadenylation from metaphase I onwards of the mRNAs that have been polyadenylated during the early phase, and delays the full polyadenylation of mRNAs that are polyadenylated after metaphase I (for review see [21]) (Fig. 1B). These waves of cytoplasmic polyadenylation and deadenylation drive meiotic progression by regulating the production of key components of meiosis: maturation promoting factor (MPF: Cdc2/Cyclin B), anaphase-promoting complex/cyclosome (APC/C) and cytostatic factor (CSF).

Two possible mechanisms emerge to explain how deadenylated mRNAs remain stable in oocytes. The first relies on the fact that polyadenylation and deadenylation occur concomitantly on mRNAs; the steady state poly(A) tail length of a specific mRNA depending on the balance between these two reactions. In such a system, polyadenylation would maintain short poly(A) tails on deadenylated mRNAs in oocytes to prevent their decay [14,15,21,22].

The second potential mechanism involves Cup, a translational repressor in *Drosophila* ovaries and early embryos [26–29]. In addition to its direct role in translational repression, Cup has been shown recently to mediate deadenylation by the CCR4-NOT complex in *Drosophila* S2 cells, through interaction with the NOT1 subunit of the complex. Remarkably, another domain of Cup prevents decapping and mRNA decay [20] thus highlighting Cup as an excellent candidate for a role in the stabilization of deadenylated mRNAs in *Drosophila* ovaries. Cup has indeed multiple functions during *Drosophila* oogenesis [30–32].

Cup targets mRNAs through interaction with specific RNA binding proteins [26,28]. One of these proteins is Bruno, an important ovarian regulator of *oskar* (*osk*) mRNA which encodes a key determinant for the formation of posterior structures of the embryo. *osk* mRNA is repressed in the oocyte during its transport to the posterior pole, where it is then translated (Fig. 1A). Although Cup/Bruno-mediated *osk* repression has not been shown to involve deadenylation, this is conceivable since *osk* translational activation at the posterior pole involves cytoplasmic poly(A) tail elongation [33–35]. In the embryo, however, Cup interacts with the RNA binding protein Smaug (Smg) to regulate *nanos* (*nos*) mRNA which encodes another essential posterior determinant [29]. Smg induces *nos* mRNA decay (see below), therefore Cup activity in mRNA stabilization through the prevention of decapping must be overcome in embryos; how this is achieved is yet to be addressed.

Notably, while a large proportion of mRNAs remains stable in oocytes even when deadenylated, mRNA decay can occur in oocytes. In mice, a subset of maternal mRNAs is degraded during meiotic maturation of the oocyte [36]. Interestingly, recent studies have shown that mRNA decay in arrested mouse oocytes involves the endo-siRNA (endogenous small interfering RNA) pathway. endo-siRNA are small non-coding RNAs (21-nt long) involved in RNA silencing. They are produced from genomic double-stranded RNAs which are generated by transcripts either forming hairpins or overlapping in opposite directions [37,38]. Although the miRNA pathway has a crucial role in maternal mRNA decay in embryos after zygotic transcription (see below), miRNA activity appears to be largely inactive in mouse oocytes [39]. Here, endo-siRNAs produced from pseudogenes target mRNAs from the corresponding genes by complementarity and induce their degradation [40–42]. Accordingly, decreased levels of endo-siRNAs in *Dicer* mutant lead to upregulation of mRNAs involved in microtubule dynamics, and to defects in meiotic spindle assembly. The mechanisms underlying this mRNA decay have not been addressed, although have been proposed to involve the endonucleolytic cleavage function of Ago2 loaded with endo-siRNAs.

3. mRNA deadenylation and decay in embryos during the maternal-to-zygotic transition

In early embryos, the control of development switches from the maternal to the zygotic genome during the maternal-to-zygotic transition (MZT). This switch occurs as a result of the massive degradation of maternal mRNAs combined with the activation of the zygotic genome. Genome-wide analyses of transcripts during the MZT in different species have revealed that 30 to 40% of maternally deposited mRNAs are completely degraded [43–45], and that in total 60% are eliminated or significantly degraded [46].

In *Drosophila*, the comparison of maternal mRNA decay in activated unfertilized eggs (without zygotic transcription) and in fertilized embryos showed that degradation of maternal mRNAs depends on two pathways that involve maternal and zygotic activities, respectively [47]. The zygotic pathway of mRNA degradation is more active than

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