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RNA Processing During Early Embryogenesis: Managing Storage, Utilisation and Destruction

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1. Introduction

The classical model of the life of a messenger RNA (mRNA) is generally depicted as a cascade of typical cellular events initiated with the transcription of the genomic sequence followed by the usual maturation of the produced transcript through splicing of the intronic regions, addition of the cap structure on its 5′ end and polyadenylation of the 3′ end. The mature mRNA is then exported out of the nucleus and sent for translation in the endoplasmic reticulum where it will serve as template/blueprint for the production of the encoded protein. The typical life cycle of an mRNA is then concluded by its decay in cellular structures that take the shape of granules called processing bodies. These well accepted steps offer a general perspective of the life and death of most mRNAs in most cellular contexts. Nonetheless, this general model does not fit well with embryogenesis mainly due to the presence of transcriptionnaly impaired cells composing the early stage embryos. In fact, the stage at which the embryo acquires the potential to transcribe its genome is widely variable between species. For instance, the mouse genome is readily activated following fertilization while in Human; transcription is initiated between the 6 and 8-cell stage. Other non-mammalian species provide more extreme situations amongst which Xenopus leavis represents a prime example of non-classical RNA management as the early embryogenesis is accomplished through 12 cell cycles conducted in the absence of transcriptional activity. In this model organism, the first embryonic cells become transcriptionally active once the embryo is composed of roughly 4,000-8,000 cells.

In the absence of transcription, the embryonic cell sustains its protein production using mRNAs found in the stocks that were stored during oogenesis. These stockpiles of transcripts are accumulated during the oocyte growth that took place in the ovary, and are generally accepted as a large component of the maternal legacy that is associated with developmental competence of the resulting embryo once the egg is fertilized. The mechanisms by which the oocyte stores these transcripts are still only partly understood.

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Since some of these transcripts are destined to be used several days or even weeks later, the cytoplasmic storage inevitably involves their stabilization and protection from degradation. Several important proteins that play key roles in mRNA stabilization have been identified, mostly from studies performed on non-mammalian model organisms. Knowledge transfer has allowed identifying orthologs in mouse and Human.

To sustain protein synthesis, the stored transcripts must be released from their stabilized state and appropriately allowed to proceed to translation by the recruitment of the initiating factors that will facilitate the binding and progression of ribosomes. On this aspect also, the mechanisms by which the mRNAs are specifically recruited to fulfill the protein requirements of the cell are still poorly understood. The involvement of several key proteins has been highlighted; however, the current model only provides a partial perspective of the recruitment processes that must involve some elements to target specific transcripts from storage that must be governed in a temporarily regulated manner.

One of the main considerations pertaining to how this spatio-temporal management may occur relies on the information encoded in the untranslated regions of the mRNAs. Indeed, elegant studies performed in model organisms have shown the importance of these non-coding regions to regulate the location of the mRNAs within the cell. So far, the mammalian oocyte and the early blastomeres have yet to show clear partitioning of the cell's cytoplasm as it is the case for other non-mammalian species. Recent evidence suggest the involvement of small non-coding RNAs namely microRNAs in the regulation of the stored maternal RNA reserve. Currently, our knowledge is based upon evidence of the complex nature of maternal RNA management, regulation of which occurs at different levels.

Once translated, the mRNAs are typically destined for decay in the processing bodies. The classical string of events includes mRNA decapping, poly(A) tail removal and complete transcript degradation by the action of nucleases. Within the early embryonic context, a large proportion of stored maternal mRNAs are believed to be destroyed without ever being translated. This apparent waste of resources is still unexplained however recent evidence suggests maternal stores must be depleted for successful embryonic genome activation. This situation stresses the importance of the decay pathway as an active aspect of early embryogenesis. Following embryonic genome activation, the blastomeres gradually adopt a more classical RNA processing strategy where, for example, environmental stimulus could drive cellular response through signal transduction leading to nuclear transcriptional events resulting in novel mRNA production to be translated.

Herein are discussed the species related similarities and divergence in transcriptional silencing during oogenesis which account for the accumulation of the maternal RNA stores. A perspective of the embryonic program that is driven by these stored transcripts will also be presented by contrasting the different strategies adopted across species. Finally, the current mechanisms regarding the management of these transcripts in a space and time dependant manner will be addressed through the presentation of known key proteins in addition to the action of small non-coding RNAs.

2. The oocyte's legacy to early development is accumulated in the ovary

Successful zygote formation begins with the fusion of a male and female gamete. Although equal contributions of nuclear material are combined from each parent resulting in transmission of half their genetic information to their offspring, the structural composition of the resulting embryo originates almost entirely from the oocyte. The oocyte endowment

includes the future zygotic cytoplasm with all the organelles and various components e.g. proteins, stocks of RNA or calcium. In fact, compared to the oocyte, the sperm transfers little cytoplasm, and even though many mitochondria exist in the sperm, those that are transferred to the oocyte's cytoplasm do not persist in development past about the 4 cell stage in rodents and in cattle (Shalgi et al. 1994; Sutovsky et al. 1996). Amongst the known spermatic contributions to zygotic composition aside from the haplotype, the spermatozoon donates a centriole that leads to the sperm aster that mediates pronuclei fusion (Sutovsky et al. 1996). More recently, protein and additional nucleic acid material originating from the spermatic micro-cytoplasm have been identified to be passed to the oocyte's cytoplasm. It is the case for phospholipase C zeta that has been shown to induce the calcium release after fertilization as part of the mechanism driving the block to polyspermy (Swann 2004) and RNA molecules either messengers or small non-coding Review: (Lalancette et al. 2008). So far the functional relevance of these RNA molecules to perform specific and essential tasks in support of early embryonic development still remains unclear. As it will be discussed later, the oocyte's cytoplasm represents a rich source of messenger (Schultz and Wassarman 1977; Gilbert et al. 2009) and small non-coding RNAs Review: (Krawetz 2005). Although some reports indicate a potential role of the spermatic RNA molecules, early embryonic development is undisputedly supported by the resources accumulated during oogenesis. As discussed below, the accumulated RNA stores support early development until the embryonic genome is activated which occurs, in most species, after several cell cycles.

Oogenesis leads to the production of the largest cells of the body enabling the accumulation of large amount of resources. Depending upon the species, the mammalian oocyte ranges from 70 to 140 μm in diameter and is much larger in reptiles, fish and birds by the time of ovulation. The description of the neuroendocrine regulation of oogenesis is far beyond the scope of the current objective. However, it is important to position the accumulation of RNA in the oocyte during oogenesis which takes place in the ovary. Briefly, upon recruitment from the ovarian reserves, a cohort of follicles each bearing an immature oocyte initiates growth which is heavily mediated by gonadotrophins secreted from the hypophysis. The follicles are composed of mainly two types of somatic cells which are granulosa and theca cells. These cells structurally form the individual unit that is a follicle within which an oocyte is found. The somatic cells work in tandem to support oogenesis by modifying hormones (progestins to androgens to estrogens in response to gonadotrophins).

As folliculogenesis progresses, the enclosed oocytes undergo oogenesis. The follicle was long believed to support the gamete's growth by communicating from the outer cell compartment towards the inside where the gamete would passively benefit (Biggers et al. 1967). The growth of both the follicle and the gamete is now known to be governed by bi-directional communication mainly between the oocyte and the granulosa cells. So far, outside towards the inside communication has been reported through direct contact through gap junctions between the somatic cells and to the oocyte. A subset of granulosa cells in close proximity to the oocyte, the cumulus cells, are further differentiated and have direct contact with the oocyte's plasma membrane through transzonal projections. The cumulus cells play a large role regulating the level of cyclic nucleotides in the oocyte which in turn prevent meiosis resumption (Conti et al. 2002). The oocyte signals back by secreting factors such as BMP15 and GDF9 that stimulates granulosa cell growth and differentiation (Hussein et al. 2006). This communication is essential to maintain a certain level of synchrony between the follicle and the gamete especially during early folliculogenesis when the gamete is still growing in size. Typically, a mammalian oocyte reaches it's full diameter

before the follicle has reached full size. The follicle will continue to grow, filling with follicular fluid, and increasing in surrounding granulosa cell population (Pedersen and Peters 1968). The relationship between the size of the follicle and of the enclosed oocyte in several mammalian species can be found in Table 1. Oocyte growth is accompanied with the accumulation of large amounts of RNA observable in the early growth phase. In mice, by about 65% of growth to full size, 95% of the RNA has accumulated, the remaining 5% occurs over the final stages of growth (Pedersen and Peters 1968).

Specie	Size of full grown oocyte	Follicular size at which full grown oocytes are found	Size of pre-ovulatory follicle	References
Human	> 105 μm	5 - 7 mm	> 20 mm	(Gougeon 1986)
Mouse	70 μm	> 2 mm	4 mm	(Rose et al. 1999)
Sheep	> 120 μm	~1.5 mm	> 5 mm	(Turnbull et al. 1977)
Bovine	> 130 μm	> 2 mm	20 - 25 mm	(Fair et al. 1995)
Pig	144 μm	> 3 mm	> 10 mm	(Knox 2005)
Rabbit	80-90 μm	650-700 μm	> 1.6 mm	(Žitný et al. 2004) (Osteen and Mills 1980) (Hulot and Mariana 1985)

Table 1. Relationship between follicular and oocyte size across different mammalian species

The build-up of maternal RNA stores is driven by heavy transcriptional activity of the gamete's genome (Tomek et al. 2002). In most mammalian species, this transcriptional activity is however, greatly reduced or completely shutdown once the oocyte reaches its full size (Table 2). Some studies show clear patterns of transcription shutdown like in the pig and in cattle (Motlik J 1984; Fair et al. 1995) By measuring the rate of ^{3}H-uridine incorporation it was shown RNA synthesis is fully active during early oogenesis, but as the oocyte grows, this activity shuts down, and by the time the oocyte is full size, activity that remains is limited to the nucleolus (Moore and Lintern-Moore 1978). In the mouse, however, the shutdown of transcription is very brief and occurs just before meiosis resumption (Rodman and Bachvarova 1976; Wassarman and Letourneau 1976).

Aside from endogenous transcription, accumulation of maternal RNA is also known to be occurring through RNA transfer from the surrounding somatic cells in non-mammalian species. In *c. elegans* or drosophila and other insects like notonecta, maternal mRNAs are transferred to the oocytes through translocation channels or cell–cell bridges that connect nurse cells and the oocytes (Hurst et al. 1999). As germ cells divide to become oocytes in the drosophila, they remain directly connected to each other by connections termed ring canals (Deng and Lin 1997). Aggregates of RNA move from the other germ cells, or from supporting cells to the oocyte in an ordered method (Hurst et al. 1999). The transfer of mRNA between cells may be motor protein mediated as mRNA can associate to form a ribo-nucleo-particle (RNP) with motor-like proteins, or proteins that associate with dyneins (Hurst et al. 1999; Schnorrer et al. 2000). This RNA accumulation through endogenous transcription and/or transfer from surrounding somatic cells and oocytes makes the

immature oocyte the most RNA rich cell of the body. Although numbers differ between studies, total RNA content differs importantly between species (Table 2).

Specie	Immature oocyte (GV stage) total RNA content	Detectable period of RNA polymerase II activity
Human	330 pg (Kocabas et al. 2006)	Growth until large diameter oocytes with condensed chromatin (Miyara et al. 2003)
Mouse	0.35 ng (Piko and Clegg 1982) 0.35-0.43 ng (Bachvarova et al. 1985) 0.45 ng (Olszańska and Borgul 1993) 0.6 ng (Sternlicht and Schultz 1981)	Arrested in full size SN phase oocytes (Bouniol-Baly et al. 1999)
Sheep	0.76 ng (Olszańska and Borgul 1993)	Oocyte size of 110 µm with Surrounded Nucleus Configuration (Russo et al. 2007)
Bovine	0.35 ng (Gilbert et al. 2009) 0.98 ng (Olszańska and Borgul 1993) 2.0 ng (Lequarre 2004) 2.4 ng (Bilodeau-Goeseels and Schultz 1997)	Arrested in full size GV3 configuration oocytes (Lodde et al. 2008)
Pig	0.65 ng (Olszańska and Borgul 1993)	Arrested in full size GV3/4 stage oocytes (Sun et al. 2004)
Rabbit	15 ng (Olszańska and Borgul 1993)	Arrested in oocytes with "Tight Chromatin" (TC) configuration (Wang et al. 2006)
Birds	1.0 µg (Japanese quail), 2.1 µg (hen) (Olszańska and Borgul 1993)	N/A

Table 2. Total RNA content in immature oocytes

In some species, transcriptional arrest is observed by the presence of a non-permissive state of chromatin and/or the depletion of RNA polymerase. The decrease in transcriptional activity is mediated by gonadotropin influence on the supporting granulosa cells (De La Fuente and Eppig 2001). Chromatin state changes are indicative of transcriptional arrest when the chromatin becomes condensed. Concurrently, there is a depletion of RNA polymerases in oocytes that have undergone DNA condensation (Bouniol-Baly et al. 1999; Miyara et al. 2003). Most pre-ovulatory oocytes in the mouse exhibit a chromatin configuration termed "surrounded nucleus" (SN). Alternatively, non-surrounded nucleus (NSN) configuration can also exist. Condensed DNA associating closely with the nucleolus characterizes SN configuration (Miyara et al. 2003). SN configuration is also related to RNA polymerase I and II activity. In SN chromatin configuration, polymerase activity is arrested

(Bouniol-Baly et al. 1999). When other species are taken into account, the conformation change in chromatin is not the same as in mice. In rabbits, sheep, humans, and cows, conformation changes are significant, but not characterized solely by SN or NSN charactersistics. The DNA still typically condenses, and can be labeled as surrounding or non-surrounding, but more descriptive stages that take into account related morphological changes have been described (Tan et al. 2009).

In rabbits, there are more terms to describe oocyte chromatin configuration as the oocyte matures. As described by Wang et al. (2006) the progression observed in the rabbit oocyte is as follows: net-like (NL), loosely condensed (LC), tightly condensed (TC), and singly condensed (SC) chromatin configurations. Transcription shuts down at the tightly condensed stage.

In human oocytes, Combelles and colleagues describe four states of chromatin related to maturation and the ability to fertilize. In the first class, class A, the oocyte is smaller in diameter and has a partially surrounded nucleolus and fibrillar chromatin distributed in the nucleoplasm. The three other classes (B, C and D) have peri-nuclear condensed chromatin and resemble the surrounded nucleolus conformation of the mouse, the difference being that oocyte diameter is larger and the chromatin is less widely distributed in the nucleoplasm. Class B has very compact chromatin and no distribution of chromatin in the nucleoplasm. Class C is the largest in oocyte diameter, and large masses of chromatin surround the nucleolus. In class D there are threads of chromatin extending in the nucleoplasm (Combelles et al. 2002). These reports are similar to Miyara and colleagues who propose a size dependant chromatin configuration change in oocytes and a subsequent decrease in polymerase activity to none in pre-ovulatory oocytes with condensed configuration.

In bovine oocyte maturation, the terms GV0-GV3 are predominantly used (Lodde et al. 2008) though SN and Non SN configurations are also referred to in literature (Tan et al. 2009). In GV0 oocytes, there is much transcription in the nucleolus and a number of morphological differences exist that distinguish the bovine oocyte from later GV stages that include erected microvilli, small clusters of immature mitochondria, few ooplasmic vesicles, the presence of a golgi apparatus, and scattered cortical granules (Lodde et al. 2008). In the later GV stages, the nucleus becomes peripheral, microvilli become bent, mitochondria become hooded, there are increasing numbers of ooplasmic vesicles, and the gogli begins to disassociate and the cortical granules become clustered before moving to the periphery of the oocyte. Intense transcriptional activity is seen in the GV0 oocyte, and then in the GV1 oocyte the activity is sparsely detected by H^3-Uridine such that by GV3 stage no transcriptional activity exists (Lodde et al. 2008). In porcine oocytes similar chromatin configuration nomenclature exists, with the exception that there is a GV4 stage, and that the later stages (GV3 and GV4) are associated with more atretic follicles (Sun et al. 2004). Overall, preovulatory oocytes largely exhibit, some form of condensed transcriptionally inactive chromatin status and a lack of polymerase activity (Bouniol-Baly et al. 1999).

3. RNA is used to sustain protein synthesis during early development before the activation of the embryonic genome

The reduction in transcriptional activity in the mature oocyte, which may even be complete transcriptional silencing, occurs during oocyte growth, and lasts until embryonic genome activation (EGA). The developmental period which occurs in the absence of transcription is referred to as the embryonic program. During this transcriptionnaly repressed period,

control over gene expression involves post-translational modifications that regulate protein activity and permit for the compensation of protein turnover or synthesis of stage specific proteins that also rely on the maternal RNA stores.

A classic example of gene expression control operating at both the translational and post-translational levels involves the action of the M-phase promoting factor (MPF). This complex regulating meiosis resumption, is composed of two subunits, a cyclin-dependant kinase (CDK1) and a regulatory cyclin unit (CCNB1) (Masui 2001). The complex has to be activated in a two step process to allow dissolution of the germinal vesicle, the first step of meiosis resumption. To begin, CDK1 and CCNB1 have to be present or have to be synthesised if they are not. Second, the complex must be activated. Depending on the species, one of the two proteins is usually present in the cytoplasm whereas the other has to be translated in a time-specific manner to allow meiosis resumption (Chesnel and Eppig 1995; Robert et al. 2002). The presence of the components of the MPF is necessary but not sufficient to grant meiotic competence. Post-translational regulation is compulsory to allow MPF activation through the dephosphorylation of the CDK1 subunit. This kind of tight recruitment regulation of both stockpiled mRNAs and proteins is ubiquitous and allows early development progression given that no transcription occurs until the embryonic genome activates.

4. The duration of transcriptional silencing is species specific

The duration of the period of transcriptional silence varies between species. While being short in the mouse oocyte, the silent period can last several days in many other species. Indeed, the mouse genome is activated as early as the end of the zygotic stage. According to previous work (Schultz 1993), while a period of minor gene activation occurs during G2 in the 1-cell embryo, the major activation occurs during the 2-cell stage. Thus, in the mouse, the maternal contribution is only required to support a single cell cycle. This is an important difference with other mammals like humans, pigs, rabbits, cattle and sheep where the embryonic genome activation occurs later, at the end of the third or fourth cell cycle (Table 3).

In other model organisms, the maternal stores can support up to 16 cell cycles, which corresponds to approximately 65,536 cells. There is an important difference between mammals and non-mammal species such as fish, amphibians, insects and birds. In zebrafish, the activation of transcription begins at cell cycle 10 (512 to 1,024 cells). The first nine cycles are controlled by a 15 minute oscillator that allows perfectly synchronous cleavage (Kane and Kimmel 1993). In Xenopus, the embryo undergoes 12 rapid 35 minutes long synchronous cleavages (4,096-8,192 cells) before detectable transcription is observed (Newport and Kirschner 1982). In drosophila, the bulk of embryo transcription begins during the 14th cell cycle (8,192-16,384 cells) (McCleland et al. 2009). Finally, the chicken represents an extreme model of embryonic program with it first transcriptional activity detected in the 16th cell cycle, when the embryo consists of about 30 to 50 thousand cells. The large variability in the number of cell cycles and the number of cells required to achieve the maternal to embryo transition in different animal species is remarkable and is a tribute to the vast amount of resources that can be stably accumulated during oogenesis.

The total time elapsed (in hours) before the EGA is also impressive in its own right. Even though the mouse reaches the point of EGA (also referred to as the maternal to zygotic transition (MZT), due to the stage during which it occurs) early, it still transpires 23 hours after fertilization (Schultz 1993). By adding the time from meiosis resumption and the MII stage arrest, which lasts around 10 hours, the total period of transcriptional silence lasts

more than 30 hours. In large mammals, the duration of RNA storage may be extended when considering that in the bovine, fully grown oocytes are typically found in follicles of 3 mm and a proportion of those oocytes already harbor transcriptionally inactive, highly condensed chromatin (GV3 stage) (Akhtar and Veenstra 2009). Oocyte growth to full size involves transcriptional silencing and includes the time for the 3 mm follicle to reach preovulatory size which requires 4 to 8 days depending on a two or three wave cycle. In addition there is the time taken to reach the other key developmental steps that are, the duration from the LH surge up to ovulation (1 day), the time for fertilization to occur, and the time for the zygote to reach the EGA 3-4 days later. Considering this timeline and that some of the maternal RNA present in these oocytes may have been stored during early stages of oocyte recruitment, and will not be enlisted for translation until the time of EGA, these RNAs will have necessitated storage for more than two weeks before they are used.
Interestingly, the number of cell cycles undergone before EGA and the duration of the transcriptional silence are two uncorrelated factors. Indeed, the number of cells at EGA may be several thousand in Drosophila and Xenopus, but transcriptional silence only lasts 3 and 7 hours in each of these species respectively, as the first cell cycles are extremely rapid (Newport and Kirschner 1982; Schultz 1993). Similarly, the chicken embryo reaches the 16th cell cycle (30,000-50,000 cells) a mere 24 hours post-fertilization (Elis et al. 2008).

Specie	Developmental stage	Number of cell cycles	References
Mouse	1-cell	0	(Schultz 1993)
Pig	4-6 cells	2-3	(Anderson et al. 2001)
Human	4-8 cells	2-3	(Braude et al. 1988)
Bovine	8-16 cells	3-4	(Memili et al. 1998)
Rabbit	8-16 cells	3-4	(Henrion et al. 1997)
Sheep	8-16 cells	3-4	(Crosby et al. 1988)
Zebrafish	512-1,024 cells	9-10	(Kane and Kimmel 1993)
Xenopus	4,096-8,192 cells	12-13	(Newport and Kirschner 1982)
Drosophila	8,192-16,384 cells	13-14	(McCleland et al. 2009)
Chicken	30,000-50,000 cells	15-16	(Elis et al. 2008)

Table 3. Developmental stage at which the embryonic genome gets activated

5. Storing RNA for later

As mentioned, the oocyte contains all the materials needed to carry out early embryo development up to the stage at which the genome activates. This is exemplified by the fact that the duration of the embryonic program is determined by the stage at which the developmental block occurs when in the presence of alpha-amanitin, an RNA polymerase II specific inhibitor. Distinctly from the textbook processes through which mRNAs are matured in the nucleus and exported, capped, and polyadenylated, to the cytoplasm where they are readily translated and then sent for destruction, these essential maternal RNA molecules involve additional steps for transcript stabilization to render them physiologically

inert, a state from which they will be recruited in a time orderly fashion to be either translated or simply sent directly for decay (Figure 1).

However, several aspects have been known for some time and parallels can be drawn from the knowledge gathered in other cell types known to store mRNAs. Additionally, it seems that a close relationship exists between factors involved in RNA storage and in RNA decay. For instance, it has been reported in numerous species that stored mRNAs are found in a deadenylated state (Eulalio et al. 2007; Zheng et al. 2008) and deadenylation is the first step in the mRNA decay pathway further. Some storage granules contain components for mRNA decay (Cougot 2004; Kedersha et al. 2005). The collection of these different protein aggregates with various cellular functions is often referred under the general terminology of processing bodies (p-bodies). Decay intermediates are typically stored in the p-bodies where decapping factors (DCP1 and DCP2) are concentrated. The mRNA can, however, resume translation by exiting the p-body, being re-adenylated, and interacting with polyribosomes (Brengues et al. 2005). This turnover is often observed to occur between periods of stress and cell growth.

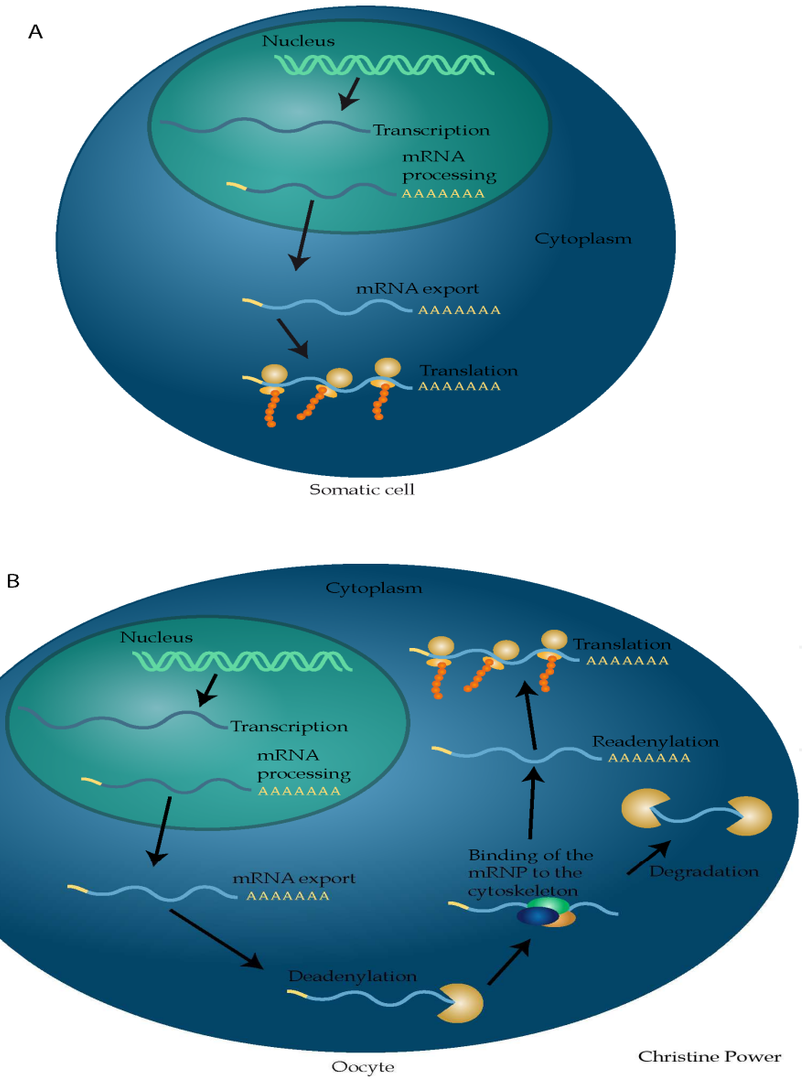


Fig. 1. The RNA pathway in a somatic cell (A) and in an oocyte (B)

The current state of knowledge regarding these processes is still fragmented as the detailed mechanisms of RNA storage in the oocyte and early embryos are still being determined. In the context of the oocyte, the mechanisms by which the transcripts must undergo to be stabilized are largely unknown, however, stored messengers are found to be deadenylated and this process does not result in RNA decay, but allows the RNA to be stored through protein interactions. Several key proteins and complexes have been identified to mitigate the poly(A) tail shortening. Such key players involve the poly(A) ribonuclease PARN in some species while in others, it can also be mediated by the Pumilio protein, which in turn interacts with the CCR4–Pop2–Not deadenylase complex (Radford et al. 2008). In drosophila the mRNA adenylation state is determined by a balance between the polyadenyl polymerase (PAP) involved in poly(A) tail lengthening and proteins with nuclease activity like the Caf1-Ccr4 complex (Eulalio et al. 2007). So far, the mammalian Ccr4 homolog has been localized in p-bodies and also acts to remove the poly(A) repeats (Zheng et al. 2008). Following this action, the length of the polyA tail of stored RNA has been estimated to be of less than 100 nucleotides reduced from over 200 nucleotides (Zheng et al. 2008). Other reports suggested that the extent of deadenylation is driven by sequence specific structures namely found in 3' untranslated region (3'UTR) of mRNAs. For examples, it has been reported that the presence of a Cytoplasmic Polyadenylation Element (CPE) motif can influence the length of the remaining poly(A) tail where deadenylation of the poly A tail from 300-400 repeats down to 40 in absence of it or preserving a length of 40-100 when the CPE motif is present (Paynton and Bachvarova 1994). In all, poly(A) tail length of stored maternal mRNAs is still vaguely characterized as it is extremely difficult to clearly fractionate the mRNA pools to isolate the ones that are stored from the others that have been recruited. So far the extent of knowledge is restricted to general means in poly(A) tail fluctuations observed between developmental stages (Bachvarova et al. 1985; Paynton et al. 1988; Paynton and Bachvarova 1994; Brevini-Gandolfi et al. 1999).

Once bearing a shorter poly(A) tail, messenger storage requires stabilization to prevent destruction. This is conducted by the binding of proteins to form stable RNPs that aggregate in the oocyte's cytoplasm (Flemr et al. 2010). It has been suggested that as an oocyte approaches full size, there is a decrease in size of p-bodies and there is an increase in abundance of mRNA binding proteins in the cytoplasm. Transcript storage during oogenesis involves the binding of proteins, especially those of the Y-box family. These proteins called FRGY1 and FRGY2 were first studied in Xenopus (Bouvet and Wolffe 1994). These conserved factors are germ cell specific nucleic acid binding proteins and are homologous to the mouse MSY2 (Gu et al. 1998). In a fully grown murine oocyte, it has been estimated that MSY2 alone accounts for about 2% of the total protein content (Yu et al. 2001). These proteins are nuclease sensitive binding elements and have high sequence homology between mammalian species where identities match from 98% to 100% when using NCBI database Blast comparison. These proteins are conserved through evolution as nucleotide sequence identity between yps in D. Melanogaster and YBX1 in Human is still 79%. The full perspective on how these proteins are involved in maternal RNA storage is still under investigation. As mentioned, RNA storage is observed in other tissues than the oocyte and as such, a general perspective can be extrapolated from the other systems. These protein bound mRNA molecules form RNPs and can either aggregate in a granule like a P-body, or remain free in the cytoplasm. A variety of granules exists and are usually described based on the cell type they have been found in. Germ cells exhibit germ cell granules in oocytes, or chromatoid bodies in sperm (Nagamori et al. 2010), in neurons, neuronal granules exist, and in somatic cells there are typically p-bodies and stress granules reviews: (Anderson and Kedersha 2009; Voronina and Pshennikova 2010). Storage granule-like structures have been

identified in single cell organisms, insects, plants, and mammals (Jansen 2001; Voronina and Pshennikova 2010). On a general perspective, storage granules share some basic RNA binding ability, often have exonuclease action, helicases, structural components, and are aggregations of RNPs (Anderson and Kedersha 2006). It is by studying the presence of these components that characterization of the granules is mainly being carried out. For instance, comparison of p-bodies and stress granules has been made as they were shown to remain functionally and spatially linked, but stress granule assembly requires eIF2α phosphorylation, but this is not necessary for p-bodies (Kedersha et al. 2005). Furthermore, eIF3, G3BP, eIF4G, and PABP-1 are found only in stress granules whereas decapping proteins are, however, found in p-bodies (Kedersha et al. 2005)

It is not known how many parallels can be drawn from the situation observed in somatic cells in comparison to the situation of long term maternal mRNAs storage. The knowledge of RNA storage in the mammalian context is still extremely fragmentary. In mouse, it was recently reported that there is a novel protein storing body that localizes in the subcortical region of the oocyte (Flemr et al. 2010). This storage form termed subcortical RNP domain (SCRD) is related to the components of a p-body as it shares similar protein components. Flemr and colleagues reported components that include "unidentified 18033 antibody-interacting protein", DDX6, YBX2 (previously termed MSY2 in the mouse and FRGY2 in xenopus), CPEB, and the exon junction complex or EJC, which is a variable complex based around 5 proteins (SRm160, DEK, RNPS1, Y14 and REF) that have a number of other interactions and are involved in enhancing nucleocytoplasmic shuttling of mRNAs (Le Hir et al. 2001). In a similar fashion to the storage mechanisms described in other cell types, two DCP1 containing bodies were proposed to be active in the mouse oocyte (Swetloff et al. 2009). Likewise, responsiveness to chemical treatments like cycloheximide and RNase A treatments (Lin et al. 2008) also helps to define the different granule types, with p-bodies being sensitive to the chemicals, unlike decapping bodies.

The makeup of storage sites is better described in other model organisms especially in drosophila; however, several distinctive features question the evolutionary conservation of these mechanisms. Perhaps these divergences may be due to the marked differences in the embryonic program duration and the number of cell cycles that must be conducted prior to the EGA. In drosophila, storage is known to be highly organized with protein sorting and delivering of the mRNA to a specific position. The sorting allows for polarity in the oocyte that helps set up the organization on the body and determines cell fate in the early embryo (Review (Bashirullah et al. 1998). For instance, in drosophila , Bicoid (bcd) polarity is mediated through several proteins such as exuperantia (exu), swallow (swa) and staufen (stau) (Schnorrer et al. 2000). Polarity is created in this case by the swa protein which interacts with a dynein light chain, and exu protein that is required for appropriate localization. Exu is also suspected to localize differently depending upon the mRNA it forms an RNP with (Jansen 2001). The polarity of stau containing complexes requires bcd polarity(Schnorrer et al. 2000). A staufen-like protein has been shown to have motor protein properties though association with cytoskeletal components (Hurst et al. 1999). In complement, transcript localization in this highly organized structure is encoded in the nucleotide sequence itself where zipcodes are part of the untranslated regions (UTR). RNA binding proteins called signal recognition proteins (SRP) can attach to this region and assist in the translocation. This interaction results in the formation of a RNP with specific cellular or cytoplasmic "address". Region specific signaling and coding is used to deliver proteins to their site of intended action. It has been proposed that this process of RNA movement is potentially less energetically demanding than protein translocation (Jansen 2001). The drosophila oocyte cytoplasm is compartmentalized by protein gradients determined by the

SRP-mRNA interaction creating a polarity that drives cell fate. These observations depict the cytoplasm has been highly structured for RNP storage where the cytoskeleton serves to anchor the RNPs awaiting to be used in the appropriate spatio-temporal manner. Unfortunately, Stau and other polarity related proteins have not been shown to function with the same effect in mammalian oocytes (Calder et al. 2008). In fact, Stau abundance has been shown to be homogeneously distributed thus raising doubts on its role in spatial organization in mammals. So far, the mammalian oocyte has not been shown to be highly and specifically compartmentalized as observed in non-mammalian models.

6. Using the stored resources

The complex series of events which orchestrate mRNA recruitment are still unclear and under continuous investigation. mRNAs can be recruited either for translation or degradation. It is still unknown if the mechanisms through which recruitment occurs are general or specific. Due to the presence of the highly organized structures in other model animals and the fact that mRNAs cannot be translated or degraded in a single wave of recruitment since development is a multi-stage process, it is believed that maternal RNA management must be under a yet unknown precise mechanism.

This need for a timely regulated management process is exemplified by the action of cyclins during the embryonic program. Cyclin degradation at the end of each cell-cycle check point is essential to allow the inactivation of cyclin-dependant kinases and in turn, this inactivation is needed to complete the essential steps that are spindle disassembly, cytokinesis and the transition into G1 phase (Irniger 2002). Obviously, new cyclin proteins have to be synthesized before each new cell division. Until EGA, this has to occur through the precise recruitment and translation of stored mRNAs to ensure the presence of the proper cyclin at the appropriate moments of early development. By similar reasoning, some stockpiled mRNAs have also to be destroyed at specific moments of early development. For example, some mRNAs involved in specific meiotic events are deleterious for further development if they are not rapidly degraded after fertilization. The dynamics of the proto-oncogene Mos which is part of the cytostatic factor necessary to halt meiosis in the second metaphase waiting for fertilization is a suitable example of this. It seems protein elimination is not sufficient as the Mos mRNA must be degraded rapidly after fertilization probably since this transcript is potentially harmful as the presence of the protein can cause a rapid embryonic arrest (Alizadeh et al. 2005). These examples illustrates that it is unlikely that maternal RNA management falls under the action of a single and global mechanism. It is expected that the different nature and roles of proteins encoded in the stored maternal transcripts require a vast array of processes directing the production of these proteins. So far, several different mechanisms have been shown to be involved to some extent in the management of at least a fraction of these stored maternal mRNAs.

7. Re-adenylation of stored mRNAs

The first step of mRNA recruitment from storage to translation is usually the lengthening of the poly(A) tail. As mentioned earlier, most mRNAs are stored in the cytoplasm with a short poly(A) tail containing less than 50 nucleotides. When the poly(A) tail of an mRNA is elongated to 200 nucleotides or more, it is recruited for translation (Kim and Richter 2006). For many stored transcripts, sequence encoded elements have been shown to be required for proper re-adenylation notably the presence of two 3'UTR cis-acting elements. The first one is the polyadenylation hexanucleotide (HEX), AAUAAA, which is always required for nuclear

and cytoplasmic polyadenylation. The HEX sequence is bound by the cleavage and polyadenylation specificity factor (CPSF). The second one is the cytoplasmic polyadenylation element (CPE), whose consensus sequence is UUUUUAU (Stebbins-Boaz et al. 1999). It is bound by the CPE-Binding protein (CPEB) and is required for the cytoplasmic polyadenylation of many mRNAs following storage (Kim and Richter 2006). The presence of a specific sequence on all transcripts is insufficient to meet the requirements of gradual use throughout the embryonic program. The time dependant constraint of transcript utilization could be met if isoforms bearing different 3'UTR with different regulatory motifs are present in the maternal pools (Tremblay et al. 2005; Pique et al. 2008). It has been proposed that RNA accumulation during oogenesis may involve the production of a heterogenic RNA population. CPEB is also believed to be involved in other aspects of transcript storage from mediating mRNA deadenylation by interacting with the poly(A) ribonuclease PARN (Radford et al. 2008) to the control mRNA translation (presented below).

When mRNA is recruited for translation, mechanisms associated with the HEX and CPE sequences become active by promoting lengthening of the poly(A) tail. This probably occurs differently in each species. Most studies on this subject have been carried on oocytes and early embryos from species of Xenopus, since their large size and availability make them particularly well suited to such studies. Thus, in these non-mammalian animals, polyadenylation is induced by the poly(A) polymerase Gld2, which binds to both CPSF and CPEB proteins. Cytoplasmic readenylation seems to occur through opposing polymerase – deadenylase activities. Both the PARN ribonuclease and the Gld2 polymerase are components of the cytoplasmic polyadenylation apparatus and the length of the poly(A) tail is controlled by balancing the rates of both of these enzymes bearing antagonistic activities. Additionaly, CPEB can influence poly(A) tail length since its phosphorylation tends to expel PARN from the cytoplasmic polyadenylation complex, which seems to indicate that this phosphorylation event is involved in mRNA recruitment for translation. Once PARN is out of the way, Gld2 can finally extend the poly(A) tail (reviewed in (Kim and Richter 2006; Radford et al. 2008).

8. Involvement of the poly(A) binding proteins

The polyadenylation process stimulates translation. This stimulation is mediated by the association of poly(A) binding proteins (PABPs) that bind the poly(A) tail of mRNAs. Each PABP contains four RNA recognition motifs (RRMs) and a carboxyl-terminus domain that serves as an anchoring site for many interacting proteins. A physical association between PABP and the mRNA cap is involved in the circularization and translational stimulation of mRNAs (Imataka et al. 1998). This physical interaction is induced through the binding of one PABP with the eukaryotic initiation factor 4G (eIF4G). In turn, eIF4G binds to eIF4E, which binds the 5' cap of mRNAs. This interaction between a PABP and eIF4G could also stimulate binding of the 40S ribosomal subunit by stabilizing the eIF4F-cap interaction (Kahvejian et al. 2001).

Two Poly(A) binding protein interacting proteins i.e. Paip1 and Paip2, are known to interact with PABPs and regulate their function. Both have opposing effects on PABPs as Paip1 shows significant similarity with the central portion of eIF4G and, like it, interacts with the ATP-dependant RNA helicase eIF4A. In the same way, Paip1 interacts with eIF3, which acts as an adapter between the ribosome and the eIF4G protein (Craig et al. 1998; Martineau et al. 2008). Paip1 stimulates the action of PABP since the binding of eIF4A on the 5' UTR of the mRNA provokes the unwinding of mRNA secondary structures. This action enhances

ribosome binding and translation initiation. Moreover, the possible interactions of Paip1 and eIF3 could link PABPs to the 40S ribosome subunit. This putative link is consistent with the idea that the 40S ribosome subunit could initiate a new translation cycle because of the proximity of the mRNA extremities. Conversely, Paip2 acts as a repressor of translation by decreasing the affinity of PABPs for polyadenylated mRNAs. As a matter of fact, Paip2 completely prevents PABP multimerization and thus prevents its poly(A)-organizing activity. The simplest model explaining Paip2 translation inhibition poses that Paip2 acts by disrupting the circularization of mRNAs. Evidence suggest that PABP cannot bind to eIF4G in the presence of Paip2 since the binding sites for Paip2 and eIF4G on PABP both overlap the second RRM (Khaleghpour et al. 2001). It was shown that Paip2 also inhibits the formation of the 80S ribosome initiation complex, demonstrating that Paip2 could affect a step that precedes the formation of this complex.

Nevertheless, the principal mode of action of Paip2 is to compete directly with Paip1 for binding PABP. Paip1 interacts with RRMs 1 and 2 of PABP whereas Paip2 interacts with RRMs 2 and 3. This overlap on RRM 2 explains the mutually exclusive binding of Paip1 and Paip2 on PABP. Thus, Paip1 and Paip2 regulation can be used to either stimulate or inhibit translation initiation. The mechanisms of Paip1/2 regulation do however, remain mostly unknown. Since Paip1 and Paip2 are both phosphoproteins, it is likely that their phosphorylation state could modulate their activities (Kahvejian et al. 2001).

9. Roles of RNA helicases

RNA molecules are highly prone to adopt secondary structures which play an important part in RNA processing. The classical example is the presence of hairpin structures in the 5′ UTR of the ferritin mRNA which prevents ribosome progression and thus control over translation. In this specific case, the proteins binding the stem-loop structure are responsive to environmental levels of iron, and appropriately, this region is referred to as the iron-response element (Kikinis et al. 1995; Cho et al. 2010). Another prime example is illustrated through the action of the stem-loop binding protein (SLBP) which binds to structures found in the 3′UTR region of histone mRNAs and regulates its translation (Allard et al. 2002; Whitfield et al. 2004). These examples clearly indicate that interactions between RNA and protein leads to important events of RNA processing involving the presence of secondary structures. These stable conformations can be destabilized by the action of RNA helicases that unwind the RNA molecules resulting in the displacement of bound proteins that can confer a new fate to the transcript.

Prokaryotic and eukaryotic genomes contain a large contingent of DNA and RNA helicases (Silverman et al. 2003). The latter are of interest to RNA processing and have been classified in five super-families that are distinguished by their respective domains and structure. Contrary to the last three super-families, members of the first two super-families form non-ring shaped complexes. From the RNA helicase database (http://www.rnahelicase.org/), the Human super-family 1 is composed of 11 members while the second super-family contains the DExD/H Proteins, a family of 62 members. RNA helicases are known to be involved in every aspect of RNA processing from transcription to mRNA splicing, including RNA transport, ribosome biogenesis and RNA decay (Cordin et al. 2006; Srivastava et al. 2010; Montpetit et al. 2011). They are generally thought as “RNA chaperones” or “maturases” that impact RNA-RNA, RNA-DNA and RNA-protein interactions (Tanner and Linder 2001).

This wide array of RNA helicases may be important for the complex regulation of the maternal RNA pools. Amongst these super-families the DEAD-box family contains the most

proteins (36 in Human). The family is named after the D-E-A-D (asp-glu-ala-asp) conserved NTP binding motif and its most prestigious member is eIF4A (Rogers et al. 2002). As mentioned earlier, eIF4A (DDX2) is present in the eukaryotic translation initiation complex and unwinds secondary structures in the mRNA to allow the binding of the 40S ribosome subunit and facilitate its progression along the 5'UTR of the mRNA (Kahvejian et al. 2001). The DEAD-box proteins are known to have helicase, unwindase in addition to RNPase activities (Linder 2006; Naarmann et al. 2010). The later activity is related to the formation and destabilization of RNPs which is integral to the state in which maternal mRNAs are stored. Moreover, the analysis of the protein composition of germ cell granules in C. elegans highlighted the presence of several DEAD-box proteins including Vasa (DDX4) and Vasa-like proteins (Bezares-Calderon et al. 2010; Updike and Strome 2010). So far, the presence of DEAD-box proteins has been confirmed in mammalian oocytes and early embryos, though their association with maternal RNA processing still remains to be demonstrated.

10. Controlling translation through eIF4E binding proteins

Another mechanism by which translation of maternal RNA could be controlled involves eIF4E binding proteins (4E-BP). These small repressors interact with eIF4E to prevent eIF4G binding and thus inhibit the formation of the eukaryotic initiation complex. This complex is named eIF4F and is responsible for cap recognition and is composed of eIF4E, the aforementioned DEAD-box protein eIF4A (DDX2) and eIF4G. eIF4G is the scaffolding protein that binds many proteins involved in translation initiation. eIF4E sequestration by a 4E-BP complex is a reversible process and is modulated by the phosphorylation of 4E-BP (Kahvejian et al. 2001).

11. The closed-loop model

The interaction between proteins localized on the 3'end of the mRNAs (PABP, PAIBP, CPEB) and the translation initiation complex localized at the 5'end involves mRNA circularization by physical interactions between both of the extremities. The closed-loop model is important for translation initiation and efficacy of protein synthesis since in addition to protecting mRNA from degradation by limiting ribonuclease access, this interaction also allows for more efficient translation. Indeed, mRNA circularization could promote ribosome recycling on the same mRNA through the physical proximity of both extremities due to their interactions. This model also protects the cell against the potentially lethal production of truncated proteins, since circularization allows efficient translation only for intact mRNAs and thus prevents the translation of partially degraded mRNA (Kahvejian et al. 2001).

12. The CPEB-Maskin model

Along these lines, the 5' UTR and the 3' UTR of mRNAs are the key regions for translational regulation. Numerous models try to elucidate the pathways responsible for the temporal regulation of maternal stores. Most of them involve different 4E-BPs, different polyadenylation systems and various ways to promote the formation of the closed-loop.
One well known model (Stebbins-Boaz et al. 1999) involves the 4E-BP Maskin protein. This factor binds both CPEB and the cap-binding translation initiation factor eIF4E. Its presence on eIF4E prevents eIF4G binding and the formation of the eukaryotic initiation complex. It was shown that Maskin-eIF4E interactions are significantly reduced during oocyte

maturation where many mRNAs are recruited for translation. The CPEB-Maskin regulation model functions so that, mRNA translation initiation is regulated by the release of Maskin from the CPEB-Maskin-eIF4E complex. The interaction between CPEB, Maskin and eIF4E forestalls the formation of the eukaryotic initiation complex by preventing eIF4G binding to eIF4E (Groisman et al. 2001). However, phosphorylation of CPEB by the protein kinase Aurora A enhances its affinity for CPSF, which binds the polyadenylation hexanucleotide HEX. CPSF binding to HEX promotes poly(A) polymerase recruitment, which elongates the poly(A) tail. PABPs can thereby bind the poly(A) tail which promotes the formation of the closed-loop through eIF4E-eIF4G interactions. eIF4G is a scaffold protein which allows the recruitment and binding of many proteins to form the eIF4F eukaryotic initiation complex. The RNA helicase eIF4A/DDX2 will join this complex to unwind the secondary structures of the 5'UTR of the mRNA. As for EIF3, it will act by promoting the recruitment of the 40S ribosomal subunit to initiate translation. Once the eIF4F complex is recruited, it journeys along the mRNA to reach the AUG initiation codon where the 60S subunit ribosome will join the complex and start mRNA translation.

The CPEB-Maskin model is probably one of the best known models of translation regulation applied to the context of maternal RNA management. Nevertheless, the portion of mRNAs regulated through this model is unknown. Furthermore, the model has been challenged as Maskin protein seems to be specific to non-mammalian species since no mammalian homologue has been identified yet despite sequence comparison (Cai et al. 2010). This discrepancy may again highlight some species specific means of regulating the early embryonic program through management of maternal RNAs.

13. A combinatorial code in the 3'UTR

The temporal control of protein production from stored maternal mRNAs through specific interactions of proteins requires the presence of a code imbedded in the UTR regions. Similarly to the HEX and CPE sequence known to drive mRNA polyadenylation, other sequences have been identified such as the embryo deadenylation element (EDEN) which is an AU-rich element found in the 3'UTR of certain mRNAs. It induces deadenylation in a subclass of mRNAs which undergoes deadenylation only after fertilization. An associated binding protein (EDEN-BP) is responsible for deadenylase recruitment such as the PARN or the CCR4–Pop2–Not complexes (Cosson et al. 2006). As an extent of these general processes, to regulate the complexe nature of maternal RNA management, it was proposed that the 3'UTR regions of stored mRNAs may contain a combinatorial code that could serve as a general molecular language to explain the temporal translation control. The proposed code involves the CPE and HEX sequences and explains how a specific mRNA is recruited for translation either early or late during oocyte maturation in mice (Pique et al. 2008). These observations were made from comparative analysis of the 3'UTR of mRNAs. The number and relative position of the two elements were shown to determine whether an mRNA is repressed or activated. An mRNA bearing a single CPE that does not overlap HEX is not repressed and translational activation will occur if the distance between the two sequences does not exceed 121 nucleotides. Furthermore, the distance between CPE and HEX will modulate the strength of activation. A maximal activation is induced by very close but non-overlapping sequences and increased distances induce a weaker polyadenylation (Pique et al. 2008). Additionally, an mRNA bearing a cluster of at least two CPEs is translationally repressed. The distance between the CPEs modulates the efficiency of the repression. An

optimal separation between two CPEs is of 10 to 12 nucleotides. These results propose that Maskin binds a heterodimer of CPEB and cannot bind efficiently on only one CPEB. The HEX sequence is involved in allowing a differential translational activation depending on early or late polyadenylation. Early polyadenylation during oocyte maturation is triggered by Aurora A kinase, which phosphorylates CPEB. This phosphorylation increases CPEB affinity for CPSF, which can bind to the HEX sequence (Pique et al. 2008). Subsequently, the process presented earlier can get under way: i.e. PARN is expelled and the polyadenylation triggered by GLD2 initiates translation.

Late polyadenylation is specific to mRNAs where one of the CPE sequences overlaps the HEX sequence and prevents CPSF from binding. In this situation, mRNAs are silenced. During oocyte maturation this occurs until the synthesis of the cytostatic factor component Mos concomitantly with the phosphorylation of CPEB by CDK1 (formerly known as Cdc2). Once the cell cycle must resume, the conditions will lead to the degradation of most CPEBs which allows CPSF to bind on the HEX sequence triggering polyadenylation and stimulating translation (Pique et al. 2008).

In addition to managing the poly(A) tail length, sequences imbedded in the transcripts have also been shown to act downstream of messenger recruitment during initiation of translation. These sequences impact the rate of translation by destabilizing the binding of the initiation complex. Indeed, typical imitation of translation is conducted through the following sequence of events: after eIF4F complex association, the 40S ribosomal subunit can bind the mRNA and scan its 5'UTR region for the start codon. During this process, most of the eIF4F initiation factors are released letting the eIF5 initiation factors bind the mRNA. This promotes the association of the large 60S ribosomal subunit at the moment of the recognition of the initiation codon (Kahvejian et al. 2001). A sequence found in the 3'UTR of some mRNA called the Differentiation Control Element (DICE) is involved in a process that can interfere with the recruitment of the 60S ribosomal subunit and thus inhibit the formation of the monosome. In this manner, the DICE complex maintains translational silencing (Naarmann et al. 2010).

Embedding the fate of the transcript in the UTR regions of mRNAs is an appealing model. However, the proposed model is incomplete as it may fit the mouse embryonic program which only lasts the duration of a single cell cycle but in other species where the embryonic program must undergo several cell cycles, the coding of the transcripts would involve an extremely complex mixture of 3'UTR isoforms. With the recent development of NextGen sequencing, surveys of embryonic transcripts can be accomplished at a very complete depth and such messenger heterogeneity has not been demonstrated so far.

14. Potential involvement of non-coding RNAs

The properties of miRNAs are still being explored, however, the diversity of these short RNAs has been recognized (Williams 2008). As well as playing roles in cellular growth and differentiation, miRNAs function to alter transcript processing. Roles also exist for degradation of mRNAs, as well as sequestering mRNAs from translation (Ma et al. 2010). Along with small interfering (siRNAs), micro-RNAs (miRNAs) have been shown to play a role in the formation of storage granules (Eulalio et al. 2007). When miRNA attach to mRNA with the help of AGO2, transcriptional silencing can occur. The complex is referred to as a microRNP and mRISC (microRNA induced silencing complex) and can associate with p-bodies or related structures (Williams 2008). In the mouse oocyte, it was recently shown that miRNA function is considerably reduced in translational repression and mRNA

degradation than previously thought (Ma et al. 2010). The authors discuss that in presence of high levels of miRNAs, the mRNAs are stabilized and this situation coincides with oocyte growth and RNA accumulation. It was also proposed that miRNA may be necessary for the maternal zygotic transition, suggesting that the miRNA activity inhibition may prepare the zygote's blastomeres for pluripotency, a program that assumes control over miRNA expression (Marson et al. 2008). The exact role the miRNAs may play in managing maternal RNAs in mammals still needs further investigation.

15. Concluding remarks

It is interesting to note that although focus has been directed at the understanding of how stored resources are managed to contribute to cell function and early embryogenesis, at least in mammals, it was shown that a large proportion of the maternal transcripts are never translated and are recruited to be sent for decay. In mouse, it has been shown that the content in maternal RNA decreases by about 19% during oocyte maturation (Bachvarova et al. 1985). Furthermore, it has also been proposed that complete degradation of maternal RNA is required for the mouse zygote to undergo the MZT (Schultz 2002). In the bovine, the EGA occurs when the embryonic RNA content are the lowest (Gilbert et al. 2009). The depletion of the maternal RNA content is massive and it is not paralleled by the amount of newly synthesized proteins during these developmental stages as determined by proteomic analysis (Massicotte et al. 2006). In addition, the abundance of ribosomal RNAs (rRNAs) during the pre-EGA stages show atypical profiles with low levels of 28S, the large rRNA component of the 60S ribosomal subunit, which may be indicative of lower translational potential in these early developmental stages (Gilbert et al. 2009). This would also support the observations of large reduction in RNA content that does not lead to massive protein synthesis thus supporting the fact that a large proportion of maternal RNAs are destroyed without ever being translated. So far, the physiological relevance of this apparent wastage is currently unknown.

Overall, it is clear that the processes that managed maternal RNAs have, for the main part, yet to be established. The knowledge so far is indicative of the complexity that underlies the regulation of the stored pools of RNAs during the embryonic program thus in absence of fully functional nuclear responsiveness. Species show marked divergence in the strategies employed to coordinate the use of the stored resources in a spatio-temporally manner. It is clear that regulation of protein synthesis from the stored pools of mRNA can be done at many different levels by interfering with the rates and efficacies during recruitment and/or initiation of translation. For every layer of potential regulation, several models are proposed and it is probable that a combination of many of these models exist to take into account the nature of the different classes of stored transcripts.

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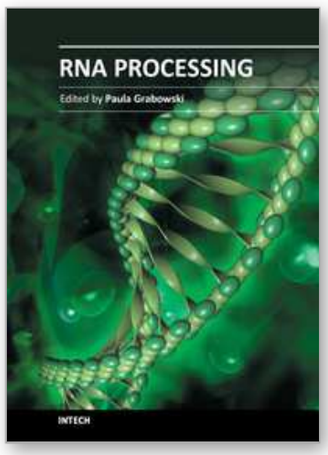
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RNA functions broadly as informational molecule, genome, enzyme and machinery for RNA processing. While these functions reflect ancient activities, they also remain vital components of contemporary biochemical pathways. In eukaryotic cells RNA processing impacts the biogenesis of RNA molecules of essentially every shape and function. The collection of articles in this volume describes the current state of understanding of the broad array of RNA processing events in animal and plant cells, key unanswered questions, and cutting edge approaches available to address these questions. Some questions discussed in this volume include, how viruses subvert the RNA processing machinery of the host cell, how the coordination of co-transcriptional RNA processing is regulated at the level of chromatin, the status of RNA processing in plant organelles, and how micro RNA machinery is biosynthesized and regulated.

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