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Invited Mini Review

Post-transcriptional and post-translational regulation during mouse oocyte maturation

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The meiotic process from the primordial stage to zygote in female germ cells is mainly adjusted by post-transcriptional regulation of pre-existing maternal mRNA and post-translational modification of proteins. Several key proteins such as the cell cycle regulator, Cdk1/cyclin B, are post-translationally modified for precise control of meiotic progression. The second messenger (cAMP), kinases (PKA, Akt, MAPK, Aurora A, CaMK II, etc), phosphatases (Cdc25, Cdc14), and other proteins (G-protein coupled receptor, phosphodiesterase) are directly or indirectly involved in this process. Many proteins, such as CPEB, maskin, eIF4E, eIF4G, 4E-BP, and 4E-T, post-transcriptionally regulate mRNA via binding to the cap structure at the 5' end of mRNA or its 3' untranslated region (UTR) to generate a closed-loop structure. The 3' UTR of the transcript is also implicated in post-transcriptional regulation through an association with proteins such as CPEB, CPSF, GLD-2, PARN, and Dazl to modulate poly(A) tail length. RNA interfering is a new regulatory mechanism of the amount of mRNA in the mouse oocyte. This review summarizes information about post-transcriptional and post-translational regulation during mouse oocyte meiotic maturation. [BMB reports 2011; 44(3): 147-157]

INTRODUCTION

Gene expression is regulated in several steps including transcription, post-transcriptional modification, translation, and post-translational modification. Among these processes, post-transcriptional and post-translational regulation provide cells with the device to respond rapidly and sensitively to internal or environmental changes. Oocytes use post-translational regulation such as phosphorylation, dephosphorylation, ubiquitination, and sumoylation to regulate the maturation process (1). The oocyte also relies on post-transcriptional regulation of pre-existing transcripts to precisely regulate maturation, because no transcriptional activity exists in the fully grown oocyte. Therefore, post-transcriptional and post-translational regulation in the oocyte are pivotal mechanisms that generate female gametes in many species. However, almost all reports about post-transcriptional and post-translational regulation are limited to *Xenopus laevis* or *Caenorhabditis elegans* oocytes. Reports about the mechanisms in mammalian species such as the mouse, are relatively few due to limitations in materials and techniques. Recently, improved techniques to handle the mammalian oocyte have been developed and more knowledge has been gained about the oocyte maturation process. As a result, several reports have provided new findings about post-transcriptional and post-translational regulation in mammalian oocytes. In this mini review, we will describe recent discoveries about these processes in the mammalian oocyte, particularly the maturation process of prophase I arrested oocytes, by a comparison with the relatively well-known results from *Xenopus* oocytes.

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DEVELOPMENT OF MOUSE OOCYTES

During early development in mouse oocytes, primordial germ cells (PGCs) are formed at the posterior proximal epiblast region of the mouse embryo (2), and the PGCs in the posterior region of the primitive streak migrate to the endoderm and residue in the hindgut (3). At embryonic day 11.5, the PGCs in the hindgut enter the genital ridge with increasing their population from 10-100 cells to 2,500-5,000 cells by mitotic division (4). The PGCs continuously proliferate by mitosis in the gonad and generate more than millions of diploid gamete precursors. The germ cells at this stage initiate meiosis to reduce their chromosome numbers from diploid to haploid. When a female is born, all oocytes in the ovary of most mammals are arrested at prophase I (diplotene) of the first meiotic cell cycle (1, 5) (Fig. 1). The arrested prophase I oocyte has prominent morphological properties, such as a large nucleus called a germinal vesicle (GV). Oocyte maturation, which alters the prophase I-arrested cell (oocyte) in meiotic metaphase II cell (egg), consists of three stages; 1) resumption of meiotic cell cycle including germinal vesicle breakdown (GVBD), chromosome condensation, and spindle formation, 2) the transition between meiosis I and meiosis II without S-phase, and 3) further arrest in meiotic metaphase II. The post-transcriptional

regulation of maternal mRNAs and post-translational regulation of proteins are critical to control the processes of fertilization and early embryogenesis as well as oocyte maturation.

OOCYTE MATURATION BY POST-TRANSLATIONAL MODIFICATION

Post-translational regulation is comparatively well investigated in recent years, whereas the mechanism of post-transcriptional regulation during oocyte maturation is largely obscure. Many reports have demonstrated that a high concentration of second messenger cAMP plays a pivotal role maintaining oocyte cell cycle arrest (6-9). The cAMP is generated by oocyte-specific adenylyl cyclase type 3 (AC3) (10) through a G-protein coupled receptor mediated signal (11, 12). Injection of an antibody against Gs, a stimulatory subunit of the trimeric G protein, causes oocyte maturation (13) and mice deficient in the *Gpr3* transcript using RNA interference (RNAi) methods reveal a stimulation of meiosis resumption in follicle-enclosed mouse oocytes (12). These results indicate that the GPR3 and Gs signals mediate cell cycle arrest in mouse oocytes. The binding of cAMPs to two regulatory subunits of the tetramer enzyme complex, cAMP dependent protein kinase A (PKA), leads to the release of the active form of the catalytic subunits. Active PKA phosphorylates several proteins including Wee1B kinase, a known substrate in the mouse oocyte (14). The kinases such as Wee1, Mik1, and Myt1 inhibit the complex by phosphorylation of two conserved residues, Thr14 and Tyr15 of Cyclin dependent kinase 1 (Cdk1) (15). Cyclin associates with Cdk1 to activate the Cdk1 kinase resulting in the generation of an M phase promoting factor (MPF) complex. MPF is a major mitotic and meiotic cell cycle modulator (16). In the mouse oocyte, Wee1B, which is activated by PKA, is involved in the inhibition of the MPF complex to arrest cell cycle. *In vivo* knockdown of Wee1B using RNAi induces oocyte maturation and polar body extrusion without hormonal stimulation (14). The Cdc25 phosphatase family removes inhibitory Cdk1 phosphates to activate MPF and promote cell cycle progression (17). Active PKA phosphorylates and inhibits cdc25 phosphatase in *Xenopus* and mouse oocytes (18, 19). Indeed, *cdc25b*$^{-/-}$ female mice are sterile, and the oocytes from knockout mice remain in a prophase arrested state after removal from the follicle (20). Active Wee1B kinase and inactive cdc25B cooperatively inactivate the Cdk1/cyclin B complex; therefore, the prophase oocyte, containing a high concentration of cAMP, remains arrested (Fig. 1).

From puberty, the oocytes are released from cell cycle arrest by a surge of luteinizing hormone (LH) and resume the meiosis

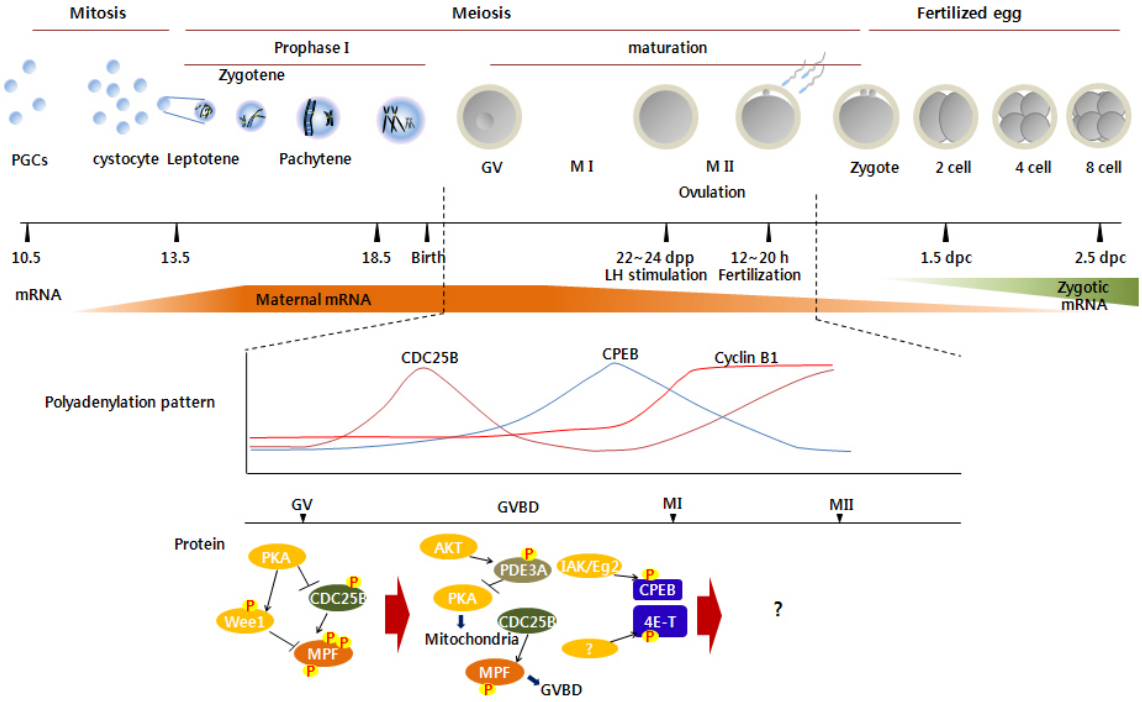

Fig. 1. The process of oogenesis and oocyte maturation. Reserved maternal mRNA gradually decreases during maturation and disappears in 2-cell zygotes. Zygote mRNAs are synthesized from the maternal to the zygotic transition (MZT) stage. The polyadenylation of many transcripts is regulated by several factors, which are associated with the 3' untranslated region during oocyte maturation. To fulfill the oocyte maturation process, many proteins are post-translationally regulated by phosphorylation, dephosphorylation, sumoylation, or degradation.

(1). The cellular mechanism of the resumption of oocyte meiosis is not well known yet. It is known that phosphodiesterase 3A (PDE3A) is the major cAMP hydrolyzing enzyme that decreases the cAMP concentration leading to the resumption of oocyte maturation in various species such as mice, rats, monkeys, and humans (21). It is supported by the facts that the mouse oocyte can be arrested at the GV state by PDE3A inhibitor treatment as well as by overexpression of the PKA catalytic subunit (21, 22). It has also been genetically demonstrated that oocytes from *pde3a* knockout mice have an increased cAMP level and fail to undergo spontaneous maturation *in vitro*. *pde3a*$^{-/-}$ oocytes undergo meiotic maturation by either an injection of a protein kinase inhibitor peptide (PKI) or by an injection of mRNA coding for Cdc25B phosphatase (23).

Although *Xenopus* oocytes are also arrested by high cAMP concentrations, the details of the cell cycle arrest mechanism appear to be different from those of mice. When *Xenopus* oocytes are removed from the follicle, the oocytes remain in stage VI and do not mature. *Xenopus* oocytes undergo GVBD through stimulation from an the exogenous signal such as progesterone treatment. In contrast, mouse oocytes spontaneously resume the cell cycle when they are removed from the follicle and surrounding cumulus cells. This observation indicates that the cell cycle blockage signal in mouse oocytes originates from the surrounding cells. Mouse oocytes restart the meiotic cell cycle following *in vivo* hormonal stimulation, which is easily observed under the microscope as GVBD. Although the exact mechanism that induces mouse oocyte maturation is still obscure, several proteins are known as regulators. Akt kinase is activated and phosphorylates PDE3A to enhance its enzymatic activity at the onset of oocyte maturation (24). Phosphorylated and activated PDE3A hydrolyzes cAMP leading to PKA inactivation through a re-association of the catalytic subunits with cAMP-free regulatory subunits. The inactivated PKA loses its ability to phosphorylate the substrates, Wee1B and Cdc25B, which are involved in the maintenance of GV oocyte arrest. As a result, the Cdk1/cyclin B complex is activated and induces GVBD, chromosome condensation, and spindle formation. After completion of the first meiosis by extrusion of the polar body, the egg starts meiosis II without DNA replication (S phase) and re-arrests at metaphase II. The arrested egg is ovulated and completes its meiotic cell cycle following fertilization with sperm (Fig. 1).

The other post-translational mechanism in mouse oocytes is tuning of the protein amount by ubiquitin-mediated protein degradation. The role of anaphase-promoting complex/cyclosome (APC/C) for protein destruction in the mitotic and meiotic cell cycle has been well summarized in several studies (25, 26); therefore, only one recent discovery will be discussed here. The major protein that is regulated by ubiquitin-mediated proteolysis is cyclin B1, a subunit of the MPF complex (Cdk1/cyclin B) in the metaphase transition (27). Recently, anaphase-promoting complex/cyclosome (APC/C), which is activated by CDH1 binding, has been shown to degrade cyclin B to prevent the onset of meiotic resumption by maintaining low Cdk1 activity in prophase I arrested oocytes (28, 29). CDC14B functions to lower Cdk1 activity by degrading cyclin B1 through activation of the Cdh1/APC/C complex in GV-arrested mouse oocytes (30).

POST-TRANSCRIPTIONAL REGULATION OF MATERNAL MRNA IN THE OOCYTE

Although almost all species use common basic machinery such as the Cdk1/cyclin complex to regulate meiosis; however, some differences in the detailed mechanism exist among species. One of the most important concepts is whether protein synthesis is indispensable during oocyte maturation. *Xenopus* and pig oocytes cannot induce GVBD in the presence of protein synthesis inhibitors (31), whereas mouse oocytes undergo GVBD in the presence these inhibitors (32). Nevertheless, protein synthesis is essential for completing meiosis in the mouse oocyte after GVBD, considering that adding cycloheximide to post-GVBD oocytes blocks polar body extrusion (32). These results show that modulating translation through post-transcriptional regulation of existing transcripts is important to control meiosis.

Post-transcriptional regulation controls many cellular mechanisms such as cell cycle, neural cell plasticity, embryo development, cancer cell occurrence, and oocyte maturation (reviewed in ref. (33-35)). Because gene transcription does not occur during mouse oocyte maturation due to the absence of the proteins involved in transcription, the post-transcriptional regulation of resident mRNA is a crucial step to accomplish all oocyte maturation processes. After fertilization, the embryo undergoes a rapid mitotic cycle, without G_1 and G_2, and reaches the maternal to zygotic transition (MZT) (36). Transcription begins from the MZT stage including lengthening of the cell cycle, annexation of G_1 and G_2 during cell proliferation, and degradation of maternal transcripts (Fig. 1). Promotion or repression of translation initiation by several proteins, and mRNA degradation are key steps among the mechanisms implicated in the post-transcriptional regulation of maternal transcripts during oocyte maturation.

Regulation of translation by complex in 5' UTR

Transcripts are translated into polypeptides by initiation, elongation, termination, and ribosome recycling. The initiation, controlled through the 5' and 3' untranslated region (UTR) of the transcripts, is the most important regulatory step in mRNA expression (37). Translation is initiated by assembly of the eIF4F complex consisting of eIF4E, eIF4G, and eIF4A on the 5' m^7Gppp capping structure of the transcript. The eIF4F complex recruits the ribosomal complex to the ribosome recognition sequence in the 5' UTR for translation initiation. Therefore, the formation of the eIF4F complex, particularly the association between mRNA bound eIF4E with eIF4G, is the most critical rate limiting steps to initiate translation (38). eIF4E has

several consensus sites for phosphorylation by several kinases to serve as a major regulator of translation initiation. The serine 209 of eIF4E is a key residue for regulation in response to serum-treatment or mitogenic and inflammatory stimuli (39-41). It is believed that eIF4E is regulated by PKC, as it has several putative PKC phosphorylation sites and is phosphorylated by PKC, at least *in vitro* (40). It turns out that MNK in fact phosphorylates eIF4E *in vivo* to enhance its affinity for the 5' cap structure in somatic cells (42). Although the significance of serine 209 phosphorylation of eIF4E during protein synthesis is unclear (43), serine 209 phosphorylation plays a role in the cellular system, as this phosphorylation has an effect on *Drosophila* growth (44) and phosphorylation with DNA damage stimulates eIF4F formation (45).

Other reports suggest that protein synthesis is more precisely modulated by the interaction between eIF4E and eIF4G than the eIF4E phosphorylation state (46). eIF4G is a scaffold protein that forms the eIF4F complex by recruiting with eIF4A, eIF4B, eIF4E, and many other proteins. The binding of eIF4G with eIF4E is accomplished by the 4E binding motif (YXXXXL ϕ, ϕ : hydrophobic residue) in the eIF4G protein (47), and the motif is found in several eIF4E binding proteins such as the eIF4E binding protein (4E-BP) and the eIF4E transporter (4E-T, eIF4ENIF) (47, 48) (Table 1). A wealth of evidence has demonstrated that 4E-BP is a major regulator of the eIF4E and eIF4G interaction. Hypophosphorylated 4E-BP, which has increased affinity for eIF4E, prevents eIF4E from associating with eIF4G. Upon phosphorylation by Akt and mTOR, 4E-BP dissociates from eIF4E. The eIF4E dissociated from 4E-BP binds to eIF4G to load the eIF4F complex on the mRNA for protein synthesis (49). In starfish oocytes, the dissociation between eIF4E and 4E-BP occurs upon the completion of GVBD, and this process is achieved by the mTOR signal (50). Activation of the mTOR or MNK pathways leads to the induction of mRNA translation in the mouse male germ cell (51). It is hypothesized that during mouse oocyte maturation, eIF4E is released from detention by 4E-BP, as protein synthesis for completing GVBD and the morphological changes increase during this process. Interestingly, Akt activity increases during mouse oocyte maturation to activate PDE3A (24). Active Akt and its downstream mTOR pathway may phosphorylate 4E-BP to allow eIF4E to associate with eIF4G in the oocyte. It would be very interesting to determine the relationship between translational regulation by 4E-BP and Akt activation in the mouse oocyte.

The eIF4E is also regulated by binding with other proteins as well as 4E-BP (Table 1). *Drosophila* germline-specific eIF4E binds to pos-1, pal-1, mex-1, and oma-1 to maintain mRNA storage and germ cell maturation (52). 4E-T is another protein that has the eIF4E binding motif and functions to transport eIF4E from the cytosol to the nucleus as its name connotes (48). In the mouse oocyte, Clast4 (the ortholog of human 4E-T) is stably expressed in the cytosol and phosphorylated by still unknown kinase(s) during oocyte maturation (53). The effect of Clast4 phosphorylation either on the protein itself or on oocyte maturation is still unclear. *Drosophila* also has the 4E-T ortholog, cup, which is a eIF4E binding and nucleocytoplasmic shuttling protein (54). Cup interacts with the nanos protein to maintain female germline stem cells, and it represses translation of *oskar* and *nanos* mRNA. Furthermore, cup controls eIF4E phosphorylation in the ovary (55). In *Xenopus* oocytes, ovary-specific eIF4E1b and 4E-T bind with cytopolyadenylation element binding protein (CPEB) to inhibit specific mRNA translation (56). The existence of mouse eIF4E1b has never been tested in the mouse oocyte, even though Clast4 is specifically expressed in ooplasm (53).

Another mechanism to regulate eIF4E is sumoylation. This modification promotes the formation of an active translation initiation complex, and stimulates translation of the proteins

Table 1. eIF4E interacting protein

Name*	Species	Function	Associated elements	Mouse oocyte expression†
4E-BP	H, X, M	Translation inhibition by competing with eIF4G	mTOR complex	ND
eIF4G	H, X, D, M	Scaffold protein of eIF4F	Paip, Mnk	Y
Mnk	H, M, C	Phosphorylates on S209 of eIF4E	eIF4G, Erk2, p38	ND
Bicoid	D	Represses translation of caudal mRNA		
Maskin	X, H, M	Interfering with formation of eIF4F by binding to CPEB and eIF4E	CPEB	Y
4E-T(CUP)	X, H, (D), M	Transport s eIF4E from cytoplasm to nucleus (represses translation of nanos and oskar mRNA)	CPEB, eIF4E, Smad, (BRE/Bruno)	Y
PML	H, M	Binds to eIF4E and prevents cap-binding, leading to decrease in mRNA transport from nucleus	mTOR, Nanog	ND
Gemin5	H, D, M	Component of gemini body Inhibition of both cap-dependent and IRES-driven translation	DDX20, SNRPD, SIP1, SMN2	ND
Neuroguidin	H, D, C, M	Represses translation of CPE-containing mRNAs	CPEB	ND
CYFIP1	H, C, M	Represses translation of mRNA bound FMRP	ACTA1, FMR1, RAC1	Y

H: human, X: xenopus, D: drosophila, C: caenorhabditis, ND: no data or not detected. *reviewed in (99, 100), †data based on ref. (101).

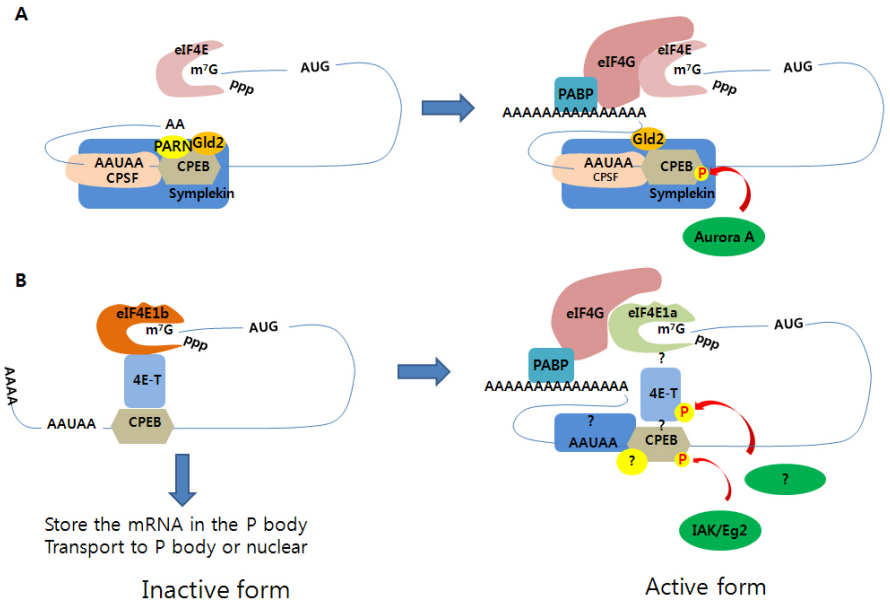

Fig. 2. The closed-loop model for post-transcriptional regulation of translation initiation. (A) While oocytes are arrested in the GV stage, CPEB, which binds to CPE in 3' untranslated region of the transcript, forms a complex with the scaffold protein symplekin, cleavage and polyadenylation specificity factor CPSF, cytoplasmic poly(A) polymerase GLD-2, and deadenylase PARN. The interplay between GLD-2 and PARN helps to balance the length of the mRNA poly(A) tail. PARN is blocked or removed to strengthen the role of GLD-2 for polyadenylation after CPEB phosphorylation by Aurora kinase. (B) 4E-T also binds with CPEB and probably with eIF4E1b. It seems that this complex hinders eIF4E1a from interacting with the cap structure to prevent translation initiation. However, the translation repression mechanism by 4E-T and 4E-T binding proteins is still unclear.

that are important for cell proliferation and preventing apoptosis (57). SUMO-1,2,3 were localized as concentrated dots in the GV of prophase I-arrested mouse oocytes and disruption of sumoylation by overexpressing the SUMO-specific isopeptidase, Senp2, leads to a defect in MII spindle organization in mature eggs (58). However, the sumoylated state of eIF4E during mouse oocyte maturation is still unknown.

Regulation of translation by 3' polyadenylation of transcript

Although the translation initiation step, particularly eIF4F complex formation in the 5' UTR, is the major target for post-transcriptional regulation, the interaction between the two complexes assembled in the 5' and 3' UTR is also a crucial point to regulate translation. When the two complexes interact, mRNA forms a "closed-loop structure" to modulate translation capacity (Fig. 2). The hexa-polyadenylation signal AAUAA, and the U-rich cytopolyadenylation element (CPE) in the 3'UTR of many mRNAs are specific cis-acting sequences in *Xenopus* oocytes to produce protein-RNA complexes. Before the beginning of *Xenopus* oocyte maturation, translation is repressed by a loop generated by several protein binding to the 5' and 3' ends of the transcript (59). The most well-known loop structure model is the protein complex consisting of CPEB, maskin, and eIF4E (60). Maskin, which binds simultaneously to CPEB on the CPE of 3' UTR and eIF4E on the 5' cap structure, is implicated in the repression of translation by obstructing the association of eIF4E with eIF4G and preventing the poly(A) addition. For example, cyclin B1 mRNA, a major regulator of oocyte maturation, has a short poly(A) tail of 20 to 40 nucleotides and is kept in a dormant state by binding to maskin (61).

CPEB phosphorylation during *Xenopus* oocyte maturation causes a poly(A) addition at the end of transcript (62). Therefore, ablation of the hexa-polyadenylation signal and the CPE sequence in the mRNA or blockage of CPEB by a CPEB specific antibody in progesterone-treated *Xenopus* oocytes interferes with the poly(A) additions of cyclin, cdk2, and c-mos mRNA (63). Eg2 (Aurora A kinase) phosphorylates CPEB at the onset of *Xenopus* oocyte maturation to sequentially bind with several factors such as cleavage and polyadenylation specificity factor (CPSF) and poly(A) polymerase (PAP) to elongate the poly(A) tail of 80 to 250 residues (64). The poly(A) binding protein (PABP) is a core protein that achieves the "active" closed-loop of transcripts by joining the elongated poly(A) tail of mRNA to eIF4G in the eIF4F complex (65). It was believed that c-mos translation, which activates the MAPK pathway to resume cell cycle progression in *Xenopus* oocytes, is regulated by this sequential binding process of several proteins (66). However, much evidence from several experiments such as immunoprecipitation and protein depletion indicate that CPEB already binds with cytoplasmic poly(A) polymerase GLD-2, deadenylase PARN, and scaffold protein symplekin on the transcript in inactivated *Xenopus* oocytes (67) (Fig. 2). GLD-2 and PARN balance the length of the poly(A) mRNA while the oocyte is arrested in the GV state. Following hormone stimulation, the phosphorylated CPEB blocks or removes PARN to strengthen the cytoplasmic poly(A) polymerase GLD-2 to add the poly(A) tail. As a result, CPEB plays a significant role in *Xenopus* oocyte maturation by dual way to repress or activate translation.

Richter *et al*. reported that kinase IAK1/Eg2 catalyzes CPEB phosphorylation and cytoplasmic polyadenylation in mouse

maturing oocytes. During this process, the proteins, which are involved in polyadenylation, are localized at the same site in *Xenopus* oocyte (68). In mice, CPEB phosphorylation is related to the regulation of mouse ovarian follicular development; therefore, CPEB knockout results in the disruption of meiotic progression at the pachytene stage. Oocyte CPEB knockdown using stage-specific expressed siRNA induces parthenogenetic cell division in oocytes, detachment from the cumulus granulosa cell layer, and spindle and nuclear anomalies (69). Although Aurora A stimulates cyclin B and mos protein synthesis and promotes meiotic resumption in the porcine system (70), the role of Aurora A kinase in the translational regulation of mouse oocytes is still ambiguous. Microinjection of Aurora A antibody during mouse oocyte maturation decreases the degree of GVBD and disturbs MI spindle organization (71). However, Aurora A is not activated at the onset of mouse oocyte maturation but is probably involved in the second meiotic process. This result indicates that other mechanisms are necessary to activate the translational regulation of maternal transcripts in mouse oocytes. Based on the observation that calcium/calmodulin-dependent kinase II (CaMK II) phosphorylates mouse CPEB (72) and that CaMK II is involved in mouse oocyte maturation (73), CaMK II has recently received attention as a novel regulator of translation in the mouse oocyte.

Although CPEB and maskin are important for regulating translation, it is controversial whether the proposed working model truly represents the actual translation regulation process in the oocyte. As pinpointed by Kozak, direct evidence for the interaction between maskin and eIF4E has not been shown yet (74). All of the evidence is indirect, and even the yeast-two hybrid experiment just revealed that the interaction is very weak (74, 75). In fact, a coimmunoprecipitation experiment showed that eIF4E1 and maskin do not bind together, and, if so, they bind weakly in *Xenopus* oocytes (56). Another question is related to the eIF4E binding consensus site. The Y and L residues at the 4E binding motif (YXXXXL) are well conserved among eIF4E binding proteins; however, this is not true for maskin (Y is replaced by T) (60). Additionally, mitosis is unexpectedly delayed by maskin depletion in Hek 293 cells, leading to the suspicion of a negative regulation of cyclin B1 by maskin *in vivo* (75). It seems that the interaction between CPEB and maskin is evident, as many data show that CPEB binds with maskin (59, 60, 76, 77). Therefore, more direct and precise experiments are needed to elucidate the relationship among CPEB, maskin, and eIF4E.

Another thing to be considered is the role of maskin in the growing oocyte. Because maskin first appears at stage VI in *Xenopus* oocytes (77, 78), it plays a role only after the oocyte is fully grown not in the growing oocyte. Recently identified *Xenopus* 4E-T creates a bridge between CPEB and ovary specific eIF4E (eIF4E1b), as maskin does in grown oocytes (56). Mouse 4E-T is stably expressed during all mouse oocyte stages and binds to CPEB and eIF4E (53). It appears that mouse 4E-T also plays the same role as maskin to inactivate mRNA translation during maturation and early development of mouse oocytes. However, no studies have reported the differences and similarities between the working mechanism of 4E-T and those of maskin. The expression and role of mouse ovary specific eIF4E (eIF4E1b) are also unclarified.

Although CPEB and its binding partners are important for regulating translation, some other mechanisms without the CPEB protein also regulate translation. Musashi1 associates with the 3' UTR of its target mRNA and prevents the initiation of translation by blocking the interaction between eIF4G and PABP (79). The deleted in azoospermia-like (Dazl) protein (*Xenopus* Xdazl, mouse Dazl, human DAZL) promotes germ cell differentiation and regulates the later stages of meiosis and the development of haploid gametes (80). The Dazl protein binds to GU rich regions in the 3' UTR and recruits additional PABP without changing the poly(A) tail length to initiate translation in *Xenopus* germ cells (81). Dazl also inhibits translation by interacting with other inhibitor proteins, deadenylase Pum2 and DAZAP1 (82, 83). DAZAP1 phosphorylation by Erk2 leads to the release of DAZAP1 from DAZL to induce the initiation of translation (82). In terms of mammalian system, DAZL mRNA and protein levels increase during pig oocyte maturation (84); however, no studies have reported on Dazl at the onset of mouse oocyte maturation. It would be very interesting to examine the existence of a closed-looped transcript in mouse oocytes and the regulatory mechanism of the transcripts by clarifying the relationship among the many proteins assembled in the 5' and 3' UTR of the maternal transcript.

An alternative model for translation regulation is cap methylation induced by the poly(A) tailing to increase the initiation of translation (85, 86). In fact, the activity of a cytoplasmic guanine-7-methyltransferase increases during oocyte maturation (87). Although poly(A) tailing and N-7 methylation of the cap synergistically stimulate translation during oocyte maturation, they might not be a critical factor, as cap methylation of certain mRNAs is not required for their translational recruitment by polyadenylation (87).

Regulation of translation by transcript degradation

Adjusting the amount of accumulated transcripts by degradation is another mechanism to determine the amount of proteins available during oocyte maturation and embryonic development. When mRNA is stained with EtBr, the amount of mRNA in the ovulated egg is 19% less than that in the full-grown mouse oocyte (88). This finding indicates that maternal mRNA is degraded during meiotic resumption. Another report proposed that maternal RNA in the oocyte gradually degrades from the onset of maturation and that almost all maternal RNA disappears at the 2-cell stage (89). The elucidated transcript degradation mechanism in budding yeast is related to dissolution of the closed-loop structure of polyadenylated transcript. The deadenylated transcript, which is subsequently decapped by the Dcp1/Dcp2 enzyme, is degraded by the 5' to 3' exonuclease Xrn1p (90). In contrast, deadenylated mRNAs du-

ring *Xenopus* oocyte maturation do not cause decapping, reflecting the absence of decapping activity in *Xenopus* oocytes (87). In the mouse oocyte, the level of DCP1A, a component of the decapping complex, is low in GV oocytes and sharply rises during meiotic maturation followed by a dramatic increase in MII eggs (91). This result suggests that DCP1A functions in the first wave of maternal mRNA degradation; however, it is unclear whether the protein plays a critical role during mouse oocyte maturation.

It seems that polyadenylation, deadenylation, and degradation of mRNA cooperate to determine the amount of protein in fully grown mouse oocytes, because the length of the poly(A) tail is correlated with translation efficiency. For example, CPE containing hypoxanthine phosphoribosyltransferase (HPRT) mRNA is polyadenylated and actively translated during mouse oocyte maturation. After the completion of maturation and fertilization, mRNA is deadenylated and declines greatly during the two-cell stage (89, 92). However, this does not mean that deadenylation always causes mRNA degradation. A significant amount of mRNA is only deadenylated without degradation during maturation. The majority of housekeeping maternal transcripts such as actin and ribosomal proteins are not cytoplasmically polyadenylated during oocyte maturation because they do not contain CPE in their 3' UTR (89). The default state of actin mRNA is deadenylated but not degraded during *Xenopus* and mouse oocyte maturation, and actin mRNA is only degraded after MBT (92).

RNA interfering (RNAi), the process of mRNA regulation by small RNA, particularly micro RNA (miRNA) and short interfering RNA (siRNA), is a marvelous discovery of the last decade. The difference between siRNA and miRNA originates from the base-pairing property. Perfect base-pairing between siRNA and its target mRNA results in cleavage of the target mRNA, whereas a mismatched and bulged structure is related to the translation repression function of miRNA. However, after the discovery of miR-196 miRNA, which binds to HoxB8 mRNA with a perfect complementarity and cleaves its target mRNA (93), the concept regarding translational repression with miRNA and cleavage of mRNA with siRNA was weakened. The siRNA and miRNA share several protein components such as RNase III Dicer to generate short double-stranded RNA and work with several argonaute proteins. The miRNAs are ~21-nucleotides-long small RNA that function post-transcriptionally by imperfectly base-pairing with the 3'-UTR of mRNA to repress protein synthesis. Although the mechanisms are not fully understood, it appears that miRNA functions by repressing the initiation of translation or deadenylating mRNA in the ribonucleoprotein complex with the argonaute and GW182 proteins (reviewed in (94)). miRNA is also involved in RNA degradation by moving the mRNA to the P bodies, which is a cytoplasmic RNA processing center containing translational repressor, RNA binding proteins, mRNA degradation enzymes, decapping enzymes, and deadenylation enzymes.

Many reports have indicated that endogenous RNAi activity occurs in the mouse oocyte (95, 96), and that Dicer is indispensable for oocyte maturation (97). However, a deficiency in Dgcr8, which is required for miRNA processing, does not affect oocyte maturation (98). This finding suggests that only endogenous siRNA, and not miRNA, regulates the RNA level in mouse oocytes (98). This result is supported by the absence of P bodies, the location in the cytosol where miRNA processes mRNA, in the mouse oocyte (91). mRNA is stored in a specific mRNA storage domain in the fully grown oocyte, therefore, it is speculated that this RNA granule is involved in the maternal RNA storage and degradation process in the oocyte (91). The reason why the miRNA mechanism is repressed and endo-siRNA is qualified to regulate maternal RNA processing is unclear.

CONCLUSION

Post-transcriptional and post-translational regulation in the oocyte been vigorously investigated for several decades. In particular, the regulatory mechanism of *Xenopus* oocyte maturation has been investigated because this specimen has a large volume of cytoplasm containing a large amount of maternal transcripts and proteins. Although post-transcriptional and post-translational regulation in mammalian oocytes had been the focus of many researchers, it is not easy to understand all of these processes. Recent technical improvements in biological, biochemical, and genetic methods has helped to open new insights into the early development of mammalian species. This information will be applied to the clinical treatments for infertility and the invention of new contraceptive drugs.

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