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REVIEW

Post-translational regulation of the maternal-to-zygotic transition

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Abstract

The maternal-to-zygotic transition (MZT) is essential for the developmental control handed from maternal products to newly synthesized zygotic genome in the earliest stages of embryogenesis, including maternal component (mRNAs and proteins) degradation and zygotic genome activation (ZGA). Various protein post-translational modifications have been identified during the MZT, such as phosphorylation, methylation and ubiquitination. Precise post-translational regulation mechanisms are essential for the timely transition of early embryonic development. In this review, we summarize recent progress regarding the molecular mechanisms underlying post-translational regulation of maternal component degradation and ZGA during the MZT and discuss some important issues in the field.

Keywords MZT · ZGA · Phosphorylation · Ubiquitination · Histone modification

Introduction

Embryogenesis begins with the fertilization of a haploid egg by a haploid sperm. Then, a highly coordinated cascade of events is initiated in the earliest stages of embryogenesis. Maternal mRNAs and proteins accumulated in the egg during oogenesis control almost all aspects of initial embryonic development, but transcription of the zygotic genome is quiescent. After several rapid cell divisions, maternal mRNAs and proteins are eliminated, the zygotic genome is activated, and developmental control is transferred from maternal components to the gene products synthesized from the zygotic genome, defined as maternal-to-zygotic transition (MZT) [1–5]. The MZT involves two major processes, including the clearance of maternal mRNA and proteins, which are necessary for oocyte maturation and the earliest stages of embryogenesis but become unnecessary or possibly harmful in embryonic development, and zygotic genome activation (ZGA), which establishes new zygotic instructions for embryogenesis [1, 2, 4].

During the MZT, there are extensive variations in the timing and duration of these events among different species, which occur between 2 h (*Drosophila*) and 2 days (mouse) after fertilization (Fig. 1) [2]. In *Caenorhabditis elegans*, about 30% maternal mRNAs appear to decay before the four-cell stage, and the first zygotic transcription can be detected in the four-cell stage, a little over 2 h after fertilization [6, 7]. In *Drosophila melanogaster,* the maternally deposited mRNAs are destabilized upon egg activation and the zygotic transcription first initiates at the cleavage cycles 8 and increases rapidly until the cleavage cycles 14 [2, 8]. In zebrafish, the zygotic genome activation occurs at around ten cell cycles after fertilization, together with maternal mRNA clearance [9]. In *Xenopus laevis*, the MZT begins at fertilization, and degradation of maternal messages begins immediately after fertilization, and ends during gastrulation, the major ZGA occurs 6 h later [10]. In mouse, a large

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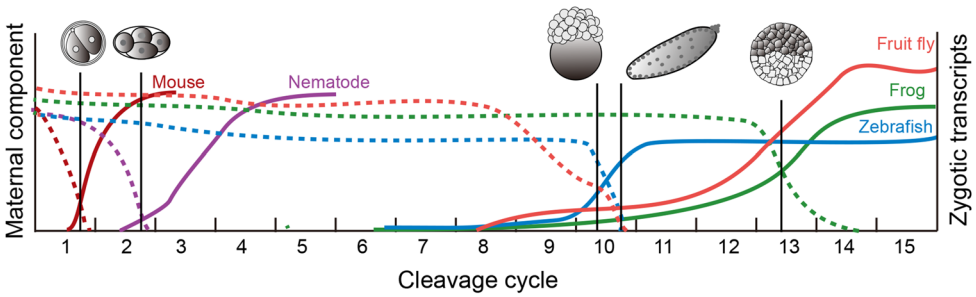

Fig. 1 Overview of the maternal-to-zygotic transition in several model organisms. Dashed curves represent the degradation profiles of destabilized maternal component in each species. The solid line curves illustrate cumulatively increase in zygotic gene expression

fraction of the maternally supplied mRNAs is degraded by the two-cell stage, and the first wave of transcription commencing occurs at the one-cell stage [2, 5]. In human, 10% of the expressed maternal mRNAs and 2% of the lncRNAs are eliminated between the four- and eight-cell stage, and the ZGA occurs at four- to eight-cell stage, 2 days after fertilization [5, 11].

The MZT is one of the most complex and crucial developmental processes in the life of an organism and multiple mechanisms at different levels regulate the clearance of the maternal components and the activation of the zygotic genome, including transcriptional, post-transcriptional, translational, and post-translational regulation [12–19]. Because the zygotic genome is inactive in the early stages of embryogenesis, post-translational regulation is particularly important in the MZT. Various protein post-translational modifications have been identified during this stage, which are essential for the timely transition of embryonic development. The focus of this review is on recent advances in our understanding of the molecular mechanisms underlying the post-translational regulation of maternal mRNA-protein degradation and zygotic genome activation during the MZT.

Post-translational regulation of maternal mRNAs clearance

At the earliest stages of embryogenesis, the transcription of the zygotic genome is quiescent and the developmental processes in the embryo rely exclusively on maternal mRNAs, which are produced by immature oocytes or nurse cells and are regulated under the control of mRNA stability, translation, and localization [3, 18, 20, 21]. During the MZT, approximately 60% of maternal mRNA levels are considerably reduced in *Drosophila* [3, 4, 22] and up to 90% of maternal mRNA is eliminated in the two-cell stage of the mouse [23, 24]. The stability of maternal mRNAs is dependent on three main features: the mRNA sequence, the 7-methylguanylate (m7G) cap, and the length of the 3′ untranslated region (UTR) [4]. Multiple mechanisms for maternal mRNA clearance have been identified, including (1) RNA-binding proteins (RBPs) that direct the maternal degradation machinery to its target maternal mRNAs, (2) small RNA-induced silencing, (3) some signaling pathways in the early embryos, (4) spatial control of transcript clearance, and (5) m^6A-dependent RNA decay, which was recently uncovered during zebrafish MZT [3, 4, 20, 25, 26]. Post-translational modifications have recently been reported to participate in the clearance of maternal mRNAs via the activation of maternal mRNA decay machinery, and the regulation of maternal mRNA clearance-related RNA-binding proteins and small RNA biogenesis.

Activation of maternal mRNA decay machinery

Little is known about the initiation of maternal mRNA decay. Maternal transcripts are destabilized in activated eggs, indicating that egg activation is necessary and sufficient to trigger maternal mRNA destabilization, while the exact link between them remains unclear [27]. Nonetheless, the post-translational cascade triggered upon egg activation has been identified to function in maternal transcript destabilization in many organisms, such as the Pan gu (PNG) Ser/Thr kinase complex, which regulates the translation of Smaug in *Drosophila* and the extracellular signal-regulated kinases 1 and 2 (ERK1/2) mediated phosphorylation is essential for the activation of BTG4 in mouse.

In *Drosophila*, the Pan gu (PNG) Ser/Thr kinase complex is a crucial regulator of the S phase to metaphase transition by ensuring adequate Cyclin B protein levels and consequently the activity of the cyclin-dependent kinase (CDK)/cyclin complex [28]. Following egg activation, the PNG kinase complex promotes the translation of a multifunctional and highly conserved RNA-binding protein (RBP), Smaug (SMG), to trigger maternal transcript clearance [27]. Smaug is responsible for both the translational repression and degradation of maternal mRNA by binding RNA stem loop structures, which are called Smaug recognition elements (SREs), through a sterile alpha motif (SAM) [29–31]. For maternal mRNA clearance, Smaug recruits the CCR4/POP2/NOT-deadenylase complex to initiate poly (A) tail shortening and subsequent mRNA elimination [32–34]. Smaug can also

work together with piRNAs and their associated proteins to promote maternal mRNA decay [35]. Microarray analyses have shown that Smaug was required for the degradation of two-thirds of unstable maternal mRNAs [8]. PNG regulates the cytoplasmic polyadenylation of *smg* mRNA via the PUM (pumilio RNA-binding family member) [8], which is an RBP and has been implicated in the deadenylation and clearance of maternal mRNAs via binding with Pumilio-binding element (PBE) and the recruitment of Nanos and the deadenylation complex [3, 4, 36]. As in *Xenopus*, PUM1 can be phosphorylated during oocyte maturation and may induce a conformational change in the complex consisting of PUM1 and cytoplasmic polyadenylation element (CPE)-binding protein (CPEB) that targets CPEB for dissociation, which is required for the translational activation of *cyclin B1* mRNA [37, 38]. Therefore, PNG may phosphorylate PUM to induce a conformational change and relieves the translational repression of Smaug. Because the restoration of polyadenylation in *png* mutants is not sufficient to rescue Smaug translation [8], one or more additional factors may act in parallel to modulate Smaug translation through *smg* mRNA's 3′UTR (Fig. 2a). The activity of PNG could also be regulated by Cyclin B/CDK1-catalyzed phosphorylation on GNU, preventing binding to PNG–PLU and the activation of PNG kinase (Fig. 2a). Thus, meiotic completion promotes the dephosphorylation of GNU and PNG kinase activation to further regulate Smaug translation [39].

A mitogen-activated protein kinase (MAPK) cascade and extracellular signal-regulated kinases 1 and 2 (ERK1/2) have also been found to activate the translation of BTG4 to promote maternal mRNA clearance in mouse [40]. Upon oocyte meiotic resumption, ERK1/2 is activated by upstream kinases and triggers CPEB1 phosphorylation and $SCF^{\beta\text{-}TrCP}$-dependent degradation. The phosphorylation and partial degradation of CPEB1 stimulates polyadenylation and translational activation of BTG4 (Fig. 2b), which belongs to the TOB/BTG family of proteins and promotes maternal mRNA degradation by recruiting the RNA deadenylation complex CCR4-NOT onto target mRNAs [41–43].

Regulation of RNA-binding proteins

RBPs regulate almost every step of RNA life, including RNA stability, translation, and localization, and are crucial for the temporal control of the maternal mRNA decay machinery [3, 20, 44, 45]. Several RBPs have been identified to bind to and direct the degradation of largely distinct subsets of maternal mRNAs [2–4], such as MEX-5/MEX-6 in *C. elegans* [46]; Smaug, Pumilio, AU-rich element-binding

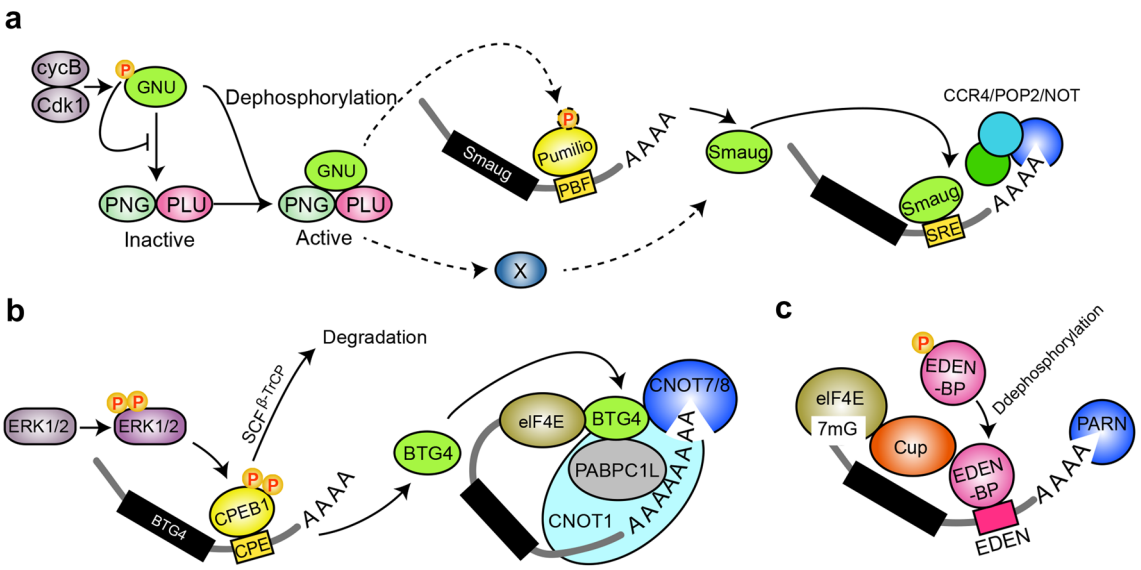

Fig. 2 Mechanisms of post-translational regulation of maternal mRNA clearance. **a** PNG-mediated polyadenylation regulates *smg* mRNA translation. Cyclin B/CDK1-catalyzed phosphorylation on GNU inhibits the interaction between GNU and PNG–PLU, resulting in the inactivation of PNG kinase. Meiotic completion promotes GNU dephosphorylation and PNG kinase activation. The active PNG kinase phosphorylates PUM and one or more additional factors, which act in parallel through the smg mRNA's 3′untranslated region (UTR) to promote the translation of Smaug. **b** ERK1/2 activates the translation of BTG4. Upon oocyte meiotic resumption, ERK1/2 is activated by upstream kinases and triggers CPEB1 phosphorylation and $SCF^{\beta\text{-}TrCP}$-dependent degradation. The phosphorylation and partial degradation of CPEB1 stimulates polyadenylation and translational activation of BTG4 to further promote maternal mRNA degradation by recruiting the RNA deadenylation complex CCR4-NOT. **c** Dephosphorylation of EDEN-BP regulates its deadenylation activity by deadenylase PARN and Cup. EDEN-BP is phosphorylated during oocyte maturation and calcium-dependently dephosphorylated following egg activation

proteins (ARE-BPs) in *Drosophila* [8, 22, 31, 47]; embryonic deadenylation element-binding proteins (EDEN-BP) in *Xenopus* [48]; and Zinc Finger Protein C3H Type 36-Like 2 (ZFP36L2) and mouse-specific Y-box protein 2 (MSY2) in mouse [49, 50]. The post-translational modifications of RBPs have been found to function in maternal transcript destabilization in many organisms, including the phosphorylation of embryonic deadenylation element-binding protein (EDEN-BP) (*Xenopus*), cytosine–uridine–guanine-binding protein (CUG-BP) (human), and MSY2 (mouse).

In *Xenopus*, EDEN-BP recognizes embryonic deadenylation element (EDEN), which is rich in uridine/purine dinucleotides, to deadenylate the maternal transcripts upon fertilization [48, 51]. One hundred and fifty-eight maternal mRNAs as binding targets for EDEN-BP have been identified by microarrays analyses [51]. EDEN-dependent deadenylation is active in early *Xenopus* embryos, whereas the quantities of EDEN-BP remain constant from fertilization to the tadpole stage in *Xenopus* [48], suggesting that temporal and spatial regulation mechanisms are necessary for its precise activation. The dephosphorylation of EDEN-BP has been shown to regulate this sequence-specific deadenylation activity (Fig. 2c) [52]. EDEN-BP is phosphorylated during oocyte maturation and calcium-dependently dephosphorylated following egg activation. EDEN-dependent deadenylation is not influenced by M-phase promoting factor (MPF) reactivation, suggesting that this regulation does not depend directly on MPF activity [52].

CUG-BP, the homolog of EDEN-BP in human, interacts with PARN deadenylase to promote deadenylation, suggesting that EDEN-BP may also cooperate with PARN to promote deadenylation and further clearance of maternal transcripts [53]. The phosphorylation of CUG-BP catalyzed by myotonin-protein kinase (DMPK) in human somatic cells is involved in the regulation of its localization (nuclear versus cytoplasmic) [54], indicating that some kinases and phosphatases may also regulate the deadenylation activity of CUG-BP by modulating its localization.

MSY2 is a DNA/RNA-binding protein that stabilizes mRNAs and inactivates the RNA degradation machinery in male mouse germ cells [55]. In mouse oocytes, MSY2 regulates the global stability of mRNA and the knockdown and disruption of *Msy2* results in an approximate 20% decrease in the amount of total mRNA [56, 57]. Following fertilization, the amounts of *msy2* mRNA and MSY2 protein decrease [58], suggesting that the decay of MYS2 is essential for maternal mRNA clearance. CDC2A-mediated phosphorylation of MSY2 has been proven to trigger the transition from maternal mRNA stability to instability [59]. Overexpression of a nonphosphorylatable form of MSY2 inhibits maternal mRNA clearance, whereas overexpression of a putative constitutively active form of MSY2 triggers maternal mRNA degradation in the absence of CDC2A. The phosphorylation of MSY2 may increase mRNA accessibility to the RNA degradation machinery as overexpressing the constitutively active form of MSY2 is far more sensitive to degradation by exogenous RNase. The decay of MYS2 upon fertilization may also be caused by a positive-feedback loop of CDK1-mediated phosphorylation of MSY2 that leads to the degradation of *msy2* mRNA [59, 60]. Therefore, the CDC2A-mediated phosphorylation of MSY2 is essential for maternal mRNA clearance. CDC2A can also phosphorylate the mRNA-decapping complex, consisting of DCP1A and DCP2, which is essential for maternal mRNA degradation through removal of the 5′-monomethyl guanosine cap [61]. However, the significance of the maturation-associated phosphorylation of DCP1A and DCP2 requires further investigation.

Small RNA biogenesis

Small RNAs have emerged as widespread regulators of gene expression by interacting with mRNA and mediating translational repression, deadenylation, and mRNA destabilization [62]. Many small RNAs have been identified as mediators of maternal mRNA clearance, such as miR-35-42, miR-51-56, and the miR-58/80-82 family in *C. elegans* [63, 64]; the miR-309 cluster and piRNA in *Drosophila* [35, 65]; miR-430 in zebrafish [26, 66]; miR-18 and miR-427 in *Xenopus*; and miR-290 in mouse [67]. Dicer is crucial for the generation of functional miRNA or siRNA by cleaving the dsRNA or pre-miRNA into their final siRNA and miRNA forms, respectively [68, 69]. In *C. elegans*, the function of Dicer must be dynamically regulated during oocyte maturation and embryogenesis as the complete disruption of Dicer blocks oocyte meiotic maturation, whereas a reduction in Dicer function allows oogenesis to proceed but results in early embryonic death [70, 71]. In mouse, an expression analysis of Dicer ZP3-cKO oocytes indicated an overabundance of mRNA transcripts, which is consistent with a loss of miRNA inhibition of translation or mRNA degradation [67], suggesting a conserved functional role of Dicer in maternal mRNAs clearance.

The phosphorylation of Dicer, which is catalyzed by ERK/MPK-1, has been proven to be important for this dynamic regulation in *C. elegans* [71, 72]. During oogenesis, ERK/MPK-1 is active and phosphorylates Dicer on two conserved residues in its RNase IIIb and double-stranded RNA (dsRNA)-binding domains to trigger Dicer's nuclear translocation and inhibit its function [71]. In oocyte maturation and fertilization, ERK/MPK-1 is inactivated, and Dicer is dephosphorylated and activated to generate small RNAs and further degrade maternal mRNAs [72]. The post-translational regulation of Dicer for maternal mRNAs clearance in other species still needs further exploration.

Post-translational regulation of maternal protein degradation

The maternal proteins stored in oocytes are essential for fertilization, the meiosis-to-mitosis transition, reprogramming, and the early stages of embryogenesis [2, 4, 5]. After fertilization, maternal proteins are quickly degraded, and a proteomic study reveals that zygotes show a reduction of approximately 900 proteins (~ 100,000 peptides) compared with oocytes in the second meiotic metaphase (MII) [73]. In eukaryotes, two major pathways for intracellular protein degradation exist, including the autophagy–lysosome pathway and the ubiquitin–proteasome pathway [74, 75]. Both of these proteolysis pathways are necessary for some maternal proteins degradation.

Autophagy regulates maternal protein degradation

Autophagy is a highly evolutionarily conserved membrane trafficking process in which cytoplasmic materials, such as long-lived proteins and organelles, are sequestered into a double-membrane autophagosome and then delivered to the lysosome for degradation [76, 77]. At least three types of autophagy have been defined, including macroautophagy, microautophagy, and chaperone-mediated autophagy [77–79]. The most extensively investigated form is macroautophagy, which is initiated from an isolated membrane followed by the formation of an autophagosome to engulf cytoplasmic cargos and then fuse with lysosomes for degradation [76, 77, 80]. More than 40 autophagy-related (ATG) proteins have been characterized, which consist of several functional units: the ULK1 kinase complex, PI3K complex, Atg9–Atg2–WIPI1/Atg18 complex, and two ubiquitin-like conjugation systems [81–83]. Recently, autophagy has been found to participate in both maternal protein and mRNA degradation.

In mouse, autophagy can be triggered by fertilization and transiently suppressed from the late one-cell to middle two-cell stages and then reactivated after the late two-cell stage. The disruption of autophagy in an oocyte fails to progress beyond the four- and eight-cell stages if the oocyte was fertilized by an *Atg5*-null sperm, indicating that autophagy is essential for preimplantation development [84]. Protein synthesis rates are decreased in autophagy-null embryos, which is likely due to amino acid insufficiency [84], suggesting that autophagy may promote maternal protein degradation for energy or amino acid recycling. During the establishment of anteroposterior (AP) polarity in the early embryogenesis of *C. elegans*, P-granules, large ribonucleoprotein complexes, localize in the germ line cytoplasm and are essential for cell fate determination [85]. In somatic cells, PGL-1, a marker of P-granules, is surrounded by autophagosomes, and a reduction of autophagy-related genes also blocks the degradation of GFP-PGL-1-positive granules in somatic cells, suggesting that autophagy may participate in the elimination of extra P-granule components in somatic blastomeres [86]. During this process, SEPA-1, which directly binds to the P-granule component PGL-3 and the autophagy protein LGG-1/Atg8, has been identified to function as a bridging molecule in the mediation of the specific recognition and degradation of P-granule components by autophagy [86]. Recently, autophagy has also been found to influence maternal mRNA degradation. In two-cell- and four-cell-stage of porcine parthenote embryos treated with 3-MA, an autophagy inhibitor, maternal mRNAs remain at high levels, but they were significantly reduced in embryos treated with rapamycin, which can activate autophagy [87]. However, the direct or indirect role of autophagy in maternal mRNA clearance is still unknown.

Ubiquitin–proteasome system regulates maternal protein degradation

The ubiquitin–proteasome system represents large machinery for protein degradation, consisting of protein ubiquitination components and a proteasome. Protein ubiquitination is an important post-translational modification in which ubiquitin, a 76-residue protein, is covalently attached to a lysine or a Ser/Thr residue in a target protein. Ubiquitination is achieved via three classes of enzymes working in sequence. E1 (ubiquitin-activating enzyme) forms a thioester bond between itself and the C-terminus of ubiquitin. Then, E2 (ubiquitin-conjugating enzyme) receives the activated ubiquitin from E1 by transthiolation. Finally, E3 (ubiquitin ligase) transfers ubiquitin from E2 to the target protein. Polyubiquitin chains conjugated on the target protein, especially Lys48-linked and Lys11-linked ubiquitin chains, can be recognized by the proteasome for further proteasomal degradation [88–91]. A proteomic analysis reveals that ubiquitination-related proteins are highly enriched in the mouse zygote [73], and many studies have identified some ubiquitin ligases with important roles in maternal protein degradation (Table 1) that are essential for meiosis-to-mitosis transition, spindle transition, and early embryonic development.

Table 1 Maternal proteins targeted for degradation in different organisms

	Substrate	E3 ligase	Function	References
Mouse	Cyclin B	APC/C	Meiosis I and II	[99]
	Cyclin B1	RFPL4	Meiosis I and II	[100]
	Emi2	$SCF^{\beta\text{-TrCP}}$	Metaphase II exiting	[205]
	TAB1	RNF114	NF-κB pathway activation	[122]
	MATER	UCHL1	Polyspermy block	[132]
Xenopus	CyclinA, Cyclin B	APC/C(CORT)	Meiosis I and II	[102]
	Mtrm	APC/C(CORT)	Polo kinase activation	[105]
	Cort	APC/C	Embryonic mitosis	[102]
	CPEB1	$SCF^{\beta\text{-TrCP}}$	Maternal mRNAs polyadenylation	[129]
C. elegans	MEI-1/katanin	$CUL\text{-}3^{MEL\text{-}26}$	Meiotic spindle degradation	[109]
	EGG-3	APC/C	MBK-2 activation	[117]
	OMA-1/2	$CRL1^{LIN\text{-}23}$, $CRL1^{FBXB\text{-}3}$, $CRL2^{ZYG\text{-}11}$	ZGA	[175]

Ubiquitin–proteasome system regulates the meiosis-to-mitosis transition

In most animals, mature oocytes are arrested at MII by Cyclin B, a maturation promoting factor (MPF), and after fertilization, the oocyte relieves the MII arrest and undergoes the transition from meiosis to mitosis. The degradation of MPF by the anaphase-promoting complex/cyclosome (APC/C), a multisubunit E3 ubiquitin ligase, is essential for this process [92]. In *Xenopus* and mouse, Emi2/XErp1, an essential cytostatic factor (CSF) component, has been identified to serve as a necessary protein for maintaining MII arrest before egg activation by inhibiting the activity of APC/C [93, 94]. Emi2/XErp1 contains three parts: an F-box domain, a C-terminal Zn^{2+}-binding region (ZBR), and a D-box. The D-box and ZBR domain have been found to inhibit APC/C activity by binding the D-box receptor on the core of the APC/C and blocking the access of substrates to the APC/C [92]. In addition, phosphorylation of Emi2/XErp1 by the Mos/MAPK/$p90^{Rsk}$ pathway promotes the association of Emi2/XErp1 with the APC/C for further inactivation [92, 95]. Upon fertilization, Ca^{2+}-induced calmodulin kinase II (CaMKII) phosphorylates Emi2/XErp1, and the phosphorylation of Emi2/XErp1 can be recognized by the polo-box domain (PBD) of polo-like kinase 1 (Plx1) [96, 97]. Plx1 further phosphorylates the DSGX3S motif of the Emi2/XErp1 protein, which is necessary for the recognition of the Skp1–Cullin–F-box (SCF) ubiquitin ligase complex [93]. SCF ubiquitin ligase catalyzes the ubiquitination of Emi2/XErp1 and promotes its degradation to reactivate the APC/C (Fig. 3) [93]. The active APC/C promotes the degradation of Cyclin B to exit MII [98, 99]. Some other E3 ligases have also been identified during this process, such as Ret Finger Protein-Like 4 (Rfpl4), a RING-type E3 ligase that accumulates in growing oocytes and quickly disappears during early embryonic cleavage. Rfpl4 could interact with Cyclin B1 and promote its degradation [100], indicating that Rfpl4 may regulate oocyte meiosis-to-mitosis transition. However, the precise mechanism still needs further investigation.

In *Drosophila*, the activation of the APC/C is regulated by a meiosis-specific adaptor protein Cortex, which acts as an activator of the APC/C and is required for cyclin degradation and the completion of meiosis during egg activation [101–104]. Cortex can interact with Polo kinase inhibitor matrimony and promote its degradation to activate Polo kinase, which is essential for chromosome segregation, centrosome dynamics, and cytokinesis [105]. During the meiosis-to-mitosis transition, Cortex need to be targeted for degradation by the APC/C following egg activation [102], which may allow mitotic Cdc20 (Fizzy) to regulate subsequent embryonic mitosis.

After the completion of meiosis triggered by fertilization, the spindle should transform from a small centrosomal meiotic spindle to a large mitotic spindle. In *C. elegans*, this spindle transition requires downregulation of the microtubule-severing katanin complex [106, 107]. The katanin complex is a p60–p80 heterodimeric complex consisting of a 'catalytic' AAA+ subunit (p60) and an 'accessory' subunit (p80), which are called MEI-1 and MEI-2, respectively, in *C. elegans* [107]. The degradation of katanin requires a cullin 3-based E3 ubiquitin ligase, a type of cullin-RING ligases (CRL), which are multisubunit enzymes composed of specific substrate-recognition modules dedicated to cullin-RING-based catalytic cores [108]. MEL-26 functions as a substrate-specific adaptor to recognize MEI-1 through its MATH (meprin and TRAF homology) domain and bind to the N terminus of CUL-3 through its Bric-a-brac, Tramtrack, and Broad (BTB) fold [109, 110]. Then, CUL-3 and MEL-26 can mediate the polyubiquitination of MEI-1 and promote its

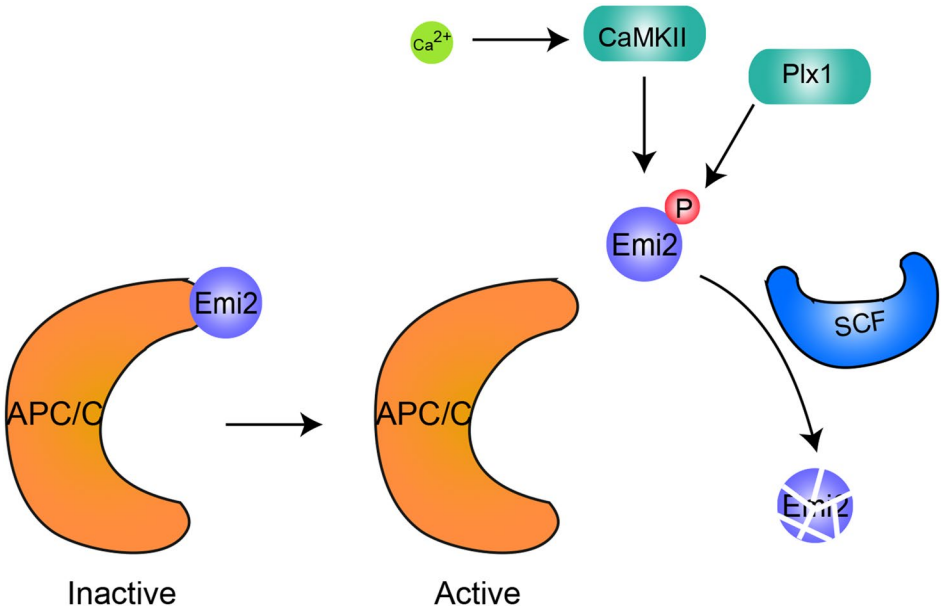

Fig. 3 Emi2 regulates the activity of the APC/C to promote the metaphase II exit. Emi2 inhibits APC/C activity by binding the D-box receptor on the core of the APC/C and blocking the access of substrates to the APC/C. Upon fertilization, Ca2+-induced calmodulin kinase II (CaMKII) phosphorylates Emi2 and the phosphorylation of Emi2 can be recognized by the polo-box domain (PBD) of polo-like kinase 1 (Plx1) for further phosphorylation on the DSGX3S motif of Emi2. The phosphorylation of Emi2 is recognized by the Skp1–Cullin–F-box (SCF) ubiquitin ligase complex, which promotes its ubiquitination and further degradation to reactivate the APC/C

degradation [111, 112]. Some other types of post-translational modification have also been reported to modulate CUL-3^{MEL-26}-mediated MEI-1 degradation. Nedd8 is a ubiquitin-like protein, and an enzymatic cascade similar to ubiquitination catalyzes neddylation [113]. As neddylation of cullin-RING ligases promotes the recruitment of the E2 into them, the neddylation and deneddylation of CUL-3 regulates the activity of cullin-RING ligases to further target MEI-1 for degradation [114]. The phosphorylation of MEI-1 catalyzed by MBK-2, a member of the dual-specificity tyrosine-related kinases (DYRKs), is also necessary for MEI-1 degradation [115, 116]. With high levels of MBK-2-dependent phosphorylation only after the completion of meiosis [117], MBK-2-mediated phosphorylation on MEI-1 may serve as a temporal regulator for the degradation of katanin after meiosis [112]. The activity of MBK-2 can also be regulated by ubiquitination. In oocytes, MBK-2 is sequestered in the cell cortex in an inactive state and depends on the pseudo-phosphatase EGG-3 [118]. EGG-3 recognizes EGG4/5 and uses their PTP domains to bind phosphorylated MBK-2 to prevent MBK-2 activation. Then, CDK-1-mediated phosphorylation activates MBK-2 during oocyte maturation [119, 120] and the APC/C activates the degradation of EGG-3 [117], which then releases active MBK-2 into the cytoplasm.

Ubiquitin–proteasome system in other maternal protein degradation

To analyze the maternal proteome in depth and identify crucial ubiquitination-related proteins in it, we previously developed and performed one-dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis (1D SDS-PAGE) and reverse-phase liquid chromatography–tandem mass spectrometry (RP-LC–MS/MS) to analyze the mature oocyte proteome [121]. A set of 625 different mouse maternal proteins has been identified and RNF114 (Ring finger 114) protein was identified as one of the predominantly expressed proteins in the later stages of mouse oocyte maturation [121], indicating that RNF114 is important for maternal protein degradation. RNF114 is predominately expressed in oocytes and in early embryonic development. The knockdown of *Rnf114* results in decreased early embryonic developmental competence. Through an unbiased screening of a protein microarray with more than 9000 proteins, 13 potential RNF114 substrates have been identified. Further ubiquitination and overexpression analyses have shown that TAB1 may be the major substrate of RNF114 during the MZT [122]. TAB1 is an activator of the MAP kinase kinase kinase (MAPKKK) MAP3K7/TAK1, which is an intracellular

hub molecule that regulates both the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways [123, 124]. The activation of the NF-κB pathway is crucial to the early development of the mouse embryo, and a previous study showed that TAB1 negatively regulated NF-κB pathway activity [125, 126]. We also found a decreased protein level of the inhibitory subunit IκBα accompanied by the upregulated phosphorylated form and the ratio of phosphorylated IκBα to total IκBα increased gradually from MII to the four-cell stage, indicating the activation of the NF-κB pathway during the MZT [122]. Therefore, RNF114-mediated ubiquitination and degradation of TAB1 may be essential to the activation of the NF-κB pathway during the MZT, directly linking maternal clearance to early embryonic development.

Some other maternal proteins have also been identified to be degraded via ubiquitin–proteasome system, such as CPEB and MATER. CPEB is a cytoplasmic polyadenylation element-binding protein that binds to the cytoplasmic polyadenylation element (CPE) and plays an important role in the translational control of maternal mRNAs in the early animal development [20]. During *Xenopus* oocyte maturation, two waves of phosphorylation of CPEB occur and play a role in differential mRNA translation or proper meiotic progression [20]. At an early stage of oocyte maturation, CPEB is phosphorylated by the kinase Aurora A on serine 174, which facilitates PARN expulsion from the RNP complex and Gld2-catalyzed polyadenylation, activating a class of maternal mRNAs [127, 128]. Then, CDC2 catalyzes six additional phosphorylation events on CPEB, which may cause conformational changes of CPEB and allow T125 phosphorylation. Polo-like kinase Plx1 binds CPEB at the phosphorylated Thr125 residue and facilitates TSG motif phosphorylation. β-TrCP, the F-box protein of $SCF^{\beta\text{-TrCP}}$, specifically recognizes the phosphorylated TSG motif, thereby targeting CPEB for degradation [129]. The polyubiquitination-dependent degradation of CPEB1 may cause a change in the CPEB/CPE ratio and result in activation of another class of mRNAs [129]. Recently, the peptidyl-prolyl *cis–trans* isomerase Pin1 has also been identified as an important factor in the promotion of CPEB destruction by interacting with CPEB and inducing its isomerization [130]. Maternal antigen that embryos require (MATER, Nlrp5) is one of the first characterized maternal effect proteins in mouse and combines with FLOPED, TLE6, and FILIA to create a subcortical maternal complex, which is essential for successful preimplantation development [5, 131]. In "gracile axonal dystrophy" (*gad*) female mice, which carry an intragenic deletion of Ubiquitin C-terminal hydrolase L1 (UCHL1), the MATER protein level increases significantly [132], suggesting that the ubiquitination of MATER is important for its stability. However, the precise mechanisms require further investigation.

Degradation of maternal plasma membrane (PM) proteins

In addition to the autophagy–lysosome pathway and the ubiquitin–proteasome pathway, endocytosis has also been found to participate in the degradation of a subset of maternal PM proteins after fertilization [133], including CAV-1 [134], RME-2 [135, 136], CHS-1 [137], and EGG-1 [138]. PM proteins destined for degradation are sorted into intraluminal vesicles (ILVs) at the endosomal membrane and form multivesicular bodies (MVBs). Then, MVBs fuse with lysosomes for degradation [139]. The sorting of maternal PM proteins to the lysosomal pathway is a selective process and maternal SNB-1 is targeted to the PM upon exocytosis but does not undergo lysosomal degradation [140]. Ubiquitination has been found to modulate the endocytosis, monoubiquitination, or K63-linked polyubiquitination of the cargo proteins required for sorting into the MVB pathway and internalization from the PM [141–143]. In *C. elegans*, K63-linked polyubiquitination is strongly induced on the endosomes of one-cell-stage embryos, which is regulated by UBC-13 and UEV-1 and induced by fertilization. In *ubc-13* and *uev-1* mutants, K63-linked polyubiquitylation is reduced and PM proteins are internalized from the PM, but they are inefficiently sorted to the MVB and targeted to lysosomes for degradation [144]. Therefore, UBC-13 and UEV-1-mediated K63-linked polyubiquitylation is required for efficient MVB sorting of maternal PM proteins and further lysosome degradation.

Post-translational regulation of ZGA

After the elimination of a subset of maternal mRNAs and proteins, zygotic genome transcription is initiated, commonly referred to as ZGA, and early embryonic developmental control passes to the zygotic genome [1, 145, 146]. ZGA is regulated in a precisely timed manner. Three broad classes of activation models have been proposed to explain ZGA timing: (1) the nucleocytoplasmic (N/C) ratio model in which a threshold ratio of nuclear components to cytoplasmic volume alleviates transcriptional repression [147], (2) the maternal clock model in which maternally deposited activating or derepressing transcription factors may determine the timing of gene expression [148], and (3) the de novo establishment of chromatin states permitting zygotic genome transcription [145, 146]. Post-translational regulation is essential for ZGA and recent findings have identified in N/C ratio-related regulation, transcriptional repression and activation, regulation of chromatin state remodeling, and histone modification [1, 145, 146].

Nucleocytoplasmic ratio-related regulation

In most species, complete or nearly complete cytokinesis follows every cleavage [2]. The enormous cell volumes are decreased two fold with each division cycle, causing the nuclear-to-cytoplasmic ratio to double, and ZGA repressors in the cytoplasm may be titrated [147], such as histones [149], replication factors [150], DNA methyltransferase xDnmt1 [151], and Tramtrack (TTK) [152]. An increased N/C ratio is achieved by rapid early embryonic cell cycles in frogs and other aquatic organisms, which are simplified versions of the cell cycles of somatic cells [147, 153, 154]. These rapid cell cycles differ from the canonical cell cycle, including a lack of gap phases (G1 and G2) and cytoplasmic volume growth, which is entirely controlled by maternally provided mRNA and protein in an autonomous manner [154]. The phosphorylation-related kinase, CDK, has been identified to participate in this process.

CDK activity is essential for cell cycle regulation. Compared with somatic cell cycles, embryonic cell cycles only contain CDK2-Cyclins A/E, which mediate DNA replication and centrosome duplication, and CDK1-Cyclins A/B, which mediate mitotic progression [155–157]. In *Xenopus*, CDK1 and CDK2 are inhibited via Wee1 kinase-mediated phosphorylation at relatively low levels and Cdc25 phosphatases eliminate this inhibitory phosphorylation during the cleavage stages, maintaining CDK1 in a primed state for activation upon cyclin binding and mitotic entry [157–160]. The activity of CDK in early stage embryos is also predominately regulated by cyclin protein synthesis and degradation [157]. The translation of cyclin protein requires polyadenylation mediated by the phosphorylation of CPEB by Aurora [127, 128]. The degradation of cyclin protein depends on APC/C ligase [92]. CDK1 also regulates Cyclin B protein levels through a CDK1-APC/C negative feedback loop, decreasing the burden of Cyclin B degradation at anaphase and supporting the rapid cyclin oscillations in embryonic cell cycles [161].

Regulation of transcriptional activators

Transcriptional activators are required for transcription regulation, which should be central components of ZGA timing modulation [1, 145], including the TFIID complex [162] and TATA-binding protein (TBP) [163–167], which bind the promoter of zygotic genes to activate transcription. Among them, many pioneer transcriptional factors have been identified as essential in the activation of zygotic genomic transcription, including Zelda in *D. melanogaster* [168], Nanog, Pou5f1, and Sox19b in zebrafish [169, 170], DUX in mouse, and DUX4 in humans [171–173]. Similar to the functional roles of transcriptional factors in somatic cells, the regulation of ZGA-related transcriptional factors includes import into the nucleus, remodeling of nucleosomes, and recruitment and elongation of RNA polymerase (RNAP) [145]. Recently, phosphorylation and ubiquitination have been found to regulate the import of ZGA-related transcriptional factors into the nucleus.

In *C. elegans*, TATA-binding protein-associated factor 4 (TAF-4) is an essential factor for TFIID formation and function [174]. During the first two cleavages cycles, OMA-1 and OMA-2 phosphorylated by the kinase MBK-2 bind to TAF-4 and sequester it in the cytoplasm, subsequently preventing TFIID formation into a stable DNA-bound complex [162]. At the four-cell stage, phosphorylated OMA-1/2 are normally degraded and then TAF-4 returns to the nucleus to form TFIID and promotes the transcriptional activation of the zygotic genome [162]. $CRL1^{LIN-23}$, $CRL1^{FBXB-3}$, and $CRL2^{ZYG-11}$ have been found to be related to the degradation of OMA-1 [175], but the precise mechanisms require further investigation. In mouse, Yap1, the Hippo pathway transcriptional regulator, has been reported to control zygotic genome transcription. Maternal deletion of Yap1 results in the downregulation of approximately 3000 ZGA transcripts [145]. The import of YAP into the nucleus is also regulated by its phosphorylation and dephosphorylation. YAP is phosphorylated at serine 112 by protein kinase A and excluded from the nucleus, whereas dephosphorylated YAP can be transported to the nucleus [176].

Chromatin remodeling allows ZGA

Chromatin consists of DNA wound around nucleosomes, which are octamers of the histones H2A, H2B, H3, and H4, and is joined together by histone linker protein H1. Chromatin conformation is necessary for transcriptional activity [177]. In *Xenopus*, although the zygotic genome is not activated after fertilization, plasmids microinjected into *Xenopus* fertilized eggs could be transcripted within 10 min [178], indicating that the chromatin state is essential for ZGA. A genome-wide map of accessible chromatin in mouse preimplantation embryos using ATAC-seq revealed that many gene loci show large open chromatin domains over entire transcribed units in late one-cell and early two-cell embryos. Along with gene expression during ZGA, sharp open chromatin peaks are gradually limited around promoter regions from the two-cell stage to the inner cell masses (ICM) blastocyst stage, indicating a unique spatiotemporal chromatin conformation during minor ZGA [179]. Recently, the three-dimensional structure of chromatin during the early mammalian development has been analyzed by an optimized Hi-C (genome-wide chromosome conformation

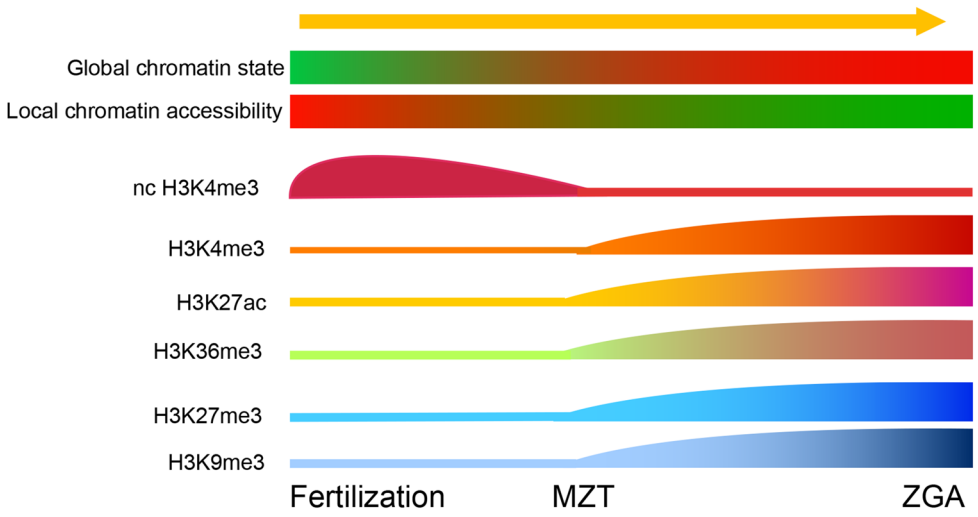

Fig. 4 Chromatin states and histone modification during ZGA. The global chromatin is more accessible during the early stages of embryogenesis, gradually changing to a more compact conformation. Local chromatin accessibility and transcription-related histone modifications appear during ZGA

capture) approach. Mature oocytes lack detectable topologically associating domains (TADs), which play important roles in regulating transcription and DNA replication [180]. After fertilization, the higher order structure of chromatin is significantly diminished, and then, chromatin organization is gradually re-established as slow TAD consolidation and chromatin compartment segregation. The establishment of the TAD structure requires DNA replication, but not zygotic genome activation. Therefore, during the early mammalian development, chromatin may exist in a markedly relaxed state after fertilization, followed by progressive maturation of higher order chromatin conformation (Fig. 4) [181, 182].

Chromatin conformation is highly regulated by histone variants and histone post-transcriptional modifications, such as methylation, acetylation, and ubiquitination [1, 183, 184]. The exchange of histone variants may stimulate promoter nucleosome changes to regulate the chromatin conformation [145].

In *Xenopus*, the H1 linker variant, H1M, persists in the chromatin until its somatic variants are synthesized at the MZT. The embryonic linker histone H1M is required for proper chromosome architecture and transcription initiation by potentially generating a less stable chromatin structure as H1M lacks multiple CDK1 phosphorylation sites and cannot bind to nuclear import receptors RanBP7 and importin β, which are necessary for H1 to condense chromatin during interphase [185]. The repressive H2A variant, macroH2A, is present in developing and mature mouse oocytes, but it is removed from the maternal genome after fertilization. The maternal macroH2A appears to contribute to its transcriptional silence and macroH2A is progressively lost as the embryo becomes transcriptionally active [186]. MacroH2A variants have a major function in maintaining nuclear organization and heterochromatin architecture [187].

In mammals, maternal and paternal genomes harbor distinct chromatin modifications and each parental genome contributes differently to the establishment of the chromatin conformation in the zygote, which is essential for zygotic gene expression [145, 188]. In maternal chromosomes, pericentric heterochromatin is marked by H3K9me3 and H4K20me3, which is established by the Suv39h and Suv4–20h histone methyltransferases (HMTs) in oocytes and by HP1 beta loaded onto chromatin upon gamete fusion [189]. Maternal chromosomes also provide polycomb repressive complex 1 (PRC1) components to paternal heterochromatin independent of the PRC2 complex, which mediates transcription repression by inhibiting chromatin remodeling or mediating chromatin compaction [190]. Nonetheless, it is accompanied by H3K27me3 of the paternal genome. This process is dependent on the RNF2 component of the PRC1 complex and is functionally critical for the regulation of transcription [189], indicating that H2Aub may also participate in this process. Therefore, the MZT is accompanied by nucleus-wide remodeling of chromatin of the paternal genome by maternally inherited components. In paternal chromosomes, protamines are replaced by maternally supplied histones after fertilization [191], but species-dependent amounts of histone and histone modification still exist in paternal chromosomes [145, 192] and paternal histone modification at particular genes may also influence zygotic gene expression [145]. For example, H3K27me3 and H3K4me3 in sperm may have roles in the establishment of a poised chromatin state in the embryo prior to ZGA in zebrafish [193]. In *Drosophila*, the oocytes also could transmit the repressive histone mark H3K27me3 to their offspring that promotes the aberrant accumulation of the active histone mark H3K27ac at regulatory regions and precocious activation of lineage-specific genes at zygotic genome activation, suggesting that maternally inherited H3K27me3 is essential for the activation of enhancers and lineage-specific genes during development [194].

Histone modification during ZGA

Histone modification is essential for the regulation of gene expression and many types of histone modification have been identified during ZGA (Fig. 4) [177, 195, 196]. Histones H3K4me3 and H3K27me3 are two important histone modifiers associated with transcription activation and repression, respectively [197]. H3K36me3 marks regions of transcriptional elongation [177]. In zebrafish, H3K4me3, H3K27me3, and H3K36me3 are not detected before the MZT [198]. After ZGA, H3K4me3, H3K27me3, and H3K36me3 emerge and approximately 80% of genes are marked by H3K4me3, including both zygotically expressed genes and inactive genes [198]. These gene loci exhibiting both H3K4me3 (transcription activation-associated marker) and H3K27me3 (transcription repression-associated marker) are similar to the "bivalent" chromatin domains in pluripotent mouse embryonic stem cells [199], which are presumed to poise genes for activation while keeping them repressed [198]. In addition, many inactive genes are associated with H3K4me3 but not H3K27me3, and H3K4me3 markers can form in the absence of both sequence-specific transcriptional activators and the stable association of RNA polymerase II, indicating that these monovalent domains may also poise genes for activation by creating a platform for the transcriptional machinery [198]. In mouse, some noncanonical H3K4me3 markers, which exist as broad peaks at promoters and in a large number of distal loci with low fold enrichment, are widely observed in full-grown and mature oocytes and are reduced in the two-cell stage. The re-establishment of canonical H3K4me3 occurs at the late two-cell stage. The removal of noncanonical H3K4me3 requires zygotic genome transcription, and the downregulation of noncanonical H3K4me3 by the overexpression of the H3K4me3 demethylases KDM5A and KDM5B is required for normal zygotic genome activation [199–202]. Two other transcription activation and repression histone modifiers, H3K27ac and H3K9me3, which are similar to H3K4me3 and H3K27me3, are also detectable in two-and eight-cell stage embryos [201].

Future perspectives on post-translational regulation of the MZT

The maternal-to-zygotic transition is a complex and highly coordinated development process that includes both material decay and generation. The temporal and spatial regulation mechanisms during the MZT are necessary for successful embryogenesis. Because there was no transcription, the post-translational regulation during MZT might play key roles to regulate both material decay and zygotic generation. While this mechanism has not been thoroughly investigated during MZT, less systematic work was performed to analyze the proteomics of phosphorylation, ubiquitination, acetylation, or other post-translational modifications during MZT. Except the above-mentioned modifications, the other post-translational modifications are even more poorly investigated during MZT, such as the SUMOylation, amidation, sulfation, N-myristoylation, and S-nitrosylation. Recently, the O-glycosylation of some mitochondrial TCA cycle enzymes has been reported to be essential for ZGA by regulating their localization, and protein palmitoylation has been found to induce the clearance of the maternal mRNA by activating miR-430 expression [203, 204]. However, the precise mechanisms are still largely unknown. Therefore, the identification of novel post-translational modifications and the investigation of their functional roles in MZT are necessary for further understanding the mechanisms underlying MZT. Although many researchers work on histone modifications during ZGA, most of their works are descriptive and correlative; detailed functional mechanism studies are required for further investigation. As many post-translational modifications could work with each other, the crosstalk between different types of post-translational modifications may also be essential for the temporal and spatial regulation of MZT. With the rapid development of proteomics, high-throughput sequencing, and gene editing tools, many open questions in the field may be addressed in the near future:

1. What initiates the MZT, degradation, or creation?
2. How is degradation linked with creation, particularly in terms of transcription?
3. How can an old network be renovated to build a new regulatory network?
4. What is the relationship between the autophagy–lysosome system and the ubiquitin–proteasome system during MZT?
5. What is the mechanism underlying substrate selection by the two degradation systems?
6. Are there new post-translational regulations during the MZT?
7. What are the key regulators of the epigenetic regulations during the MZT?

The answers to the above questions would certainly expand our knowledge regarding the MZT, deepen our understanding of the initiation of life, and help us to determine new strategies to treat infertility or other related diseases.

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