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Commentary

Losing Mom's Message: Requirement for DCP1A and DCP2 in the Degradation of Maternal Transcripts During Oocyte Maturation[1]

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The oocyte is a remarkable haploid cell that carries all the information needed to undergo a complex maturation process to become a fertilizable egg and possesses the ability to initiate the early stages of development after fertilization. During the period of oocyte growth, mRNAs are synthesized and stored, and these mRNAs are very stable at this time, with a half-life of approximately 12 days in mouse oocytes [1, 2]. By the time the oocyte reaches its full size, transcription ceases, so the oocyte must rely on these stored maternal mRNAs for oocyte maturation, fertilization, and early embryonic development until zygotic gene activation, which occurs at the 2-cell stage in the mouse [3]. Paradoxically, although maternal mRNAs are necessary for oocyte maturation and early development, the period of oocyte maturation through the 2-cell stage is marked by a dramatic degradation of select maternal transcripts, accounting for an approximately 20% decrease in the total RNA in the oocyte [4, 5]. This loss of mRNAs is necessary to remove the maternal genome so that the oocyte can undergo the maternal-to-embryonic transition to metamorphose into totipotent blastomeres [6]. In this issue of *Biology of Reproduction*, Ma et al. [7] answer some of the unknown questions about how maternal mRNA degradation occurs in the mouse oocyte during oocyte maturation.

Eukaryotic mRNAs have a 5′ cap structure and a 3′ poly(A) tail that regulate translation and mRNA stability [8]. Deadenylation of the 3′ poly(A) tail usually triggers mRNA degradation, and indeed, deadenylation is apparent in mouse oocytes during meiotic maturation [4, 9]. Removal of the 5′-monomethyl guanosine cap (decapping) renders mRNA susceptible to the 5′→3′ degradation pathway by exposing them to exonucleases that rapidly degrade the mRNA from the 5′ end [8].

Earlier work, reported largely by the Schultz lab, has shown that the stability of mRNAs during oocyte growth is maintained by the protein MSY2 (mouse specific Y-box protein 2). MSY2 is an abundant, germ cell-specific Y-box protein that binds to RNA in vitro [10, 11]. Reducing MSY2 protein using a transgenic RNA interference (RNAi) approach leads to a decrease in protein synthesis and in the total amount of RNA; in turn, this leads to abnormal meiotic spindle formation and low incidence of egg activation after fertilization [12]. Furthermore, *Msy2*$^{-/-}$ oocytes have a reduced growth rate compared with wild-type oocytes; these knockout oocytes fail to become transcriptionally quiescent when fully grown, display a decrease in mRNA stability, and do not mature properly [13]. A progressive loss of oocytes and follicles as well as disrupted ovulation also occur in *Msy2*$^{-/-}$ mice, with the result that these mice are infertile [14]. MSY2 is phosphorylated during oocyte maturation by CDC2A, a protein that is activated very early in the oocyte maturation process [10, 15]. By the time the oocyte reaches the metaphase II stage, essentially all the MSY2 protein is phosphorylated [10]. Phosphorylation of MSY2 is correlated with mRNA degradation.

Ma et al. [7] examine the role of two proteins in the transition from mRNA stability to instability during oocyte maturation. DCP1A and DCP2 are mammalian orthologs of decapping proteins originally identified in yeast [16–20]. DCP1A and DCP2 are undetectable in fully grown, immature oocytes, but their abundance increases dramatically during oocyte maturation, indicating that they are recruited (translated) during oocyte maturation. DCP1A and DCP2 are also phosphorylated during maturation, and this phosphorylation is correlated with CDC2A activation. This is shown by inhibiting CDC2A activation with roscovitine, a treatment that substantially inhibited DCP1A phosphorylation. When the terminal 0.5 kb of the 3′ untranslated region (UTR) of *Dcp1a* and *Dcp2* was fused with firefly luciferase, both cRNAs were recruited during oocyte maturation. In addition, mutating potential cytoplasmic polyadenylation elements in the 3′ UTR of both proteins reduced recruitment. Therefore, both *Dcp1a* and *Dcp2* appear to encode classic dormant maternal mRNAs. Knockdown of these proteins with RNAi efficiently prevented the maturation-associated increase of DCP1A and DCP2 without affecting meiotic maturation or metaphase II arrest, and this protein knockdown inhibited mRNA degradation. Examination of a select panel of mRNAs that are known to be degraded during meiotic maturation showed that each transcript underwent the expected degradation except when the accumulation of DCP1A and DCP2 was prevented. Additionally, transcriptome changes associated with the loss of DCP1A and DCP2 were analyzed. Ma et al. [7] found not only substantial perturbation of the transcriptome in oocytes exhibiting protein knockdown but also a predominant increase in the relative abundance of transcripts when DCP1A and DCP2 were targeted. Moreover, when accumulation of DCP1A and DCP2 was prevented using antisense morpholinos, genome activation at the 2-cell stage was inhibited by approximately 50%. These results strongly implicate DCP1A and DCP2 in the transition from RNA stability to instability during meiotic maturation in mouse oocytes.

The following model emerges from these results (Fig. 1). The mRNAs are synthesized during oocyte growth and are stabilized by MSY2. Fully grown, meiotically immature but competent oocytes are stimulated to resume meiosis, which is

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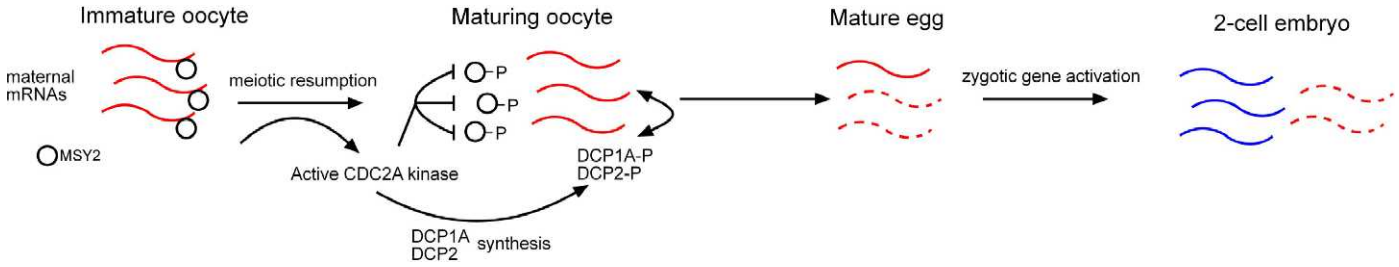

FIG. 1. Model showing the steps leading to the degradation of maternal mRNAs during oocyte maturation in the mouse oocyte.

rapidly followed by the activation of CDC2A. In turn, CDC2A phosphorylates and inhibits the activity of MSY2, rendering the RNAs more susceptible to degradation. Recruitment of DCP1A and DCP2 and their phosphorylation by CDC2A increases the mRNA degradation capacity of the maturing oocyte so that by the 2-cell stage, when zygote genome activation occurs, most of the maternal mRNA is largely degraded.

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