ples, such as the nucleo-cytoplasmic ratio or microRNA-induced mRNA degradation. Future studies may also be relevant to the field of animal cloning. Cloning experiments rely on the reprogramming of donor nuclei by enucleated eggs. Thus, the milieu that silences the zygotic genome also reprograms transferred nuclei. Hence, understanding the mechanisms that underlie zygotic genome silencing will inform the design of reprogramming strategies (*4*).

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REVIEW

Regulation of the Oocyte-to-Zygote Transition

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Oocytes, the female germ cells, contain all the messenger RNAs necessary to start a new life but typically wait until fertilization to begin development. The transition from oocyte to fertilized egg (zygote) involves many changes, including protein synthesis, protein and RNA degradation, and organelle remodeling. These changes occur concurrently with the meiotic divisions that produce the haploid maternal genome. Accumulating evidence indicates that the cell-cycle regulators that control the meiotic divisions also regulate the many changes that accompany the oocyte-to-zygote transition. We suggest that the meiotic machinery functions as an internal pacemaker that propels oocytes toward embryogenesis.

Ex ovo omnia (Everything from an egg) (*1*).

How does an egg become "everything"? The journey begins with one of the most complex cell transformations in biology: remodeling of a fertilized oocyte into a totipotent zygote. Remarkably, this transition occurs in the absence of transcription and therefore depends on messenger RNAs (mRNAs) accumulated in the oocyte during oogenesis. Fully grown oocytes contain a dizzying array of RNA messages, corresponding to 20 to 45% of all mouse genes (*2*, *3*) and 55% of all *Drosophila* genes (*4*)! These transcripts guide oocytes during two makeovers on the way to becoming zygotes: oocyte maturation and egg activation. During oocyte maturation, extracellular signals stimulate oocytes arrested in prophase of meiosis I to enter meiotic M phase and initiate the meiotic divisions (*5*). Typically, oocytes are ovulated and become competent for fertilization before reaching a second arrest point (metaphase of meiosis II in mammals). Egg activation, triggered by sperm entry in many species, completes the transformation to zygote by signaling the completion of meiosis, the formation of pronuclei, and the first mitotic division (*6*). In this Review, we discuss the changes that accompany each of these transitions, addressing strategies of gene activation, gene inactivation, and organelle remodeling.

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In with the New…

Oocyte maturation requires the synthesis of new proteins. Interdependent translational activation events ensure that proteins are produced in the correct succession (*7*). For example, early during oocyte maturation in *Xenopus*, translation of the cyclin-dependent kinase (CDK)–binding protein RINGO/Spy activates maturation promoting factor (MPF; CDK1/cyclin B1 complex). Active MPF in turn stimulates the translation of proteins needed to maintain metaphase II arrest in the matured oocyte (Fig. 1). During egg activation, additional RNAs are recruited for translation. A study comparing matured oocytes and zygotes revealed dramatic differences in polysome-associated RNAs, with nearly one-third of transcripts (29%) showing differential translation between the two stages (*8*). Oocyte polysomes were enriched for transcripts encoding proteins implicated in cellular homeostasis, whereas zygotic polysomes were enriched for transcripts implicated in macromolecular biosynthesis.

How are oocyte mRNAs activated for translation? In many cases, activation depends on liberating mRNAs from complexes that block translation initiation (*7*, *9*). For example, in mouse, clam, and *Xenopus* oocytes, mRNAs that contain cytoplasmic polyadenylation elements (CPEs) in their 3′ untranslated region are stored with short poly-adenylated [poly(A)] tails and bound by a translation-repressing complex containing the CPE-binding protein (CPEB) and its partner, Maskin. Maskin binds the cap-binding protein eIF4E, preventing the recruitment of the translation initiation factor eIF4G. During oocyte maturation, phosphorylation of CPEB stimulates polyadenylation and recruitment of poly(A)-binding protein bound to eIF4G. Incoming eIF4G displaces Maskin from eIF4E, allowing formation of the initiation complex (*7*).

As first recognized in clam oocytes (*10*), translational activation of oocyte mRNAs is often linked to poly(A)-tail extension, but the two can also occur independently. For example, in *Drosophila* eggs, cyclin B mRNA is kept translationally silenced by the RNA binding protein Pumilio (*11*). During egg activation, the PAN GU kinase activates (by an unknown mechanism) cyclin B mRNA translation and poly(A) tail extension (*4*, *11*). In *pan gu* mutants, forced expression of poly(A) polymerase is sufficient to rescue polyadenylation of cyclin B but not translation (*4*). Depletion of Pumilio has the opposite effect: translation is restored, but polyadenylation is not (*11*). These observations suggest that both polyadenylation-independent and polyadenylation-dependent mechanisms activate translation in oocytes, and a challenge for the future will be to define the requirements for each mechanism. Another important question is the extent to which microRNAs contribute to translational repression in oocytes. A recent survey of nearly 1000 *Drosophila* oocyte proteins found only 4% with increased abundance in *Dicer* mutants, suggesting that microRNAs regulate only a minority of mRNAs in oocytes (*12*).

…And Out with the Old

Oocyte maturation and egg activation also stimulate mRNA degradation. Fifteen percent of transcripts are degraded during maturation in mice (*3*). Degradation is selective and preferentially removes transcripts required for prophase arrest and oocyte maturation (*3*). Further degradation occurs after fertilization to usher the transition to zygotic control (*2*, *9*, *13*). Mechanisms of RNA degradation and activation of zygotic transcription are discussed in an accompanying Review (*14*).

Proteins are also targeted for degradation during the oocyte-to-zygote transition. Components of the ubiquitin-proteasome pathway are well represented in the oocyte transcriptome (*2*), and several studies have reported examples of protein turnover in mouse (*15*–*17*), *Xenopus* (*18*), zebrafish (*19*), and

Caenorhabditis elegans (*20*) oocytes and/or early embryos. Protein degradation often serves to inactivate proteins that are needed early in the transition but that would be harmful later. For example, CPEB functions early in oocyte maturation (described above) but is partially degraded during meiosis I (*18*). Injection of a degradation-resistant form of CPEB in *Xenopus* oocytes interfered with translation of cyclin B1 and progression to meiosis II (*18*). Similarly in *C. elegans*, successful transition from meiosis to mitosis requires degradation of the microtubule-severing complex MEI-1/MEI-2 (*20*). MEI-1 and MEI-2 are required for meiosis but, if maintained during mitosis, interfere with growth of the first mitotic spindle. Protein degradation is also used to restrict proteins to specific areas of the egg. For example, in *Drosophila*, *C. elegans*, and zebrafish, germline-specific proteins are degraded from the somatic regions of the emerging embryo (*21*). In this respect, protein degradation may be viewed as a way to partially erase the germline program of the egg to promote totipotency in the zygote. Comprehensive proteomic approaches will be needed to reveal the extent of protein degradation during the oocyte-to-zygote transition and its contribution to oocyte remodeling.

Reshuffle What's There…

Changes during the oocyte-to-zygote transition are not restricted to proteins and RNAs but also affect cellular organelles. The meiotic divisions elicit many changes in the oocyte nucleus, but organelles in the cytoplasm and at the cell periphery are also affected. Redistribution of mitochondria and endoplasmic reticulum (ER) have been documented in several organisms. In *Xenopus*, redistribution of the ER-rich mitochondrial cloud to the vegetal cortex has been linked to localization of germline determinants (*22*). During oocyte maturation in *Xenopus* and mouse, ER-derived vesicles also align underneath the plasma membrane (*23*). This redistribution may facilitate propagation of Ca^{2+} waves at fertilization (see below) by moving Ca^{2+} stores closer to the site of sperm entry. After egg activation, cortical ER clusters are re-internalized (*24*). Perhaps the most dramatic rearrangement following fertilization is the rapid fusion of cortical granules with the plasma membrane to prevent polyspermy (*23*). A similar fusion event was recently described in *C. elegans* involving vesicles rich in caveolin (*25*).

…And Time It Just Right

What signals initiate these changes? Oocyte maturation typically is started by extracellular ligands (*23*). Egg activation, in contrast, depends on Ca^{2+} signaling inside the egg. In mammals, Ca^{2+} signaling may be initiated by a sperm-specific phospholipase C (PLC-ζ), which activates phosphoinositide signaling at fertilization to generate several Ca^{2+} waves (*6*). Remarkably, the egg appears to "count" each wave, with early responses (cortical granule exocytosis) requiring fewer oscillations than later ones (resumption of the second meiotic division) (*6*).

Several lines of evidence suggest that, after these initial triggers, the cell cycle machinery assumes control of subsequent events. For example, degradation of CPEB during meiosis I in *Xenopus* depends on phosphorylation by MPF (*18*). Similarly, internalization of ER granules during egg activation in mice depends on cell cycle resumption (*24*) (Fig. 1). In *C. elegans*, mutations that prevent the first meiotic division block MEI-1 degradation and caveolin vesicle fusion (*25*, *26*). Conversely, premature entry into M phase by removal of the MPF inhibitory kinase WEE-1 jumpstarts MEI-1 degradation in immature oocytes (*26*). The remarkable dependence of several aspects of the oocyte-to-zygote transition on meiotic progression suggests that the cell cycle machinery serves as an internal master timer that drives and coordinates the transition.

Egg quality is often cited as a crucial parameter for success in assisted reproductive technologies, yet the molecular processes that contribute to egg quality remain poorly defined (*27*). Increased understanding of the signaling and remodeling events that shape the oocyte-to-zygote transition will be critical to provide more definitive criteria for what constitutes a "healthy" egg. Already, the realization that the meiotic machinery drives many aspects of the transition raises questions about the practice of removing the meiosis II spindle from oocytes during cloning (*28*).

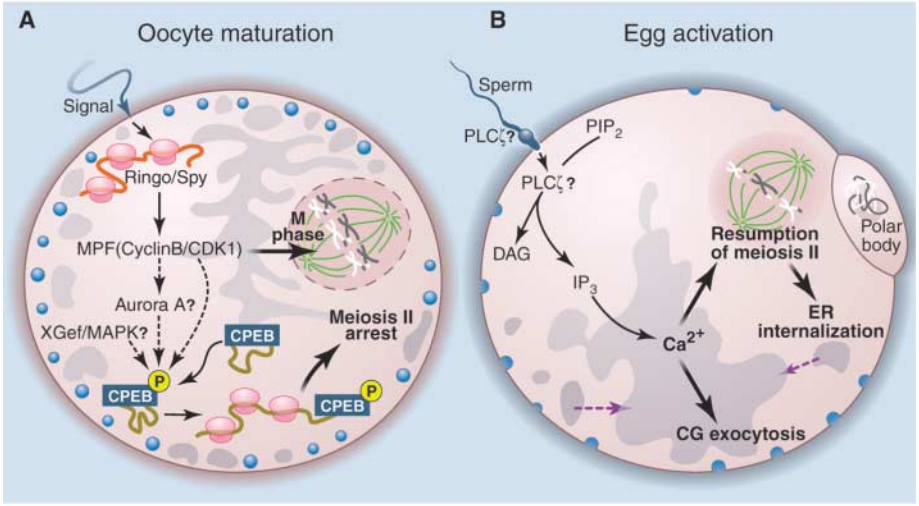

Fig. 1. Schematic of oocyte maturation and egg activation events in vertebrates. (**A**) An extracellular cue initiates oocyte maturation, stimulating the translation of specific mRNAs [for example, *Ringo/Spy* in *Xenopus*] leading to MPF activation. CPEB phosphorylation leads to translation of additional transcripts required for meiotic progression (*29*). ER-derived vesicles (gray) and cortical granules (blue) accumulate below the egg plasma membrane (Xgef, *Xenopus* guanine exchange factor; MAPK, mitogen-activated protein kinase). (**B**) Fertilization triggers egg activation in the matured oocyte. In mice, a sperm-specific phospholipase C isoform (PLC-ζ) has been proposed to be delivered into the oocyte at fertilization. Increased inositol 1,4,5-trisphosphate (IP_3) stimulates calcium (Ca^{2+}) release from the ER, which signals cortical granule exocytosis (blue) and meiosis II. Cell cycle resumption in turn drives internalization of cortical ER vesicles (purple arrows).

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