REVIEW

The Maternal-Zygotic Transition: Death and Birth of RNAs

Alexander F. Schier

Maternal gene products drive early development when the newly formed embryo is transcriptionally inactive. During the maternal-zygotic transition, embryonic transcription is initiated and many maternal RNAs are degraded. Multiple mechanisms regulate the birth of zygotic RNAs and the death of maternal RNAs. Genome activation appears to rely in part on the sequestration of transcriptional repressors by the exponentially increasing amount of DNA during cleavage divisions. Maternal RNA degradation is induced by the binding of proteins and microRNAs to the 3′ untranslated region of target RNAs.

To achieve the striking increase in cell number after fertilization, most animals devote their early development to rapid and synchronous cell cycles (*1*). Whereas the overall amount of cytoplasm in the embryo remains constant, the number of nuclei and the amount of DNA increase exponentially. During this period, mRNAs and proteins provided to the egg by the mother drive development. By contrast, the embryonic genome is transcriptionally activated only at later cell cycles. This transition from a maternal to a zygotic mode of development has been called the midblastula transition (*2*) or maternal-zygotic transition (MZT) (Fig. 1). It often coincides with cell cycle lengthening and the degradation of many maternal RNAs. Here I review our current understanding of the mechanisms that regulate the birth of zygotic RNAs and the death of maternal RNAs.

At least three mechanisms have been implicated in the silencing of the zygotic genome during early development: (i) chromatin-mediated repression, (ii) deficiencies in the transcription machinery, and (iii) transcriptional repression or abortion by rapid cell cycles. The first evidence for repressors was provided 25 years ago, when Newport and Kirschner reported that a premature increase in the number of nuclei or the amount of DNA resulted in premature initiation of cell cycle lengthening and zygotic transcription in *Xenopus* embryos (*2*, *3*). These results, and related studies in *Drosophila* and zebrafish, have suggested that the nucleo-cytoplasmic ratio and the titration of a transcriptional repressor by the exponentially increasing amount of genomic DNA determine the timing of MZT (the "excess repressor model"). The key factors that need to be titrated are still elusive, but it is conceivable that histones or other chromatin components maintain silencing until a critical amount of DNA is present (*4*, *5*). Gene-specific DNA methylation has also been implicated in repression. Depletion of the methyltransferase Dnmt1 or of Kaiso, a transcriptional repressor binding to methylated DNA, results in the premature activation of a subset of genes (*6*). These studies suggest that multiple chromatin-mediated mechanisms prevent zygotic genome activation.

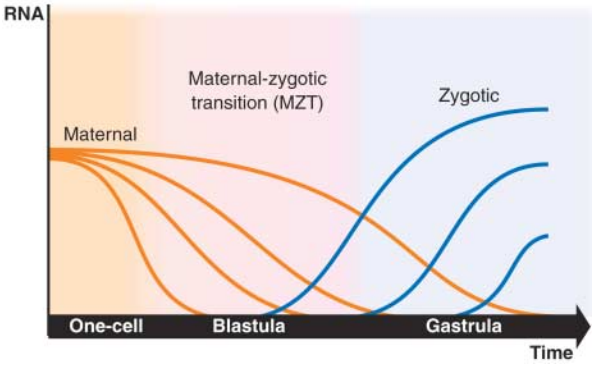

Fig. 1. The maternal-zygotic transition (MZT). Maternal RNAs are deposited by the mother into the egg and drive early development. These RNAs are degraded during different stages of embryogenesis, including blastula and gastrula stages. The embryonic genome is initially transcriptionally inactive until the MZT, when zygotic genes are starting to be transcribed.

A dearth or inactivation of components of the transcription machinery might be a second strategy for gene silencing before MZT (the "limited machinery model"). For example, premature expression of TATA-binding protein (TBP), a component of the transcriptional machinery, can induce premature activation of a subset of genes (*4*, *5*). Analogously, misexpression of strong transcriptional activators can cause precocious transcriptional activation. These conclusions are mainly based on the study of injected extrachromosomal DNA, and it therefore remains unclear to what extent the limited machinery model applies to endogenous genes.

The rapid cell cycles lacking G_1 and G_2 phases might constitute a third strategy that interferes with productive transcription during early cleavage stages (the "rapid cell cycle model"). DNA replication can interfere with transcription, and mitosis can lead to the abortion of nascent transcripts (*7*). Conversely, experimentally induced cell cycle lengthening can lead to premature transcription (*8*).

Although the excess repressor, limited machinery, and rapid cell cycle models can account for some aspects of MZT, they do not explain why several genes are already activated during early cleavage stages and why zygotic genome activation is a gradual and gene-specific process (*9*–*11*). These observations suggest that some of the mechanisms underlying zygotic genome activation remain to be discovered. Moreover, mammals activate zygotic transcription at very early cleavage stages (e.g., the mouse genome is activated at the two-cell stage) (*1*). It is conceivable that in mammals there might be sufficient time to assemble transcription complexes at early cleavage stages because the cell cycles are very long, but the exact mechanisms are elusive.

Whereas zygotic mRNAs are synthesized during embryogenesis, many maternal mRNAs are degraded. Degradation removes gene products that might interfere with later development. This regulated maternal mRNA destabilization is mediated by sequences in the 3′ untranslated region (3′ UTR) (*12*). Regulatory RNAs or proteins such as Smaug or EDEN-BP bind to these sequences and induce the deadenylation of target mRNAs, which are then prone to degradation by nucleases. Recent studies in zebrafish have identified the microRNA miR-430 as a potential link between zygotic genome activation and the decay of maternal mRNAs (*13*). MicroRNAs are short RNAs that bind to the 3′ UTR of target mRNAs to repress their translation and accelerate their decay. miR-430 targets several hundred maternally provided mRNAs by binding to complementary sites in their 3′ UTR and promoting their deadenylation. In the absence of miR-430 activity, these mRNAs accumulate and are thought to interfere with embryonic morphogenesis. miR-430 expression initiates at MZT, thus linking genome activation and maternal mRNA degradation.

In summary, multiple mechanisms regulate RNA synthesis and degradation during early embryogenesis. It remains unclear, however, whether most of the observed phenomena can be explained by a few key regulatory princi-

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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*).

References and Notes

1. P. H. O'Farrell, J. Stumpff, T. T. Su, *Curr. Biol.* **14**, R35 (2004).
2. J. Newport, M. Kirschner, *Cell* **30**, 675 (1982).
3. J. Newport, M. Kirschner, *Cell* **30**, 687 (1982).
4. N. Kikyo, A. P. Wolffe, *J. Cell Sci.* **113**, 11 (2000).
5. M. N. Prioleau, J. Huet, A. Sentenac, M. Mechali, *Cell* **77**, 439 (1994).
6. A. Ruzov *et al.*, *Development* **131**, 6185 (2004).
7. A. W. Shermoen, P. H. O'Farrell, *Cell* **67**, 303 (1991).
8. B. A. Edgar, G. Schubiger, *Cell* **44**, 871 (1986).
9. J. Yang, C. Tan, R. S. Darken, P. A. Wilson, P. S. Klein, *Development* **129**, 5743 (2002).
10. D. K. Pritchard, G. Schubiger, *Genes Dev.* **10**, 1131 (1996).
11. S. Mathavan *et al.*, *PLoS Genet.* **1**, 260 (2005).
12. W. Tadros, H. D. Lipshitz, *Dev. Dyn.* **232**, 593 (2005).
13. A. J. Giraldez *et al.*, *Science* **312**, 75 (2006).

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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

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