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Review

Cellular, biochemical and molecular mechanisms regulating oocyte maturation

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Abstract

The original model for regulation of oocyte maturation proposed by us in 1978 postulated that gap junction-mediated transmission of cAMP from the follicle cells to the oocyte inhibits meiosis and that luteinizing hormone (LH) terminates the flux of the follicle cAMP to the oocyte. A decrease in oocyte cAMP below inhibitory threshold occurs since oocytes lack the ability to generate sufficient amounts of cAMP to compensate for the phosphodiesterase activity. Our previous studies provided evidence to support this model. More recent studies in our laboratory were directed at identification of the cellular biochemical and molecular events initiated within rat oocytes upon the relief of cAMP inhibition. These studies: (i) identified an oocyte specific A kinase anchoring protein (AKAP) that is phosphorylated in oocytes resuming meiosis, (ii) confirmed that cdc25B governs meiosis reinitiation and demonstrated that its expression is translationally regulated, (iii) substantiated the indispensable role of proteasomal degradation at completion of the first meiotic division in a mammalian system, (iv) elucidated the role of MPF reactivation in suppressing interphase between the two meiotic divisions and (v) provided evidence that mos translation is negatively regulated by a protein kinase A (PKA)-mediated action of cAMP and is dependent on an active MPF. A detailed account on each of these findings is presented in this chapter.

Keywords: Oocyte; cAMP; AKAP; cdc25; MPF; Mos

Contents

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1. Introduction

Meiosis in oocytes of all animal species is arrested at the first prophase, which corresponds to the G2 phase of the cell cycle. The meiotic division in most species is reinitiated prior to ovulation in response to the pituitary leutenizing hormone (LH). In mammals, the transition from G2 to M phase of meiosis can also occur spontaneously, upon removal of the oocyte from the ovarian follicle (reviewed by Tsafriri, 1979). The observation that prophase-arrested oocytes, removed from the ovary resume meiosis spontaneously, was initially reported in 1935 and raised the idea that the ovarian follicle provides the oocyte with an inhibitory agent responsible for its meiotic arrest (Pincus and Enzmann, 1935). The nature of this agent remained a major puzzle of reproductive biology for more than four decades.

It was back in 1978 that we identified cAMP as the oocyte "meiotic arrestor" (Dekel and Beers, 1978, 1980) and thereafter, characterized its inhibitory action in rat oocytes (Aberdam et al., 1987; Dekel, 1988; Dekel et al., 1988). A meiosis-associated decrease in cAMP that has been demonstrated in parallel in Xenopus oocytes was attributed to inhibition of adenylate cyclase activity. However, since our studies revealed, unexpectedly that rat oocytes fail to generate inhibitory concentrations of cAMP (Dekel et al., 1984) we searched for an alternative mechanism that would be employed by mammalian oocytes to regulate their meiotic status. We raised the hypothesis, that cAMP generated by the somatic cells of the ovarian follicle is transmitted to the oocyte through gap junctions. We have also suggested that LH-induced reinitiation of meiosis involves breakdown of the oocyte–somatic cells communication that is followed by a decrease in intraoocyte concentrations of cAMP and results in exit from meiotic arrest (Dekel et al., 1981). This theory was later supported by experimental evidence generated by our studies in rat oocytes (Dekel et al., 1978, 1981; Dekel and Sherizly, 1983; Sherizly et al., 1988; Phillips and Dekel, 1991; Piontkewitz and Dekel, 1993) and confirmed for other mammalian species by other laboratories (reviewed by Eppig, 1985). Our recent studies were directed at a higher level of resolution of the ideas formulated by us previously. Findings generated by these studies are discussed below.

2. Identification of a novel, oocytes-specific AKAP

As mentioned already, it is well established that cAMP maintains the oocyte in meiotic arrest and that reinitiation of meiosis is subsequent to a drop in intraoocyte concentrations of this cyclic nucleotide. It has also been demonstrated that meiotic arrest in oocytes is dependent on a phosphorylation event catalyzed by protein kinase A. Along this line, modulation of intracellular concentrations of cAMP has been implicated as the mechanism that regulates PKA action in oocytes (Maller and Krebs, 1977). Later reports, however, demonstrated that PKA isoenzymes can be targeted to various subcellular loci through interaction of their regulatory (R) subunit with A kinase anchoring proteins (AKAPs) (reviewed by Scott and McCartney, 1994) suggesting a complementary mechanism for regulation of the activity of this kinase. Taking this information into account we hypothesized that subcellular compartmentalization of PKA, may provide an additional apparatus that would increase the efficiency of PKA in regulating meiosis. To test our hypothesis we examined rat oocytes for the presence of AKAPs and monitored the PKA regulatory subunits for changes in their localization during meiosis. Our studies indeed detected a 140 kDa AKAP referred to as AKAP140 that is progressively phosphorylated during meiosis (Kovo et al., 2002). This protein was not recognized by antibodies known to react with other AKAPs (AKAP 150, AKAP 149 and AKAP KL) previously identified in rat ovaries (Carr et al., 1999) suggesting that AKAP140 is a novel, hitherto unidentified RII-binding protein. Immunocytochemical analysis further revealed that the regulatory subunits of PKA underwent cellular translocation upon resumption of meiosis (Kovo et al., 2002). Similar findings were later reported for mouse oocytes (Brown et al., 2002).

Much of the evidence for the role of AKAPs in signaling has come from the use of synthetic Ht31 peptides derived from human thyroid anchoring protein. Ht31 peptides contain an amphipatihc helix domain and bind to the RII subunit of PKA with nanomolar affinity, thus competing for PKA binding to AKAPs and disrupting anchoring of the enzyme within cells (Carr and Scott, 1992). We have recently used Ht31 peptide and its inactive analogue Ht31-proline (Ht31-p) to investigate the potential role of rat oocyte specific AKAPs in PKA regulation of meiosis. The Ht31 and Ht31-p peptides were microinjected into oocytes incubated in medium containing the phsophodiesterase isobutylmethylxantine (IBMX). The oocytes were monitored for maturation at different time points after injection. As expected, non-injected oocytes incubated in IBMX-free medium resumed meiosis spontaneously. This spontaneous maturation was inhibited by the presence of IBMX in the medium. The injection of Ht31 into oocytes incubated in IBMX overcame the negative effect of the phosphodiesterase inhibitor on meiosis resumption with no such effect of its inactive analog Ht31-p.

Collectively, the information generated in our present and previous studies are compatible with the following working model: meiotic arrest is maintained by PKA, the catalytic activity of which is maintained by relatively high intraoocytes concentrations of cAMP. This inhibitory cAMP is not generated by the oocyte but rather transmitted from the follicular cells through gap junctions. This pattern of cAMP supply apparently creates a centripetal concentration gradient of the nucleotide within the oocytes (the diameter of a fully grown oocyte is 80–90 μm). Under these conditions, targeting of PKA by AKAP to its site of action may facilitate its control of meiotic arrest. Alternatively, breakdown of cell-to-cell communication, which terminates the flux of follicle cAMP to the oocyte, leads to a decrease in intraoocyte concentra-

tions of cAMP. The drop in cAMP within the oocytes, when combined with PKA translocation from its site of action may provide an efficient mechanism for downregulation of the catalytic activity of this enzyme.

3. The cdc25B isoform regulates meiosis reinitiation

Prophase-arrested oocytes are characterized by a nuclear structure, known as germinal vesicle (GV). Upon reinitiation of meiosis the GV breaks down (GVB) the chromosomes condense and the first metaphase (MI) spindle is formed. The first meiotic division is completed upon segregation of the homologous chromosomes between the oocyte and the first polar body (PBI) and is immediately followed by the transition into the second metaphase (MII). The oocyte is arrested at MII until fertilization.

Reinitiation of meiosis and its progression to MI depends on the activation of MPF (Masui and Market, 1971) the protein components of which are the catalytic p34cdc2 kinase and the regulatory cyclin B1 (Gautier et al., 1988, 1990). This p34cdc2/cyclin B1 heterodimer is initially formed as an inactive pre-MPF and is activated by the dual specificity Cdc25 phosphatase upon dephosphorylation on Thr 14 and Tyr 15 of p34cdc2 (Gould and Nurse, 1989).

We confirmed the oscillatory pattern of MPF activation in spontaneously maturing rat oocytes showing that its kinase activity is elevated immediately after reinitiation of meiosis before GVB, reaches maximal levels at metaphase I, declines just prior to the formation of PBI and rises again before entry into the second meiotic division. We have further demonstrated that MPF activation at the onset of meiosis is conditioned to the reduction in intraoocyte cAMP (Josefsberg et al., 2003). In a previous study, we demonstrated that the cAMP-mediated inhibition of MPF activation is accomplished by prevention of p34cdc2 dephosphorylation (Goren and Dekel, 1994). Our most recent experiments suggest that in parallel to suppression of MPF activation cAMP represses the synthesis of cyclinB1, minimizing the availability of pre-MPF (Josefsberg et al., 2003).

Unlike amphibians, that express a single form of cdc25, this phosphatase in mammals is represented by a multigene family comprising three isoforms A, B and C. A role for cdc25B in regulating the G2/M transition in mammalian oocytes is suggested by a recent report of impaired fertility in mice lacking this isoform (Lincoln et al., 2002). In order to substantiate the role of cdc25B in reinitiation of meiosis, we examined the pattern of expression of this isoform and explored the mode of its regulation in rat oocytes. Supporting the above-mentioned observation we showed that microinjection of neutralizing antibodies against cdc25B, but not cdc25C impaired the ability of the oocytes to undergo GVB. We also revealed that cdc25B exhibits periodic expression throughout meiosis that nicely corresponds to the oscillatory pattern of MPF activation. We showed that cdc25B expression represents a balance between degradation and translation of this protein further demonstrating for the first time that cdc25B translation is mediated by polyadenylation of its mRNA. We also visualized changes in cdc23B localization, which are associated with progression of meiosis (Gershon et al., submitted for publication). Taken together, this information supports the central role of cdc25B in regulation of reinitiation of meiosis in mammalian oocytes.

4. Inactivation of MPF: proteasomal degradation of cyclin B1

MPF activation is necessary for reinitiation of meiosis, and its elevated activity is required for the progression to MI. We have shown previously that downregulation of MPF activity at the transition between the first and the second rounds of meiosis is not associated with p34cdc2 rephosphorylation (Goren and Dekel, 1994). More recent results from our (Josefsberg et al., 2000) and other laboratories demonstrated that degradation of cyclin B1, that leads to dissociation of the p34cdc2/cyclin B1 complex serves at this stage of meiosis as the mechanism to lower kinase activity. Since cyclins are included among the cellular substrates for the proteasome, we have used the selective proteasome inhibitor MG132 in order to interfere with cyclin B degradation. These experiments revealed that inhibition of the catalytic activity of the proteasome prevented the completion of the first meiotic division and did not allow chromosomal segregation and PBI formation (Josefsberg et al., 2000).

Indispensability of proteasomal degradation is well established for the exit from M phase in both, the second meiotic and the mitotic cell cycles. The common feature of the metaphase to anaphase transition in these two examples of cell division is the separation of sister chromatids, which is absolutely dependent on proteasomal action. However, it is not clear as yet whether or not the segregation of the pairs of homologous chromosomes, which is a unique characteristic of the first meiotic division, involves protein degradation. In fact, in contrast to our report in the rat, recent studies in Xenopus oocytes have underlined the dispensability of the degradation machinery at the first meiotic division (Peter et al., 2001; Taieb et al., 2001). These last studies demonstrate that interruption of the proteasomal pathway had no effect on the completion of first meiosis and the transition into the second metaphase.

In light of this apparent discrepancy, we have reexamined the essentiality of the proteasomal-dependent degradation processes at the exit from MI using a complementary strategy. This strategy takes into account that a protein substrate marked for degradation by the proteasome is first conjugated to multiple molecules of ubiquitin. In order to inhibit proteasomal action in this study, we microinjected into oocytes methylated ubiquitin that interferes with the formation of the multi ubiquitin chain. Confirming our previous results (Josefsberg et al., 2000) we found that oocytes injected with methylated ubiquitin remained arrested at MI (Josefsberg et

al., submitted for publication). The combined results of these two studies strongly imply that, at least in the rat, proteasomal degradation is necessary for the completion of the first meiotic division.

5. MPF reactivation: suppression of interphase

As mentioned previously, MPF inactivation is transient and is followed by reactivation of this enzyme prior to the transition into the second meiotic division. What would be the role of MPF reactivation at this specific stage of meiosis? As already mentioned, meiosis is uniquely characterized by two rounds of chromosome segregation that follow DNA replication, allowing the production of progeny cells that are haploid. These two rounds of meiosis are not interrupted by interphase. Specifically, after PBI formation DNA replication does not occur, the nuclear envelope does not form and chromosomes do not decondense. The period in between the two meiotic divisions is defined as interkinesis. Does MPF reactivation secure the oocyte from entering interphase? To answer this question we utilized the p34cdc2 inhibitor, roscovitine. In this experiment, oocytes were isolated into a medium that allowed them to resume meiosis. Immediately after PBI extrusion they were individually selected and placed into roscovitine-containing medium. We found that under conditions that prevented MPF reactivation, the oocytes decondensed their chromosomes, formed a nucleus and entered interphase (Josefsberg et al., 2003). A role for MPF as a suppressor of interphase between the two meiotic divisions has been demonstrated so far only in starfish oocytes. On the other hand, regulation of interkinesis in Xenopus is attributed to the mitogen activated protein kinase (MAPK) family members which is obviously not the case in mammalian oocytes.

6. Regulation of Mos translation

Confirming previous reports in Xenopus and rodent oocytes, we have also demonstrated that the activity of the extracellular signal-regulated kinases (ERK1 and ERK2), two members of the MAPK family, is elevated in association with meiosis reinitiation (Lazar et al., 2002). The immediate regulator of MAPK is MEK, which in oocytes is activated by Mos (Posada et al., 1993), a distinct MEK kinase that is expressed exclusively in germ cells (Goldman et al., 1987; Mutter and Wolgemouth, 1987). In Xenopus oocytes, Mos is required for activation of MAPK and MPF at reinitiation of meiosis, for the suppression of DNA replication during interkinesis and for maintenance of the second meiotic arrest (Reviewed by Maller et al., 2000).

Analysis of the kinetics of MAPK activation in rodent oocytes cannot detect substantial elevation before 6 h of incubation suggesting that in mammals, unlike Xenopus, MAPK does not regulate early meiotic events (Lazar et al., 2002). Our use of PD098059, a specific and most effective MEK inhibitor indeed revealed that GVB and chromosome condensation were not disturbed when MAPK activity was low. Furthermore, inhibition of MAPK did not prevent the oocyte from completing the first round of meiosis and emitting PBI but impaired their ability to arrest at MII. These oocytes were parthenogenically activated, forming the second PB without fertilization. In some oocytes, this activation was carried further to pronucleus formation and even to progression through the first and the second mitotic divisions (Josefsberg et al., 2003). A normal progression through early meiotic events but inability to arrest at MII was also demonstrated in Mos knockout mice (Colledge et al., 1994; Hashimoto et al., 1994).

As mentioned previously, prevention of resumption of meiosis can be attained via increased intraoocyte concentration of cAMP. We have further demonstrated that under these conditions MAPK is not activated (Lazar et al., 2002). Taking into account that the upstream regulator of MAPK in the oocyte is Mos, we hypothesized that Mos could possibly mediate the effect of cAMP on the MAPK signaling cascade.

Maturing oocytes are known to be transcriptionally dormant. Protein synthesis in these oocytes is enhanced by recruitment of pooled mRNA and its selective cytoplasmic polyadenylation. Polyadenylation of mos mRNA that elicits Mos translation has been demonstrated in Xenopus oocytes and its necessity for the completion of meiosis in this species has been indicated (Sheets et al., 1995). Along this line, a recent study from our laboratory (Lazar et al., 2002) showed that meiotically arrested rat oocytes express mos-mRNA with no detectable Mos protein. The presence of Mos was initially demonstrated at 6 h after reinitiation of meiosis and was associated with mos mRNA polyadenylation. Elevated intraoocyte cAMP inhibited mos mRNA polyadenylation as well as Mos expression. The highly selective inhibitor of the catalytic subunit of PKA, 4-cyano-3-methylisoquinoline, reversed both these actions of cAMP. Polyadenylation of mos mRNA was also prevented by roscovitine, a potent inhibitor of p34cdc2 (Lazar et al., 2002).

Regulation of Mos translation by MPF that is suggested in the above-mentioned study is based on the use of roscovitine. Since this kinase inhibitor does not interfere solely with the activity of p34cdc2 we further employed the RNA interference (RNAi) technique using cyclinB1 double-stranded RNA (dsRNA) to specifically deplete the Cyclin B1 mRNA and subsequently eliminate its protein product. RNAi has been shown previously to ablate targeted mRNA in lower organisms such as C. elegance Zebrafish and Drosophila. Specific interference of gene function by dsRNA has been achieved more recently in mice (Svoboda et al., 2000; Wianny and Zernicka-Goetz, 2000). Since mammalian cells typically respond to the presence of dsRNA by an overall block of translation the successful demonstration of RNAi in the mouse may be attributed, at least in part, to the lack of this response in oocytes as well as in early embryos.

In our experiment total oocyte RNA was reverse transcribed using specific T7 RNA polymerase promoter and

sequence-linked primers followed by PCR amplification. The product was transcribed *in vitro* to produce dsRNA. The DNA template was removed and the purified dsRNA was tested by the ribonucleas protection assay. Oocytes were then transfected using cationic liposomes and examined for cyclin B1 expression after various times of incubation. We found that after 2.5 h cyclin B1 mRNA was eliminated and that this effect was followed by a substantial decrease in its protein product. As anticipated, in the absence of cyclin B1 the oocytes failed to activate MPF and did not resume meiosis. Having established the successful depletion of cyclin B1 and confirming its physiological consequences we further examined the oocytes for Mos translation. We found that the cyclin B1 dsRNA transfected oocytes possessed a relatively short mos mRNA poly (a) tail and failed to express Mos. Furthermore, these oocytes could not activate MAPK (Lazar et al., 2004). These results provide a definitive evidence for the regulation of Mos translation by an active MPF. These results combined with our previous reports (Lazar et al., 2002; Josefsberg et al., 2003) suggest that the negative action of cAMP that is mediated by PKA involves the inhibition of MPF activation to suppress Mos translation. The meiosis reinitiation-associated drop in cAMP lowers the catalytic activity of PKA that allows MPF activation further stimulating Mos translation.

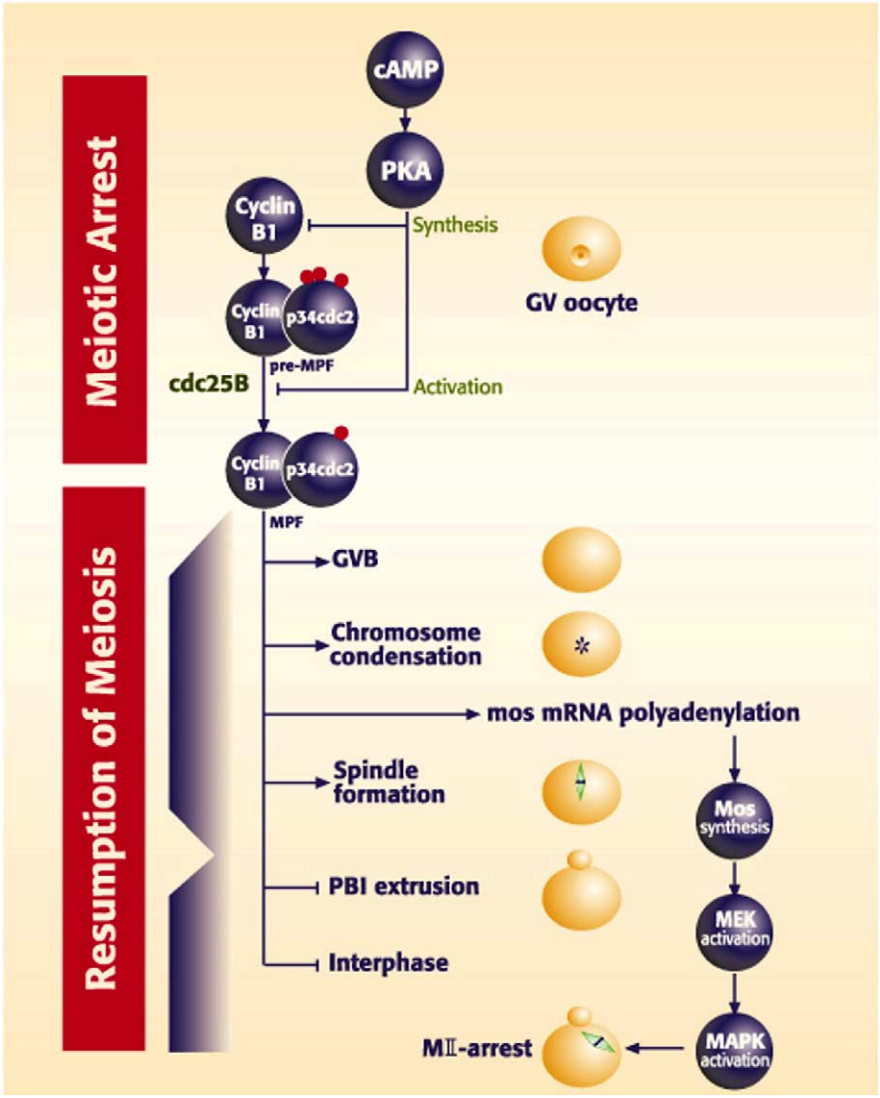

Fig. 1. The hierarchy of meiosis regulating kinases. Meiosis arrest in the oocyte is maintained by the inhibitory effect of a PKA-mediated cAMP action. This enzyme gains higher efficiency due to the interaction of its regulatory subunit with the newly discovered oocyte AKAP140. The PKA-mediated cAMP inhibition is conferred at two levels: the prevention of pre-MPF activation due to sustained phosphorylation on p34cdc2 and the repression of de-novo synthesis of cyclin B1. In response to the preovulatory LH (or following the release of the oocyte from the ovarian follicle), intraoocyte cAMP concentration drops and MPF activation is catalyzed by the B isoform of the cdc25 phosphatase. The active MPF induces resumption of meiosis, namely GVB, chromosome condensation and spindle formation. MPF activity also stimulates the polyadenylation of mos mRNA, leading to Mos synthesis and to the activation of MAPK. Inactivation of MPF at MI is necessary for the completion of the first meiotic division and the extrusion of PBI, whereas its reactivation suppresses interphase thus ensuring the tranasition into MII. The MII arrest of the oocyte is endured until fertilization by the action of MAPK.

7. Epilog

The meiotic cell cycle in mammalian oocytes is regulated at the level of protein translation and its degradation as well as by its post-translational modification. cAMP is the negative upstream key regulator of these events. Upon the decrease of intraooocyte concentrations of cAMP and PKA inactivation two different pathways are being switched on. One such pathway involves MPF activation and leads to GVB, chromosome condensation and spindle formation. The other, somewhat delayed, cascade involves Mos translation and MAPK activation. Stimulation of the later pathway will maintain the oocytes arrested at MII.

The interaction between these two major regulators of meiosis has been extensively studied in both amphibian and mammalian oocytes. Early results in these species suggested that MAPK controls MPF activity and Mos was defined therefore as the initiator of meiosis. However, the role of MAPK in MPF activation in mammals was ruled out by observations that oocytes derived from mos knockout mice, displayed a normal pattern of MPF activity despite of their inability to activate MAPK (Hashimoto, 1996). Similarly, we have also demonstrated that inhibition of MAPK in the rat does not prevent MPF activation and allows reinitiation of meiosis (Josefsberg et al., 2003). MAPK-independent MPF activation has also been suggested by recent studies in Xenopus oocyte (Gross et al., 2000) tethering the implication of Mos/MAPK pathway on p34cdc2 activation into a center of a controversial debate.

The relationships between MPF and MAPK kinetics of activation in rodents suggests that MPF might be an upstream regulator of the MAPK/Mos pathway. Surprisingly, this possibility has never been challenged in mammals. Using roscovitine, which is a potent inhibitor of p34cdc2, we proved that MAPK activation was tempered in the absence of MPF. Specificity of this MPF inhibitor was conferred by its inability to interfere with the activity of immunoprecipitated MAPK in-vitro. The inhibition of MAPK activation was correlated with the obstructive effect of roscovitine on accumulation of Mos, the upstream regulator of MAPK. Taken together, the absence of MAPK activation under inhibition of p34cdc2 via repression of Mos expression suggests a linear relationship between these three enzymes (Josefsberg et al., 2003). This linear relationship gained definitive evidence by using the mRNAi protocol for selective depletion of Cyclin B1 mRNA. In this previously mentioned study, we clearly revealed that Mos translation does not take place and that the subsequent activation of MAPK fails in the absence of an active MPF (Lazar et al., 2004). Another study in our laboratory has demonstrated recently that the expression of Mos is subjected to negative regulation by a PKA-mediated cAMP action (Lazar et al., 2002). As cAMP represses MPF activity, the linear relationship between MPF, Mos and MAPK can be extended to include cAMP and PKA as their upstream negative regulators. Our suggested model for the hierarchy of the above-mentioned regulators of meiosis in mammalian oocytes is described in Fig. 1.

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