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# Translational and post-translational modifications in meiosis of the mammalian oocyte

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**Abstract**

The fully-grown oocyte is transcriptionally inactive. Therefore, translational and post-translational modifications furnish the control mechanism of key components governing meiosis. Regulation by protein synthesis provides an irreversible unidirectional mechanism for an extended period that can be restricted by a complementary degradation of the same protein. Both processes utilize tight measures to ensure precise expression at the right time in the right place. Rapid modifications such as phosphorylation and dephosphorylation supply reversible means to regulate protein action. Information regarding these extremely exciting issues is being accumulated recently in an exponential rate. However, the vast majority of these data is generated from studies conducted on Xenopus oocytes. We fully agree with Andrew Murray's statement that ''The modern trend of promoting research on a small number of 'model' organisms will eventually deprive us of the opportunity to study interesting biology'' [Cell 92 (1992) 157]. Thus, despite all of the enormous technical difficulties resulting from the limited availability of biological material we extended our interest to mammalian model systems. Our review will attend to certain examples of such modifications in the regulatory pathway of meiosis in mammalian oocytes. 

*Keywords:* Oocyte; Meiosis; MPF; MAPK; Mos; Proteasome

## 1. Cyclic AMP is the meiotic arrestor

Fertilization is the central event in reproduction. However, this interaction between the oocyte and the sperm will not take place in gametes that have not resumed meiosis. Meiosis in the mammalian oocyte is initiated during embryonic life, proceeds up to the diplotene stage of the first prophase and is arrested around birth. Meiotic arrest persists throughout infancy until the onset of puberty. In the sexually mature female at each cycle, one or more oocytes, according to the species, respond to the hormonal stimulus and reinitiate their meiotic division. This hormonal stimulus is provided by the mid-cycle surge of the pituitary leutenizing hormone (LH) that induces both resumption of meiosis and ovulation. However, reinitiation of meiosis in mammals can also occur spontaneously, upon removal of the oocyte from the ovarian follicle (reviewed by Dekel, 1995).

The observation, that meiotically arrested oocytes, removed from the ovary spontaneously resume meiosis, 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 first clue regarding the possible identity of this inhibitory agent was provided by another study published almost 40 years later (Cho et al., 1974). This study demonstrated that the spontaneous reinitiation of meiosis could be blocked by elevation of intraoocyte concentrations of cAMP. Additionally, phosphodiesterase inhibitors, that do not elevate cAMP concentrations but rather maintain the nucleotide at amounts present in the oocyte just prior to its separation from the ovarian follicle, were equally effective in preventing maturation (Cho et al., 1974, Lindner et al., 1974). Taking these last observations into account we suggested that cAMP provided to the oocyte by the follicular cells could possibly serve as the 'meiotic arrestor'. The inhibitory effect of cAMP has been thoroughly characterized by us in rat oocytes (Dekel and Beers, 1978, 1980) and confirmed by other laboratories in other animal species. It has been later demonstrated

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that the effect of cAMP in the oocyte is mediated by the cAMP dependent protein kinase (PKA) (Maller and Krebs, 1977; Bornslaeger et al., 1986). However, the downstream effector molecules that transduce the PKA-mediated cAMP effect remain largely unknown.

## 2. MPF—the initiator of meiosis

The studies in our laboratory during the past 10 years, aimed at identification of the cellular regulators that are controlled by cAMP and determination of their specific role throughout meiosis. Rat oocytes that resume meiosis spontaneously were used as the experimental model. These oocytes that are removed from the ovary at prophase-arrest, are characterized by the presence of a nuclear structure, known as germinal vesicle (GV). At around 4 h of incubation the GV breaks down (GVB). This event is associated with chromosome condensation and is immediately followed by spindle formation. The oocyte reaches the first metaphase (MI) at 8 h of incubation. At this stage the pairs of homologous chromosomes are aligned at the equator of the fully organized spindle. The formation of the first polar body (PBI) that occurs at 11 h of incubation represents the completion of the first round of meiosis. Immediately thereafter, the spindle of the second metaphase (MII) is formed and the oocyte arrests again at this stage until fertilization (Figs. 1 and 2). The sequence of events that starts with GVB and progresses to MII leads to the production of a mature fertilizable oocyte and is, therefore, defined as oocyte maturation. If fertilized, and normally only in this case, the oocyte exits the MII-arrest. Such oocytes that have been penetrated by a sperm emit one set of the sister chromatids into the second PB (PBII) and form the male and female pronuclei (reviewed by Dekel, 1996).

The activity of a maturation promoting factor (MPF) was initially discovered in 1971 in amphibian oocytes (Masui and Market, 1971). The protein components of this factor, the catalytic p34cdc2 kinase and the regulatory cyclin B1 have been identified 17 years later (Gautier et al., 1988; Lohka et al., 1988; Gautier et al., 1990). The obligatory association of the kinase with cyclin has defined it as the first member of the cyclin dependent kinases-CDK1 (reviewed by Morgan, 1997). Further studies have shown that the formation of the p34cdc2/cyclin B1 heterodimer, known as pre-MPF, is necessary but insufficient for its activation (Solomon et al., 1990). Following the binding of cyclin B1, p34cdc2 undergoes phosphorylation on threonine 161, mediated by CDK-activating kinase (CAK) which is in itself a CDK7, cooperating with cyclin H (Morgan, 1997). Further phosphorylation on threonine 14 and tyrosine 15 are catalyzed by Wee1 and Myt1 (Mueller et al., 1995a,b). Dephosphorylation of p34cdc2 on threonine 14 and tyrosine 15 is required for its activation and is catalyzed by the dual specificity Cdc25 phosphatase (Gould and Nurse, 1989). The role of Wee1, Myt1, CAK and Cdc25 has yet to be demonstrated in mammalian oocytes.

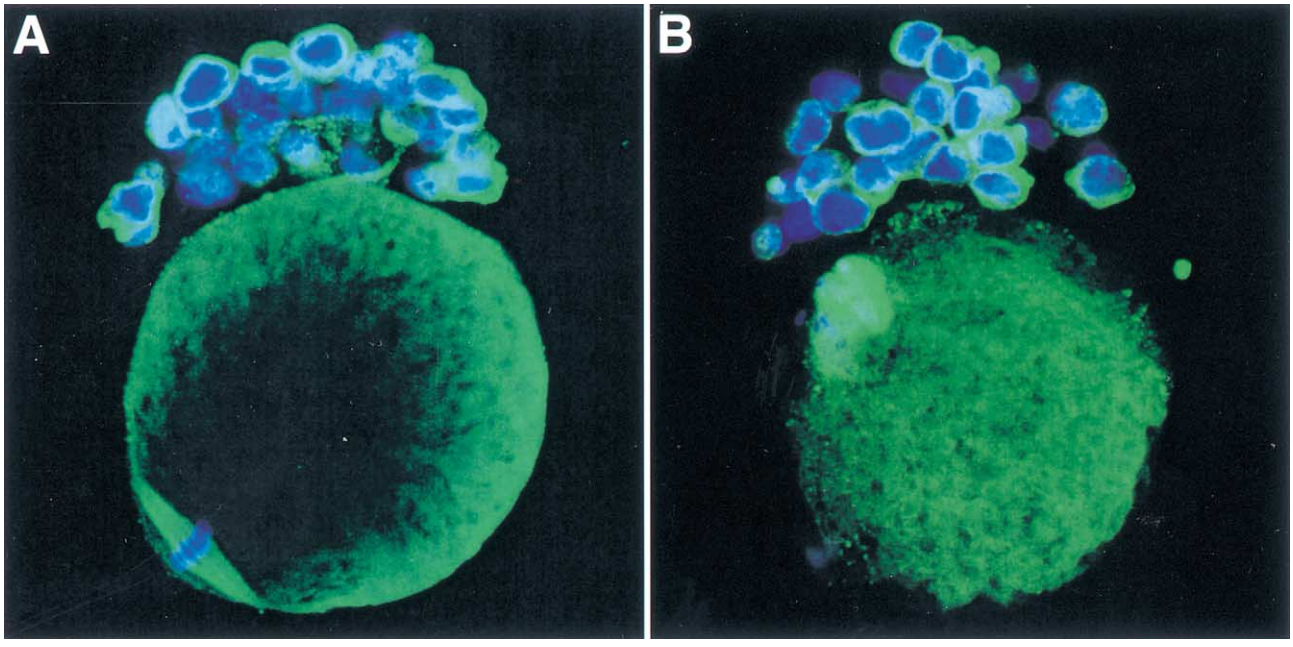


Fig. 1. Extrusion of the first PB in a spontaneously maturing rat oocyte arrested at MII. After 24 h of incubation the oocytes were fixed and double-stained for β-tubulin (fluorescent green) and DNA (blue) and examined with confocal microscopy. (A) The chromatids of one set of homologous chromosomes are arranged at the MII plate, in a longtitudal section of the spindle. The surrounding cumulus cells contain decondensed DNA. (B) The PB contains high concentration of tubulin with the remnants of the homologous chromosomes.

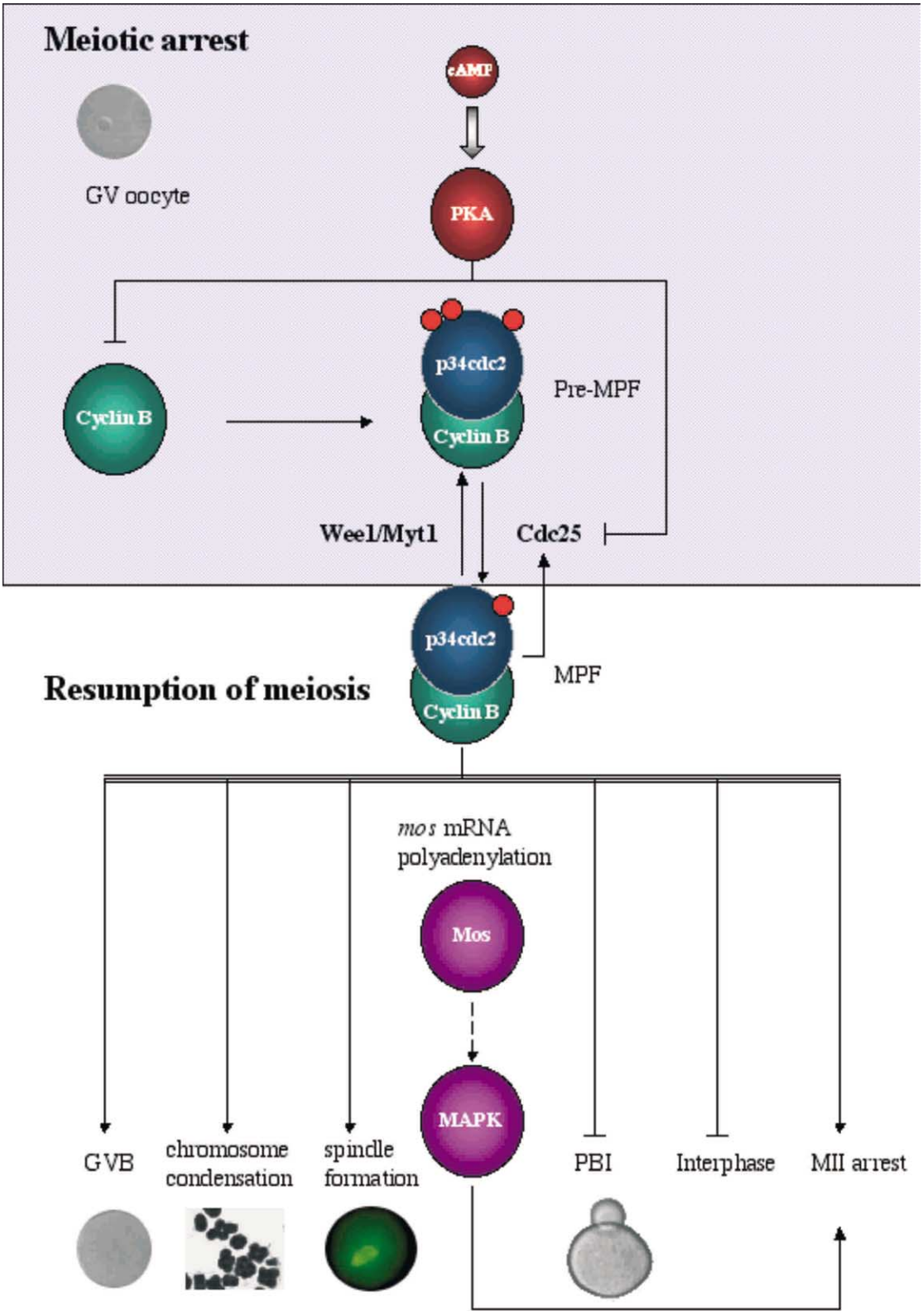


Fig. 2. Regulation of meiosis in mammalian oocytes. The GV arrested oocyte is maintained at prophase due to the inhibitory effect of PKA mediated cAMP action. The inhibition is conferred on two levels: the prevention of pre-MPF activation due to sustained phosphorylation on p34cdc2 and repression of de-novo synthesis of cyclin B1. Following the release of the oocyte from the ovarian follicle, intraoocyte cAMP concentration drops and pre-MPF undergoes activation. Active MPF elicits resumption of meiosis, namely GVB, chromosome condensation and spindle formation within 6 h of isolation. The polyadenylation of *mos* mRNA follows MPF activation, leading to Mos expression and activation of MAPK. Inactivation of MPF at MI is necessary for the extrusion of PBI, whereas its reactivation at the onset of the second meiotic division suppresses entry into interphase. The MII arrest of the oocyte is endured until fertilization by the action of both MAPK and MPF.

Histone H1 is a preferable substrate for the p34cdc2 kinase and phosphorylation of this protein is, therefore, utilized for determination of MPF activity. Using this histone H1 phosphorylation assay we demonstrated similar to other rodents (Choi et al., 1991; Fulka et al., 1992; Gavin et al., 1994; Zernicka-Goetz et al., 1997) an oscillatory pattern of MPF activity in spontaneously maturing rat oocytes. Specifically kinase activity rises immediately after reinitiation of meiosis before GVB, reaching maximal levels at MI. It declines just prior to the formation of PBI, rises again before entry into the second meiotic division and stays elevated until fertilization (Josefsberg et al., submitted).

MPF activation at the onset of meiosis is conditioned to the reduction in intraoocyte cAMP (Choi et al., 1991; Fulka et al., 1992; Gavin et al., 1994, Josefsberg et al., submitted). It has been demonstrated that cAMP mediated inhibition of MPF activation is accomplished by prevention of p34cdc2 dephosphorylation (Choi et al., 1991; Goren and Dekel, 1994). In parallel to elimination of pre-MPF activation the synthesis of cyclin B1 is repressed, thus minimizing the amount of pre-MPF (Hampl and Eppig, 1995b; Josefsberg et al., submitted).

What is the specific role of MPF in reinitiation of meiosis? Addition of roscovitine, a selective inhibitor of p34cdc2 kinase (Meijer et al., 1997), dose-dependently prevented MPF activation and GVB (Josefsberg et al., submitted). Similar results were established in Xenopus oocytes by the use of the cyclin dependent kinase inhibitor p21Cip (Frank-Vaillant et al., 1999). Under these conditions of low MPF activity the chromosomes do not condense. Quite interestingly, inhibition of MPF activity after the commitment period of the oocyte to resume meiosis, but prior to PB extrusion, prevented the exit from MI. These oocytes had a 'reversed' phenotype, in which a nucleus had reformed (Josefsberg et al., submitted). These findings suggest that in addition to the initial role of MPF at the onset of meiosis, its sustained activity is necessary to ensure meiotic progression.

## 3. Proteasomal degradation—the cutting edge of metaphase to anaphase transition

As mentioned previously, MPF activation is necessary for reinitiation of meiosis, and its elevated activity is required for the progression of MI. The role of its inactivation in regulation of the meiotic progress has been a subject of further studies. Downregulation of MPF activity that takes place just before completion of the first round of meiosis is not associated with p34cdc2 rephosphorylation (Choi et al., 1991; Goren and Dekel, 1994). Alternatively, degradation of cyclin B1 that leads to dissociation of the p34cdc2/cyclin B1 complex, serves at this stage as a mechanism to lower kinase activity (Hampl and Eppig, 1995a; Winston 1997; Josefsberg et al., 2000).

Cyclin serves as one of the cellular substrates for the proteasome (Murray, 1995). A protein substrate marked for degradation by the proteasome is first conjugated to multiple ubiquitin molecules (reviewed by Ciechanover, 1998). This reaction is catalyzed by a multi-enzymatic system, composed of E1, E2, and E3. The ubiquitin ligase (E3) that attaches ubiquitin molecules to cyclin B1 has been identified and named as the anaphase promoting complex (APC) or the cyclosome (Hershko et al., 1994; Sudakin et al., 1995 reviewed by Page and Hieter, 1999). The importance of cyclin B1 degradation at the exit from M-phase was first demonstrated in Xenopus embryos (Murray et al., 1989). This degradation is brought about by a short stretch of amino acid sequence (RxxLxxV) known as the destruction box (D-box). Studies demonstrating that a truncated form of cyclin B, lacking the D-box, thus resistant to proteolysis, prevents the exit from M-phase, established the notion that cyclin B1 degradation is essential for completion of mitosis (Murray et al., 1989; Glotzer et al., 1991; Brandeis and Hunt, 1996). The injection of a fragment that contains the D-box motif of cyclin B1 (Huchon et al., 1993) or both D-box fragments of cyclin B1 as well as cyclin B2 in Xenopus oocytes resulted in MI arrest (Yoshitome et al., 1998).

A central role for the proteasomal degradation at the exit from M-phase is suggested by our recent reports. We incubated rat oocytes in the presence of MG132, a selective proteasome inhibitor that prevented the degradation of cyclin B1 (Josefsberg et al., 2000). As a consequence, a relatively high MPF activity was maintained. In the absence of proteasomal catalytic activity the chromosomes did not segregate and cytokinesis did not occur. Similarly, interference with proteasomal degradation blocked one-cell embryos and prevented the first embryonic cleavage (Josefsberg et al., 2001). Unexpectedly the accumulated cyclin B1 in such treated zygotes was not correlated with elevated MPF activity, due to a precocious rephosphorylation of p34cdc2. In contrast to the above reports in the rat, recent studies in Xenopus oocytes have challenged the necessity of cyclin degradation at the first meiotic division and furthermore underlined the dispensability of the degradation machinery at this stage (Peter et al., 2001; Taieb et al., 2001). These last studies report that interruption of the ubiquitination pathway at several levels had no effect on the progression of meiosis I and entry into meiosis II. In light of this apparent discrepancy, emerging from studies in rat and Xenopus oocytes, the essentiality of proteasomal-dependent degradation processes at the exit from MI, needs to be further clarified.

## 4. Chromosome segregation

Demonstrations that a non-degradable cyclin B1 arrests cell division in telophase, rather than metaphase (Holloway et al., 1993), seem to suggest the existence of non-cyclin substrates that should be degraded to allow the exit from metaphase. Indeed, proteasomal action at the metaphase to anaphase transition was demonstrated to be essential for the separation of sister chromatids in mitosis (reviewed by Farr and Cohen-Fix, 1999; Nasmyth et al., 2000). Immediately following DNA replication, the sister chromatids adhere to each other through the interaction of 'adhesive' molecules that have been denominated as cohesins (Michaelis et al., 1997; Koshland and Guacci, 2000). Amongst the cohesins are the Scc1 and the SMC family of proteins (Ball and Yokomori, 2001). The cohesion molecules remain attached to the chromatids until the metaphase to anaphase transition. Cohesion is maintained by the action of a recently identified family of proteins, securins that inhibit separation of sister chromatids. This family includes Pds1 (*S. cerevisiae*) (Cohen-Fix et al., 1996), Cut2p (*S. pombe*) (Funabiki et al., 1996) and the vertebrate orthologue, vSecurin (Zou et al., 1999). The securins were shown to be degraded by the ubiquitin-proteasome dependent pathway. The non-degradable mutants of the securins blocked cells in metaphase (Orr-Weaver 1999; Nasmyth et al., 2000). Upon degradation of securin, an initial cleavage of cohesins by a separin protein is inaugurated (Uhlmann et al., 2000) and is complemented by proteasomal degradation of the entire cohesin molecule (Rao et al., 2001).

Sister chromatid segregation that takes place at the second anaphase of meiosis shares apparently similar mechanisms described above for the mitotic cell division (van Heemst and Heyting, 2000). In addition to the destruction of the securin Pds1 (Salah and Nasmyth, 2000), another different subset of proteins is apparently subjected to proteolysis at segregation of the homologous chromosomes, at the first meiotic anaphase. It has been indeed demonstrated that disjunction of homologous chromosomes in meiosis I depends on proteolytic cleavage of an exclusive meiotic cohesin molecule-Rec 8 (Klein et al., 1999; Stoop-Myer and Amon, 1999; Buonomo et al., 2000 reviewed by Stoop-Myer and Amon, 1999).

It is evident that there is a lack of information in higher eukaryotes regarding the regulation of homologous chromosomes as well as sister-chromatid maintenance of cohesion. Interference with degradation by the proteasome inhibitors employed in our study could possibly be attributed to prevention of homologous chromosomes and sister chromatids segregation resulting in the failure of treated oocytes and embryos to complete the first meiotic and mitotic division, respectively, (Josefsberg et al., 2000, 2001). This information suggests that in the rat, similar to lower organisms, proteins maintaining sister chromatid, as well as homologous chromosome cohesion, may also be subjected to degradation by the ubiquitin-proteasome machinery.

## 5. MPF reactivation controls interkinesis

As mentioned previously, MPF inactivation is transient and is followed by reactivation of this enzyme. What would be the specific role of MPF reactivation at this stage of meiosis? DNA replication (S-phase) in mitosis is followed by chromosome segregation between the resulting daughter cells. In contrast, meiosis is 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 the nuclear envelope does not form, chromosomes do not decondense and DNA replication does not take place. The period in between the two meiotic divisions is defined as interkinesis. What is the mechanism responsible for the suppression of these events? Does MPF reactivation secure the oocyte from entering interphase? To answer these questions we utilized again 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 (Josefsberg et al., submitted). This experimental strategy extends the period through which MPF is inactive. We found that under conditions that prevented MPF reactivation, the oocytes were 'misled', formed a nucleus and entered interphase. Similar findings were published only recently, in which antisense oligonucleotides against cyclin B1, eliminated its synthesis, prevented the entry into the second meiotic division and resulted in an interphase (Ledan et al., 2001).

## 6. Mos/MAPK pathway the second runner up

The activity of two members of the mitogen activated protein kinases (MAPKs), also known as extracellular signal-regulated kinases (ERK1 and ERK2), is also elevated in association with meiosis reinitiation (reviewed by Gotoh and Nishida, 1995; Abrieu et al., 2001). The immediate regulator of MAPK is MEK, which in oocytes is activated by Mos (Nebreda and Hunt, 1993; 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 plays a role in several steps along the meiotic process. In this animal species, Mos is required

for reinitiation of meiosis, eliciting the activation of MAPK and MPF (Sagata et al., 1989a). Suppression of DNA replication during interkinesis is also attributed to Mos (Furuno et al., 1994). In addition, Mos was also delineated as the cytostatic factor (CSF) responsible for the maintenance of the second meiotic arrest (Masui and Market, 1971; Sagata et al., 1989b). Recently p90Rsk was identified as a downstream element that mediates MAPK-dependent MII-arrest in Xenopus oocytes (Bhatt and Ferrell, 1999; Gross et al., 2000) and blastomers (Gross et al., 1999).

Analysis of the kinetics of MAPK activation in rodent oocytes can not detect substantial elevation before 8 h incubation (Verlhac et al., 1993; Zernicka-Goetz et al., 1997 Lazar et al., 2002). The delayed activation of MAPK suggests that in the rat, unlike Xenopus, MAPK does not regulate early meiotic events such as GVB. The use of PD098059, a specific and most effective MEK inhibitor (Alessi et al., 1995) indeed revealed that early meiotic events such as GVB and chromosome condensation were not disturbed when MAPK activity was low (Josefsberg et al., submitted). Inhibition of MAPK did not prevent the oocyte from completing the first round of meiosis and emitting PBI but impaired the ability of the oocytes 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 proceeded through the first and the second mitotic divisions, forming two and four- cell embryos. This parthenogenic embryonic division is obviously abortive and would not proceed beyond this stage.

The role of the Mos/MAPK pathway in mammalian oocytes was deciphered in the Mos knockout mice (Colledge et al., 1994; Hashimoto et al., 1994). Oocytes derived from these mutant mice are as expected, unable to activate MAPK but can proceed normally through early meiotic events, displaying a normal pattern of MPF activation (Araki et al., 1996; Choi et al., 1996, Verlhac et al., 1996). Furthermore, interkinesis in these oocytes occurs in the absence of an active MAPK. The only default of these oocytes is their inability to arrest at MII; they undergo parthenogenic activation in the absence of a sperm (Colledge et al., 1994; Hashimoto et al., 1994).

As mentioned previously, prevention of resumption of meiosis can be attained via increased intraoocyte cAMP concentration. Under these conditions MAPK is not activated (Verlhac et al., 1993, Choi et al., 1996; 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. Indeed, the expression of Mos that is initially detected at 6 h after the onset of meiosis, was reversibly prevented by cAMP (Lazar et al., 2002). The inhibitory effect of cAMP on Mos expression was also reversed by a PKA inhibitor, cyanomethylisoquinolone (4C3M) suggesting PKA mediation of the negative effect of cAMP on Mos expression (Lazar et al., 2002). Parallel observations of cAMP mediated action of PKA on Mos expression were reported in Xenopus oocytes (Frank-Vaillant et al., 1999; Qian et al., 2001).

## 7. Polyadenylation—the ending tail that starts it all

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 (reviewed by Colgan and Manley, 1997; Richter 1999). Polyadenylation of *mos* mRNA that elicits Mos translation has been demonstrated for Xenopus oocytes and its necessity for the completion of meiosis has been indicated (Sheets et al., 1994, 1995; Barkoff et al., 1998). In the frog, progesterone serves as the cue for *mos* mRNA polyadenylation. The presence of UUUUUAU-type cytoplasmic polyadenylation element (CPE) on the 3′ untranslated region (UTR) is the *cis*-acting element that marks *mos* for polyadenylation. Additionally, a hexanucleotide AAUAAA sequence is required for this process. One *trans*-acting element responding to the progesterone signal is the cytoplasmic polyadenylation element binding protein (CPEB) that binds the CPE. The necessity of its action was demonstrated when neutralizing antibodies against CPEB inhibited polyadenylation in-vivo as well as progesterone induced oocyte maturation (Stebbins-Boaz et al., 1996). Phosphorylation of CPEB was demonstrated to accompany its activation (Paris et al., 1991; Hake and Richter, 1994; de Moor and Richter, 1997; Mendez et al., 2000a,b). The kinase responsible for the activation of CPEB has been recently identified as Eg2, a serine/threonine kinase, which is related to the Aurora family (Mendez et al., 2000a). Eg2 in itself has been demonstrated to be phosphorylated shortly after progesterone administration, providing the linkage to induction of resumption of meiosis and activation of polyadenylation (Andresson and Ruderman, 1998). MPF was demonstrated to participate in the phosphorylation of Eg2 (Frank-Vaillant et al., 2000). An additional *trans*-acting element is the hexa nucleotide binding factor (HBF), also known as cleavage and polyadenylation specificity factor (CPSF), that binds the hexanucleotide (Bilger et al., 1994; Dickson et al., 1999). This last protein tethers the poly A polymerase to the mRNA capacitating the elongation of the poly(A) tail. CPEB phosphorylation by Eg2 was found to increase its affinity to CPSF, resulting in an increase in the number of RNA molecules polyadenylated (Mendez et al., 2000b). Further succeeding phosphorylation of CPEB are at-

tributed to p34cdc2 (Paris et al., 1991; Hake and Richter, 1994). The MPF mediated phosphorylation marks CPEB for degradation bringing about the closure of the polyadenylation process (de Moor and Richter, 1997; Reverte et al., 2001).

Ample evidence has been provided for the construction of the above-mentioned model, most of which has been described in amphibian oocytes. Very little is known regarding this process in mammals, reinforcing the need for further study of meiosis in higher eukaryotes. Our limited knowledge in mammalian systems includes demonstration of *mos* mRNA polyadenylation in mature mouse oocytes that is inhibited by cAMP (Goldman et al., 1988; Gebauer et al., 1994). Of the *trans*-acting element, a mouse homologue of CPEB was isolated (Gebauer and Richter, 1996) and its phosphorylation was correlated with MI (Tay et al., 2000).

Does *mos* mRNA polyadenylation occur in maturing rat oocytes? A recent study from our laboratory shows that *mos* mRNA in meiotically arrested oocytes possesses a poly A tail of about 50 bp (Lazar et al., 2002). The length of the poly A tail does not change at 4 h of incubation but is elongated to include 350 bp at 6 h and becomes even longer at 8 h. Elongation of the poly A tail is prevented by cAMP. Mediation of PKA in this action of cAMP is further suggested by the reversal of the inhibitory effect of this nucleotide by 4C3M, a potent and selective PKA inhibitor. Moreover, the activity of MPF was required for the polyadenylation of *mos* in rat oocytes. In agreement with these findings, ablation of MPF activity, by a constitutively active mutant form of Wee1, prevented polyadenylation of *mos* in Xenopus oocytes (Howard et al., 1999). Opposing results, in Xenopus oocytes, were achieved by the use of a dominant negative mutant of p34cdc2, that it had no effect on polyadenylation of mos mRNA (Ballantyne et al., 1997).

A positive feedback loop between MAPK and Mos during Xenopus oocyte maturation has been proposed previously (Matten et al., 1996; Roy et al., 1996; Faure et al., 1998). A role for MAPK in stimulating *mos* mRNA cytoplasmic polyadenylation has later been suggested (Howard et al., 1999). In disagreement with the above-mentioned observations a substantial accumulation of Mos under conditions of inhibited activity of MAPK were detected lately in both the Xenopus and the rat (Gross et al., 2000; Lazar et al., 2002).

## 8. The crosswalk between cAMP, MPF and MAPK

The meiotic cell cycle in mammalian oocytes is regulated at the level of protein translation and its degradation as well as its post-translational modification. cAMP is the negative upstream key regulator of these events. Upon the decrease of intraoocyte 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, pathway involves Mos translation and MAPK activation. Stimulation of this pathway will maintain the oocytes arrested at MII. Are these two pathways indeed parallel? The sequence of MPF and MAPK activation in Xenopus can not be disclosed by kinetic analysis, since both enzymes are activated almost simultaneously (Gotoh et al., 1991a,b; Nebreda et al., 1995). However, the activation of MAPK signaling pathway is a prerequisite for stimulation of p34cdc2 action (Sagata et al., 1989a). This is obviously not the case in rodents since oocytes of Mos deficient mice activate MPF in a pattern which is indistinguishable of that in wild type (Hashimoto, 1996). Our most recent results (Josefsberg et al., submitted, Lazar et al., 2002) not only support the idea that MPF activation is independent of the MAPK signaling pathway, but rather seem to suggest that MAPK activation is subjected to regulation by p34cdc2. Contrary to previous reports assigning an initiator role to Mos, later studies in Xenopus oocytes seem also to suggest MPF-dependent of Mos expression and MAPK activation (Nebreda et al., 1995; Frank-Vaillant et al., 1999; Howard et al., 1999).

One of the open paradigms in meiotic regulation is the explicit order of inactivation of both MAPK and MPF. The identification of Mos/MAPK pathway as the CSF suggests that only the switch-off of the pathway will allow the completion of the second meiosis. Indeed, inhibition of MAPK results in parthenogenic activation. However, phosphorylated MAPK persists after the completion of the second meiotic division and does not disappear before the first mitotic division in Xenopus (Watanabe et al., 1991), as well as in rat zygotes (N.D. unpublished results). MPF inactivation on the other hand is a pre-requisite for the exit from MII. Similarly in the mouse the expression of Mos persists during embryonic interphase (Weber et al., 1991). Further complication is presented by a recent publication in which a line is drawn connecting spindle assembly checkpoint and MAPK (Schwab et al., 2001). The spindle assembly checkpoint is a surveillance mechanism that maintains MPF in an active stage via prevention of cyclin B1 degradation (Shah and Cleveland, 2000). Rsk was shown to phosphorylate and hence activate Bub1, a component of the spindle assembly checkpoint, (Schwab et al., 2001). Since MAPK remains active at the exit from MII what then disregard the spindle assembly checkpoint? The identification of the initial event that allows for the exit from MII remains to be formulated.

## 9. Epilouge

This review has described our current understanding of regulatory pathways governing meiosis of mammalian oocytes. These and Xenopus oocytes apparently share similar regulatory components. However, variations seem to be depicted at their hierarchy along the meiotic cell cycle. Such differences uncovered herein may illustrate development of modifications in these mechanisms throughout evolution.

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