Molecular Control of Meiosis

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The animal cell cycle consists of a round of chromosomal DNA replication in S-phase, followed by segregation of the replicated chromosomes into the daughter nuclei during M-phase. In most animal cells, gap phases termed G_1 and G_2 are introduced between the M- and S-phases, respectively. Meiosis is a particular example of cell division occurring in germ cells. This specialized cell cycle consists of two successive rounds of chromosome segregation that follow a round of DNA replication. Meiosis produces progeny cells with half as many chromosomes as their parents, thus making sexual reproduction possible. This review is concerned with the factors that have been implicated in the control of meiosis, although research in progress may reveal additional regulatory processes. (Trends Endocrinol Metab 1995;6:165–169).

The entry of the oocyte into meiosis takes place in the fetal ovary and is accompanied by DNA synthesis analogous to S-phase in mitotic cells. Meiosis proceeds up to the diplotene stage of the first prophase and is arrested at diakinesis, just prior to or shortly after birth. This stage corresponds to the G_2-phase of the cell cycle and is characterized by diffused chromosomes surrounded by an intact nuclear membrane termed "germinal vesicle" (GV). Reinitiation of meiosis, which occurs in fully grown oocytes after puberty, represents transition from G_2- to M-phase and involves condensation of the interphase chromatin, dissolution of the nuclear membrane referred to as GV breakdown (GVB), spindle formation, and chromosome segregation. These oocytes complete the first meiotic division by the formation of the first polar body, which is immediately followed by their maturation into unfertilized eggs arrested at the second metaphase of meiosis. The transition between the two meiotic metaphases is not interrupted by interphase. Completion of the second meiotic division is triggered at fertilization, upon sperm penetration. The protracted nature of the meiotic division makes the oocytes and eggs an excellent model for studying the cell cycle checkpoints.

Very little was known until quite recently about the control of cell division. Extensive studies during the last ten years, however, have substantially advanced our understanding of the biochemical and molecular basis of the cell cycle machinery, with most impressive progress made toward description of the events leading to entry into M-phase. The initial landmark in this field was established by Masui and Markert (1971) and, independently, by Smith and Ecker (1971), who discovered that maturing *Rana pipiens* oocytes produce a factor that causes them to resume meiosis. This factor, which was termed "maturation-promoting factor" or MPF, has later been demonstrated in the amphibian *Xenopus laevis* (Schorderet-Slatkine and Drury 1973) and *Ambystoma mexicanun* (Reynhout and Smith 1974) and in the starfish *Asterina pectinifera* (Kishimoto and Kanatani 1976) oocytes. In addition to maturing oocytes, MPF activity has been found in mitotically dividing cells, such as cleaving blastomeres of starfish (Kishimoto et al. 1984) and amphibians (Wasserman and Smith 1978), mammalian cultured cells synchronized at M-phase (Sunkara et al. 1979), and the temperature-sensitive cdc mutants of yeast arrested at M-phase (Weintraub et al. 1982). As MPF appears to control the transition from G_2- to M-phase in both meiosis and mitosis, the acronym MPF was later proposed to mean "M-phase-promoting factor."

Another landmark in the investigation of the control of cell division was established by the purification of *Xenopus* oocyte MPF that allowed resolution of its chemical nature (Lohka et al. 1988). These and later experiments have identified MPF as a complex of two components, one of which, a 34-kD protein that is homologous to the product of the cdc2 gene of the fission yeast, is termed $p34^{cdc2}$. This protein, which is highly conserved among eukaryotes, is a serine/threonine kinase that exhibits a strong preference for histone H1 as a substrate. The second component of MPF is a 45-kD B-type cyclin. Cyclin is subjected to periodic synthesis and degradation, while the levels of $p34^{cdc2}$ remain constant throughout the cell cycle. Association with cyclin is regarded as essential for $p34^{cdc2}$ kinase activity. Another obligatory step for activation of the cyclin/$p34^{cdc2}$ complex is the removal of the phosphate from tyrosine 15 of $p34^{cdc2}$. This step is regulated by specific protein tyrosine phosphatases and kinases homologous to the protein products of the cdc25 and Wee1 genes of fission yeast, respectively [reviewed by Maller (1994)].

The central regulatory role of MPF at the onset of M-phase has been established, mostly by studies conducted on either invertebrate oocytes and eggs that resume the meiotic division or other cells that undergo mitosis [reviewed by Norbury and Nurse (1992), Maller (1994)]. On the other hand, much less knowledge is available regarding the regulatory mechanisms of meiosis in mammalian oocytes. Nevertheless, the observations reported thus far allow the inclusion of mammalian oocytes among the meiotic and mitotic cell types in which the transition from G_2- to M-phase is regulated by MPF. The studies on the meiotic cell cycle of mammalian oocytes and the specific role of MPF

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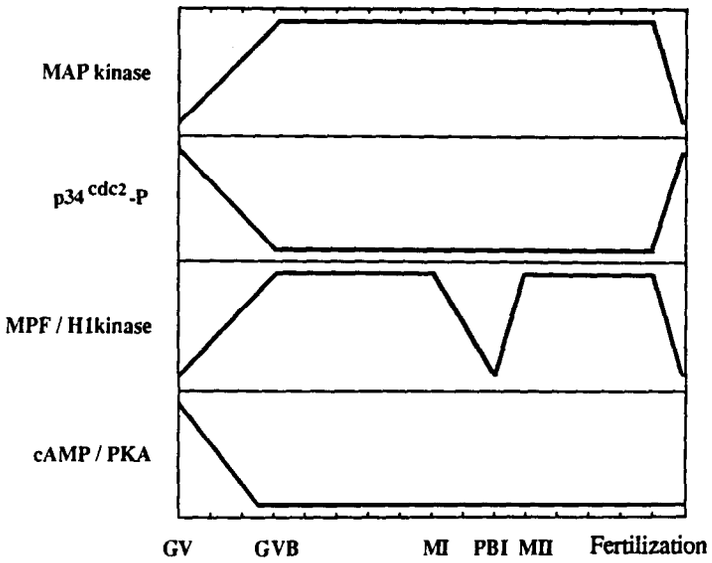

Figure 1. Regulation of meiosis in mammalian oocytes and eggs. GV, germinal vesicle; GVB, GV breakdown; MAP, mitogen-activated protein; MI, MII, meiotic phases; MPF, M-phase-promoting factor; PBI, first polar body; and PKA, cAMP-activated protein kinase.

in setting into motion the cellular machinery involved in resumption of meiosis are herein reviewed in detail. A schematic representation of the knowledge available in this field of research is presented in Figure 1.

• MPF Activity in Mammalian Oocytes and Eggs

The appearance of a cytoplasmic MPF in maturing mammalian oocytes was first suggested by Balakier and Czolowska (1977), who observed that enucleated fragments of immature mouse oocytes, when fused with interphase blastomeres from two-celled mouse embryos, induced premature dissolution of the nuclear membrane and premature chromatin condensation in the blastomeres when their nucleate sister-fragments underwent GVB. Later, fusion experiments confirmed that, in addition to the mouse, MPF is also present in maturing oocytes of other mammalian species, such as the pig and the rabbit (Fulka 1983, Fulka et al. 1986).

Mammalian oocyte MPF is fully effective when introduced into oocytes of nonmammalian species. Starfish (Kishimoto et al. 1984) as well as *Xenopus laevis* oocytes (Sorensen et al. 1985) underwent GVB following their injection with cytoplasm of maturing mouse oocytes. The use of immature starfish oocytes as recipients of cytoplasmic transfer of maturing mouse oocytes was adopted for semiquantification of changes in MPF activity during the course of meiotic maturation (Hashimoto and Kishimoto 1988). This study demonstrated that MPF activity appears initially at GVB, reaches a high level at metaphase I, and then disappears transiently at the time of first polar body emission. Thereafter, MPF activity reappears at metaphase II and remains at an elevated level until fertilization. Similar dynamic changes in MPF activity were demonstrated by electrofusion of pig GV oocytes with homologous oocytes at different stages of maturation (Mattioli et al. 1991). Determinations of H1 kinase activity throughout meiosis in pig, mouse, and rabbit (Naito and Toyoda 1991, Choi et al. 1991, Jelinkova et al. 1994) further confirmed that, during maturation of mammalian oocytes, MPF activity oscillates in exact correspondence with the meiotic cycles.

• Cyclin in Mammalian Oocytes

Information related to the role of cyclin in regulation of meiosis in mammals is scarce. Requirements for cyclin synthesis, in the first but not the second meiotic cell cycle, is denied indirectly by early reports that in mouse oocytes treated with inhibitors of protein synthesis, meiotic maturation is blocked before the first polar body emission, but GVB and chromosome condensation proceed (Wassarman and Letourneau 1976, Golbus and Stern 1976). Accordingly, a later study demonstrated that in maturing mouse oocytes, the formation of MPF requires protein synthesis during the second, but not the first, metaphase (Hashimoto and Kishimoto 1988). The recent detection of cyclin B1 and B2 transcripts in the ooplasm of growing, as well as fully grown, oocytes in the adult mouse ovary (Chapman and Wolgemuth 1992 and 1993) agrees with these early observations. Taken together, these findings suggest that, in rodent oocytes, the cyclin synthesis requirement is completed well before transition into M-phase and a pool of inactive $p34^{cdc2}$/cyclin heterodimers or "pre-MPF" is held in an inactive state by a posttranslational block.

On the other hand, in species with a longer interval between the stimulus and GVB, such as pig, cow, and sheep, de novo protein synthesis is required for GVB (Fulka et al. 1986, Moor and Crosby 1986, Hunter and Moor 1987). These observations could possibly suggest that in larger mammals accumulation of cyclin in G_2-arrested oocytes did not reach the particular threshold level sufficient to support reinitiation of meiosis, requiring further de novo synthesis of the protein. This assumption is not supported, however, by a most recent report of the presence of B-type cyclin in both growing and fully grown pig oocytes (Christmann et al. 1994). Nevertheless, it is still possible that other, as yet unknown, regulatory proteins, localized upstream to MPF, are absent from G_2-arrested porcine, bovine, and ovine oocytes, but are present in rodent oocytes.

• Dephosphorylation of $p34^{cdc2}$

Evidence that resumption of meiosis in mammalian oocytes involves tyrosine dephosphorylation of $p34^{cdc2}$ is provided by experiments using vanadate, an inhibitor of tyrosine phosphatase. This agent prevents tyrosine dephosphorylation of $p34^{cdc2}$ in mouse (Choi et al. 1992) and rat oocytes (Goren and Dekel 1994) and also blocks their spontaneous maturation (Dekel and Goren 1992, Goren and Dekel 1994).

The phosphorylated forms of $p34^{cdc2}$ present in G_2-arrested mouse and rat oocytes disappeared at 2 h after the onset of meiosis, with no further change until metaphase II (Choi et al. 1991, Goren and Dekel 1994). Histone H1 kinase activity, on the other hand, which

was high during metaphase I and II, did decrease at polar body extrusion (Choi et al. 1991). These results suggest that, in maturing mammalian oocytes, dephosphorylation of $p34^{cdc2}$ triggers its activation upon entry into the first metaphase. The previously mentioned cell cycle-dependent oscillatory pattern of MPF activity, however, which is observed upon exit from the first and entry into the second meiotic metaphase, is not associated with another round of phosphorylation/dephosphorylation of $p34^{cdc2}$.

- **Mammalian Oocyte Mitogen-Activated Protein Kinase**

The specific mode of regulation of the meiotic cell cycle in the oocyte that allows the fall in the activity of MPF at the end of meiosis I, in the absence of $p34^{cdc2}$ dephosphorylation, is not known. It is also not fully elucidated what mechanism prevents the events that are normally associated with MPF inactivation, such as chromosome decondensation, nuclear formation, and interphasic reorganization of the microtubule network. These biochemical functions could possibly be executed by a kinase other than $p34^{cdc2}$ that stays active between the two meiotic metaphases.

Members of the mitogen-activated protein (MAP) family are serine/threonine protein kinases that are activated upon their phosphorylation on specific tyrosine and threonine residues. Once activated, these kinases can phosphorylate many of the same sites that MPF does. Indeed, the presence of two isoforms of 42 kD and 44 kD of MAP kinase has been shown in mouse (Sobajima et al. 1993, Verlhac et al. 1993) and rat (Goren et al. 1994) oocytes, and MAP kinase activity that rises as the oocytes enter meiosis I and remains high throughout oocyte maturation has further been demonstrated (Sobajima et al. 1993, Verlhac et al. 1993). These findings suggest that MAP kinase could possibly phosphorylate some of the substrates modified by the active MPF, keeping the oocyte from entering interphase between metaphase I and II.

A role for MAP kinase that is not limited to the transition phase between the two meiotic metaphases is suggested by kinetic analysis of microtubule organization in maturing mouse oocytes (Verlhac et al. 1994). This study reveals that the assembly of the first meiotic spindle correlates better temporally with MAP kinase rather than with MPF activation. This study also shows that MAP kinase activation was delayed after H1 kinase activation, possibly localizing MAP kinase downstream to MPF. On the other hand, an earlier study (Sobajima et al. 1993), which uses oocyte of the same species, but shows a reverse temporal relationship between activation of these two kinases, makes it difficult to establish their relative loci along the signal transduction pathway that finally leads to resumption of meiosis in mammalian oocytes. The possibility that in mammals, as in amphibia, a common signal that induces oocyte maturation activates these two kinases in parallel cannot be excluded at this stage of our knowledge.

- **The Inhibitory Effect of cAMP**

Negative regulation of meiosis in mammalian oocytes by cAMP was originally proposed by Cho et al. (1974). These investigators demonstrated that spontaneous maturation in vitro of mouse oocytes released from their follicles can be reversibly blocked by addition of a membrane-permeant derivative of cAMP or a phosphodiesterase inhibitor. These findings were later extended to include other mammalian species and led to the hypothesis that this cyclic nucleotide could serve as the physiological inhibitor involved in the maintenance of meiotic arrest. The observations that cAMP derivatives and inhibitors of phosphodiesterase prevent LH-stimulated maturation in follicle-enclosed oocytes in vitro were in full accordance with this hypothesis. The physiological role of cAMP was also indicated by determinations of the intracellular levels of cAMP in rat and mouse oocytes. Such measurements revealed that the postovulatory mature oocytes contain lower levels of cAMP than the follicular immature oocytes. Moreover, they also demonstrated that the spontaneous maturation in vitro is preceded by a sharp drop in intraoocyte cAMP, whereas no decrease in cAMP concentrations is observed in oocytes maintained meiotically arrested by a phosphodiesterase inhibitor. Clear correlation between the meiotic status and intraoocyte levels of cAMP was also demonstrated in nonmammalian species, implicating a universal role for cAMP as a negative regulator of oocyte maturation. Furthermore, an inverse correlation between cAMP levels and proliferation, which has been described for certain somatic cell types in culture, may imply that cAMP plays a regulatory role not only in the meiotic, but also in the mitotic, cell cycle [reviewed by Dekel (1988)].

Inhibition of MPF activation by cAMP was already suggested by early fusion experiments. These studies demonstrated that *Xenopus* oocytes are induced to resume meiosis following fusion with maturing, but not with dibutyryl cAMP-arrested, mouse oocytes (Sorensen et al. 1985). On the other hand, fusion of metaphase II mouse oocytes rapidly induced GVB in dibutyryl cAMP-arrested homologous oocytes, suggesting that once cytoplasmic MPF has been activated, its ability to induce the transition of nuclei to metaphase is no longer sensitive to cAMP (Clarke and Masui 1985). More recent studies suggest that it is not the appearance of $p34^{cdc2}$, but rather posttranslational modification of this protein that is regulated by cAMP in the meiotic prophase. Specifically, it has been demonstrated that dephosphorylation of $p34^{cdc2}$ that is associated with reinitiation of meiosis of mouse and rat oocytes (Choi et al. 1991, Goren and Dekel 1994) is inhibited by isobutylmethylxanthine (IBMX), a phosphodiesterase inhibitor that maintains the intraoocyte concentration of cAMP relatively high, inhibiting the resumption of meiosis. Dephosphorylation of $p34^{cdc2}$ could be demonstrated in such oocytes after removal of IBMX. These findings offer evidence for a possible negative regulation of $p34^{cdc2}$ dephosphorylation by cAMP.

Our recent findings that treatment with vanadate effectively maintained rat oocytes in meiotic arrest that was independent of intraoocyte concentrations of cAMP (Goren and Dekel 1994) indicate that the maturation-associated decrease in intracellular concentrations of cAMP is essential, but not sufficient, for reinitiation of meiosis. They further suggest that $p34^{cdc2}$ dephosphorylation is distal to the decrease in cAMP. This idea is further supported by previous studies showing that rat oocytes undergo irreversible commitment to resume meiosis at 45–60 min after their isolation from the ovarian follicle (Dekel and Beers 1980), which is exactly the time at which the maturation-associated drop in intra-

cellular concentrations of cAMP was observed (Aberdam et al. 1987). The electrophoretically retarded phosphorylated form of $p34^{cdc2}$ that disappeared at 2 h after the onset of meiosis is still detected at this earlier time-point (Goren and Dekel 1994). This temporal analysis reveals that the irreversible commitment of rat oocytes to resume meiosis, resulting from the decrease in cAMP, occurs just prior to the dephosphorylation of $p34^{cdc2}$ that has been shown to be completed at 2 h after the onset of meiosis (Choi et al. 1991, Goren and Dekel 1994).

It has been reported that an inhibitor of cAMP-dependent protein kinase (PKA) can induce maturation in IBMX-arrested mouse oocytes (Bornslaeger et al. 1986). These observations suggest that an activated PKA mediates the negative action of cAMP on resumption of meiosis. Further experimental evidence related to the biochemical events that link the cAMP-activated PKA to other downstream regulatory elements of the cell cycle in the mammalian oocyte is not yet available. One such link can be attributed to a tyrosine phosphatase that is indirectly regulated by PKA.

• The Cytostatic Factor

As mentioned in the introduction, unfertilized eggs are arrested in the metaphase of the second meiotic cell cycle. Fertilization or other treatments that increase the intracellular calcium level release cells from metaphase arrest by inducing cyclin degradation and MPF inactivation. A cytostatic factor (CSF) responsible for the meiotic arrest was discovered at the same time that MPF was (Masui and Markeret 1971). CSF was identified by transferring cytoplasm from unfertilized to fertilized eggs. The injected cells arrested in metaphase, demonstrating that the donor unfertilized eggs contained some substance (CSF) that can arrest the cell cycle. Unlike MPF, CSF has never been purified. A number of lines of evidence indicate that the product of the proto-oncogene c-*mos* may act as a CSF. The c-mos protein product $p39^{mos}$ is a protein kinase that, in some way, blocks the ability of MPF to induce the degradation of cyclin. Like CSF, $p39^{mos}$ is calcium-sensitive, being selectively degraded by a calcium-dependent cysteine protease. Fertilization induces an increase in intracellular calcium concentrations that overcomes the ability of c-mos to prevent cyclin degradation, and the subsequent inactivation of MPF seems to induce the proteolysis of c-mos [reviewed by Norbury and Nurse (1992)].

In contrast to the advanced stage of knowledge on the specific function of $p39^{mos}$ in the control of meiosis in the frog, the regulatory role of the c-mos protein product as CSF in the second meiotic arrest of mammalian eggs is not fully established. Recent studies have shown that the amount of c-mos in activated mouse oocytes was still very high after the second polar body formation, when cyclin B was degraded and MPF activity decreased (Weber et al. 1991). These studies seem to deny the role of $p39^{mos}$ degradation in the release from metaphase II arrest in mammals. Nevertheless, previous reports on c-*mos* in mammalian oocytes does indicate that this proto-oncogene participates in oogenesis and that expression of its protein product is required for oocyte maturation. Specifically, in situ hybridization analysis of c-*mos* expression in histological sections of mouse ovaries revealed that oocytes are the predominant, if not exclusive, source of c-*mos* transcripts. The expression of c-*mos* is regulated in a developmental pattern (Mutter and Wolgemuth 1987). In agreement with these findings are the later observations that the c-mos-encoded protein product, $p39^{mos}$, is not expressed by growing oocytes. This protein has been detected in the fully grown mouse oocytes arrested in the first meiotic prophase, in GVB oocytes, in oocytes at first metaphase and anaphase, and in ovulated eggs (Paules et al. 1989). Microinjection of c-*mos* antisense oligodeoxyribonucleotides into GV mouse oocytes prevented the emission of the first polar body. Instead, the loss of c-mos function led to chromosome decondensation, formation of a nucleus after meiosis I and cleavage to two cells (Paules et al. 1989, O'Keefe et al. 1989). These studies show an absolute requirement of c-mos for the normal progression to meiosis II.

• Concluding Remarks

The pioneering studies on cell cycle regulation were performed on oocytes that resume meiosis. Furthermore, it was the female germ cell in which the presence of MPF activity had been reported initially. Vertebrate oocytes and eggs further contributed to the impressive amount of information accumulated to date on the molecular events that participate in cell duplication. The technical difficulty in obtaining a sufficient number of oocytes, but not lack of interest, however, is probably responsible for the gap in knowledge on these processes in the female gametes of mammalian species. Even though a few recent studies of rodent oocytes have helped us to gain some insight into the biochemical and molecular basis of the control of meiosis, some of the most important questions related to this specialized type of cell cycle remain to be answered.

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