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The Control of Meiotic Arrest and Resumption in Mammalian Oocytes

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1. Introduction

In mammals, following implantation of the embryo, a small number of cells from the epiblast eventually become the precursors of primordial germ cells (reviewed by Edson et al., 2009). After mitotic proliferation of the primordial germ cells, migration to the genital ridges and rapid proliferation again, meiosis is initiated in the oogonia at about day 13 of development in mice, at day 82 in bovine and during the 3rd month in humans. A last round of DNA synthesis occurs after which the oocytes enter a long meiotic prophase which consists of different stages (leptotene, zygotene, pachytene). By the time of birth, oocytes of most mammals have reached the diplotene stage, meiosis is arrested and the nucleus is referred to as a germinal vesicle (GV). The timing of progression of oocytes through meiosis in relation to birth varies in different mammals and in a few species meiotic prophase is initiated only after birth (i.e., rabbits and cats). At about the time of birth, oocytes become surrounded by follicle cells and these primordial follicles and oocytes represent a large stockpile from which, at any given time, a few are selected to grow and develop. The gradual depletion of primordial follicles through either growth or degeneration (atresia) continues until menopause.

As oocytes grow, they also acquire the competence to re-initiate meiosis. In mammals, re-initiation of meiosis in the pre-ovulatory follicle is induced by the luteinizing hormone (LH) surge. The germinal vesicle membrane breaks down [this stage is called germinal vesicle breakdown (GVBD)] and chromosomes separate from one another: one set is extruded into the first polar body, whereas the other set aligns at the second metaphase (MII) plate. In most mammals, meiosis is arrested again at this stage until activation by a spermatozoon. When mammalian oocytes that are competent to re-initiate meiosis are removed from their follicles and cultured, they undergo spontaneous resumption of meiosis with progression to MII in the absence of gonadotropins, demonstrating that a signal(s) from the follicle holds oocytes in prophase arrest. Spontaneous resumption of meiosis was first observed by Pincus & Enzmann (1935) in rabbit oocytes and was subsequently observed in oocytes from other mammalian species (Edwards, 1965). Spontaneous oocyte maturation allowed the development of *in vitro* maturation (IVM), a reproductive technology which involves artificial removal of cumulus-oocyte complexes (COC) from antral follicles and culturing them in standard cell culture conditions for 24-48 h until they reach metaphase II. A proportion of these oocytes are then competent to develop following *in vitro* fertilization (IVF).

The cellular and molecular mechanisms involved in maintaining oocyte meiotic arrest for prolonged intervals in the ovary are not fully understood. Similarly, the chain of molecular and cellular events that leads to meiotic resumption, either *in vivo* in response to the gonadotropin surge, or spontaneously *in vitro*, has not been completely elucidated even though dramatic advances have been made in recent years in understanding the control of meiosis in rodent oocytes. Research aimed at understanding the mechanisms that control meiosis has relevance for practical applications as the oocyte, in addition to its important role in determining fertility, is a major player in reproductive biotechnologies such as IVM, IVF, cloning and transgenesis. For example, in livestock species, the efficiency of *in vitro* embryo production remains low as only approximately 40% of the fertilized oocytes develop to the blastocyst stage. One reason for this inefficiency is that although the oocytes are at the correct nuclear maturation stage (MII) after IVM, several of them did not have sufficient time to complete cytoplasmic maturation; i.e., they did not have time to accumulate all the mRNAs and proteins required for early development as RNA synthesis ceased when meiosis resumed. Physiological inhibition of spontaneous nuclear maturation *in vitro* for a period of time sufficient to complete cytoplasmic maturation, will be required to improve developmental competence. Similarly, the cornerstone of any wild animal fertility preservation approach is the capacity for successful *in vitro* culture of gametes and embryos (Comizzoli et al., 2010). Moreover, IVM has the potential to exploit the large supply of oocytes available within ovaries in the case of ovariectomy or death of a wild female donor. In 2009, the International Committee for Monitoring Assisted Reproductive Technologies reported that over 200,000 babies are born annually from assisted reproductive technologies (de Mouzon et al., 2009). Currently, the use of IVM for the treatment of human infertility is not widespread due to its low efficiency (Suikkari, 2008); however, IVM represents an attractive alternative as it would reduce the use of gonadotropins for ovarian stimulation, thereby reducing side effects and costs for patients. This chapter reviews research aimed at understanding the signalling pathways involved in the control of meiotic cell cycle arrest at the diplotene (GV) stage as well as in the control of meiotic resumption (GVBD) in oocytes from selected mammalian species.

2. The control of meiosis in rodent oocytes

2.1 Early data on the role of cAMP

Cyclic adenosine monophosphate (cAMP) is a second messenger which is responsible for the transduction of hormonal signals in a wide range of organisms. Cyclic AMP is synthesized from ATP by the enzyme adenylate cyclase (AC) which is located on the inner side of the plasma membrane. Adenylate cyclase is activated by a range of signalling molecules through the activation of adenylate cyclase stimulatory G (Gs)-protein-coupled receptors and inhibited by agonists of adenylate cyclase inhibitory G (Gi)-protein-coupled receptors. Cyclic AMP is degraded to 5′-AMP by phosphodiesterase (PDE) enzymes.

Cyclic AMP was thought early on to play a critical role in the control of meiotic maturation as LH, human chorionic gonadotropin (hCG), follicle-stimulating hormone (FSH) and prostaglandin E_2 (PGE_2) were effective in inducing meiotic resumption in rat oocytes cultured in intact follicles (Tsafriri et al., 1972). Additionally, injection of dibutyryl cyclic AMP (dbcAMP) into the follicular antrum also induced GVBD while LH and PGE_2 increased cAMP levels over 20-folds in follicles suggesting that the stimulatory effect of the

hormones on maturation was mediated by cAMP (Tsafriri et al., 1972). Subsequently, several other studies, performed with cumulus-oocyte complexes cultured without follicles, provided evidence that cAMP levels within the oocyte determine meiotic status such that high levels result in meiotic arrest while low levels lead to re-initiation of meiotic maturation (Aberdam et al., 1987; Dekel et al., 1984; Schultz et al., 1983a). Therefore, cAMP appeared to have a dual role in the control of meiosis: mediation of the stimulatory action of gonadotropins on the follicle cells (oocytes do not have gonadotropin receptors) and an inhibitory effect on the oocyte itself. Challenging questions being addressed were: whether or not the oocyte itself could synthesize cAMP and whether the amount of cAMP synthesized by the oocyte was sufficient for meiotic arrest. Several studies with rodent oocytes suggested that cAMP derived from follicle cells was responsible for maintaining meiotic arrest as cAMP-elevating agents such as AC stimulators, PDE inhibitors and membrane-permeable cAMP derivatives did not inhibit meiosis in oocytes denuded of their cumulus cells [DO, (Dekel & Beers, 1978, 1980; Dekel et al., 1984; Racowsky, 1984)] and cAMP transfer from the cumulus cells to the oocyte was demonstrated (Bornslaeger & Schultz, 1985). However, other studies showed that the oocyte could synthesize cAMP and that cAMP-elevating agents could prevent GVBD in DO (Cho et al., 1974; Olsiewski & Beers, 1983; Urner et al., 1983).

2.2 Events downstream of cAMP and the control of maturation promoting factor

Maturation promoting factor (MPF) is a key regulator of the mitotic and meiotic cell cycle and integrates the signals from several pathways to control mitosis and meiosis. It is a serine-threonine kinase protein heterodimer composed of a catalytic subunit, cyclin-dependent kinase 1 (CDK1, also known as p34^{cdc2}), and a regulatory subunit, cyclin B. The activated form of MPF involves dephosphorylation at Thr14 and Tyr15 of CDK1 and its association with cyclin B (Clarke & Karsenti, 1991). For meiotic arrest to be maintained at prophase I, MPF must be kept inactive. How do high levels of cAMP in the oocyte maintain MPF inactive? In general, cAMP acts via protein kinase A (PKA). Recent studies [reviewed by Han & Conti (2006)] in mouse and Xenopus oocytes indicate that PKA directly regulates the activities of a kinase (Wee1B) and a phosphatase (Cdc25) for CDK1. High cAMP levels in oocytes result in active PKA, active Wee1B, and the phosphorylation and inactivation of CDK1 while a decrease in oocyte cAMP levels leads to PKA inactivation, Cdc25 activation, dephosphorylation of CDK1 and MPF activation. Regulation of the level of cyclin B by synthesis and degradation is also involved in the control of MPF activity (Ledan et al., 2001).

2.3 New findings on the control of meiosis in rodent oocytes

It is no longer believed that cAMP from follicle cells contributes significantly to mouse oocyte meiotic arrest. Horner et al. (2003) showed that mRNA and protein for the adenylate cyclase 3 (AC3) isoform were detected in rat and mouse oocytes and that the regulation of cAMP levels in oocytes indicated that the main AC from rat oocytes possessed properties similar to AC3 of somatic cells. Moreover, more than 50% of early antral follicles from AC3-deficient mice contained oocytes that had resumed meiosis (10-15% in wild-type oocytes), providing evidence that rodent oocytes contain a functional AC involved in meiotic arrest (Horner et al., 2003).

The development of a method to inject mouse oocytes within antral follicles allowed experiments to be performed that would shed more light on the mechanisms involved in the control of meiosis. Microinjection of a Gs antibody caused resumption of meiosis in follicle-enclosed oocytes indicating that inhibition of Gs in the oocyte leads to meiotic resumption and conversely, Gs activity in the oocyte is required to maintain meiotic arrest in the follicle (Mehlmann et al., 2002). Similarly, microinjection of a dominant negative form of Gs into mouse oocytes (also in Xenopus oocytes) caused resumption of meiosis (Kalinowski et al., 2004). Since Gs by itself has no constitutive activity, it was suspected that a receptor is required to activate Gs. A potential receptor, the orphan receptor GPR3, was identified through searching an expressed sequence tag database derived from a cDNA library obtained from mouse oocytes (Mehlmann et al., 2004). This receptor was of interest because it elevated cAMP when expressed in various cell lines. *In situ* hybridization showed that GPR3 RNA was localized in oocytes and 82% of the oocytes in antral follicles of ovaries from prepubertal GPR3 knockout mice had resumed meiosis (0% in wild-type, Mehlmann et al., 2004). Injection of GPR3 RNA into GPR3$^{-/-}$ oocytes reversed the knockout phenotype indicating that the GPR3 of the oocyte itself maintained meiotic arrest rather than the GPR3 of the follicle cells (Mehlmann et al., 2004). From these results, it appeared that the meiosis inhibitory signal was a GPR3 agonist which activated Gs and AC3; however, removal of oocytes from their follicles did not decrease Gs activation by GPR3 (Freudzon et al., 2005). Therefore, although GPR3 and Gs are required to maintain meiotic arrest, the signal from follicle cells acts by a mechanism other than providing a GPR3-activating ligand to maintain meiotic arrest.

If the signal from follicle cells to inhibit meiosis is not a GPR3-activating ligand then what are the other potential signals? The signal may act via gap junctions as initially believed, since gap junction inhibitors caused a decrease in oocyte cAMP and meiotic resumption (Norris et al., 2008; Sela-Abramovich et al., 2006). This brings us back to the original hypothesis that cAMP from somatic cells is transferred to the oocyte and inhibits meiosis. However, because the major oocyte phosphodiesterase is PDE3A (Masciarelli et al., 2004) which is inhibited by cyclic guanosine monophosphate (cGMP), and various studies showed that cGMP could be involved in meiotic arrest (Sela-Abramovich et al., 2008; Törnell et al., 1990), it was hypothesized that cGMP from the somatic cells could reach the oocyte through gap junctions, inhibit PDE3A and maintain meiotic arrest. Using Förster resonance energy transfer-based cyclic nucleotide sensors in follicle-enclosed oocytes, Norris et al. (2009) showed that cGMP does pass through gap junctions into the oocyte to contribute to the maintenance of high cAMP levels by inhibiting PDE3A.

How does LH stimulation of follicles lead to oocyte meiotic resumption? In the study from Norris et al. (2009), LH stimulation lowered cGMP levels in follicle cells and closed gap junctions. As a result, cGMP levels in the oocyte also decreased, PDE3A activity increased approximately 5-folds, oocyte cAMP decreased also approximately 5-folds and meiosis resumed (Norris et al., 2009). It is possible that LH could regulate oocyte cAMP via other mechanisms; for example, activation of Gi family G protein can inhibit AC or stimulate PDE thereby lowering cAMP. However, injection of pertussis toxin (a Gi inhibitor) into follicle-enclosed mouse oocytes did not prevent LH-induced meiotic resumption (Mehlmann et al., 2006). Similarly, the LH response was not prevented by inhibition of a Ca^{2+} elevation by injection of EGTA into follicle-enclosed mouse oocytes (Mehlmann et al., 2006) indicating that LH does not regulate cAMP in the oocytes via a Gi family G protein or calcium. Further

studies also showed that LH does not act by terminating receptor-G(s) signalling (Norris et al., 2007).

There are still a number of questions remaining to answer to complete this exciting story such as: whether there is a direct role for somatic cell cAMP in meiotic inhibition. What maintains high cGMP levels? How does LH decrease cGMP in somatic cells: through inhibition of a guanylate cyclase or stimulation of a cGMP-specific phosphodiesterase? Further studies showed that the epidermal growth factor (EGF) pathway is required for LH-induced gap junction closure and a portion or all of the cGMP decrease (Norris et al., 2010; Vaccari et al., 2009). Another important question is how do other signalling pathways that can affect meiosis fit into this model? For example, several studies demonstrated that the energy sensor adenosine monophosphate-activated protein kinase (AMPK) plays a role in controlling the resumption of nuclear maturation in mouse oocytes. Pharmacological activation of AMPK induced nuclear maturation in cumulus-enclosed and denuded oocytes that had been arrested with dibutyryl cAMP or hypoxanthine (Downs et al., 2002). Moreover, oocyte AMPK was also activated by hormones and stress; this activation preceded GVBD, and inhibiting AMPK activity blocked the effects of these stimuli (Chen et al., 2006; Chen & Downs, 2008; LaRosa & Downs, 2006, 2007). A recent study provided evidence that AMPK is also involved after GVBD to promote the completion of meiosis and to prevent premature activation (Downs et al., 2010). In conclusion, these studies show that the control of oocyte meiosis probably involves a complex network of cross-talk between several signalling pathways in the oocyte and also in cumulus cells.

3. The control of meiosis in bovine oocytes

Research on the control of meiosis in livestock species has to accommodate a number of variables not encountered in laboratory animals. For example, the majority of studies were performed with oocytes recovered from ovaries collected from slaughtered animals. Although most researchers collect oocytes from a narrow range of follicle sizes and further select the oocytes based on morphological criteria, it remains that the selected oocytes represent a mixed population originating from follicles at varying stages of development, dominance and/or atresia. Moreover, contrary to laboratory animals for which all animals in an experiment are synchronized and treated the same way, the livestock females from which the oocytes are recovered are at different stages of the estrus cycle and are exposed to different environments such as nutrition, temperature or stress level, all of which can potentially affect reproductive cells. In addition, the generation of knockout animals to study molecules of interest is currently not possible in livestock species; therefore, definitive conclusions on the role of a specific enzyme isoform in a biological process can sometimes not be reached. Our understanding of the control of oocyte meiosis in livestock species has relied on the study of the presence of mRNA and proteins, the study of protein phosphorylation and, to a large extent, on pharmacological studies.

3.1 Role of cAMP in the control of bovine oocyte meiosis

As in rodent oocytes, several early studies showed that cAMP-elevating agents could decrease meiotic maturation of bovine cumulus-enclosed oocytes (Jagiello et al., 1975, 1981). However, higher concentrations of the cAMP-elevating agents were necessary to transiently increase the percentage of bovine oocytes remaining at the GV stage after *in vitro* culture

(Jagiello et al., 1981, Sirard & First, 1988) compared to concentrations that were effective in rodent oocytes. Since AC was detected on their plasma membrane (Kuyt et al., 1988), it was concluded that bovine oocytes could possibly generate sufficient amount of cAMP for meiotic arrest. In support of this hypothesis, the AC stimulator forskolin (FSK) transiently inhibited GVBD in oocytes denuded of cumulus cells (Homa, 1988), or denuded of both cumulus cells and zona pellucida thereby eliminating the possibility that the AC in the cumulus cell projections embedded in the zona pellucida was contributing to the FSK effect (Bilodeau et al., 1993). However, transfer of cAMP from cumulus cells to the oocyte was indirectly demonstrated in a few studies. For example, the culture of COCs with FSK led to ~20 to 90-fold increases in intra-oocyte cAMP compared to oocytes from complexes cultured in control conditions, whereas the culture of denuded oocytes with FSK resulted in only 2 to 6-fold increases in cAMP levels (Bilodeau et al., 1993; Thomas et al., 2004).

The enzyme AC possesses two metal ion-binding sites in its active site and Mn^{2+} is an AC activator (Tesmer et al., 1999). Moreover, a Mn^{2+}-dependent soluble AC is present in sperm cells (Braun & Dods, 1975). Culture of bovine oocytes in the presence of $MnCl_2$ resulted in an increase in the percentage of cumulus-enclosed oocytes (CEO) remaining at the GV stage after 7 h of culture, a decrease in the percentage of oocytes reaching the MII stage after 22 h of culture, and a six fold cAMP increase in complexes (Bilodeau-Goeseels, 2001, 2003a). An increase in cAMP in oocytes from complexes in response to $MnCl_2$ was detected in the presence of FSK only. In contrast to CEO, Mn^{2+} increased the percentage of denuded oocytes resuming meiosis, but also increased cAMP in the presence of FSK only (Bilodeau-Goeseels, 2003a). These results could be explained by the fact that Mn^{2+} is an activator of AC; however, Mn^{2+} is also a cofactor for many enzymes and the addition of $MnCl_2$ to the culture medium could possibly alter the activity of other enzymes involved in meiotic progression. The fact that inhibition of protein kinase A (PKA) activity abrogated the inhibitory effect of $MnCl_2$ in bovine CEO (Bilodeau-Goeseels, 2003a) supports the former possibility. Moreover, stimulation of protein kinase C (PKC) also abrogated the inhibitory effect of Mn^{2+} on meiosis (Bilodeau-Goeseels, 2003a) suggesting that the inhibitory effect of Mn^{2+} can be due to activation of AC4, 6, or 9 as these isoforms are inhibited by PKC (Sadana & Dessauer, 2009). Taken together, these results indicate that bovine oocytes and cumulus cells may contain AC isoforms with different sensitivities to Mn^{2+}. Lastro et al., (2006) determined that bovine cumulus cells obtained from follicles 2-8 mm contained mRNA for AC isoforms 1, 3, 4, 6, and 9 and were enriched in PKC-inhibited isoforms 4 and 6 and the Ca^{2+}-stimulated isoform 1. However, the AC isoforms of bovine oocytes have not yet been determined.

3.2 Role of phosphodiesterases in the regulation of bovine oocyte meiosis

As was the case with dbcAMP, the non-specific PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX) inhibited bovine oocyte meiotic resumption partially and transiently (Sirard, 1990; Sirard & First, 1988) when used at much higher concentrations than concentrations that were inhibitory in rodent oocytes (Dekel et al., 1988; Schultz et al., 1983b; Vivarelli et al., 1983). In bovine oocytes, specific inhibition of PDE3 *in vitro* delayed spontaneous meiotic maturation and increased cAMP levels in cumulus cells and in denuded oocytes (Bilodeau-Goeseels, 2003b; Mayes & Sirard, 2002; Thomas et al., 2002). A study of PDE isoforms present in bovine follicle components showed that PDE3 accounted for 80% of the PDE activity in the oocyte, while PDE8 activity accounted for the remaining 20 and 60% of PDE activity in oocytes and cumulus cells, respectively. Inhibition of PDE8 in bovine COCs

increased cAMP levels in oocytes and delayed meiosis (Sasseville et al., 2009). Collectively, these results suggest that cAMP and PDE enzymes are involved in the control of meiosis in bovine oocytes. However, even when cAMP levels were increased substantially and/or PDE inhibitors specific for the isoforms present in oocytes were used; meiosis was generally delayed and not totally inhibited as in rodent oocytes. It is suspected that other pathways acting in synergy with cAMP are probably important for the control of meiotic arrest in bovine oocytes.

3.3 Role of AMPK in the control of bovine oocyte meiosis

Contrary to results obtained with mouse oocytes where AMPK activation led to meiotic resumption (see section 2.3), meiosis was inhibited when bovine oocytes were cultured with the AMPK activator 5′-aminoimidazole-4-carboxamide 1-β-D-ribofuranoside (AICAR, Bilodeau-Goeseels et al., 2007). The inhibitory effect of AICAR was observed in cumulus-enclosed and denuded oocytes, was reversible, increased the inhibitory effect of the AC activator FSK, was dependent on its phosphorylation by adenosine kinase and was not due to increased cAMP levels or to increased purine nucleotide synthesis (Bilodeau-Goeseels et al., 2007). Metformin [MET, one of the most widely used drugs for the treatment of type 2 diabetes and an AMPK activator (Zhou et al., 2001)], was also reported to inhibit GVBD in bovine CEO and DO by Bilodeau-Goeseels et al. (2007). In a subsequent study, however, the AMPK inhibitor Compound C (CC) did not reverse the effect of AICAR and MET and even had a significant inhibitory effect itself on bovine oocyte meiosis (Bilodeau-Goeseels et al., 2011). In mouse oocytes, CC prevented AICAR-induced maturation and on its own had a slight inhibitory effect on GVBD (Chen et al., 2006).

No changes in the ratio of Thr172 phosphorylation (phosphorylation of Thr172 of the α subunit of AMPK is required for activation) to total AMPK were detected in extracts of cumulus cells, CEO or DO that had been treated with AICAR or MET at concentrations that inhibited meiosis (Bilodeau-Goeseels et al., 2011) suggesting that the inhibitory effect of AICAR and MET on bovine oocyte meiosis was not due to AMPK activation in cumulus cells or the oocyte. Different results were obtained in another laboratory where MET inhibited meiosis in CEO but not in DO, CC accelerated GVBD and culture with 5 or 10 mM MET [2 mM was used by Bilodeau-Goeseels et al. (2007)] resulted in increased Thr172 phosphorylation in cumulus cells and oocytes from complexes (Tosca et al., 2007). The different results were likely due to the different MET concentrations used and/or the different culture conditions. In both studies, but especially in the Bilodeau-Goeseels et al. 2011 study, there was already a certain level of Thr172 phosphorylation at the onset of culture (t = 0) and this could have made small changes in Thr172 phosphorylation in response to MET (and also AICAR) difficult to detect. In conclusion, more studies are needed to determine the extent of AMPK involvement in the control of meiosis in bovine oocytes. More specifically, the determination of the effects of culture conditions on basal AMPK activation and on the effects of activators and inhibitors, as well as the identification of the upstream kinase(s) that phosphorylates Thr172 will be the next steps.

3.4 Other signalling pathways involved in the control of bovine oocyte meiosis

As mentioned above, AICAR and MET may not inhibit bovine oocyte meiosis through AMPK activation and therefore, may act through other inhibitory signalling molecules. Additionally, since the inhibitory effect of cAMP is transient and high concentrations are

required, it is possible that cAMP acts in synergy with another signalling pathway(s) to inhibit meiosis in bovine oocytes. Is the cGMP pathway as involved in the control of bovine oocyte meiosis as it is in rodent oocytes? The cGMP analog 8-bromo-cGMP as well as the guanylate cyclase stimulators atrial natriuretic peptide and protoporphyrin 1X did not have any effect on bovine oocyte meiosis after 7h of culture (Bilodeau-Goeseels, 2007), while cGMP derivatives inhibited spontaneous nuclear maturation in rat denuded oocytes (Törnell et al., 1990). The cGMP pathway can also be activated by nitric oxide (NO), which is synthesized by NO synthase (NOS) and activates soluble cytoplasmic guanylate cyclase. Inducible NOS (iNOS) inhibition studies suggested that endogenous NO is necessary for spontaneous nuclear maturation (Bilodeau-Goeseels, 2007) and/or the MI to MII transition (Matta et al., 2009; Schwarz et al., 2010). Yet, NO donors also inhibited GVBD (Bilodeau-Goeseels, 2007; Schwarz et al., 2008; Viana et al., 2007) but the inhibitory effect of the NO donor sodium nitroprusside was not through the cGMP/protein kinase G (PKG) pathway (Bilodeau-Goeseels, 2007). In mouse oocytes, NO donors reversed the inhibitory effect of NOS inhibitor on meiosis (Bu et al., 2003), demonstrating yet again differences in the control of meiosis between bovine and rodent oocytes.

There are even fewer studies on the role of other signalling pathways in the control of bovine oocyte meiosis, and meiotic resumption has not been studied as extensively as meiotic arrest in oocytes from livestock species. The role of Ca^{2+} in bovine oocyte fertilization and activation of development has been studied extensively (Tosti et al., 2002) and it appears to also be necessary for GVBD and progression of meiosis (He et al., 1997; Homa, 1995). Similarly, few studies have examined the role of PKC in bovine oocytes. Protein kinase C activation accelerated GVBD (Mondadori et al., 2008; Rose-Hellekant & Bavister, 1996) while PKC inhibition prevented GVBD (Homa, 1991). Using *in vivo* and *in vitro* experiments, Barreta et al. (2008) provided evidence that angiotensin II mediates LH-induced meiotic resumption in bovine oocytes and this event is dependent on prostaglandin E_2 or $F_{2\alpha}$ from follicular cells.

4. The control of meiosis in porcine oocytes

4.1 Role of cAMP, phosphodiesterases and AMPK

As in rodent and bovine oocytes, cAMP-elevating agents such as dbcAMP, the AC activator forskolin and non-specific and specific PDE isoform inhibitors can prevent or delay GVBD in porcine oocytes (Fan et al., 2002; Kim et al., 2008; Kren et al., 2004; Laforest et al., 2005; Racowsky, 1985). Phosphodiesterase activity in DO was almost completely inhibited by cilostamide (a PDE3 inhibitor) and PDE3A mRNA was detected by RT-PCR, suggesting that PDE3 is the main PDE in porcine oocytes (Sasseville et al., 2006). Although PDE3 activity represented only 19% of the total PDE activity in porcine COC, it potentially has a functional role in meiotic resumption as its mRNA level and activity were upregulated in COC but not in oocytes (therefore, upregulation was in cumulus cells) after 4 h of IVM. The up-regulation was gonadotropin- and cAMP-dependent (Sasseville et al., 2007). Similarly, cGMP-specific PDE activity also increased in a gonadotropin-dependent manner in porcine cumulus cells after 24 and 48 h of IVM (Sasseville et al., 2008). This PDE activity increase could potentially be responsible for a cGMP decrease leading to meiotic resumption as described in mouse follicles (see section 2.3). Although the presence and roles of AC3 or other AC isoforms and the GPR3 receptor have not yet been determined in porcine oocytes, an inhibitory role of

Gsalpha for meiotic resumption has been demonstrated as injection of an anti-Gsalpha antibody into porcine oocytes maintained in meiotic arrest with IBMX promoted cyclin B synthesis, MPF activation and GVBD (Morikawa et al., 2007). Similarly, as in mouse and Xenopus oocytes, Wee1B, the kinase which catalyzes the inhibitory phosphorylation of CDK1, is involved in meiotic arrest of porcine oocytes (Shimaoka et al., 2009).

Porcine oocytes and cumulus cells contained transcripts for at least one isoform of each of the three AMPK subunits. Moreover, AMPK activators alone or in combination with PDE inhibitors maintained porcine cumulus-enclosed oocytes in meiotic arrest (Mayes et al., 2007). As in bovine oocytes, the AMPK inhibitor CC did not reverse the effect of AMPK activators on meiosis and was itself inhibitory to oocyte nuclear maturation (Bilodeau-Goeseels et al., unpublished). Therefore, the effects of AMPK modulators on porcine oocyte meiosis are more similar to their effects on bovine oocytes compared to mouse oocytes indicating that the level of involvement of AMPK (and/or other signalling pathways affected by the AMPK modulators) is probably similar in bovine and porcine oocytes and different from rodent oocytes.

4.2 The role of mitogen-activated protein kinase in the control of porcine oocyte meiosis

4.2.1 MAPK in oocytes

Mitogen-activated protein kinase (MAPK) is universally activated in oocytes during maturation in all vertebrates studied so far. However, several studies suggested that MAPK activation in porcine oocytes is not implicated in meiotic resumption as spontaneous meiotic resumption occurred normally in porcine DO cultured with the MAPK inhibitor U0126 (Fan et al., 2003) and MAPK activation in pig oocytes occurred after GVBD (Liang et al., 2005). Moreover, microinjection of porcine oocytes with c-mos antisense RNA (c-mos is an upstream activator of MAPK) completely inhibited phosphorylation and activation of MAPK but did not have an effect on spontaneous meiotic resumption (Ohashi et al., 2003). Studies of the timing of MAPK activation and studies using inhibitors suggested that MAPK is probably involved in the regulation of meiosis after GVBD or during the MI/MII transition (Inoue et al., 1995; Lee et al., 2000; Ye et al., 2003). Similar conclusions were obtained in rodent and bovine oocytes (reviewed by Liang et al., 2007).

4.2.2 MAPK in follicular cells

Contrary to the situation in oocytes where MAPK is not necessary for GVBD, MAPK in follicular somatic cells is required for gonadotropin-induced meiotic resumption. Gonadotropins induced early and rapid MAPK activation in cumulus cells, MAPK activation in oocytes then occurred later at around the time of GVBD (Ebeling et al., 2007). The selective MEK inhibitors PD98059 and U0126 blocked FSH-induced meiotic resumption in mouse and porcine CEO but not spontaneous meiotic resumption in DO (Liang et al., 2005; Meinecke & Krischek, 2003; Su et al., 2002).

The mediator(s) between LH stimulation and MAPK activation in follicular cells as well as the mechanisms for inducing oocyte meiotic resumption following MAPK activation in follicle cells are not completely elucidated. Activation of MAPK could potentially lead to the production of a putative meiosis-inducing factor (Downs et al., 1988). However, LH

stimulation closed gap junctions (Norris et al., 2009) and inhibition of MAPK activation blocked oocyte GVBD (Liang et al., 2005) as well as LH-induced inhibition of gap junction protein Cx43 translation in rat follicle cells (Kalma et al., 2004), suggesting that a MAPK-dependent pathway mediates LH-induced breakdown of gap junction communication and thus leads to oocyte maturation. The mediator of LH-stimulated MAPK activation could potentially be PKA as increased cAMP levels in porcine cumulus cells (resulting from inhibition of cumulus cell-specific PDE) activated MAPK (Liang et al., 2005). Protein kinase C also stimulated MAPK and oocyte meiotic resumption. The epidermal growth factor (EGF) network has an important role to play in mediating LH function during oocyte meiotic resumption; therefore, EGF could potentially be a mediator of LH-stimulated MAPK activation. In porcine granulosa cells, MAPK can be activated after a transient treatment with EGF (Keel & Davis, 1999) and EGF can induce meiotic maturation in porcine oocytes (Ding & Foxcroft, 1994). Studies in other species also suggested that activation of EGF receptor triggers signalling via the MAPK pathway (reviewed by Liang et al., 2007).

In conclusion, several questions remain unanswered about the role of MAPK in oocyte meiosis. For example, if PKA and PKC activate MAPK, are there other proteins in the signalling cascade between PKA/PKC and MAPK? Similarly, what is the mediator(s) between EGF receptor and MAPK?

5. The control of meiosis in equine oocytes

An increase in follicle diameter has been positively linked with increased nuclear and cytoplasmic maturation rates in the horse; however, oocyte diameter is not directly linked to oocyte competence (Goudet et al., 1997). Similar to other domestic species such as bovine and porcine, equine oocytes used for research tend to be recovered from slaughtered animals; however, due to the large size of follicles, ultrasound guided follicular puncture is often performed on mares. Follicular punctures are not nearly as efficient as follicle scraping of slaughterhouse ovaries with only approximately 8-9 COC being recovered every 22 days (Goudet et al., 1997); however, it allows for repeated harvesting of oocytes from the same mare when its reproductive cycle is known, thereby increasing the repeatability of results.

Equine oocytes have the lowest *in vitro* nuclear maturation rates of all of the domestic species discussed in the present review (Del Campo et al., 1995); therefore, the majority of studies on equine oocyte meiosis have focused on how to improve meiosis *in vitro* rather than on how to inhibit it. The low maturation rates may be related to the fact that the LH surge that triggers *in vivo* maturation lasts 4-6 days versus a 6-8 hour period observed in ewes (Alexander & Irvine, 1987; Irvine & Alexander, 1994); therefore, equine oocytes probably have different requirements and culture conditions still need to be optimized.

5.1 The role of follicular cells in the control of equine oocyte meiosis

Follicular cells play a key role in the control of meiosis since removal of oocytes from their follicle environment leads to spontaneous meiotic resumption (Pincus & Enzmann, 1935). Equine ovaries are especially suitable for the study of the role of follicular cells due to the follicles' large size which allows the different cell types to be easily isolated. Equine oocytes cultured while still attached to the membrana granulosa resumed meiosis. However, in the presence of theca cells or in theca cell-conditioned medium, more oocytes (attached to

membrana granulosa) remained at the GV stage indicating that theca cells secrete a meiosis-inhibiting factor (Tremolada et al., 2003). These results are similar to results obtained with bovine oocytes as theca cells but not granulosa cell monolayers maintained meiotic arrest *in vitro* (Richard & Sirard, 1996).

5.2 Role of MPF, MAPK and other signalling molecules in the control of equine oocyte meiosis

The two subunits of MPF, p34^{cdc2} and cyclin B protein, are present in both immature and mature oocytes before and after *in vitro* culture (Goudet et al., 1998). Therefore, equine oocytes have all the key components required for MPF formation, suggesting a lack of MPF regulators in incompetent oocytes. Mitogen-activated protein kinase (MAPK) is present at all nuclear stages after *in vitro* culture (Goudet et al., 1998). Of the two forms of MAPK, ERK1 and ERK2, only ERK2 is detected in equine oocytes during the GV stage with decreased electrophoretic mobility due to modification by phosphorylation in Metaphase I and Metaphase II. Thus MAPK remains non-phosphorylated (inactive) in incompetent and immature oocytes but becomes phosphorylated (activated) after GVBD in competent and preovulatory oocytes (Goudet et al., 1998). The reasons for the inability to phosphorylate MAPK in incompetent equine oocytes are unknown. An extracellular calcium sensing receptor agonist, NPS R-467, increased the activity of MAPK in equine cumulus cells and oocytes (De Santis et al., 2009).

Epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I) and growth hormone had a positive effect on *in vitro* nuclear maturation of equine oocytes (Carneiro et al., 2001; Lorenzo et al., 2002; Pereira et al., 2011). Receptors for EGF have been localized in equine follicles particularly in cumulus cells and to some extent in mural granulosa cells. The addition of A-47, a specific tyrosine kinase inhibitor, inhibited maturation, suggesting that EGF has a physiological role in the regulation of equine oocyte maturation (Lorenzo et al., 2002). Contrary to other mammalian species discussed above, we are not aware of any studies on the role of cAMP in the control of equine oocyte meiosis, except for a preliminary study which concluded that the positive effect of growth hormone on equine oocyte meiosis was mediated by the PKA pathway (Lorenzo et al., 2005).

6. The control of meiosis in ovine oocytes

6.1 The role of cumulus cells in the control of ovine oocyte meiosis

The presence of cumulus cells during ovine oocyte culture may have more importance in the promotion of nuclear maturation compared to bovine oocytes: only 3.6% of ovine DO reached MII (81.3% for CEO) after 24 h of culture in a complex medium containing serum, pyruvate and hormones (Shi et al., 2009). In contrast, 40-80% of bovine DO reached the mature stage after culture without hormones (Bilodeau-Goeseels, 2001, 2003b).

A study of paracrine factors released by gonadotropin-stimulated ovine COC also highlighted some differences in the control of meiosis between rodent and ovine (and potentially other species) oocytes. Meiosis-inducing signals from gonadotropin-stimulated cumulus cells from competent oocytes acted on cumulus cells from incompetent oocytes to induce meiosis but they did not have any effect on incompetent DO (Cecconi et al., 2008). In

contrast, meiosis-stimulating factors from cumulus cells can act directly on mouse denuded oocytes (Downs, 2001). Additionally, cumulus expansion appears to be regulated by the cumulus cells themselves rather than by the oocyte as in mice (Cecconi et al., 2008; Su et al., 2003).

6.2 Role of cAMP, MAPK in the control of meiosis in ovine oocytes

Similar to bovine oocytes, meiotic resumption was only partially inhibited by cAMP-elevating agents in ovine oocytes (Jagiello et al., 1981). Ovine oocytes possess an AC enzyme as cholera toxin, a Gs activator, stimulated cAMP synthesis in isolated sheep oocytes (Crosby et al., 1985). As in other mammals, MAPK is activated at the time of GVBD in ovine cumulus cells from competent oocytes in response to gonadotropins, then later in the oocyte (Cecconi et al., 2008). Cumulus cells from incompetent oocytes (from small follicles) did not show MAPK activation even after exposure to gonadotropins. However, when co-cultured with competent complexes (and gonadotropins), more oocytes from small follicles could resume meiosis and MAPK was activated in these oocytes but not in their cumulus showing that meiotic arrest in oocytes from small follicles could be due to the inability of their surrounding cumulus cells to respond to gonadotropins (Cecconi et al., 2008).

7. Conclusion

The results obtained in rodent models suggest that, similarly to several other biological processes, oocyte nuclear maturation involves a complex network of cross-talk between several signalling pathways in oocytes and follicular cells. This review highlighted some differences between rodent and livestock species and it is anticipated that more differences will be discovered in the mechanisms controlling meiotic arrest and meiotic resumption as research progresses in non-rodent species.

8. References

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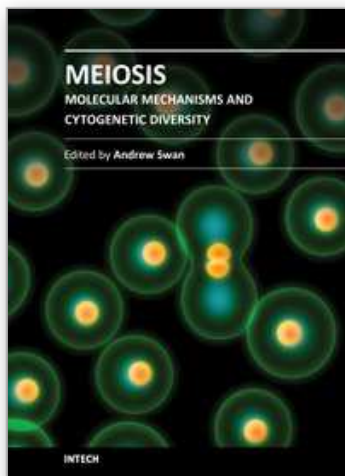
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Meiosis, the process of forming gametes in preparation for sexual reproduction, has long been a focus of intense study. Meiosis has been studied at the cytological, genetic, molecular and cellular levels. Studies in model systems have revealed common underlying mechanisms while in parallel, studies in diverse organisms have revealed the incredible variation in meiotic mechanisms. This book brings together many of the diverse strands of investigation into this fascinating and challenging field of biology.

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