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Molecular and endocrine determinants of oocyte competence

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Abstract

Mammalian female gametes are stored for many years in the ovaries in an inactive state until stimulated to grow. Activation of the resting follicle is initiated by the oocyte and requires a communication mechanism between the oocyte and the surrounding granulosa cells. Key molecular and morphological events that occur during oocyte and follicle growth and maturation include the establishment of a bi-directional communication system, granulosa cell proliferation and antrum formation, nucleolus activation and initiation of oocyte transcription, establishment of the maternal imprints and completion of the meiotic maturation. Successful accomplishment of these events furnishes the oocyte with the competency to support fertilization and to sustain early embryo development and is reflected in the molecular signatures of the oocyte and the follicular granulosa cells. The current review will consider these events and highlight the molecular and endocrine factors associated with them.

Keywords: egg, follicle, gene expression, progesterone.

Introduction

Mammalian female gametes are stored in the ovaries as inactive oocytes, arrested at the diplotene stage of meiosis and surrounded by a single layer of flattened granulosa cells until they are stimulated to grow (Erickson, 1966; Fair *et al*., 1997a). Oocyte storage can be extremely prolonged, spanning the fetal, prepubertal and reproductive lifetime of the animal. The classical studies of Lussier *et al*. (1987), indicate that in cattle, progression from the primary follicle to the tertiary follicle stage takes approximately 60 days and about 2 estrous cycles are required for a follicle to grow from antrum formation to preovulatory size. Oocyte meiotic arrest is maintained throughout follicle activation and subsequent initiation of oocyte growth and folliculogenesis. During the periovulatory period, the oocyte, completes maturation and resumes meiosis in response to luteinizing hormone (LH). Despite a relatively short duration of 24 h in cattle, the changes in the endocrine milieu and subsequent dramatic changes in the morphological and biochemical profiles of both the follicle and the oocyte which characterize the periovulatory period, profoundly affect the oocyte's competence to support fertilization and embryogenesis and the follicle's subsequent performance as the corpus luteum. The current review will highlight the key determinants of mammalian postnatal oocyte growth and development, specifically focusing on the events associated with the completion of the growth phase, maturation, and ovulation in cattle.

Activation of follicle growth

Conventional knockout or oocyte-specific deletion studies have facilitated the identification of several factors such as Sohlh2, anti Müllerian hormone (AMH) and Pten, as repressors of follicle activation, (Sun *et al*., 2008 for review). Early studies, suggested that follicle and oocyte growth was in response to signals from the granulosa cells, however, the identification of the oocyte-secreted transforming growth factor beta (TGFβ) superfamily member, growth differentiation factor 9 (GDF9), led to the revelation of the oocyte as the driving force in development beyond the primary follicle stage (Eppig, 1991; Dong *et al.*, 1996). Subsequent studies identified another factor, the oocyte-secreted and structurally related family member, BMP15 (GDF9B; Dube *et al*., 1998). Sequential profiling of the murine oocyte transcriptome according to stage of folliculogenesis, has identified that the transition from primordial to primary follicle is associated with the greatest change in the oocyte transcriptome profile. In agreement with the pioneering studies mentioned above, the key factors that were upregulated in oocytes following transition to the primary follicle stage were members of the TGF-β superfamily, including Bmp15, Gdf9, Bmp5, Bmp6, Tgfb2, andTgfb3, as well as other growth factors such as Kitld, bFgf, and Lif (Pan *et al*., 2005). Bi-directional communication between the oocyte and the granulosa cells is critical to follicle activation; in cattle this appears to be facilitated in the primordial and primary follicles through receptor-mediated endocytosis, as gap junctions are absent and the oolemma is characterized by the presence of numerous coated pits and coated vesicles in the cortical ooplasm (Fair *et al*., 1997a).

Preantral follicle development

In cattle, establishment of a direct communication system commences during the progression from the primary to the secondary follicle stage, when gap junctions are formed between the

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surface membranes of the oocyte and the surrounding granulosa cells (Fair *et al*., 1997a). Additional key morphological changes occurring at the secondary follicle stage include deposition of zona pellucida material around the oocyte, synthesis of cortical granules within the oocyte cytoplasm, nucleolus reorganisation and activation, and the first detection of RNA synthesis (Fair *et al*., 1997a, b). It is at this point in cattle and sheep, that FSHr mRNA expression was first detected (Tisdall *et al*., 1995; Xu *et al*., 1995; Bao and Garverick, 1998), implying the establishment of responsiveness to gonadotropins. The transition from the secondary follicle to the tertiary follicle stage is characterized by the continued proliferation and differentiation of the somatic cells surrounding the oocyte to form the theca interna and externa and the basal lamina. At the same time oocyte volume quadruples accompanied by proliferation of the oocyte organelles and driven by intensive mRNA and rRNA transcription (Fair *et al*., 1995, 1996, 1997a). These events appear to be driven by TGF-β superfamily members; granulosa cell-derived activin, BMP-2, -5 and -6, theca cell-derived BMP-2, -4 and -7, and oocyte-derived BMP-6 promote granulosa cell proliferation, follicle survival and prevention of premature luteinization and/or atresia, respectively (Knight and Glister, 2006). GDF9 deletion studies in mice showed that oocyte-derived GDF9 is required for the formation of transzonal projections (TZPs; Dong *et al*., 1996). TZPs form a core structural component of an elaborate bi-directional intercellular communication system between the oocyte and surrounding somatic cells that develops during follicle development and functions to meet the metabolic requirements of the growing oocyte (Eppig, 1991; Carabatsos *et al*., 1998; Li and Albertini, 2013). GDF9 and GDF9b have been identified as major players in cumulus cell metabolism, particularly glycolysis and cholesterol biosynthesis (Su *et al*., 2008). Other key factors expressed in the granulosa cells at this time include Insulin-like growth factor (IGF), IGFBP2, IGFBP3, and Type 1 IGF receptor (Armstrong *et al*., 2003), LHr (Xu *et al*., 1995), steroidogenic enzymes P450scc, P450c17, and 3β-HSD (Bao and Garverick, 1998). Follicles become increasingly FSH responsive and their growth and continued survival becomes increasingly gonadotropin dependent.

Antral follicle growth - oocyte transcription, maintenance of meiotic arrest and establishment of maternal imprints

In cattle, antrum formation occurs when follicles reach a diameter of 130-200 μm and is completely gonadotropin -dependent. Once formed, the size of the antrum increases rapidly and the granulosa cells proliferate and differentiate into mural granulosa cells and cumulus cells which surround the oocyte (Lussier *et al*., 1987; Fair *et al*., 1997a). FSH granulosa cell differentiation appears to be indirectly induced by FSH, through the activation of the PI3-K/AKT pathway (Fan *et al*., 2008).

Oocyte RNA transcription:

Early tertiary follicle stage oocytes are transcriptionally active and display at least one active nucleolus. Transcriptional activity continues as oocyte and follicle growth proceeds, the successful accumulation of messenger RNAs (mRNAs), ribosomes and polypeptides by the oocyte ultimately affects the developmental potential of the resulting ovulated egg (see review Fair, 2003). Oocyte transcription declines when oocyte diameter reaches 110 μm, the decline in transcription is associated with the completion of the oocyte growth phase, as oocyte diameter subsequently plateaus at approximately 120-130 μm, corresponding to a follicle diameter of 3 mm (Fair *et al*., 1995). Oocyte diameter will be maintained throughout maturation, fertilization, and development up to the early blastocyst stage, in contrast, the follicle can grow up to 15-20 mm in diameter before ovulation. Transcriptomic profiling of fully grown oocytes from antral follicles with differing developmental potential has identified pathways associated with RNA processing and the control of chromosome segregation to be associated with oocyte competence (Labrecque *et al*., 2013). While the analysis of the oocyte transcriptome provides valuable information, the oocyte must be sacrificed in order to carry out the analysis. Therefore, the identification of non-invasive indicators of oocyte competence would aid in the selection of optimal oocytes for assisted reproduction therapies. The analysis of follicular parameters revealed that intrafollicular steroid concentrations were not predictive of oocyte developmental potential; however, the metabolomic profile of the follicular fluid, particularly the amino acid profile was highly predictive (Matoba *et al*., 2013).. Greater mRNA abundance of LHCGR in granulosa cells, ESR1 and VCAN in thecal cells and TNFAIP6 in cumulus cells was also associated with highly competent oocytes from antral follicles (Matoba *et al*., 2013).

Maintenance of meiotic arrest

The interaction of mural granulosa cells, cumulus cells, and oocytes is essential for maintaining oocyte meiotic arrest in the fully grown oocyte, prior to the LH surge. Inhibition of oocyte cAMP-phosphodiesterase (PDE3A) activity is essential for sustaining elevated oocyte cAMP concentrations, which is crucial for maintaining meiotic arrest. Cyclic GMP diffuses into the oocyte from companion cumulus cells via gap junctions and inhibits oocyte PDE3A activity and cAMP hydrolysis, thus maintaining meiotic arrest (Norris *et al.,* 2009; Vaccari *et al*., 2009). Recently,

work in mice has identified Natriuretic peptide precursor type C (NPPC) as a key factor in this process. NPPC is produced by follicular mural granulosa cells, it stimulates the generation of cGMP by the cumulus NPPC receptor, NPR2, which is required to inhibit oocyte PDE3A activity and thereby maintain meiotic arrest (Zhang *et al*., 2010).

Establishment of maternal imprints

According to data from mice (Lucifero *et al*., 2002; Hiura *et al*., 2006), human (Geuns *et al*., 2003) and cattle (O'Doherty *et al*., 2012), DNA methylation of the maternal imprints occurs during the oocyte growth phase. The correct establishment and maintenance of methylation patterns at imprinted genes has been associated with placental function and regulation of embryonic/fetal development whereas abnormal reprogramming of maternal and/or paternal imprinted loci has been associated with reduced developmental potential. In mice, the onset of methylation coincides with the transition from primary to secondary follicles or as oocytes attain a diameter of >50 μm. In cattle, methylation onset may occur later, as maternal imprints were incompletely methylated in oocytes <100 μm. DNA methylation appears to be a progressive process, such that partially methylated intermediates can be detected in populations of oocytes (Tomizawa *et al*., 2011). In addition, the timing of DNA methylation appears to be imprint specific (O'Doherty *et al.*, 2012). In mice, CpG methylation is completed by the time oocytes reach >70 μm (Smallwood *et al*., 2011), and in cattle completion appears to occur in parallel with cessation of transcription. DNA methylation patterns are established and maintained by a family of enzymes, the DNA methyltransferases (DNMTs). They consist of five members: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. DNMT1 is regarded to be the maintenance methyltransferase (Yoder *et al*., 1997; Ooi *et al*., 2009), whereas the DNMT3 enzymes are required for establishing methylation during gametogenesis and early embryonic development (Okano *et al*., 1999). DNMT3L is highly expressed in bovine oocytes during the critical period of DNA methylation imprint acquisition, suggesting that it plays a role similar to that described in mouse (Bourc'his *et al.*, 2001; Kaneda *et al.*, 2004; O'Doherty *et al.*, 2012) in the establishment of maternal imprints.

Preovulatory follicle - Cumulus cell expansion, oocyte maturation, endocrine factors:

In cattle the LH surge induces luteinization, cumulus cell–oocyte complex (COC) expansion, final oocyte maturation, ovulation and a change in the follicular endocrine environment from E2 dominance to P4 dominance in the follicular fluid. Oocyte maturation is characterized by the breakdown of the oocyte nuclear membrane, causing the release of the nuclear contents into the cytoplasm, subsequent chromosome condensation, extrusion of the first polar body, and meiotic arrest at metaphase II (Fair, 2003 for review). Because oocytes express few or no LH receptors, it would appear that LH stimulates the (LH receptor–positive) mural granulosa cells to produce epidermal growth factor-like factors Areg, Ereg, and Btc that act on the LH receptor-negative cumulus cells in concert with GDF9/BMP15 to propagate LH signaling throughout the preovulatory follicle (Park *et al*., 2004). The direct effects of the GDF9/BMP15 and indirect effects of the LH signaling pathway through the mural granulosa promote cumulus expansion. Granulosa and cumulus cell depletion of extracellular signal-regulated kinase (ERK) 1 and 2 (also known as mitogen-activated protein kinases 1 and 3) indicate their central role in cumulus cell expansion, oocyte maturation and ovulation in response to LH (Fan *et al*., 2009). In the same study, the transcription factor CCAAT box enhancer binding protein-beta (C/EBP-β) was identified as a downstream effector of ERK1/2 in granulosa cells during ovulation and luteinization; target genes include Cyp19a1 and Sult1e1, which regulate estradiol biosynthesis and activity; Star and Cyp11a1, which are associated with granulosa cell luteinization; the EGF-like factors Areg, Ereg and Btc and the cumulus expansion factors Ptgs2, Tnfaip6, Has2, Ptx3 and Pgr. Cumulus expansion aids in the expulsion of the oocyte from the ruptured follicle and also facilitates chemoattraction of sperm towards the oocyte (Chang and Suarez, 2010).

Meiotic maturation is controlled by three key biochemical pathways: (1) maturation-promoting factor (MPF) which activates meiotic resumption resulting in germinal vesicle breakdown (GVBD); (2) anaphase promoting complex (APC) which regulates progression from GVBD through the subsequent stages of meiosis; and (3) cytostatic factor (CSF) which maintains meiotic arrest at MII. Regulation of MPF is mostly via the activity of several kinases and phosphates, whereas APC and CSF are regulated mainly by translational regulation through sequential waves of polyadenylation and deadenylation (Belloc *et al*., 2008). A recent metanalysis of previously published microarray data on various models of metaphase II –stage oocyte quality led to the identification of 56 candidate genes associated with oocyte quality across several species (O'Shea *et al*., 2012). One of the most striking aspects of the analysis was the differential expression of genes linked to mRNA and protein synthesis between models, underlining the importance of de novo protein synthesis and its regulation for successful oocyte maturation and subsequent development. Several genes that are known to be involved in oocyte maturation and/or embryonic developmental competence such as GDF9, EMI1, and PTPN1 were identified. Nuclear maturation alone is not sufficient to produce a high quality oocyte; bioinformatic analysis of preferentially populated

pathways identified Wnt signaling and the antiapoptotic PI3K/Akt pathway as being key to the maturation of a high quality oocyte. Regulation of the canonical Wnt/beta-catenin pathway interlinks with APCregulation and metaphase II arrest of an oocyte.

Factors produced by the cumulus cells and/or components of the follicular fluid such as progesterone (P4), estrogen (E2), insulin, and IGF play an important role in oocyte and follicle development. For example, during development to the preovulatory stage, intrafollicular E2 increases granulosa cell mitosis, promotes gap junction formation among granulosa cells, increases the stimulatory action of FSH on aromatase activity and regulates the expression of several steroidogenic enzymes and induces FSH and LH receptor expression in granulosa cells (Geary *et al*., 2012 for review). High concentrations of E2 within the follicular microenvironment may impact bovine oocyte maturation and competence. Data from IVP studies indicate that preovulatory follicular fluid E2 concentrations are associated with higher blastocyst development rates following in vitro maturation, fertilization, and culture (Mermillod *et al*., 1999; Van De Leemput *et al*., 1999). The switch from E2 dominance to P4 dominance in mammalian preovulatory follicular fluid in the period between the LH surge and ovulation (Dieleman *et al*., 1983) and COC cumulus cell P4 synthesis during IVM (Aparicio *et al*., 2011; Salhab *et al*., 2011) coincident with resumption of meiosis and maturation of the oocyte, implies a role for P4 in oocyte maturation. Inhibitory experiments have confirmed the functional relevance of P4 and P4 receptor signaling during oocyte maturation to oocyte acquisition of developmental competence. The membrane bound receptors PGRMC1 and mPRα appear to be involved in oocyte meiotic maturation and first mitosis, respectively, as intracytoplasmic injection of oocytes with an antibody against PGRMC1 affected chromosome segregation during oocyte meiotic maturation (Luciano *et al*., 2010) and the addition of an mPRα specific antibody during IVM reduced the percentage of oocytes progressing through the early cleavage stages (Aparicio *et al*., 2011). Furthermore, nuclear progesterone receptor (PRG) signaling during oocyte maturation appears to be important for oocyte developmental competence as blastocyst development rates were dramatically reduced when either cumulus cell P4 synthesis was inhibited using Trilostane, or PRG signaling was blocked using RU 486 during IVM (Aparicio *et al*., 2011). Further investigations are required to determine the mechanism(s) by which P4 'promotes' acquisition of developmental competence. Initial investigations by our group suggest P4 acts to protect the oocyte from apoptosis. Indeed several studies have indicated a pro-survival or anti-apoptotic role for P4 in female reproductive tissues; for example, P4 has been shown to inhibit apoptosis in the uterus (Wang *et al*., 2003), the corpus luteum (Okuda *et al*., 2004; Liszewska *et al*., 2005), and the ovarian follicle (Besnard *et al*., 2001). The main anti-apoptotic action of P4 was demonstrated to be mediated via the classical PGR in periovulatory rat granulosa cells as treatment of these cells with the PGR antagonist Org 31710 induced increased caspase 9- and caspase 3/7 activity (Friberg *et al*., 2009, 2010). At the level of the COC, in vitro maturation in media that promoted cumulus cell P4 synthesis resulted in lower rates of cumulus cells apoptosis and higher oocyte competence (Salhab *et al*., 2011). Additional studies have described a role for PGRMC1 in the mediation of the anti-apoptotic effects of P4 and sterol metabolism (Gilchrist *et al*., 2004; Hussein *et al*., 2005) implying that anti-apoptotic effects of P4 are not confined to one pathway but are due to the regulation of several key pathways and processes occurring during oocyte maturation.

Conclusion

The development of the oocyte from the resting primordial stage up to the fully competent ovulated egg involves the progression through a number of developmental checkpoints which are under the control of several key factors. These factors include: members of the TGF-β superfamily, particularly GDF9 and GDF9B, which play pivotal roles in the establishment of bi-directional communication between the oocyte and the granulosa cells, follicle activation, and initiation of transcription in the oocyte; NPPC and NPR2 which are critical to the maintenance of oocyte meiotic arrest during the oocyte phase; DNA methyltransferase enzymes which establish and maintain the maternal imprints in the oocytes, a key checkpoint in the completion of the oocyte growth phase; and finally P4 which promotes meiotic and cytoplasmic maturation and acts to protect the integrity of the oocyte genome for the next generation.

References

Aparicio IM, Garcia-Herreros M, O'Shea LC, Hensey C, Lonergan P, Fair T. 2011. Expression, regulation, and function of progesterone receptors in bovine cumulus oocyte complexes during in vitro maturation. *Biol Reprod*, 84:910-921.

Armstrong DG, Gong JG, Webb R. 2003. Interactions between nutrition and ovarian activity in cattle: physiological, cellular and molecular mechanisms. *Reprod Suppl*, 61:403-414.

Bao B, Garverick HA. 1998. Expression of steroidogenic enzyme and gonadotropin receptor genes in bovine follicles during ovarian follicular waves: a review. *J Anim Sci*, 76:1903-1921.

Belloc E, Pique M, Mendez R. 2008. Sequential waves of polyadenylation and deadenylation define a translation circuit that drives meiotic progression. *Biochem Soc Trans*, 36:665-670.

Besnard N, Horne EA, Whitehead SA. 2001. Prolactin and lipopolysaccharide treatment increased apoptosis and atresia in rat ovarian follicles. *Acta Physiol Scand*, 172:17-25.

Bourc'his D, Xu GL, Lin CS, Bollman B, Bestor TH. 2001. Dnmt3L and the establishment of maternal genomic imprints. *Science*, 294:2536-2539.

Carabatsos MJ, Elvin J, Matzuk MM, Albertini DF. 1998. Characterization of oocyte and follicle development in growth differentiation factor-9-deficient mice. *Dev Biol*, 204:373-384.

Chang H, Suarez SS. 2010. Rethinking the relationship between hyperactivation and chemotaxis in mammalian sperm. *Biol Reprod*, 83:507-513.

Dieleman SJ, Kruip TA, Fontijne P, De Jong WH, Van Der Weyden GC. 1983. Changes in oestradiol, progesterone and testosterone concentrations in follicular fluid and in the micromorphology of preovulatory bovine follicles relative to the peak of luteinizing hormone. *J Endocrinol*, 97:31-42.

Dong J, Albertini DF, Nishimori K, Kumar TR, Lu N, Matzuk MM. 1996. Growth differentiation factor-9 is required during early ovarian folliculogenesis. *Nature*, 383:531-535.

Dube JL, Wang P, Elvin J, Lyons KM, Celeste AJ, Matzuk MM. 1998. The bone morphogenetic protein 15 gene is X-linked and expressed in oocytes. *Mol Endocrinol*, 12:1809-1817.

Eppig JJ. 1991. Intercommunication between mammalian oocytes and companion somatic cells. *Bioessays*, 13:569-574.

Erickson BH. 1966. Development and senescence of the postnatal bovine ovary. *J Anim Sci*, 25:800-805.

Fair T, Hyttel P, Greve T. 1995. Bovine oocyte diameter in relation to maturational competence and transcriptional activity. *Mol Reprod Dev*, 42:437-442.

Fair T, Hyttel P, Greve T, Boland M. 1996. Nucleus structure and transcriptional activity in relation to oocyte diameter in cattle. *Mol Reprod Dev*, 43:503-512.

Fair T, Hulshof SC, Hyttel P, Greve T, Boland M. 1997a. Nucleus ultrastructure and transcriptional activity of bovine oocytes in preantral and early antral follicles. *Mol Reprod Dev*, 46:208-215.

Fair T, Hulshof SC, Hyttel P, Greve T, Boland M. 1997b. Oocyte ultrastructure in bovine primordial to early tertiary follicles. *Anat Embryol (Berl)*, 195:327-336.

Fair T. 2003. Follicular oocyte growth and acquisition of developmental competence. *Anim Reprod Sci*, 78:203-216.

Fan HY, Liu Z, Cahill N, Richards JS. 2008. Targeted disruption of Pten in ovarian granulosa cells enhances ovulation and extends the life span of luteal cells. *Mol Endocrinol*, 22:2128-2140.

Fan HY, Liu Z, Shimada M, Sterneck E, Johnson PF, Hedrick SM, Richards JS. 2009. MAPK3/1 (ERK1/2) in ovarian granulosa cells are essential for female fertility. *Science*, 324:938-941.

Friberg PA, Larsson DG, Billig H. 2009. Dominant role of nuclear progesterone receptor in the control of rat periovulatory granulosa cell apoptosis. *Biol Reprod*, 80:1160-1167.

Friberg PA, Larsson DG, Billig H. 2010. Transcriptional effects of progesterone receptor antagonist in rat granulosa cells. *Mol Cell Endocrinol*, 315:121-130.

Geary TW, Smith MF, Macneil MD, Day ML, Bridges GA, Perry GA, Abreu FM, Atkins JA, Pohler KG, Jinks EM, Madsen CA. 2012. Influence of follicular characteristics at ovulation on early embryonic survival. *J Anim Sci*. Epub ahead of print.

Geuns E, De Rycke M, Van Steirteghem A, Liebaers I. 2003. Methylation imprints of the imprint control region of the SNRPN-gene in human gametes and preimplantation embryos. *Hum Mol Genet*, 12:2873-2879.

Gilchrist RB, Ritter LJ, Armstrong DT. 2004. Oocyte-somatic cell interactions during follicle development in mammals. *Anim Reprod Sci*, 82-83:431-446.

Hiura H, Obata Y, Komiyama J, Shirai M, Kono T. 2006. Oocyte growth-dependent progression of maternal imprinting in mice. *Genes Cells*, 11:353-361.

Hussein TS, Froiland DA, Amato F, Thompson JG, Gilchrist RB. 2005. Oocytes prevent cumulus cell apoptosis by maintaining a morphogenic paracrine gradient of bone morphogenetic proteins. *J Cell Sci*, 118:5257-5268.

Kaneda M, Okano M, Hata K, Sado T, Tsujimoto N, Li E, Sasaki H. 2004. Essential role for de novo DNA methyltransferase Dnmt3a in paternal and maternal imprinting. *Nature*, 429:900-903.

Knight PG, Glister C. 2006. TGF-beta superfamily members and ovarian follicle development. *Reproduction*, 132:191-206.

Labrecque R, Vigneault C, Blondin P, Sirard MA. 2013. Gene expression analysis of bovine oocytes with high developmental competence obtained from FSH-stimulated animals. *Mol Reprod Dev*. doi: 10.1002/mrd.22177.

Li R, Albertini DF. 2013. The road to maturation: somatic cell interaction and self-organization of the mammalian oocyte. *Nat Rev Mol Cell Biol*, 14:141-152.

Liszewska E, Rekawiecki R, Kotwica J. 2005. Effect of progesterone on the expression of bax and bcl-2 and on caspase activity in bovine luteal cells. *Prostaglandins Other Lipid Mediat*, 78:67-81.

Luciano AM, Lodde V, Franciosi F, Ceciliani F, Peluso JJ. 2010. Progesterone receptor membrane component 1 expression and putative function in bovine oocyte maturation, fertilization, and early embryonic development. *Reproduction*, 140:663-672.

Lucifero D, Mertineit C, Clarke HJ, Bestor TH, Trasler JM. 2002. Methylation dynamics of imprinted genes in mouse germ cells. *Genomics*, 79:530-538.

Lussier JG, Matton P, Dufour JJ. 1987. Growth rates

of follicles in the ovary of the cow. *J Reprod Fertil*, 81:301-307.

Matoba S, Bender K, Fahey AG, Mamo S, Brennan L, Lonergan P, Fair T. 2013. Predictive value of bovine follicular components as markers of oocyte developmental potential. *Reprod Fertil Dev*. doi:10.1071/RD13007.

Mermillod P, Oussaid B, Cognie Y. 1999. Aspects of follicular and oocyte maturation that affect the developmental potential of embryos. *J Reprod Fertil Suppl*, 54:449-460.

Norris RP, Ratzan WJ, Freudzon M, Mehlmann LM, Krall J, Movsesian MA, Wang H, Ke H, Nikolaev VO, Jaffe LA. 2009. Cyclic GMP from the surrounding somatic cells regulates cyclic AMP and meiosis in the mouse oocyte. *Development*, 136:186-189.

O'Doherty AM, O'Shea LC, Fair T. 2012. Bovine DNA methylation imprints are established in an oocyte size-specific manner, which are coordinated with the expression of the DNMT3 family proteins. *Biol Reprod*, 86:1-10.

O'Shea LC, Mehta J, Lonergan P, Hensey C, Fair T. 2012. Developmental competence in oocytes and cumulus cells: candidate genes and networks. *Syst Biol Reprod Med*, 58:88-101.

Okano M, Bell DW, Haber DA, Li E. 1999. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell*, 99:247-257.

Okuda K, Korzekwa A, Shibaya M, Murakami S, Nishimura R, Tsubouchi M, Woclawek-Potocka I, Skarzynski DJ. 2004. Progesterone is a suppressor of apoptosis in bovine luteal cells. *Biol Reprod*, 71:2065-2071.

Ooi SK, O'donnell AH, Bestor TH. 2009. Mammalian cytosine methylation at a glance. *J Cell Sci*, 122:2787-2791.

Pan H, O'brien M J, Wigglesworth K, Eppig JJ, Schultz RM. 2005. Transcript profiling during mouse oocyte development and the effect of gonadotropin priming and development in vitro. *Dev Biol*, 286:493-506.

Park JY, Su YQ, Ariga M, Law E, Jin SL, Conti M. 2004. EGF-like growth factors as mediators of LH action in the ovulatory follicle. *Science*, 303:682-684.

Salhab M, Tosca L, Cabau C, Papillier P, Perreau C, Dupont J, Mermillod P, Uzbekova S. 2011. Kinetics of gene expression and signaling in bovine cumulus cells throughout IVM in different mediums in relation to oocyte developmental competence, cumulus apoptosis and progesterone secretion. *Theriogenology*, 75:90-104.

Smallwood SA, Tomizawa S, Krueger F, Ruf N, Carli N, Segonds-Pichon A, Sato S, Hata K, Andrews SR, Kelsey G. 2011. Dynamic CpG island methylation landscape in oocytes and preimplantation embryos. *Nat Genet*, 43:811-814.

Su YQ, Sugiura K, Wigglesworth K, O'brien MJ, Affourtit JP, Pangas SA, Matzuk MM, Eppig JJ. 2008. Oocyte regulation of metabolic cooperativity between mouse cumulus cells and oocytes: BMP15 and GDF9 control cholesterol biosynthesis in cumulus cells. *Development*, 135:111-121.

Sun QY, Liu K, Kikuchi K. 2008. Oocyte-specific knockout: a novel in vivo approach for studying gene functions during folliculogenesis, oocyte maturation, fertilization, and embryogenesis. *Biol Reprod*, 79:1014-1020.

Tisdall DJ, Watanabe K, Hudson NL, Smith P, McNatty KP. 1995. FSH receptor gene expression during ovarian follicle development in sheep. *J Mol Endocrinol*, 15:273-281.

Tomizawa S, Kobayashi H, Watanabe T, Andrews S, Hata K, Kelsey G, Sasaki H. 2011. Dynamic stage-specific changes in imprinted differentially methylated regions during early mammalian development and prevalence of non-CpG methylation in oocytes. *Development*, 138:811-820.

Vaccari S, Weeks II JL, Hsieh M, Menniti, FS, Conti M. 2009.Cyclic GMP Signaling Is Involved in the Luteinizing Hormone-Dependent Meiotic Maturation of Mouse Oocytes. *Biol Reprod*, 81: 595-604.

Van De Leemput EE, Vos PL, Zeinstra EC, Bevers MM, Van Der Weijden GC, Dieleman SJ. 1999. Improved in vitro embryo development using in vivo matured oocytes from heifers superovulated with a controlled preovulatory LH surge. *Theriogenology*, 52:335-349.

Wang B, Xiao C, Goff AK. 2003. Progesterone-modulated induction of apoptosis by interferon-tau in cultured epithelial cells of bovine endometrium. *Biol Reprod*, 68:673-679.

Xu Z, Garverick HA, Smith GW, Smith MF, Hamilton SA, Youngquist RS. 1995. Expression of follicle-stimulating hormone and luteinizing hormone receptor messenger ribonucleic acids in bovine follicles during the first follicular wave. *Biol Reprod*, 53:951-957.

Yoder JA, Soman NS, Verdine GL, Bestor TH. 1997. DNA (cytosine-5)-methyltransferases in mouse cells and tissues. Studies with a mechanism-based probe. *J Mol Biol*, 270:385-395.

Zhang M, Su YQ, Sugiura K, Xia G, Eppig JJ. 2010. Granulosa cell ligand NPPC and its receptor NPR2 maintain meiotic arrest in mouse oocytes. *Science*, 330:366-369.