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## Maternal control of early embryogenesis in mammals

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### Abstract

Oocyte quality is a critical factor limiting the efficiency of assisted reproductive technologies (ART) and pregnancy success in farm animals and humans. ART success is diminished with increased maternal age, suggesting a close link between poor oocyte quality and ovarian-aging. However, the regulation of oocyte quality remains poorly understood. Oocyte quality is functionally linked to ART success because the maternal-to-embryonic transition is dependent on stored maternal factors, which are accumulated in oocytes during oocyte development and growth. The maternal-to-embryonic transition consists of critical developmental processes including maternal RNA depletion and embryonic genome activation. In recent years, key maternal proteins encoded by maternal-effect genes have been determined, primarily using genetically modified mouse models. These proteins are implicated in various aspects of early embryonic development including maternal mRNA degradation, epigenetic reprogramming, signal transduction, protein translation and initiation of embryonic genome activation. Species differences exist in number of cell divisions encompassing the maternal-to-embryonic transition and maternal-effect genes controlling this developmental window. Perturbations of maternal control result in decreased oocyte quality, some of which are associated with ovarian aging.

### Keywords

Maternal-effect; Embryo; Reproductive aging; Oocyte quality; Epigenetics; Mitochondria

### Introduction

Female fertility, if defined as the percentage of pregnancy to a single insemination, is poor in humans and major domestic animals, such as dairy cows (Spencer 2013). For instance, the conception rate of the first service is only approximately 32% in high-producing cows, which is attributed primarily to the detrimental impacts of lactation on their reproductive system (Sartori *et al.* 2010). According to the statistics from the Centers for Disease Control and Prevention of the United States (CDC), approximately 10% of women of reproductive age are affected by infertility. Consequently, a growing number of patients resort to assisted

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reproductive technologies (ART) procedures. Despite much improvement during the last three decades, the average success rate is still poor with 31% pregnant from a single cycle. Of particular note, the success rate is extraordinary low when performed in women of advanced reproductive age (>35 years old), who account for 60% of patients subjected to ART (2012 ART Report from CDC). Such phenomena (usually called reproductive aging), refers to declining fertility with maternal aging and has been well documented in humans and animals (Qiao *et al.* 2014). For instance, mare fertility decreases between the late teens and early twenties. As mares age further, they become infertile and ovarian activity ceases completely (Carnevale 2008; Altermatt *et al.* 2009).

The majority of embryo mortality occurs during early developmental stages in various species, such as dairy cows (Sartori *et al.* 2010), women (Wilcox *et al.* 1988) and horses (Ginther *et al.* 1985). In a recent review, Sartori *et al.* estimated that 37% of embryo deaths occur during the first week after fertilization, primarily resulting from poor oocyte quality in dairy cows (Sartori *et al.* 2010). In women, growing evidence shows that a large proportion of cases of infertility are attributed to a reduction in oocyte quality, particularly in the case of women of advanced reproductive age (Navot *et al.* 1991). Indeed, the success rate in ART is significantly higher when women of advanced reproductive age use donor oocytes collected from young women than when using their own eggs (2012 CDC ART Report). It is also noted that *in vitro*-matured oocytes have lower developmental competence relative to *in vivo* counterparts (Lonergan *et al.* 2003; Hansen *et al.* 2010; Hinrichs 2010). Thus, oocyte quality is a critical component contributing to pregnancy success. Oocyte quality/competence is defined as the ability of oocyte to resume meiosis, cleave and develop to blastocyst stage after fertilization, to implant and develop to term in good health (Sirard *et al.* 2006).

Specifically, oocyte quality plays an important role in dictating outcome of early embryonic development. This is because the maternal-to-embryonic transition is highly dependent on stored maternal factors, such as subcellular organelles and macromolecules, which are accumulated in oocytes during the course of folliculogenesis and oogenesis. During the maternal-to-embryonic transition, key developmental events occur, including depletion of maternal mRNA transcripts, epigenetic reprogramming/chromatin remodeling, and activation of the newly-formed embryonic genome (Bettegowda *et al.* 2008). A growing list of maternal proteins encoded by maternal-effect genes have been characterized, primarily using genetically modified mouse models. These factors regulate various aspects of early embryonic development including maternal mRNA degradation, epigenetic modifications/chromatin remodeling, signal transduction, protein translation, onset of embryonic genome activation (EGA), and cell compaction.

In this review, we will summarize the maternal factors that contribute to oocyte developmental competence and functions of maternal-effect genes identified in mammals. We also discuss the relevance of these factors in relation to maternal reproductive aging.

## **Influences of maternal ovarian follicular environment on oocyte quality**

As the largest cell in the body of mammals, the oocyte develops, matures, and obtains developmental competence within the ovarian follicle. Throughout the course of oogenesis,

oocyte growth and development is dynamically regulated by various physiological, cellular and molecular events, which are modulated through the ovarian intra-follicular environment (Edson *et al.* 2009; Hsueh *et al.* 2014). To some extent, it could be argued that the intra-follicular environment dictates oocyte quality/competence, particularly in the context of the ability to resume meiosis and acquire competent cytoplasm to foster subsequent development after fertilization (Fig. 1).

The intra-follicular environment is regulated by miscellaneous endocrine, paracrine, and autocrine factors (Fig. 1) (Edson *et al.* 2009; Hsueh *et al.* 2014). The endocrine factors (e.g. FSH, LH and E2) are well established in their role in promoting granulosa cell proliferation/differentiation, cumulus expansion, ovulation and final oocyte maturation (Binelli and Murphy 2010). As mediators of endocrine signals, the paracrine factors (EGF, FGF10 etc.) produced from follicular somatic cells are critical for oocyte development and maturation in various species, including mice, horses and cows (Park *et al.* 2004; Lindbloom *et al.* 2008; Zhang *et al.* 2010). Interestingly, recent studies have shown that cell-secreted vesicles consisting of miRNAs and proteins exist in equine ovarian follicular fluid, suggesting a novel form of communication between cells within the follicle (da Silveira *et al.* 2012). The oocyte also has an active role in regulating follicular development (Su *et al.* 2009). The bidirectional communication-mediated by gap junctions—between cumulus cells and oocytes is critical for amino acid homeostasis, glycolysis and cholesterol synthesis in oocytes (Su *et al.* 2009). Two well-characterized TGF- $\beta$  family members, BMP15 and GDF9, both oocyte-specific proteins, are directly implicated in regulation of meiotic maturation (Wigglesworth *et al.* 2013), cholesterol synthesis (Su *et al.* 2008), amino acid transportation (Eppig *et al.* 2005) and glycolysis (Sugiura *et al.* 2007), which are utilized to maintain metabolism, growth and maturation of the oocyte. *GDF9*-null mice are infertile because of developmental arrest of follicles at the primary follicle stage (Dong *et al.* 1996). *BMP15* knockout mice exhibit a defective cumulus phenotype that results in subfertility, while overexpression of *BMP15* promotes growth of the ovarian follicle in mice (Yan *et al.* 2001). Moreover, BMP15 and GDF9 supplementation during *in vitro* maturation (IVM) improves oocyte developmental competence in cattle (Hussein *et al.* 2006).

The intra-follicular environment is impacted by a variety of environmental cues such as diet (Fig. 1) (Armstrong *et al.* 2001; Tilly and Sinclair 2013), the hormonal milieu (Macklon *et al.* 2006; Altermatt *et al.* 2012), chemicals (Uzumcu and Zachow 2007; Hunt *et al.* 2012) and health status [e.g. human polycystic ovary syndrome (Dunaif and Fauser 2013) and equine metabolic syndrome (Sessions-Bresnahan and Carnevale 2014)]. An inappropriate intra-follicular environment could result in poor oocyte quality/competence, which ultimately leads to infertility/subfertility. Dietary restriction causes subfertility or infertility in mice and rats (Selesniemi *et al.* 2008). In women, low body weight due to dietary restriction is linked to reduced fertility and results in significant changes in gonadotropin hormones to levels similar to those in women with ovarian insufficiency (Bates 1985). Mice on a zinc-deficient diet produced smaller fetuses and are prone to neural tube defects (Tian *et al.* 2014). In such animals, histone methylation was decreased in oocytes and retained in the maternal pronucleus after fertilization (Tian and Diaz 2013). Furthermore, increased oocyte lipid content and cellular stress are also evident in mouse studies showing poor embryo and fetal development after maternal preconception diabetes or obesity (Luzzo *et al.*

2012; Wu *et al.* 2012). The effects of environmental cues on the female reproductive system have been reviewed elsewhere (Uzumcu and Zachow 2007; Wang and Moley 2010; Fleming *et al.* 2011; Lane *et al.* 2014). Of particular note, future research on identification of specific maternal factors/oocyte stored factors that are influenced by environmental cues will improve our understanding of the mechanisms underlying the regulation of oocyte competence.

## Maternal components contributing to oocyte quality

### Spindle

The spindle is a complex subcellular structure with microtubules as fundamental machinery that gathers and segregates chromosome between daughter cells during cell division. Compared with other somatic cell types, oocytes are prone to errors in chromosome segregation that lead to aneuploid embryos/fetuses. The majority of aneuploidies in humans do not result in live offspring, making it a major cause of pregnancy failure. Thus, in human IVF clinics, a significant higher pregnancy rate from single embryo transfer was obtained if embryos are screened for euploidy compared with embryos that assessed only by morphology (Yang *et al.* 2012). Particularly, aneuploidy is commonly seen in oocytes from women of advanced reproductive age, suggesting it is a major cause of declining fertility with maternal aging (Savva *et al.* 2010; Kuliev *et al.* 2011) (Jones and Lane 2013). A similar age-associated increased aneuploidy rate is also observed in mice (Merriman *et al.* 2012). Growing evidence has shown that most errors in chromosome segregation arise during oocyte meiotic division, with various defects in the meiotic spindle (Howe and FitzHarris 2013; Jones and Lane 2013).

Therefore, much research attention has been drawn to understanding control of the first meiotic division, including microtubule-kinetochore interactions, spindle assembly, and the spindle assembly checkpoint (SAC). Due to the limitations of using human oocytes, most mechanistic research on these topics has used mouse oocytes as a model. Summaries of the control and timing of major events occurring during the metaphase I (MI) phase can be found in recent reviews (Howe and FitzHarris 2013; Jones and Lane 2013; Li and Albertini 2013).

Increased aneuploidy with maternal age has also been seen in mice (Pan *et al.* 2008; Selesniemi *et al.* 2011; Merriman *et al.* 2012), which presents a natural setting in which to search for the molecular causes of maternal age-related aneuploidy. By using this model, microarray analysis indicated that differential oocyte transcript profiles were found between old and young mice (Pan *et al.* 2008). Furthermore, time-lapse microscopy analysis indicated that there was no difference in the timing of oocytes from old mice entering anaphase of meiosis compared with young mice, suggesting oocyte aging is not likely due to defective SAC (Duncan *et al.* 2009).

Interestingly, several recent independent studies have reported a dramatic decrease in chromosome-bound cohesion proteins, with weakened chromosome cohesion in oocytes from old mice (Chiang *et al.* 2010; Lister *et al.* 2010; Merriman *et al.* 2012). Specifically, in oocytes from old mice, the distances between sister kinetochores are increased during MI

and MII, and abundance of meiotic cohesion protein REC8 is reduced. Live cell imaging followed by immunocytochemical analysis also revealed that the majority of aneuploidies are attributed to weakened centromere cohesion (Chiang *et al.* 2010).

Despite recent breakthroughs, there is still a dramatic gap in our understanding of molecular mechanisms underlying the regulation of spindle assembly and chromosome segregation in mammalian oocytes. Further studies of these topics will depend on the state-of-the-art live imaging approach to observe detailed events occurring during MI and MII, plus gene-silencing techniques as well as proteomic approaches.

## Mitochondria

Well-known as the “powerhouse” in the cell, mitochondria are subcellular organelles with double membranes and are essential for generating the majority of ATP that supplies energy for the body. They are especially important for characteristic energy-consuming events that require adequate energy stores during development such as chromosome segregation and fertilization occurring in oocytes and early embryos (Dumollard *et al.* 2007). In addition, relevant mitochondrial functions for oocyte/early embryonic development include sequestration and release of calcium, homeostasis of reduction-oxidation, and control of apoptosis.

Mitochondria are maternally inherited and possess their own genome independent of the nuclear genome. Interestingly, the mitochondrial population increases during oocyte maturation followed by an arrest of replication during cleavage stages in early embryos until mitochondrial replication recovers during gastrulation (Dumollard *et al.* 2007). Therefore, mitochondria in the early embryos originate from the maternal-stored population produced during oogenesis, implying a critical role of maternal mitochondria in early embryonic development; especially DNA of mitochondria is prone to mutations (Tilly and Sinclair 2013).

Dysfunction of mitochondria is linked to a number of human diseases, including obesity-induced diabetes, atherosclerosis and several neurodegenerative disorders (Wallace 2001; Lin and Beal 2006; Di Lisa *et al.* 2009). Around 1 in 4,000 children born in the United States are afflicted with mitochondrial diseases, which could be attributed to mutations of mitochondrial DNA (Schaefer *et al.* 2004). In recent years, there is much interest in developing novel ART to prevent transmission of mitochondrial diseases through replacement of mother’s oocyte mitochondria with mitochondria from un-afflicted donors. Pronuclear transfer or spindle transfer can be successfully performed in mice (McGrath and Solter 1983), monkey (Tachibana *et al.* 2009) and humans (Craven *et al.* 2010; Paull *et al.* 2013; Tachibana *et al.* 2013), and shows promising application in human clinics as a treatment of mitochondrial diseases. However, there are ethical and epigenetic concerns that must be addressed at the same time (Mitalipov and Wolf 2014).

Beside the genetic contribution, mitochondria are also important for early embryogenesis. Abnormal oxidative phosphorylation of mitochondria in mouse oocytes causes a defect in meiotic maturation and fertilization, thus resulting in poor early embryonic development (Van Blerkom *et al.* 1995). In alignment with this result, increased ATP content in human

oocytes is correlated with improved developmental competence of oocytes (Van Blerkom *et al.* 1995). Microinjection of mitochondria into oocytes leads to reduction of oocyte apoptosis (Perez *et al.* 2000). It is also believed that insufficient ATP production from oocyte mitochondria is responsible for errors in chromosome segregation (Schon *et al.* 2000; Eichenlaub-Ritter *et al.* 2004; Zheng *et al.* 2007). Several studies have also revealed that mitochondria DNA copy numbers in oocytes and early embryos are correlated with success rates of fertilization and early development (Santos *et al.* 2006; Spikings *et al.* 2006). Consistent with this finding, suppressed replication of mitochondria in porcine oocytes during IVM leads to poor early embryonic developmental potential (Spikings *et al.* 2007). Thus, mitochondrial membrane potential, indicative of mitochondria health, and number of mitochondria may be potential markers of oocyte competence.

Maternally inherited mitochondria are affected by maternal diabetes. Transmission electron microscopy analysis indicates mitochondrial structure of oocytes ovulated from diabetic mice is altered and mitochondrial DNA copy number is increased (Wang *et al.* 2009). Moreover, the abundance of ATP and metabolites of tricarboxylic acid cycle are reduced in these oocytes, and altered distribution of mitochondria is observed in matured oocytes (Wang *et al.* 2009). The dysfunctional mitochondria in oocytes from diabetic females may be linked to their poor developmental competence. Indeed, transfer of zygotes from diabetic to non-diabetic foster mothers causes congenital disorders and delayed growth in the offspring, indicating adverse effects of maternal diabetes occur as early as the zygote stage (Wyman *et al.* 2008).

Mitochondrial dysfunction may contribute to maternal reproductive aging. Previous studies revealed decreases in ATP content, mitochondria numbers and mitochondria DNA copy numbers in aged oocytes, and dramatic morphological changes in oocyte mitochondria occur with aging in various species, including human, rat, pig, cow, mouse and mare (Simsek-Duran *et al.* 2013; Tilly and Sinclair 2013; Rambags *et al.* 2014).

## Lipids

Lipids are hydrophobic or amphipathic molecules, whose main biological functions include storing energy, cell signaling and as structural components of cell membranes. Fatty acids are one category of lipids that functions as precursors of prostaglandins and cell membrane components. In addition, fatty acids can be stored as triacylglycerides within lipid droplets, which provide a rich source of energy upon demand. Numerous lipid droplets are seen in oocytes from certain species, including cattle, pigs and horses; these to some extent explain the darkness of the oocyte cytoplasm in these species (Dunning *et al.* 2014). Previous studies have demonstrated darkness of the oocyte cytoplasm is correlated with the oocyte quality. For example, there is a difference in the proportion of oocytes that cleave and develop to the blastocyst stage when bovine oocytes are categorized based on cytoplasm darkness (Jeong *et al.* 2009). Different darkness of oocyte cytoplasm is also linked with the ratio between saturated and unsaturated fatty acid, with the latter shown to be beneficial for oocyte developmental competence (Kim *et al.* 2001; Marei *et al.* 2009; Marei *et al.* 2010; Lapa *et al.* 2011).



To date, little direct evidence has been reported regarding the relationship between oocyte lipid content and oocyte competence. However, reduced developmental potential to the blastocyst stage was observed in mice on a diet enriched in n-3 fatty acids for 4 weeks, probably due to corresponding changes in mitochondrial distribution and increases in reactive oxygen species (ROS) levels (Wakefield *et al.* 2008). Similarly, treatment with a diet enriched in saturated fatty acids results in significant increases in oocyte lipid content, and oocytes exhibit a lipotoxicity response linked with reduced fertilization potential (Wu *et al.* 2012).

Oocyte lipid content is also affected by the follicular environment, which is—in turn—affected by changes in whole body metabolism. A well-known example to illustrate the association between maternal metabolism and oocyte quality is infertility in high producing cows. It is broadly believed that negative energy balance in post-calving high-producing cows is the primary causes of maternal metabolic disorders that alter the composition of endocrine and biochemical components in ovarian follicles, thus compromising oocyte quality (Thatcher *et al.* 2006; Thatcher *et al.* 2011). Numerous studies have attempted to supplement fatty acids to improve fertility in high producing cows (Santos *et al.* 2008; Thatcher *et al.* 2011). A diet high in  $\alpha$ -linolenic acid leads to increases in  $\alpha$ -linolenic acid content in follicular fluid, cumulus-oocyte-complexes and granulosa cells and an increased cleavage rate following *in vitro* fertilization (IVF) (Zachut *et al.* 2010).

Impacts of fatty acids on oocyte maturation and competence have also been observed using *in vitro* embryo production model systems. Supplementation with either stearic or palmitic acid into maturation medium results in defects in cumulus expansion, higher rates of cumulus cell apoptosis and delayed development to MII (Leroy *et al.* 2005).

Given the importance of lipid metabolism in oocyte developmental competence, our understanding on the key factors (enzymes) involved in this process has been limited. Future research should be directed towards understanding the profiles of regulatory genes related to lipid metabolism and their relevance to oocyte competence. This understanding will shed novel insight on developing strategies to improve oocyte developmental competence in both humans and animals.

### **Subcortical maternal complex**

The subcortical maternal complex (SCMC) is a MDa protein complex that plays an essential role in mouse preimplantation development. Localized in the subcortex of oocytes, the SCMC is assembled during oogenesis (Li *et al.* 2008a). After fertilization, the SCMC is restricted to the exposed surface of cleaved embryos ultimately making it specifically localized in outside cells of morula and blastocysts (Li *et al.* 2008a). To date, the SCMC contains a minimum of four maternal proteins: MATER, FLOPED, TLE6 and Folia (Li *et al.* 2008a). Null mutations of *Mater*, *TLE6* and/or *Floped* cause developmental arrest during cleavage divisions, and female mutant mice are infertile (Tong *et al.* 2000; Li *et al.* 2008a; Yu *et al.* 2014). In addition, *Folia* deficiency results in delayed preimplantation development with reduced fecundity, increased aneuploidy and abnormal spindle assembly (Zheng and Dean 2009). Results also indicate MATER, TLE6 and FLOPED are required for the stability of the SCMC (Li *et al.* 2008a; Zheng and Dean 2009; Yu *et al.* 2014). Interestingly, one

documented role for the SCMC is to regulate the spindle position through cytoplasmic F-actin cytoskeleton (Yu *et al.* 2014). Further research is needed to explore the complete component identities of the SCMC complex, which will shed novel insights on our understanding of the maternal control of early embryogenesis.

### Maternal-effect genes

Maternal-effect genes are genes that when dysfunctional affect the phenotype of offspring regardless of their genotype (Matzuk and Burns 2012). Maternal-effect gene products are especially critical for the early embryonic development after fertilization until massive activation of the embryonic genome occurs. The maternal-effect gene was first described in *Drosophila* 30 years ago, while the first one in mammals was disclosed in 2000 (Christians *et al.* 2000; Tong *et al.* 2000).

Different technical strategies have been used to identify maternal-effect genes in mammals since 2000. The first several maternal-effect genes were discovered in mice using conventional knockout approaches (Christians *et al.* 2000; Tong *et al.* 2000; Burns *et al.* 2003; Wu *et al.* 2003). To precisely probe the functional roles of maternal genes, for which conventional knockout strategies result in embryonic lethality, conditional knockout paired with RNAi-mediated gene silencing via oocyte injections has been used. A growing number of maternal-effect genes have been found to be essential for early embryogenesis. They are summarized in Table 1.

Despite the increased understanding of maternal control of early embryonic development in mice through the identification of maternal-effect genes, the information regarding the functional role of maternal genes has been limited in other species, particularly in domestic animals. Due to the practical limitations of using conventional gene knockout strategies in domestic animals, inhibition of mRNA and protein by injection of siRNAs or antibodies is the predominant approach used to determine the functional role of maternal-effect genes (Bettegowda *et al.* 2007; Tejomurtula *et al.* 2009; Tripurani *et al.* 2011; Lee *et al.* 2014b). We have utilized cattle as a dual-purpose model relevant to both human ART and bovine reproduction with the goal to increase understanding of molecular mediators of oocyte quality and maternal regulation of early embryogenesis. To date, our results support a critical functional role in early embryogenesis in bovine for *JY-1* (Bettegowda *et al.* 2007), *Follistatin* (Lee *et al.* 2009), *KPNA7* (Tejomurtula *et al.* 2009), *NOBOX* (Tripurani *et al.* 2011) and *SMAD4* (Lee *et al.* 2014c).

The first maternal-effect gene we studied in bovine was identified through analysis of expressed sequence tags (ESTs) from cDNA libraries of bovine oocytes (Yao *et al.* 2004). Of interest, several ESTs were noted that encode a novel oocyte-expressed transcript: *JY-1*, whose product is a bovine-specific protein. *JY-1* mRNA and protein are present exclusively in the ovary during folliculogenesis. Specifically, *JY-1* is exclusively expressed in the oocyte. Gene expression analysis showed levels of *JY-1* mRNA are maximal in the germinal vesicle stage oocytes and decline in early embryos to even undetectable levels at 16-cell stage. Microinjection of *JY-1* siRNAs into zygotes results in a dramatic decrease in the potential of embryonic development in terms of 8-16 celled embryo and blastocyst rates relative to control embryos (Bettegowda *et al.* 2007). Addition of exogenous *JY-1* protein



rescues the development of *JY-1*-deficient embryos to the blastocyst stage. Moreover, a novel model system whereby *JY-1* siRNA was injected into cumulus-enclosed oocytes (germinal vesicle stage) and meiotic arrest maintained for 48 h before IVM, was developed in our lab to examine the effect of reduced *JY-1* expression in oocytes on meiotic maturation, cumulus expansion and subsequent development potential after fertilization. Reduction of *JY-1* protein in oocytes leads to a dramatic reduction in cumulus expansion, reduced proportion of oocytes developing to MII, and decreased proportions of embryos that developed to the 8-16 cell and blastocyst stages following IVF (Lee *et al.* 2014a). Effects of oocyte *JY-1* depletion on meiotic maturation and cumulus expansion, but not subsequent embryonic development post fertilization, are rescued by supplementation of recombinant *JY-1* protein during oocyte culture, supporting a crucial functional role of maternal *JY-1* both pre- and post-fertilization (Lee *et al.* 2014a).

*KPNA7* is another bovine maternal-effect gene discovered by analyzing EST sequences from cDNA libraries of oocytes (Yao *et al.* 2004) and encodes a novel member of the importin  $\alpha$  protein family that is involved in the nuclear import of proteins > 40 kDA. *KPNA7* mRNA expression is ovary-specific in cattle with high abundance in both immature and mature oocytes and early embryos prior to the 16 cell stage followed by a sharp decrease at the morula and blastocyst stages. *KPNA7* deficiency in early embryos led to a reduced developmental potential to the blastocyst stage (Tejomurtula *et al.* 2009). In addition, compared with other importin  $\alpha$  family members, *KPNA7* possess a stronger affinity for binding with NPM2 (a maternal-effect nuclear protein), implying a critical role of *KPNA7* in the transportation of oocyte-stored nuclear proteins in early embryos (Tejomurtula *et al.* 2009).

The newborn ovary homeobox encoding gene (*NOBOX*) is also required for early embryogenesis in cattle (Tripurani *et al.* 2011). Deficiency of *NOBOX* mRNA in early embryos results in poor development potential of early embryos to the blastocyst stage, and apparent down-regulation of genes related to signal transduction, cell cycle, and transcriptional regulation during EGA (Tripurani *et al.* 2011). Furthermore, *NOBOX* deficiency in early embryos leads to decreased expression of pluripotent genes (*Pou5f1/Oct4* and *Nanog*) and reduced inner cell mass (ICM) cell number (Tripurani *et al.* 2011). Interestingly, the level of *NOBOX* mRNA in early embryos is modulated by a particular miRNA (Tripurani *et al.* 2011).

To further determine differential RNA transcripts associated with poor oocyte competence, we performed microarray analysis using a well-characterized prepubertal model of poor oocyte quality. Results showed *follistatin* mRNA abundance is positively associated with oocyte competence (Patel *et al.* 2007). Follistatin increased percentage of embryos cleaving early, percentage of embryos developing to the blastocyst stage and numbers of trophectoderm cells in resulting blastocysts (Lee *et al.* 2009). Results of comparative experiments in rhesus monkeys also showed positive actions of follistatin treatment on development of IVF embryos to the blastocyst stage and supported translational relevance of results from the bovine model (VandeVoort *et al.* 2009). Moreover, loss of function studies via microinjection of follistatin siRNAs into zygotes further confirmed the functional role of

follistatin in regulating bovine early embryonic development and cell allocation in blastocysts (Lee *et al.* 2009).

Follistatin selectively binds TGF- $\beta$  growth factor superfamily ligands, which bind to their receptors and activate SMAD signaling pathways. To increase understanding of the potential mechanism underlying follistatin's action in early embryos, experiments utilizing a combination of pharmacological and siRNA-mediated inhibition of TGF- $\beta$  superfamily signaling pathway components in the presence or absence of follistatin treatment were performed. Results to date demonstrated a functional requirement for the common SMAD (SMAD4) and SMAD2/3 (unpublished data) signaling pathways in bovine early embryonic development and suggest stimulatory actions of follistatin on blastocyst rate, but not early cleavage, are blocked when SMAD2/3/4 signaling is inhibited (Lee *et al.* 2009; Lee *et al.* 2014c). Collectively, results support a fundamental intrinsic role for follistatin and TGF- $\beta$  superfamily signaling in bovine early embryonic development.

### Relevance to oocyte aging

Altered expression of maternal-effect genes could be associated with reduced oocyte developmental competence characteristic of ovarian aging. *Dnmt1o* (oocyte-specific DNA methyltransferase 1) and *Dnmt1s* (somatic form of Dnmt1) mRNA levels are both reduced in oocytes from old animals relative to controls. (Hamatani *et al.* 2004; Pan *et al.* 2008). Moreover, nuclear importing of DNMTs is abnormal in oocytes from old animals (Zhang *et al.* 2011). However, the functional significance is unclear as methylation imprints are maintained for selected imprinted genes, and global methylation level is normal in oocytes from old animals (Lopes *et al.* 2009). Further research is necessary to clarify how reduced Dnmts affect oocyte quality in models of ovarian aging.

As a maternal-effect gene, *p73* is well known for its regulatory role in cell cycle, genome stability and apoptosis (Tomasini *et al.* 2008). Analysis of *p73* expression between oocytes of young women versus women of advanced maternal age shows that *TAp73*, *p73* isoform containing transcription transactivation (TA) domain, levels are reduced in women older than 38 (Guglielmino *et al.* 2011). Similar results were observed from mouse oocytes. Collectively, defective *TAp73* expression in old oocytes could help account for some of the declining fertility associated with maternal aging. Indeed, *TAp73*-null oocytes exhibit defects in spindle formation and result in poor blastocyst formation in mice (Tomasini *et al.* 2008).

## Mechanisms of maternal control of early embryogenesis

### Maternal control of epigenetic reprogramming following fertilization

The fusion of the oocyte and the sperm represents a remarkable moment during which highly differentiated germ cells are reprogrammed to a totipotent status. A variety of developmental events are reset to foster the correct embryonic development, including maintenance of methylation imprints, activation of the embryonic genome and lineage specification. These important developmental events are subject to regulation via epigenetic modifications (DNA methylation, histone modifications etc.)/chromatin remodeling.

Epigenetic modifications are extremely dynamic in early embryos and occur shortly after fertilization, suggesting a critical role in reprogramming the above-mentioned developmental events in early embryos (Fig. 2). For example, active DNA demethylation occurs in the male pronucleus prior to the onset of DNA replication and passive DNA demethylation follows thereafter until the morula stage (Kohli and Zhang 2013). Accordingly, chromatin organization is dramatically different between paternal and maternal pronuclei (Hemberger *et al.* 2009). This difference is characterized by an asymmetry of DNA demethylation and histone modification patterns (Sarmiento *et al.* 2004; Morgan *et al.* 2005; Hemberger *et al.* 2009). Epigenetic reprogramming is believed to resolve this dramatic difference in paternal and maternal chromatin and ensure the transition from differentiated status to totipotency. Due to the transcriptional quiescence in early embryos prior to EGA, proteins (reprogramming factors) stored during oogenesis are believed necessary for the epigenetic reprogramming in early embryos. The powerful ability of oocytes in reprogramming has been demonstrated by the success of somatic cell nuclear transfer (SCNT). Indeed, multiple maternal proteins have been reported to be critical for epigenetic reprogramming.

Recently, Tet3 has been shown to be a key modulator of active demethylation of paternal DNA after fertilization (Gu *et al.* 2011). Tet3 is specifically enriched in the paternal pronucleus where conventional DNA methyl groups (5-methylcytosine, 5mc) are oxidized to 5-hydroxymethylcytosine (5hmc), a novel DNA modification identified recently (Kriaucionis and Heintz 2009; Tahiliani *et al.* 2009; Inoue and Zhang 2011; Iqbal *et al.* 2011; Wossidlo *et al.* 2011). However, Tet3-depleted zygotes fail to exhibit 5mc to 5hmc conversion, indicating a loss of active demethylation of paternal genome. Moreover, reduced fecundity was observed in female mice deficient of *Tet3* in the germ line and depletion of *Tet3* from oocytes results in reduced reprogramming efficiency in SCNT. These data suggest active demethylation is achieved by DNA hydroxylation catalyzed by Tet3, supporting a critical role for maternal Tet3 in early embryogenesis.

The first protein identified with a documented role in controlling DNA demethylation in zygotes is DPPA3 (Nakamura *et al.* 2007). *DPPA3*-null mouse zygotes exhibit active DNA methylation in both paternal and maternal genomes, suggesting its role in prohibiting the maternal genome from active demethylation after fertilization. Additionally, binding of DPPA3 to H3K9me2-enriched nucleosomes induces a change in chromatin structure. Such change may impact Tet3 affinity for chromatin and causes reduced conversion of 5mc to 5hmc (Nakamura *et al.* 2007). This role of DPPA3 may be conserved across species as a similar functional role has been documented recently in bovine embryos (Bakhtari and Ross 2014).

Histones are also subject to dramatic reprogramming immediately after fertilization occurs, particularly in terms of histone variants and the post-translational modifications of histone tails (Fig. 2) (Beaujean 2014). It is well known that sperm DNA is highly coated with protamines and requires reorganization at fertilization to ensure successful development of embryos. Maternal histone proteins are critical for completing this reorganization. For example, protamines are rapidly replaced by oocyte-specific linker histone H1Foo (Becker *et al.* 2005). Recently, several studies also demonstrated that histone variants (H3.3) are crucial

for epigenetic regulation/chromatin remodeling which orchestrates gene expression changes in early embryos (Lin *et al.* 2013; Lin *et al.* 2014; Wen *et al.* 2014). Reprogramming of histone post-translational modifications was recently reviewed (Beaujean 2014; Lee *et al.* 2014d).

H3.3 is one such maternal histone protein important for early embryogenesis. Canonical histone H3 is expressed and deposited onto chromatin during S phase of the cell cycle while the variant H3.3 is found throughout the entire cell cycle. Maternal H3.3 is deposited onto the sperm chromatin shortly after fertilization (1h). Recently, three independent studies revealed an essential role of H3.3 during the process of reprogramming after fertilization in mice (Lin *et al.* 2013; Inoue and Zhang 2014; Wen *et al.* 2014). RNAi-mediated knockdown of H3.3 in mouse zygotes results in developmental failure at the morula stage with overly condensed chromosomes, high aneuploidy rate and failure in nucleosome assembly (Lin *et al.* 2013; Inoue and Zhang 2014), suggesting a critical role of H3.3 in chromatin remodeling in zygotes. Consistent with this idea, Wen *et al.* showed that reduction of H3.3 from mouse oocytes leads to decreased reprogramming potential and downregulation of key pluripotent genes, which could be rescued by injection of exogenous H3.3 mRNA but not H3.2 using SCNT as a model (Wen *et al.* 2014). Interestingly, only maternal H3.3 rather than H3.3 from donor somatic cells is responsible for the reprogramming success of SCNT (Wen *et al.* 2014). The requirement of H3.3 in the reprogramming process may be explained by its role in chromatin remodeling (open/closed chromatin structure) as H3.3 deficiency leads to reduced levels of H3K36me2 and H4K16ac, both markers of open chromatin (Lin *et al.* 2013).

Hira is a chaperone for H3.3. *Hira*-mutant females are infertile as embryos generated from such females and wild-type male mice fail to develop beyond zygote stage, suggesting a requirement of maternal Hira in important development events occurring in zygotes (Lin *et al.* 2014). Consistent with this idea, formation of the maternal pronucleus is blocked after knockdown of *Hira* in oocytes because of failure in nucleosome assembly in the sperm. Hira also plays a role in maternal chromatin reprogramming since *Hira* mutant oocytes fail to develop parthenogenetically. Additionally, depletion of *Hira* causes reduced levels of DNA replication and transcription in both male and female pronuclei.

### Embryonic genomic activation

Early embryos gradually develop developmental independence once EGA occurs, a developmental process by which an embryo begins to transcribe its newly formed genome. The onset of EGA varies among species (2 cell in mice, 4-8 cell in human and pig, 8-16 cell in cow and sheep). Proper EGA is critical for normal development (Lee *et al.* 2014d). Thus, many studies have been performed to determine the mechanism of EGA and gene expression profile changes occurring during the maternal-to-zygotic transition (Lee *et al.* 2014d). A growing list of maternal factors involved in regulation of EGA have been identified (Table 1). These factors include Brg1 (Bultman *et al.* 2006), Mater (official name, Nlrp5) (Tong *et al.* 2000), Padi6 (Yurttas *et al.* 2008), Hsf1 (Christians *et al.* 2000), Zar1 (Wu *et al.* 2003), Npm2 (Burns *et al.* 2003), Ctfc (Wan *et al.* 2008), Zfp3612 (Ramos *et al.* 2004), Atg5 (Tsukamoto *et al.* 2008), Ago2 (official name, Eif2c2) (Lykke-Andersen *et al.* 2008),

Basonuclin (Ma *et al.* 2006), *Ring1*, *Rnf2* (Posfai *et al.* 2012), and *Sox2* (Pan and Schultz 2011). Mutations of any one of the genes encoding these proteins cause developmental arrest at cleavage stages.

The maternal nucleolus is also required for EGA and thus critical for normal early embryonic development in mice (Vogt *et al.* 2012). In early embryos, the nucleolar precursor bodies (NPBs) undergo dramatic transformation to mature nucleoli. A recent study has shown that *LIN28*, known for its reprogramming ability in generation of induced pluripotent stem cells (iPSC), is enriched in NPB. Depletion of *Lin28* from early embryos results in developmental arrest at 2-4 cell stage, due to the failure of NPB assembly.

Maternal polycomb group (PcG) proteins are crucial for the initiation of EGA (Posfai *et al.* 2012). PcG proteins are conserved across species with an established role in transcriptional repression. In mammals, PcG proteins have at least two different classes of complexes, PRC1 and PRC2. These complexes are well known for their ability to catalyze mono-ubiquitination of histone H2A and tri-methylation of histone H3 lysine 27. Depletion of maternal *Ring1* and *Rnf2* from mouse oocytes, both components of PRC1, results in developmental arrest at 2 cell stage after fertilization with wild-type male sperm, suggesting PcG proteins are implicated in the acquisition of oocyte developmental competence during oogenesis by maintaining appropriate chromatin status.

### Maternal control of genomic imprinting

Genomic imprinting is an epigenetic process that distinguishes chromosomes inherited from mother and father and results in parent-of-origin-specific gene expression. Central to this process is the creation of differentially methylated regions (DMRs), which exhibit allele-specific epigenetic marks (Plasschaert and Bartolomei 2014). Among these marks, DNA methylation is the most-well-investigated. DMRs are hypomethylated in the expressed parental allele and hypermethylated in the non-expressed parental allele (Plasschaert and Bartolomei 2014). Disruption of DMRs results in loss of imprinting for many imprinted genes and can cause cancer and human defects (Lee and Bartolomei 2013).

Differential epigenetic marks (imprints) are placed on DMR in the germ line and must be maintained throughout development to ensure proper growth and development (Lee and Bartolomei 2013). It is especially critical for maintenance of genomic imprints during preimplantation development because both parental genomes are demethylated while the chromatin is strikingly remodeled. Mechanisms must exist that maintain allele-specific modifications of the DMRs during early development. How these discrete regions are specifically recognized and their specific epigenetic modifications subsequently maintained are poorly understood. It is likely that maternal factors are crucial during preimplantation development to perform this specialized protective role. Indeed, multiple maternal genes have been identified, whose products are involved in protecting imprinted methylation sites during preimplantation development including *DPPA3* (Nakamura *et al.* 2007); *ZFP57* (Li *et al.* 2008b); *TRIM28* (Messerschmidt *et al.* 2012) and *DNMT1* (Hirasawa *et al.* 2008).

Maternal *DPPA3* (also known as *PGC7* or *Stella*) is the first maternal protein possessing a protective role in maintenance of methylation imprints. As mentioned above, maternal

DPPA3 is required for prohibiting the maternal pronucleus from active demethylation in mouse zygotes and *DPPA3* mutants fail to develop beyond the blastocyst stage (Nakamura *et al.* 2007). Moreover, DPPA3 is also implicated in the protection of imprinted genes with paternally inherited methylation (*H19*, *Rasgrf1*). As a result, *DPPA3*-depletion from oocytes leads to reduced DNA methylation at imprinted genes. Recently, it was found that an underlying histone modification, H3K9me2, is responsible for recruiting DPPA3 to the maternal genome and some paternal imprinting control regions (ICRs), and thus prevents active demethylation by Tet3 (Nakamura *et al.* 2012).

ZFP57 is a Krüppel-associated box domain (KRAB)–zinc finger protein involved in control of genomic imprinting. During preimplantation development, *ZFP57* expression is generally of maternal origin until *ZFP57* transcription begins at the blastocyst stage (Zeng *et al.* 2004). Ablation of both maternal and embryonic *ZFP57* lead to embryonic lethality in mice (Li *et al.* 2008b). Bisulfite sequencing analysis demonstrated that mid-gestation embryos depleted of maternal and embryonic *ZFP57* have reduced DNA methylation at both maternal (*Snrpn*, *Peg1*, *Peg3*, *Peg5*) and paternal imprinted DMRs (*Gtl2* ICR) (Li *et al.* 2008b). The effect of maternal *ZFP57* depletion on methylation imprints can be found as early as the blastocyst stage, where *ZFP57* depletion results in hypomethylation of *Snrpn* that can be rescued by embryonic *ZFP57* by day 13.5. *ZFP57* mutations have also been correlated with abnormal DNA methylation at several imprinted regions in humans (Mackay *et al.* 2008).

TRIM28 is a scaffold component of a chromatin-modifying complex that mediates transcriptional activity by interaction with KRAB–zinc finger proteins, such as ZFP57, which recognize specific genomic loci (Messerschmidt *et al.* 2012). TRIM28 is responsible for recruiting epigenetic modifiers that are associated with repressive chromatin (Messerschmidt *et al.* 2012). Embryonic *TRIM28* transcription occurs at the 2-cell stage with the protein detected as early as the 4-cell stage. Maternal *TRIM28* deletion results in partial embryonic lethality in mice (Messerschmidt *et al.* 2012). *TRIM28* maternal mutant embryos display loss of methylation imprints at the *H19*, *Snrpn* and *Gtl2* ICRs but this phenotype varies between embryos (Messerschmidt *et al.* 2012). *H19* imprinted methylation is still reduced in 4- and 8-cell *TRIM28* maternal mutant embryos, indicating maternal TRIM28 is required for protection of methylation imprints from passive demethylation.

By comparison, *DPPA3* deletion has a global role in protecting the maternal genome while maternal *TRIM28* mutation has a specific effect on imprinted genes. This specificity is achieved by interaction of TRIM28 with KRAB ZFP, such as ZFP57, which is expressed in a tissue-specific fashion. Consistent with this idea, TRIM28 and ZFP57 are both enriched at DMRs of imprinted genes, such as *H19*. Thus, TRIM28 may attract epigenetic modifiers to change chromatin structures to allow transcriptional control. Indeed, multiple epigenetic modifiers have been shown to bind TRIM28 complex, including SETDB1, DNMT1, DNMT3A and DNMT3B (Iyengar and Farnham 2011).

Maternal DNMTs are also critical for the maintenance of methylation imprints during early embryonic development. The DNMT are classified into two categories: de-novo (DNMT3A, 3B, 3L) and maintenance methyltransferase (DNMT1). DNMT1 recognizes hemimethylated DNA, methylating the newly synthesized strand at each replicative cycle. It has been



demonstrated that maternal and zygotic DNMT1, but not DNMT3A and 3B, are both required for the maintenance of methylation imprints in preimplantation embryos.

Despite the above information, no universal mechanism has been reported affecting maintenance of methylation imprints of imprinted genes. For example, PGC7 selectively protects the paternally imprinted/methylated DMRs of *Rasgrf1* and *H19-Igf2* and maternally methylated DMRs of *Peg1*, *Peg3*, and *Peg10*. However, PGC7 is dispensable for the protection of the maternal DMRs of *Snrpn* and *Peg5* and the paternal DMR of *IG-DMR//Meg3*. It suggests locus-specific regulation by a cohort of modifiers on methylation imprints.

### Cell specification

During mammalian development, the first cell fate decision is clearly made upon the formation of blastocyst (at day 3.5 in mice and 6-7 after insemination in cattle), in which the outside layer of cells is termed trophectoderm (TE) and inside cells named inner cell mass (ICM). TE cells subsequently develop to the majority of placenta. ICM cells will develop into the embryo proper, and are also the source of embryonic stem cells (ESCs). Given specific localization within either ICM (*Oct4*) or TE (*Cdx2*), maternal *Oct4* and/or *Cdx2* were hypothesized to be critical for the first lineage specification event. However, it was later found that both maternal *Oct4* and *Cdx2* are dispensable for the first lineage specification (Blij *et al.* 2012; Frum *et al.* 2013).

The Hippo-YAP pathway plays an important role in this lineage decision. In outside cells, YAP is localized in the nucleus and induces the TE specific transcription factor *Cdx2* by cooperation with TEAD4 while in inside cells YAP is phosphorylated by Lats1/2, Hippo pathway kinases, blocking entry into the nucleus. Recently, a Hippo pathway member upstream of Lats1/2 and YAP, *Nf2/Merlin*, was shown to be required for YAP phosphorylation in early embryos. Zygotic *Nf2* mutant embryos exhibit mild defects in *Cdx2* expression and YAP localization while the maternal and zygotic mutants have more severe phenotypes, demonstrating a role of maternal *Nf2* in the first lineage decision.

### Conclusions and Perspectives

A competent oocyte is a major determinant of pregnancy success, not only providing genetic materials but a variety of functional maternal factors that support early embryogenesis. Despite great progress made towards identification and characterization of the maternal factors, there is still a significant gap in understanding the maternal control of maternal-zygotic-transition, especially in domestic animals, such as cows and horses. Furthermore, there is also a lack of knowledge on the influence of environmental perturbation on the expression and activity of maternal factors. Recent progress in genome sequencing, especially single-cell transcriptomic analysis, will greatly facilitate identification of maternal factors. Furthermore, functional analysis will be convenient with the robust gene engineering tools (e.g. TALEN, CRISPR/Cas9).

Oocyte quality is a dramatic concern for women of advanced age, given a growing number of women that choose to conceive in their later 30s or early 40s. To determine how oocyte quality contributes to poor fertility in women with advanced age, there is a huge interest in

effects of maternal age on spindle assembly and chromosome segregation as aneuploidy rate increases as women age. In contrast to this effect on nuclear competence, there is a limited understanding of how cytoplasmic competence/maturation is altered in women with advanced maternal age. Thus, future work should also be directed toward identifying age-associated perturbation in maternal factors. Due to ethical issues and limitations of oocyte numbers in humans, such type of work requires using relevant model such as bovine or equine, which exhibit similarities to the human female reproductive system (Malhi *et al.* 2007; Carnevale 2008).

Recently, growing attention has been paid to the long-term developmental influences of the use of ART. Aberrant epigenetic regulation is closely associated with low efficiency and the poor outcome of reproductive technologies in both agricultural animals and humans (Grace and Sinclair 2009; El Hajj and Haaf 2013). Evidence demonstrates that aberrant DNA methylation patterns are correlated with the use of reproductive technologies, including superovulation and SCNT (Farin *et al.* 2006; Market-Velker *et al.* 2010). Of particular note, superovulation in mouse models induces abnormal imprinted methylation for both paternally and maternally imprinted genes in blastocysts, suggesting maternal-effect genes are affected and are required for maintenance of genomic imprints in early embryos (Market-Velker *et al.* 2010). However, our understanding of mechanisms of epigenetic reprogramming in early embryos is far from complete. It remains to be identified which maternal factors are disturbed in response to the use of reproductive technologies (e.g. superovulation). Future investigation of the regulation of maternal control on developmental events, such as DNA methylation dynamics, in early embryos will better our understanding of the key factors that contributing to maternal reproductive aging and shed novel insights on further improvements in reproductive technologies in both agricultural animals and humans.

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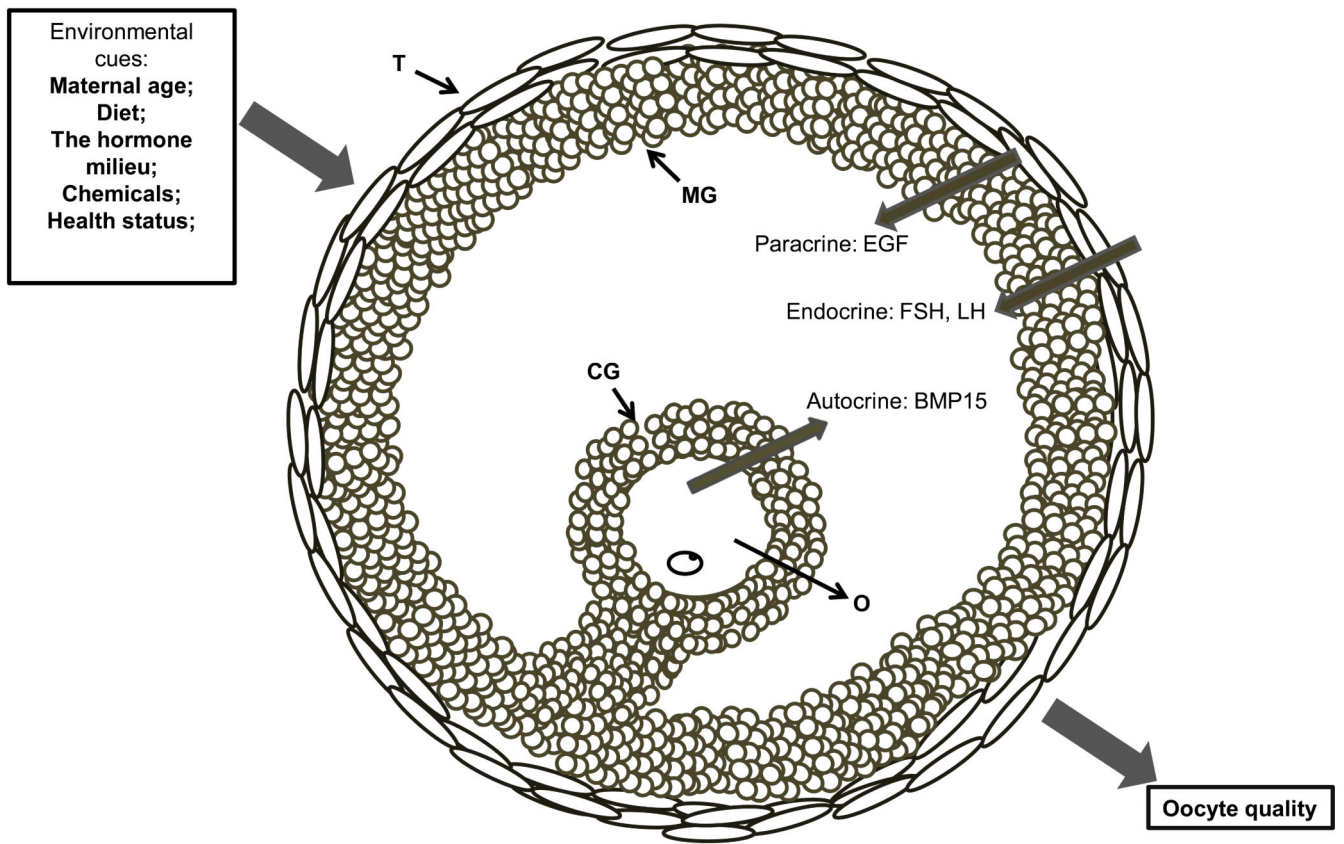
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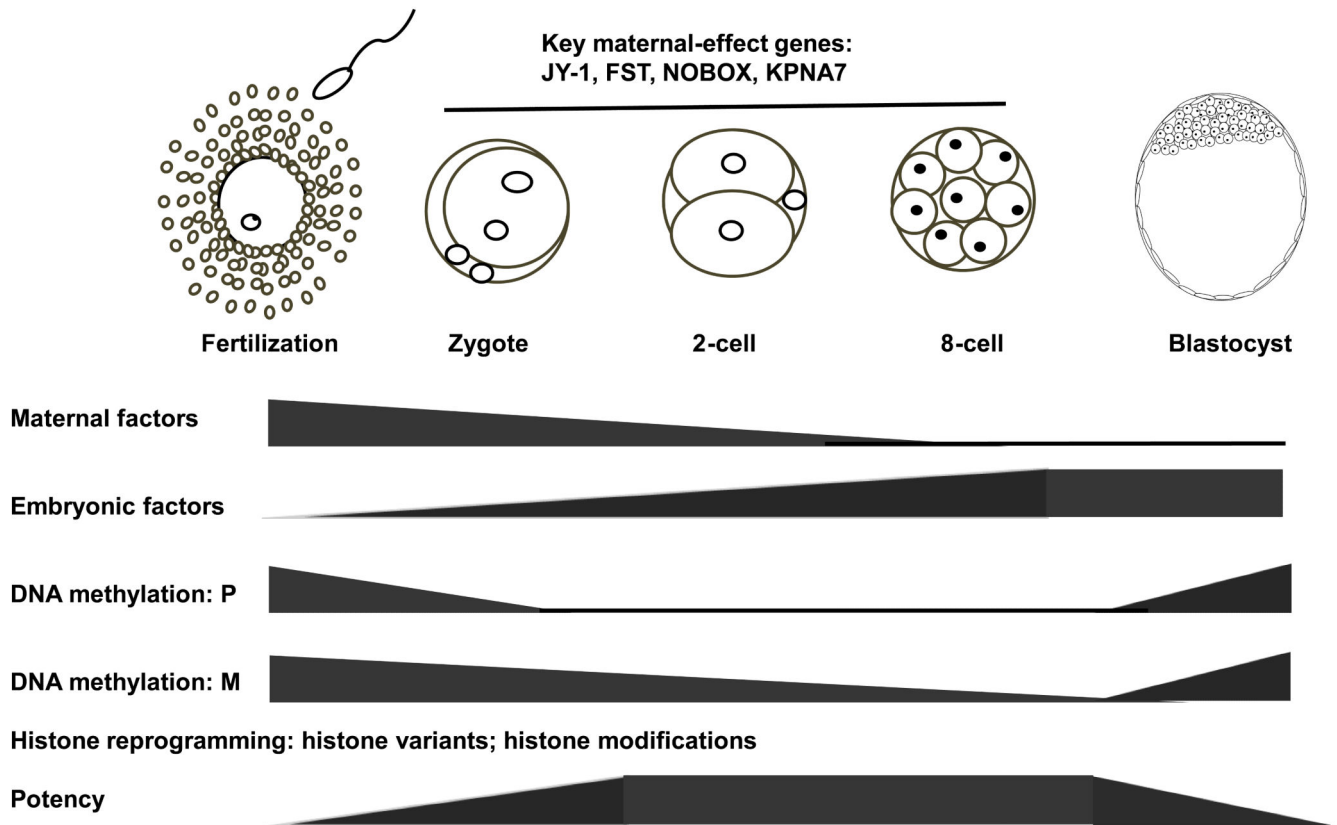


T: theca cells; MG: mural granulosa cells; CG: cumulus granulosa cells; O: oocyte

**Fig. 1.**

Oocyte acquire developmental competence in ovarian follicles. Environmental cues, such as maternal age, diet, chemicals and health status (e.g. obesity), could impact the intra-follicular environment and thus affect the oocyte developmental competence. A variety of physiological signals (paracrine, endocrine and autocrine) play a critical role in maintaining a proper intra-follicular environment that nurture a competent oocyte.

### Bovine early embryonic development



**Fig. 2.**

Dynamics of key developmental events occurring during bovine preimplantation development.

Shortly after fertilization and prior to 8-16 cell stage, when embryonic genome activation occurs, early embryonic development relies on maternal-stored factors due to transcriptional silencing during this period. The maternal factors are gradually degraded while the embryonic genome is gradually activated. Genome-wide DNA demethylation occurs in both male and female genomes immediately following fertilization. However, active DNA demethylation—that is independent of DNA replication, exclusively occurs in male genome while passive DNA demethylation, that is dependent on DNA replication, occurs in female genomes. At a certain point between morula and blastocyst stages, de novo DNA methylation is initiated for both male and female genomes. Throughout early embryogenesis, other epigenetic modifications, including histone variants and modifications, are also dynamically reprogrammed. The final goal of the regulation is to reprogram the highly differentiated germ cells (sperm and oocyte) to a totipotent embryo.

**Table 1**

A list of maternal-effect genes in mammalian early embryonic development (M: mouse; B: bovine)

Genes	Function	Species	References
<i>Ago2</i>	Degradation of maternal RNA	M	(Lykke-Andersen <i>et al.</i> 2008)
<i>Atg5</i>	Degradation of maternal protein	M	(Tsukamoto <i>et al.</i> 2008)
<i>Basonuclin</i>	Transcriptional factor	M	(Ma <i>et al.</i> 2006)
<i>Brg1</i>	Chromatin remodeling; Embryonic genome activation	M	(Bultman <i>et al.</i> 2006)
<i>Brwd1</i>	Chromatin remodeling	M	(Philipps <i>et al.</i> 2008)
<i>Ctcf</i>	Transcriptional factor; Embryonic genome activation	M	(Wan <i>et al.</i> 2008)
<i>Cdh1</i>	Cell-cell adhesion during compaction	M	(Larue <i>et al.</i> 1994; Riethmacher <i>et al.</i> 1995; De Vries <i>et al.</i> 2004)
<i>Dnmt1</i>	Maintenance of DNA methylation	M, B	(Hirasawa <i>et al.</i> 2008; Golding <i>et al.</i> 2011)
<i>Dnmt3a</i>	De novo methyltransferase	M	(Kaneda <i>et al.</i> 2010)
<i>Dnmt3l</i>	De novo methyltransferase	M	(Hata <i>et al.</i> 2002)
<i>Dicer1</i>	Degradation of maternal RNA	M	(Murchison <i>et al.</i> 2007)
<i>Dppa3</i>	Maintenance of DNA methylation	M, B	(Nakamura <i>et al.</i> 2007; Bakhtari and Ross 2014)
<i>Filia</i>	Component of SCMC, euploidy maintenance		(Zheng and Dean 2009)
<i>Floped</i>	ND		(Li <i>et al.</i> 2008a)
<i>Fmn2</i>	Meiotic progression	M	(Leader <i>et al.</i> 2002)
<i>H1foo</i>	Replacement of protamines	M	(Becker <i>et al.</i> 2005)
<i>H3.3</i>	Reprogramming; decondensation of chromatin	M	(Lin <i>et al.</i> 2013; Inoue and Zhang 2014; Wen <i>et al.</i> 2014)
<i>Hira</i>	H3.3 incorporation; rRNA transcription	M	(Inoue and Zhang 2014; Lin <i>et al.</i> 2014)
<i>Hsf1</i>	Redox homeostasis; mitochondria function	M	(Christians <i>et al.</i> 2000; Bierkamp <i>et al.</i> 2010)
<i>Kdm1b</i>	Histone H3 lysine 4 (H3K4) demethylase; de novo DNA methylation	M	(Ciccone <i>et al.</i> 2009)
<i>Mater</i>	Component of SCMC	M, B	(Tong <i>et al.</i> 2000) (Penner <i>et al.</i> 2006)
<i>mHR6A</i>	Degradation of maternal protein; chromatin remodeling	M	(Roest <i>et al.</i> 2004)
<i>Npm2</i>	Chromatin remodeling	M	(Burns <i>et al.</i> 2003; Inoue <i>et al.</i> 2011)
<i>Padi6</i>	ND	M	(Yurttas <i>et al.</i> 2008)
<i>Pdk1</i>	ND	M	(Zheng <i>et al.</i> 2010)
<i>Pms2</i>	DNA mismatch Repair	M	(Gurtu <i>et al.</i> 2002)
<i>Ring1</i>	Component of Polycomb protein; chromatin remodeling	M	(Posfai <i>et al.</i> 2012)
<i>Rnf2</i>	Component of Polycomb protein; chromatin remodeling	M	(Posfai <i>et al.</i> 2012)

Genes	Function	Species	References
<i>SEBOX</i>	ND	M	(Kim <i>et al.</i> 2008)
<i>Sox2</i>	Reprogramming gene expression;	M	(Avilion <i>et al.</i> 2003; Pan and Schultz 2011)
<i>Tap73</i>	Spindle assembly; genomic stability	M	(Tomasini <i>et al.</i> 2008)
<i>Tcl1</i>	ND	M	(Narducci <i>et al.</i> 2002)
<i>Tet3</i>	Active DNA demethylation	M,B	(Gu <i>et al.</i> 2011)
<i>Tif1a</i>	Chromatin remodeling	M	(Torres-Padilla and Zernicka-Goetz 2006)
<i>Tle6</i>	ND	M	(Yu <i>et al.</i> 2014)
<i>Trim28</i>	Maintenance of DNA methylation	M	(Messerschmidt <i>et al.</i> 2012)
<i>UCH11</i>	Block polyspermy	M	(Sekiguchi <i>et al.</i> 2006)
<i>Zar1</i>	Early embryonic development	M	(Wu <i>et al.</i> 2003)
<i>ZFP3612</i>	Degradation of maternal factors	M	(Ramos <i>et al.</i> 2004)
<i>Zfp57</i>	Maintenance of DNA methylation	M	(Li <i>et al.</i> 2008b)
<i>JY-1</i>	ND	B	(Bettegowda <i>et al.</i> 2007; Lee <i>et al.</i> 2014a)
<i>Follistatin</i>	ND	B	(Patel <i>et al.</i> 2007; Lee <i>et al.</i> 2009)
<i>SMAD4</i>	ND	B	(Lee <i>et al.</i> 2014b)
<i>NOBOX</i>	ND	M, B	(Rajkovic <i>et al.</i> 2004; Tripurani <i>et al.</i> 2011)
<i>KPNA7</i>	Nuclear importing	B	(Tejomurtula <i>et al.</i> 2009)