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OOCYTE-SPECIFIC GENE SIGNALING AND ITS REGULATION OF MAMMALIAN REPRODUCTIVE POTENTIAL

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1. ABSTRACT

Oocyte-specific genes play important roles in regulating ovarian development, principally through the proper and timely progression of oogenesis and folliculogenesis. Development of transgenic mouse models has been critical in revealing how oocyte-specific transcripts influence oocyte development and growth, integrity of the oocyte-granulosa cell complex, oocyte maturation, fertilization, and early embryonic development. Oocyte-derived genes that mediate recombination of homologous chromosomes and DNA mismatch repair include *Spo11, Atm, Dmc1, Msh5, Mlh1,* and *Msh4.* Transcripts such as *Dazla* and *Fig-alpha* regulate initial proliferation of the primordial germ cell and follicle. Transition from the primordial to primary follicle relies on the expression of growth factors *bFGF, Gdf9* and *Bmp15,* as well as on the expression of various transcripts that mediate oocyte-granulosa cell interactions. Oocyte growth is predominantly under exogenous control, however resumption of meiotic progression is dictated by genes that influence proper chromatin and spindle regulation, such as *Cdk*, *Histone H1$_{oo}$, Fmn-2, Mad2,* and *Bub3.* Maintenance of meiotic metaphase II arrest prior to fertilization is mediated primarily by *c-mos*, and successful fertilization requires the expression of zona pellucida glycoproteins (*Zp1, Zp2*, and *Zp3*) and *Cd9*. Following fertilization, maternal-effect and maternally expressed 'imprinting' genes are necessary for the completion of meiosis and for patterning early embryonic development. Recent utilization of suppressive subtractive hybridization (SSH), PCR amplification, and cDNA microarray analysis techniques alongside established transgenesis models are expanding the classification of novel oocyte-specific genes required for reproductive fitness in various species, including human.

2. INTRODUCTION

. The oocyte is a unique cell whose life cycle is characterized by alternating periods of active meiotic progression with long periods of meiotic arrest. Oogenesis is further characterized by periods of high transcriptional and translational activity, that alternate with phases of relatively low metabolic activity. In addition, the ability of an oocyte to develop into a viable embryo depends on several factors, including the accumulation of RNA transcripts and proteins throughout follicular and oocyte growth (1). The advent of transgenesis and targeted mutagenesis in rodents over two decades ago has provided invaluable tools to identify genes critical for proper mammalian development (2, 3). Since there are currently no transformed cell lines derived from oocytes, transgenic mice offer the most direct method of characterizing the various gene and protein interactions that result in competent mammalian oocytes. In addition, several ovarian pathologies observed in transgenic knockout mice have been shown to phenocopy certain human ovarian dysgeneses, thereby substantiating the value of the rodent model in understanding disruptions in human reproductive potential (4-8).

In the mouse, gestation occurs over a 20-day period, during which migrating germ cells colonize the urogenital ridge by E10-11 to form an undifferentiated gonad. At the time of sex differentiation, the genetically predetermined XX gonad develops into an ovary, under the control of both somatic and oocyte-cell specific regulation. In the fully differentiated ovary, mitotically dividing oogonia enter prophase of the first meiotic division at E13.5, and then arrest at the dictyate stage of the first meiotic prophase to form primordial follicles (9). These primordial follicles are characterized by developmentally arrested oocytes surrounded by a single layer of squamous granulosa cells (9). Upon follicular stimulation, cohorts of these primordial follicles are induced to undergo a growth phase that culminates in completion of the first meiotic division and ovulation of oocytes into the oviduct (10). Although both follicular and oocyte development are directly regulated by various growth/survival factors expressed in the somatic tissues of the developing gonad (11), experimental disruption of oocyte development during embryogenesis can lead to abnormal ovarian development or premature ovarian failure, indicating that germ-somatic cell interactions are essential for normal ovarian development (12-15). This review will cover the most current understanding of the genes specifically expressed in the murine oocyte that are responsible for germ cell development, differentiation of granulosa cells, oocyte maturation and fertilization, and early embryonic development.

3. GENES INVOLVED IN EARLY OOGENESIS AND FOLLICULOGENESIS

3.1. Mediation of homologous recombination and DNA mismatch repair

During embryonic development, oogonia enter the first meiotic division to become primary oocytes that arrest at the dictyate stage of meiotic prophase I (9). At the time of this developmental arrest, the chromosomes have already undergone condensation, followed by synapsis, homologous recombination, and chromatin decondensation (10). Oocyte-derived genes that initiate or support recombinational exchange between homologous chromosomes, and mediate DNA repair prior to arrest in prophase of meiosis I are essential for oocyte survival (16-21). Expression of the mouse ortholog of *Spo11* is necessary for generating chromatin breaks during leptotene of the first meiotic prophase (16). Disruption in *Spo11* expression impairs normal synapsis and homologous recombination, and oocytes die prior to birth (16). Chromosomes in oocytes with genetic null mutations in *Atm, Dmc1, Msh5,* or *Msh4* fail to synapse, leading to an arrest of gametogenesis, followed by apoptotic cell death resulting in sterility (17-19, 21). Targeted disruption of the DNA mismatch repair gene, *Mlh1*, drastically reduces homologous recombination and results in irreversible structural disruptions in the meiotic process (20, 22). Mutations in these genes demonstrate how losses in germ cell signaling can lead to premature ovarian failure and consequent infertility.

3.2. Primordial germ cell and follicle formation

Survival and proliferation of primordial germ cells are influenced by several factors expressed in the surrounding ovarian somatic cells, including TNF-alpha, leukemia inhibitory factor (LIF), Kit ligand (KL), and interleukin (IL-4) (11). Although the factors essential for follicle formation are not well understood, it is clear that oocyte developmental competence directly influences the expression of transcripts in surrounding follicular cells (23). Therefore, primordial follicle formation appears dependent on the timely expression of specific transcription factors that affect both primordial germ cell survival and consequent oocyte-somatic cell interactions during folliculogenesis.

Genes expressed in primordial germ cells have been implicated in survival of the developing oocyte and follicular cells. The *Dazla* gene encodes a cytoplasmic protein expressed in the developing gonads during early embryogenesis, before the onset of meiosis in the mouse and human (24, 25). Disruption of the *Dazla* gene leads to the complete absence of male and female gamete production suggesting that *Dazla* functions at the first phase of gametogenesis for the development and survival of primordial germ cells in the ovary (24, 26). Factor in the germline-alpha (*Fig-alpha)* is a basic helix-loop-helix transcription factor first expressed at E13 that persists into adulthood, and is required for perinatal formation of primordial follicles (27, 28). Primordial germ cell formation is blocked in mice that lack *Fig-alpha*, leading to infertility (27). This transcription factor also regulates the expression of the three genes that encode the zona pellucida glycoproteins, ZP1, ZP2, and ZP3 (28). These proteins work together to build the extracellular matrix found in all vertebrate eggs that is critical for oocyte growth, fertilization, and early embryo migration through the oviduct.

3.3. Transition from primordial to primary follicle

Follicular growth from the primordial to primary stage is characterized by the morphological change from a single layer of squamous pre-granulosa to cuboidal granulosa cells surrounding a primary oocyte (10). Between E16.5 and birth, oocytes express the tyrosine kinase receptor *c-kit*, and from post-natal day 7, there is a considerable accumulation of *c-kit* transcripts in growing oocytes (29). Kit ligand (KL) is first expressed in oocytes at E16.5 and in granulosa cells at E18.5 (29). Interactions between c-kit and its ligand have been shown be important for promoting the primordial to primary follicle transition in rodent ovaries (29, 30). Oocytes at mid-stage of meiotic prophase I (E16.5-17.5) co-express c-kit and KL proteins, and functional ablation of these proteins in this critical time-frame results in increased oocyte apoptosis; this suggests a temporal KL/c-kit autocrine regulatory loop in the oocyte for survival of fetal oocytes at this stage (29). Basic fibroblast growth factor (*bFGF*) is expressed in oocytes of primordial follicles, and oocyte-derived *bFGF* is believed to signal to surrounding granulosa and stromal cells to promote the transition from a primordial to a primary follicle (30). As important, *bFGF* has been shown to increase KL mRNA expression, and both bFGF and KL proteins are required for optimal promotion of the primordial to primary oocyte transition (31). *Nobox* is an oocyte-specific homeobox gene expressed in germ cell cysts and in primordial and growing oocytes (32). *Nobox*$^{-/-}$ female mice exhibit atrophic ovaries almost devoid of oocytes. The loss of *Nobox* does not affect embryonic development, germ cell proliferation, or initial primordial follicle development; however lack of NOBOX inhibits the majority of oocyte and follicle growth beyond the primordial follicle stage, while increasing the rate of atresia in oocytes postnatally (33). Also, *Nobox*$^{-/-}$ mice show a downregulation of oocyte-specific *Oct4* and *Gdf9* gene expression (33).

Growth differentiation factor 9 (Gdf9) is an oocyte-specific member of the TGF-beta superfamily of secreted growth factors (34, 35). Synthesis of *Gdf9* messenger RNA occurs in the oocyte from the primary follicle stage until after ovulation. Female mice with null mutations of *Gdf9* demonstrate that primordial and primary follicles can be formed, but there is a block in follicular development beyond the primary follicle stage, which leads to complete infertility (36). Bone morphogenetic protein-15 (Bmp15) is another oocyte-specific member of the TGF-beta superfamily closely related to Gdf9, and it has been shown to regulate granulosa cell proliferation (34). Interestingly, *Bmp15* $^{-/-}$ mice have grossly normal follicular development and are fertile, whereas mice heterozygous for inactive copies of both *Gdf9* and *Bmp15* have reduced litter sizes, an outcome that suggests inappropriate development of the oocyte-cumulus cell complex (37). In *Bmp15* homozygous null sheep, ovarian follicles do not grow beyond the primary follicle stage, but ewes heterozygous for the *Bmp15* mutation display higher ovulation rates than their wild-type counterparts (38). The higher ovulation rate in the heterozygous sheep is apparently the result of precocious maturation of small follicles due to increased FSH receptor expression and earlier expression of LH receptors on the granulosa cells (39). *In vitro* studies in rat granulosa cells, as well as the *in vivo* data in sheep that display point mutations in *Bmp15*, demonstrate that decreasing *Bmp15* expression can increase FSH receptor expression on granulosa cells (38, 40). Generation of mice with *Bmp15* point mutations similar to those in the sheep studies may elucidate whether the different phenotypes are species-dependent or point mutation-dependent.

3.4. Oocyte-granulosa cell regulatory loop

It is also important to consider oocyte-specific genes that mediate the interaction between granulosa cells and the oocyte proper. Connexin 37 (*Cx37*) is the predominant murine oocyte connexin and it is expressed in gap junctions between developing oocytes and granulosa cells (41). Gap junctions are intercellular channels that directly connect adjacent cells, allowing for diffusion of metabolites, ions, and other signaling molecules (42). Communication between the developing oocyte and granulosa cells influences overall follicular development, and oocyte-granulosa cell gap junctions do not appear until the secondary follicle stage, coinciding with the acquisition of oocyte meiotic competence (43, 44). Mice deficient in *Cx37* expression lack recognizable gap junctions, resulting in female infertility due to abnormalities in follicle growth, oocyte maturation, and control of luteinization (41).

Genes involved in the oocyte-granulosa cell regulatory loop that encode transmembrane proteins have been identified by generating an oocyte signal sequence trap (SST) library and screening oocyte-expressed sequences (45). These genes include *crb1*, which codes for a paracrine factor known to establish and maintain cellular polarities through interactions with the cytoskeleton (45, 46). A possible role of *crb1* in the mouse ovary is the organization of granulosa cells in the developing follicle (45). Another gene is *Pkd212* which encodes an integral membrane protein that forms cation channels (45, 47). Therefore, *Pkd212* may play a role in calcium events during oocyte development (45). Lastly, *Gpiap1* encodes a glycosylphosphatidylinositol (GPI)-anchored protein that may be involved in signal transduction via kinases, G-proteins, and immunoreceptors in the oocyte (45, 48).

4. OOCYTE-SPECIFIC GENES NECESSARY FOR OOCYTE GROWTH, MATURATION, AND FERTILIZATION

Follicular maturation is prompted by a series of complex and highly coordinated interactions between hormones, hormonally responsive granulosa cells, and the oocyte (49). Folliculogenesis past the primary stage, as well as initial oocyte growth, are characterized by a high rate of transcriptional activity and enhanced nucleolar activity (50). Ribosomal RNA (rRNA) synthesis comprises approximately 65% of the total RNA synthesized during the oocyte growth phase, and overall RNA content increases by about 300% during the entire growth phase (51). Protein synthesis is also high during the growth phase, but both RNA and protein synthesis in the fully grown oocyte cease upon resumption of meiosis, therefore

storage of both transcripts and proteins during oocyte growth is essential for proper resumption of meiosis, fertilization, and early embryogenesis (1, 50). It is important to note that regulation of gene expression can occur at the transcriptional, translational, and post-translational level, and that the oocyte relies on all three mechanisms to coordinate the appropriate expression of proteins during folliculogenesis and oogenesis. Some mRNAs are immediately translated during oocyte growth, whereas others are 'masked' via deadenylation, which generates short poly (A) tails to maintain the stability of the mRNA stored for long periods of time (52). As important, several proteins bind and mask mRNA via post-translational modifications, such as phosphorylation (53). An oocyte-specific RNA-binding protein necessary for stabilizing maternal mRNAs in growing oocytes, MSY2, has been identified in the mouse (54).

In vivo factors in the follicle actively inhibit oocyte maturation, and this inhibition is overcome by exposure to gonadotropins, which results in the resumption of meiosis and ovulation (55, 56). Studies in murine oocyte-granulosa cell complexes show that transcriptional activity is not required for spontaneous oocyte maturation, but that transcription is required for initiating gonadotropin-induced oocyte maturation (57, 58). One model of murine oocyte maturation contends that when follicle stimulating hormone (FSH) binds to its receptor on cumulus cells surrounding the oocyte, it stimulates the release of cAMP from granulosa cells, which in turn activates both isozymes of protein kinase A, PKA I and PKA II (58). Transient activation of PKA I temporarily inhibits oocyte maturation, but simultaneous stimulation of PKA II activates gene transcription in the oocyte that initiates germinal vesicle breakdown (GVBD) (58, 59). Spontaneous oocyte maturation results from a decrease in intra-oocyte cAMP after removal from an inhibitory follicular environment (58). Therefore, gonadotropins mediate oocyte maturation via transcriptional activity in granulosa cells, whereas the oocyte is responsible for the post-translational modifications necessary for timely expression of the transcripts (58, 60).

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4.1. Resumption and completion of first meiotic division

Resumption of maturation in a meiotically competent, fully grown oocyte requires the timed recruitment, translation, and/or degradation of several mRNAs. M-Phase promoting factor (MPF) is a protein kinase that consists of a heterodimer of cyclin-dependent kinase (Cdk1) and its regulatory subunit, cyclin B (61). Expression of *cdk1*occurs in germinal vesicle intact oocytes, but MPF activation is undetectable until GVBD (62). In mammals, MPF activation is independent of *de novo* protein synthesis of cyclin B, and is highly regulated through post-translational events, primarily reversible phosphorylation (63). MPF phosphorylates and activates the oocyte-specific linker histone $H1_{oo,}$ which aids in the formation of the definitive first meiotic metaphase plate (64, 65).

Formin-2 (*Fmn2*) is a maternal-effect gene that is expressed in oocytes and is required for progression through metaphase of meiosis I (66). Oocytes derived from *Fmn2* $^{-/-}$ females cannot correctly position the metaphase spindle during meiosis I and form the first polar body, demonstrating that *Fmn2* is required for microtubule-independent chromatin positioning during metaphase I (66). Fertilization of *Fmn2* $^{-/-}$ oocytes results in polyploid embryo formation, recurrent pregnancy loss and sub-fertility.. Although *Fmn2* is expressed in the human embryo as early as E9.5, its expression in the ovary has not been directly assessed (67). However, high sequence similarity between human and murine *Fmn2* suggests that mutations in human *Fmn2* may result in chromosomal aneuploidies leading to birth defects and/or pregnancy loss in humans (66, 67).

Transcription of spindle checkpoint genes is also critical for both the appropriate arrest at metaphase of meiosis I and for prevention of homologous chromosome missegregation during anaphase of meiosis I (68). Targeted mutagenesis of known spindle checkpoint genes, *Mad2* and *Bub3*, causes mouse embryonic lethality by E6.5 (69, 70), but gene silencing techniques that deplete protein in fully grown oocytes show that *Mad2* is required to delay the exit from meiosis I and to ensure accurate homologue separation (68). Timely expression of *Mad2* delays the onset of cyclin B (essential component of MPF) degradation during meiosis I to prevent the risk of aneuploidy. Depletion of Mad2 protein also results in abnormal polar body extrusion, suggesting that expression of Mad2 regulates proper extrusion of the first polar body, by ensuring that the meiotic spindle completes its migration to the oocyte cortex prior to completion of meiosis I (68).

4.2. Maintenance of meiotic metaphase II arrest

Ubiquitination of cyclin B lowers MPF activity to facilitate release of the MI arrest (71). In mammalian oogenesis, following completion of the first meiotic division and extrusion of the first polar body, mature oocytes enter the second meiotic division and arrests at metaphase II (MII). In vertebrates, oocytes are arrested at the second meiotic metaphase by a cytostatic factor (CSF) that is defined as the activity capable of inhibiting the transition from metaphase II to anaphase II (72). In mammalian oocytes, the gene *c-mos* encodes a serine-threonine protein kinase essential for the maintenance of the meiotic MII arrest (73-75). Transcription of *c-mos* mRNA occurs in primordial germ cells, but translational activation of *c-mos* mRNA requires cytoplasmic polyadenylation that does not occur until oocytes undergo meiotic maturation (76). Disruption of *c-mos* results in spontaneous parthenogenetic activation of oocytes, which may generate ovarian cysts and reduce fertility (73, 75). Expression of Mos activates the mitogen-activated protein (MAPK) cascade that functions in parallel with MPF activity to drive meiotic progression (77). Activation of MAP kinase plays a role in mediating the MII arrest, but is unable to regulate the MI arrest during meiosis (78). As importantly, MAP kinase inactivation is not necessary for the release of MII after fertilization, therefore the exact role of MAP kinases in regulating mammalian meiosis remains unclear (79).

4.3. Fertilization of mature oocyte

Successful fertilization in mammals requires the formation of the zona pellucida around the oocyte periphery. The mouse zona pellucida is composed of three sulphated glycoproteins, ZP1, ZP2, and ZP3 (80). As mentioned previously, the transcription factor Figα is responsible for expression of the three genes that encode these zona pellucida glycoproteins (28). Female mice with a null mutation in *Zp1* maintain a zona pellucida composed of Zp2 and Zp3 glycoproteins, but embryos generated from these females have a structurally compromised zona matrix that leads to precocious hatching (81). Female mice lacking *Zp2* expression form a thin zona matrix that cannot be sustained past the antral stage of folliculogenesis (82). The structural defect is more severe than the *Zp1* null mutation, in that the loss of the zona pellucida during folliculogenesis disrupts granulosa-oocyte interactions, consequently compromising the developmental competence of the oocyte (82). All homozygous null *Zp2* females are sterile. *Zp3* homozygous null females exhibit the most severe phenotype, which is a failure to form a zona pellucida, even during early folliculogenesis (83).

The oocyte plasma membrane contains an integral protein CD9 that functions in sperm-egg fusion (84). Ovaries from *Cd9*$^{-/-}$ females are grossly normal and hormonally responsive, and produce follicles in all developmental stages, including corpora lutea. Female *Cd9*$^{-/-}$ mice are infertile, as a result of a block of sperm penetration of oocytes during fertilization. Oocytes from *Cd9*$^{-/-}$ females subjected to intracytoplasmic sperm injection (ICSI) develop as normal embryos pre- and post-implantation (84). Therefore, decreased fertility in these females results from an inhibition of sperm binding to oocyte plasma membrane, rather than a deficiency in oocyte maturation or ovulation (84).

5. MATERNAL-EFFECT GENES REQUIRED FOR EARLY EMBRYONIC DEVELOPMENT

Maternal-effect genes encode transcripts and proteins during oogenesis that are necessary for the completion of meiosis, as well as for the activation of the embryonic genome post-fertilization (85). Although it is speculated that several hundred genes participate in the activation of the embryonic genome, relatively few maternal-effect genes have been identified in mammals (86). To date, the known mammalian maternal-effect genes include *Hsf1, Dnmt1o, Fmn-2, Zar1, Npm2, Mater, Spindlin*, and *Oogenesin 1* (66, 85, 87-93). Formin-2 (*Fmn-2*) has been discussed previously in this review for its role in mediating oocyte progression through metaphase of meiosis I (67). Of all the known genes, only *Zar1* and *Mater* are exclusively expressed in oocytes and preimplantation embryos (89, 91).

Hsf1 encodes heat shock factor-1, a transcription factor that regulates stress-inducible proteins (94). Although *hsf1* is a ubiquitously expressed gene, and oocytes from homozygous null *hsf1* females have the potential to ovulate and become fertilized, resultant embryos cannot develop properly beyond the zygotic stage (87). Fertilization of *hsf1*$^{-/-}$ oocytes by wild-type spermatozoa cannot rescue the embryonic lethality; therefore maternal *hsf1* controls early post-fertilization embryonic development (87).

DNA methyltransferases (Dnmt) maintain genomic methylation patterns in mammalian somatic cells. DNA methyltransferase-1o (Dnmt-1o) is a variant of this protein found only in mouse oocytes and preimplantation embryos (88). *Dnmt1o* homozygous null mutants are normal, but most heterozygous fetuses of homozygous females die during the last third of gestation. This demonstrates that although genomic methylation patterns were established normally in *Dnmt1o*-deficient oocytes, embryos derived from such oocytes show a loss of allele-specific expression and methylation at certain imprinted loci that are necessary for embryogenesis.

Zygote arrest 1 (Zar1) is synthesized specifically in growing oocytes and its mRNA is virtually absent throughout preimplantation embryo development (89). Ovarian development in homozygous null females (*Zar1*$^{-/-}$) is normal, and oocytes are able to progress through oogenesis and early stages of fertilization. However, most embryos from *Zar1*$^{-/-}$ females arrest at the zygotic stage, marked by a lack of syngamy between the maternal and paternal pronuclei. Therefore, Zar1 is a maternally–derived factor necessary for the completion of fertilization (89).

Nucleoplasmin 2 (*Npm2*) is another maternal-effect gene critical for the one-cell to two-cell transition (90). Expression of *Npm2* is limited to growing oocytes and is critical for nuclear and nucleolar organization during the final stages of oogenesis, as well as for histone deacetylation and heterochromatin formation around the nucleoli of oocytes and early embryos (90). Oocytes derived from *Npm2*$^{-/-}$ females are competent to undergo normal *in vitro* maturation and fertilization, but fail to complete the first mitotic division. The cause of this mitotic failure is unclear but it is characterized by cellular fragmentation immediately following the first mitotic metaphase (90). Overall levels of rRNA transcription and protein translation do not change in *Npm2*$^{-/-}$ oocytes, suggesting that Npm2 controls the activation of specific maternal mRNAs necessary for early embryogenesis (90).

Maternal antigen that embryos require' (*Mater*) is the only other known maternal-effect gene (other than *Zar1*) expressed exclusively in oocytes and preimplantation embryos (85). In wild-type oocytes, *Mater* RNA is highly expressed during oocyte and follicular growth, and although transcripts are undetectable in ovulated ova, Mater protein is present in all stages of preimplantation embryo development (91). Homozygous null (*Mater* $^{-/-}$) females exhibit normal ovarian folliculogenesis, oocyte meiotic competence, and ovulation, but *Mater* $^{-/-}$ embryos arrest at the two-cell stage (85). Thus, Mater may play a critical role in activation of the embryonic genome.

The maternal transcript for *Spindlin* is only expressed in oocytes prior to fertilization and through the 2-cell stage of embryonic development (92). The Spindlin

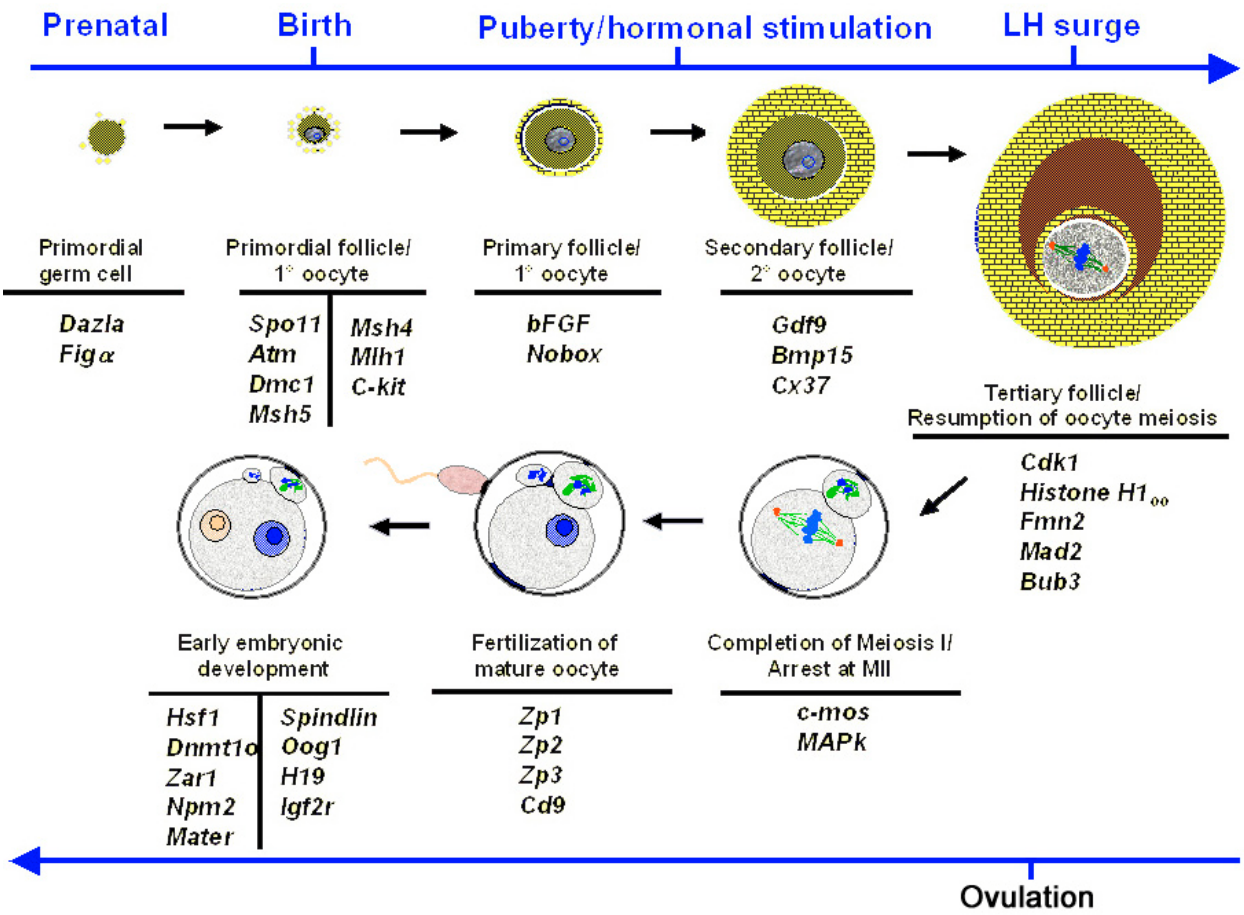

Figure 1. Summary of the expression of known oocyte-specific genes involved in reproductive function.

protein associates with the meiotic spindle and plays a role in cell-cycle regulation during the transition from meiosis to the first mitotic division (92). Transcripts of the novel gene *oogenesin1 (Oog1)* are expressed throughout oogenesis and through the first cleavage division in mouse embryos (93). Although the Oog1 protein has been shown to localize to the nuclei of both 1-cell and 2-cell embryos, functional studies still need to be performed to assess if this protein plays a critical role in folliculogenesis, oogenesis and/or zygotic transcription during early preimplantation embryo development (93).

6. MATERNALLY EXPRESSED 'GENOMIC IMPRINTING' GENES

. Several genes important for embryogenesis depend on whether a parental allele is inherited from the oocyte or spermatozoa, and are classified as 'genomically imprinted' genes (95-98). Known paternally-expressed imprinting genes include *Peg1/Mest, Igf2, Peg3,* and *Snrpn* (99-101). Known maternally-expressed imprinting genes include *H19* and *Igf2r* (99, 100). Primary imprinting of all these genes occurs during oocyte growth, and is essential for both expression and repression of maternal alleles during embryogenesis (102). Disruption of primary imprinting during oocyte growth modifies expression of both maternally and paternally expressed genes, which can ultimately disrupt embryogenesis following zygotic genomic activation (102). There are key regulatory sequences that are methylated on only one of the two parental imprinted alleles, and the allelic DNA methylation established in either the maternal or paternal germline is maintained throughout pre- and post-implantation development (103, 104). Extensive characterization of the *H19* locus has revealed that epigenetic factors (i.e. *in vitro* culture conditions) regulate the methylation status and directly affect imprinted allelic expression (99, 102, 105). Loss of *H19* imprinting in pre-implantation embryos persists post-implantation and the imprinting loss cannot be restored (106). To date, a comprehensive analysis of loss of imprinting prior to or during pre-implantation embryo development has not been conducted in any species, therefore the ramifications of this functional loss on embryo viability are unclear.

7. PERSPECTIVE

. The ability to study human oocytes/embryos is highly restricted, therefore mouse genetic models have proven invaluable for improving our understanding of the processes critical for establishing and maintaining oocyte competence and reproductive function. Gene knockout and targeted mutagenesis studies in mice provide precise functional data and can elucidate specific roles for genes

Table 1. Uncharacterized mouse genes preferentially expressed in oocyte, determined by microarray analysis and validated by RT-PCR

BLAST Identity [1,2]	**Accession no.**[1]	**% Identity** [1]
Mm 2 days pregnant adult female ovary, E330034G19Rik	AK087874	100
Mm 2 days pregnant adult female ovary, hypothetical protein E330017A01	AK087761	99
Mm expressed sequence C87414	BC052888	100
Mm similar to Nur77 downstream protein 1 (LOC381251)	XM_355193	99
Mm adult male testis, 49215201Rik	AK014932	99

Modified from 108, [1] BLAST identity , Accession no., and % Identity based on BLAST searches of GenBank database, [2] Mm, Mus musculus

Table 2. Microarray reported genes expressed in primate oocytes

BLAST identity [1]	Accession no. [1]	Species	Stage of Folliculogenesis Expressed	Reference
Dazl	AA129397	Human, Rhesus monkey	Primordial, primary, secondary	111-112
Alpha-tubulin	AA180742	Human	Unknown	112
TRF-interacting telomeric RAP1	AA434068	Human	Unknown	112
Integrin, beta-3	AA037229	Human	Unknown	112
Cellular repressor of E1A-stimulated genes	T71991	Human	Unknown	112
Growth arrest and DNA damage inducible, gamma/GADD45	T71360	Rhesus monkey	Unknown	112
Ubiquitin-conjugating enzyme E2A	AA600173	Rhesus monkey	Primordial, primary	112
Gene 33/Mig6	AA400258	Rhesus monkey	Unknown	112
Dendritic cell protein	AA101348	Rhesus monkey	Unknown	112
G_1 to S phase transition 1 (GSPT1)	AA129397	Rhesus monkey	Primordial, primary	112

[1] BLAST identity and Accession no. based on BLAST searches of GenBank database

based on their expression patterns, localization, and loss-of-function phenotype in a cell or tissue. Figure 1 summarizes the most current understanding of oocyte-specific genes involved in oogenesis, folliculogenesis, fertilization, and early embryonic development. Recent improvements in molecular biology are facilitating the identification of novel genes preferentially expressed in the oocyte that play critical roles in oogenesis and embryonic development. The use of suppressive subtractive hybridization (SSH), PCR amplification, and cDNA microarray analysis techniques provide powerful tools for the identification of novel oocyte-specific genes within and across species (107-109). The combined use SSH and cDNA microarray analysis is highly selective and surpasses previous transcriptome analyses that identified extensive lists of oocyte-expressed clones with no indication as to which clones may be key regulators in the oocyte and embryo development (109, 110). Table 1 displays uncharacterized mouse genes that are preferentially expressed in secondary oocytes versus somatic tissues recently identified via microarray analysis by Vallée and colleagues (108). Quantitative RT-PCR and high-density microarray analyses have been used to study the expression of several known genes in primate oocytes (111, 112). These analyses determined the differential expression of 95 genes in primordial primate oocytes. Table 2 summarizes the array-identified genes investigated to date in primate oocytes with confirmed expression by *in situ* hybridization. Advances in human assisted reproductive technologies (ART) are fundamentally dependent on a more accurate assessment of oocyte quality and factors that regulate consequent embryonic development. An improved understanding of gene expression and activity is critical in characterizing the mechanisms underlying the proper activation of the embryonic genome for successful embryonic development. As important, recent findings that environmental factors such as *in vitro* culture conditions can affect the expression of maternally imprinted genes validates the need for further investigation into oocyte specific genes, their regulation, and the consequences in subsequent embryo development and offspring health.

8. REFERENCES

1. R. De La Fuente & J. J. Eppig: Transcriptional activity of the mouse oocyte genome: companion granulosa cells modulate transcription and chromatin remodeling *Dev Biol* 229, 224-236 (2001)

2. J. W. Gordon, G. A. Scangos, D. J. Plotkin, J. A. Barbosa & F. H. Ruddle: Genetic transformation of mouse embryos by microinjection of purified DNA *Proc Natl Acad Sci U S A* 77, 7380-7384 (1980)

3. R. L. Brinster, H. Y. Chen, M. Trumbauer, A. W. Senear, R. Warren & R. D. Palmiter: Somatic expression of herpes thymidine kinase in mice following injection of a fusion gene into eggs *Cell* 27, 223-231 (1981)

4. S. D. Sullivan & S. M. Moenter: GABAergic integration of progesterone and androgen feedback to gonadotropin-releasing hormone neurons *Biol Reprod* 72, 33-41 (2005)

5. J. M. Emmen & K. S. Korach: Estrogen receptor knockout mice: phenotypes in the female reproductive tract *Gynecol Endocrinol* 17, 169-176 (2003)

6. L. C. Layman & P. G. McDonough: Mutations of follicle stimulating hormone-beta and its receptor in human and mouse: genotype/phenotype *Mol Cell Endocrinol* 161, 9-17 (2000)

7. A. Dierich, M. R. Sairam, L. Monaco, G. M. Fimia, A. Gansmuller, M. LeMeur & P. Sassone-Corsi: Impairing follicle-stimulating hormone (FSH) signaling *in vivo*:

targeted disruption of the FSH receptor leads to aberrant gametogenesis and hormonal imbalance *Proc Natl Acad Sci U S A* 95, 13612-13617 (1998)
8. T. R. Kumar, Y. Wang, N. Lu & M. M. Matzuk: Follicle stimulating hormone is required for ovarian follicle maturation but not male fertility *Nat Genet* 15, 201-204 (1997)
9. R. Bachvarova: Gene expression during oogenesis and oocyte development in mammals *Dev Biol (N Y 1985)* 1, 453-524 (1985)
10. F. Brambell: The development and morphology of the gonads of the mouse. Part III. The growth of the follicles. *Proc. R. Soc. Lond. (Biol.)* 103, 258-272 (1928)
11. O. Anderson, J. Heasman & C. Wylie: Early events in the mammalian germ line *Int Rev Cytol* 203, 215-230 (2001)
12. A. N. Hirshfield: Relationship between the supply of primordial follicles and the onset of follicular growth in rats *Biol Reprod* 50, 421-428 (1994)
13. S. Mazaud, C. J. Guigon, A. Lozach, N. Coudouel, M. G. Forest, H. Coffigny & S. Magre: Establishment of the reproductive function and transient fertility of female rats lacking primordial follicle stock after fetal gamma-irradiation *Endocrinology* 143, 4775-4787 (2002)
14. M. Di Giacomo, M. Barchi, F. Baudat, W. Edelmann, S. Keeney & M. Jasin: Distinct DNA-damage-dependent and -independent responses drive the loss of oocytes in recombination-defective mouse mutants *Proc Natl Acad Sci U S A* 102, 737-742 (2005)
15. M. Uda, C. Ottolenghi, L. Crisponi, J. E. Garcia, M. Deiana, W. Kimber, A. Forabosco, A. Cao, D. Schlessinger & G. Pilia: Foxl2 disruption causes mouse ovarian failure by pervasive blockage of follicle development *Hum Mol Genet* 13, 1171-1181 (2004)
16. F. Baudat, K. Manova, J. P. Yuen, M. Jasin & S. Keeney: Chromosome synapsis defects and sexually dimorphic meiotic progression in mice lacking Spo11 *Mol Cell* 6, 989-998 (2000)
17. D. L. Pittman, J. Cobb, K. J. Schimenti, L. A. Wilson, D. M. Cooper, E. Brignull, M. A. Handel & J. C. Schimenti: Meiotic prophase arrest with failure of chromosome synapsis in mice deficient for Dmc1, a germline-specific RecA homolog *Mol Cell* 1, 697-705 (1998)
18. S. S. de Vries, E. B. Baart, M. Dekker, A. Siezen, D. G. de Rooij, P. de Boer & H. te Riele: Mouse MutS-like protein Msh5 is required for proper chromosome synapsis in male and female meiosis *Genes Dev* 13, 523-531 (1999)
19. B. Kneitz, P. E. Cohen, E. Avdievich, L. Zhu, M. F. Kane, H. Hou, Jr., R. D. Kolodner, R. Kucherlapati, J. W. Pollard & W. Edelmann: MutS homolog 4 localization to meiotic chromosomes is required for chromosome pairing during meiosis in male and female mice *Genes Dev* 14, 1085-1097 (2000)
20. L. M. Woods, C. A. Hodges, E. Baart, S. M. Baker, M. Liskay & P. A. Hunt: Chromosomal influence on meiotic spindle assembly: abnormal meiosis I in female Mlh1 mutant mice *J Cell Biol* 145, 1395-1406 (1999)
21. Y. Xu, T. Ashley, E. E. Brainerd, R. T. Bronson, M. S. Meyn & D. Baltimore: Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma *Genes Dev* 10, 2411-2422 (1996)
22. S. M. Baker, A. W. Plug, T. A. Prolla, C. E. Bronner, A. C. Harris, X. Yao, D. M. Christie, C. Monell, N. Arnheim, A. Bradley, T. Ashley & R. M. Liskay: Involvement of mouse Mlh1 in DNA mismatch repair and meiotic crossing over *Nat Genet* 13, 336-342 (1996)
23. I. M. Joyce, A. T. Clark, F. L. Pendola & J. J. Eppig: Comparison of recombinant growth differentiation factor-9 and oocyte regulation of KIT ligand messenger ribonucleic acid expression in mouse ovarian follicles *Biol Reprod* 63, 1669-1675 (2000)
24. J. Seligman & D. C. Page: The Dazh gene is expressed in male and female embryonic gonads before germ cell sex differentiation *Biochem Biophys Res Commun* 245, 878-882 (1998)
25. V. Brekhman, J. Itskovitz-Eldor, E. Yodko, M. Deutsch & J. Seligman: The DAZL1 gene is expressed in human male and female embryonic gonads before meiosis *Mol Hum Reprod* 6, 465-468 (2000)
26. M. Ruggiu, R. Speed, M. Taggart, S. J. McKay, F. Kilanowski, P. Saunders, J. Dorin & H. J. Cooke: The mouse Dazla gene encodes a cytoplasmic protein essential for gametogenesis *Nature* 389, 73-77 (1997)
27. S. M. Soyal, A. Amleh & J. Dean: FIGalpha, a germ cell-specific transcription factor required for ovarian follicle formation *Development* 127, 4645-4654 (2000)
28. L. Liang, S. M. Soyal & J. Dean: FIGalpha, a germ cell specific transcription factor involved in the coordinate expression of the zona pellucida genes *Development* 124, 4939-4947 (1997)
29. L. Doneda, F. G. Klinger, L. Larizza & M. De Felici: KL/KIT co-expression in mouse fetal oocytes *Int J Dev Biol* 46, 1015-1021 (2002)
30. E. Nilsson, J. A. Parrott & M. K. Skinner: Basic fibroblast growth factor induces primordial follicle development and initiates folliculogenesis *Mol Cell Endocrinol* 175, 123-130 (2001)
31. E. E. Nilsson & M. K. Skinner: Kit ligand and basic fibroblast growth factor interactions in the induction of ovarian primordial to primary follicle transition *Mol Cell Endocrinol* 214, 19-25 (2004)
32. N. Suzumori, C. Yan, M. M. Matzuk & A. Rajkovic: Nobox is a homeobox-encoding gene preferentially expressed in primordial and growing oocytes *Mech Dev* 111, 137-141 (2002)
33. A. Rajkovic, S. A. Pangas, D. Ballow, N. Suzumori & M. M. Matzuk: NOBOX deficiency disrupts early folliculogenesis and oocyte-specific gene expression *Science* 305, 1157-1159 (2004)
34. J. A. Elvin, C. Yan & M. M. Matzuk: Oocyte-expressed TGF-beta superfamily members in female fertility *Mol Cell Endocrinol* 159, 1-5 (2000)
35. S. A. McGrath, A. F. Esquela & S. J. Lee: Oocyte-specific expression of growth/differentiation factor-9 *Mol Endocrinol* 9, 131-136 (1995)
36. J. Dong, D. F. Albertini, K. Nishimori, T. R. Kumar, N. Lu & M. M. Matzuk: Growth differentiation factor-9 is required during early ovarian folliculogenesis *Nature* 383, 531-535 (1996)
37. C. Yan, P. Wang, J. DeMayo, F. J. DeMayo, J. A. Elvin, C. Carino, S. V. Prasad, S. S. Skinner, B. S. Dunbar, J. L. Dube, A. J. Celeste & M. M. Matzuk: Synergistic roles of bone morphogenetic protein 15 and growth

differentiation factor 9 in ovarian function *Mol Endocrinol* 15, 854-866 (2001)
38. K. P. McNatty, L. G. Moore, N. L. Hudson, L. D. Quirke, S. B. Lawrence, K. Reader, J. P. Hanrahan, P. Smith, N. P. Groome, M. Laitinen, O. Ritvos & J. L. Juengel: The oocyte and its role in regulating ovulation rate: a new paradigm in reproductive biology *Reproduction* 128, 379-386 (2004)
39. G. H. Shackell, N. L. Hudson, D. A. Heath, S. Lun, L. Shaw, L. Condell, L. R. Blay & K. P. McNatty: Plasma gonadotropin concentrations and ovarian characteristics in Inverdale ewes that are heterozygous for a major gene (FecX1) on the X chromosome that influences ovulation rate *Biol Reprod* 48, 1150-1156 (1993)
40. F. Otsuka, S. Yamamoto, G. F. Erickson & S. Shimasaki: Bone morphogenetic protein-15 inhibits follicle-stimulating hormone (FSH) action by suppressing FSH receptor expression *J Biol Chem* 276, 11387-11392 (2001)
41. A. M. Simon, D. A. Goodenough, E. Li & D. L. Paul: Female infertility in mice lacking connexin 37 *Nature* 385, 525-529 (1997)
42. D. A. Goodenough, J. A. Goliger & D. L. Paul: Connexins, connexons, and intercellular communication *Annu Rev Biochem* 65, 475-502 (1996)
43. T. Fair, S. C. Hulshof, P. Hyttel, T. Greve & M. Boland: Oocyte ultrastructure in bovine primordial to early tertiary follicles *Anat Embryol (Berl)* 195, 327-336 (1997)
44. E. Anderson & D. F. Albertini: Gap junctions between the oocyte and companion follicle cells in the mammalian ovary *J Cell Biol* 71, 680-686 (1976)
45. R. A. Taft, J. M. Denegre, F. L. Pendola & J. J. Eppig: Identification of genes encoding mouse oocyte secretory and transmembrane proteins by a signal sequence trap *Biol Reprod* 67, 953-960 (2002)
46. A. I. den Hollander, M. Ghiani, Y. J. de Kok, J. Wijnholds, A. Ballabio, F. P. Cremers & V. Broccoli: Isolation of Crb1, a mouse homologue of Drosophila crumbs, and analysis of its expression pattern in eye and brain *Mech Dev* 110, 203-207 (2002)
47. C. Stayner & J. Zhou: Polycystin channels and kidney disease *Trends Pharmacol Sci* 22, 543-546 (2001)
48. V. Horejsi, K. Drbal, M. Cebecauer, J. Cerny, T. Brdicka, P. Angelisova & H. Stockinger: GPI-microdomains: a role in signalling via immunoreceptors *Immunol Today* 20, 356-361 (1999)
49. H. Picton, D. Briggs & R. Gosden: The molecular basis of oocyte growth and development *Mol Cell Endocrinol* 145, 27-37 (1998)
50. G. Kaplan, S. L. Abreu & R. Bachvarova: rRNA accumulation and protein synthetic patterns in growing mouse oocytes *J Exp Zool* 220, 361-370 (1982)
51. P. M. Wassarman & R. A. Kinloch: Gene expression during oogenesis in mice *Mutat Res* 296, 3-15 (1992)
52. R. F. Bachvarova: A maternal tail of poly(A): the long and the short of it *Cell* 69, 895-897 (1992)
53. B. V. Paynton, R. Rempel & R. Bachvarova: Changes in state of adenylation and time course of degradation of maternal mRNAs during oocyte maturation and early embryonic development in the mouse *Dev Biol* 129, 304-314 (1988)
54. J. Yu, N. B. Hecht & R. M. Schultz: Expression of MSY2 in mouse oocytes and preimplantation embryos *Biol Reprod* 65, 1260-1270 (2001)
55. A. Tsafriri, M. E. Lieberman, A. Barnea, S. Bauminger & H. R. Lindner: Induction by luteinizing hormone of ovum maturation and of steroidogenesis in isolated Graafian follicles of the rat: role of RNA and protein synthesis *Endocrinology* 93, 1378-1386 (1973)
56. J. J. Eppig: The participation of cyclic adenosine monophosphate (cAMP) in the regulation of meiotic maturation of oocytes in the laboratory mouse *J Reprod Fertil Suppl* 38, 3-8 (1989)
57. S. M. Downs, P. G. Humpherson, K. L. Martin & H. J. Leese: Glucose utilization during gonadotropin-induced meiotic maturation in cumulus cell-enclosed mouse oocytes *Mol Reprod Dev* 44, 121-131 (1996)
58. K. F. Rodriguez, R. M. Petters, A. E. Crosier & C. E. Farin: Roles of gene transcription and PKA subtype activation in maturation of murine oocytes *Reproduction* 123, 799-806 (2002)
59. S. M. Downs & M. Hunzicker-Dunn: Differential regulation of oocyte maturation and cumulus expansion in the mouse oocyte-cumulus cell complex by site-selective analogs of cyclic adenosine monophosphate *Dev Biol* 172, 72-85 (1995)
60. R. J. Webb, F. Marshall, K. Swann & J. Carroll: Follicle-stimulating hormone induces a gap junction-dependent dynamic change in [cAMP] and protein kinase a in mammalian oocytes *Dev Biol* 246, 441-454 (2002)
61. T. Tokumoto, M. Yamashita, M. Tokumoto, Y. Katsu, R. Horiguchi, H. Kajiura & Y. Nagahama: Initiation of cyclin B degradation by the 26S proteasome upon egg activation *J Cell Biol* 138, 1313-1322 (1997)
62. J. Mitra & R. M. Schultz: Regulation of the acquisition of meiotic competence in the mouse: changes in the subcellular localization of cdc2, cyclin B1, cdc25C and wee1, and in the concentration of these proteins and their transcripts *J Cell Sci* 109 (Pt 9), 2407-2415 (1996)
63. T. Choi, F. Aoki, M. Mori, M. Yamashita, Y. Nagahama & K. Kohmoto: Activation of p34cdc2 protein kinase activity in meiotic and mitotic cell cycles in mouse oocytes and embryos *Development* 113, 789-795 (1991)
64. T. Jung, R. M. Moor & J. Fulka, Jr.: Kinetics of MPF and histone H1 kinase activity differ during the G2- to M-phase transition in mouse oocytes *Int J Dev Biol* 37, 595-600 (1993)
65. M. Tanaka, J. D. Hennebold, J. Macfarlane & E. Y. Adashi: A mammalian oocyte-specific linker histone gene H1oo: homology with the genes for the oocyte-specific cleavage stage histone (cs-H1) of sea urchin and the B4/H1M histone of the frog *Development* 128, 655-664 (2001)
66. B. Leader, H. Lim, M. J. Carabatsos, A. Harrington, J. Ecsedy, D. Pellman, R. Maas & P. Leder: Formin-2, polyploidy, hypofertility and positioning of the meiotic spindle in mouse oocytes *Nat Cell Biol* 4, 921-928 (2002)
67. B. Leader & P. Leder: Formin-2, a novel formin homology protein of the cappuccino subfamily, is highly expressed in the developing and adult central nervous system *Mech Dev* 93, 221-231 (2000)
68. H. A. Homer, A. McDougall, M. Levasseur, K. Yallop, A. P. Murdoch & M. Herbert: Mad2 prevents aneuploidy and premature proteolysis of cyclin B and securin during meiosis I in mouse oocytes *Genes Dev* 19, 202-207 (2005)

69. M. Dobles, V. Liberal, M. L. Scott, R. Benezra & P. K. Sorger: Chromosome missegregation and apoptosis in mice lacking the mitotic checkpoint protein Mad2 *Cell* 101, 635-645 (2000)
70. P. Kalitsis, E. Earle, K. J. Fowler & K. H. Choo: Bub3 gene disruption in mice reveals essential mitotic spindle checkpoint function during early embryogenesis *Genes Dev* 14, 2277-2282 (2000)
71. E. Ledan, Z. Polanski, M. E. Terret & B. Maro: Meiotic maturation of the mouse oocyte requires an equilibrium between cyclin B synthesis and degradation *Dev Biol* 232, 400-413 (2001)
72. Y. Masui & C. L. Markert: Cytoplasmic control of nuclear behavior during meiotic maturation of frog oocytes *J Exp Zool* 177, 129-145 (1971)
73. N. Hashimoto, N. Watanabe, Y. Furuta, H. Tamemoto, N. Sagata, M. Yokoyama, K. Okazaki, M. Nagayoshi, N. Takeda, Y. Ikawa & *et al.*: Parthenogenetic activation of oocytes in c-mos-deficient mice *Nature* 370, 68-71 (1994)
74. M. H. Kim, X. Yuan, S. Okumura & F. Ishikawa: Successful inactivation of endogenous Oct-3/4 and c-mos genes in mouse preimplantation embryos and oocytes using short interfering RNAs *Biochem Biophys Res Commun* 296, 1372-1377 (2002)
75. W. H. Colledge, M. B. Carlton, G. B. Udy & M. J. Evans: Disruption of c-mos causes parthenogenetic development of unfertilized mouse eggs *Nature* 370, 65-68 (1994)
76. F. Gebauer & J. D. Richter: Synthesis and function of Mos: the control switch of vertebrate oocyte meiosis *Bioessays* 19, 23-28 (1997)
77. Q. Y. Sun, H. Breitbart & H. Schatten: Role of the MAPK cascade in mammalian germ cells *Reprod Fertil Dev* 11, 443-450 (1999)
78. C. Tong, H. Y. Fan, Y. Chen da, X. F. Song, H. Schatten & Q. Y. Sun: Effects of MEK inhibitor U0126 on meiotic progression in mouse oocytes: microtuble organization, asymmetric division and metaphase II arrest *Cell Res* 13, 375-383 (2003)
79. H. Y. Fan & Q. Y. Sun: Involvement of mitogen-activated protein kinase cascade during oocyte maturation and fertilization in mammals *Biol Reprod* 70, 535-547 (2004)
80. J. D. Bleil & P. M. Wassarman: Structure and function of the zona pellucida: identification and characterization of the proteins of the mouse oocyte's zona pellucida *Dev Biol* 76, 185-202 (1980)
81. T. Rankin, P. Talbot, E. Lee & J. Dean: Abnormal zonae pellucidae in mice lacking ZP1 result in early embryonic loss *Development* 126, 3847-3855 (1999)
82. T. L. Rankin, M. O'Brien, E. Lee, K. Wigglesworth, J. Eppig & J. Dean: Defective zonae pellucidae in Zp2-null mice disrupt folliculogenesis, fertility and development *Development* 128, 1119-1126 (2001)
83. T. Rankin, M. Familari, E. Lee, A. Ginsberg, N. Dwyer, J. Blanchette-Mackie, J. Drago, H. Westphal & J. Dean: Mice homozygous for an insertional mutation in the Zp3 gene lack a zona pellucida and are infertile *Development* 122, 2903-2910 (1996)
84. K. Miyado, G. Yamada, S. Yamada, H. Hasuwa, Y. Nakamura, F. Ryu, K. Suzuki, K. Kosai, K. Inoue, A. Ogura, M. Okabe & E. Mekada: Requirement of CD9 on the egg plasma membrane for fertilization *Science* 287, 321-324 (2000)
85. Z. B. Tong, L. Gold, K. E. Pfeifer, H. Dorward, E. Lee, C. A. Bondy, J. Dean & L. M. Nelson: Mater, a maternal effect gene required for early embryonic development in mice *Nat Genet* 26, 267-268 (2000)
86. J. Dean: Oocyte-specific genes regulate follicle formation, fertility and early mouse development *J Reprod Immunol* 53, 171-180 (2002)
87. E. Christians, A. A. Davis, S. D. Thomas & I. J. Benjamin: Maternal effect of Hsf1 on reproductive success *Nature* 407, 693-694 (2000)
88. C. Y. Howell, T. H. Bestor, F. Ding, K. E. Latham, C. Mertineit, J. M. Trasler & J. R. Chaillet: Genomic imprinting disrupted by a maternal effect mutation in the Dnmt1 gene *Cell* 104, 829-838 (2001)
89. X. Wu, M. M. Viveiros, J. J. Eppig, Y. Bai, S. L. Fitzpatrick & M. M. Matzuk: Zygote arrest 1 (Zar1) is a novel maternal-effect gene critical for the oocyte-to-embryo transition *Nat Genet* 33, 187-191 (2003)
90. K. H. Burns, M. M. Viveiros, Y. Ren, P. Wang, F. J. DeMayo, D. E. Frail, J. J. Eppig & M. M. Matzuk: Roles of NPM2 in chromatin and nucleolar organization in oocytes and embryos *Science* 300, 633-636 (2003)
91. Z. B. Tong, L. Gold, A. De Pol, K. Vanevski, H. Dorward, P. Sena, C. Palumbo, C. A. Bondy & L. M. Nelson: Developmental expression and subcellular localization of mouse MATER, an oocyte-specific protein essential for early development *Endocrinology* 145, 1427-1434 (2004)
92. B. Oh, S. Y. Hwang, D. Solter & B. B. Knowles: Spindlin, a major maternal transcript expressed in the mouse during the transition from oocyte to embryo *Development* 124, 493-503 (1997)
93. N. Minami, A. Aizawa, R. Ihara, M. Miyamoto, A. Ohashi & H. Imai: Oogenesin is a novel mouse protein expressed in oocytes and early cleavage-stage embryos *Biol Reprod* 69, 1736-1742 (2003)
94. X. Xiao, X. Zuo, A. A. Davis, D. R. McMillan, B. B. Curry, J. A. Richardson & I. J. Benjamin: HSF1 is required for extra-embryonic development, postnatal growth and protection during inflammatory responses in mice *Embo J* 18, 5943-5952 (1999)
95. T. M. DeChiara, E. J. Robertson & A. Efstratiadis: Parental imprinting of the mouse insulin-like growth factor II gene *Cell* 64, 849-859 (1991)
96. M. M. Lau, C. E. Stewart, Z. Liu, H. Bhatt, P. Rotwein & C. L. Stewart: Loss of the imprinted IGF2/cation-independent mannose 6-phosphate receptor results in fetal overgrowth and perinatal lethality *Genes Dev* 8, 2953-2963 (1994)
97. F. Guillemot, T. Caspary, S. M. Tilghman, N. G. Copeland, D. J. Gilbert, N. A. Jenkins, D. J. Anderson, A. L. Joyner, J. Rossant & A. Nagy: Genomic imprinting of Mash2, a mouse gene required for trophoblast development *Nat Genet* 9, 235-242 (1995)
98. Y. Marahrens, B. Panning, J. Dausman, W. Strauss & R. Jaenisch: Xist-deficient mice are defective in dosage compensation but not spermatogenesis *Genes Dev* 11, 156-166 (1997)
99. C. Walsh, A. Glaser, R. Fundele, A. Ferguson-Smith, S. Barton, M. A. Surani & R. Ohlsson: The non-viability

of uniparental mouse conceptuses correlates with the loss of the products of imprinted genes *Mech Dev* 46, 55-62 (1994)
100. H. Sasaki, P. A. Jones, J. R. Chaillet, A. C. Ferguson-Smith, S. C. Barton, W. Reik & M. A. Surani: Parental imprinting: potentially active chromatin of the repressed maternal allele of the mouse insulin-like growth factor II (Igf2) gene *Genes Dev* 6, 1843-1856 (1992)
101. T. Kaneko-Ishino, Y. Kuroiwa, N. Miyoshi, T. Kohda, R. Suzuki, M. Yokoyama, S. Viville, S. C. Barton, F. Ishino & M. A. Surani: Peg1/Mest imprinted gene on chromosome 6 identified by cDNA subtraction hybridization *Nat Genet* 11, 52-59 (1995)
102. Y. Obata, T. Kaneko-Ishino, T. Koide, Y. Takai, T. Ueda, I. Domeki, T. Shiroishi, F. Ishino & T. Kono: Disruption of primary imprinting during oocyte growth leads to the modified expression of imprinted genes during embryogenesis *Development* 125, 1553-1560 (1998)
103. R. Feil & S. Khosla: Genomic imprinting in mammals: an interplay between chromatin and DNA methylation? *Trends Genet* 15, 431-435 (1999)
104. A. Razin & H. Cedar: DNA methylation and genomic imprinting *Cell* 77, 473-476 (1994)
105. A. S. Doherty, M. R. Mann, K. D. Tremblay, M. S. Bartolomei & R. M. Schultz: Differential effects of culture on imprinted H19 expression in the preimplantation mouse embryo *Biol Reprod* 62, 1526-1535 (2000)
106. M. R. Mann, S. S. Lee, A. S. Doherty, R. I. Verona, L. D. Nolen, R. M. Schultz & M. S. Bartolomei: Selective loss of imprinting in the placenta following preimplantation development in culture *Development* 131, 3727-3735 (2004)
107. F. Zeng, D. A. Baldwin & R. M. Schultz: Transcript profiling during preimplantation mouse development *Dev Biol* 272, 483-496 (2004)
108. M. Vallee, C. Gravel, M. F. Palin, H. Reghenas, P. Stothard, D. S. Wishart & M. A. Sirard: Identification of Novel and Known Oocyte-Specific Genes Using Complementary DNA Subtraction and Microarray Analysis in Three Different Species *Biol Reprod* (2005)
109. F. Zeng & R. M. Schultz: Gene expression in mouse oocytes and preimplantation embryos: use of suppression subtractive hybridization to identify oocyte- and embryo-specific genes *Biol Reprod* 68, 31-39 (2003)
110. A. Rajkovic, M. S. C. Yan, M. Klysik & M. Matzuk: Discovery of germ cell-specific transcripts by expressed sequence tag database analysis *Fertil Steril* 76, 550-554 (2001)
111. H. A. Pan, S. J. Tsai, C. W. Chen, Y. C. Lee, Y. M. Lin & P. L. Kuo: Expression of DAZL protein in the human corpus luteum *Mol Hum Reprod* 8, 540-545 (2002)
112. J. A. Arraztoa, J. Zhou, D. Marcu, C. Cheng, R. Bonner, M. Chen, C. Xiang, M. Brownstein, K. Maisey, M. Imarai & C. Bondy: Identification of genes expressed in primate primordial oocytes *Hum Reprod* 20, 476-483 (2005)

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