Reproductive Medicine and Biology 2006; **5**: 175–182 doi: 10.1111/j.1447-0578.2006.00139.x

Review Article

Role of oocyte-specific genes in the development of mammalian embryos

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Studies on oocyte-specific genes are important in understanding the genetic pathways essential for folliculogenesis, oogenesis and early embryogenesis. Although the molecular mechanisms regulating oocyte growth and embryo development in mammals have partially been unraveled by gene knockout studies, many aspects concerning reproduction remain to be determined. Development of mammalian embryos starts with the fusion of sperm and egg. After fertilization, the first major developmental transition, maternal to zygotic transition, occurs at the specific stages of preimplantation development in each mammal. The transition is called zygotic gene activation (ZGA) or embryonic genome activation. The ZGA is one of the most important events that occur during preimplantation development; however, the mechanism of the event remains unknown. Because the development until the transition is maintained by maternally inherited proteins and transcripts stored in the oocytes, it is highly likely that these products play an important role in the initiation of ZGA. Several maternal-effects genes that are specifically expressed in oocytes have been identified and their involvement in preimplantation development has been revealed. Therefore, to study oocyte-specific gene regulation would help not only to understand the precise mechanisms of mammalian development, but also to show the mechanisms of reproductive disorders, such as premature ovarian failure and infertility. (Reprod Med Biol 2006; **5**: 175–182)

Key words: embryo development, maternal-effect gene, oocyte-specific gene, oog1, oogenesis.

INTRODUCTION

DEVELOPMENT OF MAMMALIAN embryos has been studied for more than 50 years.[1] The culture of mammalian embryos has been intensively examined in mice. The studies have lead to the successful *in vitro* culture of embryos, however, the precise mechanism of mammalian development has not yet been elucidated.

The development of one-cell mouse embryos, except for embryos of some inbred strains and their F1 hybrids, is blocked at the two-cell stage, a phenomenon that has been termed 'the two-cell block'.[2–4] Cross-breeding experiments have shown that maternally inherited developmental information plays an important role in controlling early cleavage of the mouse embryo.[3] In addition, the transfer of cytoplasm from non-blocked embryos into blocked embryos recovers the developmental competence of two-cell embryos *in vitro*.[5] These results suggest that the gene products such as mRNAs and/or proteins stored in oocytes play important roles in the development of embryos. The developmental arrest *in vitro* can be overcome by modifying the culture conditions; the addition of ethylenediaminetetracetic acid (EDTA)[6,7] and deletion of phosphate[8] can eliminate the developmental arrest *in vitro*. It has also been shown that isolated mouse ampulla maintained in organ culture can overcome the two-cell block in the mouse[9] and hamster.[10] These observations indicate that the maternal factors involved in the embryonic development are closely associated with developmental environment. Therefore, to study the gene functions in oocytes provides information about the relationship between maternal factors and embryonic development in mammals.

In the present review, the role of oocyte-specific genes in early embryogenesis is discussed.

ZYGOTIC GENE ACTIVATION AND EMBRYO DEVELOPMENT IN MAMMALS

THE MATERNAL TO zygotic transition is the first major transition that occurs after fertilization. This developmental program is initially directed by maternally inherited proteins and transcripts, and the transcripts

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Received 30 March 2006; accepted 26 April 2006.

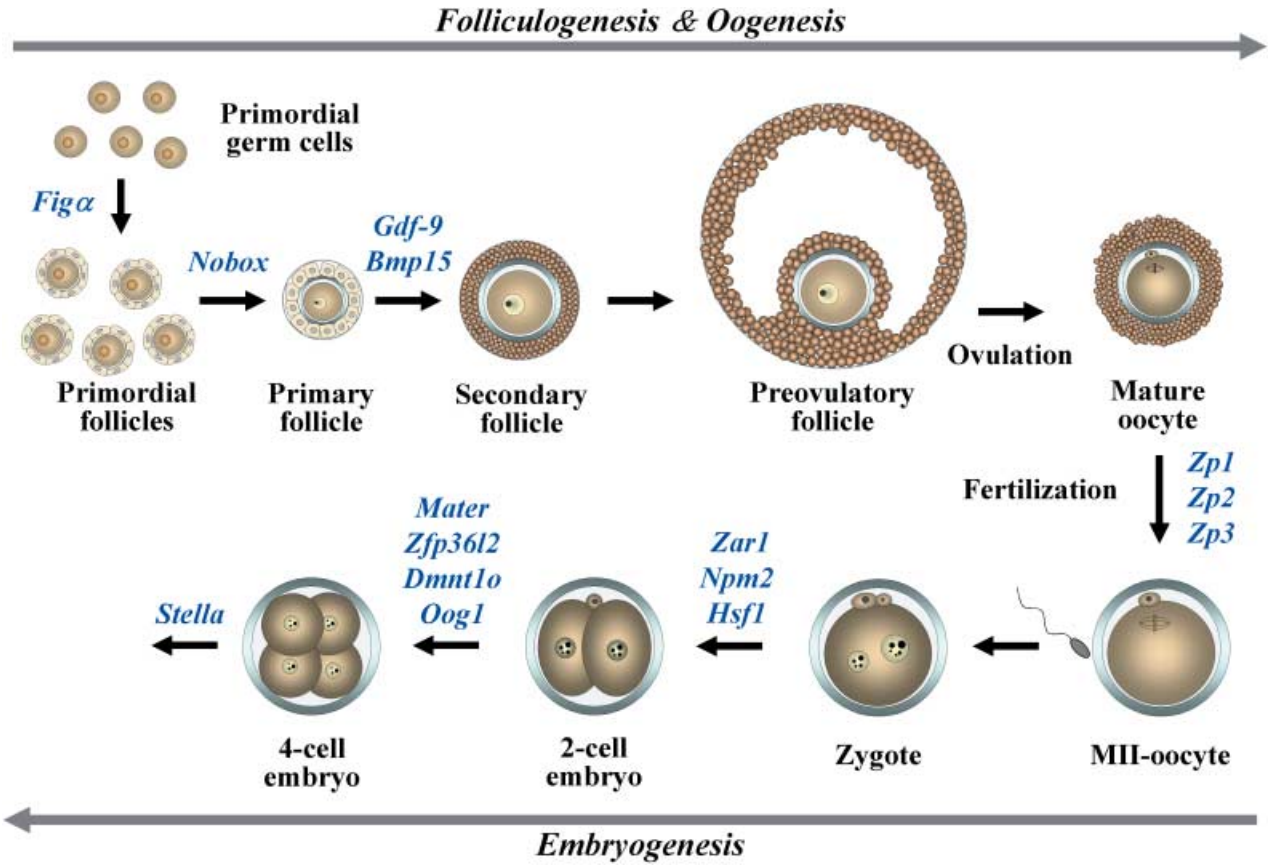

Figure 1 Summary of the expression of oocyte-specific genes involved in folliculogenesis, oogenesis and early embryogenesis.

are mostly replaced by newly synthesized ones. In mammals, zygotic gene activation (ZGA) has been shown to be a two-step process consisting of minor and major phases.[11] In the mouse, the minor ZGA phase is initiated at the late one-cell stage (G2 phase) with very weak transcriptional activity.[12–18] Consequently, some of the proteins are synthesized at the early two-cell stage (G1/S) for the next phase of ZGA, the major phase.[19–24] It has been reported that reporter genes microinjected into the pronuclei of one-cell mouse embryos are transcribed during the minor ZGA phase.[17,25–28] Because the translation of maternal RNA is required for the initiation of ZGA, the proteins stored in oocytes are utilized in the early event of transcription at the late one-cell stage.[29] The regulation of the initiation of the transcription and the following first mitotic events are mainly controlled by maternally inherited products. At the G2 phase of the second cell cycle, the major ZGA phase, which is characterized by an increase of transcriptional and translational activity, occurs and results in a dramatic change in the pattern of protein synthesis.[11,19,27,30–32] In many mammalian species, development of one-cell embryos is blocked at various early stages *in vitro*. It has been reported that the time of developmental arrest *in vitro* coincides with the time of ZGA,[33] suggesting that there might be a relationship between the developmental arrest in culture and transcriptional activity of embryos.

ROLE OF OOCYTE-SPECIFIC GENES

THE GENE PRODUCTS expressed specifically in oocytes play important roles in folliculogenesis, fertilization and preimplantation development (Fig. 1).[34] One of the most exciting molecules expressed in oocytes is a member of the transforming growth factor β (TGF-β) superfamily, growth differentiation factor 9 (*Gdf-9*), which is obligatory for proper folliculogenesis beyond the primary stage and fertility in female mice.[35–38] Another oocyte-specific member of TGF-β superfamily is bone morphogenetic protein 15 (*Bmp15*), which is a single copy gene on the X chromosome in mammals.[39] Ovarian

follicles in sheep homozygous *Bmp15* mutations do not normally grow beyond the primary follicle stage.[40,41] *Bmp15* null mice are phenotypically different from sheep and have minimal ovarian histopathological defects and smaller litter sizes than wild type mice.[42] Genes encoding several other growth factors are also expressed in mammalian oocytes: *Bmp6*,[43] *Tgf-β2*[44] and fibroblast growth factor 8 (*Fgf8*).[45] Recent studies have revealed key roles of the oocyte in folliculogenesis and have shown that bidirectional communication between the oocyte and somatic cells is essential for development of an egg so it can undergo fertilization and embryogenesis.[46,47] Although these growth factors and other unknown factors are known to be involved in folliculogenesis, many of their specific functions are not well characterized.

A factor in the germline, alpha (FIGα) is a basic helix-loop-helix (bHLH) transcription factor first detected in oocytes at 13.5 dpc. Female mice lacking *Figα* are unable to form primordial follicles which results in massive depletion of oocytes and sterility.[48] *Figα* has also been implicated in the coordinate expression of the three zona pellucida genes (*Zp1*, *Zp2*, *Zp3*) that encode the mouse egg coat.[49,50]

MATERNAL-EFFECT GENES IN EARLY DEVELOPMENT

DURING OOCYTE GROWTH and follicular development oocytes accumulate maternal-effect factors necessary for early embryogenesis, which occurs in the absence of de novo transcription of either parental genome (Fig. 1).[27] Maternal-effect genes, which are well documented in lower species such as *Drosophila melanogaster* and *Xenopus laevis*, encode transcripts or proteins in the egg during oogenesis that play pivotal roles after fertilization.[51,52] As described above, ZGA occurs at the 1- to two-cell stages and is a critical event that is indispensable for further embryonic development in mice.[25] It is speculated that several hundred genes participate in the activation,[53] indicating that some of the maternal-effect genes might be involved in the ZGA. However, relatively few maternal-effect genes have been identified in mammals. Until now, eight maternal-effect genes, such as *Mater*, *Hsf1*, *Dnmt1o*, *Pms2*, *Zar1*, *Npm2*, *stella* and *Zfp36l2* have been identified in mice, and knockout models of these genes have shown that many of the maternal-effect genes are involved in the early embryogenesis, especially at the 1- to two-cell stages.[54–61]

The maternal antigen that embryo required (MATER) was first identified as an ooplasm-specific protein encoded by a single-copy gene that is transcribed in growing oocytes.[62] Homozygous null *Mater* males and heterozygous females have normal fertility, although homozygous females are sterile. Although folliculogenesis, ovulation, fertilization and the first cleavage appear normal, early embryos lacking MATER are unable to progress beyond the two-cell stage.[60] Heat-shock factor-1 (*Hsf1*) was also identified as a maternal-effect gene. Embryos lacking HSF1 are blocked mainly at the one-cell stage and show ultrastructural abnormality in the nuclei at the two-cell stage.[55] Dnmt1o, an oocyte-specific DNA methyltransferase, maintains genomic methylation during preimplantation development.[57] Although DNMT1o accumulates in nuclei of early growing oocytes, but is sequestered in the cytoplasm of mature oocytes,[63] it is required for the maintenance of the methylation pattern specifically at the 8-cell stage.[57] *Pms2* has also been shown to act as a maternal-effect gene which functions in DNA mismatch repair.[56] Recently, oocyte-specific gene, *Zar1* (zygote arrest 1) and *Npm2* (nucleoplasmin 2) have been identified using subtractive hybridization.[54,64] Homozygous null *Zar1* female are sterile because the embryos from the female are arrested at the 1- to two-cell stage. ZAR1 is detected after resumption of meiosis, it persists in one-cell embryos and rapidly disappears at the two-cell stage, suggesting a critical role in the oocyte-to-embryo transition.[61] *Npm2* knockout females have fertility defects because of reduced cleavage to the two-cell stage. In *Npm2* null oocytes and zygotes, absence of coalesced nucleolar structures and loss of heterochromatin and deacetylated histone H3 are observed, suggesting that *Npm2* is critical for nuclear and nucleolar organization and embryonic development.[54] *Stella* is a germ cell-specific maternal-effect gene and embryos without STELLA are compromised in preimplantation development and rarely reach the blastocyst stage.[58] The effects of lack of STELLA become evident shortly after fertilization, with progressively fewer embryos exhibiting normal development during preimplantation stages. A SAP-like domain and a splicing factor motif-like structure of *Stella* suggest possible roles in chromosomal organization or RNA processing. Zinc finger protein 36 like 2 (*Zfp36l2*) is also reported to be one of the maternal-effect genes.[59] *Zfp36l2* null females apparently cycle and ovulate normally, and their ova can be fertilized; however, the embryos do not progress beyond the two-cell stage of development. ZFP36l2 belongs to an unusual family of zinc finger proteins containing tandem zinc-binding motifs characterized by three cysteines followed by one histidine (CCCH). Through this zinc finger, the protein can bind to mRNA containing class II AU-rich

elements; binding is then followed by degradation of the target mRNA.[65]

FUNCTION OF GERM CELL-SPECIFIC GENES IN GAMETOGENESIS

RECENTLY, NOVEL GENES that are specifically expressed in the ovary and testis have been reported. *Gasz* is one of the newly identified germ cell-specific genes, encoding a protein containing four ankyrin repeats (ANK), a sterile-alpha motif (SAM) and a basic leucine zipper (bZIP) domain.[66] Mouse *Gasz* is shown to be expressed in oocytes at all stages of oogenesis, pachytene spermatocytes, round spermatids and preimplantation embryos at the mRNA and protein revels. Therefore, it is likely that GASZ functions as a cytoplasmic signaling molecule in germ cells, because the protein has a motif that is important for protein–protein interaction. Furthermore, *Gasz* orthologs are present in rats, cows, baboons, chimpanzees and humans, indicating that the gene has an evolutionally conserved function in germ cell.[67]

Newborn ovary homeobox-encoding gene (NOBOX) is a transcription factor containing a homeobox domain.[68] *Nobox* is expressed in germ cell cysts, and in primordial and growing oocytes during folliculogenesis (Fig. 1). Lack of NOBOX accelerates postnatal oocyte loss and abolishes the transition from primordial to growing follicles in mice.[69] *Nobox*$^{-/-}$ mice also show a down-regulation of genes preferentially expressed in the oocyte including *Oct4*, *Mos*, *Rfpl4*, *Fgf8*, *Zar1*, *Dnmt1o*, *Bmp15*, *H1oo* and *Gdf9*, whereas ubiquitous genes such as *Bmp4*, *Kit* and *Bax* are unaffected. Thus, NOBOX might have a direct role in the regulation of the oocyte-specific gene expression during folliculogenesis, oogenesis and early embryogenesis.

ROLE OF AN OOCYTE-SPECIFIC GENE, OOG1 DURING MOUSE PREIMPLANTATION DEVELOPMENT

WE PREVIOUSLY IDENTIFIED an oocyte-specific novel gene, *Oogenesin* (*Oog1*), that encodes 326 amino acids containing a leucine zipper and a leucine rich repeat which appears to be necessary for protein–protein interactions.[70,71] More interestingly, OOG1 localized in the nuclei at late one-cell and early two-cell stages, the time when the zygotic genome activation occurs in mice. The zygotic genome activation relies on transcripts and proteins stored in the oocyte during oogenesis. However, the molecular mechanisms governing these events are largely unknown. Recently, another group identified three additional *Oog1*-like genes (*Oog2*, *3*, *4*) containing a leucine rich repeat, speculating that this family functions by mediating protein–protein interactions.[72] To identify the interacting proteins of OOG1, we carried out a yeast two-hybrid screening using a GV oocyte cDNA library and found that RAL guanine nucleotide dissociation stimulator (RALGDS) is the potential binding partner of OOG1.[73] RALGDS is one of the Ras effector proteins, exchanging a GDP-bound inactive state RAL to a GTP-bound active state RAL in a RAS-dependent manner.[74,75] We also showed that RAS-binding domain (RBD) of RALGDS is indispensable for the interaction with OOG1 and that OOG1 interact with activated RAS. It has been reported that the leucine-rich repeats binds to the GTP-binding motif of G-proteins.[76] It is probable that leucine-rich repeats of OOG1, GTP-binding motif of RAS and RBD of RALGDS play an important role in the interaction of these proteins. RALGDS transcript is detected in GV oocytes and pre-implantation embryos until the end of the four-cell stage and the protein is localized in the cytoplasm in oocytes and preimplantation embryos. Interestingly, the protein appears in the nucleus rather than the cytoplasm between late one-cell and late two-cell stages, suggesting that RALGDS-OOG1 complex is formed after the activation of RAS and functions in the nucleus of the one- to two-cell stage embryos.[73] In a colocalization experiment, it was shown that OOG1 expression is necessary for the nuclear localization of RALGDS in transfected HeLa cells. Because the expression profiles and localization of OOG1 and RALGDS are quite similar in the late one-cell and early two-cell stage embryos,[71,73] the interaction between OOG1 and RALGDS probably occurs in mouse embryos.

A NEW INSIGHT INTO GENE FUNCTION USING BIOFORMATICS

THE CURRENT DATABASES provide many kinds of biological information, including gene expression, gene mapping, DNA and protein sequences, and protein structure and function, for example: National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/), European Molecular Biology Laboratory (EMBL; http://www.ebi.ac.uk/embl/) and DNA Data Bank of Japan (DDBJ; http://www.ddbj.nig.ac.jp/Welcome-j.html). Furthermore, programs designed to search these databases, such as BLAST (http://www.ncbi.nlm.nih.gov/blast), are helpful for scientists using these large data sets. Therefore, the combined use

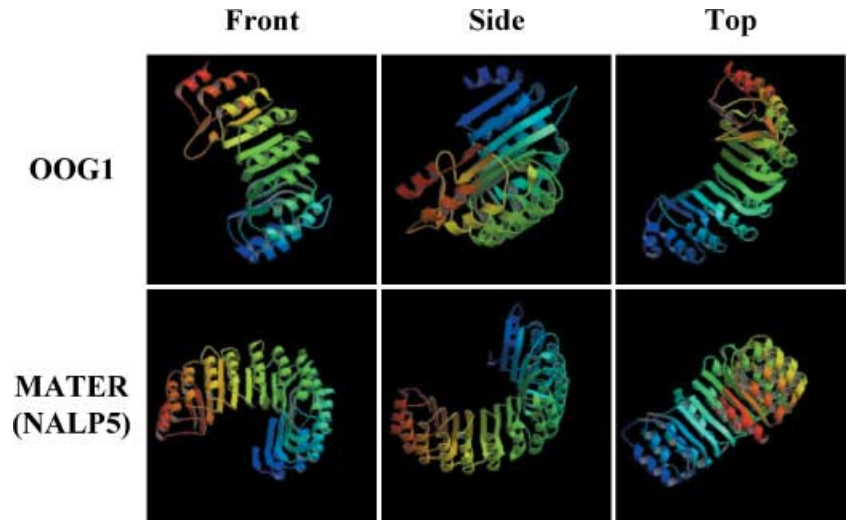

Figure 2 3D structures of OOG1 and MATER/NALP5. The structures of OOG1 and MATER were predicted by Modbase using the March 2005 mouse (*Mus musculus*) draft genome data and the August 2005 mouse draft genome data, respectively.

of molecular genetics and bioinformatics is a powerful approach to investigate the function of the gene of interest.

Recently, it has been reported by the *in silico* approach that some of the oocyte-specific genes, including *Oogenesin* and *Mater* (also known as *Nalp5*), are organized in clusters to map near the chromosome ends.[72,77,78] Although most oocyte-specific genes organized in clusters are paralogous genes, they seem to have individual biological roles, that is, *Nalp9A-F* that are clustered at vicinity regions of *Nalp5* are not able to compensate the absence of *Mater* product in *Mater* (*Nalp5*)$^{-/-}$ mice.[60,77] Interestingly, using the Genome Browser of UCSC Genome Bioinformatics (http://genome.ucsc.edu/cgi-bin/hgGateway), we found that the MATER and OOG1 share a similar tertiary structure (Fig. 2). Because a MATER lacking-embryo is unable to progress beyond the two-cell stage,[73] OOG1 might have the same function as well as MATER during early embryogenesis.

CONCLUSIONS

IDENTIFICATION AND CHARACTERIZATION of genes preferentially expressed in oocytes would be extremely useful in unraveling their oocyte specific functions in oogenesis, folliculogenesis, fertilization and early embryogenesis. Therefore, understanding the biological functions of oocyte-specific genes using genetics, genomics, proteomics and bioinformatics would help to accelerate the elucidation of the mechanisms involved in mammalian development.

ACKNOWLEDGMENTS

THE PRESENT WORK was supported in part by a Grants-in-Aid for Scientific Research (No. 16380187) from the Japan Society for the Promotion of Science and a grant from The INAMORI foundation to N. M.

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