



Maternal effect factors that contribute to oocytes developmental competence: an update

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Abstract

Oocyte developmental competence is defined as the capacity of the female gamete to be fertilized and sustain development to the blastocyst stage. Epigenetic reprogramming, a correct cell division pattern, and an efficient DNA damage response are all critical events that, before embryonic genome activation, are governed by maternally inherited factors such as maternal-effect gene (MEG) products. Although these molecules are stored inside the oocyte until ovulation and exert their main role during fertilization and preimplantation development, some of them are already functioning during folliculogenesis and oocyte meiosis resumption. This mini review summarizes the crucial roles played by MEGs during oocyte maturation, fertilization, and preimplantation development with a direct/indirect effect on the acquisition or maintenance of oocyte competence. Our aim is to inspire future research on a topic with potential clinical perspectives for the prediction and treatment of female infertility.

Keywords Maternal effect genes · Folliculogenesis · Oocyte competence · Embryonic genome activation · Preimplantation development

Introduction

Oocyte developmental competence is the capacity of a mature female gamete to be fertilized and sustain the initial phases of embryonic development until the blastocyst stage [1–3].

During folliculogenesis, many factors contribute to the production of a good quality oocyte, and abnormalities in this process lead to infertility and recurrent failure of assisted reproductive technologies (ART). Infertility is a pathology affecting up to 15% of couples worldwide [4], with 40% of

the causes that might be either maternal or paternal, and 20% attributed to both partners [5, 6]. Regardless of the main causes of infertility, adverse reproductive outcomes in humans are mainly due to advanced maternal age, because of its well-known double impact: the progressive depletion of the ovarian reserve and a heavier insult on oocyte quality. This impact mainly results in an exponential increase in the blastocyst aneuploidy rates especially beyond the age of 35 [7]. Nevertheless, oocyte quality is not defined only based on its euploid chromosomal constitution, but also by several other aspects that concur to its capacity to reach the blastocyst stage and implant. For instance, critical roles are covered by mechanisms ensuring correct (i) epigenetic reprogramming, (ii) cell division pattern, and (iii) DNA damage response. Before embryonic genome activation (EGA), all these events are governed by maternally inherited factors, which are carried by the oocyte and inevitably affect embryo competence downstream. These factors encompass several maternal-effect gene (MEG) products transcribed during folliculogenesis by the oocyte itself or its surrounding follicle cells through a tightly regulated bidirectional communication. Although MEGs are stored inside the oocyte during its growth [8] and exert their main role during fertilization and

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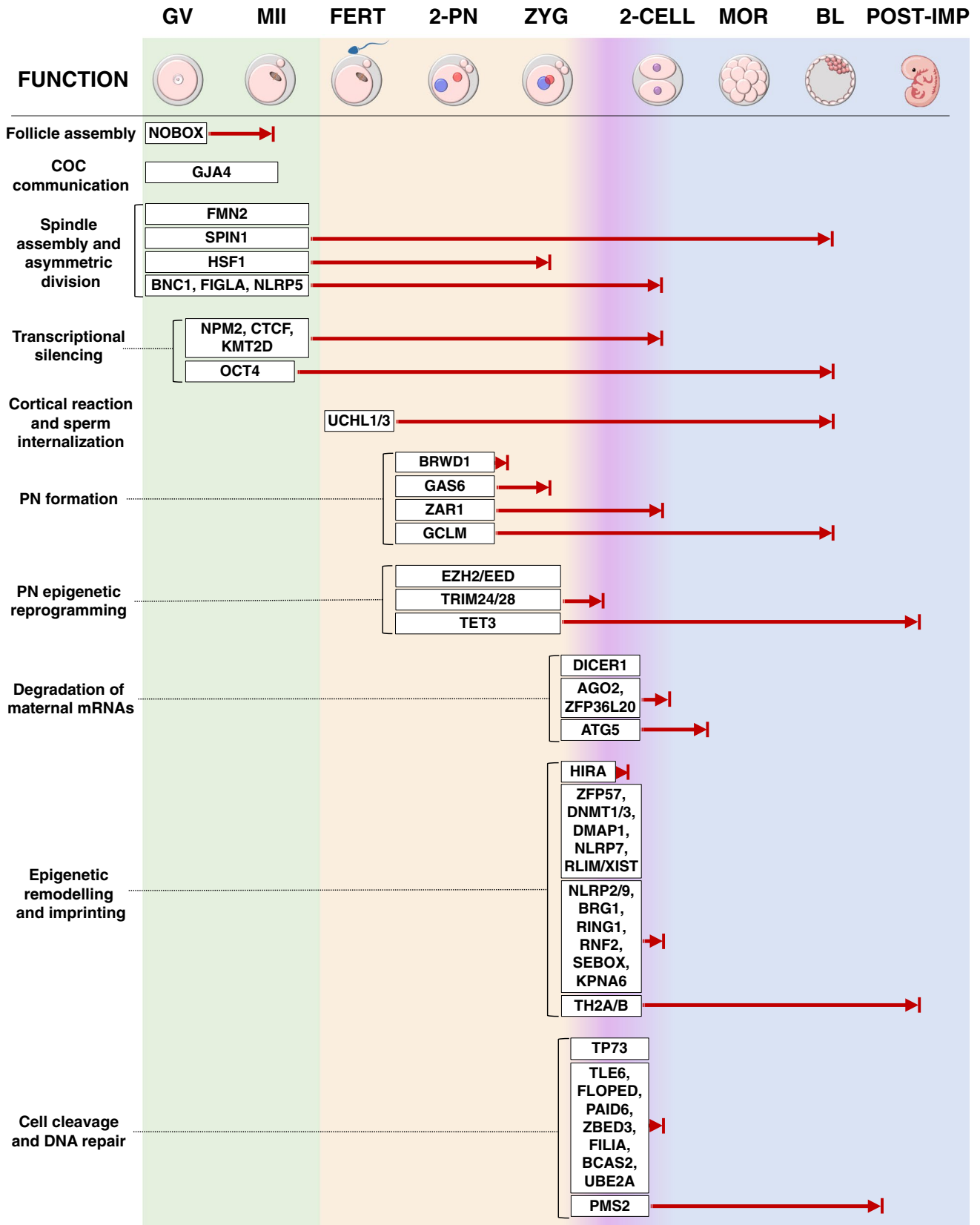


Fig. 1 Summary of 53 maternal-effect gene (MEG) products active during oocyte growth and meiosis resumption (green box), fertilization (orange box) and early preimplantation development (blue box). The purple-shaded area represents the moment when the embryonic genome activation occurs. MEGs are grouped according to their specific function and located depending on the site where they exert their main activity. For each MEG, the lethality stage observed in experimental models is indicated with a red arrow. All the experiments were performed in the mouse, except for *Spind1*, whose lethality was detected in the porcine model. The absence of the red arrow indicates that the lethality stage is not yet available. GV, germinal vesicle; MII, metaphase II; FERT, fertilization; PN, pronuclei; ZYG, zygote; MOR, morula; BL, blastocyst; POST-IMP, post-implantation; COC, cumulus-oocyte complex

preimplantation development, some of them already interact with the autocrine, paracrine, and biomechanical pathways that orchestrate folliculogenesis and oocyte meiosis resumption. The aim of this review is to summarize the crucial roles played by MEGs during oocyte maturation, fertilization, and preimplantation development.

Material and methods

For each area discussed, a systematic bibliographical search was performed, without temporal limits, using PubMed Central, Web of Science, and Scopus search engines employing the keyword maternal-effect gene in combination with folliculogenesis; oocyte growth; meiosis; oocyte competence; fertilization; embryonic genome activation; and preimplantation development. A total of 1513 papers were yielded and further selected based on our focus. Following the manual elimination of duplicates, this selection process retrieved 116 papers that were cited in the manuscript.

Maternal-effect gene products that regulate early embryonic development

Preimplantation from the zygote to the blastocyst stage is a developmental window full of hurdles. These very early stages rely almost completely on the developmental capacity of the oocyte to regulate a sequence of key events that guide the zygote from a maternal to an embryonic control. Soon after fertilization, paternal chromatin decondensation [9–12], pronuclei (PN) DNA demethylation and fusion [9, 13], epigenetic reprogramming, EGA [14], and early embryo cell divisions are the main processes under the control of maternal factors. In the zygote, the large number of transcripts stored in the oocyte during folliculogenesis undergoes elimination or inactivation, except for a small group of MEG products that survives erasure and plays a critical role at the time of maternal-to-embryonic transition, when further development goes under the control of the embryo. In the next paragraphs and in **Fig. 1**, we will detail the main

roles of MEGs involved in oocyte growth, meiosis resumption and progression to the metaphase II stage, fertilization, and preimplantation development.

MEGs with a role in oocyte growth, meiosis resumption, and progression to the metaphase II stage

Folliculogenesis is the process of growth and maturation from the primordial follicle, enclosing a primary oocyte arrested at the prophase meiosis I (MI), to the fully grown antral follicle, ready to ovulate a metaphase II (MII) oocyte. It entails timely morphological and functional changes mostly based on the bi-directional communication between the oocyte and the surrounding somatic cells [15]. While MEG products are well-known for their critical function at the time of maternal-to-embryonic transition in preimplantation embryos [14], here we highlight twelve of them that contribute also to follicle assembly and oocyte-cumulus cells communication, spindle assembly and asymmetric division, and transcriptional silencing during the GV to MII transition (**Fig. 1**, green area). Some interrelate with biomechanical pathways operating at the time of primordial follicle activation [16, 17], whereas others cooperate with autocrine and paracrine signalling cascades important for meiosis resumption, asymmetrical division, and oocyte epigenetic reprogramming.

By interacting with the Notch pathway, the newborn ovary homeobox-encoding gene (**NOBOX**) product is involved in the bi-directional communication between oocyte and granulosa cells, critical for follicle assembly [18]. This role becomes evident in *Nobox* knockout female mice lacking primary and secondary follicles [19]. Lastly, disruption of *Nobox* has been associated with non-syndromic ovarian failure in mice [19], as well as with premature ovarian insufficiency (POI) in women with specific mutations of this gene [20–22].

During folliculogenesis, the interaction between follicular cells and oocytes is facilitated by endocrine and paracrine signalling and intercellular gap junctional communication. Gap junction alpha-4 protein (CX37) is a gap junction connexin required in developing follicles [23]; the targeted deletion of its gene (*Gja4*) causes arrested folliculogenesis at the early antral stage, impaired oocyte maturation and meiotic competence, and premature follicles luteinization [24, 25]. During meiotic maturation, the prophase I-arrested oocyte undergoes nuclear envelope breakdown, chromosome recombination and condensation, and homolog segregation towards opposite poles thanks to the activity of the meiotic spindle [26, 27]. These events result in unequal cytokinesis and extrusion of the first polar body (PB-I), containing half genetic material. Then, meiotic maturation progresses with spindle reassembly, until the arrest at the MII oocyte ready for fertilization [27]. Some

MEGs, including *Fmn2*, *SPIN1*, *Hsf1*, *Bnc1*, *Figla*, and *Nlrp5*, are involved in spindle assembly and asymmetric division. Formin-2 (**FMN2**) is the first actin nucleator during microtubules extension, migration, and spindle formation, a process regulated by the Rho-family GTPase RhoA ending with PB-I extrusion [28]. Female mice lacking FMN2 produce oocytes incapable of completing MI, resulting, when fertilized, in polyploid embryos with a consequently high incidence of pregnancy losses [29]. Spindlin-1 (**SPIN1**) is essential for chromosome stability and MII maintenance [30]. Its aberrant expression is associated with the extrusion of larger PB and a decreased blastocyst development [30]. Heat shock transcription factor 1 (**HSF1**) is known for its role in oogenesis and preimplantation development [31, 32], where its absence causes arrest at the zygote stage [33]. Interestingly, *Hsf1* knockout mouse oocytes lack of *Hsp90a* expression and display delayed germinal vesicle breakdown (GVBD), altered G2/M transition, partial MI block, and defective asymmetrical division [34]. Basenuclin 1 (**BNC1**), a zinc-finger protein involved in the regulation of rRNAs transcription, is localized in the nucleolus of mouse oocytes and zygotes [35]. Experimental *Bnc1* inactivation causes the formation of dark granules in the ooplasm [36], aberrant expression and activity of RNA polymerase I and II [37, 38], defective PB-I extrusion [36], and developmental arrest at the two-cell stage [36]. Folliculogenesis-specific basic helix-loop-helix α (**FIGLA**) is a transcription factor, whose deficiency arrests meiotic progression by dysregulating the transcription of *Syp3*, *Rad51*, *Cpeb1*, and *Ybx2* meiosis-related genes [37]. During follicle growth, FIGLA is also implicated in the interaction between oocytes and granulosa cells and in the coordination of zona pellucida (ZP) genes expression [39–41]. Interestingly, heterozygous mutations of *Figla* have been observed in patients with POI [42], suggesting its involvement in the pathogenesis of this condition [43]. Another MEG involved in asymmetric division is *NACHT*, *LRR* and *PYD* domains-containing protein 5 (*Nlrp5*, also known as Mater), whose transcripts and proteins are detected in oocytes of primary follicles and throughout folliculogenesis [44]. In growing oocytes, by interacting with the phosphoinositide 3-kinase pathway, NLRP5 participates in the F-actin polymerization during meiosis resumption [45]. Further evidence correlated its nucleolar localization during follicle growth with a specific type of chromatin organization [46] associated with oocyte developmental potential [47]. In particular, the great majority of *Nlrp5*-null fully grown antral oocytes displays a not-surrounded nucleolus (NSN) type of chromatin that is characteristic of developmentally incompetent female gametes, as opposed to SN oocytes that, instead, show a ring of chromatin around the nucleolus and are potentially developmentally competent [48, 49]. The

compacted SN chromatin conformation is strictly associated with the global transcriptional silencing occurring in the final stages of oocyte growth that is essential to establish its developmental competence. Extensive chromatin modifications, including changes in histone methylation or acetylation, participate in this event, and transcription does not significantly resume until EGA [50–52]. Two additional factors associated with the oocyte's chromatin organization and developmental competence are NPM2 and OCT4. Nucleoplasmin-2 (**NPM2**) is an oocyte-specific nuclear protein detected from the primary to the antral follicle and involved in chromatin remodelling at the time of fertilization and during early embryonic development [14, 53]. NPM2 is essential for the oocyte chromatin compaction during the final stages of maturation [54]. Indeed, *Npm2*^{-/-} fully grown antral oocytes show an NSN type of chromatin [47, 55, 56]. These oocytes progress correctly through meiosis with no alterations in spindle formation and chromosomal segregation, although, after fertilization, they arrest their development at the two-cell stage [53]. As for Octamer-binding transcription factor 4 (**Oct4**), besides its role in the maintenance of pluripotency in primordial germ cells and in the blastocyst inner cell mass (ICM) [57], its protein is also present in fully grown antral developmentally competent SN and their derived MII oocytes [58, 59]. Although its role in oogenesis has not yet been detailed, OCT4 and a network of Oct4-regulated genes may represent a developmental link between the female gamete and the pluripotency of the preimplantation embryo [1, 60].

Among the best characterized epigenetic modifications, recent evidence supports that the accumulation of H3K4me3 in the late oocyte growth stages contributes to its transcriptional silencing [61, 62]. Lysine (K)-specific methyltransferase 2D (**KMT2D**) is a histone 3 lysine 4 (H3K4) methyltransferase, thought to be involved in most of the promoter-specific chromatin modifications during oogenesis and early embryo development. Conditional *KMtd2* knockout female mice show increased serum gonadotropin hormones, decreased serum oestradiol, altered folliculogenesis, premature ovarian follicle loss, and developmental arrest between the one- and four-cell stage [50].

Alongside with its function in somatic epigenetic regulation and reprogramming [63], CCCTC-binding factor (**CTCF**) has an important role in the establishment and maintenance of maternal imprinting during oocyte growth. Specifically, CTCF binding inhibits the methylation of the imprinting control region in female germ cells [64]. Using RNA interference (RNAi), the depletion of maternal *Ctcf* from growing mouse oocytes induced defects in maternal gene expression that, in turn, caused meiotic defects in eggs, mitotic defects in embryos, and apoptosis [65].

MEGs with a role during fertilization

Fertilization is a sequence of strictly controlled events involving the entry of the sperm inside the oocyte, the fusion of their PNs, and the establishment of the embryonic genome. In this paragraph, we will describe those MEGs acting at the time of cortical reaction and sperm internalization, PN formation, and subsequent epigenetic reprogramming of the parental genomes (**Fig. 1**, orange area).

The binding between sperm and oocyte ZP is the first process required for fertilization; it is regulated by several factors like ADAMs, Integrins, CRISP1, IZUMO, and JUNO. By triggering acrosomal exocytosis, this event allows the passage of the male gamete through the ZP and ends with sperm-egg fusion [66, 67]. Soon after this phase, sperm-derived factors, such as phospholipase C zeta 1, trigger the release of cortical granules, whose enzymes modify and harden the ZP, preventing polyspermy [68]. Concurrently, the second oocyte meiotic division and PB-II release take place. Within this context, two MEGs, *ubiquitin carboxyl-terminal hydrolase isozyme L1* and *L3* (*Uchl1* and *Uchl3*), play an important role as, if inhibited in MII oocytes, they induce aberrant cortical granules release and, as a consequence, meiotic spindle defects and fertilization block [69]. Their key maternal effect role beyond fertilization and during preimplantation was shown in embryos from *Uchl1* knockout females failing to undergo morula formation [69].

Immediately after internalization, the sperm nucleus undergoes a series of changes to form the male PN, which migrates towards and fuses with the female PN, resulting in the diploid zygote. During PNs formation and maturation, significant epigenetic reprogramming of the parental genomes occurs to allow the access and transcription of genes needed for the zygote further development [70]. First, active demethylation of the paternal genome takes place, whereas in the maternal genome, it mostly occurs passively [27, 71]. When demethylation is complete, the two PNs move closer together and fuse [27]. A group of four MEGs, *Gas6*, *Zar1*, *Brwd1*, and *Gclm*, are known for their role at the time of PNs formation. *Growth arrest-specific protein 6* (*Gas6*) RNAi-treated oocytes arrested at MII stage, exhibited no exocytosis of cortical granules, and impaired PNs formation, suggesting that the decreased *Gas6* expression influences sperm head decondensation [72]. Although *zygote arrest protein 1* (*Zar1*) null mice have a normal oogenesis, more than 80% of their embryos arrest at the one-cell stage, with separated maternal and paternal PNs. The remaining embryos display marked reduction in the synthesis of the transcription-requiring complex, and none of them develops beyond the two-cell stage [73]. *Bromodomain and WD repeat domain containing 1* (*Brwd1*) encodes a putative transcriptional regulator acting on chromatin through interactions with the Brg1-dependent SWI/SNF chromatin

remodelling pathway [74]. *Brwd1*-mutant oocytes do not show any morphological alteration, but are defective in the oocyte–embryo transition, suggesting an altered transcription of genes involved in the developmental progression beyond the 2-PN stage [75]. Finally, mice lacking maternal glutamate cysteine ligase modifier subunit (*Gclm*) show a decreased glutathione concentration in ovulated oocytes, and although fertilization occurs, they have a reduced rate of male PN formation, decreased development to the blastocyst stage, reduced implantation, and smaller litter size [76].

During paternal PN maturation, methylcytosine dioxygenase TET3 (**TET3**) is particularly abundant and has recently been shown to contribute to the genome-wide loss of 5-methylcytosine, the main responsible of its epigenetic reprogramming [77]. Female mice depleted of *Tet3* in the germline show severely reduced fertility and their heterozygous mutant offspring suffer from an increased incidence of developmental failures [9]. **TRIM24** and **TRIM28** are transcription intermediary factors that interact with numerous proteins involved in chromatin organization and zygotic genome activation in the PNs. In particular, TRIM24 enters the PNs to interact with sites enriched with chromatin remodellers BRG-1 and SNF2H. Zygotes lacking *Trim24* proceed their development only until the two- to four-cell stage transition, because of mis-localization of RNA polymerase II and impaired expression of SNF2H-dependent genes [78]. In bovine oocytes, *TRIM28* knockdown, instead, alters histone methylation at the two-cell stage [79]. Two other MEGs with histone methyltransferase activity are the *histone-lysine N-methyltransferase EZH2* and the *polycomb protein EED*, part of a single multimeric complex (*Ezh2/Eed*). Depletion of the maternal *Ezh2* allele affects the preferential localization of EED to the maternal PN in early zygotes, causing alterations to the parental histones' methylation profile, and severe growth retardation in newborns [66].

MEGs with a role during preimplantation development

Shortly after fertilization, a second wave of transcriptional activation begins in mouse [80], involving the final transition from an oocyte to an embryonic control of development. This dynamic process, known as EGA, aims at restoring totipotency to the zygote. It takes place predominantly at the two-cell stage in mice and the eight-cell stage in humans. In this paragraph, we will describe MEGs that contribute to the degradation of maternal mRNAs and proteins, epigenetic remodelling, and imprinting, all essential for EGA. Then, we will highlight those MEGs involved in the processes of early cell cleavage and DNA repair [81] (**Fig. 1**, purple-blue area).

MEGs like *Ago2*, *Dicer1*, *Atg5*, and *Zfp3612* [82–85] participate in the timely degradation of subgroups of maternal mRNAs that facilitates the transition between embryonic

developmental stages. Protein argonaute-2 (**AGO2**) and endoribonuclease Dicer (**DICER1**) are the best-known endonucleases of the RNA-induced silencing complex (RISC) [84, 85]. Specifically, *Ago2* transcript is expressed in mouse oocytes and throughout preimplantation development and localizes in mRNA degradation P-bodies. RNAi of *Ago2* leads to developmental arrest at the two-cell stage, by inactivating zygotic transcripts and stabilizing those maternal mRNAs that are normally degraded [86]. Another factor whose function is important at the time of mouse EGA is autophagy-related gene 5 (**ATG5**), which is a regulator of maternal transcripts degradation. In this case, though, when the maternal gene is experimentally knocked out, the paternal transcript can compensate its lack [82].

The embryonic development arrest in a transgenic mouse model also showed the involvement of **ZFP36L2** in maternal mRNA turnover in normal embryogenesis, by binding mRNAs and destabilizing proteins [78].

In the rich sub-group of MEGs regulating epigenetic remodelling and imprinting, two histone variants, *histone H2A* and *H2B types* (**Th2A** and **Th2B**), are highly expressed in oocytes and contribute to the activation of the paternal genome after fertilization, by influencing its chromatin state [79]. Interestingly, the loss of TH2A/TH2B does not cause histological alterations to folliculogenesis, whereas the resulting oocytes display reduced developmental competence and altered paternal genome activation [87]. Zinc finger protein 57 (**ZFP57**), then, is a transcriptional repressor required for the post-fertilization maintenance of both maternal and paternal methylation imprints [88]. DNA methyltransferase 1 (**DNMT1**) and its associated protein DNMT1-associated protein 1 (**DMAP1**) are involved in the maintenance of embryonic stem cell pluripotency [89, 90] and preserve the correct methylation at the differentially methylated regions (DMRs) of all imprinted genes [82]. Homozygous *Dmap1*^{-/-} embryos show a lethal phenotype [89]. Among the methyltransferase family, *Dnmt3a* and *Dnmt3b* are expressed in both male and female germlines and are required for de novo methylation of the DMRs and for the acquisition of functional imprints [83]. Specifically, embryos derived from *Dnmt3a*⁻, *Dnmt3b*⁻, and *Dnmt3a/Dnmt3b*-deficient oocytes show growth retardation and died at early post-implantation stages [84]. Three members of the Nlrp family are involved in the regulation of genome imprinting. Germline mutations in *Nlrp2*, whose knockdown in mouse oocytes leads to arrest at the 2-cell stage [85], result in a familial imprinting disorder (Beckwith–Wiedemann syndrome) in humans, suggesting that this gene might have a function in the establishment and/or maintenance of DNA methylation [86]. **NLRP7**, in association with **FILIA**, is required for the establishment or maintenance of the appropriate oocyte imprint. In fact, women affected from familial recurrent hydatidiform mole, due to mutations in both genes, show abnormal maternal

imprinting patterns [91]. Recently, evidences of a **NLRP9** function during preimplantation development are emerging: when mated with wild-type males, *Nlrp9*-deficient mice are fertile, but produce less and slower-growing blastocysts; on the contrary, when fertilized in vitro, development arrested at the two-cell stage after asymmetric cell divisions [92].

In early mammalian development, one of the two X chromosomes is randomly silenced in each female cell as a result of X chromosome inactivation. This choice is then transmitted to all daughter cells through mitosis, such that the adult female is a mosaic of two different cell lineages [93]. Maternal RING finger LIM domain-interacting protein (**RLIM**) is a ubiquitin ligase required for imprinted X chromosome inactivation by triggering the expression of the X-linked *Xist* [68]. A recent study demonstrated that knock-down of RLIM improved the developmental rate of cloned male pig embryos. This effect might be due to the suppression of *Xist* transcription and the consequent upregulation of several X-linked and autosomal genes required for blastocyst development [69].

Another group of molecules that participate in epigenetic remodelling and regulate DNA transcription are HIRA, BRG1, RING1, and RNF2. **HIRA**, a chaperone for the histone variant H3.3, is a protein required for the extensive chromatin reprogramming that occurs during oogenesis, fertilization, and mouse development beyond the zygote stage. In fact, Hira-mutant oocytes show strongly reduced DNA replication and transcription levels, essential for the first cleavage [10, 70]. *Transcription activator BRG1* encodes a catalytic subunit of the SWI/SNF-related chromatin remodelling complex which regulates transcription involved in zygotic gene expression reprogramming during the two-cell stage. In particular, *BRG1*-depleted mouse zygotes arrest at the two-cell stage displaying reduced gene expression and lower dimethyl-H3K4 levels [94]. **RING1** and **RNF2** are components of the polycomb-repressive complex 1 (PRC1), essential for proper EGA, replication, and cell cycle progression in early embryos. Genetic ablation of both genes in oocytes results in loss of chromatin-bound PRC1, induction of massive transcriptional mis-regulation during oocyte growth, and developmental arrest at the two-cell stage. These results support that PRC1 acts in the female germline to establish developmental competence by silencing differentiation-inducing genes and defining an appropriate chromatin organization [95]. Two other genes, *Kpna6* and *Sebox*, whose mechanism of action is still unclear, have been highlighted experimentally for their role in regulating DNA transcription at the very beginning of preimplantation development. Oocytes lacking importin $\alpha 7$ (**KPNA6**) show correct fertilizability but arrest at the two-cell stage [96]. The *homeobox protein SEBOX* RNAi at the PN stage, instead, led to arrested embryo development between the two-cell (85% of cases) and the four-/eight-cell (15%) stage.

Specifically, in *Sebox*-knockdown two-cell embryos, the embryonic transcriptional activity is reduced, with critical maternal mRNAs not fully degraded and several EGA markers under-expressed [97, 98].

During preimplantation development, soon after EGA, embryos go through several cell divisions and transit from totipotency to pluripotency, and their cells start their differentiation towards trophectoderm or ICM [99].

Early embryonic symmetrical cell division requires the action of maternally inherited complexes, such as the subcortical maternal complex (SCMC), the spindle assembly checkpoint (SAC), and strictly regulated mechanisms of DNA repair. The SCMC assembles underneath the oolemma and is essential to progress beyond the first embryonic cell division [100]. TLE6, NLRP5, PADI6, FLOPED, and FILIA are the main components of the SCMC; however, recently novel members, such as NLRP2, NLRP7, NLRP9, NLRP4, FILIA, and ZBED3, have been identified [92, 101, 102]. As described above, NLRP2, NLRP7, NLRP9, and FILIA have a role also in the establishment of genomic imprints and post-zygotic methylation maintenance [92, 101].

In the mouse, genetic ablation of individual components provides evidence that the SCMC is required for normal cleavage and development [103]. Transducin-like enhancer protein 6 (TLE6) is a transcriptional co-repressor [104, 105], and, together with FLOPED and NLRP5, its transcripts accumulate and reach the highest abundance in fully grown oocytes. The *oocyte-expressed protein homolog* (*Floped*) expression was detected in growing oocytes, and the protein is present in the subcortex of eggs where it overlaps with cortical F-actin but extends further into the cytoplasm. Although genetic ablation of either *Floped* and/or *NLRP5*, and the subsequent impairment of the SCMC, does not affect oocyte development up to fertilization, mutant embryos fail to reach the cleavage stage, thereby resulting in infertility [43]. Peptidylarginine deiminase 6 (PADI6) is a germ cell-specific enzyme mainly located in the cortex of eggs and preimplantation embryos. It is responsible for amino acid citrullination, a process crucial for the formation of the cytoplasmic lattices (CPLs), a fibrillar matrix composed of proteins and RNAs. Also, PADI6 has been identified as a member of the SCMC, because it co-localizes with its other components, and it is detectable from the oocyte to the blastocyst stage [106, 107]. Specifically, in mice oocytes, the absence of PADI6 protein results in impaired embryonic transcription, reduced ribosomal component levels, and dysregulated de novo protein synthesis, thus causing arrest at the zygote-to-embryo transition [107, 108].

To guarantee a correct segregation of genetic materials into daughter cells, eukaryotic organism developed the SAC complex to prevent premature metaphase-anaphase transition until all chromosomes successfully attach to the bipolar spindle. It has been reported that SAC is one of the main

mechanisms essential for the regulation of mitotic cell cycle progression in cleavage stage embryos [109]. By regulating the activity of SAC, FILIA and TP73 ensure a correct spindle formation and chromosome alignment. Alterations to these processes are among the most common causes of embryonic aneuploidies [110]. FILIA (also known as KHDC3) enables SAC activity by guiding the interaction of AURKA, PLK1, and γ -tubulin to the microtubule-organizing center, and the attachment of MAD2 to kinetochores. Depletion of maternal *Filia* transcripts impairs mouse preimplantation development, and defects in the human homolog could play a similar role and cause recurrent miscarriages [111]. Tumor protein p73 (TP73) regulates SAC activity by interacting with its BUBR1 and BUB1 components; in fact, TP73-null mice are infertile and produce oocytes with spindle abnormalities [112].

In the early embryonic stages of development, to preserve and maintain the integrity of the genome, cells activate complex DNA repair mechanisms to prevent mutations caused by endogenous and exogenous factors. In response to a DNA damage, DNA repair proteins can stop cell cycle progression, allowing genome correction. If the damage cannot be repaired, a proapoptotic pathway is activated, resulting in cell death [113]. During early embryogenesis, DNA transcription is inactive; thus, the embryo's ability to repair DNA is restricted to the function of maternally inherited DNA repair proteins, such as BCAS2, PMS2, and UBE2A [114–116]. Breast carcinoma amplified sequence 2 (BCAS2) plays an important role in the DNA damage response through the replication protein A (RPA) complex, a key regulator in the maintenance of genome integrity [117]. Maternal BCAS2 depletion leads to developmental arrest at the two-/four-cell stage [114]. Mouse zygotes deficient in the mismatch repair endonuclease PMS2 show unrepaired replication errors in early cell divisions, suggesting a role of maternal *Pms2* in DNA mismatch repair [115].

Conclusions

With the beginning of preimplantation development, the major hurdle encountered by the embryo is the transition from a maternal to an embryonic control of development, a phase strictly regulated by maternal-effect factors like MEGs [118]. These molecules are the cargo that the oocyte inherits during folliculogenesis and oocyte maturation also via a mutual communication with its companion cumulus cells. MEGs therefore represent the molecular link between folliculogenesis and preimplantation development, thereby covering a key role in the acquisition and maintenance of oocytes developmental competence. Yet, the whole network of molecular regulations and all the mechanisms and pathways governed in this choreography still need to be unveiled.

Here we described the role of MEGs not only during pre-implantation development, but also their contribution to the acquisition of oocytes developmental competence during folliculogenesis. Our view aims at inspiring future research on a topic with potential clinical perspectives for the prediction and treatment of female infertility.

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Author Contribution FI, GF, and DS conducted the literature search. FI, GF, DC and MZ drafted the manuscript. FI, GF, DC, DS and MZ designed the figure. All other authors reviewed the manuscript and contributed to its summary and discussion.

Declarations

Conflict of Interest The authors declare no competing interests.

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