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Oocyte competence develops: nuclear maturation synchronously with cytoplasm maturation

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Review Article

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Summary

Human oocyte maturation is a lengthy process that takes place over the course of which oocytes gain the inherent ability to support the next developmental stages in a progressive manner. This process includes intricate and distinct events related to nuclear and cytoplasmic maturation. Nuclear maturation includes mostly chromosome segregation, whereas rearrangement of organelles, storage of mRNAs and transcription factors occur during cytoplasmic maturation.

Human oocyte maturation, both in vivo and in vitro, occurs through a process that is not yet fully understood. However, it is believed that the second messenger, cyclic adenosine monophosphate (cAMP), plays a pivotal role in the upkeep of the meiotic blocking of the human oocyte. Relatively high levels of cAMP in the human oocyte are required to maintain meiosis blocked, whereas lower levels of cAMP in the oocyte enable meiosis to resume. Oocyte cAMP concentration is controlled by a balance between adenylate cyclase and phosphodiesterases, the enzymes responsible for cAMP generation and breakdown.

In addition to nuclear maturation, the female gamete requires a number of complicated structural and biochemical modifications in the cytoplasmic compartment to be able to fertilize normally. According to ultrastructural studies, during the transition from the germinal vesicle stage to metaphase II (MII), several organelles reorganize their positions. The cytoskeletal microfilaments and microtubules found in the cytoplasm facilitate these movements and regulate chromosomal segregation.

The aim of this review is to focus on the nuclear and cytoplasmic maturation by investigating the changes that take place in the process of oocytes being competent for development.

Introduction

During foetal life, human oocytes often become arrested in prophase I of meiosis. The oocytes are still in the dictyate phase at birth, and each ovary has more than 500,000 healthy, primordial follicles (Varghese *et al.*, 2021). Cohorts of oocytes are taken out of this non-growing pool and start to develop during the woman's reproductive life. The initial follicular development phase, which produces a few layers of granulosa cells (GCs) surrounding the oocyte, is primarily characterized by a rise in oocyte size. After oocytes develop their cytoplasm, follicular development focuses on the proliferation and differentiation of GCs (Tukur *et al.*, 2020). In follicles, this differentiation promotes the development of antral cavities. In the antral phase, which is brought on by the anterior pituitary's release of follicle-stimulating hormone (FSH), fluid gathers between GCs. A central cavity is formed, with the mural GCs situated on the perimeter (Gougeon, 2010). The oocyte remains surrounded by closely related granulosa cells, referred to as cumulus cells, forming the compact cumulus–oocyte complex (Turathum *et al.*, 2021). At this stage of development, gonadotrophin is needed for the follicles to continue to grow. From the early antral stage until the preovulatory stage, the follicles grow under the control of FSH (Hsueh *et al.*, 2015). The pre-ovulatory surge of luteinizing hormone (LH) triggers germinal vesicle breakdown (GVBD) at the late follicular phase (middle of the menstrual cycle), and chromosomes move from metaphase I to telophase I (Arroyo *et al.*, 2020). The extrusion of the first polar body and the development of the secondary oocytes, both of which contain a diploid chromosomal complement, signify the end of the first meiotic division.

After the first meiotic division is finished, the second one is quickly started, and the oocytes reach the metaphase II stage before ovulation (Levi *et al.*, 2011).

Oocyte maturation is basically divided into nuclear and cytoplasmic maturation. Nuclear maturation is the process of the resumption of meiosis and advancing on to metaphase II. MII Cytoplasmic maturation is known as the preparation of oocyte cytoplasm for fertilization and embryonic development (Trebichalská *et al.*, 2021). These two processes, meanwhile, are not entirely distinct from one another. By controlling cytoplasmic maturation, nuclear maturation is regulated.

Despite the fact that immature oocytes taken from antral follicles may resume meiosis in vitro, cytoplasmic maturation seems to happen asynchronously with nuclear maturation (Mandelbaum *et al.*, 2021). This is most likely the major cause of the reduced embryo generation rates seen when oocytes are matured in vitro. Therefore, knowledge of the oocyte maturation process is crucial in order to improve the success rate of in vitro embryo formation and provide therapies for different types of infertility.

In this review, we will take a look at the mechanisms, signals mediating local control and the changes that occur during the oocyte maturation process.

Nuclear maturation

The process of nuclear maturation initiates when meiosis resumes in the GV oocyte from the diplotene stage, which is marked by chromosomal condensation and GVBD. Following GVBD, the oocyte passes through metaphase I (MI), anaphase I (AI) and telophase I (TI) until finally completing the first meiotic division. Then quickly advances through MII of the second meiotic division, where a second meiotic arrest takes place (second meiotic blockage) (He *et al.*, 2021).

The structure of the nuclear membrane, including the GV, is preserved by proteins known as laminins. Cyclin-dependent kinase 1 (CDK1) increases nuclear envelope destabilization during GVBD by phosphorylating the laminins (Adhikari & Liu, 2014). Simultaneously with the disintegration of the nuclear envelope, chromosome condensation occurs and the metaphase plate forms. The protein degradation that takes place during the transition from metaphase to anaphase is regulated by the anaphase promoter complex (APC), which is accountable for the ubiquitination of a number of different protein substrates (Landim-Alvarenga & Maziero, 2018).

Following sperm entrance into an MII oocyte, chromosomes are segregated and the formation of the nuclear envelope brings an end to meiosis with the expulsion of the second polar bodies (PB) (Greaney *et al.*, 2018). The embryonic development process begins with the union of female and male pro-nuclei after the extrusion of the second PB (Georgadaki *et al.*, 2016).

Nuclear modifications during oocyte maturation and fertilization are required for appropriate embryonic development, which are synchronized with the movement of genetic material and organelles as well as metabolic alterations in the cytoplasm.

Meiotic arrest regulation in the GV

An essential factor in controlling the maturation of oocytes is cAMP (Ramos Leal *et al.*, 2018; Strączyńska *et al.*, 2022). Meiosis arrest is maintained by a high concentration of cAMP in the oocyte, whereas a reduction in cAMP levels permits meiosis to resume (Pan & Li, 2019). A balance between the enzymes adenyl cyclase (AC) and PDE, which are responsible for cAMP production and breakdown, respectively, controls the concentration of cAMP in the oocyte (Landim-Alvarenga & Maziero, 2018). Oocyte cAMP synthesis is regulated by G protein-coupled receptors (GPR3), which are required for adenyl cyclase activation (Richards & Ascoli, 2018).

Natriuretic peptide precursor C (NPPC) is present in the mural granulosa cells on the follicular wall, while natriuretic peptide receptor 2 (NPR2) is expressed by the cumulus cells surrounding the oocytes (Alam & Miyano, 2020). The NPPC in mural granulosa cells can bind to NPR2 receptors in cumulus cells to produce cyclic guanosine monophosphate (cGMP), which then enters oocytes through gap junctions to inhibit the activity of phosphodiesterase (PDE3A). This maintains a high level of cAMP in oocytes. Oocytes with high concentrations of cAMP inhibit maturation-promoting factor (MPF) activity through a protein kinase A (PKA)-dependent mechanism (Gilchrist *et al.*, 2016).

The MPF is a protein made up of a catalytic subunit, CDK1 and a regulatory subunit, cyclin B and is regulated by phosphorylation of CDK1 at its tyrosine 15 and threonine 14 sites. The phosphorylation is carried out by the kinase Wee1B, while the dephosphorylation is accomplished by the phosphatase Cdc25 (Landim-Alvarenga & Maziero, 2018). Wee1B and Cdc25 activity is directly regulated by the PKA (Filatov *et al.*, 2019) (Figure 1).

Meiosis resumption

Various exogenous factors are required for the resume of meiosis. LH can lead to a reduction in the expression of NPPC receptors in the granulosa cell (GC) and resulting in a lack of cGMP transfer to the oocyte (Arroyo *et al.*, 2020). Concurrently, the LH surge leads to a disruption in the gap junctions that connect the oocyte and the GC. Epidermal growth factors such as the epiregulin, amphiregulin and beta-cells cause a breakdown in the oocyte-to-GC gap junction (Richani & Gilchrist, 2018). The decrease in cGMP causes an increase in PDE3 activity, which in turn leads to a precipitous fall in cAMP levels in the oocyte (Gershon *et al.*, 2019). As cAMP levels drop, PKA activity is dampened, and Cdc25 is nuclear translocated. The buildup of the phosphatase Cdc25 in the nucleus is what drives both the activation of the MPF and the delivery of Wee1B into the cytoplasm. In both the mitotic and meiotic cycles, MPF activation causes chromosomal condensation, nuclear envelope breakdown (GVBD) and cytoplasmic preparation for the M phase(Oh *et al.*, 2010) (Figure 1).

Mitogen-activated protein Kinase (MAPKs)

Recent studies have shown that, in addition to MPF, the mitogen-activated protein kinase (MAPK) cascade is a major regulatory mechanism that drives the advancement of the meiotic cell cycle in oocytes (Sha *et al.*, 2017). MAPK, which is also known as extracellular-regulated kinase (ERK), has two isoforms, ERK1 (p44) and ERK2 (p42), which are extensively expressed in the oocyte. Direct activation of MAPK occurs through phosphorylation of threonine-183 and tyrosine-185 in the activation loop by MAPK kinase (also known as MAPK-ERK kinase 1, MEK1) (Tabatabaie *et al.*, 2022). Phosphorylation is also required for MEK activation, and MOS, the product of the proto-oncogene c-mos, acts as an upstream activator of MEK in the oocyte. MOS was first discovered in cells transformed by the Moloney murine leukaemia virus (Cao *et al.*, 2020; Papkoff *et al.*, 1982). It is a 39-kDa Ser/Thr protein kinase that is expressed only in germ cells (Liang *et al.*, 2007). In CC,

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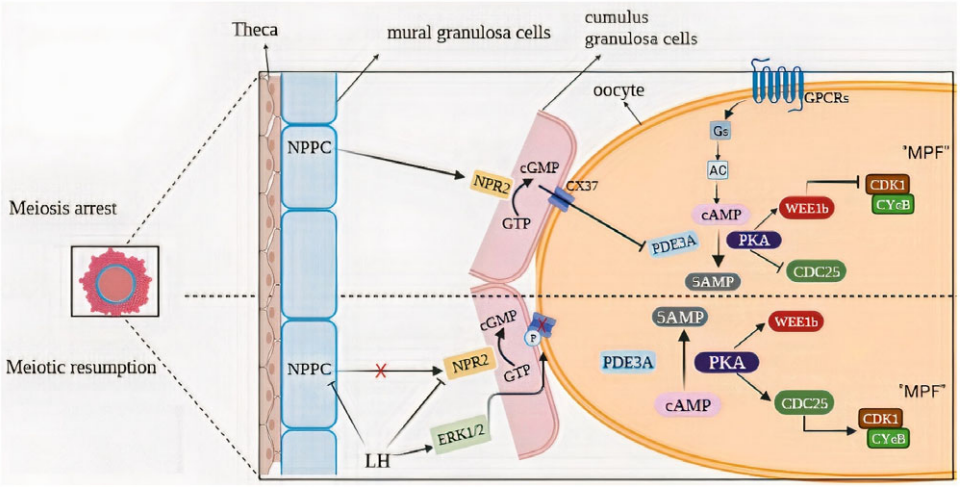

Figure 1. Mechanisms of meiotic prophase maintenance and gonadotropin-induced meiosis resumption. (A) In fully developed follicles, prophase I-arrested oocytes need the production and maintenance of high levels of cAMP, which are generated by activating the GPCR/Gs/AC pathway. Inhibition of phosphodiesterase 3A (PDE3A) prevents cAMP degradation and keeps cAMP levels high in the oocyte. Natriuretic peptide precursor type C (NPPC) is made by mural granulosa cells (GCs) and induces the production of cyclic guanosine monophosphate (cGMP) by NPR2 (a guanylyl cyclase) existing in cumulus GCs. In the oocyte, cGMP enters via Cx37 gap junctions and blocks cAMP hydrolysis by PDE3A. cAMP stimulates the activity of protein kinase A (PKA), which in turn stimulates the activity of the Wee1B kinase and inhibits the activity of the CDC25B phosphatase, resulting in the inactivation of CDK1. (B) A preovulatory level rise of LH induces gap junctions across the follicle to close, shutting off cGMP delivery to the oocyte. As a result, PDE3A's ability to hydrolyze cAMP is subsequently enhanced. Low levels of cAMP and PKA can no longer activate WEE1B and inactivate CDC25B and CDK1 becomes dephosphorylated and catalytically active.

RAS/RAF trigger MAPK activation (Das & Arur, 2022). Through the suppression of several negative regulators and the activation of cdc25 phosphatase, the MAPK, when activated, enhances MPF stability in the oocyte. coincides with or precedes GVBD, MAPK is activated in the oocyte, and its levels rise steadily throughout oocyte maturation, staying high until meiosis II (Landim-Alvarenga & Maziero, 2018).

Regulation of oocyte transcripts required for nuclear maturation

Oocytes actively take part in the meiotic maturation process, guaranteeing that they advance to the mature stage. During maturation, oocyte transcripts undergo a predominately large degradation; yet, this phenomenon seems to be a selective process (Su *et al.*, 2007). It is clear that transcripts and/or proteins linked to oocyte meiotic arrest at the GV stage are degraded or have significantly reduced expression levels. As an illustration, translation of CDH1, a co-activator of the anaphase-promoting complex/cyclosome (APC/C) that suppresses cyclin B1 levels by ubiquinylation and upholds meiotic arrest, is 70% lessened (Holt *et al.*, 2011).

However, transcripts implicated in signalling pathways like ERK/MAPK and PI3/AKT that are crucial for controlling oocyte meiosis and maintaining meiotic arrest during MII are still present (Su *et al.*, 2007). While it has been demonstrated that certain maternal-effect transcripts degrade during this transition, other transcripts seem to remain stable.

During oocyte maturation and/or fertilization, unusual transcript maintenance or degradation may be detrimental to oocyte quality and undermine developmental competence(Krajnik *et al.*, 2023).

However, the majority of transcripts in the oocyte are destroyed during maturation. Many additional transcripts undergo polyadenylation and connect with the polysomes to undergo translation (Chen *et al.*, 2011; Sha *et al.*, 2019). Recent investigations have shown various patterns of oocyte transcripts in conjunction with the polysomes using wide-genome profiling of maternal mRNAs, showing active translational control throughout maturation. It has been proven via the use of this standpoint that during oocyte maturation, almost 7600 transcripts are actively translated while many others are repressed (Chen *et al.*, 2011).

Message ribonucleoprotein (mRNP) complexes allow for the storage of these transcripts so that they can be translated when required (Hafidh *et al.*, 2011). Additionally, they might be spread throughout the whole oocyte's cytoplasm or concentrated within a particular area of it. More research clarified the oocyte gene expression profile from various angles. Depending on their functions, the expression of a number of genes was associated with DNA, chromatin, RNA, transcription, kinases, membrane receptors, ion channels, mitochondria, structural nuclear proteins and phospholipases as well as to apoptosis, cell cycle, secretory pathways, exocytosis, endocytosis and other processes (Virant-Klun *et al.*, 2013). In addition to recognized genes like DAZL, BMP15, or GDF9, Assou *et al.* discovered 1,514 additional genes that were up-regulated in human oocytes. They included transcription factors like OTX2, SOX15 and SOX30, meiosis-related genes like PTTG3 (securing) and AURKC (Aurora kinase), as well as newly unreported growth factors including TNFSF13/APRIL, FGF9, FGF14 and IL4 (Assou *et al.*, 2006). In a similar investigation, Gasca *et al.* examined a collection of immature oocytes, mature MII oocytes that had not been fertilized and cumulus cells. The high gene expression levels of BRCA1 and 2, ATM, TP53, RB1, BUB1, MAD2, APC and ACTB were examined in all samples. All samples exhibited ACTB and MAD2 expression. Since MI and MII oocytes had significant levels of RBBP7, RBBP4 and RBL2 expression, it was possible that this transcription regulatory pathway may be active during oocyte maturation. Following oocyte maturation, the DNA repair marker BARD1 is expressed (Gasca *et al.*, 2007). Additionally, the research by Wells and Patrizio revealed that several germ cell-specific genes, such as DAZL, and genes involved in meiosis, like SYCP2, SGOL2 and

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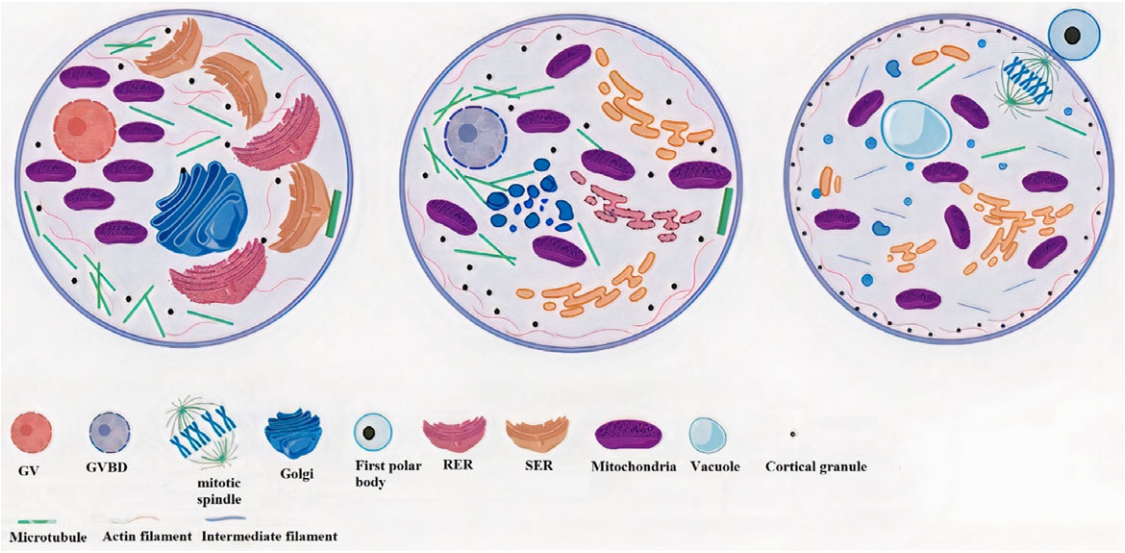

Figure 2. A summary of the distribution of cytoplasmic organelles and the cytoskeleton during oocyte maturation. In germinal vesicle (GV) oocytes, mitochondria are clustered around the GV; the Golgi apparatus is more concentrated in the interior than at the cortex; and the endoplasmic reticulum (ER), cortical granules, microtubules and microfilaments are evenly distributed throughout the cytoplasm. Oocytes undergo a number of morphological changes in stage germinal vesicle breakdown, including the relocation of mitochondria away from the perinuclear region, the fragmentation and aggregation of the Golgi apparatus in the central part of the oocyte, the localization of the ER in cortical regions, the condensation of microtubules around the chromosomes, and the dense accumulation of microfilaments in the subcortical region. At metaphase II, the first polar body has been extruded, spindles have formed underneath the first polar body, and intermediate filaments are uniformly dispersed throughout the cytoplasm. Also, the Golgi apparatus is further fractured and distributed throughout the oocyte; cortical granules travel towards the cortical cytoplasm and arrest in the cortex.

MSH2, were among those that were up-regulated in mature oocytes (Wells & Patrizio, 2008).

It's interesting to note that there seem to be two distinct methods of translational inhibition during oocyte maturation: one is transcript degradation, as was previously shown (Cui *et al.*, 2006), and the other appears to be independent of degradation. In this latter case, translation appears to be repressed by the translocation of transcripts that remain stable, from the polysome to the subpolysome/RNP compartment (Chen *et al.*, 2011).

Well-known cell cycle regulators (Ccnb1 and Mos) have been found among the transcripts undergoing active translation during the GV-MII transition, along with elements of the anaphase-promoting complex and the spindle assembly checkpoint (Mad2, Bub1b and Sogl2). A group of transcripts that code for transcriptional regulators and chromatin remodellers are also members of this class (Sánchez & Smitz, 2012).

Recent research has shown two key regulators of translation during oocyte maturation: CPEB and DAZL. CPEB increases Dazl mRNA translation when to the MI stage advances; after that, the DAZL protein stimulates the translation of its own mRNA, creating a positive feedback loop. Although DAZL's function has previously been suggested to have as a translational regulator during oocyte maturation (Cauffman *et al.*, 2005), Chen *et al.* (Chen *et al.*, 2011) have recently shown that DAZL has a clear and significant function during this late period.

Cytoplasmic maturation

Meiotic advancement, which is indicative of nuclear oocyte maturation, is not sufficient to ensure successful embryonic development; further alterations to the cytoplasm, or cytoplasmic maturation, are required (Trebichalská *et al.*, 2021). Cytoplasmic maturation is comprised of both structural and molecular alterations that take place in the oocyte between the GV stage and the finish of the MII stage (Landim-Alvarenga & Maziero, 2018). These changes include appropriate spatial and temporal dynamics of organelles that rearrange and store mRNA, proteins and transcription factors necessary for egg maturation, fertilization and early embryogenesis (Kang *et al.*, 2023). For the oocyte to attain high developmental potency, adequate alteration of the location, shape and biochemical characteristics of organelles must take place. During maturation, oocyte organelles such as the Golgi and mitochondria relocate from the oocyte's periphery to a position in close proximity to the nucleus. The Golgi complex-derived cortical granules (CGs) travel from the centre of the oocyte to the periphery and attach to the membrane (Ferrer-Vaquer *et al.*, 2019).

Rearrangement of the cytoskeleton

During oocyte development, dynamic redistribution of organelles takes place within an incredibly enormous volume (relative to somatic cells). It makes sense that the oocyte and early embryo may have developed a particular shape to aid with organelle location and distribution.

The cytoskeleton, because of its adaptability and dynamic nature, plays a crucial role in the rearrangement of oocyte organelles and may be altered to meet the oocyte's specific requirements. Three different kinds of filaments make up this structure: microfilaments, intermediate filaments and microtubules. Microtubules in GV-stage oocytes are distributed in a rather even pattern. A similar distribution of microfilaments is also seen in the ooplasm. In the MII stage, mature oocyte microtubules and microfilaments mostly congregate in the cortical cytoplasm. Furthermore, microtubules, which may be seen as well-organized meiotic spindles, are often found in a direction perpendicular to the surface of the oocyte; they are barrel-shaped, anastral and centriole-free (Fan & Sun, 2019). Intermediate filaments are still not adequately comprehended in comparison to microfilaments and microtubules (Mao *et al.*, 2014) (Figure 2).

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Also, new research shows that the cytoplasmic lattices of oocytes can play a key role in regulating the position and movement of the organelle mediated by cytoskeleton (microtubule) (Lin *et al.*, 2017). The cytoplasmic lattices (also known as cytoskeletal sheets, plaques, lamellae and fibrillar arrays) are missing in oocytes that are not developing but significantly increase in number as the oocyte grows and finally property prominently in the entirely grown oocyte (Qin *et al.*, 2019). Previous investigations into the molecular make-up of the lattices revealed that the lattices served as a reservoir for ribosomes or maybe intermediate filaments (Yurttas *et al.*, 2008). More recently, studies using immunoelectron microscopy discovered that peptidylarginine deiminase 6 (PADI6), which is a very plentiful oocyte and embryo-restricted maternal protein, binds specifically to the lattices (X. Liu *et al.*, 2017). In terms of expression, PADI6 protein is visible in the cytoplasm of oocytes as soon as they start to mature, and it is present in embryos until the blastocyst stage of development, which is resembling to that of the lattices (Innocenti *et al.*, 2022). Along with PADI6, two other maternal factors, MATER and FLOPED, have been identified to localizing to and being necessary for lattice formation (Bebbere *et al.*, 2016; Lu *et al.*, 2017). Both MATER and FLOPED exhibit PADI6-like expression patterns in oocytes and early embryos (Paonessa *et al.*, 2021). These results suggest that the distribution of organelles via microtubules during oocyte maturation may be directly influenced by the lattices.

Endoplasmic reticulum and Mitochondria

The endoplasmic reticulum (ER) of the human oocyte serves as a reserve for the Ca2+ required for oocyte activation (Wakai *et al.*, 2019). Upon fertilization, the entry of sperm into the oocyte initiates a series of intricate intracellular signalling cascades, ultimately leading to oocyte activation, a pivotal process essential for the commencement of embryonic development. Specifically, the entry of sperm into the oocyte triggers the activation of phospholipase C zeta (PLCζ), an enzyme predominantly present in the sperm head (Saunders *et al.*, 2002). PLCζ assumes a pivotal role in inducing Ca2+ oscillations within the oocyte by catalyzing the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (Nomikos *et al.*, 2013). IP3, acting as a second messenger, binds to IP3 receptors located on the ER membrane, leading to the opening of calcium channels and subsequent release of calcium ions from the ER lumen into the cytoplasm. This abrupt rise in cytoplasmic calcium levels initiates a cascade of essential downstream events crucial for oocyte activation, such as CG exocytosis, resumption of meiosis and initiation of embryo development (Stein *et al.*, 2020).

In contrast to oocytes in the GV stage, which exhibit a thin network of ER, mature human oocytes have ER arranged in discrete clusters (2–5 m) throughout the cell (Kang *et al.*, 2023; Palmerini *et al.*, 2022). Several researches showed time solidarity between the emission of Ca2+ and development of ER clusters at the cortex of mature MII-stage oocytes (FitzHarris *et al.*, 2003; Kline *et al.*, 1999). The redistribution of ER throughout maturation appears to be controlled by microtubules and microfilaments, similar to other organelles (mitochondria) (Kang *et al.*, 2023). Another restructuring characteristic connected to oocyte competence is the morphology and changing position of the mitochondria surrounding the spindle. These organelles establish a border that encloses the developing spindle and compressing chromosomes (Dalton & Carroll, 2013). According to Van Blerkom, this redistribution is assumed to be essential to build high adenosine triphosphate (ATP) concentrations in areas with a high need for energy (Van Blerkom, 2011).

Findings from electron microscopy and confocal studies of oocytes suggest that throughout maturation, mitochondria seem to undergo an orderly clustering and also move in close proximity to the ER (Takahashi *et al.*, 2016). Numerous investigations have indicated that in somatic cells, near physical contacts between ER and mitochondria promote organelle interaction via concerted signalling processes. For instance, it was observed that mitochondrial-derived ATP activated ER membrane Ca2+ pumps, which then sent Ca2+ signals to the mitochondria and changed their metabolic rate. Furthermore, by controlling local Ca2+ concentrations and the rate of Ca2+ signalling events, mitochondria can function as a Ca2+ buffer (Silva *et al.*, 2020). Based on studies, it is probable that the ER and mitochondria in oocytes interact functionally, and that this interaction affects both ATP production and Ca2+ regulation (Wang *et al.*, 2020). Furthermore, the efficient interaction between these two organelles in oocytes may turn out to be a crucial factor in effective embryonic development (L. Liu *et al.*, 2001) (Figure 2).

Golgi complex and cortical granules

The GV oocytes each have many Golgi complexes that are dispersed throughout the cytoplasm and are surrounded by numerous tiny vesicles. There are two types of vesicles that may be seen: smooth vesicles with uneven size and electron density are visible close to the trans face of the Golgi complex, whereas coated vesicles that resemble pinocytosis granules are detected next to the cis face (Landim-Alvarenga & Maziero, 2018). During the course of oocyte maturation, the number and size of Golgi complexes present in the oocyte's cytoplasm both decrease and become fragmented. The fragmented Golgi apparatus is dispersed throughout the oocyte in MI, and this pattern is also preserved in MII oocytes (Satouh & Sato, 2023).

The Golgi complex is the place where the CG were first derived (Trebichalská *et al.*, 2021). At the ultrastructural level, the CGs all seem to have the same size (0.2 μm to 0.6 μm) and have a similar morphology (M. Liu, 2011). Cortical granules are scattered in the cytoplasm of GV oocytes. At the end of the maturation process, in MII oocytes, the granules are located on the inner surface of the cell membrane. The arrangement described herein represents a pre-fertilization distribution mechanism enacted prior to sperm entry and subsequent oocyte activation (Reader *et al.*, 2017). After the fusion of sperm and oocyte, a significant surge in intracellular calcium levels ensues (as noted in section 2.2 Endoplasmic reticulum). Subsequent to this rise in calcium concentration, protein kinases such as protein kinase C (PKC) and Ca2+/calmodulin-dependent protein kinase II (CaMKII) become activated, phosphorylating various specific proteins associated with CGs within the oocyte (Tsaadon *et al.*, 2008). These proteins often play pivotal roles in facilitating the activity of the exocytosis machinery or in regulating the fusion of CGs with the oocyte's plasma membrane. Notable examples of such proteins include Soluble N-ethylmaleimide-sensitive factor Attachment Protein REceptors and Rab GTPases (M. Liu, 2011). Within CGs, oocytes house a variety of hydrolytic enzymes, such as proteases, peroxidases and glycosaminoglycans (Georgadaki *et al.*, 2016).

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Oocytes employ specific strategies to prevent polyspermy. These strategies can generally be categorized into two types: the 'oocyte membrane block' to sperm penetration and the 'zona reaction' (Mio *et al.*, 2012).

The oocyte membrane block begins with depolarization triggered by an influx of Na+ ions, altering the membrane potential from negative to positive. This depolarization then activates voltage-gated calcium channels on the oocyte membrane, allowing Ca2+ to enter from the extracellular space into the oocyte cytoplasm. The increase in intracellular calcium levels that follows serves as a pivotal signalling event for the rapid block to polyspermy. This rapid change in potential effectively inhibits sperm penetration and attachment to the oocyte membrane, providing a transient barrier against polyspermy. Referred to as the 'fast block' to polyspermy, this mechanism occurs within seconds. However, this 'fast block' mechanism is unlikely to play a significant role in preventing polyspermy during the fertilization process in humans (Carvacho *et al.*, 2018; Mio *et al.*, 2012).

The second proposed mechanism is initiated by the attachment of sperm to the oocyte membrane, triggering a Ca2+ oscillation event. This occurrence results in an increase in intracellular Ca2+ concentration, which in turn triggers the release of CGs from beneath the oocyte membrane into the perivitelline space through exocytosis (Lin *et al.*, 2017) (Figure 2). Following the exocytosis of CGs, a 'slow block' to polyspermy occurs within the zona pellucida, the extracellular envelope surrounding the oocyte (Mio *et al.*, 2012). The contents of these cortical granules, including proteinases such as tissue-type plasminogen activator (tPA), peroxidase and N-acetylglucosaminidase, play critical roles in this process. The proteinases modify the zona pellucida, making it less receptive to sperm binding by catalyzing the proteolysis of ZP2 and causing ZP hardening (Sun, 2003). Similarly, peroxidase, an oocyte-specific protein stored within cortical granules, contributes to the polyspermy block by participating in the formation of the fertilization envelope post-cortical reaction (M. Liu, 2011). Specifically, N-acetylglucosaminidase released during fertilization inactivates the sperm GalTase-binding site on ZP, effectively blocking subsequent sperm binding (Zitta *et al.*, 2006). These enzymatic actions collectively modify the structure of sperm receptors like ZP2 and ZP3, creating a barrier that prevents additional sperm penetration and thus ensures monospermy. This 'slow block' typically occurs within 5 to 8 minutes after oocyte activation and is considered the primary mechanism for preventing polyspermy in humans (Mio *et al.*, 2012).

In exploring the contentious issue of polyspermy prevention, Professor Brian Dale and colleagues have critically examined whether mechanisms actively repel supernumerary sperm from oocytes, or if the natural sperm-to-oocyte ratios inherently minimize the need for specific polyspermy prevention mechanisms. They suggest that monospermia is likely maintained through a combination of controlled sperm-oocyte encounters and specialized molecular and structural features within the oocyte (Dale & DeFelice, 2011).

Professor Dale argues that the fusion of cortical granules with the plasma membrane represents a slow structural change, transforming the oocyte's receptive external investment into a hardened protective layer for the developing embryo, rather than functioning solely to repel sperm. Additionally, he asserts that polyspermy is observed in aged oocytes both in vivo and in vitro. He contests the prevailing notion of 'polyspermy-blocking mechanisms' in mammalian oocytes, primarily based on in vitro experiments using oocytes stripped of their external coats, which may not accurately reflect natural fertilization processes (Dale & DeFelice, 2011).

It's important to note that Figure 2 has been adapted from a previously published study conducted by Trebichalská et al (Trebichalská *et al.*, 2021). Slight modifications were made to the original figure to better align it with the focus of the current research.

Conclusion

The available information reviewed above demonstrates unequivocally that oocyte maturation is a complicated process that involves many 'arrest and resume' processes and is strictly controlled during the reproductive cycle. The basic paradigm of meiotic maturation in the oocyte is the precise management of intracellular cAMP's spatial and temporal regulation to control the activation of the MPF. This process is accomplished by significant modifications in the level of expression of transcripts associated with the arrest of meiosis in the oocyte or the stabilization of transcripts that are crucial for oocyte maturation. Although oocyte nuclear and cytoplasmic maturation occur simultaneously, they are nevertheless autonomous phenomena. Cytoplasmic maturation takes place with the reorganization of organelles, most notably the active mitochondria and ER in the oocyte cytoplasm. Cytoplasmic maturation is crucial for oocytes to achieve fertilizable and post-fertilization developmental competence during maturation. Many of the processes described here are intracellular, while others are subject to paracrine regulation that is modulated by the close relationships between follicular cells and the oocyte. All of the activities that take place are essential to producing a functioning gamete that has the potential to develop into a healthy embryo after fertilization.

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