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REVIEW

Endoplasmic reticulum in oocytes: spatiotemporal distribution and function

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Abstract

Endoplasmic reticulum in oocytes The storage and release of calcium ions (Ca2+) in oocyte maturation and fertilization are particularly noteworthy features of the endoplasmic reticulum (ER). The ER is the largest organelle in the cell composed of rough ER, smooth ER, and nuclear envelope, and is the main site of protein synthesis, transport and folding, and lipid and steroid synthesis. An appropriate calcium signaling response can initiate oocyte development and embryogenesis, and the ER is the central link that initiates calcium signaling. The transition from immature oocytes to zygotes also requires many coordinated organelle reorganizations and changes. Therefore, the purpose of this review is to generalize information on the function, structure, interaction with other organelles, and spatiotemporal localization of the ER in mammalian oocytes. Mechanisms related to maintaining ER homeostasis have been extensively studied in recent years. Resolving ER stress through the unfolded protein response (UPR) is one of them. We combined the clinical problems caused by the ER in in vitro maturation (IVM), and the mechanisms of ER have been identified by single-cell RNA-seq. This article systematically reviews the functions of ER and provides a reference for assisted reproductive technology (ART) research.

Keywords Oocyte maturation · Endoplasmic reticulum (ER) · Calcium oscillations · Stress · Mitochondria

The structure of ER

The ER is the main site for the synthesis and transport of various biomolecules and is defined as an interconnected network with continuous membranes [1, 2]. The ER consists of a nuclear envelope, smooth tubules, and rough lamellae.

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The different structures that make up the ER perform very diverse and specialized functions within the cell. The nuclear envelope consists of two lipid bilayers, the inner nuclear membrane and the outer nuclear membrane, and shares a common lumen with the peripheral ER [3]. The nuclear envelope is attached to form part of the peripheral ER, and the lamellae are essentially composed of two lipid bilayers with an intermediate lumen, with curved regions located only at the membrane edge [4].

Specifically, the rough ER is defined by a high density of ribosomes on the cytoplasmic surface and is the primary site for synthesis, folding, and post-translational modification of secreted or membrane-bound proteins [5]. Far fewer ribosomes are present on the membrane surface of the smooth ER tubules, which are highly curved and smooth [5]. The tubular network is dynamic, constantly rearranging and growing, and consists of three-way junctions connecting individual tubules [6]. Tubules and sheets have very different structural features and thus play different roles in different cellular processes [7, 8].

ER tubules and lamellae are present in all eukaryotic cells, and the ratio of lamella to tubules varies in different cell types and reflects the different functions of these cells

[9]. For example, the rough ER structure of specialized cells that synthesize a large number of secreted proteins, such as pancreatic secretory cells and B lymphocytes, is mainly composed of sheets. Cells involved in processes including lipid synthesis, calcium signaling, and other organelle contact sites have ERs that are mainly composed of tubules. Mural granulosa cells (MGCs), adrenal cells, hepatocytes, and muscle cells that synthesize lipid hormones are all examples of specialized cells dominated by a tubular network. Calcium signaling occurs at the site of contact between the plasma membrane (PM) and the adjacent cortical ER, and the morphology and intracellular location of ER subdomains contribute to the function of these structures and thus the specialized cells in which they reside.

The ER is also the major reservoir of intracellular Ca^{2+} [7, 10, 11]. The typical cytoplasmic concentration of Ca^{2+} is approximately 100 nM, while the Ca^{2+} concentration in the ER lumen is 100–800 μM, and the extracellular Ca^{2+} concentration is approximately 2 mM. The multifunctional nature of this organelle requires numerous proteins, unique physical structures, and coordination and response to changes in the intracellular environment [12]. The ER of oocytes also has similar structure and function, but oocytes need to undergo highly dynamic changes, and the structure and function of the ER will also have corresponding adaptation and coordination.

Function of the oocyte ER

Functional protein synthesis occurs through translation of maternal messenger RNA (mRNA) and is critical for proper oocyte development and maturation. The ability of the ER to store and release free Ca^{2+} in the cytoplasm is also important. Therefore, maintenance of ER homeostasis may be a key mechanism for folliculogenesis and oocyte maturation (Fig. 1).

A prevalent mode of calcium regulation upon oocyte activation is the release of PLC zeta by sperm into the oocyte cytoplasm. PLC zeta then cleaves PIP_2 into IP_3 and DAG. The binding of IP_3 to IP_3Rs located on the SER membrane causes a conformational change that allows the release of Ca^{2+}, triggering Ca^{2+} oscillations. The combined action of STIM proteins in the ER membrane and Orai channels in the PM mediates the maintenance of cellular Ca^{2+} homeostasis. This coupling process is initiated in response to depletion of Ca^{2+} stores in the ER, which triggers STIM protein activation. Thereafter, the opening of the Orai1 Ca^{2+} channel located in the PM allows the influx of extracellular Ca^{2+}. The accumulation of misfolded or unfolded proteins in the lumen disrupts ER homeostasis and activates ER stress. Activation of ER stress can trigger the UPR, a signal transduction pathway that senses the fidelity of protein folding in the ER lumen. The MAM is a physically coupled structure between mitochondria and the ER in cells. MFN includes two isoforms, MFN1 and MFN2. MFN2 on the ER membrane and MFN1 or MFN2 on the mitochondrial outer membrane can form a homotypic or heterotypic structural complex. MFN1/2 are located on the outer mitochondrial membrane and OPA1, located on the inner mitochondrial membrane, mediates mitochondrial fusion. MAM is involved in the regulation of mitochondrial fission. Fission 1 (FIS1), located on the mitochondrial outer membrane, recruits mitochondrial DRP1, which is mainly located in the cytoplasm, to the fission site of the mitochondrial outer membrane.This image was originally created by Kang Xin and Wang Jing.

ER stress in oocytes

The ER is the main intracellular organelle responsible for protein synthesis. During these processes, the ER plays a crucial role in meeting the increased protein demands of the oocyte. This task is accomplished through proper protein synthesis, folding, modification, and transport [13].

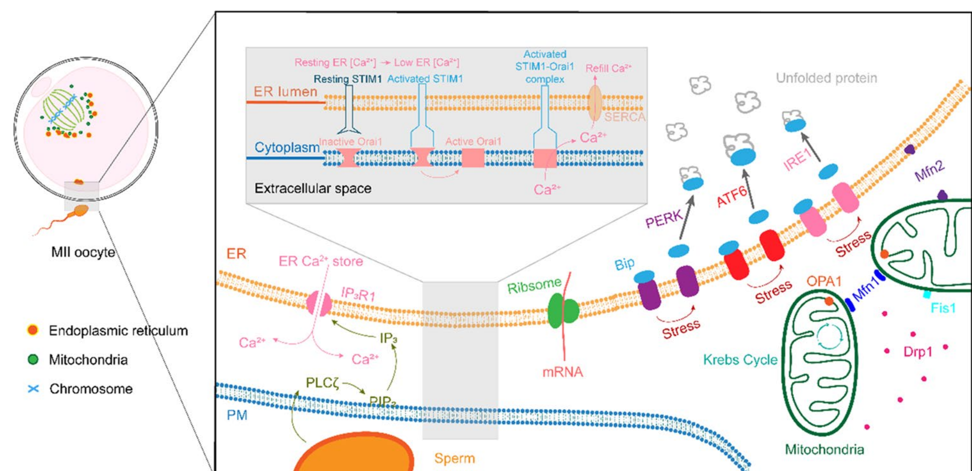

Fig. 1 The function of ER in oocyte

Developing gametes and embryos may experience various types of exogenous stress in in vitro culture systems, some of which adversely affect ER function and protein synthesis, leading to ER stress and UPR signaling being activated [14–16]. ER proteostasis surveillance is mediated by the UPR, a signal transduction pathway that senses the fidelity of protein folding in the ER lumen [17]. Misfolded proteins are retained in the ER for proper folding or targeted for degradation by ER-associated degradation (ERAD) mechanisms [18]. The accumulation of misfolded or unfolded proteins in the lumen disrupts ER homeostasis and activates ER stress. Activation of ER stress can trigger the UPR, which is designed to maintain cellular homeostasis and normal ER function [19].

Although the exact molecular mechanism of UPR in mammalian oocyte development is poorly described, it is generally believed that three ER transmembrane proteins, protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1), and the ER molecular chaperone-binding immunoglobulin protein BiP (also known as glucose-regulated protein 78 or GRP78), trigger the UPR response to ER stress [16]. As an adaptive response, the UPR mitigates misfolded protein accumulation and restores ER function. PERK signaling reduces the translocation of new proteins to the ER lumen and prevents protein overload, while the ATF6 and IRE1 pathways regulate the transcriptional activation of various genes including those responsible for increased ER translocation, protein folding, export, degradation, and other functions. However, if ER stress becomes prolonged or too severe for UPR-based relief, apoptosis is induced through activation of the C/EBP homologous protein (CHOP), Jun N-terminal kinase (JNK), and caspase 12 pathways [13].

The oocyte ER affects Ca^{2+} oscillations during fertilization

Ca^{2+} oscillations are a hallmark of mammalian fertilization and regulate the transition of oocytes to early embryos [11, 20]. Decades of studies on different species have finally identified the origin of stimulation in sperm-carried phospholipase C zeta (PLC zeta), a pervasive pattern of calcium regulation upon oocyte activation involving sperm transfer of phospholipase. PLC zeta is released into the oocyte cytoplasm [21]. PLC zeta then cleaves phosphatidylinositol 4,5-bisphosphate (PIP_2) into 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) [22]. Downstream of this signaling pathway, the binding of IP_3 to IP_3 receptors (IP_3Rs) located on the smooth endoplasmic reticulum (SER) membrane causes a conformational change that allows the release of Ca^{2+} from the organelle lumen, triggering the release of Ca^{2+} from the ER and leading to an increase in intracellular Ca^{2+} levels [23]. The initial rise in Ca^{2+} is followed by repeated Ca^{2+} transients, termed Ca^{2+} oscillations, that stimulate oocyte activation and embryonic development [24, 25]. The metaphase II (MII) oocytes respond to gamete fusion by Ca^{2+} oscillations. The amplitude, frequency, and duration of these oscillations are then decoded by downstream regulators into signals that trigger fertilization events, namely, further cumulus cell release, exit from MII, second polar body (PBII) extrusion, and pronucleus formation.

In oocytes, therefore, the ability of the ER to store and release free Ca^{2+} in the cytoplasm is important. The ER is central to the mechanism that generates intracellular Ca^{2+}oscillations at the time of fertilization [26–29]. The mechanism of Ca^{2+} release in mature oocytes has been widely described, and in this context, this review will describe the changes that the ER undergoes during oocyte maturation as part of cytoplasmic reorganization and are associated with the acquisition of developmental competence.

Changes in the structure and distribution of the ER in oocytes

Mouse oocyte maturation is associated with a marked reorganization of the ER [30], during which the distribution of the ER undergoes major changes guided by microtubules and filaments, ranging from a network of cytoplasmic accumulation at the germinal vesicle (GV) stage to a distinctive cortical cluster network in MII [31, 32]. Multiple lines of evidence suggest that this redistribution of the ER is important in preparing the oocyte to trigger Ca^{2+} oscillations upon fertilization [28, 31–33]. What needs to be understood is to study the time course and mechanism of ER reorganization during oocyte maturation. The ER first reorganizes upon GV breakdown (GVBD) into a dense network of membranes that wrap and invade the developing meiotic spindle [28]. GVBD is critical for initiating ER reorganization, as ER structure does not change in GV-arrested oocytes of mice [31]. The microtubule inhibitor nocodazole and the inhibition of cytoplasmic dynein prevented ER reorganization. Thus, ER redistribution of GVBD is dynein-driven and cell cycle-dependent [32]. Some proteins play a critical role in microtubule-mediated organelle redistribution via cytoplasmic lattices (CPLs) [26, 34]. CPLs are ascribed with key roles in oocyte maturation, which is causatively related to microtubule and organelle dynamics by controlling the translational processes [35]. Peptidylarginine deiminase 6 (PADI6) and maternal antigen that embryos require (MATER), localized to CPL, are required for the formation of CPL [35, 36]. PADI6/CPL complex is involved in regulating microtubule-mediated organelle localization and redistribution

during oocyte maturation. The PADI6/CPL complex may regulate organelle localization and redistribution by promoting the formation of stable acetylated microtubules [35]. MATER may work in concert with PADI6 and microtubule to orchestrate organelle redistribution during oocyte maturation [26]. Moreover, the mRNA vector Staufen and calreticulin are constantly expressed and selectively localize during oocyte maturation. At the GV stage both proteins display a dispersed distribution localization throughout the cytoplasm. Progressing to the MII stage, Staufen tends to aggregate to the cortical cluster of ER, while calreticulin assumes a pattern possibly coincidental with the position of the meiotic spindle that may mediate cytoskeletal remodeling during oocyte maturation [37]. After GVBD, a dense network of ER surrounds the spindle during its migration into the oocyte cortex. Later, the endoplasmic reticulum was reshaped into the characteristic cortical clusters of MII dependent not on microtubules but on microfilaments [32].

During maturation, human oocytes show altered ER distribution patterns and changes in IP_3R abundance, similar to those observed in mice [28]. Human GV-stage oocytes are characterized by an ER organized into a fine mesh that extends throughout the cortex and cell interior, whereas MII oocytes have large and distinct clusters of 2–3 mm in diameter throughout the cortex and cell interior. Moreover, in MII oocytes, ER clusters are not absent in the cortex near the MII spindle, consistent with the presence of microvilli on the spindle surface of oocytes in humans, unlike in mice [28]. In addition, during the GV-MII transition, Western blot analysis shows that oocytes have a 50% increase in IP_3R, while their capacity to release Ca^{2+} in response to IP_3 nearly doubles [31]. Thus, in a manner similar to mouse models, during maturation, human oocytes undergo changes in the distribution and composition of ER elements, which explains the increased capacity to release Ca^{2+}. However, human MII oocytes matured in vitro from GV stage oocytes are unable to support this increase in IP_3R abundance and Ca^{2+} releasing capacity despite the normal distribution of ER clusters of 2–3 mm. This suggests that the response to IP_3 may be reduced [28]. The similar distribution of the ER clusters and IP_3R further suggests that the ER clusters are specialized sites for the initiation and propagation of Ca^{2+} oscillations in oocytes [38].

Some research results suggest that the diabetic condition adversely affects the ER distribution pattern during mouse oocyte maturation and early embryo development [33]. In vitro matured oocytes have been reported to have lower developmental capacity. However, these results should be interpreted with caution as they are obtained using residual GV stage oocytes from stimulated in vitro fertilization (IVF) cycles, i.e., oocytes that are not representative of normal humans. Furthermore, in such experiments, GV-stage oocytes are cultured in the absence of cumulus cells, a condition known to profoundly affect many cellular and biochemical aspects of the maturation process [30].

These experiments demonstrate that ER reorganization during oocyte maturation is a complex multistep process involving distinct microtubule-dependent and filament-dependent stages and suggest a role for dynein in cytoplasmic changes [33]. These changes are an indispensable step in oocyte fertilization.

ER and mitochondria cooperate to complete oocyte maturation

Organelle rearrangement is another major theme of oocyte maturation [39]. Organelle positioning and movement in oocytes are largely mediated by microtubules and their associated motor proteins [30, 32]. The coordination of cytoskeleton and ER has been well summarized in previous reviews and will not be discussed here [30, 40]. Elements of the ER and other organelles whose functions are regulated during maturation are also redistributed according to precise spatiotemporal control [35]. For example, during spindle migration into the cortex, a clump of mitochondrial and ER elements surrounds the spindle, providing energetic and spatial information for the localization of the actin nucleation factor FMN2, which facilitates spindle displacement [41, 42].

Mitochondria and ER are involved in a variety of cellular processes including regulation of lipid biosynthesis and metabolic energy, Ca^{2+} homeostasis, and apoptosis [18, 27, 43, 44]. Interactions and functional interactions between these two organelles have also been reported in mouse oocytes. The ER forms a fine reticular network with large ER-rich clusters in the cortex of MII oocytes, as mitochondria appear to facilitate Ca^{2+} oscillations upon fertilization through a Ca-ATPase-driven Ca^{2+} pumping mechanism [45].

The mitochondrion-associated ER membrane (MAM) is a physically coupled structure between mitochondria and the ER in cells. and ER stress and other processes play a key role. These physiological functions of MAM are very important for the maturation of oocytes [45–47]. In recent years, studies have found that a variety of proteins on MAMs are involved in the maturation of oocytes (Fig. 1).

MAM is involved in regulating the fusion process of mitochondria. In MAM, the GTPase mitofusin (MFN) is mainly located on the outer mitochondrial membrane, and MFN includes two isoforms, MFN1 and MFN2. MFN1 or MFN2 on the mitochondrial outer membrane can form a homotypic or heterotypic structural complex, thereby building a bridge between the ER and mitochondria. MFN1/2 are located on the outer mitochondrial membrane, and another mitochondrial fusion GTPase, optic atrophy 1 (OPA1), located on the inner mitochondrial membrane mediates mitochondrial

fusion [47]. Using live-cell fluorescence imaging analysis, it is found that the ER is attracted to sites where *Mfn* is overexpressed, suggesting that MFN contributes to the bridge connecting mitochondria and ER [47]. In particular, MFN2-induced mitochondrial aggregation resulted in discrete ER networks and reduced ER Ca^{2+} storage. The lack or increase inMFN2 can lead to ER morphology and mitochondrion-ER physical and functional problems [48]. Aberrant ER morphology may impair ER Ca^{2+} homeostasis through ER-mitochondrion communication.

MAM is involved in the regulation of mitochondrial fission. Fission 1 (FIS1), located on the mitochondrial outer membrane, recruits mitochondrial dynamin-related protein 1 (DRP1), which is mainly located in the cytoplasm, to the fission site of the mitochondrial outer membrane, and DRP1 forms a ring structure through oligomerization, enabling the mitochondrial membrane to undergo fracture. BAP31 is a protein located on the ER membrane and can regulate the degradation and apoptosis pathways of misfolded proteins. When FIS1 binds to BAP31 in MAM, apoptotic signals are transmitted to the ER, thereby initiating the apoptotic pathway.

Clinical problems caused by the distribution of oocyte ER

In addition to the aforementioned genetic changes, ER has attracted clinical attention in terms of the different distribution and morphology of ER during in vitro maturation and fertilization of human oocytes [49]. Aggregates of SER (SERa) in oocytes are one of the cytoplasmic malformations of the oocyte. Several researchers reported that oocytes with SERa (SERa +) resulted in significantly lower fertilization rate, blastocyst rate, and pregnancy rate than controls [50]. Pregnancies in women with affected gametes are accompanied by a higher incidence of obstetric problems [50]. Indeed, partially mature oocytes recovered from treatment cycles of ovulation induction with gonadotropins displayed large aggregates of smooth ER, manifesting as single or multiple translucent vacuole-like structures 10–80 μm in diameter. The cause of this deformity is unknown. Their incidence is related to the duration and dose of gonadotropins used for stimulation. No SERa is observed in oocytes from unstimulated patients [51]. This, further, may support that exposure to in vivo (IVO) gonadotropins during the final stages of oocyte maturation and may induce the emergence of SERa, but it does not affect pregnancy outcomes or increase the newborn malformation rate [52].

SERa is thought to contribute to chromosome segregation errors and abnormal cell division [53]. SERa is associated with cytoskeletal changes, including increased spindle length and cortical actin disturbance [54]. Overall, SERa may negatively affect fertilization and post-fertilization events, with effects on embryo quality, implantation, and fetal development [55, 56]. The presence of SERa is associated with lower chances of successful pregnancy [57]. A reduction in the live birth rate with an increasing proportion of SERa oocytes is observed [58]. For these reasons, the effect of SERa on embryonic and obstetric outcomes has been assessed. In several studies, the presence of SERa + oocytes or their use in IVF has been described to be associated with malformations or genetic abnormalities in neonates [55, 56]. ESHRE guidelines recommend against using SERa + oocytes in IVF [49]. However, a recent study showed that healthy babies can be born from oocytes that display ER abnormalities [59]. Knowledge about this issue is still limited, and more systematic research is needed [60]. At present, transcriptomic research on various stages of oocyte development is increasing [61]. This review integrates the research results in recent years to provide a reference.

Gene abnormalities associated with the ER in oocytes

Transcriptomics

The ER may play an important role in the deterioration of oocyte quality during oocyte aging [62]. An analysis of transcriptomic data from single cell RNA-seq has shown that 32-week mice are involved in protection in GV oocytes compared to 5-week mice with downregulation of a group of genes under ER stress, including adiponectin receptor 2 (AdipoR2), interleukin 1 receptor-associated kinase 1 (Irak1), regulator of calcineurin 1 (Rcan1), and methionine sulfoxide reduction regulator of enzyme B1 (Msrb1) [62]. The expression of AdipoR2 has been shown in cow, pig, goat, and rat oocytes. Multiple studies have shown that adiponectin supplementation positively affects meiotic progression and initial embryonic development during in vitro maturation (IVM) of human, mouse, goat, and porcine oocytes [63].

Calcium normally acts as an activator of enzymes through the ER or mitochondria. By analyzing transcriptomic data, it was found that calcium signaling in IVM oocytes may be dysfunctional. The Kyoto Encyclopedia of Genes and Genomes (KEGG) results show that IVM and IVO oocytes can be clearly separated according to the expression of 52 genes involved in the calcium signaling pathway. In addition, the mean intensity of calcium signals is also reduced in human IVM oocytes compared to human IVO oocytes. Genes encoding PM proteins related to calcium transport are all downregulated; however, genes encoding ER and mitochondrial membrane proteins are upregulated [64].

Transcription of VDAC family members is significantly reduced in human IVM oocytes relative to IVO oocytes [64]. Voltage-dependent anion channel (VDAC) is a mitochondrion-associated Ca^{2+} transporter that regulates oocyte activation and is also known as mitochondrial porin [65]. Located on the outer mitochondrial membrane, VDACs act as gatekeepers for the entry and exit of mitochondrial metabolites, thereby controlling cross-talk between mitochondria and the rest of the cell. VDACs are also key players in mitochondria-mediated apoptosis [66]. VDAC2 is an autophagy inhibitor that exerts its function by inhibiting ovarian autophagy [67].

The mRNA expression levels of genes (*ITPR1*, *ITPR2*, *ITPR3*, *STIM1*, and *SERCA*) encoding ER membrane proteins are elevated in IVM oocytes [64]. *ITPR* encodes IP_3R, as previously described [68]. The combined action of STIM proteins in the ER membrane and Orai channels in the PM mediates the maintenance of cellular Ca^{2+} homeostasis [69]. The two proteins undergo a dynamic coupling process within the ER-PM junction region. This coupling process is initiated in response to depletion of Ca^{2+} stores in the ER, which triggers STIM protein activation. Thereafter, the opening of the Orai1 Ca^{2+}channel located in the PM allows the influx of extracellular Ca^{2+} [70–72]. However, it has actually been shown not to be necessary for store-operated Ca^{2+} entry in fertilized mouse eggs by research, in which they found that Ca^{2+} influx was not perturbed in fertilized eggs from double knockout STIM1/STIM2 mice or in Orai knockouts [73]. Rather, TRPM7 and Cav3.2 channels appear to mediate Ca^{2+} influx.

The mRNA expression levels of genes (*ORAI1*, *ORAI2*, *ORAI3*, *PKA*) encoding PM proteins are elevated in IVO oocytes, and the temporal and spatial regulation of PKA activity is critical for oocyte meiosis recovery [64, 74].

Furthermore, genes encoding calmodulin (CAM) and calcium/calmodulin-dependent protein kinase II (CAMKII) exhibited different expression profiles between IVM and IVO oocytes. The mRNA expression levels of *CAM1*, *CAM2*, and *CAM3* are elevated in IVO oocytes, and the mRNA expression levels of *CAMK2A* are elevated in IVM oocytes [64]. These differences persist at the protein level according to immunostaining and dot blot analysis. CAM is associated with oocyte maturation [75]. The inhibition of cell death mediated by the pentose phosphate pathway is due to the inhibitory phosphorylation of caspase-2 by CaMKII [76].

To demonstrate the effect of calcium concentration on human oocyte development, human IVO oocytes are fertilized, and the embryos are cultured in calcium-free medium. Fertilized embryos develop to the blastocyst stage at a lower rate than normal controls. Studies have shown that nearly all genes encoding membrane proteins in calcium metabolism pathways are downregulated, suggesting a potential barrier to uptake. Excessive calcium release leads to ER stress, which induces apoptosis and autophagy. In this study, genes involved in the ER stress pathway are not stably expressed, suggesting that ER is involved in releasing calcium and maintaining calcium concentrations in the cytoplasm, inducing apoptosis, and blocking development due to stress. Therefore, inhibiting the ER stress response will improve the maturation and development of human IVM oocytes.

Characteristic transcriptomic changes in oocytes with SER

The transcriptomes of human MII SERa + oocytes and normal MII oocytes without SERa (SERa-) have been analyzed by a microarray method, and gene expression profiles have been also analyzed. In SERa + oocytes, the most significantly enriched Gene Ontology (GO) term for upregulated genes is the GoLoco (otherwise known as GPR or "G-protein regulatory") motif, including the *RAP1GAP*, *GPSM3*, and *GPSM1* genes. Proteins containing the GoLoco motif control mitotic spindle organization, microtubule interactions, and chromosome segregation during cell division. Among them, GPSM1 (G protein signaling regulator 1) localizes to the ER membrane of the Golgi apparatus and controls spindle orientation, while RAP1GAP (RAP1 GTPase-activating protein) is involved in cell proliferation, differentiation, and embryogenesis [61].

Since SER is an important component of calcium signaling, differentially expressed genes that may have an effect on calcium signaling are valuable. Study found that in SERa + oocytes, 4 downregulated (*FAT1*, *ITGA10*, *LMAN2*, and *TGM4*) and 7 upregulated (*DLK1*, *DSPP*, *EYS*, *MMP28*, *PCDHB13*, *PCDHB8*, and *PCDHGA12*) genes encode proteins that bind at least a calcium atom or proteins whose function is calcium-dependent [61].

In addition, SERa + oocytes and SERa- oocytes have the following differences: a group of genes downregulated in SERa + oocytes are genes involved in cell division and mitotic/meiotic regulation, spindle assembly, and chromosome division. Specifically, low expression levels of the *NEK2* and *CROCC* genes may alter the centrosome cycle in which centrosome duplication and segregation occur. Decreased expression of *HAUS8*, *MAU2*, and *BIRC5* may alter microtubule formation, sister chromatid cohesion, chromosome alignment and segregation, and cell division within the mitotic spindle [61].

SERa + oocytes, compared with normal oocytes, involved mitochondrial structure and respiratory activity, suggesting that SERa may also reflect perturbations in the functional connection between the ER and mitochondrial network. Defects in calcium regulation of mitochondrial and energetic ATP homeostasis may have negative downstream developmental effects in SERa + oocytes.

Conclusion and perspectives

The ER plays an important role in both oocyte maturation and embryonic development and is a major site for protein synthesis, trafficking, and folding. For development to proceed properly, the oocyte also undergoes an appropriate calcium signaling response to initiate development and embryogenesis.

In terms of omics data, the correlation between mRNA and protein expression is weaker in oocytes than in other somatic cells. This insignificant correlation has been observed in many cell types but is especially pronounced in oocytes probably because of the storage of the mRNA pool [77]. In addition, intrinsic differences between individual oocytes still exist, and extrapolation of conclusions requires confirmation from subsequent experiments, as shown by mouse and human transcriptome studies. Additionally, it is difficult to reconcile the results described about transcriptomic analyses in oocytes matured in vitro vs in vivo, because fully-grown oocytes are transcriptionally silent up until the 2-cell stage or beyond depending on the species and regardless of the method of stimulating maturation (in vitro or in vivo). A comprehensive meta-analysis involving multiple datasets is still lacking. Great care is also needed when performing this analysis and only comparable elements should be included. Continued refinement of computer analysis tools will ultimately help improve our understanding of biological complexity. The proposed studies need to be considered and further validated to confirm that the results obtained are still applicable after implementation in humans, facilitating translation to the clinic.

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Author contribution All authors contributed to the study conception and design. Xin Kang and Jing Wang performed the literature search and wrote the manuscript and prepared the figure. LiyingYan revised the manuscript.

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Data Availability The data and material in this article are available.

Declarations

Conflict of interest The authors declare no competing interests.

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