Science Bulletin 70 (2025) 2365–2376

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Review

Human oocyte quality and reproductive health

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ARTICLE INFO

Article history:
Received 23 January 2025
Received in revised form 26 February 2025
Accepted 11 April 2025
Available online 21 April 2025

Keywords:
Hypothalamic-pituitary-gonadal axis
Granulosa cells
Human oocyte quality
Female fertility
Reproductive health

ABSTRACT

Declining female fertility is a health issue that has received broad global attention. Oocyte quality is the key limiting factor of female fertility, and key processes affecting oocyte quality involve the secretion of and response to hormones, ovarian function, oogenesis, oocyte maturation, and meiosis. However, compared with other species, the research and understanding of human oocyte quality and human reproductive health is limited. This review highlights our current understanding of the physiological factors and pathological factors related to human oocyte quality and discusses potential treatments. In terms of physiology, we discuss the regulation of the hypothalamic-pituitary-gonadal axis, granulosa cells, key subcellular structures, maternal mRNA homeostasis, the extracellular matrix, the maternal microenvironment, and multi-omics resources related to human oocyte quality. In terms of pathology, we review hypothalamic-pituitary-gonadal defects, ovarian dysfunction (including premature ovarian insufficiency and polycystic ovary syndrome), human oocyte development defects, and aging. In terms of the pathological aspects of human oocyte development and quality defects, nearly half of the reported pathogenic genes are involved in meiosis, while the remainder are involved in maternal mRNA regulation, the subcortical maternal complex, zona pellucida formation, ion channels, protein transport, and mitochondrial function. Furthermore, we outline the emerging scientific prospects and challenges for future explorations of the biological mechanisms behind infertility and the development of clinical treatments. This review seeks to deepen our understanding of the mechanisms regulating human oocyte quality and to provide novel insights into clinical female infertility characterized by defects in oocyte quality and oocyte development.

1. Introduction

Declining female fertility has become a major health issue and currently affects 10%–15% of couples globally [1]. Factors determining oocyte quality are complex and involve the processes of hormone regulation, ovarian function, granulosa cell proliferation, oogenesis, oocyte maturation, and meiosis. The hypothalamic-pituitary-gonadal (HPG) axis initiates gonadal steroid production and thus regulates ovary development, follicular development, and oogenesis. Human oocytes are generated during fetal life, and in the initial stage primordial germ cells, which are the progenitors of oocytes in the gonads, migrate to the genital ridge and transform into oogonia at 5–6 weeks post-conception [2]. After several rounds of mitotic proliferation, nests of oogonia are formed [3]. At 11–12 weeks of gestation, the oogonia initiate meiosis and differentiate into oocytes at the diplotene stage of prophase I [3]. Oocytes in primordial follicles are maintained in a state of growth arrest and are surrounded by a single layer of flattened granulosa cells [4]. Activated primordial follicles develop into primary follicles, which are characterized by the transformation of flattened granulosa cells into cuboidal granulosa cells [4], and the oocytes then enter into a growth phase corresponding to the formation of secondary follicles. In this process, the volume of the oocytes increases rapidly following a dramatic increase in transcriptional activity [5]. Oocytes subsequently accumulate a large amount of maternal mRNA to support oocyte maturation and embryo development. The resulting fully-grown oocytes are maintained under germinal vesicle (GV) arrest until puberty, at which time a surge of gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) triggers meiotic resumption and GV breakdown. This indicates the start of metaphase I (MI) and is followed by spindle assembly and chromosome alignment. MI oocytes extrude the first polar body and enter metaphase II (MII).

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https://doi.org/10.1016/j.scib.2025.04.045
2095-9273/

Meiosis is then arrested for a second time at MII until fertilization [6]. During fertilization, the oocytes acquire full developmental competence. The normal process of granulosa cell proliferation is directly associated with oocyte activation, growth, and maturation, and any defects in the HPG axis, ovary development, oogenesis, oocyte maturation, or meiosis will reduce oocyte quality and lead to reduced female fertility.

The current understanding of human oocyte quality remains limited, and in this review, we highlight recent advances in studies of the physiological factors and pathological factors affecting oocyte quality and human reproductive health. In terms of physiology, we summarize the studies on the secretion of and response to hormones, granulosa cells, key subcellular structures, maternal mRNA homeostasis, the extracellular matrix, the maternal microenvironment, and the multi-omics landscape of human oocytes. In terms of pathology, we focus on HPG defects, ovarian dysfunction, human oocyte developmental defects, and aging, we discuss the underlying genetic factors, and we present the molecular basis of these defects and the associated signaling pathways. Because there have been limited new advances in our understanding of human oocytes, we include some important findings in mouse oocytes for reference to enhance the exploration of related issues on human oocyte quality control. In addition, we discuss potential treatment strategies for improving human oocyte quality.

2. Physiological regulation of oocyte development

2.1. The HPG axis

The HPG axis controls the secretion of various reproductive hormones such as gonadotropin-releasing hormone (GnRH), gonadotropins, LH, and FSH [7]. The hypothalamic kisspeptin neurons and GnRH neurons induce the secretion of GnRH [8], which stimulates the secretion of gonadotropins (LH and FSH), which in turn control the processes of ovary development, oogenesis, and oocyte growth and maturation (Fig. 1). FSH hemostasis is regulated by antagonism between inhibin and activin, where activin promotes the release of FSH from pituitary cells, while inhibin, which is produced by the ovary, inhibits FSH secretion. *Inhbb* deficiency in mice causes loss of function of both activin B and inhibin B, and *Inhbb*-deficient female mice present increasing FSH levels, indicating that inhibin B is dominant over activin B [9,10]. There has been little research into the neuroendocrinology of the HPG axis over the past twenty years. However, it has recently been reported that muscle-derived myostatin can function as an endocrine hormone and can promote FSH synthesis and regulate ovarian function in mice [11]. Furthermore, the known thyrotropin-releasing hormone mediates a novel transient neurohormonal circuit that controls hatching in fish [12]. It is therefore worth investigating whether these new pathways also play key roles in human infertility.

2.2. Granulosa cells support oocyte growth

Oocytes originating from primordial germ cells are physically coupled to the somatic supporting cells (granulosa cells) during their development into follicles. Granulosa cells support oocyte activation, growth, and maturation, while the oocyte can in turn regulate the activity of granulosa cells (Fig. 2). Thus, normal granulosa cell function is essential for ensuring oocyte quality. Specificity protein 1 (SP1) governs the formation of primordial follicles in mice by regulating pre-granulosa cell development [13], while the PI3K/PTEN/AKT pathway and cAMP activity in the ovaries are known to regulate the activation of primordial follicles [14]. During the primordial-to-primary follicle transition in mice, glycolysis activity is increased in granulosa cells and is decreased in oocytes,

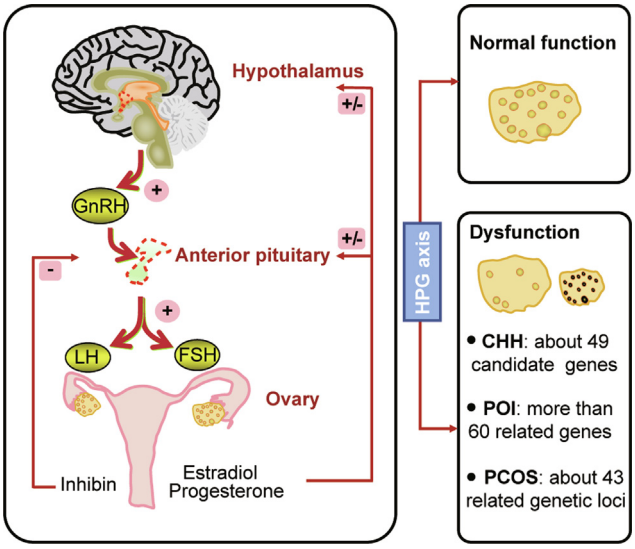

Fig. 1. The HPG axis and ovary function. Kisspeptin stimulates GnRH neurons in the hypothalamus to release GnRH. GnRH in turn promotes the secretion of gonadotropins including FSH and LH, which maintain the normal function of the ovary. The sex hormones (estradiol, progesterone, and inhibin) produced by the ovaries can generate feedback to the HPG axis. Dysfunction of the HPG axis causes ovary dysfunction, including CHH, POI, and PCOS. The image was designed in Adobe Illustrator and the ScienceSlides software.

thus promoting the activation of primordial follicles through mTOR signaling [15]. Poly (ADP-ribose) polymerase 1 (PARP1) is expressed in pre-granulosa cells and determines primordial follicle activation by catalyzing the PARylation of YY1 and inducing endoplasmic reticulum stress [16]. Gap junctions provide two-way communication between oocytes and granulosa cells, which is essential for ensuring oocyte quality. Deficiency in connexin43 (CX43) or connexin37 (CX37) in mice disrupts the communication between oocytes and granulosa cells thus causing oocyte growth arrest and female infertility [17]. The factors secreted by oocytes, such as IGF-I, GDF9, and BMP15, have been reported to regulate granulosa cell growth and proliferation in a paracrine manner [18,19]. Recently, R-spondin2 (RSPO2) has been shown to function as a secreted activator of the WNT/β-catenin signaling pathway in a similar manner. RSPO2 deficiency impairs oocyte and granulosa cell communication and granulosa cell proliferation, thus leading to follicular growth arrest and female infertility [20]. Autophagy also plays an essential role in granulosa cell differentiation by degrading the transcription factor Wilms Tumor 1 (WT1), which is essential for ovarian function [21]. Lysine-specific demethylase 1 (LSD1) affects the formation of FSH-induced antral follicles by promoting autophagy and suppressing *Wt1* expression in granulosa cells [22]. Advanced oxidation protein products, which show elevated levels in women with premature ovarian insufficiency (POI), impair autophagic flux and lysosomal biogenesis via the ROS-mTOR-TFEB signaling pathway [23]. Cytoplasmic polyadenylation element binding protein 3 (CPEB3) affects mRNA homeostasis in granulosa cells leading to the gradual loss of follicles and subsequent infertility [24]. FSHR and LHCGR are essential for the cellular response to FSH and LH. Fucosyltransferase 8 (FUT8) regulates the N-glycosylation of FSHR and its response to FSH. FUT8 deficiency inhibits the communication between granulosa cells and oocytes and reduces transzonal projection formation causing reduced oocyte developmental competence and female infertility [25]. *LARS2*, *SIRT1*, *LONP1*, *C1QL1*, *TAp63*, *BRE*, and *BMI1* are reported to affect granulosa cell proliferation, and defects in these genes induce granulosa cell apoptosis resulting in female infertility [26]. Furthermore, microRNAs also influence the function of gran-

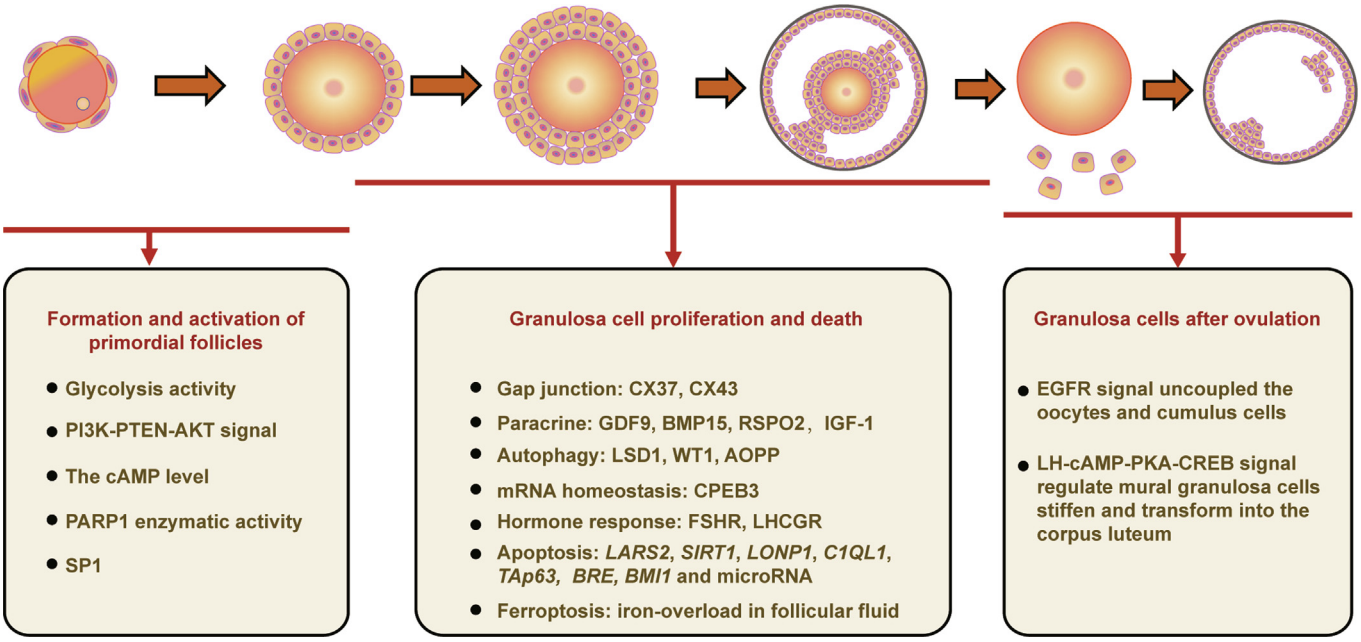

Fig. 2. The physiological regulation of granulosa cells. Factors and their involved pathways affecting the normal function of granulosa cells are summarized. The image was designed in Adobe Illustrator.

ulosa cells. For example, mir-484 in human follicular fluid induces mitochondrial dysfunction and granulosa cell apoptosis via the regulation of *YAP1* expression [27]. Mir-143-3p/mir-155-5p regulates follicular dysplasia by modulating glycolysis in granulosa cells in PCOS [28]. Follicular fluid with excessive levels of iron can trigger granulosa cell ferroptosis, and this is associated with endometriosis-related infertility [29]. After ovulation, the EGFR signal induces the retraction of transzonal projections and uncoupling of the oocyte from the cumulus cells [30]. The granulosa cells remaining within the follicles stiffen and transform into the corpus luteum, and this process is regulated by focal adhesion assembly, which is stimulated by the LH (hCG)-cAMP-PKA-CREB signaling cascade [31].

2.3. Subcellular structures control oocyte quality and development

2.3.1. Spindle assembly in human oocytes

The bipolar spindle is required for chromosome separation in both mitosis and meiosis (Fig. 3). Spindle assembly consists of microtubule nucleation and spindle bipolarization, and centrosomes contribute to both microtubule polymerization and spindle bipolarization during mitosis. In contrast to mitotic cells, centrosomes are degenerated during oogenesis in most species, including worms, flies, mice, and humans [32]. In mouse oocytes, multiple acentriole microtubule organizing centers (aMTOCs) can functionally substitute for centrosomes [33]. Compared to mouse oocytes, the prominent aMTOCs are absent throughout human female meiosis [34], indicating distinct mechanisms of spindle assembly in human oocytes.

The process of spindle assembly in human oocytes has recently been described, and a novel distinct microtubule nucleator has been identified that has been termed the human oocyte microtubule organizing center (huoMTOC) [35]. The huoMTOC is formed at the cortex and moves to the nucleus before nuclear envelope breakdown (NEBD), and it serves as a nucleation center for microtubules around chromosomes after NEBD. The huoMTOC is comprised of several core components, namely CCP110, CKAP5, DISC1, and TACC3. These components are expressed during NEBD

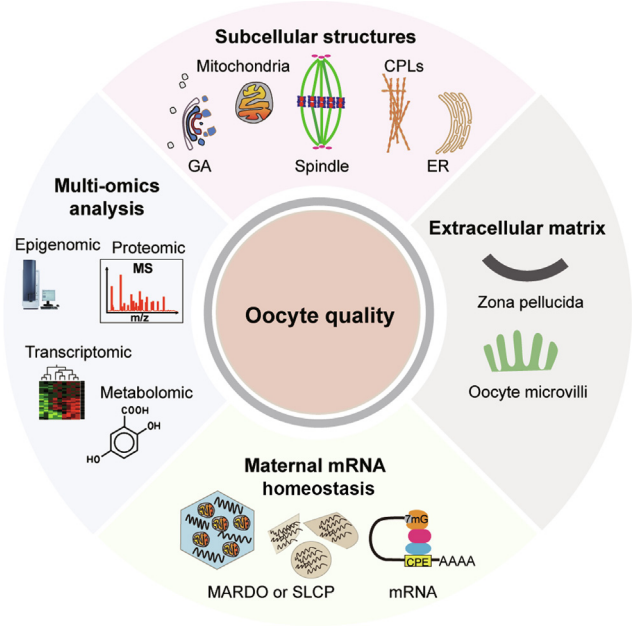

Fig. 3. Physiological regulation of oocytes**.** The key subcellular structures, maternal mRNA homeostasis, the extracellular matrix, maternal mRNA, and proteins identified by multi-omics analysis determine human oocyte quality. GA: Golgi apparatus; ER: endoplasmic reticulum; CPLs: cytoplasmic lattices; MARDO: mitochondria-associated membraneless compartment; SLCP: sponge-like cortical partition. The image was designed in Adobe Illustrator and the ScienceSlides software.

and are subsequently recruited to kinetochores for microtubule nucleation. Mutations in *TACC3* cause the failure of spindle microtubule polymerization in human oocytes, suggesting that the huoMTOC is essential for spindle assembly in human oocytes.

Following microtubule polymerization, microtubules are sorted and arranged to establish spindle bipolarity. In the absence of centrosomes, the original poles are formed through the coalescence of microtubule minus ends, and these are referred to as "minor poles"

[36]. Multiple minor poles combine to form kinetochore clusters and establish multipolar intermediates during prometaphase I. The establishment of bipolar spindles relies on the functions of *HAUS6*, *KIF11*, and *KIF18A*, which are responsible for microtubule amplification, spindle elongation, and the maintenance of spindle structure homeostasis. Mutations in these key genes disrupt spindle bipolarity in human oocytes. The minor poles are then aggregated into two opposing major poles, which are then organized and focused by the nuclear mitotic apparatus (NuMA) protein [37]. Through these distinct mechanisms, human oocytes assemble a bipolar spindle in a lengthy process that does not involve centrosomes or prominent aMTOCs.

2.3.2. Mitochondrial remodeling of human oocytes

Mitochondria play diverse roles in oocyte function and are a major factor affecting oocyte quality (Fig. 3), and mitochondrial dysfunction is associated with poor developmental competence in aging oocytes [38]. Compared with mitotic cell mitochondria, oocyte mitochondria have several specific characteristics, including spherical morphology, fragmented mitochondrial networks with few cristae, and high mtDNA content [38]. Previous studies on mitochondria and oocyte quality have mainly been performed using transgenic mouse models [39–41], and disruptions in genes associated with mitochondrial fusion and division in mice have been shown to significantly decrease oocyte quality. For example, the deletion of *DRP1* and *MFN1* causes mitochondrial dysfunction and reduced oocyte quality [39,40]. In human primordial germ cells, the mitochondria are round with small vesicular cristae near the nuclei, while oocyte mitochondria in primordial follicles and primary follicles contain round or irregular mitochondria with typical parallel or arched cristae [42]. In growing oocytes, the number of mitochondria increases, and these disperse throughout the ooplasm. In MII oocytes, mitochondria aggregate and exhibit smooth endoplasmic reticulum tubules and vesicles [42]. In 2016, a non-membrane-bound compartment containing RNA, mitochondria, and other organelles named the Balbiani body was reported in vertebrate early oocytes, including human oocytes [43]. Subsequent studies showed that mammalian oocytes, including human oocytes, store mRNAs in a mitochondria-associated membraneless compartment (MARDO) [44]. In addition, Rodríguez-Nuevo et al. [45] proposed that human oocytes maintain a ROS-free metabolism by remodeling the mitochondrial electron transport chain through the elimination of complex I. This suggests that oocyte mitochondria may have been remodeled throughout evolution to play a specific role in oocyte maturation and embryo development [44]. However, the purification and isolation of sufficient oocyte mitochondria for omics analysis and functional assays is difficult. Because complex I is absent in early human oocytes, how oocytes adjust the electron transport chain and which complexes provide the primary energy metabolism in human oocytes remain unknown. A recent study in somatic cells showed that mitochondria can be remodeled into two distinct subpopulations depending on energy demands [46]. Furthermore, the 187AA form of CYTB, which is encoded by mtDNA, was reported to be essential for follicle development and female fertility [47]. All of these studies indicate the specificity of oocyte mitochondria. However, although mitochondrial remodeling during oogenesis, oocyte growth, and oocyte maturation is related to dynamic changes in mitochondrial morphology, structure, and activity as well as the TCA cycle, the key factors and pathways regulating these processes have remained poorly understood. Thus, the mechanisms of oocyte mitochondria remodeling require further investigation.

2.3.3. Other subcellular structures regulating oocyte development

During oocyte meiotic maturation, human oocytes reorganize the Golgi apparatus and endoplasmic reticulum to coordinate cortical granule release and calcium oscillations in response to fertilization [48]. The endoplasmic reticulum and the Golgi apparatus also affect oocyte quality by regulating the glycosylation of key molecules such as ZP1 and PANX1 [49,50]. Cytoplasmic lattices, which are cytoskeletal structures specifically seen in mammalian oocytes, are essential for embryo development competence [51]. By using super-resolution microscopy, quantitative mass spectrometry, and cryo-electron tomography, Jentoft et al. [52] confirmed that cytoplasmic lattices are formed from arched filaments and are assembled by the subcortical maternal complex proteins that localize to the cytoplasm of oocytes and preimplantation embryos. Furthermore, endolysosomal vesicular assemblies (ELVAs), which are specialized non-membrane-bound compartments composed of endolysosomes, autophagosomes, and proteasomes, are observed in mouse oocytes and are essential for mouse embryo survival by accumulating protein aggregates [53]. However, whether ELVAs exist in human oocytes and if so what their role is in human oocyte quality need to be confirmed.

2.4. The extracellular matrix and the maternal microenvironment

The zona pellucida (ZP) is a viscoelastic extracellular matrix surrounding all mammalian oocytes and early embryos. Compared with mice (which express ZP1–3), the human ZP is composed of four glycosylated proteins (ZP1–4) [54]. The ZP proteins harbor a ZP domain, and it has been shown that the ZP domain of ZP2 and ZP3 is responsible for the polymerization of ZP proteins into filaments [55]. The ZP facilitates the interconnections between transzonal projections and oocyte microvilli and the formation of gap junctions [56,57]. After recognizing and binding to the ZP of first polar body oocytes, the sperm attempt to pass through the ZP and fuse with the oocyte plasma membrane to form a zygote. As soon as the first sperm reaches the oocyte plasma membrane, the ZP hardens to prevent polyspermy [58]. Recent studies have shown that cleavage of the N-terminal region of ZP2 triggers the oligomerization of the protein. This oligomerization promotes the cross-linking of ZP filaments that hardens the ZP and blocks polyspermy [58]. Deficiency of ZP proteins in mice impairs ZP assembly and female fertility, and this is characterized by a thinner ZP or absent ZP leading to reduced oocyte ovulation, fertilization failure, and embryo development arrest [59–61]. Oocyte microvilli are another important component of the extracellular matrix of oocytes, and deletion of radixin in mice impairs the formation of oocyte microvilli and causes oocyte growth and follicle development delays leading to reduced female fertility [62]. Furthermore, ARP2/3 deficiency in mouse and human oocytes re-organizes the cortex and induces cortical contractions that affect oocyte quality [63]. The secreted proteins, metabolites, and small molecules in the follicular fluid and blood may affect oocyte quality and follicle development. Urinary trypsin inhibitor (UTI) is a serine proteinase inhibitor enriched in follicular fluid, blood, and urine, and *Uti*-deleted female mice show severely reduced fertility characterized by disorganized corona radiata. However, wild-type mice transplanted with *Uti*-deficient ovaries can give birth normally, indicating that UTI is supplied from the systemic circulation [64]. Neonatal ketone bodies are essential for the primordial reservoir in newborn mice [65], and a hyperglycemic environment also reduces oocyte quality. It is reported that pregestational hyperglycemia causes insufficient demethylation of oocyte TET3, which results in an increased risk of glucose intolerance in the offspring [66]. Furthermore, maternal obesity can induce meiotic defects and epigenetic alterations in fetal oocytes [67]. Thus, the extracellular matrix and maternal microenvironment are essential for oocyte quality by affecting the bidirectional communication between oocytes and cumulus cells during the process of fertilization (Fig. 3).

2.5. Maternal mRNA homeostasis maintains oocyte quality

Maternal mRNA accumulation is primarily regulated by transcription factors. After the transition from primordial follicles to primary follicles, oocytes undergo growth with enlarged volumes accompanied by sharply increased transcription activity. Transcription is silenced during oocyte maturation and early embryogenesis before embryonic genome activation [68], and thus large amounts of mRNAs accumulate in the growing phase to support subsequent oocyte maturation, meiosis, and early embryo development (Fig. 3). Membraneless organelles formed by phase separation play a general role in maternal transcript storage and stability. In mammalian oocytes (including human oocytes), a ZAR1-mediated MARDO or YBX2-mediated sponge-like cortical partition is responsible for maternal mRNA storage and stability [44,69]. In Drosophila oocytes, the oskar ribonucleoprotein granules undergo a liquid-to-solid phase transition, which is essential for embryonic development [70]. In addition, N6-methyladenosine (m6A) and 5-methylcytosine (m5C) are associated with maternal mRNA stability during oocyte maturation and the maternal-to-zygotic transition in mice [71,72]. Recent studies have identified several critical factors that regulate maternal mRNA turnover in mouse oocytes. The length of the poly(A) tail controls the stability and translation of maternal mRNA [73]. BTG4 is essential for maternal mRNA clearance and deadenylation by functioning as an adaptor of the CCR4-NOT complex [74], and CNOT6L is a catalytic subunit of the CCR4-NOT deadenylase complex that mediates maternal mRNA decay in combination with ZFP36L2 [75]. PABPN1L, a poly(A)-binding adapter for BTG4, couples with the CCR4-NOT deadenylase complex to promote maternal mRNA clearance [76]. mRNA transporter 4 (MTR4) is an RNA helicase involved in RNA surveillance and determines the volume of mouse oocytes, and *Mtr4* deficiency in oocytes impairs the accumulation of transcripts in the cytoplasm leading to smaller oocytes [77]. The function of BTG4 and ZFP36L2 in human oocytes was further confirmed by human genetic studies [78,79]. Despite these findings, novel maternal factors, unknown signaling pathways, and specific regulatory mechanisms are still worthy of further exploration in human oocytes.

2.6. Multi-omics dynamics in human oocytes

The application of multi-omics technologies such as epigenomics, transcriptomics, proteomics, and metabolomics has provided a deep understanding of the biological processes of human oocyte maturation, fertilization, and embryo development.

2.6.1. Epigenomics

DNA methylation, histone modification, and non-coding RNA are the main types of epigenetic regulation in oocytes. The DNA methylation pattern is established by DNMTs in a transcription-dependent manner during the oocyte growth phase [80–82], and the methylome in oocytes is maintained by stella, which prevents the *de novo* methylation that is normally mediated by DNMT1 [83]. Both parental genomes undergo global DNA demethylation at the time of fertilization, and methylation is re-established after implantation [84–87]. SETD2 is crucial for embryonic development by establishing the maternal epigenome [82]. The distribution of H3K4me3 and H3K27me3 modifications in human oocytes is similar to that of somatic cells, but the pattern in human early embryos is distinct. The H3K27me3 modification is globally removed prior to zygotic genome activation (ZGA) and is re-established at the morula stage. Global *de novo* H3K4me3 methylation is present in pre-ZGA embryos, but this is reprogrammed into a somatic-like pattern after ZGA [88]. The parental 5-hydroxymethylcytosine that is present during human preimplantation development regulates the gene expression of early lineage specification [89]. Oocyte TET3 is responsible for the epigenetic regulation of the maternal inheritance of glucose intolerance [66], and the mitochondrial dysfunction caused by Drp1 deficiency can affect the maternal epigenome leading to embryonic development arrest [39]. Endogenous small interfering RNAs, which are more active in mouse oocytes than somatic cells, can regulate gene expression [90,91]. A class of short PIWI-interacting RNAs has been observed in both human and monkey oocytes [92]. There also exists bulk long non-coding RNAs (lncRNAs) in human and mice oocytes, most of which are degraded prior to ZGA. Sirena1, the most abundant lncRNA in mouse oocytes, is involved in RNA interference and mitochondrial distribution, but *Sirena1* knockout has no effects on female fertility [93]. Thus, the role of small RNAs and lncRNAs in oocytes needs to be further confirmed.

2.6.2. Transcriptomics

Two studies in 2013 and 2018 reported the most complete transcriptomic landscape of human oocytes and early embryos, respectively [94,95]. During the growth phase, human oocytes accumulate a large amount of maternal mRNA, and this is degraded by maternal and zygotic decay both before and after ZGA to drive cell-cycle progression and subsequent embryonic development [45,46]. Comparative transcriptome analysis of maternally biased genes (MBGs) and paternally biased genes (PBGs) in the preimplantation stages showed that MBGs are present at the 4-cell stage while PBGs are present at the 8-cell stage. The MBGs were shown to be essential for the initiation of embryonic genome activation, while the PBGs were shown to affect embryo compaction and trophectoderm specification [28].

2.6.3. Proteomics

The first proteomes of human GV and MII oocytes were reported in 2016 and identified 2154 proteins and provided a list of human maturation-specific proteins [96]. A single-cell quantitative proteomic analysis of human GV and MII oocytes matured *in vivo* compared to those matured *in vitro* showed high heterogeneity, and there was little correlation between mRNA and protein changes during maturation [97]. The proteome of human pre-implantation embryos was reported at the single-cell level in 2023, and this showed the stage-specific protein expression and proteomic patterns during the maternal-to-zygotic transition [98]. The proteomic dynamics before and around ZGA were distinct in humans and mice, and proteins encoded by ZGA transcripts were associated with the first lineage specification. The comparative analysis of proteomic profiles between poor-quality human embryos and good-quality embryos also provided potential candidates associated with preimplantation development failure [99].

2.6.4. Metabolomics

Due to the limited availability of biological samples, studies on metabolic patterns in mammalian oocytes and embryos have been sparse, and there have been no metabolomics studies in human oocytes. The metabolic landscape of mouse oocytes showed that arachidonic acid-regulated polyunsaturated fatty acid levels decrease and that the serine-glycine-one-carbon pathway is activated during meiotic maturation [100]. Two-cell embryos remain in a reductive state with high methionine, polyamine, and glutathione metabolism, while blastocysts maintain a more oxidative state with higher mitochondrial tricarboxylic acid cycle activity [101]. Taken together, these studies systematically provide an omics landscape of human oocytes and embryos, thus providing a foundation for identifying specific factors that affect human oocyte quality (Fig. 3).

3. Pathological factors affecting oocyte quality

3.1. HPG defects

The HPG axis controls human sexual development and reproductive capacity via GnRH, FSH, and LH [8]. Dysfunction of the HPG axis in females can result in hypogonadism manifesting as hormonal disorders, absent or delayed puberty, and infertility [102]. The hypogonadism can present as hypergonadotropic or hypogonadotropic hypogonadism. Hypogonadotropic hypogonadism can be summarized as low sex hormone levels along with low or normal FSH/LH [102]. Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder that results from abnormal GnRH secretion and action, leading to delayed puberty and infertility. As reviewed by Young et al. in 2019, nearly 43 genes are associated with CHH [88]. Recent studies have identified another six genes associated with CHH, namely *PRDM13*, *NDNF1, NOS1*, *MADD*, *POGZ*, and *NEUROG3*. PRDM13 regulates the GABAergic cell fate in the cerebellum and kisspeptin neuron development in the hypothalamus, and defects in *PRDM13* cause CHH [103]. *NOS1* defects in hypothalamic neurons affect the secretion of GnRH [104]. *NDNF* mutants impair GnRH neuron migration, thus inducing severe GnRH deficiency and CHH [105]. A splice site variant in *MADD* (pathogenic gene for DEEAH syndrome) and a heterozygous *de novo* mutation in *POGZ* (pathogenic gene for White-Sutton syndrome) have been reported to affect hormone expression causing CHH [106,107]. Biallelic *NEUROG3* variants cause malabsorptive diarrhea and insulin-dependent diabetes mellitus and also present with CHH, but only rarely [108]. The role of *MADD*, *POGZ*, and *NEUROG3* in CHH needs to be further confirmed by functional assays and genetic studies. These genes are enriched in GnRH neuron migration and axon projection pathways (19/49), GnRH neuron homeostasis (11/49), GnRH neuron fate and differentiation (8/49), and gonadotrophin defects (8/49) (Table 1).

Hypergonadotropic hypogonadism is characterized by low sex hormones and high FSH/LH levels, and women with hypergonadotropic hypogonadism usually present with ovarian failure. Women with karyotype (45, X), also termed as Turner syndrome, present with primary amenorrhea, improper sexual development, and irreversible ovarian failure [109]. Partial X chromosome deletions such as X11q also impair ovarian function [109]. Furthermore, mutations in *AR*, *NR5A1*, *SRY*, and *WT1* affect sex determination and differentiation leading to infertility [8]. Mutations in luteinizing hormone receptor (*LHCGR*) cause female infertility characterized by primary amenorrhea, oligomenorrhea, and anovulation due to LH resistance [110].

3.2. Ovary dysfunction

As the location where oogonia, oocyte growth, follicle development, oocyte maturation, meiosis, and apoptosis occur, the female ovary is critical for oocyte quality and human reproduction. POI and polycystic ovary syndrome (PCOS) are two major ovarian disorders (Fig. 1). POI is characterized by deficient ovarian function before the age of 40 years and usually presents as hypergonadotropic hypogonadism [111]. Chromosome abnormalities can explain up to 13% of POI cases [111,112]. *FMR1* is the most common monogenic cause of fragile X syndrome with clinical implications in POI [113]. As reviewed by Jiao et al. and Huhtaniemi et al. in 2018, 31 genes have been associated with syndromic or non-syndromic POI [111]. Recently, a large cohort study of POI (1030 cases vs. 5000 controls) in China identified 20 novel POI-associated genes [114], while a cohort study of 375 POI patients in Europe identified another 9 candidate genes [115]. Thus nearly 60 genes have been associated with the development of POI. A total of 45.00% (27/60) of these genes are involved in meiosis, with 23 of the 27 being enriched in homologous recombination and DNA damage repair. A total of 28.33% (17/60) of the candidate genes participate in follicle assembly, activation, growth and development, and granulosa cell proliferation and differentiation (Table 2). Five genes (8.33%) affect the process of oocyte maturation and ovulation. The remaining genes take part in primordial germ cell mitosis (3/60), cell death (3/60), immunity (1/60), autophagy (1/60), and post-transcription regulation (1/60) (Table 2). The function of *CCDC150* and *CCDC185* are unknown. Most of these genes and variants have not been verified by functional assays, and the causal relationship between mutations and POI and the associated regulatory mechanisms and key targets need further study.

Table 1
Pathways of 49 genes associated with CHH.

Gene function	No. of genes	Associated genes
GnRH neuron migration and axon projection	19	*KAL1, PROK2, PROKR2, SEMA3A, PLXNA1, SEMA3E, NSMF, HS6ST1, WDR11, SOX10, FEZF1, IGSF10, DCC, NTN1, TUBB3, SMCHD1, CCDC141, NDNF, POGZ*
GnRH neuron homeostasis	11	*GNRH1, KISS1, KISS1R, TAC3, TACR3, LEP, LEPR, PCSK1, DXML2, KLB, NOS1*
GnRH neuron fate and differentiation	8	*FGF8, FGFR1, SOX2, CHD7, FGF17, IL17RD, PRDM13, NEUROG3*
Gonadotrophin defects	8	*GNRHR, NROB1, PNPLA6, POLR3B, POLR3A, FSHB, LHB, MADD*
Neuron degeneration	3	*OTUD4, RNF216, STUB1*

PCOS is another example of ovarian dysfunction and is characterized by hyperandrogenemia, oligomenorrhea, amenorrhea, chronic anovulation, and polycystic ovarian morphology [116]. It affects 6%–8% of women of reproductive age worldwide [117,118]. PCOS is highly associated with obesity, insulin resistance, and endocrine abnormalities. Familial clustering and phenotype heritability of PCOS indicate a genetic contribution to PCOS [119], and thus the determinants of PCOS are complex and involve both genetic and environmental factors. Genome-wide association studies in East Asian and European populations identified 43 genetic loci that were significantly associated with PCOS [117,118]. Candidate genes in these loci were enriched in pathways related to obesity, insulin metabolism, menopause, hyperandrogenism, anovulation, and inflammation. Epigenetic changes also play a role in PCOS, and it is reported that PCOS traits can be transmitted to multiple generations in mice through an altered landscape of DNA methylation [120]. Common hypomethylation signatures are also present in women with PCOS, indicating a conserved mechanism in humans [120]. It has been shown that lncMAP3K13-7:1 can inhibit the expression of *DNMT1* leading to *CDKN1A* promoter hypomethylation, which leads to ovarian granulosa cell proliferation in PCOS [121]. Studies have proposed that gut microbes and microbial metabolites in the circulation affect ovarian function leading to PCOS [122]. For example, the microbial metabolite agmatine from intestinal *Bacteroides vulgatus* activates the farnesoid X receptor pathway and promotes PCOS in female mice [123], and modifying the gut microbiota can alleviate PCOS via the gut microbiota-bile acid-interleukin-22 axis [124]. The secondary metabolite AT-C1 from intestinal fungus can also promote the development of PCOS via the gut AhR-IL-22 axis [125].

3.3. Human oocyte developmental defects

The genetic factors affecting human oocyte development have remained poorly understood for many years, but emerging studies indicate that human oocyte development defects have Mendelian

Table 2
Pathways of 60 genes associated with POI.

Gene function		No. of genes	Associated genes
primordial germ cells proliferation and differentiation		3	*NANOS3, PRDM1, LGR4*
Meiosis	Meiosis initiation	2	*MEIOSIN, STRA8*
	Homologous recombination and DNA damage repair	23	*STAG3, SMC1B, REC8, SYCE1, PSMC3IP, SPIDR, HFM1, MSH4, MSH5, MCM8, MCM9, CSB-PGBD3, NUP107 KASH5, CPEB1, MCMDC2, NUP43, RFWD3, SHOC1, SLX4, HROB, HELQ, SWIS*
	Meiosis resumption	1	*H1-8*
	Spindle microtubule assembly	1	*CENPE*
Follicle	Follicle assembly	1	*FIGLA*
	Follicle activation	3	*LHX8, NOBOX, SOHLH1*
	Follicle growth and development	11	*GDF9, BMP15, BMPR2, AMH, AMHR2, FOXL2, WT1, NR5A1, FSHR, KHDRBS1, BMP6*
	GC proliferation and differentiation	2	*HMMR, HSD17B1*
Oocyte maturation and ovulation		5	*ZAR1, ZP3, ALOX12, PPM1B, MST1R*
Cell death		3	*FMR1, EIF4ENIF1, PGRMC1*
Immunity		1	*NLRP11*
Autophagy		1	*SPATA33*
Post-transcription regulation		1	*ELAVL2*
Unknown		2	*CCDC150, CCDC185*

GC: granulosa cells.

inheritance patterns [49,126]. The widely used whole-exome sequencing technique has now identified 37 mutant genes that are reported to be responsible for defects in human oocyte quality and oocyte development.

3.3.1. Disruption of meiosis

Meiosis is essential for oogenesis and oocyte maturation and for converting primordial germ cells into haploid oocytes. Nearly half of the identified genes (17/37, 45.95%) associated with reduced oocyte quality and development defects are involved in meiosis (Fig. 4a and Table 3). Spindle assembly is one of the key events in meiosis. *TUBB8*, *TUBA4A*, *KIF11*, *HAUS6*, *KIF18A*, and *TACC3* are involved in human spindle assembly (Fig. 4a), and variants in these genes cause human oocyte meiotic arrest [35,36,126]. It is worth noting that dominant mutations in *TUBB8,* the first pathogenic gene shown to cause oocyte meiotic arrest, account for the etiology of oocyte metaphase I arrest in up to 30% of patients [126]. During meiosis, DNA double-strand breaks and homologous chromosome recombination are essential for genome diversity and proper chromosome segregation during the first meiotic division [127]. Mutations in genes involved in double-strand break formation such as *REC114*, *MEI1*, *MEI4*, and *TOP6BL* are responsible for early embryonic arrest and hydatidiform mole formation [128–131]. The AAA + ATPase thyroid hormone receptor interactor 13 (TRIP13) monitors meiotic recombination progression and functions as a surveillance protein, and bi-allelic missense mutations in *TRIP13* are responsible for oocyte MI arrest (Fig. 4) [132]. Six reported genes code for checkpoint proteins that mediate cell cycle progression for oocyte maturation, fertilization, and embryo development (Fig. 4a, b and Table 3). *CHEK1* and *MOS* have been shown to be a cause of zygote arrest [133,134]. *FBOX43*, *CDC20*, and *CDC23* encode subunits of the CDC20-APC/C complex and have been shown to cause oocyte maturation arrest and early embryonic arrest [135–137]. *WEE2* encodes an oocyte meiosis-inhibiting kinase, and variants in *WEE2* reduce the phosphorylation of CDK1 and impair maturation-promoting factor activity causing fertilization failure [138].

3.3.2. Dysregulation of maternal mRNA dynamics

The accumulation and timely degradation of maternal mRNA is essential for oocyte quality and embryo development competence. A total of 16.22% (6/37) of the identified mutant genes participate in maternal mRNA regulation in human oocytes (Fig. 4 and Table 3). In 2017, *PATL2* was the first gene reported to cause human oocyte GV arrest, and the RNA-binding protein PATL2 was shown to be essential for maternal mRNA accumulation and stability [139]. *LHX8* and *TBPL2* regulate mRNA transcription in human oocytes, and variants in these genes cause human oocyte maturation arrest [140,141]. BTG4 and ZFP36L2 are adaptors of the CCR4-NOT deadenylate complex and promote the decay of maternal mRNAs in early embryonic development, and variants in *BTG4* and *ZFP36L2* cause human zygote arrest and early embryonic arrest [78,79]. In addition, PABPC1L is essential for maternal mRNA translation activation, and *PABPC1*L variants cause early embryonic arrest by impairing the ERK pathway [142].

3.3.3. Deficiency of the subcortical maternal complex

The subcortical maternal complex is a maternally inherited multiprotein complex that localizes to the cell subcortex. This structure, which is unique to oocytes and preimplantation embryos, is essential for early embryo development in mammals, including humans. A total of 18.92% (7/37) of the reported pathogenic genes are members of the subcortical maternal complex (Fig. 4 and Table 3). Familial inherited *NLRP7* and *KHDC3L* variants have been reported to cause hydatidiform mole [143,144], *TlE6* was found to be responsible for fertilization failure [145], *PADI6* was identified as the first mutant gene responsible for early embryonic arrest [146], and variants in *NLRP2*, *NLRP5*, and *OOEP* have been reported to be responsible for human early embryonic arrest [147,148].

3.3.4. Anomalies in the ZP

The human ZP matrix is a delicate network of thin interconnected filaments and is essential for oocyte quality, and 10.81% (4/37) of the identified pathogenic genes affect ZP assembly (Fig. 4 and Table 3). In 2014, mutant *ZP1* was shown to follow an autosomal recessive inheritance pattern leading to abnormal oocytes lacking a ZP [49]. A recurrent heterozygous missense mutation in *ZP3* was reported to be responsible for empty follicle syndrome by impairing ZP formation and the communication between cumulus cells and oocytes [149]. Homozygous mutations in *ZP2* cause IVF failure due to a thinner ZP and defective sperm binding, although the oocytes of ZP2 patients can be fertilized by ICSI [150]. One reported individual shared a heterozygous missense mutation in *ZP2* and a heterozygous frameshift mutation in *ZP3* and was also infertile due to ZP defects, which indicated a dosage effect of ZP mutations. Ovastacin, which is coded by *ASTL*, functions by triggering ZP hardening as part of the cortical reaction upon fertilization, and recessive variants in *ASTL* cause fertilization failure [151].

3.3.5. Other genes

In 2019, a novel autosomal dominant disease named "oocyte death" was reported, and *PANX1* was found to be the pathogenic gene [50]. *PANX1* encodes the ion channel pannexin, and variants in *PANX1* cause aberrant glycosylation and channel activity leading to oocyte death [50]. *KPNA7* encodes the karyopherin α7 protein, which mediates the transport of proteins between the nucleus and cytoplasm in oocytes, and variants in *KPNA7* impair nuclear protein transport causing preimplantation embryo arrest [152]. *COX15* is a main component of mitochondrial respiratory chain

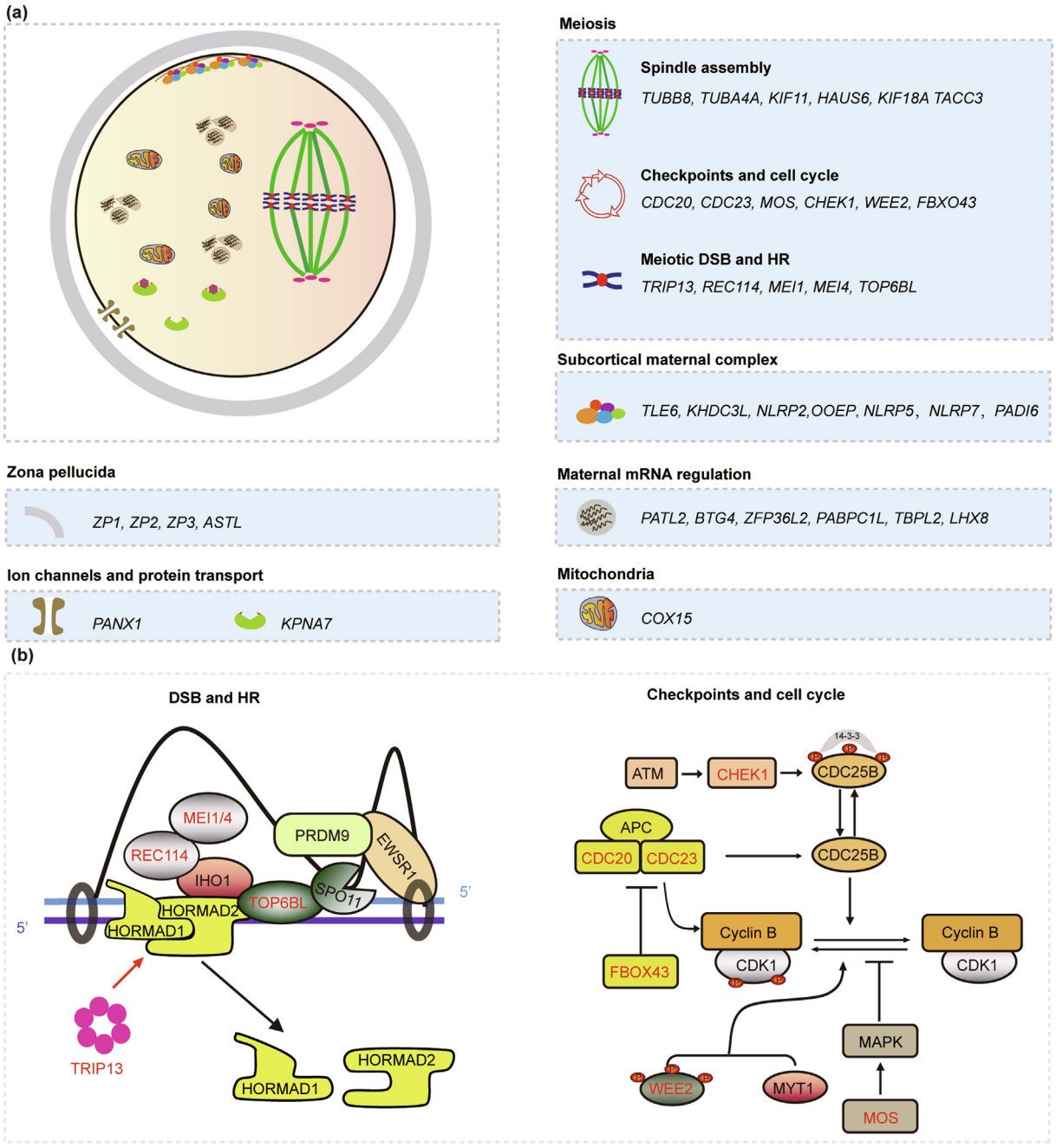

Fig. 4. Pathogenic genes related to human oocyte defects and related pathways. (a) The pathogenic genes in oocyte development-related pathways. (b) The signaling pathways involved in double-strand break (DSB) formation, homologous recombination (HR), checkpoints, and cell cycle regulation. Genes in which mutations have been shown to reduce oocyte quality and induce developmental defects are marked in red. The image was designed in Adobe Illustrator.

IV (Table 3), and *COX15* mutations have been reported to cause human oocyte defects by activating ferroptosis, thus expanding the spectrum of human infertility to include mitochondrial disorders [41].

3.4. Aging

Oocyte quality declines with increasing maternal age, and this is closely related to reduced fertility. To explore the characteristics of oocyte quality decline related to maternal aging, several studies have reported changes in the transcriptomes, proteomes, and translatomes of aging oocytes [153–157]. Microarray and single-cell RNA sequencing studies have shown that maternal age affects genes involved in chromosome stability, RNA splicing, transcriptional regulation, oxidative phosphorylation, cell cycle regulation, protein trafficking, and immune function [155–157]. The function of *TOP2B*, a candidate for age-related oocyte quality decline, was preliminarily confirmed, and *Top2b* deletion in mice caused early embryo arrest at the 2-cell stage [157]. Single-cell proteomics analysis showed that proteostasis and meiosis-related proteins are decreased in aged oocytes [153]. Multi-omics analysis of mouse oocytes showed that decreased translational efficiency is associated with changes in the proteome, especially changes associated with YTHDF3-mediated m6A modification [154]. However, this mechanism is not conserved in human oocytes, and the translation activity in human oocytes is regulated by the alternative splicing

Table 3
Pathways of 37 pathogenic genes involved in human oocyte defects.

Gene function		No. of genes	Pathogenic genes
Meiosis	Spindle assembly	6	*TUBB8, TUBA4A, KIF11, HAUS6, KIF18A, TACC3*
	Meiotic double-strand break formation and homologous recombination	5	*TRIP13, REC114, MEI1, MEI4, TOP6BL*
	Checkpoints and cell cycle	6	*CDC20, CDC23, MOS, CHEK1, WEE2, FBXO43*
Maternal mRNA regulation		6	*PATL2, BTG4, ZFP36L2, PABPC1L, TBPL2, LHX8*
Subcortical maternal complex		7	*TLE6, KHDC3L, NLRP2, NLRP5, NLRP7, PADI6, OOEP*
Zona pellucida		4	*ZP1, ZP2, ZP3, ASTL*
Ion channels and protein transport		2	*PANX1, KPNA7*
Mitochondria		1	*COX15*

factor SRSF6 instead of YTHDF3 m6A modification [154]. In addition, spatiotemporal transcriptomic analysis showed that Forehead Box P1 (FOXP1) is a regulator of ovarian aging, and FOXP1 deficiency inhibited CDKN1A transcription and resulted in POI in mice [158]. These comprehensive analyses showed the physiological changes that occur in aging oocytes and identified numerous age-related markers, but causal relationships between changes in marker expression and age-related oocyte quality decline are lacking. Therefore, identifying corresponding causal genes, proteins, metabolites, and pathways is essential for understanding the age-related decline in oocyte quality.

4. Strategies for improving oocyte quality and female fertility

Oocyte quality is the key limiting factor for female fertility, and researchers have put great effort into strategies for improving oocyte quality and female fertility. Several studies have reported that sex steroid hormone treatments can partly recover HPG axis function and restore typical serum concentrations of LH and FSH in some patients, but the underlying mechanisms remain unknown [159]. Gut microbiota transplantation, bile acid, and interleukin-22 can alleviate the phenotype of PCOS [124], but there are currently no proven treatments for restoring normal ovarian function. Mitochondrial replacement therapies, including germinal vesicle transfer, pronuclear transfer, maternal spindle transfer, and first or second polar body transfer are potential treatments for overcoming poor oocyte quality caused by aging [8]. Furthermore, work with assisted reproduction technologies has indicated the proper windows for intervention and treatment of patients with oocyte defects. For example, supplementation with *TRIP13* and *WEE2* cRNA can restore meiotic maturation, fertilization ability, and subsequent embryonic development competence in human oocytes [132,138]. The CHK1 inhibitor PF477736 and the MPS1 inhibitor AZ3146 can rescue the zygote arrest phenotype and MI arrest phenotype caused by *CHEK1* and *CDC23* variants, respectively [134,136]. Ferrostatin-1, an inhibitor of ferroptosis, can alleviate the oocyte ferroptosis phenotype caused by *COX15* deficiency [41]. In addition, several small-molecule compounds, including nicotinamide mononucleotide, N-acetylcysteine, and spermidine, have been reported to effectively improve the quality of aged mouse oocytes [160–162]. However, the safety of these methods and their effects on offspring as well as other ethical concerns should be considered and evaluated. There is still a lack of proven and effective methods for restoring oocyte quality, and this remains a significant challenge for researchers and clinicians.

5. Perspectives

Although recent advances have expanded our understanding of human oocyte quality and female reproductive health, a full understanding of the complex mechanisms affecting oocyte quality remains elusive. A series of studies have systematically mapped the omics landscapes of human oocytes and have provided the bulk of the available data. Using these resources, it is imperative to explore the key factors and signaling pathways involved in regulating human oocyte quality. To date, a total of 49 genes associated with CHH, 60 genes associated with POI, and 37 genes associated with oocyte development defects have been identified that affect human oocyte quality and female fertility. It is urgent to verify their functions and explore their underlining regulatory mechanisms and related pathways. Discovering additional genes will further improve the genetic diagnoses of clinical patients and the evaluation of human oocyte quality. Targeting these factors and their associated signaling pathways via small molecule inhibitors and agonists will likely bring breakthroughs for restoring human oocyte quality. The development of the therapeutic interventions should be designed according to the gene function and their pathogenic modes. For mutants that function in a dominant negative manner, the use of a C-terminal amide marking system for protein degradation may be a possible treatment [163]. For mutant proteins involved in cell cycle regulation, inhibitors, and antagonists can be screened that will allow the oocytes or embryos to skip the corresponding phase. For genes and pathways associated with aging or oocyte degeneration, small molecules or compounds that function as anti-oxidants can be used as therapeutic agents.

Recent insights into human oocyte quality also present new opportunities for future mechanistic explorations. The specific huoMTOC structure and the related mechanism of minor pole-mediated spindle bipolarization have been described in human oocytes, indicating the specific mechanism of human oocyte spindle assembly [36]. Thus, more elaborate studies of the human oocyte spindle and a revision of our current understanding of related mechanisms will contribute new knowledge on the mechanism of spindle assembly. Secondly, mammalian oocyte mitochondria are distinct compared to mitochondria in somatic cells, and they undergo remodeling during oocyte growth, maturation, and embryonic development [45]. However, due to limited sample availability, the specific mechanisms behind human oocyte mitochondria remodeling have remained poorly understood. Thirdly, rapid developments in artificial intelligence have suggested important applications of these tools in genetic counseling and the precise diagnosis of human oocyte defects.

Advances in our understanding of human oocyte quality will pave the road to improved female reproductive health and will inspire new ideas for elucidating novel mechanisms. With the application of cutting-edge technology and increased studies focusing on human oocyte development, the ultimate goal of restoring human oocyte quality might be realized in the future.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (82325021, 82288102, 32130029, 82371662, 82422033, and 82271685), the Project of the Shanghai Municipal Science and Technology Commission (23QA1401800), the Fund of Fudan University and Cao'ejiang Basic Research (24FCB01), and

the New Cornerstone Science Foundation through the XPLORER PRIZE. Lei Wang is a SANS Exploration Scholar.

Author contributions

Lei Wang and Qing Sang supervised and designed the project. Zhihua Zhang and Tianyu Wu wrote the manuscript. Lei Wang, Qing Sang, and Zhihua Zhang revised the manuscript.

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