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Follicular metabolic dysfunction, oocyte aneuploidy and ovarian aging: a review

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Abstract
With the development of modern society and prolonged education, more women choose to delay their childbearing age, which greatly increases the number of women aged older than 35 years with childbearing needs. However, with increasing age, the quantity and quality of oocytes continue to fall, especially with increasing aneuploidy, which leads to a low in vitro fertilization (IVF) success rate, high abortion rate and high teratogenesis rate in assisted reproduction in women with advanced maternal age. In addition to genetics and epigenetics, follicular metabolism homeostasis is closely related to ovarian aging and oocyte aneuploidy. Glucose, lipid, and amino acid metabolism not only provide energy for follicle genesis but also regulate oocyte development and maturation. This review focuses on the relationships among follicular metabolism, oocyte aneuploidy, and ovarian aging and discusses potential therapeutic metabolites for ovarian aging.

Keywords Metabolism, Infertility, Ovarian aging, DNA repair, Meiotic defects, Mitochondrial quality, Genetics, Epigenetics

Ovarian aging and dilemma of advanced maternal age

The dilemma of ovarian aging faced by women over the age of 35 is the decline in female ovarian function. Ovarian aging is mainly manifested as a decrease in the quantity and quality of oocytes, especially when oocyte euploidy robustly decreases. Women have a limited number of germ cells. There are approximately 2 million oocytes at birth, and the number of oocytes decreases to approximately 400,000 during puberty. The number of primary follicles drops sharply after 37 ~ 38 years of age, from 25,000 to approximately 1,000 during menopause [1, 2]. Moreover, oocyte quality greatly declines, which is mainly reflected in the increase in oocyte meiotic defects and aneuploidy in aged women [3]. Moreover, ovarian aging affects multiple systems, ultimately leading to infertility and related diseases, such as menstrual irregularities and sexual disorders [4, 5]. Therefore, research on reproductive aging, which promotes the quantity and quality of oocytes, is urgently needed. This approach will help women achieve better pregnancy outcomes at advanced reproductive ages.

Causes of ovarian aging

The process of meiosis and ovarian aging

Abnormal meiosis and aneuploidy are important manifestations of age-related oocyte senescence and ovarian aging. The observation of human oocyte meiosis showedthat human natural fertility and age exhibit

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an inverted U-shaped curve, which is caused by the U-shaped curve of human oocyte aneuploidy [6]. There are three main causes of aneuploidy [7]: (i) nondisjunction (NDJ); (ii) premature sister chromatid separation (PSCS); and (iii) reverse segregation (RS). The incidence of NDJ in human generally decreases with increasing age, while the incidence of PSCS and RS increases [8]. These error types depend on age, and lowest incidence of error combinations occurs during middle age from 24 to 29 [9]. Previous animal studies have suggested that the generation of aneuploidy in aged oocytes is associated with many factors, such as cohesion dysfunction, spindle assembly, spindle assembly checkpoint (SAC) dysfunction, genetics, and epigenetics [10]. These factors are age-dependent and vary throughout the reproductive lifespan. For young oocytes, specific gene mutations or polymorphisms can increase the risk of aneuploidy [11]. As age increases, the functionality of the SAC weakens, leading to improper chromosome segregation. Abnormalities in homologous chromosome pairing and crossover events can also raise the risk of aneuploidy. Furthermore, changes in epigenetic factors, such as DNA methylation and histone modifications, can impair the normal function of oocytes, contributing to an increased risk of aneuploidy [12].

Cohesion dysfunction and oocyte aneuploidy

Cohesion dysfunction is one of the main causes of aneuploidy [13]. The cohesin complexes exist in chromosome arms and centromere regions and are composed of SMC1, SMC3, SCC1 (RAD21 in humans) and SCC3 (STAG1 or STAG2 in humans). A ring structure formed by SMC1, SMC3, and RAD21 allows DNA to pass in and out freely. An α-kleisin subunit (SCC1/RAD21) works to bind SMC1 and SMC3 together. During metaphase II (MII), separase cleaves the kleisin subunit and finally removes the complex from chromosomes, making the sister chromatids segregate correctly [14–16]. One study reported that the deletion of STAG2, the gene encoding STAG, can lead to aneuploidy of human bladder cells [17]. Another study revealed that Chl1 promoted SCC2 to combine to DNA, and chl1 mutant cells exhibited many condensation defects, resulting in sister chromatids in yeast cells separating too early [18]. These findings suggest that any disruption in the function of cohesive proteins can have profound consequences on chromosomal stability, potentially leading to genetic disorders [19].Therefore, understanding the mechanisms by which cohesive proteins operate and interact with other cellular components is crucial for developing targeted therapies for diseases associated with chromosomal instability, and future research can focus on delving deeper into the molecular interactions between cohesive proteins and DNA, as well as other regulatory factors, so as to reveal new therapeutic targets.

Spindle functions and oocyte aneuploidy

Errors in spindle assembly are also important causes of oocyte aneuploidy. During meiosis, chromosomes are attached to spindle microtubules and are thus properly aligned at the equator of the spindle, where they form a stable bipolar spindle. An intact meiotic spindle is the key to correct separation of chromosomes. A malformed spindle may lead to chromosome fusion failure and mis-segregation [20–22]. Studies have demonstrated that spindle assembly errors exist in aged mice. Several genes associated with spindle assembly, including Sirt6, Numa1, Ran, and Tpx2, show abnormal expression in aged mouse oocytes. Moreover, aged mouse oocytes at the MI and MII stages also exhibited spindle damage and chromosomal misalignment [23–24].

In somatic cells and germline cells, there is a widespread spindle-check mechanism called the spindle-assembly checkpoint (SAC) that controls chromosome separation. SAC proteins mainly contain Mad1, Bub1, Mps1, and Cdc20. The mechanism focuses on chromosome kinetochores to detect chromosome attachment failure, so as to prevent incorrect separation of chromosomes [25–26].The signal produced by checkpoint only stops when all kinetochores are bound to microtubules, and then anaphase will be allowed to begin [27–29]. Overall analysis of mouse oocyte transcripts revealed that the transcript levels of SAC proteins (BubR1 and Bub1) decreased with age and were related to oocyte aneuploidy [30]. However, the effect of age on SAC and the mechanism of how it affects oocyte aneuploidy are still unclear and need further study.

DNA damage and oocyte aneuploidy

Most of the primordial follicles remained in diplotene for an extended period. During this time, various factors lead to DNA damage, which causes apoptosis. DNA damage includes two forms: single-strand breaks (SSBs) and double-strand breaks (DSBs) [31–32]. DNA DSBs are complex and can cause additional damage to cells, possibly leading to chromosomal instability and improper chromosomal segregation [33]. One study reported that DSBs increase in aged primordial follicles, and the expression of the key DNA DSB repair genes BRCA1, MRE11, Rad51, and ATM decreases in oocytes, suggesting the accumulation of DSBs is a hallmark of aging and is associated with declining oocyte quality and function. This explains why advanced maternal age is often associated with higher rates of infertility, miscarriages, and chromosomal disorders such as Down syndrome, emphasizing the need for further research into therapeutic approaches to mitigate DNA damage and improve fertility in aging

populations [34]. DSBs in oocytes can indeed lead to chromosomal abnormalities, potentially resulting in aneuploidy [35]. If DSBs persist and are not repaired correctly, they can interfere with the normal progression of meiosis. Persistent DSBs can hinder the proper alignment and segregation of chromosomes, leading to aneuploidy [36]. DNA DSB repair works in two forms: homologous recombination (HR) and non-homologous end joining (NHEJ), among which HR plays a dominant role in oocytes DNA repair. HR failure leads to lots of chromosomal changes, including deletions, translocations, and chromosome loss, in multiple cell types [37]. HR in oocytes reacts quickly. When DSBs occur, HR is activated to repair the damage. If the damage is extensive and cannot be repaired, oocytes may undergo apoptosis to prevent the propagation of damaged genetic material. When DSBs are repaired by NHEJ, the process can be error-prone, leading to insertions, deletions, or translocations [38]. These errors can cause structural chromosomal abnormalities that may not be lethal but can affect chromosomal segregation during meiosis.

In addition, DNA damage can also manifest as telomere shortening, which can lead to problems such as aneuploidy and miscarriage [39]. Through real-time quantitative reverse transcriptase polymerase chain reaction (Q-PCR) and immunochemical methods, one study found that the relative telomere length (RTL) in female oocytes of reproductive age was much shorter than that in young female oocytes, resulting in aneuploidy, miscarriage, and other genetic diseases [40]. Another study reported that aneuploid human polar bodies have significantly less telomeric DNA than euploid polar bodies of sibling oocytes, suggesting that oocytes with defective telomeric DNA are more likely to grow into aneuploidy during later meiosis period [41]. Both studies underscore that DNA damage, particularly at telomeres, is a central driver of chromosomal instability. Telomere shortening and dysfunction act as a "biological clock" that limits cellular lifespan and contributes to age-related declines in oocyte quality and embryonic viability. When telomeres become critically short, they lose their protective function, leading to DSBs. This triggers DNA damage responses and can result in chromosomal fusions, breaks, or mis-segregation during cell division.The inability to maintain telomere integrity and repair DNA damage leads to errors in chromosome segregation, resulting in aneuploidy. This is particularly critical in oocytes and embryos, where even minor chromosomal imbalances can have severe consequences. Moreover, the dysfunction of genes essential for DNA double-strand break repair, such as BRCA1 and BRCA2, can disrupt spindle assembly and checkpoint mechanisms, leading to meiotic aneuploidy [42–44]. These remind us that enhancing the efficiency of DNA repair pathways, particularly in aging oocytes, could reduce the accumulation of DSBs and improve chromosomal stability.

Mitochondrial quality and oocyte quality

Mitochondria are important organelles for cell growth. They are the primary sources of cellular energy and can regulate intracellular Ca2 + homeostasis [45]. In somatic cells, mitochondria play a number of central roles within cells, including regulating cell death and signalling pathways, iron metabolism, and the biosynthesis of several organic compounds. As folliculogenesis, oocyte growth, and maturation progress, the whole process needs a large amount of energy and is accompanied by changes in the quantity, quality and distribution patterns of mitochondria in oocytes [46]. Mitochondria contain rich genetic material DNA, namely, mtDNA, and oocytes ensure the stability of single-parent transmission and the generation of mitochondrial genomes [47]. During oocyte maturation, the copy number of mtDNA per cell increases dramatically from approximately 200 to 400,000. Previous studies have shown that in both animal and human models, the copy number and function of mtDNA in oocytes continue to decrease with age [48]. The instability of mtDNA associated with aging contributes to mtDNA mutations accumulating in oocytes, playing an important part in decreasing oocyte quality and the risk of passing mitochondrial abnormalities to offspring. Moreover, the mitochondria distribution changes greatly either, from the center of the cytoplasm to the pericortical region, and eventually distributes throughout the ooplasm [49].

A decrease in the quantity and quality of mitochondria is one of the main causes of ovarian aging and a decrease in oocyte quality. The levels of mtDNA and adenosine triphosphate (ATP) are important criteria for measuring the quality of oocytes [50]. One study demonstrated that oocyte and polar body mtDNA copy numbers were much lower in patients with a reduced ovarian reserve than in women with a normal one, thus leading to mitochondrial dysfunction [51]. Another study showed that reduced ATP levels due to a decrease in mitochondrial quantity and quality lead to errors in chromosome separation during meiosis, resulting in aneuploidy. Abnormal mitochondrial function also leads to abnormal Ca2 + homeostasis. An increased Ca2 + concentration disrupts oocyte redox homeostasis and oxidative phosphorylation, impairs mitochondrial function and leads to oocyte apoptosis [52]. These studies collectively underscore the central role of mitochondrial dysfunction in oocyte quality, chromosomal stability, and reproductive outcomes. While they differ in their specific focus, they converge on the importance of mitochondrial health in preventing aneuploidy and oocyte apoptosis. Future research should aim to unravel the underlying mechanisms and develop targeted therapies to improve mitochondrial function,

thereby enhancing fertility and reducing the risk of aneuploidy.

Oxidative damage to oocytes caused by excessive accumulation of free radicals is an important reason for the decline in oocyte quality. Oxidative stress (OS) means an imbalance in the redox system. Reactive oxygen species (ROS) are the main byproducts of the mitochondrial respiratory chain and are generated by reduced nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase, NOX). ROS include many substances, such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($^{\cdot}OH$) [53]. Cells, including oocytes, require proper ROS to activate intracellular signalling pathways [54]. However, if the ROS produced is unable to be scavenged by the endogenous antioxidant system, then there occurs OS [55].

Mitochondrial quality control (MQC) improves mitochondrial function and oocyte quality. MQC is a comprehensive regulatory mechanism of mitochondrial quality and is an endogenous cellular protective program that maintains mitochondrial homeostasis and function. Mitochondrial quality comprises several components such as biosynthesis, dynamics, autophagy, and control of mitochondrial protein homeostasis [56]. MQC maintains mitochondrial homeostasis by coordinating various processes, such as biogenesis, mitochondrial fission, fusion, proteolysis and mitophagy [57]. As oocytes age, their mitochondrial function often deteriorates, leading to decreased energy production, increased oxidative stress, and impaired cellular function. MQC mechanisms help to counteract these detrimental effects and improve the quality of aged oocytes [36]. By enhancing MQC mechanisms such as mitophagy, mitochondrial biogenesis, and dynamics, as well as protecting against oxidative stress and maintaining proteostasis and mtDNA integrity, the quality of aged oocytes can be significantly improved, thereby potentially enhancing fertility outcomes in older individuals [37].

Control of mitochondrial protein homeostasis relies on mitochondrial proteases, including caseinolytic protease(ClpP) and ATP-dependent Lon protease 1(LONP1). Recently, our work has revealed that mitochondrial LONP1 is important in oocyte development and maturation. LONP1 interacts with apoptosis-inducing factor mitochondrial associated 1 (AIFM1) directly. LONP1 knockout in oocytes makes AIFM1 to transfer from the cytoplasm to the nucleus. This leads to loss of ovarian reserve and sterility in mice. In addition, we found that mouse oocytes with reduced expression of LONP1 show mitochondrial dysfunction, abnormal meiotic progression and increased DNA damage [58]. These findings underscore the importance of mitochondrial health in reproductive biology and suggest that targeting mitochondrial quality control pathways could be a promising strategy for improving fertility and reducing aneuploidy, particularly in aging populations.

Genetics and ovarian aging

Genetics also contributes greatly to oocyte aging [59]. Recently, many genome-wide association studies (GWAS) related to oocyte senescence have been conducted [60]. One study performed a GWAS meta-analysis and identified a new locus on chromosome 22, which includes a genetic variant encoding the fusion-associated protein SFI1. This mutation causes abnormalities in spindle assembly, leading to aneuploidy [61]. Another study used single-cell methylation/transcriptome parallel sequencing technology (scM&T-seq) to conduct in-depth bioinformatics analysis of young and aged oocytes in the GV and MII stages. A study assessed 290 genetic sites associated with ovarian aging by collecting changes in the age of natural menopause (ANM) in approximately 200,000 women of European descent. The sites identified are involved in lots of DNA-damage response (DDR) processes which are important in shaping the ovarian reserve and its rate of depletion, demonstrating that genetic determinants are important in ovarian aging [62]. Genetic factors play a pivotal role in ovarian aging, influencing spindle assembly, DNA damage response, epigenetic regulation, and ovarian reserve depletion. Advances in GWAS and single-cell multi-omics technologies have deepened our understanding of these mechanisms, offering new opportunities for personalized fertility preservation and therapeutic interventions. Future research should focus on translating these genetic insights into clinical applications while addressing ethical and social challenges to improve reproductive outcomes for aging women.

Epigenetics and ovarian aging

With the continuous development of epigenetics, a connection between epigenetics and oocyte meiosis has been reported [63–68]. Epigenetic modifications refer to processes that regulate gene function, do not affect DNA sequence, and can be inherited through cell division. The major changes include DNA methylation, histone modification, noncoding RNA regulation, and RNA N6-methyladenosine (m6A) methylation [69]. One study found that lysine methylation and ubiquitination were upregulated while lysine acetylation was downregulated in granulosa cells (GCs) in aged mice [70]. This finding suggests that epigenetic inheritance is involved in ovarian aging. In aged oocytes, the activity of the acetylation regulatory gene TAp73 and histone deacetylase (HDAC) decreased, which negatively affected the deacetylation of certain histones (H4K12) in human MII oocytes [71]. The experiment revealed that inhibition of meiotic histone deacetylation leads to deacetylation failure, leading to meiotic

abnormalities and aneuploidy. Additionally, aneuploidy in fertilized mouse oocytes increases, eventually leading to embryo death during early developmental stages. Taken together, these findings suggest that epigenetics is a central regulator of oocyte meiosis, quality, and aging, with histone modifications, DNA methylation, and noncoding RNAs playing pivotal roles. Age-related epigenetic dysregulation disrupts chromosomal stability, leading to aneuploidy and reduced fertility. Understanding and targeting these epigenetic mechanisms offer promising avenues for improving oocyte quality, delaying ovarian aging, and enhancing reproductive outcomes. Future research should focus on translating these insights into clinical applications while exploring the broader implications of epigenetic inheritance for fertility and health. Oocyte growth and maturation require abundant RNA accumulation and posttranscriptional regulation [72]. N6-methyladenosine modifies a lot of mRNAs, and regulates RNA metabolism and gene expression precisely in a variety of physiological processes. Recent studies have shown that m6A modifications and regulatory factors are crucial for ovarian development and that abnormalities in these modifications are closely related to ovarian aging. Defects in m6A modifications defects can lead to oocyte maturation disorders and female infertility [73]. As age increases, the levels of m6A modifications in the ovaries change [38]. These specific changes may vary depending on species and individual differences. Methyltransferases (such as METTL3 and METTL14) and demethylases (such as FTO and ALKBH5) are responsible for altering m6A modifications on RNA. With ovarian aging, the expression levels and activities of these enzymes change, leading to alterations in m6A modification levels, which affect mRNA stability and translation efficiency [74]. This results in changes in the expression levels of essential proteins, impacting oocyte development and maturation. Changes in m6A modifications may also lead to disruptions in cell cycle regulation and apoptosis processes, as well as abnormalities in signaling pathways, thereby reducing the quantity and quality of oocytes [75].

Noncoding RNAs control a variety of cellular functions by regulating specific signalling pathways, and their role in ovarian aging cannot be ignored. Long noncoding RNAs (lncRNAs) play an important role in gene expression. By interacting with miRNAs, lncRNAs regulate their mRNA targets, and finally work to regulate abundant cellular processes [76]. One study used NanoString technology to conduct a high-throughput analysis of the expression profiles of 68 lncRNAs from the cumulus cells of women from different age groups and proposed that the downregulation of lncRNAs in granulosa cells of aged women may affect the expression of dysregulated protein-coding genes during reproductive aging [77]. Circular RNAs (CircRNAs) are a diverse class of endogenous noncoding RNAs (NcRNAs) that are produced from exons, introns, or untranslated regions of protein-coding genes or intergenic regions [78]. By analysing circRNAs related to ovarian aging, another study found that the NcRNAs whose expression significantly changed were significantly enriched in metabolic processes, regulatory secretion pathways, redox processes, steroid hormone biosynthesis, and insulin secretion pathways related to ovarian aging, indicating that they are important in the process of ovarian aging [79].Moreover, some classes of NcRNAs probably have an effect on mitochondrial biology. They are thought to mediate anterograde and retrograde mitochondria-nuclear crosstalk and regulate cell growth at both transcriptional and posttranscriptional levels [80]. Noncoding RNAs are critical regulators of gene expression, metabolic pathways, and mitochondrial function, playing a central role in ovarian aging. Dysregulation of lncRNAs and circRNAs in aged ovaries contributes to metabolic dysfunction, hormonal imbalances, and mitochondrial decline, ultimately impairing oocyte quality and fertility. Understanding the mechanisms by which ncRNAs influence ovarian aging offers new opportunities for therapeutic interventions and biomarkers to improve reproductive outcomes in aging women. Future research should focus on translating these insights into clinical applications while exploring the broader implications of ncRNAs for reproductive health and aging.

Metabolic abnormalities and oocyte aneuploidy

Although the mechanisms of ovarian aging and increased aneuploidy have been continuously studied, the relationship between metabolism and ovarian aging has been poorly studied. Oocyte meiosis requires energy, metabolites, molecular signalling, and protein posttranslational modifications from a variety of substrates, including glucose, lipids, and amino acids [81]. Recently, metabolic analysis of aged ovaries has improved the understanding of the biological and physiological mechanisms underlying oocyte aneuploidy and quality decline. As women age, the ovarian microenvironment undergoes substantial changes, including alterations in nutrient availability, mitochondrial function, and oxidative stress levels. These metabolic shifts can directly impact the quality of oocytes, leading to an increased incidence of chromosomal abnormalities such as aneuploidy. A metabolomic analysis of follicular fluid found significant differences in the levels of eight identified metabolites [four amino acids (creatine, histidine, methionine and trans-4-hydroxyproline), two lipids (mevalonate and choline), one nucleotide (the N2,N2-dimethylguanosine) and one peptide (gamma-glutamylvaline)] between old and young women [82]. These differences may be related to the quantity and quality of oocytes from women receiving assisted reproductive technology (ART). Another study

using targeted metabolomics and lipidomic analyses of oocytes in different age groups reported that the levels of many metabolites, such as phospholipids and nicotinamide adenine dinucleotide (NAD+), significantly differed with age [83]. These studies show that metabolic disorder is one of the core driving forces of ovarian aging, which damages the function of oocytes through multiple pathways such as energy depletion, oxidative damage, and epigenetic dysregulation. Targeting key metabolic pathways may provide a new strategy for delaying ovarian aging and improving fertility in aged women.

Carbohydrate metabolism and ovarian aging

Carbohydrate classification and function

Carbohydrates are the most common organic substances and play vital roles in living organisms. These compounds can be divided into monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Carbohydrates are mainly present in forms of glucose and glycogen in the human body [84–85]. Carbohydrates are essential energy substances for humans, and 70% of the energy required by the human body comes from their oxidation [86]. Glycoproteins and glycolipids are important components of cell membranes, and proteoglycans are structural components of connective tissues such as cartilage and bone [87]. Moreover, carbohydrates are involved in the formation of bioactive substances. Many important enzymes and hormones are glycoproteins. Most of the plasma proteins and membrane proteins involved in immune, recognition and transport functions are glycoproteins. Carbohydrates can also be used as carbon sources for the synthesis of other biomolecules, such as lipids and amino acids [88–90].

Glucose and follicle development

The process of follicular growth and maturation requires energy. Glucose metabolism in the oocyte cytoplasm is one of the main pathways of energy metabolism in oocytes [91]. The ATP production rate and efficiency affect oocyte development and maturation. It is believed that primary germ cells (PGCs) mainly carry out carbohydrate catabolism through anaerobic glycolysis to reduce the oxygen supply and avoid excessive oxidative stress [92]. As oocytes continue to develop, the demands for pyruvate and oxygen increase, and the utilization of glucose decreases gradually. Mature oocytes mainly depend on pyruvate oxidation to obtain energy. Pyruvate is mainly transported from follicular fluid and granulosa cells to oocytes. Glycolysis and transamination can produce pyruvate, and glycolysis is the main source of pyruvate production [93]. Glucose metabolism in follicles can be classified into four categories. (i) Glycolysis produces ATP, pyruvate and lactic acid. (ii) The pentose phosphate pathway (PPP) provides ribose to synthesize DNA and RNA and Nicotinamide adenine dinucleotide phosphate(NADPH) to reduce ROS in oocytes. (iii) Oxidative phosphorylation (OXPHOS) oxidizes glucose and releases energy to support the synthesis of large amounts of ATP. It has been suggested that oocytes metabolize glucose mainly through OXPHOS because OXPHOS can supply energy more efficiently than glycolysis and the tricarboxylic acid cycle. (iv) The hexosamine biosynthesis pathway (HBP) and other polyol pathways comprise the fourth category. The HBP is mainly involved in the synthesis of extracellular matrix (ECM), regulates the development of cumulus cells, and is also related to O-linked glycosylation [94]. O-linked glycosylation can regulate protein activity and cellular signal transduction [95].

Aerobic glycolysis and OXPHOS are interdependent pathways, and both are essential for energy production during oocyte and embryonic development [96]. Granulosa cells and oocytes prefer different energy substrates during follicle maturation. Granulosa cells are more dependent on glycolysis, while oocytes are more dependent on the OXPHOS pathway [97]. These pathways control cellular energy metabolism during meiosis. If these pathways are interrupted due to maternal aging, mitochondrial dysfunction occurs, resulting in reduced ATP production. This ultimately impairs the meiosis process of oocytes and reduces oocyte quality [98].

Glucose metabolism and ovarian aging

An appropriate concentration of glucose can improve the maturation and developmental potential of oocytes, while a low or high concentration of glucose harms the oocyte meiosis process [99]. Low glucose concentrations reduce PPP and glycolysis, thereby limiting the availability of substrates for nucleic acid synthesis and energy production [100]. A study demonstrated that reducing mitochondrial activity in pigs and cattle inhibits glycolytic activity in the cumulus-oocyte complex (COCs), reducing lactic acid production and meiosis maturation [101–102]. However, high glucose levels lead to active ATP production, higher ROS production, increased glycosylation levels and decreased concentrations of glutathione (GSH), resulting in stress that damages the quantity and quality of oocyte growth [103]. Another study reported that glucose consumption and lactic acid production were greater in granulosa cells from older cows than in those from younger cows, indicating an increased demand for ATP and increased glycolytic activity. This leads to an increase in ROS accumulation. A decrease in the mtDNA copy number in older cows indicated a deterioration in mitochondrial function, which affected the quality of the oocytes [104]. As Fig. 1 shows, the sequencing data of Smits showed that pyruvate, fumarate and α-ketoglutarate and other metabolites related to glycolysis and tricarboxylic acid cycle (TCA

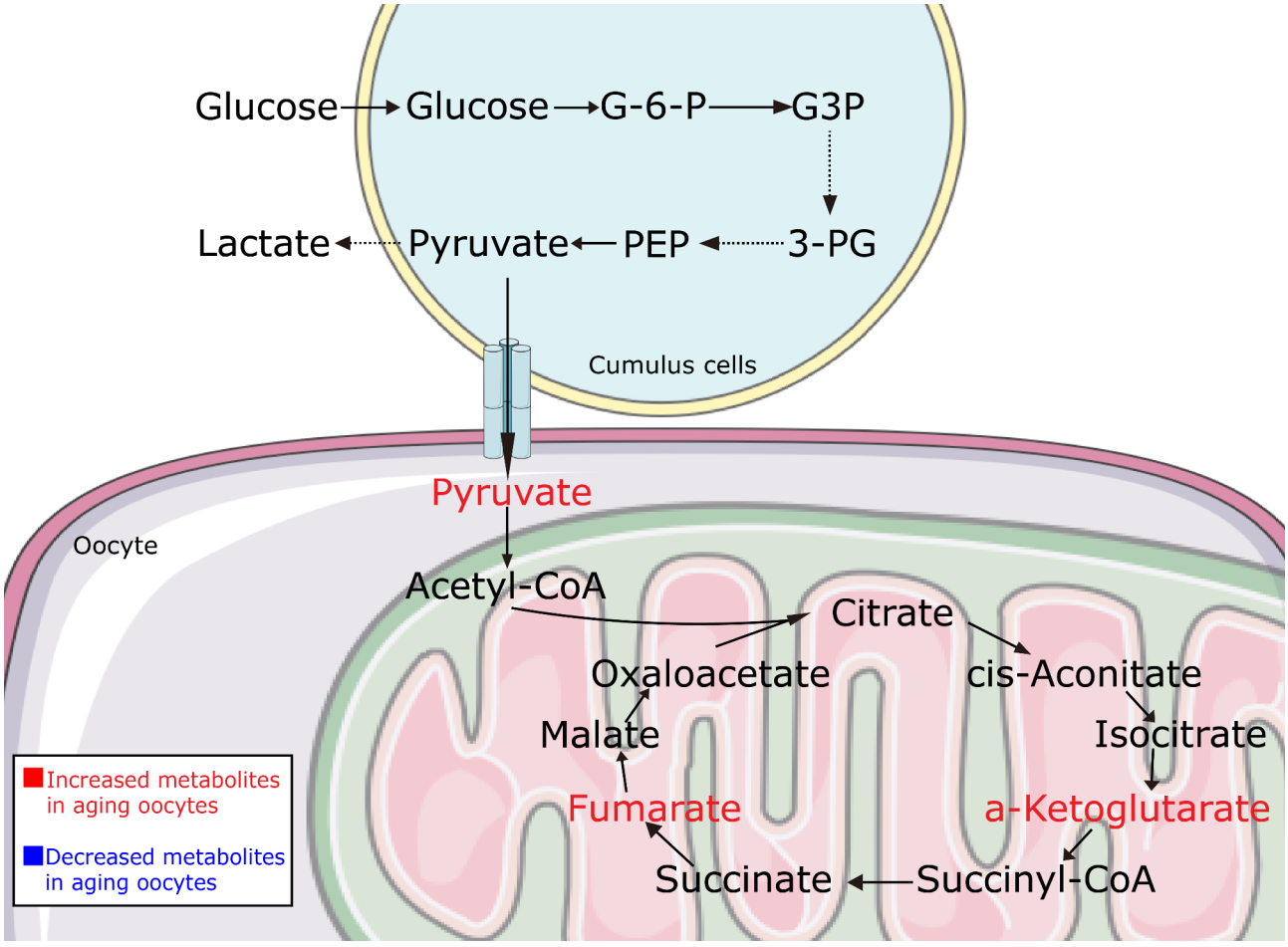

Fig. 1 Overview of age-related changes in carbohydrate metabolism in MI oocytes [105, 114]

cycle) increased significantly in aging MI oocytes, suggesting that these metabolic pathways were active in aging MI oocytes [105].

Nonenzymatic reactions (glycation) happen between reducing sugars and the amino groups of proteins, nucleotides and lipids. The products of these reactions, as are called early glycation products, continue to form advanced glycation end products (AGEs) through complex reaction steps [106]. Most of the biological effects of AGEs are mediated through specific receptors (receptors for AGEs [RAGEs]) present on the cell surface, and the interaction triggers OS and inflammation [107]. AGEs increase the production of ROS, leading to oxidative stress. The accumulation of AGEs indirectly promotes DNA damage in oocytes, resulting in mutations and chromosomal abnormalities. This affects the genetic integrity of the oocyte and can lead to issues with fertilization and embryo development. AGEs impair mitochondrial function, reducing the energy supply necessary for oocyte maturation and development. Mitochondrial dysfunction can lead to decreased ATP production, further affecting oocyte viability. The increased oxidative stress and cellular damage induced by AGEs can also trigger apoptotic pathways, leading to increased oocyte apoptosis. AGEs interfere with cellular signaling pathways that are crucial for oocyte maturation and function. This disruption can hinder the proper maturation of oocytes, affecting their quality and developmental potential [108–110]. Moreover, disordered glucose metabolisminfluencesmitochondrialqualitycontrol, thus affecting the progression of autophagy and leading to accelerated oocyte aging [111]. One study found that the administration of niacinamide mononucleotide (NMN) in mice could rescue the decreased ovarian reserve by improving the level of mitochondrial autophagy in granulosa cells [112]. Another study concluded that mitochondrial mass in humans, mice and *Drosophila* decreased with age and was associated with the decline of oocyte quality, suggesting the necessity of further systematic studies on oocytes during maternal aging using different systems [113]. These findings suggest that abnormal glucose metabolism plays a critical role in the aging process of oocytes by disrupting mitochondrial quality and function, thereby impairing energy production.

Understanding the metabolic drivers of oocyte aging not only provides insights into the biological mechanisms of reproductive decline but also opens new avenues for therapeutic strategies to combat age-related infertility.

The figure above shows the marked changes in carbohydrate metabolites in aged oocytes during MI. In aged ovaries, pyruvate from cumulus cells enters oocytes through gap junctions, and then provides energy to oocytes through tricarboxylic acid cycle (TCA cycle). Metabolites related to glycolysis and TCA cycle, such as pyruvate, fumarate and α-ketoglutarate, were significantly increased in aged MI oocytes, suggesting that glycolysis and TCA cycle are active in aged MI oocytes.

Lipid metabolism and ovarian aging

Lipid classification and function

Lipids play important roles in many biological processes, such as storing energy, forming cell membranes, and participating in intracellular and intercellular signal transduction. Lipids are divided into eight categories according to the International Lipid Classification and Nomenclature Committee: fatty acyls, sphingolipids, glycerolipids, glycerophospholipids, saccharolipids, polyketides, sterol lipids, and prenol lipids (derived from condensation of isoprene subunits) [115]. Fatty acids (FAs) are the main components of fatty acyls, and there are three major groups of FAs, namely, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs). Fatty acids can be esterified to form triglycerides, which are stored in lipid droplets and decomposed to produce ATP when cells have urgent demands for energy. Sphingolipids, glycerolipids, and glycerophospholipids are important components of cellular membranes. Cholesterol is the most abundant and important sterol and is the substrate for the synthesis of fat-soluble vitamins and steroid hormones. Isopentenyl diphosphate and dimethylallyl diphosphate synthesize prenol lipids mainly via the mevalonate (MVA) pathway. Farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) are key intermediates in the biosynthesis of prenol lipids. They can modify an array of proteins through protein prenylation [116].

Lipid and follicle development

Lipids are an important source of energy [117].Fatty acids are observed widely in the follicular environment. The observation of fatty acids in oocytes, cumulus cells, other follicular cells, and follicular fluid suggests that active lipid activities occur in the follicle during oocyte maturation [118].

As follicles grow, the lipid droplets related to mitochondria and the endoplasmic reticulum increase, indicating increased oocyte lipid metabolism [119]. In oocytes, lipids are stored in the form of triacylglycerol, while free fatty acids are located within the cytoplasm. Free fatty acids can be transported directly to mitochondria and oxidized via β-oxidation [120]. Lipids provide an essential energy source for the metabolic activities required during follicle growth and oocyte maturation. Fatty acids are metabolized to generate ATP, supporting cellular processes within the follicle. Lipids are key components of cell membranes [121]. Phospholipids and cholesterol help maintain the structural integrity and fluidity of cell membranes in follicular cells, ensuring proper cell function and communication. Lipids act as signaling molecules in various pathways that regulate follicle development. For example, steroid hormones like estrogen and progesterone, derived from cholesterol, are crucial for the growth and maturation of follicles [122]. Lipid rafts facilitate the clustering of signaling receptors and proteins, playing a role in the regulation of signal transduction during folliculogenesis [123]. Dysregulation of lipid metabolism can lead to impaired follicle development and associated fertility issues [124]. One study reported that inhibiting mitochondrial fatty acid β-oxidation prevents oocyte meiosis, showing the importance of lipid metabolism for oocyte development [125].

Lipid metabolism and ovarian aging

Lipid droplets consist of many lipids, such as triacylglycerol and cholesteryl esters. Triacylglycerol is the major constituent of lipid droplets and is the most abundant lipid in oocytes. Different species are observed to have different intracellular lipid levels [126]. It has been reported that lipid droplets are closely associated with mitochondria [127]. Lipid droplets accumulate during oocyte growth and increase in size with oocyte maturation [128], indicating the importance of lipid droplets in oocyte maturation [129]. Lipid droplets play a crucial role in oocyte maturation and quality, serving as energy reservoirs and interacting closely with mitochondria. Oxidative stress and dysregulated lipid metabolism can impair oocyte development, while interventions like salidroside demonstrate the potential to improve oocyte quality by modulating lipid dynamics [130–132]. Future research should focus on understanding the mechanisms of lipid metabolism in oocytes and developing targeted therapies to enhance fertility outcomes.

Fatty acids can be activated to acyl-coenzyme A in β-oxidation and provide ATP during this process. β-oxidation is closely related to oocyte meiotic resumption. It was reported that the inhibition of fatty acid β-oxidation in both COCs and denuded oocytes could reduce the oocyte maturation rate [133]. Fatty acids are also important for prostaglandin (PG) biosynthesis, which is critical for signal transduction, and suitable biosynthesis of PGE2 is important when follicles develop and mature. In addition, compared with those

in young control individuals, aged mares were observed to have less amount of free fatty acids in oocytes while more in cumulus cells [134]. Figure 2 shows that a study found a significant increase in carnitine in aged MI oocytes from sequencing data [105]. Although there are many studies on fatty acid metabolism during the process of ovarian aging, the changes in fatty acids in aged oocytes and granulosa cells are not particularly clear at present. Similarly, the role of different fatty acids in follicular development and oocyte maturation is ambiguous. For example, one study reported that oleic acid in follicular fluid plays a role in the quality of oocytes and embryo, while another study showed that high levels of oleic acid could reduce the quality of embryos and the blastocyst formation rate [135–136]. Additionally, treating COCs with excessive doses of linolenic acid leads to oocytes expanding and maturing poorly. However, 50 μM linolenic acid increased the oocyte maturation rate and blastocyst formation rate [137]. a study reported that omega-3 fatty acids may contribute to the delay of ovarian aging and improve oocyte quality at advanced maternal age, while a diet rich in omega-6 fatty acids may play the opposite role [138]. Several studies have shown that high maternal dietary omega-3 fatty acid levels disrupt oocyte mitochondria and decrease embryo development [139]. A clinical study revealed that there was no correlation between the omega-3 index and IVF outcomes [140]. However, a recent study showed that women taking omega-3 supplements had a 1.51-fold greater probability of conceiving than control women [141]. The concentration of fatty acids must be considered when evaluating the quality of oocytes with the addition of fatty acids. Different types and concentrations of fatty acids may affect the maturation process of oocytes differently. Lipid metabolism plays a critical role in ovarian aging and oocyte quality, with specific fatty acids exhibiting complex effects. Future research should focus on understanding the mechanisms underlying these effects and developing targeted interventions to optimize lipid metabolism for improved reproductive outcomes. Balancing lipid homeostasis through dietary or therapeutic strategies may offer new avenues for delaying ovarian aging and enhancing fertility.

The figure above shows the lipid metabolites that undergo significant changes in aged MI oocytes. In aged MI oocytes, carnitine, which is involved in energy

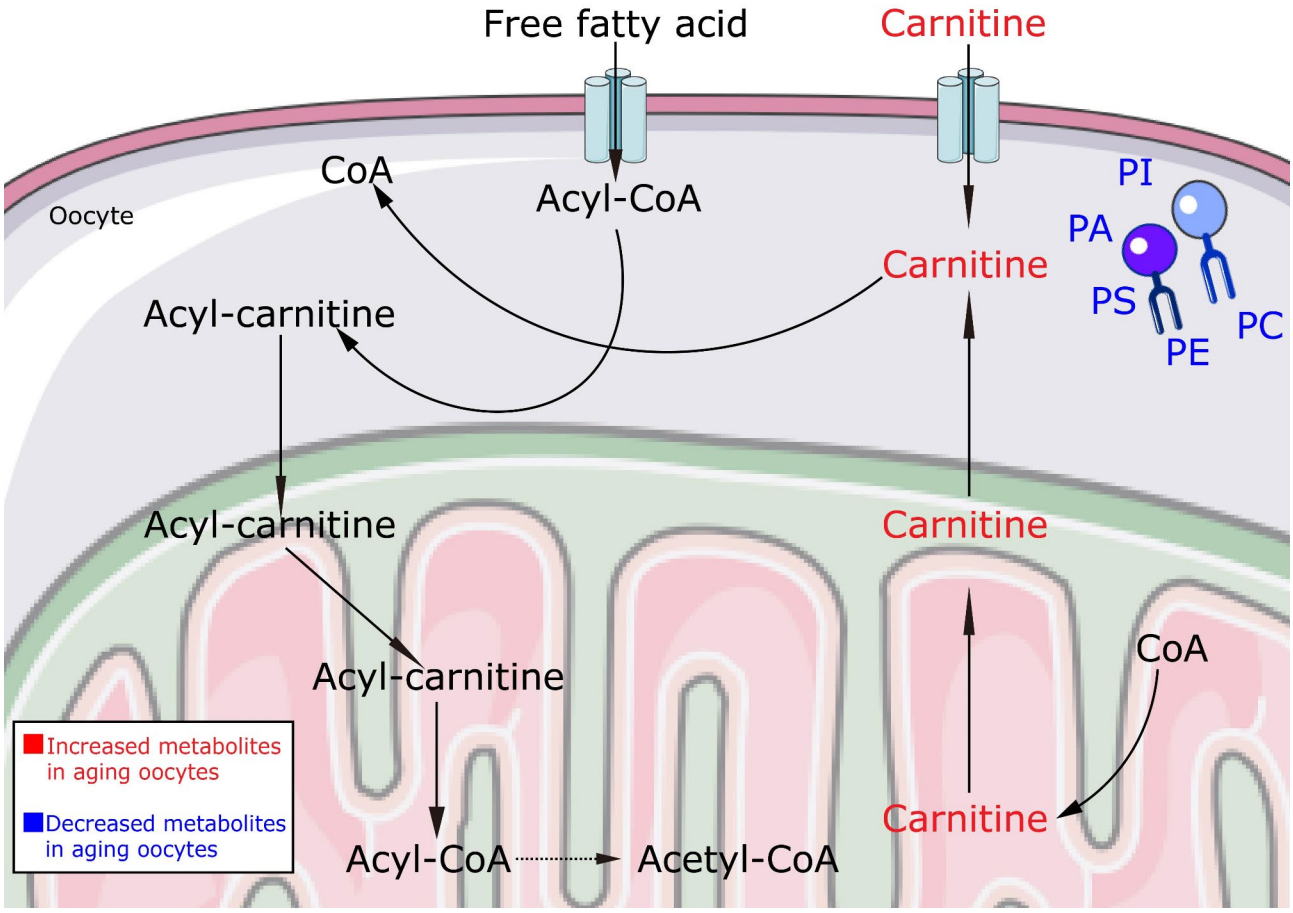

Fig. 2 Overview of age-related changes in lipid metabolism in MI oocytes [105, 114]

metabolism, was significantly increased. Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI) are five types of phospholipids that play an important role in the composition of cell membranes. With age, the levels of these phospholipids decreased significantly.

The mevalonate pathway and ovarian aging

MVA is a precursor of nonsteroidal isoprenoids, which are lipid anchors for GTP-binding proteins, such as Ras, Rho, and Rac. MVA is important for cholesterol synthesis and cell growth control [142]. The mevalonate pathway is designed to synthesize HMG-CoA from acetyl-CoA via the catalysis of HMG-CoA synthase. Mevalonic acid is then produced by the catalysis of HMG-CoA reductase (HMGCR) and is subsequently phosphorylated to mevalonate-5 pyrophosphate by the key enzyme phosphomevalonate kinase (PMVK). Decarboxylation of mevalonate-5 pyrophosphate results in the formation of isopentenyl diphosphate (IPP), which is further converted to dimethylallyl pyrophosphate (DMAPP) via catalysis by IPP isomerase. Farnesyl diphosphate synthase (FPPS) catalyses the condensation of DMAPP and IPP to form farnesyl diphosphate (FPP), and geranylgeranyl diphosophate synthase (GGPPS) catalyses the condensation of IPP and FPP to form geranylgeranyl diphosohate (GGPP) [143–144]. Geranylgeraniol (GGOH), an alcohol derivative of GGPP, is a key metabolic derivative of the cholesterol pathway. GGOH can restore the function of cells lacking mevalonate kinase (MVK) and can also prevent the cytotoxicity caused by statins [145]. Farnesol (FOH), an alcohol derivative of FPP, is generated by the dephosphorylation of FPP and is also an activator of the mevalonate pathway [146]. FOH has many biological functions, such as signal transduction and quorum sensing, and can regulate cell proliferation [147].

Overview of the MVA pathway and key genes involved in regulating the MVA pathway in metaphase I granulosa cells (MIGCs). Previous sequencing data of our research group showed that in aged MIGCs, the regulatory genes of MVA pathway showed an overall downward trend.

In addition, FPP and GGPP can also be used for post-translational modifications (PTMs) and prenylation of proteins containing the CaaX motif. Protein prenylation is a widely occurring PTM in which FPP or geranylgeranyl pyrophosphate serve as lipid donors. These lipid moieties are transferred to cysteine residues, resulting in the formation of covalent thioether bonds [148]. Protein prenylation is indispensable for the signal transduction function of GTP-binding proteins. Various diseases, including insulin resistance, islet dysfunction, and abnormal ovarian metabolism, can occur if protein prenylation is disrupted [149]. One study found that a lack of geranylgeranyl diphosphate synthase 1 (Ggps1) in myometrial cells leads to impaired uterine contraction and dystocia in mice [150]. This finding reveals that GGPPS is an important target for regulating protein prenylation and is highly important for regulating metabolic homeostasis.

Mevalonate pathway inhibition has a significant effect on reproductive processes. Another study reported that statins impair mouse preimplantation development by inhibiting the mevalonate pathway and modulating HIPPO signalling, an important regulator of the trophectoderm (TE) lineage. As the whole-transcriptome analysis showed, processes such as cholesterol biosynthesis, HIPPO signalling, cell lineage specification and the endoplasmic reticulum (ER) stress response are related to the gene expression dysregulation induced by statin treatment. The study explored the mechanism of connection between the mevalonate pathway and ER stress. GGPP supplementation inhibited the stress-responsive genes in embryos treated with statins from being upregulated. Further studies revealed that the MVA pathway activates RAC1, which is a small GTPase to keep cellular homeostasis in preimplantation embryos, and regulates differentiation (TE lineage specification) through another small GTPase named RHOA [151]. As Fig. 3 shows, our previous studies revealed that the overall downregulation of the mevalonate pathway in aged granulosa cells, which results in a deficiency of the LHR/EGF pathway in aged GCs, plays a key role in malignant defects and aneuploidy in aged oocytes. It was also found that the MVA metabolite GGOH could rescue meiotic defects, decrease aneuploidy rates and upregulate gene expression associated with meiosis in aged oocytes through protein prenylation. Moreover, GGOH treatment improved the reproductive outcome of aged mice [152]. The MVA pathway plays a crucial role in oocyte quality and embryonic development by regulating cholesterol synthesis, signal transduction, and cellular homeostasis. Dysfunction of the MVA pathway is a key driver of ovarian aging, and its restoration may serve as a potential strategy to improve fertility in women of advanced maternal age. Therefore, investigating the role of the MVA pathway in human ovarian aging and developing targeted interventions to delay ovarian aging and enhance reproductive health may become an important direction for future research.

Amino acid metabolism

Amino acid classification and function

Amino acids are the basic units of proteins and are involved in specific structural forms and biochemical activities [153]. The amino acids obtained by natural protein hydrolysis are mostly α-amino acids, with a total of 22 types. Non-protein amino acids, such as citrulline, ornithine, and hydroxyproline, are derivations of

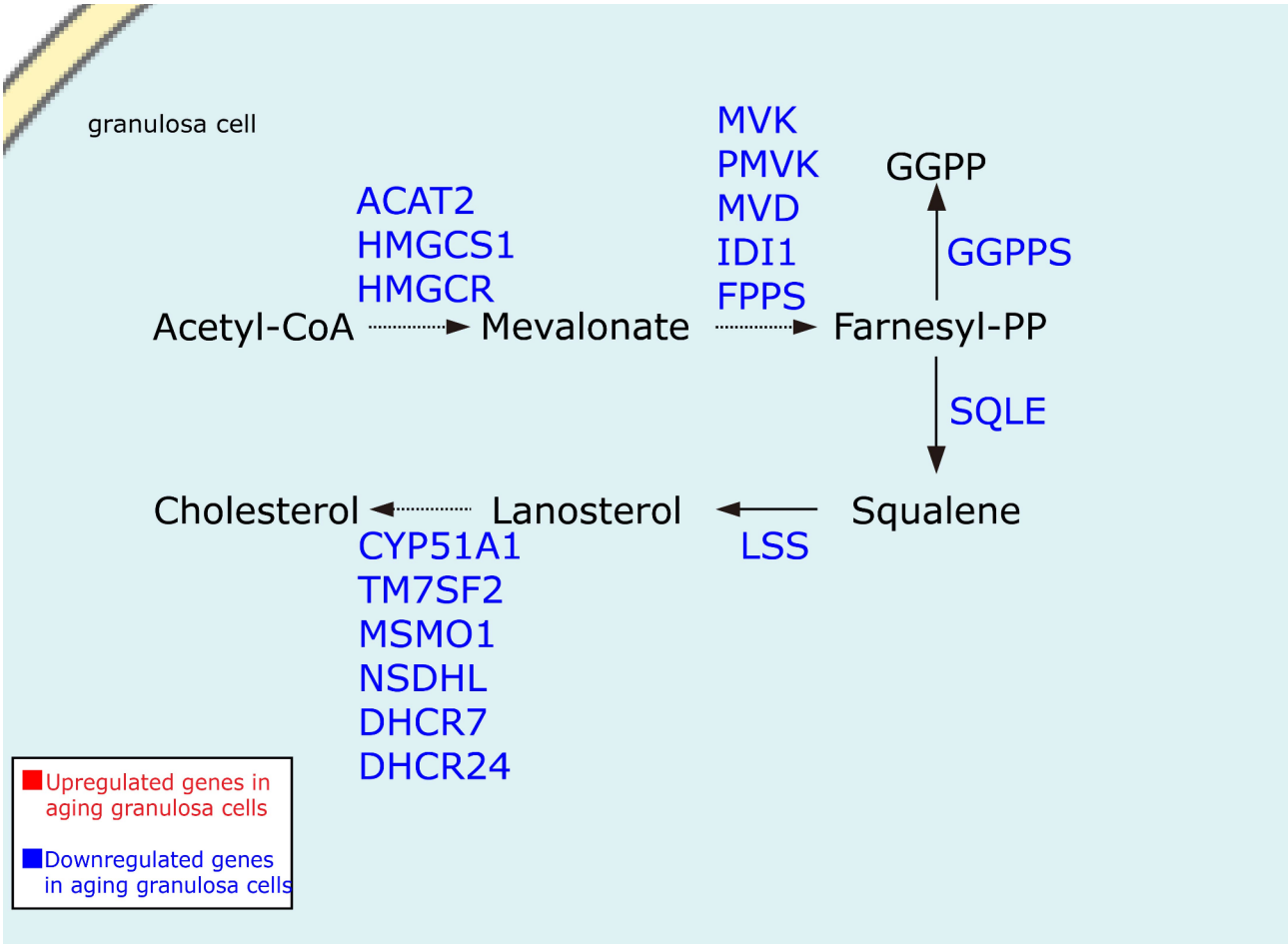

Fig. 3 Overview of age-related changes in Mevalonate pathway in Metaphase I Granulosa Cells (MIGCs) [143]

proteinogenic amino acids but cannot be directly incorporated into protein molecules [154]. Many amino acids, such as tyrosine and tryptophan, are precursors to hormones and neurotransmitters that sustain neural responses and communication in the body. Amino acids also serve as an energy source for the body, helping to maintain metabolism and energy levels. Glutathione, which is generated by the combination of glutamic acid, cysteine and glycine, is a key antioxidant in the human body that helps to remove excess ROS in the body to maintain the normal redox environment [155]. Glutathione is a key component in maintaining proper immune system functioning, which helps to fight infections. This destroys disease-causing microorganisms and infected cells and allows cells to perform normal functions [156].

Amino acids and follicle development

As precursors of proteins and nucleic acids, amino acids participate in protein synthesis, energy production, intracellular buffering and other processes to regulate oocyte development [157]. The transport and metabolism of various amino acids in oocytes, granulosa cells, and cumulus cells are observed at different stages of follicular development [158]. Studies have shown that disordered amino acid metabolism causes ovarian function to decline and leads to a series of diseases, such as premature ovarian failure and polycystic ovary syndrome [159–160]. One study analysed the amino acid content in the ovaries of mice of different ages through an ultraperformance liquid chromatography (UPLC) system and found that the levels of several amino acids in the aged group were significantly greater than those in the young group [161]. These findings indicate that aging disrupts amino acid metabolism, which in turn impairs ovarian function and oocyte development. This metabolic dysregulation likely contributes to the decline in oocyte quality and fertility observed with advancing age. From a broader perspective, these findings underscore the critical role of metabolic homeostasis in maintaining reproductive health and suggest that interventions targeting amino acid metabolism—such as dietary adjustments, supplementation, or pharmacological modulation—could potentially mitigate age-related ovarian dysfunction. Furthermore, these insights highlight the need for further research

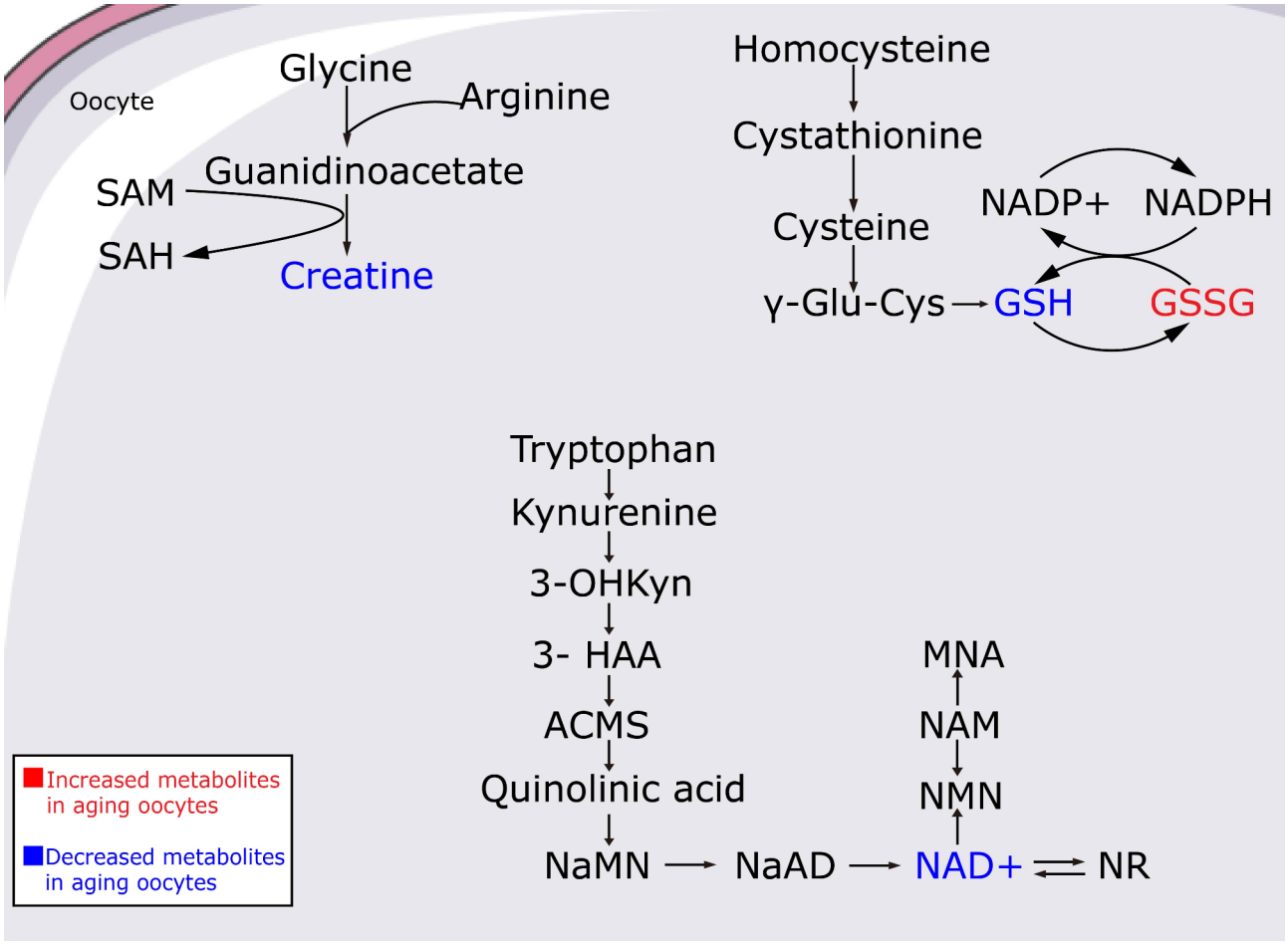

Fig. 4 Overview of age-related changes in amino acid metabolism in MI oocytes [105, 114]

into the specific mechanisms linking metabolic changes to oocyte aging, which could pave the way for innovative strategies to preserve fertility in aging individuals [162].

Amino acids and ovarian aging

As age increases, the levels of amino acid metabolites in oocytes change dramatically, as shown in Fig. 4. This results in abnormalities in various amino acid metabolic pathways and thus leads to the dysfunction of the redox system [163]. This dysfunction is characterized by continuous accumulation of ROS and a decline in oocyte quality. Amino acid metabolism is closely related to oxidative stress levels. Abnormal amino acid metabolism can impair ovarian function and oocyte growth. One study performed a metabolomic analysis of homocysteine levels in follicular fluid. The authors concluded that high homocysteine levels impair follicular development and increase the miscarriage rate. Moreover, homocysteine levels were reduced by chemical treatment and can weaken the pro-oxidative effect of homocysteine, thus improving the quantity and quality of oocytes [164]. Therapeutic amino acids can improve ovarian function by regulating the redox system. A study reported that a mixture of essential amino acids (EAAs) can activate the antioxidant defence system under special conditions, thus relieving oxidative stress in ovary caused by aging [165]. Amino acid metabolism can regulate ovarian function by regulating oxidative stress levels. Many studies have shown that glutathione, which consists of glutamic acid, cysteine and glycine, can participate in the redox process in the body to remove excess ROS and reduce oxidative stress levels [166]. Another study found through nontargeted metabolomics that arginine was significantly reduced in the ovaries of aged mice [167]. Research groups have shown through in vivo and in vitro experiments that an appropriate amount of spermidine can restore the quality of aged oocytes [168]. Microtranscriptome analysis demonstrated that arginine restores mitochondrial function by inducing mitochondrial autophagy, thereby inhibiting excessive ROS production and reducing oxidative stress-induced apoptosis. This beneficial effect is conserved across species. This study demonstrated that amino acid metabolism can also improve the oxidative stress level in aged oocytes

by improving mitochondrial function [169]. Moreover, amino acids such as glutamine and arginine can support mitochondrial health and function. Tryptophan can influence the production of anti-inflammatory molecules. By reducing inflammation, these amino acids help create a more favorable environment for ovarian function and follicle development [170]. Amino acids contribute to detoxification processes in the body. For example, glycine, glutamine, and cysteine form glutathione, which helps detoxify harmful substances and reduce oxidative damage in ovarian tissues. Amino acids are the building blocks of proteins, including those involved in the repair and maintenance of ovarian cells. By providing the necessary components for protein synthesis, they support the regeneration and proper functioning of ovarian tissue [171].

One study found that Nesfatin-1, a peptide of 82 amino acids, inhibits the proliferation of ovarian cells by reducing the phosphorylation of mammalian target of rapamycin (mTOR), which is expressed in oocytes and granulosa cells throughout follicular development, regulating oocyte metabolism, proliferation, and differentiation [172–173], and supplementation with leucine can reactivate the mTOR signalling pathway, thus significantly alleviating this inhibition [174]. The cystine/glutamate transporter (xCT) is a key protein involved in cystine transport. Watanabe found that aged mice with genetically disrupted xCT (xCT^{KO}) were inhibited in the mTOR pathway due to cystine deficiency, thus inhibiting follicular activation and obtaining a greater follicular reserve at older ages to maintain fertility [175]. These findings suggest that activation of the mTOR signalling pathway by amino acids is important for maintaining oocyte quality. Amino acids play a critical role in maintaining oocyte quality by regulating the mTOR pathway and other metabolic processes. Leucine and cystine are particularly important for mTOR activation, supporting oocyte maturation and follicular development. Nesfatin-1 and the xCT-cystine-mTOR axis highlight the complex interplay between nutrient signaling and ovarian function. Future research should focus on optimizing amino acid supplementation and modulating the mTOR pathway to improve fertility outcomes, particularly in aging or metabolically compromised individuals. These insights offer promising avenues for enhancing reproductive health and delaying ovarian aging.

Mammalian oocyte maturation and development are unique biological processes regulated by a variety of modifications [176–178]. Abnormalities in PTMs related to amino acid metabolism disorders caused by aging hinder the regulation of the oocyte maturation process and eventually lead to a decrease in oocyte quality [179]. Lysine succinylation (Ksuc) is an important PTM that is widely conserved in eukaryotic and prokaryotic cells and plays an important role in many pathophysiological processes. One study detected Ksuc level in the ovaries of premature ovarian insufficiency (POI) mice of different ages by immunoblotting and immunohistochemistry, and the results revealed that the level increased in both groups. Histological assessments and hormone level analyses revealed that higher Ksuc levels reduced the ovarian index and anti-Müllerian hormone and estrogen levels and increased follicular atresia [180]. These findings suggest that Ksuc is closely associated with ovarian senescence, highlighting the critical role of balanced amino acid metabolism in maintaining ovarian function and oocyte quality during aging. These results not only emphasize the importance of PTMs in regulating oocyte maturation and development but also suggest that targeting Ksuc and related metabolic pathways could offer novel therapeutic strategies to mitigate age-related ovarian decline. This study warrants further investigation into how other modifications interact with Ksuc to influence oocyte quality and ovarian longevity.

The figure shows the amino acid metabolites that are significantly changed in aging oocytes during MI. Creatine levels decreased in aging MI oocytes. The levels of both glutathione(GSH) and its oxidation products oxidized glutathione(GSSG) significantly changed in relation to oxidative damage, indicating that glutathione plays a role in alleviating oxidative damage in aging oocytes. With age increasing, the abundance of nicotinamide adenine dinucleotide(NAD+) decreased, while the precursors nicotinamide mononucleotide (NMN), kynurenine, and nicotinamide riboside(NR) showed few changes, which may indicate impaired NAD+ biosynthesis in aging oocytes.

Conclusion

The purpose of this review is to elucidate the connection between metabolism and ovarian aging to explore strategies for treating ovarian aging and oocyte quality decline in aged women. With respect to human natural fertility, oocyte quality and age, an inverted U-shaped curve is observed, and the ovarian function of women older than 38 years decreased rapidly. Aneuploidy is an important cause of a decrease in oocyte quality. Ovarian metabolism plays an important role in regulating ovarian functions and oocyte growth. Carbohydrate metabolism affects ovarian function by affecting the body's redox system and mitochondrial quality control. The mevalonate pathway is an important pathway in lipid metabolism. Experiments have shown that the addition of mevalonate pathway intermetabolites can effectively alleviate ovarian aging and improve the quality of oocytes. Moreover, the amino acid pathway affects ovarian function through oxidative stress, the mTOR signalling pathway and PTM regulation. Further research on ovarian metabolism may

shed light on ovarian aging and oocyte aneuploidy and provide new therapeutic targets for anti-ovarian aging.

Abbreviations

IVF	In vitro fertilization
NDJ	Nondisjunction
PSCS	Premature sister chromatid separation
RS	Reverse segregation
SAC	Spindle-assembly checkpoint
SSBs	Single-strand breaks
DSBs	Double-strand breaks
HR	Homologous recombination
Q-PCR	Real-time quantitative reverse transcriptase polymerase chain reaction
RTL	Relative telomere length
ATM	Ataxic Telangiectasia Mutation
mtDNA	Mitochondrial DNA
OS	Oxidative stress
ROS	Reactive oxygen species
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
$O_2.^-$	Superoxide
H_2O_2	Hydrogen peroxide
$^{\cdot}OH$	Hydroxyl radicals
MQC	Mitochondrial quality control
LONP1	ATP-dependent Lon protease 1
AIFM1	Apoptosis-inducing factor mitochondrial associated 1
GWASs	Genome-wide association studies
scM&T-seq	Single-cell methylation/transcriptome parallel sequencing technology
ANM	Age of natural menopause
DDR	DNA-damage response
m6A	N6-methyladenosine
HDAC	Histone deacetylase
lncRNAs	Long noncoding RNAs
GCs	Granulosa cells
CircRNAs	Circular RNAs
NcRNAs	Noncoding RNAs
ART	Assisted reproductive technology
PGCs	Primary germ cells
ATP	Adenosine triphosphate
PPP	Pentose phosphate pathway
NADPH	Nicotinamide adenine dinucleotide phosphate
OXPHOX	Oxidative phosphorylation
HBP	Hexosamine biosynthesis pathway
ECM	Extracellular matrix
COCs	Cumulus-oocyte complex
AGEs	Advanced glycation end products
RAGEs	Receptors for AGEs
PDK1	Pyruvate dehydrogenase kinase isozyme 1
FAs	Fatty acids
SFAs	Saturated fatty acids
MUFAs	Monounsaturated fatty acids
PUFAs	Polyunsaturated fatty acids
MVA	Mevalonate
FPP	Farnesyl pyrophosphate
GGPP	Geranylgeranyl pyrophosphate
FAO	Fatty acid β-oxidation
PG	Prostaglandin
HMGCR	HMG-CoA reductase
PMVK	Phosphomevalonate kinase
IPP	Isopentenyl diphosphate
DMAPP	Dimethylallyl pyrophosphate
FPPS	Farnesyl diphosphate synthase
FPP	Farnesyl diphosphate
GGPPS	Geranylgeranyl diphosohate synthase
GGPP	Geranylgeranyl diphosohate
GGOH	Geranylgeraniol
FOH	Farnesol
MVK	Mevalonate kinase
PTM	Posttranslational modification
Ggps1	Geranylgeranyl diphosphate synthase 1
TE	Trophectoderm
ER	Endoplasmic reticulum
UPLC	Ultraperformance liquid chromatography
EAAs	Essential amino acids
GSH	Glutathione
mTOR	Mammalian target of rapamycin
Ksuc	Lysine succinylation
POI	Premature ovarian insufficiency
NMN	β-Nicotinamide Mononucleotide
NR	Nicotinamide riboside
NAD+	Nicotinamide adenine dinucleotide
MI	Metaphase I
MII	Metaphase II
MIGC	Metaphase I granulosa cells
TCA cycle	Tricarboxylic acid cycle
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PS	Phosphatidylserine
PA	Phosphatidic acid
PI	Phosphatidylinositol
GSSG	Oxidized glutathione

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Author contributions
DW designed and wrote the main manuscript, CL prepared figures and help build frameworks, LD modify frameworks and revise the manuscript. All authors read and approved the final version of the article.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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