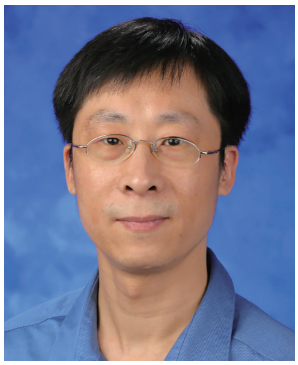


孙建伟, 博士、教授、博士生导师。2019年入选“云南省高层次人才”青年人才, 2021年获云南省“杰出青年”基金资助。以通讯/第一作者身份在*JCB*、*Oncogene*、*JBC*、*JCS*等国际一流学术期刊发表文章近20篇。中国生物物理学会线粒体分会理事, 国家自然科学基金委同行评议专家, 云南省自然科学基金评审专家库专家。现主持国家自然基金面上项目、云南高层次人才青年项目、云南省重点项目等。实验室目前的主要研究方向为: (1) 肿瘤转移相关基因的筛选与机制研究; (2) 线粒体功能调控失调在疾病发生中的作用及机制; (3) 钙池操纵的钙内流(SOCE)介导线粒体功能调控肿瘤发生恶化及抗药性的分子机制。

线粒体调控卵母细胞发育潜能的研究进展

董瑞# 关瑞琪# 高亚可# 郎啟春 沈俊岭* 孙建伟*

(云南大学生命科学中心, 云南省细胞代谢与疾病重点实验室,
省部共建云南生物资源保护与利用国家重点实验室, 生命科学学院, 昆明 650500)

摘要 卵母细胞的发育潜能与雌性生育能力密切相关。线粒体是卵母细胞中含量最丰富的细胞器, 在卵母细胞成熟和胚胎发育中具有重要的作用。卵母细胞成熟过程中所需的能量和调控信号在很大程度上依赖于线粒体的功能和活性, 线粒体功能障碍会导致雌性不孕。线粒体因其在卵母细胞和胚胎发育中的关键作用, 可作为评估卵母细胞发育潜能和雌性生育力的标志指标。该文从mtDNA、线粒体动力学、线粒体能量代谢和线粒体质量控制四个方面, 综述了线粒体如何调控卵母细胞发育潜能, 为线粒体调控在生殖医学研究方面提供借鉴和参考。

关键词 卵母细胞; 线粒体; 雌性不孕; 线粒体质量控制

Research Progress of Mitochondria in the Regulation of Oocyte Developmental Potential

DONG Rui#, GUAN Ruiqi#, GAO Yake#, LANG Qichun, SHEN Junling*, SUN Jianwei*

(*Center for Life Sciences, Yunnan Key Laboratory of Cell Metabolism and Diseases, State Key Laboratory for Conservation and Utilization of Bio-Resources in Yunnan, School of Life Sciences, Yunnan University, Kunming 650500, China*)

Abstract The quality of oocytes is closely related to female fertility. Mitochondria are the most abundant organelles in oocytes and involved in the development of oocytes and early embryos. The required energy and

收稿日期: 2023-10-27 接受日期: 2023-12-12
国家自然科学基金(批准号: 82273460、32260167)、云南省应用基础研究基金(批准号: 202101AV070002)和云南大学研究生科研创新项目(批准号: KC-22223074、ZC-23236399)资助的课题
#共同第一作者
*通信作者。Tel: 13658714542, E-mail: jlshen@ynn.edu.cn; Tel: 13822222004, E-mail: jwsun@ynn.edu.cn
Received: October 27, 2023 Accepted: December 12, 2023
This work was supported by the National Natural Science Foundation of China (Grant No.82273460, 32260167), the Yunnan Applicative and Basic Research Program (Grant No.202101AV070002) and the Yunnan University Graduate Research Innovation Project (Grant No.KC-22223074, ZC-23236399)
#These authors contributed equally to this work
*Corresponding authors. Tel: +86-13658714542, E-mail: jlshen@ynn.edu.cn; Tel: +86-13822222004, E-mail: jwsun@ynn.edu.cn

signal transduction occurring during each critical stage of oocyte maturation largely depend on the function and activity of mitochondria. Mitochondria, due to their crucial role in oocyte and embryonic development, serve as markers for evaluating oocyte viability and quality. Herein, this paper reviews the progress of mitochondrial DNA, mitochondrial dynamics, mitochondrial energy metabolism and mitochondrial quality control that regulate oocyte development, which provides a reference for mitochondrial regulation in reproductive medicine research.

Keywords oocytes; mitochondria; female infertility; mitochondrial quality control

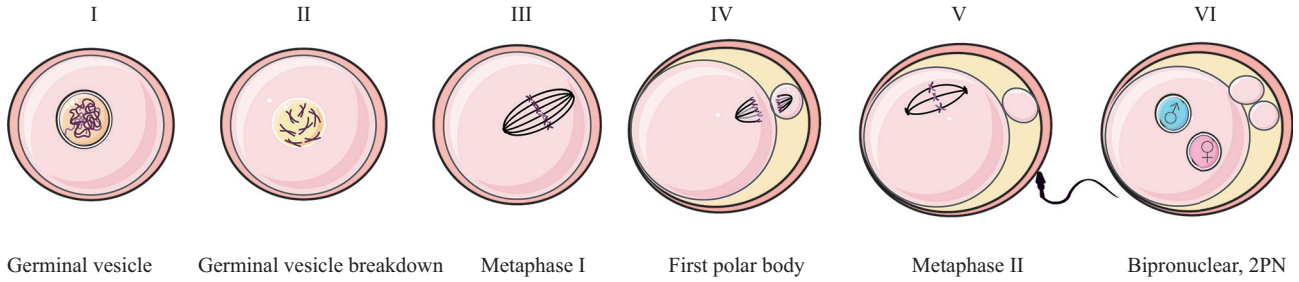
在哺乳动物胚胎发育早期阶段, 原始生殖细胞(primordial germ cells, PGCs)作为卵母细胞和精原细胞的直接前体, 在受到局部细胞因子的刺激后主动迁移定植于性腺中, 并分化为卵原细胞和精原细胞, 形成第一个生殖细胞群。卵原细胞进入第一次减数分裂, 成为原始卵母细胞[1-3]。女性的卵巢中, 原始卵母细胞最初由单层鳞状颗粒细胞包裹形成原始卵泡; 周围颗粒细胞(granulosa cells, GCs)不断复制扩增, 逐渐出现卵泡腔, 卵泡腔中充满卵泡液, 为卵母细胞生长提供环境与营养[4]。此间卵母细胞大量积累卵胞质、脂质、mRNA、蛋白质等, 还会经历细胞器, 例如线粒体、内质网等复制与重排。随着卵母细胞体积的增大, 细胞核内的遗传物质不断积累, 直到当卵母细胞获得生发囊泡破裂(germinal vesicle breakdown, GVBD)的能力[5]。卵母细胞开始恢复第一次减数分裂, 随后纺锤体开始组装, 纺锤体牵引染色体迁移, 最终导致不对称细胞分裂的发生, 以及第一极体的排出[6]。受精前, 卵母细胞会停滞在第二次减数分裂的中期(metaphase II, MII), 精子与MII期卵母细胞结合后恢复并完成第二次减数分裂, 排出第二极体[7](图1)。

线粒体(mitochondria)作为细胞内重要双层膜细胞器, 负责有氧呼吸、能量转化和多种信号通路调控。线粒体的功能和卵母细胞的发育潜能密切相关, 线粒体功能失调通常会引起卵母细胞的发育异常并导致雌性不孕。越来越多小鼠模型的研究显示, 线粒体在卵母细胞发育成熟过程中起着至关重要的作用, 特别是参与纺锤体迁移[8-9]。卵母细胞的质量是胚胎发育潜力的前提, 其不仅为受精后的胚胎发育提供母源的遗传物质, 还会将线粒体基因组传递至胚胎。本论文综述了线粒体在调控卵母细胞成熟和发育潜能中作用的研究进展, 以期为生殖医学中卵母细胞质量控制相关的研究提供借鉴和参考。

1 线粒体调控卵母细胞的发育潜能

1.1 mtDNA丰度及异质性影响卵母细胞质量

线粒体遗传物质(mitochondria DNA, mtDNA)是一种环状DNA, 包含与线粒体组装相关蛋白亚基的遗传信息, 其具有自我复制的能力[11]。线粒体基质中存在核糖体, 其负责合成线粒体DNA编码



I: 在卵母细胞发育的早期阶段, 遗传物质复制积累, 染色质高度疏松, 形似泡状, 此时被称为生发囊泡(germinal vesicle, GV)阶段; II~IV: 生发囊泡破裂(germinal vesicle breakdown, GVBD)后, 纺锤体完成组装并牵引染色体迁移, 伴随第一极体的排出, 卵母细胞完成第一次减数分裂; V: 受精前的卵母细胞停滞在第二次减数分裂中期(MII), 等待与精子结合; VI: 受精过程触发并完成第二次减数分裂, 卵母细胞排出第二极体, 形成双原核。
I: in the early stage of oocyte development, genetic material replicates and accumulates, which is called the stage of GV (germinal vesicle); II-IV: after the GVBD (germinal vesicle breakdown), the spindle completes the assembly and pulls the chromosome to migrate, and the oocyte completes the first meiosis with the discharge of the first polar body; V: before fertilization, the oocytes stagnate in MII (the second meiotic metaphase), waiting to combine with the sperm; VI: fertilization triggers and completes the second meiosis, and discharges the second polar body to form a double pronucleus.

图1 哺乳动物卵母细胞减数分裂过程示意图(根据参考文献[10]改编)

Fig.1 Schematic diagram of meiosis process of mammalian oocytes (adapted from reference [10])

的蛋白质[12]。此外，也有一些核编码的线粒体蛋白质参与mtDNA复制与修复[13-14]。卵母细胞受精后mtDNA复制不会立即发生，在每一轮受精卵细胞分裂为子细胞的过程中，卵母细胞来源的线粒体逐渐被稀释，均匀分散到各个胚胎细胞中[15-17]；为保证每个卵裂球有足够的mtDNA拷贝数，线粒体存在受精前阈值[18-19]。卵母细胞中的mtDNA复制积累发生在生发囊泡(germinal vesicle, GV)阶段[20]，随后mtDNA拷贝数急剧增加，在人类成熟卵母细胞中mtDNA拷贝数范围为2×10^4至1.04×10^6[21-23]。SANTOS等[24]研究表明，成功受精的卵母细胞中mtDNA拷贝数平均为250 454，未受精卵母细胞为163 698，退化卵母细胞组的平均拷贝数为44 629，因此mtDNA含量对受精结果至关重要，是卵母细胞质量的重要标志。此外，编码线粒体DNA聚合酶γ(DNA polymerase subunit gamma, DPOG)的*POLG*基因缺失或变异会导致mtDNA耗竭，线粒体DPOG功能障碍导致严重的进行性多系统疾病，包括帕金森综合征和过早绝经[25]；据报道，一名携带杂合子*POLG*变异的妇女具有卵巢发育不全的特征[26]。由此可见，mtDNA的丰度会影响卵母细胞的质量。

此外，mtDNA的异质性也与卵母细胞及胚胎质量有关。与核DNA不同，哺乳动物mtDNA主要通过母系遗传[27]。mtDNA由于缺少组蛋白保护，更易发生缺失与突变，从而导致线粒体疾病的发生。mtDNA复制或线粒体翻译途径异常引起的线粒体疾病与不孕症相关[28-29]。从体外受精(*in vitro* fertilization, IVF)或卵胞质内单精子注射(introcytoplasmic sperm injection, ICSI)反复失败的女性患者中收集外周血进行测序，结果分析表明这些不孕妇女携带更多的mtDNA变异，特别是在D-loop区。目前报道有16个mtDNA变异与早期胚胎发育缺陷的风险增加有关，证明mtDNA变异与不孕妇女早期胚胎发育缺陷有关[30]。mtDNA异质性突变在卵母细胞中很常见，并且根据突变位置和突变负荷的不同，它们可能会增加新生儿患氧化磷酸化(oxidative phosphorylation, OXPHOS)病的风险。有研究报道在患有“散发性”Kearns-Sayre综合征(Kearnss-Sayre syndrome, KSS)和进行性外部眼肌麻痹(progressive external ophthalmoplegia, PEO)患者的卵母细胞和肌肉组织中发现了一种特定缺失重排的mtDNA，这种致病性缺失可通过母亲传递给后代[31-32]。mtDNA遗传瓶颈理论表明在PGCs分化为初级卵母细胞阶段可以有效地过滤掉mtDNA突变，并通过限制mtDNA含量维持mtDNA同质性[33]，在卵母细胞的早期阶段，通过药物干预可以改善mtDNA异质性[34]。此外，线粒体ROS(reactive oxygen species)水平升高与mtDNA异质性有关[35-36]。一项研究报道了早发性卵巢功能不全(premature ovarian insufficiency, POI)女性的mtDNA变异的数量增加，POI人群的ROS水平显著高于对照组[37]。

1.2 卵母细胞中的线粒体动力学调控

在卵母细胞和胚胎发育的每个关键步骤中，所必需的能量和发生的信号调节在很大程度上依赖于线粒体动力学调控[38-40]。线粒体是细胞信号级联平台，因此由线粒体膜动力学调节的线粒体网络不断经历重塑和分离，以参与调节细胞信号转导和能量代谢[41]。随着细胞能量需求的不断变化，线粒体的大小和形态结构也在不断演变，它们可以自由地移动，也可以依附于其他细胞器，从而发挥其功能。线粒体锚定在位于细胞骨架的驱动蛋白马达上，随后沿着细胞骨架运输到特定位置，从而在卵母细胞发育过程中完成其动态分布[42]。小鼠卵母细胞成熟过程中线粒体的形态变化如下：在GV期前，球形或椭圆形线粒体均匀分布在整个细胞质中[43]；在GV期，大部分线粒体靠近卵母细胞的细胞膜，为细胞内蛋白质合成、分泌以及卵母细胞–颗粒细胞相互作用提供能量[17,44]；随着卵母细胞恢复减数分裂，线粒体为响应GVBD发生逐渐向细胞核迁移。小鼠卵母细胞中线粒体核周积累是第一次减数分裂前期的特征[45]：线粒体通过动力蛋白介导聚集在纺锤体周围，并与纺锤体一起向卵母细胞皮质迁移。然而，在细胞分裂时，线粒体并不是平均分离，大量线粒体留在卵母细胞中，只有少量损伤线粒体随第一极体排出[46]。随后线粒体向核周的区域重新积累，这可能为RNA转录等活动提供能量[47]。在第二次减数分裂中期线粒体又均匀分布在整个卵母细胞中，以维持卵母细胞的基础代谢[44]。

此外，线粒体通过融合和分裂改变其在细胞中的位置和形态结构，以维持线粒体稳态和正常功能，这对提供能量、抗应激、信号转导和减数分裂至关重要[48]。线粒体发生裂变和融合可以改变线粒体的内膜面积、膜间空间、基质和外膜的相对比例、基质密度以及线粒体之间的结构连接，以响应能量需求变化[49]。氧化磷酸化受损、mtDNA缺乏和ROS

过量会诱导线粒体融合发生[50-51]。线粒体融合可以通过扩大线粒体内膜(inner mitochondrial membrane, IMM)改善能量供应, 也可以促进健康和有缺陷的线粒体之间的物质交换和互补, 确保mtDNA的完整性和线粒体呼吸功能的恢复[52-53]。在卵母细胞发育过程中线粒体的超微结构随着卵泡发育时期变化, 呈现一定的变化规律。在人类卵母细胞中线粒体的变化趋势为: 在原始生殖细胞中, 细胞核附近分布着白色基质和小囊泡样嵴的椭圆形线粒体, 在PGC迁移到性腺并分化为卵原细胞的过程中, 线粒体数量显著增加, 早期原始卵泡的卵母细胞线粒体含有更致密的基质, 并具有层状嵴[54]。初级卵泡中的卵母细胞大多含有圆形或不规则的线粒体, 其基质较为松散, 显示出典型的平行拱形嵴[55]。在生长卵泡期, 卵母细胞中线粒体大量复制, 数量变多, 并分散在卵质中, 呈现出空泡结构和拱形嵴, 线粒体的活跃度相对较低[43,56]。在受精卵中, 线粒体集中在原核周围。在胚胎第一次卵裂过程中, 具有致密基质和少量拱形嵴的圆形或卵圆形线粒体逐渐被具有疏松基质和大量横嵴的细长线粒体所取代, 直到胚胎发育到4-cell时期胚胎细胞内的线粒体最终呈现出更典型的体细胞内线粒体形式(有大量横嵴的细长线粒体)。

线粒体动力学调控主要由线粒体膜中的GTP酶: DRP1(dynamin-1-like protein)[57]、OPA1(optic atrophy 1)[58]和MFNs(mitofusin)[59]介导。这些功能蛋白从以下三个方面影响卵母细胞质量发生变化。首先, 线粒体裂变通过多细胞器重排维持卵母细胞内信号调节。通过卵母细胞特异性*Drp1*缺陷小鼠分析发现, *Drp1*基因缺陷小鼠的卵母细胞中线粒体与其他细胞器(内质网和分泌囊泡等)高度聚集, 导致Ca^{2+}信号转导受损、与分泌相关的细胞间通讯受损[60]。其次, 线粒体在卵母细胞染色体分离中发挥重要作用。着丝粒蛋白F(centromere protein F, CENP-F)是外动粒的一种成分蛋白, 也是动粒–微管(kinetochore microtubule, K-MT)附着的关键调节因子[61]。在减数分裂过程中, APC/C复合体(anaphase-promoting complex)负责介导黏连蛋白(cohesion)发生降解, 驱动染色体分离[62]。DRP1是CENP-F的效应蛋白, 小鼠卵母细胞中核包膜分解后DRP1被CENP-F募集到动粒中, 通过与APC2(cullin homology protein)结合调节APC/C活性, 进而调控小鼠卵母细胞中的减数分裂细胞周期。DRP1缺失导致黏连蛋白过早降解, 染色体发生分离, 影响卵母细胞第一次减数分裂[63]。MFNS分为两种类型, 即MFN1(mitofusin 1)和MFN2(mitofusin 2), MFN1/2可以通过与MIRO(mitochondrial Rho GTPase)蛋白相互作用, 将线粒体锚定在细胞骨架上, 从而将其与驱动蛋白马达联系起来, 促使细胞质中的线粒体移动到特定区域[64]。卵母细胞中敲除*Mfn2*, 线粒体则不会定位在纺锤体周围[65]。而在*Mfn2*过表达的卵母细胞中, 线粒体一直存在于纺锤体周围, 导致纺锤体运动和染色体分离失败, 最终使多数卵母细胞停滞在MI期[66-67]。Mfns的表达在不同阶段受到精确调控, Mfns过量或缺乏会导致线粒体动力学和能量代谢异常, 最终阻碍卵母细胞减数分裂和胚胎发育[68]。最后, 线粒体动力学还参与调控卵母细胞mRNA的储存。在小鼠卵母细胞减数分裂成熟过程中, 线粒体相关核糖核蛋白结构域(mitochondria-associated ribonucleoprotein domain, MARDO)中会积累mRNA, 线粒体相关的无膜区室控制线粒体分布并调节母体mRNA的储存、翻译和衰变, 以确保哺乳动物的生育能力稳定[69-70]。

1.3 线粒体调控卵母细胞的能量代谢

卵母细胞中ATP产生的主要来源是线粒体氧化磷酸化, 抑制卵母细胞线粒体氧化磷酸化会引起卵母细胞内ATP水平的急剧下降, 而抑制糖酵解对ATP水平没有影响。卵母细胞摄取和代谢葡萄糖的能力很差, 卵母细胞中的线粒体需依靠卵丘细胞糖酵解生成的丙酮酸产生能量, 支持卵母细胞减数分裂成熟到第二次减数分裂中期II(MII)阶段[71-73]。参与调控线粒体代谢相关的关键因子, 也在卵母细胞生成以及成熟过程中发挥重要作用。我们列举了以下几种线粒体代谢相关蛋白在卵母细胞生长过程中所发挥的调控作用。

烟酰胺腺嘌呤二核苷酸(nicotinamide adenine nucleotide, NAD)在卵巢衰老中具有关键作用。吲哚胺2,3-双加氧酶1(indoleamine 2,3-dioxygenase 1, IDO1)或喹啉酸磷酸核糖转移酶(quinolinate phosphoribosyl transferase, QPRT)是NAD从头合成过程中的关键酶, 这两个基因遗传丢失会导致雌鼠卵巢NAD水平降低, 卵母细胞质量受损, 活性氧和纺锤体异常增加, 最终导致受精能力下降和早期胚胎发育受损, 在突变小鼠中补充烟酰胺核糖(nicotiamideRiboside, NR), 可增加卵巢储备并改善卵母

细胞质量[74-76]。线粒体ROS水平对维持卵母细胞质量至关重要。ROS的生理水平可调节卵母细胞正常功能，而其过度积累导致氧化应激(oxidative stress, OS)发生[77]。MitoQ(mitoquinolmesylate)是一种有效改善体外卵母细胞质量的药物[78]，MitoQ保护卵巢类器官在卵子发生和卵泡生成过程中免受氧化应激，恢复卵母细胞中的线粒体膜电位，促进卵泡生长和成熟。100 nmol/L MitoQ刺激小鼠雌性种系干细胞(female germ line stem cell, FGSC)，可有效清除FGSC内的ROS，减轻氧化损伤，从而降低由H_2O_2诱导的细胞凋亡。

沉默信息调节因子3 (sirtuin 3, SIRT3)是一种线粒体去乙酰化酶，属于NAD依赖性蛋白脱乙酰酶家族，主要存在于线粒体中，通过脱乙酰化调节线粒体蛋白功能，SIRT3参与线粒体生物活性和葡萄糖代谢调控[79]。GCs的SIRT3缺失可以通过改变泛醌NADH脱氢酶Fe-S蛋白1(recombinant NADH dehydrogenase ubiquinone Fe-S protein 1, NDUFS1)的乙酰化状态诱导线粒体氧化应激，导致颗粒细胞葡萄糖代谢发生损伤，诱导卵母细胞受损[80]。位于线粒体膜的磷酸甘油酸转位酶5(phosphoglycerate mutase 5, PGAM5)与细胞凋亡和线粒体自噬有关，PGAM5在卵丘细胞中高表达并与衰老呈正相关，且参与维持衰老颗粒细胞的线粒体动力学和代谢重编程。PGAM5在衰老卵丘细胞中经历活化并转移到线粒体外膜，磷酸化DRP1，从而催化线粒体发生分裂；当*PGAM5*被敲除后，衰老卵丘细胞的线粒体功能和代谢被部分逆转[81]。

1.4 线粒体清除机制影响卵母细胞发育潜能

细胞能够识别线粒体功能障碍，并有多种调节方式挽救线粒体功能，清除无法恢复的线粒体，维持功能性线粒体网络，重建线粒体稳态平衡，线粒体功能障碍会导致雌性小鼠不孕[82]。线粒体的质量控制除了mtDNA质量控制外，还包括线粒体未折叠蛋白反应(mitochondrial unfolded protein response, mtUPR)和线粒体自噬(mitophagy)的方式[83-84]，通过将异常线粒体蛋白清除和调控线粒体丰度响应卵母细胞活动。

线粒体未折叠蛋白反应可以在线粒体功能障碍期间，通过感知线粒体(未折叠蛋白)应激并诱导线粒体蛋白折叠、限制线粒体蛋白输入和抑制线粒体蛋白翻译来恢复功能失调的线粒体活性[85]。线粒体中未折叠或错误折叠的蛋白质被酪蛋白分解肽酶P(mitochondrial caseinolytic protease P, CLPP)降解，降解产物通过肽转运蛋白HAF-1输出到细胞质中[86]。CLPP是卵母细胞和胚胎发育以及卵母细胞线粒体功能和动力学所必需的，缺乏CLPP会导致mTOR途径激活，加速卵巢卵泡储备的消耗[87-88]。*Clpp*基因敲除雌性小鼠虽然产生较少数量的成熟卵母细胞和2-cell胚胎，但是无法发育至囊胚时期。此外，参与线粒体蛋白泛素化清除的酶发生紊乱也会影响卵母细胞质量。膜相关锌指蛋白5(membrane-associated RING-CH 5, MARCH5)是线粒体外膜定位的E3泛素连接酶，参与调节线粒体的融合，在小鼠卵母细胞减数分裂成熟中起关键作用。注射March5-siRNA导致卵母细胞线粒体功能障碍，活性氧水平增加，ATP含量降低以及线粒体膜电位降低，导致纺锤体形成的能力下降，动粒–微管脱离比例增加[89]。F-box和富含亮氨酸的重复蛋白5(F-box and leucine-rich repeat protein 5, Fbxl5)作为E3泛素连接酶参与损伤线粒体清除。Fbxl5耗竭诱导异常的线粒体动力学发生，Fbxl5沉默导致卵母细胞减数分裂失败、GVBD和极性体挤出率降低[90]。线粒体ATP依赖性lon蛋白酶1(lon protease 1, LONP1)是维持体细胞线粒体和细胞稳态的关键蛋白质，参与调节mtUPR和线粒体动力学[91]。LONP1直接与线粒体相关细胞凋亡诱导因子1(apoptosis inducing factor mitochondria-associated 1, AIFM1)相互作用，LONP1缺失会导致AIFM1从细胞质转运到细胞核，引起小鼠卵母细胞凋亡。患有LONP1致病变异的女性卵巢中缺乏大的窦卵泡，表现为不孕并出现卵巢早衰的病症[92]。

线粒体自噬是一种降解、清除衰老及损伤线粒体的特殊自噬形式，是线粒体应激反应的最后手段。线粒体膜上的PTEN诱导激酶1(PTEN induced putative kinase 1, PINK1)和E3泛素连接酶PRKN(parkin RBR E3 ubiquitin protein ligase)负责调控线粒体自噬。PINK1积聚在受损的线粒体外膜蛋白上，激酶结构域面向细胞质，该区域可磷酸化附着在线粒体外膜蛋白上的泛素，这些磷酸泛素链将PRKN募集到线粒体并激活其潜在的E3泛素连接酶活性，PRKN进一步泛素化线粒体外膜蛋白，然后募集受体，如OPTN(optineurin)或CALCOCO2/NDP52(calcium binding and coiled-coil domain 2)，组装成损伤线粒

体自噬体[93-94]。CCCP(一种诱导线粒体自噬的解偶联剂: carbonyl cyanide 3-chlorophenylhydrazone)处理生长的卵母细胞, 诱导PRKN介导的线粒体自噬发生, 卵母细胞减数分裂出现MI中期停滞, 通过显微注射编码*RAB7*的mRNA或使用RAB7激活剂ML098处理, 均可有效挽救在CCCP处理卵母细胞中观察到的所有缺陷, 表明RAB7可能在PINK1-PRKN介导的线粒体自噬中发挥调节作用; 在卵巢衰老过程中收集GV卵母细胞, 发现PINK1和PRKN蛋白水平随年龄相关性增加, 导致线粒体自噬体形成缺陷以及受损线粒体积累[95]。卵母细胞中生长停滞特异性蛋白6(growth arrest specific protein 6, GAS6)可通过调节线粒体自噬相关基因来维持线粒体活性; Gas6沉默的MII卵母细胞中线粒体自噬相关基因的表达水平降低, Gas6耗竭的MII卵母细胞表现出线粒体积累和聚集[96]。线粒体自噬有助于及时清除受损或功能失调的线粒体, 防止其释放有害物质, 维护卵母细胞的健康状态。

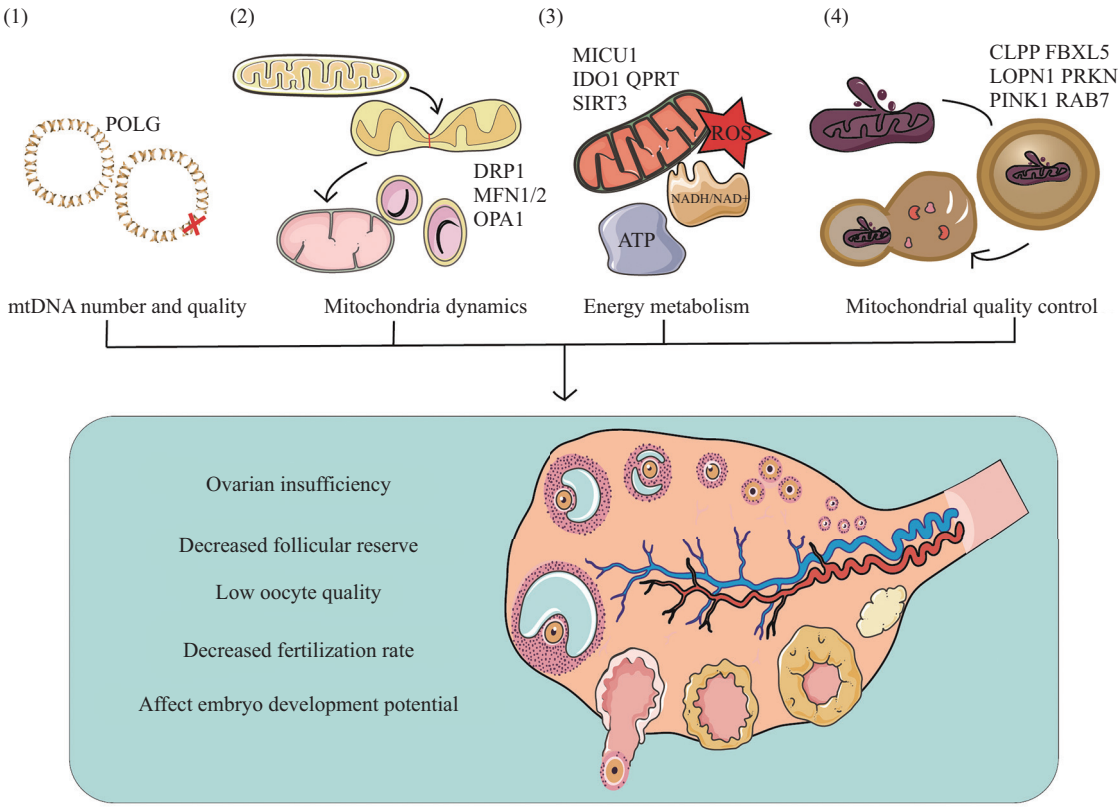
通过清除老化的线粒体, 维持新陈代谢活跃的线粒体数量, 有助于提供足够的能量, 支持卵母细胞正常发育和生殖过程。受损线粒体清除的调控涉及多个分子机制, 在卵母细胞中, 一些关键因子在这一过程中发挥重要作用, 但具体机制仍需深入研究。对于线粒体清除机制在卵母细胞中的作用及其具体调控机制的深入研究, 有助于更好地理解卵母细胞质量控制的分子基础, 为不育症等相关疾病的治疗提供新的理论和实践依据。

综上所述, 线粒体功能调控对于卵母细胞发育成熟至关重要, mtDNA、线粒体动力学、线粒体能量代谢和线粒体清除机制四个方面参与调控卵母细胞发育过程。其中mtDNA丰度影响卵母细胞的成熟和受精潜能, mtDNA异质性会导致卵母细胞携带线粒体遗传疾病风险; 线粒体的动力学网络变化响应卵母细胞的能量需求及信号调控; 与此同时, 线粒体氧化磷酸化的产物与副产物对卵母细胞的发育也产生重要影响。最后, 线粒体质量控制可保证卵母细胞内线粒体正常行使功能(图2)。

2 展望

卵母细胞成熟包括细胞核和细胞质成熟。核成熟主要涉及染色体分离, 而细胞质成熟涉及一系列复杂的过程: 细胞器重排和能量、mRNA、蛋白质和转录因子储存等[97]。卵母细胞含有大量的线粒体, 线粒体在卵母细胞细胞核及细胞质成熟中均发挥作用, 在卵母细胞发育过程中, 线粒体的形态以及分布与卵母细胞生长时期具有相关性, 成熟卵母细胞的线粒体形状与其他体细胞不同, 其不含有丰富的线粒体嵴, 卵母细胞低活性形态线粒体可以避免较少的mtDNA异质性产生, 从而维持线粒体遗传的稳定性, 保证胚胎线粒体的质量。许多与不孕症相关的线粒体疾病是由线粒体DNA突变或核编码线粒体相关蛋白基因变异引起的, 然而并非这些所有变异都会导致不孕症[88]。虽然线粒体在调控卵母细胞发育中起着重要作用, 但关于与线粒体功能障碍相关不孕症的遗传研究却很少。有些mtDNA缺陷综合征相关的不孕症报告的病例尚未得到遗传证实。许多线粒体疾病受双基因组系统(核基因组和线粒体基因组)的调控, 研究人员可以根据核基因组和线粒体基因组的新排列组合来构建细胞系统及动物胚胎, 该技术将成为研究线粒体如何调控胚胎发育的有力工具。在临床上, 试图通过线粒体移植(mitochondrial replacement therapies, MRT)来防止线粒体突变引起的遗传疾病, 但这可能会因核质相互作用不和谐而产生复杂和不可预测的结果, 该手术目前在很多国家是被禁止的[98]。

线粒体功能调控在卵母细胞发育及成熟中发挥重要的作用, 卵母细胞线粒体功能异常会引起卵母细胞及早期胚胎发育异常, 进而导致雌性不孕。随着线粒体调控卵母细胞发育的相关研究越来越多, 我们也有了许多可以评估与线粒体相关女性不孕症的候选标志基因。随着外显子组和全基因组测序等技术在不孕症研究中的应用越来越广泛, 可能会发现更多与不孕症相关的线粒体变异, 并更充分地确定发病机制。但目前线粒体在调控卵母细胞的发育潜能及雌性生殖中的作用还有很多是未知的, 仍需要进一步探究。随着高龄孕妇越来越多, 我们也应该更关注衰老对于卵母细胞质量的影响。卵巢衰老诱导的氧化应激, 通常与线粒体功能障碍有关, 导致卵巢细胞凋亡, 卵巢活性以及卵母细胞的数量和质量的整体下降[99]。衰老卵母细胞的线粒体功能障碍和纺锤体组装异常最终可能导致卵母细胞非整倍性增加[100]。因此, 可通过对卵母细胞内线粒体质量的评估, 及时对这类不孕症进行干预, 以改善妊娠结局。随着临床实践中采用新方法来预防和干预线



(1) 线粒体DNA的丰度、异质性与卵母细胞质量和胚胎发育潜能相关, 若参与mtDNA复制与修复相关的蛋白受损, 卵母细胞质量则会受影响, 例如POLG; (2) 线粒体的超微形态变化与在卵母细胞中的分布响应卵母细胞不同生长阶段的能量需求; 编码线粒体动力学相关蛋白DRP1、MFN1/2、OPA1的基因缺失会导致卵母细胞发育潜能低下; (3) 线粒体氧化磷酸化产物及副产物(ROS、ATP和NADPH等)会影响卵母细胞生长发育和凋亡; (4) 为了支持卵母细胞的正常成长, 需要清除老化的线粒体, 保持新陈代谢活跃线粒体的数量, 若参与线粒体清除的蛋白发生功能失调, 会导致雌性不孕和卵巢早衰。红色×表示mtDNA损伤。

(1) the abundance and heterogeneity of mitochondrial DNA (mtDNA) are related to the quality of oocytes and the developmental potential of embryos. If proteins involved in mtDNA replication and repair are damaged, the quality of oocytes will be affected, such as POLG; (2) the ultrastructural changes of mitochondria and their distribution in oocytes respond to the energy requirements of oocytes at different growth stages; the deletion of genes encoding mitochondrial dynamics related proteins, such as DRP1, MFN1/2 and OPA1, will lead to low developmental potential of oocytes; (3) mitochondrial oxidative phosphorylation products and by-products (ROS, ATP and NADPH, etc.) will affect the growth and apoptosis of oocytes; (4) in order to support the normal growth of oocytes, it is necessary to remove the aging mitochondria and keep the number of metabolically active mitochondria. If the proteins involved in mitochondrial clearance are dysfunctional, it will lead to female infertility and premature ovarian failure. Red × shows mtDNA damage.

图2 线粒体功能调节对卵母细胞发育和雌性不孕的影响

Fig.2 The effects of mitochondria function on oocyte development and infertility

粒体疾病的发生, 有效评估线粒体功能异常人群的生育能力变得日益重要。因此, 进一步探究线粒体对配子和胚胎发育的影响, 对于生殖医学的长足发展具有重要的意义。

参考文献 (References)

[1] SAITOU M, YAMAJI M. Primordial germ cells in mice [J]. Cold Spring Harb Perspect Biol, 2012, doi: 10.1101/cshperspect.a008375.

[2] RICHARDSON B E, LEHMANN R. Mechanisms guiding primordial germ cell migration: strategies from different organisms [J]. Nat Rev Mol Cell Biol, 2010, 11(1): 37-49.

[3] SAITOU M, BARTON S C, SURANI M A. A molecular programme for the specification of germ cell fate in mice [J]. Nature, 2002, 418(6895): 293-300.

[4] PICTON H, BRIGGS D, GOSDEN R. The molecular basis of oocyte growth and development [J]. Mol Cell Endocrinol, 1998, 145(1/2): 27-37.

[5] GOUGEON A. Regulation of ovarian follicular development in primates: facts and hypotheses [J]. Endocr Rev, 1996, 17(2): 121-55.

[6] NORRIS R P, RATZAN W J, FREUDZON M, et al. Cyclic GMP from the surrounding somatic cells regulates cyclic AMP and meiosis in the mouse oocyte [J]. Development, 2009, 136(11): 1869-78.

[7] STRĄCZYŃSKA P, PAPIS K, MORAWIEC E, et al. Signaling mechanisms and their regulation during *in vivo* or *in vitro* maturation of mammalian oocytes [J]. Reprod Biol Endocrinol, 2022,

20(1): 37.

[8] PASQUARIELLO R, ERMISCH A F, SILVA E, et al. Alterations in oocyte mitochondrial number and function are related to spindle defects and occur with maternal aging in mice and humans [J]. Biol Reprod, 2019, 100(4): 971-81.

[9] PAN Z N, LIU J C, JU J Q, et al. LRRK2 regulates actin assembly for spindle migration and mitochondrial function in mouse oocyte meiosis [J]. J Mol Cell Biol, 2022, doi: 10.1093/jmcb/mjab079.

[10] DUAN X, SUN S C. Actin cytoskeleton dynamics in mammalian oocyte meiosis [J]. Biol Reprod, 2019, 100(1): 15-24.

[11] CAVELIER L, JOHANNISSON A, GYLLENSTEN U. Analysis of mtDNA copy number and composition of single mitochondrial particles using flow cytometry and PCR [J]. Exp Cell Res, 2000, 259(1): 79-85.

[12] GREEN D E. Mitochondria: structure, function, and replication [J]. N Engl J Med, 1983, 309(3): 182-3.

[13] WIEDEMANN N, PFANNER N. Mitochondrial machineries for protein import and assembly [J]. Annu Rev Biochem, 2017, 86: 685-714.

[14] BYKOV Y S, RAPAPORT D, HERRMANN J M, et al. Cytosolic events in the biogenesis of mitochondrial proteins [J]. Trends Biochem Sci, 2020, 45(8): 650-67.

[15] AIKEN C E, CINDROVA-DAVIES T, JOHNSON M H. Variations in mouse mitochondrial DNA copy number from fertilization to birth are associated with oxidative stress [J]. Reprod Biomed Online, 2008, 17(6): 806-13.

[16] PIKÓ L, TAYLOR K D. Amounts of mitochondrial DNA and abundance of some mitochondrial gene transcripts in early mouse embryos [J]. Dev Biol, 1987, 123(2): 364-74.

[17] BREVINI T A, VASSENA R, FRANCISCI C, et al. Role of adenosine triphosphate, active mitochondria, and microtubules in the acquisition of developmental competence of parthenogenetically activated pig oocytes [J]. Biol Reprod, 2005, 72(5): 1218-23.

[18] EL SHOURBAGY S H, SPIKINGS E C, FREITAS M, et al. Mitochondria directly influence fertilisation outcome in the pig [J]. Reproduction, 2006, 131(2): 233-45.

[19] WAI T, AO A, ZHANG X, et al. The role of mitochondrial DNA copy number in mammalian fertility [J]. Biol Reprod, 2010, 83(1): 52-62.

[20] BARRITT J A, KOKOT M, COHEN J, et al. Quantification of human ooplasmic mitochondria [J]. Reprod Biomed Online, 2002, 4(3): 243-7.

[21] REYNIER P, MAY-PANLOUP P, CHRÉTIEN M F, et al. Mitochondrial DNA content affects the fertilizability of human oocytes [J]. Mol Hum Reprod, 2001, 7(5): 425-9.

[22] STEUERWALD N, BARRITT J A, ADLER R, et al. Quantification of mtDNA in single oocytes, polar bodies and subcellular components by real-time rapid cycle fluorescence monitored PCR [J]. Zygote, 2000, 8(3): 209-15.

[23] MAY-PANLOUP P, CHRÉTIEN M F, JACQUES C, et al. Low oocyte mitochondrial DNA content in ovarian insufficiency [J]. Hum Reprod, 2005, 20(3): 593-7.

[24] SANTOS T A, EL SHOURBAGY S, ST JOHN J C. Mitochondrial content reflects oocyte variability and fertilization outcome [J]. Fertil Steril, 2006, 85(3): 584-91.

[25] LUOMA P, MELBERG A, RINNE J O, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study [J]. Lancet, 2004, 364(9437): 875-82.

[26] BEKHEIRNIA M R, ZHANG W, EBLE T, et al. POLG mutation in a patient with cataracts, early-onset distal muscle weakness and atrophy, ovarian dysgenesis and 3-methylglutaconic aciduria [J]. Gene, 2012, 499(1): 209-12.

[27] LUO S, VALENCIA C A, ZHANG J, et al. Biparental inheritance of mitochondrial DNA in humans [J]. Proc Natl Acad Sci USA, 2018, 115(51): 13039-44.

[28] ZHANG J, BAO Y, ZHOU X, et al. Polycystic ovary syndrome and mitochondrial dysfunction [J]. Reprod Biol Endocrinol, 2019, 17(1): 67.

[29] DAS M, SAUCEDA C, WEBSTER N J G. Mitochondrial dysfunction in obesity and reproduction [J]. Endocrinology, 2021, doi: 10.1210/endocr/bqaa158.

[30] SU W P, LI C J, LIN L T, et al. Boosting mitochondrial function and metabolism in aging female germ cells with dual ROCK/ROS inhibition [J]. Biomed Pharmacother, 2023, 163: 114888.

[31] CHEN X, PROSSER R, SIMONETTI S, et al. Rearranged mitochondrial genomes are present in human oocytes [J]. Am J Hum Genet, 1995, 57(2): 239-47.

[32] MORAES C T, DIMAURO S, ZEVIANI M, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome [J]. N Engl J Med, 1989, 320(20): 1293-9.

[33] JACOBS L, GERARDS M, CHINNERY P, et al. mtDNA point mutations are present at various levels of heteroplasmy in human oocytes [J]. Mol Hum Reprod, 2007, 13(3): 149-54.

[34] LATORRE-PELLICER A, LECHUGA-VIECO A V, JOHNSTON I G, et al. Regulation of mother-to-offspring transmission of mtDNA heteroplasmy [J]. Cell Metab, 2019, 30(6): 1120-30,e5.

[35] HÄMÄLÄINEN R H, MANNINEN T, KOIVUMÄKI H, et al. Tissue- and cell-type-specific manifestations of heteroplasmic mtDNA 3243A>G mutation in human induced pluripotent stem cell-derived disease model [J]. Proc Natl Acad Sci USA, 2013, 110(38): E3622-30.

[36] KUMAR M, PATHAK D, KRIPLANI A, et al. Nucleotide variations in mitochondrial DNA and supra-physiological ROS levels in cytogenetically normal cases of premature ovarian insufficiency [J]. Arch Gynecol Obstet, 2010, 282(6): 695-705.

[37] DEMAIN L A, CONWAY G S, NEWMAN W G. Genetics of mitochondrial dysfunction and infertility [J]. Clin Genet, 2017, 91(2): 199-207.

[38] ZOU W, JI D, ZHANG Z, et al. Players in mitochondrial dynamics and female reproduction [J]. Front Mol Biosci, 2021, 8: 717328.

[39] UDAGAWA O, ISHIHARA N. Mitochondrial dynamics and interorganellar communication in the development and dysmorphism of mammalian oocytes [J]. J Biochem, 2020, 167(3): 257-66.

[40] FREDERICK R L, SHAW J M. Moving mitochondria: establishing distribution of an essential organelle [J]. Traffic, 2007, 8(12): 1668-75.

[41] GIACOMELLO M, PYAKUREL A, GLYTSOU C, et al. The cell biology of mitochondrial membrane dynamics [J]. Nat Rev Mol

Cell Biol, 2020, 21(4): 204-24.
[42] KRUPPA A J, BUSS F. Motor proteins at the mitochondria-cytoskeleton interface [J]. J Cell Sci, 2021, doi: 10.1242/jcs.226084.
[43] PEPLING M E, WILHELM J E, O'HARA A L, et al. Mouse oocytes within germ cell cysts and primordial follicles contain a Balbiani body [J]. Proc Natl Acad Sci USA, 2007, 104(1): 187-92.
[44] STOJKOVIC M, MACHADO S A, STOJKOVIC P, et al. Mitochondrial distribution and adenosine triphosphate content of bovine oocytes before and after *in vitro* maturation: correlation with morphological criteria and developmental capacity after *in vitro* fertilization and culture [J]. Biol Reprod, 2001, 64(3): 904-9.
[45] VAN BLERKOM J. Microtubule mediation of cytoplasmic and nuclear maturation during the early stages of resumed meiosis in cultured mouse oocytes [J]. Proc Natl Acad Sci USA, 1991, 88(11): 5031-5.
[46] DALTON C M, CARROLL J. Biased inheritance of mitochondria during asymmetric cell division in the mouse oocyte [J]. J Cell Sci, 2013, 126(Pt 13): 2955-64.
[47] NISHI Y, TAKESHITA T, SATO K, et al. Change of the mitochondrial distribution in mouse ooplasm during *in vitro* maturation [J]. J Nippon Med Sch, 2003, 70(5): 408-15.
[48] ARCHER S L. Mitochondrial dynamics: mitochondrial fission and fusion in human diseases [J]. N Engl J Med, 2013, 369(23): 2236-51.
[49] HEINE K B, HOOD W R. Mitochondrial behaviour, morphology, and animal performance [J]. Biol Rev Camb Philos Soc, 2020, 95(3): 730-7.
[50] JENDRACH M, MAI S, POHL S, et al. Short- and long-term alterations of mitochondrial morphology, dynamics and mtDNA after transient oxidative stress [J]. Mitochondrion, 2008, 8(4): 293-304.
[51] TONDERA D, GRANDEMANGE S, JOURDAIN A, et al. SLP-2 is required for stress-induced mitochondrial hyperfusion [J]. Embo J, 2009, 28(11): 1589-600.
[52] LIESA M, SHIRIHAI O S. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure [J]. Cell Metab, 2013, 17(4): 491-506.
[53] CAI Q, TAMMINENI P. Alterations in mitochondrial quality control in Alzheimer's disease [J]. Front Cell Neurosci, 2016, 10: 24.
[54] MOTTA P M, NOTTOLA S A, MAKABE S, et al. Mitochondrial morphology in human fetal and adult female germ cells [J]. Hum Reprod, 2000, 15(Suppl 2): 129-47.
[55] BAKER T G, FRANCHI L L. The fine structure of oogonia and oocytes in human ovaries [J]. J Cell Sci, 1967, 2(2): 213-24.
[56] WASSARMAN P M, JOSEFOWICZ W J. Oocyte development in the mouse: an ultrastructural comparison of oocytes isolated at various stages of growth and meiotic competence [J]. J Morphol, 1978, 156(2): 209-35.
[57] FREZZA C, CIPOLAT S, MARTINS DE BRITO O, et al. OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion [J]. Cell, 2006, 126(1): 177-89.
[58] ALEXANDER C, VOTRUBA M, PESCH U E, et al. OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28 [J]. Nat Genet, 2000, 26(2): 211-5.
[59] ZüCHNER S, MERSIYANOVA I V, MUGLIA M, et al. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A [J]. Nat Genet, 2004, 36(5): 449-51.
[60] UDAGAWA O, ISHIHARA T, MAEDA M, et al. Mitochondrial fission factor Drp1 maintains oocyte quality via dynamic rearrangement of multiple organelles [J]. Curr Biol, 2014, 24(20): 2451-8.
[61] HOLT S V, VERGNOLLE M A, HUSSEIN D, et al. Silencing Cenp-F weakens centromeric cohesion, prevents chromosome alignment and activates the spindle checkpoint [J]. J Cell Sci, 2005, 118(Pt 20): 4889-900.
[62] MUSACCHIO A, SALMON E D. The spindle-assembly checkpoint in space and time [J]. Nat Rev Mol Cell Biol, 2007, 8(5): 379-93.
[63] ZHOU C J, WANG X Y, DONG Y H, et al. CENP-F-dependent DRP1 function regulates APC/C activity during oocyte meiosis I [J]. Nat Commun, 2022, 13(1): 7732.
[64] MISKO A, JIANG S, WEGORZEWSKA I, et al. Mitofusin 2 is necessary for transport of axonal mitochondria and interacts with the Miro/Milton complex [J]. J Neurosci, 2010, 30(12): 4232-40.
[65] VAN BLERKOM J, DAVIS P, ALEXANDER S. Differential mitochondrial distribution in human pronuclear embryos leads to disproportionate inheritance between blastomeres: relationship to microtubular organization, ATP content and competence [J]. Hum Reprod, 2000, 15(12): 2621-33.
[66] WANG X H, YIN S, OU X H, et al. Increase of mitochondria surrounding spindle causes mouse oocytes arrested at metaphase I stage [J]. Biochem Biophys Res Commun, 2020, 527(4): 1043-9.
[67] ZHANG M, BENER M B, JIANG Z, et al. Mitofusin 2 plays a role in oocyte and follicle development, and is required to maintain ovarian follicular reserve during reproductive aging [J]. Aging, 2019, 11(12): 3919-38.
[68] ZHANG J H, ZHANG T, GAO S H, et al. Mitofusin-2 is required for mouse oocyte meiotic maturation [J]. Sci Rep, 2016, 6: 30970.
[69] CHENG S, ALTMEPPEN G, SO C, et al. Mammalian oocytes store mRNAs in a mitochondria-associated membraneless compartment [J]. Science, 2022, 378(6617): eabq4835.
[70] ZHAO S, HENG N, WANG H, et al. Mitofusins: from mitochondria to fertility [J]. Cell Mol Life Sci, 2022, 79(7): 370.
[71] BIGGERS J D, WHITTINGHAM D G, DONAHUE R P. The pattern of energy metabolism in the mouse oöcyte and zygote [J]. Proc Natl Acad Sci USA, 1967, 58(2): 560-7.
[72] JOHNSON M T, FREEMAN E A, GARDNER D K, et al. Oxidative metabolism of pyruvate is required for meiotic maturation of murine oocytes *in vivo* [J]. Biol Reprod, 2007, 77(1): 2-8.
[73] DALTON C M, SZABADKAI G, CARROLL J. Measurement of ATP in single oocytes: impact of maturation and cumulus cells on levels and consumption [J]. J Cell Physiol, 2014, 229(3): 353-61.
[74] YANG Q, LI H, WANG H, et al. Deletion of enzymes for *de novo* NAD^+ biosynthesis accelerated ovarian aging [J]. Aging Cell, 2023, 22(9): e13904.
[75] YANG Q, CONG L, WANG Y, et al. Increasing ovarian NAD^+ levels improve mitochondrial functions and reverse ovarian ag-

ing [J]. Free Radic Biol Med, 2020, 156: 1-10.
[76] MIAO Y, CUI Z, GAO Q, et al. Nicotinamide mononucleotide supplementation reverses the declining quality of maternally aged oocytes [J]. Cell Rep, 2020, 32(5): 107987.
[77] PRASAD S, TIWARI M, PANDEY A N, et al. Impact of stress on oocyte quality and reproductive outcome [J]. J Biomed Sci, 2016, 23: 36.
[78] WANG J, DU H, MA L, et al. MitoQ protects ovarian organoids against oxidative stress during oogenesis and folliculogenesis *in vitro* [J]. Int J Mol Sci, 2023, doi: 10.3390/ijms24020924.
[79] HE X, ZENG H, CHEN J X. Emerging role of SIRT3 in endothelial metabolism, angiogenesis, and cardiovascular disease [J]. J Cell Physiol, 2019, 234(3): 2252-65.
[80] ZHANG Q, REN J, WANG F, et al. Mitochondrial and glucose metabolic dysfunctions in granulosa cells induce impaired oocytes of polycystic ovary syndrome through Sirtuin 3 [J]. Free Radic Biol Med, 2022, 187: 1-16.
[81] LI C J, LIN L T, TSAI H W, et al. Phosphoglycerate mutase family member 5 maintains oocyte quality via mitochondrial dynamic rearrangement during aging [J]. Aging Cell, 2022, 21(2): e13546.
[82] KASAPOĞLU I, SELI E. Mitochondrial dysfunction and ovarian aging [J]. Endocrinology, 2020, doi: 10.1210/endocr/bqaa001.
[83] PALOZZI J M, JEEDIGUNTA S P, MINENKOVA A V, et al. Mitochondrial DNA quality control in the female germline requires a unique programmed mitophagy [J]. Cell Metab, 2022, 34(11): 1809-23,e6.
[84] GREEN D R. Mitochondrial quality control: just walk away [J]. Cell Metab, 2021, 33(6): 1069-71.
[85] SONG J, HERRMANN J M, BECKER T. Quality control of the mitochondrial proteome [J]. Nat Rev Mol Cell Biol, 2021, 22(1): 54-70.
[86] NARGUND A M, FIORESE C J, PELLEGRINO M W, et al. Mitochondrial and nuclear accumulation of the transcription factor ATFS-1 promotes OXPHOS recovery during the UPR(mt) [J]. Mol Cell, 2015, 58(1): 123-33.
[87] WANG T, BABAYEV E, JIANG Z, et al. Mitochondrial unfolded protein response gene Clpp is required to maintain ovarian follicular reserve during aging, for oocyte competence, and development of pre-implantation embryos [J]. Aging Cell, 2018, 17(4): e12784.
[88] SELI E, WANG T, HORVATH T L. Mitochondrial unfolded protein response: a stress response with implications for fertility and reproductive aging [J]. Fertil Steril, 2019, 111(2): 197-204.
[89] ZHOU Q, XU K, ZHAO B W, et al. Mitochondrial E3 ubiquitin ligase MARCH5 is required for mouse oocyte meiotic maturation [J]. Biol Reprod, 2023, 108(3): 437-46.
[90] WANG S, WU X, WANG H, et al. Role of FBXL5 in redox homeostasis and spindle assembly during oocyte maturation in mice [J]. Faseb J, 2023, 37(8): e23080.
[91] GIBELLINI L, DE GAETANO A, MANDRIOLI M, et al. The biology of Lonp1: more than a mitochondrial protease [J]. Int Rev Cell Mol Biol, 2020, 354: 1-61.
[92] SHENG X, LIU C, YAN G, et al. The mitochondrial protease LONP1 maintains oocyte development and survival by suppressing nuclear translocation of AIFM1 in mammals [J]. EBioMedicine, 2022, 75: 103790.
[93] ASHRAFI G, SCHWARZ T L. The pathways of mitophagy for quality control and clearance of mitochondria [J]. Cell Death Differ, 2013, 20(1): 31-42.
[94] ROBERTS R F, TANG M Y, FON E A, et al. Defending the mitochondria: the pathways of mitophagy and mitochondrial-derived vesicles [J]. Int J Biochem Cell Biol, 2016, 79: 427-36.
[95] JIN X, WANG K, WANG L, et al. RAB7 activity is required for the regulation of mitophagy in oocyte meiosis and oocyte quality control during ovarian aging [J]. Autophagy, 2022, 18(3): 643-60.
[96] KIM K H, KIM E Y, KO J J, et al. Gas6 is a reciprocal regulator of mitophagy during mammalian oocyte maturation [J]. Sci Rep, 2019, 9(1): 10343.
[97] WATSON A J. Oocyte cytoplasmic maturation: a key mediator of oocyte and embryo developmental competence [J]. J Anim Sci, 2007, 85(13 Suppl): E1-3.
[98] CUMMINS J M. Mitochondria: potential roles in embryogenesis and nucleocytoplasmic transfer [J]. Hum Reprod Update, 2001, 7(2): 217-28.
[99] TESARIK J, GALÁN-LÁZARO M, MENDOZA-TESARIK R. Ovarian aging: molecular mechanisms and medical management [J]. Int J Mol Sci, 2021, doi: 10.3390/ijms22031371.
[100] ZHANG F L, LI W D, ZHU K X, et al. Aging-related aneuploidy is associated with mitochondrial imbalance and failure of spindle assembly [J]. Cell Death Discov, 2023, 9(1): 235.