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人类卵母细胞发育的生理与病理机制

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摘要 正常的卵母细胞发育是成功受精和开启胚胎发育的保障, 对于人类繁衍生育至关重要. 卵母细胞发育是一个复杂而精细的过程, 伴随着卵泡的生长和减数分裂的进行, 受基因、遗传和环境等多种因素的调控. 该过程起始于女性胎儿时期, 先后经历原始生殖细胞和卵原细胞, 随后进入减数分裂. 卵母细胞在女性出生后就停滞在第一次减数分裂前期, 青春期在激素的刺激下, 恢复减数分裂, 启动纺锤体组装, 并完成纺锤体的双极化. 随后, 通过不对称分裂排出第一极体, 并进入第二次减数分裂, 很快停滞在第二次减数分裂中期, 发育为成熟卵子. 卵子受精后排出第二极体完成第二次减数分裂. 其中任一过程出现异常都会导致卵母细胞发育缺陷和不孕. 随着高分辨活细胞成像、辅助生殖和高通量测序等技术的发展, 人们对人类卵母细胞发育有了新的认识, 例如, 发现人类卵母细胞微管组织中心、人独特的纺锤体双极化过程以及卵子发育异常新致病基因等. 本文主要介绍人类卵母细胞发育过程、生理和病理机制、临床不孕患者遗传诊断及潜在干预策略. 最后, 对未来探索人类卵母细胞发育过程的生理和病理机制及临床干预策略进行了展望.

关键词 卵母细胞发育, 减数分裂, 突变, 女性不孕, 辅助生殖

人类繁衍依赖于发育成熟的卵子与精子融合形成受精卵. 卵母细胞作为人类繁衍生育的重要源头, 除了负责将亲本的遗传信息传递给后代外, 还为早期胚胎发育提供蛋白、底物、能量等支持. 卵母细胞的发育是一个长期的过程, 并伴随着减数分裂的进行, 始于女性胎儿时期, 胎儿出生后减数分裂处于停滞阶段, 直到青春期随着女性体内的激素水平升高恢复减数分裂, 最终发育为成熟的卵子, 等待与精子结合受精. 卵母细胞发育过程是一个复杂而严格的生理过程, 该过程受基因和遗传等诸多因素精确调控[1]. 目前, 多项研究发现人卵母细胞在其发育过程中存在独特的生理过程和调控机制. 卵母细胞发育的任何环节出现差错都会导致卵母细胞发育缺陷, 并影响后续的受精和胚胎发育过程, 最终可能导致女性不孕.

近年来, 不孕不育的比例逐渐升高, 辅助生殖技术的出现, 包括体外受精(*in vitro* fertilization, IVF)和胞浆内单精子注射(intracytoplasmic sperm injection, ICSI), 帮助部分患者成功生育, 但仍有很多患者遭受IVF/ICSI反复失败. 患者主要表现为卵子成熟障碍、受精失败和早期胚胎停滞, 其原因并不明确. 直到2016年, 国内研究团队首次报道了卵子成熟障碍的第一个致病基因*TUBB8*, 并明确该疾病为新型孟德尔遗传病[2]. 在过去十年间, 国内外研究团队相继报道了37个明确导致IVF/ICSI失败的致病基因, 并解析了部分突变基因致

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病的病理机制. 这些研究证实遗传因素在人类卵母细胞发育和女性生殖过程中发挥重要作用. 目前, 这些基因已被广泛应用于临床不孕患者的遗传检测中, 为不孕患者明确了病因, 从遗传学角度预测IVF/ICSI治疗结局, 并提出个性化的治疗策略.

在全球范围内, 生殖健康日益严峻, 正受到前所未有的关注. 卵母细胞的发育与质量是生殖健康的前提和基础. 因此, 充分了解人类卵母细胞发育的生理与病理机制, 对于促进人类生殖健康具有重要的意义. 本文旨在综述人类卵母细胞发育过程、生理病理机制以及潜在的临床干预策略. 这有助于理解人卵母细胞发育过程的独特机制, 并为相关患者的遗传咨询及靶向治疗奠定基础, 对人类生殖医学及其临床应用方面具有指导意义.

1 卵母细胞发育过程

1.1 生殖细胞分化

卵母细胞的发育过程起始于原始生殖细胞(primordial germ cells, PGCs)的形成. 在人类妊娠的第3~4周, PGCs首先出现于靠近尿囊的卵黄囊背侧壁的内胚层, 形成约100个细胞簇的簇状结构[3]. 随后, 它们沿后肠背系膜向生殖腺嵴迁移, 并于第7周完成在生殖腺的定植, 与中胚层细胞共同转化为卵巢或睾丸[4]. 雌性PGCs对于卵巢的形成和维持是必不可少的, 如果没有生殖细胞, 性腺会发生退化[5]. 卵巢中的PGCs会进一步分化为卵原细胞(oogonia), 该生殖细胞通过有丝分裂不断增殖, 此时由于卵原细胞的不完全分裂形成了多个细胞胞质相连的合胞体(germline cyst), 外层包裹着为生殖细胞发育储存营养的体细胞, 该结构称为生殖细胞巢(germ cells nests). 妊娠的第20周, 卵原细胞数量达到顶峰, 约600万个[6]. 此后, 卵原细胞有丝分裂速率逐渐下降, 并在约第28周结束, 卵原细胞的有丝分裂活性是卵母细胞池的重要决定因素. 与此同时, 卵原细胞的闭锁率逐渐增加, 绝大多数生殖细胞将经历闭锁. 妊娠的第8–13周, 部分卵原细胞开始DNA复制并进入减数分裂过程, DNA合成的开始标志着卵原细胞阶段的结束, 进入减数分裂阶段的生殖细胞被称为卵母细胞.

1.2 卵泡发育

卵泡是卵母细胞发生与发育的基本功能单位, 其发育过程包括多个阶段[7]. 卵母细胞被单层扁平前颗粒细胞围绕形成原始卵泡(primordial follicle)[8]. 原始卵泡在人类妊娠的第15周出现, 到胎儿出生时大约有100万个[9]. 但是, 随着年龄的增长, 这些卵泡会发生闭锁并逐渐减少, 到青春期时只剩下约40万个. 在此期间, 卵泡进入一个漫长的发育休眠期. 随着青春期的到来, 女性体内的激素水平发生翻天覆地的变化, 原始卵泡被激活进入生长阶段, 卵母细胞的体积增大并形成透明带(zona pellucida), 其周围的前颗粒细胞分化成单层立方状颗粒细胞, 此时卵泡发育为初级卵泡(primary follicle). 随着颗粒细胞有丝分裂扩增, 卵母细胞周围单层颗粒细胞变为多层, 卵泡发育成为次级卵泡(secondary follicle)[10]. 伴随着月经周期的到来, 卵泡刺激素(follicle stimulating hormone, FSH)水平升高, 约10~20枚次级卵泡进一步发育形成有空腔的窦状卵泡(antral follicle). 此时, 颗粒细胞进一步分化为壁颗粒细胞(mural granulosa cell)和卵丘颗粒细胞(cumulus granulosa cells), 其中卵丘颗粒细胞包裹卵母细胞形成卵丘-卵母细胞复合体(cumulus-oocyte complex, COC)[11]. 窦状卵泡中FSH阈值最低的一个卵泡会被选中优先发育为优势卵泡, 即排卵前卵泡(preovulatory follicle)[12], 其余的卵泡逐渐退化闭锁(图1).

1.3 卵母细胞减数分裂成熟

卵泡的发育过程伴随着卵母细胞减数分裂的进行. 卵母细胞减数分裂成熟是卵母细胞发育过程中的重要环节, 包括第一次减数分裂(meiosis I)和第二次减数分裂(meiosis II). 胎儿时期, 卵原细胞在间期完成DNA复制后, 进入第一次减数分裂前期, 该时期根据染色体形态可细分为细线期、偶线期、粗线期、双线期和终变期, 其中包含大量染色体行为, 如DNA双链断裂产生、同源重组、同源染色体联会等[13]. 卵母细胞会停滞在前期的双线期, 该时期的卵母细胞RNA合成活跃, 其细胞核增大形成生发泡(germinal vesicle, GV), 称为GV期卵母细胞. 根据染色质的形态, GV期卵母细胞又可以分为染色质分散且不围绕核仁分布的非包围核仁(non-surrounded nucleolus, NSN)型和染色质高度浓缩并围绕核仁分布的包围核仁(surrounded nucleolus, SN)型卵母细胞[14]. 青春期后, 排卵前黄体生成素(luteinizing hormone, LH)水平升高, 卵母细胞周围的卵丘颗粒细胞发生扩展变得松散, 卵母细胞恢复减数分裂[15], GV期卵母细胞发生生发泡破裂(germinal vesicle break-

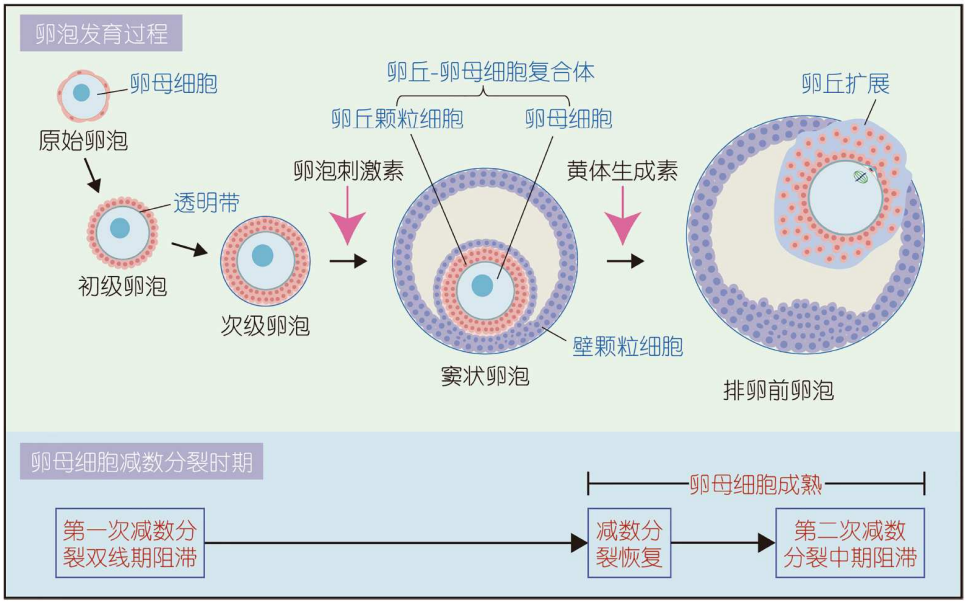

图 1 卵泡发育和卵子减数分裂过程
Figure 1 The process of follicular development and oocyte meiosis

down, GVBD)进入第一次减数分裂中期(metaphase I, MI). MI期卵母细胞完成纺锤体组装, 染色体整齐排列在赤道板上[16]. 随后, 纺锤体从中心向细胞膜附近迁移, 到达皮质下后完成不对称分裂并排出第一极体. 卵母细胞迅速进入第二次减数分裂, 其纺锤体在极短的时间内完成解聚和再组装, 并停滞在第二次减数分裂中期(metaphase II, MII)(图1)[17]. MII期卵母细胞为成熟卵母细胞, 也称为卵子. 最终, 随着LH水平达到峰值, 卵子从卵泡中释放到输卵管中等待与精子融合, 成功受精后的卵子排出第二极体并完成减数分裂.

2 卵母细胞发育的调控机制

卵母细胞发育是一个受众多分子严格调控的复杂过程. 卵母细胞发育潜能在卵母细胞成熟过程中逐渐获得, 卵母细胞成熟分为细胞核成熟和细胞质成熟. 核成熟包括减数分裂的阻滞和恢复、纺锤体组装和迁移、极体排出等. 胞质成熟涉及细胞器重组、mRNA和蛋白质的稳态调控等. 卵母细胞发育过程中任何事件调控异常都会导致卵母细胞成熟异常, 并进一步影响后续的受精和胚胎发育.

2.1 减数分裂同源重组

同源重组(homologous recombination, HR)是减数分裂的关键事件, 也是同源染色体正确分离的保障[18]. 减数分裂重组异常会导致卵子发生失败或产生非整倍体卵子, 从而导致女性生育力低下、流产、不孕或出生缺陷[19,20]. 同源重组受众多分子的精确调控[21], 并在哺乳动物中高度保守[22]. 卵母细胞在第一次减数分裂的细线期阶段, 染色体重排形成染色质环, 并固定在由黏连蛋白复合物、HORMA结构域蛋白(HORMAD1和HORMAD2)和轴元件蛋白质(SYCP2和SYCP3)组成的染色体轴上[23]. 减数分裂重组起始于DNA双链断裂(DNA double-strand breaks, DSBs)产生, DSBs不是随机引入基因组中的, 而是有偏好性地发生在由甲基转移酶PRDM9介导的组蛋白H3三甲基化(H3K4me3和H3K36me3)标记的热点区域[24]. 这些热点区域位于染色质环上, 而DSBs的启动发生在染色体轴上. 因此, 染色质环上的热点区域与未联会染色体轴之间的相互作用是DSBs产生所必需的. EWSR1可以通过与磷酸化的REC8(pREC8)相互作用, 促进PRDM9结合的DSBs位点与染色体轴的连接[25]. DSBs的形成依赖于位于染色体轴上的拓扑异构酶SPO11-TOPOVIBL复合物的催化[26]. 在染色体轴上以HORMAD1为锚定位点形成减数分裂特异性前DSB重组体(pre-DSB recombinosomes), 其主要成员包括REC114, MEI1, MEI4, ANKRD31和IHO1, 该重组体负责将SPO11-TOPO-

VIBL靶向到PRDM9依赖的DSBs热点，并催化DSBs的形成[27,28]. 另外，DSBs的数量也受到前DSB重组体的严格调控[29]，过度产生DSBs将导致联会和DSBs修复的严重缺陷[30,31]. 同源染色体的DSBs修复和联会是同时发生且相互依赖的[32]. DSBs形成后经酶切产生具有3′末端的游离DNA单链(ssDNA). 从细线期到偶线期的过渡期间，端粒附着在核膜上，并沿核膜移动，促进同源染色体的配对识别[33]. 偶线期阶段，重组酶RAD51和DMC1与ssDNA结合，通过单链侵入产生异源双链DNA[34]. 同时，同源染色体进行联会，SYCP1相关蛋白开始介导联会复合体(synaptonemal complex, SC)的组装[35]，SYCP1的N端和C端位点分别在同源染色体对的中线和染色体轴上进行自组装，然后装载SYCE2-TEX12蛋白，使SC沿着整个染色体轴延伸[36]. 粗线期阶段，SC组装完成，同源染色体配对成功，完成联会过程[23]. 在双线期阶段，DSB修复完成，同源染色体形成交叉，实现同源染色体非姐妹染色单体的基因交叉互换. 随后，联会复合体在TRIP13的调控下被降解[37]. 进入终变期后，染色体被进一步压缩，二价体从核膜上分离，等待后续同源染色体的分离.

2.2 卵母细胞GV期阻滞和恢复

卵母细胞和精母细胞的减数分裂存在很多差异，其中，精母细胞减数分裂过程是连续的，而卵母细胞减数分裂是不连续的，这也体现了卵母细胞减数分裂调控的复杂性. 卵母细胞减数分裂的阻滞与恢复受到成熟促进因子(maturation promoting factor, MPF)的调控. MPF是异二聚体，由调节亚基细胞周期蛋白B(Cyclin B)和催化亚基周期蛋白依赖激酶(cyclin dependent kinase 1, CDK1)组成，其稳定性和活性受到多种因子的调控. 卵母细胞发育到双线期(GV期卵母细胞)时，卵泡壁颗粒细胞分泌C型钠肽(natriuretic peptide precursor type C, NPPC)与卵丘颗粒细胞中的NPPC受体NPR2结合，并催化产生环磷酸鸟苷(cyclic guanosine monophosphate, cGMP). cGMP通过间隙连接COX37(connexin 37)通道进入卵母细胞，并抑制磷酸二酯酶3A(phosphodiesterase 3A, PDE3A)的活性，阻止环磷酸腺苷(cyclic adenosine monophosphate, cAMP)的水解，从而导致卵母细胞内的cAMP水平升高. 高水平的cAMP是维持卵母细胞GV阻滞的前提[38,39]. 随后，cAMP会持续激活蛋白激酶A(protein kinase A, PKA)，并磷酸化激活WEE2活性并抑制CDC25B的活性，WEE2通过磷酸化CDK1的Thr14和Tyr15位点使其失活，而CDC25B调控CDK1的去磷酸化使其激活. CDK1在磷酸化WEE2和CDC25B的共同调控下维持失活状态[40]. 与此同时，卵母细胞内的后期促进复合物/细胞周期体(anaphase promoting complex/cyclosome, APC/C)作为E3泛素连接酶，能够通过泛素化Cyclin B来促进其降解. CDK1的失活和Cyclin B的降解导致MPF失活，并诱导卵母细胞阻滞在GV期[41,42](图2).

体内LH峰的出现诱导GV期卵母细胞减数分裂恢复. LH与壁颗粒细胞表面的LH受体结合并诱导cAMP的产生. cAMP水平的增加激活颗粒细胞中PKA活性，并促进细胞产生和释放表皮生长因子(epidermal growth factor, EGF). EGF激活下游卵丘颗粒细胞中丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)的活性，进而破坏卵丘颗粒细胞与卵母细胞之间的缝隙连接，阻断卵丘颗粒细胞中的cGMP进入卵母细胞. 卵母细胞中cGMP水平降低并激活PDE3A，进一步导致cAMP水平降低和PKA活性减弱. 此时，WEE2的活性被抑制，而CDC25B活性被激活. CDK1发生去磷酸化并被激活. 同时，APC/C的活性被抑制，促进Cyclin B的积累. CDK1的激活和Cyclin B的积累导致MPF恢复活性，并诱导卵母细胞发生GVBD，这标志着减数分裂的恢复[42,43](图2). 卵母细胞完成第一次减数分裂并进入第二次减数分裂，随后不久，卵母细胞阻滞在中期，形成MII期卵母细胞，等待精子受精.

2.3 人卵母细胞纺锤体组装

纺锤体精确组装对于有丝分裂和减数分裂过程中染色体的正确分离至关重要. 纺锤体的形成过程主要包括微管成核(microtubule nucleation)和纺锤体双极化(spindle bipolarization). 在体细胞中，中心体作为主要的微管组织中心(microtubule organizing center, MTOC)介导有丝分裂微管成核和纺锤体的组装. 但卵母细胞与体细胞不同，许多卵母细胞不存在中心体. 研究发现，在爪蟾和小鼠卵母细胞中，由无中心粒的微管组织中心(acentriolar microtubule organizing center, aMTOCs)介导微管成核与纺锤体形成[44,45]. 但是在人卵中，一直未观察到aMTOC的存在，因此，此前的观点普遍认为，人卵母细胞中没有微管组织中心，并且人卵母细胞中双极纺锤体组装的确切机制并不清楚.

2022年，研究者使用2000多颗人类卵母细胞进行三维高分辨率成像观察，首次发现人卵母细胞中存在

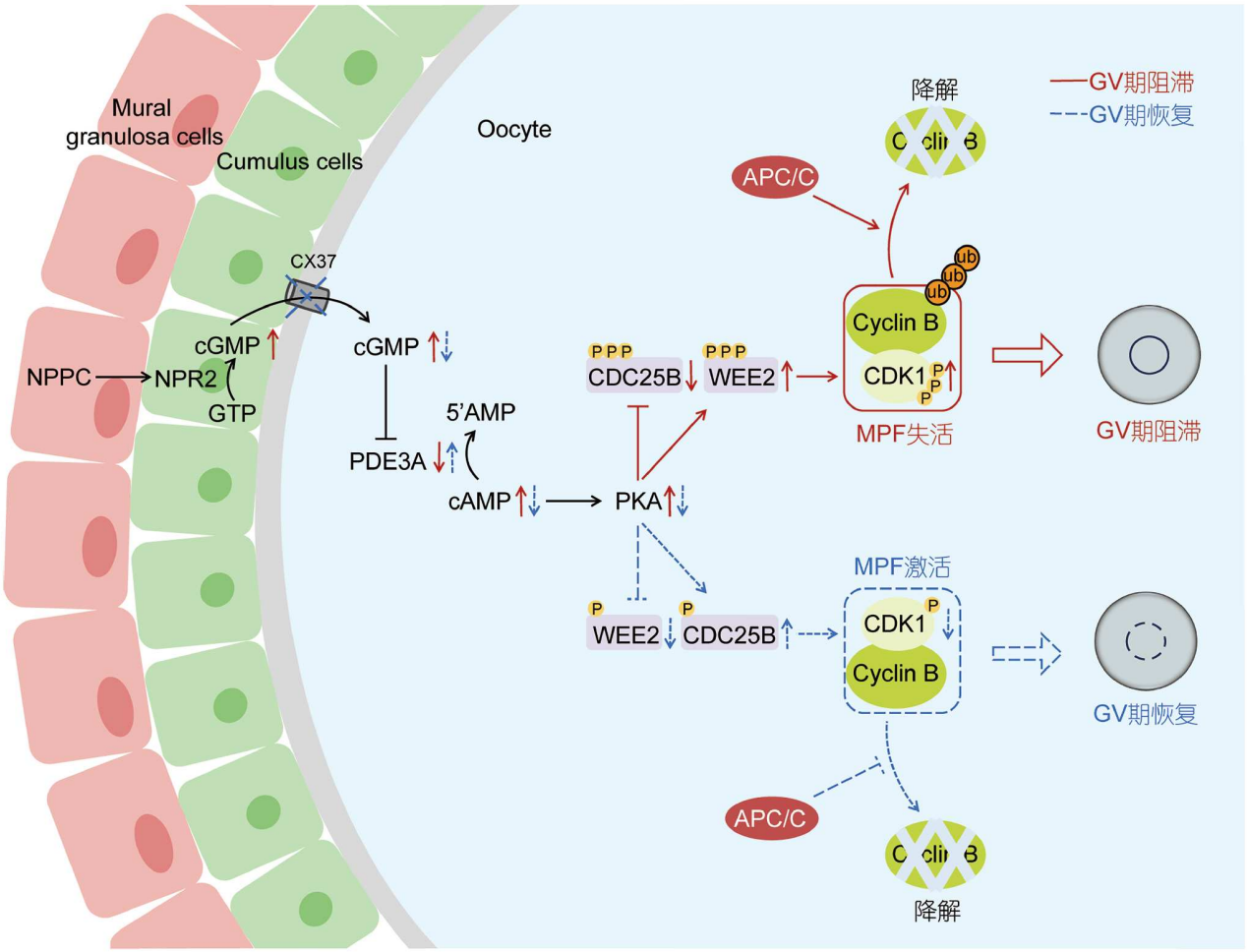

图 2 卵母细胞GV期阻滞和恢复的调控机制
Figure 2 Regulatory mechanism of GV arrest and resumption in oocytes

与众不同的微管组织中心，负责启动人卵子中纺锤体的组装，并将其命名为人类卵母细胞微管组织中心(human oocyte microtubule organizing center, huoMTOC)[46]. 利用人MI期卵母细胞，对86个中心体和纺锤体相关蛋白进行免疫荧光染色定位筛选，最终鉴定到huoMTOC的重要成员TACC3，CKAP5，CCP110和DISC1，它们在人类MI期卵母细胞中定位在动粒和纺锤体微管上，这与它们在有丝分裂过程中的定位截然不同. 这4个蛋白对于维持huoMTOC的正常功能必不可少. 人GV期卵母细胞在恢复减数分裂时在皮质下形成单个的huoMTOC，并在核膜破裂(nuclear envelope breakdown，NEBD)之前迁移到核膜附近. NEBD后，huoMTOC碎片化并被募集到染色的动粒上启动微管成核，随着微管的聚合，huoMTOC的成员也被募集到纺锤体微管上，促进人卵母细胞纺锤体的组装(图3). huoMTOC与小鼠卵母细胞中的aMTOC相比，其数量、定位和组成方面表现出截然不同的特征，说明人类卵母细胞已经进化出启动微管成核和纺锤体组装的独特机制.

纺锤体微管成核后，一旦启动微管聚合，成簇的微管会发生一系列的形态变化，最终组装为双极状纺锤体. 纺锤体双极化是纺锤体组装的另一个关键步骤. 双极化异常会导致单极或多极纺锤体形成，最终导致细胞染色体不稳定和非整倍性[47]. 相较于有丝分裂细胞和小鼠卵母细胞，人类卵母细胞的纺锤体双极化需要更长的时间，这也就提示人卵母细胞纺锤体双极化存在特殊的调控机制，但其机制一直未知. 2024年，研究者通过免疫荧光和活细胞成像对人卵母细胞纺锤体组

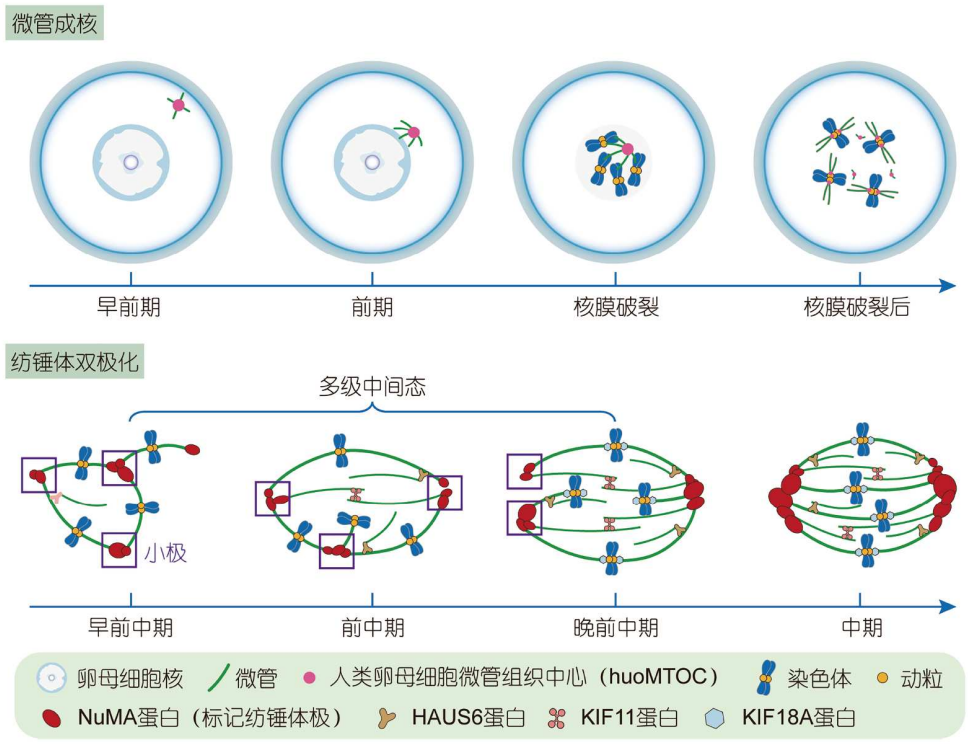

图 3 人类卵母细胞纺锤体组装的独特机制
Figure 3 Unique mechanisms of spindle assembly in human oocytes

装进行了高分辨率的观察，首次描述了人卵母细胞纺锤体双极化的时空变化过程[48]. 人卵母细胞NEBD后，多个动粒聚集促进纺锤体微管的聚合，并且纺锤体内的微管不断扩增. 在早期的前中期阶段，由于动粒的随机分布和聚集，动粒上成核微管的负端会随动粒聚集形成多个小极(minor poles)，纺锤体形态进一步伸长形成多极纺锤体中间态并维持较长的时间. 随后，多个小极进一步聚集成两个位置相对的大极，最终组装成双极纺锤体(图3). 研究者通过筛选鉴定到3个蛋白(HAUS6，KIF11和KIF18A)在人卵母细胞纺锤体双极化过程的不同阶段发挥重要功能. HAUS6通过调控微管扩增为双极化过程提供物质基础；KIF11通过调控反向平行微管间的连接和相对滑动促进纺锤体双极化；KIF18A通过抑制微管的过度生长维持双极纺锤体稳态. 这三个基因功能异常会导致人卵母细胞不同程度的纺锤体双极化异常，从而导致卵母细胞成熟障碍、受精失败及早期胚胎发育停滞[48]. 这些发现为人卵纺锤体组装过程提供了新的认识，包括纺锤体微管成核和双极化，并揭示了人卵母细胞纺锤体组装的独特调控机制.

2.4 卵母细胞纺锤体稳定

双极纺锤体负责驱动细胞分裂过程中染色体的分离，纺锤体的稳定是染色体正确分离的前提. 在卵母细胞减数分裂过程中，染色体分离错误会导致非整倍体(aneuploid)的卵子产生，继而导致胚胎发育异常，并引发流产或唐氏综合征等遗传疾病. 大约25%~50%的人类卵子属于非整倍体卵子，并且非整倍体比例随着年龄增长而增加[49]. 相较于其他哺乳动物，例如猪、牛和小鼠，人卵母细胞经常组装形成形态异常或断裂的不稳定多极纺锤体，最终导致染色体分离错误. 然而，人卵母细胞纺锤体不稳定的机制一直未能成功探究. 2022年，德国研究团队发现驱动蛋白KIFC1在卵母细胞纺锤体稳定中发挥重要作用[50]. 人卵母细胞中缺乏KIFC1，而该蛋白在其他哺乳动物卵母细胞中高度表达. 在牛卵母细胞中下调KIFC1导致纺锤体不稳定和非整倍体比例升高，成功模拟人类卵母细胞纺锤体的不稳定性. 随后，研究者将纯化的KIFC1重组蛋白注射到人卵母细胞中，结果证明引入外源KIFC1蛋白可以挽救人卵母细胞纺锤体不稳定，并降低非整倍体比例. 该

研究明确缺乏KIFC1蛋白是导致人类卵母细胞纺锤体不稳定的重要因素.

2.5 纺锤体组装检验点

纺锤体组装检验点(spindle assembly checkpoint, SAC)是监控染色体精确分离的关键分子调控机制, 在卵母细胞减数分裂过程中发挥重要作用. SAC蛋白最早在酿酒酵母中鉴定到, 主要成员包括MAD1, MAD2, BUB1, BUB3, BUBR1及MPS1[51]. 这些检验点蛋白在酵母和人体内高度保守[52]. 减数分裂进入中期后, 当染色体上的动粒与纺锤体微管连接存在异常时, SAC被激活, 动粒招募SAC蛋白MAD2, BUB3, BUBR1, 并与APC/C共激活因子CDC20结合组成有丝分裂检验点复合物(mitotic checkpoint complex, MCC)[53], 并在MPS1磷酸化的作用下, 其他SAC蛋白也会聚集到异常连接的动粒上. MCC通过螯合CDC20抑制APC/C的活性, 保护Securin和Cyclin B不被APC/C靶向降解, 防止在纺锤体组装存在异常时分裂提前进入后期. 当所有动粒都被微管捕获, 并整齐排列到赤道板, 微管负端的动力蛋白促进SAC蛋白从动粒上脱落, SAC失活[54]. 同时, MCC解聚并释放CDC20, 游离的CDC20激活APC/C, 导致Securin和Cyclin B降解, 促进染色体分离, 减数分裂进入后期[55]. SAC蛋白功能缺失导致小鼠卵母细胞减数分裂进程加快、纺锤体组装异常、染色体错误分离、非整倍体增加等表型[56~60].

2.6 纺锤体迁移

纺锤体迁移是保证卵母细胞不对称分裂排出极体的关键步骤. 在第一次减数分裂过程中, 纺锤体在卵母细胞中央形成, 迁移到皮质层, 随后同源染色体分离, 卵母细胞不对称分裂产生一个大的卵子和一个小的极体[61]. 减数分裂纺锤体迁移与有丝分裂不同, 卵母细胞纺锤体迁移不依赖于微管, 而是由肌动蛋白组成的微丝介导的[62,63]. 研究发现Arp2/3复合物和Formin家族成员FMN2在微丝成核和卵母细胞纺锤体迁移中发挥关键作用, 其中, Arp2/3复合物主要负责分支状微丝成核, 而FMN2主要参与线性微丝成核[64~67]. 在迁移前, FMN2使围绕纺锤体的肌动蛋白成核, 肌动蛋白产生的推力启动纺锤体迁移[64,68]. 当纺锤体随机移动到与皮质层距离足够近时, 染色质产生的Ran-GTP信号通过Cdc42/N-WASP或Rac-WAVE2信号通路激活皮层上Arp2/3复合物[69], 促进细胞质肌动蛋白网络成核, 从而驱动细胞质流动产生动力, 使纺锤体迅速向皮质层移动[70]. 同时, Ran-GTP信号介导ERM(ezrin/radixin/moesin)去磷酸化调节卵母细胞皮质极化, 主要表现在该区域F-actin大量聚集, 形成肌动蛋白帽(actin cap)[71]. 除了FMN2, 研究表明Formin家族成员FMNL1[72], FHOD1[73], FMNL2[74]和FMNL3[75]在卵母细胞纺锤体迁移过程中也发挥重要作用, 这些蛋白的缺失会导致小鼠卵母细胞纺锤体迁移失败. 此外, 许多小GTP酶包括RhoA[76,77], Cdc42[78], Rab3a[79], Rab7[80], Rab8a[81], Rab35[82]等功能缺失会导致卵母细胞纺锤体迁移异常.

2.7 极体排出

卵母细胞减数分裂极体排出是一种特殊的胞质分裂方式, 该过程由皮质膜突起和收缩环共同协调完成[83]. 收缩环是由微丝与肌球蛋白II形成的腰带环状束. 极体排出之前, 纺锤体迁移到皮质层的Actin cap区域. 在第一次减数分裂中期向后期转变期间, 纺锤体中间形成收缩环, 在肌球蛋白II的作用下, 收缩环产生动力将质膜向内拉, 形成分裂沟. 收缩环不断收缩, 分裂沟加深, 直至第一极体排出[84]. 随后, 第二次减数分裂纺锤体形成, 并平行于皮层的Actin cap区域. 卵子受精后, 纺锤体旋转约90°至垂直位置, 收缩环形成并收缩, 卵子排出第二极体[66,85,86]. 研究发现GTP酶RhoA可以调节纺锤体的旋转, 并在胞质分裂过程中促进收缩环的组装和分裂沟的形成[87,88]. 此外, 另一种GTP酶Cdc42通过调节Actin cap的形成参与卵母细胞极体排出. 在爪蟾卵母细胞中, 抑制Cdc42的活性导致收缩环形成和第一极体排出失败[89,90]. 此外, Cdc42的功能在小鼠卵母细胞中是保守的, 该蛋白功能缺失不影响小鼠卵母细胞纺锤体的组装、迁移以及染色体分离, 但由于收缩环收缩缺陷导致极体排出失败[91].

2.8 卵母细胞MII期阻滞和恢复

MII期卵母细胞阻滞主要依赖于细胞静止因子(cytostatic factor, CSF), CSF是一种蛋白质复合物, 其成员在第二次减数分裂期间逐渐升高. 丝氨酸/苏氨酸蛋白激酶MOS对于维持CSF活性必不可少[92]. MOS/MEK/MAPK级联通路介导PP2A招募并结合CSF复合物关键成员早期有丝分裂抑制子2(early mitotic inhibitor 2, EMI2, 也称为FBXO43), 促使EMI2去磷酸化并激活. 活化的EMI2通过结合APC/C共激活因子细胞分裂周期蛋白20(cell division cycle 20, CDC20)抑制APC/C的活

性, 进而抑制Cyclin B的降解, 并维持MPF的稳定(图4). 此外, MOS/MEK/MAPK级联通路可以维持纺锤体的稳定, 最终使卵母细胞阻滞在第二次减数分裂中期, 形成成熟的MII期卵母细胞[93].

成熟的卵子与精子结合受精诱导减数分裂恢复. 精子与卵母细胞融合后, 储存在卵母细胞内质网中的钙离子被释放, 引发钙离子震荡. 钙离子激活钙离子/钙调蛋白依赖性蛋白激酶II(calcium/calmodulin dependent protein kinase II, CaMKII)和Polo样激酶1(polo like kinase 1, PLK1), 并磷酸化EMI2, 导致EMI2失活并降解. EMI2降解后释放APC/C, 进而降解Cyclin B. 同时, CaMKII还可以磷酸化激活WEE2, WEE2通过磷酸化抑制CDK1的活性[94,95]. 最终, MII期卵母细胞中的MPF活性降低并恢复减数分裂(图4). 此外, APC/C的激活还会降解分离酶抑制蛋白Securin, 激活分离酶Separase, 并切割黏连蛋白Cohesin, 从而促进姐妹染色单体的分离, 排出第二极体, 完成第二次减数分裂[96,97].

2.9 RNA稳态调控

原始卵泡激活后, 卵母细胞基因组持续活跃转录生成大量RNA, 并经过转录后加工被转运到卵胞质中长期储存, 为后续转录沉默的减数分裂、受精和合子基因组激活前胚胎发育提供重要的物质基础. 卵子发生过程中, 卵母细胞的基因表达发生了动态变化, 这些变化是由一组活跃的转录因子共同协调调控的, 包括卵母细胞特异性转录因子FIGLA, NOBOX, LHX8, SOHLH1, SOHLH2, TBPL2等[98]. 鼠模型证实这些转录因子的缺失会导致卵母细胞基因表达异常, 最终导致不同程度的卵母细胞和卵泡发育缺陷[99~104]. 转录形成前体mRNA需要进一步在细胞核中进行转录后加工, 包括加帽、剪切和加尾, 才能最终被转运到细胞质中发挥功能. 这个过程涉及多种蛋白复合物的参与. 研究发现poly(A)结合蛋白PABPN1通过液-液相分离形成细胞核内的特定功能区域NPAD(nuclear poly(A) domain)调控卵子发生过程中mRNA的转录后加工. 卵母细胞特异性敲除*Pabpn1*的小鼠完全不孕, 表现为卵泡发育受阻、卵巢早衰、排卵失败等表型[105]. mRNA的剪切是转录后加工的重要环节. RNA剪切因子SRSF3, hnRNPH1和BCAS2功能缺失导致卵母细胞剪切异常, 最终影响卵母细胞和卵泡的发育[106~108]. 此外, 近期研究发现RNA解旋酶MTR4参与形成RNA监管机制, 确保母源性mRNA的正常加工和胞质转运. *Mtr4*基因敲除卵母细胞无法在细胞质中积累足够的母源性mRNA, 并且无法发育到正常大小[109]. 通过检查机制的mRNA被转运到细胞质, 卵母细胞通过控制Poly(A)的长度控制母源性mRNA的翻译, 其中PATL2和PABPC1L被证明在卵母细胞翻译激活和抑制中发挥重要作用, 这两个蛋白功能缺失会导致人和小鼠卵母细胞成熟异常[110~113].

卵母细胞在发育后期转录停止, 直到受精后胚胎基因组被激活才重新开启. 在此期间, 卵母细胞需要依赖之前储存的mRNA来翻译产生新的蛋白质. 母源性mRNA存储对于卵母细胞受精和早期胚胎的发育至关重要. 研究人员发现, 未翻译的mRNA和RNA结合蛋白通过相分离的方式聚集在线粒体的周围, 形成一种无膜区域保护mRNA不被降解, 称为线粒体相关的核糖核酸蛋白域(mitochondria-associated ribonucleoprotein, MARDO). RNA结合蛋白ZAR1促进MARDO的凝聚和线粒体聚集, ZAR1功能丧失会导致MARDO形成失败和mRNA减少[114]. 与此同时, 另一团队的研究人员发现在人类和小鼠卵母细胞中存在一种由RNA结合蛋白YBX2可逆相变介导的类海绵状皮质分区, 该分区通过YBX2介导的液滴状和凝胶状相分离的转换维持卵母细胞母源性mRNA的长期稳定[115]. 卵母细胞受精后, 伴随着卵母细胞减数分裂成熟和排卵, 储存的母源性mRNA在母源-合子转换(maternal-zygotic transition, MZT)过程中被广泛降解, 母源性mRNA降解是决定早期胚胎发育潜力的关键事件[116]. 在该过程中, BTG4介导CNOT7/CNOT8与EIF4E相互作用, 并将CCR4-NOT去腺苷酸酶招募到母源性mRNA上. 随后, 母源性mRNA发生去腺苷酸化并被降解[117]. 研究发现BTG4和CCR4-NOT的催化亚基CNOT6L功能缺失导致小鼠卵母细胞母源性mRNA降解缺陷和早期胚胎发育异常[117,118]. 此外, ZFP36L2是CNOT6L的功能调控蛋白, 卵母细胞特异性敲除*Zfp36l2*导致小鼠卵母细胞成熟缺陷[119]. 这些研究说明卵母细胞通过精确调控mRNA的转录、加工、监控、储存以及降解维持卵胞质中mRNA的稳态, 这对于卵母细胞胞质成熟、受精和早期胚胎发育至关重要.

2.10 蛋白质稳态调控

卵母细胞从出生时就已经存在于卵巢中, 小鼠的卵母细胞在卵巢中储存一年以上, 而人类的卵母细胞在卵巢中储存数十年. 在此期间, 卵母细胞必须维持健

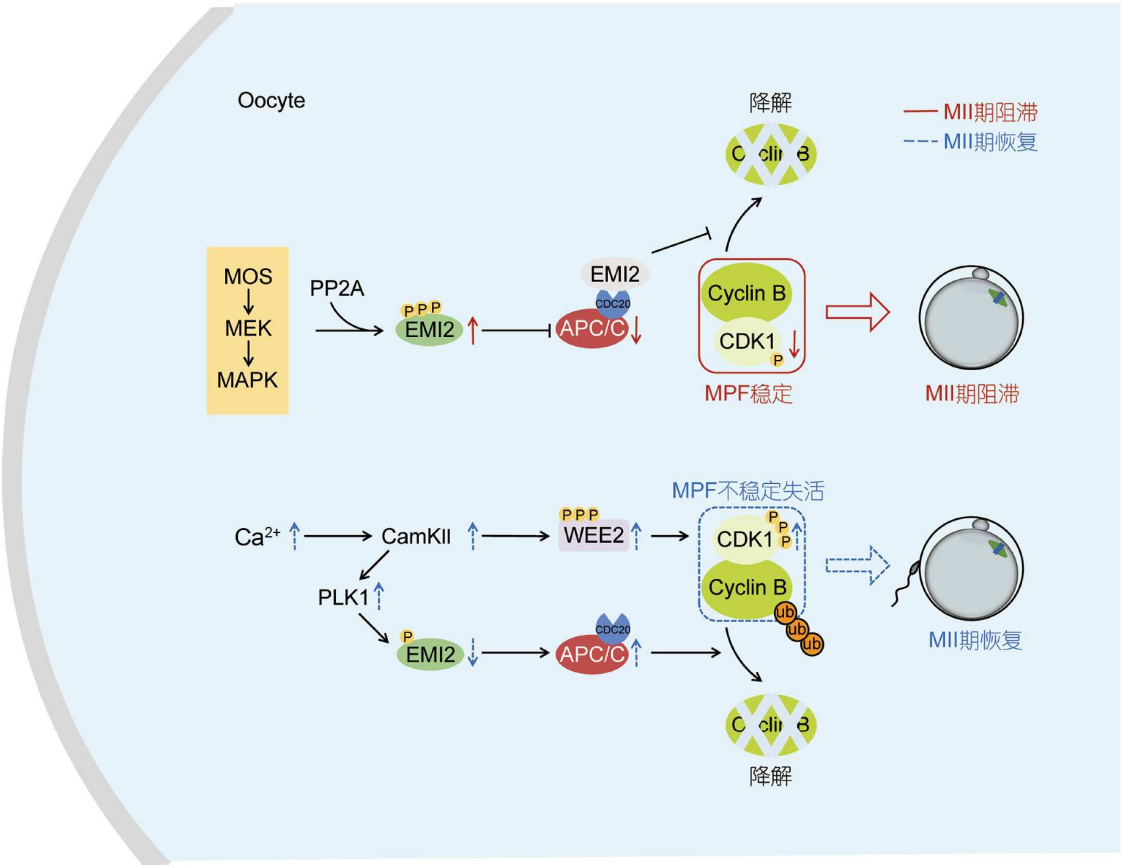

图 4 卵母细胞MII期阻滞和恢复的调控机制
Figure 4 Regulatory mechanism of MII arrest and resumption in oocytes

康的蛋白稳态确保下一代的顺利产生. 但是卵母细胞长期维持蛋白稳态的调控机制一直未知. 2024年, 研究者通过脉冲追踪实验发现小鼠卵母细胞和卵巢体细胞中许多蛋白异常稳定, 其半衰期远高于其他细胞和器官, 包括肝脏, 心脏, 大脑等. 这些超长寿蛋白在线粒体、蛋白质稳态、染色质维持和细胞骨架中具有重要功能. 进一步分析提示哺乳动物通过分子伴侣和细胞抗氧化物延长蛋白质寿命并增强蛋白质稳态, 从而维持卵母细胞在卵巢中的长期储存[120]. 除此之外, 线粒体未折叠蛋白反应(mitochondrial unfolded protein response, mtUPR)是一种细胞适应机制, 负责应对线粒体中的蛋白质折叠错误和稳态失衡[121]. 卵母细胞含有大量线粒体, 当线粒体发生损伤或错误折叠蛋白积累时, mtUPR激活核编码的伴侣蛋白和相关蛋白酶的表达, 如热休克蛋白HSP70和酪蛋白质水解酶P(CLPP). HSP70帮助修正错误折叠蛋白, 并促进新合成蛋白质的正确折叠. CLPP转运到线粒体基质中促进错误折叠蛋白的分解, 并启动一系列反应来重建蛋白质稳态[122]. *Clpp*敲除导致雌鼠完全不孕, 主要表现为卵母细胞和胚胎发育缺陷以及卵巢储备下降. 进一步分析发现CLPP缺失导致线粒体体积变小且功能紊乱[123]. 这些研究说明卵母细胞蛋白质稳态调控的重要性.

2.11 线粒体功能调控

线粒体(mitochondria)是卵母细胞中含量最丰富的细胞器, 其主要功能是合成ATP为卵母细胞发育提供能量, 同时还参与调控细胞内信号传递、氧化还原反应和钙离子稳态等[124]. 线粒体具有自己的遗传物质, 即线粒体DNA(mitochondrial DNA, mtDNA), 并通过母系遗传的方式遗传给后代. 线粒体和mtDNA的数量在卵母细胞发育过程中不断变化. 从PGC向卵原细胞发育过程中, 线粒体的数量由约10个增加到约200个. 双线期卵母细胞中含有约5000个线粒体, 而成熟的卵子中, 线粒体数量超过100000个, 每个线粒体中有一个或

两个mtDNA拷贝[125,126]. 卵母细胞发育过程中线粒体和mtDNA的增加是一种遗传机制, 可以确保细胞中存在足够数量的细胞器和基因组可以分配到各个早期胚胎细胞中, 因为mtDNA复制在早期胚胎细胞中不会开启[127]. 同时, 大量的mtDNA会成比例地稀释卵母细胞中mtDNA突变的数量, 从而有效降低后代遗传致病突变的风险[128].

在卵母细胞发育过程中, 线粒体除了数量上发生改变外, 其形态和分布也发生变化. 原始卵母细胞具有圆形空泡化的线粒体, 嵴密度低, 分布于整个细胞质中. 在卵母细胞生长和成熟过程中线粒体保持圆形, 伴有嵴密度增加[129]. 线粒体向高能量消耗区域的运动对于卵母细胞成熟至关重要. 在完全生长的卵母细胞中, 线粒体以簇状分布在整个细胞质中, 然后GVBD前聚集在生发泡周围, 随后在MI期纺锤体周围聚集, 并随纺锤体迁移至皮质区. 最后, 在卵母细胞完成第一次减数分裂后重新分布于细胞质中[129,130]. 研究发现, 卵母细胞纺锤体的迁移依赖于线粒体在纺锤体周围的聚集和动态分布[63]. 线粒体通过不断地融合和分裂维持其正常的分布、形态和功能. 线粒体融合通过交换转移RNA或蛋白质, 使一个线粒体能够补偿另一个线粒体的功能缺陷, 而线粒体分裂将受损的线粒体成分与健康成分分开, 并通过线粒体自噬将其在溶酶体内降解[131]. 线粒体融合和分裂主要由位于线粒体外膜的MFN1/2、位于线粒体内膜的OPA1和线粒体膜中的GTP酶DRP1调控[132~134]. 卵母细胞特异性敲除*Dpr1*导致卵母细胞中线粒体的分裂、形态和分布异常, 并造成小鼠卵泡成熟和排卵功能障碍[135]. 另外, 卵母细胞特异性敲除*Mfn1*会导致线粒体功能障碍, 并影响卵母细胞和卵泡的发育[136]. 敲除小鼠模型证明线粒体融合和分裂对于维持线粒体正常功能的重要性. 除此之外, 当卵母细胞线粒体损伤时, 线粒体通过线粒体自噬(mitophagy)方式清除受损线粒体, 控制线粒体质量并维持线粒体稳态[137], 对卵母细胞质量起保护作用.

2.12 内质网功能调控

内质网(endoplasmic reticulum, ER)是由膜构成扁囊、小管或小泡连接形成的网状膜系统, 主要负责细胞蛋白质合成和加工以及脂质合成, 并且是细胞储存Ca^{2+}的主要场所. ER在卵母细胞成熟过程中经历了重新分布和结构变化. 在小鼠中, GV期卵母细胞中, ER均匀分布在整个卵胞质中. MI期卵母细胞中ER围绕新形成的纺锤体紧密排列, ER的这种动态分布有助于FMN2的定位和纺锤体向皮质层迁移的启动[64]. 近期, 研究发现肌动蛋白成核因子FMNL2对于维持MI期卵母细胞中ER的分布和功能至关重要[74]. 在成熟的MII期卵子中, ER被极化, 成簇的ER位于减数分裂纺锤体对侧的皮质层[138,139]. ER在人类GV期卵母细胞中的分布与小鼠卵母细胞中的分布相似. 然而, 人类MII期卵子中成簇的ER不仅存在于皮质层, 而且存在于整个卵母细胞中, 并没有明显的极性分布. 卵母细胞发育过程中ER分布动态变化可能与其响应Ca^{2+}释放刺激的能力变化有关. 卵子受精后, ER释放Ca^{2+}在胞质中产生Ca^{2+}震荡信号, 卵子通过该信号对精子融合受精产生一系列反应, 包括皮质颗粒外排、第二极体排出、第二次减数分裂完成和原核形成等[140]. 精子来源的磷脂酶Cζ(PLCζ)是诱导卵子ER释放Ca^{2+}的原始激活因子[141]. PLCζ通过将4,5-二磷酸磷脂酰肌醇(PIP2)水解产生1,4,5-三磷酸肌醇(IP3), 并与定位在ER膜表面的肌醇1,4,5-三磷酸受体(IP3R)结合. IP3R是一种钙离子通道, 与IP_3结合后引起构象变化, 通道开放将钙离子释放到卵胞质中[142]. ER释放Ca^{2+}产生的Ca^{2+}震荡对驱动卵子激活和随后的胚胎发育至关重要.

3 人卵母细胞发育缺陷的遗传学机制

卵母细胞发育过程中受到众多基因的精确调控, 调控基因功能紊乱会导致卵母细胞发育缺陷, 并影响后续受精和胚胎发育过程. 近年来, 随着分子生物学和遗传学的发展, 人类卵母细胞发育缺陷的致病基因被不断报道, 目前已经发现37个导致人类卵母细胞发育缺陷的致病基因, 携带这些致病基因突变的不孕患者表现为多种临床表型, 包括卵母细胞成熟障碍、受精失败和早期胚胎停滞等表型(表1).

3.1 同源重组异常

减数分裂DSBs的形成对于卵母细胞减数分裂和卵母细胞发育至关重要. 在DSBs形成过程中, 减数分裂特异性前DSB重组体负责将拓扑异构酶SPO11招募到DSBs热点区域催化DSBs形成. 研究发现该复合物成员编码基因*REC114*(REC114 meiotic recombination protein), *MEI1*(meiotic double-stranded break formation protein 1)和*MEI4*(meiotic double-stranded break formation protein 4)突变都会导致女性不孕. *REC114*双等位基因突变破坏蛋白与MEI4相互作用, 并影响MEI4的稳

表 1 人卵母细胞发育缺陷的突变基因[a)]

Table 1 Mutated genes responsible for developmental defects in human oocytes

致病基因	遗传模式	功能	表型	参考文献
REC114	AR	调控同源重组DSB形成	多精受精和早期胚胎停滞	[143]
MEI1	AR	调控同源重组DSB形成	早期胚胎停滞和着床失败	[144]
MEI4	AR	调控同源重组DSB形成	早期胚胎停滞	[19]
TBPL2	AR	调控基因转录	卵母细胞成熟障碍, 卵母细胞退化以及早期胚胎停滞	[145]
LHX8	AD	调控基因转录	卵母细胞成熟障碍	[146]
KPNA7	AR	介导蛋白质核转运	早期胚胎停滞	[147]
TUBB8	AR/AD	组装人卵纺锤体微管	卵母细胞成熟障碍、受精障碍、多原核、合子分裂失败、早期胚胎停滞、植入失败以及非整倍体	[2,148,149]
TUBA4A	AD	组装人卵纺锤体微管	卵母细胞成熟障碍和早期胚胎停滞	[150]
TACC3	AR	介导人卵纺锤体微管成核	卵母细胞成熟障碍	[46]
HAUS6	AR	调控人卵纺锤体双极化	成熟障碍、受精失败或早期胚胎停滞	[48]
KIF18A	AR	调控人卵纺锤体双极化	成熟障碍、受精失败或早期胚胎停滞	[48]
KIF11	AR	调控人卵纺锤体双极化	成熟障碍、受精失败或早期胚胎停滞	[48]
TRIP13	AR	调控纺锤体组装检验点	卵母细胞成熟障碍和合子分裂失败	[151]
MAD2L1BP	AR	调控纺锤体组装检验点	卵母细胞成熟障碍	[152]
CDC23	AR	调控细胞周期进程	卵母细胞成熟障碍	[153]
CDC20	AR	调控后期促进复合体活性	卵母细胞成熟障碍、受精失败或早期胚胎停滞	[154~156]
FBOX43	AR	调控后期促进复合体活性	早期胚胎停滞	[157]
WEE2	AR	调控成熟促进因子活性	受精失败	[158,159]
MOS	AR	调控MAPK级联通路活性	早期胚胎停滞	[160,161]
CHK1	AD	调控细胞周期检查点	原核融合失败和合子分裂停滞	[162,163]
PATL2	AR	调控mRNA翻译抑制	卵母细胞成熟障碍, 受精失败和早期胚胎停滞	[111,164,165]
PABPC1L	AR	调控mRNA翻译激活	卵母细胞成熟障碍	[112,166]
BTG4	AR	调控母源mRNA降解	合子分裂失败	[167,168]
ZFP36L2	AR	调控母源mRNA降解	早期胚胎停滞	[169]
ZP1	AR	组装卵母细胞透明带	透明带异常、空卵泡、卵母细胞退化和受精障碍	[170,171,174]
ZP2	AR/AD	组装卵母细胞透明带	透明带异常、空卵泡、卵母细胞退化和受精障碍	[173,174]
ZP3	AD	组装卵母细胞透明带	透明带异常、空卵泡、卵母细胞退化和受精障碍	[171,172,174]
ASTL	AR	介导透明带蛋白切割	受精异常和早期胚胎停滞	[175,176]
PADI6	AR	组成皮质下母源复合体	早期胚胎停滞和葡萄胎	[177,182,183]
TLE6	AR	组成皮质下母源复合体	早期胚胎停滞	[178]
OOEP	AR	组成皮质下母源复合体	早期胚胎停滞	[179]
NLRP2	AR	组成皮质下母源复合体	早期胚胎停滞	[180]
NLRP5	AR	组成皮质下母源复合体	早期胚胎停滞和葡萄胎	[179~181,183]
NLRP7	AR/AD	组成皮质下母源复合体	葡萄胎	[183]
KHDC3L	AR	组成皮质下母源复合体	葡萄胎	[184]
PANX1	AR/AD	细胞膜表面通道蛋白	卵母细胞死亡	[185,186]
COX15	AR	参与组装线粒体复合体IV	卵母细胞成熟障碍和退化	[187]

a) AD: 常染色体显性(autosomal dominant); AR: 常染色体隐性(autosomal recessive)

定性, 从而导致卵母细胞发育缺陷, 最终导致患者表现为多精受精和早期胚胎停滞等表型[143]. *MEI1*双等位基因突变导致其功能受损, 进而导致患者早期胚胎停滞和着床失败等临床表型[144]. *MEI4*双等位基因突变通过破坏蛋白与DNA的结合影响DSBs形成, 最终导致患者表现为早期胚胎停滞的表型[19].

3.2 转录调控异常

TBPL2(TATA-box binding protein like 2)是卵母细胞特异高表达的转录因子, 在GV及早期卵母细胞中可

以与基因上的TATA box结合，参与调控mRNA的转录起始. 研究发现, 小鼠卵母细胞中缺乏TBPL2导致卵母细胞特异性基因转录异常，并导致卵母细胞发生缺陷和不孕. 目前发现, 女性携带*TBPL2*纯合或复杂合突变会导致卵母细胞成熟障碍、卵母细胞退化以及早期胚胎停滞的表型[145].

LHX8(LIM homeobox 8)也是一种生殖细胞特异性转录因子, 在哺乳动物卵巢中高表达. 它负责调控许多基因的转录，这些基因在卵母细胞发生早期对卵母细胞的维持和分化起着关键作用. 与TBPL2类似，小鼠LHX8缺失也会导致卵母细胞转录功能缺陷, 从而导致卵母细胞发生异常. 女性携带*LHX8*杂合突变导致卵母细胞成熟障碍[146].

KPNA7(karyopherin subunit alpha 7)是卵母细胞和早期胚胎中特异高表达的α核转运蛋白，负责将包括转录因子在内的多种蛋白转运至细胞核内发挥功能. 女性携带*KPNA7*双等位基因突变影响其核转运能力，导致合子基因组激活受损，最终表现为早期胚胎停滞表型[147].

3.3 纺锤体组装异常

卵母细胞的发育过程伴随着减数分裂的进行，其中纺锤体组装是卵母细胞发育和减数分裂过程中的重要事件. 研究发现人卵母细胞的纺锤体组装在微管组成、微管成核及双极化过程中存在物种特异性调控机制.

TUBB8(tubulin beta 8 class VIII)是灵长类特异性β-微管蛋白, 其在人卵母细胞中特异性高表达, 也是构成卵母细胞纺锤体最主要的β-微管蛋白. *TUBB8*是人卵母细胞成熟障碍的第一个致病基因[2]. *TUBB8*突变导致女性不孕的遗传模式和临床表型具有多样性. 目前发现*TUBB8*的杂合、复杂合与纯合突变都可通过显性负效应或功能丧失等影响纺锤体的正常组装. 携带*TUBB8*突变的患者主要的临床表型为MI阻滞，但由于不同突变位点的致病性存在差异，部分患者也表现为受精障碍、多原核、合子分裂失败、早期胚胎停滞、植入失败以及非整倍体等表型[2,148,149]. 此外, TUBA4A (tubulin alpha-4A chain)是一种α-微管蛋白, 与β-微管蛋白组成异源二聚体共同组装卵母细胞纺锤体. 近期研究发现, *TUBA4A*杂合突变也会导致卵母细胞成熟障碍和早期胚胎停滞[150].

最近，国内研究团队发现了人卵母细胞MTOC (huoMTOC)组装和纺锤体双极化形成的全新机制. 研究发现，huoMTOC关键分子*TACC3*双等位基因突变会破坏微管和纺锤体组装，从而导致卵母细胞成熟障碍[46]. 而在人卵母细胞双极纺锤体组装过程中, 关键蛋白*HAUS6*, *KIF18A*双等位基因突变和*KIF11*杂合突变也导致纺锤体双极化组装失败，进而导致卵母细胞成熟障碍、受精失败或早期胚胎停滞[48].

3.4 细胞周期调控异常

TRIP13(thyroid hormone receptor interactor 13)广泛表达于动物各种组织, 是调控SAC的关键分子, 在有丝分裂和减数分裂中均发挥重要作用. *TRIP13*不同类型突变会导致不同疾病，其中破坏性较弱的错义突变会破坏其调控HORMAD2的能力，使SAC调控出现异常, 最终导致卵母细胞成熟障碍. 携带*TRIP13*纯合或复杂合错义突变的患者均表现为卵母细胞成熟障碍(MI阻滞)或合子分裂失败[151]. 与TRIP13类似，MAD2L1BP (MAD2L1-binding protein)在分裂中期，通过结合MAD2L1促进后期进入，女性携带*MAD2L1BP*突变会导致卵母细胞成熟障碍[152].

人卵母细胞减数分裂过程中APC/C的调控对于卵母细胞的发育至关重要. CDC23(cell division cycle protein 23 homolog)是APC/C的关键成员之一, 对于卵母细胞退出减数分裂至关重要. 小鼠模型显示CDC23缺失导致APC/C功能受损, Cyclin B异常累积, 导致卵母细胞MI期停滞. 女性携带*CDC23*双等位基因突变导致卵母细胞成熟障碍和不孕[153]. CDC20(cell division cycle 20)是APC/C的共激活因子, 通过调控APC/C活性, 促进Securin和Cyclin B的降解，完成分裂中后期转换. *CDC20*双等位基因突变导致人卵母细胞成熟障碍、受精失败或早期胚胎停滞[154~156]. FBXO43(f-box protein 43)通过抑制APC/C活性建立并维持卵母细胞在第二次减数分裂中期的停滞直至受精. 女性携带*FBXO43*双等位基因突变表现为早期胚胎停滞表型[157].

WEE2(wee1-like protein kinase 2)是卵母细胞特异性蛋白酪氨酸激酶，可磷酸化并抑制CDK1活性，在卵母细胞受精后, 通过磷酸化CDK1使卵母细胞退出第二次减数分裂，并促进原核形成. *WEE2*双等位基因突变导致WEE2功能受损, 磷酸化CDK1能力减弱, 并导致卵母细胞无法形成原核, 最终导致受精失败[158,159].

MOS(MOS proto-oncogene, serine/threonine kinase)是ERK1/2信号分子的激活剂，参与调节MAPK级联通

路, 在维持卵母细胞MII期停滞中发挥关键作用. *MOS*双等位基因突变损害其蛋白表达和ERK1/2的磷酸化, 导致卵母细胞母源性mRNA清除和线粒体功能紊乱, 最终导致早期胚胎停滞[160,161].

CHK1(checkpoint kinase 1)也是一种丝氨酸/苏氨酸蛋白激酶, 参与检查点介导的细胞周期停滞, 并负责在DNA损伤或未复制的DNA存在时激活DNA修复, 它通过CDC25C-CDK1通路引起受精卵G2/M期转换阻滞. *CHK1*杂合突变导致CHK1活性异常增加, 并造成CDK1活性无法恢复, 最终导致受精卵原核融合失败和合子分裂停滞[162,163].

3.5 RNA调控异常

PATL2(protein PAT1 homolog 2)是一种在卵母细胞中特异高表达的RNA结合蛋白, 参与抑制RNA翻译, 并调控卵母细胞中众多基因的表达. 女性携带*PATL2*双等位基因突变主要表现为卵母细胞成熟障碍, 由于突变位点的功能破坏性不同亦可造成受精失败和早期胚胎停滞表型[111,164,165].

PABPC1L(poly(A) binding protein cytoplasmic 1 like)是卵母细胞和早期胚胎中一种重要的poly(A)尾结合蛋白, 通过调控poly(A)尾长度进而调控mRNA的翻译. *PABPC1L*双等位基因突变影响蛋白表达, 并通过影响PABPC1L与mRNA的结合降低蛋白的翻译激活功能. 携带该基因突变的患者主要表现为卵母细胞成熟障碍的表型[112,166].

BTG4(BTG anti-proliferation factor 4)是一种CCR4-NOT复合物的衔接蛋白, 其特异性在成熟卵母细胞和早期胚胎中表达, 调控母源mRNA降解. *BTG4*双等位基因突变影响其与CNOT7相互作用, 进而影响CCR4-NOT复合物降解母源mRNA, 最终导致合子分裂失败[167,168]. 此外, ZFP36L2(ZFP36 ring finger protein like 2)同样参与母源mRNA降解, 其通过结合CNOT6L招募CCR4-NOT复合物的组装. *ZFP36L2*双等位基因突变破坏合子的母源mRNA降解, 进而导致早期胚胎停滞[169].

3.6 透明带异常

透明带是卵母细胞外的一种由多种糖蛋白组成的细胞外基质, 在卵母细胞成熟、受精及早期胚胎发育过程中发挥重要作用. 人卵母细胞透明带主要由4种透明带蛋白组成: ZP1, ZP2, ZP3和ZP4. 2014年, 研究发现, *ZP1*纯合突变导致女性不孕, 患者因ZP1蛋白缺乏导致卵母细胞缺乏透明带进而导致发育异常[170]. 其后又陆续发现*ZP2*和*ZP3*的致病突变. *ZP2*纯合突变导致透明带变薄和结构异常进而导致IVF失败, 而*ZP3*杂合突变导致卵母细胞缺乏透明带导致卵母细胞退化[171~174]. 由于不同ZP蛋白的功能以及不同突变位点对蛋白功能破坏有所差异, ZP1-3突变患者表型存在多样性, 主要包括透明带形态异常或缺失、空卵泡、卵母细胞退化、受精障碍和早期胚胎发育异常等.

ASTL(astacin like metalloendopeptidase)是卵母细胞特异性膜受体, 对精子和卵子的黏附至关重要, 在受精过程中发挥着关键作用. 当精子穿过透明带与卵母细胞融合后, ASTL通过切割ZP2蛋白, 使透明带结构发生变化, 阻止其他精子继续结合和穿过透明带, 进而阻止多精受精. *ASTL*双等位基因突变导致ASTL功能损失, 从而导致受精异常和早期胚胎停滞[175,176].

3.7 皮质下母源基质复合体异常

母源效应蛋白在卵母细胞成熟、受精和早期胚胎发育中起重要作用. 皮质下母源复合体(subcortical maternal complex, SCMC)作为哺乳动物保守的母源效应蛋白复合物在早期胚胎发育过程中发挥至关重要的作用. 目前已经发现SCMC基因*PADI6*[177], *TLE6*[178], *OOEP*[179], *NLRP2*[180], *NLRP5*[179~181]双等位基因突变导致受精异常和早期胚胎发育停滞. 此外, 部分SCMC基因*PADI6*[182,183], *KHDC3L*[184], *NLRP7*[183]与*NLRP5*[183]突变也会导致葡萄胎.

3.8 卵母细胞退化和死亡

2019年, 研究者报道了一种新的孟德尔遗传疾病“卵母细胞死亡”, 并鉴定到致病基因*PANX1*[185]. 患者表现为卵子受精前或受精后出现发黑、皱缩和退化的现象. PANX1(pannexin-1)是一种跨膜的通道蛋白, 允许包括ATP在内的小分子和离子等通过, 并介导细胞内与细胞外环境的交流. PANX1是一种高度糖基化的蛋白. *PANX1*杂合突变通过影响其蛋白的糖基化导致PANX1通道的异常激活, 最终导致卵母细胞死亡. 随后, 研究发现*PANX1*纯合突变同样会导致患者卵母细胞死亡和不孕[186].

COX15(cytochrome c oxidase assembly homolog COX15)是线粒体呼吸链复合体IV的关键成员, 参与催化血红素A生物合成, 其对于线粒体复合体IV组装至关

重要. COX15突变破坏蛋白自身的正常表达, 并导致蛋白功能异常. 机制研究发现*COX15*缺陷导致卵母细胞内Fe^{2+}和ROS累积, 进而导致线粒体功能紊乱, 并激活铁死亡通路导致卵母细胞退化[187].

4 衰老与肥胖对卵母细胞的影响

4.1 卵母细胞衰老调控

随着年龄的增长, 女性卵母细胞质量和生育能力下降. 衰老导致卵母细胞质量下降的分子基础是多因素的. 线粒体功能障碍是衰老的标志之一. 在各组织中mtDNA的拷贝数和功能随着年龄的增长持续下降. 越来越多的证据支持线粒体功能障碍是导致生殖衰老的重要原因. 与年轻小鼠相比, 生育能力下降的年老小鼠卵母细胞中的mtDNA拷贝数显著降低[188]. 人类卵母细胞mtDNA的含量是卵母细胞受精和胚胎发育潜能的关键因素[189]. 与年轻女性相比, 老年女性卵母细胞mtDNA的含量显著减少[190]. 此外, mtDNA缺失和突变是导致线粒体功能紊乱的重要因素. 研究发现, 老年女性卵母细胞中mtDNA缺失和突变比例显著高于年轻女性[191,192], 这说明mtDNA缺失和突变随着女性年龄的增长而积累. ROS是线粒体氧化磷酸化的副产物, 其异常累积会导致细胞氧化损伤. 卵母细胞通过合成抗氧化物质清除ROS维持细胞内氧化还原稳态. 研究发现小鼠卵巢中抗氧化基因*Prdx3*和*Txn2*的表达水平随着年龄的增长降低[193]. 老年女性卵巢中抗氧化酶SOD和PRDX4编码基因的表达显著低于年轻女性[194,195], 表明衰老导致卵巢和卵母细胞抗氧化能力降低. 此外, 线粒体功能相关蛋白的表达也受年龄的影响, 线粒体运输蛋白MIRO1在老龄动物卵母细胞中的表达显著降低, 该蛋白缺失导致卵母细胞质量下降[196]. 以上结果说明卵母细胞线粒体功能障碍是衰老影响卵母细胞质量的关键因素.

卵母细胞中与年龄相关的非整倍体是导致卵母细胞质量下降的另一个主要因素. 随着年龄增长卵母细胞更容易发生减数分裂染色体分离错误和非整倍体. 衰老导致非整倍体发生率升高的机制较多. 黏连蛋白产生的内聚力在减数分裂过程中保障姐妹染色单体连接, 并防止分离错误. 研究发现小鼠和人类卵母细胞染色体内聚力在衰老过程中逐渐降低[197,198]. SAC功能异常会导致非整倍体卵子的产生. 年龄增加会破坏小鼠卵母细胞SAC-APC/C轴导致姐妹染色单体分裂错误增加, 过表达分离酶抑制蛋白Securin和SAC成员MPS1能够改善年龄依赖的染色体分离错误的增加[199]. 人类和小鼠卵母细胞转录组分析发现SAC成员的表达呈年龄依赖性下降[200,201]. 另外, 纺锤体的稳定对于卵母细胞减数分裂成熟和染色体整倍性至关重要. 形态学观察发现老年女性卵母细胞中存在明显染色体排列和纺锤体结构异常[202]. 老龄小鼠卵母细胞双极纺锤体形成的时间延长, 并且形成多极纺锤体的比例增加[203]. 除此之外, 年龄相关的着丝粒碎片化、端粒变短和DNA损伤增加等都会导致卵母细胞非整倍体增加和卵母细胞质量下降[204].

近年来, 多组学分析逐渐应用于探究卵母细胞衰老的机制研究. 通过单细胞转录组、翻译组和蛋白组分析, 研究人员发现在小鼠衰老过程中, 卵母细胞中大多数基因的翻译效率显著降低, 这与m^6A识别因子YTHDF3的表达下降相关. YTHDF3功能缺陷抑制RNA翻译效率并降低卵母细胞质量. 进一步对人类卵母细胞衰老过程中的翻译图谱进行分析, 发现人类卵母细胞衰老过程中表观遗传修饰调节因子的翻译变化与小鼠类似, 但是YTHDF3在人卵母细胞中表达很低, 因此, 人类卵母细胞衰老过程中的翻译调控并非由m^6A介导, 而与剪接因子SRSF6相关[205]. 充分了解衰老导致的卵母细胞质量下降的机制, 有助于探索改善高龄女性卵母细胞质量的干预策略.

4.2 肥胖与卵母细胞质量

肥胖是常见的具有跨代传递倾向的慢性代谢疾病. 女性肥胖不仅影响新陈代谢, 还对生殖健康产生危害. 同龄肥胖女性比正常体重女性由于排卵异常导致不孕的风险更高[206,207]. 肥胖女性与正常女性相比对促性腺激素的响应较差, 卵母细胞获取率降低, 卵母细胞质量及胚胎发育率下降, 流产风险增加[207~209]. 高脂饮食诱导的肥胖小鼠卵母细胞纺锤体组装异常和非整倍体比例显著升高[210,211]. 另外, 研究人员在肥胖女性不孕患者的卵母细胞中也观察到了类似的现象[212]. 肥胖逐渐成为影响卵母细胞质量和女性生殖健康的重要因素. 大量的人类和动物临床数据证实肥胖影响卵母细胞质量机制是多方面的, 包括调控表观遗传修饰和线粒体功能等.

研究发现, 肥胖小鼠卵母细胞中代谢相关基因的DNA甲基化发生变化[213]. 随后, 研究人员发现, 肥胖小鼠卵母细胞中*Stella*基因表达降低, 造成受精卵中雌

原核去甲基化和胚胎发育异常. 肥胖小鼠卵母细胞中过表达*Stella*可以恢复受精卵的表观遗传重塑, 并部分改善早期胚胎和胎儿生长中与母体肥胖相关的发育缺陷[214]. 此外, 肥胖会导致小鼠褪黑素分泌不足, 进而通过cAMP/PKA/CREB通路导致DNA甲基转移酶(DNA methyl-transferase, DNMT)高表达, 引起肥胖小鼠卵母细胞基因组甲基化升高, 并且肥胖导致的甲基化异常能够部分遗传到子代的卵母细胞[215]. 这些研究说明表观遗传修饰在肥胖诱导的卵母细胞质量下降中发挥重要作用.

早期胚胎中的线粒体主要来自卵母细胞, 所以线粒体的数量和功能不仅影响卵母细胞本身, 而且直接影响子代的健康. 研究发现肥胖影响小鼠卵母细胞中线粒体分布, 并导致线粒体嵴减少, 腔泡增多[216,217]. 肥胖小鼠卵母细胞中ROS水平显著升高, 进一步研究发现肥胖小鼠卵母细胞中SIRT3和SIRT7蛋白水平显著降低, 外源补充SIRT3或SIRT7可以改善母鼠肥胖相关的卵母细胞减数分裂缺陷和氧化应激[218,219]. 除此之外, 肥胖可诱发成熟卵母细胞mtDNA单核苷酸突变增加, 机制研究发现肥胖可通过抑制AMPKa活性来增加细胞中LonP1含量, 继而诱发ATF5蛋白被POLG募集到mtDNA突变的启动子区来大量复制突变的mtDNA[220]. 这些研究为改善肥胖诱发的卵母细胞质量降低提供理论基础和基因靶点.

5 临床遗传诊断和潜在干预策略

5.1 遗传诊断的必要性

近年来, 不孕不育的比例逐年提升, 据统计, 目前大约有15%的育龄夫妇存在生育困难. IVF/ICSI技术的广泛应用极大地提高了生育困难夫妇的生育率. 然而, 在临床中有一类患者遭受IVF/ICSI反复失败, 其原因并不明确. 2016年, 第一个卵母细胞成熟障碍致病基因*TUBB8*被报道, 揭示了该疾病是一种孟德尔遗传病. 其后, 随着遗传学和测序技术快速发展, 已经有37个基因被报道其突变会通过影响女性卵母细胞质量导致IVF/ICSI失败和女性不孕(表1), 这些研究充分说明了遗传因素是导致IVF/ICSI失败的重要原因之一. 目前, 已知致病基因被应用于临床不孕患者的遗传诊断. 针对辅助生殖失败的患者, 遗传诊断可以帮助医生尽快明确致病原因, 并选择合适的治疗方案. 避免因盲目尝试IVF/ICSI而给患者造成严重的心理负担和经济损失.

5.2 潜在干预策略

目前, 针对卵母细胞发育缺陷, 已经开展了一些干预策略的探索. 患者卵母细胞携带致病突变会通过破坏蛋白功能导致卵母细胞成熟、受精和胚胎发育异常. 多项研究证明向患者卵母细胞中注射mRNA回补可以有效挽救患者的表型. *TRIP13*突变会导致患者的卵母细胞无法成熟, 并停滞在MI期. 回补野生型*TRIP13* mRNA的患者卵子能够成熟, 并且可以成功受精并发育到囊胚[151]. 另外, *WEE2*和*CDC20*突变都导致卵母细胞受精失败, mRNA回补后的卵母细胞可以受精并卵裂发育成囊胚[154,158]. 此外, 针对性的小分子抑制剂也可以有效改善基因突变导致的卵母细胞或胚胎异常. *CHK1*突变引起的CHK1激酶活性增加导致合子第一次有丝分裂失败. CHK1抑制剂PF477736可以有效挽救突变小鼠和患者受精卵阻滞表型, 并且处理后形成的小鼠囊胚在移植后能产生健康后代[163]. *PANX1*突变通过异常激活通道导致卵子死亡. PANX1通道抑制剂Probenecid可以挽救小鼠模型卵子死亡的表型, 但是处理后的卵母细胞无法排出第一极体成熟[185]. COX15功能缺失造成线粒体功能紊乱并激活铁死亡通路导致卵子退化. 铁死亡抑制剂Ferrostatin-1在体内和体外可以部分逆转COX15缺陷导致的卵子退化表型[187]. 但是基于伦理和安全评估问题, mRNA回补和小分子抑制剂处理的干预策略并没有应用于临床治疗, 目前仍处于探索阶段.

线粒体是除细胞核以外唯一含有DNA的动物细胞器, mtDNA突变会导致线粒体功能异常, 并通过母系遗传的方式传递给后代. 线粒体是卵母细胞质量的标志之一, 其数量和功能异常将降低卵母细胞及胚胎发育潜能. 为了改善线粒体异常的卵母细胞质量并防止线粒体突变通过卵母细胞遗传, 研究者提出了一种替代疗法: 线粒体置换治疗(mitochondrial replacement therapy, MRT)[221]. MRT是将有线粒体疾病患者的卵母细胞或受精卵中的遗传物质转移到去核的、拥有正常线粒体的细胞内, 目前主要有三种方式: 母体纺锤体移植(maternal spindle transfer, MST)、原核移植(pronuclear transfer, PNT)和极体移植(polar body transfer, PBT). MST和PNT在过去十数年间被广泛研究, 并进行了安全性验证[222,223], 而PBT目前还在试验探索阶段. MRT最大的争议在于核周围的线粒体容易随着遗传物质一起转入新的细胞, 大约不到5%, 但这种残留的mtDNA目前无法完全清除. 基于伦理和安全性原因, 包括中国

和美国在内的多数国家目前禁止MRT用于治疗不孕不育. 2016年, 美国的研究团队在墨西哥利用MST技术帮助一名中东母亲生下了世界上首位“三亲婴儿”, 并且没有检测到线粒体基因变异[224]. 截至目前, 该技术仍面临着技术、伦理及社会等诸多方面的争议, 其长期影响依旧尚不明确, 需要更多的安全性研究和评估.

卵母细胞质量下降除了遗传学因素, 还有许多因素也会导致卵母细胞质量降低, 其中活性氧(reactive oxygen species, ROS)氧化损伤被认为是影响卵母细胞质量的重要因素[225,226]. 抗氧化药物目前被认为可能具有改善卵母细胞质量, 提高女性生育能力的潜力. 辅酶Q10是线粒体呼吸链中的关键电子载体, 也是跨线粒体内膜的质子转运蛋白, 是ATP生成所需的. 此外, 辅酶Q10是一种强效的抗氧化剂, 能够中和自由基, 减少脂质过氧化和DNA损伤. 临床研究表明辅酶Q10可以改善卵母细胞质量, 提高成熟率并降低非整倍体率[227,228]. 尽管大量研究表明辅酶Q10对于改善卵泡环境和卵母细胞质量有效果, 但是这种效果对于妊娠结局是否有明显提升目前仍有争议[229]. 除了辅酶Q10外, 维生素(如维生素C)[230]和烟酰胺单核苷酸[231]等抗氧化剂也被认为可以改善卵母细胞质量. 但是目前这些抗氧化剂缺乏临床试验的有力支持, 其对女性妊娠结局等是否存在显著改善需要进一步研究.

人类的生育能力和生殖寿命随着年龄的增长而急剧下降. 衰老是导致卵母质量下降的重要因素, 衰老对于卵母细胞的影响是多方面的, 包括ROS累积、DNA损伤、线粒体损伤、卵泡微环境改变等. 逆转衰老引起的卵子质量下降对于延长女性的生殖寿命至关重要. 研究发现亚精胺可以改善老龄小鼠卵母细胞质量, 该小分子通过增强线粒体自噬水平, 提高线粒体功能, 降低ROS积累和DNA损伤水平, 恢复老龄小鼠的生殖力[232]. 另外, 卵泡微环境决定卵母细胞发育潜能, 研究发现年轻的卵泡环境能够显著改善老龄小鼠卵母细胞的成熟率、胚胎发育潜力和活产率[233]. 衰老是一个系统性问题, 改善或逆转衰老导致的卵母细胞质量下降仍需要进一步的研究.

目前, 研究报道了许多改善卵母细胞质量的潜在干预策略, 例如抗氧化剂等药物治疗, 其安全性与可行性在动物试验中得到了一定验证, 但在人体组织和临床研究中仍然不足, 未来的工作应着重评估这些方法在人类应用中的安全性和可行性. 随着全球老龄化进程不断加剧, 女性的生育年龄因为各种因素逐渐推迟. 生育意愿下降和晚育趋势凸显, 带来了生殖衰老和生育力下降的挑战. 因此, 未来深入探究卵巢衰老和年龄因素导致的卵子质量下降的机制, 显得尤为重要. 此外, 线粒体在遗传、衰老和肥胖等因素导致的卵子质量下降中扮演着至关重要的角色, 未来以线粒体生物发生为切入点, 可能为寻找更多改善卵母细胞质量及ART的方法提供新思路.

干细胞治疗在生殖医学领域取得了突破性进展. 2025年1月, 美国食品药品监督管理局(FDA)批准了首个基于诱导多能干细胞(induced pluripotent stem cell, iPSC)的女性卵巢健康疗法(Fertilo)在美国进行三期临床试验. Fertilo是卵巢支持细胞技术, 该技术利用iPSC衍生的年轻卵巢支持细胞在体外与未成熟的卵母细胞共培养使卵母细胞自然成熟. 与传统的持续10-14天高剂量的激素刺激卵母细胞成熟的方法相比, 该方法治疗周期仅需要2~3天. 并且减少了过量激素治疗产生的副作用. 2024年12月在秘鲁, 世界上第一例使用Fertilo技术受孕的活体人类成功分娩. Fertilo技术展示了基于iPSC疗法在解决生殖医学领域系列关键问题方面的潜力, 该技术也成为临床治疗不孕不育的新希望.

6 总结与展望

1978年, 人类历史上的首例试管婴儿出生, 在过去的40多年里, 辅助生殖技术迅猛发展. 辅助生殖技术的广泛应用使我们能够在体外评估卵母细胞发育、受精和早期胚胎发育的情况, 并将IVF/ICSI失败的表型分类精细化, 这也推动了此方向的遗传学研究. 近10年来, 已有37个致病基因被鉴定, 充分说明遗传因素在人类卵子和早期胚胎发育异常中发挥重要作用, 这都为临床医生的精确遗传诊断提供了理论依据. 同时, 高分辨活细胞成像技术在生殖医学研究中的应用, 帮助我们更清晰地捕捉到人卵母细胞发育成熟、受精及早期胚胎发育过程中的关键分子事件, 如纺锤体及线粒体等的独特动态变化过程, 为深入认识人类卵子和早期胚胎发育过程提供便利. 此外, 有研究通过借助小鼠模型探索改善卵母细胞质量的策略, 并取得了一定的成效, 这些都为未来改善人类卵母细胞质量和提高女性生育力提供指导和借鉴.

尽管当前该领域的研究取得了一些进展, 但由于人类卵母细胞的独特性, 对人类卵母细胞发育的调控机制及不孕患者遗传病因的了解仍然有限. 在多组学交叉、多维度分析和数据资源开放的时代, 未来通过

整合基因组、转录组、蛋白质组和表观基因组等分析, 例如, 对不同发育阶段卵母细胞进行分析建立卵母细胞发育过程多组学图谱, 对不同年龄阶段女性的卵母细胞进行分析建立年龄相关的卵母细胞老化多组学图谱, 这些分析将有助于发现更多卵母细胞发育生理机制相关的关键因素. 同时, 通过对携带突变、肥胖、不孕等女性患者卵母细胞进行多组学分析, 将有助于揭示卵母细胞发育潜在的病理机制. 除此之外, 单细胞多组学交叉研究还可以克服人类卵母细胞样本数目少的限制, 并且交叉验证可以帮助科学家们发现新的生物标记物和治疗靶点. 此外, 应进一步挖掘卵母细胞发育缺陷相关的致病基因, 并涉及更广泛的突变类型(基因组结构变异、拷贝数变异)、遗传模式(双基因遗传和寡基因遗传)和突变区域(非编码区)等. 卵母细胞发育过程中除了受自身内部调控外, 还受到复杂而精密的外部调控, 包括颗粒细胞、卵泡液及卵巢微环境等调控. 越来越多的IVF/ICSI患者的参与也将提供更多宝贵的临床样本, 包括卵母细胞、颗粒细胞、卵泡液和原位组织等, 通过对这些样品进行多组学分析或高分辨率成像研究可以发掘人类卵母细胞发育过程中内部和外部的调控机制, 这将有益于系统地阐明卵母细胞发育过程中新的生理和病理机制. 目前, 临床中针对卵母细胞发育缺陷的治疗手段非常有限, 特别是明确携带已知致病基因突变的患者完全缺乏有效的干预策略. 近年来, 研究者开发了多种基因突变的不孕小鼠模型, 这将有利于针对不同的遗传因素进行个性化的干预策略探索. 但是, 基于物种的差异性导致部分突变基因的小鼠模型与患者表型存在差异, 这就限制了针对这些基因突变患者开展干预策略的探索. 近几年, 研究人员发现, 与小鼠相比, 树鼩与人的亲缘关系更近, 它是灵长类动物的近亲, 它们与人类在分子和生理方面都有高度的相似性[234,235]. 目前, 研究人员已完成树鼩基因组高精度测序组装及注释[234,236~238]. 因此, 树鼩在今后探索人类卵母细胞发育缺陷的干预策略等生殖领域具有广阔的应用前景. 另外对于灵长类特异基因, 可以考虑用猴模型进行功能验证和干预探索. 随着这些进展和努力, 预计将发现更多导致卵母细胞发育异常及女性不孕的遗传因素, 更加系统深入地认识人类卵母细胞发育的生理和病理机制, 为不孕患者最终的精确遗传诊断和个性化治疗奠定基础.

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Summary for “人类卵母细胞发育的生理与病理机制”

Physiological and pathological mechanisms of human oocyte development

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Normal oocyte development ensures successful fertilization and embryo development, playing a crucial role in human reproduction. This intricate process involves follicle growth and meiosis and is regulated by various factors, including genes, genetics, and environment. The development of oocytes begins during the female fetal stage. Oocytes undergo the stages of primordial germ cell and oogonium, and then enter meiosis. After birth, oocytes were arrested at the diplotene of prophase in meiosis I. Until puberty, under the stimulation of hormones, oocytes resume meiosis and develop into mature oocytes. Only mature oocytes can fuse with sperm for fertilization, and extrude the second polar body to complete meiosis. The maturation process of oocytes primarily consists of nuclear and cytoplasmic maturation. Nuclear maturation encompasses the arrest and resumption of meiosis, spindle assembly and migration, as well as polar body extrusion, etc. On the other hand, cytoplasmic maturation involves organelle reorganization, mRNA metabolism regulation, and protein homeostasis regulation, etc. With advancements in technologies such as high-resolution live cell imaging, assisted reproduction, and molecular biology, researchers have gained new insights into human oocyte development. For instance, they have discovered the microtubule organization center in human oocytes, the human-specific spindle bipolarization process, and the spindle stability mechanisms in human oocytes.

Any abnormality in the process of oocyte development can lead to oocyte maturation defect, which further affects fertilization and embryonic development, ultimately resulting in female infertility. Previous studies have demonstrated that genetic variation, obesity, and aging are important factors influencing oocyte development. In recent years, with the advancements in high-throughput sequencing technology and genetics, more pathogenic genes responsible for human oocyte developmental defects have been reported. Currently, there are 37 known pathogenic genes, and patients carrying mutations in these genes exhibit a variety of clinical phenotypes, including oocyte maturation arrest, fertilization failure, and early embryonic arrest. These studies fully demonstrate that genetic factors are a significant cause of female infertility, and further emphasize the necessity of clinical genetic diagnosis.

In clinical practice, the number of infertile patients suffering from repeated IVF/ICSI failures due to oocyte developmental defects is gradually increasing. Exploring effective intervention strategies is crucial for promoting reproductive health. Many studies have explored intervention strategies for oocyte developmental defects, including mitochondrial replacement therapy, antioxidant therapy, and small-molecule drug treatment. However, the feasibility and safety of these intervention strategies need to be further evaluated in human tissue and clinical studies. In addition, stem cell therapy has made a breakthrough in the field of reproductive medicine, exhibiting significant potential in improving women’s reproductive health. This technology has also brought new hope for the clinical treatment of infertility.

This review introduces the developmental process of human oocytes, physiological and pathological mechanisms, genetic diagnosis for infertility patients, and potential intervention strategies. Finally, we provided a perspective on exploring the physiological and pathological mechanisms of human oocyte development, as well as clinical intervention strategies in the future.

oocyte development, meiosis, mutation, female infertility, assisted reproduction

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