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人类卵母细胞和早期胚胎发育异常的遗传学研究进展

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摘要　卵母细胞和早期胚胎的正常发育是获得健康后代的关键, 遗传因素在卵母细胞成熟和早期胚胎发育过程中发挥重要作用。调控卵母细胞和早期胚胎发育的关键基因突变可导致卵母细胞成熟障碍、受精失败或早期胚胎发育停滞, 进而导致不孕或早期流产等。随着全基因组测序和全外显子组测序技术的广泛应用, 越来越多的致病基因突变被发现, 为不孕患者提供了可靠的诊疗靶点。该文系统回顾了导致人类卵母细胞成熟、受精和早期胚胎发育异常的致病基因, 以期促进其在辅助生殖遗传咨询中的应用。

关键词　卵母细胞; 受精; 早期胚胎; 基因突变

Genetic Research Progress on Abnormal Development of Human Oocytes and Early Embryos

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Abstract　The normal development of oocytes and early embryos is crucial for obtaining healthy offspring, and genetic factors play significant roles in the processes of oocyte maturation and early embryo development. Mutations in key genes that regulate the development of oocytes and early embryos can lead to disturbances in oocyte maturation, fertilization failure, or early embryo developmental arrest, ultimately resulting in infertility or early miscarriage. With the widespread application of whole-genome sequencing and whole-exome sequencing technologies, an increasing number of pathogenic gene mutations have been discovered, providing reliable diagnostic and

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therapeutic targets for patients with infertility. This article systematically reviews the pathogenic genes that lead to the abnormalities of human oocyte maturation, fertilization, and early embryonic development, aiming to promote its application in assisted reproduction.

Keywords oocyte; fertilization; early embryo; gene mutation

世界卫生组织2023年报告显示，全球有17.5%左右的成年人受不孕不育症影响[1]。女性因素至少占据了不孕症病因的35%, 遗传、内分泌、生理、解剖结构和免疫等因素的异常都可能影响女性的生育潜能[2]。越来越多的不孕患者正在寻求辅助生殖技术(assisted reproduction technology, ART)治疗。通过ART, 特别是控制性卵巢刺激(controlled ovarian stimulation, COH)、体外受精(*in vitro* fertilization, IVF)和卵胞质内单精子注射(intracytoplasmic sperm injection, ICSI)技术的应用，许多不孕女性有机会使用自己的卵子获得健康后代。然而，许多女性由于空卵泡综合征、卵母细胞成熟障碍、受精障碍、早期胚胎发育阻滞等, 导致IVF和/或ICSI反复失败[3]。据估计大约有一半的不孕症病例涉及遗传因素[4], 近年来随着全外显子组和全基因组测序技术的应用，科学家逐渐揭示出了导致人类卵母细胞和早期胚胎发育异常的不孕症基因[5], 本文将重点介绍这些致病基因的最新研究进展, 并讨论其他相关遗传病因。

1 卵母细胞成熟障碍的致病基因

女性生殖细胞相继经历两次减数分裂过程，从二倍体生殖细胞变成可被受精的单倍体生殖细胞。在青春期之前，卵母细胞停滞在第一次减数分裂的间期，此时期的卵母细胞含有一个明显的细胞核即生发泡(geminal vesicle, GV), 称为GV期卵母细胞。在青春期，黄体生成素(luteinizing hormone, LH)的释放可恢复第一次减数分裂，GV期卵母细胞经过染色质凝聚、生发泡破裂(geminal vesicle breakdown, GVBD)进入第I次减数分裂中期(metaphase I, MI)形成双极纺锤体，随后排出第一极体(first polar body, PB1)并迅速进入第II次减数分裂中期(metaphase II, MII), MII期卵母细胞直到与获能的精子受精后才能排出第二极体(second polar body, PB2)完成第二次减数分裂。至今已报道多种基因变异可通过影响纺锤体和微管组装、转录和翻译、细胞周期调控等重要事件引起卵母细胞成熟障碍或胚胎发育阻滞，进而导致IVF/ICSI的反复失败(图1和表1)。

1.1 微管相关基因

TUBB8(tubulin beta 8 class VIII)基因是第一个被报道的可导致卵母细胞成熟障碍的微管蛋白编码基因[6]。其编码的蛋白由444个氨基酸组成，属于灵长类特异的β-微管蛋白，主要在人类卵母细胞和早期胚胎的不同阶段特异性表达[6]。α/β微管蛋白是微管的结构单元，而微管在减数分裂纺锤体的形成中起关键作用[7]。*TUBB8*变异的遗传模式复杂，纯合、复合杂合或者杂合变异均可致病，现今已报道了130

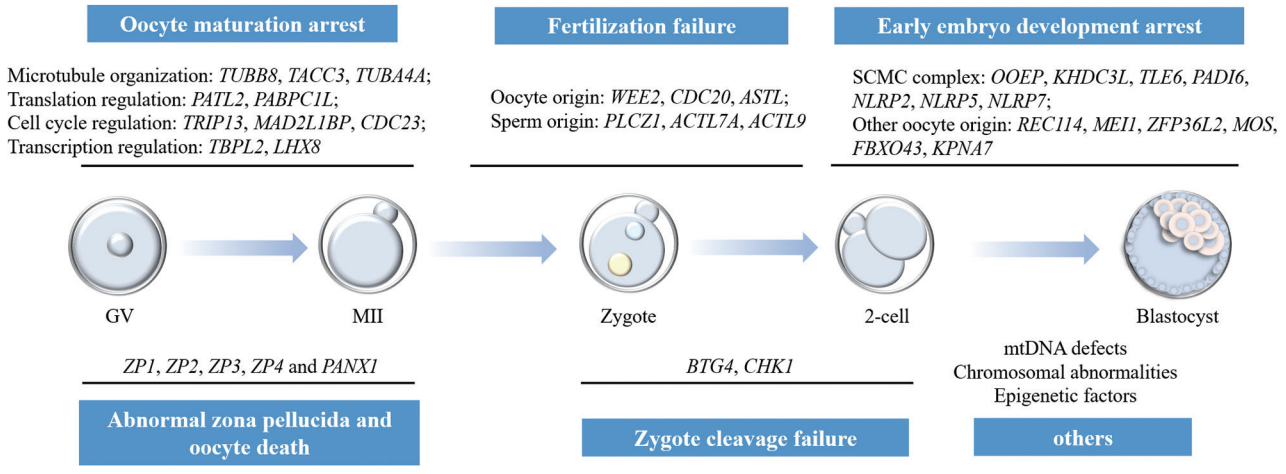

图1 人类卵母细胞和早期胚胎发育异常的遗传病因

Fig.1 The genetic etiology of human oocyte and early embryo development abnormalities

表1 影响人类卵母细胞和早期胚胎发育的致病基因

Table 1 Pathogenic genes involved in human oocyte and early embryo development

主要表型 Main phenotype	基因 Gene	遗传模式 Mode of inheritance	参考文献 References
Oocyte maturation arrest	*TUBB8*	AR/AD	[6,8,9-12]
	TACC3	AR	[13]
	TUBA4A	AD	[14-15]
	PATL2	AR	[16-19]
	PABPC1L	AR	[26]
	TRIP13	AR	[30-31]
	MAD2L1BP	AR	[34]
	CDC23	AR	[42]
	TBPL2	AR	[46]
	LHX8	AD	[51]
Oocyte death	*PANX1*	AR/AD	[63]
Empty follicle syndrome	*ZP1*	AR	[55,57,59,61]
	ZP2	AR/AD	[61]
	ZP3	AD	[58-59,61]
	ZP4	AD	[62]
Fertilization failure	*WEE2*	AR	[66-67]
	CDC20	AR	[69-70]
	ASTL	AR	[72]
	PLCZ1	AR	[78]
	ACTL7A	AR	[76-78]
	ACTL9	AR	[79]
Zygote cleavage failure	*BTG4*	AR	[81]
	CHK1	AD	[82]
Early embryonic arrest	*OOEP*	AR	[83]
	KHDC3L	AR	[83,85]
	TLE6	AR	[83]
	PADI6	AR	[83-84]
	NLRP2	AR	[83]
	NLRP5	AR	[83,86]
	NLRP7	AR/AD	[86]
	REC114	AR	[87]
	MEI1	AR	[88]
	ZFP36L2	AR	[89]
	MOS	AR	[91]
	FBXO43	AR	[92]
	KPNA7	AR	[93]

AD: 常染色体显性遗传; AR: 常染色体隐性遗传。

AD: autosomal dominant; AR: autosomal recessive.

多种*TUBB8*基因变异, 其变异改变了α/β-微管蛋白异源二聚体的组装和卵母细胞减数分裂纺锤体的组装[6,8-9]。TUBB8蛋白的不同突变可导致卵母细胞和胚胎表型的多样性, 其主要表现为MI期卵母细胞成熟阻滞, 其次还表现为受精障碍、多原核、受精卵分裂失败、早期胚胎发育阻滞、植入失败和胚胎非整倍体等[8,10-12]。TUBB8蛋白的不同变异可以导致多种蛋白结构异常, 并可能以不同方式破坏TUBB8与其他微管结构蛋白的相互作用[8], 变异的复杂性可能是其表型多样性的主要原因。尽管表型多样, *TUBB8*是卵母细胞成熟障碍最常见的致病基因, 大约30%的卵母细胞成熟障碍患者中可检测到*TUBB8*

致病变异[6]。

调控卵母细胞微管结构和纺锤体组装基因的致病变异是卵母细胞成熟障碍的重要遗传病因。除*TUBB8*的变异外, 国内团队最新研究发现人类卵母细胞的微管组织中心(microtubule organizing center, MTOC)是人卵母细胞纺锤体组装的关键驱动因素, 而编码MTOC关键组分的*TACC3*(transforming acidic coiled-coil-containing protein 3)双等位基因变异已被证明会影响微管的成核和减数分裂纺锤体的组装, 从而导致卵母细胞成熟停滞[13]。此外, 最近两个团队相继报道编码α-微管蛋白的*TUBA4A*(tubulin alpha-4A chain)基因, 其杂合变异导致微管稳定性降低, 引发卵母细胞成熟障碍、受精卵分裂障碍和早期胚胎发育停滞[14-15]。

1.2 翻译调控基因

PATL2(protein PAT1 homolog 2)基因编码高度保守的卵母细胞特异性信使核糖核蛋白体(messenger ribonucleoprotein, mRNP)翻译抑制因子, 可调控众多参与卵母细胞成熟和早期胚胎发育基因的表达[16]。*PATL2*基因特异性地在未成熟卵母细胞中表达, 随着卵母细胞的成熟, *PATL2*的表达量逐渐减少[17]。现已有多篇文章报道*PATL2*双等位基因突变可导致女性不孕, 主要表现为卵母细胞成熟阻滞(GV或MI阻滞), 可伴有受精失败和早期胚胎发育停滞[16,18-19]。值得一提的是, *PATL2*基因的突变仅影响女性生育力, 带有其纯合截短变异的男性生育力正常[19]。

PABPC1L[poly(A) binding protein cytoplasmic 1 like]基因编码一种特殊的PABP[poly(A)-binding protein], PABP在卵母细胞成熟时的mRNA poly(A)修饰和翻译激活过程中起关键作用[20]。在爪蟾卵母细胞成熟期间, PABPC1L结合poly(A)以增强mRNA的稳定性[21], 并促进翻译抑制因子Maskin-eIF4E的解离以及eIF4G-eIF4E的相互作用以启动翻译[22]。Pabpc1l在小鼠GV、MI、MII期卵母细胞以及1-细胞和2-细胞胚胎中表达, 在合子基因组激活后被体细胞PABP(Pabpc1)取代[23]。*Pabpc1l*敲除的雌性小鼠因母源mRNA(*Ccnb1*、*c-Mos*和*Dazl*等)翻译激活受损而无法产生成熟的卵母细胞[24], 伴有卵丘扩张和排卵缺陷[24-25]。最近GUO等[26]报道*PABPC1L*双等位基因变异可导致以卵母细胞成熟障碍为主要特征的女性不孕症, 这与在爪蟾和小鼠中的表型相似。

1.3 细胞周期调控基因

TRIP13(thyroid hormone receptor interactor 13)基因编码了一个由432个氨基酸组成的蛋白质, 即AAA-ATP酶, 其是纺锤体组装检查点的关键组成部分[27]。*TRIP13*基因在有丝分裂和减数分裂中均发挥关键作用, 其在全身多种组织中均有表达[27], TRIP13蛋白维持有丝分裂纺锤体组装检查点(spindle assembly checkpoint, SAC)的沉默并可参与减数分裂重组过程[28]。不同类型的*TRIP13*双等位基因变异会通过对有丝分裂和减数分裂产生不同影响而导致不同的疾病, 包括威尔姆斯瘤(Wilms tumor)和女性不孕症[29-31]。具体而言, 其纯合无义变异或影响剪接过程的致病变异导致TRIP13蛋白功能的完全丧失进而影响有丝分裂过程, 而错义变异则引起轻微的TRIP13蛋白表达水平减少并影响卵母细胞的减数分裂过程, *TRIP13*错义变异导致的女性不孕以卵母细胞减数分裂阻滞和受精卵分裂异常为主要特征[30-31]。值得注意的是, 将*TRIP13*的cRNA注射到来自该不孕患者的卵子中能够挽救其卵母细胞成熟障碍的表型, 这对未来的临床治疗具有重要意义[31]。

MAD2L1BP(MAD2L1-binding protein)基因编码MAD2(mitosis arrest deficient 2, 又名MAD2L1)结合蛋白。MAD2蛋白是有丝分裂检查点复合物(mitotic checkpoint complex, MCC)的关键组成部分, MAD2L1BP可以构象特异性地结合MAD2并招募TRIP13以促进MCC的解体和细胞周期的进展[32]。先前曾报道*Mad2l1bp*全身敲除小鼠在出生后不久死亡并且其肝糖原减少[33]。最近HUANG等[34]发现, MAD2L1BP为人类卵母细胞成熟所需, MAD2L1BP的纯合截短变体影响了其与MAD2的结合, 导致患者因卵母细胞成熟障碍而不孕。

CDC23(cell division cycle protein 23 homolog)基因编码后期促进复合体/细胞周期体(anaphase-promoting complex/cyclosome, APC/C)的一种核心亚基, 又称APC8。APC/C是一种高度保守的E3泛素连接酶, 在细胞周期的中后期转换中起到重要作用[35]。APC/C激活后可以驱动Securin和Cyclin B1的泛素化和降解, 进而促进分离酶对染色体分离的作用[36]。目前已发现15~17个APC/C核心亚基, 其组成具有种间差异[37]。小鼠APC2亚基的缺失可导致雌鼠不孕[38], APC3亚基的缺失则会因Cyclin B1的异常累积导致有丝分裂中期阻滞[39], 而在人体细胞

中APC6或APC15的缺失会导致有丝分裂后期明显延迟[40]。此外, 有报道称APC8的降解会使APC/C失活并导致哺乳动物细胞中Cyclin B1和Securin的异常积累[41], 而小鼠卵母细胞Cdc23的降调会导致卵母细胞阻滞在MI期[31]。与之相似, *CDC23*的纯合错义变异可导致以卵母细胞成熟障碍为特征的女性不孕, CDC23变异蛋白表达水平降低可能通过异常的Cyclin B1和Securin累积而影响染色体的分离[42]。

1.4 生殖细胞特异性转录因子

TBPL2(TATA-box binding protein like 2)基因编码脊椎动物卵母细胞特异表达的转录因子[43]。TBPL2能够结合到TATA盒, 与TFIIA(transcription initiation factor IIA)和TFIIB(transcription initiation factor IIB)相互作用, 介导RNA聚合酶II的转录起始[44-45]。TBPL2在哺乳动物雌性生殖细胞的发育中发挥着重要作用, TBPL2可结合到卵母细胞中活跃基因的启动子上并调控它们的表达, 缺乏*Tbpl2*的雌性小鼠因卵泡发生缺陷、卵母细胞特异性表达基因下调以及成熟卵子缺失而不孕[43]。*TBPL2*纯合突变的不孕患者主要表现为卵母细胞成熟阻滞和退变, 还伴有受精失败与早期胚胎发育停滞表型[46]。

LHX8(LIM/homeobox protein Lhx8)基因编码一种女性生殖细胞特异性转录因子, 该转录因子主要在哺乳动物的卵巢中表达[47]。*LHX8*调控早期卵母细胞发生过程中多种重要基因的转录。全身性敲除*Lhx8*会破坏卵母细胞特异性基因的表达, 导致新生小鼠卵母细胞丢失而不孕[47-48]。在原始卵泡中条件性敲除*Lhx8*则会因初级卵泡死亡和次级卵泡库储备减少导致雌鼠不孕[49]。另一项研究发现, *Lhx8*的缺失会导致小鼠卵母细胞中DNA损伤大幅增加, 导致卵巢储备的过早耗竭[50]。*LHX8*同样在人类生殖发挥关键作用, *LHX8*杂合变异在患有卵母细胞成熟障碍的不孕女性中明显增多, 而在正常对照人群中没有检测到其变异, 这些变异会导致LHX8蛋白的截短和核定位的改变并损伤其功能[51]。

2 透明带异常和卵子死亡的致病基因

2.1 透明带异常

透明带是一种对卵母细胞成熟、排卵、诱导精子顶体反应、防止多精受精以及植入前胚胎发育至关重要的细胞外基质[52]。小鼠透明带由3种透明带蛋白(zona pellucida, ZP)——ZP1、ZP2和ZP3组成, 而人类透明带由4种透明带蛋白——ZP1、ZP2、ZP3和ZP4聚合而成。透明带首次出现在卵母细胞开始生长时, 随着卵母细胞的增大而继续增厚, 不同哺乳动物成熟卵母细胞的透明带厚度在2~20 μm, 人类卵子的透明带(18 μm)比小鼠卵子的透明带(6 μm)厚约3倍[53]。透明带的厚度和形态与卵母细胞的发育潜能以及妊娠结局相关[54]。

*Zp1*纯合敲除的雌鼠表现为ZP变薄和生育力降低; *Zp2*和*Zp3*纯合敲除的雌鼠透明带缺失并完全不孕, 表现出卵巢较小、窦卵泡和排卵数量减少、卵丘细胞减少并排列紊乱等[55-56]。这些结果提示卵子周围透明带的存在对其发育至关重要, 并且ZP1和ZP3对透明带纤维的组装而言缺一不可, 缺少ZP1则使得透明带纤维之间交联异常并使分裂期的胚胎变得极为脆弱, 导致胚胎在植入子宫前丢失[55]。2014年科研人员首次在反复IVF/ICSI助孕失败的患者中鉴定到*ZP1*基因的纯合变异[57], 2017年CHEN等[58]在3个空卵泡综合征大家系中鉴定到*ZP3*基因的杂合变异, 随后越来越多的*ZP1*、*ZP2*和*ZP3*基因的致病性变异被报道, 其中*ZP1*基因的致病变异可达到51%, 这些变异导致透明带变薄或缺失、空卵泡综合症、卵母细胞退变或受精失败, 进而导致女性不孕[59-61]。最近亦有文献报道, *ZP4*基因的杂合错义变异导致患者卵子透明带异常[62], 这再次证实了透明带蛋白在卵母细胞成熟和胚胎发育中的重要作用(图1和表1)。

2.2 卵子死亡

PANX1是Pannexin-1蛋白家族的3个成员之一, 作为通道蛋白在细胞间通信过程中起重要作用[87]。ZHANG等[63]于2019年发现*PANX1*基因杂合致病变异导致了一种新的孟德尔遗传病表型, 称为“卵母细胞死亡”。携带PANXI变异的患者卵母细胞在受精前或受精后表现出细胞质的萎缩和变黑[63]。在HeLa细胞和非洲爪蟾卵母细胞中的功能研究表明, 突变改变了PANX1蛋白的糖基化模式, 造成PANX1通道活性异常[63]。这些发现提示蛋白糖基化水平改变和通道蛋白活性异常是导致女性不孕症的潜在病因(图1和表1)。

3 受精失败的致病基因

卵母细胞与精子受精后形成受精卵, 涉及从减数分裂到有丝分裂的转变, 其中包括一系列受到精

密调控的复杂过程, 如精子获能、精子和卵子识别、顶体反应、精子穿过透明带、精卵质膜融合、卵子激活、原核形成等[64]。卵母细胞到合子的过渡中发生一系列重要事件, 包括蛋白质和RNA的降解、蛋白质的合成和细胞器的重塑等[65]。以上过程中发生的任何异常都可能导致受精失败(图1和表1)。

3.1 卵母细胞特异表达的基因

WEE2(Wee1-like protein kinase 2)基因编码WEE激酶家族中的卵母细胞特异性激酶WEE2, 又名Wee1B[66]。WEE2是一种酪氨酸激酶, 在卵母细胞GV期和MII期起着关键的调控作用。在GV期卵母细胞中, 它通过抑制成熟促进因子催化亚基——细胞周期蛋白依赖性激酶1(cyclin-dependent kinase 1, CDK1)的活性来维持减数分裂的静止状态。WEE2调控成熟促进因子的能力对于MII期卵母细胞同样重要, 人类和小鼠卵母细胞中WEE2表达减少会使成熟促进因子活性升高, 导致MII阶段的退出异常和原核形成失败, 即受精失败[66]。近年来的研究表明, *WEE2*基因的纯合或复合杂合变异会使患者因受精失败而不孕[66-67]。这些患者的卵母细胞形态正常, 通过ICSI受精能使其排出第二极体, 但不能形成双原核受精卵。功能研究表明, *WEE2*的致病变异明显降低了CDK1的抑制性磷酸化水平, 导致原核形成障碍而受精失败[66-67]。

CDC20(cell division cycle 20)基因在多种组织中均有表达, 其编码的CDC20蛋白是APC/C的共激活因子, 它们共同促进减数分裂和有丝分裂中后期转换。CDC20分子可以结合到APC/C上, 形成APC/CCDC20复合物, 促使Securin和Cyclin B的降解, 抑制CDK1和CDK2的活性, 进而促进姐妹染色体单体的分离[68]。有研究表明, *CDC20*基因的纯合致病变异可导致人卵母细胞成熟障碍、受精失败和早期胚胎发育阻滞[69-70]。另外, *CDC20*纯合或复合杂合突变也可导致非梗阻性无精子症[71]。

除*WEE2*、*CDC20*等基因造成的原核形成障碍外, 临床上还可见其他受精障碍问题, 如多原核的形成。关于受精卵多原核形成的具体机制目前仍不完全清楚, 但多精受精是其重要原因之一。有研究在多原核的不孕姐妹中检测到*ASTL*基因的纯合剪接变异, 该基因编码的皮质颗粒蛋白酶Ovastacin可在透明带反应过程中负责剪切ZP2蛋白以防止多精受精[72], 这与*Astl*敲除雌鼠的表型相似[73]。

3.2 卵母细胞激活因子调控基因

除卵母细胞特异表达的因子异常造成的受精失败外, 目前已鉴定到多个扰乱卵子激活和精子获能等过程的致病基因。*PLCZ1*(sperm specific phospholipase C zeta 1)编码一种精子携带的卵母细胞激活因子, *PLCZ1*基因的表达水平降低或致病变异已被证明会导致精子功能障碍和受精失败[74-75]。ACTL7A(actin-like 7A)和ACTL9(actin-like 9)都属于肌动蛋白相关蛋白家族。ACTL7A在精子的细胞核和顶体下层板内动态分布, 将顶体固定在核膜上[76]。ACTL9在前顶体小泡融合和精子核周层形成中也起着关键作用。近年来有多个研究表明, *ACTL7A*或*ACTL9*基因变异的男性不育患者的精子中PLCZ1表达水平降低并且定位异常, 导致完全受精失败[77-79]。此外, 精子DNA的碎片化也与受精率异常和自然妊娠率降低有关[80]。以上结果提示, 对病因不明的受精过程异常病例, 除考虑卵子源性致病基因外, 还需要考虑男方精子问题, 通过筛查上述可能影响精子获能和卵子激活等过程的基因, 进一步提高不孕夫妇遗传病因的解释率。

4 受精卵分裂障碍和早期胚胎发育停滞的致病基因

4.1 受精卵分裂障碍致病基因

卵子和精子形成受精卵后, 其雌原核和雄原核将亲本遗传物质汇合并随之发生第一次有丝分裂, 即受精卵分裂过程, 随后开始胚胎发育。临床上有些夫妇可以取到形态正常的卵母细胞并成功受精, 但受精卵无法正常分裂。现今已报道了2个基因的致病变异可特异性地导致受精卵分裂障碍。BTG4(B cell translocation gene 4)作为CCR4-NOT转录复合物亚单位7(CCR4-NOT transcription complex subunit 7, CNOT7)和真核翻译起始因子4E(eukaryotic translation initiation factor 4E, EIF4E)之间的连接桥梁, 三者共同促进母源mRNA的降解。2020年首次报道*BTG4*基因的纯合变异通过破坏BTG4突变蛋白与CNOT7之间的相互作用而影响母源mRNA的降解, 导致受精卵分裂障碍[81]。随后, 2021年CHEN等[82]报道编码细胞周期检查点激酶1的*CHK1*(serine/threonine-protein kinase Chk1)基因, 其杂合变异使得CHK1激酶活性增高, 通过CDC25C-CDK1通路引起受精卵G_2/M期转换阻滞, 携带*CHK1*变异的患者表现为伴有原核核膜破裂障

碍的受精卵阻滞(图1和表1)。

4.2 早期胚胎发育停滞致病基因

皮质下母源复合体(subcortical maternal complex, SCMC)是一种多蛋白复合物，在卵母细胞和早期胚胎中特异表达。SCMC调控母源合子转换过程中的多个重要事件，如细胞骨架重塑、减数分裂纺锤体定位、细胞器重排、受精卵对称分裂等；此外，研究表明SCMC在卵和胚胎表观重编程以及mRMA翻译过程中也发挥重要作用[83]。目前研究提示人卵母细胞中的SCMC主要由8种蛋白质组成：OOEP(也称FLOPED)、KHDC3L(也称FILIA)、TLE6、PADI6、NLRP2、NLRP5(也称MATER)、NLRP7和ZBED3[83]。除ZBED3未曾被报道影响人卵或胚胎发育的致病变异外，其他7种SCMC组分的双等位基因变异均可导致植入前早期胚胎发育延迟或阻滞[83]。值得注意的是，部分SCMC成分如PADI6[84]、KDHC3L[85] 、NLRP5[86]和NLRP7[86]的变异，还可造成人类葡萄胎的表型，其表型差异的具体机制有待深入探究(图1和表1)。

除了上述SCMC母源基因外，其他影响减数分裂和母源mRNA降解等过程的母源基因变异也可能导致早期胚胎阻滞。*REC114*(meiotic recombination protein REC114)是参与减数分裂DNA双链断裂的重要基因，对确保正确的DNA重组和染色体配对起着关键作用。*REC114*变异导致的功能障碍，可通过异常的DNA双链断裂引发受精和早期胚胎发育异常[87]。*MEI1*(meiosis inhibitor protein 1)是减数分裂染色体联会的必需基因，同样在减数分裂DNA双链断裂形成中起关键作用，其双等位基因变异与胚胎阻滞和着床失败有关[88]。*ZFP36L2*(zinc finger protein 36-like 2)编码一种RNA结合蛋白，可作为CNOT6L(CCR4-NOT transcription complex subunit 6-like)的接头蛋白促进母源mRNA降解，其双等位变异可因母源mRNA降解缺陷而导致早期胚胎发育阻滞[89]。

MOS(Moloney sarcoma oncogene)编码一种ERK通路的上游激酶，在脊椎动物卵母细胞中显著高表达，作为细胞静止因子维持卵母细胞MII期停滞。*MOS*基因的双等位变异导致卵母细胞形态异常，产生大的极体并导致不孕[90]。此外，MOS蛋白的突变还可降低其下游ERK1/2的磷酸化，影响卵母细胞皮质F-actin组装并损伤线粒体功能，导致植入前胚胎发育阻滞和碎片化[91]。*FBXO43*(F-box protein 43)同样在细胞静止因子介导的卵母细胞减数分裂停滞以及早期胚胎发育中发挥重要作用，其纯合的功能丧失变异使患者表现为早期胚胎发育阻滞[92]。

最近，研究人员在植入前胚胎阻滞的患者中发现了*KPNA7*(karyopherin subunit alpha 7)基因的变异，这些突变导致KPNA7蛋白质水平降低，影响KPNA7与其底物RSL1D1(ribosome L1 domain protein 1)的结合能力，并影响KPNA7的核转运活性[93]。这提示细胞核转运过程在胚胎发育中同样具有重要作用，将来可能有更多调控该过程的基因变异被报道。

5 其他影响卵母细胞和胚胎发育的遗传因素

除了上述已知的单基因变异致病因素外，还有其他遗传因素在卵泡发生、卵子质量和胚胎发育中发挥作用，这些因素包括线粒体DNA(mitochondrial DNA, mtDNA)拷贝数异常和突变、各种染色体异常(非整倍体、染色体平衡或非平衡异位、嵌合体等)以及多基因的致病性变异等(图1)。

线粒体是一种半自主的细胞器，对细胞功能起着关键作用，包括产生ATP、调控凋亡、维持钙平衡和生成活性氧自由基。线粒体基因组缺乏核小体，因此对基因毒性损害，尤其是对活性氧高度敏感，据估计mtDNA的突变速率约为核基因组的20倍[94]。有研究表明，mtDNA缺失的积累可导致线粒体功能障碍和ATP产生受损，从而干扰卵子的受精和随后的胚胎发育[95-96]。ZHAO等[97]最近报道了关于mtDNA变异与早期胚胎发育缺陷之间的相关性分析，发现患有早期胚胎发育缺陷的不孕女性携带更多的mtDNA变异，特别是在D环区域、*ATP6*基因和*CYTB*基因中。mtDNA的缺陷可能决定了线粒体功能的改变，影响细胞氧化磷酸化和ATP供应，导致卵母细胞成熟、受精或胚胎发育的异常。

染色体异常在植入前胚胎的发育阻滞中起着关键作用，近乎70%的发育停滞胚胎显示出染色体错误，包括多倍体、单倍体、嵌合体或混乱的染色体组成[98-99]。通过植入前遗传学检测和二代测序技术评估染色体异常与胚胎发育能力的关系，结果提示片段重复和染色体单体导致显著的胚胎发育阻滞，而三体和片段缺失对胚胎发育阻滞没有明显影响[100]。最新研究显示，减数分裂和有丝分裂非整倍

体的发生率与囊胚形态分级密切相关, 停止发育的胚胎中非整倍体的发生率可高达94%, 其中以影响多个染色体的有丝分裂非整倍体为主[101]。

6 结语与展望

目前已经报道了36个核基因变异, 其可导致卵子成熟障碍、受精失败和早期胚胎发育停滞。这些基因的变异遵循孟德尔遗传模式, 包括显性遗传和隐性遗传以及新发突变。在本综述中, 我们详细介绍了这些致病基因在人类卵母细胞和早期胚胎发育过程中的具体作用, 其中一些基因的变异仅对人类早期生殖过程中的特定过程产生影响, 而有些基因(如*TUBB8*)的变异可以导致一系列表型。这些变异将为个体化的遗传咨询和患者潜在治疗奠定基础, 也将成为生殖医学中精准治疗的目标。

除核基因组的单基因突变外, 线粒体DNA缺陷、染色体异常、表观遗传变化以及多基因变异等因素都与女性不孕相关, 全面开发新的筛选策略鉴定这些因素并了解它们的功能有助于我们更广泛地理解早期胚胎发育异常的遗传风险, 并有助于不孕夫妇选择可能的替代治疗方案节约治疗成本。随着全基因组测序和高通量分析工具的深入开发, 未来将有更多的遗传病因会被生殖遗传领域的研究人员挖掘出来, 以扩大我们对基因组变异和生殖健康之间相互作用的理解。

深入了解这些遗传因素致病的分子机制可以为精准治疗提供手段。通过解析致病突变对自身编码蛋白、相互作用蛋白以及下游通路的影响, 可以选择或开发针对靶蛋白的小分子抑制剂或激活剂。例如, *CHK1*基因功能获得突变使其编码的CHK1蛋白激酶活性升高引起下游蛋白的抑制性磷酸化增强而致病, 选用靶向CHK1蛋白的抑制剂可以成功使患者和小鼠阻滞的受精卵发育成优质囊胚[82]。针对功能失活突变, 通过引入外源蛋白质或合成cRNA, 可以纠正卵子或早期胚胎的基因缺陷, 研究人员通过向卵母细胞中注射其野生型cRNA拯救了携带*WEE2*[66]、*CDC20*[70]和*TRIP13*[31] 等失活突变女性的不孕表型。自体线粒体显微注射和生殖细胞核转移也可作为改善不孕女性卵子质量和胚胎发育的潜在方法, 然而仍需要进一步验证其有效性和安全性。此外, 患者还可以考虑使用捐赠的卵子或胚胎。

我们对与女性不孕症相关的遗传病因, 特别是与减数分裂缺陷、卵母细胞和胚胎非整倍体以及卵母细胞成熟、受精和早期胚胎发育异常相关的遗传因素的了解仍然有限。揭示女性不孕症的遗传病因对于提高IVF/ICSI成功率以及为患者提供更有针对性和更加有效的治疗方案至关重要, 未来需要更多相关领域的从业人员一起携手努力, 共同深耕, 圆千万不孕夫妇的助孕梦。

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