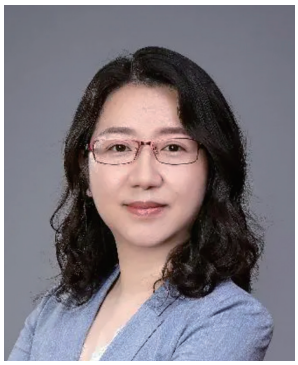

霍然博士，现为南京医科大学教授、博士生导师，生殖医学与子代健康全国重点实验室PI、副主任，中国生理学会生殖学科专业委员会理事、中国动物学会生殖生物学分会理事、中国性学会女性生殖医学分会委员、江苏省研究型医院学会生殖医学专业委员会副主任委员、江苏省“青蓝工程”中青年学术带头人、江苏省“六大高峰人次”及“333高层次人才”培养对象。实验室长期从事生殖医学研究，近年来的研究兴趣主要聚焦在母源效应因子在卵母细胞成熟、卵–胚转换及早期胚胎发育过程中的作用和机制，及其与临床女性生殖障碍的相关性研究。先后主持国家973计划课题1项，国家自然科学基金项目6项，作为课题骨干参与国家重点研发计划重点专项和973项目4项；已在*Dev Cell*、*Cell Death Differ*、*Aging Cell*、*EMBO Rep*、*Cell Mol Life Sci*、*Development*、*Hum Reprod*、*Bio Reprod*等本领域重要期刊上发表SCI论文70余篇；参编《生殖病理学》等专著；研究成果先后获全国妇幼健康自然科学奖一等奖、全国妇幼健康科学成果一等奖、江苏省科学技术奖二等奖等省、部级科研奖励8项；获授权发明专利4项。

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母源因子在哺乳动物卵母细胞向胚胎转变中的作用

钟欧[1] 孙小燕[1,2] 霍然[1]*

([1]南京医科大学生殖医学与子代健康全国重点实验室, 南京 211166; [2]苏州市立医院, 苏州 215008)

摘要 卵母细胞在形成过程中合成和储存了大量由母源效应基因(maternal effect genes, MEGs)编码的母源因子(maternal factors), 它们在卵母细胞和早期胚胎发育过程的多个环节(包括母源mRNAs的合成与积累、细胞器的有序排列、表观遗传重编程、受精后卵子的激活、合子基因组激活的启动以及母源转录物的清除等)中起到关键作用。该综述按照卵母细胞成熟至受精后早期胚胎发育的时间线，详细阐述了母源因子对哺乳动物卵母细胞和早期胚胎发育关键进程的影响，同时描述了母源因子的表达调控和定位。研究发现，MEGs的变异与一系列不良生殖结局有关。在人类中，这些变异可能导致不孕症、胎儿结构性发育缺陷和出生子代患有多位点印记障碍的风险增加。深入研究母源因子及其调控机制有助于更好地理解卵母细胞和早期胚胎发育的生理过程，提高不孕症诊断和治疗的精确性，并为预防相关疾病提供新的策略。

关键词 母源效应基因; 母源因子; 卵母细胞; 胚胎; 母体到合子的转变

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*通信作者。Tel: 025-86869394, E-mail: huoran@njmu.edu.cn

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*Corresponding author. Tel: +86-25-86869394, E-mail: huoran@njmu.edu.cn

The Role of Maternal Factors during the Oocyte-to-Embryo Transition in Mammals

ZHONG Ou[1], SUN Xiaoyan[1,2], HUO Ran[1]*

([1]*State Key Laboratory of Reproductive Medicine and Offspring Health, Nanjing Medical University, Nanjing 211166, China*; [2]*Suzhou Municipal Hospital, Suzhou 215008, China*)

Abstract During oocyte formation, a substantial number of maternal factors, encoded by MEGs (maternal effect genes), are synthesized and stored. These factors play crucial roles in various aspects of oocyte and early embryo development, including the synthesis and accumulation of maternal mRNAs, orderly arrangement of organelles, epigenetic reprogramming, egg activation after fertilization, initiation of zygotic genome activation, and clearance of maternal transcripts. This review presents a comprehensive analysis of the impact of maternal factors on key processes in mammalian oocyte and embryo development, while also discusses the regulation of expression and localization of these factors. Researches have demonstrated that variations in MEGs are associated with a range of adverse reproductive outcomes. In humans, these variants can result in infertility, and an increased risk of fetal structural defects and offspring with multilocus imprinting disorders. By in-depth studies of maternal factors and their regulatory mechanisms, this review can improve the understanding of the physiological processes of oocyte and early embryonic development. This knowledge has the potential to improve the accuracy of infertility diagnosis and treatment, as well as provides new strategies for the prevention of related diseases.

Keywords maternal effect genes; maternal factors; oocyte; embryo; maternal-zygotic transition

哺乳动物受精卵最初处于全基因组转录沉默状态, 此时精子成分对胚胎发育没有作用[1-2]。胚胎早期发育事件主要由卵母细胞中预先存在的母源RNA和蛋白质所调控。受精后, 胚胎经历了母体到合子的转变(maternal-zygotic transition, MZT), 发育由母体基因组控制转变成由合子基因组控制。MZT涉及两个重要的过程: 合子基因组激活(zygotic genome activation, ZGA)和母体转录物(包括mRNA和蛋白质)的清除, 两者都是胚胎发育所必需的。从母体到胚胎发育的转变是一个渐进的过程。在小鼠胚胎中, 1细胞晚期阶段可以检测到少量的基因转录, 这标志着初级基因组激活(minor ZGA)的开始; 在2细胞晚期阶段, 数千个其他基因被大规模激活, 称为主要基因组激活(major ZGA); 随后在8细胞、桑椹胚和囊胚阶段胚胎还会经历几轮额外的激活, 每个阶段都伴随着母体转录物的降解[1]。在人类中, minor ZGA和major ZGA分别发生在2细胞和4~8细胞阶段[1]。

母源效应基因(maternal effect genes, MEGs)最早在果蝇中被发现[3]。直到2000年, 研究者们才在小鼠体内发现第一个哺乳动物MEG[4]。此后, 越来越多的此类基因被陆续报道。通过使用传统的基因敲除手段(traditional knockout, TKO)或卵母细胞特异性条件敲除技术(oocyte specific conditional knockout, oCKO), 人们已在动物模型中鉴定出八十多种哺乳动物发育所需的母源因子(表1)。这些母源因子参与了卵母细胞成熟和早期胚胎发育的一系列关键事件, 包括细胞器的排列[5]、细胞骨架的组装[6]、卵母细胞和早期胚胎的表观遗传修饰和印记维持[7]、染色质重塑[8]、合子基因组激活[9]、母源转录物降解[10]以及细胞命运决定[11]等(图1)。此外, 有证据表明母源因子还可以影响胚胎植入后的发育, 此过程中母源因子异常可导致胎儿出现结构性缺陷[12]。

1 母源因子对卵母细胞成熟的影响

1.1 母源因子与卵母细胞胞质成熟

卵母细胞的细胞质成熟是决定卵母细胞质量的

表1 哺乳动物母源因子

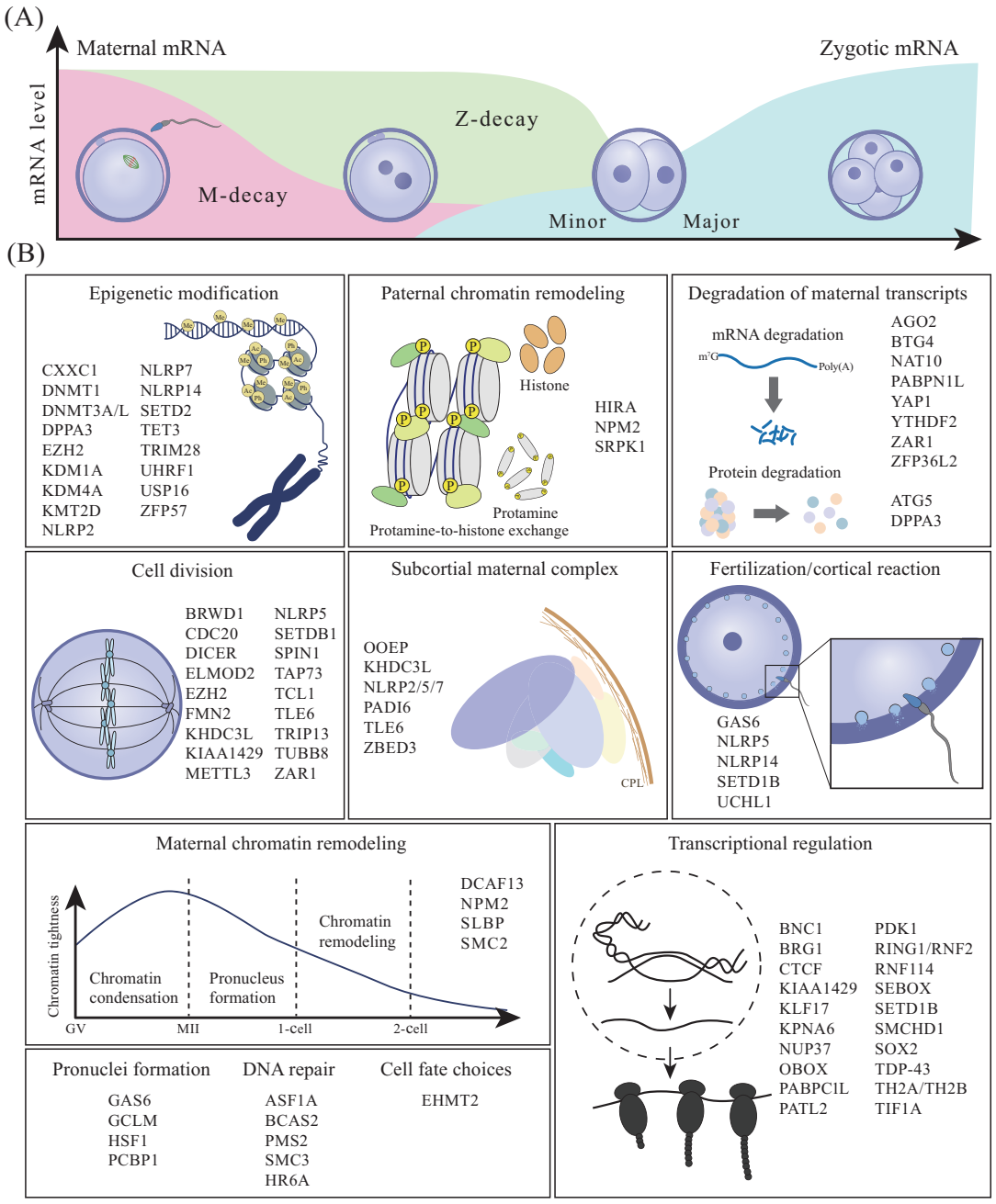
Table 1 Mammalian maternal factors

基因简写 Gene symbol	基因全称 Full name of gene	功能 Function	参考文献 References
Ago2	Argonaute RISC catalytic component 2	Degradation of maternal mRNA	[10]
Asf1a	Anti-silencing function 1A histone chaperone	DNA repair	[13]
Atg5	Autophagy related 5	Degradation of maternal protein	[14]
Bcas2	BCAS2 pre-mRNA processing factor	DNA repair	[15]
Bnc1	Basonuclin zinc finger protein 1	Transcriptional regulation	[16]
Brg1 (*Smarca4*)	BRM/SWI2-related gene 1	Transcriptional regulation	[17]
Brwd1	Bromodomain and WD repeat domain containing 1	Cell division	[18]
Btg4	BTG anti-proliferation factor 4	Degradation of maternal mRNA	[19]
Cdc20	Cell division cycle 20	Cell division	[20]
Ctcf	CCCTC-binding factor	Transcriptional regulation	[21]
Cxxc1	CXXC finger protein 1	Epigenetic modification	[7]
Dcaf13	DDB1 and CUL4 associated factor 13	Maternal chromatin remodeling	[8]
Dcaf2	DDB1-Cullin-4-associated factor-2	Maintenance of genomic stability	[22]
Dicer	Dicer 1, ribonuclease III	Cell division; the production of small RNA	[23]
Dnmt1	DNA methyltransferase 1	Epigenetic modification	[24]
Dnmt3α/l	DNA methyltransferase 3 alpha/DNA methyltransferase 3 like	Epigenetic modification	[25]
Dppa3/Stella/Pgc7	Developmental pluripotency associated 3	Epigenetic modification; degradation of maternal protein	[26-27]
Elmod2	ELMO domain containing 2	Cell division; organelle distribution	[28]
Ezh2	Enhancer of zeste homolog 2	Cell division; epigenetic modification	[29]
Ehmt2	Euchromatic histone lysine methyltransferase 2	Cell fate choices	[11]
Floped (*Ooep*)	Oocyte expressed protein	SCMC; CPL formation	[30]
Fmn2	Formin 2	Cell division	[31]
Gas6	Growth arrest specific 6	Ca^{2+} homeostasis; cortical reaction; pronucleus formation	[32]
Gclm	Glutamate-cysteine ligase modifier subunit	Pronucleus formation	[33]
Hira	Histone cell cycle regulator	Paternal chromatin remodeling	[34]
Kdm1a	Lysine demethylase 1A	Epigenetic modification	[35]
Kdm4a	Lysine demethylase 4A	Epigenetic modification	[36]
Khdc3l (*Filia*)	KH domain containing 3	SCMC; cell division	[37]
Kiaa1429 (*Virma*)	Vir like m^6A methyltransferase associated	Transcriptional regulation; cell division	[38]
Klf17	KLF transcription factor 17	Transcriptional regulation	[39]
Kmt2d (*Mll2*)	Lysine methyltransferase 2D	Epigenetic modification	[40]
Kpna6	Karyopherin alpha 6	Transcriptional regulation	[41]
Mettl3	Methyltransferase 3	Cell division	[42]
Nat10	*N*-acetyltransferase 10	Degradation of maternal mRNA	[43]
Nlrp2	NLR family pyrin domain containing 2	SCMC; epigenetic modification	[44]
Nlrp5 (*Mater*)	NLR family pyrin domain containing 5	SCMC; organelle distribution; CPL formation; cell division; cortical reaction	[5,45-47]
Nlrp7	NLR family pyrin domain containing 7	SCMC; epigenetic modification	[48-49]
Nlrp14	NLR family pyrin domain containing 14	Ca^{2+} homeostasis; epigenetic modification	[50]
Npm2	Nucleophosmin/nucleoplasmin 2	Maternal/paternal chromatin remodeling	[51-52]
Nup37	Nucleoporin 37	Transcriptional regulation	[9]
Obox	Oocyte specific homeobox	Transcriptional regulation	[53]
Pabpn1l	Poly(A) binding protein nuclear 1 like	Degradation of maternal mRNA	[54]
Pabpc1l	Poly(A) binding protein cytoplasmic 1 like	Transcriptional regulation	[55]

续表1

基因简写 Gene symbol	基因全称 Full name of gene	功能 Function	参考文献 References
Padi6	Peptidyl arginine deiminase 6	SCMC; CPL formation	[56]
Patl2	PAT1 homolog 2	Transcriptional regulation	[57]
Pcbp1	Poly(rC) binding protein 1	Pronucleus formation	[58-59]
Pdk1	3-phosphoinositide-dependent protein kinase 1	Transcriptional regulation	[60]
Pms2	Postmeiotic segregation increased 2	DNA repair	[61]
Ring1/Rnf2	Ring finger protein 1/2	Transcriptional regulation	[62]
Rnf114	Ring finger protein 114	Transcriptional regulation	[63-64]
Sebox	SEBOX homeobox	Transcriptional regulation	[65]
Setd1b	SET domain containing 1B	Transcriptional regulation; cortical reaction	[66]
Setd2	SET domain containing 2	Epigenetic modification	[67]
Setdb1	SET domain bifurcated histone lysine methyltransferase 1	Cell division	[68]
Slbp	Stem-loop binding protein	Maternal chromatin remodeling	[69]
Smc2	Structural maintenance of chromosomes 2	Maternal chromatin remodeling	[70]
Smc3	Structural maintenance of chromosomes 3	DNA repair	[71]
Smchd1	Structural maintenance of chromosomes flexible hinge domain containing 1	Transcriptional regulation	[72]
Sox2	SRY-box transcription factor 2	Transcriptional regulation	[73]
Srpk1	SRSF protein kinase 1	Paternal chromatin remodeling	[74]
Spin1	Spindlin 1	Cell division	[75]
Tap73	Transformation related protein 73	Cell division	[76]
Tdp-43	Transactive response DNA binding protein 43 kDa	Transcriptional regulation	[77]
Tet3	Tet methylcytosine dioxygenase 3	Epigenetic modification	[78]
Th2a/Th2b	Histone variants TH2A/TH2B	Transcriptional regulation	[79]
Tif1α	Transcription intermediary factor 1 alpha	Transcriptional regulation	[80]
Tle6	Transducin-like enhancer of split 6	SCMC; CPL formation; cell division	[6]
Trim28	Tripartite motif-containing 28	Epigenetic modification	[81]
Trip13	Thyroid hormone receptor interactor 13	Cell division	[82]
Tubb8	Tubulin beta 8 class VIII	Cell division	[83]
Ube2a (*Hr6a*)	Ubiquitin conjugating enzyme E2 A	DNA repair	[84]
Uchl1	Ubiquitin C-terminal hydrolase L1	Cortical reaction	[85]
Uhrf1	Ubiquitin like with PHD and ring finger domains 1	Epigenetic modification	[86]
Usp16	Ubiquitin specific peptidase 16	Epigenetic modification	[87]
Yap1	Yes1 associated transcriptional regulator	Degradation of maternal mRNA	[88-89]
Ythdf2	YTH N^6-methyladenosine RNA binding protein F2	N^6-methyladenosine reader; degradation of maternal mRNA	[90-91]
Zar1	Zygote arrest 1	Cell division; degradation of maternal mRNA	[92-93]
Zbed3	Zinc finger BED-type containing 3	SCMC; organelle distribution	[94]
Zfp36l2	ZFP36 ring finger protein like 2	Degradation of maternal mRNA	[95]
Zfp57	ZFP57 zinc finger protein	Epigenetic modification	[96]

关键因素之一, 它包括母源mRNAs的合成、积累以及细胞器的有序排列[97]。母源mRNAs的积累和储存对卵母细胞成熟和胚胎发育至关重要。PATL2(PAT1 homolog 2)是一种卵母细胞特异性RNA结合蛋白, 最近研究表明, PATL2与EIF4E(eukaryotic translation initiation factor 4E)和CPEB1(cytoplasmic polyadenylation element binding protein 1)结合以调节未成熟卵母细胞中母源mRNAs的表达。*Patl2*敲除小鼠的生发泡期(germinal vesicle, GV)卵母细胞表现出母源mRNAs表达水平降低和蛋白质合成水平下降[57]。人



A: 小鼠MZT过程中转录组的动态变化。B: 母源因子根据其主要功能的大致分类。

A: dynamic changes of the transcriptome during MZT in mice. B: maternal factors are roughly classified according to their main functions.

图1　母源因子调控卵母细胞和早期胚胎发育过程

Fig.1　Maternal factors regulate the development of oocytes and early embryos

类*PATL2*双等位基因突变会导致卵母细胞成熟障碍，从而导致女性不育[98]。母源*Ring1*(ring finger protein 1)和*Rnf2*(ring finger protein 2)敲除诱导卵母细胞成熟过程中大量转录调控错误发生，并且使胚胎在2细胞阶段发育停滞[62]。

卵母细胞的细胞质成熟还包括皮质颗粒(cortical granule, CG)、线粒体、内质网和细胞骨架等细胞器有序排列[97]。皮质颗粒是源自高尔基复合体的膜性细胞器，在受精过程中发挥重要作用[97]，此内容在下文(2.1 母源因子对受精过程的影响)进行详细描述。线粒体是卵母细胞ATP能量供应站，线粒体重排异常和ATP水平下降会导致卵母细胞成熟障碍以及受精失败[97]。NLRP5(NLR family pyrin domain containing 5)是被发现的第一个母源因子，除了在卵母细

胞和胚胎的皮层下富集外, 其还定位于核膜和线粒体, 表明它可能在线粒体中发挥作用。缺乏NLRP5的卵母细胞线粒体定位和活性状态异常, 线粒体池被过早激活[5]。另外, NLRP5还与卵母细胞中内质网分布有关[45]。另一个母源因子ELMOD2(ELMO domain containing 2)也被证明其缺失会导致卵母细胞线粒体分布异常, 以及ATP水平显著降低[28]。肌动蛋白细胞骨架(F-actin)在细胞分裂中起着重要作用, 其介导纺锤体的迁移和锚定, 并促进着丝纤维的形成, 避免染色体分离错误的发生[97]。FMN2(formin 2)是动态F-actin组装和减数分裂纺锤体迁移所必需的。FMN2缺失的卵母细胞在减数分裂I期间, 纺锤体不能正确定位并且第一极体形成失败[31]。除了调节细胞器的分布外, 母源因子还可以影响胞质晶格(cytoplasmic lattice, CPL)的形成。CPL是一种由蛋白质和RNA组成的纤维基质, 被认为是卵母细胞积累和储存蛋白质的场所[99]。皮质下母体复合物(subcortial maternal complex, SCMC)定位于CPL, 并且其组分是形成CPL所必需的。在SCMC缺陷卵母细胞中发现CPL消失, 并且缺陷胚胎在2细胞阶段停滞[56]。ZBED3(zinc finger BED-type containing 3)是SCMC的下游蛋白, 在母源ZBED3缺失的卵母细胞中, 细胞器分布异常[94]。

1.2 母源因子与卵母细胞核成熟

在卵母细胞发育和成熟过程中, 细胞核的形态和结构动态变化。最初, 卵母细胞转录活跃, 染色质处于疏松状态。而在GV后期, 染色质开始浓缩, 并在减数分裂成熟过程中进一步浓缩。在卵母细胞完全成熟之前, 染色质较少凝聚, 不局限于核仁周围, 称为无包裹核仁(non-surrounded nucleolus, NSN)构型。当卵母细胞完全成熟时, 基因组转录终止, 染色质显示出浓缩的核仁周围环, 称为包裹的核仁(surrounded nucleolus, SN)构型。“NSN-SN转换”是小鼠卵子发生的关键事件, 也是胚胎正常发育的主要前提[97]。

母源因子在卵母细胞染色质凝聚、减数分裂等事件中发挥重要作用。近期的研究表明, SMC2(structural maintenance of chromosomes 2)是凝聚蛋白复合体的核心成分, *Smc2*敲除导致GV期卵母细胞染色质凝聚缺陷, NSN比例维持高水平, 胚胎于1细胞期停滞[70]。卵母细胞染色体凝聚关键因子NPM2(nucleophosmin/nucleoplasmin 2)缺失, 导致卵母细胞中核仁分散, DNA无定形并在核仁周围凝聚失败[52]。在哺乳动物中, 卵母细胞从窦卵泡分离出时, 胞内的cAMP水平降低, 减数分裂自发恢复, 而高水平cAMP使减数分裂恢复受阻[97]。母源SETDB1(SET domain bifurcated histone lysine methyltransferase 1)缺失时, 由于PKA信号通路被错误调节导致卵母细胞维持高水平cAMP, 卵母细胞减数分裂恢复失败, 生发泡破裂(GV break-down, GVBD)延迟[68]。ZAR1(zygote arrest 1)缺失的卵母细胞也表现出延迟的减数分裂恢复和第一极体释放[92]。随着越来越多的母源因子被发现和验证, 卵母细胞中母源因子调控网络才逐渐清晰。

1.3 母源因子与卵母细胞表观遗传修饰建立

表观遗传修饰可以引起基因表达的遗传变化, 但不会改变核苷酸序列[97]。母源因子通过调控DNA甲基化、RNA甲基化及组蛋白修饰等表观遗传修饰参与卵母细胞成熟过程。DNA甲基化是研究最广泛的表观遗传修饰, 发生在胞嘧啶残基的5′碳位置(m^5C)。卵母细胞中DNA甲基化在胎儿出生后的卵泡发育阶段发生, 覆盖了大约40%的基因组[67]。SETD2(SET domain containing 2)是一种H3K36me3甲基转移酶, 指导卵母细胞中DNA甲基化的正确建立。在*Setd2*敲除的卵母细胞中发现基因组上的H3K36me3缺失, 导致基因组DNA甲基化建立异常, 最终导致卵母细胞成熟障碍和受精后单细胞期停滞[67]。CXXC1(CXXC finger protein 1)缺失导致卵母细胞DNA甲基化水平降低, H3K4me3积累不足并影响H3K27me3、H2AK119ub1和H3K36me3的分布[7]。

近期多项研究发现, RNA甲基化修饰参与卵母细胞发育和成熟。N^6-腺苷酸甲基(N^6-methyladenosine, m^6A)转移酶编码基因*Mettl3*敲除后, GV期卵母细胞直径变短、数量明显下降, 并且细胞内mRNA稳定性降低, 最终卵母细胞减数分裂成熟失败[42]。我们团队发现, m^6A甲基转移酶KIAA1429(vir like m^6A methyltransferase associated)缺失可能通过影响与卵子发生相关的外显子跳跃事件, 使GV期卵母细胞RNA代谢异常, 导致卵母细胞GVBD失败并失去减数分裂能力[38]。m^6A阅读蛋白YTHDF2(YTH N^6-methyladenosine RNA binding protein F2)缺陷通过降低母源mRNA衰变速率并干扰合子基因组激活, 导致MZT失败[90]。而大量有关DNA和RNA甲基化修饰调控卵母细胞发育、细胞命运及早期胚胎发育的机制仍有待揭示。

另外，组蛋白修饰是重要的表观调控者，常见的组蛋白修饰有四种形式，包括乙酰化、脱乙酰化、甲基化和磷酸化。母源NPM2通过调节组蛋白乙酰化水平，促使鱼精蛋白从父源染色质中移除[52]。H3K4me3参与成熟卵母细胞中基因组沉默状态的维持。母体缺乏主要的H3K4me3组蛋白甲基转移酶KMT2D(lysine methyltransferase 2D)，导致卵母细胞基因组沉默缺陷[40]。表观遗传修饰异常将有损卵母细胞中母源因子的累积和功能实现，阐明其机制将有助于开发潜在的生物标志物及治疗靶点。

2 母源因子对胚胎发育的影响

2.1 母源因子对受精过程的影响

成熟卵母细胞从细胞周期停滞状态最终过渡到可以支持胚胎发生状态的过程被称为卵子激活。卵子激活由受精触发，受精会使卵子内游离钙离子浓度增加，从而启动卵子激活的下游分子事件[100]。最近研究发现，NLRP14(NLR family pyrin domain containing 14)对保持钙离子振荡和早期胚胎发育至关重要。NLRP14缺失的卵母细胞由于线粒体分布、形态和活性的改变而导致细胞质功能和钙稳态紊乱[50]。此外，UHRF1(ubiquitin like with PHD and ring finger domains 1)[50]和NLRP5[45]也被证明与卵母细胞钙稳态调控有关。

卵子激活涉及一系列事件，包括CG胞吐以防止多精受精、卵母细胞减数分裂阻滞的释放以及单倍体雌性原核的形成[100]。母源因子在卵子激活过程中动态变化，为受精卵的发育提供必要的支持。受精后，CG分泌金属蛋白Ovastacin，通过剪切小鼠卵子周围透明带中的ZP2(zona pellucida glycoprotein 2)以阻止其他精子进入卵子。母源UCHL1(ubiquitin C-terminal hydrolase L1)是一种去泛素酶，可以抑制卵母细胞中CG的功能[85]。此外，CG在皮质中的锚定依赖于NLRP5，其异常将可能导致多精子受精[46]。在哺乳动物中，原核形成是卵子激活和受精的标志性事件。我们团队发现，母源PCBP1[Poly(rC) binding protein 1]是卵子激活过程中原核形成所必需的[58]。完全发育的卵母细胞中的全局转录沉默是受精和早期胚胎发育的先决条件。我们前期也发现PCBP1在维持早期卵母细胞转录沉默状态中发挥关键作用[59]。此外，在正常条件下，由于原核形成不同步，在受精卵雌雄原核形成时，雄性原核比雌性原核大。但母源SMC2缺失后，卵母细胞染色质凝聚失败，导致雌性原核大于雄性原核，胚胎阻滞于1细胞期[70]。精子DNA在受精时进入卵细胞中，此时父源基因组发生快速、高效的解压缩，用母源组蛋白替换包裹精子DNA的鱼精蛋白，完成“鱼精蛋白–组蛋白置换”[74]。母源NPM2通过调节组蛋白乙酰化水平去除父源染色质[51]。随后另一种母源组蛋白伴侣因子HIRA(histone cell cycle regulator)负责将组蛋白H3.3装配到父源DNA上[34]。此过程中，母源SRPK1(SRSF protein kinase 1)催化精子中的鱼精蛋白磷酸化并启动染色质重构进程[74]。

在受精后，卵母细胞从减数分裂阻滞状态中释放，并排出第二极体完成第二次减数分裂。然而，研究表明一些母源因子的缺失将会影响第二次减数分裂完成。在*Setdb1*敲除的卵母细胞中观察到MII(metaphase II)期不稳定的动粒微管附着，导致染色体分离缺陷[68]。另一项研究描述了NLRP5缺陷的MII卵母细胞中存在严重的着丝粒内聚减弱和频繁的染色体错位发生[47]。

母源因子通过调控卵子内游离钙离子浓度，诱发卵子激活的分子级联反应，以参与受精过程并支持受精卵的正常发育。

2.2 母源因子对植入前胚胎发育的影响

受精后，胚胎基因组仍然在一段时间内保持沉默，在受精卵分裂到一定时期后，胚胎基因组迅速激活，同时母源积累的RNA逐渐降解，最终完成从母源控制到胚胎控制的转变。合子基因组的激活通常经历两个阶段，即minor ZGA与major ZGA。在小鼠卵母细胞向胚胎转变过程中，RNA聚合酶II(RNA polymerase II, Pol II)通过装载、预配置和起始转录“三步走”的模式参与ZGA[53]。最近的研究表明，OBOX(oocyte specific homeobox)是ZGA的关键调节因子，其促进Pol II预配置，使其从初始靶点迁移到ZGA基因启动子和增强子区域。缺乏OBOX的胚胎ZGA受损并阻滞于2到4细胞期[53]。DNA/RNA结合蛋白TDP-43(transactive response DNA binding protein 43 kDa)可促进转录延伸，母源TDP-43缺失导致major ZGA基因上Pol II与染色质结合减少，胚胎在2细胞期停滞[77]。我们团队研究发现，母源KLF17(KLF transcription factor 17)通过影响Pol II的招募从而参与小鼠ZGA的调控过程。母源*Klf17*敲除的胚胎ZGA激活障碍并部分在2细胞期阻滞，而向这些胚胎中注射外源性*Klf17* mRNA，

能够部分挽救ZGA和早期胚胎发育的缺陷[39]。此外, 在哺乳动物中多种母源因子均参与调控ZGA。SMCHD1(structural maintenance of chromosomes flexible hinge domain containing 1)是一种母体表达的染色质调节因子。敲除母源*Smchd1*后, 小鼠2细胞期胚胎中*Dux*和*Zscan4*(*Dux*和*Zscan4*为启动和维持minor ZGA基因表达的两个关键基因)表达量增加, 从而抑制ZGA状态的退出[72]。母源YAP1(Yes1 associated transcriptional regulator)缺失使胚胎2细胞期延长, 向4细胞期进展延迟, 并导致合子基因*Rpl13*和*Rrm2*的转录破坏[88]。我们团队发现, 一种泛素连接酶RNF114(ring finger protein 114), 可以对早期胚胎中的特定底物(如TAB1[63]和CBX5[64])进行精准泛素化降解, 保证ZGA的顺利进行。综上所述, 卵母细胞提供的母源因子可以直接调控合子基因组转录网络, 激活早期合子基因转录。

除了直接控制转录外, 母源因子还参与染色质修饰, 调控染色质活性, 为基因转录提供合适的染色质状态。BRG1(BRM/SWI2-related gene 1)是染色质重塑复合体的催化亚基, 是核小体重塑和α珠蛋白基因座转录激活所需的染色质修饰因子。母源BRG1缺失的卵母细胞可以完成减数分裂并受精, 然而受精后的胚胎在2细胞期停滞并且有约30%的ZGA相关基因转录减少[17]。DCAF13(DDB1 and CUL4 associated factor 13)缺失的卵母细胞受精后染色质松动不足, 2细胞胚胎中基因转录明显减少, 并在此期发育停滞[8]。除了染色质结构的局部重塑外, 母源因子还参与调控染色体高阶结构。CTCF(CCCTC-binding factor)可以促进或抑制不同基因组结构域的相互作用[101]。耗尽母体储存的CTCF, 会导致卵母细胞的减数分裂缺陷和胚胎的有丝分裂缺陷, 这些缺陷伴随着ZGA的异常[21]。母源因子在卵母细胞成熟过程中参与表观遗传修饰建立, 在早期胚胎发育时又参与表观遗传重编程。DNA甲基化由DNA甲基转移酶DNMT3A和DNMT3B建立, 并由DNMT1维持, 非催化蛋白DNMT3L作为辅因子, 在它们缺失的情况下, 甲基化从基因组中去除。DNA甲基化重编程发生在人类胚胎发育的植入前和植入后期, 此时DNA甲基化模式发生去除和重建。研究表明基因组去甲基化部分是由SCMC介导DNMT1(DNA methyltransferase 1)导致的[44]。母源DNMT1缺失的小鼠胚胎显示出全基因组去甲基化和印记基因的单等位基因表达缺失[24]。

母源因子与受精后细胞命运决定有关。EHMT2(euchromatic histone lysine methyltransferase 2)在4细胞和8细胞阶段驱动H3K9me2的积累, 以调控4细胞阶段基因子集转录的及时终止。母源EHMT2缺失后, 合子基因调控网络会受到严重破坏, 导致ICM(inner cell mass)谱系发育延迟和谱系分离, 并导致胚胎反复植入失败[11]。这表明母源表达的EHMT2可能有助于后期基因表达模式的正确编程, 从而有助于最佳的谱系形成, 但需要长期研究来证实这一观点。

受精后, 胚胎经历合子基因组激活和母体转录物清除来完成MZT, 母源因子在这两个过程中均发挥重要调控作用。母源因子与母体转录物清除之间的关系在下文(3.3 母源因子的降解)中详述。

2.3 母源因子对植入后胚胎发育的影响

在目前研究的MEGs中, 有八种(包括*Dnmt1*、*Dnmt3a*、*Dnmt3l*、*Kdm1b*、*Nlrp2*、*Trim28*、*Tet3*、*Zfp57*)与小鼠植入后胚胎发育缺陷有关, 其中仅有*NLRP2*在人类中被报道[12]。MITCHELL教授[102]对MEGs与胎儿结构性缺陷之间的联系进行了全面综述。这些基因大多与受精后合子基因组甲基化印记有关, 其缺失会导致母体印记基因的低甲基化, 胚胎大多在妊娠中期前死亡, 并且大多表现为胎盘缺陷、生长障碍、心包水肿、神经管缺陷和心脏缺陷等表型。上述基因基本只在动物模型中研究, 目前在人类中被报道的会导致植入后胚胎发育缺陷的突变基因仅涉及*NLRP2*。在一个近亲家庭中, 母亲被鉴定出携带*NLRP2*纯合移码突变, 其子代在出生后被发现患有巨舌、脐膨出、耳皱褶、右腹股沟疝、睾丸隐降和新生儿低血糖[12]。目前的研究表明, 这些基因突变对植入后胚胎发育是致命的。但是, 研究大多在动物模型中进行, 因此需要进一步探究MEGs对人类植入后胚胎发育的影响。

3 母源因子的调控

3.1 母源mRNA的稳定和翻译控制

受精后的胚胎开始进行细胞分裂和发育, 这需要大量蛋白质合成。由于胚胎在开始时还没有自己的基因表达机制, 此时胚胎依赖于母源mRNA来合成所需的蛋白质。随着胚胎的发育, 这些母源mRNA数量逐渐减少, 胚胎自身的基因开始激活并通过转录和翻译产生蛋白质。这个过渡期是胚胎发育的关键阶段,

它确保了胚胎在早期具备必要的蛋白质来维持生命活动的顺利发展。因此，母源mRNA的稳定和翻译调控对卵母细胞成熟和早期胚胎发育至关重要。

真核基因转录后的初始产物(heterogeneous nuclear RNA, hnRNA)需要先经过加工修饰才能形成成熟的mRNA。 hnRNA变成mRNA过程中，hnRNA的5′末端增加m7pGppp帽子，3′末端增加多聚腺苷酸Poly(A)尾巴，通过中间剪接去掉内含子才能成为成熟的mRNA。Poly(A)尾一般由数十个至数百个腺苷酸连接而成，在卵母细胞成熟至胚胎发育的转变过程中动态变化。目前认为这种Poly(A)尾结构可能与卵母细胞中储存mRNA的翻译激活以及受精后母源mRNA的清除有关[103]。

在卵母细胞生长过程中，mRNA通过聚腺苷化获得长Poly(A)尾(250~300个腺苷残基)，这有助于mRNA从细胞核输出。出核后，长Poly(A)尾在细胞质中由CPEB(CPE-binding protein)和PARN[Poly(A)-specific ribonuclease]介导缩短。mRNA以短Poly(A)尾(20~30个腺苷残基)储存在细胞质中，使其处于翻译抑制状态。在卵母细胞成熟和受精时，CPEB磷酸化使PARN分离后，Poly(A)尾得以延长，此时Poly(A)尾与5′端帽子建立连接，形成“帽–尾闭环”，从而激活mRNA的翻译[104]。受精后，胚胎ZGA启动，合子mRNA陆续取代母源mRNA，此时母源mRNA发生去烯基化开始降解，当Poly(A)尾变短(<25个腺苷残基)时，Poly(A)结合蛋白分离，TUT4/7(terminal uridylyl transferase 4/7)使mRNA的短A尾尿苷化，随后mRNA被下游衰变因子识别并清除[105](图2 A)。

Poly(A)结合蛋白[Poly(A) binding protein, PABP]家族参与调控mRNA的许多关键生物过程，包括从细胞核输出，保护mRNA脆弱的3′端免受核外非特异性降解，通过与翻译起始因子eIF4G(eukaryotic translation initiation factor 4 gamma)的相互作用促进翻译以及参与Poly(A)尾巴脱腺苷[106]。PABPC1L[Poly(A) binding protein cytoplasmic 1 like]结合在mRNA的Poly(A)尾部，促进其多聚腺苷化。母源PABPC1L缺失会破坏mRNA在卵母细胞成熟过程中的翻译激活，其表现为减数分裂缺陷、NSN-SN染色质重组失败和基因组转录沉默状态异常[106]。PABPN1L[Poly(A) binding protein nuclear 1 like]将BTG4(BTG anti-proliferation factor 4)募集到Poly(A)尾部，是母体mRNA衰变所必需的[54]。PABPN1[Poly(A) binding protein nuclear 1]结合在TUT4/7作用后的3′-尿苷化转录本上，招募外切酶DIS3L2(Dis3 like 3′-5′ exoribonuclease 2)到其靶点，促进母源mRNA的衰变[107]。化学修饰会影响mRNA的活性、定位和稳定性[108]。除了常见的末端修饰，如m^7G帽和Poly(A)尾之外，m^6A是最丰富的mRNA修饰之一，该修饰异常可能影响细胞核中mRNA的输出和剪接体的形成[108]。输出的甲基化mRNA被细胞质中的YTHDF2识别。YTHDF2是m^6A阅读器也是母源因子，通过识别m^6A修饰的mRNA介导母源mRNA降解过程[90]。U尾(即mRNA尾链尿苷化修饰)也是最近引起广泛关注的热点，在小RNA的生成和mRNA的衰变中有重要作用[108]。在胚胎干细胞和某些癌细胞中，前体miRNA进入细胞质后会被TUT4/7尿苷化，U尾阻止DICER(dicer 1, ribonuclease III)加工并募集外切酶DIS3L2来降解前体miRNA。然而，在一些分化细胞中，大多数前体miRNA被TUT2/4/7单尿苷化，从而促进了DICER加工[108]。DICER也是母源因子之一，缺乏DICER的卵母细胞存在减数分裂缺陷并且不能正常发育成熟[23]。U尾与mRNA衰变的关系将在“3.3 母源因子的降解”部分详细阐述。

除了mRNA Poly(A)尾和mRNA修饰调控外，母源mRNA也受到体细胞的影响。生殖细胞分化需要周围体细胞创造独特的微环境。尽管把卵母细胞分离出来在体外培养其也能成熟并成功受精，但人们普遍认为，在没有体细胞接触的情况下，卵母细胞受精和胚胎发育会受到影响。这些缺陷可能是由于卵母细胞的细胞质成熟受到破坏导致的[109]。体细胞分泌的生长因子AREG(amphiregulin)通过PI3K-AKT-mTOR通路调控卵母细胞中mRNA子集的翻译[109]。

2022年，我国“人类早期胚胎翻译组图谱及合子基因组激活因子研究”工作组开发了超低输入的Ribo-RNA-lite(R2-lite)方法，对人类卵子和早期胚胎进行了翻译组与转录组联合测序，首次描绘了人类卵子向胚胎转变过程中的翻译组图谱[110]。此技术可以在超低输入的条件下进行翻译组与转录组的联合测序，从而更加准确地揭示基因的转录以及翻译调控过程。通过对新兴技术的开发和应用，我们对MZT过程中母源mRNA的转录翻译调控有了更深入的了解。在未来，超敏组学和低输入组学等技术的不断创新和改良，有望为人类健康和疾病治疗带来更多的突破。

3.2 母源因子的储存

在哺乳动物中，转录在卵母细胞生长的最后阶

段停止, 只有在受精后合子基因组被激活时才会恢复。卵母细胞在成熟过程中积累mRNA和蛋白质, 以满足早期胚胎发育的需要。

母源mRNA主要存储在线粒体相关核糖核酸蛋白结构域(mitochondria-associated ribonucleoprotein domain, MARDO)中[93]。在卵母细胞生长过程中, 线粒体膜电位的增加诱导MARDO在线粒体周围的组装。母源ZAR1的表达促进了MARDO聚合和线粒体聚集, 而ZAR1的降解则驱动了MARDO溶解和母源mRNA衰变[93]。此外, 研究发现部分母源mRNA也储存在卵母细胞胞质的RNA颗粒中, 例如皮层下RNP结构域(subcortical RNP domain, SCRD)[111]和生殖颗粒[112], 这些RNA颗粒与母源mRNA的稳定和翻译相关。

卵母细胞积累和储存蛋白质的位置是细胞质晶格[99]。蛋白质储存在CPL上可能有三方面的作用。第一, 阻止母源蛋白质过早进入细胞核。例如, 细胞质中UHRF1的保留对于受精后母体基因组的被动去甲基化至关重要, UHRF1过早进入卵母细胞核会导致基因组超甲基化[113]。第二, 保护蛋白质免受降解。例如, 微管蛋白以一种不溶性的形式储存在CPL上, 以免受降解机制的影响, 以及避免体细胞负反馈回路的调节。这种储存形式使卵母细胞中的微管蛋白比体细胞中积累得更多[114]。小鼠卵母细胞含有的α-微管蛋白和β-微管蛋白水平显著高于HeLa细胞[115]。第三, 阻止蛋白质进入线粒体或组装成核糖体等复合物, 而这可能会影响胚胎有丝分裂过程中细胞器和细胞骨架的功能[116]。

3.3 母源因子的降解

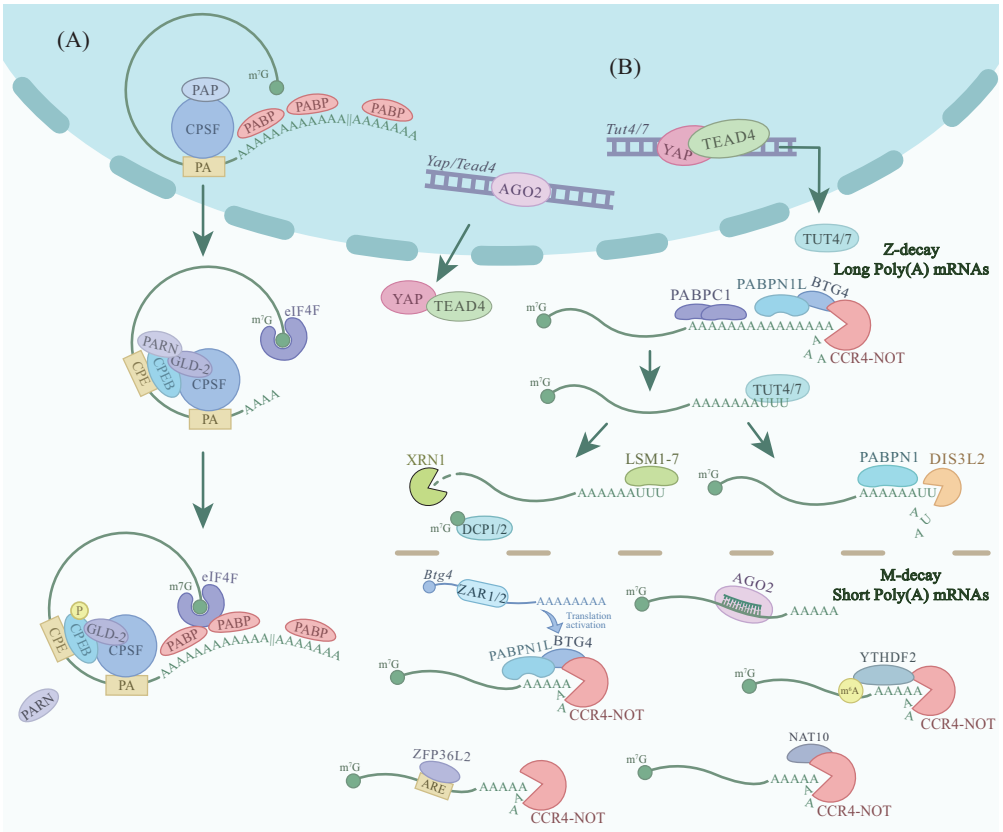
从母体到胚胎发育控制的转变主要依赖于卵母细胞生长过程中储存的分子。受精后, 发育控制权逐渐移交给胚胎自身, 此时胚胎大部分母源mRNA被清除, 使母体与胚胎的成分能够发挥各自的作用。对动物模型的研究表明, 母体转录本的清除是通过两条连续的途径完成的: 第一种途径完全由卵母细胞生长过程中积累的母源因子介导(M衰变), 而第二种途径依赖于ZGA启动后的胚胎转录产物(Z衰变)[89] (图2B)。CCR4-NOT复合体是真核生物中介导RNA降解的重要组分。在M衰变中, BTG4通过与PABPN1L相互作用将CCR4-NOT复合体募集到mRNA上[19]。AGO2(argonaute RISC catalytic component 2)通过siRNA与母源mRNA结合, 促进其降解, 并且AGO2还能激活合子表达*Yap1*和*Tead4*来参与Z衰变[10]。ZFP36L2[117]与YTHDF2[91]招募CCR4-NOT复合体到mRNA上。NAT10通过维持CCR4-NOT的活性来促进母源mRNA衰变[43]。另外, 还发现ZAR1翻译激活*Btg4*, 参与小鼠母源mRNA的衰变[92]。Z衰变是小鼠胚胎发育所必需的。母源YAP1和合子TEAD4介导小鼠胚胎中Z衰变途径的激活。ZGA后, TEAD4触发合子*Tut4/7*表达和mRNA 3′低聚尿苷化, 并与母源mRNA去烯基化机制(包括BTG4和CCR4-NOT)协同作用来清除母源转录本。卵母细胞特异性*Yap1*敲除小鼠中, 4细胞胚胎母源转录本清除失败[89]。大多数mRNA在衰变开始时会经历去烯基化。TUT4/7使短A尾的mRNA尿苷化, LSM1~7复合体与U尾结合, 并促进DCP1/2复合体脱帽, 随后mRNA被5′-3′外切酶XRN1(exoribonuclease 1)降解; 或者U尾被外切酶DIS3L2识别, 从mRNA的3′端开始降解[105](图2B)。关于母源因子降解的更多详细机制, FAN等[118]进行了全面的综述。

蛋白水解的两个主要机制是泛素–蛋白酶体系统(ubiquitin-proteasome system, UPS)和自噬[119]。母源蛋白质的大量降解是由UPS介导的。母源DPPA3除了在细胞核中维持雌性原核DNA甲基化状态外[26], 还在细胞质中参与胚胎的囊泡运输, 可能是UPS途径的上游调节因子, 参与母源蛋白质的泛素化降解[27]。自噬是继UPS之后的第二大已知的蛋白质降解途径, 也是细胞质中脂质或小细胞器等其他分子的降解途径[119]。自噬在受精后不久被激活, *Atg5*是自噬相关基因, 介导早期胚胎母源蛋白的降解。母源ATG5缺失的胚胎在着床前发育阶段阻滞[14]。研究表明, UPS和自噬的活性似乎与胚胎质量相关[119]。

4 母源因子与生殖健康

4.1 母源效应基因与女性不孕

母源基因突变是指母体基因型中影响子代表型的突变。携带MEGs缺陷的雌性是健康的, 但有生殖失败的风险, 通常是由于其子代的早期胚胎发育停止或印记障碍。目前已有很多研究证明了MEGs突变与不孕的关系。ALAZAMI等[120]在2015年首次报道, 母源*TLE6*突变会导致人类胚胎死亡。三名沙特女性患者的胚胎由于*TLE6*单一突变而无法进行



A: 卵母细胞中, 母源mRNA的Poly(A)尾依赖性调控过程。B: 母源mRNA的清除(M衰变和Z衰变)。

A: Poly(A) tail-dependent regulation of maternal mRNA in oocytes. B: clearance of maternal mRNA (M-decay and Z-decay).

图2　在母体到合子的转变过程中, 母源mRNA的调控与降解

Fig.2　Regulation and degradation of maternal mRNA during maternal-zygotic transition

早期卵裂, 导致不孕。目前, 在生殖障碍的女性中已经发现了数种MEGs突变, 具体包括*PATL2*、*TUBB8*、*NLRP2*、*NLRP5*、*NLRP7*、*PADI6*、*TRIP13*、*BTG4*、*CDC20*、*KHDC3L*、*OOEP*、*ZFP36L2*。自然妊娠的早期胚胎死亡率很难被检测到, 因为其在临床诊断之前可能已经发生妊娠丢失。因此, 在缺乏特异性分析的情况下, 由于MEGs突变导致的胚胎停滞可以在早期的遗传筛查中进行预防, 以避免突变携带者进行无效的辅助生殖治疗, 从而减轻患者身体、经济和情绪压力。这些发现对卵母细胞发育和成熟障碍、受精失败、反复种植失败及反复妊娠丢失等生殖障碍疾病的理解、诊断以及潜在干预靶点的开发和应用有重要意义。

4.2　母源效应基因与印记疾病

母源基因突变除了是女性不孕的原因外, 还与突变携带者子代的印记障碍有关。印记疾病是由于遗传和表观遗传变异改变了印记基因的有效基因剂量而引起的, 印记基因的表达通常受原生亲本的限制[121]。印记紊乱影响胚胎的生长发育, 并与人类严重发育障碍疾病有关, 包括Beckwith-Wiedmann综合征(Beckwith-Wiedmann syndrome, BWS)、Angelman综合征和Silver-Russell综合征等[121]。BWS是一种表现为胎儿过度生长的人类印记障碍疾病, 由染色体11p15.5上印记基因簇中的许多基因失调引起。研究发现BWS胎儿的母亲存在*NLRP2*纯合子移码突变[12]。此外, 在50%以上的复发性葡萄胎女性中检测到*NLRP7*的纯合或复合杂合致病变异、缺失或重排[48]。随后基因*KHDC3L*被确定为复发性葡萄胎的第二个致病基因, 解释了另外5%的病例[121]。这些葡萄胎的特点是完全失去了母体印记, 是一种严重的印记紊乱。除此之外, 研究报道NLRP5、PADI6、TLE6、OOEP、UHRF1、ZAR1等母源因子可能与印记紊乱有关, ELBRACHT等[121]对两者之间的关系进行了全面综述。虽然其中涉及的分子机制尚不完全清楚, 但这些研究表明母源因子在基因组印记中

起重要作用。

4.3 母源因子在辅助生殖技术中的应用与前景

辅助生殖技术(assisted reproductive technology, ART), 如体外受精(*in vitro* fertilization, IVF)和卵胞质内单精子注射(intracytoplasmic sperm injection, ICSI), 被广泛用于解决人类不孕症。母源因子在生殖健康和ART中扮演着关键角色。在自然受孕过程中, 母源因子可以影响卵母细胞的质量和基因表达, 从而影响受精卵和胚胎的发育。MEGs的变异可能是一部分女性出现的无法解释的不良生殖结局的潜在病因。通过胚胎植入前遗传学检测, 为携带致病性MEGs基因型的女性选择健康胚胎进行移植, 将有望提高ART成功率、降低出生缺陷风险。然而, 有研究表明, ART会影响MZT重编程, 导致基因组印记紊乱[122]。因此, 阐明母源因子对印记基因维持的作用与机制, 并探究ART对母源因子分布及功能干扰的原理, 可能为改善ART效率和安全性提供有效思路和干预靶点。综上, 母源因子研究有望在生殖健康促进和辅助生殖技术革新中崭露头角, 有助于医生优化不孕病因筛查策略、为患者制定更有利的治疗方案, 并最大程度地提高妊娠率和生出健康子代的机会。

5 总结与展望

母源因子在哺乳动物卵母细胞向胚胎转变过程中扮演着不可或缺的角色, 涉及到多个关键环节, 包括母源mRNA的合成与积累、细胞器的有序排列、表观遗传重编程、受精后卵子激活、染色质重塑、合子基因组激活和母体转录物清除等。母源因子在这些环节中的作用对于确保卵细胞成熟和早期胚胎正常发育至关重要。然而, 当前对母源因子的研究仍存在局限性。尽管已经识别出一些重要的母源因子, 但对于它们的相互作用关系和如何调控特定发育过程的机制, 我们的理解仍不充分, 还需要更多深入的研究。此外, 当前的研究主要集中在少数几种模式动物上, 尚缺乏对不同物种和发育阶段的比较分析。

技术方法上的挑战也是当前研究面临的关键难题。母源因子的作用机制复杂, 需要更为精细的实验设计和分析方法。胚胎发育的某些关键阶段(如major ZGA启动)的时间窗非常短。目前的瞬时测定法通常不能准确区分母体和合子的基因产物和功能差异, 因此开发能够捕捉这些短暂变化的、精准识别母源因子作用的高效技术也是当务之急。此前, 由于哺乳动物胚胎样本的起始材料获取困难, 同时缺乏超敏组学技术, 该领域的单细胞和低输入组学研究受到了一定的限制。然而, 随着组学的进步和单细胞分析策略的创新, 基于高通量组学技术对微量或单细胞进行分析已成为可能[110,123]。在未来, 单细胞和低输入多组学技术有望成为研究母源因子在卵母细胞和早期胚胎发育中功能的重要工具。利用多组学技术对单个细胞的遗传、表观遗传、转录和翻译等动态信息进行全面分析, 有望揭示母源因子在胚胎发育过程中的时空表达模式和在细胞命运决定中的作用。

总之, 未来的研究应该致力于深入理解母源因子在哺乳动物卵母细胞向胚胎转变过程中的作用机制, 持续探索和发现新的研究方法, 以解决当前研究中存在的不足, 克服所面临的挑战。这一领域的进步将为我们提供一个更为完整的母源调控网络景观, 这不仅有助于揭示早期胚胎发育的奥秘, 也将为辅助生殖技术的优化以及胚胎发育障碍相关疾病的预防和治疗提供新的思路。

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