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评 述 生殖健康专辑

卵母细胞发育的代谢调控

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摘要 有序均衡的代谢活动对卵母细胞发育至关重要. 早期的研究多集中于影响卵母细胞成熟的外源性营养素, 而很少关注细胞内的代谢酶与代谢物. 因此, 全面解析代谢模式特征有助于阐明卵母细胞发育的分子调控机制. 近年来, 关于细胞代谢与表观遗传修饰之间的密切联系被广泛报道; 此外, 母源环境改变所导致的卵母细胞代谢紊乱, 可能会通过表观修饰影响早期胚胎发育及子代健康. 本文将对卵母细胞成熟过程中代谢调控的研究进展进行综述, 并从卵子表观修饰角度探讨母源环境异常影响子代健康的潜在机制, 以期提高卵母细胞质量, 改善女性生殖健康.

关键词 卵母细胞, 代谢, 母源环境, 表观遗传, 生殖健康

哺乳动物卵母细胞发育是一个复杂且漫长的过程. 在雌性胎儿中, 原始生殖细胞迁移到生殖脊, 在那里它们通过有丝分裂进行增殖并且从卵原细胞转化为初级卵母细胞[1]. 在出生前后, 卵泡中的卵母细胞发育至减数第一次分裂前期, 也称为生发泡(germinal vesicle, GV)期. 随后, 卵母细胞将维持减数分裂停滞很长一段时间(人类数年, 小鼠数月). 青春期后, 卵母细胞在促性腺激素的刺激下恢复减数分裂. 伴随着染色质浓缩、纺锤体组装、同源染色体分离和第一极体排出, 卵母细胞完成减数第一次分裂随后到达减数第二次分裂中期(metaphase II, MII)[2]. 此时, 卵母细胞完成核成熟, 在第二次减数分裂中期再次停滞, 等待受精[3]. 卵母细胞的生长和成熟对于营养和化学环境的变化非常敏感[4], 并且对于女性生育力和后代健康都存在长期影响.

适时的、良好平衡的代谢对于卵母细胞的减数分裂成熟和获得较高发育潜能是至关重要的[5]. 20世纪60年代, Biggers等人[6]最先提出了哺乳动物卵母细胞代谢的基本模式, 主要涉及培养基中营养物质的利用. 随后的几年中, 人们在这一领域取得了一系列的突破性进展和发现. 例如, 完全生长的卵母细胞几乎不能通过糖酵解代谢葡萄糖[7,8], 卵泡细胞为卵母细胞提供足够的丙酮酸以完成减数分裂成熟过程[9,10]. 大量研究已表明, 脂肪酸氧化对卵母细胞减数分裂恢复和其发育潜能也至关重要[11~13]. 卵母细胞与周围的体细胞之间存在缝隙连接, 它能够促进特定代谢物的转移, 例如丙酮酸[7]、丙氨酸[14]、还原型烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide phosphate hydrogen, NADPH)和磷酸核糖焦磷酸[15].

目前, 一系列组学技术被广泛应用于生殖医学研究领域中[16], 例如, 代谢组学可以对低分子量代谢物进行鉴定和定量, 反映出细胞中的代谢状态和事

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件[17,18]. 通过多组学关联分析能够为全面呈现配子发生及早期胚胎发育的代谢特征提供方法与技术支持. 本文将对参与卵母细胞成熟的主要代谢途径进行综述, 描述表观遗传修饰的代谢调控机制, 并讨论卵母细胞代谢紊乱在母源环境影响子代健康中的介导作用.

1　代谢对卵母细胞成熟的影响

代谢是卵母细胞质量的重要决定因素[19]. 卵母细胞成熟过程具有动态、快速的特征, 需要多种代谢化合物的参与, 如碳水化合物[20,21]、脂肪酸[22,23]、氨基酸[24,25]、嘌呤和嘧啶[26~28](图1). 下文将详细阐述上述代谢物在卵母细胞成熟过程中的代谢调控.

卵母细胞的代谢活动不能完全从卵泡(尤其是颗粒细胞)中分离出来, 颗粒细胞为卵母细胞的生存、滋养和调节创造了必要的环境[29]. 由于卵母细胞缺乏进行糖酵解等关键代谢过程的能力, 因此它依赖于与颗粒细胞的合作来为其提供必要的代谢物质. 尽管卵母细胞在这个过程中起主导作用, 但卵母细胞与颗粒细胞之间的沟通是相互依赖且双向的, 这对于信号分子和营养物质的传递至关重要[30].

在卵母细胞成熟过程中, 细胞质的成熟具有决定性的作用. 这一过程涵盖了母源mRNA的合成、激活、降解, 以及细胞器有序排列和细胞骨架的重组. 母源mRNA的转录与降解需要多种代谢物和代谢途径的参与, 细胞器和细胞骨架的运动也需要线粒体提供足够水平的ATP才能完成, 这需要卵母细胞在代谢水平上进行精确的调控.

1.1　卵母细胞的碳水化合物代谢

碳水化合物代谢包括糖酵解、磷酸戊糖途径(pentose phosphate pathway, PPP)、己糖胺生物合成途径(hexosamine biosynthesis pathway, HBP)和多元醇途径, 这些内容已由Thompson团队[20]和Gilchrist团队[19]系统综述. 一般来说, 人们已经广泛认识到碳水化合物代谢对卵母细胞的生长[31]、成熟[32]和发育能力是

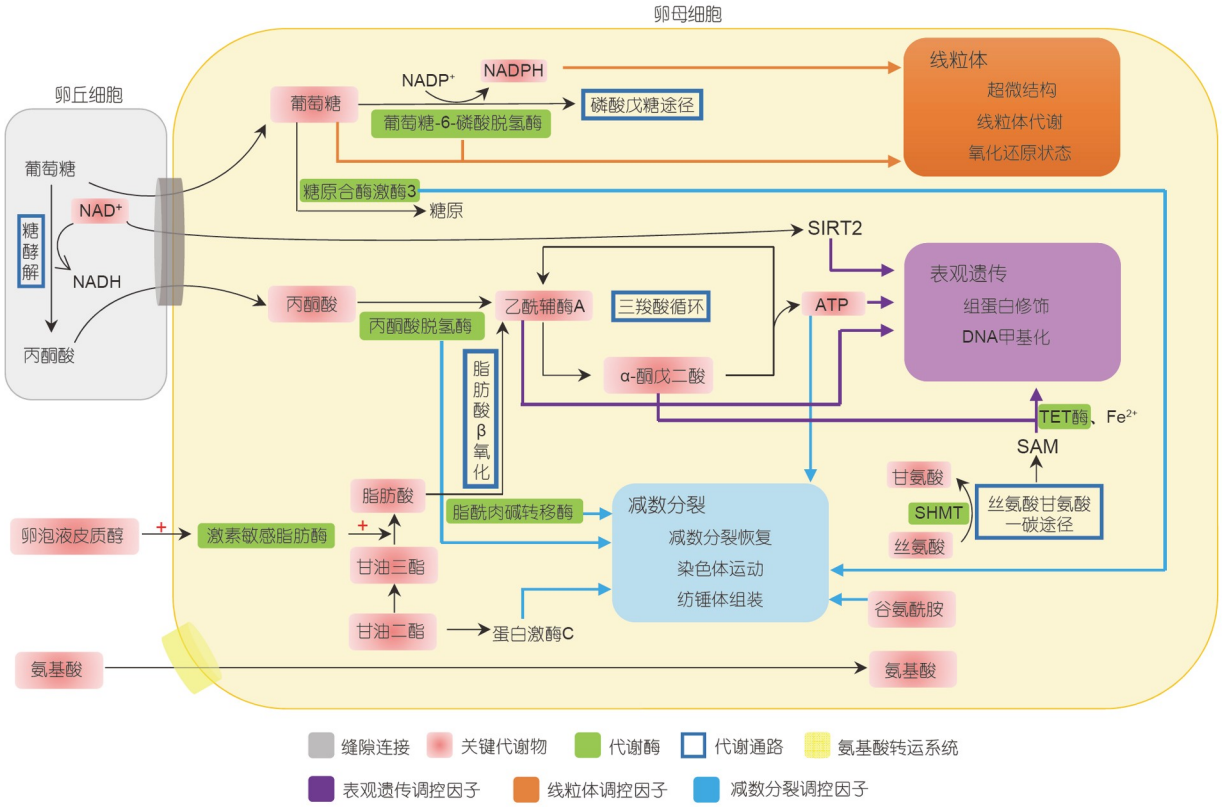

图 1　卵母细胞发育过程中线粒体、表观遗传和减数分裂的代谢调控

Figure 1　Metabolic regulation of mitochondria, epigenetics, and meiosis during oocyte development

至关重要的[33]. 有趣的是, 卵母细胞代谢葡萄糖的能力是有限的[34,35], 但是能够通过缝隙连接或卵泡液直接从卵丘细胞中摄取并利用丙酮酸. 有研究认为, 卵母细胞对葡萄糖利用能力有限的原因是其糖酵解关键酶——磷酸果糖激酶活性低下[36]. 最近, Akin等人[37]也证实, 在小鼠体内卵丘卵母细胞复合物(cumulus oocyte complexes, COCs)中, 卵丘细胞中存在较为活跃的糖酵解, 而具有低糖酵解活性的卵母细胞会使其葡萄糖利用更加偏向PPP.

丙酮酸通过丙酮酸脱氢酶(pyruvate dehydrogenase, PDH)分解代谢为乙酰辅酶A(acetyl-CoA, CoA)进入三羧酸(tricarboxylic acid, TCA)循环以产生三磷酸腺苷(adenosine triphosphate, ATP)和其他代谢中间体[38]. 在丙酮酸脱氢酶E1亚基α1(也称为PDHA1)缺乏的小鼠中, 卵母细胞减数分裂过程出现明显缺陷, 这一现象突出了丙酮酸代谢相关酶的重要性[39]. 通过对丙酮酸脱氢酶激酶(pyruvate dehydrogenase kinase, PDK)进行敲降和过表达分析, 本团队[40]已经证明PDK1和PDK2具有促进减数分裂成熟的作用, 而由PDK3介导的Ser293-PDHA1磷酸化会抑制PDH的活性. 最近, 本团队[41]发现, TCA循环中三个关键组分的丰度在MII卵母细胞中经历了急剧增加, 柠檬酸盐增加了5倍, 顺乌头酸盐增加了6倍, 延胡索酸盐增加了2倍. 此外, PDH复合物的三种酶(包括PDHA1、二氢硫辛酸转乙酰酶和二氢硫辛酸脱氢酶)的积累在卵母细胞成熟期间都有升高[41]. 这些结果表明, 卵母细胞成熟需要较高活性的丙酮酸代谢和TCA循环. 有趣的是, 卵母细胞中丙酮酸的代谢存在一种Warburg效应, 它引导丙酮酸远离TCA循环并代谢成乳酸[42]. 即使在氧含量充足、线粒体功能正常时, 这种方式产生ATP的效率仍然是低的. 所以, 必须有诸如脂肪酸等其他替代的能量产生来源, 以支持基础TCA活性和ATP产生[43]. 这些研究表明, 葡萄糖/脂肪酸平衡在卵母细胞和胚胎发育中的关键作用. 糖原合酶激酶3b(glycogen synthase kinase 3b, GSK3b)最初被认为是参与糖代谢调节的酶, 但其实它作为一个丝/苏氨酸蛋白激酶的生物学功能远不止于此. 研究已证实, GSK3b在小鼠卵母细胞的减数分裂中起到关键作用, 尤其在染色体的分离过程中[44,45].

研究人员还在不同物种中探索了参与PPP的酶的功能[15,46~49]. 在PPP的氧化阶段, NADPH伴随葡萄糖-6-磷酸氧化成核糖-5-磷酸而产生, 这是氧化还原稳态和核苷酸合成所不可或缺的[15,20,46]. 类似的是, 本团队[41]发现, PPP的几个关键中间体在卵母细胞成熟期间表现出显著变化. 例如, 葡萄糖-6-磷酸盐和葡萄糖酸内酯增加约30倍, 葡糖醛酸增加约10倍, 表明PPP过程是活跃的. 此外, PPP限速酶葡萄糖-6-磷酸脱氢酶的敲降不仅导致卵母细胞中过量的活性氧(reactive oxygen species, ROS)产生, 还会导致受精后的二细胞胚胎发育停滞[41]. 通过使用抑制剂, Kang等人[50]也发现, 只有PPP而非糖酵解、HBP或多元醇途径是非哺乳动物斑马鱼卵母细胞成熟所必需的. 己糖胺生物合成途径生成N连接乙酰糖在细胞外基质产生透明质酸[20]. 有证据证明, 在成熟的最后阶段, 葡萄糖利用率的增加是通过HBP形成的这种功能基质达到的[51,52]. 同时, 只有少数HBP产物参与O连接的蛋白质糖基化. 最近的研究表明, COCs中HBP活性的破坏显著阻碍小鼠和牛的成熟和受精过程[53,54].

1.2 卵母细胞的脂质代谢

在哺乳动物卵母细胞中, 甘油三酯是最丰富的脂质[55], 脂肪酶将其切割成甘油主链和具有不同链长和饱和度的脂肪酸[5]. 许多研究已证实, 卵母细胞中不可缺少的脂代谢途径主要是脂肪酸的β-氧化(fatty acid oxidation, FAO)[11~13,22,23,56]. 脂肪酸的特性在于高能量值, 与碳水化合物或其他物质相比, 能够产生更多的ATP. 通过使用特异性抑制剂, 已经证明FAO是减数分裂恢复[11]、成熟[57]和早期胚胎发育[13,58]所必需的. 在培养基中补充左旋肉碱会增加FAO活性, 促进卵母细胞成熟[59~61]. 脂肪酸β-氧化过程中的关键酶脂酰肉碱转移酶(carnitine palmitoyl transferase, CPT)也被证实参与调控小鼠卵母细胞的减数分裂以及后续的胚胎发育[12,62]. 此外, 左旋肉碱还能够调节葡萄糖代谢并增强参与氧化呼吸链的酶的活性[63]. 鉴于人卵母细胞和卵丘细胞中不存在参与肉碱生物合成途径的转录物[64], 通过在体外培养期间向培养基中补充左旋肉碱, 对于改善人卵母细胞质量具有巨大潜力.

除能量供应这一功能外, 脂肪酸代谢也在其他方面调节卵母细胞的减数分裂. 甘油二酯(diacylglycerol, DAG)会与蛋白激酶C(protein kinase C, PKC)中保守的C1结构域结合从而使PKC活化, 以调节细胞周期和细胞凋亡[65]. 而PKC已被证实其同工酶参与了哺乳

动物卵母细胞发育过程中的多个关键步骤, 如减数分裂恢复、纺锤体组装和激活[66~68]. 本团队[41]发现, 多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)在小鼠卵母细胞减数分裂恢复期间大幅下调. 具体地说, 花生四烯酸(arachidonic acid, ARA)的下降使得NF-κB激活蛋白(NF-κB activating protein, NKAP)和B细胞易位基因4(B-cell translocation gene 4, BTG4)积累, 分别触发减数分裂装置的装配和母源RNA降解. 有报道称, ARA可以进一步分解为类花生酸从而影响卵母细胞质量[69]. ARA也可以调节缝隙连接的活跃程度, 以调节颗粒细胞与卵母细胞间的小代谢物和分子的转运[70]. 另一方面, 脂肪酸对牛卵母细胞的影响似乎是不同的, 这取决于脂肪酸的类型[71]. PUFA在低生理剂量下会改善牛卵母细胞的质量[72], 而饱和脂肪酸却会损害其质量[73]. 因此, 脂肪酸在哺乳动物卵母细胞中的作用还有待进一步探讨. 此外, 值得注意的是, 胆固醇水平在从GV到MII期卵母细胞转变的过程中降低[41]. 与此一致的是, 研究人员发现, 过量的胆固醇可以对小鼠卵母细胞产生欺骗作用, 使它们表现得好像已经受精(从MII停滞中释放), 从而破坏受精和减数分裂之间的正常同步性, 并且使它们的功能失调[74].

在脂代谢的调控方面, Liu等人[75]的报道中指出, 卵泡中的脂质代谢会受到颗粒细胞或血液循环中的激素调节. 在排卵前, 卵丘细胞中的1型11β-羟基类固醇脱氢酶在促黄体生成素(luteinizing hormone, LH)或人绒毛膜促性腺激素(human chorionic gonadotropin, hCG)的存在下会将皮质酮催化成活性皮质醇[76]. Keay等人[77,78]发现, 当皮质醇浓度和皮质醇与皮质酮比率上升时, 会出现更好的IVF结果, 包括成功的卵母细胞受精、胚胎植入和临床妊娠. Simerman等人[79]发现, 卵泡液中皮质醇与卵丘细胞脂滴数是负相关的, 而与卵母细胞的成熟数量正相关. 一项对人卵泡的研究表明, 皮质醇可以与卵丘细胞和卵母细胞中的激素敏感脂肪酶(hormone-sensitive lipase, HSL)互作或增加HSL的表达[80], 以促进甘油三酯分解成游离脂肪酸[79]. 因此, 由皮质酮转化为皮质醇控制的脂解可能是调控卵母细胞减数分裂恢复的重要机制.

1.3　卵母细胞的氨基酸代谢

氨基酸通过一系列专门转运系统转运到细胞中并发挥重要作用, 包括蛋白质合成、能量产生、有机渗透剂和细胞内缓冲剂. 在过去的研究中, 人们对植入前胚胎中的氨基酸进行了广泛的研究[81~83]. 然而, 对于哺乳动物卵母细胞生长和发育过程中氨基酸的代谢过程知之甚少.

人们通常用底物特异性和是否存在钠离子特异性协同转运来定义氨基酸的转运系统[84,85]. Colonna等人[86]首先探究了整个卵子发生过程中分离的小鼠卵母细胞中的氨基酸转运系统. 虽然完全生长的GV卵母细胞缺乏A-转运系统, 但是他们证明了L-和ASC-系统的利用. Van Winkle等人[87,88]在后来的研究中表明, 在未成熟的卵母细胞中, 甘氨酸转运主要通过经由Xc^-系统的GLY转运系统和半胱氨酸/谷氨酸转运系统. 同样, β, L, GLY, Xc^-和b_0^+系统也在成熟卵母细胞中被成功检测到[88~91]. Pelland等人[84]测量了小鼠卵母细胞中9种氨基酸的转运特性, 并确定了11种传统方法定义的氨基酸转运系统的活性. GLY, β和Xc^-在发育中的卵母细胞中具有低活性, 并且在减数分裂过程中明显上调. L, b_0^+和asc/ASC系统似乎在卵母细胞的发育和成熟过程中具有组成性活性. 与此相一致, 卵母细胞表现出不同的氨基酸转运模式[84].

据报道, 当在含有[^{14}C]L-丙氨酸的培养基中培养小鼠卵丘细胞封闭或将卵丘细胞剥除的卵母细胞时, 卵丘细胞封闭组的卵母细胞中含有较高的放射性[24]. 与小鼠卵母细胞相比, *Slc38a3*(编码两对丙氨酸具有底物偏好的钠偶联中性氨基酸转运蛋白的转录物)在卵丘细胞中大量表达[14]. 迄今为止已得到证实的是, 在颗粒细胞存在的情况下, 甘氨酸、丙氨酸、牛磺酸和赖氨酸进入卵母细胞的转运速率会得到增强[24,84,87]. 这些发现强烈暗示, 卵母细胞和卵泡细胞之间的代谢合作会涉及氨基酸的摄取. 令人惊讶的是, 卵泡细胞并没有赋予封闭的卵母细胞额外的氨基酸转运能力, 在某些情况下, 它们似乎抑制了小鼠卵母细胞对亮氨酸的摄取[84].

卵母细胞中存在的许多转运系统表明了其利用来自外部环境的氨基酸的能力. 谷氨酸已被认为是一种有效的能量底物以支持卵母细胞的发育. 例如, 使用谷氨酸作为唯一的能量来源足以启动COCs内小鼠卵母细胞的减数分裂恢复, 但不能使其通过MII阶段[92]. 在培养液中添加谷氨酰胺可以促进牛、仓鼠、犬、兔和恒河猴卵母细胞的成熟[25,82,93~95]. 谷氨酰胺、天冬氨酸

和缬氨酸也可以有助于阻止猪卵母细胞的多精受精[96].

甘氨酸是抗氧化剂谷胱甘肽(glutathione, GSH)的重要组成部分, 其参与哺乳动物的多种细胞内信号转导途径和生物功能的调节. Zander-Fox等人[97]的研究中已经表明, 甘氨酸在卵母细胞的发育中起重要作用. Tartia等人[98]发现, 甘氨酸转运蛋白1(glycine transporter 1, GLYT1)在小鼠未成熟的GV卵母细胞中是静止的, 其中也含有很少的内源性甘氨酸. 然而, 在排卵开始的几个小时内, GLYT1介导的甘氨酸转运在卵母细胞中被激活, 并且卵母细胞能够使用这些甘氨酸来调节自身体积. 这些观察结果表明, 在卵母细胞中存在甘氨酸依赖性细胞体积调节机制. 使用6 mmol/L甘氨酸处理猪卵母细胞可以使ROS水平降低, 增强线粒体功能, 从而减少细胞凋亡并且调节与发育和细胞凋亡相关的基因表达, 进而对卵母细胞体外成熟和后续的囊胚发育产生有利影响[99]. Yu等人的研究还表明, 甘氨酸可以通过调节细胞内钙离子水平增强线粒体功能[100], 缓解内质网应激[101], 从而提高卵母细胞的体外发育潜能. 此外, 本团队[41]将丝氨酸甘氨酸-一碳途径(serine glycine-one-carbon pathway, SGOC)中的核心酶丝氨酸羟甲基转移酶2(serine hydroxymethyltransferase2, SHMT2)通过注射siRNA耗竭, 发现小鼠卵母细胞中丝氨酸/甘氨酸的比率降低, 说明SHMT2的敲降影响了丝氨酸向甘氨酸的转化, 为氨基酸参与卵母细胞的表观遗传调控提供了证据.

1.4 卵母细胞的核苷酸代谢

嘌呤和嘧啶核苷酸不仅组成核酸和能量载体ATP, 而且作为前体参与核苷酸辅因子的合成. 虽然近十年来人们已广泛认知一些核苷酸对减数分裂成熟的意义, 但对这些分子在卵母细胞中的代谢和合成知之甚少. 大量研究表明, 环鸟苷一磷酸(cyclic guanosine monophosphate, cGMP)和环腺苷一磷酸(cyclic adenosine monophosphate, cAMP)是调节卵母细胞减数分裂停滞和恢复的必要因素[26,28,102,103]. cGMP抑制磷酸二酯酶是嘌呤类物质使减数分裂保持抑制的机制[104]. 颗粒细胞通过利钠肽系统产生cGMP, 然后通过缝隙连接扩散进入卵母细胞中, 继而抑制PDE3A的cAMP水解活性[105]. 肌酐5-磷酸脱氢酶(inosine-5′-monophosphate dehydrogenase, IMPDH)是GTP从头生物合成中的限速酶, 可将肌酐5-磷酸转化成黄苷5-磷酸. IMPDH参与鸟嘌呤核苷酸生物合成以维持卵母细胞的减数分裂阻滞[27,106,107]. 最近, Ni等人[108]发现, 抑制卵母细胞IMPDH活性会损害卵母细胞减数分裂和发育能力.

次黄嘌呤和肌苷也涉及维持卵母细胞GV期的阻滞[27,109]. 本团队[41]的代谢组学数据显示, 黄苷和肌苷水平在卵母细胞成熟期间显著下降. 这大概反映了降低肌苷和黄苷水平以允许减数分裂恢复的必要性. 同时, 本团队还发现在减数分裂成熟的过程中, 许多核苷酸相关代谢物的丰度增加, 包括肌苷单磷酸(14倍)和胞苷(5倍). 卵母细胞中活跃的核苷酸代谢可能促进嘧啶底物的积累, 为胚胎发育早期合成DNA和RNA提供物质基础.

1.5 卵母细胞微环境的代谢调控

在COCs中, 存在一个广泛的碳水化合物、氨基酸和脂质代谢转移网络, 以支持卵母细胞的发育和成熟[30,110,111]. 卵母细胞通过分泌特定因子, 对卵丘细胞的代谢进行微调, 以满足自身代谢需求[112,113]. 此外, 这种动态关系会随着卵泡的生长和对各种激素刺激的响应而发生变化[30,110,114]. 因此, 研究卵丘细胞及周围卵泡液中的代谢产物和副产物, 有助于人们更深入了解卵母细胞成熟过程中的代谢调控机制.

COCs中, 糖酵解过程主要由卵丘细胞完成, 它将葡萄糖代谢为丙酮酸, 然后通过缝隙连接将丙酮酸转移到卵母细胞中[7,115]. 与卵巢储备正常的年轻女性(年龄小于35岁)相比, 老年女性卵巢储备功能减退(diminished ovarian reserve, DOR)的患者卵泡液中葡萄糖水平降低, 而乳酸水平升高. 这可能与卵丘细胞中葡萄糖摄取增加、乳酸产生增加以及血小板型磷酸果糖激酶表达增加有关[116].

一些氨基酸, 包括L-丙氨酸和L-组氨酸, 在小鼠中通过缝隙连接从卵丘细胞转运到卵母细胞, 因为卵母细胞不能从环境中直接摄取这些氨基酸[14]. 一项研究调查了卵母细胞周围环境中D-天冬氨酸与年龄相关的水平, 发现该氨基酸不参与蛋白质合成, 但可以诱导激素的合成与释放(例如, 在大鼠中注射该物质, 可增加LH、睾酮、孕酮和催乳素的血清水平)[117~119]. 在卵泡液中, D-天冬氨酸水平随着年龄增长, 往往在D-天冬氨酸含量较高的卵泡液中能观察到发育水平和形态学特征较好的MII卵母细胞[120].

在卵母细胞中, 胆固醇是合成类固醇激素的重要

底物之一, 也是细胞膜的重要成分之一. 卵丘细胞通过从头合成的方式产生胆固醇, 这是卵母细胞中胆固醇的主要来源. 此外, 胆固醇也与卵丘细胞从卵泡液中摄取一些脂蛋白的过程有关, 这些脂蛋白中含有胆固醇和其他脂质成分[110]. 在卵母细胞成熟过程中, 游离的脂肪酸是小鼠卵母细胞的重要能量来源之一. 一些短链脂肪酸, 如丙酸盐和丁酸盐, 是COCs的重要能量来源. 这些脂肪酸可能通过线粒体β-氧化途径被氧化成乙酰辅酶A, 然后进入三羧酸循环, 最终产生ATP作为能量来源.

在人类生殖过程中, 年龄是一个重要的影响因素, 随着年龄的增长, 女性的生育能力会逐渐下降. 通过对人卵泡液进行代谢组学分析, 发现大于35岁的女性鞘磷脂、磷脂酰肌醇和甘油磷脂代谢增强, 这表明这些代谢物可能与年龄相关的生育能力下降有关[121]. 载脂蛋白是运输脂质的蛋白质, 这些蛋白质以异源复合物的形式结合并转运脂质(HDL, LDL等). 在老年女性卵泡液中, 载脂蛋白A1和载脂蛋白CII水平下降, 而载脂蛋白E的水平增加, 这表明随着年龄的增长, 脂质转运和代谢发生了变化[122]. 这些复合物在老年女性卵泡液中的分布也发生了变化, 这表明年龄对卵母细胞成熟过程中的脂质代谢具有调节作用. 总的来说, 现有的数据表明, 在卵母细胞成熟的微环境中, 脂质水平、载脂蛋白水平及二者的相互作用水平呈现明显的年龄相关性, 这些发现为进一步了解年龄对女性生育能力的影响提供了重要的线索. 卵母细胞在这一过程中的调节作用, 及其所处微环境中的这些代谢变化, 是否可以在临床层面作为判断配子质量的指标仍有待进一步研究.

1.6　卵母细胞的胞质成熟与代谢

卵母细胞的细胞质成熟是决定其质量的核心因素之一, 这一成熟过程对卵母细胞的受精能力及随后的胚胎发育起着决定性的影响. 这包括母源mRNA的合成、活化、降解以及细胞器的有序排列等一系列复杂的过程[123]. 随着卵泡的生长, 卵母细胞生长和减数分裂所必需的基因开始转录并储存在细胞质中. 当减数分裂恢复后, 卵母细胞中的转录因染色体凝集而停止, 而储存在卵母细胞中的母源mRNA则逐渐被消耗和降解. 尽管在GV期完全生长的卵母细胞中存在大量的母源mRNA, 但它们在减数分裂成熟前处于翻译休眠状态[124~126]. 本团队[41]发现, ARA在胞质成熟的一些环节中发挥作用. 经过ARA处理的小鼠卵母细胞中, NKAP水平降低了70%, B细胞转位基因4(B cell translocation gene 4, BGT4)水平降低了80%. NKAP水平的降低会导致卵母细胞在减数分裂过程中纺锤体和染色体聚集失败. 而BGT4作为母源mRNA调控的关键因子, 调控母源mRNA的降解. 这表明在减数分裂恢复过程中ARA的下降有助于BGT4的积累, 并引发母源mRNA的降解. 在翻译水平上, 最新的研究表明, 人卵母细胞GV阶段高翻译效率的基因主要位于细胞质中, 而MII阶段高翻译效率的基因主要参与细胞核或染色体的调控[127]. 这一发现表明, 细胞质和细胞核基因的表达不是同时上调, 更可能是细胞质到细胞核基因的顺序上调, 意味着卵母细胞要首先准备其他胞质内的结构, 然后调节细胞核和染色体事件, 以实现MII卵母细胞的成熟.

卵母细胞成熟过程中会发生大量的细胞器和细胞骨架的重组, 这一过程需要消耗大量能量, 所以, 线粒体需要在精确的时间和位置提供足够水平的ATP以供能量. 能量代谢在卵母细胞的成熟过程中起着至关重要的作用, 因此ATP的含量已被作为评估人类[128,129]和小鼠[130]卵母细胞发育的指标. 纺锤体的形成和染色体的运动依赖于特定马达蛋白的表达和活性, 而这些马达蛋白的能量来源是ATP[131]. 先前的研究表明, ATP浓度的增加对于牛和人卵母细胞成熟都是必要的[132]. 含有较高ATP浓度的卵母细胞显示出显著增高的受精率和胚胎率[133]. 较低的卵母细胞ATP浓度会导致哺乳动物卵母细胞在体外成熟过程中阳性纺锤体形成率的降低[134]. 通过使用氧化磷酸化抑制剂处理小鼠卵母细胞以降低其ATP含量, 这导致具有核成熟、有正常纺锤体形成和染色体排列的卵母细胞百分比下降[135]. 由于发育完全的卵母细胞将葡萄糖代谢为丙酮酸的能力有限, 由线粒体支持的氧化磷酸化是卵母细胞ATP的主要来源. 因此, 扰乱线粒体功能的因素会成为卵母细胞胞质成熟的障碍. 由于线粒体的遗传完全来自母体, 卵母细胞中线粒体功能受损会对早期胚胎产生直接影响, 例如卵裂停滞、异常胞质分裂和卵裂球碎裂, 这些异常结果可能是由线粒体驱动的细胞凋亡导致的[136]. 这些发现有助于人们更好地理解卵母细胞的胞质成熟过程以及其在受精和胚胎发育中的作用, 为改进卵母细胞的质量提供了新的思路.

2 代谢调控卵母细胞的表观修饰

母源环境的紊乱可以对卵母细胞的质量产生不利影响. 即使将胎儿从应激环境转移到正常的子宫环境, 也可能会导致胎儿生长迟缓和发育缺陷. 由于这些胎儿的畸形情况在母体环境受到损伤之后很长一段时间才会表现出来, 因此母体营养对卵母细胞的影响可能通过表观遗传途径得以延续. 表观遗传学的一种重要机制就是印记, 其决定了基因按照亲本来源的特异性方式表达. 这种印记的表观遗传基础在于CpG序列的甲基化作用. 印记的建立过程主要发生在亲代的生殖系中, 并且在胚胎发育时期得到维持[137]. 细胞遗传信息的表观遗传机制在很大程度上是由DNA甲基化和组蛋白的翻译后修饰实现的[138]. 如果生殖细胞无法建立或维持其特异的表观遗传模式, 可能会导致胎儿生长异常、胎盘衰竭以及人类疾病的发生.

对糖尿病小鼠卵母细胞发育过程中的几个印迹基因甲基化状态进行研究, 结果显示母体糖尿病改变了Peg3差异甲基化区域(differential methylation region, DMR)的甲基化模式, 但H19和另一印记基因*Snrpn*的DMR甲基化状态无明显变化[139]. 此外, 在糖尿病小鼠的卵母细胞成熟过程中, 还观察到组蛋白H3和H4的乙酰化模式存在差异[140]. 与之形成鲜明对比的是, 无论是肥胖母鼠还是其后代, 卵母细胞印记基因的DNA甲基化均未发生改变, 但代谢相关基因的DNA甲基化却发生了变化. 在肥胖小鼠的卵母细胞中, 瘦素启动子的甲基化水平显著上升, 而过氧化物酶体增殖物激活受体(peroxisome proliferator- activated receptor, PPAR)启动子的DNA甲基化水平则降低[141]. 值得一提的是, 罗格列酮能够使肥胖小鼠的卵母细胞发育能力恢复正常[142], 这表明它的作用靶点PPARγ可能是调节代谢从而控制卵母细胞质量的关键因子. 若生殖细胞无法建立或维持其甲基化模式, 可能导致胎儿生长异常、胎盘衰竭和人类疾病发生[143].

现在人们认识到代谢物的动态变化影响表观遗传修饰的累积和去除. 许多对于DNA和组蛋白的化学修饰是来源于细胞代谢途径中间体的加合物[144]. 例如, 甲基化和乙酰化修饰取决于*S*-腺苷甲硫氨酸(*S*-adenosyl-methionine, SAM)[145]和乙酰辅酶A[146]的可用性. 此外, 它们还对两种物质非常敏感, 一种为去修饰酶辅因子如α-酮戊二酸(α-ketoglutaric acid, α-KG)和烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD^+), 另一种为表观遗传酶抑制剂的结构类似物的一类代谢物如*S*腺苷高半胱氨酸和2-羟基戊二酸(2-hydroxyglutaric acid, 2-HG)[147]. 因此, 染色质中的这些标记具有整合表观遗传调控与代谢状态的能力.

卵母细胞中DNA甲基化的建立伴随着卵母细胞的生长, 并且在小鼠卵母细胞的GV期基本完成[148]. 尽管如此, CpG和非CpG从头DNA甲基化在减数分裂成熟期间增加[148,149]. DNA甲基化的主要供体是SAM, 它是SGOC产生的关键代谢物[150,151]. SGOC途径是由叶酸和甲硫氨酸循环组成的代谢网络. 它的产物包括维持核苷酸、蛋白质和脂质生物合成的关键代谢物; 并且它还会促进甲基转移酶的反应, 从而塑造表观遗传[152]. 本团队[41]注意到, 甲硫氨酸循环中的许多代谢物(如SAM和5-甲硫腺苷)和转硫途径中间体(如谷氨酸和焦谷氨酸)在减数分裂恢复中升高. SHMT2是SGOC的核心酶, 在卵母细胞中的耗竭会导致SAM水平降低和平均基因组甲基化的减少. 此外, 来自*Shmt2*敲降卵母细胞的胚胎只有30%能够在第1.5天发育到二细胞, 并且这些受精卵的母体原核中H3K4me3的水平有着显著降低. 事实上, 胞嘧啶甲基化消耗了一个碳供体SAM, 并且胞嘧啶去甲基化过程经由TET酶介导的氧化反应需要α-KG和Fe^{2+}参与. 同样, 组蛋白甲基化和去甲基化也涉及相同类型的代谢物, 如SAM和α-KG. 尽管代谢产物与卵子发生过程中表观遗传修饰的直接证据仍然缺乏, 但已有的研究表明, 代谢物能够调控早期胚胎的组蛋白修饰. Zhao等人[153]揭示了在小鼠植入前胚胎发育期间发生代谢重塑, 并且增加2-HG含量会阻止受精后整体组蛋白甲基化标记的消除. Nagaraj等人[154]发现, 在体外培养小鼠受精卵的培养基中缺乏丙酮酸会使胚胎在二细胞期停滞, 并且H3K4Ac, H3K427Ac和H3K427me3这些表观基因组标记减少. 在分子机制方面, TCA循环的线粒体酶亚基进入早期胚胎的细胞核, 其对于产生表观遗传重塑的关键代谢物是必需的. 总之, 这些研究结果强调了代谢调节在卵母细胞和胚胎发育过程中表观遗传重塑的重要性.

NAD^+不仅作为关键酶的经典辅因子发挥作用, 而且能充当控制多种细胞信号转导途径的多功能调节剂[155,156]. 在哺乳动物中, 根据前体利用率的不同, 细胞中NAD^+的合成有三种途径: 在从头合成途径中来自色氨酸, 在Preiss-Handler途径中来自烟酸, 以及在补

救途径中来自烟酰胺核苷、烟酰胺单核苷酸(nicotinamide mononucleotide, NMN)和烟酰胺(niacinamide, NAM)[157]. 组蛋白修饰与细胞中的许多基本生物学过程相关. 一个新兴的观点是, 减数分裂阶段依赖的组蛋白修饰对哺乳动物卵母细胞的发育和成熟至关重要[158]. 组蛋白乙酰化的稳态水平, 由组蛋白乙酰转移酶和组蛋白脱乙酰酶(histone deacetylase, HDAC)控制. 目前已有17种同型的哺乳动物HDAC被鉴定出来[159], 它们通常分为三类: Ⅰ类(HDAC1, 2, 3和8)、Ⅱ类(HDAC4, 5, 6, 7, 9和10)和Ⅲ类(Sirtuins1, 2, 3, 4, 5, 6和7). 其中, Sirtuins是NAD^+依赖性赖氨酸脱酰基酶和ADP核糖基酶的保守进化的家族[138,160]. 与对照组相比, 烟酰胺单核苷酸腺苷酸转移酶2(nicotinamide mononucleotide adenylyltransferase 2, NMNAT2)缺失的小鼠卵母细胞中NAD^+含量低了60%, 组蛋白H4K16的乙酰化水平相应增加[161]. 此外, Li等人[162]也发现, SIRT2控制的组蛋白H4K16的去乙酰化对于维持卵母细胞减数分裂装置的稳定是必需的. 因此, NAD^+依赖性Sirtuins活性对于组蛋白乙酰化的调节是必须的, 而组蛋白乙酰化会进一步参与卵母细胞发育和成熟的控制.

总的来说, 母体的营养状况和环境因素在卵母细胞和早期胚胎的发育过程中起着至关重要的作用, 并且这些影响可能通过表观遗传途径得以延续.

3　卵母细胞代谢紊乱对子代健康的影响

在“健康和疾病的发育起源假说”中假定, 在关键的发育窗口期间, 不良的环境暴露会影响出生前的生长轨迹, 并且会改变生命后期的患病风险[163]. 从荷兰饥饿冬季中幸存下来的女性的后代, 在60岁时的脂肪沉积显著较高[164,165], 与未暴露于产前饥饿的女性相比, 她们的胰岛素样生长因子2编码基因的甲基化水平普遍较低[166]. 本团队[167,168]发现, 母体肥胖导致小鼠早期胚胎发育延迟和胎儿生长迟缓. 来自胚胎移植实验的证据表明, 这些缺陷表型归因于卵母细胞内的因素[169,170]. 值得注意的是, 卵母细胞对营养、化学和内分泌环境的改变特别敏感. 因此, 卵母细胞中的代谢紊乱可能起着纽带的作用, 它将母源环境的改变与子代表型相连接. Saben等人[171]证明, 母体饮食诱导的代谢综合征在小鼠模型中导致异常的线粒体跨代遗传, 该过程可能是通过雌性生殖细胞完成的. 事实上, 肥胖会导致卵母细胞质量下降, 包括减数分裂异常, 线粒体功能障碍以及氧化应激现象[40,167,172~180]. 本团队[180]最近发现, 烟酰胺磷酸核糖基转移酶(nicotinamide phosphoribosyltransferase, NAMPT)减少造成的NAD^+不足是导致肥胖小鼠卵母细胞质量受损的重要原因之一. 重要的是, 体内补充或体外添加烟酸能够改善肥胖个体卵母细胞的缺陷表型. 与之相类似的是, 肥胖小鼠口服褪黑素不仅减少了ROS的产生, 而且防止了减数分裂缺陷的产生, 从而改善了早期胚胎发育的潜力[177].

此外, 有报道称高龄产妇也会影响卵母细胞质量[181], 这是造成生殖结局不佳的主要原因[182]. 值得注意的是, 衰老伴随着多种组织和细胞NAD^+水平的逐渐下降[183]. 本团队和其他团队[161,184,185]发现, 老年小鼠卵母细胞中的NAD^+含量降低. Wu等人[161]证明, NMNAT2-NAD^+-SIRT1是介导母体年龄对卵母细胞减数分裂成熟的影响的重要途径. 同时, Miao等人[185]发现, 体内补充NMN恢复了老化卵母细胞中的NAD^+水平, 具体表现为受精能力和胚胎发育潜力增强. 然而, 这些代谢物是否影响以及如何影响生殖结局和子代健康, 在很大程度上仍然是未知的[186]. 最近, 新的研究表明, 卵母细胞代谢物, 特别是NAD^+和甲基供体SAM, 可以通过果蝇中的代谢重编程介导母体营养问题对后代的影响[187]. 但是, 哺乳动物卵母细胞暴露于异常的母源环境是否存在类似的代谢转变机制还尚不清楚.

4　代谢组学分析在生殖生物学中的应用进展

哺乳动物卵母细胞的代谢分析始于20世纪80年代, 最初使用放射性标记的底物来确定卵母细胞在发育和成熟过程中所需要的代谢产物. 这些研究包括对葡萄糖和丙酮酸的利用、核糖核苷和次黄嘌呤的摄取以及在卵母细胞发育过程中氨基酸的转运等的揭示[6,27,35,84,188~191]. 这些发现极大地提高了人们对卵母细胞代谢调控的认知, 并深化了人们对生殖生物学中这一关键领域的理解.

如今, 对卵母细胞、颗粒细胞以及卵泡液的谢组学分析已经成为当前的研究热点. 代谢组学分析致力于鉴定并量化细胞内外的全部代谢物, 不仅局限于单一物质, 还能全面研究卵母细胞和卵泡环境中的所有生化组成. Dai等人[192]通过液相色谱-串联质谱(liquid

chromatography coupled with tandem mass spectrometry, LC-MS/MS)分析，对子宫内膜异位症和不孕不育患者的卵泡液进行非靶向代谢物分析，鉴定出55种上调和67种下调的代谢物. 在子宫内膜异位症患者卵泡液中，磷脂酰肌醇显著升高，而溶血磷脂酰肌醇(lysophosphatidylinositol, LPI)减少. 这种脂代谢失调可能导致获卵数和成熟卵母细胞数减少. 有趣的是，通过给药LPI可以挽救血红素对卵丘-卵母细胞复合体扩张的阻断作用, 并刺激排卵相关基因的表达. 这一发现可能为子宫内膜异位症患者的生育治疗提供新的思路. Li等人[193]最近的研究中，运用液相色谱-质谱联用(LC-MS)技术对早期胚胎的代谢物进行了分析，鉴定了246种常见和重要代谢途径中的代谢物. 这一研究精细描绘了早期胚胎发育各个阶段的代谢活性的动态变化，这为进一步研究胚胎发育提供了参考，并为预测和改善胚胎质量的生物标志物的发现提供了新机会. 同样地，Ravisankar等人[194]在对恒河猴的研究中也运用了该技术，研究并鉴定和定量了恒河猴卵泡液中的代谢物组成，为进一步研究卵泡发育提供了基础. Gao等人[195]通过整合代谢组学和转录组学的方法, 揭示了猪卵母细胞在成熟过程中的代谢模式. 研究结果表明, 大多数氨基酸和碳水化合物在减数分裂成熟过程中增加，而脂质代谢物与核苷酸在从GV到MII阶段的转变中明显减少. 这一发现为了解卵母细胞成熟的分子机制提供了重要的线索. 在探索空气污染与卵母细胞质量的关系时，Hwang等人[196]采用了代谢组学技术. 他们发现卵泡液中的许多代谢特征与空气污染物暴露有关，而且存在一部分与卵母细胞质量相关的代谢途径也与空气污染物的暴露相关联. 这一发现有助于进一步理解空气污染对生殖健康的影响，并可能为预防生殖缺陷提供更有效的手段. 代谢组学的数据为研究卵母细胞发育的代谢调控提供了一个重要的宏观模式，也是预测卵母细胞质量的重要手段. 通过研究代谢组学数据，可以更深入地了解卵母细胞发育过程中的代谢调控机制，预测和改善卵母细胞的质量，从而预防生殖缺陷的发生.

5 总结与展望

目前，卵母细胞代谢物动力学分析仍存在许多限制，例如，可用于组学研究的材料稀缺和当前代谢组学分析结果覆盖率低等. 在这方面，一个适用于生殖细胞的代谢组学分析系统的发展，有望彻底改变人们所理解的卵子发生的代谢调控. 此外，卵母细胞不能完全脱离其卵泡来单独看待. 卵和它的伴随体细胞之间的代谢偶联对维持二者的正常功能都是必不可少的. 因此, 阐明卵母细胞和颗粒细胞之间的代谢互作将进一步改善辅助生殖技术的体外培养系统. 现有的证据表明，母源环境暴露可以通过表观遗传修饰作用于一代或者多代. 需要更深入地探讨母源环境变化影响胚胎和后代发育的机制，特别是卵母细胞代谢紊乱在其中的作用(图2). 由此可见，筛选并鉴定出上述过程的主要介导因素，对于干预和治疗女性生殖疾病和子代出生缺陷具有重要意义.

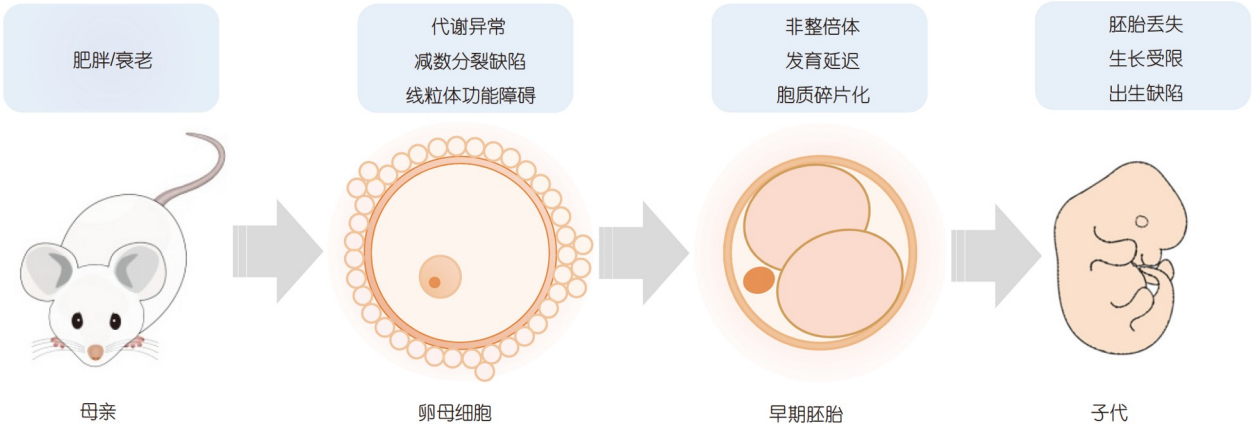

图 2 母源环境对卵母细胞代谢和胚胎发育及生殖结果产生影响的示意图

Figure 2 Schematic diagram of the influence of maternal environment on oocyte metabolism, embryo development, and reproductive outcomes

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Metabolic control of oocyte development

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Well balanced and timed metabolism is essential for oocyte development. The effects of extrinsic nutrients on oocyte maturation have been widely reported, but intrinsic control of oogenesis by intracellular metabolites and metabolic enzymes has received little attention. The comprehensive characterization of metabolic patterns could lead to more complete understanding of regulatory mechanisms underlying oocyte development. Recently the close contact between cellular metabolism and epigenetic modifications has been widely reported. In addition, oocytes metabolic disorders caused by changes in the maternal environment may affect early embryonic development and offspring health through epigenetic modifications. Here we summarize the findings on metabolic regulation in oocyte maturation. And we discuss the potential mechanisms of maternal environmental abnormalities affecting offspring health from the perspective of oocyte epigenetic modification, with a view to improving oocyte quality and female reproduction.

oocyte, metabolism, maternal environment, epigenetics, reproductive health

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