内分泌调控与代谢疾病——糖尿病早期防治 DOI:10.13406/j.cnki.cyxb.003976

孕期运动改善子代糖脂代谢的表观遗传学机制探讨

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【摘 要】代谢性疾病全球流行,孕期不良代谢状态可通过宫内编程增加子代远期代谢疾病风险。研究表明,孕期母体规律运动不仅能改善母体健康,更能显著改善子代糖脂代谢,其保护效应可持续至成年。表观遗传重编程是其中关键机制。母体运动可逆转母体宫内不良环境诱导的异常表观遗传修饰,包括DNA甲基化、组蛋白修饰、非编码RNA。本文就孕期运动改善子代代谢健康的表观遗传学机制进行综述,以期为代谢性疾病的早期干预提供新视角。

【关键词】母体运动;子代;糖脂代谢;表观遗传学
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The epigenetic mechanism by which maternal exercise during pregnancy improves glucose and lipid metabolism in offspring

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【**Abstract**】Metabolic diseases are becoming a global pandemic, and adverse maternal metabolic conditions during pregnancy can increase the long-term risk of metabolic disease in offspring via developmental programming. Studies have shown that regular maternal exercise not only improves maternal health but also significantly improves glucose and lipid metabolism in offspring, and such protective effect can last till adulthood. Epigenetic reprogramming is a key underlying mechanism. Maternal exercise can reverse aberrant epigenetic modifications induced by adverse intrauterine environment, including DNA methylation, histone modification, and non-coding RNA. This article reviews the epigenetic mechanisms by which maternal exercise during pregnancy improves offspring metabolic health, aiming to provide new perspectives for early-life intervention in metabolic diseases.

【**Key words**】maternal exercise; offspring; glucose and lipid metabolism; epigenetics

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代谢性疾病,特别是2型糖尿病(type 2 diabetes,T2D)和肥胖症,正以惊人的速度演变为全球性健康危机。数据预测显示,到2050年,全球成年糖尿病患者人数预计将达到8.53亿[1],而在年轻群体中,5~14岁和15~24岁人群的肥胖患病率已分别高达15.6%和14.2%[2]。日益普遍的久坐生活方式和高能量饮食模式共同推动了糖尿病和肥胖症患者数量的空前增长。虽然遗传与环境因素在代谢性疾病的发生中扮演着关键角色,但其确切的发病机制尚未完全阐明。因此,深入揭示其潜在机制,并强化早期预防和干预策略尤为重要且迫切。

“健康与疾病的发育起源假说”(developmental origins of health and disease,DOHaD)为理解慢性疾病的发生提供了重要视角。DOHaD理论指出,宫内不良环境暴露是子代罹患慢性疾病的关键风险因素[3]。大量流行病学与临床观察证实,母亲不健康的生活方式和代谢异常与子代肥胖、T2D及

心血管疾病的高发相关[4-9]。动物模型研究也观察到类似现象：母亲孕前及妊娠期高脂饮食（high-fat diet，HFD）可导致子代糖脂代谢紊乱[10-12]。因此，亟需有效干预措施阻断母体不良代谢的代际传递。

规律体育活动是维持健康不可或缺的要素，也是对抗代谢紊乱的重要辅助手段[13]。越来越多的证据表明，母体运动不仅对母亲自身有益，也能为子代带来显著的代谢益处。然而，其背后的生物学机制，尤其是表观遗传调控在其中扮演的角色尚不明确。鉴于胚胎期子代健康受到表观遗传机制的精密调控[14]，深入探究母体运动如何通过这一途径影响子代，具有重要的科学价值和临床意义。本文旨在从表观遗传学角度，探讨母体运动改善子代代谢健康的分子机制，为代谢性疾病早期干预提供新见解。

1 母体运动对子代代谢的益处

孕期进行规律的体育锻炼已被广泛研究，其益处涵盖母体自身及子代健康。对于母亲而言，运动可明显降低先兆子痫、妊娠期高血压、妊娠期糖尿病（gestational diabetes mellitus，GDM）、孕期体质量过度增加、分娩并发症及产后抑郁等风险，且研究证实并不会增加死产、新生儿并发症或不良出生体质量的风险[15-16]。对于子代，则观察到母体运动的后代脂肪量减少、应激耐受性增强以及神经行为成熟度提高[15,17-18]。基于这些证据，诸多国家和国际组织均建议，对于无运动禁忌证的孕妇，应鼓励她们在孕期继续或开始进行适度的体育锻炼，并强调体育活动是维持孕妇整体健康状态的关键因素[16,19-21]。《中国妊娠期糖尿病母儿共同管理指南（2024版）》也明确指出，妊娠前和妊娠早期规律运动可明显降低孕妇发生 GDM 的风险；对于已患 GDM 的孕妇，规律运动能有效改善其糖代谢状况，并减少母儿不良结局的发生；建议无运动禁忌证的 GDM 孕妇，每周至少进行 5 d、每天 30 min，或每周累计不少于 150 min 的中等强度运动[20]。

目前探讨母体运动对子代代谢稳态影响的人体研究，主要集中于子代的婴儿期。Kusuyama J 等[22]的综述系统总结了孕期运动对母体及子代的影响。多项研究结果提示，孕期体育锻炼可能对预防新生儿或儿童期的肥胖及代谢紊乱具有积极作用[23-26]。例如，有研究发现孕妇在孕中期维持较高的运动水平，能够减轻其自身胰岛素敏感性下降对新生儿脂肪堆积产生的不利影响[27]。然而，也存在部分研究报道孕期运动可能对儿童期子代产生不良影响，或者观察到肥胖孕妇子代的早期代谢危险因素似乎不受孕期生活方式干预的影响[28-30]。人体研究结果的不一致性可能与运动干预的时机选择、运动类型、样本量大小以及评估方法（如多数研究依赖问卷调查，其准确性存在局限）有关。此外，相较于动物模型，人体研究更为复杂，受多种内外部因素影响，如外部因素（运动时间、睡眠、饮食、药物）和内部因素（年龄、激素水平、种族、遗传背景及孕前身体状况）都可能调节母体运动对子代代谢的作用效果[31]。综上所述，当前关于母体运动对子代远期代谢健康影响的临床证据尚存争议，未来需要通过更大规模的临床试验，深入研究不同人群中母体运动的长期代际效应，并探索最适宜的运动类型、强度与频率。

动物研究则为深入探究母体运动对成年子代代谢健康的长期影响提供了有力支持。大量的研究证据显示，母体在孕前及孕期进行运动，能够有效减轻母体 HFD 对子代糖脂代谢造成的负面影响，减少子代脂肪含量及脂滴大小，改善葡萄糖耐量和胰岛素敏感性，并降低总胆固醇及低密度脂蛋白胆固醇水平[10,32-41]。Kasper P 等[42]进一步发现，母代运动后，子鼠肝脏呈现出与母鼠相似的代谢特征，表现为 AMP 活化蛋白激酶（AMP-activated protein kinase，AMPK）-过氧化物酶体增殖物激活受体-γ 辅激活因子-1α（peroxisome-proliferator-activated-receptor-γ-coactivator-1α，PGC-1α）信号轴活性增强，肝脏脂质代谢发生有益改变。这些结果一致表明，母体运动能够明显改善不良宫内环境对子代代谢健康的长远危害。

2 母体运动改善子代代谢的表观遗传机制

尽管研究已明确证实孕期母体运动具有代际代谢益处，但其影响子代代谢的具体机制仍处于初步探索阶段。宫内不良环境暴露子代的代谢特征表明，其基因表达经历了持久性改变。表观遗传修饰被认为是介导这种持久、可遗传性发育编程改变的关键分子机制之一[43]。DNA 序列不变的情况下，基因的表达发生可遗传性的变化。常见的表观遗传机制包括 DNA 甲基化、组蛋白修饰和非编码 RNA 调控。母体营养过剩和肥胖状态可改变修饰酶活性或表观遗传底物的可用性，这些底物参与卵母细胞发育或宫内环境中的表观遗传标记添加或去除过程，进而影响子代的表观遗传模式[44]。鉴于母代运动能够逆转母体不良环境对子代代谢的负面影响，阐明其促进子代代谢稳态的分子机制对预防代谢性疾病的代际传播至关重要。大量研究聚焦于表观遗传学，提示其可能是其中的核心机制。

2.1 DNA 甲基化

DNA 甲基化通常是指在 DNA 分子胞嘧啶第 5 位碳原子上添加甲基基团形成 5-甲基胞嘧啶的化学修饰过程，多发生于胞嘧啶-鸟嘌呤二核苷酸（CpG 位点），尤其是在基因启动子区富集的 CpG 岛。高度甲基化通常会阻碍转录因子结合或招募抑制性蛋白复合物，导致基因沉默；而低甲基化则允许基因表达。研究发现，血液或胰岛细胞中的 DNA 甲基化状态与 T2D 的发生发展显著相关[45-46]。此外，多项研究揭示了 DNA 甲基化与肥胖的关联[47-49]。越来越多证据表明，母体肥胖可诱导表观遗传改变，影响子代表型，增加子代成年后肥胖及心脏代谢疾病风险[50]。孕妇孕前超重或肥胖状态显著影响新生儿脐带血 DNA 甲基化模式[51]。1 项研究发现，胎盘和脐带中羟酰辅酶 A 脱氢酶三功能多酶复合物亚基 α

（hydroxyl acyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha，*HADHA*）和溶质载体家族2成员8（Solute carrier family 2 member 8，*SLC2A8*）基因的甲基化及表达水平与子代6岁时体质量、身高、体质指数（body mass index，BMI）、胰岛素抵抗稳态模型评估（homeostasis model assessment of insulin resistance，HOMA-IR）等代谢指标相关[52]。因此，DNA甲基化是当前研究母体运动影响子代代谢的热点表观遗传机制之一。

孕期运动干预可改变母体血液及脐带血DNA甲基化模式[53]。孕期饮食与运动干预可缓解妊娠期糖尿病在子代脐带血中呈现的甲基化特征[54]。与对照组相比，接受生活方式干预的孕妇，其子代脐带血全基因组范围内379个DNA甲基化位点（涉及370个基因）发生明显改变，这些基因功能富集于脂肪代谢和组织发育通路；其中22个位点与子代出生后3年内BMI相关[55]。除脐带血研究外，胎盘研究也提供了支持：孕前1年及孕期休闲体育活动与胎盘DNA甲基化变化相关[56]。运动干预组女性胎盘羰基还原酶1（carbonyl reductase 1，*CBR1*）基因CpG位点启动子区显著低甲基化，且其甲基化水平与妊娠晚期空腹血糖及胰岛素抵抗水平呈正相关[57]。

动物实验在不同代谢相关组织中亦得到类似结果。母体肥胖增加*PGC-1α*启动子CpG-260位点甲基化水平，母代运动可有效逆转这一效应[58]。2项独立研究也发现，母代运动促进胎儿肌肉*PGC-1α*启动子DNA去甲基化，并且这种改变可持续至子鼠12月龄，改善其运动耐力与代谢功能[59-60]。与久坐组相比，母体运动增加PR结构域蛋白16（PR domain containing 16 protein，*Prdm16*）启动子DNA去甲基化，促进棕色脂肪组织发育，从而在高能量饮食暴露时预防子代肥胖[61]。运动孕鼠和孕妇的血清及胎盘超氧化物歧化酶3（placental superoxide dismutase 3，SOD3）水平升高。升高的SOD3在胎儿肝脏中激活AMPK/十十一易位（Ten-eleven translocation，TET）信号轴，导致葡萄糖代谢基因启动子DNA去甲基化，改善葡萄糖耐量[62]。近期1项研究发现，母代运动诱导的丝氨酸蛋白酶抑制剂A3C（adipokine serine protease inhibitor A3C，SERPINA3C）通过促进子代脂肪组织Krüppel样因子4（Krüppel-like factor 4，*Klf4*）启动子去甲基化，增强Klf4表达，进而抑制子代脂肪炎症[37]。

2.2 组蛋白乙酰化

组蛋白修饰研究主要集中于甲基化、乙酰化及磷酸化。组蛋白修饰在调节骨骼肌、脂肪组织等代谢器官中代谢基因表达方面至关重要[63]。有研究发现，HFD母鼠所生子代出生后第1天，其肝脏组蛋白H3第9位赖氨酸（histone 3 on lysine 9，H3K9）乙酰化水平明显升高，而H4K16乙酰化、H3K27二甲基化及H3K9三甲基化水平未发生改变[64]。虽然直接探究母体运动与组蛋白修饰关系的研究相对有限，但先前有证据揭示，母体孕前肥胖通过可通过组蛋白H3K9me3修饰抑制异柠檬脱氢酶2（isocitrate dehydrogenase 2，*IDH2*），损害子代骨骼肌线粒体生物合成，导致全身性胰岛素抵抗[12]。关于母代运动的有益作用，有研究发现，母代运动通过诱导胎盘SOD3表达来抵消母体HFD的有害影响。SOD3有助于稳定组蛋白H3第4位赖氨酸三甲基化这一激活标记，并防止WD重复域82（WD repeat-containing 82，WDR82）蛋白的羰基化，从而维持正常的组蛋白修饰状态[65]。然而，组蛋白修饰在介导母体运动改善子代糖脂代谢中的具体作用机制有待更加深入地研究。

2.3 非编码RNA

微小RNA（microRNA，miRNA）是非编码RNA的重要组成部分，长约21~23个核苷酸，参与调控多种生理和病理过程。研究发现，miRNA在糖脂代谢中发挥关键作用[66-70]。目前，关于母体运动如何通过miRNA改善子代代谢健康的研究相对较少。然而，有研究提示miRNA表达的改变可能在子代代谢性疾病的表观遗传胎儿编程中发挥重要作用。一项研究发现，肥胖与正常体质量妇女所生婴儿的循环miR-155、miR-181a和miR-221水平存在差异[71]。动物模型显示，HFD暴露的雄性大鼠子代miR-34a-5p表达升高，且与其葡萄糖、甘油三酯、总胆固醇和低密度脂蛋白胆固醇水平呈正相关[72]。另一项研究表明，母体脂肪细胞衍生的小细胞外囊泡miRNA是胎儿肥胖的潜在调节因子[73]。

多项研究表明，母体运动可诱导母体本身、胎盘及子代的miRNA表达变化。孕期14周有氧运动训练干预增加了母体血浆miR-21-3p水平[74]。母体运动逆转了HFD抑制胎盘miR-495-5p水平，从而抑制了miR-495-5p靶向的分选蛋白7（sorting nexin 7，Snx7）并调节胎盘犬尿喹啉酸代谢途径[75]。1项研究显示，母体运动明显改变了成年子代肝脏中3种与胆固醇生物合成及表观遗传修饰调控相关miRNA的表达水平[10]。另一项研究表明，母体运动干预可逆转肥胖孕鼠子代下丘脑miR-505-5p的高表达，并减少孕期HFD摄入量[76]。这些发现表明，miRNA可能作为母体运动介导代际代谢调节的重要表观遗传媒介。由于miRNA可以透过胎盘[77]，母体运动改变的miRNA是否可以进一步影响子代，以及是否可以开发基于miRNA的干预药物，值得进一步研究。

除miRNA外，非编码RNA还包括长链非编码RNA（long non-coding RNA，lncRNA）、环状RNA（circular RNA，circRNA）等，它们不编码蛋白质但可通过多种机制调节基因表达。已有综述总结了非编码RNA在母体营养不良影响子代代谢疾病中的作用[78]。然而，lncRNA、circRNA等在母体运动影响子代代谢中作用的研究报道极少，是需要未来重点探索的方向。

3 孕期运动通过表观遗传学改善子代糖脂代谢的潜在机制

大量证据表明，肥胖和糖尿病均会改变卵母细胞和精子中的DNA与组蛋白甲基化水平、组蛋白修饰状态及非编码

RNA（如miRNA）[79]。动物模型的跨代研究揭示，表观遗传程序在生殖细胞中尤为活跃，表观遗传模式的擦除、重建与维持等过程可受到产前和（或）产后环境暴露的影响[80]。因此，孕期运动可能通过影响胚胎发育关键时期的表观遗传变化，最终改善子代的代谢健康轨迹[22]。

值得注意的是，表观遗传学可受多种环境因素影响，肠道微生物群及其代谢产物是其中备受关注的一环。现有证据表明，孕期饮食与运动可明显改变母体肠道微生物组成[81-84]。关于肠道微生物的代际作用，研究表明，通过不同方法改变母体微生物群，可经由涉及微生物代谢物、炎症细胞因子调节的分子信号传导或肠道上皮修饰等机制，引起母体及子代代谢的持久改变[85]。无菌（germ-free，GF）小鼠的子代成年后摄入HFD表现出肥胖特征，包括体质量增加和葡萄糖耐量受损。然而，孕期补充短链脂肪酸（short-chain fatty acid，SCFA）使GF母鼠的子代获得了抵抗肥胖的能力。当幼鼠断奶后接受HFD时，这种保护作用被证实由SCFA-G蛋白偶联受体41（G-protein-coupled receptor 41，GPR41）和SCFA-G蛋白偶联受体43（G-protein-coupled receptor 43，GPR43）轴介导[86]。因此，肠道菌群组成的改变及其代谢产物的产生，很可能在介导母体运动对子代代谢的积极影响中扮演着重要角色。

肠道微生物群可产生多种生物活性代谢物，其中部分可作为表观遗传底物、辅助因子或表观遗传酶活性调节剂，通过影响DNA或组蛋白修饰所需的供体底物参与表观遗传调控，进而修饰宿主基因表达[87-90]。肠道菌群可产生叶酸，叶酸参与一碳代谢，促进S-腺苷甲硫氨酸（S-Adenosylmethionine，SAM）生成，为DNA和组蛋白甲基化提供甲基。一项前瞻性队列研究显示，母体充足的叶酸水平可能有助于减轻与母体肥胖相关的儿童负面代谢影响[91]。动物研究也报道，孕期补充叶酸可减少HFD喂养大鼠雄性子代的肝脏脂肪变性[92]。胆碱是另一种参与一碳代谢的重要营养素，是表观遗传调控的甲基供体，其代谢也受肠道微生物影响。研究表明，母体消耗胆碱的肠道细菌减少了甲基供体可用性，影响胆碱代谢，并改变了成年小鼠及其子代的全基因组DNA甲基化模式[93]。在母体肥胖模型中补充胆碱可改善雄性子代的糖脂代谢[94-95]。肠道菌群还可调节表观遗传修饰酶活性。肠道微生物群分解膳食纤维产生大量SCFA（如乙酸盐、丙酸盐、丁酸盐）。其中丁酸盐和丙酸盐被认为是组蛋白去乙酰化酶（histone deacetylase，HDAC）的抑制剂。抑制HDAC活性导致组蛋白赖氨酸残基乙酰化水平升高，通过松弛染色质结构促进基因转录[96]。SCFA也可作为系统微生物诱导宿主染色质状态变化的介质，可直接转化（乙酸）或氧化（丙酸和丁酸）为组蛋白乙酰基转移酶底物乙酰辅酶A[97]。Kimura I等[86]发现，孕期来自母体肠道微生物群的SCFA被胚胎交感神经、肠道和胰腺中的GPR41和GPR43感知，影响胎儿代谢和神经系统发育。该研究揭示了母体肠道环境、SCFA与代谢综合征发育起源间的密切联系。总之，这些研究初步表明，肠道微生物群衍生的代谢物可能通过充当连接微生物与宿主表观遗传调控的桥梁，部分解释母体运动带来的代际代谢益处，这有待未来深入探索和验证。

4 结 语

代谢性疾病的全球性流行构成了前所未有的公共卫生挑战，而孕期肥胖及相关代谢性疾病患病率的急剧攀升，使得这一挑战更为严峻。其影响深远而复杂，不仅直接损害母体健康，更可能通过宫内编程效应对子代的长期健康产生深远的负面影响。运动作为一种安全、经济且可及的健康生活方式，其价值在孕期健康管理中日益凸显。大量研究证据不断证实：母体运动不仅为母亲自身带来多重健康效益，更能为子代提供重要的代谢保护，且这些有益影响可能持续至成年期。在探索其作用机制的过程中，表观遗传调控逐渐崭露头角，被视为介导母体运动代际保护效应的关键机制。从DNA甲基化、组蛋白修饰到非编码RNA调控，关键分子和通路的发现为理解母体运动如何重编程子代代谢提供了重要线索。然而，目前对具体机制的认识仍是“冰山一角”。不同运动模式（类型、强度、频率、时机）对特定表观遗传标记的影响是否存在差异、表观遗传改变如何在代际间稳定传递并长期维持其效应、这些机制在不同人群中是否存在异质性等许多关键问题仍亟待解答。目前基于人体的深入研究仍然有限，限制了结论的普适性和临床转化。未来需要设计并实施严谨的大规模随机对照临床试验，进一步验证母体运动在不同人群中的长期代际效应，并深入探究何种运动方案能为母婴带来最大化的健康收益。同时，亟需结合多组学技术和动物模型，解析母体运动诱导的保护性表观遗传重编程机制，识别更多关键调控节点，在生命最早的窗口期实现对代谢性疾病的源头预防和阻断，为改善代际健康开辟新的路径。

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