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综 述

DNA甲基化在早期营养程序化中的作用及临床意义研究进展

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摘 要：生命早期营养环境不仅与儿童早期生长发育相关，也影响成年期健康，大量流行病学和动物研究表明早期营养程序化是其重要的生理病理机制。DNA甲基化是营养程序化的重要机制之一，在DNA甲基转移酶的催化作用下，DNA特定碱基共价结合甲基基团，进而调节基因表达。本文总结了DNA甲基化在生命早期过度喂养致关键代谢器官“异常发育规划”继而引起子代远期肥胖、代谢紊乱中的作用，探索通过膳食营养干预调节DNA甲基化水平，以“去编程”的方式早期预防或逆转机体代谢紊乱发生的临床意义。

关键词：早期过度喂养；肥胖；营养程序化；DNA甲基化；膳食

Research progress on the role and clinical significance of DNA methylation in early nutritional programming

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Abstract: Early life nutritional environment is not only associated with the growth and development of children, but also affects the health of adults. Numerous epidemiological and animal studies suggest that early nutritional programming is an important physiological and pathological mechanism. DNA methylation is one of the important mechanisms of nutritional programming, which is catalyzed by DNA methyltransferase, a specific base of DNA covalently binds to a methyl group, to regulate gene expression. In this review, we summarize the role of DNA methylation in the “abnormal developmental planning” of key metabolic organs caused by excessive nutrition in early life, resulting in long-term obesity and metabolic disorders in the offspring, and explore the clinical significance of regulating DNA methylation levels through dietary interventions to prevent or reverse the occurrence of metabolic disorders in the early stage in a “deprogramming” manner.

Key words: early overnutrition; obesity; nutritional programming; DNA methylation; diet

1 早期营养环境与发育编程

大量的临床和动物研究显示，生命早期不良的营养环境与成年期的肥胖及糖尿病、高血压、高血脂等代谢综合征的发生密切相关[1, 2]。“健康和疾病起源学说”(developmental origins of health and disease, DOHaD) 认为胎儿宫内发育时期及生后早期经历着复杂的编程过程，包括组织器官的结构、代谢功能的表现等。胎儿可适应不良环境以保证生存，一旦超出胎儿的适应能力，则会出现异常编程，产生不利且长期的后果[3]。1998 年，Lucas 将在发育的关键或敏感时期遭遇不良营养环境，机体重要代谢器官的结构及生理功能发生重新设定并持续至成年，增加个体在随后生命过程中罹患肥胖、代谢综合征等疾病的发生风险定义为“营养程序化”(nutritional

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programming)[4]。营养程序化的敏感时期可以从胎儿期、婴儿期甚至延伸到青春期。

目前有关营养程序化的机制包括：1) 通过DNA甲基化、组蛋白修饰、非编码RNA、基因组印记等表观遗传修饰介导代谢程序化改变；2) 重要代谢器官如肝脏、肌肉及脂肪的结构和功能发生持续性改变；3) 多种内分泌轴信号通路调控变化和重塑，引起永久性代谢改变[5]。母孕期及婴儿生后早期的营养状况 (营养过剩或营养不良) 可导致子代适应性发育，产生生命早期表型的“可塑性”[6, 7]。大量研究表明，心脏、胰腺、肝脏和下丘脑的组织重塑是对早期不良营养环境的一种程序化改变，表观遗传效应被认为是这种“记忆”背后的一种机制[8, 9]。在生殖细胞和胎儿发育及生后早期，没有基因突变的表观遗传修饰更容易被不良环境诱导，相对稳定地传递到成人，并诱发成年后代的代谢综合征的发生[10]。

2 营养程序化与DNA甲基化

DNA甲基化是研究最多的可遗传表观学机制之一，是指在DNA甲基转移酶 (DNA methyltransferases, DNMTs) 的作用下，甲基供体S-腺苷甲硫氨酸 (S-adenosylmethionine, SAM) 上的甲基共价结合到DNA胞嘧啶5号碳原子上，形成5甲基胞嘧啶 (5-methylcytosine, 5mC)，而不改变DNA序列的可遗传变化[11–13]，如图1所示。DNMT3A、DNMT3B及其辅因子DNMT3L参与DNA甲基化的从头建立，而DNMT1在复制及有丝分裂的过程中维持DNA甲基化模式，但目前有研究发现DNMT3A、DNMT3B也参与到了DNA甲基化的维持中，这三种DNMTs都是胚胎或新生期发育过程中DNA甲基化模式正确构建所必需的[11, 14–16]，小鼠缺乏DNMT1具有胚胎致死性[17]。大量研究证实启动子或增强子区域DNA甲基化可通过抑制转录因子的结合或形成转录抑制复合物，稳定地沉默基因表达，这个过程常伴随着组蛋白修饰和染色质结构的变化，间接抑制转录。与启动子DNA甲基化不同，基因体DNA甲基化修饰可能激活转录过程，这可能与基因体中包含沉默元件相关，可能起到替代启动子，预防基因体内部转录起始的作用[18–20]。

DNA甲基化过程是动态可逆的，在复制过程中由于缺乏DNMTs的维持作用，5mC可发生被动去甲基化，而甲基胞嘧啶双加氧酶 (ten-eleven translocation methylcytosine dioxygenases, TETs) 可将5mC逐步氧化为5-羟甲基胞嘧啶 (5-hydroxymethylcytosine, 5hmC)、5-甲酰胞嘧啶 (5-formylcytosine, 5fC) 和5-羧基胞嘧啶 (5-carboxylcytosine, 5caC)，随后可以被胸腺嘧啶DNA糖基化酶 (thymine DNA glycosylase, TDG) 迅速切除，通过碱基切除修复 (base-excision repair, BER) 机制完成主动去甲基化[21, 22]，如图1所示。

DNA甲基化的水平受到衰老、营养、环境暴露、生活方式等影响，与DNMTs、TETs及甲基供体SAM水平密切相关。SAM来自于甲基营养素维生素 (叶酸、核黄素、维生素B12、维生素B6、胆碱) 和氨基酸 (蛋氨酸、半胱氨酸、丝氨酸、甘氨酸) 等，这些物质的代谢不平衡会导致DNA甲基化的模式改变[23]。生命早期既是机体组织、器官、系统不断发育成熟的窗口期，亦是DNA甲基化模式构建的重要阶段，DNA甲基化模式在胚胎、胎儿期及生后早期经历两次去除及重新建立，对子代正常生长发育十分重要，且对营养环境敏感[13, 24, 25]。在这一窗口期营养紊乱引起的表观遗传改变可能会持续到成年期，使个体发生代谢改变，从而导致远期代谢紊乱的发生[26]。临床及动物研究表明，在母孕期、哺乳期或子代生后早期的过度喂养可导致子代关键代谢器官的DNA甲基化异常，这与远期的肥胖、胰岛素抵抗、2型糖尿病 (type 2 diabetes, T2D)、非酒精性脂肪肝等的发生密切相关，而在哺乳期或生后早期通过补充甲基供体饮食，可逆转表观遗传编程异常导致的肥胖及糖耐量受损[26–29]。本文围绕DNA甲基化在生命早期过度营养致机体代谢改变中的作用进行综述。

3 早期过度营养通过DNA甲基化影响代谢程序化

3.1 临床研究

已有研究显示，人类早期营养环境与DNA甲基化变化相关。荷兰的回顾性研究显示，经历围产期饥荒的子代个体，在60年后与未暴露于饥荒的同性兄弟姐妹相比，胰岛素样生长因子2基因位点DNA甲基化水平降低，首次证明早期营养条件可导致人类表观遗传的改变且持续一生[30]。而近年来Sharp等人的研究发现，相较于正常体重母亲后代，肥胖母亲后代在脐血中存在不同的DNA甲基化差异位点且子代出现明显的肥胖。其中与母亲肥胖相

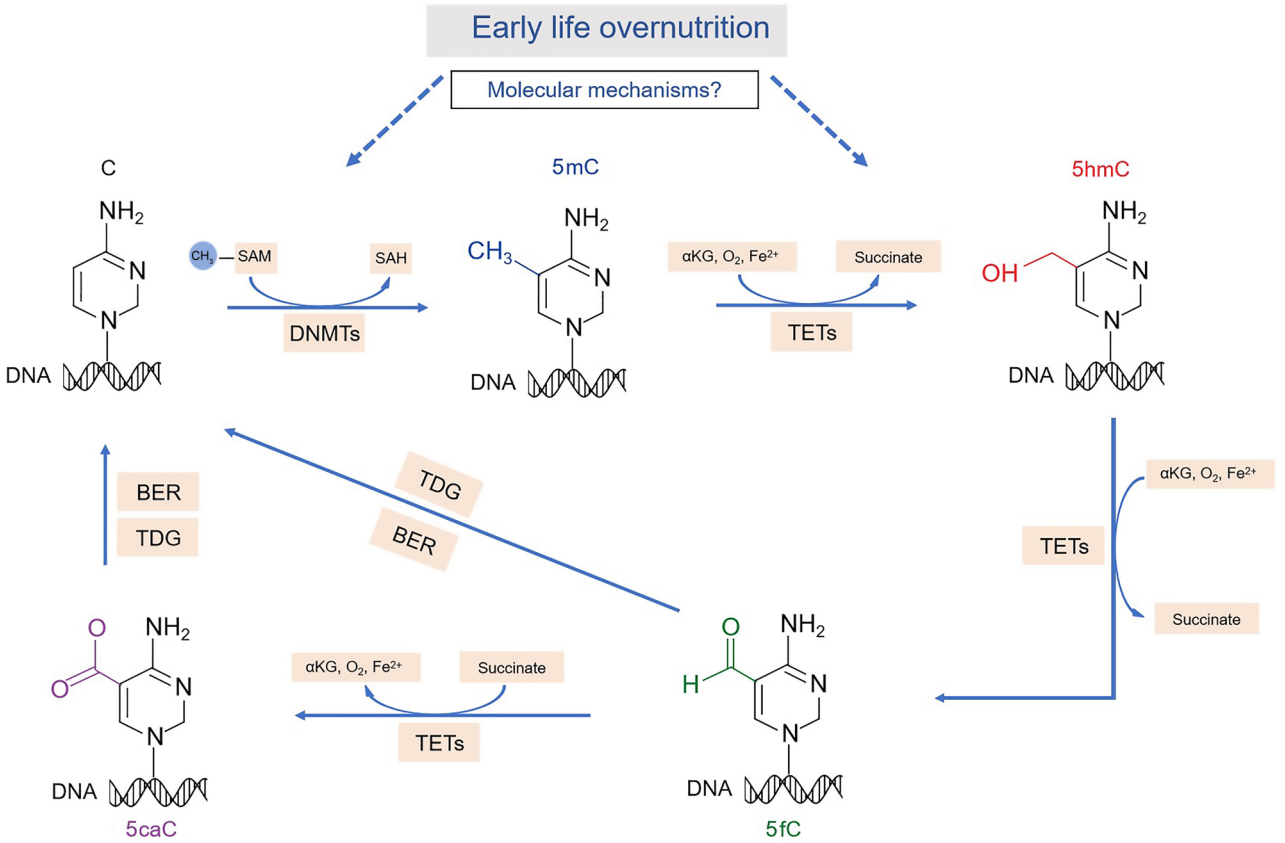

图 1. DNA甲基化模式调控机制

Fig. 1. Regulatory mechanisms of DNA methylation patterns. C: cytosine; 5mC: 5-methylcytosine; 5hmC: 5-hydroxymethylcytosine; 5fC: 5-formylcytosine; 5caC: 5-carboxylcytosine; DNMTs: DNA methyltransferases; SAM: S-adenosylmethionine; SAH: S-adenosyl-homocysteine; TDG: thymine DNA glycosylase; BER: base-excision repair; αKG: α-ketoglutarate; TETs: ten-eleven translocation methylcytosine dioxygenases. This iron (Fe^{2+})-catalyzed reaction concomitantly convert αKG and oxygen (O_2) to succinate and carbon dioxide (CO_2).

关的高甲基化与后代肥胖呈正相关，而与母亲肥胖相关的低甲基化与后代肥胖呈负相关，表明 DNA 甲基化可能介导子代肥胖的发生过程[31]。最新研究发现，肥胖母亲后代相较于正常体重母亲后代外周血中胰岛素分泌相关基因 DNA 甲基化发生了明显改变[32]。全基因组甲基化测序发现，与非糖尿病母亲后代相比，糖尿病母亲后代的外周血白细胞中与 T2D 和单基因糖尿病相关的基因，及参与胰腺发育、维持 β 细胞对葡萄糖的反应性和胰岛素分泌的 WNT 和 Notch 信号通路出现差异性甲基化，说明生命早期暴露于高血糖的环境影响参与 β 细胞功能基因的甲基化，并增加暴露者患 T2D 的风险[33]。相似的，孕期高血糖暴露的母亲增加其子代肥胖及新生儿瘦素血症的风险，可能通过 DNA 甲基化调节瘦素途径参与了儿童肥胖的发生[34]。

最近 Robinson 等人在雅芳父母与子女纵向研究队列研究 (Avon Longitudinal study of Parents and Children, ALSPAC) 中发现，婴儿期体重快速增长与儿童期单个 CpG 位点甲基化增加有关，且其中一个位点甲基化水平在青春期超重 / 肥胖青少年中更高[35]。儿童 / 青少年 BMI/ 肥胖与儿童 / 青少年 DNA 甲基化关系的研究显示二者存在关联性，提供了大量远期肥胖发生的可能预测指标[36–40]。研究发现超重或肥胖合并胰岛素抵抗的青少年外周血瘦素和脂联素启动子的甲基化状态显著下降，提示 DNA 甲基化可能参与了肥胖及其相关代谢并发症的发生和发展[39]。以上研究证实母亲孕期的肥胖可导致子代 DNA 甲基化水平的差异，儿童青少年超重 / 肥胖与 DNA 甲基化模式相关，但不能推论因果关系。

3.2 动物研究

3.2.1 DNA甲基化与下丘脑

大脑是在生后早期经历成熟的一个关键器官，

下丘脑 - 垂体轴是机体食物摄入及能量代谢平衡的重要调节器。越来越多的证据表明，围产期暴露于不良营养环境导致终生代谢紊乱发生，可能是由于调节能量平衡的下丘脑通路潜在发育程序化改变所致 [41]。研究证实母亲孕期或生后早期高脂饮食母鼠子代出现肥胖及代谢异常，同时在哺乳期调整每窝的仔数为 3 只 (小窝喂养) 诱导生后营养过剩，则加剧了这些改变。这些母鼠后代下丘脑抑制食欲的前阿黑皮质素 (proopiomelanocortin, POMC) 基因的甲基化水平增加，而促进食欲的神经肽 Y (neuropeptide Y, NPY) 基因呈现低甲基化改变，调节二者转录活性及表达水平，POMC 和 NPY 作为食欲调节的重要分子，在控制能量平衡中起着关键作用 [42, 43]。

近年来，Li 等人通过下丘脑神经元及非神经元细胞的基因组 DNA 甲基化图谱分析发现这两种细胞间 DNA 甲基化差异大多是在生后建立的，强调了生后早期亦是小鼠下丘脑细胞类型特异性表观遗传模式形成的关键窗口期 [44]。已有研究表明小窝喂养的大鼠在哺乳期摄乳量增加，乳汁蛋白质含量显著降低，脂质含量增多，其生后体重迅速增加，且成年期出现肥胖、胰岛素抵抗、糖耐量异常 [45]。Plagemann 等人在小窝喂养的大鼠中发现下丘脑 POMC 启动子两个 Sp1 相关 DNA 结合序列高甲基化，影响瘦素和胰岛素对 POMC 表达的调节作用，POMC 表达降低，子代摄食增多 [46]。此外，生后早期过度喂养可提高下丘脑胰岛素受体启动子 (insulin receptor promoter, IRP) 区域 DNA 甲基化水平，参与下丘脑胰岛素抵抗发生的过程 [47]。这些下丘脑基因的表观遗传变化，涉及胰岛素信号转导基因、POMC 和 NPY 等基因，通过表观遗传修饰规划大脑饱腹感通路，可能永久地增加了能量摄入。

3.2.2 DNA甲基化与脂肪组织

研究表明胚胎、胎儿期或生后早期均是白色脂肪组织 (white adipose tissue, WAT) 发育的高度敏感期，此时遭遇不良营养环境可导致子代肥胖与代谢紊乱的发生 [48, 49]。一项利用转录组测序及全基因组简化亚硫酸盐测序 (reduced representation bisulfite sequencing, RRBS) 结合分析的结果显示，孕前及妊娠期肥胖的母鼠子代 WAT 中脂肪生成的基因表达明显上调，包括体内成脂调节因子 [过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ, PPARγ)、C/EBP-α、C/EBP-β、Zfp423]、脂合成相关关键酶及核转录因子 (FASN, SREBP-1c)，这与肥胖母鼠子代前脂肪细胞分化增加及发育相关基因的 DNA 甲基化变化有关 [50]。

婴儿期和青春期是生后脂肪细胞分化成熟的关键期 [51]。脂肪酸代谢的关键酶硬脂酰辅酶 A 去饱和酶 -1 (stearoyl-CoA desaturase-1, SCD1) 能将饱和脂肪酸 (如棕榈酸和硬脂酸) 转化为单不饱和脂肪酸 (如棕榈油酸和油酸)，以此作为底物合成甘油三酯。研究发现摄入的多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 中 n-6/n-3 PUFA 比值过高可导致肥胖的发生 [52, 53]，而孕期补充中链脂肪酸的大鼠可预防其子代晚期暴露于高脂饮食导致的肥胖 [54]。哺乳期高脂饮食大鼠母乳脂肪酸中长链脂肪酸含量增加，中链脂肪酸比例下降，不饱和脂肪酸中 n-6/n-3 PUFAs 比值增加，其后代生殖周白色脂肪 (epigonadal white adipose tissue, eWAT) 中脂肪代谢关键酶 SCD1 启动子区域甲基化水平显著降低，与转录因子 PPARγ 结合增加，SCD1 表达水平及活性增加，子代 eWAT 成脂转录信号增强，内脏脂肪含量明显增加，说明母乳中的脂肪酸可能是生后早期的关键代谢改变因素 [55]。棕色脂肪组织 (brown adipose tissue, BAT) 是机体重要的产热脂肪组织，孕期及哺乳期高脂饮食的大鼠，其子代 BAT 结构及功能紊乱，ACAA2、ACSL1 及 COX7A1 等产热和脂肪酸氧化相关基因甲基化水平增高，表达水平下调，导致成年期产热代谢及脂肪酸氧化异常，能量代谢障碍，出现肥胖及代谢异常 [56, 57]。

3.2.3 DNA甲基化与肝脏

一项全基因组分析显示，小鼠及人类的胎儿和新生儿肝脏许多基因的 DNA 甲基化水平发生了明显的变化，提示 DNA 甲基化在肝脏发育规划中可能起到了重要作用 [58, 59]。高脂、高能量饮食喂养母孕鼠，其子代出现代谢紊乱，而肝脏 DNA 整体甲基化比例显著高于普通饲料喂养的母鼠子代，且这些基因大多是在启动子区域发生了高甲基化，同时 mRNA 及蛋白表达水平下降，如 PPARγ 和肝脏 X 受体 a，其与肝脏脂质代谢密切相关 [60]。相似的，在母鼠孕期及哺乳期高脂饮食喂养的子代中，细胞周期蛋白依赖性激酶抑制剂 1A (cyclin dependent kinase inhibitor 1A, Cdkn1a) 特定 CpG 位点及第一外显子呈现出低甲基化状态，Cdkn1a 表达上调。Cdkn1a 是一种细胞周期抑制剂，能够抑制肝细胞生长，提示高脂饮食的母鼠子代可能存在早期肝功能障碍，且更易出现持续肝功能障碍 [61]。母亲孕前期高脂饮

食持续到哺乳期，其子代肝脏胰岛素受体底物 2 (insulin receptor substrate 2, Irs2) DNA 甲基化水平增高，表达水平降低，而抑制胰岛素功能的丝裂原活化蛋白激酶激酶 4 (mitogen-activated protein kinase kinase 4, Map2k4) 基因则呈现出低甲基化，表达水平相应增加，使其子代患糖尿病风险增加 [62]。

最近，有研究表明出生后的饮食可以调节肝脏基因表观遗传修饰，以适应营养环境的改变。在高脂蔗糖饮食致肥胖的母鼠哺乳期间补充甲基供体可减少子代 20 周龄时肝脏脂质积累，证明生后早期甲基营养素的保肝作用。生后早期甲基供体补充也对应于更高的肝脏瘦素受体表达以及 DNMTs 变化，这表明 DNA 甲基化参与了肝脏转录组谱和代谢改变 [28, 63]。

3.2.4 DNA甲基化与肌肉组织

一项母孕期高脂饮食小鼠子代骨骼肌代谢异常的研究证实，母孕期高脂饮食的小鼠子代出现肥胖、胰岛素抵抗，其与骨骼肌胰岛素抵抗密切相关的核转录因子 Nr4a1 (nuclear receptor subfamily 4 group A member 1) 启动子呈低甲基化，表达明显下降。而运动治疗后 Nr4a1 甲基化水平及表达恢复正常，且小鼠的胰岛素抵抗得到了明显的改善 [64]。相似的，同一高脂喂养的母孕鼠模型中，子代骨骼肌中促进能量消耗的重要基因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, PGC1α) 启动子高甲基化，与基因表达呈负相关，子代出现胰岛素抵抗及代谢异常，而母亲运动有助于降低子代 PGC1α 启动子甲基化水平，恢复 PGC1α 及其靶基因表达，改善子代 9 月龄时的代谢功能障碍 [65]。Liu 等人研究发现早期过度喂养的成年雌性大鼠会出现明显的骨骼肌胰岛素抵抗，而在肌肉组织中，两个关键胰岛素信号基因胰岛素受体底物 1 (insulin receptor substrate 1, Irs1) 和胰岛素依赖性葡萄糖转运蛋白 4 (glucose transporter 4, Glut4) 的启动子出现 DNA 甲基化增加，这些变化与肌肉中 Irs1 和 Glut4 的表达降低相关 [66]。因此早期的过度喂养可通过 DNA 甲基化调节肌肉组织关键代谢分子表达，程序化影响成年期子代骨骼肌代谢。

3.2.5 DNA甲基化与胰腺组织

Dhawan 等人研究表明，出生后 DNA 甲基化在胰岛 β 细胞的发育及功能成熟中发挥着重编程的作用。DNMT3A 通过抑制胰岛 β 细胞中关键基因启动新陈代谢程序，从而使胰岛素能够对机体血糖水平的变化做出反应，调节机体代谢。构建胰岛 β 细胞 DNMT3A 特异性敲除小鼠模型，发现其胰岛 β 细胞失去了感受葡萄糖刺激的胰岛素分泌功能，如同未成熟的胰岛 β 细胞，餐后血糖调节功能异常，表明在发育过程中 DNA 甲基化参与了胰岛 β 细胞成熟的表观遗传学机制 [67]。早期过度营养环境可引起子代胰岛素抵抗，通过基因组规模的 DNA 甲基化分析，Li 等人观察到衰老和小窝喂养均可导致胰岛广泛的 DNA 甲基化改变，且二者影响的区域有显著重叠，这表明小窝喂养的小鼠胰岛中表观遗传衰老加速。且断奶和成年期与胰岛素分泌有关的基因 L 型钙通道 α1I (calcium channel, voltage-dependent, α1I, Cacna1i) 和钠通道蛋白 10 型 α 亚基 (sodium channel protein type 10 subunit α, Scn10a) 的 DNA 甲基化增加，胰岛 β 细胞功能下降，且子代表现出对葡萄糖反应异常，证实了胰岛的表观遗传重塑可能介导了早期过度喂养动物胰岛素分泌受损的过程 [68]。

DNA 甲基化修饰既是动态的，可因环境刺激而改变的，又是稳定的，可通过跨代遗传方式对子代产生重要影响 [69]。在动物模型中已证实，亲代暴露于环境因素会在未暴露的子代中引起表型效应 [70]。因此积极探索 DNA 甲基化在早期过度喂养致子代肥胖及代谢紊乱发生过程中的具体机制 (图 2)，进一步采取可能的针对性治疗措施对母亲及子代健康都是至关重要的。

4 营养调节DNA甲基化在生命早期肥胖及代谢紊乱治疗中发挥的作用

生命早期表观遗传模式的建立易受到环境的影响，目前有越来越多的研究证实不同营养干预可调节整体 DNA 甲基化水平，或在基因的特定位点修饰 DNA 甲基化模式，影响远期代谢 [71–74]。营养可通过改变 DNA 甲基化所需的底物 (SAM、S- 腺苷 -L- 高半胱氨酸、甲基供体) 或改变 DNMTs 及 TETs 的表达或活性影响 DNA 甲基化过程 [23, 25]。

研究发现高脂或高脂蔗糖饮食致肥胖的母孕鼠在孕期、哺乳期补充蛋氨酸，可改善子代成年期肥胖及肝脏脂质堆积，这与 DNMTs 表达水平变化、致肥胖相关基因 (PPARγ, FASN, Adiponectin) DNA 甲基化水平及表达水平的改变密切相关 [63, 71]。相似的，另一项研究发现哺乳期间给肥胖母鼠的子代口服补充生理剂量瘦素，可通过其调节下丘脑 POMC

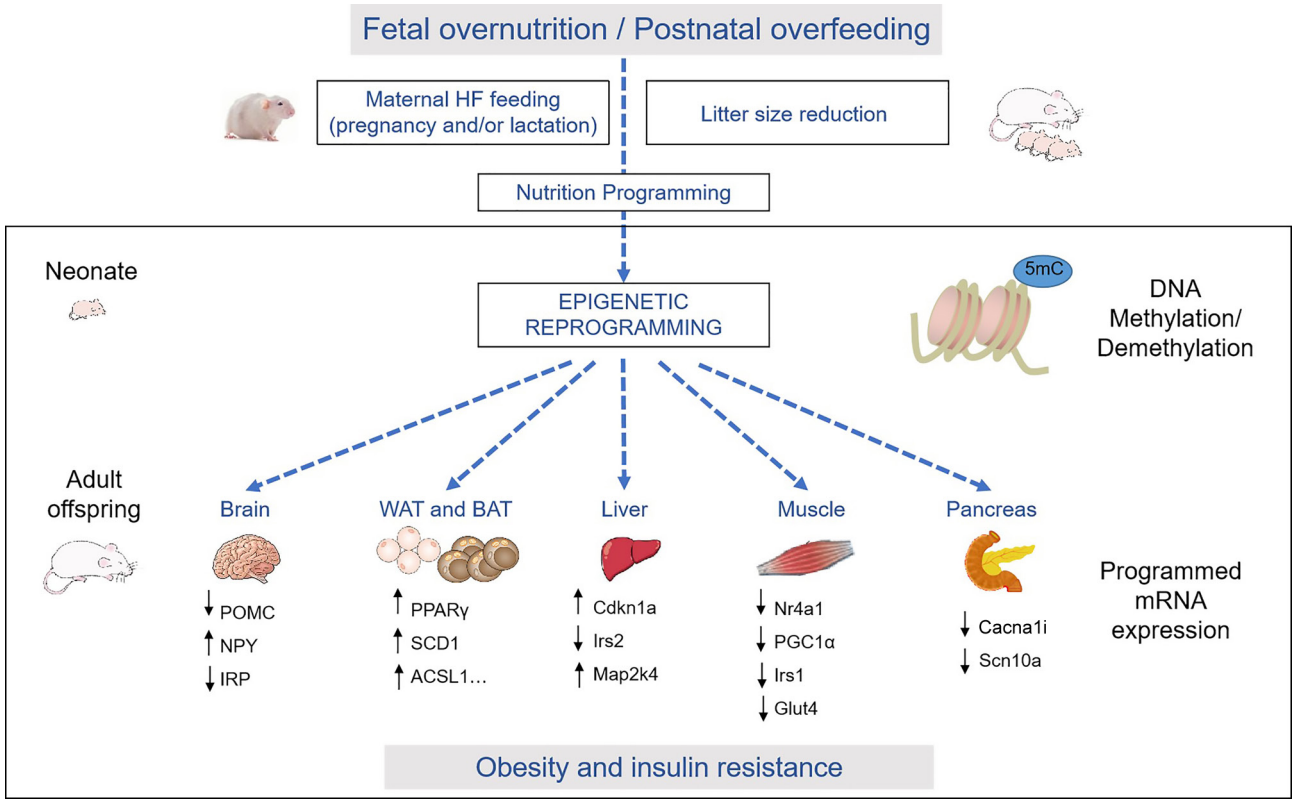

图 2. DNA甲基化在早期过度喂养致各组织器官代谢程序化中的分子机制

Fig. 2. Molecular mechanisms of DNA methylation in early overnutrition causing metabolic programming in various tissues and organs. HF: high fat; WAT: white adipose tissue; BAT: blown adipose tissue; 5mC: 5-methylcytosine; POMC: proopiomelanocortin; NPY: neuropeptide Y; IRP: insulin receptor promoter; PPARγ: peroxisome proliferator-activated receptor γ; SCD1: stearoyl-CoA desaturase-1; ACSL1: acyl-CoA synthetase long chain family member 1; Cdkn1a: cyclin dependent kinase inhibitor 1A; Irs2: insulin receptor substrate 2; Map2k4: mitogen-activated protein kinase kinase 4; Nr4a1: nuclear receptor subfamily 4 group A member 1; PGC1α: peroxisome proliferator-activated receptor γ coactivator-1α; Irs1: insulin receptor substrate 1; Glut4: glucose transporter 4; Cacna1i: calcium channel, voltage-dependent, α1I; Scn10a: sodium channel protein type 10 subunit α.

甲基化改善成年期超重及肥胖，且在断乳后暴露于高脂饮食时更能够抵抗肥胖及其相关并发症的发生[75, 76]。Liu 等人在早期过度喂养的小窝模型中发现，断奶后早期适当控制能量摄入可通过调节下丘脑 POMC 及 NPY 的 DNA 甲基化及表达水平，逆转早期过度喂养对下丘脑食欲调节机制的营养程序化影响，从而对体重稳态的调节产生更持久的影响[73]。尽管甲基供体可以改变 DNA 甲基化模式，但对于导致表观遗传标记变化的必要剂量和饮食暴露的确切持续时间及干预窗口期尚不明确，亟待进一步研究。

5 总结与展望

综上所述，早期过度喂养会引起 DNA 甲基化修饰改变，导致远期肥胖及代谢异常的发生和发展。调节组织器官中关键分子的甲基化及表达水平，进而改善代谢紊乱，似乎是一种“逆转编程”治疗代谢异常的可行途径，为预防儿童及成年疾病开辟了新思路。但仍然存在一些问题。目前大多数的研究仍是通过寻找候选基因，报告单个基因位点的表观遗传修饰，而高通量技术进行全基因组甲基化筛查，可以更全面地评估生后早期营养对表观遗传规划的影响。此外，将早期过度营养与肥胖表观遗传规划联系起来，关键是要确定哪些饮食因素和信号通路可以驱动表观遗传修饰，进一步研究通过营养干预改变表观修饰，如何特异性作用于某些靶器官而不对全身甲基化水平产生影响，明确干预窗口期、持续的时间及剂量，以确定代谢性疾病的表观遗传编程是否可以在以后的生活中预防或逆转，探索生命早期存在的预测未来代谢性疾病风险的表观遗传标记。

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