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母乳成分改变影响子代脂肪肝发生的研究进展

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摘 要：近年来，哺乳期不良母体因素导致的乳汁成分改变对个体生长发育以及代谢性疾病发生的影响受到越来越多的关注。乳汁作为哺乳动物出生早期唯一的营养来源，其成分的改变可能会影响子代整体代谢稳态，进而导致子代代谢性疾病的发生。大量的动物实验表明，哺乳期不良母体因素可改变乳汁成分，同时导致哺乳期子代脂肪肝，并且可持续至成年。该文将就哺乳期不良母体因素导致乳汁成分改变对子代脂肪肝发生的影响及其可能机制进行综述，旨在更新哺乳期不良母体因素对子代肝脏脂代谢功能影响的认识，并为产妇的健康饮食提供参考。

关键词：哺乳期；乳汁成分；脂肪肝；表观遗传修饰；外源物
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Influence of changes in breast milk composition on fatty liver of offspring: an update

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Abstract: In recent years, more and more attention has been paid to the influence of changes in breast milk composition, which may be caused by adverse maternal factors during lactation, on the individual growth and development and the occurrence of metabolic diseases in offspring. Breast milk is the only source of nutrients in the early life of mammals, and changes in its composition may affect the homeostasis of integral metabolism in offspring, and consequently lead to metabolic diseases. A large number of animal experiments have shown that adverse maternal status during lactation can change the composition of breast milk, and simultaneously lead to fatty liver in suckling infants, and even continue to adulthood. This review focused on effects of changes in breast milk composition on fatty liver in offspring and the possible underlying mechanisms. This review may help us to update the understanding how adverse maternal factors affect lipid metabolism function of the offspring, and to provide a reference for the maternal diet during lactation.

Key words: lactation; breast milk composition; fatty liver; epigenetic modification; xenobiotics

脂肪肝，又称为肝脏脂肪变性，是常见的代谢性疾病，主要病理表现为甘油三酯在肝细胞中过度蓄积。如不加干预，脂肪肝可能会发展成脂肪性肝炎、肝硬化，甚至肝细胞癌。流行病学和动物研究表明，哺乳期母体不良因素可导致子代脂肪肝等代谢性疾病易感[1-2]。母亲的乳汁为哺乳动物出生早期的重要营养来源，它也是联系哺乳期母亲和子代的重要纽带。因此，乳汁的成分改变直接决定着子代出生早期的发育状况，并很可能参与了母体不良因素所致子代脂肪肝的发生。文献提示，乳汁成分与

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哺乳期母体所处的环境和摄食习惯密切相关[3]。母体饮食结构改变会导致乳汁中固有成分的含量或比例发生变化[3]，如哺乳期母亲低蛋白饮食导致乳汁总蛋白含量下降[4]。此外，当哺乳期母亲暴露于某些可通过乳汁排泄的外源物后可导致乳汁被污染[5]。

乳汁的营养成分决定着哺乳期婴儿的发育状况[6]。哺乳动物出生后数小时内，由宫内胎盘提供葡萄糖转换为摄入富含脂肪的乳汁供能，肝脏由宫内以葡萄糖分解代谢为主转为出生后早期以脂质的分解代谢为主，这种能量代谢模式的适应性改变如被干扰，可能造成子代严重的肝脏脂代谢障碍[7]。因此，哺乳期不良母体因素致乳汁固有营养成分比例失调或被外源性物质污染时，可能会干扰子代在生命早期肝脏代谢的发育编程，从而导致脂肪肝的发生，甚至会持续至成年[8]。本文将对哺乳期不良母体因素通过影响乳汁成分造成子代脂肪肝的现象和可能机制进行综述。

1　哺乳期不良母体因素导致子代脂肪肝

有研究表明，哺乳期不良母体因素会导致后代肝脏脂肪变性[1-2]，而目前研究较多的哺乳期不良母体因素主要包括母体饮食结构改变和母体外源物暴露。

1.1　母体饮食结构改变导致后代脂肪肝

母体饮食结构的改变主要包括营养过剩或营养不良，哺乳期营养过剩是诱发子代脂肪肝等代谢性疾病的危险因素。动物研究表明，哺乳期母鼠摄入高亚油酸饮食(能量占比12.3%)可导致3周龄子代肝脏脂肪变性、肝脏中甘油三酯蓄积，病理表现为肝实质细胞中有脂滴，存在微泡型和大泡型脂肪变性[9]。哺乳期母鼠高果糖饮食会导致3周龄子代肝游离脂肪酸和甘油三酯含量增加，肝细胞内脂质蓄积，并伴有胰岛素抵抗[10-11]。给予高脂饮食的哺乳期母犬，其3周龄子代肝重增加，肝甘油三酯含量增加[12]。除此之外，哺乳期母鼠低蛋白饮食可使其3周龄子代肝脏线粒体功能障碍[13]，肝重和肝组织中甘油三酯含量明显增加[14]。

生命早期营养环境变化可导致机体代谢编程改变，影响正常的生理代谢功能并持续至成年，甚至使得生命后期对代谢性疾病的危险因素更加敏感。有研究表明，哺乳期给予高脂饮食的母鼠，断乳后即使给予正常膳食，其出生后60天子代仍表现为脂肪肝等各种代谢综合征易感[15]。另一项哺乳期母鼠高脂饮食的研究显示，其3周龄子代表现为胰岛素抵抗、肝脏脂肪酸氧化减少和甘油三酯蓄积，并会持续至出生后82天[16]。给予哺乳期母鼠能量占比0.2%的高胆固醇饮食，其11周龄子代肝脏脂质摄入增加，肝脏病理切片发现有大量空泡[17]。以上证据提示，哺乳期母体饮食的结构改变会导致子代脂肪肝，并可持续至成年。

1.2　母体外源物暴露改变导致子代脂肪肝

母体外源物暴露也是导致子代脂肪肝发生的主要原因之一。在美国，哺乳期妇女的饮酒很常见，酒精被认为是增加产奶量、促进哺乳的饮品[18]。哺乳期大鼠乙醇的过量摄入可导致其3周龄幼仔血脂异常和胰岛素抵抗[18]，肝细胞内含有脂滴的液泡蓄积，表现为大泡脂肪变性、小叶炎性细胞浸润和微肉芽肿[19]。吡咯里西啶生物碱(pyrrolizidine alkaloids, PAs)是一种存在于中草药中的肝毒性物质，可通过乳汁排泄[20]。早期病例报道，一名2月男婴因被喂服含有毒性PA——倒千里光碱(retrorsine, RTS)的草药，肝脏活检发现有脂肪沉积[21]。尼古丁是存在于香烟烟雾中的一种毒性物质，哺乳期妇女因主动或被动吸烟暴露于尼古丁的机会很大[22]。动物研究表明，哺乳期暴露于尼古丁的大鼠其雄性后代出生后180天肝脏甘油三酯持续蓄积，病理表现为微泡脂肪变性、肝细胞中存在脂滴、门静脉炎性浸润、肝细胞变性和实质性坏死[23-24]。以上证据表明，哺乳期母亲外源物暴露也可导致子代脂肪肝的发生并持续至成年。

2　哺乳期不良母体因素对乳汁成分的影响

乳汁是婴幼儿获取重要营养物质的主要来源。乳汁的主要成分包括氨基酸、核苷酸、糖类、蛋白质、脂质等各种营养物质和微量元素[6]。研究表明，哺乳期不良母体因素会改变乳汁成分[3]，而乳汁中很多成分的改变与脂代谢相关[6]，提示哺乳期不良母体因素导致的乳汁成分改变可能与子代脂肪肝的发生有关。

2.1　母亲饮食结构改变

乳汁成分的改变可能会干扰子代在生命早期肝脏代谢的发育编程，从而使肝脏代谢性疾病的发生率增加，甚至会持续至成年[8]。哺乳期母亲饮食结构的改变可影响乳汁中各种成分的量或比例，虽然没有直接证据显示乳汁成分改变可造成子代脂肪肝，但乳汁中的许多营养物质已被证实与成年脂肪肝的发生密切相关。哺乳期母亲高脂饮食会改变乳汁成分的比例，如通常会降低碳水化合物和蛋白

质，增加脂肪酸含量[3]，而脂肪酸的过量摄入与成年大鼠脂肪肝的发生关系密切[25]。还有研究显示，哺乳期母亲摄入亚麻籽会增加母乳中瘦素和17-β雌二醇浓度[26]，而成年动物血清高瘦素水平会促进肝脏炎症反应和脂肪变性[27]。此外，哺乳期母亲高碳水化合物饮食会增加乳汁中总脂质的比例[28]，而饮食中总脂质比例的增加可能会导致成年肝脏超负荷代谢，进而导致肝脏炎症和脂质蓄积[29]。哺乳期母亲高维生素A饮食则会导致乳汁中唾液酸的含量升高[30]，而血清高唾液酸水平与成人肝脂肪变性风险密切相关[31]。

除上述一些营养过剩的研究外，还有许多关于母体营养受限导致乳汁成分改变的研究。有文献表明，哺乳期母亲低蛋白饮食会降低乳汁中总蛋白的含量[4]，而低蛋白饮食会诱导成年大鼠肝脂肪变性[32]。动物研究表明，哺乳期母亲低脂饮食会降低乳汁中硬脂酸的比例，同时增加乳汁中棕榈酸的比例[33]，而棕榈酸可通过抑制肝细胞中胰岛素信号转导并诱导肝脂质蓄积[34]。低维生素C饮食会降低母乳中的维生素C的含量[35]，而维生素C是人体所必需的维生素，有抗氧化、促进细胞新陈代谢、促进脂肪酸的代谢的作用[36]。流行病学研究表明，低维生素C水平饮食的受试者中肝脏有不同程度的脂质蓄积[37]，提示乳汁维生素C缺乏可能会影响子代肝脏的脂质代谢。

2.2 母体暴露于外源物

乳汁中的外源物含量很少超过母亲摄入量的1%~2%[38]，一般不至于给乳儿带来危害。但少数外源物在乳汁中排泄量较大，应考虑对乳儿的危害。一般相对分子质量小于200的化合物及同时具有亲水和亲脂性的物质较易通过细胞膜，且在母体血浆中处于游离状态才能进入乳汁。乳汁的pH值略低于血浆，碱性物质更容易自乳汁排泄，而酸性化合物较难经乳汁排泄[39]。此外，哺乳期外源物暴露对乳汁成分也会产生不利影响。哺乳期母体尼古丁暴露会减少乳汁中总脂质含量及各种必需脂肪酸的含量[40]，从而导致子代肝脏脂代谢紊乱，最终导致脂肪肝的发生[41]。尼古丁也会通过母乳排泄[22]，尼古丁可通过增加氧化应激和肝细胞凋亡诱导成年动物肝脂肪变性[41]，是否对幼年子代有同样影响还有待研究证实。此外，大量研究报道，哺乳期母体乙醇摄入会对母乳的产生、产量、成分、味道和排出产生不利影响，进而影响婴幼儿的发育[42]。动物研究表明，哺乳期大鼠乙醇的摄入会诱导子代肝脂肪变性[43]，这可能是乳汁乙醇暴露所介导的。

除上述毒物暴露会污染乳汁外，还有一些药物也可经乳汁排泄，例如β受体阻滞剂、地西泮和锂盐等临床上常用的药物[5]。当母体暴露于这些药物时，药物可经乳汁造成婴幼儿暴露并对其发育造成影响。含有PAs的紫草科植物玻璃苣是一种民间常用的具有催乳功效的中草药，常用作哺乳期妇女补剂[44]，PAs也被证实存在于哺乳期妇女可食用的各种类型的谷物、蜂蜜或乳制品中[45]，而PAs可通过乳汁传递给子代[20]。此外，依非韦伦是临床上应用最广泛的抗逆转录病毒药物之一，依非韦伦治疗的艾滋病感染母亲其乳汁和子代血清中均发现有一定程度的药物残留。依非韦伦被证实与用药者的血脂异常相关，可诱导肝脂肪变性和高胆固醇血症[46]。

3 哺乳期不良母体因素导致子代脂肪肝的可能机制

3.1 改变肝脏线粒体功能

研究报道，某些乳汁固有成分如脂肪酸含量的改变可能导致线粒体功能障碍[47]。多项证据表明，线粒体功能障碍与肝脏脂代谢紊乱有关。生理情况下，机体生成的脂肪酸可进入线粒体进行β-氧化，但当机体摄入脂质含量过多或暴露于外源物时，可能导致线粒体功能障碍，脂肪酸β-氧化减少，最终导致肝脂质蓄积[2]。有研究表明，哺乳期母亲高脂饮食会增加乳汁中脂肪酸的含量[3]，脂肪酸水平增加则会使大鼠肝脏线粒体中脂肪酸β-氧化超负荷，诱导线粒体功能障碍[47]，主要表现为组成呼吸链(mitochondrial respiratory chain, MRC)的线粒体电子传输链复合物(electron transport chain, ETC)I减少，MRC活性降低，还可导致MRC解偶联，肝脏线粒体的DNA拷贝数和抗氧化酶含量降低[2]。

除了乳汁固有成分改变外，一些可以经乳汁暴露的外源物(如乙醇和尼古丁)也会引起子代线粒体功能障碍。乙醇已被证实会损害线粒体功能和体内脂质平衡[48]，尼古丁也可诱导线粒体氧化功能障碍和增加肝细胞凋亡[41]。以上证据表明，乳汁固有成分改变或经乳汁暴露的外源物可能通过直接诱导子代线粒体氧化功能障碍引起肝脂肪变性。

3.2 改变调控脂代谢的核受体表达

肝细胞脂肪酸的摄取、合成、氧化代谢和/或甘油三酯排出障碍均可造成脂肪肝的发生，参与这四个步骤的关键基因表达受多种转录调控因子和核受体的调控。其中，孕烷X受体(pregnane X receptor,

PXR)是调控脂质代谢，与脂肪肝发生密切相关的核受体[49]。PXR激活后可增加肝脂肪酸摄取转运体长链脂肪酸转运蛋白(cluster of differentiation 36, CD36)的表达，抑制脂肪酸氧化基因肉碱棕榈酰转移酶1α (carnitine palmitoyltransferase 1α, CPT1α)表达[49]。某些通过乳汁排泄的外源物或乳汁中固有的成分比例失调可激活PXR。乙醇和尼古丁可通过乳汁排泄，其中尼古丁可诱导人肝细胞中过氧化物酶体增殖物激活受体γ共激活因子-1α (peroxisome proliferator-activated receptor γ coactivator-1alpha, PGC-1α)对PXR的反式激活[50]，持续8周给予27.5%的乙醇也可增加成年小鼠肝PXR的表达[51]。高脂饮食也可激活成年小鼠PXR[52]。此外，在高脂或高胆固醇饮食的小鼠的肝脏中，肝X受体α (LXRα)的表达增加，而肝X受体α (LXRα)可作用于脂质合成基因胆固醇调节元件结合蛋白1c (sterol regulatory element binding protein1c, SREBP1c)，使其转录增加，最终导致脂质蓄积，并且这种改变可延续至成年甚至跨代[53-54]。由此我们推测，母体高脂饮食或暴露于外源物导致的乳汁成分改变可能激活仔鼠肝脏核受体并干扰脂代谢。

3.3　改变肠道菌群组成

肠道菌群在新生儿出生后立即在其肠道中定植，这一过程与新生儿摄入的乳汁密切相关。哺乳动物早期肠道菌群的建立和相互作用受到乳汁中的低聚糖等化合物驱动和调节[55]。人乳中的低聚糖可以特异性地促进子代肠道中益生菌(如双歧杆菌)的生长[55]。同时，乳汁中的双歧杆菌和乳酸杆菌等益生菌也可直接传递给子代[56]。哺乳期不良因素所致的乳汁成分改变可能会影响新生儿肠道菌群的定植，早期肠道中某些有益菌群的减少可能会导致脂肪肝的发生。研究表明，哺乳期间患乳腺炎的母亲经青霉素治疗会使乳汁中的乳酸杆菌和双歧杆菌减少，并且会导致子代肠道病菌过度生长[57]。有研究表明，双歧杆菌、乳酸杆菌和嗜热链球菌的混合物可通过增加小鼠肝脏天然杀伤性T细胞和减少炎症信号来减轻饮食引起的肝脂肪变性和胰岛素抵抗[58]。

此外，乳汁中产短链脂肪酸(short chain fatty acids, SCFAs)菌含量减少也可能导致脂肪肝的发生。研究报道，脂肪肝患者产SCFAs的肠道微生物减少[59]。丁酸是目前研究最为清楚的一种SCFAs，其含量变化与脂肪肝的关系密切。例如，饮水补充丁酸钠可减轻小鼠的肝脏炎症反应和脂肪堆积[60]，而大鼠摄入产丁酸益生菌则可减轻高脂饮食诱导的肝脂肪变性[61]。丁酸可通过激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)来降低SREBP1c的表达，从而改善肝细胞内脂肪生成[62]。高脂饮食(能量占比45%)或乙醇(日摄入量0.02 mL/g)会导致成年小鼠中布劳特氏菌(Blautia)等产SCFAs菌减少[63-64]。可经乳汁排泄的β-内酰胺类抗生素在生命早期会导致婴儿肠道菌群内的产SCFA菌漆斐菌科(Lachnospiraceae)的水平降低[65]。以上文献提示，哺乳期不良母体因素所致的乳汁成分改变可能使子代肠道中双歧杆菌等益生菌或产SCFAs菌减少，从而导致子代脂肪肝的发生。

3.4　表观遗传学机制

表观遗传是指由非DNA序列改变引起、可遗传的基因表达水平的改变，包括DNA甲基化、组蛋白修饰、microRNA调控和染色质重塑等修饰调控方式。表观遗传修饰在疾病的发育编程中有着重要作用，在生命早期(宫内和/或哺乳期)，当生长发育的环境因素改变时，子代的表观遗传修饰也会发生相应的改变，从而影响脂代谢相关基因的表达和脂代谢表型，甚至延续至成年[66-68]。哺乳期母鼠高脂饮食所致乳汁脂质成分的改变可能会导致子代肝脏中脂代谢相关基因发生表遗传修饰，从而导致基因表达持续改变，进而导致成年脂肪肝易感[69]。

新生子代通过摄入乳汁中的脂肪酸在肝脏生成脂酰辅酶A和酮体等代谢产物，这些脂肪酸代谢中间产物可抑制组蛋白乙酰化酶或去乙酰化酶，从而影响参与脂质代谢的基因表达[70]。如果新生儿摄入母乳的脂肪含量减少，可能会引起脂质代谢相关基因的表观遗传修饰改变，最终导致脂质蓄积并持续至成年[71]。SCFAs是最有效的组蛋白脱乙酰酶(histone deacetylase, HDAC)抑制剂[72]，乳汁成分改变或外源物暴露所致的子代产SCFAs菌减少可能会导致受HDAC调控的PPARα靶基因被抑制，从而减少子代脂肪酸β氧化，最终导致脂肪肝的发生[73]。另有文献表明，给予高脂或高胆固醇饮食的小鼠，其肝脏中检测到与脂代谢合成相关的调控基因LXRα启动子区H3K9组蛋白甲基化水平降低[53-54]。除了组蛋白修饰外，microRNA也会参与肝脏脂质代谢的调控。miR-122是高度特异表达于肝脏的一种microRNA，其表达增加可通过影响糖酵解途径和柠檬酸循环来增加肝脏甘油三酯的合成[74]。已有研究表明，高脂饮食可通过上调miR-122的表达导致Sirt1的表达下调，从而抑制肝激酶B1 (liver kinase B1, LKB1)/AMPK途径，促进肝脂质合成，诱导成

年小鼠脂肪肝的发生[75]。虽然已知哺乳期母亲高脂饮食会增加乳汁中脂质含量，但上述基因的表观遗传修饰改变是否与摄入乳汁的成分改变有关，还有待进一步研究证实。

4 总结与展望

哺乳期母体不良因素增加后代代谢综合征易感性的现象已经十分明确。有研究通过将肥胖母鼠和对照小鼠子代进行交叉喂养，发现摄入正常母鼠乳汁的肥胖鼠子代体重和肝脏甘油三酯含量与正常子代无异，但由肥胖母鼠喂养的正常子代表现出明显的摄食量增加和非酒精性脂肪肝，同时发现肥胖母鼠乳汁中瘦素含量较正常鼠显著增加[76]，该结果提示母乳成分改变比母体本身因素对子代脂肪肝发生的影响更大。母体不良因素所致的乳汁成分改变对子代发育的影响已受到越来越多的关注，尤其对于成年子代代谢性疾病的影响值得深入研究，而其发生机制还需进一步证实。乳汁成分改变引起子代脂肪肝的发生原因存在多种可能，甚至需要综合考虑多种因素的协同作用，例如，经肠道菌群消化的乳汁成分如何影响子代线粒体功能、调控核受体和表观遗传修饰酶的活性。

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