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核受体在胎源性非酒精性脂肪肝病中的作用

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摘　要：非酒精性脂肪肝病 (nonalcoholic fatty liver disease, NAFLD) 是全球最常见的慢性肝病之一，以肝脏实质细胞脂肪变性为特征，可导致更严重的肝病。越来越多的流行病学和动物研究证明，NAFLD 的发生具有发育起源。在成人 NAFLD 的发生发展过程中，核受体作为一种转录因子，在环境或激素信号作用下，调控肝脏脂肪酸代谢相关基因的表达，从而参与或干预 NAFLD 的发生。近年来研究显示，生命早期不良环境也会影响核受体的表达和功能，经表观遗传修饰引起其自身或其下游基因表达发生持续性改变，可能参与调控胎源性 NAFLD 的发生。本文旨在对核受体在胎源性 NAFLD 中的作用及调控机制进行综述。

关键词：发育源性疾病；非酒精性脂肪肝病；脂肪酸代谢；核受体；表观遗传修饰
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The role of nuclear receptors in fetal-origin non-alcoholic fatty liver disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is one of the most commonly chronic liver diseases worldwide. It is characterized by hepatic steatosis, which may lead to more severe liver disease. A growing number of epidemiological and animal studies have demonstrated that NAFLD is a development-originated disease. Nuclear receptors (NRs) are known as transcription factors that regulate the expression of genes related to metabolism of fatty acid in the liver, responding to environment or hormonal signaling. Thereby, NRs participate in or interfere with the occurrence of NAFLD. Recent studies showed that adverse environment in the early life affects expression and function of the NRs, and epigenetic modifications participate in the continuous alteration of NRs expression or its downstream target genes. Therefore, NRs may be involved in the occurrence of fetal-origin NAFLD. The role of NRs in fetal-origin NAFLD was reviewed in this manuscript.

Key words: development-originated diseases; non-alcoholic fatty liver disease; fatty acid metabolism; nuclear receptors; epigenetic modification

非酒精性脂肪肝病 (non-alcoholic fatty liver disease, NAFLD) 是一种无过量饮酒和其他明确的肝脏损伤因素所导致的肝脏疾病，以肝脏实质细胞脂肪变性为特征，包括单纯脂肪肝和非酒精性脂肪肝炎 (nonalcoholic steato-hepatitis, NASH)[1]。目前，NAFLD 已成为一种危害全球人类健康的常见慢性肝脏疾病，其患病率正在逐年增加。我国 NAFLD 患病率在 2018 年就已高达 32.9%[2]，全球 NAFLD 的发病率目前也已接近 32.4%[3]。传统观点认为，NAFLD 的发生主要与不健康的生活方式和遗传因素有关[4]。近年来，基于流行病学调查和动物研究证实，不良环境因素或疾病造成父 / 母亲身体健康

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状况的改变可影响其子代成年 NAFLD 的发生，提示 NAFLD 的发生具有发育起源 [5-6]。

脂肪酸的摄取、合成、β- 氧化和 (或) 输出异常是 NAFLD 发生的直接原因 [7]。在 NAFLD 发生过程中，四条脂代谢通路起了重要作用：(1) 脂肪酸在肝脏的摄取增加；(2) 从头脂肪合成增加；(3) 脂肪酸的氧化减少；(4) 肝内极低密度脂蛋白分泌障碍。

1 NAFLD的发育起源

20 世纪 90 年代初，英国学者 Barker 基于大规模流行病学调查结果提出“成人疾病的胎儿起源”假说 [8]。随后，国际上在 2003 年正式提出“健康和疾病的发育起源”(developmental origins of health and disease, DOHaD) 假说，认为人类在发育过程的早期 (包括胎儿、婴儿、儿童时期) 遭受的各种环境不良因素将会影响整个生命过程中的健康状况，造成疾病易感，甚至疾病的发生 [8]。近年来研究发现，NAFLD 也具有发育起源 [6]。

流行病学研究表明，宫内环境对儿童 NAFLD 的发生十分重要，低或高出生体重儿童 NAFLD 的发生率是正常儿童的两倍 [9]。出生时宫内发育受限的新生儿在成年患 NAFLD 的易感性也增加 [10]。此外，妊娠时患有糖尿病的母亲，其分娩的死婴肝脏有明显的肝脂肪变性 [11]，这提示子代肝脏脂肪变性在宫内即可发生。但目前受精卵形成前父体不良因素与子代 NAFLD 发生的相关流行病学的证据较少。研究显示，母体妊娠期高血胆固醇或糖尿病的宫内子代肝脏发生脂肪变性等病理改变 [12-13]，并且母体妊娠期高血糖、肥胖的成年子代肝脏出现了脂肪变性 [14-15]；父体高血糖可能增加了成年子代患 NAFLD 的风险 [16]。多种动物模型表明母体在孕期和 (或) 哺乳期摄入高脂饮食诱导了子代成年 NAFLD 的发生 [17-18]。孕期啮齿类和非人类灵长类动物母亲营养过剩可明显增加子代成年患 NAFLD 的几率 [19]；妊娠和哺乳期小鼠和非人类灵长类动物母亲高脂饮食均会导致宫内或成年子代肝脏脂肪变性，并造成 NASH 的易感性增加 [20-21]。同样地，父体高脂饮食也会导致成年后代脂肪合成增加和肝脂肪变性 [22]。除了这些营养过剩的模型外，母体孕期摄食限制也会造成啮齿动物和绵羊子代的成年 NAFLD 易感 [23-24]，而父体低蛋白饮食会增加后代成年小鼠体重并伴有 NAFLD[25]。

此外，生命早期暴露于环境有害物质会造成啮齿类动物生命后期 NAFLD 易感，如双酚 A、有机锡、多环芳烃、全氟化物、邻苯二甲酸盐、砷、细颗粒物 (fine particulate matter, PM2.5)、烟草烟雾等 [26-32]。本实验室在大鼠模型中也发现，孕期母鼠暴露于酒精、咖啡因、地塞米松可引起胎儿宫内发育迟缓及子代成年期 NAFLD 易感 [11, 33-34]。以上研究均表明，NAFLD 具有胎儿发育起源。

2 胎源性NAFLD发生的可能原因

成年 NAFLD 的主要病理表现为肝实质细胞内 TG 的蓄积。肝脏 TG 的蓄积主要是由于脂肪酸的摄取、合成增加和 (或) β- 氧化、输出抑制引起 [7]。肝细胞可通过脂肪酸转位酶 (又称分化簇 36，cluster of differentiation 36, CD36)、脂肪酸转运蛋白 (fatty acid transport protein, FATP)、脂肪酸结合蛋白 1 (fatty acid binding protein 1, FABP1) 等转运体摄取血中的游离脂肪酸 (free fatty acid, FFA)。脂肪酸的从头合成由脂肪酸合成酶 (fatty acid synthase, FASN) 等酶介导，受到固醇调节元件结合蛋白 -1c (sterol regulatory element-binding protein-1c, SREBP1c) 的调控。TG 在肝脏中的分解代谢主要依赖于甘油三酯脂肪酶 (adipose triglyceride lipase, ATGL) 将 TG 脂解成脂肪酸，然后脂肪酸在细胞质中转化为酯酰辅酶 A 后，和肉碱载体一起经肉碱棕榈酰转移酶 1α (carnitine-palmitoyl transferase 1α, CPT1α) 转运至线粒体内膜，在线粒体脂肪酸氧化酶系的作用下进行脂肪酸 β- 氧化。微粒体 TG 转运蛋白 (microsomal triglyceride transfer protein, MTTP) 将载脂蛋白 B 脂质化为富含 TG 的极低密度脂蛋白 (very low density lipoprotein, VLDL)，在脂质输出中发挥重要作用 (图 1)。

与成年 NAFLD 发生途径相比，胎源性 NAFLD 有其自身的特征。人们猜测胎源性 NAFLD 可能起源于早期不良环境 [35]。Nobili 等 [36] 提出了宫内营养不良或营养过剩引起的脂质变性的编程机制可能是成年 NAFLD 的易感因素。在哺乳动物中，仅部分参与成人脂肪酸代谢途径的基因在胎肝中表达 [37-38]，一些参与肝脏脂肪合成和 β- 氧化的关键基因的表达受到抑制，如胎儿肝脏的线粒体较少，脂肪酸 β- 氧化限速酶 CPT1α 的表达量较低，糖异生很少或没有 [39]。这可能是因为胎儿 (或胎仔) 在宫内主要依赖碳水化合物代谢提供的能量，出生后才改为依赖乳汁中的脂质供能 [40]。胎儿时期的 FFA 绝大部分来源于母体循环 [41]，当孕期母血中 FFA 水平过高，而胎儿肝脏未发育成熟，缺乏具有足够代谢来自母

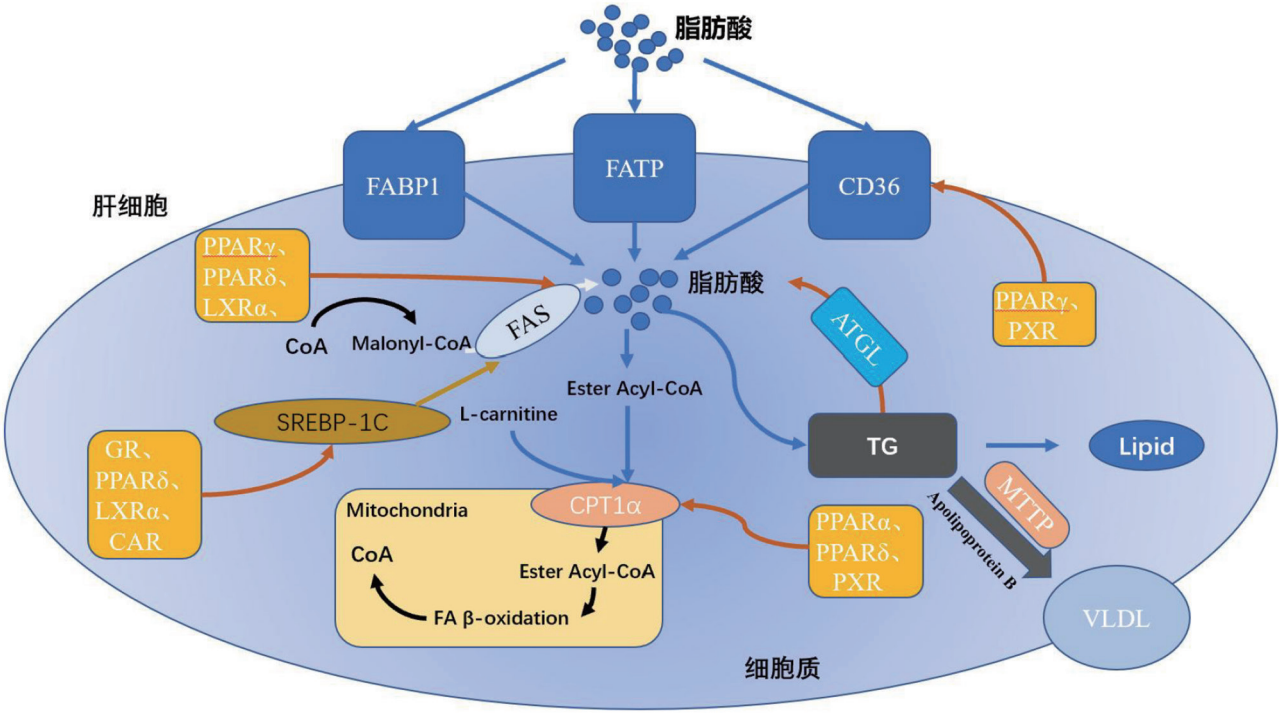

图1　成年肝脏脂肪酸摄取、合成、β-氧化和分泌示意图及其主要相关基因

体 FFA 的线粒体和基因，这种脂代谢障碍可能会在宫内被编程并持续至成年，表现为成年子代肝脏脂肪酸 β 氧化功能减弱 [42-43]。此外，来自灵长类动物肥胖母亲的胎肝中 FASN 和 SREBP1 的基因表达上调 [35]，宫内的 FFA 从头合成功能增强也可能会持续至成年，诱发成年子代肝脏脂肪合成增加 [6]。以上结果提示，胎源性 NAFLD 的发生可能主要与脂肪酸合成和 β- 氧化途径的障碍有关，且这种功能缺陷从宫内时期就已经存在。

3　核受体在胎源性NAFLD中的作用

核受体是由 48 个成员组成的转录因子超家族，构成了肝脏中重要的转录调控网络 [44]。核受体是一类配体依赖性的转录调节因子，受到多种内源性及外源性物质激活，进而调控其下游靶基因的表达。其蛋白质结构包括配体结合域和 DNA 结合域，配体与核受体的配体结合域结合后，核受体激活并与辅激活因子形成异源二聚体或两个激活的核受体形成同源二聚体进入细胞核，通过 DNA 结合域结合到下游靶基因启动子区的核受体反应元件上，促进靶基因的转录表达。核受体是调控肝脏脂肪酸合成、β- 氧化和转运等过程的一类重要转录因子，参与 NAFLD 的发生，在机体的生长发育、新陈代谢、细胞分化等多种生理过程中也发挥着重要的作用 [45-46]。核受体的激活具有配体依赖性，配体包括多种内源物 (如胆固醇、胆汁酸、脂肪酸、葡萄糖、激素等) 和外源物 (如药物、环境毒物等)[47]。亲代的内外环境改变可能激活子代的核受体，从而调控子代的脂代谢功能。更好地理解核受体在胎源性 NAFLD 发生发展中的作用及调控机制，可有助于发现预防和治疗胎源性 NAFLD 的新靶点。

在肝脏中，主要的核受体包括糖皮质激素受体 (glucocorticoid receptor, GR)、过氧化物酶体增殖剂激活受体 (peroxisome proliferator-activated receptors, PPARs)、肝脏 X 受体 (liver X receptor, LXR)、孕烷 X 受体 (pregnane X receptor, PXR)、雄甾烷受体 (constitutive androstane receptor, CAR)、法尼醇 X 受体 (farnesoid X receptor, FXR) 等，它们在脂质摄取、合成、分解和转运等各个环节均起到重要的调控作用 [46](图 1)。事实上，多数核受体在宫内已有表达，并且参与了胎儿肝脏分化、发育等至关重要的生理过程 [48-49]。因此，我们总结了近年来核受体在胎源性 NAFLD 发生过程中的作用及其编程机制 (表 1)。

3.1　GR与胎源性NAFLD

基础水平的糖皮质激素 (glucocorticoid, GC) 是决定胎儿成熟和出生后命运的关键，GC 主要通过 GR 与多种转录因子交互作用，参与调控细胞的增殖、分化及代谢过程 [64]。宫内胎儿 GC 主要来源

于母亲，出生后的 GC 依赖自身肾上腺合成 [65]。胎盘 2 型 11β- 羟类固醇脱氢酶 (11β-hydroxysteroid dehydrogenase type 2, 11β-HSD2) 为 GC 灭活酶，其表达和活性可调控胎儿从母体获得 GC 的水平 [66]。GR 几乎参与肝脏脂代谢的全部过程，最主要的机制可能与脂质合成相关。CCAAT 增强子结合蛋白 α (CCAAT/enhancer binding protein α, C/EBPα) 主要在肝细胞中表达并调节 SREBP1c 基因表达，GC 可以通过 GR 与 C/EBPα 相互作用，参与肝脏脂代谢通路的调控 [67]。

本实验室研究结果提示，孕期母鼠暴露于咖啡因 [50] 后，GR 介导了其成年子代 NAFLD 的发生。上述外源物一方面刺激母体 GC 水平升高，一方面抑制胎盘 11β-HSD2 表达，导致胎儿过度暴露于母源性 GC。宫内高 GC 水平激活胎肝 GR-C/EBPα 通路导致子代肝脏脂质合成功能增强，并延续至出生后 [68-72]。此外，地塞米松是一种产科常用的合成糖皮质激素类药物，孕期母鼠暴露于地塞米松后，地塞米松通过胎盘进入胎儿激活肝脏 GR，抑制血管紧张素转换酶 2 -Mas 受体 (angiotensin coverting enzyme2- Mas receptor, ACE2-MasR) 信号通路，从而使肝脏 TG 合成功能增强，β- 氧化功能减弱。这种作用可延续至出生后，最终导致成年子代 NAFLD 发生 [34]。另外，Zhao 等 [73] 研究发现孕期母体补充甜菜碱可以持续性抑制子代 GR 表达和脂质合成基因甲基化水平，从而有效地缓解了成年后糖皮质激素诱导的雌性子代大鼠肝脂质蓄积，也提示了 GR 在胎源性 NAFLD 中的作用。

3.2 PPARs与胎源性NAFLD

PPARs 在许多细胞类型中充当脂质代谢的主要调节因子，根据结构不同可以分为 α、γ、δ 三种类型。在成年个体，PPARα 通过调控脂肪酸 β- 氧化相关酶系如 CPT1α 的表达 [52]，在脂肪酸的 β- 氧化中扮演着关键角色。PPARγ 主要参与脂质摄入相关基因 CD36 以及脂质合成相关基因 FASN、硬脂酰辅酶 A 去饱和酶 1 (stearyl coenzyme A dehydrogenase-1, SCD1) 的表达调控 [52]。PPARδ 可能通过增加 VLDL 受体的表达来增加 TG 外排，从而减少 TG 在肝脏中的蓄积 [74]。近年来发现，PPARs 在胎源性 NAFLD 中的作用不可忽视。Fornes 等 [75] 发现，PPARγ 和 PPARδ 在妊娠期糖尿病大鼠的胎儿肝脏中发生明显改变，并介导了胎儿肝脏脂代谢的性别差异：在雄性胎儿中，PPARγ 表达增加导致肝脏中 TG 和胆固醇的含量增加，而雌性胎儿肝脏中 PPARδ 表达增加导致胎儿肝脏中 TG 和 FFA 的含量降低。除此以外，PPARs 可能参与了母体在孕期和 (或) 哺乳期不良饮食所致的子代 NAFLD 发生。在摄食限制母鼠的肥胖后代中，肝脏中的 TG 含量显著增加并伴随 PPAR γ 表达升高 [76]；母鼠孕期低蛋白饮食导致其子代肝脏 PPARα 的表达下调，进而引起脂肪酸 β- 氧化减弱，肝脏发生脂质变性 [77]；母鼠高脂饮食所致子代成年 NAFLD 中，苯扎贝特通过增加子代肝脏 PPARα/PPARγ 的比值改善了肝脏脂肪变性，提示 PPARs 在母亲高脂饮食所致子代 NAFLD 中起着重要作用 [78]；母鼠孕期高维生素摄入也会导致子代肝脏脂质蓄积增加，并伴有 PPARγ 基因表

表1 核受体在胎源性NAFLD中可能调控的基因以及发挥的作用

核受体类型	可能调控的脂代谢相关基因	在胎源性NAFLD中可能的作用
GR	SREBP1c (主要)[50]	从头脂肪合成[11]
PPARs		
①PPARα:	CPT1α[51-52];	脂肪酸β-氧化[51-52]
②PPARγ:	FASN、CD36、SCD113	从头脂肪合成和脂肪酸摄入[52]
③PPARδ:	SREBP1c、FASN[53]; CPT1α[54]	从头脂肪合成和脂肪酸β-氧化[53-54]
LXRα	SREBP1c、FASN[55-56]	从头脂肪合成[55-56]
PXR	PPARα、CPT1α、PPARγ、CD36[57]	脂肪酸摄取和脂肪酸β-氧化[57]
CAR	SREBP1c、ACC[58-59]	从头脂肪合成和脂肪酸β-氧化[58-59]
FXR	SREBP1c 、LDLR等[60-61]	几乎参与脂代谢全部过程[60-63]

GR，glucocorticoid receptor，糖皮质激素受体；PPARs，peroxisome proliferators-activated receptors，过氧化物酶体增殖物激活受体家族；LXR，liver X receptor，肝脏X受体；PXR，pregnane X receptor，孕烷X受体；CAR，constitutive androstane receptor，组成性雄甾烷受体；FXR，farnesoid X receptor，法尼酯X受体；SREBP1c，sterol regulating element binding protein，1c固醇调节元件结合蛋白-1c；CPT1α，carnitine palmitoyltransferase 1α，肉碱棕榈酰转移酶1α；FASN，fatty acid synthase，脂肪酸合酶；CD36，cluster of differentiation 36，分化簇36；SCD1，stearoyl-CoA desaturase 1，硬脂酰辅酶A去饱和酶1；ACC，acetyl CoA carboxylase，乙酰辅酶A羧化酶；LDLR，low density lipoprotein receptor，低密度脂蛋白受体。

达增加[79]。Li 等[80]发现高血糖父体的后代肝脏中 PPARα 的表达下调，可能诱导胎血 TG 水平升高和胎肝 TG 蓄积。

3.3　LXR与胎源性NAFLD

LXRs 在人类中以两种亚型存在，即 LXRα 和 LXRβ。LXRα 是调节脂肪合成基因表达的主要亚型，而 LXRβ 更多地调控参与胆固醇代谢途径的基因[55]。LXRα 在 NAFLD 中扮演双重角色。LXRα 激活可以增加其靶基因 SREBP1c 和 FASN 的表达，促进肝脏合成脂肪酸，诱发脂肪肝；同时它也可以抑制炎症并改善高胆固醇血症[56]。近年来，考虑到 LXRs 在调节脂肪酸稳态、胆固醇稳态和糖异生中的作用，越来越多的研究探讨了 LXRs 在胎源性 NAFLD 中的作用。Ma 等[32]发现孕期和哺乳期母体尼古丁暴露的雄性子代在出生后第 180 天表现出明显的血和肝 TG 水平升高，并且肝脏 FASN 和 LXRα 表达显著增加，提示 LXRα 可能介导了肝脏 TG 合成途径改变。孕期母鼠 (F0 代) 摄入高脂饮食导致小鼠 F1 代和 F2 代 LXRα 和 LXRβ 表达增加，促进肝脏脂肪生成，发生脂肪肝[81]。生命早期双酚 A 暴露可增加子代成年患 NAFLD 的易感性[26,82]，同时最近研究发现，双酚 A、邻苯二甲酸酯和有机磷酸酯等环境化合物可作为配体，与 LXRα 直接结合影响其下游靶基因表达[83]。

3.4　PXR与胎源性NAFLD

PXR 参与调控多个脂代谢途径，PXR 活化与脂肪酸的摄取、合成增加以及 β- 氧化抑制有关[84]。目前，尚无明确研究证实 PXR 可介导胎源性 NAFLD，但研究提示 PXR 很可能参与了胎源性 NAFLD 的发生[57]。Sui 等[85]研究发现，在人化 PXR 小鼠成年雄性后代的主动脉中，围产期双酚 A 暴露可增加人化 PXR 小鼠的 CD36 表达，但不会增加野生型小鼠的 CD36 表达。由于 CD36 在肝脏脂肪酸摄取中发挥重要作用，故我们推测 PXR 可能同样在围产期双酚 A 暴露所致的子代成年 NAFLD 发生中扮演重要角色。此外，孕早期暴露于 PXR 激动剂孕烯醇酮 (pregnenolone 16α-carbonitrile, PCN) 的小鼠子代出生后 PXR 及其下游靶基因表达持续增加[63]，而 PCN 激活 PXR 后可致成年小鼠发生肝脂质变性[86]。以上结果提示，生命早期 PXR 激活可造成子代出生后 PXR 下游脂代谢相关基因的持续表达改变，并可能导致肝脂质蓄积。

3.5　其他核受体与胎源性NAFLD

其他核受体如 CAR、FXR 等在肝脏脂代谢调控以及 NAFLD 发生发展中可能也扮演着重要的角色。CAR 主要作用为抑制脂肪酸的合成 (如抑制 SREBP-1c 表达)[87]。目前 CAR 与胎源性 NAFLD 的相关文献较少。Bright 等[88]研究证实孕中晚期给予小鼠 CAR 激动剂 TCPOBOP 后可以激活宫内子代 CAR 的表达，而活化的 CAR 可通过抑制肝脏脂肪合成和促进 β- 氧化改善成年小鼠脂肪肝[58]。这提示 CAR 可能对胎源性 NAFLD 的发生具有保护作用。FXR 能够参与肝脏乃至全身的 TG 代谢[62]，FXR 基因敲除小鼠表现为明显的肝脏脂质沉积、高脂血症和胰岛素抵抗[89]。但与 CAR 一样，FXR 是否参与胎源性 NAFLD 的调控尚不明确。

4　核受体对胎源性NAFLD的调控机制

在发育源性 NAFLD 的发生发展过程中，核受体对脂代谢基因的持续调控主要与表观遗传修饰有关。另外，糖皮质激素 - 胰岛素样生长因子 1 (glucocorticoid insulin-like growth factor 1, GC-IGF1) 宫内编程机制也介导了 GR 对胎源性 NAFLD 的调控。

4.1　表观遗传修饰

表观遗传学是指在 DNA 序列没有改变的情况下基因功能的可逆和可遗传性改变，这些改变主要包括 DNA 甲基化、组蛋白修饰以及微小 RNA (microRNA, miRNA) 调控等[90]。在胎源性 NAFLD 中，表观遗传修饰参与核受体对胎源性 NAFLD 的调控主要涉及两方面：一方面，核受体发生表观遗传修饰影响其自身表达来调节肝脏脂代谢；另一方面，核受体通过招募和 (或) 调控表观遗传修饰酶对下游靶基因进行表观遗传修饰而调节肝脏脂代谢 (图 2)。

动物研究表明，在妊娠期糖尿病大鼠的胎肝中，低水平的 miR-130 导致雄性 PPARγ 表达升高，增加肝脏脂肪蓄积；而 miR-9 降低则导致雌性胎儿 PPARδ 表达增加，表现为脂质水平降低[75]。另外，父亲高血糖的成年子代肝中 PPARα 的启动子区域 (-852~-601) DNA 甲基化增高，PPARα 的表达受到抑制进而导致 CPT1α 下调[80]。此外，核受体与下游靶基因 DNA 结合位点结合后，招募或调控能重塑染色质构象的组蛋白修饰酶，如组蛋白乙酰转移酶 (histone acetyltransferase, HATs) 或组蛋白去乙酰化酶 (histone deacetylase, HDACs)，形成多蛋白复合物进而参与下游靶基因的表观遗传修饰[91-93]。孕期母鼠咖啡因暴露导致宫内子代暴露于母源性高 GC，激活 GR-C/EBPα 通路，抑制下游 NAD^+ 依赖

的去乙酰化酶 1 (sirtuin 1, SIRT1) 表达。SIRT1 是一种组蛋白去乙酰化酶，其表达降低促进 SREBP1c 和 FASN 组蛋白特定位点乙酰化水平的增加以及基因的转录表达，从而增加了雌性子代肝脏脂肪酸合成，并延续至出生后 [50]。在成年子代遭受慢性应激后 SIRT1 表达会进一步降低，导致 SREBP1c 和 FASN H3K14 和 H3K27 位点乙酰化水平升高，促使雌性成年子代大鼠肝脏脂肪酸从头合成增加，诱发 NAFLD[50]。孕期和哺乳期母体尼古丁暴露的雄性子代肝脏 LXRα 蛋白表达增加，与 FASN 启动子上的 LXR 响应元件 (liver X receptor response element, LXRE) 结合，促进 FASN 组蛋白 H3K9、H3K14 位点乙酰化水平增高 [32]。

4.2 GC-IGF1宫内编程改变

GR 介导的胎源性 NAFLD 存在“两种编程”机制。前文已经介绍，孕期外源物暴露导致子代肝脏脂质合成功能增强，这是由于 GR 与下游靶基因位点结合后调控和招募相应表观遗传修饰酶，持续增加下游靶基因表达，此谓之“第一种编程”[67]。此外，GR 对 IGF1 存在抑制作用，后者可促进肝脏脂质从头合成。孕期外源物暴露子代出生后肝脏 GR 活性降低，IGF1 信号通路增强并增加脂肪酸合成，称为“第二种编程”[50,67]。

IGF1 是妊娠晚期和出生后体重增长及发育相关的主要因子，在调节代谢方面，肝脏 IGF1 可通过 IGF1R/ 蛋白激酶 B (protein kinase B, AKT) 增加 SREBP1c 表达，促进肝脏 TG 合成 [94]。孕期外源物暴露使得宫内胎儿暴露于高 GC 环境下，通过激活 GR 抑制胎肝 IGF1 表达 [95]，可能与高 GC 促使 GR 入核增加与 C/EBPβ 结合并抑制 IGF1 转录有关 [94]。出生后胎儿脱离了母源性高 GC 环境，而且由于在宫内时胎儿肾上腺功能受到母源性高 GC 的抑制 [33, 96]，所以出生后子代自身 GC 合成功能受限，GR 活化减少解除了对 IGF1 表达的抑制，导致肝脏高 IGF1[50, 94]，脂质合成功能增强，成年子代患 NAFLD 的易感性显著增加。

5 总结与研究展望

核受体在胎源性 NAFLD 的发生发展中起着至关重要的调控作用，核受体响应生命早期不良环境后经表观遗传修饰可对其下游基因表达进行调控，进而影响脂代谢途径。生命早期不良因素暴露后，母体 PXR、PPARγ 的激活可能通过调控下游 CD36 或 SCD1 的持续性表达来增加子代脂肪酸的摄取，母体 GR、PPARγ、PPARδ、LXRα、CAR 的激活可能通过调控下游 FASN 和 (或) SREBP1c 的持续性表达来增加子代脂肪酸从头合成，母体 PXR、PPARα、PPARδ、CAR 的激活可能通过调控下游 CPT1α 或 ACC 的持续性表达来减少子代脂肪酸的氧化。

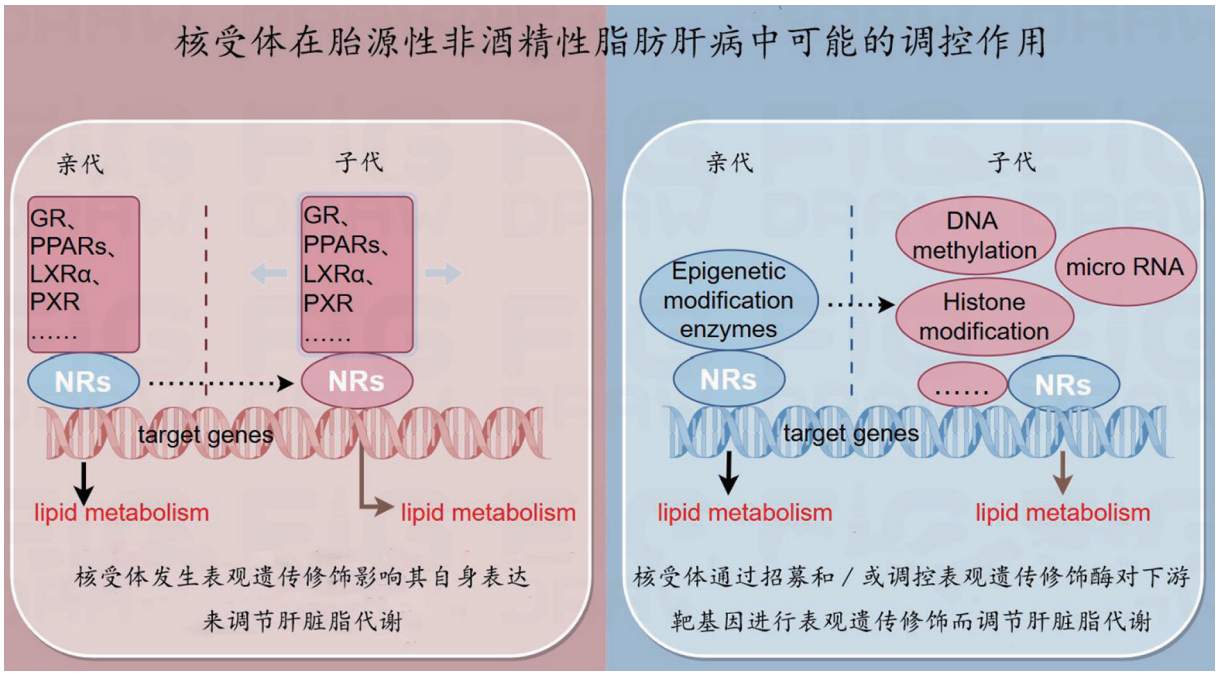

图2 核受体在胎源性非酒精性脂肪肝病中可能的调控作用

因此，了解它们在胎源性 NAFLD 的病理生理中的作用对于探寻有效的治疗靶标具有重要意义。目前，已有研究提出将核受体作为 NAFLD 的潜在治疗靶点，如苯扎贝特通过增加动物子代肝脏 PPARα/PPARγ 的比率来加强脂肪酸 β- 氧化，从而改善孕期高脂饮食引起的子代脂代谢紊乱和肝脂质变性 [97]。但值得注意的是，核受体的作用较为广泛，在针对核受体进行胎源性 NAFLD 干预治疗时，还应密切关注核受体相关的不良反应，如胆固醇、胆汁酸代谢紊乱等症状。

[参　考　文　献]

[1] Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet, 2021, 397: 2212-24

[2] Zhou J, Zhou F, Wang W, et al. Epidemiological features of NAFLD from 1999 to 2018 in China. Hepatology, 2020, 71: 1851-64

[3] Younossi ZM. Non-alcoholic fatty liver disease - a global public health perspective. J Hepatol, 2019, 70: 531-44

[4] Sarin SK, Kumar M, Eslam M, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol, 2020, 5: 167-228

[5] Itoh H, Kanayama N. Developmental origins of nonalcoholic fatty liver disease (NAFLD). Adv Exp Med Biol, 2018, 1012: 29-39

[6] Wesolowski SR, Kasmi KC, Jonscher KR, et al. Developmental origins of NAFLD: a womb with a clue. Nat Rev Gastroenterol Hepatol, 2017, 14: 81-96

[7] Ten Hove M, Pater L, Storm G, et al. The hepatic lipidome: from basic science to clinical translation. Adv Drug Deliv Rev, 2020, 159: 180-97

[8] Carpinello OJ, DeCherney AH, Hill MJ. Developmental origins of health and disease: the history of the barker hypothesis and assisted reproductive technology. Semin Reprod Med, 2018, 36: 177-82

[9] Newton KP, Feldman HS, Chambers CD, et al. Low and high birth weights are risk factors for nonalcoholic fatty liver disease in children. J Pediatr, 2017, 187: 141-6

[10] Nobili V, Alisi A, Panera N, et al. Low birth weight and catch-up-growth associated with metabolic syndrome: a ten year systematic review. Pediatr Endocrinol Rev, 2008, 6: 241-7

[11] Patel KR, White FV, Deutsch GH. Hepatic steatosis is prevalent in stillborns delivered to women with diabetes mellitus. J Pediatr Gastroenterol Nutr, 2015, 60: 152-8

[12] Dumolt JH, Ma M, Mathew J, et al. Gestational hypercholesterolemia alters fetal hepatic lipid metabolism and microRNA expression in Apo-E-deficient mice. Am J Physiol Endocrinol Metab, 2019, 317: E831-8

[13] Balachandiran M, Bobby Z, Dorairajan G, et al. Placental accumulation of triacylglycerols in gestational diabetes mellitus and its association with altered fetal growth are related to the differential expressions of proteins of lipid metabolism. Exp Clin Endocrinol Diabetes, 2021, 129: 803-12

[14] Chang E, Hafner H, Varghese M, et al. Programming effects of maternal and gestational obesity on offspring metabolism and metabolic inflammation. Sci Rep, 2019, 9: 16027

[15] Zhang W, Su R, Feng H, et al. Transgenerational obesity and alteration of ARHGEF11 in the rat liver induced by intrauterine hyperglycemia. J Diabetes Res, 2019, 2019: 6320839

[16] Shi X, Li X, Hou Y, et al. Paternal hyperglycemia in rats exacerbates the development of obesity in offspring. J Endocrinol, 2017, 234: 175-86

[17] Zhou Y, Peng H, Xu H, et al. Maternal diet intervention before pregnancy primes offspring lipid metabolism in liver. Lab Invest, 2020, 100: 553-69

[18] Wentzel P, Eriksson UJ, Herrera E. High-fat diet in pregnant rats and adverse fetal outcome. Ups J Med Sci, 2019, 124: 125-34

[19] Li M, Reynolds CM, Segovia SA, et al. Developmental programming of nonalcoholic fatty liver disease: the effect of early life nutrition on susceptibility and disease severity in later life. Biomed Res Int, 2015, 2015: 437107

[20] Grant WF, Gillingham MB, Batra AK, et al. Maternal high fat diet is associated with decreased plasma n-3 fatty acids and fetal hepatic apoptosis in nonhuman primates. PLoS One, 2011, 6: e17261

[21] Mouralidarane A, Soeda J, Visconti-Pugmire C, et al. Maternal obesity programs offspring nonalcoholic fatty liver disease by innate immune dysfunction in mice. Hepatology, 2013, 58: 128-38

[22] Ornellas F, Souza-Mello V, Mandarim-de-Lacerda CA, et al. Programming of obesity and comorbidities in the progeny: lessons from a model of diet-induced obese parents. PLoS One, 2015, 10: e0124737

[23] Wolfe D, Gong M, Han G, et al. Nutrient sensor-mediated programmed nonalcoholic fatty liver disease in low birthweight offspring. Am J Obstet Gynecol, 2012, 207: 308. e301-6

[24] Gnanalingham MG, Williams P, Wilson V, et al. Nutritional manipulation between early to mid-gestation: effects on uncoupling protein-2, glucocorticoid sensitivity, IGF-I receptor and cell proliferation but not apoptosis in the ovine placenta. Reproduction, 2007, 134: 615-23

[25] Watkins AJ, Dias I, Tsuro H, et al. Paternal diet programs offspring health through sperm- and seminal plasma-specific pathways in mice. Proc Natl Acad Sci U S A, 2018, 115: 10064-9

[26] Jiang Y, Xia W, Zhu Y, et al. Mitochondrial dysfunction in early life resulted from perinatal bisphenol A exposure contributes to hepatic steatosis in rat offspring. Toxicol Lett, 2014, 228: 85-92

[27] Foulds CE, Treviño LS, York B, et al. Endocrine-disrupting chemicals and fatty liver disease. Nat Rev Endocrinol, 2017, 13: 445-57

[28] Quist EM, Filgo AJ, Cummings CA, et al. Hepatic

mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). Toxicol Pathol, 2015, 43: 546-57

[29] Maranghi F, Lorenzetti S, Tassinari R, et al. In utero exposure to di-(2-ethylhexyl) phthalate affects liver morphology and metabolism in post-natal CD-1 mice. Reprod Toxicol, 2010, 29: 427-32

[30] Ditzel EJ, Nguyen T, Parker P, et al. Effects of arsenite exposure during fetal development on energy metabolism and susceptibility to diet-induced fatty liver disease in male mice. Environ Health Perspect, 2016, 124: 201-9

[31] Wang X, Yang Y, Zhu P, et al. Prenatal exposure to diesel exhaust PM(2.5) programmed non-alcoholic fatty liver disease differently in adult male offspring of mice fed normal chow and a high-fat diet. Environ Pollut, 2019, 255: 113366

[32] Ma N, Nicholson CJ, Wong M, et al. Fetal and neonatal exposure to nicotine leads to augmented hepatic and circulating triglycerides in adult male offspring due to increased expression of fatty acid synthase. Toxicol Appl Pharmacol, 2014, 275: 1-11

[33] Shen L, Liu Z, Gong J, et al. Prenatal ethanol exposure programs an increased susceptibility of non-alcoholic fatty liver disease in female adult offspring rats. Toxicol Appl Pharmacol, 2014, 274: 263-73

[34] Liu H, He B, Hu W, et al. Prenatal dexamethasone exposure induces nonalcoholic fatty liver disease in male rat offspring via the miR-122/YY1/ACE2-MAS1 pathway. Biochem Pharmacol, 2021, 185: 114420

[35] Thorn SR, Baquero KC, Newsom SA, et al. Early life exposure to maternal insulin resistance has persistent effects on hepatic NAFLD in juvenile nonhuman primates. Diabetes, 2014, 63: 2702-13

[36] Cianfarani S, Agostoni C, Bedogni G, et al. Effect of intrauterine growth retardation on liver and long-term metabolic risk. Int J Obes, 2012, 36: 1270-7

[37] Rando G, Tan CK, Khaled N, et al. Glucocorticoid receptor-PPARα axis in fetal mouse liver prepares neonates for milk lipid catabolism. eLife, 2016, 5: e11853

[38] Baker PR, Friedman JE. Mitochondrial role in the neonatal predisposition to developing nonalcoholic fatty liver disease. J Clin Invest, 2018, 128: 3692-703

[39] Kim SR, Kubo T, Kuroda Y, et al. Comparative metabolome analysis of cultured fetal and adult hepatocytes in humans. J Toxicol Sci, 2014, 39: 717-23

[40] Bell RM, Coleman RA. Enzymes of glycerolipid synthesis in eukaryotes. Annu Rev Biochem, 1980, 49: 459-87

[41] Shekhawat P, Bennett MJ, Sadovsky Y, et al. Human placenta metabolizes fatty acids: implications for fetal fatty acid oxidation disorders and maternal liver diseases. Am J Physiol Endocrinol Metab, 2003, 284: E1098-105

[42] Gregorio BM, Souza-Mello V, Carvalho JJ, et al. Maternal high-fat intake predisposes nonalcoholic fatty liver disease in C57BL/6 offspring. Am J Obstet Gynecol, 2010, 203: 491-8

[43] Alfaradhi MZ, Fernandez-Twinn DS, Martin-Gronert MS, et al. Oxidative stress and altered lipid homeostasis in the programming of offspring fatty liver by maternal obesity. Am J Physiol Regul Integr Comp Physiol, 2014, 307: R26-34

[44] Frigo DE, Bondesson M, Williams C. Nuclear receptors: from molecular mechanisms to therapeutics. Essays Biochem, 2021, 65: 847-56

[45] Mazzoccoli G, Vinciguerra M, Oben J, et al. Non-alcoholic fatty liver disease: the role of nuclear receptors and circadian rhythmicity. Liver Int, 2014, 34: 1133-52

[46] Cave MC, Clair HB, Hardesty JE, et al. Nuclear receptors and nonalcoholic fatty liver disease. Biochim Biophys Acta, 2016, 1859: 1083-99

[47] Chen T. Nuclear receptor drug discovery. Curr Opin Chem Biol, 2008, 12: 418-26

[48] Clifton VL, Cuffe J, Moritz KM, et al. The role of multiple placental glucocorticoid receptor isoforms in adapting to the maternal environment and regulating fetal growth. Placenta, 2017, 54: 24-9

[49] Duttaroy AK. Fetal growth and development: roles of fatty acid transport proteins and nuclear transcription factors in human placenta. Indian J Exp Biol, 2004, 42: 747-57

[50] Hu S, Xia L, Luo H, et al. Prenatal caffeine exposure increases the susceptibility to non-alcoholic fatty liver disease in female offspring rats via activation of GR-C/EBPα-SIRT1 pathway. Toxicology, 2019, 417: 23-34

[51] Ip E, Farrell GC, Robertson G, et al. Central role of PPARα-dependent hepatic lipid turnover in dietary steatohepatitis in mice. Hepatology, 2003, 38: 123-32

[52] Kumar DP, Caffrey R, Marioneaux J, et al. The PPAR α/γ agonist saroglitazar improves insulin resistance and steatohepatitis in a diet induced animal model of nonalcoholic fatty liver disease. Sci Rep, 2020, 10: 9330

[53] Qin X, Xie X, Fan Y, et al. Peroxisome proliferator-activated receptor-δ induces insulin-induced gene-1 and suppresses hepatic lipogenesis in obese diabetic mice. Hepatology, 2008, 48: 432-41

[54] Bojic LA, Telford DE, Fullerton MD, et al. PPARδ activation attenuates hepatic steatosis in $Ldlr^{-/-}$ mice by enhanced fat oxidation, reduced lipogenesis, and improved insulin sensitivity. J Lipid Res, 2014, 55: 1254-66

[55] Zhang X, Xu Y, Bai Q, et al. Inhibition of LXR signaling by SULT2B1b promotes liver regeneration after partial hepatectomy in mouse models of nonalcoholic fatty liver disease. Am J Physiol Gastrointest Liver Physiol, 2020, 319: G87-96

[56] Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. Nat Rev Endocrinol, 2018, 14: 452-63

[57] Dai Y, Luo J, Xiang E, et al. Prenatal exposure to retrorsine induces developmental toxicity and hepatotoxicity of fetal rats in a sex-dependent manner: the role of pregnane X receptor activation. J Agric Food Chem, 2021, 69: 3219-31

[58] Dong B, Saha PK, Huang W, et al. Activation of nuclear receptor CAR ameliorates diabetes and fatty liver disease. Proc Natl Acad Sci U S A, 2009, 106: 18831-6

[59] Chow JD, Jones ME, Prelle K, et al. A selective estrogen

receptor α agonist ameliorates hepatic steatosis in the male aromatase knockout mouse. J Endocrinol, 2011, 210: 323-34

[60] Caron S, Huaman Samanez C, Dehondt H, et al. Farnesoid X receptor inhibits the transcriptional activity of carbohydrate response element binding protein in human hepatocytes. Mol Cell Biol, 2013, 33: 2202-11

[61] Singh AB, Dong B, Kraemer FB, et al. Farnesoid X receptor activation by obeticholic acid elevates liver low-density lipoprotein receptor expression by mRNA stabilization and reduces plasma low-density lipoprotein cholesterol in mice. Arterioscler Thromb Vasc Biol, 2018, 38: 2448-59

[62] Zhang Y, Lee FY, Barrera G, et al. Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. Proc Natl Acad Sci U S A, 2006, 103: 1006-11

[63] Wang P, Liu G, Nie Y, et al. Epigenetic memory is involved in the persistent alterations of drug-processing genes in adult mice due to PCN-activated PXR during early life. Toxicol Sci, 2019, 172: 98-108

[64] Shi XT, Zhu HL, Xu XF, et al. Gestational cadmium exposure impairs placental angiogenesis via activating GC/GR signaling. Ecotoxicol Environ Saf, 2021, 224: 112632

[65] Busada JT, Cidlowski JA. Mechanisms of glucocorticoid action during development. Curr Top Dev Biol, 2017, 125: 147-70

[66] Yu P, Zhou J, Ge C, et al. Differential expression of placental 11β-HSD2 induced by high maternal glucocorticoid exposure mediates sex differences in placental and fetal development. Sci Total Environ, 2022, 827: 154396

[67] Liu K, Wang G, Li L, et al. GR-C/EBPα-IGF1 axis mediated azithromycin-induced liver developmental toxicity in fetal mice. Biochem Pharmacol, 2020, 180: 114130

[68] Chapman K, Holmes M, Seckl J. 11β-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev, 2013, 93: 1139-206

[69] Chen M, Wang T, Liao ZX, et al. Nicotine-induced prenatal overexposure to maternal glucocorticoid and intrauterine growth retardation in rat. Exp Toxicol Pathol, 2007, 59: 245-51

[70] Liang G, Chen M, Pan XL, et al. Ethanol-induced inhibition of fetal hypothalamic-pituitary-adrenal axis due to prenatal overexposure to maternal glucocorticoid in mice. Exp Toxicol Pathol, 2011, 63: 607-11

[71] Xu D, Zhang B, Liang G, et al. Caffeine-induced activated glucocorticoid metabolism in the hippocampus causes hypothalamic-pituitary-adrenal axis inhibition in fetal rats. PLoS One, 2012, 7: e44497

[72] Xu D, Chen M, Pan XL, et al. Dexamethasone induces fetal developmental toxicity through affecting the placental glucocorticoid barrier and depressing fetal adrenal function. Environ Toxicol Pharmacol, 2011, 32: 356-63

[73] Zhao N, Yang S, Jia Y, et al. Maternal betaine supplementation attenuates glucocorticoid-induced hepatic lipid accumulation through epigenetic modification in adult offspring rats. J Nutr Biochem, 2018, 54: 105-12

[74] Zarei M, Barroso E, Palomer X, et al. Hepatic regulation of VLDL receptor by PPARβ/δ and FGF21 modulates non-alcoholic fatty liver disease. Mol Metab, 2018, 8: 117-31

[75] Fornes D, White V, Higa R, et al. Sex-dependent changes in lipid metabolism, PPAR pathways and microRNAs that target PPARs in the fetal liver of rats with gestational diabetes. Mol Cell Endocrinol, 2018, 461: 12-21

[76] Hyatt MA, Gardner DS, Sebert S, et al. Suboptimal maternal nutrition, during early fetal liver development, promotes lipid accumulation in the liver of obese offspring. Reproduction, 2010, 141: 119-26

[77] Sato N, Sudo K, Mori M, et al. Early gestational maternal low-protein diet diminishes hepatic response to fasting in young adult male mice. Sci Rep, 2017, 7: 9812

[78] Magliano DC, Bargut TC, Carvalho SN, et al. Peroxisome proliferator-activated receptors-α and γ are targets to treat offspring from maternal diet-induced obesity in mice. PLoS One, 2013, 8: e64258

[79] Reza López SA, Poon AN, Szeto IM, et al. High multivitamin intakes during pregnancy and postweaning obesogenic diets interact to affect the relationship between expression of PPAR genes and glucose regulation in the offspring. J Nutr Biochem, 2013, 24: 877-81

[80] Li X, Shi X, Hou Y, et al. Paternal hyperglycemia induces transgenerational inheritance of susceptibility to hepatic steatosis in rats involving altered methylation on Pparalpha promoter. Biochim Biophys Acta Mol Basis Dis, 2019, 1865: 147-60

[81] Li J, Huang J, Li JS, et al. Accumulation of endoplasmic reticulum stress and lipogenesis in the liver through generational effects of high fat diets. J Hepatol, 2012, 56: 900-7

[82] Long Z, Fan J, Wu G, et al. Gestational bisphenol A exposure induces fatty liver development in male offspring mice through the inhibition of HNF1b and upregulation of PPARγ. Cell Biol Toxicol, 2021, 37: 65-84

[83] Mozzicafreddo M, Cuccioloni M, Bonfili L, et al. Environmental pollutants directly affect the liver X receptor α activity: kinetic and thermodynamic characterization of binding. J Steroid Biochem Mol Biol, 2015, 152: 1-7

[84] Zeng H, Lin Y, Gong J, et al. CYP3A suppression during diet-induced nonalcoholic fatty liver disease is independent of PXR regulation. Chem Biol Interact, 2019, 308: 185-93

[85] Sui Y, Park SH, Wang F, et al. Perinatal bisphenol A exposure increases atherosclerosis in adult male PXR-humanized mice. Endocrinology, 2018, 159: 1595-608

[86] Hoekstra M, Lammers B, Out R, et al. Activation of the nuclear receptor PXR decreases plasma LDL-cholesterol levels and induces hepatic steatosis in LDL receptor knockout mice. Mol Pharm, 2009, 6: 182-9

[87] Ahn HY, Kim HH, Hwang JY, et al. Effects of pioglitazone on nonalcoholic fatty liver disease in the absence of

constitutive androstane receptor expression. PPAR Res, 2018, 2018: 9568269

[88] Bright AS, Herrera-Garcia G, Moscovitz JE, et al. Regulation of drug disposition gene expression in pregnant mice with car receptor activation. Nucl Receptor Res, 2016, 3: 101193

[89] Tanaka N, Takahashi S, Matsubara T, et al. Adipocyte-specific disruption of fat-specific protein 27 causes hepatosteatosis and insulin resistance in high-fat diet-fed mice. J Biol Chem, 2015, 290: 3092-105

[90] Ling C, Rönn T. Epigenetics in human obesity and type 2 diabetes. Cell Metab, 2019, 29: 1028-44

[91] Cai D, Liu H, Zhao R. Nuclear receptors in hepatic glucose and lipid metabolism during neonatal and adult life. Curr Protein Pept Sci, 2017, 18: 548-61

[92] Gong Y, Cao R, Ding G, et al. Integrated omics approaches to characterize a nuclear receptor corepressor-associated histone deacetylase in mouse skeletal muscle. Mol Cell Endocrinol, 2018, 471: 22-32

[93] Romagnolo DF, Zempleni J, Selmin OI. Nuclear receptors and epigenetic regulation: opportunities for nutritional targeting and disease prevention. Adv Nutr, 2014, 5: 373-85

[94] Hwa V, Fang P, Derr MA, et al. IGF-I in human growth: lessons from defects in the GH-IGF-I axis. Nestle Nutr Inst Workshop Ser, 2013, 71: 43-55

[95] Liu Y, Xu D, Feng J, et al. Fetal rat metabonome alteration by prenatal caffeine ingestion probably due to the increased circulatory glucocorticoid level and altered peripheral glucose and lipid metabolic pathways. Toxicol Appl Pharmacol, 2012, 262: 205-16

[96] Xu D, Bai J, Zhang L, et al. Prenatal nicotine exposure-induced intrauterine programming alteration increases the susceptibility of high-fat diet-induced non-alcoholic simple fatty liver in female adult offspring rats. Toxicol Res, 2014, 11: 112-20

[97] Lynch C, Chan CS, Drake AJ. Early life programming and the risk of non-alcoholic fatty liver disease. J Dev Orig Health Dis, 2017, 8: 263-72