基础研究

· 综述 ·

肝细胞因子与非酒精性脂肪性肝病

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【摘要】 非酒精性脂肪性肝病（NAFLD）是目前最常见的慢性肝病，其特点是肝脏内脂肪大量堆积（脂肪变性）。肝细胞因子指由肝脏分泌的具有自分泌、旁分泌或内分泌活性的蛋白质，主要功能为调节脂质和葡萄糖代谢。研究发现，在发生肝脏脂肪变性时，许多肝细胞因子的表达会发生变化，包括成纤维细胞生长因子 21、性激素结合球蛋白、adropin、血管生成素样蛋白 8、胎球蛋白 A、视黄醇结合蛋白 4、hepassocin、硒蛋白 P 和白细胞衍生趋化因子 2 等，它们抑制或者促进NAFLD的形成，在该过程中发挥重要作用。

【关键词】 肝细胞因子；非酒精性脂肪性肝病；肝脂肪变性
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【**Abstract**】 Nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease, is characterized by a large accumulation of fat in the liver. Hepatokines are a kind of proteins secreted by the liver which regulate lipid and glucose metabolism in autocrine, paracrine or endocrine ways. Studies showed that the expression of many hepatokines are changed when hepatic steatosis occurred, including fibroblast growth factor 21, sex hormone-binding globulin, adropin, fetuin A, retinol binding protein 4, angiopoietin-like protein 8, hepassocin and leukocyte cell-derived chemotaxin 2. These hepatokines can inhibit or promote the formation of NAFLD, and therefore play important roles in this process.

【**Key words**】 Hepatokines; Nonalcoholic fatty liver disease; Liver steatosis
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非酒精性脂肪性肝病（NAFLD）以肝脏脂肪变性为主要特点，而其发病机制目前尚未完全知晓。肝细胞因子是肝脏分泌的具有调控糖脂代谢功能的蛋白质。研究表明，许多肝细胞因子在NAFLD的各个发病环节都发挥了重要作用，但目前研究较多的集中在肝细胞因子如何参与NAFLD的形成。因此，本文就此作一综述。

1　NAFLD 概况

NAFLD 是一种除酒精和其他明确损肝原因以外的以肝脏内脂肪过度堆积（脂肪变性）为主要特

征的肝病综合征。随着疾病的进展,NAFLD可表现为单纯性脂肪肝、非酒精性脂肪肝炎(NASH),甚至肝硬化及肝细胞癌[1]。目前,NAFLD逐渐成为最常见的慢性肝病,其发病率在全世界范围中约占25%[2-3]。由于与腹型肥胖、胰岛素抵抗、血脂异常、葡萄糖耐受不良等密切相关,NAFLD被认为是代谢综合征的肝脏表现。NAFLD患者死亡的主要原因包括心血管疾病、恶性肿瘤、肝脏疾病等[4]。

2 NAFLD 的发病机制

NAFLD 的发病机制至今尚未完全明确,目前流行的假说为“多次打击”假说[5]。第一次“打击”是肝脏脂肪聚集。由于血浆游离脂肪酸的再酯化、从头脂肪生成、膳食脂肪酸等肝脏内的脂肪酸代谢异常,导致NAFLD患者的肝脏脂肪异常累积[6]。在胰岛素抵抗状态下,胰岛素抑制脂肪组织脂肪分解以及肝糖异生的作用减弱,而仍然保留促进肝细胞脂肪合成的能力,使得肝细胞内脂肪累积进一步加剧[7]。由于脂肪在肝细胞内过度累积,肝细胞遭到严重的损害[8]。在后续的氧化应激、内质网应激、炎性反应和线粒体功能障碍等多次“打击”下,受损的肝细胞对这些因素的敏感性增加,进一步造成炎性细胞浸润、炎性反应转导途径激活、肝细胞凋亡,从而使得单纯性脂肪肝转变为 NASH、肝硬化甚至肝癌[5,9]。

3 肝细胞因子简介

肝脏是人体重要的代谢器官,具有分泌胆汁、调节物质代谢、防御和免疫、解毒等功能。肝细胞因子指由肝脏分泌的具有自分泌、旁分泌或内分泌活性的蛋白质,主要功能为调节脂质和葡萄糖代谢。胎球蛋白 A 是 1989 年第一个被发现在代谢性疾病中发挥作用的肝细胞因子,其能够抑制胰岛素受体酪氨酸激酶的活性[10]。随后发现,肝细胞因子与许多疾病的发生、发展都密切相关,如心血管疾病、2 型糖尿病、肥胖症、NAFLD、代谢综合征等[11]。

研究显示,在肝脏发生脂肪变性时,许多蛋白质的分泌都会发生改变[12]。其中包含多种肝细胞因子。这些肝细胞因子能通过促进脂肪肝形成、肝纤维化和诱导机体产生胰岛素抵抗等多种途径参与NAFLD的发生、发展。其中,一些肝细胞因子通过调节有关受体的表达、促进肝细胞自噬、调控肝脏脂质生成相关的基因、转录因子和关键酶的表达等抑制NAFLD 的形成,如成纤维细胞生长因子21(FGF21)、性激素结合球蛋白(SHBG)和adropin。而另一些肝细胞因子通过调控肝脏的糖脂代谢酶表达、肝细胞脂质含量、促进肝脏脂质生成和聚集等途径促进 NAFLD 的形成,如血管生成素样蛋白 8(ANGPTL8)、胎球蛋白 A、视黄醇结合蛋白 4(RBP4)、硒蛋白 P、hepassocin和白细胞衍生趋化因子 2(LECT2)。

4 抑制 NAFLD 形成的肝细胞因子

4.1 FGF21 FGF21 是一种主要产生于肝脏的蛋白质,具有调节碳水化合物和脂代谢的功能[13]。研究表明,在成人NAFLD患者中,血清FGF21水平较正常对照明显升高[14]。而在儿童NAFLD患者中,关于血清FGF21水平变化的研究报道并不一致。Alisi等[15]研究发现,儿童NAFLD患者血清FGF21水平较对照组显著降低。Reinehr等[16]发现,与正常组儿童相比,儿童NAFLD患者血清FGF21水平无明显差异。结果的不一致可能与受试人群种族、NAFLD诊断手段不同有关。

肝组织水平的研究显示,随肝脏甘油三酯含量的升高,血清FGF21水平及肝FGF21 mRNA的表达均明显升高[17]。进一步逐步线性回归分析发现,血清FGF21水平是NAFLD患者肝脏脂肪变性的唯一独立预测因子[17]。而对于FGF21如何调控肝脏脂肪含量,目前认为可能存在以下两种机制。其一,FGF21调控肝脏脂肪含量可能与抑制极低密度脂蛋白受体(VLDLR)表达有关。研究发现,沉默小鼠体内FGF21的表达后,小鼠肝脏的甘油三酯聚集程度明显增加,VLDLR mRNA、激活转录因子 4(ATF4)蛋白表达及真核生物翻译起始因子 2α(eIF2α)磷酸化水平显著上升[18]。在细胞水平使用FGF21蛋白处理Huh-7肝细胞后,细胞内 VLDLR 和 ATF4 表达及eIF2α磷酸化水平明显降低。提示FGF21可能通过抑制eIF2α-ATF4通路,下调肝脏VLDLR的表达,从而减少肝脏的脂肪聚集[18]。其二,FGF21可以通过促进肝细胞自噬,调控肝脏脂肪含量。研究表明,在肥胖伴胰岛素抵抗的小鼠中,过表达FGF21后,小鼠肝细胞内脂肪滴的数量和大小均明显下降[19]。使用FGF21处理HepG2细胞后,细胞内溶酶体、自噬体增多,自噬相关蛋白Beclin-1、ATG12和LC3B的表达明显上调,LC3B-Ⅰ向LC3B-Ⅱ的转换也明显增加;同时研究人员还观察到了细胞中双膜自噬体和自噬溶酶体内的脂质隔离(脂质过氧化的特征)[19]。这些结果表明,FGF21能够通过促进肝细胞自噬和肝脏脂质过氧化,减少肝脏脂肪含量。

4.2 SHBG SHBG 主要在肝脏中产生,负责性激素的转运[20]。NAFLD 患者循环中 SHBG 水平较

低[21]。在糖尿病患者中，NAFLD与血清SHBG水平呈负相关[22]。循环中SHBG水平随肝脏内脂肪含量的增加而降低[23-25]。在 C57BL/ksJ-db/db 小鼠（NAFLD模型）中过表达SHBG后，小鼠肝脏重量及肝脏内脂肪累积程度显著减少，调控肝脏脂质生成的关键转录因子过氧化物酶体增殖物活化受体 γ（PPARγ）和肝脏脂质生成关键酶，包括乙酰辅酶 A 羧化酶、脂肪酸合成酶和 ATP 柠檬酸裂解酶的mRNA及蛋白表达水平均明显降低[26]。上述结果说明，SHBG可能通过抑制肝脏脂质生成的关键转录因子和关键酶的表达，从而减少肝脏脂肪生成。

4.3　Adropin　Adropin 是一种由能量稳态相关基因 Echo 编码的蛋白质，主要表达于大脑和肝脏中[27]。研究发现，与对照组相比，NAFLD患者血清adropin水平明显降低[28]。在饮食诱导性肥胖小鼠体内过表达adropin，小鼠肝脏脂肪脂肪变性减轻，但小鼠肥胖或饮食摄入未受影响。进一步研究发现，adropin能抑制小鼠体内肝脏脂肪生成基因和脂肪组织中PPARγ的表达，从而减少肝脏脂肪生成[27]。

5　促进 NAFLD 形成的肝细胞因子

5.1　ANGPTL8　ANGPTL8 又称甜菜碱（betatrophin），在人类中主要表达于肝脏中，而在小鼠中富含于肝脏、白色脂肪组织和棕色脂肪组织[29]。研究发现，在NAFLD患者和各种脂肪肝的小鼠模型中，血清ANGPTL8水平均明显升高[30]。多元逐步线性回归分析显示，人体血清ANGPTL8水平是肝细胞脂质含量的独立决定因素[31]。动物实验中，在高脂饮食大鼠和小鼠体内抑制ANGPTL8表达后，大鼠肝脏的甘油三酯含量相对下降 66%；小鼠肝脏的甘油三酯含量相对下降 37%[32]。细胞实验中，使用游离脂肪酸干预HepG2和Huh7细胞，能增加细胞内甘油三酯含量，同时伴有ANGPTL8 mRNA的表达上调。而干扰ANGPTL8的表达后，游离脂肪酸诱导的细胞内甘油三酯聚集显著减少[33]。这些结果说明ANGPTL8能够通过增加肝脏脂肪含量，从而参与脂肪肝的形成。

5.2　胎球蛋白 A　胎球蛋白 A 又称 α2-HS-糖蛋白（α2-HS-glycoprotein），主要表达于肝脏中[34]。von Loeffelholz等[35]发现NAFLD患者血清胎球蛋白 A 水平均明显上升，并与肝脏脂质含量呈正相关。另外有研究表明，随着血清胎球蛋白 A 水平升高，基于腰围、体重指数、血清甘油三酯和谷丙转氨酶计算所得的脂肪肝指数也随之增加[36]。研究发现，在NAFLD患者及对照人群中，肝脏中胎球蛋白 A mRNA表达与固醇调节元件结合蛋白 1c 和磷酸烯醇式丙酮酸激酶mRNA表达呈正相关，提示肝组织中的胎球蛋白 A 可能参与调节脂质和葡萄糖代谢[37]。但胎球蛋白 A 作用于肝脏糖脂代谢的具体机制还需要进一步研究。

5.3　RBP4　RBP4 主要在肝脏和脂肪组织表达，负责血液中维生素 A 的转运[38]。血清RBP4水平变化在不同人种、年龄及不同样本量的研究结果均不一致[39-40]。而Zhou等[41]的荟萃分析表明，NAFLD患者血清 RBP4 水平与对照组相比无明显差异。Yan等[42]发现，中国人的血清 RBP4 水平与肝脏脂肪含量（HFC）无关。当人体 HFC 低于 6.34% 时，血清RBP4水平与 HFC 呈正相关。并且这一关联不受体重指数、腰围、体重等因素影响[43]。此外，Schina等[44]发现，肝组织RBP4表达评分与肝脏脂肪变性等级呈正相关。

5.4　Hepassocin　Hepassocin因在大鼠肝脏再生中表达上调而被发现[45]。NAFLD患者血清hepassocin水平明显高于对照人群[46]。动物实验中，使用hepassocin干预小鼠后，小鼠肝脏脂质生成和聚集增加，NAFLD活动度积分升高。而降低小鼠体内的hepassocin表达后，小鼠体内的肝脏脂质生成相关蛋白、甘油三酯、NAFLD活动度积分等指标均有明显降低[46-47]。基于HepG2细胞的实验表明，hepassocin能通过细胞外信号调节激酶 1/2 通路诱导肝脏脂肪生成和聚集[47]。

5.5　硒蛋白 P　硒蛋白 P 是一种主要由肝脏产生的分子量为60 000的糖蛋白，其能够作为载体蛋白将硒运送至机体各个组织器官[48]。NAFLD患者血清硒蛋白 P 水平明显升高，并与NAFLD的患病率呈正相关[49]。研究发现，随着血清硒蛋白 P 水平升高，受试者的肝衰减指数（与肝脏脂肪累积成负相关）明显降低。而另一项研究则表明，在怀孕的女性中，NAFLD患者的脂肪肝指数与血清硒蛋白 P 水平呈正相关[50]。这些结果说明硒蛋白 P 的血清水平与肝脏脂肪累积呈正相关[51]。

5.6　LECT2　LECT2 主要由肝细胞分泌，是一种中性粒细胞趋化蛋白[52]。研究发现，与对照组相比，NAFLD患者血清LECT2血清水平更高[53]。动物实验发现，循环LECT2水平与小鼠肝脏甘油三酯含量呈正相关[54]。

目前，NAFLD 的发病机制仍尚未完全明确。最新的研究表明，肝细胞因子与NALFD的形成过程密切相关，肝细胞因子能调节肝脏脂质和葡萄糖代谢

关键酶的表达、肝脏脂肪含量、肝细胞自噬等多个方面。临床上可以通过检测肝细胞因子的水平，作为血清生物标志物，辅助NAFLD的早期诊断。但是，目前关于肝细胞因子与NAFLD发生、发展的关系，主要集中在肝细胞因子如何参与脂肪肝的形成过程，其他发病环节如肝纤维化形成、胰岛素抵抗等的研究较少。此外，多数研究仅停留在血清肝细胞因子水平与NAFLD的相关性，缺乏相应动物、细胞实验阐明肝细胞因子在脂肪肝形成中的具体作用。未来尚需要大量多角度、更深入的研究，探索肝细胞因子在NAFLD发生、发展中的具体作用，为NAFLD的精准诊断和临床治疗提供实验依据。

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