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文献综述 REVIEW

非酒精性脂肪性肝炎的发病机制: 病理生理学和分子生物学

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Mechanisms of non-alcoholic steatohepatitis: pathophysiology and molecular biology

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Abstract

Non-alcoholic steatohepatitis (NASH), characterized by liver fatty infiltration, inflammation, hepatocellular injury and fibrosis, may easily develop into liver cirrhosis and hepatocellular carcinoma. The increased flow of FFAs (free fatty acids) to the liver and the *de novo* lipogenesis in the liver lead to fat overload. Lipotoxicity can induce oxidative stress, inflammatory reaction and apoptosis. Subsequently chronic liver injury activates a fibrogenic response that accelerates the evolution of NASH towards end-stage liver disease. Further research on pathophysiology and molecular biology is beneficial to clinical diagnosis and management of NASH.

Key Words: Non-alcoholic steatohepatitis; Pathophysiology; Molecular biology

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摘要

非酒精性脂肪性肝炎以肝脏脂肪浸润、炎症、肝细胞损害和纤维化为特征, 可进一步发展为肝硬化及肝癌. 游离脂肪酸向肝内转运和肝脏脂肪酸的从头合成导致肝细胞内脂肪超负载. 脂毒性引起氧化应激、炎症反应和肝细胞凋亡. 随后慢性肝损伤激活纤维化反应发展至终末期肝病. 对非酒精性脂肪性肝炎病理生理学和分子生物学发病机制的深入研究将有利于临床诊断和治疗.

关键词: 非酒精性脂肪性肝炎; 病理生理学; 分子生物学

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0 引言

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)被认为是代谢综合征在肝脏中的表现, 后者包括内脏性肥胖、胰岛素抵抗(insulin resistance, IR)、血脂异常及高血压病. 有一部分NAFLD患者可进一步发展为非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH). 虽然这一具体过程尚不清楚, 但目前认为NASH以脂肪浸润、肝细胞损害、炎症和纤维化为其特征. 本文将对NASH的病理生理学和分子生物学发病机制进行综述, 旨在为临床诊断和治疗提供依据.

1 导致肝脏中脂肪沉积的因素

以甘油三酯(triglycerides, TG)为主的脂肪在肝内沉积是发展为NAFLD和NASH的绝对必要条件, 远距离产生的内分泌激素(如胰岛素)以及局部产生的激素和细胞因子共同调控着肝脏的脂肪代谢.

1.1 IR IR是指体内周围组织对胰岛素的敏感性降低, 如肌肉、脂肪组织对胰岛素促进葡萄糖摄取的作用不敏感. 为克服IR, 机体分泌更多的胰岛素并减少胰岛素的清除[1], 从而导致其他组织脏器(如肝脏)的代谢变化. NAFLD患者常表现为高IR: 一方面是肌肉组织对葡萄糖的摄取

■背景资料
非酒精性脂肪性肝病(NAFLD)被认为是代谢综合征在肝脏中的表现, 后者包括内脏性肥胖、胰岛素抵抗(IR)、血脂异常及高血压病. 有一部分NAFLD患者可进一步发展为非酒精性脂肪性肝炎(NASH). NASH以肝脏脂肪浸润、炎症、肝细胞损害和纤维化为特征, 可进一步发展为肝硬化及肝癌. 游离脂肪酸向肝内转运和肝脏脂肪酸的从头合成导致肝细胞内脂肪超负载. 脂毒性引起氧化应激、炎症反应和肝细胞凋亡. 随后慢性肝损伤激活纤维化反应发展至终末期肝病. 本文将对NASH的病理生理学和分子生物学发病机制进行综述, 旨在为临床诊断和治疗提供依据.

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■研发前沿
尽管关于NASH的发病机制有了大量新的研究资料, 但IR、炎症和纤维化三者间相互作用的具体过程, 脂肪肝、NASH和心血管危险因素之间的联系, 各种FFAs的不良反应, 符合NASH发病机制的动物模型建立等问题都有待进一步解决.

减少及脂肪组织分解加速导致游离脂肪酸(free fatty acids, FFAs)增多; 另一方面则是胰岛素对肝葡萄糖生成(hepatic glucose production, HGP)抑制减弱[2-4]. 糖尿病患者IR较NAFLD更为严重, 但NAFLD患者的IR是独立于糖尿病和/或肥胖的代谢缺陷[2,5].

1.2 肝脏的脂肪代谢障碍 肝脏的脂肪代谢障碍可能与FFAs的浓度, 脂肪酸的氧化合成以及极低密度脂蛋白(very low density lipoprotein, VLDL)有关. NAFLD患者脂肪分解加速, 大量FFAs向肝中转运, 示踪研究显示肝中脂肪的氧化不仅没有减少而是增加, 同时VLDL也相应增加[6], 提示FFAs可能是脂肪代谢障碍最为重要的因素. 增加的FFAs即可来自于脂肪细胞和高脂饮食, 也可通过肝内从头合成(*de novo* lipogenesis, DNL)产生[7]. 人类和动物研究均发现内脏性脂肪的分解及FFAs动员至门静脉导致肝内IR[3,5]. 在动物中给予高脂饮食出现肝细胞脂肪变性和HGP增加, 而在人类中低热低脂饮食则减少肝中40%-80%的脂肪[8]. 向肝内转运的FFAs不仅出现在脂肪餐后, 即使是禁食的受试者也可通过动员腹部脂肪转运FFAs至肝[9], 提示血液中FFAs可能优先通过门静脉转运, 导致肝内脂肪沉积. DNL是肝内FFAs增加的另一来源. 在正常人禁食情况下, DNL对肝内FFAs的贡献约5%左右, 而在NAFLD患者中, DNL对肝内FFAs的贡献增加至25%左右[10]. 胰岛素通过固醇调节元件结合蛋白-1(sterol regulatory element binding protein-1, SREBP-1)以及葡萄糖通过碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, ChREBP)转录调控DNL[11].

1.3 脂肪因子 脂肪组织(尤其是内脏性脂肪)的增加伴随着胰岛素增敏因子和抗炎因子的减少以及致炎因子的增加. 炎症因子反过来通过调节脂肪细胞分泌代谢而增强IR. Kanda *et al*[12]研究表明单核细胞趋化蛋白-1(monocyte chemotactic protein-1, MCP-1)通过募集巨噬细胞在脂肪组织中产生炎症, 加重脂肪肝和IR. NAFLD患者脂联素(adiponectin)水平降低, 且与肝脏TG的含量成负相关[13], 这可能与他抑制包括肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)在内的多种炎症因子有关[14]. 瘦素(leptin)一方面参与肝内TG沉积和促炎效应, 另一方面调节氧化应激反应[15-17]. 抵抗素(resistin)在啮齿类是由脂肪细胞和单核细胞产生, 而在人类主要是由脂肪组织中的间质细胞产生[18]. 肝内抵抗素在NASH患者中显著增加, 并被炎症细胞所调节[19]. 最近发现内脏性脂肪还能分泌一种致炎细胞因子, 即内脏脂肪素(visfatin)[20], 也可能参与到NASH的发生中.

1.4 过氧化物酶体增殖物激活受体 过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)属于配体激活的转录因子中的核受体超家族, 根据其结构及功能可分为3种亚型: PPARα、PPARβ/δ及PPARγ. 人工合成的PPARγ配体(噻唑烷二酮类)已经用于治疗糖尿病, 而PPARα配体(贝特类)则用于治疗高脂血症. PPARγ激动剂通过活化AMP激活的蛋白激酶(AMP-activated protein kinase, AMPK)促进胰岛素敏感的脂肪组织摄取和存储FFAs, 同时抑制肝脏脂肪酸的合成[21]. PPARα和PPARγ均有抗炎效应, 并能改善脂肪沉积引起的IR[22]. 近年来在NASH患者中发现给予PPARγ激动剂治疗后, 脂联素水平显著增加, 而抵抗素、TNF-α、IL-6和C-反应蛋白(C-reactive protein, CRP)水平则显著减低, 并且肝脏脂肪变性明显改善[23].

2 肝细胞脂肪超负载的损害机制

细胞中的脂肪超负载(fat-laden)可引起各种直接或间接的脂毒性作用. 代谢调节异常、线粒体损害和氧化应激损伤肝细胞, 并引发基因表达异常, 最终导致炎症反应和细胞死亡[24].

2.1 线粒体功能障碍和氧化应激 FFAs的β氧化、活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)的产生均在线粒体中进行. 而研究发现NASH患者无论线粒体结构还是功能都发生异常. 越来越多的证据表明IR和脂肪超负载导致线粒体功能障碍, ROS和RNS生成增加[25]. 其中ROS又可抑制细胞色素c氧化酶, 破坏含铁硫蛋白氧化还原酶的呼吸链以及损害线粒体DNA(mitochondrial DNA, mtDNA)[26], 形成恶性循环. TNF-α诱导一氧化氮合酶-2(nitric oxide synthase-2, NOS-2)增加RNS产物[27], 然后RNS通过硝基化酪氨酸残基破坏呼吸链或者直接损害DNA[28]. 研究表明给*ob/ob*小鼠喂养尿酸饮食后, 尿酸与过氧亚硝酸盐反应形成无活性的含氮尿酸盐, 从而减少细胞色素c的破坏以及脂质过氧化物的生成[29]. FFAs增加还可活化细胞色素P450亚族CYP2E1和CYP4A10/4A14, 导致ROS增加和线粒体呼吸链解偶联[25,30]. 线粒体中的胆固醇也被证实与NASH患者的炎症浸润有关[31]. 现在研究还发现非线粒体来源

的ROS, 例如来源于过氧化物酶体和微粒体的ROS, 枯否细胞(kupffer cells, KCs)和肝星状细胞(hepatic stellate cells, HSCs)产生的ROS, 也都参与到NASH的氧化应激中[32-33]. NASH患者中反映脂质氧化损害的指标(硫巴比妥酸反应物、丙二醛、羟基壬烯醛、硝基酪氨酸蛋白、8-羟基-2'脱氧鸟嘌呤核苷和硫氧还蛋白)增加, 而反映抗氧化的因子(辅酶Q10、铜锌超氧化物歧化酶、过氧化氢酶和谷胱甘肽转移酶)减少[34-36], 提示氧化应激在促进和维持细胞损害的过程中起重要作用.

2.2 NASH中肝细胞的坏死和凋亡 尽管机体存在抗氧化应激系统, 但持续过度的细胞毒性仍可导致细胞坏死和/或凋亡[37-38]. 与对照组相比, NASH患者中抗凋亡因子Bcl-2继发性增加[39], 提示测定血浆中凋亡产物以及抑制死亡受体介导的凋亡有可能为NASH的诊断和治疗提供线索.

2.3 NASH与基因表达调控 转录因子Sp1和Sp3已被证实参与到NASH的发生发展过程, 他们通过激活Ⅰ型胶原的表达促进纤维化的形成[40], 而转录因子CCAAT增强子结合蛋白-β(CCAAT enhancer binding protein-β, C/EBP-β)则参与脂肪代谢、炎症反应和内质网应激等过程[41]. 调控抗氧化基因表达的转录因子Nrf-1和调控氧化应激适应性反应的转录因子APE/Ref-1在NASH患者中均显著升高[42]. 新近研究发现PI3K-Akt-PTEN信号转导通路缺陷的小鼠在40 wk后发展为NASH, 在80 wk后则发展为肝癌[43], 提示炎症反应和血管生成可能是两者的共同之处.

3 NASH中的炎症和纤维化

除了肝细胞损害外, 炎症和纤维化也是从脂肪变性过渡到脂肪性肝炎的重要特征. 在慢性肝病患者中, 肝脏炎症是肝纤维化发生发展的独立危险因素. 因此细胞损害, 炎症和纤维化三者之间关系密切.

3.1 肝脏中的炎症信号通路 在动物模型和NASH患者中, 肝脏NF-κB的表达显著增加, 活化的NF-κB通过信号转导通路介导肝脏炎症、脂肪变性和IR[44-45]. 在基因敲除IκB激酶β(IκB kinase β, IKKβ)小鼠中, 给予高脂饮食后仍然保留对胰岛素的敏感性, 而另一项研究认为基因敲除IKKγ/NEMO(NF-κB essential modulator, NEMO)的肝细胞引起脂肪性肝炎和肝细胞癌[46-47]. 这一方面说明NF-κB调控的复杂性, 另外一方面说明完全抑制NF-κB活性可能导致肿瘤发生.

TNF诱导的c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)信号转导通路也参与到NASH中的炎症和IR. 同时敲除JNK-1和JNK-2的小鼠肝脏炎症和IR均显著降低[48], 而仅敲除JNK-2的小鼠则与野生型小鼠相近[49], 提示抑制JNK-1对减轻脂肪沉积引起的肝细胞损害更为有效.

TNF-α和IL-6在NASH患者中显著增加, 他们受NF-κB、JNK或p38 MAPK等信号转导通路调控[50]. 在*ob/ob*小鼠和高脂饮食模型中, 抑制TNF-α能够显著减轻脂肪变性、炎症和肝细胞损害[51]. 另外的研究则发现敲除TNF-α或TNFR1基因的小鼠在脂肪性肝炎、脂质过氧化和肝细胞损害方面与野生型小鼠差异不大[45]. IL-6也是一个存在争议的细胞因子, 他可通过JAK-STAT信号转导通路促进肝细胞再生而减轻小鼠脂肪肝[52]. 尽管如此, IL-6缺陷的小鼠却能改善IR[53], 这可能与JAK-STAT通路的负性调控分子家族细胞因子信号转导抑制因子(suppressors of cytokine signaling, SOCS)有关. 其中SOCS-1和SOCS-3可以阻断胰岛素受体信号导致IR[54]. SOCS还可干扰瘦素受体信号, 可能与瘦素抵抗有关.

3.2 其他致炎机制 近来研究认为模式识别受体(pattern recognition receptors, PRRs)也参与到NASH的炎症过程中, 这与肠道细菌代谢产物入血后作用于KCs有关. PRRs包括Toll样受体(Toll-like receptors, TLRs)和其他识别内毒素等细胞代谢产物的受体[55-56]. TLRs活化后通过NF-κB促进炎症因子和致纤维化因子的分泌[57]. 在NASH患者和动物模型中发现IL-8和MCP-1也通过NF-κB途径而表达增加, 他们分别促进中性粒细胞和单核细胞的浸润[50,58].

3.3 肝纤维化机制 虽然肝纤维化和肝硬化是所有慢性肝病的最终结果, 但NASH所致肝纤维化与其他肝损害所致肝纤维化有所不同. NASH所致纤维化主要发生在小叶中央区, Disse腔周围纤维组织较厚, 而包绕肝细胞团的纤维组织较薄. NASH的致纤维化因素除了HSCs外, 还与脂肪因子、氧化应激和IR密切相关.

4 结论

FFAs向肝内转运和肝脏脂肪酸的从头合成导致肝细胞内脂肪超负载. 脂毒性和细胞死亡激活炎症反应信号转导通路, 促进炎症细胞浸润, 加重细胞损害及纤维化. 尽管关于NASH的发病机

■应用要点
对非酒精性脂肪性肝炎病理生理学和分子生物学发病机制的深入研究将有利于临床诊断和治疗.

■同行评价
本文内容新颖, 逻辑性强, 参考文献引用合理, 是一篇临床实用性较强的优秀文章.

制有了大量新的研究资料, 但IR、炎症和纤维化三者间相互作用的具体过程, 脂肪肝、NASH和心血管危险因素之间的联系, 各种FFAs的不良反应, 符合NASH发病机制的动物模型建立等问题都有待进一步解决. 只有研究更加深入, 才能最终找到NASH的有效诊断和治疗方法.

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• 消息 •

世界华人消化杂志计量单位标准

本刊讯 本刊计量单位采用国际单位制并遵照有关国家标准, GB3100-3102-93量和单位. 原来的“分子量”应改为物质的相对分子质量. 如30 kD改为M_r 30 000或30 kDa(M大写斜体, r小写正体, 下角标); “原子量”应改为相对原子质量, 即Ar(A大写斜体, r小写正体, 下角标); 也可采用原子质量, 其单位是u(小写正体). 计量单位在+、－、±及-后列出. 如37.6±1.2℃, 45.6±24岁, 56.4±0.5 d. 3.56±0.27 pg/ml应为3.56±0.27 ng/L, 131.6±0.4 mmol/L, t = 28.4±0.2℃. BP用kPa(mmHg), RBC数用×10^{12}/L, WBC数用×10^9/L, WBC构成比用0.00表示, Hb用g/L. M_r明确的体内物质以mmol/L, nmol/L或mmol/L表示, 不明确者用g/L表示. 1 M硫酸, 改为1 mol/L硫酸, 1 N硫酸, 改为0.5 mol/L硫酸. 长10 cm, 宽6 cm, 高4 cm, 应写成10 cm×6 cm×4 cm. 生化指标一律采用法定计量单位表示, 例如, 血液中的总蛋白、清蛋白、球蛋白、脂蛋白、血红蛋白、总脂用g/L, 免疫球蛋白用mg/L; 葡萄糖、钾、尿素、尿素氮、CO_2结合力、乳酸、磷酸、胆固醇、胆固醇酯、三酰甘油、钠、钙、镁、非蛋白氮、氯化物; 胆红素、蛋白结合碘、肌酸、肌酐、铁、铅、抗坏血酸、尿胆元、氨、维生素A、维生素E、维生素B_1、维生素B_2、维生素B_6、尿酸; 氢化可的松(皮质醇)、肾上腺素、汞、孕酮、甲状腺素、睾酮、叶酸用nmol/L; 胰岛素、雌二醇、促肾上腺皮质激素、维生素B_{12}用pmol/L. 年龄的单位有日龄、周龄、月龄和岁. 例如, 1秒, 1 s; 2分钟, 2 min; 3小时, 3 h; 4天, 4 d; 5周, 5 wk; 6月, 6 mo; 雌性♀, 雄性♂, 酶活性国际单位IU = 16.67 nkat, 对数log, 紫外*uv*, 百分比%, 升L, 尽量把1×10^{-3} g与5×10^{-7} g之类改成1 mg与0.5 μg, hr改成h, 重量γ改成mg, 长度m改成mm. 国际代号不用于无数字的文句中, 例如每天不写每d, 但每天8 mg可写8 mg/d. 在一个组合单位符号内不得有1条以上的斜线, 例如不能写成mg/kg/d, 而应写成mg/(kg•d), 且在整篇文章内应统一. 单位符号没有单、复数的区分, 例如, 2 min不是2 mins, 3 h不是3 hs, 4 d不是4 ds, 8 mg不是8 mgs. 半个月, 15 d; 15克, 15 g; 10%福尔马林, 40 g/L甲醛; 95%酒精, 950 mL/L酒精; 5% CO_2, 50 mL/L CO_2; 1∶1 000肾上腺素, 1 g/L肾上腺素; 胃黏膜含促胃液素36.8 pg/mg, 改为胃黏膜蛋白含促胃液素36.8 ng/g; 10%葡萄糖改为560 mmol/ L或100 g/L葡萄糖; 45 ppm = 45×10^{-6}; 离心的旋转频率(原称转速)用r/min, 超速者用*g*; 药物剂量若按体质量计算, 一律以“/kg”表示. (常务副总编辑: 张海宁 2009-05-08)