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文献综述 REVIEW

瘦素、脂联素在慢性肝病中的研究进展

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Advances in understanding the roles of leptin and adiponectin in the pathogenesis of chronic liver diseases

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Abstract
Leptin and adiponectin are adipokines that are abundantly expressed in adipose tissue and have multiple biological effects related to the development of human diseases. More and more studies have demonstrated that adipokines play important roles in the pathogenesis of steatosis, steatohepatitis and liver fibrosis, especially nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C (CHC). This paper reviews the recent advances in understanding the roles of leptin and adiponectin in the pathogenesis of liver diseases.

Key Words: Adipokine; Leptin; Adiponectin

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摘要
瘦素脂联素是脂肪细胞分泌的细胞因子, 发挥多种生物学作用并与一系列人类疾病相关. 越来越多的研究发现瘦素脂联素等细胞因子在肝脏脂变、炎症坏死及纤维化方面起重要作用, 尤其是非酒精性肝病(nonalcoholic fatty liver disease, NAFLD)、慢性丙型肝炎方面. 本文就瘦素脂联素在慢性肝病中的进展作一总结.

关键词: 脂肪因子; 瘦素; 脂联素

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■背景资料
脂肪因子主要是由脂肪组织分泌的一组具有生物活性的多肽激素, 他们调节不同组织产生多种生物学作用. 目前认为脂肪因子与不同病因引起的严重肝病密切相关, 其中以瘦素与脂联素研究最为广泛深入.

0 引言
白色脂肪组织在成人表达丰富, 主要有三方面作用: 储存能量; 将三酰甘油水解为游离脂肪酸, 供应组织能量; 释放脂肪因子. 脂肪因子(瘦素、脂联素、抵抗素等)主要是由脂肪组织分泌的一组具有生物活性的多肽激素, 他们进入血液循环系统, 调节不同组织产生不同生物学作用. 目前认为脂肪因子与不同病因[非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)、丙型肝炎及酒精性肝病]引起的严重肝病进展密切相关, 其中以瘦素、脂联素的研究最为广泛深入.

1 瘦素脂联素的生物学作用
1.1 瘦素 瘦素是肥胖基因(obese, ob)编码产物, 通过与其受体结合在体内发挥多种生物学作用, 调节摄食、能量代谢、生殖、造血、免疫等生理功能, 参与炎性反应、损伤修复等病理生理过程, 瘦素受体(leptin receptors, OBRs)属于Ⅰ类细胞因子受体家族, 由胞外区、跨膜区、胞质区三部分组成. 瘦素受体有6种亚型, 即OBRa、OBRb、OBRc、OBRd、OBRe、OBRf. 他们的差异在于胞内结构域的长度及氨基酸序列组成的不同, 这些受体被分为长型和短型2种, 其中OBRb为长型受体, 其余5种亚型受体为短型受体. OBRb型受体是瘦素的功能性受体, 主要分

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■研发前沿
肝脏在代谢综合征中的核心作用, 因而大量研究关注脂肪因子在脂肪肝中的作用及慢性丙型肝炎相关的代谢综合征. 脂肪因子为肝病治疗方面提供新的靶点, 尤其是脂联素显示出更有前景的治疗作用.

布于中枢神经系统, 外周组织也广泛表达, 包括肝脏, OBRb经Janus激酶2(Janus kinase 2, JaK2)/信号转导蛋白激活转录因子3(signal transducer and activator of transcription3, Stat3)介导瘦素的主要生物学作用. 以OBRa为主的短型受体多分布于脂肪、骨骼肌、肝等外周组织, OB-R分布的不同和广泛性, 决定了瘦素作用的多样性[1].

瘦素分泌与脂肪含量成正比, 并通过下丘脑通路产生抗肥胖信号, 调节脂肪吸收, 与交感兴奋及能量过剩时的能量消耗有关. 近来研究发现瘦素介导的能量消耗可能与改变肝脏线粒体能量代谢有关[2]. 瘦素缺陷的ob/ob小鼠发生明显脂肪变, 提示瘦素可以预防脂肪肝, 其机制为直接激活肝脏磷酸腺苷蛋白激活酶(adenosine monophosphate-activated protein kinase, AMPK)信号通路, 间接通过中枢神经通路[3]. 瘦素缺陷还可以引起全身脂肪营养障碍, 补充瘦素可以改善脂肪肝. 与之相反存在脂肪肝肥胖患者其瘦素水平升高, 这可能与肝脏瘦素抵抗有关. 瘦素抵抗机制可能为营养学参与其中, 因为果糖可以干扰Stat3信号诱导的高瘦素血症及肝脏瘦素抵抗[4]. 另一机制可能与升高的细胞因子信号3(cytokine signaling-3, SOCS3)有关, 其损害受体后信号, 导致AMPK活化信号减弱. 大麻素受体(cannabinoid receptor, CB1)信号活化是瘦素抵抗的另一机制[5].

瘦素还参与天然免疫及适应性免疫. ob/ob肥胖的小鼠免于刀豆蛋白A诱导的自身免疫性疾病及T细胞介导的肝炎[6]. 瘦素缺陷的动物更易感染细菌及病毒, 给予内毒素刺激后肝脏毒性及病死率更高. 因而一般认为瘦素作为促炎因子, 保护机体免于微生物感染[7].

促纤维化作用是瘦素的另一特征. 给予瘦素而非限制饮食可以逆转ob/ob小鼠的纤维化缩小, 提示瘦素具有强效促纤维化作用. 瘦素经多种细胞发挥其促纤维化作用, 瘦素活化库普弗细胞和巨噬细胞, 刺激内皮细胞分泌转化生长因子β[8]. 更重要的是瘦素经ObRb直接作用于肝星状细胞(hepatic stellate cell, HSC), 促进星状细胞增殖抑制其凋亡, 促进Ⅰ型前胶原的表达及分泌, 上调基质金属蛋白组织抑制因子1(tissue inhibitor of matrix metalloproteinase, TIMP-1)的表达[9]. 此外瘦素可以激活辅酶Ⅱ(nicotinamide adenine dinucleotide phosphate, NADPH)产生氧自由基, 调整细胞趋化因子的表达及凋亡小体的吞噬[10]. 瘦素缺乏的大鼠可以改变肝脏部分切除术及毒物损伤后的肝脏再生, 然而, 恢复血瘦素水平没能挽救肝部分切除术后肝脏再生, 提示持续的瘦素缺乏对肝细胞再生能力产生复杂的干扰[11]. 最近研究发现瘦素与癌症进展相关, 与其直接及间接增加血管生成有关. 瘦素作用于内皮细胞上调星状细胞表达血管内皮细胞生长因子, 实验性脂肪肝炎模型中发现瘦素缺乏可以减少血管生成及癌前疾病形成[12]. 此外, ObR在人类肝癌组织高表达, 而分化不良的肝细胞癌(hepatocellular carcinoma, HCC), 其血管化作用较强, ObR表达较多, 提示体外瘦素或瘦素受体与肝癌的血管生成有关[13]. 瘦素还促进了胆管癌细胞的增殖及迁移. 因而瘦素在慢性肝脏疾病中可以通过加速纤维化, 诱导血管生成及直接作用于肿瘤细胞等方面促进癌症发生. 而另外一方面瘦素干预免疫系统可能产生有益的作用, 最近报道在异种移植模型中给予瘦素可以增加自然杀伤细胞的数目并减少肿瘤大小[14].

1.2 脂联素 脂联素是由脂肪组织分泌的一种蛋白质, 是脂肪组织中特异表达的脂肪因子. 正常人血浆中含量丰富, 脂联素在血浆中以球状结构域、全长脂联素(脂联素三聚体、六聚体、高聚体)等形式存在. Yamauchi等首次克隆出人和小鼠脂联素受体, 研究发现高度保守的脂联素受体(adiponectin receptor, AdipoR)有两种构成: AdipoR1和AdipoR2. 人体多种组织细胞表面均有脂联素受体的分布和表达. AdipoR1在全身各组织广泛表达, 在骨骼肌最丰富, 在内皮细胞及其他组织亦有表达, 是球形脂联素的高亲和力受体, 对全长脂联素亲和力低, AMPK是其下游主要信号分子; AdipoR2主要在肝脏表达, 对全长及球形脂联素都有中等程度的亲和力, 而PPARa是其下游主要信号分子. T-钙粘蛋白, 脂联素另一受体其具体信号通路研究不清. 脂联素与其受体结合, 在机体能量代谢、炎症、免疫等方面发挥重要的调节作用[15].

脂联素水平与机体脂肪含量呈负相关, 可以增强肝脏、骨骼肌、脂肪组织对胰岛素的敏感性, 在肥胖2型糖尿病患者中其水平下降. 与瘦素相似, 脂联素调节机体脂质分布, 并在肝脏损伤时发挥保护肝脏及抗纤维化作用. 酒精性及非酒精性肝病研究中发现给予脂联素可以缓解炎症坏死及脂肪变, 其机制可能是脂联素抑制肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)表达[16]. 此外, 减少食物中饱和脂肪酸含量可以增加脂联素分泌, 对酒精性肝损伤具

有保护作用[17]. 相反, 长期慢性酒精暴露, 可降低血脂联素水平. 相应的给予肥胖大鼠(对氨基半乳糖或脂多糖敏感)脂联素可以改善肝损伤, 降低TNF-α并增加过氧化物酶体增殖激活受体(peroxisome proliferator -activated receptor-alpha, PPAR-α)表达[18]. ob/ob小鼠中研究发现适度增加脂联素水平可以减少炎症, 增加脂肪组织表达PPAR-γ, 其机制是脂联素通过信号分子将肝脏、骨骼肌的三酰甘油转运至脂肪组织, 从而增加这些组织对胰岛素的敏感性[19]. 这与采用噻唑烷二酮类药物诱导人脂联素水平增加机制相似[20].

虽然脂联素及瘦素都可以抵消异位脂肪沉积, 然而他们在炎症方面具有不同的作用. 一般来说脂联素降低炎症程度, 刺激分泌抗炎因子, 如白介素-10(interleukin-10, IL-10), 封闭核因子κB(nuclear factor-κB, NF-κB), 抑制TNF-α、IL-6等炎症因子释放[21]. 此外脂联素可以有效抑制动脉粥样硬化的发生[22]. 同样炎症亦可以封闭脂联素分泌, 尤其是肥胖患者, 脂肪组织炎症加剧了血脂联素水平降低. 肝脏方面, 瘦素缺失ob/ob的小鼠, 免于T细胞介导的肝脏炎症, 而缺乏瘦素及脂联素的脂肪代谢紊乱的小鼠没有免于炎症, 表明脂联素在保护肝损伤方面起重要作用, 给予脂联素后ob/ob小鼠及脂肪代谢紊乱小鼠都免于炎症损伤而给于瘦素加剧了炎症[23]. 因而我们认为脂联素对那些代谢综合征为表现的全身及肝脏炎症起负性调节作用[24]. 然而应慎重看待这个结论, 因为在一些情况下(如经历缺血再灌注的肝脏脂肪变性)脂联素会产生不利作用[25].

近来大量研究表明脂联素具有抗肝纤维化作用, 与瘦素在肝纤维化中的作用相反. Kamada等发现四氯化碳(carbon tetrachloride, CCl_4)诱导的肝损伤中, 脂联素基因敲除的小鼠比野生型小鼠形成更广泛的纤维化, 这表明脂联素具有抗纤维化作用, 且此种作用不依赖于代谢作用[26]. 脂联素在NASH进展早期有保护作用其机制可能是通过抑制TNF-α及抗纤维化作用[27]. Ding等发现脂联素通过维持HSC静息状态抑制其增殖而发挥抗纤维化作用[28]. 最近有研究发现脂联素球状结构域刺激人星状细胞可以激活AMPK途径抑制血小板衍生生长因子(platelet-derived growth factor, PDGF)诱导的星状细胞的增殖及迁移, 同时降低IL-1引起的单核细胞趋化蛋白1(monocyte chemoattractant protein-1, MCP-1)的产生[29]. 体外研究还发现高分子量脂联素可以抑制PDGF激活的hTERT(永生化人星状细胞系)和大鼠原代HSC的增殖及迁移, 其作用机制AMPK通过以下途径抑制星状细胞增殖: (1)抑制AKT途径. (2)通过诱导抗氧化应激酶而抑制氧化应激(reactive oxygen species, ROS)依赖性的产物. (3)增加细胞周期依赖性激酶抑制剂(cyclin-dependent kinase inhibitors p21cip, p21)及(cyclin-dependent kinase inhibitors p27kip, p27)的表达[30]. 目前认为脂联素抗纤维化的关键机制是作用于HSC脂联素受体, 活化AMPK通路. AMPK是AdipoR1下游的信号分子, 但最近有研究发现干扰AdipoR2信号通路足以封闭实验性脂肪性肝炎损伤[31]. 脂联素受体信号通路在慢性肝病中的作用有待进一步研究. 关于脂联素与肝癌的研究很少, 最近一项研究发现脂联素缺乏的小鼠给予胆碱缺乏的氨基酸饮食, 其发生肝癌的机率增加, 然而脂联素这种作用是通过降低肝损伤还是对癌细胞的直接作用还有待证实[32]. 有报道提示脂联素可以通过抑制肿瘤血管生长, 下调(Rho kinase, Rock; IFN-inducible protein 10, IP10)Rock/IP10/mmp 9信号通路抑制肝癌生长及肿瘤的转移[33]. 最近还发现脂联素缺乏还可以延迟肝再生, 但相关研究还很少[34].

2 瘦素脂联素在NAFLD病毒性肝炎及肝硬化人群中的研究

2.1 *瘦素及脂联素与NFALD人群研究* 与实验室获得的资料不同, 不同研究中NAFLD患者血瘦素水平变化不一致. 循环瘦素水平在NASH患者升高, 重症患者更高, 脂联素水平变化与体质量指数无关[35]. 儿童NASH患者与之相似, TNF-α及瘦素预测NAS评分>5[36]. 而另一项成人研究发现瘦素水平与脂变严重程度直接相关而与炎症及纤维化无关[37,38]. 还有一些研究没有发现NASH患者与对照人群中瘦素水平存在显著差异[39]. 总之与动物实验得到结论不同, 瘦素的抗纤维化作用在人群研究中并不完全一致.

在一组非肥胖非糖尿病NASH患者中, 脂联素水平下降与胰岛β细胞功能失调有关, 此外脂联素还与纤维化相关[40]. 一项肥胖患者研究发现血脂联素水平与肝脏组织病理学相关且可以预测NAFLD患者肝脏组织病理学严重性[41,42]. 也有研究发现脂联素可以作为血清标志物预测儿童NAFLD患者脂肪变性的进展[43]. Bugianesi等研究发现脂联素水平与内源性葡萄糖生成受抑制有关, 可以预测存在代谢综合征[44]. 脂联素水

■创新盘点
本文总结近年来瘦素脂联素在肝脏脂变、炎症坏死及纤维化及病毒性肝炎肝硬化等方面研究进展, 对于认识脂肪因子在慢性肝病的作用有一定意义.

■应用要点
近10年来越来越多的研究证实脂肪因子与肝脏疾病的病理生理存在相关性. 随着脂肪因子在慢性肝病领域中的深入研究, 脂肪因子将为肝病治疗方面提供新的靶点.

平与肝脏脂肪含量及内源性葡萄糖产生呈负相关提示脂联素可能联系肝脏脂肪含量及胰岛素抵抗[45]. 一项研究发现肝脏中可以检测到低度水平脂联素表达, NASH患者肝脏中脂联素及AdipoR2 mRNA水平比单纯脂变患者表达降低, 此外AdipoR2的表达与转氨酶及纤维化分期呈负相关[46]. 而Vuppalanchil等在肝脏中没能检测出脂联素mRNA表达, 且他们还发现NASH患者中AdipoR2表达比单纯脂肪变的患者高[47]. 近来研究发现脂联素而非瘦素参与病态肥胖患者的早期肝脏疾病[48]. 还有研究发现联合采用稳态模型评估法(homeostasis model assessment method, HOMA)及血清脂联素与瘦素的比值可作为预测NAFLD患者肝损伤严重程度的非侵入性方法[49]. 综合上述资料, 一般来说脂联素水平可以用来预测肝脏脂肪变及肝脏疾病严重程度[50], 虽然可以预测到什么程度, 是直接作用, 还是与胰岛素抵抗有关, 还有待阐明. 尽管如此, 肥胖及胰岛素抵抗患者的脂联素水平下降所营造的促炎环境及个体患者对脂毒性的易感性决定那个患者最终从单纯脂变进展为NASH, 甚至肝硬化.

2.2 瘦素及脂联素在病毒性肝炎人群中的研究 瘦素在胰岛素抵抗脂肪变性及慢性丙型肝炎肝损伤中的作用目前尚未阐明. 有研究发现丙型肝炎患者瘦素水平较健康人群偏高[51], 而其他研究中结果相反[52]. 同时一些研究中发现瘦素与肝纤维严重程度呈正相关[53], 而在另外一些实验中未能证实[52]. 瘦素与HCV诱导的脂变之间关系也不很清楚, 一些研究提示瘦素水平与脂肪变存在相关性[54], 另外一项研究发现瘦素水平与感染基因1型患者的脂肪变有关, 而与基因3型无关[55]. 而其他研究没能证实瘦素水平与脂变分级存在关系[52].

与NAFLD不同, 脂联素水平在丙型肝炎患者的研究不一致. 一些研究发现丙型肝炎感染患者的脂联素水平与健康人群变化不大, 脂联素水平与病理组织血变化无相关. 低脂联素水平与高病毒载量及感染基因2型病毒相关[56]. 另外一项研究没有发现脂联素、瘦素、IL-6水平与组织病理学特征存在任何关系[57]. 一项研究发现丙型肝炎患者中血脂联素水平较高[58], 儿童急性病毒性肝炎中也有类似发现[59]. 而丙型肝炎基因3型患者脂联素水平低, 这与是否存在脂变无关, 成功抗病毒治疗后脂联素水平增加, 提示病毒直接影响脂联素, 低脂联素水平提示缺乏抗病毒应答[60]. 近来研究提示高水平总脂联素及高分子量脂联素与丙型肝炎患者中存在的细胞免疫应答受抑制相关, 提示脂联素在调节慢性丙型肝炎免疫方面起作用[61]. 慢性乙型肝炎患者中, 脂联素水平变化与慢性丙型肝炎患者相似[62]或较低[63]. 有关中国人群中慢性乙型肝炎患者研究报道发现脂联素保护患者免于发生胰岛素抵抗及肝脏脂肪变性, 但对肝功能变化无影响, 脂联素对肝脏损伤的作用可能独立于病毒因素[64]. 此外, 脂联素水平在进展期肝纤维化增加并与纤维化分期呈相关性[65].

2.3 瘦素及脂联素在肝硬化人群中研究 至于终末期肝病脂肪因子变化可能与病因无关, 而与分解代谢或炎症状态的存在有关. 病毒性肝硬化研究中发现游离瘦素水平未发生变化, 而结合瘦素水平增加, 游离瘦素与脂肪含量相关, 结合瘦素与能量消耗及分解状态的存在有关[66]. 类似研究报道游离瘦素与代谢参数呈正相关, 结合瘦素及可溶性瘦素受体与促炎因子及交感神经活动呈相关性[67]. 肝硬化患者瘦素水平升高的可能机制是肾脏提取物脂联素下降导致皮下脂肪库释放脂联素增加, 而肝内提取物瘦素水平较对照组变化不明显[68].

与脂联素保肝作用看似相反, 循环血脂联素水平在肝硬化小鼠及人类是增加的, 增加的循环脂联素水平(而肝脏提取物脂联素水平下降)伴随疾病进展及门脉压力增高[69]. 原发性胆汁性肝硬化患者脂联素水平升高, 提示脂肪因子的清除可能经胆汁分泌排出[70].

3 结论

近10年来越来越多的研究证实脂肪因子与肝脏疾病的病理生理存在相关性. 肝脏在代谢综合征中的核心作用, 因而大量研究关注脂肪因子在脂肪肝中的作用及慢性丙型肝炎相关的代谢综合征. 细胞培养及动物模型的研究证实脂肪因子与肝损伤及修复存在直接的强有力的相关性. 而在人群中的研究结果存在争议, 可能与疾病本身固有复杂性有关. 脂肪因子为肝病治疗方面提供新的靶点, 尤其是脂联素显示出更有前景的治疗作用.

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■同行评价
本文重点突出，对于了解瘦素、脂联素在慢性肝病中的研究进展有意义.

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• 消息 •

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本刊讯 本刊采用“顺序编码制”的著录方法, 即以文中出现顺序用阿拉伯数字编号排序. 提倡对国内同行近年已发表的相关研究论文给予充分的反映, 并在文内引用处右上角加方括号注明角码. 文中如列作者姓名, 则需在“Pang等”的右上角注角码号; 若正文中仅引用某文献中的论述, 则在该论述的句末右上角注码号. 如马连生[1]报告……, 潘伯荣等[2-5]认为……; PCR方法敏感性高[6-7]. 文献序号作正文叙述时, 用与正文同号的数字并排, 如本实验方法见文献[8]. 所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准, 通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献, 包括世界华人消化杂志(http://www.wjgnet.com/1009-3079/index.jsp)和*World Journal of Gastroenterology*(http://www.wjgnet.com/1007-9327/index.jsp). 期刊: 序号, 作者(列出全体作者). 文题, 刊名, 年, 卷, 起页-止页, PMID编号 ; 书籍: 序号, 作者(列出全部),书名, 卷次, 版次, 出版地, 出版社, 年, 起页-止页.