世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2011年7月8日; 19(19): 2036-2042
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

# 脂联素在非酒精性脂肪肝中的作用及机制

张征波, 孙晓琦, 钱 斐, 薛博瑜

■背景资料
非酒精性脂肪肝的发病机制主要与胰岛素抵抗、氧化应激及炎症等相关. 研究发现脂肪组织分泌的脂肪因子参与了非酒精性脂肪肝整个病程. 因此目前对脂肪因子及其相互作用的研究是一大热点. 而脂肪因子之一的脂联素与NAFLD发病机制关系更为密切. 脂联素具有抗脂质沉积、抗炎、抗脂质过氧化的作用.

张征波, 孙晓琦, 钱斐, 薛博瑜, 南京中医药大学第一临床医学院 江苏省南京市 210046
江苏省科技计划基金资助项目, No. BS2002036
**作者贡献分布**: 本文综述由张征波、孙晓琦及钱斐完成; 薛博瑜审校.
**通讯作者**: 薛博瑜, 教授, 主任中医师, 博士生导师, 210046, 江苏省南京市, 南京中医药大学第一临床医学院.
xueboyu9502@sina.com.cn
收稿日期: 2011-04-30 修回日期: 2011-06-19
接受日期: 2011-06-21 在线出版日期: 2011-07-08

## Role of adiponectin in the pathogenesis and treatment of nonalcoholic fatty liver disease

Zheng-Bo Zhang, Xiao-Qi Sun, Fei Qian, Bo-Yu Xue

Zheng-Bo Zhang, Xiao-Qi Sun, Fei Qian, Bo-Yu Xue, the First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing 210046, Jiangsu Province, China
Supported by: the Science and Technology Project of Jiangsu Province, No. BS2002036
Correspondence to: Professor Bo-Yu Xue, the First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing 210046, Jiangsu Province, China. xueboyu9502@sina.com.cn
Received: 2011-04-30 Revised: 2011-06-19
Accepted: 2011-06-21 Published online: 2011-07-08

## Abstract
Adiponectin is an insulin-sensitizing adipokine possessing multiple beneficial effects on nonalcoholic fatty liver disease. This adipokine is secreted from adipocytes into the circulation as three oligomeric isoforms: trimer, hexamer and the high molecular weight (HMW) oligomeric complex. Adiponectin binds to its receptor to exert its effects on target organs. The hepatoprotective activities of adiponectin have been demonstrated by many clinical and experimental studies. Decreased level of serum adiponectin represents an independent risk factor for (NAFLD and liver dysfunction in humans. In animals, elevation of circulating adiponectin by either pharmacological or genetic approaches leads to a significant alleviation of hepatomegaly, steatosis and necro-inflammation associated with various liver diseases. In adiponectin knockout mice, there is a pre-existing condition of hepatic steatosis and mitochondrial dysfunction, which might contribute to increased vulnerability of these mice to secondary liver injuries induced by obesity and other conditions. This review aims to summarize the recent advances in research of the structural, molecular and cellular mechanisms underlying the hepatoprotective properties of adiponectin.

Key Words: Adiponectin; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Insulin resistance

Zhang ZB, Sun XQ, Qian F, Xue BY. Role of adiponectin in the pathogenesis and treatment of nonalcoholic fatty liver disease. Shijie Huaren Xiaohua Zazhi 2011; 19(19): 2036-2042

## 摘要
脂联素是由脂肪细胞分泌的胰岛素敏感性脂肪因子, 其对非酒精性脂肪肝病(NAFLD)有多种有益作用. 在循环中脂联素有3种低聚亚型, 包括三聚体、六聚体及高分子量低聚复合物. 脂联素通过与靶器官上脂联素受体结合来发挥效应, 其保肝作用已经在临床和实验室研究中证明. 脂联素的下降是NAFLD及肝脏功能损害的独立危险因素. 在动物实验中, 通过药物或基因疗法使循环中的脂联素增高可导致肝肿大、脂肪变、坏死炎症及其相关肝脏疾病. 脂联素敲除的小鼠, 会发生肝脂肪变和线粒体功能损害, 这致使小鼠易于遭受脂肪肝病的二次打击. 本文旨在综述近年来对于脂联素在NAFLD中的保肝作用及机制的研究成果.

**关键词: 脂联素; 非酒精性脂肪肝; 非酒精性脂肪性肝炎; 胰岛素抵抗**

张征波, 孙晓琦, 钱斐, 薛博瑜. 脂联素在非酒精性脂肪肝中的作用及机制. 世界华人消化杂志 2011; 19(19): 2036-2042
http://www.wjgnet.com/1009-3079/19/2036.asp

## 0 引言
在许多国家非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)是最普遍的慢性肝脏损伤之一[1,2]. NAFLD包括了从单纯肝脂肪变性, 非酒精性脂肪性肝炎(nonalcoholic steatohepatitis,

■同行评议者
高泽立, 主任医师, 上海交通大学医学院附属第九人民医院周浦分院消化科

NASH), 到肝纤维化, 肝硬化以及肝细胞癌等一系列的疾病过程[3]. 在西方国家其总发病率达15%-40%, 在亚洲达到9%-40%[4], 并且本病的发病率在过去15年里大幅提高, 主要是因为其与肥胖、2型糖尿病这两大世界性流行病密切相关[5]. NAFLD患者的死亡率明显高于年龄及性别相关的普通人群[6]. 本病进展到NASH及肝硬化的过程很缓慢, 并且只有一小部分患者能发展到致命的肝脏疾病. 多数NAFLD病例中, 代谢性及心血管疾病的发病率增加的危险性要比肝脏疾病大得多[7,8]. 事实上, NAFLD是代谢综合征的肝脏表现, 与胰岛素抵抗有关的心血管危险因素, 包括肥胖、高血压、血脂异常及2型糖尿病[9]并称为代谢综合征. NAFLD与代谢综合征的关系在很多横向、前瞻性研究中被证实[8]. NAFLD显著增加糖尿病的危险性, 并且他比肥胖本身更能预示代谢异常的进展[10]. 最近的研究揭示了NAFLD与多数心血管疾病危险因素之间的关系[7]. NAFLD能独立于包括代谢综合征组分在内的其他预后因素而预示心血管疾病的发展. 增加对这一疾病的理解以及研究其治疗方法在临床实践中是一个重要问题.

## 1 NAFLD的发病机制

尽管NAFLD的发病机制在很大程度上未被完全了解, 但现在认为胰岛素抵抗、氧化应激及炎症在本病的发展过程中起着重要的作用[11,12]. 脂肪肝本身就是一种胰岛素抵抗的状态. 肝脏脂质的积聚能导致肝脏胰岛素抵抗, 而这种肝胰岛素抵抗可能发生在外周胰岛素效应的改变之前, 也可能诱导外周胰岛素抵抗[13,14]. 胰岛素通过其敏感器官, 如肝脏、骨骼肌及脂肪组织调节营养物质的摄取、氧化和储存. 外周胰岛素抵抗损害了机体从血液摄取葡糖糖进入骨骼肌和脂肪组织的能力; 血清中的游离脂肪酸也可能因为胰岛素抑制脂肪分解的失败而增高[15,16]. 在肝脏, 胰岛素抵抗与肝细胞内的脂肪代谢产物(酯酰辅酶A, 二酰甘油、神经酰胺等)含量增加有关[17-19]. 在血液循环中游离脂肪酸增加的前提下, 因胰岛素抵抗而产生的高胰岛素血症增强了肝脏脂肪酸的摄取及脂质的生成[1,20]. 另外, 线粒体β氧化的缺陷, 脂肪酸合成的增强以及富含三酰甘油的极低密度脂蛋白(very low density lipoprotein, VLDL)的分泌缺陷都是肝脏脂质沉积的原因[21-23]. 越来越多的动物模型证据证实了二次打击学说是NAFLD进展的机制[24-26]. 这一学说认为, 第1次打击是指脂肪肝(脂肪沉积), 紧接着导致了脂肪性肝炎; 潜在的第2次打击包括内毒素、酒精消耗、病毒感染等, 而这些打击增加了肝脏脂质的沉积, 并导致肝细胞的损伤, 增加肝脏氧化应激和炎症. 脂毒性和细胞因子、促炎因子的释放在这一过程中有重要作用. 此外, 脂肪性肝炎的中的炎症发展能进一步妨碍胰岛素信号通路[27]. 组织学上, 脂肪性肝炎表现为肝细胞核气球样变性, 肝细胞凋亡, 马洛里玻璃样变和炎症病灶[28]. NAFLD患者循环中游离脂肪酸水平很高, 且与肝脏疾病严重程度关联度很高. 游离脂肪酸的超载通过诱导促炎因子如TNF-α而表现出脂质毒性[29].

## 2 脂联素与NAFLD相关性

最近的研究显示, 内脏脂肪组织是与代谢及炎症相关的组织, 能起到传递信息及调节大脑、肝脏、肌肉和心血管系统的功能及代谢的作用[30,31]. 脂肪组织分泌的促炎和抗炎脂肪因子间的平衡失调有助于NAFLD的发病[32]. 对脂肪组织内分泌、免疫、炎症的相互作用的调控可能为NAFLD的治疗提供新的治疗靶点. 如, 患严重营养障碍的患者注射了瘦素后可逆转NAFLD[33,34]. 然而, 在NAFLD伴肥胖的情况下, 血清瘦素升高并且肝脏对瘦素的抗脂质沉积作用产生耐受[35-37]. 因此瘦素的注射不太可能成为NAFLD患者的有效疗法. 肿瘤坏死因子(tumor necrosis factor α, TNF-α)这一促炎因子干扰胰岛素的信号通路, 促进脂质沉积, 可能在NASH发病过程中有临时性作用[32]. 循环中的TNF-α含量及肝脏表达的1型受体在NASH时增高, 但这不能用来区分脂肪性肝炎和脂肪变性[38-40]. 中和TNF-α的活性能改善动物的脂肪肝[41]. 相反的, 在实验性TNF-α及其1型受体敲除的小鼠中营养性的脂肪肝炎仍然能产生. 这表明这一脂肪因子可能不是NAFLD必不可少的调节因子[42,43].

与瘦素和TNF-α相比, 脂联素与NAFLD发病机制关系更为密切. 与其他细胞因子不同, 血清脂联素水平与肥胖及其并发症负相关[44], 且与肝酶水平亦呈负相关[45]. 大量的在不同族群间的流行病学调查显示, 脂联素水平降低是NAFLD及肝功能障碍的独立危险因子. 与健康人群相比, NASH患者的脂联素水平至少降低50%以上[46]. 从单纯脂质沉积到脂肪性肝炎的发病过程中, 脂联素的表达下降了20%-40%[46,47]. 更重要的是, 在NASH患者中较低的脂联素水平

**■研发前沿**
脂肪因子脂联素调节非酒精性脂肪肝发病过程中脂质代谢, 炎症及脂质过氧化的机制是目前的研究热点.

**■相关报道**
在脂联素与NAFLD的相关性研究中, Hui发现脂联素水平降低是NAFLD及肝功能障碍的独立危险因子. Xu等通过动物研究发现, 在酒精饮料和非酒精性脂肪性肝炎的动物模型, 外源性脂联素降低肝肿大, 消耗脂肪的积累, 抑制肝脏炎症, 降低肝肿瘤坏死因子的表达及血浆浓度.

预示着更严重的炎症程度, 表明脂联素缺乏是脂肪肝, 脂肪性肝炎和肝损伤等发展的重要危险因素[46-49]. 在2型糖尿病患者中, 血浆脂联素浓度与肝脏脂肪含量呈负相关[50]. 动物研究表明, 脂联素具有对各种形式的肝损伤, 包括由$CCl_4$诱导、LPS/*D*-半乳糖胺、药物、胆管结扎及蛋氨酸缺乏饮食所引起的肝损有很强的保护能力[51-55]. 在酒精饮料和NASH的动物模型, 外源性脂联素降低肝肿大, 消耗脂肪的积累, 抑制肝脏炎症, 降低肝TNF的表达及血浆浓度[56]. 脂联素基因敲除小鼠表现出一种增强的$CCl_4$所致的肝纤维化. 脂联素的表达缺乏可能会加速肝肿瘤在NASH模型的小鼠体内的形成[57]. 在众多的脂肪因子中, 脂联素由于具有胰岛素敏感增敏及抗炎作用, 因此他可能成为治疗NAFLD的新方法.

## 3 脂联素治疗NAFLD的机制

3.1 脂联素及其受体的结构和功能 脂联素是脂肪细胞分泌的由244个氨基酸组成的蛋白质, 在血浆中以低分子量和高分子量多聚体形式存在. 脂联素有AdipoR1和AdipoR2两种受体, 他们的结构高度相关, 有66.7%的同源性, 均为包含7个跨膜区域的蛋白质, 两种受体在多种组织器官都有表达[58], 但主要分布于肌细胞和肝组织, AdipoR1主要分布于骨骼肌, AdipoR2主要分布于肝脏[59]. 脂联素与其受体结合后, 发挥多种重要的生物学作用. 脂联素具有抗糖尿病、抗肥胖、抗动脉粥样硬化及抗炎效应, 可以减少体脂肪并且改善肝脏和外周的胰岛素敏感性. 最近几个实验室通过AdipoR1/2基因敲除小鼠对AdipoR1和AdipoR2的生理作用进行研究, AdipoR1/2基因敲除小鼠表现出轻微的胰岛素抵抗. 在AdipoR1/R2双敲除小鼠, 脂联素与受体结合能力和活性下降, 从而增加组织中三酰甘油含量, 导致炎症和氧化应激. 这些数据支持在葡萄糖和脂质代谢的调节中脂联素及其受体AdipoR1和AdipoR2的生理作用.

3.2 脂联素抗肝脂肪沉积功能的受体后信号转导机制 在骨骼肌、肝脏、心脏、内皮、脂肪细胞、脑等主要靶器官, 脂联素激活AMP激活蛋白激酶(AMP-activated protein kinase, AMPK)[60-65]. 值得注意的是, 在这些靶组织脂联素大多数生物效应被AMPK显性负性形态的表达所抑制, 这表明AMPK在调解脂联素活性上决定性的作用. APPL1是一种含有PH结构域衔接蛋白, 拥有磷酸结合域和亮氨酸拉链基序, 他是一种关键的信号分子, 使脂联素与脂联素受体结合及激活下游的AMPK[66]. 脂联素增强APPL1同时结合AdipoR1和AdipoR2的能力, 这些反应能关键性的磷酸化和激活AMPK. 研究还表明, APPL1在代谢综合征的重要作用[67,68], AMPK活化后紧接着磷酸化乙酰辅酶A羧化酶(ACC)并抑制其活性. 抑制ACC活性会抑制脂质合成, 并且通过阻断丙二酰CoA、CPT-1(脂肪酸氧化的限速酶)的生产增强脂肪酸氧化. 此外, 激活的AMPK下调固醇调节元件结合蛋白1c的表达(SREBP1c), 后者调节胆固醇和脂质合成. 下调的SREBP1c使在脂肪生成过程中涉及的基因下调, 这些基因包括ACC, 脂肪酸合成酶(FAS), 以及甘油三磷酸酰基转移酶(GPAT)等[63,69,70].

PPARα是一种转录因子控制编码脂肪酸氧化酶的基因的转录, 包括FATP, 酰基辅酶A氧化酶(ACOX)和长链酰基辅酶A合成酶(LCAS). 脂联素通过PPARγ共激活剂PGC-1刺激PPARα的活性[71]. 这些信号通路为脂联素所介导而导致脂肪氧化增强, 从而降低脂质合成及防治脂肪肝. 以上这些是脂联素介导对NAFLD脂代谢方面的调节, 从脂肪的氧化及脂肪酸的合成环节脂联素是重要的调控因子, 而上调体内脂联素及肝脏脂联素受体的表达, 从而通过AMPK这一中介调控下游转录因子, 调控所涉及各脂代谢酶, 最终达到调控肝脏脂质代谢平衡的目的.

3.3 脂联素在NAFLD中的抗炎抗、抗纤维化作用 炎性细胞因子在肝脏出现大规模或局灶性肝损伤时, 对肝脏炎症, 肝细胞死亡, 纤维化, 以及再生进行调节[72]. 脂联素水平与某些炎症介质负相关, 包括IL-6和C-反应蛋白, 与抗炎因子正相关, 如IL-10[73,74]. 他通过抑制TNF-α的表达和抑制其活性, 对抗其在肝脏的功能[55,56,75,76]. 在肝脏, 细胞因子如白介素-6(interleukin-6, IL-6)和TNF, 主要产自Kupffer细胞和肝星状细胞(hepatic stellate cells, HSC), 部分来自炎症肝细胞[77,78]. 脂联素可通过抑制Kupffer细胞活化HSC, 改善NASH和肝纤维化. 在来源于猪血的巨噬细胞中, 脂联素抑制由LPS诱导的TNF-α和IL-6的产生, 而诱导IL-10的表达. 脂联素部分通过介导减弱NF-κB的核易位弱化炎症细胞因子的产生, 而这一过程是通过IKK-b/NF-κB通路来实现的[79]. 脂联素也可以诱导抗炎细胞因子IL-1受体拮抗剂(interleukin-1-receptor antagonist, IL-1RA)的表达[80,81]. 脂联素的抗炎作用也可能涉及巨噬细胞

Toll样受体4(Toll-like receptor-4, TLR-4)信号转导通路[82].

肝脏损害过程中星状细胞向肌成纤维细胞转化是纤维化的关键步骤. 被激活的星状细胞增加细胞外基质的积聚. 研究发现两种脂联素受体均在星状细胞中表达. 因此脂联素能使星状细胞保持静止状态, 能抑制血小板衍生生长因子刺激的星状细胞的激活和迁移, 并能减少通过AMPK依赖通路介导的单核细胞趋化蛋白的分泌. 另外, 脂联素还能调节一种星状细胞激活后产生的促纤维化因子TGF-β1的表达. 通过抑制AdipoR2的表达能诱导TGF-β1的表达, 而如果使AdipoR2过表达则可降低TGF-β1的mRNA水平.

3.4 脂联素对于线粒体功能的调节作用 线粒体功能异常是NAFLD的核心机制之一. NASH患者肝脏线粒体功能呈现超微结构的病变并且线粒体内呼吸链复合物(mitochondrial respiratory chain complex, MRC)的活性也下降[83,84]. 在这种情况下, 活性下降的呼吸链能使活性氧(reactive oxygen species, ROS)积聚, 后者能氧化脂肪而产生脂质过氧化物, 脂质过氧化物反过来能引起脂肪性肝炎、坏死、炎症和纤维化. 脂肪性肝炎增加的线粒体ROS能直接破坏线粒体DNA、呼吸链多肽, 能诱导NF-κB的活化及肝脏合成TNF-α[85]. MRC调控的氧化磷酸化反应直接调节细胞内ROS活化, 防止脂质沉积及肝脏脂质过氧化物得产生.

研究发现当小鼠缺乏脂联素时甚至用普通饲料喂养也会表现出脂质沉积. 这种脂质沉积现象可能是线粒体功能异常的直接后果[75]. 脂联素能恢复线粒体呼吸链活力, 能通过调节线粒体的功能降低线粒体脂质过氧化物的水平. 线粒体内膜上的转运子解偶联蛋白2(UCP2)介导了脂联素对于MRC活性的益处. UCP2的蛋白及mRNA水平在脂联素敲除的小鼠是下降的, 并且脂联素治疗后升高. 过度表达脂联素受体2上调肝UCP2、过氧化氢酶、超氧化物歧化酶1的mRNA水平. 此外, 脂联素对MRC活力的影响戏剧性的在UCP2缺乏小鼠中降低了, 提示了增加UCP2的表达是脂联素作用于线粒体的重要机制. 众所周知UCP2具有通过抑制线粒体产生ROS抗氧化活力的特性. 他还能抑制巨噬细胞、Kupffer细胞产生促炎因子. 大量证据显示UCP2可能在脂肪肝病程中扮演重要角色. 以上这些表明了UCP2与脂联素间的关系. 尽管脂联素促进UCP2表达的机制尚不清楚, 有待研究.

## 4 结论

脂联素是一种脂肪细胞大量分泌的244个氨基酸组成的蛋白质激素, 通过与靶器官的AdipoR1/2结合发挥生物学效应. 与其他脂肪因子相比脂联素与NAFLD的关系更密切. 脂联素水平降低是NAFLD及肝功能障碍的独立危险因子, 其具有良好的抗脂质沉积、抗炎症、抗纤维化、抗脂质过氧化作用并能增加胰岛素敏感性. 脂联素在治疗NAFLD的作用越来越被重视. 尽管这些知识在这几年不断完善, 但其中具体的分子及细胞机制仍然在很大程度上未知. 目前针对NAFLD总的治疗策略是: (1)生活方式干预; (2)针对代谢综合征的组分进行改善胰岛素抵抗、减肥、降压、降糖、调脂等治疗; (3)针对肝脏损伤进行治疗, 抑制氧应激, 改善肝纤维化; (4)如进展至终末期肝病, 可考虑肝移植. 然而, 来自2009年欧洲肝病年会的2项研究显示, 长期生活方式改变及胰岛素增敏剂治疗能改善生化学指标, 但仅有50%的NASH患者组织学得到改善. 同时NAFLD的基础治疗还存在诸多缺陷, 肥胖患者单纯控制糖脂代谢紊乱和改善胰岛素抵抗很少能使脂肪性肝炎逆转; 对于体质量指数正常的NAFLD患者, 减肥无助于脂肪肝的消退; 还有一点非常重要, 治疗代谢综合征的某些药物用于NAFLD患者容易导致肝毒性, 诱发或加剧肝损伤. 因此寻找有效地特异性治疗NAFLD的靶标, 并针对靶标寻找经济、有效且副作用少的药物迫在眉睫. 而利用脂联素及其激动剂治疗NAFLD代表一种全新的治疗方法, Xu等[86]研究黄芪提取物黄芪苷可以使脂肪细胞脂联素分泌增加, 减轻NAFLD小鼠胰岛素抵抗, 治疗NAFLD. 由此可见基于脂联素的NAFLD治疗可能成为NAFLD的新疗法, 而其作用机制的研究为临床研发新药提供了理论基础, 拓展了新的策略和思路.

**■创新盘点**

本综述对近几年的研究报道做了概述, 认为脂肪因子脂联素在非酒精性脂肪肝发病过程中的作用机制是研究热点. 围绕脂肪因子尤其是脂联素对非酒精性脂肪肝的胰岛素增敏、调节脂质代谢、抗炎、抗纤维化、抗脂质过氧化、保护肝脏等作用及其分子机制进行总结. 提出脂联素及其激动剂可以成为NAFLD的新型治疗方法, 并且这也可能成为NAFLD的研究新方向.

## 5 参考文献


1 Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; 346: 1221-1231
2 Farrell GC. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? *J Gastroenterol Hepatol* 2003; 18: 124-138
3 Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; 116: 1413-1419
4 Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; 43:

**■应用要点**

本文对脂联素在NAFLD发病过程中的肝脏保护作用进行综述. 对脂联素、胰岛素增敏、调节脂质代谢、抗炎、抗纤维化、抗脂质过氧化、保护肝脏等作用及其分子机制有了较系统的认识, 为将来运用脂联素及其激动剂治疗NAFLD及研发新药提供了参考价值.


S99-S112

5 Adams LA, Angulo P. Recent concepts in non-alcoholic fatty liver disease. *Diabet Med* 2005; 22: 1129-1133

6 Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008; 49: 608-612

7 Targher G, Marra F, Marchesini G. Increased risk of cardiovascular disease in non-alcoholic fatty liver disease: causal effect or epiphenomenon? *Diabetologia* 2008; 51: 1947-1953

8 Watanabe S, Yaginuma R, Ikejima K, Miyazaki A. Liver diseases and metabolic syndrome. *J Gastroenterol* 2008; 43: 509-518

9 Machado M, Cortez-Pinto H. Non-alcoholic steatohepatitis and metabolic syndrome. *Curr Opin Clin Nutr Metab Care* 2006; 9: 637-642

10 Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007; 30: 2940-2944

11 Machado M, Cortez-Pinto H. Non-alcoholic fatty liver disease and insulin resistance. *Eur J Gastroenterol Hepatol* 2005; 17: 823-826

12 Mehta K, Van Thiel DH, Shah N, Mobarhan S. Nonalcoholic fatty liver disease: pathogenesis and the role of antioxidants. *Nutr Rev* 2002; 60: 289-293

13 Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y, Berria R, Buzzigoli E, Sironi AM, Cersosimo E, Ferrannini E, Defronzo RA. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. *Gastroenterology* 2007; 133: 496-506

14 Vuguin P, Raab E, Liu B, Barzilai N, Simmons R. Hepatic insulin resistance precedes the development of diabetes in a model of intrauterine growth retardation. *Diabetes* 2004; 53: 2617-2622

15 Blaak EE. Fatty acid metabolism in obesity and type 2 diabetes mellitus. *Proc Nutr Soc* 2003; 62: 753-760

16 DeFronzo RA, Gunnarsson R, Björkman O, Olsson M, Wahren J. Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest* 1985; 76: 149-155

17 Banerji MA, Buckley MC, Chaiken RL, Gordon D, Lebovitz HE, Kral JG. Liver fat, serum triglycerides and visceral adipose tissue in insulin-sensitive and insulin-resistant black men with NIDDM. *Int J Obes Relat Metab Disord* 1995; 19: 846-850

18 Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, Liu Y, Narra K, Hoehn KL, Knotts TA, Siesky A, Nelson DH, Karathanasis SK, Fontenot GK, Birnbaum MJ, Summers SA. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell Metab* 2007; 5: 167-179

19 Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. *Am J Physiol Endocrinol Metab* 2003; 285: E906-E916

20 Assimacopoulos-Jeannet F, Brichard S, Rencurel F, Cusin I, Jeanrenaud B. In vivo effects of hyperinsulinemia on lipogenic enzymes and glucose transporter expression in rat liver and adipose tissues. *Metabolism* 1995; 44: 228-233

21 Minehira K, Young SG, Villanueva CJ, Yetukuri L, Oresic M, Hellerstein MK, Farese RV, Horton JD, Preitner F, Thorens B, Tappy L. Blocking VLDL secretion causes hepatic steatosis but does not affect peripheral lipid stores or insulin sensitivity in mice. *J Lipid Res* 2008; 49: 2038-2044

22 Grefhorst A, Hoekstra J, Derks TG, Ouwens DM, Baller JF, Havinga R, Havekes LM, Romijn JA, Kuipers F. Acute hepatic steatosis in mice by blocking beta-oxidation does not reduce insulin sensitivity of very-low-density lipoprotein production. *Am J Physiol Gastrointest Liver Physiol* 2005; 289: G592-G598

23 Dentin R, Benhamed F, Hainault I, Fauveau V, Foufelle F, Dyck JR, Girard J, Postic C. Liver-specific inhibition of ChREBP improves hepatic steatosis and insulin resistance in ob/ob mice. *Diabetes* 2006; 55: 2159-2170

24 Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998; 114: 842-845

25 Brunt EM. Nonalcoholic steatohepatitis. *Semin Liver Dis* 2004; 24: 3-20

26 Charlton M. Noninvasive indices of fibrosis in NAFLD: starting to think about a three-hit (at least) phenomenon. *Am J Gastroenterol* 2007; 102: 409-411

27 de Luca C, Olefsky JM. Inflammation and insulin resistance. *FEBS Lett* 2008; 582: 97-105

28 Liou I, Kowdley KV. Natural history of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2006; 40 Suppl 1: S11-S16

29 Feldstein AE, Werneburg NW, Canbay A, Guicciardi ME, Bronk SF, Rydzewski R, Burgart LJ, Gores GJ. Free fatty acids promote hepatic lipotoxicity by stimulating TNF-alpha expression via a lysosomal pathway. *Hepatology* 2004; 40: 185-194

30 Antuna-Puente B, Feve B, Fellahi S, Bastard JP. Adipokines: the missing link between insulin resistance and obesity. *Diabetes Metab* 2008; 34: 2-11

31 Kamada Y, Takehara T, Hayashi N. Adipocytokines and liver disease. *J Gastroenterol* 2008; 43: 811-822

32 Tilg H, Hotamisligil GS. Nonalcoholic fatty liver disease: Cytokine-adipokine interplay and regulation of insulin resistance. *Gastroenterology* 2006; 131: 934-945

33 Javor ED, Ghany MG, Cochran EK, Oral EA, DePaoli AM, Premkumar A, Kleiner DE, Gorden P. Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy. *Hepatology* 2005; 41: 753-760

34 Javor ED, Cochran EK, Musso C, Young JR, Depaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. *Diabetes* 2005; 54: 1994-2002

35 Huang XD, Fan Y, Zhang H, Wang P, Yuan JP, Li MJ, Zhan XY. Serum leptin and soluble leptin receptor in non-alcoholic fatty liver disease. *World J Gastroenterol* 2008; 14: 2888-2893

36 Kim IK, Kim J, Kang JH, Song J. Serum leptin as a predictor of fatty liver in 7-year-old Korean children. *Ann Nutr Metab* 2008; 53: 109-116

37 Marra F. Leptin and liver tissue repair: do rodent models provide the answers? *J Hepatol* 2007; 46: 12-18

38 Crespo J, Cayón A, Fernández-Gil P, Hernández-Guerra M, Mayorga M, Domínguez-Díez A, Fernández-Escalante JC, Pons-Romero F. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology* 2001; 34: 1158-1163

39 Ribeiro PS, Cortez-Pinto H, Solá S, Castro RE, Ra-

malho RM, Baptista A, Moura MC, Camilo ME, Rodrigues CM. Hepatocyte apoptosis, expression of death receptors, and activation of NF-kappaB in the liver of nonalcoholic and alcoholic steatohepatitis patients. *Am J Gastroenterol* 2004; 99: 1708-1717
40 Younossi ZM, Jarrar M, Nugent C, Randhawa M, Afendy M, Stepanova M, Rafiq N, Goodman Z, Chandhoke V, Baranova A. A novel diagnostic biomarker panel for obesity-related nonalcoholic steatohepatitis (NASH). *Obes Surg* 2008; 18: 1430-1437
41 Li Z, Yang S, Lin H, Huang J, Watkins PA, Moser AB, Desimone C, Song XY, Diehl AM. Probiotics and antibodies to TNF inhibit inflammatory activity and improve nonalcoholic fatty liver disease. *Hepatology* 2003; 37: 343-350
42 Deng QG, She H, Cheng JH, French SW, Koop DR, Xiong S, Tsukamoto H. Steatohepatitis induced by intragastric overfeeding in mice. *Hepatology* 2005; 42: 905-914
43 Schnyder-Candrian S, Czarniecki J, Lerondel S, Corpataux J, Ryffel B, Schnyder B. Hepatic steatosis in the absence of tumor necrosis factor in mice. *Cytokine* 2005; 32: 287-295
44 Trujillo ME, Scherer PE. Adiponectin--journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005; 257: 167-175
45 López-Bermejo A, Botas P, Funahashi T, Delgado E, Kihara S, Ricart W, Fernández-Real JM. Adiponectin, hepatocellular dysfunction and insulin sensitivity. *Clin Endocrinol* (Oxf) 2004; 60: 256-263
46 Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology* 2004; 40: 46-54
47 Shimada M, Kawahara H, Ozaki K, Fukura M, Yano H, Tsuchishima M, Tsutsumi M, Takase S. Usefulness of a combined evaluation of the serum adiponectin level, HOMA-IR, and serum type IV collagen 7S level to predict the early stage of nonalcoholic steatohepatitis. *Am J Gastroenterol* 2007; 102: 1931-1938
48 Musso G, Gambino R, Biroli G, Carello M, Fagà E, Pacini G, De Michieli F, Cassader M, Durazzo M, Rizzetto M, Pagano G. Hypoadiponectinemia predicts the severity of hepatic fibrosis and pancreatic Beta-cell dysfunction in nondiabetic nonobese patients with nonalcoholic steatohepatitis. *Am J Gastroenterol* 2005; 100: 2438-2446
49 Aygun C, Senturk O, Hulagu S, Uraz S, Celebi A, Konduk T, Mutlu B, Canturk Z. Serum levels of hepatoprotective peptide adiponectin in non-alcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2006; 18: 175-180
50 Bajaj M, Suraamornkul S, Piper P, Hardies LJ, Glass L, Cersosimo E, Pratipanawatr T, Miyazaki Y, DeFronzo RA. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab* 2004; 89: 200-206
51 Ikejima K, Okumura K, Kon K, Takei Y, Sato N. Role of adipocytokines in hepatic fibrogenesis. *J Gastroenterol Hepatol* 2007; 22 Suppl 1: S87-S92
52 Kamada Y, Tamura S, Kiso S, Matsumoto H, Saji Y, Yoshida Y, Fukui K, Maeda N, Nishizawa H, Nagaretani H, Okamoto Y, Kihara S, Miyagawa J, Shinomura Y, Funahashi T, Matsuzawa Y. Enhanced carbon tetrachloride-induced liver fibrosis in mice lacking adiponectin. *Gastroenterology* 2003; 125: 1796-1807
53 Masaki T, Chiba S, Tatsukawa H, Yasuda T, Noguchi H, Seike M, Yoshimatsu H. Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice. *Hepatology* 2004; 40: 177-184
54 Matsumoto H, Tamura S, Kamada Y, Kiso S, Fukushima J, Wada A, Maeda N, Kihara S, Funahashi T, Matsuzawa Y, Shimomura I, Hayashi N. Adiponectin deficiency exacerbates lipopolysaccharide/D-galactosamine-induced liver injury in mice. *World J Gastroenterol* 2006; 12: 3352-3358
55 Thakur V, Pritchard MT, McMullen MR, Nagy LE. Adiponectin normalizes LPS-stimulated TNF-alpha production by rat Kupffer cells after chronic ethanol feeding. *Am J Physiol Gastrointest Liver Physiol* 2006; 290: G998-G1007
56 Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest* 2003; 112: 91-100
57 Kamada Y, Matsumoto H, Tamura S, Fukushima J, Kiso S, Fukui K, Igura T, Maeda N, Kihara S, Funahashi T, Matsuzawa Y, Shimomura I, Hayashi N. Hypoadiponectinemia accelerates hepatic tumor formation in a nonalcoholic steatohepatitis mouse model. *J Hepatol* 2007; 47: 556-564
58 Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; 26: 439-451
59 Kadowaki T, Yamauchi T, Kubota N. The physiological and pathophysiological role of adiponectin and adiponectin receptors in the peripheral tissues and CNS. *FEBS Lett* 2008; 582: 74-80
60 Tsao TS, Tomas E, Murrey HE, Hug C, Lee DH, Ruderman NB, Heuser JE, Lodish HF. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. *J Biol Chem* 2003; 278: 50810-50817
61 Wang Y, Lam KS, Chan L, Chan KW, Lam JB, Lam MC, Hoo RC, Mak WW, Cooper GJ, Xu A. Post-translational modifications of the four conserved lysine residues within the collagenous domain of adiponectin are required for the formation of its high molecular weight oligomeric complex. *J Biol Chem* 2006; 281: 16391-16400
62 Cheng KK, Lam KS, Wang Y, Huang Y, Carling D, Wu D, Wong C, Xu A. Adiponectin-induced endothelial nitric oxide synthase activation and nitric oxide production are mediated by APPL1 in endothelial cells. *Diabetes* 2007; 56: 1387-1394
63 Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, Eto K, Akanuma Y, Froguel P, Foufelle F, Ferre P, Carling D, Kimura S, Nagai R, Kahn BB, Kadowaki T. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002; 8: 1288-1295
64 Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, Kumada M, Sato K, Schiekofer S, Ohashi K, Funahashi T, Colucci WS, Walsh K. Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat Med* 2004; 10: 1384-1389
65 Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, Suzuki R, Satoh H, Tsuchida A, Moroi M, Sugi K, Noda T, Ebinuma H, Ueta Y, Kondo T, Araki E, Ezaki O, Nagai R, Tobe K, Terauchi Y, Ueki K,

**■同行评价**
本文内容新颖, 可读性较好, 具有一定的科学价值.

Minokoshi Y, Kadowaki T. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. *Cell Metab* 2007; 6: 55-68

66 Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, Fang Q, Christ-Roberts CY, Hong JY, Kim RY, Liu F, Dong LQ. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. *Nat Cell Biol* 2006; 8: 516-523

67 Chandrasekar B, Boylston WH, Venkatachalam K, Webster NJ, Prabhu SD, Valente AJ. Adiponectin blocks interleukin-18-mediated endothelial cell death via APPL1-dependent AMP-activated protein kinase (AMPK) activation and IKK/NF-kappaB/PTEN suppression. *J Biol Chem* 2008; 283: 24889-24898

68 Saito T, Jones CC, Huang S, Czech MP, Pilch PF. The interaction of Akt with APPL1 is required for insulin-stimulated Glut4 translocation. *J Biol Chem* 2007; 282: 32280-32287

69 Woods A, Azzout-Marniche D, Foretz M, Stein SC, Lemarchand P, Ferré P, Foufelle F, Carling D. Characterization of the role of AMP-activated protein kinase in the regulation of glucose-activated gene expression using constitutively active and dominant negative forms of the kinase. *Mol Cell Biol* 2000; 20: 6704-6711

70 Tomita K, Tamiya G, Ando S, Kitamura N, Koizumi H, Kato S, Horie Y, Kaneko T, Azuma T, Nagata H, Ishii H, Hibi T. AICAR, an AMPK activator, has protective effects on alcohol-induced fatty liver in rats. *Alcohol Clin Exp Res* 2005; 29: 240S-245S

71 You M, Considine RV, Leone TC, Kelly DP, Crabb DW. Role of adiponectin in the protective action of dietary saturated fat against alcoholic fatty liver in mice. *Hepatology* 2005; 42: 568-577

72 Carter-Kent C, Zein NN, Feldstein AE. Cytokines in the pathogenesis of fatty liver and disease progression to steatohepatitis: implications for treatment. *Am J Gastroenterol* 2008; 103: 1036-1042

73 Choi KM, Ryu OH, Lee KW, Kim HY, Seo JA, Kim SG, Kim NH, Choi DS, Baik SH. Serum adiponectin, interleukin-10 levels and inflammatory markers in the metabolic syndrome. *Diabetes Res Clin Pract* 2007; 75: 235-240

74 Engeli S, Feldpausch M, Gorzelniak K, Hartwig F, Heintze U, Janke J, Möhlig M, Pfeiffer AF, Luft FC, Sharma AM. Association between adiponectin and mediators of inflammation in obese women. *Diabetes* 2003; 52: 942-947

75 Park PH, Thakur V, Pritchard MT, McMullen MR, Nagy LE. Regulation of Kupffer cell activity during chronic ethanol exposure: role of adiponectin. *J Gastroenterol Hepatol* 2006; 21 Suppl 3: S30-S33

76 Zhou M, Xu A, Tam PK, Lam KS, Chan L, Hoo RL, Liu J, Chow KH, Wang Y. Mitochondrial dysfunction contributes to the increased vulnerabilities of adiponectin knockout mice to liver injury. *Hepatology* 2008; 48: 1087-1096

77 Choi S, Diehl AM. Role of inflammation in nonalcoholic steatohepatitis. *Curr Opin Gastroenterol* 2005; 21: 702-707

78 Jarrar MH, Baranova A, Collantes R, Ranard B, Stepanova M, Bennett C, Fang Y, Elariny H, Goodman Z, Chandhoke V, Younossi ZM. Adipokines and cytokines in non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2008; 27: 412-421

79 Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. *Biochem Biophys Res Commun* 2004; 316: 924-929

80 Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, Maeda K, Nagaretani H, Kishida K, Maeda N, Nagasawa A, Funahashi T, Matsuzawa Y. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. *Circulation* 2004; 109: 2046-2049

81 Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun* 2004; 323: 630-635

82 Yamaguchi N, Argueta JG, Masuhiro Y, Kagishita M, Nonaka K, Saito T, Hanazawa S, Yamashita Y. Adiponectin inhibits Toll-like receptor family-induced signaling. *FEBS Lett* 2005; 579: 6821-6826

83 Pérez-Carreras M, Del Hoyo P, Martín MA, Rubio JC, Martín A, Castellano G, Colina F, Arenas J, Solis-Herruzo JA. Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. *Hepatology* 2003; 38: 999-1007

84 Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001; 120: 1183-1192

85 Fromenty B, Robin MA, Igoudjil A, Mansouri A, Pessayre D. The ins and outs of mitochondrial dysfunction in NASH. *Diabetes Metab* 2004; 30: 121-138

86 Xu A, Wang H, Hoo RL, Sweeney G, Vanhoutte PM, Wang Y, Wu D, Chu W, Qin G, Lam KS. Selective elevation of adiponectin production by the natural compounds derived from a medicinal herb alleviates insulin resistance and glucose intolerance in obese mice. *Endocrinology* 2009; 150: 625-633

编辑 李军亮 电编 何基才