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文献综述 REVIEW

PNPLA3 I148M (rs738409) SNP与肝硬化及肝细胞癌关系的研究进展

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■背景资料
我国肝细胞癌发病率呈逐年增高趋势, 在我国约70%的肝细胞癌(hepatocellular carcinoma, HCC)发生于肝硬化的基础上. 近年来研究显示含patatin样磷脂酶域3(patatin-like phospholipase domain containing 3, *PNPLA3*)基因突变与肝脂肪变性及纤维化相关联, 其与肝硬化、肝细胞癌的相关性研究越来越得到重视.

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Progress in understanding association of PNPLA3 I148M (rs738409) single nucleotide polymorphism with hepatocellular carcinoma and hepatic cirrhosis

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Abstract
Patatin-like phospholipase domain containing 3 (PNPLA3), also called adiponutrin, is mainly expressed in the hepatocellular membrane and involved in lipid metabolism. The rs738409 genetic variant causes an isoleucine-to-methionine substitution at amino acid position 148 (I148M). Recently, genome-wide association studies have described associations of PNPLA3 I148M with plasma liver enzyme levels, steatosis and fibrosis severity. Studies found that PNPLA3 I148M is associated with progression of alcoholic liver cirrhosis, clinical outcome and prognosis of alcohol related hepatocellular carcinoma (HCC), and clinical outcomes of chronic hepatitis C. PNPLA3 I148M plays an important role in liver disease progression, which can be an independent risk factor for HCC.

Key Words: Liver cirrhosis; Hepatocellular carcinoma; Patatin-like phospholipase domain containing 3

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摘要
含patatin样磷脂酶域3(patatin-like phospholipase domain containing 3, PNPLA3), 又称脂肪营养素. 大量位于肝细胞膜上并参与脂质代谢. rs738409处基因突变致148位异亮氨酸被蛋氨酸取代(148 isoleucine to Methionine protein variant, I148M). 近年来全基因组分析显示PNPLA3 I148M与肝脏脂肪含量、血清肝酶水平、纤维化程度明显相关, 研究显示PNPLA3 I148M与酒精性肝硬化进程及其所致肝细胞癌的临床转归及预后、慢性丙型肝炎的临床转归显著相关. PNPLA3 I148M在肝病进展中扮演重要角色, 可作为肝细胞癌的一个独立危险因素.

关键词: 肝硬化; 肝细胞癌; 含patatin样磷脂酶域3

核心提示: 含patatin样磷脂酶域3(patatin-like phospholipase domain containing 3)与酒精性肝硬化及其所致肝细胞癌显著相关, 并与丙型肝炎肝硬化临床转归相关.

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)的发病率占是全球恶性肿瘤的第5位, 死亡率位居恶性肿瘤第3位. 研究[1]显示, 2003-2007年, 在同期全球184个国家或地区中, 我国肝细胞癌发病率水平男性居第5位, 女性居第6位. 肝癌是中国目前仅次于肺癌的最主要恶性肿瘤, 并有继续增高趋势[1]. 在我国, 约70%的HCC发生于肝硬化的基础上. 我国肝硬化的主要病因目前仍为病毒性肝炎进展所致, 但酒精性肝病所致肝硬化近年来呈现升高趋势. 除却肝硬化进展所致HCC之外, HCC的发病还与肥胖、环境因素、化学毒素、家族史及基因遗传因素有关. 近年来通过全基因组分析中发现, 含patatin样磷脂酶域3(patatin-like phospholipase domain containing 3, PNPLA3) rs738409单核苷酸多态性(single nucleotide polymorphisms, SNP)与肝脂肪变性及纤维化相关联[2,3].

1 PNPLA3的一般特性

PNPLA3位于22号染色体上, 又称为脂肪营养素(adiponutrin), 属于patatin样磷脂酶家族[4]. 主要表达于人体脂肪组织、肝、肌肉、骨骼、皮肤及巨噬细胞中, 尤其在肝组织中表达最高[5,6]. PNPLA3在体外表现出脂肪酶及酰基转移酶活性[7], 该表达呈现对脂肪细胞分解供能的正调节[8]; 但其在体内的生物学功能目前尚未明确. PNPLA3 rs738409 C>G非同义单核基因多样性造成了148位异亮氨酸被蛋氨酸取代(148 isoleucine to methionine protein variant, I148M)变异, 暨第22号染色体rs738409处碱基胞嘧啶(C)被鸟嘌呤(G)所替代, 导致第148位氨基酸由异亮氨酸(I)变成蛋氨酸(M). 目前认为I148M变异损害了肝细胞内甘油三酯的水解, 暨增加了甘油三酯在肝细胞内的蓄积[9].

最新研究显示, PNPLA3还参与到肝星状细胞的视黄醇代谢中[10]. 肝星状细胞参与肝纤维化[11], 而视黄醇是一种脂溶性微量营养素, 被认为在调控细胞的增殖、分化、癌变[12]及肝细胞脂质代谢中扮演重要角色[13]. Pirazzi等[10]的研究观察到PNPLA3在胰岛素调控下促进肝星状细胞中的视黄醇释放到细胞外且PNPLA3的过表达还降低了细胞内脂滴. 而PNPLA3 I148M变异则不具备此项功能. 值得注意的是细胞内视黄醇酯的水平与慢性肝损伤中星状细胞的修饰有关. 此项实验提出PNPLA3、肝星状细胞及视黄酸代谢与慢性肝病易感性之前存在潜在关联.

2 PNPLA3 I148M与丙氨酸氨基转移酶(alanine aminotransferase, ALT)、门冬氨酸氨基转移酶(aspartate aminotransferase, AST)水平及Child-Pugh分级的相关性研究

2008年, Romeo等[2]通过对“达拉斯心脏研究”(Dallas Heart Study, DHS)在西班牙人、非洲人及欧美人中展开全基因组分析. 结果显示: PNPLA3 I148M(rs738409), 在西班牙人中与血清ALT水平存在明显相关性. Stickel等[14]在对1043例有长期大量饮酒史的德国人进行组间对照研究证实: rs738409(GG)与肝硬化及血清ALT水平升高存在着关联; 研究同时发现: rs738409(GG)与AST水平升高存在着一个稳健的生物学基础. 但此项研究中以AST为基础的统计学分析显示*P*值略低于ALT为基础的统计学分析. 该差异或许与AST存在肝外来源有关. Li等[15]在对中国非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)患者的研究中也发现: 随着携带危险等位基因的拷贝数增加, ALT呈现显著增长; AST虽也呈现增长趋势, 但缺乏统计学显著差异. 同时, Valenti等[16]在对186例意大利肝硬化患者的实验中也证实: rs738409(GG)与血清AST及ALT升高存在关联. Nakamura等[17]及Takeuchi等[18]也在对日本丙型肝炎性肝硬化及酒精性肝硬化患者的研究中也证实了此项发现. 然而Nischalke等[19]在对512例肝硬化及肝癌患者的对照研究发现: PNPLA3 I148M变异与血清肝酶指标之间并无显著相关. Trépo等[20]在对923例的受试者进行的对照实验研究中也发现rs738409与ALT、AST并无显著相关. PNPLA3 I148M变异是否与ALT、AST水平存在相关性, 还有待大样本实验研究证实.

Tian等[21]在对1221例酒精性肝硬化患者的对照实验中发现: rs738409高危险性G等位基因与肝硬化疾病进展的严重程度相关, 统计学分析显示, 在Child-Pugh级别分别为A、B、C(其中C为最严重等级)的肝硬化患者中, rs738409(G)等位基因的频率分别为0.70、0.75、0.77. Trépo等[20]的实验却恰恰相反, 并未得出rs738409与Child-Pugh分级的相关性. rs738409是否与肝硬化程度相关, 可否作为肝硬

■研发前沿
研究显示PNPLA3 I148M与酒精性肝硬化进程及酒精性肝硬化所致肝细胞癌的临床转归及预后、慢性丙型肝炎的临床转归显著相关, 但*PNPLA3*基因突变介导肝细胞癌形成的机制仍有待进一步研究探讨.

■相关报道
2010年, Tian等通过对PNPLA3域常见的17种变异基因及306例有单核苷酸多样性家族史并有大量饮酒史的混血儿(为欧洲与美洲原住民混血)的研究中发现: PNPLA3 rs738409与酒精性肝硬化间存在着显著相关性, 并独立于其他变量, 如年龄、酒精摄入量及饮酒时间.

化发展趋势的一项预测因子, 还有待其他大样本临床试验来证实.

3 PNPLA3 I148M与酒精性肝硬化的研究进展

2010年, Tian等[21]通过对PNPLA3域常见的17种变异基因及306例有单核苷酸多样性家族史并有大量饮酒史的混血儿(为欧洲与美洲原住民混血)的研究中发现: PNPLA3 rs738409与酒精性肝硬化间存在着显著相关性并独立于其他变量, 如年龄、酒精摄入量及饮酒时间. Stickel等[14]在对1034例有长期饮酒史的德国患者的研究中发现: PNPLA3 I148M变异与酒精性肝硬化相关, 同时, 酒精性肝硬化携带rs738409(GG)基因型的比值比(odd ratio, OR)值为(3.6, 95%CI: 1.95-6.64)与Tian等[21]的实验数据相符. Dutta等[22]在对120例印度长期酗酒者与健康人群的对照实验中同样得到PNPLA3与北印度人群中酒精性肝硬化的发生存在易感性. Nischalke等[19]在对512例欧洲肝硬化、肝癌患者的研究也证实上述研究结果, 同时发现PNPLA3 I148M(GG)基因型个体的肝活检较同等状态下脂质沉积野生型(C)个体显现出严重的炎症改变及肝损伤. Way等[23]、Falleti等[24]、Guyot等[25]均在各自实验中证实上述研究结果. Burza等[26]在对384例意大利酒精摄入危险量者(每日酒精摄入量为男性≥36 g乙醇; 女性≥24 g乙醇)的研究中发现: PNPLA3 I148M增加了肝硬化的发病率(P<0.001), 且在酒精摄入为危险量时, 年长者(≥24岁)中酒精性肝硬化发病率高于年轻者(<24岁). 由于此项研究为回顾性研究, 研究设计可能存在选择偏倚, 此项研究成果还有待前瞻性研究证实. Trépo等[20]对欧洲酒精性肝硬化患者的研究中发现: rs738409 G等位基因频率在酒精性肝病患者中持续增长, 与纤维化严重度呈显著相关, 却与脂肪化程度不相关. 考虑到酒精摄入同时也是众所周知肝脂肪化的诱发因子, rs738409与酒精性肝硬化脂肪化程度间的相关性是否因此被掩盖, 还需更多相关研究证实.

4 PNPLA3 I148M与丙型肝炎肝硬化的研究进展

Valenti等[27]在对819例意大利慢性丙型肝炎患者的研究中发现: rs738409基因型与肝脂肪变性的相关性独立于目前已知的其他危险因素. 10%的慢性丙型肝炎患者携带rs738409 GG基因型, 其中约50%存在肝硬化高危险性. 实验发现PNPLA3 I148M变异与慢性丙型肝炎进展存在相关性, 影响了慢性丙型肝炎的脂肪化进程. 从而证实PNPLA3 I148M变异与慢性丙型肝炎肝硬化患者中发生HCC危险性存在相关性. 同时Corradini等[28]对221例意大利丙型肝炎肝硬化患者进行研究也证实了这一发现. 而后Falleti等[24]在对483例意大利肝硬化患者的对照研究中发现: rs738409 G等位基因在非病毒性肝硬化(酒精或代谢性肝硬化)中出现频率远远高于病毒性肝硬化, 但与空白对照组相比, rs738409仍与丙型肝炎肝硬化存在显著差异. 但有趣的是, Nischalke等[19]的实验却否认了这一相关性. 通过322例肝硬化患者的对照研究, Nischalke等[19]发现: PNPLA3 I148M变异与丙型肝炎肝硬化发生HCC的危险性并无明显相关. 而Guyot等[25]在对253例丙型肝炎肝硬化患者及279例酒精性肝硬化患者的对照研究中同样发现: rs738409基因型在丙型肝炎肝硬化中的分布并不符合Hardy-Weinberg平衡, rs738409 G等位基因与丙型肝炎肝硬化患者的预后及转归并不存在相关性. Nakamura等[17]在对260例日本丙型肝炎肝硬化患者的研究中再次证实: PNPLA3 rs738409基因型与慢性丙型肝炎患者的脂肪肝改变或肝硬化间并不存在相关性.

Dunn等[29]在对101例丙型肝炎行原位肝移植手术患者的研究中发现: 移植供体存在rs738409 GC或GG型基因变异的患者肝移植后出现纤维化或丙型肝炎所致死亡或移植物失功的危险性呈2.53倍高于CC基因型. rs738409基因型因作为预测丙型肝炎移植后转归的重要因素. 此项发现对于丙型肝炎移植选择供体及指导早期抗病毒治疗具有重要意义.

PNPLA3 I148M变异与丙型肝炎相关性, 我们必须考虑到: Valenti等[27]的实验中并未将感染丙型肝炎病毒(hepatitis C virus, HCV)人群同时伴有酒精摄入的患者排除, 实验存在纳入标准不完善, 存在选择偏倚; Nakamura等[17]的样本量过少, 确立肝硬化诊断时并未使用肝活检, 而是采用影像学辅助诊断, 可能存在偏倚. 所以该矛盾结论的产生可能与实验存在纳入标准不够完善、样本量少等因素有关. PNPLA3 I148M变异是否与丙型肝炎肝硬化无关、是否能够作为丙型肝炎早期抗病毒治疗指标还有待接下来临床

大规模实验验证.

5 PNPLA3 I148M与肝癌的研究进展

近年来全基因组分析发现PNPLA3 I148M变异与肝脂肪化及纤维化间存在显著相关[2,3]. PNPLA3(rs738409 C>G)单核苷酸多态性参与肝炎症改变及纤维化进程的调节中[30]; 其中rs738409 G等位基因与肝脂肪变性[31-36]及纤维化严重程度[37-40]均相关. 众所周知, 肝纤维化及肝脂肪变性与HCC发生有关. 事实上, 近来研究发现, PNPLA3 rs738409变异造成了外周循环血中促炎因子及细胞间黏附分子-1水平增加[41], 而具备抗炎、抗纤维化及抑制肿瘤特性[42]的脂联素水平下降[42,43], 因此PNPLA3 I148M与HCC的相关性越来越受到重视.

Nischalke等[19]对512例欧洲肝硬化及肝癌患者的研究中发现PNPLA3 I148M在健康对照组或丙型肝炎相关肝硬化及肝癌中的分布并无显著差异, 与之相比, 在酒精性肝硬化及肝癌患者中, 携带PNPLA3 I148M变异者则呈明显上升趋势. 其危险等位基因G频率分别高达53.7%, 该基因型与酒精性肝硬化进展为HCC的危险度相关. Falleti等[24]的实验得出上述结果, 并显示: rs738409(GG)等位基因是无论病毒性、代谢性/酒精性肝硬化发生HCC的一个独立预测因子, 与性别呈协同作用, 并与HCC发生呈显著相关. Takeuchi等[18]对638例日本肝癌患者的研究得到上述结果, 同时发现: 有酒精性肝病基础, 携带rs738409(GG), 同时体质量指数(body mass index, BMI)<25 kg/m^{2}的患者生存率普遍低于BMI高于25 kg/m^{2}的患者, 此项结论并未在C/G, C/C基因型或非酒精性脂肪肝病中发现. Valenti等[27,44]在对意大利肝癌患者的研究中发现: 在酒精性肝病或非酒精性脂肪肝的患者中, PNPLA3 I148M变异与发病年龄早、肝硬化历史短、诊断肝癌时非晚期肝硬化(Child A)、HCC呈现低分化级别有显著相关. Hassan等[45]对美国肝癌患者进行的研究发现: 携带rs738409(GG)基因型的肝癌患者, 其生存周期远远短于CC型或CG型: 其平均存活时间仅为16.8 mo(95%CI: 9.9-23.7), 而CC或CG型肝癌患者则可达25.9 mo(95%CI: 21.5-30.3), GG基因型可作为死亡率的一个独立危险因素. Ezzikouri等[46]在对437例慢性丙型肝炎肝硬化摩洛哥人进行的研究中发现: PNPLA3 rs738409(GG)基因型与HCC发展呈正相关性, rs738409(GG)基因型发生HCC的风险三倍高于rs738409(CC)基因型. Trépo等[47]在对7项共2503例欧洲肝硬化患者进行个体病例数据的荟萃分析时发现: rs738409(G)与酒精性肝硬化所致HCC的相关性(OR = 2.20, 95%CI: 1.80-2.67, $P = 4.71\times10^{-15}$)显著高于慢性丙型肝炎肝硬化所致HCC(OR = 1.55, 95%CI: 1.30-2.34, $P = 3.52\times10^{-2}$).

Guyot等[25]在对法国579例于1999-01/2007-12确诊为肝硬化患者的随访研究中, 发现与rs738409(CC)型相比, rs738409(GG)患者中酒精性肝硬化所致HCC呈现高发病率, G等位基因同时还与HCC的死亡率相关. 在此基础上, 通过统计学分析, 提出了关于存在酒精性肝硬化基础且携带rs738409(GG)基因型患者, 预计HCC发病率的公式: 年龄×0.05085-1.88790×女性性别+BMI×0.09712+rs738409 (GG)×0.78377. 该公式符合Kaplan-Meier法. 但是否在其他人种中也同样具备统计学意义, 还需要进一步的临床研究验证.

关于PNPLA3 I148M潜在介导肿瘤形成的机制, 目前研究显示包括: PNPLA3 I148M变异通过增加肿瘤坏死因子α(tumour necrosis factor α)及白介素-6(interleukin-6)的释放, 形成肝内低级别炎症[48], 通过调控脂肪因子的释放、影响胰岛素抵抗及炎症反应[42], 促进脂肪形成及提高脂肪酸的细胞可用性为快速生长的细胞供能[49,50], 脂毒性影响细胞内信号传导通路[51], 脂质过氧化作用所致氧化应激及线粒体损伤[52].

6 结论

随着肝癌发病率逐年提升, 关于PNPLA3 I148M与肝硬化、肝癌相关性的研究也日益受到重视. 但关于PNPLA3 I148M如何介导肝硬化或肝癌进展的机制, 仍需大量实验证实. 也留有许多问题有待解决, 例如: PNPLA3 I148M在我国肝硬化中与何种病因所致肝硬化相关? 是否与肝癌进展有关? 可否将*PNPLA3*基因筛查加入常规筛选中以降低肝癌发生率? 能否通过Kaplan-Meier法基于大样本提出更为合理的估算肝癌生存率公式? 是否存在针对PNPLA3 I148M的靶向治疗将成为下一步临床研究的热点.

■**创新盘点**
本综述首次对*PNPLA3*基因突变与肝硬化、肝细胞癌研究进展进行综述, *PNPLA3*基因突变存在显著种族差异, 目前尚缺乏中国相关性研究完善这一空白.

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■应用要点
*PNPLA3*基因突变与酒精性肝硬化发病率显著相关; 可作为预测丙型肝炎移植后转归的重要因素; 在肝病进展中扮演重要角色, 可作为肝细胞癌的一个独立危险因素.

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■名词解释

PNPLA3: 又称为脂肪营养素(adiponutrin), 属于patatin样磷脂酶家族. 148位异亮氨酸被蛋氨酸取代(148 isoleucine to methionine protein variant, I148M): 第22号染色体rs738409处碱基胞嘧啶(C)被鸟嘌呤(G)所替代, 导致第148位氨基酸由异亮氨酸(I)变成蛋氨酸(M).

■同行评价
本综述详细介绍PNPLA3 rs738409 SNP与肝硬化以及肝癌发生之间的关系, 具有一定的研究价值, 综述语言流畅.

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