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文献综述 REVIEW

PNPLA3 rs738409基因多态性在肝病中的作用

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Role of PNPLA3 polymorphism in pathogenesis of liver diseases

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Abstract

Hepatic fat accumulation, a common phenomenon in nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD), is associated with liver inflammation development and disease progression. Besides, hepatic fat accumulation is also seen in HCV-infected patients, which influences the response to anti-HCV therapy. Although the causes of fatty accumulation in the above three diseases are different, hereditary factors causing fatty accumulation have attracted more and more attention. PNPLA3, a member of patatin-like phospholipase family, has the activity of triglyceride hydrolase and can influence the liver fatty metabolism. In recent years, PNPLA3 polymorphism has become a hot topic in research of NAFLD, ALD, and HCV, and important results have been achieved. This article describes the expression of PNPLA3 in human tissues and review recent progress in understanding the role of PNPLA3 polymorphism in the pathogenesis of the above three liver diseases.

Key Words: PNPLA3; Polymorphism; Nonalcoholic fatty liver disease; Alcoholic liver disease; Hepatitis C virus

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摘要

肝脏脂肪蓄积是非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)、酒精性肝病(alcoholic liver disease, ALD)的普遍现象, 并与炎症发展、疾病进程有关, 在丙型肝炎病毒(hepatitis V virus, HCV)感染患者中也多见报道, 并影响抗HCV治疗效果. 虽然引起三者脂肪蓄积的因素不尽相同, 但是不同肝病的肝细胞脂肪蓄积的遗传因素越来越引起人们关注. PNPLA3作为patatin样磷脂酶家族成员, 考虑其可能有三酰甘油水解酶活性从而影响肝脏脂肪代谢. 近年来PNPLA3 rs738409基因多态性成为NAFLD、ALD、HCV的研究热点并取得诸多重要成果. 本文就PNPLA3在人体内的表达及其rs738409基因多态性在上述疾病中的研究现况作一综述.

关键词: PNPLA3; **多态性; 非酒精性脂肪肝; 酒精性肝病; 丙型肝炎病毒**

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0 前言

PNPLA3(patatin-like phospholipase domain containing 3)是一种属于patatin样磷脂酶家族的非分泌性蛋白[1], 具有非特异的脂肪酰基水解酶活性[2-4]. PNPLA3在人体的表达受到多种

■背景资料
PNPLA3是一种属于patatin样磷脂酶家族的非分泌性蛋白, 具有非特异的脂肪酰基水解酶活性, 该基因rs738409(C>G)变异的PNPLA3丧失脂肪酰基水解活性, 从而导致肝脏脂肪蓄积. 目前研究表明PNPLA3 rs738409(C>G)变异与非酒精性脂肪肝(NAFLD)、酒精性肝病(ALD)及HCV感染患者的易感性、脂肪变、纤维化进展密切相关.

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■研发前沿
PNPLA3 rs738409多态性对HCV感染患者疾病进展和抗病毒疗效的影响是目前研究的热点和重点.

因素的影响, 如饮食、肥胖、胰岛素水平等. 其rs738409(C>G)变异与肝脏脂肪代谢、非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)、酒精性肝病(alcoholic liver disease, ALD)、丙型肝炎病毒(hepatitis V virus, HCV)感染患者的疾病进展相关, 近年来在国外被广泛研究, 但国内未见相关研究报道, 对其成果也缺乏综合整理与分析. 为紧跟国际前沿, 本文就PNPLA3分子机制、影响因素及其rs738409基因多态性在临床肝病中的研究现状作一综述.

1 PNPLA3的分子特性及其表达调控

PNPLA3是一个由481个氨基酸组成的非分泌性蛋白, 又称为adiponectin, 属于patatin样磷脂酶家族[1]. PNPLA3结构与非钙离子依赖的磷脂酶A2(PNPLA2)相似, 具有非特异的脂肪酰基水解酶活性[2-4]. 体外实验证实PNPLA3有三酰甘油水解酶和部分酰基甘油转酰基酶活性, 但其在体内表达的生物学活性尚无统一结论.

PNPLA3基因位于22号染色体(22q13.31)[5]. 目前, PNPLA3基因多态性研究最多和最热的是rs738409 C>G位点, 该位点编码PNPLA3蛋白的148位氨基酸, C>G转换使异亮氨酸转化为蛋氨酸, 蛋氨酸将阻止底物结合到有催化活性的47位丝氨酸上[6], 从而使其丧失脂肪酰基水解活性[4,6]. 因此, PNPLA3I148M通过阻止甘油三酯水解而增加甘油三酯的蓄积. 此外还有rs6006460、rs2294918、rs2281135等位点, 但PNPLA 3rs738409(I148M)变异与肝脏脂肪代谢、NAFLD、ALD、HCV感染患者的相关性最强.

人体PNPLA3主要表达在肝脏, 其次为皮肤和脂肪组织[7]. PNPLA3的表达由脂肪组织及肝脏代谢调控[1,8,9]. 根据目前研究, PNPLA3的表达受以下因素影响: (1)饮食: PNPLA3 mRNA在空腹状态下很低, 进食碳水化合物后明显升高[1,8,9]. 相关实验表明, 2 d的低热量饮食可以将PNPLA3 mRNA表达降低至原来的1/3[10]. Perttilä等[11]通过染色体免疫沉淀反应发现PNPLA3启动子区存在碳水化合物反应元件(ChRE, carbohydrate response element), 葡萄糖通过该元件结合蛋白(ChREBP)在转录水平调节PNPLA3的表达; (2)体质量指数(body mass index, BMI)和肥胖: PNPLA3 mRNA在肝脏中的表达与BMI和肥胖及肝脏脂肪含量正相关[12,13]; (3)胰岛素和葡萄糖: 二者都可以刺激脂肪组织中PNPLA3的表达: 胰岛素正常的高血糖患者PNPLA3水平为正常人的2.2倍; 血糖正常而伴有高胰岛素血症患者为正常人的2.5倍; 高血糖高胰岛素血症患者为正常人的4.8倍[10]; (4)基因变异: PNPLA3 rs738409G等位基因与NAFLD及健康人群的低水平PNPLA3相关, 即该位点变异可导致其蛋白和mRNA表达下降[14]. 但是在HCV感染患者中因存在PNPLA3抵抗, 故PNPLA3 rs738409基因突变与其表达在HCV感染患者中不存在相关性[14].

2 PNPLA3 rs738409基因多态性对组织代谢、肝脏酶学的影响

(1)增加肝内细胞脂质沉积: 研究表明[11]在存在过量游离脂肪酸的情况下, PNPLA3 rs738409突变增加甘油三酯在细胞内的蓄积. 在人体及体外实验研究均表明PNPLA3 rs738409突变影响apo-B脂蛋白的分泌, 且该突变通过降低极低密度脂蛋白(very low-density lipoprotein, VLDL)而提高肝细胞内脂质沉积[15]; (2)降低血脂水平: Krarup等[16]对1 357例糖调节异常的个体进行分析发现rs738409G等位基因与下降的空腹血清甘油三脂和血清总胆固醇水平显著相关. Palmer等[17]也发现rs738409G等位基因的肥胖患者具有更低的血清甘油三脂水平; (3)对血清胰岛素及胰岛素敏感性的影响: 多数研究表明rs738409G等位基因对肝内及外周胰岛素抵抗没有影响[16,18], rs738409基因突变与血清胰岛素、胰岛素敏感性和糖耐量不相关[12,19-21]. 但Palmer等[17]的研究提出PNPLA3 I148与胰岛素抵抗相关. Wang等[22]在最近的研究报道中也有类似的发现; (4)对脂肪细胞大小的影响: 与CC型患者相比, GG型患者脂肪细胞更小[18]; (5)对肝脏酶学的影响: 多项研究均表明PNPLA3 rs738409基因突变可引起普通人群[23]、肥胖人群[19]、肝病患者肝脏酶学谷丙转氨酶(alanine aminotransferase, ALT)、天冬氨酸氨基转移酶(aspartate aminotransferase, AST)增高, 且该基因变异对肝损伤的影响从儿童时期即开始[19]. Li等[23]对1532例墨西哥群体进行大样本、随机对照研究发现PNPLA3 rs738409变异与ALT显著相关; 在男性患者中, 与AST也相关, 可能与性激素水平有关.

3 PNPLA3基因多态性与临床肝病的关系

3.1 PNPLA3基因多态性与NAFLD的关系 多项

研究表明PNPLA3 rs738409变异增加脏脂肪蓄积, 与成人及儿童的NAFLD严重程度有关, 并最终增加脂肪性肝炎(non-alcoholic steatohepatitis, NASH)的发生风险[24-28]. (1)PNPLA3 rs738409突变与肝脏脂肪含量显著相关: GG型患者肝脏脂肪含量高于CC型患者2.7倍. 调整年龄、性别、BMI、糖尿病、酒精摄入和种族等因素的影响, PNPLA3变异与肝脏脂肪含量的相关性依然非常显著[12,28-33], 研究证明PNPLA3基因是肝脏脂肪变的独立危险因素[33], 能够增加肝脏的脂肪蓄积[18,19]. 此外, 其他研究还表明PNPLA3 rs738409突变与内脏脂肪、皮下脂肪、胰腺脂肪不相关, 唯独增加肝内脂肪蓄积[20]; (2)与NAFLD的易感性相关: 多项研究表明PNPLA3 rs738409突变增加NAFLD的易感性[28,29,34]; (3)PNPLA3 rs738409突变与NAFLD患者肝损伤相关: 该位点突变可引起NAFLD患者血清ALT升高[19,28,29,34,35], AST升高[19,36]. 此外, PNPLA3 rs738409 GG基因型与NAFLD患者的肝组织下脂肪变、炎症评分、纤维化、M-D小体相关, 即与肝组织损伤程度及疾病进展相关[27,28,37-39]. 经过对529例NAFLD和932例健康对照的日本群体进行全基因组关联分析, Kawaguchi等[37]研究发现PNPLA3 rs738409多态性与NAFLD发生的相关性最强($P = 1.4\times10^{-10}$), 并且与Matteoni等[40]提出的NAFLD组织损伤程度分级最为相关. 该研究表明PNPLA3 rs738409基因突变与NAFLD严重性及NASH进展强烈相关. 另一项研究也表明rs738409G等位基因与NASH的易感性、严重性及纤维化的发生相关[41]; (4)PNPLA3 rs738409突变可能与NAFLD的预后相关: 研究显示rs738409SNP与透明质酸、HbA1c、肝内铁沉积相关[37], 三者均为NAFLD预后相关的临床指标; (5)PNPLA3基因突变与总胆固醇、低密度脂蛋白水平显著相关[29,42], 可引起总胆固醇累计[29], 高密度脂蛋白下降[20].

3.2 PNPLA3多态性与ALD的关系 2010年, Tian等[43]首次报道了PNPLA3 rs738409多态性与酒精性肝病之间的相关性: 该位点突变与过量饮酒、发生酒精性肝病及酒精性肝硬化相关. 随后, 众多研究者对此进行了进一步深入研究. Trépo等[44]对330例ALD患者进行研究发现: PNPLA3 rs738409G等位基因与ALD患者发生脂肪变、纤维化和肝硬化显著相关, 多因素分析显示该基因型为ALD患者发生肝硬化的最强独立危险因素. Stickel等[45]对1 047例ALD患者及376例高危饮酒者的德国样本进行研究发现: 与没有肝损伤的酒精性肝病患者相比, rs738409GG基因型在酒精性肝硬化患者中明显增高($OR = 2.79$), 在ALT升高的酒精性肝炎患者中也明显升高($OR = 2.33$), 这表明PNPLA3 rs738409GG基因型与饮酒者发生肝损害、酒精性肝炎、酒精性肝硬化相关.

3.3 PNPLA3多态性与HCV感染患者的关系 (1)PNPLA3 rs738409G等位基因与HCV感染患者的脂肪变及其严重程度有关. Valenti等[46]发现rs738409突变影响HCV患者脂肪变进展. 经分析972例HCV-1型白种人, Clark等[47]发现了PNPLA3危险等位基因和明显的脂肪变(肝细胞脂肪含量>5%)、严重脂肪变(肝细胞脂肪含量>32%)之间的相关性; (2)PNPLA3 rs738409G等位基因与HCV患者纤维化进展有关. Valenti和Trépo等[46,48]通过分析欧洲大样本HCV患者, 2011年首次报道了rs738409G等位基因不仅与HCV感染者组织性确定的肝脏脂肪变有关, 还与其纤维化进展及肝硬化有关; (3)PNPLA3基因突变对抗HCV治疗效果的影响: Valenti等[46]只是在HCV-1和HCV-4型患者中发现PNPLA3 rs738409G等位基因与抗HCV治疗效果有关, GG基因型患者持续性病毒应答(sustained virologic response, SVR)率10%, CG/CC基因型SVR率36%($P = 0.02$), 然而在所有基因型HCV患者中未发现PNPLA3 rs738409基因突变与SVR率之间存在相关性. 另一项由意大利和澳大利亚联合开展的对602例HCV患者进行研究[49]也得到同样结论: PNPLA3 rs738409GG基因型与PegIFNα联合利巴韦林的抗HCV治疗的SVR率之间缺乏相关性, 而与HCV-1/HCV-4型的严重纤维化或肝硬化患者的SVR和早期病毒学应答(early virological response, EVR)相关[41]. 但是Trépo在他们的样本中不能复现Valenti的研究结果. 且经过对Clark等[47]和Valenti等研究中的1 500多例患者进行分析发现PNPLA3基因多态性对PegIFN联合利巴韦林治疗的SVR率很少或没有影响.

3.4 PNPLA3多态性与肝癌发生的相关性 PNPLA3 rs738409G等位基因增加肥胖人群发生肝细胞癌的概率[49]. 有研究发现PNPLA3 rs738409GG基因型是酒精性肝硬化患者发生肝癌的危险因素, 与正常人相比, 其肝癌发生的*OR*值为16.8[50]. Corradini等[51]的研究发现PNPLA3 rs738409GG型患者发生肝细胞癌的概率更高. 多因素分析也确实显示rs738409GG基因型是HCC发生的独立危险因素, 其*OR*值为2.23[51].

■相关报道

Valenti等只是在HCV-1和HCV-4型患者中发现PNPLA3 rs738409G等位基因与抗HCV治疗效果有关, 然而在所有基因型HCV患者中未发现PNPLA3 rs738409基因突变与SVR率之间存在相关性. 该研究提示PNPLA3 rs738409变异可能与抗HCV疗效相关, 但是抗HVC疗效受到基因分型、纤维化程度、机体免疫等因素的影响, 因此有必要对HCV感染患者进行分层分组的进一步研究, 以明确该位点与抗HCV疗效的关系.

■创新盘点

本文对近几年来PNPLA3相关文献进行了综合整理和阐述，重点介绍了PNPLA3多态性与临床肝病(NAFLD、ALD、HCV感染患者、HCC)的相关性，内容新颖，资料详实.

4 结论

PNPLA3属于patatin样磷脂酶家族, 具有非特异的脂肪酰基水解酶活性[2-4]. PNPLA3 I148M变异蛋白通过阻止甘油三脂水解而增加肝脏脂肪蓄积. PNPLA3在人体内主要表达在肝脏[7], 其在体内的表达受到饮食、肥胖、胰岛素水平、基因变异等因素的影响. PNPLA3 rs738409(C>G)变异可引起普通人群、肥胖人群及肝病患者(NAFLD、ALD、HCV感染患者)的肝脏酶学(ALT、AST)增高[19,23]. 该位点的突变与临床肝病(NAFLD、ALD、HCV感染患者)发生的易感性、肝脂肪变、肝脏损害及纤维化进展相关. PNPLA3基因多态性与抗HCV治疗效果之间的关系尚未得出统一结论, 因此有必要进一步开展该方面研究. 此外, 研究还发现该位点变异是肥胖人群、ALD患者发生肝细胞癌的危险因素, 但相关研究还极少, 故需更多相关研究进一步论证.

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■应用要点
本文内容新颖、资料丰富、思路清晰，为读者了解PNPLA3的作用、研究现状及研究热点提供了重要的资料.

■同行评价
本文内容新颖, 对PNPLA3的作用机制以及今后临床肝病的后续研究有一定的指导意义.

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