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文献综述 REVIEW

PNPLA3基因在非酒精性脂肪性肝病中的作用

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■背景资料
非酒精性脂肪性肝病(NAFLD)在世界范围内发病率成日益上升趋势, 而NAFLD致病机制中的遗传易感性越来越得到人们关注. 多项实验证实PNPLA3基因突变与NAFLD密切相关, 但关于其致病机制仍无详细阐释.

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Advances in understanding the role of PNPLA3 in the pathogenesis of non-alcoholic fatty liver disease

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Abstract
The incidence of non-alcoholic fatty liver disease (NAFLD) is rising worldwide. Investigation of genes involved in the pathogenesis of NAFLD is significant for replenishing treatment scheme and improving prognosis. Multiple studies have established a correlation between patatin-like phospholipase domain-containing 3 (PNPLA3) gene mutation and the pathogenesis of NAFLD, suggesting that PNPLA3 may affect lipid metabolism. However, the precise mechanism remains to be elucidated. Some researchers believed that PNPLA3 as a patatin-like protein might have triglyceride hydrolysis activity and therefore affect fat metabolism in the liver, while some others thought that PNPLA3 mutation might interfere with the lipid transfer process. In this paper, we give an overview of the PNPLA3 gene and its expression, and explore the correlation between PNPLA3 gene mutation and the pathogenesis of NAFLD.

Key Words: Patatin-like phospholipase domain-containing 3; Adiponectin; Non-alcoholic fatty liver disease; Gene mutation

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摘要
非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)在世界范围内发病率成日益上升趋势, 其相关基因研究对完善其致病机制, 补充其治疗方案及改善预后至关重要. 目前, 国内外多项实验证实含patatin样磷脂酶域3(PNPLA3)基因突变与NAFLD密切相关, 考虑其与肝脏脂代谢有关, 但就其致病机制仍无详细阐释. 部分文献认为PNPLA3作为patatin样磷脂酶家族, 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. 也有文献认为PNPLA3突变干扰了脂质转运的过程. 本文详细介绍PNPLA3基因及其表达, 并就PNPLA3基因突变与NAFLD相关性进行综述.

关键词: 含patatin样磷脂酶域3; 脂肪滋养蛋白; 非酒精性脂肪性肝病; 基因突变

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0 引言
非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是一种无过量饮酒史, 以肝实质细胞脂肪变性、坏死、炎性细胞浸润等为特征的临床病理综合征. NAFLD在世界范围内发病率成日益上升趋势, 流行病学调查示西方

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国家NAFLD的发病率为20%-30%[1,2], 在我国上海地区NAFLD的发病率为15%[3]. NAFLD的致病机制一般认为与肥胖、2型糖尿病、高脂血症、胰岛素抵抗综合征等密切相关. 但现在越来越明确基因突变也是NAFLD发病的危险因素之一. 目前, 国外很多研究证实PNPLA3基因突变与NAFLD发病密切相关, 但中国仍鲜有这方面研究. 对PNPLA3基因的深入研究对完善NAFLD致病机制, 补充其治疗方案及改善预后至关重要.

1 PNPLA3基因

含patatin样磷脂酶域3(patatin-like phospholipase domain containing 3, PNPLA3)位于22号染色体上, 所编码的蛋白又被称为adiponectin, 蛋白由481个氨基酸组成的, 属于patatin样磷脂酶家族[4]. patatin是一种可溶的蛋白质, 在马铃薯根茎中广泛存在, 具有脂肪酰化水解酶活性[5]. PNPLA3位于细胞膜与脂滴之间, 两者紧密联系在一起, 高盐、高pH值等无法将两者分开. PNPLA3可能有针对性的存在于内质网新生膜脂滴形成的专门区域. 另外, PNPLA3也可能通过内质网转高尔基体转运机制, 从内质网膜转运到脂滴上. PNPLA3也可能在膜和脂滴之间执行不同功能[6]. PNPLA3蛋白的生物学功能尚不十分清楚. 生物结构上与PNPLA3结构最为类似的是PNPLA2, PNPLA2已被证实具有三酰甘油水解酶和酰基甘油转酰基酶活性[7]. 部分体外实验证实PNPLA3有三酰甘油水解酶和部分酰基甘油转酰基酶活性, 但其在体内所表达的生物学活性仍无统一结论. 例如: 人类肾脏胚胎细胞PNPLA3的过度表达并没有引起细胞内三酰甘油的改变[8]. 小RNA干扰机制PNPLA3敲除也没有影响3T3-L1细胞中三酰甘油含量[9]. 人类组织中cDNA的PCR表明, PNPLA3表达主要在肝脏, 其次为皮肤和脂肪细胞. 但在小鼠体内, PNPLA3的表达主要集中在脂肪组织. 实验比较小鼠肝细胞和星状细胞PNPLA3的分布, 发现PNPLA3 mRNA水平在星状细胞是含量只有肝细胞内的23%[10]. 最近报道显示, PNPLA3在小鼠肝脏内皮细胞及库普弗细胞(Kupffer cells)中均没有表达[11]. 因此, PNPLA3很可能主要在肝细胞内表达[10]. PNPLA3的表达由脂肪组织和肝脏的代谢所调控. PNPLA3 mRNA水平在空腹状态下很低, 进食碳水化合物时显著升高[4,8,12]. 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[13]. 另外有实验表明, PNPLA3 mRNA在肝脏中的表达与体质量指数(BMI)成正相关[14]. 而肥胖人群和消瘦人群PNPLA3 mRNA在脂肪组织中的表达未有统一结论, 一些实验未见明显差异[15], 而一些实验表明肥胖人群中PNPLA3 mRNA表达水平增强[16].

2 PNPLA3基因突变与NAFLD

2.1 PNPLA3基因突变与NAFLD 应用基因组相关性研究(genome-wide association studies, GWAS)方法研究NAFLD的历史并不长, 目前完整GWAS在NAFLD方面研究的报道文献主要有2篇. 1篇是对236例女性NAFLD患者的队列研究, 该研究未设对照组, 此项研究并未显示PNPLA3与NAFLD的相关性, 其具体原因仍不清楚, 研究者认为可能与样本过小以及研究对象只有女性有关[17]; 另外1篇对来自4组研究[Old Order Amish; Age, Gene/Environment Susceptibility-Reykjavik study (AGES); Family Heart; Framingham Heart Studies]中的7 176个体进行了研究, 充分证明了PNPLA3与NAFLD密切相关[18].

目前关于PNPLA3突变[rs738409[G], 编码I148M]与NAFLD相关性研究结论主要为以下几个方面. 首先, PNPLA3突变与肝脏脂肪含量的相关性显著, 并且PNPLA3rs738409[G]纯合子者肝脏脂肪含量高于不携带者2倍多. 若排除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仍非常显著[19-22]; 其次, PNPLA3突变在一些人群中发现引起了肝脏相关酶学的升高. Romeo等[19]发现在西班牙裔美国人中谷丙转氨酶(alanine aminotransferase, ALT)升高, 在其他非洲裔美国人和欧美裔美国人肝酶未有明显改变. 而Yuan等[23]的相关研究表明PNPLA3突变在欧美白人和印度籍亚洲人都引起ALT的升高. Huang等[10]研究发现PNPLA3等位基因rs738409[G]与血清谷草转氨酶(aspartate aminotransferase, AST)浓度相关. 另外, Romeo等[19]发现PNPLA3 rs738409突变在11 000欧裔美国人有总胆固醇累计效应. 相关研究证实, 经过多次修正实验后, PNPLA3基因突变与总胆固醇, 低密度脂蛋白水平显著相关[24].

2.2 PNPLA3基因突变在NAFLD致病机制方面研究 NAFLD的致病机制一般认为与肥胖、2型糖尿病、高脂血症、胰岛素抵抗综合征等密切相关. 虽然肥胖人群中肝脏PNPLA3呈高表达, 但其在脂肪代谢中的作用及其生理学底物仍未

■研发前沿
NAFLD的致病机制一般认为与肥胖、2型糖尿病、高脂血症、胰岛素抵抗综合征等密切相关. 但现在越来越明确基因突变也是NAFLD发病的危险因素之一. PNPLA3基因突变与NAFLD的关系是现阶段研究热点, 值得我们深入探讨.

■相关报道
2008年Rome等首次应用基因组相关性研究(GWAS)方法证明PNPLA3突变[rs738409(G), 编码I148M]与NAFLD发病相关, PNPLA3基因突变与肝脏脂肪含量增加显著相关并与肝脏炎症密切相关.

明确. PNPLA3相比其他器官在肝脏中的高表达水平, 意味着其在肝脏代谢中一个不为我们所知的作用. 相关研究示在体外培养PNPLA3-I148M突变肝细胞中三酰甘油含量增加且动物实验中PNPLA3突变小鼠的肝脏三酰甘油的含量也会增加. 细胞分离的研究显示, 90%的野生型PNPLA3存在与细胞膜和脂滴分割之间, 突变的PNPLA3没有改变蛋白质亚细胞的分布. 因此, 学者认为PNPLA3-I148M通过限制三酰甘油水解引起其在肝脏的聚集. 可能机制是PNPLA3突变将表达蛋白中异亮氨酸变为甲基氨酸, 这将限制底物与蛋白催化位点的结合, 从而限制了三酰甘油水解酶的活性. 这一猜测在生物学结构模型上得到了证实. 结构模型表明氨基酸的替代没有扰乱催化对残留(Ser-47和Asp-166)的位置或方向, 更确切地说, 是甲基氨酸的侧链的延伸到催化区域,干扰丝氨酸与底物的结合[25].

需要引起我们重视的是, 人类野生型PNPLA3的过度表达并没有改变小鼠肝脏三酰甘油的水平, 考虑PNPLA3可能不是肝脏中主要的三酰甘油水解酶. 而突变型PNPLA3的过度表达引起了小鼠肝脏中三酰甘油含量的升高. 这些实验表明小鼠三酰甘油在体内的聚集主要是因为PNPLA3突变后变异蛋白的表达, 而野生型蛋白活性的缺失并不是主要因素[25].

另外, 研究者考虑PNPLA3的突变引起三酰甘油在肝脏中的聚集与影响水解酶辅酶因子的活性或影响底物与另外的脂酶结合有关. 许多三酰甘油水解酶, 包括在脂肪组织中起主要作用的PNPLA2都需要蛋白辅助因子来完成酶的活性. 但类似的PNPLA3辅助因子仍未被发现. 在体外实验中, 突变的酶并没有干扰野生型蛋白的作用, 但在体内是否和底物或必需的辅助因子相互作用仍不可知[25]. 也有研究表明肝脏的脂肪积聚可能是由于富含三酰甘油的脂蛋白从肝脏释放到血液循环的过程受到影响导致的, 相关结果表示, PNPLA3基因突变在欧亚混血儿人群中与apoB-containing脂蛋白分数密切相关. 研究表明每个等位基因PNPLA3变异可以使apoB载脂蛋白分数下降3%, 而在群体水平脂蛋白的浓度变异应该小于1%. 研究者考虑PNPLA3可能通过参与餐后肝脏脂蛋白包装而参与apoB脂蛋白的新陈代谢[24]. 也有文献证明PNPLA3突变可以抑制微粒体的转运蛋白从而影响肝脏脂肪含量[26].

一些文章表明PNPLA3 rs738409[G]突变携带者肝脏ALT水平升高, 实验中PNPLA3突变对肝酶的影响排除了血脂紊乱和其他肝脏疾病, 考虑其可能与肝脏炎症及肝细胞损伤相关[27,28]. 然而目前不清楚是PNPLA3的变异引起肝脏脂质存储导致使肝脏酶学升高, 或是PNPLA3本身的变异对肝功能有影响导致轻微的肝脏功能障碍和肝脏炎症. ALT是反映肝功能的指标中特异性和敏感性较高的, 因肝脂肪堆积产生的轻微肝功能损伤可能引起ALT的升高. 研究者还怀疑肝功能的受损也可能来自于胆固醇水平升高[28].

最近研究考虑, 尽管PNPLA3在体外具有三酰甘油水解酶的作用, 但其在进食碳水化合物是的表达上调考虑其在体内可能是在脂肪形成方面起作用, 而不是脂质代谢方面[10]. 有研究表示, 服用特定的饮食后的低密度脂蛋白受体敲除小鼠PNPLA3的表达模式与葡萄糖六磷酸脱氢酶(glucose-6-phosphate dehydrogenase, G6PD)的表达模式相近[11]. G6PD是细胞内参与磷酸戊糖途径催化酶, 他是NADP生成NADPH过程中的关键酶. NADPH作为体内的供氢体, 在三酰甘油合成过程中其重要作用[29,30]. 因为PNPLA3的表达模式与G6PD的表达模式相近, 考虑PNPLA3在脂质合成上起相应作用. 另外, PNPLA3与G6PD在不同代谢条件下相似变化也证明两者在脂质合成上的相关作用. 禁食时PNPLA3与G6PD在肝脏表达水平减低[31]. 在注射胰岛素后, 脂肪中PNPLA3和G6PD水平升高[15,32]. 假如我们认证PNPLA3与G6PD在脂质合成上具有相似的作用, 那PNPLA3突变引起脂肪在肝脏中聚集的现象又如何解释? 考虑其在PNPLA3的突变是否干扰了肝外脂质的合成以至于相对较多的脂肪在肝脏聚集, 但目前仍缺乏相关研究解释其具体机制.

总之, 目前关于PNPLA3突变与NAFLD致病相关机制研究热点主要在其脂质分解作用. 但部分学者考虑到PNPLA在进食碳水化合物后的高表达这一现象认为PNPLA3具有脂质合成作用. 除此之外, 目前仍不能排除PNPLA3突变对肝脏脂代谢转运过程影响及在分子生物水平上影响其他基因的调控, 干扰转录因子作用机制[33].

2.3 PNPLA3基因突变在脂肪肝治疗方面意义

PNPLA3基因变异rs738409(C→G)与肝脂肪沉积增加有关, 并在西班牙裔效果更加明显. 动物模型表明, PNPLA3表达可以通过饮食中碳水化合物来调节. 这些研究结果表明, 当饮食中碳

水化合物尤其是糖摄入过高, 携带着GG基因型的西班牙裔孩子对脂肪肝有明显易感性. 基于脂肪肝遗传易感性特殊饮食干预在该人群中治疗效果优于单纯脂肪肝治疗[34]. PNPLA3的表达在脂肪细胞分化时上调, 饮食和禁食时差异性调节, 考虑他的作用在能量动员, 脂肪组织和肝脏的脂肪储存作用可能是相似的. 生物学信息已揭示其突变将影响其蛋白质的功能. 因此, PNPLA3与肝酶的密切联系引导我们思考PNPLA3是否可以作为肝酶治疗的新的药物作用位点[28]. NAFLD的病态肥胖患者中, 相关尸检及肝脏穿刺活检表明, 只有10%-20%的患者肝脏表现为非单纯性脂肪肝, 出现了肝细胞变性及纤维化[35,36]. 这引发我们对NAFLD疾病预后相关因素的思考. 很多研究表明, PNPLA3突变是NAFLD疾病单纯性脂肪肝向脂肪肝肝炎进展的危险因子, 可能影响肝脏纤维化进展过程[37-39]. 因此考虑PNPLA3可以作为NAFLD疾病预后预测因子[40].

3 PNPLA3基因突变与其他肝脏疾病

一些文献表明PNPLA3与酒精性肝病严重性也有密切联系. 研究中PNPLA3突变者Child-Pugh分数增高. 因此, 考虑rs738409[G]突变不仅和肝脏脂肪量密切相关, 也加重酒精性肝病肝损伤及肝脏纤维化程度. 文献中作者大胆推论, PNPLA3 rs738409[G]突变结果与人类很多复杂疾病密切相关, 可能是人类那些可预防的致死疾病的最重要基因修饰[41]. 另外, 最新研究表明, PNPLA3突变推进了慢性丙型肝炎脂肪化及纤维化的进程, 考虑其可以作为慢性丙型肝炎预后预测因子及潜在的药物治疗靶点[42].

4 结论

PNPLA3是patatin样磷脂酶家族一员, 体外实验证明其具有三酰甘油水解酶的活性, 但具体机制仍不清楚. PNPLA3基因变异rs738409(C→G)与NAFLD相关性于2008年首次报道后相关研究很多. PNPLA3突变影响NAFLD的具体机制目前主要考虑与脂质分解有关. 但PNPLA3突变是否影响肝脏脂代谢转运过程或在分子生物水平上影响其他基因的调控, 干扰转录因子等作用机制仍需更多的研究来探讨. PNPLA3基因突变研究提示我们发展NAFLD治疗的新的酶学位点药物的可能, 并扩展NAFLD预后危险因素研究的思路. 目前PNPLA3的研究仍处在起步阶段, 是西方NAFLD发病机制方面的研究热点, 但在中国这方面研究仍很少. 中国关于NAFLD基因多态性的研究并未提及PNPLA3与NAFLD的相关性[43]. 但台湾关于肥胖儿童NAFLD研究表明, PNPLA3突变增加了肥胖儿童患NAFLD的危险性[44]. 而日本方面相关研究也证实了PNPLA3突变与NAFLD相关性[45]. 因此, PNPLA3突变对NAFLD的影响可能不存在种族差异, 值得我们进行深入研究.

■创新盘点

本综述首次对PNPLA3突变与NAFLD相关性进行综述. 中国相关研究很少, 而对其深入研究对完善其致病机制, 补充其治疗方案及改善预后至关重要.

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■**应用要点**
PNPLA3突变是NAFLD疾病单纯性脂肪肝向脂肪肝肝炎进展的危险因子, 可能影响肝脏纤维化进展过程. 因此考虑PNPLA3可以作为NAFLD疾病预后预测因子.

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■同行评价
本文创新性、可读性较好, 具有较好的科学和理论价值.

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或$T_{\frac{1}{2}}$, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var.glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *Cl*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.