

ChREBP及其靶基因*PNPLA3*在非酒精性脂肪性肝病发病中的作用

季玲, 李昌平

季玲, 李昌平, 四川省泸州医学院附属医院消化内科 四川省泸州市 646000

季玲, 主要从事消化系统疾病的研究。

作者贡献分布: 本文由季玲综述; 李昌平选题和审校。

通讯作者: 李昌平, 教授, 646000, 四川省泸州市太平街25号, 泸州医学院附属医院消化内科. 506854209@qq.com

电话: 0830-3161276

收稿日期: 2013-11-05 修回日期: 2013-11-19

接受日期: 2013-11-29 在线出版日期: 2014-01-18

Role of ChREBP and its target gene *PNPLA3* in pathogenesis of nonalcoholic fatty liver disease

Ling Ji, Chang-Ping Li

Ling Ji, Chang-Ping Li, Department of Gastroenterology, the Affiliated Hospital of Luzhou Medical College, Luzhou 646000, Sichuan Province, China

Correspondence to: Chang-Ping Li, Professor, Department of Gastroenterology, the Affiliated Hospital of Luzhou Medical College, 25 Taiping Street, Luzhou 646000, Sichuan Province, China. 506854209@qq.com

Received: 2013-11-05 Revised: 2013-11-19

Accepted: 2013-11-29 Published online: 2014-01-18

Abstract

Nonalcoholic fatty liver disease (NAFLD) is a clinical and pathological syndrome caused by excessive triglyceride accumulation in liver cells. Its hepatic histological changes are similar to those of alcoholic liver disease (ALD), but the patients do not have a history of heavy alcohol drinking. NAFLD includes nonalcoholic simple fatty liver (NASFL), nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty hepatitis related to liver fibrosis and cirrhosis. At present, the detailed pathogenesis of NAFLD is unclear. Many studies have reported the relationship between ChREBP and its target gene *PNPLA3* and NAFLD occurrence. ChREBP and *PNPLA3* are associated with liver fat content and inflammation. This article reviews the role of ChREBP and its target gene *PNPLA3* in the pathogenesis of NAFLD, in order to provide a theoretical basis for further research of the occurrence and treatment of NAFLD.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

Key Words: Nonalcoholic fatty liver disease; *ChREBP* gene; *PNPLA3* gene; Insulin resistance

Ji L, Li CP. Role of ChREBP and its target gene *PNPLA3* in pathogenesis of nonalcoholic fatty liver disease. *Shijie Huaren Xiaohua Zazhi* 2014; 22(2): 179-183 URL: <http://www.wjgnet.com/1009-3079/22/179.asp> DOI: <http://dx.doi.org/10.11569/wjcd.v22.i2.179>

摘要

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是肝细胞内大量甘油三酯聚集而引起的临床病理综合征, 肝的组织学改变与酒精性肝病(alcoholic liver disease, ALD)相似, 但无过量饮酒史. NAFLD包括非酒精性单纯性脂肪肝、非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)、NASH相关肝纤维化和肝硬化. 目前其详细发病机制尚不清楚, 但国内外已有较多关于ChREBP及其靶基因*PNPLA3*与NAFLD发病关系的研究, 证实了ChREBP和*PNPLA3*与肝内脂肪含量及炎症相关. 本文主要综述了ChREBP及其靶基因*PNPLA3*在NAFLD发病过程中的作用, 为脂肪肝的发生和治疗提供更多的理论基础.

© 2014年版权归百世登出版集团有限公司所有.

关键词: 非酒精性肝病; *ChREBP*基因; *PNPLA3*基因; 胰岛素抵抗

核心提示: 对ChREBP和*PNPLA3*在非酒精性肝病中的作用机制的深入研究, 将有利于对非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)等疾病的治疗提供新理论依据, 成为解决这系列健康问题的新途径. 对于消除人们对于NAFLD所带来的潜在的恐惧将具有极大的现实效果.

季玲, 李昌平. ChREBP及其靶基因*PNPLA3*在非酒精性脂肪性肝病发病中的作用. 世界华人消化杂志 2014; 22(2): 179-183 URL: <http://www.wjgnet.com/1009-3079/22/179.asp> DOI: <http://dx.doi.org/10.11569/wjcd.v22.i2.179>

■背景资料

随着生活水平、饮食习惯的改变和代谢综合征等患病率的上升, 非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)的发病率也在不断上升, 且有低龄化趋势. 影响范围甚广, 严重危害着人民的身心健康, 国内外已有较多关于ChREBP及其靶基因*PNPLA3*与NAFLD发病关系的研究, 但其发病机制仍不明确.

■同行评议者

孙学英, 教授, 哈尔滨医科大学第一附属医院

■研发前沿

NAFLD的发病可能是遗传-环境-代谢-应激等因素所致,但越来越多研究认为ChREBP、PNPLA3基因在NAFLD的发病中起着相当重要的作用。ChREBP、PNPLA3基因与NAFLD的关系日益成为现阶段的研究热点。

0 引言

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是无过量饮酒史但肝病理学改变与酒精性肝病相似的临床病理综合征。按严重程度分为脂肪变性、脂肪肝、肝纤维化和坏死^[1],最终可发展成肝硬化、肝癌^[2-6]。近年NAFLD成日益上升趋势,成为我国发达地区和富裕人群的常见病^[7,8]。据统计全世界成人约10%-30%有NAFLD, 70%以上肥胖、糖尿病患者患有NAFLD, 肥胖儿童10%-50%患有NAFLD^[9],在我国上海地区NAFLD的发病率为15%^[9]。目前其发病机制尚不完全清楚,可能是遗传环境、代谢应激等所致,常与肥胖、高脂血症、胰岛素抵抗等代谢综合征相关^[10,11]。本文主要综述ChREBP(碳水化合物反应元件结合蛋白)及其靶基因PNPLA3基因(脂肪滋养蛋白或者含patatin样磷脂酶域3)在NAFLD发病中的作用。

1 碳水化合物反应元件结合蛋白

2001年Yamashita等^[12]发现碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, ChREBP),是一种与肝丙酮酸激酶(liver pyruvate kinase, LPK)基因启动子区的碳水化合物反应元件(carbohydrate response element, ChRE)相结合的蛋白。目前大量研究示ChREBP的靶基因主要是控制如肝型丙酮酸激酶(liver pyruvate kinase, LPK)、脂肪酸合酶(fatty acid synthase, FAS)、乙酰辅酶A羧化酶(acetyl-coenzyme A carboxylase, ACC)等糖脂代谢过程中酶类的表达^[13]。在肝的代谢中起重要作用。

1.1 ChREBP的结构与功能 ChREBP属于转录因子Mondo-家族^[14],是由864个氨基酸组成的碱性螺旋-环-螺旋/亮氨酸拉链(bHLH/ZIP)大分子DNA结合蛋白,含聚脯氨酸区(PRO)、核定位信号区(nuclear localization signal, NLS)、亮氨酸拉链区(bHLH/ZIP)和类亮氨酸拉链(ZIP-like)区域(ZIP样区)(图1)^[15]等多个结构域,还含有cAMP依赖蛋白激酶(protein kinase A, PKA)和AMP活化蛋白激酶(AMP-activated protein kinase, AMPK)的磷酸化位点,包括可以被PKA磷酸化的Ser196、Ser626、Thr666以及AMPK的磷酸化位点ser568(图1)。低糖时,ChREBP以不活泼的磷酸化形式存在于胞质中, Ser196和Thr666位点磷酸化。在高糖条件下,葡萄糖激活ChREBP,并去磷酸化进入细胞核变成有活性的ChREBP结合在葡萄糖反应基因的ChRE上,促进其转录。

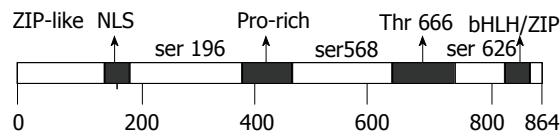


图1 ChREBP上的功能域和PKA及AMPK的磷酸化位点示意图。Ser196、Ser626和Thr666是PKA的3个磷酸化位点, Ser568是AMPK的磷酸化位点。PKA: 蛋白激酶; AMPK: AMP活化蛋白激酶。

1.2 ChREBP的作用机制及其表达的调控与活性调节 ChREBP是葡萄糖过程中的关键转录因子^[16],需异二聚体伴侣才能与ChRE序列结合并调控转录,只有Mlx存在时,ChREBP才能结合到葡萄糖反应基因的ChRE上并激活其转录。ChREBP还可能通过其他因子共同调节。研究发现高浓度葡萄糖激活ChREBP表达,而胰高血糖素、游离脂肪酸(free fatty acid, FFA)、cAMP抑制其表达^[17]。而ChREBP活性的调节通过磷酸化位点的磷酸化和去磷酸化从细胞质到细胞核的转移以及转录活性的激活两个水平上进行调节。除此还有其他调节机制,如cha等报道肝x受体(liver x receptor, LXR)在转录水平上调控其表达; Hashimoto等^[18]也证实了甲状腺激素可以上调其表达水平。Li等^[14]也发现通过葡萄糖敏感组件(glucose-sensing module, GSM)的方式能控制ChREBP对葡萄糖的调节作用。

1.3 ChREBP在NAFLD中的作用 过多脂质堆积会出现肥胖、脂肪肝、胰岛素抵抗等代谢综合征。敲除ChREBP基因的ob/ob小鼠体质量明显下降,代谢综合症状也明显改善,且肝细胞内异常表达的糖酵解、脂质合成基因也得到了纠正^[19]。Dentin等^[20]研究示抑制肝ChREBP可以纠正小鼠脂肪肝和葡萄糖耐受情况,缓解小鼠的代谢综合征情况。所以抑制ChREBP活性可削弱高碳水化合物引起的过多脂质沉积、改善肥胖症状,成为解决肥胖、脂肪肝等新途径。ChREBP通过对成脂相关的基因的转录调控在肝脂质合成中起重要的决定因子的作用^[21]。所以ChREBP在NAFLD的进展中起重要作用。

2 脂肪滋养蛋白或者含patatin样磷脂酶域3

目前NAFLD越来越多地被重视,有研究指出接触了相似危险因素的个体间NAFLD的发病率差异较大以及病程亦不同,这提示遗传、基因多态性与NAFLD发病及进程相关,目前磷脂酶家族成员A3(PNPLA3, SNP rs738409, 编码1148M)引起了广泛关注。国外许多报道证明PNPLA3基因多态性与NAFLD发生和发展有相关性^[22,23]。

■相关报道

He等推断PNPLA3变异导致了肝甘油三酯的聚集, Dentin等研究示抑制肝ChREBP可以纠正小鼠脂肪肝和葡萄糖耐受情况,削弱高碳水化合物引起的过多脂质沉积、改善肥胖症状。他们可能成为解决肥胖、脂肪肝等新途径。

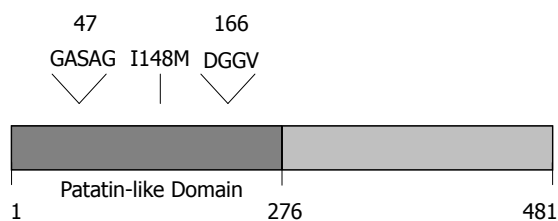


图2 PNPLA3蛋白的patatin样结构域示意图。PNPLA3是含有patatin样结构域蛋白, 由481个氨基酸编码的N端结构域含有两个经典的保守序列, 第148位的异亮氨酸, 位于两端保守序列之间, 蛋氨酸(Met148)替代异亮氨酸(Ile148)之后, 使其失去水解酶的活性, 增加了人体肝脏脂肪聚集的风险。

2.1 PNPLA3概述及调节 PNPLA3(patatin-like phospholipase domain containing family member A3)又称脂肪滋养蛋白, 属patatin类磷酸酯酶结构域蛋白家族, 该家族蛋白在C末端有一个共有的patatin类结构域^[24], 位于22号染色体, 编码一种由481个氨基酸组成的非分泌性蛋白(图2)。PNPLA3主要在肝细胞内表达^[25], 主要定位在细胞膜脂间, 并可能在细胞膜和脂滴之间执行不同功能^[26]。徐静等^[27]发现PNPLA3在肝脂质代谢中起重要作用, 其表达水平的改变与脂肪合成密切相关。而PNPLA3可通过胆固醇应答元件结合蛋白1(sterol regulatory element binding protein-1, SREBP-1)结合到*PNPLA3*启动子区SREs上进行调节, 且*PNPLA3*启动子上游-4931--4915 bp之间的CHRE序列与ChREBP结合后激活PNPLA3转录^[28], 促进脂肪合成并影响糖代谢。PNPLA3还受营养因素、葡萄糖、胰岛素和LXR的激活剂T0901317调节^[29]。

2.2 PNPLA3基因与NAFLD 研究发现*PNPLA3*基因是一易感NAFLD的关键遗传因素^[30-34], 与胰岛素抵抗密切相关^[34-36], Wang等^[37]在最近的研究报道中也有类似的发现。国内外很多研究示PNPLA3多态性与肝脂肪含量、血ALT水平增加有关^[38-41], 还与酒精性肝病、病毒性肝炎甚至肝癌的疾病进展密切相关^[41-43]。其突变可引起普通人群^[44]、肥胖人群^[45]、肝病患者谷丙转氨酶(alanine aminotransferase, ALT)、天冬氨酸氨基转移酶(aspartate aminotransferase, AST)增高, 且该基因与肝炎、肝纤维化的发展也有密切联系^[39,40,46]。*PNPLA3*突变是NAFLD疾病单纯性脂肪肝向肝炎进展的危险因子, 可能影响肝纤维化进展过程^[47,48]。He等^[49]推断PNPLA3变异导致了肝甘油三酯的聚集, Basantani等^[50]也推断*PNPLA3*基因是参与了脂肪合成且其突变体能增强其脂肪合成的功能。Romeo等^[32]发现在

11000例欧裔美国人中*PNPLA3*突变后有胆固醇累计现象。Sookoian等^[31]也发现PNPLA3变异与NAFLD密切相关。这些都是以不同种族地区的人为研究对象, 说明在不同种族及地区PNPLA3多态性与肝脂肪含量及肝炎症有关且其变异也可能是不同种族地区间其易感性和肝脂肪含量差异的原因之一, 所以*PNPLA3*基因突变与总胆固醇、低密度脂蛋白明显相关^[51]。因此, PNPLA3在NAFLD的发病中起重要作用。

3 结论

有关非酒精性肝病的防治研究中, 已初步证明ChREBP在糖脂代谢过程中发挥重要作用, 可能具有延缓脂肪肝发生进展的作用, 对治疗糖脂类代谢紊乱、肝疾病等有重大意义。PNPLA3与NAFLD的发生密切相关, 国内外虽有较多研究, 但其具体机制仍未阐明, 未来仍需更多研究来证实其对NAFLD的致病和病变发展的影响。对ChREBP和PNPLA3在非酒精性肝病中的作用机制的深入研究, 将有利于对NAFLD等疾病的治疗提供新的作用靶点及理论依据, 成为解决这系列健康问题的新途径。

4 参考文献

- 1 Brunt EM. Pathology of nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2010; 7: 195-203 [PMID: 20195271 DOI: 10.1038/nrgastro.2010.21]
- 2 Lam B, Younossi ZM. Treatment options for nonalcoholic fatty liver disease. *Therap Adv Gastroenterol* 2010; 3: 121-137 [PMID: 21180596 DOI: 10.1177/1756283X09359964]
- 3 Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis* 2010; 28: 155-161 [PMID: 20460905 DOI: 10.1159/000282080]
- 4 Bellentani S, Marino M. Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). *Ann Hepatol* 2009; 8 Suppl 1: S4-S8 [PMID: 19381118]
- 5 Schmoldt A, Benthe HF, Haberland G. Digitoxin metabolism by rat liver microsomes. *Biochem Pharmacol* 1975; 24: 1639-1641 [DOI: 10.1016/0006-2952(75)90094-5]
- 6 Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011; 34: 274-285 [PMID: 21623852 DOI: 10.1111/j.1365-2036.2011.04724.x]
- 7 Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJ, Chutaputti A. What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific? *J Gastroenterol Hepatol* 2007; 22: 794-800 [PMID: 17498218 DOI: 10.1111/j.1440-1746.2007.04952.x]
- 8 Fan JG. [Advances in research on nonalcoholic fatty liver disease]. *Zhonghua Ganzangbing Zazhi* 2008; 16: 801-803 [PMID: 19032857 DOI: 10.1016/j.jhep.2008.10.010]

■创新盘点

ChREBP以及*PNPLA3*基因与胰岛素抵抗、肝炎、肝纤维化的发展程度有着密切的联系, 但目前关于这方面的报道仍较少。本文探讨了ChREBP及其靶基因*PNPLA3*与NAFLD发病关系的研究以及他们对NAFLD的影响。

■应用要点

ChREBP调控糖酵解和脂肪生成途径,在肝脂肪变性、肥胖症、2型糖尿病、胰岛素抵抗等方面起重要作用,PNPLA3与肝炎、肝纤维化的发展程度也有密切的联系,因此他们可以为脂肪肝的发生和治疗提供更多的理论基础。

- 9 Fan JG, Farrell GC. Epidemiology of non-alcoholic fatty liver disease in China. *J Hepatol* 2009; 50: 204-210 [PMID: 19014878]
- 10 Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. *Diabetes Care* 2005; 28: 1757-1762 [PMID: 15983331]
- 11 向国卿, 孟宪云, 张浩, 台文霞, 孟晓丹, 王炳元. 脂肪肝相关危险因素的评估. *世界华人消化杂志* 2009; 17: 1038-1041
- 12 Yamashita H, Takenoshita M, Sakurai M, Bruick RK, Henzel WJ, Shillinglaw W, Arnot D, Uyeda K. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. *Proc Natl Acad Sci U S A* 2001; 98: 9116-9121 [PMID: 11470916]
- 13 李小山, 何松. ChREBP及其靶基因在高脂大鼠非酒精性脂肪肝中的表达. *重庆医学* 2011; 40: 1671-8348
- 14 Li MV, Chang B, Imamura M, Pongvarin N, Chan L. Glucose-dependent transcriptional regulation by an evolutionarily conserved glucose-sensing module. *Diabetes* 2006; 55: 1179-1189 [PMID: 16644671]
- 15 符白英, 王继文, 韩春春. ChREBP和Mix在调控葡萄糖反应基因表达中的作用. *中国生物化学与分子生物学报* 2007; 23: 977-980
- 16 卢建雄, 陈粉粉, 杨公社. 调控糖酵解和生脂的重要转录因子: 碳水化合物反应元件结合蛋白. *生理科学进展* 2006; 37: 266-269
- 17 刘振山, 李齐发, 李学斌, 谢庄. 糖类应答元件结合蛋白-葡萄糖信号途径中的转录因子. *生命的化学* 2006; 26: 302-304
- 18 Hashimoto K, Ishida E, Matsumoto S, Okada S, Yamada M, Satoh T, Monden T, Mori M. Carbohydrate response element binding protein gene expression is positively regulated by thyroid hormone. *Endocrinology* 2009; 150: 3417-3424 [PMID: 19324998 DOI: 10.1210/en.2009-0059]
- 19 郑芳. 碳水化合物反应元件结合蛋白研究进展. *医学研究生学报* 2011; 24: 1008-8199
- 20 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 [PMID: 16873678]
- 21 程维肖, 赵和平. 动态观察非酒精性脂肪肝大鼠肝脏ChREBP的表达. *山西医科大学学报* 2009; 40: 308-311
- 22 Krawczyk M, Grünhage F, Zimmer V, Lammert F. Variant adiponutrin (PNPLA3) represents a common fibrosis risk gene: non-invasive elastography-based study in chronic liver disease. *J Hepatol* 2011; 55: 299-306 [PMID: 21168459 DOI: 10.1016/j.jhep.2010.10.042]
- 23 Chen W, Chang B, Li L, Chan L. Patatin-like phospholipase domain-containing 3/adiponutrin deficiency in mice is not associated with fatty liver disease. *Hepatology* 2010; 52: 1134-1142 [PMID: 20648554 DOI: 10.1002/hep.23812]
- 24 Kienesberger PC, Oberer M, Lass A, Zechner R. Mammalian patatin domain containing proteins: a family with diverse lipolytic activities involved in multiple biological functions. *J Lipid Res* 2009; 50 Suppl: S63-S68 [PMID: 19029121 DOI: 10.1194/jlr.R800082-JLR200]
- 25 李冬阳, 林连捷, 郑长青. PNPLA3基因在非酒精性脂肪性肝病中的作用. *世界华人消化杂志* 2011; 19: 1796-1801
- 26 Soni KG, Mardones GA, Sougrat R, Smirnova E, Jackson CL, Bonifacino JS. Coatamer-dependent protein delivery to lipid droplets. *J Cell Sci* 2009; 122: 1834-1841 [PMID: 19461073 DOI: 10.1242/jcs.045849]
- 27 徐静, 辛永宁, 宣世英. PNPLA3基因多态性与非酒精性脂肪性肝病关系的研究进展. *临床肝胆病杂志* 2012; 28: 316-320
- 28 Perttilä J, Huaman-Samanez C, Caron S, Tanhuanpää K, Staels B, Yki-Järvinen H, Olkkonen VM. PNPLA3 is regulated by glucose in human hepatocytes, and its I148M mutant slows down triglyceride hydrolysis. *Am J Physiol Endocrinol Metab* 2012; 302: E1063-E1069 [PMID: 22338072 DOI: 10.1152/ajpendo.00125.2011]
- 29 Huang Y, He S, Li JZ, Seo YK, Osborne TF, Cohen JC, Hobbs HH. A feed-forward loop amplifies nutritional regulation of PNPLA3. *Proc Natl Acad Sci U S A* 2010; 107: 7892-7897 [PMID: 20385813 DOI: 10.1073/pnas.1003585107]
- 30 Valenti L, Alisi A, Galmozzi E, Bartoli A, Del Menico B, Alterio A, Dongiovanni P, Fargion S, Nobili V. I148M patatin-like phospholipase domain-containing 3 gene variant and severity of pediatric nonalcoholic fatty liver disease. *Hepatology* 2010; 52: 1274-1280 [PMID: 20648474 DOI: 10.1002/hep.23823]
- 31 Sookoian S, Castaño GO, Burgueño AL, Gianotti TF, Rosselli MS, Pirola CJ. A nonsynonymous gene variant in the adiponutrin gene is associated with nonalcoholic fatty liver disease severity. *J Lipid Res* 2009; 50: 2111-2116 [PMID: 19738004 DOI: 10.1194/jlr.P900013-JLR200]
- 32 Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; 40: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]
- 33 Kotronen A, Johansson LE, Johansson LM, Roos C, Westerbacka J, Hamsten A, Bergholm R, Arkkila P, Arola J, Kiviluoto T, Fisher RM, Ehrenborg E, Orholm-Melander M, Ridderstråle M, Groop L, Yki-Järvinen H. A common variant in PNPLA3, which encodes adiponutrin, is associated with liver fat content in humans. *Diabetologia* 2009; 52: 1056-1060 [PMID: 19224197 DOI: 10.1007/s00125-009-1285-z]
- 34 Li X, Zhao Q, Wu K, Fan D. I148M variant of PNPLA3 confer increased risk for nonalcoholic fatty liver disease not only in European population, but also in Chinese population. *Hepatology* 2011; 54: 2275 [PMID: 21793025 DOI: 10.1002/hep.24567]
- 35 Johansson LE, Lindblad U, Larsson CA, Råstam L, Ridderstråle M. Polymorphisms in the adiponutrin gene are associated with increased insulin secretion and obesity. *Eur J Endocrinol* 2008; 159: 577-583 [PMID: 18728122 DOI: 10.1530/EJE-08-0426]
- 36 Palmer CN, Maglio C, Pirazzi C, Burza MA, Adiels M, Burch L, Donnelly LA, Colhoun H, Doney AS, Dillon JF, Pearson ER, McCarthy M, Hattersley AT, Frayling T, Morris AD, Peltonen M, Svensson PA, Jacobson P, Borén J, Sjöström L, Carlsson LM, Romeo S. Paradoxical lower serum triglyceride levels and higher type 2 diabetes mellitus susceptibility in obese individuals with the PNPLA3 148M variant. *PLoS One* 2012; 7: e39362 [PMID: 22724004 DOI: 10.1371/journal.pone.0039362]
- 37 Wang CW, Lin HY, Shin SJ, Yu ML, Lin ZY, Dai CY, Huang JF, Chen SC, Li SS, Chuang WL. The

- PNPLA3 I148M polymorphism is associated with insulin resistance and nonalcoholic fatty liver disease in a normoglycaemic population. *Liver Int* 2011; 31: 1326-1331 [PMID: 21745282 DOI: 10.1111/j.1478-3231.2011.02526.x]
- 38 Speliotes EK, Butler JL, Palmer CD, Voight BF, Hirschhorn JN. PNPLA3 variants specifically confer increased risk for histologic nonalcoholic fatty liver disease but not metabolic disease. *Hepatology* 2010; 52: 904-912 [PMID: 20648472 DOI: 10.1002/hep.23768]
- 39 Rotman Y, Koh C, Zmuda JM, Kleiner DE, Liang TJ. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. *Hepatology* 2010; 52: 894-903 [PMID: 20684021 DOI: 10.1002/hep.23759]
- 40 Kollerits B, Coassin S, Kiechl S, Hunt SC, Paulweber B, Willeit J, Brandstätter A, Lamina C, Adams TD, Kronenberg F. A common variant in the adiponutrin gene influences liver enzyme values. *J Med Genet* 2010; 47: 116-119 [PMID: 19542081 DOI: 10.1136/jmg.2009.066597]
- 41 Trépo E, Gustot T, Degré D, Lemmers A, Verset L, Demetter P, Ouziel R, Quertinmont E, Vercruysse V, Amininejad L, Deltenre P, Le Moine O, Devière J, Franchimont D, Moreno C. Common polymorphism in the PNPLA3/adiponutrin gene confers higher risk of cirrhosis and liver damage in alcoholic liver disease. *J Hepatol* 2011; 55: 906-912 [PMID: 21334404 DOI: 10.1016/j.jhep.2011.01.028]
- 42 Trépo E, Pradat P, Potthoff A, Momozawa Y, Quertinmont E, Gustot T, Lemmers A, Berthillon P, Amininejad L, Chevallier M, Schlué J, Kreipe H, Devière J, Manns M, Trépo C, Sninsky J, Wedemeyer H, Franchimont D, Moreno C. Impact of patatin-like phospholipase-3 (rs738409 C > G) polymorphism on fibrosis progression and steatosis in chronic hepatitis C. *Hepatology* 2011; 54: 60-69 [PMID: 21488075 DOI: 10.1002/hep.24350]
- 43 Trepo E, Guyot E, Ganne-Carrie N, Degre D, Gustot T, Franchimont D, Sutton A, Nahon P, Moreno C. PNPLA3 (rs738409 C > G) is a common risk variant associated with hepatocellular carcinoma in alcoholic cirrhosis. *Hepatology* 2012; 55: 1307-1308 [PMID: 22162034 DOI: 10.1002/hep.25518]
- 44 Li Q, Qu HQ, Rentfro AR, Grove ML, Mirza S, Lu Y, Hanis CL, Fallon MB, Boerwinkle E, Fisher-Hoch SP, McCormick JB. PNPLA3 polymorphisms and liver aminotransferase levels in a Mexican American population. *Clin Invest Med* 2012; 35: E237-E245 [PMID: 22863562]
- 45 Romeo S, Sentinelli F, Cambuli VM, Incani M, Congiu T, Matta V, Pilia S, Huang-Doran I, Cossu E, Loche S, Baroni MG. The 148M allele of the PNPLA3 gene is associated with indices of liver damage early in life. *J Hepatol* 2010; 53: 335-338 [PMID: 20546964 DOI: 10.1016/j.jhep.2010.02.034]
- 46 Santoro N, Kursawe R, D'Adamo E, Dykas DJ, Zhang CK, Bale AE, Calí AM, Narayan D, Shaw MM, Pierpont B, Savoye M, Lartaud D, Eldrich S, Cushman SW, Zhao H, Shulman GI, Caprio S. A common variant in the patatin-like phospholipase 3 gene (PNPLA3) is associated with fatty liver disease in obese children and adolescents. *Hepatology* 2010; 52: 1281-1290 [PMID: 20803499 DOI: 10.1002/hep.23832]
- 47 Valenti L, Al-Serri A, Daly AK, Galmozzi E, Rametta R, Dongiovanni P, Nobili V, Mozzi E, Roviario G, Vanni E, Bugianesi E, Maggioni M, Fracanzani AL, Fargion S, Day CP. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology* 2010; 51: 1209-1217 [PMID: 20373368 DOI: 10.1002/hep.23622]
- 48 Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology* 2011; 53: 1883-1894 [PMID: 21381068 DOI: 10.1002/hep.24283]
- 49 He S, McPhaul C, Li JZ, Garuti R, Kinch L, Grishin NV, Cohen JC, Hobbs HH. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. *J Biol Chem* 2010; 285: 6706-6715 [PMID: 20034933 DOI: 10.1074/jbc.M109.064501]
- 50 Basantani MK, Sitnick MT, Cai L, Brenner DS, Gardner NP, Li JZ, Schoiswohl G, Yang K, Kumari M, Gross RW, Zechner R, Kershaw EE. Pnpla3/Adiponutrin deficiency in mice does not contribute to fatty liver disease or metabolic syndrome. *J Lipid Res* 2011; 52: 318-329 [PMID: 21068004 DOI: 10.1194/jlr.M011205]
- 51 Kollerits B, Coassin S, Beckmann ND, Teumer A, Kiechl S, Döring A, Kavousi M, Hunt SC, Lamina C, Paulweber B, Kutalik Z, Nauck M, van Duijn CM, Heid IM, Willeit J, Brandstätter A, Adams TD, Mooser V, Aulchenko YS, Völzke H, Kronenberg F. Genetic evidence for a role of adiponutrin in the metabolism of apolipoprotein B-containing lipoproteins. *Hum Mol Genet* 2009; 18: 4669-4676 [PMID: 19729411 DOI: 10.1093/hmg/ddp424]

■同行评价

本文对ChREBP、PNPLA3两种蛋白的分子结构、功能和在脂肪肝的发生中的作用进行了综述,有一定的科学意义。

编辑 田滢 电编 闫晋利





Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-3177-9906

Telephone: +852-6555-7188

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1009-3079

