世界华人消化杂志 2013年10月18日; 21(29): 3067-3071
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

肝X受体与肝脏疾病

贺晓敏, 柳长柏

贺晓敏, 柳长柏, 三峡大学分子生物学研究所 湖北省宜昌市 443002
贺晓敏, 硕士, 主要从事基因治疗方向的研究.
国家自然科学基金资助项目, No. 81070348
作者贡献分布: 本文综述由贺晓敏完成; 柳长柏审校.
通讯作者: 柳长柏, 教授, 硕士生导师, 443002, 湖北省宜昌市西陵区大学路8号, 三峡大学分子生物学研究所. cbliu@ctgu.edu.cn
电话: 0717-6397179
收稿日期: 2013-06-28 修回日期: 2013-08-07
接受日期: 2013-08-29 在线出版日期: 2013-10-18

Liver X receptors and liver diseases

Xiao-Min He, Chang-Bai Liu

Xiao-Min He, Chang-Bai Liu, Institute of Molecular Biology, China Three Gorges University, Yichang 443002, Hubei Province, China
Supported by: National Natural Science Foundation of China, No. 81070348
Correspondence to: Chang-Bai Liu, Professor, Institute of Molecular Biology, China Three Gorges University, 8 Daxue Road, Xiling District, Yichang 443002, Hubei Province, China. cbliu@ctgu.edu.cn
Received: 2013-06-28 Revised: 2013-08-07
Accepted: 2013-08-29 Published online: 2013-10-18

Abstract
Liver X receptors (LXRs) are members of the nuclear receptor superfamily, which have important roles in cholesterol metabolism, glucose metabolism, lipid metabolism and inflammatory reactions. Although liver X receptors are expected to become targets for the treatment of liver fibrosis, nonalcoholic hepatitis, viral hepatitis and other liver diseases, they may lead to liver steatosis. Therefore, it is of great importance to understand the direct target genes of LXRs for regulation of cholesterol metabolism and inflammatory reactions and find specific LXRs agonists or antagonists.

Key Words: Liver X receptors; Hepatic lipogenesis; Liver fibrosis; Hepatitis

He XM, Liu CB. Liver X receptors and liver diseases. Shijie Huaren Xiaohua Zazhi 2013; 21(29): 3067-3071 URL: http://www.wjgnet.com/1009-3079/21/3067.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i29.3067

摘要
肝X受体(liver X receptors, LXRs)是核受体超家族的成员, 在胆固醇代谢、糖代谢、脂代谢和炎症反应的过程中发挥着重要作用, 有望成为非酒精性脂肪性肝炎、病毒性肝炎和肝纤维化等肝脏疾病的治疗靶点, 其不良反应则是可能导致肝脂肪病变. 因此, 了解LXRs调节胆固醇代谢及炎症反应的直接靶基因及其机制, 研发特异性的LXRs激动剂或拮抗剂, 对研究肝脏疾病及LXRs的临床应用将是很好的途径.

关键词: 肝X受体; 肝脏的脂肪生成; 肝纤维化; 肝炎

核心提示: 本文阐述了肝X受体(liver X receptors, LXRs)有望成为非酒精性脂肪性肝炎、病毒性肝炎和肝纤维化等肝脏疾病的治疗靶点的优势及可能导致肝脂肪病变的劣势, 为研发特异性的LXRs激动剂或拮抗剂及肝脏疾病的探讨提供了新思路.

贺晓敏, 柳长柏. 肝X受体与肝脏疾病. 世界华人消化杂志 2013; 21(29): 3067-3071 URL: http://www.wjgnet.com/1009-3079/21/3067.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i29.3067

0 引言
核受体是一组依赖配体激活的转录因子, 可对其靶基因的表达进行调节, 从而调控机体新陈代谢、发育、增殖和炎症反应[1]. 肝X受体(liver X receptors, LXRs)是核受体超家族成员之一, 需被氧化型的胆固醇或胆固醇生物合成途径中的一些中间代谢产物激活[2]. 随着细胞学、分子生物学等基础医学科学的发展和应用, 人们对LXR的研究和认识不断深入, 发现其在肝脏疾病中发挥着极其复杂的作用. 本文将就LXR与肝脏疾病关系的最新进展进行简要阐述.

■背景资料
本文简要阐述了肝X受体(liver X receptors, LXRs)与肝脏疾病关系的最新进展, 意在解读LXR对肝脏疾病的利弊, 探讨其存在的问题, 为肝病的治疗提供可能的发展方向.

■同行评议者
胡国信, 副教授, 主任医师, 南昌大学第一附属医院传染科; 李永翔, 教授, 主任医师, 博士生导师, 普外腔镜外科主任, 安徽医科大学第一附属医院普外科

■研发前沿
本文介绍的LXR对肝病有利有弊，目前着重于研究LXRs调节脂质代谢及炎症反应的直接靶基因及其机制，旨在研发特异性的LXRs激动剂或拮抗剂，使其应用于临床.

1 LXR的概况

LXR可分为两个亚型, 即: LXRα和LXRβ, 二者的DNA结合域和配体结合域有大约80%的氨基酸同源性. LXRα仅在脾脏、肝脏、脂肪组织、肠、肺、肾及巨噬细胞中有高表达, 而LXRβ则几乎在所有组织中都有表达[3]. 作为核受体家族的成员, LXRs由4个独立的区域组成: (1)氨基端配体非依赖的转录活化域; (2)具有两个锌指结构的DNA结合域; (3)缺乏配体时可招募共抑制物的铰链区;(4)羧基端疏水的配体结合域及转录活化域[4].

大量研究表明, 一些氧化的胆固醇衍生物是LXRs的天然激动剂, 包括22(R)-羟基胆甾醇、20(S)-羟基胆甾醇、24(S)-羟基胆甾醇、24(S), 25-环氧胆甾醇、27-羟基胆甾醇及胆固醇生物合成中的一些中间产物[5]. 此外, 一些来源于植物的复合物如植物固醇β谷甾醇以及D-葡萄糖和D-葡萄糖六磷酸[6]也可以活化LXRs. 除天然的激动剂之外, 一些合成和半合成的复合物也能激活LXRs, 例如T0901317和GW3965, 他们已广泛应用到对LXRs信号研究上, 但他们对LXR的亚型并没有选择性[7]. 最近有研究证实, 一些复合物可以特异性的结合到LXR的其中一个亚型上. 例如一些喹啉砜类化合物[8]、N,N-二甲基-3β-羟基-胆酰胺[9]和WAY-252623[10]已经被证实对LXRβ有更高的亲和力.

LXRs被天然或合成配体激活后, 可与视黄醇类X受体(retinoid X receptors, RXRs)形成异二聚体复合物, 进而结合到靶基因启动子区LXR反应元件(liver X receptor response element, LXRE)上, 从而诱导一系列与脂代谢和糖代谢相关的靶基因的表达. LXRE是一组被4个随机核苷酸分隔的核心序列为AGGTCA的正向重复序列[11].

LXRs是机体的胆固醇感应器[12]; 也是肝脏脂肪更新的关键调节因子[13]; 并反向调节巨噬细胞中炎症因子基因的表达, 例如抑制包括IL-6和单核细胞趋化蛋白-1(monocyte chemotactic protein 1, MCP-1)等一些炎症因子的产生[14]. 最近的研究还发现, LXRs具有调节免疫应答的能力, 应用其配体可减轻小鼠动脉粥样硬化和接触性皮炎, 抑制抗原刺激的T细胞增殖[15].

2 LXR与肝脏疾病

2.1 LXR与肝脏的脂肪生成 LXRs与肝脏的脂代谢密切相关, 可通过上调固醇调节元件结合蛋白(sterol regulatory element binding protein 1c, SREBP-1c)表达参与肝脏中脂肪酸的生物合成[16,17]. SREBP-1c的下游靶基因包括乙酰辅酶a羧化酶(acetyl CoA carboxylase, ACC)[18], 脂肪酸合成酶(fatty acid synthase, FAS)[19]和硬脂酰基-辅酶a脱氢酶(stearoyl-CoA desaturase 1, SCD1)[20], 这3个基因的启动子都含有功能性的LXREs, 而其表达直接被LXRs调节. 研究表明LXRα$^{-/-}$和LXRαβ$^{-/-}$(双基因敲除)小鼠的SREBP-1c及其靶基因, 包括FAS和SCD-1的表达都被下调, 使肝脏及血浆中的甘油三酯水平(triglyceride, TG)下降[21]; 而LXRβ$^{-/-}$小鼠体内SREBP-1c和脂肪生成相关基因的表达仍然正常, 说明LXR的两个亚型中, LXRα在肝脏脂肪生成的调节中发挥重要作用. 人工合成的LXRs激动剂T0901317可增加野生型小鼠和LXRβ$^{-/-}$小鼠肝脏ACC、FAS和SCD-1的表达, 但对LXRα$^{-/-}$或LXRαβ$^{-/-}$小鼠则无此作用. 类似的现象在特异性高表达肝脏LXRα和LXRα特异性配体的小鼠中也能观察到, 进一步证实了LXRα通过上调SREBP-1c的表达促进肝脂肪生成[22-24].

最新研究表明, 糖类调节元件结合蛋白(carbohydrate response element-binding protein, ChREBP)也是LXRs的直接靶基因, 他是葡萄糖敏感转录因子, 可将肝脏中过剩的糖类转化为脂质. *ChREBP*基因的启动子包含两个LXREs, 用T0901317处理野生型小鼠后可增加ChREBP的mRNA水平和蛋白活性, 脂肪生成相关基因ACC、FAS和SCD-1的表达也都被上调[25].

血管生成素类似蛋白3(angiopoietin like protein3, Angptl3)是肝脏中的一个蛋白, 可增加血浆中TG和高密度脂蛋白(high density lipoprotein, HDL)、胆固醇水平. 最近的研究发现, Angptl3可增加肥胖/糖尿病小鼠模型和野生型小鼠血浆中的TG水平, 且Angptl3是LXR的一个直接的靶基因, 其激动剂T0901317处理Angptl3$^{-/-}$小鼠并不能增加血浆中的TG水平[26].

Zhou等[23]发现在脂肪酸转移酶(fatty acid transferase, FAT)/CD36的启动子区域有功能性的LXREs, 并证实LXR配体可诱导其表达. T0901317处理FAT/CD36$^{-/-}$小鼠时, 肝脂肪性变减轻, 脂肪生成减少.

又有研究指出LXR可能通过促进肝脏中低密度脂蛋白-甘油三酯积累, 也可能通过磷脂转运蛋白(phospholipid transfer protein, PLTP)促进中低密度脂蛋白的分泌引起高甘油三酯血症[27].

T0901317处理野生型小鼠可上调PLTP的蛋白表达及活性[28].

以上研究都表明, LXRs可通过结合LXREs上调SREBP-1c、ChREBP、Angptl3及其下游相关功能蛋白的表达, 导致高甘油三酯血症和肝脂肪病变, 甚至脂肪肝的形成.

2.2 LXR与肝炎 LXRs参与调节胆固醇代谢[29]和炎症反应[30], 与非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)的发病密切相关[31]. 研究表明LXRs的活化可促进胆固醇的逆向转运, 增加肝脏内胆汁酸合成过程中的限速酶的转录, 促进胆固醇转变为胆汁酸[32], 加速低密度脂蛋白受体(low density lipoprotein receptor, LDLR)的降解, 从而减少肝细胞内胆固醇的摄取[33], 调节胆固醇代谢. 此外, 研究还显示体外培养的巨噬细胞经细菌感染或脂多糖刺激后, LXRs的活化可抑制一些炎性因子的表达[34]. 用LXRs激动剂GW3965刺激大鼠原代肝巨噬细胞可通过抑制肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)的表达，从而减轻肝脏炎症[35]. 胆固醇代谢失衡及肝脏内大量游离脂肪酸的堆积将加速NASH的病理进程[36], 研究表明过量饮食胆固醇会加重高脂模型小鼠的肝脏炎症, 而LXRs的活化可减轻肝脏炎症, 也会减少肝脏中胆固醇的积累[37,38]. 因此, LXRs的活化可能有抑制NASH的作用.

除NASH外, LXRs也参与了病毒性肝炎的病理进程. HBx是乙型肝炎病毒(hepatitis B virus, HBV)基因组编码的一种蛋白, 能增强HBV前基因组的转录及HBV的复制[39]. 研究证明HBx可通过活化LXRα诱导脂肪生成因子SREBP1和FAS的表达[40]. 进一步研究还证实LXRα可以介导伴随HBV感染的肝脂肪性变等疾病, 其机制正是由于HBx与LXRα相互作用, 增强LXRα的表达与活性, 细胞内脂质积累, 造成肝脏代谢的紊乱, 引起肝炎等疾病[41]. 由此可见, LXRα促进了HBV感染所致的肝脏疾病.

研究发现, LXRs也可能抑制丙型肝炎病毒(hepatitis C Virus, HCV)的感染. Agnello等[42], Monazahian等[43]证实LDLR对HCV进入细胞是必需的. HCV会与极低密度脂蛋白(very low density lipoprotein, VLDL)形成复合物, VLDL在脂蛋白脂肪酶的作用下变成中等密度脂蛋白(intermediate density lipoprotein, IDL)、低密度脂蛋白(low density lipoprotein, LDL), 而IDL或LDL与HCV形成的复合物可以被肝细胞膜上的LDLR识别, 并进而摄取进入细胞. Zelcer等[33]研究表明E3泛素连接酶(Inducible degrader of the low-density lipoprotein receptor, IDOL)是LXRs的靶基因, 他可在转录后水平调节LDLR的表达, 促进LDLR的降解. 最近Zeng等[44]研究也证实LXRs内源性和外源性激动剂都可上调IDOL的表达, 进一步促使LDLR的降解, 显著的抑制了HCV的感染.

2.3 LXRs与肝纤维化 肝星状细胞(hepatic stellate cell, HSC)位于肝窦内皮细胞与肝细胞之间的狄氏间隙内, 在肝纤维化进程中起着关键作用[45]. 静止的HSC富含视黄酯、甘油三酯类和胆固醇酯, 并表达许多脂肪生成相关转录因子和脂肪生物合成因子[46]. 肝损伤后, HSC被活化转分化成肌成纤维细胞(myofibroblastic, MFB), 并表达Ⅰ型胶原和α-平滑肌肌动蛋白(α-Smooth muscle actin, α-SMA)等标志蛋白, 丧失视黄酯和脂滴储存能力; 同时一些脂肪合成相关转录因子表达降低, 与肝纤维化密切相关[47,48].

Beaven等[49]用LXRs激动剂处理野生型及LXRαβ$^{-/-}$小鼠HSC时发现, LXRs活化可抑制野生型小鼠HSC中Ⅰ型胶原、α-SMA和一些促炎因子的表达, 以及MFB形成和肝纤维化的发生, 而在LXRαβ$^{-/-}$小鼠HSC中则无此现象. 研究还发现, LXRs的活化可诱导活化的HSC逆转为静止细胞; 且LXRαβ$^{-/-}$小鼠更易导致肝纤维化. 表明LXRs有可通过抑制HSC的活化达到抗肝纤维化效应.

3 结论

由于具有促进肝脏内胆固醇的清除, 缓解炎症反应, 减轻NASH; 抑制HSC的活化; 促进LDLR降解, 抑制HCV进入细胞等特征, LXRs有望作为一些肝病的治疗靶点. 然而LXRs的活化可上调脂肪生成基因的表达, 导致肝脂肪病变. 因此, 未来研究应该着重于揭示LXRs调节胆固醇代谢及炎症反应的直接靶基因及其机制, 研发特异性的LXRs激动剂或拮抗剂, 避免LXRs诱导的肝脂肪病变. SR9238是一种新的人工合成LXR反式激动剂, 可有效抑制肝脏的脂肪生成、炎症反应及肝脏脂质积累, 但会抑制血浆内胆固醇的水平[50]. 因此还有待进一步开发LXRs选择性激动剂或拮抗剂并探讨其在治疗肝病中的应用.

4 参考文献

1 Müllenbach R, Weber SN, Lammert F. Nuclear receptor variants in liver disease. *J Lipids* 2012;

■相关报道

LXRs激动剂或拮抗剂的研发很值得期待, Griffett人工合成的LXRs激动剂SR9238可有效抑制肝脏的脂肪生成及炎症反应，这令人很惊喜, 但其可能抑制血浆内胆固醇的水平, 因此还有待进一步开发LXRs选择性激动剂或拮抗剂.

■创新盘点

本文全面总结了LXR对肝脏疾病的利弊, 旨在为其激动剂或拮抗剂的研发及临床应用提供新的思路.

2012: 934707 [PMID: 22523693 DOI: 10.1016/j.cell.2010.09.032.]

2 Geyeregger R, Zeyda M, Stulnig TM. Liver X receptors in cardiovascular and metabolic disease. *Cell Mol Life Sci* 2006; 63: 524-539 [PMID: 16389454]

3 Wójcicka G, Jamroz-Wiśniewska A, Horoszewicz K, Bełtowski J. Liver X receptors (LXRs). Part I: structure, function, regulation of activity, and role in lipid metabolism. *Postepy Hig Med Dosw* (Online) 2007; 61: 736-759 [PMID: 18063918]

4 Lee JH, Zhou J, Xie W. PXR and LXR in hepatic steatosis: a new dog and an old dog with new tricks. *Mol Pharm* 2008; 5: 60-66 [PMID: 18072748]

5 Janowski BA, Grogan MJ, Jones SA, Wisely GB, Kliewer SA, Corey EJ, Mangelsdorf DJ. Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta. *Proc Natl Acad Sci U S A* 1999; 96: 266-271 [PMID: 9874807]

6 Mitro N, Mak PA, Vargas L, Godio C, Hampton E, Molteni V, Kreusch A, Saez E. The nuclear receptor LXR is a glucose sensor. *Nature* 2007; 445: 219-223 [PMID: 17187055]

7 Ohkoshi N, Shoji S. Reversible ageusia induced by losartan: a case report. *Eur J Neurol* 2002; 9: 315 [PMID: 11985643]

8 Bernotas RC, Singhaus RR, Kaufman DH, Travins JM, Ullrich JW, Unwalla R, Quinet E, Evans M, Nambi P, Olland A, Kauppi B, Wilhelmsson A, Goos-Nilsson A, Wrobel J. 4-(3-Aryloxyaryl)quinoline sulfones are potent liver X receptor agonists. *Bioorg Med Chem Lett* 2010; 20: 209-212 [PMID: 19932617 DOI: 10.1016/j.bmcl.2009.10.132]

9 Kratzer A, Buchebner M, Pfeifer T, Becker TM, Uray G, Miyazaki M, Miyazaki-Anzai S, Ebner B, Chandak PG, Kadam RS, Calayir E, Rathke N, Ahammer H, Radovic B, Trauner M, Hoefler G, Kompella UB, Fauler G, Levi M, Levak-Frank S, Kostner GM, Kratky D. Synthetic LXR agonist attenuates plaque formation in apoE-/- mice without inducing liver steatosis and hypertriglyceridemia. *J Lipid Res* 2009; 50: 312-326 [PMID: 18812595 DOI: 10.1194/jlr.M800376-JLR200]

10 Hu B, Unwalla RJ, Goljer I, Jetter JW, Quinet EM, Berrodin TJ, Basso MD, Feingold IB, Nilsson AG, Wilhelmsson A, Evans MJ, Wrobel JE. Identification of phenylsulfone-substituted quinoxaline (WYE-672) as a tissue selective liver X-receptor (LXR) agonist. *J Med Chem* 2010; 53: 3296-3304 [PMID: 20350005 DOI: 10.1021/jm100034x]

11 艾正琳, 陈东风, 王晓敏. 肝X受体的研究进展. 世界华人消化杂志 2005; 13: 2013-2015

12 Zhao C, Dahlman-Wright K. Liver X receptor in cholesterol metabolism. *J Endocrinol* 2010; 204: 233-240 [PMID: 19837721 DOI: 10.1677/JOE-09-0271]

13 Schultz JR, Tu H, Luk A, Repa JJ, Medina JC, Li L, Schwendner S, Wang S, Thoolen M, Mangelsdorf DJ, Lustig KD, Shan B. Role of LXRs in control of lipogenesis. *Genes Dev* 2000; 14: 2831-2838 [PMID: 11090131]

14 Myhre AE, Agren J, Dahle MK, Tamburstuen MV, Lyngstadaas SP, Collins AJ, Foster SJ, Thiemermann C, Aasen AO, Wang JE. Liver X receptor is a key regulator of cytokine release in human monocytes. *Shock* 2008; 29: 468-474 [PMID: 17724434]

15 Pascual-García M, Valledor AF. Biological roles of liver X receptors in immune cells. *Arch Immunol Ther Exp* (Warsz) 2012; 60: 235-249 [PMID: 22696047 DOI: 10.1152/physrev.00004.2011]

16 Higuchi N, Kato M, Shundo Y, Tajiri H, Tanaka M, Yamashita N, Kohjima M, Kotoh K, Nakamuta M, Takayanagi R, Enjoji M. Liver X receptor in cooperation with SREBP-1c is a major lipid synthesis regulator in nonalcoholic fatty liver disease. *Hepatol Res* 2008; 38: 1122-1129 [PMID: 18684130 DOI: 10.1111/j.1872-034X.2008.00382.x]

17 Fang DL, Wan Y, Shen W, Cao J, Sun ZX, Yu HH, Zhang Q, Cheng WH, Chen J, Ning B. Endoplasmic reticulum stress leads to lipid accumulation through upregulation of SREBP-1c in normal hepatic and hepatoma cells. *Mol Cell Biochem* 2013; 381: 127-137 [PMID: 23703028 DOI: 10.1007/s11010-013-1694-7]

18 Talukdar S, Hillgartner FB. The mechanism mediating the activation of acetyl-coenzyme A carboxylase-alpha gene transcription by the liver X receptor agonist T0-901317. *J Lipid Res* 2006; 47: 2451-2461 [PMID: 16931873]

19 Joseph SB, Laffitte BA, Patel PH, Watson MA, Matsukuma KE, Walczak R, Collins JL, Osborne TF, Tontonoz P. Direct and indirect mechanisms for regulation of fatty acid synthase gene expression by liver X receptors. *J Biol Chem* 2002; 277: 11019-11025 [PMID: 11790787]

20 Chu K, Miyazaki M, Man WC, Ntambi JM. Stearoyl-coenzyme A desaturase 1 deficiency protects against hypertriglyceridemia and increases plasma high-density lipoprotein cholesterol induced by liver X receptor activation. *Mol Cell Biol* 2006; 26: 6786-6798 [PMID: 16943421]

21 Repa JJ, Liang G, Ou J, Bashmakov Y, Lobaccaro JM, Shimomura I, Shan B, Brown MS, Goldstein JL, Mangelsdorf DJ. Regulation of mouse sterol regulatory element-binding protein-1c gene (SREBP-1c) by oxysterol receptors, LXRalpha and LXRbeta. *Genes Dev* 2000; 14: 2819-2830 [PMID: 11090130]

22 Lund EG, Peterson LB, Adams AD, Lam MH, Burton CA, Chin J, Guo Q, Huang S, Latham M, Lopez JC, Menke JG, Milot DP, Mitnaul LJ, Rex-Rabe SE, Rosa RL, Tian JY, Wright SD, Sparrow CP. Different roles of liver X receptor alpha and beta in lipid metabolism: effects of an alpha-selective and a dual agonist in mice deficient in each subtype. *Biochem Pharmacol* 2006; 71: 453-463 [PMID: 16325781]

23 Zhou J, Febbraio M, Wada T, Zhai Y, Kuruba R, He J, Lee JH, Khadem S, Ren S, Li S, Silverstein RL, Xie W. Hepatic fatty acid transporter Cd36 is a common target of LXR, PXR, and PPARgamma in promoting steatosis. *Gastroenterology* 2008; 134: 556-567 [PMID: 18242221 DOI: 10.1053/j.gastro.2007.11.037]

24 Ferré P, Foufelle F. SREBP-1c transcription factor and lipid homeostasis: clinical perspective. *Horm Res* 2007; 68: 72-82 [PMID: 17344645]

25 Cha JY, Repa JJ. The liver X receptor (LXR) and hepatic lipogenesis. The carbohydrate-response element-binding protein is a target gene of LXR. *J Biol Chem* 2007; 282: 743-751 [PMID: 17107947]

26 Shimizugawa T, Ono M, Shimamura M, Yoshida K, Ando Y, Koishi R, Ueda K, Inaba T, Minekura H, Kohama T, Furukawa H. ANGPTL3 decreases very low density lipoprotein triglyceride clearance by inhibition of lipoprotein lipase. *J Biol Chem* 2002; 277: 33742-33748 [PMID: 12097324]

27 Grefhorst A, Elzinga BM, Voshol PJ, Plösch T, Kok T, Bloks VW, van der Sluijs FH, Havekes LM, Romijn

JA, Verkade HJ, Kuipers F. Stimulation of lipogenesis by pharmacological activation of the liver X receptor leads to production of large, triglyceride-rich very low density lipoprotein particles. *J Biol Chem* 2002; 277: 34182-34190 [PMID: 12097330]
28 Cao G, Beyer TP, Yang XP, Schmidt RJ, Zhang Y, Bensch WR, Kauffman RF, Gao H, Ryan TP, Liang Y, Eacho PI, Jiang XC. Phospholipid transfer protein is regulated by liver X receptors in vivo. *J Biol Chem* 2002; 277: 39561-39565 [PMID: 12177004]
29 de Boussac H, Pommier AJ, Dufour J, Trousson A, Caira F, Volle DH, Baron S, Lobaccaro JM. LXR, prostate cancer and cholesterol: the Good, the Bad and the Ugly. *Am J Cancer Res* 2013; 3: 58-69 [PMID: 23359865]
30 Steffensen KR, Jakobsson T, Gustafsson JÅ. Targeting liver X receptors in inflammation. *Expert Opin Ther Targets* 2013; 17: 977-990 [PMID: 23738533 DOI: 10.1517/14728222.2013.806490]
31 Musso G, Gambino R, Cassader M. Cholesterol metabolism and the pathogenesis of non-alcoholic steatohepatitis. *Prog Lipid Res* 2013; 52: 175-191 [PMID: 23206728 DOI: 10.1016/j.plipres.2012.11.002]
32 Naik SU, Wang X, Da Silva JS, Jaye M, Macphee CH, Reilly MP, Billheimer JT, Rothblat GH, Rader DJ. Pharmacological activation of liver X receptors promotes reverse cholesterol transport in vivo. *Circulation* 2006; 113: 90-97 [PMID: 16365197]
33 Zelcer N, Hong C, Boyadjian R, Tontonoz P. LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. *Science* 2009; 325: 100-104 [PMID: 19520913 DOI: 10.1126/science.1168974]
34 Hong C, Tontonoz P. Coordination of inflammation and metabolism by PPAR and LXR nuclear receptors. *Curr Opin Genet Dev* 2008; 18: 461-467 [PMID: 18782619 DOI: 10.1016/j.gde.2008.07]
35 Wang YY, Dahle MK, Steffensen KR, Reinholt FP, Collins JL, Thiemermann C, Aasen AO, Gustafsson JA, Wang JE. Liver X receptor agonist GW3965 dose-dependently regulates lps-mediated liver injury and modulates posttranscriptional TNF-alpha production and p38 mitogen-activated protein kinase activation in liver macrophages. *Shock* 2009; 32: 548-553 [PMID: 19295476 DOI: 10.1097/SHK.0b013e3181a47f85]
36 吴涛, 季光. 非酒精性脂肪性肝病的代谢发病机制. 世界华人消化杂志 2009; 17: 2908-2914
37 Wouters K, van Bilsen M, van Gorp PJ, Bieghs V, Lütjohann D, Kerksiek A, Staels B, Hofker MH, Shiri-Sverdlov R. Intrahepatic cholesterol influences progression, inhibition and reversal of non-alcoholic steatohepatitis in hyperlipidemic mice. *FEBS Lett* 2010; 584: 1001-1005 [PMID: 20114046 DOI: 10.1016/j.febslet.2010.01.046.]
38 陈洁, 郑瑞丹, 徐成润, 伍伟平. LXRα在大鼠非酒精性脂肪肝组织中的表达及其意义. 中华实验和临床病毒学杂志 2009; 4: 265-268
39 Murakami S. Hepatitis B virus X protein: a multifunctional viral regulator. *J Gastroenterol* 2001; 36: 651-660 [PMID: 11686474]
40 Kim K, Kim KH, Kim HH, Cheong J. Hepatitis B virus X protein induces lipogenic transcription factor SREBP1 and fatty acid synthase through the activation of nuclear receptor LXRalpha. *Biochem J* 2008; 416: 219-230 [PMID: 18782084 DOI: 10.1042/BJ20081336]
41 Na TY, Shin YK, Roh KJ, Kang SA, Hong I, Oh SJ, Seong JK, Park CK, Choi YL, Lee MO. Liver X receptor mediates hepatitis B virus X protein-induced lipogenesis in hepatitis B virus-associated hepatocellular carcinoma. *Hepatology* 2009; 49: 1122-1131 [PMID: 19105208 DOI: 10.1002/hep.22740]
42 Agnello V, Abel G, Elfahal M, Knight GB, Zhang QX. Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. *Proc Natl Acad Sci U S A* 1999; 96: 12766-12771 [PMID: 10535997]
43 Monazahian M, Böhme I, Bonk S, Koch A, Scholz C, Grethe S, Thomssen R. Low density lipoprotein receptor as a candidate receptor for hepatitis C virus. *J Med Virol* 1999; 57: 223-229 [PMID: 10022791]
44 Zeng J, Wu Y, Liao Q, Li L, Chen X, Chen X. Liver X receptors agonists impede hepatitis C virus infection in an Idol-dependent manner. *Antiviral Res* 2012; 95: 245-256 [PMID: 22713431 DOI: 10.1016/j.antiviral.2012.06.004]
45 高润平, 齐晓艳. 肝纤维化的发生机制与治疗进展. 世界华人消化杂志 2006; 14: 2263-2269
46 Tacke F, Weiskirchen R. Update on hepatic stellate cells: pathogenic role in liver fibrosis and novel isolation techniques. *Expert Rev Gastroenterol Hepatol* 2012; 6: 67-80 [PMID: 22149583 DOI: 10.1586/egh.11.92]
47 Blaner WS, O'Byrne SM, Wongsiriroj N, Kluwe J, D'Ambrosio DM, Jiang H, Schwabe RF, Hillman EM, Piantedosi R, Libien J. Hepatic stellate cell lipid droplets: a specialized lipid droplet for retinoid storage. *Biochim Biophys Acta* 2009; 1791: 467-473 [PMID: 19071229 DOI: 10.1016/j.bbalip.2008.11.001]
48 Tsukamoto H, Zhu NL, Asahina K, Mann DA, Mann J. Epigenetic cell fate regulation of hepatic stellate cells. *Hepatol Res* 2011; 41: 675-682 [PMID: 21504520 DOI: 10.1111/j.1872-034X.2011.00804.x]
49 Beaven SW, Wroblewski K, Wang J, Hong C, Bensinger S, Tsukamoto H, Tontonoz P. Liver X receptor signaling is a determinant of stellate cell activation and susceptibility to fibrotic liver disease. *Gastroenterology* 2011; 140: 1052-1062 [PMID: 21134374 DOI: 10.1053/j.gastro.2010.11.053]
50 Griffett K, Solt LA, El-Gendy Bel-D, Kamenecka TM, Burris TP. A liver-selective LXR inverse agonist that suppresses hepatic steatosis. *ACS Chem Biol* 2013; 8: 559-567 [PMID: 23237488 DOI: 10.1021/cb300541g]

■同行评价
本文内容较新颖, 条理较清晰, 有一定指导意义.

编辑 田滢 电编 鲁亚静