PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 June 21; 13(23): 3159-3163
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Metabolism of high density lipoproteins in liver cancer

Jing-Ting Jiang, Ning Xu, Chang-Ping Wu

Jing-Ting Jiang, Chang-Ping Wu, Department of Tumor Biological Treatment, the Third Affiliated Hospital of Suzhou University, Changzhou 213003, Jiangsu Province, China
Ning Xu, Section of Clinical Chemistry & Pharmacology, Lund University S-221 85 Lund, Sweden
Correspondence to: Jing-Ting Jiang, Department of Tumor Biological Treatment, the Third Affiliated Hospital of Suzhou University, Changzhou 213003, Jiangsu Province, China. jjtnew@163.com
Telephone: +86-519-6180978 Fax: +86-519-6621235
Received: 2007-04-10 Accepted: 2007-05-12

Abstract

Liver plays a vital role in the production and catabolism of plasma lipoproteins. It depends on the integrity of cellular function of liver, which ensures homeostasis of lipid and lipoprotein metabolism. When liver cancer occurs these processes are impaired and high-density lipoproteins are changed.

Key words: High density lipoproteins; Metabolism; Liver cancer

Jiang JT, Xu N, Wu CP. Metabolism of high density lipoproteins in liver cancer. *World J Gastroenterol* 2007; 13(23): 3159-3163

http://www.wjgnet.com/1007-9327/13/3159.asp

INTRODUCTION

Liver cancer is often followed procession of chronic hepatitis or cirrhosis, therefore hepatic function is damaged obviously on these bases, which may significantly influence lipid and lipoprotein metabolism *in vivo*[1,2]. In this review we summarized the high density lipoproteins (HDL) metabolism in liver cancer.

Biologic character and physiological functions of HDL

HDL are a heterogeneous mixture of spherical macromolecules which differ in size (80-120A), and chemical composition (apolipoprotein A- I , apolipoprotein A- Ⅱ)[3]. ApoA- I is present on the majority of HDL particles and constitutes 70% of the apolipoprotein content of HDL particles[4], It is involved in the metabolic interconversions that occur as a result of cholesteryl ester transfer protein (CETP), lecithin: cholesterol acyltransferase (LCAT) and lipase activities and their role in the formation of mature HDL and in reverse cholesterol transport[5]. And Kunitake *et al*[6] reported that the pre-beta sub-population can be observed directly in fresh plasma by immunoelectrophoresis. It contains phospholipid and free and esterified cholesterol. But, protein constitutes 90% of its mass, and the protein moiety of this subpopulation exhibits markedly lower helicity than that of high density lipoproteins isolated by ultracentrifugation. It was utilized gelose gradient polyacrylamide gel and divided α-HDL to HDL_{2a}, HDL_{2b} and HDL_3[7], also in association with a few molecules of sphingomyelin and phosphatidylcholine, β-HDL was divided β_1-, pre β_2- and pre β_3-HDL[8-11].

The majority of the HDL particles contain apoA-I. Differences in the quantitative and qualitative content of lipids, apolipoproteins, enzymes, and lipid transfer proteins result in the presence of various HDL subclasses, which are characterized by differences in shape, density, size, charge, and antigenicity[7]. It is accepted that a low level of HDL cholesterol is an important cardiovascular risk factor[12]. Also, the liver is a major source of the plasma lipoproteins[4]. These data indicate that the putative primary site of human HDL synthesis is in the liver[13,14]. Epidemiological studies have shown that obesity is a risk factor for hepatocellular carcinoma[15].

Metabolism of HDL in liver

It is a relative balance in metabolism of cholesterol and lipoprotein under normal liver function, it was influence of metabolism in lipoprotein with liver disease[16], and an impaired lipid metabolism is often found in patients with chronic liver diseases[17]. HL activity is suppressed by estradiol and increased by testosterone[18,19], estradiol to advance in liver cancer, but testicular hormone secrete ability is depressed, it was confirmed that transgenic overexpression of HL in either mice or rabbits decreased HDL-C levels[20, 21].

In addition, in the hepatocellular metabolism of long-chain fatty acids suggest that increased fatty acid oxidation by way of extra mitochondrial pathways results in a corresponding increase in the generation of hydrogen peroxide, thus, oxidative stress leads to alterations in gene expression and in DNA itself, which may also contribute to nonneoplastic liver injury and to tumorigenesis in other tissues[22]. As a result of lipid peroxidation probably play significant roles in clonal expansion and hepatocellular carcinoma progression[15]. Liver cancer is frequent malignant tumor, most of them based liver cirrhosis, and hepatic function was damaged obviously, analysis of the

cholesterol (Chol) and triglyceride (TG) fractions. Liver diseases were classified into chronic hepatitis (CH), liver cirrhosis (LC), hepatocellular carcinoma (HCC), and metastatic liver cancer, and each fraction was compared among these diseases. Metastatic liver cancer showed a lower HDL-fraction level, but higher levels of the other parameters than HCC. the HDL fraction level in HCC and metastatic liver cancer, and the LDL level in LC and metastatic liver cancer differed between survivors and patients who died. Lipid analysis in liver diseases by this method showed results reflecting the pathologic conditions and may be clinically useful[23].

Metabolism of reverse cholesterol transport of HDL in liver cancer

Reverse cholesterol transport (RCT) is a pathway transporting cholesterol from extrahepatic cells and tissues to the liver, and perhaps intestine, for excretion. That antiport process is determined at least partially by the HDL concentration in the blood[24], uptake of cholesterol from cells by specific acceptors, esterification of cholesterol within HDL by LCAT transfer of cholesterol to the apoB-containing lipoproteins (cholesterol transfer); remodeling of HDL and uptake of HDL cholesterol by the liver and possibly also by kidney and small intestine through lipoprotein receptors[9]. CETP is an important determinant of lipoprotein function, especially high density lipoprotein metabolism, and contributes to the regulation of plasma HDL levels[25]. So high density lipoprotein plays a key role in the reverse cholesterol transport pathway in liver[26,27].

The liver contributes free cholesterol to the plasma lipoproteins which participate in the process of reverse-cholesterol transport. But when cells were incubated with equivalent concentrations of isolated lipoproteins, HDL was much more effective in promoting [14C] cholesterol efflux than LDL, suggesting that unesterified cholesterol is initially transferred to HDL and then to LDL[28]. Serum concentrations of apolipoprotein A- I and A-Ⅱ were determined in patients with hepatic metastases of colorectal cancer, with primary liver cancer and with cirrhosis. In all three liver diseases, the HDL fraction and apolipoproteins A- I and A-Ⅱ showed significantly low values[29]. To establish whether there is any significant relationship between high-density lipoprotein cholesterol concentrations and biopsy-documented liver disease, 169 patients had needle biopsies, serum cholesterol, and HDLC evaluated. In both men and women, HDLC decreased strikingly and significantly in acute alcoholic hepatitis and in acute viral hepatitis, compared to controls. Men and women with inactive alcoholic liver disease and chronic active hepatitis showed moderate decreased in HDLC. Patients with primary and metastatic hepatic neoplasms also had strikingly decreased HDLC[30].

Cell surface receptor influence HDL metabolism in liver cancer

Hepatoma cell lines serve as a suitable model for the study of hepatic receptors for lipoprotein in man[31]. The experiments also demonstrate that the responses at least of some of the receptors of the hepatoma cells in culture resemble those of hepatocytes *in vivo* and in *vitro*[32].

The importance of hepatic apolipoprotein (apo) E in lipoprotein metabolism is evidenced by the fact that the level of apoE expression determines the fate of LDL and HDL3[33]. Although studies in recombinant cells indicate that scavenger receptor class B, type I (SR-BI) can promote cholesterol efflux, investigations in transgenic mice overexpressing or deficient in SR-BI support its physiological function as selectively sequestering cholesteryl esters from high density lipoproteins[34].

Impaired capacity of acute-phase high density lipoprotein particles to deliver cholesteryl ester to the hepatoma cell line[35] suggest that plasma high-density lipoproteins are cleared from the circulation by specific receptors and are either totally degraded or their cholesteryl esters are selectively, delivered to cells by receptors such as the scavenger receptor class B type I (SR-BI)[36]. The fact that the capacity for cellular cholesterol efflux from HUH-7 cells is slightly impaired by AP-HDL (compared with HDL) is supports the concept that scavenger receptor class B, type I (SR-BI), of the human hepatoma cell line, increased HDL binding with cholesterol loading that was specific for HDL3, and hepatic tissue can modulate its recognition of HDL. Hepatic membranes from a patient lacking normal hepatic LDL receptors bound apo A-I HDL normally. These data indicate that a saturable, specific regulatable receptor for apo E-free HDL is present in human liver[37].

Lipids or proteins of α-HDL are removed from the circulation by at least 2 direct pathways, which involve the selective uptake of lipids by scavenger receptor B1 (SR-BI) and the holoparticle uptake by apoE or apoA- I receptors[38-41]. ApoE-containing HDLs, which constitute the minority of HDLs, are internalized by hepatic apoE receptors (LDL receptor and LDL receptor-related protein)[42]. Tall and colleagues have suggested the presence of a hepatic leptin-regulated HDL receptor, which regulates HDL-C levels by mediating holoparticle uptake into liver cells[43].

Adjustment of hepatic lipase to HDL in liver cancer

HDL plays a key role in the lipids of binding and delivery, and is a key enzyme in lipoprotein adjustment. Hepatic lipase (HL) hydrolyzes phospholipids and triglycerides in all lipoprotein classes[44,45]. HL is a lipolytic enzyme involved in the metabolism of plasma lipoproteins, especially HDLs[46].

Genetic factors have been shown to play an important role in determining interindividual variation in plasma HDL-C levels[47]. HL may hydrolyze phospholipids of surface layers from HDL and plasma membrane and thereby enable the flux of cholesteryl esters from the lipoprotein core into the plasma membrane[48,49].

It is important role of hepatic triacylglycerol lipase (H-TGL) in promoting the liver uptake of HDL free and esterified cholesterol[50]. But hepatic lipase can enhance the delivery of high-density lipoprotein cholesterol to cells by a process which does not involve apoprotein catabolism[51]. Hepatic lipase (HL) gene transcription is almost exclusively limited to hepatocytes[52]. Hepatic lipase mediates an

increase in selective uptake of high-density lipoprotein-associated cholesteryl esters[53]. Approximately 28% of the HDL phosphatidylcholine was hydrolyzed by the hepatic lipase. The stimulation of free cholesterol delivery was dose-dependent up to a level of 100 micrograms of HDL free cholesterol/ml of extracellular medium, and was directly related to the extent of phosphatidylcholine hydrolysis. The enhanced cellular accumulation of HDL free cholesterol observed with hepatic lipase appears to be due to the phospholipase activity of this enzyme[54].

Hepatic lipase stimulates the internalization of apoprotein (apo) B-containing lipoproteins by hepatocytes independent from lipolysis. In this study, the role of HL in the hepatic metabolism of apo A-I-containing lipoproteins, i.e. HDL, was investigated. To explore the role of these molecules for the HL effect on selective CE uptake, hepatoma cells were depleted of proteoglycans or Chinese hamster ovary (CHO) cells deficient in proteoglycan synthesis were used. Proteoglycan-deficiency reduced the HL-mediated increase in selective uptake by more than 80%[53].

The inverse correlation between HL activity and HDL-C[55], is due to hepatic lipase stimulation of the uptake of high density lipoprotein cholesterol by hepatoma cells[54]. Hepatoma cells exposed to hepatic lipase-modified HDL, showed an increased uptake of HDL free cholesterol relative to cells exposed to control HDL[30].

Regulation HDL in liver cancer by protein kinase

Protien kinase C is a key molecule in signal transduction pathway, and significant control role in cell growth and deterioration[56]. It plays an important role in many of HDL effects on cells[57]. There is close correlation between carcinogenesis in liver and abnormalities in PKC-α abnormality expression[58,59]. HDL receptor-mediated translocation and efflux of intracellular cholesterol occurs through activation of protein kinase C[60]. Activation of protein kinase C enhances and inhibition of PKC suppresses apolipoprotein-mediated cholesterol efflux[60,61]. High density lipoprotein stimulates multiple signaling pathways. HDL-induced activation of the mitogen-activated protein kinase (MAPK) pathway can be mediated by protein kinase C[62], and high expression in liver tissue[56].

PROSPECT

The liver plays a vital role in the production and clearance of a large number of lipoproteins and is an important determinant of the plasma levels of various lipids[63]. Lipid analysis in liver diseases by this method showed results reflecting the pathologic conditions and may be clinically useful[23]. It may be a good indicator of the hepatic protein synthetic ability during the perioperative period after hepatectomy[64]. Drinking instant coffee powder, in addition to increased uptake HDL-cholesterol, resulted in amelioration of abnormal lipoprotein profiles occurred in hepatoma-bearing rats and has the ability to induce cell cycle arrest and apoptosis in hepatoma cells and to suppress tumor cell invasion. It could also exhibit these effects that lead to the inhibition of tumor growth and metastases[65]. High density lipoprotein as a potential carrier for delivery of a lipophilic antitumoral drug into hepatoma cells[66], to supply a new treatment method in liver cancer.

REFERENCES

1 **Jiang J**, Nilsson-Ehle P, Xu N. Influence of liver cancer on lipid and lipoprotein metabolism. *Lipids Health Dis* 2006; **5**: 4
2 **Tietge UJ**, Boker KH, Bahr MJ, Weinberg S, Pichlmayr R, Schmidt HH, Manns MP. Lipid parameters predicting liver function in patients with cirrhosis and after liver transplantation. *Hepatogastroenterology* 1998; **45**: 2255-2260
3 **Assmann G**, Schriewer H. HDL cholesterol: biochemical aspects (author's transl). *Klin Wochenschr* 1980; **58**: 749-756
4 **Lewis GF**, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res* 2005; **96**: 1221-1232
5 **Skinner ER**. High-density lipoprotein subclasses. *Curr Opin Lipidol* 1994; **5**: 241-247
6 **Kunitake ST**, La Sala KJ, Kane JP. Apolipoprotein A-I-containing lipoproteins with pre-beta electrophoretic mobility. *J Lipid Res* 1985; **26**: 549-555
7 **von Eckardstein A**, Huang Y, Assmann G. Physiological role and clinical relevance of high-density lipoprotein subclasses. *Curr Opin Lipidol* 1994; **5**: 404-416
8 **Barrans A**, Jaspard B, Barbaras R, Chap H, Perret B, Collet X. Pre-beta HDL: structure and metabolism. *Biochim Biophys Acta* 1996; **1300**: 73-85
9 **Fielding CJ**, Fielding PE. Molecular physiology of reverse cholesterol transport. *J Lipid Res* 1995; **36**: 211-228
10 **Asztalos BF**, Sloop CH, Wong L, Roheim PS. Two-dimensional electrophoresis of plasma lipoproteins: recognition of new apo A-I-containing subpopulations. *Biochim Biophys Acta* 1993; **1169**: 291-300
11 **Castro GR**, Fielding CJ. Early incorporation of cell-derived cholesterol into pre-beta-migrating high-density lipoprotein. *Biochemistry* 1988; **27**: 25-29
12 **Gordon DJ**, Rifkind BM. High-density lipoprotein--the clinical implications of recent studies. *N Engl J Med* 1989; **321**: 1311-1316
13 **Eggerman TL**, Hoeg JM, Meng MS, Tombragel A, Bojanovski D, Brewer HB. Differential tissue-specific expression of human apoA-I and apoA-II. *J Lipid Res* 1991; **32**: 821-828
14 **Garcia A**, Barbaras R, Collet X, Bogyo A, Chap H, Perret B. High-density lipoprotein 3 receptor-dependent endocytosis pathway in a human hepatoma cell line (HepG2). *Biochemistry* 1996; **35**: 13064-13071
15 **Caldwell SH**, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S97-S103
16 **Davis R**, Bryson HM. Levofloxacin. A review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. *Drugs* 1994; **47**: 677-700
17 **Cicognani C**, Malavolti M, Morselli-Labate AM, Zamboni L, Sama C, Barbara L. Serum lipid and lipoprotein patterns in patients with liver cirrhosis and chronic active hepatitis. *Arch Intern Med* 1997; **157**: 792-796
18 **Brinton EA**. Oral estrogen replacement therapy in postmenopausal women selectively raises levels and production rates of lipoprotein A-I and lowers hepatic lipase activity without lowering the fractional catabolic rate. *Arterioscler Thromb Vasc Biol* 1996; **16**: 431-440
19 **Tan KC**, Shiu SW, Pang RW, Kung AW. Effects of testosterone replacement on HDL subfractions and apolipoprotein A-I containing lipoproteins. *Clin Endocrinol* (Oxf) 1998; **48**: 187-194
20 **Busch SJ**, Barnhart RL, Martin GA, Fitzgerald MC, Yates MT, Mao SJ, Thomas CE, Jackson RL. Human hepatic triglyceride lipase expression reduces high density lipoprotein and aortic cholesterol in cholesterol-fed transgenic mice. *J Biol Chem* 1994; **269**: 16376-16382
21 **Santamarina-Fojo S**, Haudenschild C, Amar M. The role of hepatic lipase in lipoprotein metabolism and atherosclerosis. *Curr Opin Lipidol* 1998; **9**: 211-219

22 **Ockner RK**, Kaikaus RM, Bass NM. Fatty-acid metabolism and the pathogenesis of hepatocellular carcinoma: review and hypothesis. *Hepatology* 1993; **18**: 669-676
23 **Ooi K**, Shiraki K, Sakurai Y, Morishita Y, Nobori T. Clinical significance of abnormal lipoprotein patterns in liver diseases. *Int J Mol Med* 2005; **15**: 655-660
24 **Sviridov D**, Nestel P. Dynamics of reverse cholesterol transport: protection against atherosclerosis. *Atherosclerosis* 2002; **161**: 245-254
25 **Hirano R**, Igarashi O, Kondo K, Itakura H, Matsumoto A. Regulation by long-chain fatty acids of the expression of cholesteryl ester transfer protein in HepG2 cells. *Lipids* 2001; **36**: 401-406
26 **Sviridov D**, Sasahara T, Pyle LE, Nestel PJ, Fidge NH. Antibodies against high-density lipoprotein binding proteins enhance high-density lipoprotein uptake but do not affect cholesterol efflux from rat hepatoma cells. *Int J Biochem Cell Biol* 1997; **29**: 583-588
27 **Genest JJ**, McNamara JR, Ordovas JM, Martin-Munley S, Jenner JL, Millar J, Salem DN, Schaefer EJ. Effect of elective hospitalization on plasma lipoprotein cholesterol and apolipoproteins A-I, B and Lp(a). *Am J Cardiol* 1990; **65**: 677-679
28 **Sviridov D**, Fidge N. Pathway of cholesterol efflux from human hepatoma cells. *Biochim Biophys Acta* 1995; **1256**: 210-220
29 **Hachem H**, Favre G, Raynal G, Blavy G, Canal P, Soula G. Serum apolipoproteins A-I, A-II and B in hepatic metastases. Comparison with other liver diseases: hepatomas and cirrhosis. *J Clin Chem Clin Biochem* 1986; **24**: 161-166
30 **Kanel GC**, Radvan G, Peters RL. High-density lipoprotein cholesterol and liver disease. *Hepatology* 1983; **3**: 343-348
31 **Wadsack C**, Hirschmugl B, Hammer A, Levak-Frank S, Kozarsky KF, Sattler W, Malle E. Scavenger receptor class B, type I on non-malignant and malignant human epithelial cells mediates cholesteryl ester-uptake from high density lipoproteins. *Int J Biochem Cell Biol* 2003; **35**: 441-454
32 **Tamai T**, Patsch W, Schonfeld G. Regulation of lipoprotein receptors on a rat hepatoma cell line. *Atherosclerosis* 1988; **69**: 29-37
33 **Charpentier D**, Tremblay C, Rassart E, Rhainds D, Auger A, Milne RW, Brissette L. Low- and high-density lipoprotein metabolism in HepG2 cells expressing various levels of apolipoprotein E. *Biochemistry* 2000; **39**: 16084-16091
34 **Mulcahy JV**, Riddell DR, Owen JS. Human scavenger receptor class B type II (SR-BII) and cellular cholesterol efflux. *Biochem J* 2004; **377**: 741-747
35 **Artl A**, Marsche G, Pussinen P, Knipping G, Sattler W, Malle E. Impaired capacity of acute-phase high density lipoprotein particles to deliver cholesteryl ester to the human HUH-7 hepatoma cell line. *Int J Biochem Cell Biol* 2002; **34**: 370-381
36 **Huard K**, Bourgeois P, Rhainds D, Falstrault L, Cohn JS, Brissette L. Apolipoproteins C-II and C-III inhibit selective uptake of low- and high-density lipoprotein cholesteryl esters in HepG2 cells. *Int J Biochem Cell Biol* 2005; **37**: 1308-1318
37 **Hoeg JM**, Demosky SJ, Edge SB, Gregg RE, Osborne JC, Brewer HB. Characterization of a human hepatic receptor for high density lipoproteins. *Arteriosclerosis* 1985; **5**: 228-237
38 **Krieger M**. Charting the fate of the "good cholesterol": identification and characterization of the high-density lipoprotein receptor SR-BI. *Annu Rev Biochem* 1999; **68**: 523-558
39 **Trigatti B**, Rigotti A, Krieger M. The role of the high-density lipoprotein receptor SR-BI in cholesterol metabolism. *Curr Opin Lipidol* 2000; **11**: 123-131
40 **Curtiss LK**, Boisvert WA. Apolipoprotein E and atherosclerosis. *Curr Opin Lipidol* 2000; **11**: 243-251
41 **Tall AR**, Jiang Xc, Luo Y, Silver D. 1999 George Lyman Duff memorial lecture: lipid transfer proteins, HDL metabolism, and atherogenesis. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1185-1188
42 **Mahley RW**. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 1988; **240**: 622-630
43 **Silver DL**, Wang N, Tall AR. Defective HDL particle uptake in ob/ob hepatocytes causes decreased recycling, degradation, and selective lipid uptake. *J Clin Invest* 2000; **105**: 151-159
44 **Cohen JC**, Vega GL, Grundy SM. Hepatic lipase: new insights from genetic and metabolic studies. *Curr Opin Lipidol* 1999; **10**: 259-267
45 **Thuren T**. Hepatic lipase and HDL metabolism. *Curr Opin Lipidol* 2000; **11**: 277-283
46 **Su Z**, Zhang S, Nebert DW, Zhang L, Huang D, Hou Y, Liao L, Xiao C. A novel allele in the promoter of the hepatic lipase is associated with increased concentration of HDL-C and decreased promoter activity. *J Lipid Res* 2002; **43**: 1595-1601
47 **Cohen JC**, Wang Z, Grundy SM, Stoesz MR, Guerra R. Variation at the hepatic lipase and apolipoprotein AI/CIII/AIV loci is a major cause of genetically determined variation in plasma HDL cholesterol levels. *J Clin Invest* 1994; **94**: 2377-2384
48 **Lambert G**, Chase MB, Dugi K, Bensadoun A, Brewer HB, Santamarina-Fojo S. Hepatic lipase promotes the selective uptake of high density lipoprotein-cholesteryl esters via the scavenger receptor B1. *J Lipid Res* 1999; **40**: 1294-1303
49 **Collet X**, Tall AR, Serajuddin H, Guendouzi K, Royer L, Oliveira H, Barbaras R, Jiang XC, Francone OL. Remodeling of HDL by CETP in vivo and by CETP and hepatic lipase in vitro results in enhanced uptake of HDL CE by cells expressing scavenger receptor B-I. *J Lipid Res* 1999; **40**: 1185-1193
50 **Dugi KA**, Vaisman BL, Sakai N, Knapper CL, Meyn SM, Brewer HB, Santamarina-Fojo S. Adenovirus-mediated expression of hepatic lipase in LCAT transgenic mice. *J Lipid Res* 1997; **38**: 1822-1832
51 **Bamberger M**, Lund-Katz S, Phillips MC, Rothblat GH. Mechanism of the hepatic lipase induced accumulation of high-density lipoprotein cholesterol by cells in culture. *Biochemistry* 1985; **24**: 3693-3701
52 **Chang SF**, Scharf JG, Will H. Structural and functional analysis of the promoter of the hepatic lipase gene. *Eur J Biochem* 1997; **247**: 148-159
53 **Rinninger F**, Mann WA, Kaiser T, Ahle S, Meyer N, Greten H. Hepatic lipase mediates an increase in selective uptake of high-density lipoprotein-associated cholesteryl esters by human Hep 3B hepatoma cells in culture. *Atherosclerosis* 1998; **141**: 273-285
54 **Bamberger M**, Glick JM, Rothblat GH. Hepatic lipase stimulates the uptake of high density lipoprotein cholesterol by hepatoma cells. *J Lipid Res* 1983; **24**: 869-876
55 **Dugi KA**, Brandauer K, Schmidt N, Nau B, Schneider JG, Mentz S, Keiper T, Schaefer JR, Meissner C, Kather H, Bahner ML, Fiehn W, Kreuzer J. Low hepatic lipase activity is a novel risk factor for coronary artery disease. *Circulation* 2001; **104**: 3057-3062
56 **Carter CA**. Protein kinase C as a drug target: implications for drug or diet prevention and treatment of cancer. *Curr Drug Targets* 2000; **1**: 163-183
57 **Deeg MA**, Bowen RF, Oram JF, Bierman EL. High density lipoproteins stimulate mitogen-activated protein kinases in human skin fibroblasts. *Arterioscler Thromb Vasc Biol* 1997; **17**: 1667-1674
58 **Tu LC**, Chou CK, Chen HC, Yeh SF. Protein kinase C-mediated tyrosine phosphorylation of paxillin and focal adhesion kinase requires cytoskeletal integrity and is uncoupled to mitogen-activated protein kinase activation in human hepatoma cells. *J Biomed Sci* 2001; **8**: 184-190
59 **Perletti G**, Tessitore L, Sesca E, Pani P, Dianzani MU, Piccinini F. Epsilon PKC acts like a marker of progressive malignancy in rat liver, but fails to enhance tumorigenesis in rat hepatoma cells in culture. *Biochem Biophys Res Commun* 1996; **221**: 688-691
60 **Mendez AJ**, Oram JF, Bierman EL. Protein kinase C as a mediator of high density lipoprotein receptor-dependent efflux of intracellular cholesterol. *J Biol Chem* 1991; **266**: 10104-10111
61 **Francis GA**, Tsujita M, Terry TL. Apolipoprotein AI efficiently binds to and mediates cholesterol and phospholipid efflux from human but not rat aortic smooth muscle cells. *Biochemistry* 1999; 38: 16315-16322
62 **Grewal T**, de Diego I, Kirchhoff MF, Tebar F, Heeren J, Rinninger F, Enrich C. High density lipoprotein-induced

signaling of the MAPK pathway involves scavenger receptor type BI-mediated activation of Ras. *J Biol Chem* 2003; **278**: 16478-16481
63 **Cooper ME**, Akdeniz A, Hardy KJ. Effects of liver transplantation and resection on lipid parameters: a longitudinal study. *Aust N Z J Surg* 1996; **66**: 743-746
64 **Katsuramaki T**, Hirata K, Kimura Y, Nagayama M, Meguro M, Kimura H, Honma T, Furuhata T, Hideki U, Hata F, Mukaiya M. Changes in serum levels of apolipoprotein A-1 as an indicator of protein metabolism after hepatectomy. *Wound Repair Regen* 2002; **10**: 77-82
65 **Miura Y**, Ono K, Okauchi R, Yagasaki K. Inhibitory effect of coffee on hepatoma proliferation and invasion in culture and on tumor growth, metastasis and abnormal lipoprotein profiles in hepatoma-bearing rats. *J Nutr Sci Vitaminol* (Tokyo) 2004; **50**: 38-44
66 **Lou B**, Liao XL, Wu MP, Cheng PF, Yin CY, Fei Z. High-density lipoprotein as a potential carrier for delivery of a lipophilic antitumoral drug into hepatoma cells. *World J Gastroenterol* 2005; **11**: 954-959

S- Editor Liu Y **L- Editor** Alpini GD E- Editor Wang HF