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Review:

Lipids changes in liver cancer*

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Abstract: Liver is one of the most important organs in energy metabolism. Most plasma apolipoproteins and endogenous lipids and lipoproteins are synthesized in the liver. It depends on the integrity of liver cellular function, which ensures homeostasis of lipid and lipoprotein metabolism. When liver cancer occurs, these processes are impaired and the plasma lipid and lipoprotein patterns may be changed. Liver cancer is the fifth common malignant tumor worldwide, and is closely related to the infections of hepatitis B virus (HBV) and hepatitis C virus (HCV). HBV and HCV infections are quite common in China and other Southeast Asian countries. In addition, liver cancer is often followed by a procession of chronic hepatitis or cirrhosis, so that hepatic function is damaged obviously on these bases, which may significantly influence lipid and lipoprotein metabolism in vivo. In this review we summarize the clinical significance of lipid and lipoprotein metabolism under liver cancer.

Key words: Lipids, Lipoprotein, Liver cancer
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INTRODUCTION

The liver is a major organ in energy metabolism, and plays a critical role in the production metabolism of lipid and lipoprotein, regulating their synthesis and degradation (Tietge *et al*., 1998); Liver function depends on the integrated activity of different hepatic cells and the injury of the organ could result in disintegrated intracellular functions (Sherlock, 1995); Changed lipid and lipoprotein metabolism homeostatically is one of the foundations in various liver diseases, and is regulated by related substances (Lewis and Rader, 2005). In addition, hepatic cells can draw help from lipoprotein receptor of the cells surface to absorb and clear lipoprotein metabolic products. Liver produced lipoprotein, as most of VLDL (very low density lipoprotein) and part of HDL (high density lipoprotein), and could keep opposite balanced state of lipid and lipoprotein metabolism by this way in vivo (Pangburn *et al*., 1981).

Most plasma proteins and endogenous lipoproteins were synthesized in liver (Levi, 1972; Albers *et al*., 1977), but the synthesis and secretion depended on the integrity of hepatocellular function (Eisenberg and Levy, 1975), and is influenced by normal lipid and lipoprotein metabolism in liver diseases (Davis and Bryson, 1994).

Liver cancer was the fifth malignant tumor in the world (Parkin *et al*., 2001), and was infected with hepatitis B virus (HBV) and hepatitis C virus (HCV) which were common in China (Shi *et al*., 2005), which is major remote cause of liver cancer (Nissen and Martin, 2002; Guan *et al*., 2004). The mortality of liver cancer was 20.4/100000 in China, occupied 18.8% of all malignant tumors, and it was next to gastric cancer only. Compared to other countries in the world the mortality of liver cancer in China occupies the first place (Zhang *et al*., 1999). The earlier period of liver cancer is often followed by hepatic cirrhosis process, so that liver function is damaged obviously by hepatic cirrhosis (Sherlock and Dooley, 1993), and influences lipid normal metabolism in liver. Severe liver diseases could disorder lipoprotein

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metabolism and change lipid and lipoprotein level in serum (Cooper *et al*., 1996; Motta *et al*., 2001; Ooi *et al*., 2005). In this article we specially discuss the changes of lipid and lipoprotein and the clinical significances in liver cancer.

INFLUENCE OF LIVER CANCER ON TG METABOLISM

Patients with liver cancer are often followed by liver diseases. Liver cancer and chronic liver disease influence blood fat level (Cicognani *et al*., 1997). Motta *et al*.(2001) detected that triglyceride (TG) level decreased 28.8% in 40 cases with liver cancer, and the reduction of TG levels observed in their study series may be explained on the basis of the relationship between cytokines and lipids (Malaguarnera *et al*., 1994). Lipid metabolism products such as Tnf-α, IL-1, IL-6, and IFN-α are produced by tumor cells (Langstein and Norton, 1991; Tracey *et al*., 1988). In fact cytokines inhibited lipolysis (Gifford and Lohmann-Matthes, 1987). Hepatic cells are damaged simultaneously in hepatocarcinogenesis, and in patients with this pattern, hepatic TG lipase activity significantly decreases (Hiraoka *et al*., 1993). The X protein of hepatitis B virus (HBx) plays a major role in hepatocellular carcinoma. Apolipoprotein B (apoB) in the liver is an important glycoprotein for transport of VLDL and low density lipoproteins (LDL). In liver cells hyper-express of HBx causes negative accommodation of microsome TG transfer protein, could increase the expression of β-d-mannoside-1, 4-N-acetylglucosaminyl transferase-III (GnT-III), and causes inhibition of apoB secretion and accumulation of intracellular TG and cholesterol (Tch) (Kang *et al*., 2004), but serum TG level in liver cancer did not obviously decrease compared with lipoprotein(a) (Lp(a)), Tch and HDL (Ooi *et al*., 2005).

INFLUENCE OF LIVER CANCER ON CHOLESTEROL METABOLISM

Cholesterol metabolism is a normal regulation process which first transformed choloic acid and desoxycholic acid through biliary system in liver, then as bile salt was passed to bowels through biliary system (Rothblat and Phillips, 1986). When hepatic inadequacy occurred because of liver cancer and chronic liver disease, form, esterification and evacuation of cholesterol were blocked, which causes changes of plasma cholesterol level (Cooper *et al*., 1996; Motta *et al*., 2001; Ooi *et al*., 2005; Heeren *et al*., 2004; Kanel *et al*., 1983; Popescu *et al*., 2003); and it was also discovered that serum cholesterol level was negative correlated with occurrence and mortality of some cancers by epidemiologic study (Law and Thompson, 1991; Williams *et al*., 1981). Study of the correlation between total serum cholesterol and tumor showed that the cholesterol level in patients who died of cancer was significantly lower than that in those who survived (Cambien *et al*., 1980).

Liver cancer is a wasting disease, and with patient's condition process, tumor cells proliferated and needed to intake large amount of cholesterol as raw material for cytomembrane synthesis (Funahashi *et al*., 1989). Tumor cells cholesterol intake, synthesis and changes of membrane content suggested that endogenous cholesterol may play an important role in tumor pathobiology (Dessì *et al*., 1994), and cholesterol metabolic products participated in duplication of DNA and regulation of oncogene protein (Casey *et al*., 1989).

Eighty percentage of endogenous cholesterol in serum is synthesized in liver cell cytomicrosome (Krisans, 1996), since there are cholesterol synzymes in cytomicrosome (Grünler *et al*., 1995). Developing from chronic hepatitis to liver cirrhosis resulted in reduced hepatic cell fibrosis and hydroxy-methyl-glutaryl coenzyme A (HMGCoA) reducase synthesis. With patient's condition aggravating, cholesterol synthesis in liver reduced and serum cholesterol content gradually depressed, especially in liver cancer, which explained that serum cholesterol content depressed significantly when patient's condition aggravated and liver function lesion intensified (Ooi *et al*., 2005; Cooper *et al*., 1996).

Protein kinase C (PKC) is hypso-expressed in liver cancer, also is the major molecule in cell signal transduction pathway, and plays an important role in cell growth and aggravation (Carter, 2000). In cancerization of liver cells the abnormality of cell signal transduction plays a key role, and the abnormal expression of PKC-α is closely correlated with genesis and development of liver cancer (Tu *et al*., 2001;

Perletti *et al*., 1996). HDL receptor-mediated translocation and efflux of intracellular cholesterol occur through activation of PKC (Mendez *et al*., 1991), while activation of PKC enhances and inhibition of PKC suppresses apolipoprotein-mediated cholesterol efflux (Mendez *et al*., 1991). HDL causes serum cholesterol level to significantly decrease in liver cancer (Motta *et al*., 2001).

CHANGE OF LIPOPROTEIN IN LIVER CANCER

Liver is a major source of the endogenous lipoproteins in vivo, meanwhile, and it is the main site of the synthesis, storage, transport and degradation of lipid (Lewis and Rader, 2005). Each protein is influenced by liver disease in a different way and serum lipoprotein concentrations with faster turn-over are more reduced with respect to those with slower turn-over (Phillips, 1960).

Metabolism of Lp(a) in liver cancer

The liver is the main site of Lp(a) synthesis (Malaguarnera *et al*., 1994; 1996; Kraft *et al*., 1989). In the view of healthy controls, Lp(a) level in liver cancer patients' serum strikingly decreased compared with that of the normal (Samonakis *et al*., 2004), and it was found Lp(a) level decreased in liver cancer and cirrhotic patients. Lp(a) is produced by the liver and it is expected that its levels may decrease in patients with chronic liver disease (Samonakis *et al*., 2004). That liver plays an important role in lipid metabolism and so it is quite certain that a malfunction of liver cells might influence serum Lp(a) levels. Several factors such as hormones, cytokines, genetics and nutrition may be involved in different way, with each single protein being synthetized by the liver (Phillips, 1960). Several inflammatory and tumoral diseases are characterized by the production and delivery of cytokines influencing serum Lp(a) levels (Higuchi *et al*., 1988), so serum Lp(a) is significantly lower in patients with liver cancer (Samonakis *et al*., 2004). The mechanisms by which the tumours induce cachexia involve inflammatory cytokine production, which is responsible for a wide number of metabolic disorders, essentially involving lipid metabolism (Langstein and Norton, 1991). Serum Lp(a) level changes during inflammatory disease (Maeda *et al*., 1989); and also liver damage is linked to reduced Lp(a) serum levels (Malaguarnera *et al*., 1996; Kostner, 1983). Geiss *et al*.(1996) longitudinally observed patients showing a marked increase in Lp(a) concentration from 7 mg/dl in acute stage to 32 mg/dl in convalescence, and acute hepatitis is associated with decreased Lp(a) serum levels.

Obvious Lp(a) half-life is brief in vivo (3.3~3.9 d) (Krempler *et al*., 1983), and influenced early by liver function alterations (Malaguarnera *et al*., 1994). Then Lp(a) is synthesized and metabolized independently of other plasma lipoproteins, at the same time the serum Lp(a) level is not influenced by various dietary manipulations (Albers *et al*., 1977). Thus, Lp(a) is a substance involved in lipid and proteic metabolism, and can be a sensitive and early marker of liver malfunction. It is concluded that Lp(a) might be useful in the follow-up of liver cancer patients and that ferritin and α-fetoprotein can be used for a more complete evaluation of the liver function (Motta *et al*., 2001), for analyzing the Lp(a) level in vivo, and for evaluating the liver functional status of hepatoma patients (Malaguarnera *et al*., 1996; Motta *et al*., 2001; Samonakis *et al*., 2004), but the increased Lp(a) serum level was found in hepatoma patients (Basili *et al*., 1997).

Metabolism of HDL and LDL in liver cancer

HDL comprises a heterogeneous mixture of spherical macromolecules which differ in size (80~120 Å) and chemical composition; the main structural proteins are apoA-I (apolipoprotein A-I) and apoA-II (apolipoprotein A-II) (Assmann and Schriewer, 1980). The apoA-I is present on most HDL particles and constitutes 70% of the apolipoprotein content of HDL particles; it is not only the structural protein of HDL, but also the activator of lecithin cholesterol acyl transferase (LCAT) (Lewis and Rader, 2005), and most HDL particles contain apoA-I (Katsuramaki *et al*., 2002). 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 (von Eckardstein *et al*., 1994).

Reverse cholesterol transport (RCT) is a pathway transporting cholesterol from extrahepatic cells

and tissues to the liver, which antiport process is determined at least partially by the HDL concentration in the blood (Sviridov and Nestel, 2002); HDL plays an important role in cleaning the cholesterol (Fielding and Fielding, 1995). Cholesterol ester transfer protein (CETP) is an important determinant of lipoprotein function, especially HDL metabolism, and contributes to the regulation of plasma HDL levels (Hirano *et al*., 2001). Therefore, HDL plays a key role in the reverse cholesterol transport pathway in liver (Sviridov *et al*., 1997; Genest *et al*., 1990). But when cells are incubated with equivalent concentrations of isolated lipoproteins, HDL is much more effective in promoting 14C cholesterol efflux than LDL, suggesting that unesterified cholesterol is initially transferred to HDL and then to LDL (Sviridov and Fidge, 1995), indicating that the primary site of human HDL synthesis is putatively in the liver (Eggerman *et al*., 1991; Garcia *et al*., 1996). In earlier period of liver cancer it often follows hepatic cirrhosis process, so that liver function is damaged obviously by hepatic cirrhosis (Sherlock and Dooley, 1993). Ooi *et al*.(2005) analyzed lipids in liver diseases by agarose gel electrophoresis, and differential staining and simultaneous analysis of the lipid and lipoprotein fractions, including chronic hepatitis (CH), liver cirrhosis (LC), hepatocellular carcinoma (HCC), and metastatic liver cancer, with each fraction being compared among these diseases. Metastatic liver cancer showed lower HDL-fraction level, but higher levels of the other parameters than HCC. When the subjects were classified into survivors and patients who died, 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, with atypical patterns being frequently observed in patients who died. There were 6 atypical patterns, of which 4 (slow α-HDL, abnormal LDL, Lp-X (lipoprotein X) and Lp-Y (lipoprotein Y)) were associated with liver diseases. Slow alpha HDL appeared during slight bile stagnation and was accompanied by increases in the apoE (apolipoprotein E) level and the HDL particle size. The LDL level in LC and metastatic liver cancer differed between survivors and patients who died, also the function of the entire liver decreases in LC while HCC develops in the LC stage in patients.

To establish whether there is any significant relationship between high density lipoprotein cholesterol (HDLC) concentrations and biopsy-documented liver disease, Kanel *et al*.(1983) reported that 169 patients had needle biopsies, serum cholesterol and HDLC evaluated. HDLC decreased strikingly and significantly in acute alcoholic hepatitis and in acute viral hepatitis; compared to controls, patients with inactive alcoholic liver disease and chronic active hepatitis showed moderate decrease in HDLC, and patients with primary and metastatic hepatic neoplasms also had strikingly decreased HDLC (Booth *et al*., 1991). The patient's condition proceeded, developed and changed, it caused HDL physiology function to change (Motta *et al*., 2001; Kanel *et al*., 1983; Montaguti *et al*., 1975; Rubies-Prat *et al*., 1983; Skipski *et al*., 1975).

Hepatic lipase can adversely affect the HDL2 selectively, hydrolyze the TG and lipoprotein in it (Dugi *et al*., 1997). After lipoprotein of HDL2 is hydrolyzed, the cholesterol/phospholipid (C/PC) ratio on the surface increased, promoted cholesterol and its lipid flowing into hepatic cell, which is favourable for liver to uptake HDL2 cholesterol and lipid to synthesize bile acid. At the same time, HDL2 is changed into HDL3 and enters the blood circulation. Liver can take cholesterol and its lipid from tissue outside of liver. This process plays an important role in the antiport of cholesterol, and the phospholipase A1 activity of hepatic triglyceride lipase (H-TGL) in stimulating the delivery of HDL esterified cholesterol into liver cells (Marques-Vidal *et al*., 1994).

Hepatic lipase (HL) mediates increase in selective uptake of HDL-associated cholesteryl esters (Rinninger *et al*., 1998), and stimulates the internalisation of apoB-containing lipoproteins by hepatocytes independent from lipolysis. The HDL role in the hepatic metabolism of apoA-I-containing lipoproteins, i.e. HDL was investigated, which explored the role of these molecules in the HL effect on selective cholesterol esters 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% (Rinninger *et al*., 1998), and caused the inverse correlation between HL activity and HDLC (Dugi *et al*., 2001), so that hepatic lipase stimulates the uptake of HDLC by hepatoma cells (Bamberger *et al*., 1983).

Hepatoma cells exposed to hepatic lipase-modified HDL, showed increased uptake of HDL free cholesterol relative to cells exposed to control HDL, and resulted in the decrease of HDLC level in vitro (Kanel *et al*., 1983). It was confirmed that transgenic overexpression of HL in either mice or rabbits decreased HDLC levels (Busch *et al*., 1994; Santamarina-Fojo *et al*., 1998). HL activity is suppressed by estradiol and increased by testosterone (Brinton, 1996; Tan *et al*., 1998), and when patients' estradiol level with HCC was high, the secreting ability of testosterone will be cut down, which decreases HDLC level too. Experiment in vitro showed the capacity for cellular cholesterol efflux from HUH-7 cells is slightly impaired by acute-phase (AP)-HDL. Compared with HDL, it is supportive of scavenger receptor class B, type I (SR-BI). Hepatic tissue can modulate its recognition of HDL. The human hepatoma cell line, increases HDL binding with cholesterol loading that is specific for HDL3, and hepatic membranes from a patient lacking normal hepatic LDL receptors bound apoA-I HDL normally, indicating that a saturable, specific regulatable receptor for apoE-free HDL is present in human liver, and that there is a free HDL apoE which can be saturated and regulated specially in humen liver (Hoeg *et al*., 1985).

INFLUENCE OF LIVER CANCER ON APOLIPOPROTEINS

Serum concentrations of apoA-I and apoA-II were determined in liver cancer, and the HDL fraction and apoA-I and apoA-II showed significantly low values (Hachem *et al*., 1986). The liver participated in the reaction converting proapoA-I to the mature apoA-I; and also the proportion of proapoA-I showed a tendency toward increase with advance in liver damage (Matsuura *et al*., 1988). With the short half-life, changes of the serum apoA-I levels may be a good indicator of the hepatic protein synthesis ability during the perioperative period after hepatectomy (Krempler *et al*., 1980; Katsuramaki *et al*., 2002). It also serves as an excellent parameter for predicting liver function after orthotopic liver transplantation (Tietge *et al*., 1998; Malmendier *et al*., 1992).

The uptake and composition of cholesterol increased to satisfy the requirement of proliferation in malignant tumor cells which obviously increases cholesterol in its membrane. And the activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to reduce the rate-limiting enzyme of cholesterol composition has increased. Lipids or proteins of α-HDL are removed from the circulation by at least 2 direct pathways involving the selective uptake of lipids by scavenger receptor B and the holoparticle uptake by apoE or apoA-I receptors (Curtiss and Boisvert, 2000; Krieger, 1999; Tall *et al*., 2000; Trigatti *et al*., 2000). Silver *et al*.(2000) suggested the presence of a hepatic leptin-regulated HDL receptor, which regulates HDLC levels by mediating holoparticle uptake into liver cells, after internalization of triglyceride-rich lipoproteins (TRL) in hepatoma cells, TRL particles are immediately disintegrated in the early endosomal compartment. This involves the targeting of lipids and apoB along the degradative pathway and the recycling of TRL-derived apoE through recycling endosomes (Heeren *et al*., 2004).

Lipoprotein metabolism is determined by the importance of hepatic apoE, and expression level determines the fate of LDL and HDL3 (Charpentier *et al*., 2000). Slow α-HDL appeared during slight bile stagnation and was accompanied by increases in the apoE level and the HDL particle size with liver cancer (Ooi *et al*., 2005).

The redistribution of apoE from HDL to apoB-containing lipoproteins upon activated lipogenesis in hepatoma cells occurs intracellularly and is not attributable to decrease in HDL production (Fazio and Yao, 1995), although studies in recombinant cells indicated that SR-BI can promote cholesterol efflux (Mulcahy *et al*., 2004). Investigations of transgenic mice overexpressing or deficient in SR-BI indicate its physiological function as selectively sequestering cholesteryl esters from HDLs (Artl *et al*., 2002), which result in plasma HDLs being cleared from the circulation by specific receptors, and being either totally degraded or their cholesteryl esters being selectively delivered to cells by receptors such as the SR-BI, which suggested that apoC-II and apoC-III inhibit selective uptake of low- and high-density lipoprotein cholesteryl esters in HepG cells (Huard *et al*., 2005).

INFLUENCE OF LIVER CANCER ON FATTY ACID METABOLISM

The liver is a critical organ in fatty acids of metabolism (Cowen and Campbell, 1977). Fatty acid is also the source of liver triacylglycerol (Donnelly *et al*., 2005). The extracellular free fatty acids (FFA) pool in tumors undergoes continuous turn-over, probably utilizing adipose tissue deposits as a source (Mermier and Baker, 1974), and plasma FFA are increased in tumor bearing animals (Frederick and Begg, 1956).

Available evidence (Ockner *et al*., 1993) is consistent with the possibility that selected changes in the hepatocellular metabolism of long-chain fatty acids may contribute significantly to this process, which in turn leads to alterations in gene expression and in DNA itself. Moreover, certain intermediates of extramitochondrial fatty acid oxidation (e.g., the long-chain dicarboxylic fatty acids) impair mitochondrial function and are implicated as modulators of gene expression through their interaction with the peroxisome proliferator-activated receptor, which may also contribute to nonneoplastic liver injury and to tumorigenesis in other tissues. FFA concentrates in the serum of mice with mammary tumors. Similar results have been reported by various authors (Iguchi *et al*., 1989; Kumar *et al*., 1991; Lin *et al*., 1992). Bravo *et al*.(1990) found increased unsaturated FFA concentrations in transplantable Friend leukemic cell tumors, and someone believed that they represented a metabolic and energy substrate for the tumor itself (Spector, 1967). Morris hepatoma 7777 cells freshly isolated from highly malignant tumors grown in the hindlimb of buffalo rats actively convert ketone bodies to cholesterol and fatty acids. The results are discussed in terms of the known and proposed metabolic pathways for lipid synthesis from ketone bodies, particularly that from 3-hydroxybutyrate (Hildebrandt *et al*., 1995).

Hanai *et al*.(1993) evaluated 17 hepatectomized cases (12 cases of hepatocellular carcinoma and 5 cases of metastatic liver cancer). The cancerous tissues and the noncancerous reference tissues were separated, and the fatty acids were determined as methyl esters by gas chromatography. In HCC, the levels of α-linolenic acid (omega-3) and docosahexaenoic acid in liver cancer tissue were significantly less than those in the reference tissues, and eicosanoid production and the compositions of precursor fatty acids were determined in human cancerous and reference liver tissues.

But the FFA in ascitic fluid improves diagnosis in malignant abdominal tumors (Greco *et al*., 1995). The elevation of FFA in ascitic fluid allows discrimination between malignant and non-malignant ascites. The fasting concentration of FFA in the ascitic fluid was determined in 14 patients with malignant ascites and in 19 patients with liver cirrhosis. In malignant ascites FFA levels were increased more than three times compared with that in cirrhotic ascites. Palmitic acid was the most representative saturated FFA, while unsaturated FFA were represented, in decreasing order, by oleie, linoleic and arachidonic acids. The ratio of unsaturated to saturated FFA was higher in neoplastic patients.

Available evidence (Ockner *et al*., 1993) is consistent with the possibility that selected changes in the hepatocellular metabolism of long-chain fatty acids may contribute significantly to this process, nonneoplastic liver injury, and tumorigenesis in other tissues.

de Alaniz and Marra (1994) also demonstrated significant contribution of the stearoyl-CoA desaturase system to the high levels of oleic acid present in this kind of hepatoma cells. Peroxisome proliferators comprise a diverse group of chemicals which are regarded as rodent hepatocarcinogens and/or liver tumor promoters (Palut, 1997).

Cyclooxygenase-2 (COX-2) is an isoform of cyclooxygenase, which is the key enzyme converted arachidonic acids to prostaglandins. Hu (2003) evaluated that COX-2-prostanoid pathway plays important and complex roles in the pathogenesis of various liver diseases and provides the rationale for further testing COX-2 inhibitors as clinical agents for HCC chemoprovention. Kondo *et al*.(1999) reported increased levels of COX-2 in hepatocellular carcinoma, examined the expression of COX-2 protein by immunohistochemistry in 53 patients with HCC, and found 17% of samples showing a high COX-2 expression, and 37% of samples expressed COX-2 at a moderate level.

Cyclooxygenase (COX) is a key enzyme in the synthesis of prostanoids. Koga *et al*.(1999) investigated the expression of COX-2 and COX-1 in human HCC tissues using the above-mentioned methods to show high expression of COX-2 in well-differentiated

HCC and low expression in advanced HCC, in contrast to its continuous expression during colorectal carcinogenesis, which suggested that COX-2 may play a role in the early stages of hepatocarcinogenesis. Shiota *et al*.(1999) studied twenty-eight of 29 (97%) patients with HCC showing a positive staining and immunohistochemically examined expression of this enzyme in cancerous and non-cancerous tissues of HCC.

COX2-prostanoid pathway may also be involved in malignant invasion during hepatocarcinogenesis (Bae *et al*., 2002). Keler *et al*.(1992) showed that dietary linoleic acid increases hepatoma growth. Fish oil was found to inhibit hepatic carcinogenesis (Ramesh and Das, 1995) and decrease growth (Fox and Hay, 1992). It is probable that this effect of linoleic acid is mediated through prostaglandin E2 (PGE2). Portal PGE2 had also been shown to suppress liver-associated immunity, and promote the formation of hepatic metastases (Okuno *et al*., 1995). Albumin carries fatty acids and is suggested to act as an antioxidant; polyunsaturated fatty acids (linoleic, arachidonic, eicosapentaenoic and docosahexaenoic acids) inhibit growth of human hepatoma cells at low albumin concentration (0.5%) (Hostmark and Lystad, 1992).

Ramesh and Das (1995) studied a diethylnitrosamine (DEN) induced hepatoma model, the effect of fish oil, a rich source of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), ground nut oil, oleic acid (OA) and linoleic acid (LA), and found that a 'high fat' diet and lipid peroxidation can modulate DEN-induced hepatocarcinogenesis in rats. The metabolism of arachidonic acid (AA), EPA, and DHA was examined in HepG2 cells, with the results suggesting that the levels of AA and DHA in both types of cells were regulated more severely than EPA and that the activity of fatty acid desaturation might be different between n-6 and n-3 families (Fujiyama-Fujiwara *et al*., 1992).

Polyunsaturated fatty acids killed incubated human tumor cells (Bégin *et al*., 1985), suggesting that treatment of malignancy with polyunsaturated fatty acids may have considerable potential while being associated with a high level of safety. The effects of essential fatty acids on cell proliferation and cell viability of 3 human tumor and 4 normal cell lines were tested in vitro; the treatment of cancer with polyunsaturated fatty acids containing 3, 4, and 5 double bonds has potential clinical usefulness (Bégin *et al*., 1986).

CONCLUSION

It is thus evident that 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 (Cooper *et al*., 1996) which were analyzed in liver diseases, showed results reflecting the pathologic conditions, and may be clinically useful (Ooi *et al*., 2005); and also it may be a good indicator of the hepatic protein synthetic ability during the perioperative period after hepatectomy (Katsuramaki *et al*., 2002). Drinking instant coffee powder results in amelioration of abnormal lipoprotein profiles that occurred in hepatoma-bearing rats, and instant coffee powder has the ability to suppress tumor cell invasion by reducing oxidative stresses in vitro, leading to the inhibition of tumor growth and metastases (Miura *et al*., 2004). According to the metabolic characteristic of lipoids and lipoprotein (Chu *et al*., 2001; Kader *et al*., 1998), high-density lipoprotein has been used as a potential carrier for delivery of a lipophilic antitumoral drug into hepatoma cells (Lou *et al*., 2005).

The above discussion showed that analysis of serum level of lipid and lipoprotein in liver cancer reflected the condition of liver lipid and lipoprotein metabolism and hepatic cell impairment exactly, and will be an adjunct method for determination of observed pathogenetic condition, curative effect and estimating prognosis, and also will be used as a new method for hepatoma therapy.

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