Mechanisms and significance of lipoprotein(a) in hepatocellular carcinoma

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BACKGROUND: The liver plays a key role in the metabolism of plasma apolipoproteins, endogenous lipids and lipoproteins. Hepatocellular carcinoma is one of the most common fatal malignant tumors in China and in other Southeast Asian countries. It has been demonstrated that plasma lipid profiles are changed in liver cancer.

DATA SOURCES: A MEDLINE database search was performed to identify relevant articles using the keywords "hepatocellular carcinoma" and "lipoprotein(a)". The search was conducted and research articles were reviewed from 1960 to 2008.

RESULTS: Production and homeostasis of lipids, apolipoproteins and lipoproteins depend on the integrity of hepatocellular functions, which ensures normal lipid and lipoprotein metabolism in vivo. When hepatocellular injury or liver cancer occurs these processes can be impaired. It has been suggested that plasma levels of apolipoprotein(a) (apo(a)) and/or lipoprotein(a) (Lp(a)) may be considered as sensitive markers of hepatic impairment.

CONCLUSIONS: Plasma levels of apo(a) and Lp(a) display significant correlations with hepatic status. Most studies demonstrated that the plasma levels of apo(a) and Lp(a) can be considered as an additional clinical index of liver function.

(KEY WORDS: lipoprotein(a); apolipoprotein(a); metabolism; hepatocellular carcinoma)

Introduction

Normal metabolism and homeostasis of carbohydrates, amino acids and lipids in vivo depend on integrated liver function. Most plasma apolipoproteins and endogenous lipids and lipoproteins, including apolipoprotein(a) (apo(a)) and lipoprotein(a) (Lp(a)), are synthesized in the liver.[1,2] Hepatocellular injury or chronic liver diseases including hepatocellular carcinoma (HCC) may result in a distinctly abnormal pattern of plasma lipids, apolipoproteins and lipoproteins, which may be related to or regulated by various cytokines and/or metabolic cellular substances, or tumor factors, although the detailed mechanisms are not fully understood.[3]

HCC is the fifth most malignant tumor in the world.[4] It has been confirmed to be related to HBV and HCV infections, and HBV is quite common in China.[5-7] The mortality of HCC is about 20.4/100 000 in China, and comprises 18.8% of all malignant tumors. Compared to other countries, the mortality from HCC is higher in China.[8,9] HCC is frequently accompanied by chronic HBV infection and hepatic cirrhosis, therefore liver function is clearly impaired in HCC because of chronic hepatocellular damage.[1,10,11] Studies[2,12-14] demonstrated that severe chronic liver diseases are associated with disordered lipoprotein metabolism and changed plasma patterns of lipid and lipoprotein. However, aberration of apo(a) and Lp(a) in HCC has not been fully addressed. This review especially focused on the clinical significance of the metabolic mechanisms of apo(a) and plasma levels of Lp(a) in HCC.

Gene location, expression of apo(a) and structure of Lp(a)

The core components of Lp(a) are neutral lipid and an apoB-100 molecule, which are covalently connected by a disulfide bond and surrounded by
hydrophilic apo(a). The density of Lp(a) is between those of LDL and HDL. apo(a) is a high molecular weight glycoprotein, 250-838 kDa. Marcovina et al. reported that a total of 34 different apo(a) isoforms have been identified in populations. The heterogeneity of apo(a) determines the changes in plasma Lp(a) concentrations, and there is a clear negative correlation between the molecular weight of apo(a) and the plasma Lp(a) concentration.

Lp(a) has a simple Mendelian dominant inheritance, which is controlled by the alleles Lp and Lp. In 1986, Hasstedt et al. reported that the plasma Lp(a) concentration is controlled by three alleles, i.e., Lp, Lp, and Lp. Pedigree analysis indicated that the size polymorphism of Lp(a) is controlled by a series of alleles of a single point. The apo(a) gene which is located in q26-27 of chromosome 6 in humans has a linkage to the plasminogen (PGN) gene, and is inherited in a codominant Mendelian model. apo(a) mRNA (14 kb) encodes for a mature protein of 4529 amino acid residues in the presence of a signal peptide with 19 amino acid residues. A high-degree homology exists between the molecular structures of the apo(a) gene and the PGN gene. In addition, the apo(a) gene contains two structural regions which are similar to the Kingle region of the PGN gene. The high-degree homology between the apo(a) gene and the PGN gene determines the biological actions of Lp(a).

The polymorphism of the apo(a) gene mainly results from differences in the repeat numbers of a Kingle4-like structure, which has a high-degree homology with that of the PGN gene. The plasma Lp(a) concentration of apo(a) Type B is ten times as many as that of apo(a) type S4. Researchers have suggested that the levels of Lp(a) are determined by a main apo(a) gene and a polygenic background.

In general, the plasma Lp(a) level is quite stable, unaffected by sex, age, diet or other physical factors. Increased plasma Lp(a) level may be considered as an important and independent risk factor for atherosclerosis and cardiovascular diseases. There is a direct correlation between the structural polymorphism of the apo(a) gene and the occurrence of cardiovascular diseases.

Hepatic production of Lp(a) and clinical importance
The liver is the major organ of energy metabolism, and plays a critical role in both the production and catabolism of lipids, apolipoproteins and lipoproteins. Lp(a), mainly produced and taken up by the liver, maintains a stable plasma concentration of Lp(a). Serum Lp(a) level can change in many pathophysiological processes including inflammatory disease and also in liver damage. In general, hepatocellular damage may be linked to a reduced Lp(a) serum level. Geiss et al. longitudinally observed hepatitis patients who showed a marked increase in Lp(a) concentration from 7 mg/dl in acute stage to 32 mg/dl in convalescence, thus acute hepatitis is associated with decreased Lp(a) serum levels.

Plasma Lp(a) concentration is mainly correlated with its hepatic rate of synthesis, but not clearly related to the decomposition or distribution of Lp(a) in plasma. Plasma Lp(a) levels are positively correlated with atherosclerosis and thrombosis. The pro-thrombotic role of Lp(a) is due to the structure of apo(a) that is very similar to that of PGN in addition to the role of apo(a) in promoting thrombosis by interference with the physiological function of PGN. Several clinical and laboratory experiments have shown that Lp(a) competitively inhibits the combination of PGN with platelets, macrophages and endothelial cells, and it also inhibits the activation of PGN on the surface of endothelial cells. Epidemiological investigations demonstrated that plasma Lp(a) concentration is closely related to early myocardial infarction, the plasma Lp(a) concentration is even closely related to the severity of coronary artery disease and the liver is the main location of Lp(a) metabolism.

Changes of Lp(a) in HCC
The liver is the main organ of Lp(a) synthesis. Lp(a) level in serum from HCC patients is strikingly decreased compared with that of normal subjects, and Lp(a) level decreases in cirrhotic patients. Other factors such as hormones, cytokines, genetics and nutrition may be involved differently, with each single protein being synthesized by the liver. Lp(a) is produced by the liver and its levels may decrease in patients with chronic liver diseases. Inflammatory liver diseases including HCC are characterized by the production and delivery of cytokines influencing serum Lp(a) levels. In general, serum Lp(a) level is significantly lower in patients with chronic liver diseases and HCC. The mechanisms by which the tumors induce cachexia involve inflammatory cytokine production, which is responsible for a large
number of metabolic disorders, essentially involving in lipid metabolism.\textsuperscript{[45, 46]}

The half-life of Lp(a) is about 3.3-3.9 days in human plasma,\textsuperscript{[32]} which is influenced in the early stage when liver function is impaired.\textsuperscript{[18]} Lp(a) is synthesized and metabolized independently in other plasma lipoproteins, and its level is not influenced by various dietary manipulations.\textsuperscript{[45]}

Hepatocellular injury and/or chronic liver diseases which are frequently found in HCC may result in an abnormal pattern of plasma lipids, apolipoproteins and lipoproteins. It has been reported that serum Lp(a) level is significantly lower in HCC patients.\textsuperscript{[40, 46]}

Similar results were observed in our recent studies (in press). In addition, Geiss et al\textsuperscript{[33]} found that patients with acute hepatitis showed a marked increase in Lp(a) concentration, i.e., 7 mg/dl in the acute stage and 32 mg/dl in convalescence. Lp(a) together with ferritin and alpha-fetoprotein are sensitive early markers to evaluate liver function.\textsuperscript{[13]}

We concluded that in general apo(a) and Lp(a) plasma levels display a significant correlation with hepatic status. The plasma levels of apo(a) and Lp(a) can be considered as an additional clinical index for liver function. The relation of apo(a) and Lp(a) to HCC and its clinical significance need further investigation.

Funding: None.

Ethical approval: Not needed.

Contributors: WCP and XN proposed the idea, structure and content of this article. JJT wrote the main body of the article. ZXG did the revision and final proofreading of the article. JJT is the guarantor.

Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Received May 28, 2008
Accepted after revision October 18, 2008