World Journal of Hepatology

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DOI: 10.4254/wjh.v8.i1.1

World J Hepatol 2016 January 8; 8(1): 1-8
ISSN 1948-5182 (online)

TOPIC HIGHLIGHT

2016 Advances in Hepatitis B Virus

Metabonomic window into hepatitis B virus-related hepatic diseases

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Author contributions: Hou Q searched the literature and drafted the review; Duan ZJ supervised the review.

Supported by Liaoning Natural Science Foundation of China, No. 2013B003.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Received: April 29, 2015
Peer-review started: May 7, 2015
First decision: August 11, 2015
Revised: November 23, 2015
Accepted: December 17, 2015
Article in press: December 18, 2015
Published online: January 8, 2016

Abstract

Metabonomics has recently been widely used to discover the pathogenesis and find potential metabolic markers with high sensitivity and specificity. Furthermore, it develops new diagnosis and treatment methods, increases early phase diagnosis rates of certain diseases and provides a new basis for targeted therapy. This review mainly analyzes the research progress of the metabonomics of hepatitis B virus (HBV)-related hepatic diseases, hoping to discover some potential metabolic markers for identification of HBV-related hepatic diseases from other etiologies and for HBV-related hepatitis, liver cirrhosis and hepatocellular carcinoma. This can contribute to early discovery, diagnosis and treatment, eventually increasing the survival rate of HBV-related hepatic diseases.

Key words: Metabonomics; Hepatitis B virus-related hepatic diseases; Hepatitis B; Hepatitis B virus-related liver cirrhosis; Hepatitis B virus-related hepatocellular carcinoma

Core tip: This review mainly analyzes the research progress of the metabonomics of hepatitis B virus (HBV)-related hepatic diseases, hoping to discover some potential metabolic markers which can distinguish HBV-related hepatic diseases from other etiologies and discover potential metabolic markers of HBV-related hepatitis, liver cirrhosis and hepatocellular carcinoma, which can contribute to early discovery, diagnosis and treatment.

Hou Q, Duan ZJ. Metabonomic window into hepatitis B virus-related hepatic diseases. *World J Hepatol* 2016; 8(1): 1-8 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i1/1.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i1.1

METABONOMICS AND THE LIVER IN BRIEF

The main function of the liver is the synthesis and metabolism of various proteins, polysaccharides and fats and the detoxification of the body's normal metabolic wastes, such as uric acid, drugs and chemical products[1,2]. There are many hepatic diseases that threaten health. However, because of a lack of effective early diagnosis methods, a large number of the diseases are in the middle to late stages when detected, which seriously affects the prognosis. Therefore, it is important to find tumor markers with high sensitivity and specificity as well as to elucidate the pathogenesis.

Metabonomics, a branch of systematic biology, is a recent newly developing subject. It aims to explore biological systems, like the changes in metabolites of the cells, tissues and certain organisms in the environment of exogenous stimulations, especially studying metabolites weighing less than 1000. Metabonomics integrates gene regulation, post-transcriptional regulation and the interaction of the pathways together, which makes different metabolites manifest significant biological phenotypes through the stages of the cell directly. Compared to the vast information in genomics, transcriptomics and proteomics, there is more information about apparent learning[3]. Thus, metabonomics has recently been widely used to discover the pathogenesis, finding potential metabolic markers with high sensitivity and specificity and exploring new diagnosis and treatment methods in order to increase early phase diagnosis rates of certain diseases and provide a new basis for targeted therapy[4].

The morbidity of hepatocellular carcinoma (HCC) ranks 5th and its mortality ranks 3rd as a malignancy worldwide[5]. The incidence in southeast Asia and Africa is especially high, about 20 per 100000 population[6]. HCC has many risks with HBC as the primary one, causing 780000 death yearly[7]. The evolutionary progress of chronic hepatic disease is from chronic hepatitis B (CHB), hepatitis B virus (HBV)-related cirrhosis to HBV-related HCC. Nowadays, liver biopsy is the golden criteria in differentiating hepatic fibrosis, liver cirrhosis (LC) and HCC but cannot be used universally because of the invasiveness. Abdominal ultrasound is still the first screening method for hepatic diseases. It is widely used clinically because it is noninvasive and cheap. However, its sensitivity is affected by the machine, operators and different states of the disease. The sensitivity of diagnosing early cirrhosis is especially low, only 32% to 65% in HCC[8,9]. However, as a widely used clinical serum biomarker for HCC, alpha fetoprotein shows no increase in 80% of small HCC and its overall sensitivity is just 70%[8-11]. Some liver fibrosis indexes, such as hyaluronic acid, procollagen type Ⅲ, procollagen type Ⅳ and laminin, can indicate early hepatic cirrhosis by analyzing the proliferation and degeneration of hepatic fibrosis. However, its sensitivity and specificity remain unknown[12]. As an essential metabolic organ, any organic disease of the liver will lead to changes in the whole body's metabolism, causing widespread concern for medical staff. Research on the relationship between hepatic diseases and metabonomics has been increasing yearly. This review mainly analyzes the research progress of the metabonomics of HBV-related hepatic diseases, hoping to discover some potential metabolic markers for identification of HBV-related hepatic diseases from other etiologies and for HBV-related hepatitis, LC and HCC. It can contribute to early discovery, diagnosis and treatment, eventually increasing the survival rate of HBV-related hepatic diseases.

THE METABONOMIC WINDOW INTO HBV-RELATED HEPATIC DISEASES

CHB

Chronic HBV infection is a global problem, mainly in developing countries and especially in southeast Asia and Africa. About 600000 people die of acute or chronic HBV infection each year[13]. Chronic HBV infection can result in hepatitis, hepatic fibrosis and even LC and HCC. Presently, the main treatment methods for chronic HBV infection are interferon treatment[14-16], nucleotide analogue treatment[17-19], immune treatment[20-22], *etc.* Although they can reduce the transformation from CHB to LC and HCC, their cure rates still need to improve. In the meantime, the pathogenic pathway of chronic HBV infection is still unclear. In the metabonomic study of patients with chronic HBV infection, some metabolites with a significant difference were found, which may provide some basis for discovering a pathogenic pathway and ideas for new targeted therapy.

As shown in Table 1, there are 2 studies concerning CHB. Zhou *et al*[23] analyzed the metabolites in serum from CHB patients and a control group by liquid chromatography-mass spectrometry (LC-MS) and discovered 12 metabolites with a difference that were involved in fatty acids, amino acids, bile acids and energy metabolism and other pathways[24]. To date, there are still few metabonomic studies about CHB so it is a research domain that needs to be expanded. Autoimmune hepatitis (AIH) is an inflammatory reaction of the liver caused by autoantibodies. Early diagnosis can result in successful treatment. However, due to the unknown pathogenesis, the diagnostic rate is low and the prognosis cannot be estimated. Wang *et al*[25] studied metabonomic characteristics of AIH by nuclear magnetic resonance (NMR) for the first time, providing a basis for researching the pathogenesis of AIH and discovering potential metabolic markers further. About 11% of patients with nonalcoholic steatohepatitis (NASH) will develop LC after 15 years and 7% will develop HCC through LC or directly after 6.5 years[26]. The metabolic changes of NASH refer to the metabolism of fatty acids, carbohydrates and bile acids[27-29]. The metabonomic research for chronic hepatitis C has discovered that the

Table 1 Summary of metabolomic studies of chronic hepatitis B

Ref.	Year	Species	Tissue	Platform	Up-regulated	Down-regulated
Zhou *et al*[23]	2012	Human CHB 30 N 30 CHB/N	Serum	LC-MS	Cortisol, GCA, GCDCA, LysoPC (15:0), LysoPE (22:6), C16:1-CN	Tryptophan, C10-CN, C10:1-CN, C8-CN, C6-CN
Soga *et al*[24]	2011	Human CHB 7 N53 CHB/N	Serum	CE-TOM LC-MS	γ-Glu-Thr	

CHB: Chronic hepatitis B; LC-MS: Liquid chromatography-mass spectrometry; GCA: Glycocholic acid; GCDCA: Glycochenodeoxycholic acid; LysoPC: Lysophosphatidylcholine; LysoPE: Lysophosphatidylethanolamine; CN: C16:1-acylcarnitine.

Table 2 Summary of metabolomic studies of hepatitis B virus-related liver cirrhosis

Ref.	Year	Species	Tissue	Platform	Up-regulated	Down-regulated
Liu *et al*[42]	2013	Human LC 42 N 18 LC/N	Serum	NMR LC-MS	L-phenylalanine, C16 sphinganine, alpha-CEHC, LysoPC (18:1), linoelaidic acid, PC (18:4/20:1), bilirubin	L-carnitine, decanoyl-L-carnitine, phytosphingosine, 3α, 6α, 7α, 12α-tetrahydroxy-5β-cholan-24-oic acid PC (14:1/14:1), LysoPC (16:0)
Wang *et al*[39]	2012	Human LC 63 N 31 LC/N	Urine	GC-MS UPLC-TOFMS	Prolile, citrate, aconitate, 3,4-dihydroxyphenylacetate, taurohyocholate, glycocholate, glycoursodeoxycholate	Threonine, hippurate, 2-aminobutyrate, cis-aconitate, pyroglutamate, alpha-hydroxyisobutyrate, 3-hydroxyisovalerate, alpha-hydroxyhippurate, estrone
Zhou *et al*[23]	2012	Human CIR 30 N 30 CIR/N	Serum	LC-MS	GCA, GCDCA, CN	Tryptophan, LysoPC (20:5), LysoPC (0:0/14:0), LysoPC (22:6), LysoPC (14:0/0:0), LysoPE (20:4), C10-CN, C10:1-CN, C8-CN, C6-CN
Yin *et al*[41]	2009	Human LC25 N25 LC/N	Serum	RRLC	Taurocholic acid fragment, GCA, bilirubin, TCDCA fragment, GCDCA, oleic acid fragment, taurocholic acid fragment, carnitine fragment, L-acetylcarnitine	Hypoxanthine, lysoPC C18:2, LPC C18:3, LPC C16:1, LPC C18:0, Hypoxanthine fragment, inosine, taurine, 6-methylnicotinic acid
Xue *et al*[40]	2009	HBV infected human LC20 non-LC 20 LC/non-LC	Serum	GC-MS	Acetic acid, hexanoic acid, 1-naphthalenamine, butanoic acid	Sorbitol, D-Lactic acid, phosphoric acid, D-glucitol, glucose

HBV: Hepatitis B virus; LC-MS: Liquid chromatography-mass spectrometry; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; LC: Liver cirrhosis; PC: Phosphatidylcholine; NMR: Nuclear magnetic resonance; Alpha-CEHC: 2,5,7,8-Tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman; LysoPC: Lysophosphatidylcholine; LysoPE: Lysophosphatidylethanolamine; UPLC-TOFMS: Ultra-high performance liquid chromatography-time of flight-mass spectrometer; CN: C16:1-acylcarnitine; GC-MS: Gas chromatography-mass spectrometer.

up-regulation of AKR1B10 expression in urine leads to abnormal glucose metabolism[30]. In studies about acute alcoholic hepatitis, Rachakonda *et al*[31] detected metabolites that were distinctly different from those in alcoholic LC that were involved in the metabolic process of fatty acids, bile acids, proteins and carbohydrates.

LC

LC is the terminal stage of chronic liver diseases (CLD), with a high morbidity worldwide. Chronic HBV infection is an important pathogenic factor of LC[32] and the evolution of HBV-related LC is a gradual progress[33]. Due to a lack of specific diagnostic methods, the incidence rate of LC is 3.7 per 100 person-years in HBV carriers[34] and the 5 years survival rate of decompensated LC patients is only 14% to 35%[35,36], while 70% to 90% of HBV-related HCC developed from decompensated LC[37,38]. To date, there are still few valuable markers for early diagnosis of HBV-related LC and it is especially important to detect potential biomarkers with a higher sensitivity and specificity.

Table 2 shows 5 studies regarding the metabonomics of HBV-related LC, 4 of them based on serum and 1 based on urine. According to the Child-Pugh scores, all the LC patients were classified into three groups, A, B and C. Wang *et al*[39] carried out a urinary metabonomic study on the different stages of HBV-related LC and healthy controls using a gas chromatography-mass spectrometer (GC-MS) and ultra performance liquid chromatography time-of-flight mass spectrometry. They found metabolites with a significant difference in the three groups of LC, which may be potential metabolic markers in different stages of LC, providing a basis for the estimate of progress. Differently from the other three studies, Xue *et al*[40] chose patients with CHB as a control group and found nine metabolites with an obvious difference in total. The study also further verified the distinguishing ability by SAS software, showing that five out of twenty LC patients in Child-Pugh A were misdiagnosed as patients with CHB due to the small

sample size. Zhou *et al*[23] and Yin *et al*[41] analyzed the metabolites in the serum of a HBV-related LC group and healthy control group by LC-MS and NMR, with both methods discovering metabolites with differences[42]. Among these five articles, only one used hepatitis B patients as a control group and the others chose healthy volunteers. In these present studies, we still lack research that uses CHB patients as a control group. The identification sensitivity of potential metabolic markers in patients with early HBV-related LC and patients with CHB found in present studies should be further discussed.

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are two diseases relevant to metabolic disorders of bile acid. Due to the insidious onset and lack of effective diagnostic methods with high specificity, patients are usually in an advanced stage when diagnosed[43]. Trottier *et al*[44] analyzed the metabolic changes of 17 bile acids in patients with these two diseases by LC-MS. Compared to healthy volunteers, the primary bile acid in serum in the two diseases increased significantly, which may be associated with impairment of the enterohepatic circulation. Compared with PBC, the levels of secondary bile acid in the PSC group decreased obviously. It suggests that PBC is only relevant to the impairment of the extrahepatic bile duct, while PSC involves both the intrahepatic and extrahepatic bile duct. Furthermore, Bell *et al*[45] also drew similar conclusions by LC-MS. Acute-on-chronic liver failure (ACLF) is acute liver failure resulting from the acute deterioration of liver function on the basis of CLD, which can be accompanied by multiple organ failure at the same time. Due to its yearly increasing incidence and high mortality rate, ACLF is receiving more and more attention from the medical profession[46]. Amathieu *et al*[47,48] studied the metabonomic characteristics of LC patients with and without ACLF and detected obvious differences in the metabolic features of the two groups. Nie *et al*[49] discovered 17 potential markers by comparing HBV-related ACLF with HBV-related LC in Child-Pugh A and 11 of them had improved survival after treatment, which has implications for the early diagnosis and prognosis assessment of ACLF. Lian *et al*[50] researched metabolic differences in alcoholic LC and HBV-related LC by LC-MS and found that oleamide and myristamide increased significantly in patients with alcoholic LC but decreased distinctly in patients with HBV-related LC, which indicated that they both could be used as specific metabolic markers to distinguish alcoholic LC from HBV-related LC. By GC-MS and LC-MS, Fitian AI, Soga *et al*[24] and Fitian *et al*[51] found that some bile acids and dicarboxylic acids increased in hepatitis C virus (HCV)-related LC. Also, γ-glutamyl dipeptides were mentioned in both studies and there was thought to be some expressed differences in different types of hepatic diseases. Therefore, it can be used as a potential metabolic marker to differentiate various hepatic diseases. So far, metabonomics of various hepatic diseases is still in the primary stages, lacking the metabolomic difference analysis comparing the diverse types of hepatic diseases. Therefore, the field of metabonomics of hepatic diseases needs further research.

HCC

In China, over 80% of HCC cases resulted from chronic HBV infection, an evolutionary progress from CHB to LC and eventually to HCC[32,33]. To improve the diagnostic rate for early HCC, potential biomarkers with high specificity which can be adopted to screen the HBV-related LC need to be explored. Some metabolites which are specifically expressed in HBV-related HCC may provide a new horizon for the targeted treatment of HCC in the future.

In Table 3, 4 studies from China exploring metabolomics of HBV-related HCC are shown, complying with the regional differences of HCC. The potential metabolic markers found in these studies involve the metabolism pathways of fatty, amino and bile acids, energy and so on. Liu *et al*[52] researched the metabolomic characteristics of liver tissue in 10 patients with liver carcinoma by LC-MS. Based on the comparison of the central area of the tumor and distant tissue, 14 metabolites were found with obvious differences and 9 of them[53-55] have also been mentioned in other studies. However, beta-sitosterol, quinaldic acid, arachidyl carnitine, tetradecanal and oleamide have rarely been mentioned, possibly because the levels of these 5 metabolites are too low in serum to be detected. It indicates that although metabolic profiling of tissue cannot reflect the changes of systemic metabolism in the human body, it could actually reflect the changes of metabolic characteristics of certain tissues or organs. Li *et al*[56] compared the metabolomic characteristics of HBV infected HCC host cells HepG2.2.15 with HCC host cell HepG2 by NMR and found that 11 metabolites were obviously different. N-acetyl glucosamine kinase had a significantly increased expression in HepG2.2.15 and was involved in the hexosamine biosynthesis pathway, which demonstrated that the hexosamine biosynthesis pathway was activated in HBV infected cells, providing a new thought for studying targeted therapy for HBV infection in the future. Zhou *et al*[23] and Yin *et al*[41] analyzed the metabolites of HBV-related HCC and normal bodies by LC-MS and found some potential biomarkers of metabolism involved in the metabolism of fatty acid, phosphoric acid, amino acid and glucose. Both studies found that the expression of glycochenodeoxycholic acid, lysophosphatidylcholine and glycocholic acid were significantly different in patients with HCC.

Besides the infection with HBV, infection with HCV, the addition of alcohol and steatohepatitis are also important pathogenic factors in HCC. We found 3 studies regarding HCV-related HCC[51,57,58] from the United States. Compared to the research of HBV-related HCC, other body fluid samples were added, as well as serum, containing metabolomic characteristics of HCV-related HCC and LC. Bowers *et al*[57] analyzed the metabolomic

Table 3 Summary of metabolomic studies of hepatitis B virus-related hepatocellular carcinoma

Ref.	Year	Species	Tissue	Platform	Up-regulated	Down-regulated
Li *et al*[56]	2015	Human	Liver	NMR	Fructose-bisphosphatealdolase, glucose-6-phosphate isomerase, alpha-enolase, citrate synthase	4-hydroxyphenylpyruvate dioxygenase
		Hepatoblastoma cell line HepG2.2.15/HepG2	Host cell		Phosphoglycerate kinase 1 Triosephosphate isomerase Sussinate dehydrogenase Malate dehydrogenase	Fumarylacetoacetase
Liu *et al*[52]	2013	Human	Liver	UPLC-MS	Sitosterol-beta, L-phenylalanine, LysoPC [18:2 (9Z, 12Z)], quinaldic acid glycerophosphocholine, LysoPC (18:0)	Arachidyl carnitine
		HCC 10			LysoPE (18:0/0:0), chenodeoxycholic acid glycine conjugate	Tetradecanal
		Central/distant			LysoPE [18:3 (9Z, 12Z, 15Z)/0:0] LysoPC [22:6 (4Z, 7Z, 10Z, 13Z, 16Z, 19Z)] M LysoPC [20:4 (5Z, 8Z, 11Z, 14Z)]	Oleamide
Zhou *et al*[23]	2012	Human HCC 30 N 30 HCC/N	Serum	LC-MS	GCA, GCDCA, C16:1-CN	Tryptophan, C10:1-CN, C8-CN, C10-CN, C6-CN, LysoPC (20:5) LysoPC (0:0/14:0), LysoPC (20:3), LysoPC (14:0/0:0)
Yin *et al*[41]	2009	Human HCC 24 N 25 HCC/N	Serum	LC-MS	Taurocholic acid, GCA, bilirubin, TCDCA, GCDCA, oleic acid, taurocholic acid, carnitine, L-acetylcarnitine	Hypoxanthine, phytosphingosine, dihydrosphingosine, LPC C18:2, LPC C18:3, LPC C16:1, LPC C18:0 phytosphingosine, inosine, hypoxanthine, taurine, 6-methylnicotinic acid

LC-MS: Liquid chromatography-mass spectrometry; LysoPC: Lysophosphatidylcholine; LysoPE: Lysophosphatidylethanolamine; LPC: Lysophosphatidylcholine; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; UPLC-TOFMS: Ultra-high performance liquid chromatography-time of flight-mass spectrometer; CN: C16:1-acylcarnitine; HCC: Hepatocellular carcinoma.

characteristics in serum and urine from HCV-related HCC and chronic hepatitis C patients by LC-MS. Fitian *et al*[51] and Baniasadi *et al*[58] also studied the diversity of serum metabolomics in patients with HCV-related HCC and LC, resulting in some potential metabolic markers with significant differences being detected. There are increasing numbers of people addicted to alcohol with the speeding pace of modern society and about 1/3 of HCC cases result from alcohol worldwide[59]. Nahon *et al*[60] analyzed the metabolic changes of alcoholic LC and HCC by NMR and discovered that the metabolites in a group of alcoholic LC without HCC were apparently different from that of alcoholic LC with large HCC. Glutamine decreased greatly, while metabolites such as glutamate and glycoprotein increased sharply. It indicated that glutamine degradation and glycolysis might be the main metabolic pathway of energy in hepatoma cells. With the improvement of living standards and the changes in lifestyle, the incidence of non-alcoholic fatty liver disease is increasing yearly and is currently up to 30% in developed countries[61,62]. Excessive deposition of fat in the liver can cause NASH, liver fibrosis, LC and even HCC[63]. Beyoğlu *et al*[64] specifically analyzed the research about non-alcoholic HCC in their review. Most of the research used healthy people as the control group, while a small part used patients with LC. The potential metabolic markers detected were involved in the metabolic processes of fatty acids, bile acids and so on. There are some differences between the metabolic markers found in this research and in the research on HBV-related HCC. More research is needed to find the pathogenesis in order to provide the basis for targeted treatment of HCC of different etiologies in the future.

PROSPECTS

Metabonomics is still in the beginning and developing stage but it has drawn wide attention from the medical community. There are some short comings in its analysis technology and data analysis methods which require further completion and improvement. At present, metabonomics is just applied to common diseases. In our review, there are some obvious metabonomic differences between HBV-related hepatic diseases and other liver diseases, which have some research value and may provide evidence for detecting specific markers and elucidating the pathogenesis of HBV-related hepatic diseases. With the continuous development of medical technology, the prospect of metabonomics is immeasurable. It is expected to develop and enhance clinical diagnosis and treatment in the future, with genomics, transcriptomics and proteomics.

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