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**Metabonomic window into hepatitis B virus-related hepatic diseases**

Hou Q *et al*. Metabonomics in HBV-related hepatic diseases

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**Abstract**

Metabonomics recently has been widely used in discovering the pathogenesis, finding potential metabolic markers with high sensitivity and specificity. Furthermore, developing new diagnosis and treatment methods, elevate early phase diagnosis rates of certain disease and provide new basis for targeted therapy. This review mainly analyzes the research progress of metabonomics of hepatitis B virus (HBV)-related hepatic diseases, hoping to discover some potential metabolic markers of identification of HBV-related hepatic diseases from other etiologies, and of HBV-related hepatitis, liver cirrhosis and hepatocellular carcinoma. It can contribute to the early discovery, diagnose and treatment,and eventually raise 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

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**Core tip:** This review mainly analysis the research progress of 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 the potential metabolic markers of HBV-related hepatitis, liver cirrhosis and hepatocellular carcinoma, which can contribute to the early discovery, diagnose and treatment.

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**METABONOMICS AND THE LIVER IN BRIEF**

The main function of the liver is the synthesis and metabolism of various protein, polysaccharide and fat, detoxification of the body’s normal metabolic wastes such as uric acid, intaked drugs and chemical products[1,2]. There are so many hepatic diseases that threat our health. However, because of lacking effective early diagnosis methods, a large number of the diseases have been in middle-late stage when detected. It affects the prognosis seriously. So it is of great importance to find the tumor markers with high sensitivity and specificity, and to explicit the pathogenesis as well.

Metabonomics, a branch of systematic biology, is a newly developing subject in the recent decades. It aims at exploring biological systems like the change of metabolite of the cell, tissue and certain organism in the environment of exogenous stimulations, and expecially studying the metabolites weight less than 1000. Metabonomics integrates the gene regulation, post-transcriptional regulation and pathways’s interaction together, which makes different metabolites manifest significant biological phenotypes through cell’s stage directly. Comparing to the vast information in genomics, transcriptomics and proteomics, it contains more information about apparent learning[3]. Thus, metabonomics recently has been widely used in discovering the pathogenesis, finding potential metabolic markers with high sensitivity and specificity, and furthermore, exploring new diagnosis and treatment methods, in order to raise the early phase diagnosis rates of certain disease and provide new basis for targeted therapy[4].

Hepatocellular carcinoma (HCC), as a malignancy, its morbidity ranks 5th and its mortality ranks 3rd worldwide[5]. The incidence in Southeast Asia and Africa is especially high, about 20 per 100000 population[6]. HCC has many risks and HBC is the primary one, which causes 780000 death yearly[7]. The evolution progress of chronic hepatic disease is from chronic hepatitis B (CHB), HBV-related cirrhosis to HBV-related HCC. Nowdays, liver biopsy is the golden criteria in differentiating hepatic fibrosis, liver cirrhosis (LC) and HCC, but it can’t be operated universally because of the invasion. Abdominal ultrasound is still the first screening method for hepatic diseases. It is widely used in clinic because it is noninvasive and cheap. However, its sensitivity is affected by the machine, operators and different states of the disease. The sensitivity in diagnosing early cirrhosis is especially low, the sensitivity in HCC is only 32% to 65%[8,9]. As a widely used serum biomarker for HCC in clinic, alpha fetoprorotein (AFP), however, shows no increase in 80% of the small HCC, and, its overall sensitivity is just 70%[8-11]. Some liver fibrosis indexes, such as hyaluronic, procollagen type Ⅲ, procollagen type Ⅳ and laminin, can possibly indicate the 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 liver will lead to the changes of the whole body’s metabolism, which appealed to widespread concern of medical staff. In the recent decades, the researches of the relationship between hepatic diseases and metabonomics are increasing yearly. This review mainly analyzes the research progress of metabonomics of hepatitis B virus (HBV)-related hepatic diseases, hoping to discover some potential metabolic markers of identification of HBV-related hepatic diseases from other etiologies, and of HBV-related hepatitis, LC and HCC. It can contribute to the early discovery, diagnose and treatment,and eventually raise the survival rate of HBV-related hepatic diseases.

**THE METABONOMIC WINDOW INTO HBV-RELATED HEPATIC DISEASES**

***CHB***

Chronic HBV infection is a global problem and mainly happens in developing countries, 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, even LC and HCC. Presently, the main treatment methods of chronic HBV infection are interferon treatment[14-16], nucleotide analogues 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 be further improved. In the meantime, the pathogenic pathway of chronic HBV infection is still unclear. In metabonomics study of patients with chronic HBV infection, we found some metabolites with significant difference, which may provide some basis for discovering pathogenic pathway and new ideas for the new target therapy.

As shown in Table 1, there are 2 researches concerning CHB. Zhou*et al*[23] analyzed the metabolites in serum from CHB patients and control group by liquid chromatography-mass spectrometry(LC-MS), discovered 12 metabolites with difference, which were involved in fatty acids metabolism, amino acids metabolism, bile acids metabolism, energy metabolism and other pathways[24]. Nowadays, metabonomics studies about CHB are still few, so it is a research domain which still needs to be expanded. Autoimmune hepatitis (AIH) is an inflamatory reaction of the liver caused by autoantibodies. It is the early diagnosis that can achieve successful treated. However, due to the unknown pathogenesis, the diagnostic rate is low and the prognosis can not be estimated. Wang *et al*[25] have studied metabonomic characteristics of AIH by nuclear magnetic resonance(NMR) for the first time, which provides a basis for researching the pathogenesis of AIH and discovering the potential metabolic markers further. About 11% patients of nonalcoholic steatohepatitis (NASH) will develop to LC after 15 years, and 7% will develop into HCC through LC or directly after 6.5 years[26]. The metabolic changes of NASH refer to the metabolism of fatty acid, carbohydrate and bile acid[27-29]. The metabonomic researches to chronic hepatitis C have discovered that the up-regulation of AKR1B10 expression in urine lead to abnormal glucose metabolism[30]. In the studies about acute alcoholic hepatitis (AAH), Rachakonda*et al*[31] detected the metabolites which were distinctly different from that in alcoholic LC, and were involved in the metabolic process of fatty acids, bile acids, proteins and carbohydrate.

***LC***

LC is the terminal stage of chronic liver diseases (CLD) with a high morbidity worldwidely. Chronic HBV infection is an important pathogenic factor of LC[32], and the evolution of HBV-ralated LC is a gradual progress[33]. Due to lack of specific diagnostic methods, the incidence rate of LC was 3.7 per 100 person-years in HBV carriers[34], and the 5-years survival rate of decompensated LC patients of is only 14% to 35%[35,36], while 70% to 90% of HBV-related HCC was 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 that is detecting potential biomarkers with higher sensitivity and specificity.

In Table 2, there are 5 articles researching the metabonomics of HBV-related LC, 4 of them were based on the serum and 1 based on the 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 by gas chromatography-mass spectrometer (GC-MS) and ultra performance liquid chromatography time-of-flight mass spectrometry (UPLC-TOEMS). They have found the metabolites with significant difference in the three groups of LC, which may be the potential metabolic markers in different stages of LC and can provide basis for the estimate of progress. Different from the other three articles, Xue[40] chose patients with CHB as control group, and found nine metabolites with obvious difference in total. The study also further verified the distinguishing ability by SAS software, which showed that five of twenty LC patients in Child - pugh A were misdiagnosed as patients with CHB due to the small sample rearch. Zhou *et al*[23] and Yin *et al*[41] analyzed the metabolites in the serum of HBV-related LC group and healthy control group by LC-MS and NMR, and both methods have discovered the metabolites with differences[42]. Among above five articles, only one took hepatitis B patients as control group, while the others chose the healthy volunteers. In present studies, we still lack researches taking CHB patients as 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 types of diseases relevant to metabolic disorder of bile acid. Due to the insidious onset and lacking of effective diagnosis methods with high specificity, patients are mostly in advanced stage when are diagnosed[43]. Trottier *et al*[44] have analysed the metabolic changes of 17 bile acids of patients with the above two diseases by LC-MS. Compared to the healthy volunteers, the primary bile acid in serum in the two diseases increased significantly, which might be associated with the impairment of 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 extrahepatic bile duct, while PSC involves both the intrahepatic and extrahepatic bile duct. Furthermore, Bell *et al*[45] have also drawn the similar conclusion by LC-MS. Acute-on-chronic liver failure (ACLF) is an acute liver failure resulting from the acute deterioration of liver function on the basis of CLD, which can accompany with multiple organs failure at the same time. Because of its yearly increasing incidence and high mortality rate, ACLF is getting more and more attention of the medical profession[46]. Amathieu *et al*[47,48] studied the metabonomic characteristics of LC patients with ACLF and without ACLF, and detected the 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 improved in the survival patients after treatment, which has implications for the early diagnosis and prognosis assessment of ACLF. Lian *et al*[50] researched metabolic differences of 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 both of them 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*[24,51] found that some bile acids and dicarboxylic acids increased evidently in hepatitis C virus-related LC.There into,γ-glutamy1 dipetides was mentioned in both the two researches above, and it was thought to have some expressing differences in different types of hepatic diseases. So it can be used as the potential metabolic markers in differentiating various hepatic diseases. So far, Metabonomics on various hepatic diseases is still in primary stage, lacking the metabolomic difference analysis compared between the diverse types of hepatic diseases. So the field of metabonomics on the hepatic diseases needs futher researches.

***HCC***

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

As shown in Table 3, we have searched 4 studies exploring metabolomics regrading HBV-related HCC, they are all from China, complying with the regional differences of HCC. The potential metabolic markers we found in these studies involve metabolism pathway of fatty acid, amino acid, bile acid，energy and so on. Liu *et al*[52] have researched the metabolomic characteristics of liver tissue in 10 patients with liver carcinoma by LC-MS. Based on the comparison of central area of the tumor and distant tissue, we found 14 metabolites with obvious differences, and 9 of them[53-55] have also been mentioned in other studies. However, sitosterol-beta, Quinalic acid, Arychidyl carnitine, Tetradecanal and Oleamide have rarely been mentioned, which possibly due to the levels of this 5 metabolites are too low in serum to be detected. It indicates that although metabolic profiling of tissue cannot reflect the changes of systemic metabolic in 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, andfound 11 metabolites were obviously different. Thereinto N-acetyl glucosamine kinase (NAGK) had significantly increased expression in HepG2.2.15 and was involved in hexosamine biosynthesis pathway, which demonstrated hexosamine biosynthesis pathway was activated in HBV infected cells, and it provided a new thought for studying the target therapy to HBV infection in the furture. Zhou *et al*[23] and Yin *et al*[41] analyzed the metabolities 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 the two studies above found the expression of glycochenodeoxycholic acid (GCDCA), lysophosphatidylcholine (LysoPC) and glycocholic acid (GCA), were significant difference in patients with HCC.

Besides the infection of HBV, the infection of hepatitis C virus (HCV), alcohol addition and steatohepatitis are also the important pathogenic factors of HCC. We have searched 3 studies regarding HCV-related HCC[51,57,58] from the United States. Compared to the researches of HBV-related HCC, they added more about other body fluid samples in addition to serum, and contained the metabolomic characteristics of HCV-related HCC and LC. Bowers *et al*[57] have analyzed the metabolomic characteristics in serum and urine from HCV-related HCC and chronic hepatitis C patients by LC-MS. Fitian *et al*[51], Baniasadi *et al*[58] have also studied the diversities of serum metabolomics in patients with HCV-related HCC and LC, as a result, some potiential metabolic markers with significant differences were detected. There are more and more people addicted to alcohol with the speeding pace of modern society, and about 1/3 HCC patiences are resulted from alcohol worldwide[59]. Nahon*et al*[60] analyzed the metabolic changes of alcoholic LC and HCC by NMR and discovered that metabolites in 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 pathways of energy in hepatoma cells. With the improvement of living standards and the changes of lifestyle, the incidence of non-alcoholic fatty liver disease (NAFLD) is increasing yearly, and it is up to 30% in the developed countries currently[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 researches about the non-alcoholic HCC in their review, and most of the researches took the normal people as the control group, while a small part took the patients with LC. The potential metabolic markers they detected were involved in the metabolic process of fatty acid, bile acid and so on. There are some differences between the metabolic markers found in the researches above and in the researches about the HBV-related HCC. To provide the basis for the target treatment of HCC of different etiologies in the future, we need to do more researches to find the pathogenesis.

**PROSPECT**

Metabonomics is still in the begining and developing stage, but it has drawn wide attention from medical community. There are some shortages in its analysis technology and data analysis methods, which require further completion and improvement. At present, metabonomics is just applied to the common diseases, in our review, there are some obvious metabonomic differences between HBV-related hepatic diseases and other liver diseases, so it has certain research value, and may provide evidence for detecting specific markers and expliciting 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 the clinical diagnosis and treatment in the future, as the genomics, transcriptomics and protcomics.

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| **Table 1 Summary of metabolomic studies of chronic hepatitis B** |
| Ref. | Year | Species | Tissue | Platform | Up-regulated | Down-regulated |
| Zhou *et al*[24] | 2012 | Human CHB 30 N 30CHB/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*[25] | 2011 | HumanCHB 7 N53CHB/N | serum | CE-TOMLC-MS |  ɤ-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.

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| **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*[43] | 2013 | HumanLC 42 N 18LC/N | Serum | NMRLC-MS | L-Phenylalanine, C16 Sphinganine, Alpha-CEHC, LysoPC (18:1),Linoelaidic acid, PC (18:4/20:1), Bilirubin | L-Carlitine, Decanoyl-L-carnitine, Phytosphingosine, 3α, 6α, 7α, 12α-Tetrahydroxy-5β-cholan-24-oic AcidPC (14:1/14:1),LysoPC (16:0) |
| Wang *et al*[40] | 2012 | HumanLC 63 N 31LC/N | Urine | GC-MSUPLC-TOFMS |  Prolile, Citrate, Aconitate, 3,4-Dihydroxyphenylacetate, Taurohyocholate, Glycocholate, Glycoursodeoxycholate | Threonine, Hippurate, 2-Aminobutyrate, cis-Aconitate, Pyroglutamate, Alpha-Hydroxyisobutyrate, 3-Hydroxyisovalerate, Alpha-hydroxyhippurat, Estrone |
| Zhou *et al*[24] | 2012 | HumanCIR 30 N 30CIR/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*[42] | 2009 | HumanLC25 N25LC/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, Hypoxinthine fragment, Inosine, Taurine, 6-Methylnicotinic acid |
| Xue *et al*[41] | 2009 | HBV infected HumanLC20 non-LC 20LC/non-LC | Serum | GC/MS | Acetic acid, Hexanoic acid, 1-Niphthalenamine, Butanoic acid | Sorbitol, D-Lactic acid, Phosphoric acid, D-glucitol, Glucose |

CHB: Chronic hepatitis B; LC-MS: Liquid chromatography-mass spectrometry; GCA: Glycocholic acid; TCDCA: Taurochenodesoxycholic 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.

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| **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*[61] | 2015 | Humanhepatoblastoma cell line HepG2.2.15/HepG2  | Liver host cell | NMR | Fructose-bisphosphatealdolase, Glucose-6-phosphate isomerase, Alpha-enolase, Citrate synthase,Phosphoglycerate kinase 1,Triosephosphate isomeraseSussinate dehydrogenaseMalate dehydrogenase | 4-Hydroxyphenylpyruvate dioxygenase,Fumarylacetoacetase |
| Liu *et al*[56] | 2013 | HumanHCC 10central/distant | Liver | UPLC-MS | sitosterol-beta, L-phenylalanine, LysoPC [18:2 (9Z, 12Z)], Quinalic acid Glycerophosphocholine, LysoPC (18:0)LysoPE (18:0/0:0), Chenodeoxycholic acid glycine conjugate,

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| LysoPE [18:3 (9Z, 12Z, 15Z)/0:0], |
| LysoPC [22:6 (4Z, 7Z, 10Z, 13Z, 16Z, 19Z)] MLysoPC [20:4 (5Z, 8Z, 11Z, 14Z)] |

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| Arychidyl carnitine |
| Tetradecanal |
| Oleamide |

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| Zhou *et al*[24] | 2012 | HumanHCC 30 N 30HCC/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*[42] | 2009 | HumanHCC 24 N 25HCC/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: Taurochenodesoxycholic acid; GCDCA: Glycochenodeoxycholic acid; UPLC-TOFMS: Ultra-high performance liquid chromatography-time of flight-mass spectrometer; CN: C16:1-acylcarnitine; HCC: Hepatocellular carcinoma.