

## Impact of hepatitis B virus infection on hepatic metabolic signaling pathway

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### Abstract

A growing body of epidemiologic research has demonstrated that metabolic derangement exists in patients with hepatitis B virus (HBV) infection, indicating that there are clinical associations between HBV infection and host metabolism. In order to understand the complex interplay between HBV and hepatic metabolism in greater depth, we systematically reviewed these alterations in different metabolic signaling pathways due to HBV infection. HBV infection interfered with most aspects of hepatic metabolic responses, including glucose, lipid, nucleic acid, bile acid and vitamin metabolism. Glucose and lipid metabolism is a particular focus due to the significant promotion of gluconeogenesis, glucose aerobic oxidation, the pentose phosphate pathway, fatty acid synthesis or oxidation, phospholipid and cholesterol biosynthesis affected by HBV. These altered metabolic pathways are involved in the pathological process of not only hepatitis B, but also metabolic disorders, increasing the occurrence of complications, such as hepatocellular carcinoma and liver steatosis. Thus, a clearer understanding of the hepatic metabolic pathways affected by HBV and its pathogenesis is necessary to develop more novel therapeutic strategies targeting viral eradication.

**Key words:** Hepatitis B virus infection; Nucleic acid metabolism; Metabolic derangement; Metabolic signaling pathway; Glucose metabolism; Lipid metabolism; Bile acid metabolism; Vitamin metabolism

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**Core tip:** Currently, hepatitis B virus (HBV) infection still poses a serious threat to public health, and causes

approximately 1 million deaths annually due to HBV-related liver diseases. Thus, investigation into the complex host cellular responses to HBV infection is a crucial area of research. Multiple epidemiologic data have proved that patients with HBV infection often have metabolic disorders. Therefore, we systematically reviewed the alterations in metabolic response to HBV infection with regard to molecular mechanisms. Deciphering the detailed interplay mechanisms would contribute to our understanding of HBV-induced pathological processes and may lead to nutritional therapies as new anti-HBV treatments.

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## INTRODUCTION

Chronic hepatitis B (CHB) is a serious global health concern, which is estimated to affect approximately 350 million people worldwide and carries a significantly increased risk of serious liver disorders including liver cirrhosis, hepatic decompensation or hepatocellular carcinoma (HCC). Approximately, one million deaths occur each year due to CHB and its complications<sup>[1,2]</sup>. However, the intrinsic mechanisms of hepatitis B virus (HBV)-induced diseases are unclear, and no complete cure is currently available for CHB. Thus, an investigation of the complex host responses to HBV infection is a crucial area of research, which in turn could provide a more thorough understanding of the pathogenesis and potential novel targets in antiviral drug discovery.

The HBV genome (3.2 kb) is a partially double-stranded, relaxed circular DNA, mainly controlled through the transcriptional activation of four promoters (core, X, pre-S1 and pre-S2/S) and two enhancers (EnhI and EnhII)<sup>[3-6]</sup>. The recruitment of cellular transcription factors to the binding sites of HBV genome could regulate virus transcription. Some of these transcription factors are ubiquitous nuclear receptors such as C-AMP-response element binding protein, specificity protein 1, prospero-related homeobox protein and nuclear respiratory factor 1; some are liver-enriched nuclear receptors such as hepatocyte nuclear factor 4, alpha (HNF4a), CAAT enhancer-binding protein, peroxisome proliferator-activated receptors, alpha/retinoid X receptors, alpha (PPARa/RXRa) and farnesoid X receptor (FXR)<sup>[7,8]</sup>.

Interestingly, the native role of most HBV-bound transcription factors is the coordination and control of hepatic metabolism<sup>[8]</sup>. For example, HNF4a plays a key role in glucose metabolism in the liver<sup>[9]</sup>. PPARa

controls fatty acid  $\beta$ -oxidation and is a crucial regulator of genes involved in the cellular fasting response<sup>[10]</sup>. FXR, activated by bile acids, is a molecular link between lipid metabolism and bile acid<sup>[11]</sup>. Thus, it indicates that HBV has adopted a smart mode of regulation, which is similar to that of major hepatic metabolic genes, implying that there is an association between metabolism and HBV infection. Our previous work also suggested that activation of fatty acid oxidation-associated PPARa was required for fasting-induced HBV transcription<sup>[12]</sup>.

Accumulating epidemiologic evidence has shown that there is still debate regarding the clinical associations between HBV infection and host metabolism. For instance, patients with chronic HBV infection, compared with healthy adults, have lower triglyceride (TG) and high-density lipoprotein (HDL) levels, but a higher adiponectin level<sup>[13]</sup>. A review by Janicko *et al.*<sup>[14]</sup> described strong correlations between CHB and the metabolic syndrome, non-alcoholic fatty liver disease or dyslipidemia, whereas an inconclusive association between diabetes mellitus and CHB has also been described. However, in metabolic signaling pathways, an increasing number of studies have shown that HBV modulates all aspects of host hepatic metabolism. In order to understand the unique interplay between HBV and hepatic metabolism in greater depth, we systematically reviewed these alterations in metabolic signaling pathways due to HBV infection.

## HBV AND GLUCOSE METABOLISM

Glucose homeostasis is regulated by balancing the output and the storage of glucose<sup>[15]</sup>. Glucose metabolism in hepatocytes can be divided broadly into two categories: anabolism and catabolism, including gluconeogenesis, glycolysis, aerobic oxidation and the pentose phosphate pathway.

Previous studies indicated that HBV infection could affect either gluconeogenesis or glucose aerobic oxidation. According to the study by Park<sup>[16]</sup>, hepatitis B virus X protein (HBx) functions as an important positive regulator of gluconeogenesis. In HBx-overexpressing (HBxTg) mice and inducible nitric oxide synthase (iNOS)-knocked out HBxTg mice, increased HBx expression significantly up-regulated the gene expression of hepatic key gluconeogenic enzymes (PEPCK, G6Pase) and the production of hepatic glucose, leading to hyperglycemia and impaired glucose tolerance. These effects are considered to be mediated through the nitric oxide (NO)/JNK pathway. However, other studies have demonstrated that HBV can promote glucose aerobic oxidation. By combining proteomics, metabolomics and molecular biological assays in HepG2.2.15 and HepG2 cell models, Li *et al.*<sup>[17]</sup> provided a holistic view of the interplay between host metabolism and HBV. They pointed out that enzymes which regulate the glycolysis pathway, such

as fructose-bisphosphate aldolase, alpha enolase, triosephosphate isomerase, phosphoglycerate kinase 1 and glucose-6-phosphate isomerase, and enzymes involved in the tricarboxylic acid (TCA) cycle, including malate dehydrogenase, citrate synthase and succinate dehydrogenase, are all significantly up-regulated in HepG2.2.15 cells, subsequently leading to elevated levels of corresponding intermediates, such as lactate in glycolysis and fumarate, succinate and 2-oxoglutarate in the TCA cycle. These data suggested that glycolysis and the TCA cycle are stimulated in host cells due to HBV infection. In addition, another study revealed that a HBV pre-S2 mutant could induce aerobic oxidation *via* activation of MTOR signaling, which may contribute to HBV tumorigenesis<sup>[18]</sup>.

Furthermore, HBV infection could promote the pentose phosphate pathway (PPP). Overexpression of HBx caused the nuclear translocation and activation of NF-E2-related factor 2, resulting in up-regulation of glucose-6-phosphate dehydrogenase, which is the first and rate-limiting enzyme of the PPP converting glucose-6-phosphate into 6-phosphogluconolactone<sup>[19]</sup>. Enhancement of the PPP by HBx-mediated elevation of G6PD provided host cells with more ribose for nucleotide biosynthesis to support their proliferation, which might contribute to HBV-associated hepatocarcinogenesis. The change in G6PD was also supported by a systems biology model<sup>[17]</sup>. It was reported that G6PD participating in the PPP was markedly increased, accompanied by elevated nucleotide levels, such as AMP, ADP, uridine 59-diphosphate and inosine-59-monophosphate.

## HBV AND LIPID METABOLISM

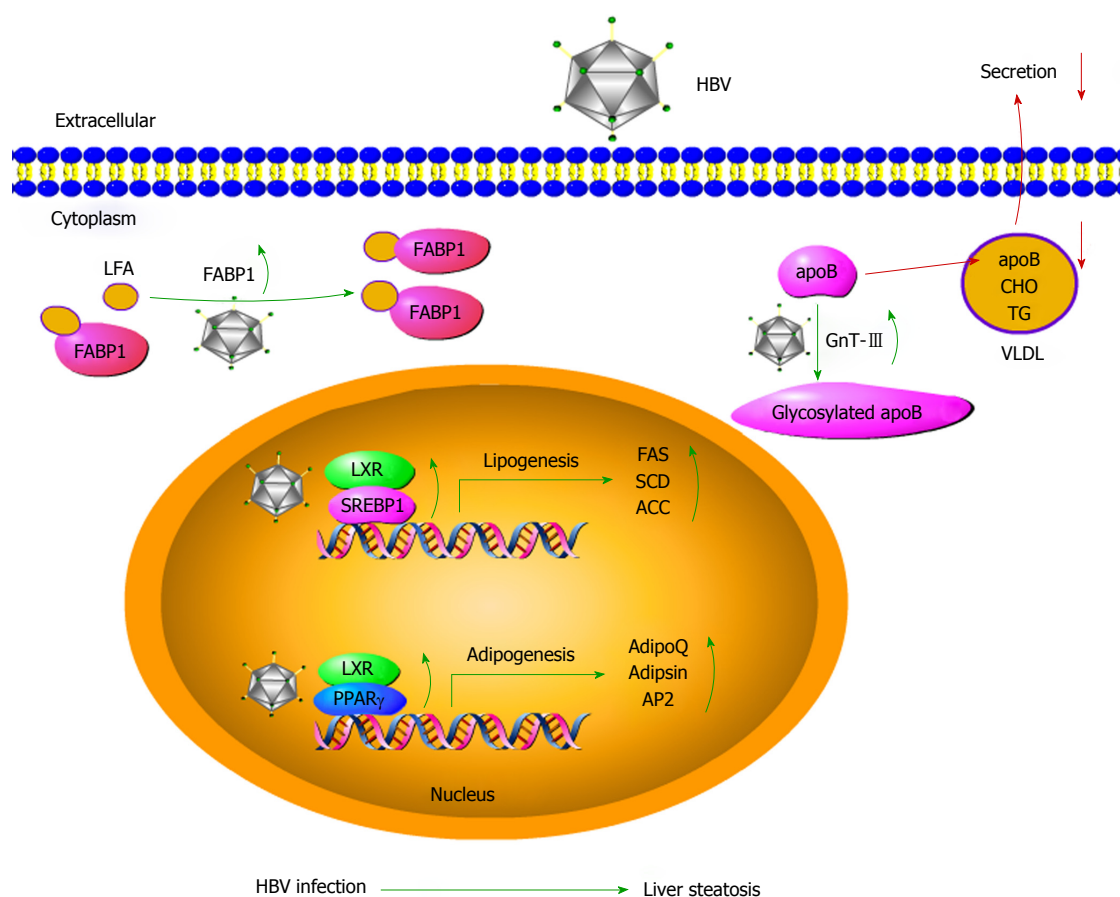
The liver, the main organ for the synthesis and circulation of lipids (*e.g.*, fatty acids, fats, phospholipids and cholesterol), oxidation of fatty acids and the production of ketone bodies, plays an important role in lipid metabolism<sup>[20]</sup>.

A significant amount of basic research has indicated that HBV infection has an effect on fatty acid metabolism. Many, but not all, studies have shown that HBV can promote the synthesis of fatty acids. Based on HPLC/MS analysis and two-dimensional electrophoresis (2-DE), fatty acid binding 5 and Acyl-CoA binding protein implicated in fatty acid metabolism and synthesis, which can bind Acyl-CoA and fatty acids with high affinity, are markedly increased in hepatitis B virus transgenic mice (HBV-Tg mice)<sup>[21]</sup>. HBV-influenced genes in lipid biosynthetic pathways in HBV-Tg mice were identified by cDNA microarray analysis, in which retinol binding protein 1 (RBP1), sterol regulatory element binding protein 2 (SREBP2), ATP citrate lyase and fatty acid synthase (FAS) were all strongly upregulated<sup>[22]</sup>. However, in contrast to the above studies, Wang *et al.*<sup>[23]</sup> recently proposed that up-regulation of HBx could facilitate fatty acid oxidation (FAO) and subsequently maintain intracellular NADPH

and ATP levels under glucose deprivation, which is of great importance for HCC cell survival under conditions of metabolic stress.

Recently, accumulating evidence from experimental investigations has suggested that HBV infection is a potential trigger of liver steatosis. HBx can induce hepatic steatosis at all aspects, such as increasing fatty acid binding, promoting lipid synthesis and inhibiting secretion of apolipoprotein (Figure 1). Fatty acid binding protein 1 (FABP1), responsible for the uptake, metabolism and transport of long-chain fatty acids (LFA)<sup>[24]</sup>, plays a key role in intracellular fatty acid utilization and transport<sup>[25]</sup>. Forced expression of HBx induced liver steatosis through up-regulation of FABP1, whereas gene silencing of FABP1 blocked lipid accumulation in both *in vivo* and *in vitro* models<sup>[26]</sup>. LXR, SREBP1 and PPAR $\gamma$  are master regulators in hepatic lipogenesis: LXR directly induces expression of SREBP1, which up-regulates lipogenic genes<sup>[27]</sup>; activation of LXR also stimulates adipocyte differentiation through induction of PPAR $\gamma$  expression<sup>[28]</sup>. Both are suggested to be of vital importance in hepatic lipid accumulation. Several studies have demonstrated that HBx increased the gene expression and transcriptional activity of LXR-mediated SREBP1 and PPAR $\gamma$ , thereby inducing the expression of hepatic lipogenic genes (fatty acid synthase, stearoyl-CoA desaturase, acetyl-CoA carboxylase) and adipogenic genes (adipsin, adiponectin, aP2/adipose fatty acid-binding protein), finally accompanied by the accumulation of lipid droplets<sup>[29-32]</sup>. Apolipoprotein B (apoB), required for the secretion and assembly of low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL), is assembled into a secretion-competent particle with lipids<sup>[33-35]</sup>. It has been reported that HBx mediated aberrantly glycosylated apoB by elevating the expression of N-Acetylglucosaminyltransferase III (GnT-III) resulted in inhibition of apoB secretion as well as intracellular accumulation of cholesterol and triglyceride<sup>[36]</sup>.

In addition, phospholipid and cholesterol metabolism are also altered by the presence of HBV. Phosphatidylcholine (PC) is a major component of the biological membrane<sup>[37]</sup>, and acts as a precursor for the synthesis of lipid signaling molecules<sup>[38]</sup>. In comparison with HepG2, the key enzymes participating in PC synthesis, such as choline-phosphate cytidyltransferase A, choline kinase a, choline phosphotransferase 1 and choline/ethanolamine phosphotransferase 1 are all up-regulated in HepG2.2.15 cells, consistent with the elevated levels of phosphocholine and reduced levels of choline<sup>[17]</sup>. These results strongly indicate that HBV infection can promote the biosynthesis of PC. Cholesterol, a type of lipid different from triglyceride and phospholipid, has two essential metabolic fates: conversion into bile acids or steroid hormones<sup>[39]</sup>. HBV-infected humanized mice displayed a significant increase in human genes related to the uptake, biosynthesis, and transcriptional regulation of cholesterol, such as low-density lipoprotein receptor (LDLR), hydroxy-



**Figure 1** The molecular mechanisms contributing to liver steatosis following hepatitis B virus infection. Hepatitis B virus (HBV) infection can induce the accumulation of lipids *via* three different regulatory mechanisms, including elevated expression of FABP1, up-regulation of LXR, SREBP1 and PPAR $\gamma$  and increased expression of Gnt-III. On the one hand, up-regulation of FABP1 would increase fatty acid binding and transport. On the other hand, induction of LXR-mediated SREBP1 and PPAR $\gamma$  would result in increased transcriptional activity of hepatic lipogenic genes (FAS, SCD, ACC) and adipogenic genes (adipoQ, adipsin, AP2). In addition, elevation of Gnt-III would cause glycosylation and dysfunction of apoB, finally leading to reduced secretion of VLDL (containing apoB, CHO and TG). LFA: Long-chain fatty acids; FABP1: Fatty acid binding protein 1; FAS: Fatty acid synthase; SCD: Stearoyl-CoA desaturase; ACC: Acetyl-CoA carboxylase; adipoQ: Adiponectin; AP2: aP2/adipose fatty acid-binding protein; apoB: Apolipoprotein B; Gnt-III: N-Acetylglucosaminyltransferase III; CHO: Cholesterol; TG: Triglyceride; VLDL: Very low density lipoproteins.

methylglutaryl-coenzyme A reductase (HMGCR) and SREBP2<sup>[40]</sup>. Another study provided evidence that HBV exacerbated hepatic cholesterol accumulation *via* up-regulation of LDLR and HMGCR in HepG2 cells<sup>[41]</sup>.

## HBV AND NUCLEIC ACID METABOLISM

It is well known that the main function of the nucleotide is the biosynthesis of nucleic acids. Many studies have reported that DNA damage can cause abnormalities in nucleic acid metabolism<sup>[42]</sup>. HBV infection also influences this process *via* HBx-induced DNA damage, which may result in the onset of hepatocarcinogenesis<sup>[43]</sup>. Thus, identifying the distinguishing nucleic acid metabolites under HBx induction may help to understand the occurrence of HCC. A new study<sup>[44]</sup> using a systematic approach combining metabolomics and mRNA microarray analysis indicated that HBx could initially induce DNA damage and then disrupt nucleic acid metabolism, resulting in a significant decrease in DNA damage-related genes (BRCA1, TP53, RPA1, DDB1, TCEA1

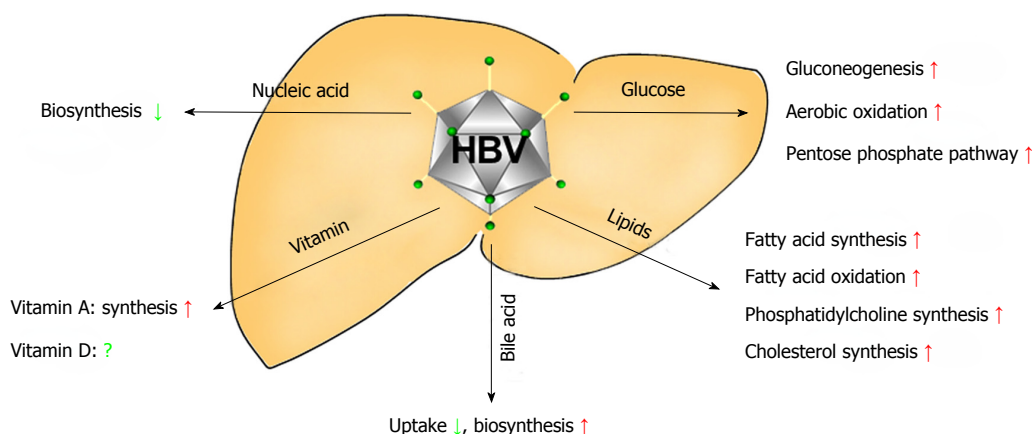
and NHEJ1) and intermediates of nucleic acid metabolism (guanosine, inosine and uridine), which in turn blocked DNA repair and probably contributed to the development of HCC.

## HBV AND BILE ACID METABOLISM

Bile acid, mainly synthesized in the liver from cholesterol, plays a key role in the digestion and absorption of lipids<sup>[45]</sup>. Human NTCP (SLC10A1), located in the basolateral membrane of hepatocytes, functions as a main transporter to mediate entry of bile salts from portal blood into hepatocytes<sup>[46]</sup>.

Recently, the detection of NTCP, acting as a functional entry receptor for HBV, clearly represents a typical milestone in our knowledge of HBV infection<sup>[47]</sup>. HBV exploits NTCP for species-specific entry into hepatocytes<sup>[48]</sup>. Hence, emerging evidence demonstrated the probable association between HBV infection and bile acid. Yan *et al.*<sup>[49]</sup> showed that the HBV pre-S1 lipopeptide efficiently blocked the uptake of bile salts





**Figure 2** Changes in the hepatic metabolic signaling pathway induced by hepatitis B virus infection. Alterations in related signaling pathways (including glucose, lipids, nucleic acids, bile acids and vitamins) following hepatitis B virus (HBV) infection are marked and highlighted in this figure. The influence of HBV infection on vitamin D metabolism is unclear.

by NTCP, suggesting that HBV infection may limit the physiological function of NTCP. Reduced bile salts could promote compensatory bile acid synthesis to maintain its homeostasis<sup>[50,51]</sup>. This compensation was confirmed by the strong induction of hCYP7A1 (the rate-limiting enzyme converting cholesterol to bile acid), decreased FXR (the positive transcription factor of SHP) nuclear translocation and significant reduction of SHP (the corepressor of hCYP7A1 transcription) in human liver-chimeric uPA/SCID mice infected with HBV<sup>[40]</sup>.

## HBV AND VITAMIN METABOLISM

Vitamin A, including retinol, retinal and retinoic acid, plays a critical role in visual function as well as cell growth and differentiation<sup>[52]</sup>. Previous data provided evidence that retinoic acid could enhance HBV transcription and replication through activation of RXRa<sup>[53,54]</sup>. Most interestingly, another study demonstrated that HBV infection could promote retinol metabolism-related proteins RBP, CRBP1 and ALDH1 as shown by 2-DE and MS/MS analysis<sup>[55]</sup>. It is reasonable that more retinol would be pumped into cells and converted into retinoic acid during HBV infection. HBV infection may up-regulate retinoic acid by promoting retinol metabolism and thereby facilitating self-replication through activation of RXRa, leading to an increased risk of liver damage, which was considered a positive feedback<sup>[56]</sup>.

Vitamin D, including its bioactive vitamin D metabolite [1,25(OH)<sub>2</sub>D<sub>3</sub>] and stable, easy-to-quantify metabolite (25(OH)D<sub>3</sub>), plays an emerging role in metabolic and inflammatory liver diseases<sup>[57]</sup>. A study has demonstrated a significant association between low levels of serum 25(OH)D<sub>3</sub> and high HBV DNA levels in CHB patients<sup>[57]</sup>. However, the molecular mechanism underlying inverse seasonal fluctuations of HBV DNA and 25(OH)D<sub>3</sub> serum levels still remains to be elucidated.

## CONCLUSION

In conclusion, we have systematically outlined the hepatic metabolic responses to HBV infection in this review. According to the above observations, multiple studies combining systematic approaches and molecular biological assays found that, from the molecular mechanism perspective, HBV infection interfered with the hepatic metabolic signaling pathway (Figure 2), including glucose, lipid, nucleic acid, bile acid and vitamin metabolism, ultimately resulting in metabolic derangement. Furthermore, these altered metabolic pathways may also contribute to the pathological processes of other HBV-induced diseases, such as hepatocellular carcinoma. Therefore, in this review, deciphering the molecular mechanisms of the metabolic pathways during HBV infection has shed new light on the pathological processes, and provides a new, revolutionary, potential means of directly fighting against this virus.

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