World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i31.7017

World J Gastroenterol 2016 August 21; 22(31): 7017-7029
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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REVIEW

Roles of hepatocyte nuclear factors in hepatitis B virus infection

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Author contributions: Kim DH and Kang HS contributed equally to this work; Kim DH, Kang HS and Kim KH analyzed the literature and wrote the manuscript.

Supported by Konkuk University in 2016.

Conflict-of-interest statement: No conflicts of interest.

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Manuscript source: Invited manuscript

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Received: March 29, 2016
Peer-review started: April 5, 2016
First decision: May 12, 2016
Revised: June 2, 2016
Accepted: June 28, 2016
Article in press: June 29, 2016
Published online: August 21, 2016

Abstract

Approximately 350 million people are estimated to be persistently infected with hepatitis B virus (HBV) worldwide. HBV maintains persistent infection by employing covalently closed circular DNA (cccDNA), a template for all HBV RNAs. Chronic hepatitis B (CHB) patients are currently treated with nucleos(t)ide analogs such as lamivudine, adefovir, entecavir, and tenofovir. However, these treatments rarely cure CHB because they are unable to inhibit cccDNA transcription and inhibit only a late stage in the HBV life cycle (the reverse transcription step in the nucleocapsid). Therefore, an understanding of the factors regulating cccDNA transcription is required to stop this process. Among numerous factors, hepatocyte nuclear factors (HNFs) play the most important roles in cccDNA transcription, especially in the generation of viral genomic RNA, a template for HBV replication. Therefore, proper control of HNF function could lead to the inhibition of HBV replication. In this review, we summarize and discuss the current understanding of the roles of HNFs in the HBV life cycle and the upstream factors that regulate HNFs. This knowledge will enable the identification of new therapeutic targets to cure CHB.

Key words: Hepatitis B virus; Hepatocyte nuclear factor; Covalently closed circular DNA; Replication

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Core tip: Hepatitis B virus (HBV) infection is the leading cause of chronic liver disease and death worldwide. Persistent HBV infection is a major risk factor for chronic hepatitis and is the leading cause of liver disease, including cirrhosis and hepatocellular carcinoma. In the HBV life cycle, hepatocyte nuclear factors (HNFs) play critical roles in covalently closed circular DNA transcription. Control of HNF expression

and function could regulate HBV replication. Therefore, understanding the upstream cellular factors or signals involved in the regulation of HNFs is important for controlling HBV replication.

Kim DH, Kang HS, Kim KH. Roles of hepatocyte nuclear factors in hepatitis B virus infection. *World J Gastroenterol* 2016; 22(31): 7017-7029 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i31/7017.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i31.7017

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is responsible for global public health problems and greatly increases the risk of liver diseases, including chronic hepatitis B (CHB), liver cirrhosis, and hepatocellular carcinoma (HCC). Although effective vaccination and approved nucleos(t)ide analog (NA) drugs have greatly contributed to reducing the number of newly infected individuals and the development of HBV-related liver diseases, sustained clearance of HBsAg or HBV DNA in liver tissues of CHB patients is rarely achieved using current NA drugs because of the inability of NAs to inactivate covalently closed circular DNA (cccDNA), a template for all HBV RNAs.

The HBV genome has four open reading frames (ORFs: PreC/C, P, preS1/S2/S, and X), which encode the precore and core proteins, polymerase, surface proteins, and HBx, respectively[1]. A unique feature of the HBV genome is the conversion of the 3.2-kb partially double-stranded relaxed circular DNA (rcDNA) into cccDNA in the nucleus[2,3], where five types of HBV RNAs are transcribed from the cccDNA. The production of HBV mRNAs is effectively regulated by complex interactions with various transcription factors. For example, transcription factors such as hepatocyte nuclear factors (HNFs) and CCAAT/enhancer binding protein (C/EBP) are critical for viral RNA production; these factors bind to HBV enhancers and promoters[4-7]. Interferon regulatory elements (IREs), which are present in the enhancer I (Enh I) region, regulate HBV gene expression[8]. Estrogen can suppress HBV Enh I activity by up-regulating estrogen receptor-α (ER-α), which binds to the enhancer region of HBV cccDNA and alters HNF4α binding[9]. By contrast, the androgen receptor binds to androgen-responsive elements present in HBV enhancers and thereby increases the transcription of HBV mRNAs[10]. The opposite effects of these two representative sex hormone receptors could explain the gender differences in HBV infection (males are more vulnerable than females to HBV-related HCC development). Accumulating evidence has indicated that the transcription of HBV genes is regulated by precise and ordered recruitment of chromatin modifiers and various host factors, including transcription factors, IREs, and sex hormones. Because there are no drugs that can inhibit cccDNA function, a thorough understanding of the mechanism of cccDNA transcription by cellular or viral factors will be useful for the development of drugs targeting cccDNA. This review will focus on the host factors, mainly HNFs, related directly or indirectly to the expression and regulation of HBV genes.

SHORT OVERVIEW OF THE HBV LIFE CYCLE

HBV is a prototype virus of the Hepadnaviridae family. According to the Baltimore classification, HBV is a Group Ⅶ virus, *i.e.*, a double-stranded DNA virus that replicates through a single-stranded RNA intermediate. HBV has a complex life cycle involving reverse transcription. The genomic structure of HBV is unique and is referred to as circular partial duplex DNA, consisting of circular double-stranded DNA (dsDNA) with one strand that is only partially complete. The HBV life cycle has more complicated stages than most other viruses; these stages are explained below in a simplified form. A graphical scheme of the HBV life cycle is depicted in Figure 1. For more detail, the reader is referred to a comprehensive review of the HBV life cycle[1].

HBV infects hepatocytes but not hepatoma cell lines such as HepG2 or Huh7. This lack of a suitable cell infection system has hampered the study of the mechanism of virus entry (and other infection steps), and, therefore, the development of entry inhibitors. The recent identification of sodium-taurocholate cotransporting polypeptide, also known as NTCP, as a functional receptor for HBV entry has opened the door for the study of the molecular mechanisms of HBV infection[11,12]. NTCP is a transporter involved in the uptake of bile salts, and the preS1 domain of the viral large envelope protein (L-HBsAg) interacts directly with NTCP as an essential step for viral entry; therefore, poorly differentiated hepatocytes such as Huh7 or HepG2 cells, which express negligible amounts of NTCP, are not susceptible to HBV infection[13,14].

A unique feature of L-HBsAg is myristoylation at its N-terminus, which enables its association with the plasma membrane. The highly conserved motif 9-NPLGF(F/L)P-15 in the receptor-binding region of L-HBsAg is also crucial for viral infection[15,16]. Although there is limited information regarding the processes of plasma membrane fusion and endosomal migration after HBV binding, several studies have demonstrated that the virus enters cells *via* clathrin-mediated endocytosis[17-19].

After entering the cell, the virus undergoes uncoating and core disassembly, and its genome enters the cell nucleus[20]. Nuclear import is mediated by nuclear localization signals of capsid proteins, and nuclear entry of the encapsidated, deproteinized

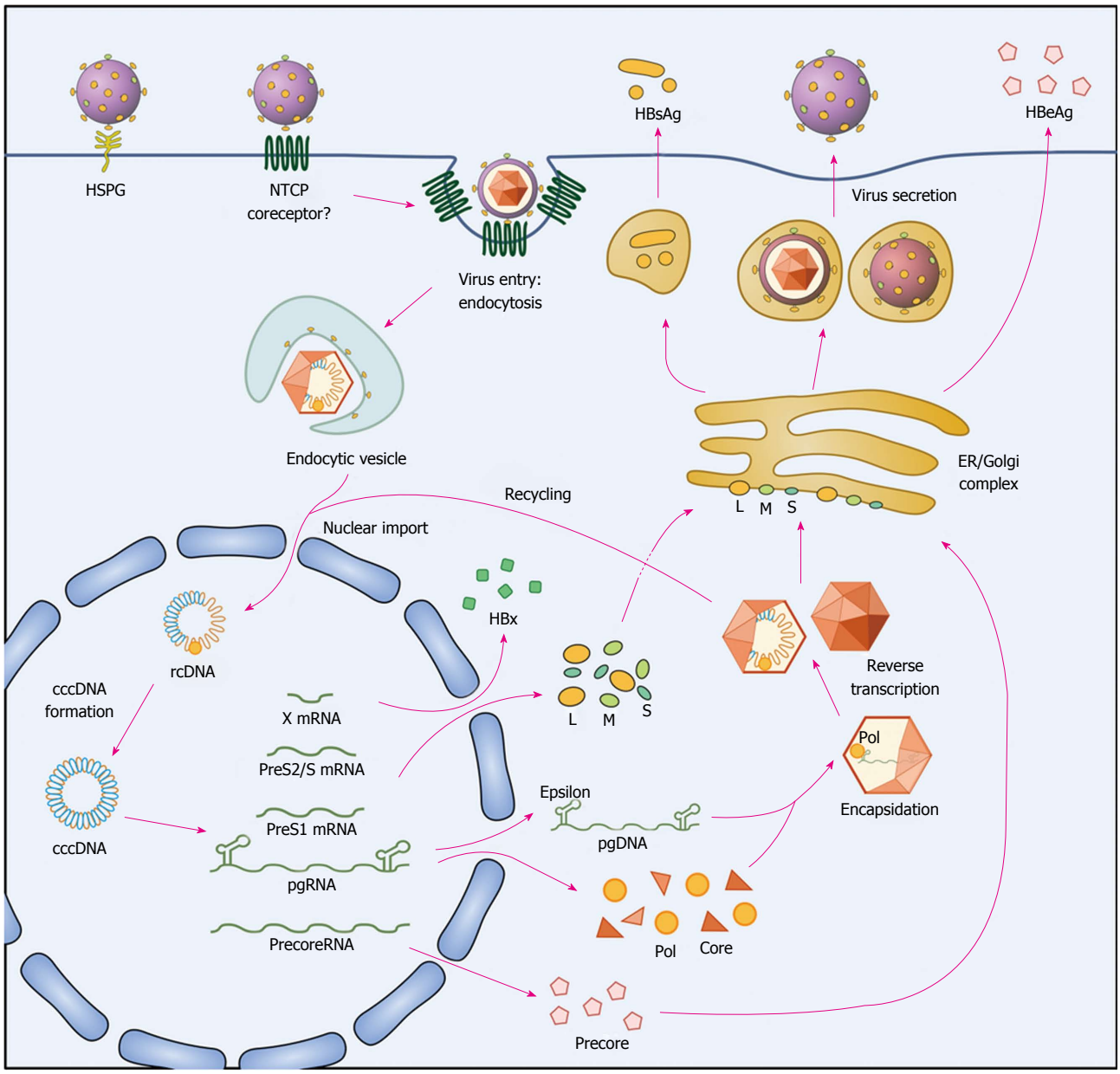

Figure 1 The life cycle of hepatitis B virus. Hepatitis B virus (HBV) binds to the surface receptor NTCP and enters hepatocytes, and its genome is released into the nucleus. The relaxed circular HBV genome (rcDNA) is repaired and forms covalently closed circular DNA (cccDNA), which serves as a template for the transcription of viral mRNAs (pregenomic (pg), precore, HBx, PreS1, and PreS2/S RNA). The HBV mRNAs are translated into the large (L), middle (M), and small (S) surface, precore, core, polymerase (pol), and HBx proteins. pgRNA and pol are encapsidated into the capsid, and viral DNA is reverse-transcribed. Assembled HBV virions are secreted from hepatocytes.

relaxed circular (rc) DNA uses the importin-α/importin-β receptor pathway[21]. Although the size of the genome-containing nucleocapsid of HBV is close to the functional diameter of the nuclear pore complex, the capsid was suggested not to release the viral genome before nuclear import. Unlike the capsids of other viruses, such as herpes virus, adenovirus, and influenza virus, the HBV capsid enters the nuclear basket in its intact form[22]. Only capsids with a mature genome enter the basket and consequently liberate the genome through the interaction with nucleoporin 153 (Nup153) in the nuclear basket of the nuclear pore complex[23].

Inside the nucleus, rcDNA is repaired (see below) by the host repair system to form cccDNA, which is stable and difficult to remove throughout HBV infection and therefore plays an important role in viral persistence and recurrence[24]. The cccDNA acts as a transcriptional template for five types of viral RNAs: the pregenomic RNA (pgRNA) and precore RNA (both 3.5-kb), 2.4-kb and 2.1-kb HBsAg RNAs, and 0.7-kb HBx RNA. The precore RNA is the template for the production of HBeAg; the core and polymerase proteins are translated from pgRNA, which also serves as a template for reverse transcription to produce the HBV DNA.

Packaging of the pgRNA and polymerase protein

into the viral capsid is initiated by a *cis*-acting element called epsilon, which acts as the packaging signal[25]. The epsilon, polymerase, and core proteins form the nucleocapsid. This process is referred to as encapsidation; when encapsidation is completed, polymerase begins reverse transcription of the pgRNA to generate the minus-strand DNA. The template pgRNA is simultaneously degraded by RNase H activity of polymerase before the synthesis of the plus-strand begins. After several rounds of strand transfer, formation of the circular genomic DNA is complete[26]. Genome-containing nucleocapsids interact with the envelope proteins in the ER-Golgi complex and form enveloped mature virions. The preS1, preS2, and S domains of surface proteins have different functions according to their transmembrane topology. The preS1 domain is located partially at the surface and partially on the internal side during virion maturation. The internal side of PreS1, which slightly overlaps with the PreS2 domain, interacts with core particles necessary for envelope formation[27], whereas the surface side of PreS1 interacts with a cellular receptor for virus entry. The infectious mature virions, known as Dane particles, exit the cell *via* the ER and Golgi apparatus, although the details of this process have not yet been completely revealed.

cccDNA AS A TEMPLATE FOR HBV TRANSCRIPTION

cccDNA plays a central role in HBV transcription and replication. cccDNA forms a minichromosome in the nucleus and becomes the source for pgRNA and other viral RNAs production, and virus replication occurs through reverse transcription of the pgRNA into rcDNA. NA drugs can inhibit reverse transcription and are currently used as a treatment for HBV[28,29]. However, these drugs are unable to affect cccDNA, which is upstream of the NA target site. To inhibit cccDNA transcription and to prevent the production of viral mRNAs, it is important to better understand how cccDNA is produced and functions.

Host factors involved in cccDNA formation

HBV rcDNA is converted to cccDNA *via* an intermediate form, protein-free rcDNA[30,31]. This process is referred to as repair; following plus-strand DNA synthesis by gap-filling, viral polymerase and short RNA oligomers (also called RNA primers) attached to the 5′-termini of minus-strand and plus-strand DNA should be removed[32]. Identification of the host factors involved in rcDNA to cccDNA conversion will provide potential new therapeutic targets to prevent cccDNA formation. A recent *in vitro* study suggested that host tyrosyl-DNA-phosphodiesterase 2 (TDP2) is involved in the removal of viral polymerase covalently linked to the 5′-end of minus-strand DNA[33]. However, knockout of the TDP2 gene does not block cccDNA formation during HBV infection of permissive hepatoma cells and does not prevent intracellular amplification of duck hepatitis B virus cccDNA[34]. Intriguingly, the knockdown of TDP2 increases the formation of HBV cccDNA[34]. Although several host enzymes, such as TDP2 and topoisomerase[35], were suggested to be involved in cccDNA biogenesis, the mechanisms of rcDNA repair and the host factors associated with cccDNA formation are largely unknown. Further studies aimed at revealing these steps are highly warranted.

Role of HBx in cccDNA function

HBx is essential for cccDNA transcription; therefore, the inhibition of HBx prevents HBV replication[36]. Accumulating evidence suggests that cccDNA transcription is epigenetically controlled. cccDNA forms a minichromosome in the nucleus and associates with histones, including H2A, H2B, H3, and H4. HBV transcription and replication is regulated by the acetylation status of cccDNA-bound histones and non-histone proteins[37]. Our understanding of the role of HBx in viral replication was considerably advanced by the finding that nuclear HBx binds to cccDNA and modifies the epigenetic regulation of cccDNA function. HBx recruits chromatin regulators such as P300 and other acetyltransferases to cccDNA and enhances viral transcription[38]. Conversely, if HBx is mutated so that it is unable to recruit acetyltransferases, cccDNA acetylation is reduced by histone deacetylases (HDACs), and the level of viral transcription and replication is reduced[38]. Moreover, occult HBV infection is demonstrated by epigenetic inactivation of cccDNA, and reactivation of cccDNA from this state is controlled by the epigenetic function of HBx[32].

Elimination or inactivation of cccDNA

Complete cure of HBV infection requires the elimination of cccDNA in liver tissues. Several studies have attempted to eliminate cccDNA by applying genome editing technologies. A zinc finger nuclease (ZFN) that was genetically designed to bind specifically to HBV cccDNA was shown to inhibit viral replication[39]. Engineered transcription activator-like effector endonucleases (TALENs) efficiently inactivated the HBV genome[40]. The RNA-guided clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system has been employed to cleave cccDNA[41]. However, genome editing technologies have numerous unresolved issues, including the *in vivo* delivery of genome editing molecules to HBV-infected hepatocytes, which is the key hurdle for clinical application of this technology.

Cytokines were recently shown to play an important role in the control of cccDNA. APOBEC3A and 3B, which are induced by high doses of interferon-alpha (IFN-α) or by the activation of lymphotoxin-β receptor, cause cytidine deamination in HBV cccDNA, which is subsequently degraded by a cellular endonuclease[42].

Table 1 Hepatocyte nuclear factors and other transcription factors involved in hepatitis B virus transcription

Factor	Binding site	Effect on viral enhancers/promoters	Ref.
HNF1α	PreS1	Activation	[60]
	Enh Ⅱ	Activation (interaction with hB1F)	[61]
	Enh Ⅱ	Suppression (mutant HBV core promoter)	[50]
	Enh Ⅱ	Activation	[62]
	Enh Ⅱ	Activation (mutant HBV core promoter)	[49]
HNF3β	Enh Ⅰ	Activation (interaction with STAT3)	[48]
	Enh Ⅰ	Suppression (HepG2)/ Activation (SK-Hep1)	[68]
	Enh Ⅱ	Suppression	[67]
	Enh Ⅱ	Activation	[66]
HNF4α	EnhII/PreS1	Activation	[73]
	Enh Ⅱ	Activation	[130]
HNF6	PreS2	Suppression	[78]
C/EBP	Enh Ⅰ	Suppression	[83]
	Enh Ⅱ	Activation	[81]
	Enh Ⅱ	Activation	[46]
	Enh Ⅱ	Activation	[80]
FXR/RXR	Enh Ⅱ	Activation	[99]
HLF	Enh Ⅱ	Activation	[6]
NF1	PreS2	Activation	[101]
	Enh Ⅰ	Suppression	[102]
SP1	Enh Ⅱ	Activation	[104,105]
	PreS1	Activation	[106]
	PreS2	Activation	[107]

HBV: Hepatitis B virus.

Because cccDNA is epigenetically regulated by HBx[38] and by the host antiviral factor IFN-α[43], the control of epigenetic factors that control cccDNA transcription may also be used to inactivate cccDNA. Epigenetic changes in cccDNA alter the binding of various liver-enriched transcription factors to its enhancer region. Therefore, understanding the interaction between transcription factors and enhancers will be important for cccDNA inactivation.

Structure of enhancers in HBV cccDNA and their regulatory transcription factors

Although HBV has a small genome, it has a large number of transcriptional regulatory sequences that have various roles. Genome transcription and replication can be stimulated or suppressed by the association or dissociation of numerous host factors. In particular, HNFs are the host factors that are present in hepatocytes in high concentrations, interact with viral components and play important roles in viral replication.

The HBV genome has four overlapping ORFs and contains several promoters, enhancers, a polyadenylation sequence, and an encapsidation signal. Four promoters are responsible for the transcription of the four ORFs. Two regions in the HBV genome, called Enh Ⅰ and Enh Ⅱ, have gene enhancer activity. Enh Ⅰ is a region of approximately 300 nucleotides located between the ORFs S and X[44]. Enh Ⅱ is a region of approximately 200 nucleotides, is located before the core promoter and overlaps with the core upstream regulatory sequence.

General transcription factors that bind to HBV promoters or enhancers include nuclear factor 1 (NF1), specificity protein 1 (SP1), activator protein 1 (AP1), TATA-binding protein (TBP), prospero-related homeobox protein 1 (PROX1), c-AMP-response element-binding protein (CREB), nuclear factor-kappa B (NF-κB), octamer transcription factor 1 (OCT1), and nuclear respiratory factor 1 (NRF1).

The hepatotropic nature of HBV infection is primarily mediated by hepatocyte-restricted expression of the viral receptor NTCP; however, the liver-enriched transcription control factors also play essential roles in the life cycle of HBV. Representative examples include hepatocyte nuclear factor 1α (HNF1α), hepatocyte nuclear factor 3β (HNF3β), hepatocyte nuclear factor 4α (HNF4α), hepatocyte nuclear factor 6 (HNF6), and CAAT enhancer-binding protein (C/EBP). A detailed description on these factors is provided in Table 1, and the binding sites of these factors to HBV enhancers and promoters are depicted in Figure 2.

REGULATION OF HBV GENE EXPRESSION BY HNFs AND miRNAs

Host factors that regulate HBV gene expression include transcription factors and microRNAs (miRNAs). Host transcription factors, especially liver-enriched factors, regulate the transcription of HBV cccDNA by binding to viral enhancers and promoters, whereas liver-enriched miRNAs regulate HBV gene expression post-transcriptionally.

HNFs are typical examples of liver-enriched transcription factors; they are highly expressed in the liver in comparison with other organs and affect viral transcription and the production of a number of liver proteins that are essential to maintain liver function and homeostasis. HNFs regulate cccDNA transcription by directly interacting with HBx, which enhances the DNA-binding activity of HNFs[4,45,46].

DNase Ⅰ protection analysis revealed that several distinct ubiquitous and liver-specific cellular factors bind in concert to the HBV enhancer regions[5]. Transcription factors interact with the cognate HBV DNA sequences, and multiple transcription factors might bind competitively to the same DNA sequence region[6]. Such competitive binding can occur when transcription factors share their consensus binding motif. Several transcription factors sometimes physically interact with each other to form dimers or multimers, resulting in regulation of the transcriptional activity of target genes[47,48].

The level of HBV transcription varies with the extent of transcription factor binding to HBV DNA, which can be altered by mutations in the HBV genome. When a

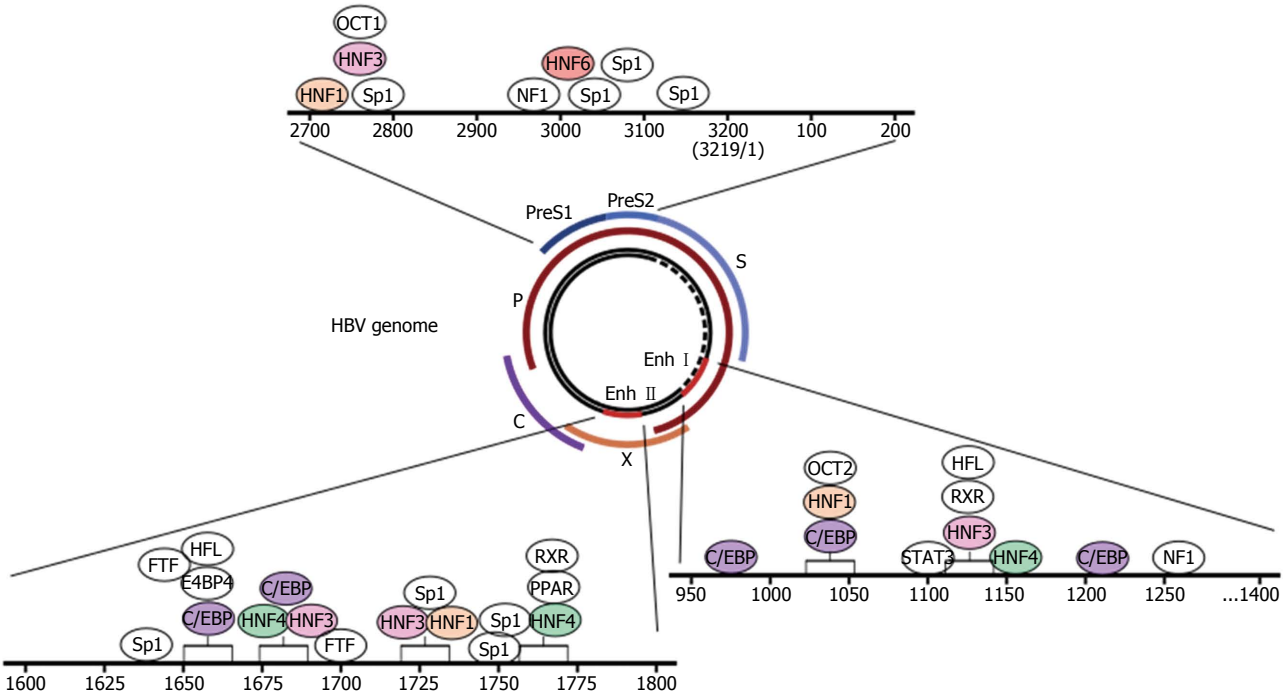

Figure 2 Schematic representation of transcription factor-binding regions in HBV enhancers and promoters. The inner circle represents the 3.2-kb hepatitis B virus (HBV) genome (partially double-stranded circular DNA). The outer lines indicate the four open reading frames (ORFs). There are four viral promoters located just before the ORFs and two enhancers (Enh Ⅰ and Enh Ⅱ). Various transcription factors can bind to the enhancers and promoters as indicated. The boxes represent competing binding regions.

new mutation allows a transcription factor to bind to a new region in HBV DNA, HBV replication is stimulated, resulting in progression to fulminant hepatitis[49]. A naturally occurring double nucleotide mutation in the HBV core promoter was shown to convert a nuclear receptor binding site to an HNF1 binding site, resulting in the suppression of RNA transcription *via* interactions between HNF1 and the mutant HBx[50].

miRNAs play a number of essential roles as biological regulators[51-53] and are involved in various biological processes[54-56], disease progression, and pathogen infection[56-59]. miRNAs are short RNAs (approximately 20 nucleotides) that are processed by Drosha and Dicer. By binding to the untranslated or coding regions of the target transcripts, miRNAs induce mRNA degradation or inhibit translation. A large number of miRNAs are involved in the transcription and replication of HBV and can cause HBV pathogenesis. When hepatocytes are infected with HBV, the expression of cellular miRNAs increases, and they regulate HBV gene expression directly by targeting viral mRNAs, or indirectly by controlling epigenetic factors such as DNA methyl transferase (DNMT) or HDAC[44].

Understanding the relationship among transcription factors, miRNAs, regulatory sequences, and the functional consequences of their binding is very important for understanding HBV-mediated pathogenesis.

HNF1α

Although there is some controversy regarding the role of HNF1α in the regulation of HBV genes, HNF1α is known to affect HBV transcription by controlling most of the HBV regulatory elements, including preS1 promoter, core promoter, HBx promoter, and Enh Ⅱ, in cccDNA. HNF1α has been reported to stimulate viral transcription by 7-fold in Huh7 cells through binding to the preS1 promoter[60]. HNF1 up-regulates Enh Ⅱ activity by interacting with either the hB1F[61] or B element in Enh Ⅱ[62]. In the absence of HNF1α, the concentration of HBV pgRNA is decreased, resulting in decreased genome replication[63]. The emergence of new binding sequences for HNF1 by mutation in transplant-transmitted HBV was able to lead to increased viral replication and fulminant hepatitis[49].

In contrast to these observations, HNF1α does not interact with the wild-type viral core promoter, although it binds a mutant HBV core promoter, which has an HNF1α-binding sequence, and reduces precore RNA transcription[50,64]. HNF1α has no effect on the HBx promoter or core promoter[61]. In HNF1α-null HBV transgenic mice, the levels of intracellular viral replication intermediates are increased several fold[65]. It is evident that HNF1α plays important roles in the regulation of HBV transcription, although the authentic role of HNF1α during the natural course of HBV infection remains unclear.

HNF3β

A binding motif for HNF3α and HNF3β was identified within Enh Ⅱ and the TGTTTGTTT sequence was mapped as an essential motif for the specific interaction between DNA and the HNF3 protein[66]. This motif is

critical for the regulation of Enh Ⅱ activity by HNF3, and the introduction of mutations into this motif alters Enh Ⅱ activity. Competitive binding of HNF3β and HNF4 to a region (positions 1650-1674) of HBV Enh Ⅱ was also observed[66]. HNF3 cooperates with other molecules such as NF1 and STAT3. Interleukin-6 (IL-6) and epidermal growth factor (EGF) stimulate the cooperative interaction between HNF3 and STAT3, which leads to the activation of Enh Ⅰ[48].

The effect of HNF3 on HBV enhancer activity differs depending on the tested system. HNF3β inhibits HBV replication in mouse NIH 3T3 fibroblasts[67] and reduces enhancer activity in HepG2 cells, whereas it increases enhancer activity in SK-Hep1 cells[68]. In mice, HNF3β inhibits HBV replication[67,69]. It appears that HNF3 inhibits HBV replication in hepatocytes in cooperation with other molecules.

HNF4α

HNF4α exists as either a homo- or heterodimer and acts as a key regulator of approximately 40% of hepatocyte genes[70]. HNF4α can also bind to various HBV enhancer regions[4,44] and is the main activator of HNF1α expression through binding to the HNF1α promoter[71]. The inhibition of HNF4α using siRNA effectively reduces HBV transcription and replication in cells and in mice[72]. When HNF4α is absent, the level of HBV pgRNA is reduced, resulting in decreased replication[64]. The overexpression of HNF4α in HepG2.1 cells increases the activity of the preS, preS2/S, and core promoters, but has no effect on the Enh I/X promoter[73]. The suppression of HBV replication by transforming growth factor-β1 (TGF-β1) can be restored by ectopic expression of HNF4α[74].

The effect of HNF4α on HBV replication appears to be clinically relevant. A retrospective study demonstrated that the HNF4α expression level was increased in CHB patients, whereas HNF3β was down-regulated[75]. The expression level of HNF4α was inversely correlated with the clinical outcomes of CHB patients[76]. Overall, HNF4α is a key transcription factor in the regulation of the HBV life cycle and in the maintenance of hepatocyte function.

HNF6

HNF6 is involved in liver homeostasis processes such as glucose metabolism, bile homeostasis, and liver cell proliferation[77]. HNF6 inhibits HBV gene expression and replication in HepG2 cells by suppressing the activity of the preS2/S promoter[78]. Interestingly, HNF6 is regulated by CYP2C12, which is expressed in a female-specific manner. Therefore, the regulation of HNF6 by CYP2C12 might explain why HBV replication is suppressed in females compared to males[79].

C/EBP

C/EBPα, a liver-enriched transcription factor, can form homodimers or heterodimers and plays critical roles in the regulation of hepatocyte-specific genes[45]. C/EBP binds to at least five regions of HBV promoters and enhancers (Figure 2). C/EBP promotes HBV transcription by transactivation of Enh Ⅱ[80] and synergistically activates Enh Ⅱ through interaction with HBx[47]. Consistent with this finding, the anti-HBV effect of interleukin 4 (IL-4) was attributed to the down-regulation of C/EBPα in Hep3B cells[81].

Low C/EBP concentrations increase the activity of the viral core promoter, whereas high concentrations suppress core promoter activity[82]. Similarly, C/EBP binds to HBV Enh Ⅰ and represses HBV transcription activity[83]. Although the role of C/EBP in HBV gene regulation is controversial, C/EBP appears to act as a proviral factor activating viral enhancers and promoters.

miRNAs related to HBV gene expression

miRNAs can regulate HBV replication either indirectly, by targeting cellular proteins that are essential for HBV replication, or directly, by targeting viral RNAs. miRNA-18a prevents the expression of ER-α, which represses HBV transcription *via* interaction with HNF4α[84] Several miRNAs, including miRNA-1, 148a, 152, 210, and 449a, are involved in the regulation of HBV replication, mainly by targeting host epigenetic regulators such as DNMT and HDAC[85-89].

A number of miRNAs can directly target HBV transcripts. Among them, the most well-known miRNA is miRNA-122, which is abundant in hepatocytes and has received increasing attention because several studies have shown that it reduces the level of viral expression by binding to a highly conserved site in 3.5-kb pgRNA[90-92]. miRNA-199a-3p and miRNA-210 suppress HBV replication by binding to the 2.1-kb RNA and 2.4-kb RNA, respectively[93]. miRNA-125a-5p inhibits HBV translation by binding to the 2.1-kb RNA[94]. Using a 3D array system, Kohno et al. found that miRNA-1231 suppresses HBV replication by targeting the core mRNA[95]. Bioinformatics analyses have suggested several putative miRNA-binding sites on HBV RNAs, including the following: miRNA-199a-3p, 125a-5p, 210, and 345 are predicted to bind the 3.5-kb RNA; miRNA-let7, 196b, and 511, 2.4-kb RNA; miRNA-433, 2.1-kb RNA; and miRNA-205, 0.7-kb RNA[93,94,96,97].

There is a report that viral RNA can target host miRNA. Viral HBx RNA directly down-regulates the tumor suppressor miRNAs miRNA-15a and miRNA-16-1[98]. This study suggests that HBV can induce HCC development by viral RNA-mediated down-regulation of specific tumor suppressor miRNAs. The various targets of miRNAs involved in HBV replication are shown in Figure 3.

Others

Nuclear receptors are known to regulate the activity of HBV enhancers and promoters. Farnesoid X receptor (FXR) and retinoid X receptor (RXR) are reported to form heterodimers and increase the activity of Enh Ⅱ and

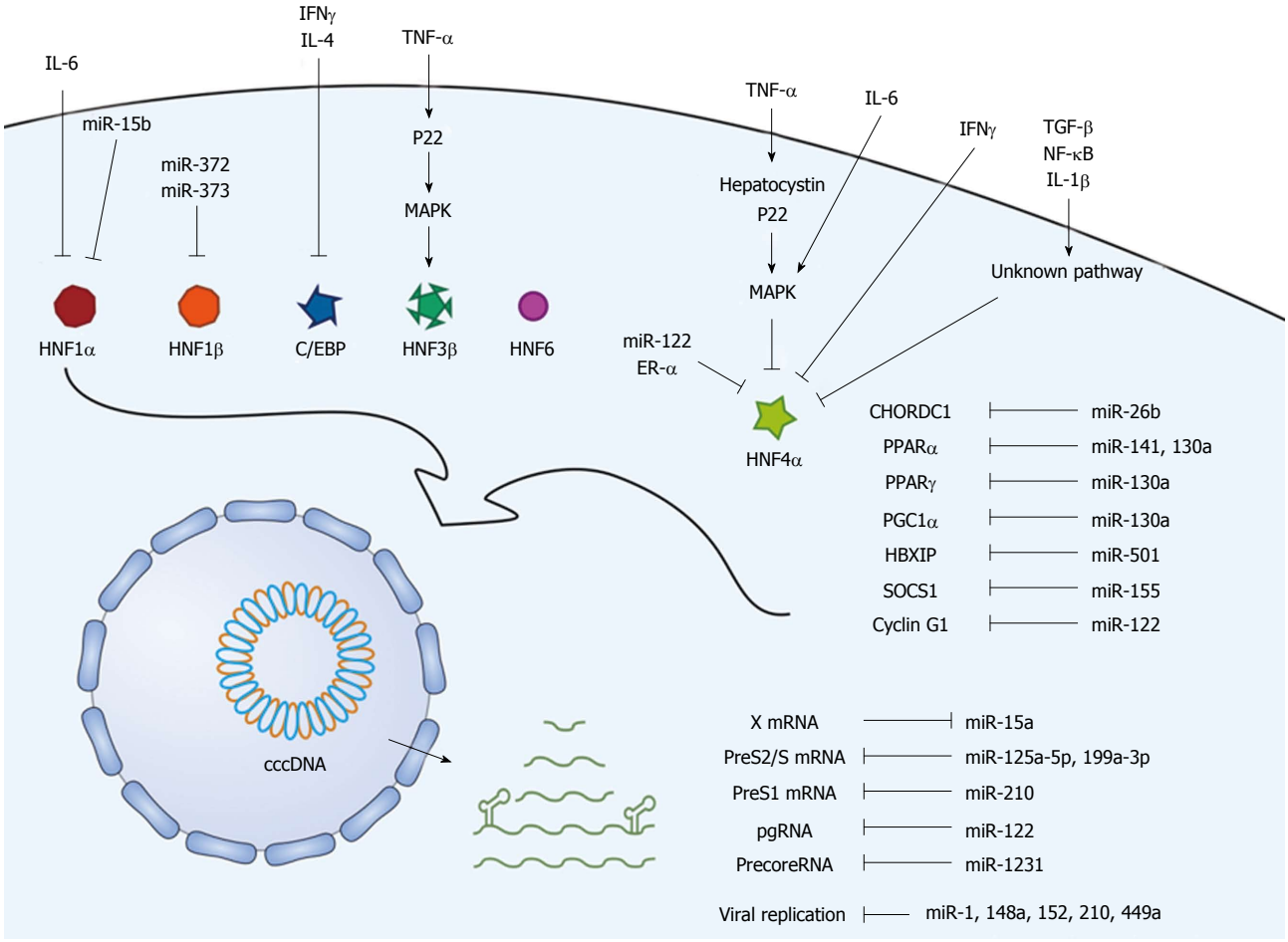

Figure 3 Scheme of regulatory factors associated with HBV transcription and translation. The upstream regulators, including cytokines, mediators, and signaling molecules, regulate liver-enriched transcription factors. In addition, miRNAs regulate the transcription factors and viral transcripts. These upstream factors and miRNAs exert positive or negative effects on HBV transcription and replication. HBV: Hepatitis B virus.

the core promoter[99]. Peroxisome proliferator-activated receptors (PPARs) and RXRs form heterodimers and increase the activity of the Enh Ⅰ/X promoter[73,100].

Many nuclear factors have also been shown to be involved in HBV regulation. The binding of NF-1 to the S gene promoter is essential for HBV surface RNA transcription[101]; however, NF-1 binding to Enh Ⅰ suppresses the activity of the HBV enhancer[102]. Nuclear factor Y (NF-Y) can activate the S promoter by binding to the CCAAT element[103]. SP1 binds to GC-rich DNA sequences on HBV enhancers and promoters and up-regulates the activity of Enh Ⅱ[104,105] and the PreS1[106] and PreS2[107] promoters. HLF binds to the Enh Ⅱ region and increases the transcription of pgRNA and precore RNA[6]. Testicular orphan receptor 4 (TR4) reduces core promoter activity by blocking HNF4α binding through a protein-protein interaction[108]. Cysteine- and histidine-rich domain-containing 1 (CHORDC1) binds HBV enhancers and activates gene transcription[109]. Other factors involved in HBV regulation include nuclear respiratory factor 1 (NRF1)[110], activator protein 1 (AP1)[111], TATA-binding protein (TBP)[112], CREB[113], and OCT1[45].

UPSTREAM FACTORS RELATED TO HNF REGULATION

Six families of liver-enriched transcription factors [HNF-1, HNF-3, HNF-4, HNF-6, C/EBP, and D-binding protein (DBP)] have been characterized to date. As discussed above, most of these factors, except DBP, are critically involved in HBV gene expression and replication. Therefore, understanding the upstream cellular factors or signals involved in the regulation of liver-enriched transcription factors is important to grasp the complicated cellular networks related to the HBV life cycle. For example, the activation of extracellular signal-regulated kinase (ERK) inhibits HBV replication by down-regulating HNF4α and up-regulating HNF3β[114]. A detailed description of these factors and signals is presented in Figure 3 and Table 2.

Cellular factors and signaling pathway involved in HNF regulation

Extracellular signals such as cytokines can affect HBV by dysregulating liver-enriched transcription factors. IL-4 suppresses HBV core promoter activity and inhibits

Table 2 Upstream factors and signals involved in the regulation of hepatocyte nuclear factors and other factors related to hepatitis B virus replication

Regulating factor	Target molecule	Effect on target molecule	Effect on HBV replication	Ref.
TGF-β	HNF4α	Decrease	Decrease	[74]
ER-α		-	Decrease	[9]
NF-κB		Decrease	Decrease	[119,120]
MAPK		Decrease	Decrease	[119,121]
TNF-α → Hepatocystin → MAPK		Decrease	Decrease	[118]
TNF-α → P22 → MAPK		Decrease	Decrease	[114]
IFN-γ		Decrease	Decrease	[117]
IL-6 → MAPK		Decrease	Decrease	[116]
miRNA-122		Decrease	Decrease	[124]
IL-4	C/EBP	Decrease	Decrease	[81]
IFN-γ		Decrease	Decrease	[117]
IL-6	HNF1α	Decrease	Decrease	[116]
miRNA-15b		Decrease	Increase	[122]
miRNA-372, miRNA-373	HNF1β	Decrease	Increase	[123]
TNF-α → P22 → MAPK	HNF3β	Increase	Decrease	[114]
miRNA-26b	CHORDC1	Decrease	Decrease	[109]
miRNA-141	PPARα	Decrease	Decrease	[125]
NF-κB → miRNA-130a		Decrease	Decrease	[128]
miRNA-122	Cyclin G1	Decrease	Decrease	[90]
miRNA-501	HBXIP	Decrease	Increase	[128]
miRNA-155 → JAK/STAT	SOCS1	Decrease	Decrease	[129]

HBV: Hepatitis B virus.

pgRNA synthesis by down-regulating C/EBPα[81]. IL-6 controls HBV replication by reducing the levels of HNF4α and HNF1α[115,116]. IFN-γ also regulates the HNF4α and C/EBP levels and affects HBV replication[117]. Recently, we demonstrated that cytokine-mediated up-regulation of hepatocystin/80K-H impairs HBV replication by down-regulating HNF4α through the Ras/MAPK pathway[118] and also reported that p22-FLIP, a cleavage product of c-FLIP formed upon TNF-α stimulation, reduces the HNF4α level but increases the HNF3β level *via* the ERK pathway, thereby strongly impairing HBV replication[115].

NF-κB suppresses HBV replication by inhibiting HNF4α[119,120]. The activation of ERK1/2 and stress-activated protein kinase 1/c-jun NH_2-terminal kinase (SAPK/JNK) also inhibits HBV replication through negative regulation of HNF4α[119,121]. ER-α suppresses HBV by physical interaction with HNF4α[9], which supports the observation that males are more vulnerable to HBV infection than females.

miRNAs involved in HNF regulation

As described above, miRNAs can directly regulate HBV by targeting viral RNAs. In this subsection, we provide a brief overview of the miRNAs that exert an indirect effect on HBV by controlling liver-enriched transcription factors that are involved in HBV replication. The control of HNF1α by miRNA-15b is reported to promote HBV replication[122], and the control of HNF1β by miRINA-372 and 373 up-regulates HBV gene expression[123]. miRNA-122 is also able to control HBV replication by inhibiting HNF4α[124].

In addition to targeting HNFs, miRNAs can also target other nuclear factors. miRNA-26b inhibits CHORDC1 expression, thereby suppressing HBV enhancer activity[109]. miRNA-141 represses HBV replication by targeting PPARα, which binds and *trans*-activates HBV enhancers[125]. Ectopic expression of miRNA-141 suppresses PPARα expression, decreasing viral transcription in HBV-transfected HepG2 cells. The expression of miRNA-130a is stimulated by NF-kB/p65 and inhibits HBV replication by down-regulating PGC1α and PPARγ[126]. The level of C/EBP is reduced by miR-155, the expression of which is increased by diet-induced activation of NF-κB[127].

During HBV infection, host antiviral signaling can contribute to viral clearance *via* the induction of miRNAs transcription. Other miRNAs that have been reported to affect HBV replication by controlling cellular proteins other than liver-enriched transcription factors include miRNA-122 targeting cyclin G1[90], miRNA-501 targeting HBXIP[128], and miRNA155 targeting SOCS1[129].

CONCLUSION

Host factors, mainly HNFs, are indispensable for the survival and maintenance of HBV in hepatocytes. These factors regulate cccDNA transcription and mediate host antiviral responses. Although our knowledge of HBV-related host factors has increased, the overall understanding of the cellular networks related to cccDNA transcription is still very limited. Numerous recent studies have revealed that miRNAs play key roles in the HBV life cycle. Systematic understanding of the complex interactions between HBV and host miRNAs is needed. Currently, there is no way to eliminate cccDNA in infected hepatocytes, which would be required for complete CHB cure. Therefore,

understanding the molecular network that determines how cccDNA is activated by extrinsic and intrinsic factors will provide us a chance to inactivate or halt the cccDNA function until drugs that eliminate cccDNA are developed.

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P- Reviewer: Cunha C, Liu LF **S- Editor**: Yu J **L- Editor**: A **E- Editor**: Ma S

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ISSN 1007-9327

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