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## Hepatitis B and circadian rhythm of the liver

Ivana Skrlec, Jasminka Talapko

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### Abstract

The circadian rhythm in humans is determined by the central clock located in the hypothalamus's suprachiasmatic nucleus, and it synchronizes the peripheral clocks in other tissues. Circadian clock genes and clock-controlled genes exist in almost all cell types. They have an essential role in many physiological processes, including lipid metabolism in the liver, regulation of the immune system, and the severity of infections. In addition, circadian rhythm genes can stimulate the immune response of host cells to virus infection. Hepatitis B virus (HBV) infection is the leading cause of liver disease and liver cancer globally. HBV infection depends on the host cell, and hepatocyte circadian rhythm genes are associated with HBV replication, survival, and spread. The core circadian rhythm proteins, REV-ERB and brain and muscle ARNTL-like protein 1, have a crucial role in HBV replication in hepatocytes. In addition to influencing the virus's life cycle, the circadian rhythm also affects the pharmacokinetics and efficacy of antiviral vaccines. Therefore, it is vital to apply antiviral therapy at the appropriate time of day to reduce toxicity and improve the effectiveness of antiviral treatment. For these reasons, understanding the role of the circadian rhythm in the regulation of HBV infection and host responses to the virus provides us with a new perspective of the interplay of the circadian rhythm and anti-HBV therapy. Therefore, this review emphasizes the importance of the circadian rhythm in HBV infection and the optimization of antiviral treatment based on the circadian rhythm-dependent immune response.

**Key Words:** Circadian rhythm; Clock genes; Hepatitis B virus; Immune system; Liver

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**Core Tip:** Some studies in the literature contribute to the association of the circadian rhythm and liver pathophysiology associated with hepatitis B virus (HBV) infection. However, this is the first review to report the latest molecular mechanisms of HBV infection, including cellular circadian rhythm disorders, circadian clock-related immune response, therapeutic strategies in improving health outcomes, and the significance of personalized medicine and chronotherapy in treating chronic HBV infections.

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## INTRODUCTION

The circadian rhythm in humans is determined by the central clock found in the hypothalamus's suprachiasmatic nucleus (SCN) which receives light signals from the retina[1]. Endogenous functional circadian rhythms are active in peripheral tissues. For example, the circadian clock in humans, expressed in almost every cell, consists of a whole range of transcription-translation feedback loops[2]. Furthermore, all peripheral clocks in every tissue are synchronized by the central clock in the SCN[3]. Therefore, circadian clock genes and clock-controlled genes (CCG) exist in almost all cell types. Approximately 10%-40% of the genome is encoded in a circadian manner[4]. Furthermore, most physiological processes, such as lipid metabolism, immune system regulation, and infection severity, are under circadian control, and therefore circadian rhythm disorders can result in pathophysiological changes downstream[4,5].

The liver has a vital role in maintaining energy homeostasis within the body. The primary biochemical reactions within the liver are involved in the breakdown and generation of glucose, which is associated with fatty acid metabolism[6]. In addition, the metabolic functions of the liver show rhythmic fluctuations with a periodicity of 24 h[6]. Hepatitis-causing viruses depend closely on hepatocytes for replication, survival, and spread[6]. In addition, viral infection can disrupt the hepatocytes' circadian rhythm[5]. Circadian rhythm transcription factors alter liver metabolism and are linked with various conditions, including viral infection, fatty liver disease, diabetes, and hepatocellular carcinoma (HCC)[1].

What makes the hepatitis B virus (HBV) significantly different from other hepatotropic viruses is its global impact on human health[7], namely, infections caused by this virus result in liver disease, which is a growing global problem[8]. According to the World Health Organization (WHO), it is estimated that 296 million people lived with chronic hepatitis B in 2019, and that 1.5 million new infections are detected each year[9]. Furthermore, due to HBV infection in 2019, mainly from cirrhosis and HCC, about 820000 people died[10]. Hepatitis B can develop in an acute or chronic form[11]. Most infected people do not have any symptoms, which does not mean that there is no disease. Symptoms of acute infection usually occur 2 mo to 3 mo after infection and are nonspecific[12,13].

The HBV begins to multiply within the first 3 d of infection[14]. Whether and to what extent liver damage occurs depends on the infected person's immune system, the infectious dose, and the site of virus entry. Tissue compatibility antigens and interferon promote the viral antigens' [hepatitis B surface antigen (HBsAg), hepatitis B envelope antigen (HBeAg), and hepatitis B core antigen (HBcAg)] exposure to cytotoxic T lymphocytes[15]. If there is no adequate response by these cells, milder signs of the disease occur, which may progress to the development of chronic hepatitis[16]. About 10% of acute HBV infections progress to a chronic form[17]. Chronic HBV can be clinically manifested as mild conditions to severe chronic hepatitis[18], which, in untreated cases, results in 8%-20% of cases with cirrhosis and HCC[19]. Persistent hepatitis is a mild disease that occurs in 8%-10% of patients, occasionally causing elevated aminotransferases, but generally does not progress toward cirrhosis and has a favorable prognosis[20]. HBV plays a significant role in the development of HCC, which can occur many years after chronic infection[21]. Still, typically the HBV is not a cytopathogen, and cell damage is thought to be mediated by a persistently unproductive immune response[17].

Therefore, this mini-review highlights the significance of the circadian rhythm in HBV infection, and the effectiveness of therapy in relation to the circadian rhythm-dependent immune response.

## HBV

The epidemiological model of the spread of HBV and human immunodeficiency virus (HIV) is the same, but HBV is 50-100 times more infectious than HIV[22]. The source of infection is people with HBV infection[23]. However, the geographical prevalence of HBV infection varies[24]. In addition, it depends



on several factors, such as different modes of transmission in the population and the age at which the infection originated, which relates to the likelihood of progression to chronic infection[25].

HBV is mainly transmitted by percutaneous or mucosal exposure to infected blood or body fluids [26]. Perinatal transmission is the primary route of infection in endemic regions[27], while the most direct route in the low-endemic regions is sexual transmission[28]. Globally, the epidemiology of HBV infection is changing, influenced by infant vaccination programs and migration between low- and high-prevalence populations[29]. On the basis of the available data, it is estimated that the prevalence of new chronic HBV cases is 70% in developing countries[30].

On the basis of the prevalence of the HBsAg, the epidemiology of HBV in certain areas of the world can be classified into one of three categories (Table 1)[31]: Low prevalence areas (< 2%), medium prevalence areas (2%-7%), and high prevalence areas (> 8% HBsAg prevalence)[32]. These categories are important for understanding the transmission and outcome of infection, and the consequences of chronic hepatitis B[25].

### **Biology and life cycle of HBV**

HBV is a DNA virus with ten known genotypes, labeled A-J. HBV belongs to the group of hepatotropic viruses from the family Hepadnaviridae, genus Orthohepadnavirus[33]. It is a small round virus of a very complex structure, 42 nm in diameter, with a double shell (Dane particle) (Table 2)[33]. Genotypes are divided into subgenotypes due to the significant variability of the nucleotide sequences[34]. They are based on a more than 4% difference along the entire genome. In addition, HBV genotypes and subgenotypes are related by geographical distribution, and also related to the pathogenesis and outcome of HBV infection (Table 3)[35].

The HBV genome has 3.2 kb long, relaxed circular, partially double-stranded DNA (rcDNA)[36]. The minus strand is complete, while the plus strand is regularly incomplete with a stable 5' end, but an inconsistent 3' end. The 5' end of the plus strand is covalently linked to the RNA with a 5' cap formation. In addition, the viral polymerase (reverse transcriptase) is covalently bound to the 5' end of the minus strand[36,37].

Linear DNA is the direct precursor of viral DNA that is randomly incorporated into the hepatocytes' DNA throughout infection. Incorporated DNA has no role in virus replication[37,38]. The HBV genome is highly compact, with four open reading frames (ORFs) overlapping multiple times and encoding seven proteins[39]. All ORFs are identical orientations and encoded by the negative strand of DNA[40]. Thanks to the ORFs, the coding capacity increases, and DNA is transcribed one and a half to two times because there is no stop codon[41]. In addition to ORF, there are six start codons, four promoters, and two transcription enhancers[42].

ORF C encodes the nuclear core antigen HBc and envelope E antigen (HBe)[39]. The precore protein in serum indicates active virus replication[43]. The presence of HBeAg in serum suggests prevented or decreased virus replication. HBeAg can repress the cellular immune response to HBsAg, thereby reducing perinatal transmission and promoting chronic infection[37,44]. The longest ORF is the P gene, encoding most of the virus genome (80%) and viral polymerase (reverse transcriptase)[45]. The ORF X encoding hepatitis B protein X (HBx) activates viral RNA transcription[37,38]. HBx causes the progression of the cell cycle and is essential for activating the transcription of covalently closed circular DNA (cccDNA) and pregenomic RNA (pgRNA) after infection[37]. ORF S codes three different sizes of the surface S antigen (S-small, M-medium, and L-large HBs)[46]. The M- and L-HBs have additional PreS2 and PreS1 domains[39]. The PreS1 region, present in L-HBsAg, possesses a binding domain for the sodium taurocholate co-transporting polypeptide (NTCP) receptors, essential for viral internalization[37,47]. HBsAg are embedded in the outer lipid envelope, and the inner nucleocapsid structure contains the DNA genome, HBcAg, and viral polymerase (reverse transcriptase)[48]. In addition, HBeAg is between the nucleus and the outer shell[49].

HBV replicates in hepatocytes *via* pgRNA (Figure 1)[35]. The entry of the virus into the hepatocyte is the first step in its life cycle[50]. After the virus enters the liver, S-HBsAg recognizes heparan sulfate proteoglycans (HSPG) on the hepatocytes, and binds them with low affinity[51]. A high-affinity interaction between the PreS1 region of the L-HBs protein and NTCP follows[52]. Later, the virus envelope and the hepatocytes' membrane merge, releasing the nucleocapsid into the cytoplasm[53]. After the capsid shell is removed, the viral genome is transferred to the nucleus. As a result, viral DNA enters the nucleus of the hepatocytes. The relaxed circular (rc) genome is restored, resulting in cccDNA [54]. Viral DNA can be integrated into the hepatocytes' DNA, and is a constant HBsAg source[55]. The cccDNA is a template for pgRNA production and the transcription of all viral mRNAs[37]. On this basis, cccDNA in the hepatocytes can stimulate virus replication[56]. The cccDNA is associated with cellular histones and forms a minichromosome. Each viral protein has a promoter and mRNA, except for reverse transcriptase, translated from the same pgRNA as the virus core protein[37,44]. The onset of infection is indicated by the expression of core proteins and polymerase from pgRNA. HBc is a phosphoprotein and a subunit of the viral nucleocapsid. The core proteins are constructed into nucleocapsids, icosahedral shells of 120 dimers[57]. They merge with RNA and are assembled into core particles. Viral DNA synthesis takes place in the core particles, followed by packaging of pgRNA and polymerase[37,47]. Upon completing viral DNA synthesis by reverse transcription, viral particles can exit the hepatocytes in two ways. First, while envelope protein levels are low, core particles recycle and

**Table 1** Prevalence of hepatitis B surface antigen

	Low prevalence area (< 2%)	Area of medium prevalence (2%-7%)	Area of high prevalence (> 8%)
Geographical areas	United states, Canada, and Western European countries	Parts of Russia, border Eurasian, and Asian-African areas	Asia, sub-Saharan Africa, South, and Central America
% of the world population	12%	43%	45%

**Table 2** Classification of hepatitis B virus

Genus	Orthohepadnavirus
Family	Hepadnaviridae
Species	HBV
Genotypes	A-J
Virion	42 nm, spherical
Envelope	Yes (HBs)
Genome	Circular ds/ssDNA
Genome size	3.2 kb
Sensitivity	Acid-sensitive
Virus antigens	HBsAg, HBcAg, HBeAg, polymerase

HBV: Hepatitis B virus; HBs: Hepatitis B surface protein; ds/ssDNA: Double-stranded/single-stranded DNA; HBsAg: Hepatitis B surface antigen; HBcAg: Hepatitis B nuclear core antigen; HBeAg: Hepatitis B envelope E antigen.

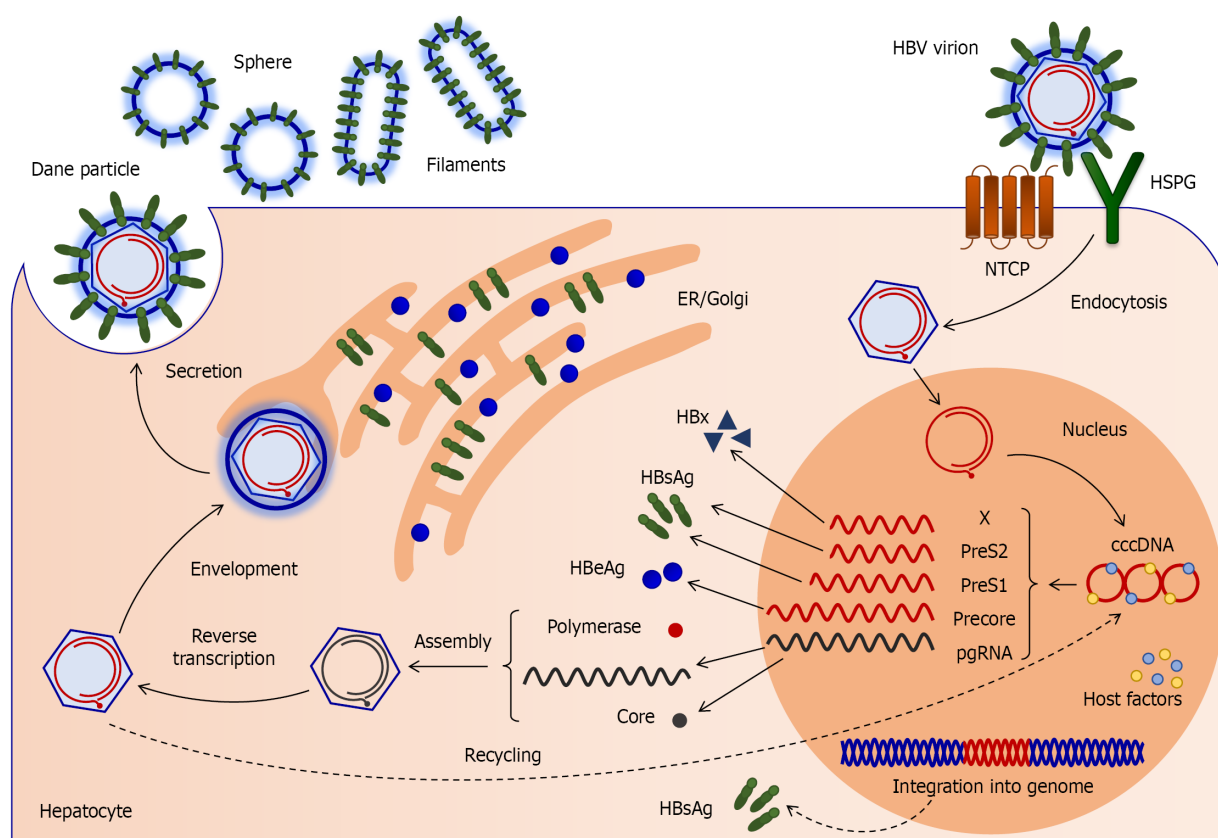
**Table 3** Prevalence of hepatitis B virus genotypes and subgenotypes

Genotype	Subgenotype	Prevalence
A	A1 -A6	Africa, India, Northern Europe, USA
B	B1-B8	Asia, USA
C	C1-C14	Asia, USA
D	D1-D9	India, Middle East, Southern Europe, USA
E	F1-F4	West and South Africa
F		Central and South America
G		Europe, USA
H		Central and South America, California (USA)
I	I1-12	Vietnam
J		Japan

USA: United States.

enter the nucleus, resulting in the replenishment of cccDNA[37,39]. Later, the core particles gather with the envelope proteins in the endoplasmic reticulum, enter the secretory pathway, and are discharged from hepatocytes into the blood[58]. In addition to infectious virions (Dane particles), incomplete subviral particles are secreted by secretory pathways (such as spheres and filaments lacking nucleocapsid proteins and naked nucleocapsids)[59]. The virus emerges on the surface of the hepatocytes by budding, and can thus infect another cell[52]. Once created in the cell nucleus, the cccDNA minichromosome is very difficult to eliminate from infected cells, where it can survive until the death of the host cell[56].





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**Figure 1 Hepatitis B virus life cycle.** Hepatitis B virus (HBV) enters hepatocytes via interaction with the heparan sulfate proteoglycan (HSPG), followed by the sodium taurocholate co-transporting polypeptide (NTCP) receptor. The virus envelope and the hepatocytes' membrane merge, releasing the nucleocapsid into the cytoplasm. The viral genome is transferred to the nucleus after the capsid is removed. The relaxed circular genome is restored in the nucleus, resulting in covalently closed circular DNA (cccDNA), and viral DNA could be integrated into the host DNA. Integrated viral DNA is a constant source of hepatitis B surface antigen (dashed line). The cccDNA is a template for pregenomic RNA (pgRNA) production and the transcription of all viral mRNAs. In addition, the cccDNA is associated with host factors and cellular histones, and forms a minichromosome. The core proteins are constructed into nucleocapsids together with pgRNA. Viral polymerase converts the pgRNA to relax circular DNA, resulting in a mature nucleocapsid. The core particles can recycle and replenish cccDNA (dashed line), or gather with the envelope proteins in the endoplasmic reticulum and Golgi, and enter the secretory pathway. Through the secretory process, virions gain surface antigens and are secreted as infectious virions-Dane particles. Also, incomplete subviral particles are secreted, such as spheres and filaments lacking nucleocapsid proteins. HSP: Heparan sulfate proteoglycan; NTCP: Sodium taurocholate co-transporting polypeptide receptor; cccDNA: Covalently closed circular DNA; pgRNA: Pregenomic RNA; HBx: Hepatitis B protein X; HBsAg: Hepatitis B surface antigen; HBe: E antigen; ER: Endoplasmic reticulum.

## CIRCADIAN RHYTHM

The molecular basis of the circadian rhythm includes transcriptional and translocation feedback loops. In addition, the circadian rhythm is driven by the circadian locomotor output cycles kaput (CLOCK), and brain and muscle ARNTL-like protein 1 (BMAL1 or ARNTL) transcription factors. In contrast, transcription repressors are period (PER) and cryptochrome (CRY) transcription factors. The central transcription factors that make up the activation and positive part of the molecular clock are BMAL1 and CLOCK. The heterodimer CLOCK-BMAL1 enters the nucleus, where it initiates transcription by binding to a specific sequence, the E-box, in promoters of the target genes. CLOCK's main downstream goals include *BMAL1* and its repressors, cryptochrome (*CRY1*, *CRY2*), and period (*PER1*, *PER2*, and *PER3*) and multiple CCG[60]. CRYs and PERs accumulate during the positive loop in the cytoplasm. They are controlled by F-box/LRR-repeat protein 3 (FBXL3) and casein kinase 1 (CK1)  $\epsilon$  and CK1 $\delta$ [4, 61]. CK1 $\epsilon$  and CK1 $\delta$  phosphorylate PERs for degradation, while FBXL3 stimulates CRYs degradation. If CK1 $\epsilon$  phosphorylates heterodimer PER-CRY, it enters the nucleus and suppresses the CLOCK-BMAL1 heterodimer. By suppressing their activator, CRYs and PERs suppress their own expression[62]. Posttranslational phosphorylation of CRYs and PERs promotes their degradation, which triggers a new circadian cycle, with increased binding of the CLOCK-BMAL1 heterodimer to the E-box of CCG[2,63].

The second regulatory loop includes the retinoic acid receptor-related orphan receptor (*ROR*)  $\alpha$  and *ROR* $\gamma$ , and the *REV-ERB* $\alpha$  and *REV-ERB* $\beta$  genes. The CLOCK-BMAL1 heterodimer initiates their transcription by binding to the E-box elements of their promoters. RORs and REV-ERBs receptors bind to the ROR element (RORE). *REV-ERB* $\alpha$  and  $\beta$  inhibit transcription, while *ROR* $\alpha$  and  $\gamma$  stimulate expression of target genes. RORs and REV-ERBs together create cyclic fluctuations in the expression of

many CCG, including the regulation of *BMAL1* transcription[6,64]. REV-ERB $\alpha$  accumulates rapidly and prevents *BMAL1* transcription, while ROR $\alpha$  accumulates more slowly and promotes *BMAL1* transcription. In this way, the stability and robustness of the rhythmicity of the internal clock system are enhanced[2,63].

An additional independent feedback loop includes the helix-loop-helix e40 family (DEC1 or BHLHE40) and DEC2 (BHLHE41) that prevent CLOCK-BMAL1 activity[65]. The CLOCK-BMAL1 heterodimer stimulates the expression of *DEC1* and *DEC2* by binding to the E-box of their promoters. Conversely, DECs suppress transcription of genes with E-box elements in the promoter, including transcription of itself and *CRY*s and *PER*s, due to its binding to the E-box[66]. In addition, the CLOCK-BMAL1 heterodimer affects the expression of other CCG by stimulating D-box binding protein (DBP) transcription, by binding to E-box elements on the promoter[67]. DBP rhythmically triggers genes with D-box elements in the promoter[2,4].

The transcriptional and translational feedback loop creates rhythms in the expression and levels of downstream CCG[4]. All of these connected feedback loops create a circadian rhythm. For example, CCGs containing RORE elements in promoters are transcribed during the active phase. In contrast, the genes' promoters containing E-box and D-box elements are transcribed during the resting phase[63].

The circadian rhythm is controlled at the transcriptional and posttranslational levels, including cellular pathways, transcription factors, epigenetic changes, and posttranslational modifications[68]. Many posttranslational modifications of clock elements include acetylation, phosphorylation, ubiquitylation, and sumoylation[4,63]. Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, interfere with the target genes' transcription and post-transcriptional expression, including clock genes[69]. Different patterns of histone modifications, such as histone deacetylase sirtuin 1 (SIRT1), or microRNA, can be direct and indirect modulators in maintaining different aspects of circadian rhythm function[53,70].

### **Liver physiology and circadian rhythm**

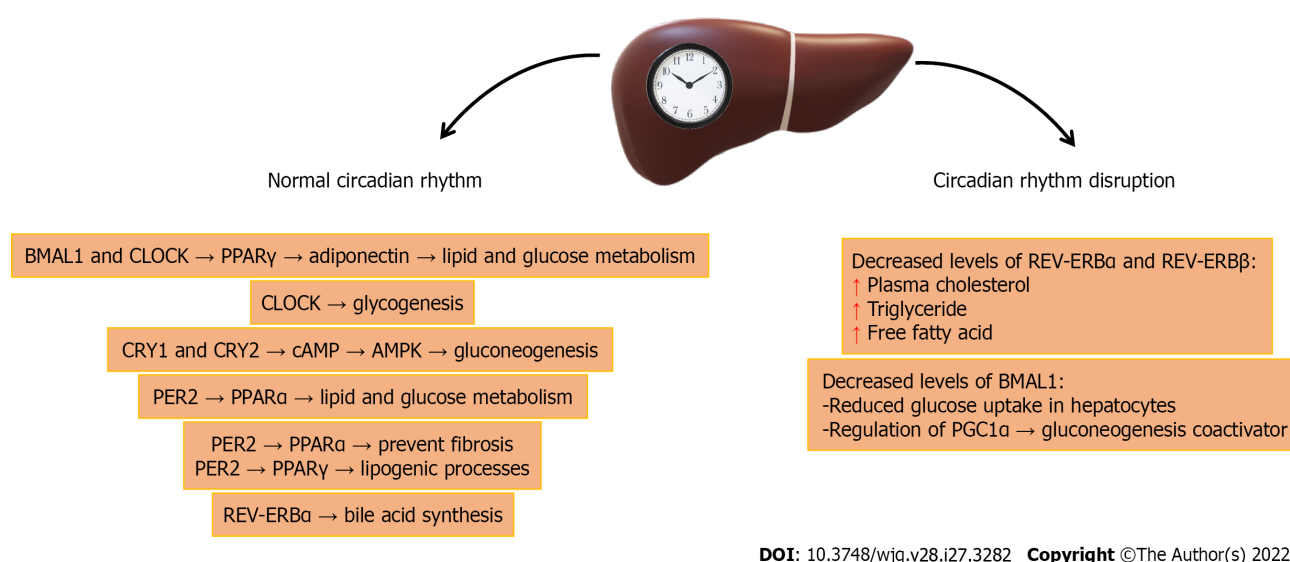
With a lack of environmental signs, such as the alternation of light and dark, food intake affects the circadian rhythm of the liver[6]. Circadian rhythms largely control different genes, levels of proteins, and the enzymes in the liver[2]. The circadian rhythm and liver metabolism are connected through the peroxisome proliferator-activated receptors (PPARs)  $\alpha$  and  $\gamma$ [6,71]. PPAR $\alpha$  controls the transcription of genes participating in lipid and glucose metabolism, while PPAR $\gamma$  is involved in lipogenic processes because it binds eicosanoids from omega-3 or omega-6 fatty acids[4,72]. Both genes are rhythmically expressed, and their expression is controlled by PER2, which directly regulates *BMAL1* transcription (Figure 2). The binding of PPAR $\alpha$  to PPAR response elements (PPRE) in the *BMAL1* promoter leads to its transcription. Also, PPAR $\alpha$  interacts with PER2 in the liver to impact the expression of target genes[73]. In the positive feedback loop in the liver, BMAL1 and CLOCK control the circadian oscillations of PPAR $\alpha$ [4], and thus the expression of enzymes participating in glucose and lipid homeostasis, and the biosynthesis of bile acids and apolipoproteins[6]. REV-ERB $\alpha$  is implicated in the control of bile acid synthesis[74]. Adiponectin, triggered by BMAL1 and CLOCK *via* the transcription of PPAR $\gamma$  and its coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), is involved in glucose and lipid metabolism[75].

In addition, gluconeogenesis is controlled in a circadian manner in the liver *via* CRY1 and CRY2, which prevent signaling *via* the secondary messenger cyclic adenosine monophosphate (cAMP)[76]. Moreover, AMP-activated protein kinase (AMPK) can influence circadian cycle length by phosphorylating CRYs and directing it to degradation[4]. Activation of ROR $\alpha$  in the liver may impact lipid metabolism and control hepatic steatosis by triggering AMPK[77]. Furthermore, CLOCK controls glycogenesis in the liver by acting on glycogen synthase 2 expression[78]. Disorders of the *CLOCK* and *BMAL1* genes lead to impaired glucose homeostasis[6]. Histone deacetylase SIRT1 prevents hepatic steatosis by controlling lipid homeostasis by positive binding of PPAR $\alpha$  and PGC1 $\alpha$  coactivators, or by direct action on BMAL1[70].

### **Circadian rhythm and HBV**

There is a functional association between virus replication and circadian dysfunction in the pathogenesis of liver disease[79]. HBV has been revealed to impact the liver clock genes and disrupt the internal molecular clock in order to make better use of hepatocytes for self-replication[80]. HBV is randomly incorporated into the human genome, yet there are sites where it is incorporated more frequently, such as circadian rhythm-related elements, *CLOCK*, and *BMAL1*. Those elements are one way that the circadian rhythm is associated with diseases caused by HBV infection[81]. HBV replicates in the liver where around 20% of genes exhibit a rhythmic expression pattern, implying that the virus has successfully evolved to persist in the liver[5,50]. Integrated copies of HBV, which have regulatory elements similar to circadian rhythm genes, present additional circadian rhythm motifs in the infected cell, resulting in undesirable oscillations of specific genes, or disrupted circadian rhythms of the hepatocytes, and are a risk factor for cancer[50].

The circadian rhythm impacts gene expression in the liver and thus HBV replication[50]. In patients with HBV infection, a reduction in *BMAL1* and an increase in *REV-ERB $\alpha$*  and *REV-ERB $\beta$*  transcription have been observed compared to healthy subjects, which indicates that circadian rhythm gene transcription is impaired in HBV infection[50]. In hepatocytes, decreased expression or deletion of *REV-*



**Figure 2 Role of circadian rhythm genes in liver metabolism.** BMAL1: Brain and muscle ARNTL-like protein 1; CLOCK: Circadian locomotor output cycles kaput; PPAR: Peroxisome proliferator-activated receptors; CRY: Cryptochrome; PER: Period; ROR: Retinoic acid receptor-related orphan receptor; cAMP: Cyclic adenosine monophosphate; AMPK: AMP-activated protein kinase; PGC1 $\alpha$ : PPAR coactivator 1 $\alpha$ .

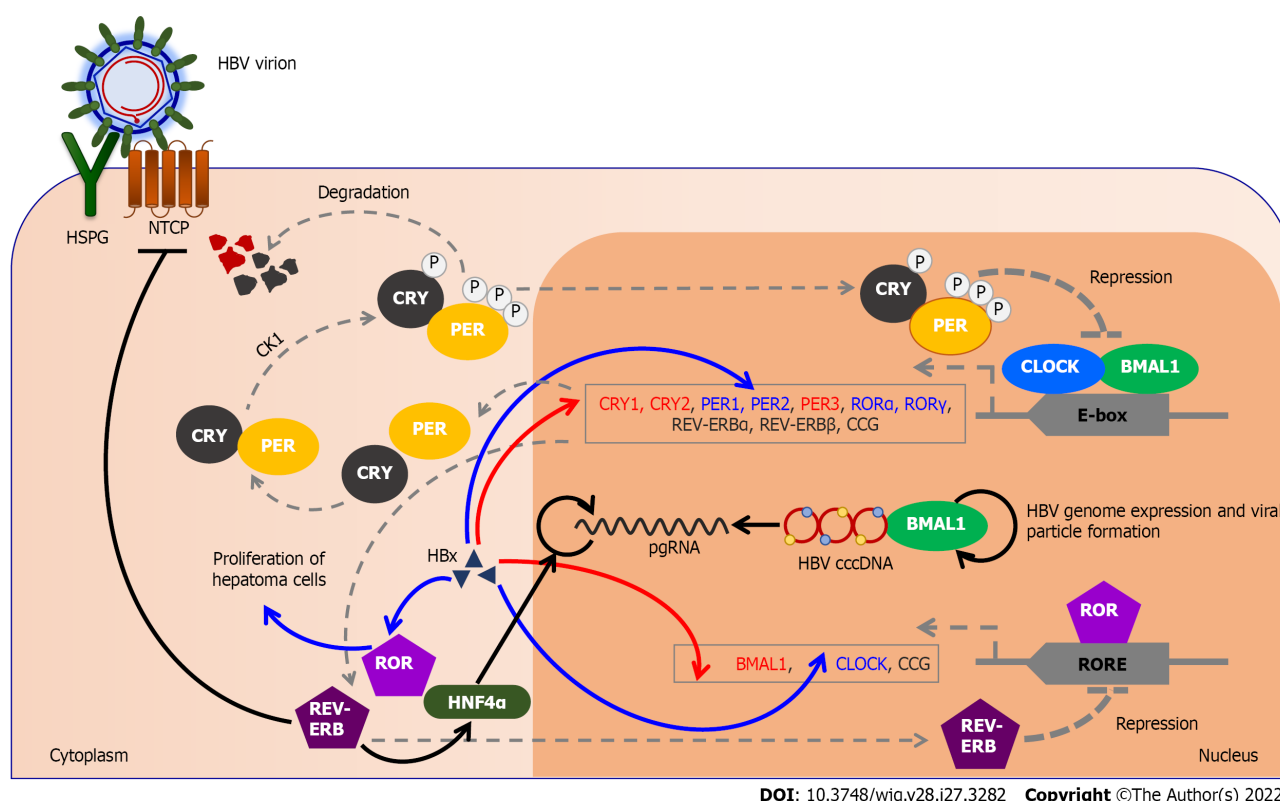
*ERBa* and *REV-ERB $\beta$*  in hepatocytes increases plasma cholesterol, triglycerides, and free fatty acid levels [63]. In addition, *REV-ERB* binds and controls *NTCP* expression, and stimulation of *REV-ERB* prevents HBV from entering the hepatocytes [50]. The *NTCP* receptor has a circadian pattern in hepatocytes [82]. Decreased expression of *BMAL1* in hepatocytes leads to reduced glucose uptake. In addition, *BMAL1* regulates the transcription of the *PGC1 $\alpha$*  gene, a coactivator of gluconeogenesis [63]. Thus, *PPAR $\alpha$*  can prevent the development of fibrosis [63], and it is known that HBV dysregulates *PPAR $\alpha$*  and *PPAR $\gamma$*  [6]. Also, *BMAL1* binds HBV DNA, and controls viral genome expression and new viral particle formation [50].

The impaired circadian rhythm in HCC may favor the selective survival of cancer cells and facilitate carcinogenesis [83]. An increased risk of developing HCC is linked with chronic HBV infection. The HBx protein is linked with HCC due to the disturbance of cell proliferation [19]. It is a possible cause of significantly reduced transcription levels of the *BMAL1*, *PER3*, *CRY1*, *CRY2*, and *CK1 $\epsilon$*  genes in HCC [84]. At the same time, elevated HBx expression in HCC results in increased *CLOCK*, *PER1*, and *PER2* expression [1,85]. In addition, abnormal expression of *REV-ERBa* was observed in a cell line that stably expressed HBV [86]. The circadian rhythm acts *via* *REV-ERBa* in the liver on hepatocyte nuclear factor 4 alpha (*HNF4 $\alpha$* ), and thus directs the action of glucocorticoid receptors on energy metabolism (Figure 3). Consequently, the interactions between *CRY* and glucocorticoid receptors affect carbohydrate metabolism, hence transacting *PER2* [87]. *HNF4 $\alpha$*  increases the transcription of pgRNA in hepatoma cells and thus affects HBV biosynthesis [88]. In addition, P2-*HNF4 $\alpha$*  inhibits the expression of *BMAL1*, leading to the localization of P1-*HNF4 $\alpha$*  from the nucleus to the cytoplasm. *BMAL1* is expressed in healthy hepatocytes, but tumor growth is prevented if *BMAL1* expression is induced in *HNF4 $\alpha$* -positive tumor cells [89]. The possible reason for the inhibition of tumor growth is that *BMAL1* mediates the transcription of *P53* pathway genes, a well-known tumor-suppressor gene [90]. DNA viruses rely more on host transcription for gene expression; however, *BMAL1* deficiency increases virus replication. *REV-ERB $\alpha$*  has a protective effect because it reduces the inflammatory response, thus decreasing the severity of the disease. Thus, *REV-ERBa* agonists inhibit HBV replication, while *BMAL1* promotes virus replication. Nevertheless, as *BMAL1* stimulates oscillations in genes that metabolize drugs and sensitivity to toxicity, it also promotes HBV infection in hepatocytes [91].

HBV infection leads to overexpression of *ROR $\alpha$*  and *ROR $\gamma$*  [92]. *ROR $\gamma$*  overexpression is associated with promoter methylation and HBx protein. Furthermore, HBx-induced *ROR $\gamma$*  may facilitate the proliferation and migration of hepatoma cells [93], and *ROR $\alpha$*  may be a possible diagnostic and prognostic biomarker for disease severity [94]. Overexpression of *ROR $\alpha$* , *CRY2*, and *PER1* is associated with a better survival of HCC patients, and regulating the circadian rhythm gene may help in the chronotherapy of such patients [94]. HBV infection leads to disruptions of the *CLOCK* gene and its downstream circadian genes and other CCGs [2]. All the above indicates that circadian rhythm disorders caused by a virus may contribute to the pathogenesis of cancer.

### Immunopathogenesis of chronic HBV infection and circadian rhythm

Clinical manifestations of chronic hepatitis B result from a cellular and humoral immune response to the recognized target antigenic viral epitopes, HBcAg and HBsAg [21]. Integration of HBV into the



**Figure 3 Relationship between circadian rhythm genes and hepatitis B virus replication.** Gray dashed lines indicate normal circadian rhythm in hepatocytes. Black arrows show the association between core clock proteins and hepatitis B virus (HBV) entry into hepatocytes and its replication. Increased levels of REV-ERB protein prevent the entry of HBV into hepatocytes by impaired action on the sodium taurocholate co-transporting polypeptide (NTCP) receptor. Brain and muscle ARNTL-like protein 1 (BMAL1) protein binds HBV DNA and thus controls viral genome expression and the formation of new viral particles. In infected hepatocytes, REV-ERB through HNF4 $\alpha$  mediator increases pregenomic RNA (pgRNA) transcription, while HNF4 $\alpha$  inhibits BMAL1 expression, promoting HBV replication. Red arrows indicate circadian rhythm genes inhibited by hepatitis B protein X (HBx) protein (BMAL1, CRY1, CRY2, and PER3). Conversely, HBx increases CLOCK, PER1, PER2, and ROR $\gamma$  gene expression (indicated by blue arrows). Increased expression of ROR $\gamma$  leads to the proliferation of hepatoma cells. BMAL1: Brain and muscle ARNTL-like protein 1; cccDNA: Covalently closed circular DNA; CCG: Clock-controlled genes; CLOCK: Circadian locomotor output cycles kaput; CK1: Casein kinase 1; CRY: Cryptochrome; HBx: Hepatitis B protein X; HNF4 $\alpha$ : Hepatocyte nuclear factor 4 alpha; HSP: Heparan sulfate proteoglycan; NTCP: Sodium taurocholate co-transporting polypeptide receptor; PER: Period; pgRNA: Pregenomic RNA; ROR: Retinoic acid receptor-related orphan receptor; RORE: ROR element.

hepatocytes' genome serves as a constant source of HBsAg during chronic infection. It may induce dysfunctional T-cell responses, and favor harmful immunopathology and disease progression to fibrosis and cirrhosis[95]. Hepatocytes expressing HBcAg are recognized and attacked by cytotoxic CD8<sup>+</sup> lymphocytes (CTL)[96]. The increase in alanine aminotransferase is the result of hepatocyte lysis[97]. HBcAg has strong immunogenicity and can cause the antigen-specific T-cell responses necessary for controlling HBV infection. HBcAg stimulates the production of interleukin 6 (IL-6), IL-10, IL-17A, IL-22, IL-23, and transforming growth factor  $\beta$  (TGF $\beta$ ) by peripheral blood mononuclear cells[98]. In addition, the immunosuppressive cytokine IL-10 negatively controls the expansion of Th17 cells, which plays a part in the existence and promotion of HBV infection[46]. Persistent HBV infection is marked by a poor immune response due to the poor response of CD4<sup>+</sup> lymphocytes in the early phases of infection. This results in qualitatively and quantitatively weaker CD8<sup>+</sup> T cell responses[21].

In addition to other viral proteins, HBeAg is also important for the persistence of infection, as it suppresses the humoral and cellular immune response to HbcAg, weakens the action of CTL on HbcAg, and allows the maintenance of the infection[99]. The predominance of Th-1 over the Th-2 cytokine response, with the production of IL-2, interferon-alpha (IFN- $\alpha$ ), and lymphotoxin- $\beta$  receptor (LT- $\beta$ R), is responsible for virus elimination during acute and chronic HBV infections[100]. Conversely, the predominance of Th-2 cytokine response is responsible for maintaining chronic infection, with IL-4, IL-5, and IL-10, which enhance the humoral immune response[98].

Many innate and adaptive immune system elements are under circadian regulation[1], and the adaptive immune response mediates virus removal and liver disease[95]. Cellular immune rhythms are synchronized with the central clock in the SCN[6]. Innate and adaptive immune system cells have a molecular clock that controls their rhythmic activity over 24 h[101]. Certain functions of the innate immune system rely on the hepatocytes' circadian rhythm[5,65]. Increased amounts of pro-inflammatory hormones such as growth hormone, prolactin, and melatonin and cytokines such as IL-1 and TNF- $\alpha$  are present during the rest period. In addition, immune rhythms are affected by hormonal



rhythms, so cortisol regulates the number of naive T cells. Epinephrine influences the number of CTL cells over 24 h[102].

Furthermore, the transcription factor CRY2 links the circadian rhythm and the innate immune system [103]. Moreover, CLOCK and BMAL1 control transcription of the pattern recognition receptor, which is involved in nucleic acid detection during viral infections[104]. ROR $\gamma$  regulates the differentiation of Th17 cells, which secrete IL-17, an essential regulator of pro-inflammatory signaling[93]. REV-ERB $\alpha$  has a protective effect in various inflammatory processes[105]. Additionally, the suppression of REV-ERB receptors elevates virus-associated mortality by promoting the inflammatory response[106]. The circadian hormone melatonin has protective and antiviral actions and a role in the inflammatory response[105]. Melatonin increased IFN- $\gamma$  levels during viral infection, decreased Venezuelan equine encephalomyelitis virus (VEE) levels, and reduced mortality rates in mice infected with VEE. The protective impact of melatonin is associated with increased IL-1 $\beta$  production because it acts as a cytokine modulator and antioxidant[107]. This shows the positive role of the circadian rhythm in regulating antiviral immunity[91].

## ANTIVIRAL THERAPY

There are two main drugs for HBV infection therapy: Nucleoside/nucleotide analogs (NAs), which interfere with viral DNA synthesis during reverse transcription, and IFN- $\alpha$ [108,109]. NAs effectively inhibit virus replication and may suppress the generation of new cccDNA[109]. Existing drugs can suppress virus replication, slow fibrosis progression, and decrease infectivity, but rarely remove the cccDNA responsible for HBV persistence[108]. Therefore, the development of therapy aims to achieve a "functional healing" state, *i.e.*, the removal of cccDNA from hepatocytes[110,111]. However, in the treatment of HBV infection, NAs rarely eliminate the virus, that is, they do not eradicate HBV from the liver[95]. This is because each HBV surface protein (S, M, and L) has an HBsAg determinant. Therefore, HBsAg circulates in the bloodstream of HBV patients, mainly in non-infectious subviral spheres and filaments[95].

Alternative therapeutic strategies are based on silencing viral genes using RNA interference (RNAi) [108] and antisense oligonucleotide (ASO) technology[110]. Both approaches are based on the effective suppression of HBV replication in patients with chronic HBV infection[108,110]. RNAi is a mechanism for silencing genes after transcription, and can be used in mammalian cells against viral infections[108]. ASO technology prevents HBV antigen production by targeting all HBV genome transcripts in infected hepatocytes[10,110]. It is based on NAs that act on viral polymerase but do not influence the cccDNA transcription[110]. ASO and other nucleic acid-based therapies may potentially decrease the tolerogenic outcome of the high HBsAg levels characteristic of chronic infection[63,110].

### Role of circadian rhythm in antiviral therapy

One of the principles of personalized medicine is to optimize the time of day for administration of drugs whose action is affected by the circadian rhythm[5,112]. Circadian oscillations can affect vaccine responses to viral pathogens[91]. The direct impact of the circadian rhythm on the cellular and humoral immune reaction is mediated by melatonin and cortisol. Research on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown that melatonin can affect circadian clocks and modulate the immune response during viral infections and thus impact virus replication[113]. Therefore, vaccination in the morning or evening may impact the immune response to the vaccine[114]. Thus, it was observed that patients vaccinated against the SARS-CoV-2 in the morning had significantly lower C-reactive protein levels compared to patients vaccinated in the evening[115]. Making a simple effort to determine the appropriate time for administration of drugs or vaccine can improve the drug's effectiveness and reduce side effects[5]. However, studying the interaction of the circadian rhythm and virus replication may lead to a better knowledge of viral infections and the associated immune response, discovery of new antiviral targets, improvement of existing treatments, and therapy for chronic infections[5]. Chronic infection is linked with a weakened immune response, and poor T-cell responses that fail to control HBV replication[50]. The effectiveness of current antiviral therapies could be enhanced by modulating the timing of vaccine administration. For example, the engineered T cell receptor activity showed a circadian pattern upon antigen activation. However, this daily effect was attenuated in *CLOCK* mutant mice, emphasizing the importance of timing T cell therapy to maximize antiviral immunity[1].

Many studies show that the efficacy or toxicity of treatment depends on the dosing time in many diseases. Also, inter-individual variations in the circadian rhythm resulting from lifestyle differences should be considered[116]. The efficiency of the DNA virus vaccine can be enhanced by specifying the time of day for vaccination. For example, some studies have found that patients immunized in the morning produce a more significant antibody response to hepatitis A and influenza vaccines[1,117]. In addition, morning vaccination is considered to significantly increase responses to viral-specific antibodies, compared to afternoon vaccination[1]. As viruses are intracellular pathogens that replicate within host cells, given the high association of circadian rhythm transcription factors with cell

transcription, the circadian rhythm plays a vital role in determining host susceptibility to viral infections and the immune response[1].

Circadian clock-modulating small molecules may help inhibit or activate circadian rhythm proteins and enzymes in viral infections. Thus, the small molecule SRT2183 modulates the circadian clock that inhibits SARS-CoV-2 replication[118] because it modulates physiological and circadian rhythm gene expression[119]. Inhibiting *BMAL1* expression and overexpression of *REV-ERB* via circadian rhythm-modulating small molecules may prevent dengue virus, hepatitis C virus, Zika virus, and HIV1 virus replication. In addition, clock genes have antiviral abilities that can be applied to HBV[120]. One of the effective circadian clock-modulating small molecules in treating HBV infections is GSK4112, a synthetic ligand for REV-ERB, but it is not suitable for *in vivo* use due to its poor pharmacokinetic properties. In contrast, ARN5187 is a REV-ERB $\beta$  agonist with dual function, an inhibitor of REV-ERB and autophagy [121]. SR9009 is a REV-ERB $\alpha$  agonist based on the chemical structure of GSK4112. It has better pharmacokinetic properties than GSK4112 and affects many oncogenes. In addition, REV-ERB $\alpha$  is known to regulate cancer development by inhibiting proliferation[121], and hence SR9009 inhibits *BMAL1* and prevents the entry and replication of HBV into hepatocytes[50].

Challenges associated with antiviral drug development, including circadian clock-modulating small molecules, may be adverse effects or suboptimal pharmacokinetics. Therefore, for an antiviral agent to succeed, the target drug should be distributed locally to avoid unfavorable consequences on other tissues.

## CONCLUSION

Interaction exists between viruses and the circadian rhythm of hepatocytes. Infection susceptibility depends on the infectivity of the inoculum, the mode of transmission, the length of exposure to the virus, and the time of the day infection occurs[1]. Understanding how HBV interacts with the circadian rhythm of hepatocytes may influence the treatment of infections[1]. Viruses are among the most critical human carcinogens[6], and pharmacotherapy and chronotherapy should be united to treat or prevent viral infections[1]. Research on the impact of viral infections on the circadian rhythm may help detect new antiviral targets and optimize the timing of immune-based therapies[1]. The main challenge in treating HBV infection is eradicating or silencing the cccDNA[50]. By acting on specific components of the circadian rhythm, such as REV-ERB and *BMAL1*, HBV can be prevented from entering hepatocytes and producing new virions. In addition to lifestyle changes, circadian rhythm-focused approaches may provide new therapeutic options in treating HBV infections[63].

## FOOTNOTES

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