

## Host cellular microRNA involvement in the control of hepatitis B virus gene expression and replication

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(miRNAs), their growth factors and their downstream agents is required for the initiation and completion of pathogenesis in the liver. miRNAs are thought to exert a profound effect on almost every aspect of liver biology and pathology. Accumulating evidence indicates that several miRNAs are involved in the hepatitis B virus (HBV) life cycle and infectivity, in addition to HBV-associated liver diseases including fibrosis, cirrhosis and hepatocellular carcinoma (HCC). In turn, HBV can modulate the expression of several cellular miRNAs, thus promoting a favorable environment for its replication and survival. In this review, we focused on the involvement of host cellular miRNAs that are directly and indirectly associated with HBV RNA or HBV associated transcription factors. Exploring different facets of the interactions among miRNA, HBV and HCV infections, and the carcinogenesis and progress of HCC, could facilitate the development of novel and effective treatment approaches for liver disease.

**Key words:** Hepatitis B virus; Gene expression; Gene replication; Transcription; MicroRNA

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**Core tip:** A large number of studies have demonstrated that the synergistic collaboration of a number of microRNAs (miRNAs), their growth factors and their downstream agents is required for the initiation and completion of pathogenesis in the liver. miRNAs are thought to exert a profound effect on almost every aspect of biology and pathology. In this review, we focused on the miRNAs that play an important role in hepatitis B virus replication and gene expression, and summarized the involvement of host cellular miRNAs that are directly and indirectly associated with hepatitis B virus (HBV) RNA or HBV associated transcription factors.

### Abstract

A large number of studies have demonstrated that the synergistic collaboration of a number of microRNAs

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## INTRODUCTION

MicroRNAs (miRNAs) participate in crucial biological processes, including development, differentiation, apoptosis, and proliferation<sup>[1,2]</sup>, by either inhibiting target mRNA translation or inducing its degradation by pairing with complementary sequences within the 3'-untranslated regions (3'-UTRs) of targeted transcripts at the post-transcriptional and/or translational level<sup>[3]</sup>. There are more than 2500 homo sapiens miRNAs (1881 precursors, 2588 mature; data taken from miRbase 21; <http://www.mirbase.org/>), each of which can influence hundreds of gene transcripts<sup>[4]</sup>. Several miRNAs can regulate a specific mRNA, engendering substantial complexity with respect to their capacity to modulate fundamental biological processes.

MiRNAs are crucial in normal liver development<sup>[5]</sup> and biological processes, including liver differentiation, hepatocyte development, and many metabolic functions.

Recent studies have demonstrated that the profiling of miRNAs facilitates the classification of various tumors (whereas mRNA profiles are relatively inaccurate), which suggests that miRNAs possess a high potential for facilitating cancer diagnosis<sup>[6]</sup>. Another study using sequencing demonstrated that a set of miRNAs account for the majority of the differences in miRNA profiles among cell lineages and tissues<sup>[7]</sup>. A large number of miRNAs are expected to be involved in critical aspects of liver physiology, because the liver serves as an endocrine and exocrine organ with numerous functions, including carbohydrate, lipid and amino-acid metabolism, urea synthesis, detoxification of drugs and toxic endogenous compounds, bile production and plasma protein secretion<sup>[8]</sup>. The dysregulation of tissue and serum miRNA expression has also been observed in the context of specific liver pathologies, including hepatitis, cirrhosis, and liver cancers, as well as chronic cholestasis<sup>[9]</sup>.

MiRNAs are typically transcribed from genes in the nucleus by RNA polymerase II into initial transcripts of either monocistronic or polycistronic primary-miRNAs (pri-miRNAs; Figure 1). These pri-miRNAs are further processed *via* the canonical pathway (by Drosha-DGCR8)<sup>[10]</sup> into hairpin-shaped precursor miRNAs (pre-miRNAs). These pre-miRNAs are exported *via* Exportin-5/RanGTP<sup>[11]</sup> from the nucleus into the cytoplasm, where they undergo cleavage by the RNase III enzyme known as Dicer, as well as TBRP<sup>[12]</sup>, which produces an imperfect miRNA duplex. This duplex then splits, thereby generating a single-stranded mature miRNA that is loaded onto the RNA-induced silencing complex<sup>[12]</sup>, which is then guided to the target mRNA through interactions with members of the Argonaute family. Due to

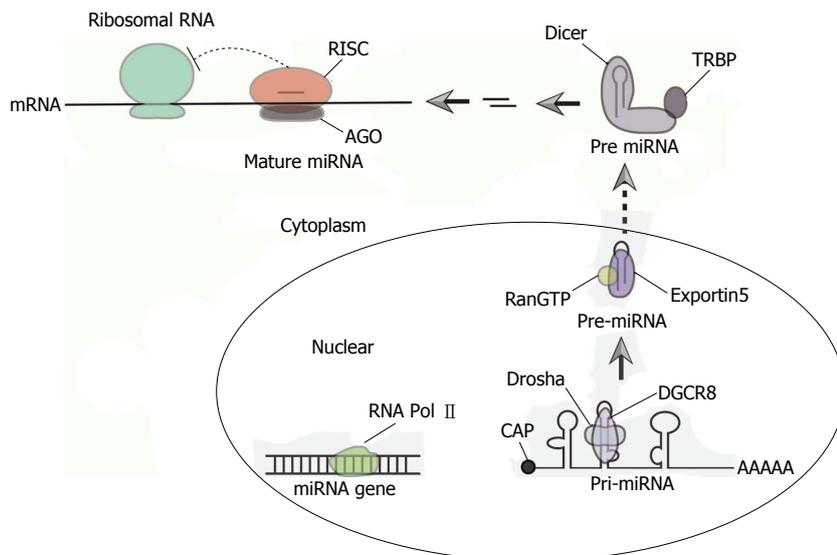
complementarity with its target gene sequence, mature miRNA principally induces either translational repression or mRNA degradation<sup>[13]</sup>. However, several reports have indicated that miRNAs and their associated protein complexes (micro-ribonucleoproteins or microRNPs) can also post-transcriptionally stimulate gene expression *via* direct and indirect mechanisms<sup>[14,15]</sup>. miRNAs primarily regulate mRNAs by interacting with their 5' end (5p) and 3'-UTR, although it has recently been suggested that the miRNA target sites may be located in the 5'-UTR or even at simultaneous 5'-UTR and 3'-UTR interaction sites<sup>[16]</sup>.

In the following section, we review recent advances in the understanding of the involvement of miRNA in the control of hepatitis B virus (*HBV*) gene expression and replication.

## HBV INFECTION

The estimated number of new hepatocellular carcinoma (HCC) cases rose to 564300, with 548600 of these patients dying (*i.e.*, 97.2% of those receiving a diagnosis of HCC). The World Health Organization estimates that 2 billion people worldwide have been infected with the HBV, which represents the most common cause of HCC and, furthermore, that 350 million people have chronic-type HBV infection<sup>[9]</sup>. Because the current therapeutic options for HCC patients are limited, there is an urgent need to analyze the molecular oncogenic mechanisms of HCC, to determine novel targets for specific systemic therapy and to detect novel biomarkers for early diagnosis. The biology and lifecycle of the HBV remains to be elucidated, but it is presumed to involve the following processes<sup>[17]</sup>: (1) entry into hepatocytes *via* the fusion of viral and cellular membranes, such that the viral capsid is transported into the nucleus; (2) the HBV-relaxed circular genome is released into the nucleus and converted to 1-50 covalently closed circular DNA (cccDNA); (3) 3.2 kb cccDNA contains four major open reading frames of the pre-core/core gene, the polymerase gene, the *preS1/L-*, *preS2/M-*, and *Surface/S-* gene, and the *X* gene. The genes are transcribed into subgenomic RNA (sgRNA) and pregenomic RNA (pgRNA), HBV surface antigen, HBV core protein, viral reverse DNA polymerase, and X protein, as well as pgRNA; (4) following nuclear export, the pgRNA is translated into the core protein and viral polymerase. The sgRNA is translated into regulatory X-protein and three envelope proteins; and (5) complex formation and reverse transcription of pgRNA produces an RNA-containing nucleocapsid. RNA-containing nucleocapsids mature into DNA-containing nucleocapsids within the cytoplasm.

Accumulating evidence indicates that several miRNAs are involved in the HBV life cycle and infectivity, in addition to HBV-associated liver diseases including fibrosis, cirrhosis and HCC. In turn, HBV can modulate the expression of several cellular miRNAs, thus promoting a favorable environment for its replication and



**Figure 1 Schematic illustration of microRNA biogenesis.** mRNA: Messenger RNA; RISC: RNA-induced silencing complex; AGO: Argonaute; Pre-miRNA: Premature-microRNA; Pri-miRNA: Primary-microRNA; RNA pol II: RNA polymerase II.

**Table 1 Direct interactions of microRNAs with hepatitis C virus and hepatitis B virus RNA**

| Host miRNA  | Binding location        | Function                  | Expression | Ref. |
|-------------|-------------------------|---------------------------|------------|------|
| miR-20a     | X and polymerase        | Inhibits HBV replication  | Up         | [23] |
| miR-92a-1   | X and polymerase        | Inhibits HBV replication  | Up         | [23] |
| miR-122     | Core and DNA polymerase | Inhibits HBV replication  | Down       | [20] |
| miR-125a-5p | HBsAg                   | Inhibits HBV replication  | Up         | [22] |
| miR-199a-3p | HBsAg                   | Inhibits HBV replication  | Up         | [21] |
| miR-205     | HBx                     | Suppresses HBx production | Down       | [25] |
| miR-210     | PreS1                   | Inhibits HBV replication  | Up         | [21] |
| miR-1231    | HBx/HB core             | Inhibits HBV replication  | Up         | [26] |

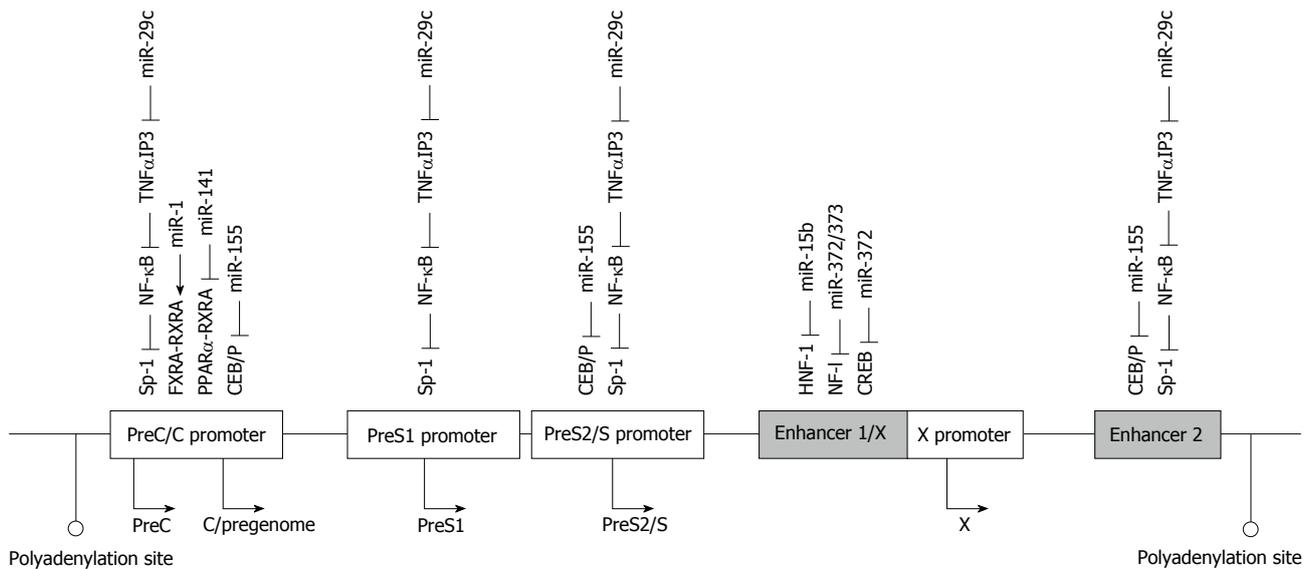
HBsAg: Hepatitis B surface antigens; HBV: Hepatitis B virus; HBx: HBV X.

survival. Several studies exploring the involvement of HBV in hepatocytes utilized HepG2.2.15 cells, derived from HepG2 and containing a stable transfected full-length *HBV* genome (ayw subtype), hepatitis B surface antigens (HBsAg) and hepatitis B e antigens (HBeAg), thereby supporting full HBV replication<sup>[18]</sup>.

### DIRECT INTERACTION BETWEEN HBV TRANSCRIPTS AND HOST miRNAs

Although HBV is a DNA virus, its transcripts may be targeted and regulated by several cellular miRNAs similar to those of HCV (Table 1). The direct interaction between HCV RNA and miR-122, which results in a stable heterotrimeric structure, enhances HCV translation and protects against HCV RNA degradation<sup>[19]</sup>. Conversely, all of the interactions reported thus far between host cellular miRNAs, including miR-122, and HBV RNA transcripts inhibit HBV genome replication. Chen *et al.*<sup>[20]</sup> demonstrated that miR-122, a liver-specific miRNA, down-regulates *HBV* gene expression and replication, as determined using HBsAg and HBeAg. MiR-122 can inhibit *HBV* gene expression by interacting with the target sequence coding for nucleotides 2738-2760 and

by targeting sequences located at the coding region of the mRNA for viral polymerase and the 3'-UTR region for the core protein of the HBV genome, *via* base-pairing interactions. Chen *et al.*<sup>[20]</sup> also demonstrated an inverse linear relationship *in vivo* between miR-122 levels and viral load in the peripheral blood mononuclear cells of HBV-positive patients. Zhang *et al.*<sup>[21]</sup> demonstrated that miR-199a-3p and miR-210 effectively reduced HBsAg expression in HepG2 2.2.15 cells containing an integrated *HBV* genome. Bioinformatics analysis indicated a putative binding site for miR-199a-3p in the HBsAg coding region and a putative binding site for miR-210 in the HBV pre-S1 region<sup>[21]</sup>. Comparison of the expression levels of miR-199a-3p and miR-210 between HepG2 2.2.15 cells and the parent cell line (*i.e.*, HepG2 cells) revealed a 9-fold increase in miR-199a-3p and miR-210 in HepG2 2.2.15 cells compared with HepG2 cells<sup>[21]</sup>. Potenza *et al.*<sup>[22]</sup> reported that miR-125a-5p can interact with the HBV surface antigen and interfere with its expression, thus reducing the amount of HBsAg secreted. A recent study by Jung *et al.*<sup>[23]</sup> demonstrated that HBV infection transactivates c-Myc, after which it up-regulates the miR-17-92 cluster. Conversely, miR-20a and miR-92a can down-regulate HBV pregenomic



**Figure 2 Summary of the effect of miRNAs on hepatitis B virus transcription.** Binding sites of ubiquitous and hepatocyte-enriched transcription factors within *HBV* promoter and enhancer regions as well as miRNAs that can modulate target transcription factors are indicated. The various *HBV* promoter and enhancer sites are schematically depicted as boxes. *HBV*: Hepatitis B virus.

RNA by directly targeting its *X* and polymerase gene, indicating that these miRNAs suppress *HBV* replication by creating a negative feedback loop. *HBV X* protein (*HBx*) plays a crucial role in the development of HCC by inducing epigenetic changes within host genetic and epigenetic architecture, including aberrations in DNA methylation, histone modifications, and miRNA expression<sup>[24]</sup>. Zhang *et al.*<sup>[25]</sup> demonstrated that *HBx* can down-regulate miR-205, otherwise known as down-regulated miRNA in HCC, by inducing hypermethylation of the miR-205 promoter within cells. In turn, miR-205 suppresses *HBx* expression by directly targeting *HBx* mRNA. Kohno *et al.*<sup>[26]</sup> recently demonstrated that in *HBV*-transfected HepG2 cells, the overexpression of hsa-miR-1231 is associated with the suppression of *HBV* replication and *HBV* core reduction. The mechanism by which these interactions between host cellular miRNAs and *HBV* RNA transcripts affect infectivity could involve the maintenance of a suitable reduction in virus antigen level and virion production, thereby contributing to a persistent, chronic *HBV* infection or latent *HBV* state.

## CELLULAR miRNAs CONTROL HBV TRANSCRIPTION BY TARGETING TRANSCRIPTION FACTORS

In addition to direct interactions, several miRNAs regulate *HBV* replication by targeting *HBV*-associated genes, including transcription factors (Table 2 and Figure 2).

*HBV* contains a 3.2-kb partially double-stranded DNA genome with four promoters (*i.e.*, core, pre-S1, pre-S2/S, and *X* promoters) and two enhancer regions (ENI and ENII), which are involved in viral transcription regulation and thus play a central role in the control of

*HBV* replication<sup>[27]</sup>. The transcription of *HBV* cccDNA is tightly regulated according to epigenetic mechanisms, such as DNA methylation, acetylation, and histone modifications<sup>[28]</sup>. *HBV* utilizes a number of ubiquitous and liver-enriched transcription factors, in addition to nuclear receptors in hepatocytes, to cause the efficient transcription of the *HBV* gene by binding to *HBV* promoter/enhancer elements<sup>[27]</sup>. The control of *HBV* during transcription thus influences both *HBV* gene expression and replication. Zhang *et al.*<sup>[29]</sup> demonstrated that miR-1 enhanced *HBV* core promoter transcription activity by augmenting the expression of farnesoid *X* receptor alpha (*FXRα*), a liver-enriched transcription factor activated by bile acids. *FXRα* can function as a transcription factor by binding to the *HBV* enhancer II and core promoter in heterodimers with retinoid *X* receptor α (*RXRα*). Zhang *et al.*<sup>[29]</sup> also demonstrated that miR-1 targets deacetylase 4 and E2F transcription factor 5, thus suppressing *HBV* replication. Liver-specific miR-122 is part of a complicated signaling network for *HBV* infectivity, through which it can down-regulate *HBV* replication as discussed above. For instance, the inhibition of miR-122 causes an increase in cellular heme oxygenase-1, which can decrease *HBV* cccDNA levels<sup>[30]</sup>. Cyclin G<sub>1</sub> is one target of miR-122 and is involved in the regulation of *HBV* replication. Wang *et al.*<sup>[31]</sup> demonstrated that interactions between cyclin G<sub>1</sub> and p53 block the specific binding of p53 to *HBV* enhancer elements and simultaneously abrogate p53-mediated inhibition of *HBV* transcription. Fan *et al.*<sup>[32]</sup> reported an inverse correlation between the expression levels of miR-122 and *NDRG3* (a member of the N-myc downstream-regulated gene) in *HBV*-related HCC specimens, which might accelerate *HBeAg* and *HBsAg* secretion and *HBV* DNA replication. miR-372/373 represses *PRKACB* and *NFIB* by targeting its 3'-UTR,

**Table 2** MicroRNAs that control hepatitis B virus gene replication and expression through cellular targets

| MiRNAs      | Cellular targets     | Effects on HBV biology or pathogenesis  | Expression | Ref. |
|-------------|----------------------|---|------------|------|
| miR-1       | HDAC4/E2F5           | Increases HBV replication by augmenting FXRA activity                               | Down       | [29] |
| miR-15b     | HNF1 $\alpha$        | Promotes HBV replication and expression of HBV antigens, including HBx protein      | Down       | [39] |
| miR-29c     | TNFAIP3              | Suppresses HBV DNA replication and cell proliferation and inhibits apoptosis of HCC | Down (HCC) | [41] |
| miR-122     | Cyclin G1            | Suppresses HBV replication  | Down       | [31] |
|             | (HO-1)               | Promotes HBV expression by inhibiting HO-1 expression                               |            | [30] |
|             | NDRG3                | Inhibits viral replication and HBV HCC proliferation                                |            | [32] |
| miR-125b    | SCNN1A               | Inhibits HBV expression   | Down       | [42] |
| miR-141     | PPARA                | Suppresses HBV replication by inhibiting PPARA-HBV promoter interaction             |            | [44] |
| miR-155     | C/EBP                | Elevates HCC levels/promotes HCC cell growth  | Up         | [46] |
| miR-372/373 | NFIB                 | Promotes HBV replication  | Up         | [33] |
| upmiR-372   | CREB                 | Promotes HBV replication  |            | [34] |
| miR-501     | HBIP (HBx inhibitor) | Promotes HBV replication  | Up         | [45] |

HBV: Hepatitis B virus; HBx: HBV X; CREB: cAMP-response element binding protein; C/EBP: CCAAT/enhancer binding protein beta; HCC: Hepatocellular carcinoma; HNF1 $\alpha$ : Human hepatocyte nuclear factor 1  $\alpha$ .

resulting in reduced expression of HBV<sup>[33,34]</sup>. PPKACB induces the phosphorylation of cAMP-response element binding protein (CREB) and dissociates CREB from its promoter. CREB is required for the expression of all HBV transcription units in the binding of viral enhancer I<sup>[35]</sup>. NFIB is significantly down-regulated in HBV-associated liver cirrhosis (LC), compared with non-LC tissues, whereas pre-miR-372 is increased significantly in liver cirrhosis. Together, these independent findings confirm that *HBV* genomic nuclear factor I sites play important and complex roles in the regulation of HBV expression<sup>[36-38]</sup>. Conversely, a recent study has reported that peroxisome proliferator-activated receptor (PPAR)- $\gamma$  and the HBx down-regulate miR-122 transcription. Dai X reported that miR-15b promotes HBV replication by augmenting HBV enhancer I activity *via* direct targeting of human hepatocyte nuclear factor 1 $\alpha$ , while HBV replication and antigen expression, particularly of the HBx protein, repress the expression of miR-15b<sup>[39]</sup>.

The miR-29 family members miR-29a, miR-29b, and miR-29c exert a suppressive action on tumors and are downregulated in several types of cancer, in which miR-29 directly targets DNA methyltransferase 3A and -3B, two key enzymes involved in DNA methylation, in addition to methylation-silencing tumor suppressor genes, such as fragile histidine triad and WW domain containing oxidoreductase<sup>[40]</sup>. Wang *et al*<sup>[41]</sup> reported that miR-29c functions as a tumor-suppressive gene by targeting TNFAIP3, a key regulator in inflammation and immunity. Furthermore, this interaction results in the suppression of HBV replication, as indexed by HBsAg/HBeAg secretion and HBV DNA replication.

Zhang *et al*<sup>[42]</sup> used a miRNA microarray to assess miRNA expression during HBV infection *in vitro*. miR-125b expression was decreased in both HepG2-HBV1.3 (a HepG2 cell line transiently transfected with an HBV expression plasmid) and HepG2.2.15 cells. Furthermore, the ectopic expression of miR-125b inhibited HBV DNA intermediates and the secretion of HBsAg and HBeAg. miR-125b also reduced SCNN1A mRNA and protein levels. Using a dual luciferase assay,

SCNN1A was shown to be one of the targets of miR-125b, indicating that miR-125b inhibits HBV expression by targeting the *SCNN1A* gene. These results suggest a potential role of miRNA in HBV infection.

The core promoters pre-S1 promoter, X promoter, ENI and ENII all contain a PPAR $\alpha$  binding site; these regions are transactivated in the presence of RXR $\alpha$  and PPAR $\alpha$ <sup>[27]</sup>, suggesting that PPAR $\alpha$  likely plays a critical role in HBV biogenesis. miRNA 141, a member of the miR-200 family, plays a central role in epithelial mesenchymal transition<sup>[43]</sup>. Hu *et al*<sup>[44]</sup> demonstrated that miR-141 can repress HBV replication effectively, and further that miR-141 inhibitor transfection precipitates a marked increase in HBsAg/HBeAg expression, which had no significant effect on HBV DNA replication, through direct targeting of the PPAR $\alpha$  mRNA 3'-UTR.

MiR-501 expression was significantly up-regulated in hepatocellular carcinoma tissues, in which the level of HBV replication remained high<sup>[45]</sup>. Down-regulating miR-501 significantly inhibited HBV replication but did not influence the growth of HepG2.2.15 cells<sup>[45]</sup>. Luciferase reporter and western blot assays revealed that HBx-interacting protein, an HBV replication inhibitor, is a potential target of miR-501<sup>[45]</sup>.

Although the association between miR-155 and HBV replication remains to be demonstrated, it has been reported that CCAAT/enhancer binding protein beta, which can bind to HBV promoters and enhancers, is one target of miR-155<sup>[46]</sup>.

## CONCLUSION

In this review, we focused on the role of miRNAs in *HBV* gene expression and replication. The available evidence suggests that several miRNAs mediate HBV RNA accumulation. miRNAs might have other functions specific to individual miRNAs, cell types or tissue environments and may also play a suppressive role in multi-target gene expression, thereby suggesting that miRNAs may serve as novel targets for therapeutic interventions. Despite progress in drug discovery and

development, as evidenced by novel protease inhibitors and polymerase inhibitors, the clinical use of direct-acting antivirals is limited due to poor compliance and rapid-onset drug resistance. The use of imatinib mesylate, a platelet-derived growth factor receptor, and other tyrosine kinase inhibitors, as molecular targets against HCC progression, has been proposed<sup>[47,48]</sup>; however, clinical trials have indicated a lack of efficacy using this approach<sup>[49]</sup>. The development of more effective, cost efficient, and better-tolerated novel treatments is crucial to control the development of hepatitis, cirrhosis, and hepatocellular carcinoma. Exploring different facets of the interactions among miRNA, HBV and HCV infections, and the carcinogenesis and progression of HCC could facilitate the development of novel and effective treatment approaches for liver disease.

Although relatively poorly understood in the context of human cancers, evidence continues to accumulate indicating that long non-coding RNAs play a crucial role in regulating numerous developmental and biological genomic pathways<sup>[50]</sup>.

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