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A double-edged sword: The HBV-induced non-coding RNAs alterations in hepatocellular carcinoma

Tianxing LIU[1]; Hongyan DIAO[2,*]

[1] Department of Cell and Systems Biology, University of Toronto, Toronto, Ontario, M5S1A1, Canada
[2] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, 310003, China

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Abstract: Non-coding RNAs are speculated to exert important regulatory functions at the level of gene expression, oncogenesis, and many other pathologies. Hepatitis B virus (HBV) infection is a leading cause of hepatocellular carcinoma (HCC), and some studies have shown that the expression of non-coding RNAs has an assignable effect on the development of HBV-induced HCC. In this context, the functions and molecular mechanisms of the HBV-induced non-coding RNA expression in the development of hepatoma have attracted increasing attention. This review covers the progress in the exploration of the relationship between HBV-induced hepatoma and non-coding RNA expression, cataloging the recent reports about the roles of non-coding RNAs in HBV-induced hepatoma into five classes, including (1) modulation of metabolism in hepatic cancer, (2) aggravation of inflammation and hepatic fibrosis, (3) alteration of the tumor immune microenvironment, (4) non-coding RNA N6-methyladenosine modification, and a seemingly opposite process, (5) the suppression of the progression of HBV-related HCC. All evidence supports non-coding RNAs as promising novel targets for the early diagnosis and treatments for HCC.

Introduction

The chronic infection of hepatitis B virus (HBV) causes long-term damage to human health. HBV infection is a global pandemic; around 350–400 million people are chronically infected with HBV. Approximately 800,000 people die every year due to complications of HBV infection. Chronically infected persons have an increased lifetime risk for cirrhosis and hepatocellular carcinoma (HCC) (Mamuye *et al.*, 2020). The incidence rate of HCC is ranked fifth among all oncological diseases, and it is also one of the major oncological diseases worldwide that lead to death. HCC is also the most common primary liver cancer, as the incidence rate of HCC after HBV infection is up to 80%.

The human genome comprises both coding and non-coding genes. With the increase in research about the human genome, the functions of coding genes have been elucidated to a great extent, including their functions in infectious diseases and cancers (Atianand *et al.*, 2017; Zhang *et al.*, 2020). The majority (more than 90%) of the entire human genome consists of non-coding regions. Despite the growing academic interest toward the non-coding regions of genomes, their functions are still not fully understood. Among the non-coding genes, non-coding RNA represents the family of RNAs that are not translated into proteins and include long non-coding RNA (lncRNA), microRNA (miRNA), circle RNA (cirRNA), and so on. These non-coding RNAs have been found to act as regulators in the process of gene expression and the subsequent oncogenesis and other pathologies. The expression level of non-coding RNA is also reported to be affected by viral infections, which would lead to consequent changes in the host immune system (Chen *et al.*, 2021a; Henzinger *et al.*, 2020; Ozata *et al.*, 2019).

HBV infection is a common cause of chronic hepatic pathologies such as HBV-induced hepatic fibrosis and HCC, and it alters the patients' genomes and the compositions of coding and non-coding RNAs (Li *et al.*, 2019a). For instance, the level of lncRNA AK001796 is highly correlated with the tumor size and pathological stages in HCC patients (Han *et al.*, 2019). Histopathological sections also show that the infiltration of immune cells also changes the levels and the composition of non-coding RNAs (Zeng *et al.*, 2014). During the development of these pathologies, the dynamic interactions among HBV, hepatocytes, and the host immune system lead to different stages of pathogenesis. Specifically,

*Address correspondence to: Hongyan Diao, diaohy@zju.edu.cn
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the HBV-infected asymptomatic carriers show normal hepatic functions but are HBV-positive during the immune tolerance stage. As soon as the immune system is abnormally disturbed, the HBV-affected hepatocytes are damaged and eliminated, which leads to chronic liver injury, inflammation, and liver regeneration.

Although HBV infection is a leading cause of HCC, the molecular mechanism of HBV infection in the development of HCC is not fully understood yet. Non-coding RNA is likely to play a role in this process because there are already some reports confirming the changes in non-coding RNA expression in the development of HBV-induced HCC. Therefore, this article will review the functions of the HBV-induced non-coding RNAs, combining our research results, in the development of hepatoma.

Main Text

Hepatitis B virus modulates metabolism in hepatic cancer via non-coding RNA

The development of HCC is a complex, multifaceted process with multiple stages, which is also controlled intrinsically by genes and extrinsically by the environment. Evidence already supports the critical role played by non-coding RNA in the development of HCC by interacting with oncogenes or antioncogenes and altering the metabolic states of cancer cells (Chen *et al*., 2021b; Feng *et al*., 2019; Wong *et al*., 2018). When the tumor tissue is growing at a high rate, the blood vessels around the cancer cells are not capable of supporting them with sufficient nutrients and oxygen, thus placing these cancer cells under a hypoxic microenvironment. Under hypoxic conditions, cancer cells then switch their metabolic pathways to the glycolytic process to provide the energy for tumor growth, where glucose can be catabolized anaerobically to lactate via glycolysis (Liu *et al*., 2019). This transition from aerobic glycolysis to anaerobic fermentation is also closely related to the malignancy of tumors and their metastasis (Zhang *et al*., 2018).

Particularly, one subfamily of non-coding RNA, miRNA, is reported to be a regulator of the metabolic reprogramming in cancer cells, where miRNAs induce the degradation of the target genes or suppress the gene expression post-translationally (Subramaniam *et al*., 2019). Our research revealed that the p-protein in HBV (HBp) could modulate the glycolytic pathway to promote tumor growth and metastasis (Chen *et al*., 2021b). HBp increases the energy production via the miRNA-30b-5p/MINPP1 axis by accelerating the conversion of glucose into lactate and 2,3-bisphosphoglycerate (2,3-BPG) during tumorigenesis. HBp is also shown to selectively exert its function in the HBV-positive HCCs, but not in other non-HCC cell lines (Chen *et al*., 2021b). In addition to miRNA, lncRNA can also modulate the glucose metabolism in cancer cells by affecting the functioning of mitochondria (Li *et al*., 2019b). These findings support non-coding RNAs as a new target in the treatment for HCC that can regulate the glycolysis in HCC cells.

Hepatitis B virus aggravates inflammation and hepatic fibrosis via non-coding RNA and thus promotes tumorigenesis

The hepatic inflammation-fibrosis-cancer trajectory is a typical development process after HBV infection (Nomair *et al*., 2021). After the HBV infection, the liver of most patients undergoes chronic inflammation, which induces fibrosis and the occurrence of HCC (Lok, 2009). Non-coding RNA, especially lncRNA, is also involved in this inflammatory pathway.

Liver fibrosis-associated lncRNA1 (lnc-LFAR1) is identified to promote fibrogenesis in the liver via the nuclear-factor-kappa B (NF-κB)-mediated macrophage activation (Zhang *et al*., 2017b). Lnc-LFAR1 assists the binding between Smad2/3 and TGFβ R1 and enhances its phosphorylation, which further activates hepatic stellate cells (HSCs) to enhance the production of extracellular matrix (ECM). The level of miR-132 is elevated in chronic hepatitis B, posthepatitic cirrhosis, and HBV-related HCC, and the expression of miR-132 is positively correlated with the expression of HBx (Santella *et al*., 2019). We compared the peripheral blood mononuclear cells in terms of transcriptome between the HBV carrier and the patients with chronic hepatitis B with long-term medication and found that lncRNA ENST00000519726 (lncRNA-HEIM) was highly expressed in monocytes and further upregulated upon HBV infection. Furthermore, lncRNA-HEIM can activate hepatic stellate cells in patients with chronic hepatitis B with long-term medication (Yao *et al*., 2021).

In addition to the activation of immune cells, non-coding RNA also links cell proliferation with hepatitis, hepatic fibrosis, and HCC. For instance, one of the key proteins of HBV, the HBV-encoded X protein (HBx), upregulates the expression of both lncRNA and miRNA to induce HCC (Sartorius *et al*., 2020; Zhang *et al*., 2017a). After the HBV infection, these specific miRNAs bind to the promoters to enhance the transcription of genes for HBV proliferation and subsequently cause inflammation.

Hepatitis B virus promotes the expression of non-coding RNA in the tumor immune microenvironment (TIME)

TIME is a dynamic network consisting of blood vessels, immune cells, fibroblasts, extracellular matrix, cytokines, and chemokines, which is closely related to the development of cancers (Desbois and Wang, 2021). Previous research has reported that TIME prevents the escaping of the cancerous cells to suppress cancer development, mainly via the immune surveillance system (Schreiber *et al*., 2011). The activation of immune cells in TIME, such as T cells, B cells, macrophages, natural killer (NK) cells, and dendritic cells, plays an immunosuppressive role in tumorigenesis in general (Gaudino and Kumar, 2019). However, the composition of different cell types can have differential impacts on the development of cancers; for instance, the increase in the proportion of regulatory T (Treg) cells would promote cancerogenesis (Fridman *et al*., 2017).

Within the TIME, non-coding RNA is also closely related to immunomodulatory signaling. LncRNA LincR-Cer2-5'AS regulates the number and the migration of T helper 2 cells by binding to GATA-3 and forming a regulatory circuit in the gene expression (Hu *et al*., 2013). Moreover, exosomal microRNAs can even affect the extracellular matrix (ECM) surrounding the tumor, influencing both the immune system activation and immune cell recruitment (Que *et al*., 2016; Sun *et al*., 2018b). The persistent presence of HBV in the liver tissue suppresses the expression of microRNA-34a, leading to enhanced production of chemokine CCL22, which recruits Treg cells to facilitate immune escape, and,

consequently, the growth of tumors (Yang *et al.*, 2012). Previous studies also identified that some lncRNAs could potentially modulate gene expression related to inflammatory conditions in the TIME (Nong *et al.*, 2021).

When it comes to HCC specifically, some non-coding RNAs activate the macrophages, NK cells, and effector T cells in TIME (Pi *et al.*, 2021). For a clearer understanding of the composition of immune cells in HCC TIME and their functions, we investigated 22 subtypes of immune cells in 735 HCC patients based on the gene expression profiling of HCC cases from the public database. The resulting HCC TIME-specific immunophenotypes can be used to further study the links among genotypes, immunophenotypes, prognosis, and clinical features, allowing for novel immunosignatures for the clinical assessment of HCC prognosis (Chen *et al.*, 2020).

Combining the immune modulation and the TIME, tumor immunotherapy aims to activate and restore the functioning of immune cells so that the development of cancer can be suppressed (Makarova-Rusher *et al.*, 2015). Now, the HCC immunotherapeutic targets derived from the TIME research greatly contribute to the clinical interventions against HCC, particularly those therapies enhancing the programmed death-ligand 1 (PDL-1), which have been applied clinically on a large scale (Nishida and Kudo, 2017). Research also points out that miR-200c is re-expressed through HBV-induced signal transducer and activator of transcription 3 (STAT3) activation in adulthood, and the overexpression of miR-200c would downregulate PD-L1 and reverse the antiviral CD8+ T cell exhaustion in HBV-related HCC (Sun *et al.*, 2018a). Therefore, the composition of TIME can be used as biomarkers for the prognosis and as targets for treatment in many cases of tumors, including but not limited to HCC, lung cancer, and breast cancer (Fridman *et al.*, 2017; Zeng *et al.*, 2019; Zhang *et al.*, 2021).

Non-coding RNAs suppress the progression of hepatitis B virus-related hepatocellular carcinoma

In most cases, HBV alters the non-coding RNA expression to elevate the expression levels of oncogenic genes, thus leading to the development of cancer. But several studies have reported the suppressive effect of non-coding RNAs on HCC development (Deng *et al.*, 2020; Gan *et al.*, 2021). Another mechanism of HBV infection-mediated repression of the development of HCC is by reducing the expression of miR-15a and miR-16-1. These miRNAs subsequently cause the increase in the expression of Anillin (ANLN), which is negatively correlated with clinical outcomes and survival of the HCC patients. MiR-15a and miR-16-1 target the 3′ UTR of ANLN to suppress the growth, colony formation, and sphere formation of the cancer cells (Lian *et al.*, 2018). It is also possible that HBV activates the suppressive transcription factor, sal-like protein 4 (SALL4), which then downregulates the expression of miR-200c (Sun *et al.*, 2018a). The HBV-pSTAT3-SALL4-miR-200c axis is proposed to have a role in the regulatory process of PD-L1 in HBV infection and the development of HCC, and disrupting the axis can be a likely therapeutic strategy to reverse the immune failure caused by retroviral infections. Similarly, the suppressive role of non-coding RNAs in HCC development is also identified in the lncRNAs-mediated downregulated replication of HBV. For instance, miR-192-3p suppresses the replication of HBV by interacting with NF-κB. This signaling pathway confirms the regulatory role of miR-192-3p in HBV infection and its possible suppressive role in the development of HCC (Wang *et al.*, 2019).

Bidirectional role of non-coding RNA N6-methyladenosine (m6A) modification in hepatitis B virus-related hepatocellular carcinoma

A newly emerged focus of RNA research is m6A modification, which takes place not only on mRNAs but also on non-coding

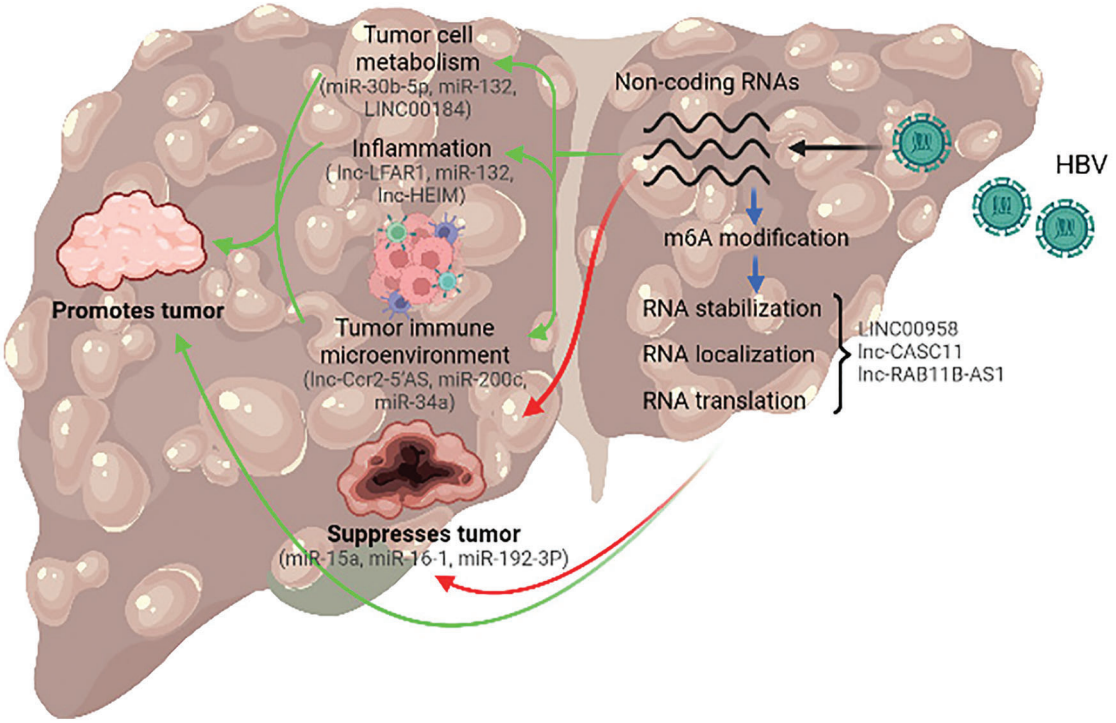

FIGURE 1. Function of hepatitis B virus-related non-coding RNAs in hepatocellular carcinoma.

RNAs such as lncRNAs. Besides mediating the RNA expression levels, m6A modification can also change the RNA stability, localization, and translation at the post-transcriptional level.

The enhanced modification of m6A mediated by methyltransferase 3 (METTL3) upregulates the expression level of LINC00958 by stabilizing the RNA transcript, which then aggravates the HCC malignant phenotypes (Zuo *et al.*, 2020). Another lncRNA implicated in m6A modification is cancer susceptibility candidate 11 (CASC11), which serves a promotive role in tumorigenesis and metastasis. The two mechanisms underlying this process of tumor development involve the ubiquitin-conjugating enzyme E2T (UBE2T) and an m6A reader protein YT521-B homology domain family 2 (YTHDF2), respectively. CASC11 lowers the m6A level of UBE2T and thus stabilizes it by recruiting an increased amount of human AlkB homolog H5 (Chen *et al.*, 2021). The RNA METTL16, similar to METTL3, serves as a link between m6A modification and the development of HCC. METTL16 is reported to directly bind to a lncRNA RAB11B-AS1, which enhances the m6A modification of RAB11B-AS1. The modification subsequently regulates the proliferation, migration, and metastasis of HCC cells (Dai *et al.*, 2022). A similar m6A reader protein named YTHDF1 was found to be highly expressed in HCC patients and was especially higher in patients at the later stages of HCC (Zhao *et al.*, 2018). There is a high possibility of a positive correlation between the YTHDF1 level and the pathological stage with YTHDF1-mediated tumor metabolism.

However, the increase in m6A modification level also likely suppresses the invasion and metastasis of HCC, as the methyltransferase-like 14 (METTL14)-induced methylation of the adenosine base at the nitrogen-6 position serves as a suppressor of HCC cell migration. This suppression is regulated by the positive regulation of the processing of the primary microRNA 126, which links the interaction between METTL14 and the microprocessor complex subunit DGCR8 (Ma *et al.*, 2017). In short, different non-coding RNAs undergoing m6A modification changes can be either cancer-promotive or cancer-suppressive, depending on the regulatory pathways.

Conclusions

Viral infections have already been officially confirmed as high-risk factors for cancers, such as HPV infection-induced cervical cancer, which is also the reason for the broad application of vaccinations against HPV among populations. The chronic hepatic inflammation induced by HBV was thought to be the main mechanism of HBV-induced HCC, but recent findings on the modulatory role of HBV on the cancer-causing genes via non-coding RNA have also attracted increasing attention in this field (Fig. 1). In most cases, HBV promotes non-coding RNA expression by altering the levels of HBV transcription factors. Not only do non-coding RNAs take part in the transcriptional and translational processes of the coding genes, but they can also directly modify the signaling proteins to affect oncogenesis. Some of the molecular mechanisms are still unclear, such as the mechanisms underlying the elevation of miR-132 and its consequent HCC afterward (Santella *et al.*, 2019). All these unsolved questions are the future directions of our research, and we have already discovered that HBV destabilizes one of the lncRNAs to halter the development of HBV-related HCC through the regulation of mitochondrial functions and carbohydrate metabolism. As the roles and the mechanisms of non-coding RNAs are increasingly elucidated, novel targets for early diagnosis and treatments for cancers will be possible in the near future, providing more directions for future studies in this area.

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