ISSN:2790-167X DOI: 10.56028/aehssr.4.1.15.2023

Potential carcinogenic mechanism of hepatitis B virus X protein (HBX) mediated by microRNA (miRNA)

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Abstract. The hepatocellular carcinoma (HCC) is the sixth most common cancer in the world. The hepatitis B virus (HBV) is crucial in the growth of HCC. Hepatitis B virus X protein (HBX) has been linked in numerous studies to the clinical prognosis of patients with hepatocellular carcinoma, but the exact mechanism is still unknown. Short non-coding RNAs identified as miRNAs have a significant influence in many malignancies. Numerous research conducted recently have discovered a strong connection between HBX and miRNA. In order to offer thoughts on the diagnosis and care of people with advanced hepatocellular carcinoma who have hepatitis B virus infection, this article examines recent study findings.

Keywords: hepatocellular carcinoma, hepatitis B virus, HBX, miRNA.

HCC, the sixth most common malignancy worldwide, is extremely aggressive, and patients frequently have poor prognoses because of a late diagnosis. 350 million people worldwide have chronic hepatitis B virus infection, which can cause a number of illnesses include hepatic steatosis and HCC. S, P, C, and X, which each encode four viral proteins, are the four open reading frames (OFR) that make up the HBV gene sequence. Among these, HBX has a direct impact on host cell signal transduction, DNA repair, and gene expression, all of which are directly associated to the development of HCC. A class of tiny, non-coding RNA molecules known as miRNAs controls transcription in cells adversely. According to reports, HBX can affect several different pathways and activities through regulating the expression and activity of genes, the expression and activity of epigenetic molecules like miRNA, and the regulation of methylation and acetylation. For the therapeutic management of HCC patients, understanding the aberrant expression of miRNA in the HBV viral host is crucial.

1. miRNA can affect the activity of liver cancer stem cells (CSCs)

Cancer stem cells have the potential to stimulate tumor growth, encourage tumor spread, maintain the tumor microenvironment, cause tumor recurrence, and prolong tumor survival. According to studies, blocking miRNA-5188 can considerably improve the prognosis of HCC-negative mice. MiRNA-5188 was found to be enhanced in malignant liver cells. According to studies, miR-5188 directly targets FoxO1, interacts with β-catenin in the cytoplasm, prevents β-catenin from translocating into the nucleus, and stimulates the activation of the Wnt signaling pathway, all of which encourage carcinogenesis, EMT, and the production of C-Jun. Additionally, miR-5188 expression is stimulated by c-jun transcription, creating a positive feedback loop. An key part of it involves HBX. Hepatitis X protein (HBX) mediates the miR-5188/FoxO1/-catenin/c-Jun feedback loop via Wnt signaling. MiR-5188 inhibition may reduce CSC survival, and miR-5188 as a possible cancer target may be instructive for the clinical management of HCC [1]. Additionally, altered hepatic progenitor cells(HPCs) can develop hepatocellular cancer. It was discovered that HBX and transforming growth factor-1 (TGF-1) were both expressed at high levels. Additional research has revealed that HBX and TGF-1 drive HPCs to differentiate into liver cancer stem cells and support the EMT process. A potential molecular target for HPCs treatment in the treatment of HCC may be offered by the finding that the miRNA miR-199a-3p is considerably up-regulated in HPCs and that it can enhance the malignant transformation of HPCs [2].

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2. Tumor-suppressor genes can be downregulated by miRNA to speed up the development of HCC

High levels of miRNA-3928v are seen in HBV (+) HCC tissues, where they bind to the voltage-dependent anion channel 3 (VDAC3) receptor to advance HCC growth, migration, and invasion. Early Growth Response Factor 1 (EGR1) nuclear translocation is promoted by HBX protein by boosting its expression, and miR-3928V promoter expression is increased by NF- κ B signal transduction. Through the signal transduction pathway involving NF- κ B and EGR1, HBX causes the synthesis of miRNA-3928v. The tumor suppressor gene VDAC3's expression is subsequently downregulated[3]. A tumor suppressor gene called zinc finger and homeobox 2 (ZHX2) is linked to HCC, and ZHX2 expression is frequently inhibited when HBX is expressed. Additional research revealed that HBX was the mechanism by which miR-155 expression was considerably elevated in HCC patients [4].

3. hepatic epithelial-mesenchymal(EMT) transition is encouraged by miRNA

EMT in liver tissue is frequently seen to change into a more invasive phenotype in HCC patients. In HCC tissues, miR-520C-3P expression was noticeably upregulated. Additional research has revealed that the interaction between the transcription factor HBX and miR-520C-3P might boost its expression. And by targeting PTEN and turning on the AKT-NFkB signaling pathway, the increased miRNA facilitates the EMT process. MiR-520C-3P, a novel regulator of HBV, is crucial to the development of HCC. It is a potential molecular therapeutic target and novel biomarker for HBV patients [5].

4. miRNA modulation of tumor cell proliferation adversely

According to research, HBX small interfering RNA (siRNA) can stop the proliferation of MHCC97H cells and the development of tumors. In HCC patients who received HBX-siRNA treatment, MiR-137 was strongly expressed. MiR-137's expression can be restored and its methylation can be reduced by HBX gene knockout. The inhibition of HCC cell proliferation by HBX-siRNA was reversed by miR-137 downregulation and Notch1 inhibition. MiRNA-137, which targets Notch1, prevents tumor cell growth and invasion in patients receiving HBX-siRNA treatment. This shows that inhibiting miRNA-137 might improve a patient's prognosis [6]. An independent predictor of a poor prognosis, even in patients receiving therapeutic hepatectomy, is alpha-fetoprotein (AFP), a tumor marker for HCC. The study discovered a strong correlation between HBX expression and APF. Analysis of HCC samples connected to HBV revealed a negative correlation between the expression of AFP and the concentrations of miR-1236 and miR-329. This shows that miR-1236 and miR-329 may be downregulated by HBX in order to increase AFP expression. AFP reduces the pro-apoptotic action of chemotherapy medications, encourages the growth of liver cancer cells, and eventually speeds up the disease's progression [7].

5. Long non-coding RNA is a mediator for miRNA in the malignant process of host cells

LncRNAs are a kind of RNA molecules that have a length more than 200 nucleotides and have either no or very little capacity to transcribe proteins. It is crucial for crucial cell life processes such cell differentiation, cell cycle control, and epigenetic regulation. It also serves as a crucial biomarker for a number of tumors as well as a critical predictor for determining prognosis. A new family of lncRNAs discovered in HCC, LINC01352, can bind to estrogen receptor (ERα) to create a complex and limit the proliferation and metastasis of HCC cells. But HBX has the ability

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to block this impact. Additional research revealed that LINC01352 was downregulated, which raised the production of miR-135b and triggered the Wnt/-catenin signaling pathway to accelerate tumor growth. By controlling miR-135b, the LINC01352 and ER complex may be a key target to influence patient prognosis [8]. In addition, research on sorafenib, an innovative targeted oral kinase inhibitor used to treat advanced HCC, has discovered a strong correlation between lncRNAs and the drug resistance of HCC cancer cells. Long non-coding RNA TRERNA1 has a higher expression level when HBX is present. According to additional research, TRERNA1 can influence the expression of NRAS through controlling miR-22-3p, which ultimately results in sorafenib resistance in HCC cells [9].

6. miRNA contributing to the development of liver fibrosis

Chronic hepatitis can cause ongoing liver cell damage, inflammation, necrosis, aberrant proliferation, and the deposition of collagen in the extracellular matrix (ECM), all of which can progress to cirrhosis. An significant cause of death is the development of regenerative nodules brought on by intrahepatic fibrous tissue hyperplasia. The amount of the enzyme prolyl 4-hydroxylase subunit 2 (P4HA2), which is strongly associated to the manufacture of collagen, is markedly increased in the liver tissues of HBV transgenic mice, patients with clinical cirrhosis, and those with liver cancer. Additional research has revealed that miR-30E, which can target the 3' untranslated region of P4HA2 mRNA in HCC, is inhibited by HBX, which therefore increases the production of P4HA2. This offers a fresh approach to treating patients with cirrhosis and HBV infection [10].

MiRNA is a significant class of short non-coding RNA that is crucial in HCC. This article provides numerous examples of how essential a function miRNA serves in HCC. Currently, more thorough research is still required to understand long-term chronic infections in clinical patients. Finding new molecular targets and advancing the creation of new medications are made possible by investigating the precise carcinogenic mechanism of miRNA.

References

[1] Lin, X., et al., HBX-induced miR-5188 impairs FOXO1 to stimulate β-catenin nuclear translocation and promotes tumor stemness in hepatocellular carcinoma. Theranostics, 2019. 9(25): p. 7583-7598.

[2] Dong, K.S., et al., TGF-β1 accelerates the hepatitis B virus X-induced malignant transformation of hepatic progenitor cells by upregulating miR-199a-3p. Oncogene, 2020. 39(8): p. 1807-1820.

[3] Zhang, Q., et al., miR-3928v is induced by HBx via NF-κB/EGR1 and contributes to hepatocellular carcinoma malignancy by down-regulating VDAC3. J Exp Clin Cancer Res, 2018. 37(1): p. 14.

[4] Song, X., et al., HBV suppresses ZHX2 expression to promote proliferation of HCC through miR-155 activation. Int J Cancer, 2018. 143(12): p. 3120-3130.

[5] Liu, Y., et al., Upregulation of miR-520c-3p via hepatitis B virus drives hepatocellular migration and invasion by the PTEN/AKT/NF-κB axis. Mol Ther Nucleic Acids, 2022. 29: p. 47-63.

[6] Gao, Y., et al., Hepatitis B virus X protein boosts hepatocellular carcinoma progression by downregulating microRNA-137. Pathol Res Pract, 2020. 216(6): p. 152981.

[7] Zhang, C., P. Liu, and C. Zhang, Hepatitis B virus X protein upregulates alpha-fetoprotein to promote hepatocellular carcinoma by targeting miR-1236 and miR-329. J Cell Biochem, 2020. 121(3): p. 2489-2499.

[8] Huang, P., et al., HBx/ERα complex-mediated LINC01352 downregulation promotes HBV-related hepatocellular carcinoma via the miR-135b-APC axis. Oncogene, 2020. 39(18): p. 3774-3789.

[9] Song, W., et al., TRERNA1 upregulation mediated by HBx promotes sorafenib resistance and cell proliferation in HCC via targeting NRAS by sponging miR-22-3p. Mol Ther, 2021. 29(8): p. 2601-2616.

ISSN:2790-167X DOI: 10.56028/aehssr.4.1.15.2023
[10] Feng, G.X., et al., Hepatitis B virus X protein promotes the development of liver fibrosis and hepatoma through downregulation of miR-30e targeting P4HA2 mRNA. Oncogene, 2017. 36(50): p. 6895-6905.