Review

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The function of HBx in HBV-induced hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the second cause cancer death in the world. HCC is frequently diagnosed at advanced stages with intrahepatic metastasis or vascular invasion and has a poor prognosis with a high mortality rate. In the world, hepatitis B virus (HBV) caused over 50% HCC, making it the most common carcinogen after tobacco. Notably, accumulating evidence suggests HBV X gene (HBx) play an important role in tumorigenesis of HBV-related HCC. In this review, we will summarize the functions of HBx proteins in tumorigenesis and discuss their potential implications in cancer therapy.

Keywords: Hepatocellular carcinoma (HCC); hepatitis B virus (HBV); HBV X gene (HBx)

1 Introduction

Liver cancer is the fifth most common cancer in the world¹. It is estimated that every year about more than 500,000 people death for Hepatocellular carcinoma (HCC)². hepatitis B virus (HBV) is a kind of multi-functional regulatory protein and mainly promote HCC development³. It is a kind of double link DNA virus. It's contained four open reading frame, respectively coded 4 kinds of protein S, X, E, C⁴. A multifunctional protein HBx is encoded by the X gene of HBV, It has reported that HBx has multifunctional, including transcriptional activation⁵⁻¹¹, epigenetic regulation¹²⁻¹⁴, apoptosis regulation¹⁵, DNA repair regulation¹⁶⁻¹⁸ and so on.

2 Correlation between HBx and hepatocellular carcinoma

HBx often restructured in the host cell genome¹⁹. In recent years, more and more significant advancement in the molecular mechanisms about the role of in HCC. Continuous replication in the host is an important process of HCC. In the process of chronic liver disease, the regeneration of infected hepatocytes leads to the integration of HBx into the host gene. It is an important biological process in the early stages of HCC. HBx transgenic mice are more likely to develop HCC²⁰, and replication of HBV will be enhance when HBx integrated into the host genome²¹.

3 HBx, transcriptional control

HBx was recruited to HBV replication cells in cccDNA microchromosomes to increase transcription of the nuclear cccDNA microchromosome^{22,23}. In the absence of HBx, cccDNA-bound histones are hypo-acetylated, and cccDNA transcription was significantly less pgRNA. HBx protein can blocks the inhibitory activity on

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HBV transcription by binding to PRMT1 methyltransferase, the Tudor-domain protein Spindlin-1 and the SETDB1 histone methyltransferase²⁴⁻²⁶. HBx can reinforce HBV replication, through induction of miR-101 to downregulation of DNMT3A expression²⁷. The genome-wide analysis of HBx chromatin recruitment in HBV replicating cells revealed a specific binding of HBx to a large number target sequences, including protein-coding genes and non-coding RNAs²⁸.

4 Correlation between HBx and Epithelial-mesenchymal transition (EMT)

Epithelial-mesenchymal transition (EMT) plays an important role in tumor metastasis. SRC signaling is critical to the development of EMT and can promote the expression of metalloproteinases (MMPs) in a variety of ways²⁹. HBx stimulates SRC by destroying tight junctions and promotes the development of EMT. This process is correlation with tyrosine phosphorylation of β -catenin in the Ecadherin complex³⁰. In addition, HBx-mediated upregulation of SNAIL protein by inhibited E-cadherin expression. Recent studies have shown that HBx activates PI3K-AKT signaling pathway to stabilize SNAIL protein to promote development of HCC³¹.

5 HBx and cancer metabolism reprogram

Metabolic reprogramming is a symbol of cancer physiological changes. Cancer cells can mainly use glycolytic for energy metabolism. So it allows cells to use glycolytic intermediates for various macromolecule biosynthesis, in order to meet the materials of cell rapid proliferation of and energy demand. Glucose-6-phosphate dehydrogenase (G6PD) is the first rate-limiting enzyme for the pentose phosphorylation pathway, which is highly expressed in human hepatitis B and HBV-associated hepatocellular carcinoma, infected with chronic hepatitis B virus (HBV) X protein (HBx) stimulates activation of the Nrf2 activation pathway to promote G6PD expression³².

In HCC, HBx protein can directly binding with MDM2 and inhibiting its ubiquitin-directed self-degradation. This change activated the Wnt/ β -catenin pathway, so promotes the stem-like properties of OV6(+) liver CSCs³³.

6 Conclusions

HBV has been regarded as the major dangerous factor for liver cancer. HCC is the most common global cancer. However, the mechanism of HBV-mediated pathogenesis still unknown. Evidence suggests that HBx plays a vital role in the development of HCC. HBx protein is involved in transcriptional regulation, signal transduction, cell cycle progression, apoptosis, and protein degradation pathway. Because HBX protein function is so diverse, so more and more research is needed to explore its unknown function. To clarify the role of HBx in the development and progression of hepatocellular carcinoma from the perspective of biology could provide a new research strategy for the future clinical treatment of liver cancer.

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