Review

The Biological Function of Hepatitis B Virus X Protein in Hepatocellular Carcinoma

Qiaodong Xu, Songgang Gu, Jiahong Liang, Zhihua Lin, Shaodong Zheng, and Jiang Yan

Department of Biliary-Pancreatic Minimally Invasive Surgery, The First Affiliated Hospital of Shantou University Medical College, Shantou, P.R. China

Hepatocellular carcinoma (HCC) is one of the major malignant tumors that lead to death. Chronic hepatitis B virus infection is an important risk factor for HCC initiation. HBx protein, encoded by the HBV X gene, is a significant factor that promotes HBV-related HCC, although the exact molecular mechanism remains unclear. This article summarizes the pathological roles and related mechanisms of HBx in HCC. HBx plays a carcinogenic role by promoting cell proliferation, metastasis, and angiogenesis and inhibiting apoptosis in HCC. A detailed study of the biological functions of HBx will help to elucidate the mechanism of hepatocarcinogenesis and lead to the development of novel therapeutic targets for the treatment of HBV-related HCC.

Key words: Hepatocellular carcinoma (HCC); Hepatitis B virus (HBV); Carcinogenic mechanism; Hepatitis B virus X (HBx) protein

INTRODUCTION

Liver cancer is one of the most common fatal tumors worldwide. It ranks second in terms of cancer-related mortality and morbidity due to liver cancer has been ranked sixth among the major types of cancers. GLOBOCAN 2012, published by the International Agency for Research on Cancer (IARC), reported approximately 782,500 new cases of liver cancer and 745,500 deaths in 2012 worldwide. Hepatocellular carcinoma (HCC) accounted for 70%–90% of primary liver cancers. Chronic hepatitis B virus (HBV) infection is a risk factor for HCC induction. It is estimated that currently there are over 350 million HBV carriers globally. However, the underlying mechanism of HBV-associated HCC remains unclear. Hepatitis B virus X (HBx) protein, encoded by the HBV X gene, is a multifunctional protein responsible for HBV-related hepatocarcinogenesis. Numerous studies have thoroughly explored the roles that HBx played in the initiation and development of HCC and its molecular mechanisms. In this article, we comprehensively summarize the biological function of HBx in HCC by regulating a variety of biological processes, such as cell proliferation, cell invasion or metastasis, angiogenesis, and cell apoptosis.

THE HBV GENOME AND MOLECULAR MECHANISMS OF HBV INFECTION-RELATED HCC (HBV-HCC)

HBV, belonging to the Hepadnaviridae family, is a partially double-stranded and looped DNA virus. Its genome contains four overlapping open reading frames (ORFs) encoding four proteins. These are pre-S/S (virus surface protein), C (virus core protein), P (virus polymerase), and X (HBx protein).

HBV infection is involved in the carcinogenesis of HCC by chronic inflammation, integration of DNA into the host genome and viral proteins (see Fig. 1), through the following concrete mechanisms. (1) Cytotoxic T lymphocytes, induced by immune system activation after HBV infection, attack HBV-infected hepatocytes. Necrosis of liver cells then causes inflammation, resulting in further liver cirrhosis by activating fibroblasts leading to liver fibrosis. This is consistent with the fact that over...
80% of HCC patients may have liver fibrosis cirrhosis. Additionally, inflammation and immune responses caused by HBV infection can generate oxidative stress and produce reactive oxygen species (ROS). It is well known that ROS causes oxidative damages to DNA by interrupting repair mechanisms. The accumulation of DNA mutations also results in the development of HCC. (2) The HBV genome integrates into the host genome in 85% to 90% of HBV-HCC cases, whereas host genes in the HBV integration region can undergo further mutation. This causes host cell genome instability and disorders of various intracellular signaling pathways, which are beneficial for promoting HCC development. (3) Viral proteins encoded by the HBV genome also play carcinogenic roles. The surface protein is often localized on the endoplasmic reticulum with its truncated mutant, causing endoplasmic reticulum stress followed by the oxidative damage of DNA and host cell genome instability. HBx has long been considered a key protein in malignant transformation and is an important factor in the onset of HBV-HCC. Next, we summarize the biological function and carcinogenic mechanisms of HBx in HBV-HCC.

**HBx PROTEIN**

The X ORF of HBV genome encodes the HBx protein. HBx is a small, approximately 17-kDa multifunctional protein. A number of studies have shown HBx stimulated HBV replication and transcription. Recent studies have concluded that HBx plays an important role in the carcinogenesis of HBV-HCC. Among the Hepadnaviridae family, only woodchuck hepatitis virus and HBV encode the HBx protein. Intriguingly, virus-associated liver cancer occurs only in hosts infected by these two viruses. Transgenic mouse experiments have confirmed that HBx overexpression can induce HCC. Additionally, HBx can increase the rate of HCC formation in c-myc transfection mice and reduce the incubation period of HCC occurrence by diethylnitrosamine. Although HBx is closely related to the onset and progression of HBV-HCC, the exact molecular mechanisms remain unknown. Here we will combine the current knowledge to elucidate the pathological function and related mechanisms of HBx in HCC from different perspectives.

**HBx AND CELL PROLIFERATION**

Recent studies have demonstrated that HBx plays critical roles in carcinogenesis through the promotion of HCC cell proliferation. Du et al. reported that IncRNA highly upregulated in liver cancer (HULC) promoted proliferation of hepatoma cells through suppression of p18 and HULC was upregulated by HBx. Hu and colleagues reported that HBx upregulated IncRNA UCA1. UCA1 was physically associated with enhancer of zeste homolog 2 (EZH2), which suppresses p27Kip1 and results in the enhancement of cell proliferation. Huang et al. found that HBx could upregulate the expression of
DBH-AS1 and consequently promoted cell proliferation through activation of MAPK signaling in HCC\textsuperscript{33}. MicroRNAs are a new class of small noncoding RNAs that are 18 to 25 nucleotides in length. Recent work has revealed that expression of several miRNAs was altered in HBV-HCC; simultaneously aberrant expression of miRNAs played an important biological role by acting on downstream target genes. HBx plays critical roles in promoting cell proliferation through regulating miRNAs. HBx promotes aberrant HCC cell proliferation via the downregulation of miR-132, miR-429, miR-205, miR-15b, and miR-145 and the upregulation of miR-221\textsuperscript{24–29}.

**HBx AND CELL INVASION OR METASTASIS**

HBx promotes HCC invasion and metastasis by multiple mechanisms. Liu et al. reported that HBx increases the expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) by activating the nuclear factor \(k\)-B (NF-\(k\)-B) pathway. The upregulation of VEGF and MMPs promotes HCC cell invasion and metastasis\textsuperscript{30}. Han and colleagues found that the HBx protein is also localized to peroxisomes to increases the level of cellular ROS. The peroxisome-localized HBx increased the expressions of MMPs and decreased the expression of E-cadherin, which facilitated HCC cell invasion\textsuperscript{31}. Zhang et al. reported that HBx increased the expressions of MMPs and promoted HCC cell invasion and metastasis\textsuperscript{32}. HBx plays a critical role in enhancing HCC cell invasion through regulating miRNAs and lncRNAs. Xu and colleagues found that HBx suppressed p53-mediated activation of miR-148a, which resulted in the upregulation of hematopoietic pre-B-cell leukemia transcription factor-interacting protein (HPIP). HPIP increased the expression of mTOR through the AKT/ERK/FOXO4/ATF5 pathway, which resulted in HCC cell invasion and metastasis\textsuperscript{33}. Arzumanyan et al. reported that HBx increased the expressions of miR-373, a positive regulator of E-cadherin expression. The downregulation of E-cadherin is associated with the enhancement of the cell invasion ability of HCC\textsuperscript{34}. Kong et al. found that the upregulation of miR-29a by HBx promotes HCC cell by targeting PTEN\textsuperscript{35}. A study by Zhao and colleagues reported that HBx elevates oncoprotein AEG-1 expression to promote HCC cell migration by downregulating miR-375 and miR-136\textsuperscript{36}. Huang and colleagues discovered that the lncRNA Dreh was downregulated by HBx using chip sequencing technology and HBx transgenic mice. They also found that lncRNA Dreh inhibited metastasis via the downregulation of vimentin\textsuperscript{37}.

**HBx AND ANGIOGENESIS**

HCC is a kind of highly vascularized solid tumor. Angiogenesis is important for the growth and metastasis of HCC. Previous studies showed that HBx stimulated angiogenesis during hepatocarcinogenesis. It was reported that HBx stimulated the transcription of VEGF, a known angiogenic factor\textsuperscript{38}. Moon and colleagues found that HBx induced angiogenesis by increasing the transcriptional activity and protein level of hypoxia-inducible factor-1\(\alpha\) (HIF-1\(\alpha\))\textsuperscript{39}. A study by Lu et al. found that HBx upregulated endothelin 1 (END1) indirectly by suppressing miR-1. END1 plays a crucial role in promoting angiogenesis in HCC by activating the PI3K/AKT pathway\textsuperscript{40}. Study from another group reported that HBx contributed to angiogenesis by downregulation of Lethal-7 through activating STAT3\textsuperscript{41}. Moreover, HBx increases the expression of MTA1 (metastasis-associated protein 1) coregulator via NF-\(k\)-B signaling by the suppression of miR-661 to induce angiogenesis\textsuperscript{42}. HBx induces the expression of miR-7, miR-107, and miR-21 and results in the downregulation of mammary serine protease inhibitor (Maspin). The repressed Maspin makes a contribution to angiogenesis in HCC\textsuperscript{43}.
expression of p21^{CIP/WAF1}. Similarly, p53 modulates apoptosis by interaction with ASPP1 and ASPP2. Nude mice experiments have confirmed that sensitivity of malignant cells to apoptotic stimuli decreased and tumor growth was promoted after knockdown of the ASPP1 and ASPP2 genes. Zhao and coworkers found that, by analyzing 51 pairs of carcinoma samples and adjacent normal tissues, the expression of ASPP1 and ASPP2 was reduced due to promoter hypermethylation. Interestingly, HBx overexpression in hepatoma cells induced methylation of the ASPP2 promoter region. Hence, HBx may inhibit p53-mediated apoptosis by downregulating ASPP2. In addition, HBx could inhibit Fas-mediated apoptosis by the upregulation of the SAPK/JNK pathway and prevent cell apoptosis by upregulating SATB1 and HURP (hepatoma upregulated protein) expression in HCC.

HBx-induced apoptosis also contributes to chemotherapy drug resistance in HCC. As mentioned above, HBx can directly bind to p53 and cause inactivation of p53, or it can inhibit p53 through regulating Cox-2, thus inhibiting p53-induced apoptosis. Furthermore, Cheng and colleagues discovered that knockdown of HBx increased apoptosis induced by cisplatin. MDR1 (multidrug resistance 1) is upregulated when tumor cells switch from chemotherapeutic drug sensitivity to resistance. HBx was found to activate HIF-1α that promotes expression of MDR1 in the H411E cell line. Another study showed that in the Hep3B cell line, HBx increased antiapoptosis upon cisplatin treatment by upregulating HURP via the p38/MAPK pathway. In addition, HBx also promoted the expression of survivin, an antiapoptosis protein. Huang and colleagues discovered that HBx caused resistance to bortezomib in HBV-HCC, and the resistance could be antagonized by an inhibitor of MEK signaling.

CONCLUSION AND PROSPECTIVE

Multiple molecules and signaling pathways are involved in the formation and progression of HBV-HCC, and HBx is a key factor in hepatocarcinogenesis. We have summarized the various malignant biological functions of HBx in HCC, including regulation of cell proliferation, invasion and metastasis, apoptosis, and angiogenesis in the related molecular mechanisms.

However, the exact functions and molecular mechanisms of HBx in HCC have not yet been elucidated. Further study of the biological functions of HBx will help to elucidate the mechanism of hepatocarcinogenesis and promote the development of novel therapeutic targets for the treatment of HBV-HCC. In addition to present studies concentrating on trials of HBx in vitro, the functions of HBx must also be thoroughly explored in vivo.

ACKNOWLEDGMENT: The authors declare no conflicts of interest.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5):E359–86.
3. Gelband H, Chen CJ, Chen W, Franceschi S, Hall SA, London WT, McGlynn KA, Wild CP. Liver Cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, editors. Cancer: Disease control priorities, 3rd ed., Vol 3. Washington (DC): The World Bank; 2015.
4. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: From genes to environment. Nat Rev Cancer 2006;6(9):674–87.
5. Yang HI, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, Wang LY, Lu SN, You SL, Chen DS, Liaw YF, Chen CJ; REVEAL-HBV Study Group. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(16):1134–43.
6. Martin-Vilchez S, Lara-Peazzi E, Trappero-Marugan M, Moreno-Otero R, Sanz-Cameno P. The molecular and pathophysiological implications of hepatitis B X antigen in chronic hepatitis B virus infection. Rev Med Virol. 2011;21(5):315–29.
7. Okuda K. Hepatocellular carcinoma. J Hepatol. 2000;32(1 Suppl):225–37.
8. Higgs MR, Chouteau P, Lerat H. ‘Liver let die’- Oxidative DNA damage and hepatotropic viruses. J Gen Virol. 2014;95(Pt 5):991–1004.
9. Matsubara K, Tokino T. Integration of hepatitis B virus DNA and its implications for hepatocarcinogenesis. Mol Biol Med. 1990;7(3):243–60.
10. Koshy R, Maupas P, Muller R, Hoschfische PH. Detection of hepatitis B virus-specific DNA in the genomes of human hepatocellular carcinoma and liver cirrhosis tissues. J Gen Virol. 1981;57(Pt 1):95–102.
11. Shafritz DA, Shoval D, Sherman HI, Hadziyannis SJ, Kew MC. Integration of hepatitis B virus DNA into the genome of liver cells in chronic liver disease and hepatocellular carcinoma. Studies in percutaneous liver biopsies and post-mortem tissue specimens. N Engl J Med. 1981;305(18):1067–73.
12. Sukawati CH, El-Khobar KE, Ie SI, Anfuso B, Muljono DH, Tiribelli C. Significance of hepatitis virus infection in the oncogenic initiation of hepatocellular carcinoma. World J Gastroenterol. 2016;22(4):1497–512.
13. Pollicino T, Cacciola I, Saffioti F, Raimondo G. Hepatitis B virus PreS/S gene variants: Pathobiology and clinical implications. J Hepatol. 2014;61(2):408–17.
14. Hildt E, Urban S, Lauer U, Hoschfischer PH, Ekel A, ER-localization and functional expression of the HBV transactivator MHVst. Oncogene 1993;8(12):3359–67.
15. Xu C, Zhou W, Wang Y, Qiao L. Hepatitis B virus-induced hepatocellular carcinoma. Cancer Lett. 2014;345(2):216–22.
16. Decorsiere A, Mueller H, van Breugel PC, Abdul F, Gerossier L, Beran RK, Livingston CM, Niu C, Fletcher SP, Hantz O, Strubin M. Hepatitis B virus X protein identifies the Smc5/6 complex as a host restriction factor. Nature 2016;531(7594):386–9.
17. Murphy CM, Xu Y, Li F, Nio K, Rieszka-Blanco N, Li X, Wu Y, Yu Y, Xiong Y, Su L. Hepatitis B virus X protein promotes degradation of SMCS6 to enhance HBV replication. Cell Rep. 2016;16(11):2846–54.
THE BIOLOGICAL FUNCTION OF HBx IN HCC

18. Feitelson MA. Hepatitis B virus in hepatocarcinogenesis. J Cell Physiol. 1999;181(2):188–202.
19. Kim CM, Koike K, Saito I, Miyamura T, Jay G. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. Nature 1991;351(6324):317–20.
20. Yu DY, Moon HB, Son JK, Jeong S, Yu SL, Yoon H, Han YM, Lee CS, Park JS, Lee CH, Hyun BH, Murakami S, Lee KK. Incidence of hepatocellular carcinoma in transgenic mice expressing the hepatitis B virus X-protein. J Hepatology. 1999;31(1):123–32.
21. Du Y, Kong G, You X, Zhang S, Zhang T, Gao Y, Ye L, Zhang X. Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18. J Biol Chem. 2012;287(31):26302–11.
22. Hu JJ, Song W, Zhang SD, Shen XH, Qiu XM, Wu HZ, Gong PH, Lu S, Zhao JJ, He ML, Fan H. HBx-upregulated lncRNA UCA1 promotes cell growth and tumorigenesis by recruiting EZH2 and repressing p27Kip1/CDK2 signaling. Sci Rep. 2016;6:23521.
23. Huang JL, Ren TY, Cao SW, Zheng L, Wang Q. HBx-related long non-coding RNA DBH-AS1 promotes cell proliferation and survival by activating MAPK signaling in hepatocellular carcinoma. Oncotarget 2015;6(32):33791–804.
24. Wei X, Tan C, Tang C, Ren G, Xiang T, Qiu Z, Liu R, Wu Z.Epigenetic repression of miR-132 expression by the hepatitis B virus x protein in hepatitis B virus-related hepatocellular carcinoma. Cell Signal. 2013;25(5):1037–43.
25. You X, Liu F, Zhang T, Li Y, Ye L, Zhang X. Hepatitis B virus X protein upregulates oncogene Ralb1 to result in the dysregulation of lipogenesis and proliferation of hepatoma cells. Carcinogenesis 2013;34(7):1644–52.
26. Zhang T, Zhang J, Cui M, Liu F, You X, Du Y, Gao Y, Zhang S, Lu Z, Ye L, Zhang X. Hepatitis B virus X protein inhibits tumor suppressor miR-205 through inducing hypermethylation of miR-205 promoter to enhance carcinogenesis. Neoplasia 2013;15(11):1282–91.
27. Wu CS, Yen CJ, Chou RH, Chen JN, Huang WC, Wu CY, Yu YL. Downregulation of microRNA-15b by hepatitis B virus X enhances hepatocellular carcinoma proliferation via fucosyltransferase 2-induced Globo H expression. Int J Cancer 2014;134(7):1638–47.
28. Bandopadhyay M, Banerjee A, Sarkar N, Panigrahi R, Datta S, Pal A, Singh SP, Biswas A, Chakrabarti S, Chakravarty R. Tumor suppressor micro RNA miR-145 and onco micro RNAs miR-21 and miR-222 expressions are differentially modulated by hepatitis B virus X protein in malignant hepatocytes. BMC Cancer 2014;14:721.
29. Chen JJ, Pang YS, Huang SF, Ai JG, Wang HX, Zhang LP. HBx protein-induced upregulation of microRNA-221 promotes aberrant proliferation in HBV related hepatocellular carcinoma by targeting estrogen receptor-alpha. Oncol Rep. 2015;33(2):792–8.
30. Liu LP, Liang HF, Chen XP, Zhang WG, Yang SL, Xu T, Ren L. The role of NF-kappaB in hepatitis B virus X protein-mediated upregulation of VEGF and MMPs. Cancer Invest. 2010;28(5):443–51.
31. Han JM, Kang JA, Han MH, Chung KH, Lee CR, Song WK, Jun Y, Park SG. Peroxisome-localized hepatitis Bx protein increases the invasion property of hepatocellular carcinoma cells. Arch Virol. 2014;159(10):2549–57.
32. Zhang F, Wang Q, Ye L, Feng Y, Zhang X. Hepatitis B virus X protein upregulates expression of calpain small subunit 1 via nuclear factor-kappaB/p65 in hepatoma cells. J Med Virol. 2010;82(6):920–8.
33. Xu X, Fan Z, Kang L, Han J, Jiang C, Zheng X, Zhu Z, Jiao H, Lin J, Jiang K, Ding L, Zhang H, Cheng L, Fu H, Song Y, Jiang Y, Liu J, Wang R, Du N, Ye Q. Hepatitis B virus X protein represses miRNA-148a to enhance tumorigenesis. J Clin Invest. 2013;123(2):630–45.
34. Arzumanany A, Friedman T, Kotei E, Ng JO, Lian Z, Feitelson MA. Epigenetic repression of E-cadherin expression by hepatitis B virus x antigen in liver cancer. Oncogene 2012;31(5):563–72.
35. Kong G, Zhang J, Zhang S, Shan C, Ye L, Zhang X. Upregulated microRNA-29a by hepatitis B virus X protein enhances hepatoma cell migration by targeting PTEN in cell culture model. PLoS One 2011;6(5):e19518.
36. Zhao J, Wang W, Huang Y, Wu J, Chen M, Cui P, Zhang W, Zhang Y. HBx elevates oncoprotein AEG-1 expression to promote cell migration by downregulating miR-375 and miR-136 in malignant hepatocytes. DNA Cell Biol. 2014;33(10):715–22.
37. Huang JF, Guo YJ, Zhao CX, Yuan SX, Wang Y, Tang GN, Zhou WP, Sun SH. Hepatitis B virus X protein (HBx)-related long noncoding RNA (lncRNA) down-regulated expression by HBx (Drech) inhibits hepato-cellular carcinoma metastasis by targeting the intermediate filament protein vimentin. Hepatology 2013;57(5):1882–92.
38. Lee SW, Lee YM, Bae SK, Murakami S, Yun Y, Kim KW. Human hepatitis B virus X protein is a possible mediator of hypoxia-induced angiogenesis in hepatocarcinogenesis. Biochem Biophys Res Commun. 2000;268(2):456–61.
39. Moon EJ, Jeong CH, Jeong JW, Kim KR, Yu DY, Murakami S, Kim CW, Kim KW. Hepatitis B virus X protein induces angiogenesis by stabilizing hypoxia-inducible factor-1alpha. FASEB J. 2004;18(2):382–4.
40. Lu JW, Liao CY, Yang WY, Lin YM, Jin SL, Wang HD, Yuh CH. Overexpression of endothelin-1 triggers hepatocarcinogenesis in zebrafish and promotes cell proliferation and migration through the AKT pathway. PLoS One 2014;9(1):e85318.
41. Wang Y, Lu Y, Toh ST, Sung WK, Tan P, Chow P, Chung AY, Jooi LL, Lee CG. Lethal-7 is down-regulated by the hepatitis B virus x protein and targets signal transducer and activator of transcription 3. J Hepatol. 2010;53(1):57–66.
42. Bui-Nguyen TM, Pakala SB, Sirigiri DR, Martin E, Murad F, Kumar R. Stimulation of inducible nitric oxide by hepatitis B virus transactivator protein HBx requires MT1A coregulator. J Biol Chem. 2010;285(10):6980–6.
43. Chen WS, Yen CJ, Chen YJ, Chen YJ, Wang LY, Chiu SJ, Shih WL, Ho CY, Wei TT, Pan HL, Chen PH, Hung MC, Chen CC, Huang WC. miRNA-7/21/107 contribute to HBx-induced hepatocellular carcinoma progression through suppression of maspin. Oncotarget 2015;6(28):25962–74.
44. Michieli P, Cheddad M, Lin D, Pierce JH, Mercer WE, Givol D. Induction of WAF1/CIP1 by a p53-independent pathway. Cancer Res. 1994;54(13):3391–5.
45. Miyashita T, Reed JC. Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell 1995;80(2):293–9.
46. Shin TH, Paterson AJ, Kudlow JE. p53 stimulates transcription from the human transforming growth factor alpha promoter: A potential growth-stimulatory role for p53. Mol Cell Biol. 1995;15(9):4694–701.
factor receptor promoter by human p53. Mol Cell Biol. 1996;16(11):6009–19.
48. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature 2000;408(6810):307–10.
49. Shibata T, Aburatani H. Exploration of liver cancer genomes. Nat Rev Gastroenterol Hepatol. 2014;11(6):340–9.
50. Lee SG, Rho HM. Transcriptional repression of the human p53 gene by hepatitis B viral X protein. Oncogene 2000;19(3):468–71.
51. Feitelson MA, Zhu M, Duan LX, London WT. Hepatitis B x antigen and p53 are associated in vitro and in liver tissues from patients with primary hepatocellular carcinoma. Oncogene 1993;8(5):1109–17.
52. Elmore LW, Hancock AR, Chang SF, Wang XW, Chang S, Callahan CP, Geller DA, Will H, Harris CC. Hepatitis B virus X protein and p53 tumor suppressor interactions in the modulation of apoptosis. Proc Natl Acad Sci USA 1997;94(26):14707–12.
53. Wang XW, Gibson MK, Vermeulen W, Yeh H, Forrester K, Sturzbecher HW, Hoeijmakers JH, Harris CC. Abrogation of p53-induced apoptosis by the hepatitis B virus X gene. Cancer Res. 1995;55(24):6012–6.
54. Yun C, Lee JH, Park H, Jin YM, Park S, Park K, Cho H. Chemotherapeutic drug, adriamycin, restores the function of p53 protein in hepatitis B virus X (HBx) protein-expressing liver cells. Oncogene 2000;19(45):5163–72.
55. Kobayashi S, Matsushita K, Saigo K, Urashima T, Asano T, Hayashi H, Ochiai T. P21WAF1/CIP1 messenger RNA expression in hepatitis B, C virus-infected human hepatocellular carcinoma tissues. Cancer 2001;91(11):2096–103.
56. Samuels-Lev Y, O’Connor DJ, Bergamaschi D, Trigante G, Hsieh JK, Zhong S, Campargue I, Naumovski L, Crook T, Lu X. ASPP proteins specifically stimulate the apoptotic function of p53. Mol Cell 2001;8(4):781–94.
57. Zhao J, Wu G, Bu F, Lu B, Liang A, Cao L, Tong X, Lu X, Wu M, Guo Y. Epigenetic silence of ankyrin-repeat-containing, SH3-domain-containing, and proline-rich-region-containing protein 1 (ASPP1) and ASPP2 genes promotes tumor growth in hepatitis B virus-positive hepatocellular carcinoma. Hepatology 2010;51(1):142–53.
58. Diao J, Khine AA, Sarangi F, Hsu E, Iorio C, Tibbles LA, Woodgett JR, Penninger J, Richardson CD. X protein of hepatitis B virus inhibits Fas-mediated apoptosis and is associated with up-regulation of the SAPK/JNK pathway. J Biol Chem. 2001;276(11):8328–40.
59. Kuo TC, Chao CC. Hepatitis B virus X protein prevents apoptosis of hepatocellular carcinoma cells by upregulating SATB1 and HURP expression. Biochem Pharmacol. 2010;80(7):1093–102.
60. Cheng AS, Yu J, Lai PB, Chan HL, Sung JJ. COX-2 mediates hepatitis B virus X protein abrogation of p53-induced apoptosis. Biochem Biophys Res Commun. 2008;374(2):175–80.
61. Cheng AS, Wong N, Tse AM, Chan KY, Chan KK, Sung JJ, Chan HL. RNA interference targeting HBx suppresses tumor growth and enhances cisplatin chemosensitivity in human hepatocellular carcinoma. Cancer Lett. 2007;253(1):43–52.
62. Han HK, Han CY, Cheon EP, Lee J, Kang KW. Role of hypoxia-inducible factor-alpha in hepatitis-B-virus X protein-mediated MDR1 activation. Biochem Biophys Res Commun. 2007;357(2):567–73.
63. Huang P, Zhuang B, Zhang H, Yan H, Xiao Z, Li W, Zhang J, Tang Q, Hu K, Koeffler HP, Wang J, Yin D. Hepatitis B virus X protein (HBx) is responsible for resistance to targeted therapies in hepatocellular carcinoma: Ex vivo culture evidence. Clin Cancer Res. 2015;21(19):4420–30.