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Oncogenesis and transforming viruses: the hepatitis B virus and hepatocellularcarcinoma – the etiopathogenic link

Alvin TC Lee [1] and Caroline GL Lee [1,2]

[1] Division of Medical Sciences, National Cancer Center, Singapore, [2]Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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1. ABSTRACT

Hepatocellular carcinoma (HCC) is one of the world's leading fatal malignancies. Chronic infection with the hepatitis B virus (HBV) has been implicated with the development of HCC. For the past three decades, intensive research has focused on the role of HBV in hepatocarcinogenesis. Various HBV-associated models have emerged, but increasing evidence points to two major HBV-specific mechanisms that contribute to the development of HCC. The first is the integration of the viral genome into the host chromosome causing *cis*-effects, resulting in loss of tumor suppressor gene functions, and/or activation of tumor-promoting genes. The second mechanism involves the expression of *trans*-activating factors derived from the HBV genome, which have the potential to influence intracellular signal transduction pathways and alter host gene expression. A major player involved in this form of viral transactivation is the X protein (HBx). The HBx protein was found to display pleiotropic functions and has been implicated in the malignant transformation of chronically-infected liver cells. By disrupting cellular gene expression, viral products such as HBx may modulate cellular growth, repair and death, consequently resulting in the transformation of hepatocytes to an oncogenic state.

2. INTRODUCTION

The number of chronic Hepatitis B virus (HBV) carriers worldwide is estimated to be more than 350 million (1) and deaths from liver cancer caused by HBV infection was found to be as high as one million per year (2, 3). The major manifestation of primary liver cancer is hepatocellular carcinoma (HCC). Approximately one million new cases of HCC are reported worldwide every year, and the 5-year survival is at a disheartening low rate of 3% (4). The most viable treatment options are limited to surgical resection and liver transplantation, while the other current treatments are mainly for palliation. Unfortunately, the number of resectable cases remains small, as HCC patients frequently have complicated conditions including multi-focality of the tumor, early vascular invasion and concurrent liver cirrhosis at the time of diagnosis.

Development of HCC is epidemiologically linked to chronic HBV infection. Patients with chronic HBV infection are at a hundred times higher risk of developing HCC compared to uninfected individuals, and in some countries, an estimated 80% of all HCCs occur in HBV-infected individuals (5). The association between chronic HBV infection and HCC remains poorly understood, but increasing evidence points to two major HBV-specific

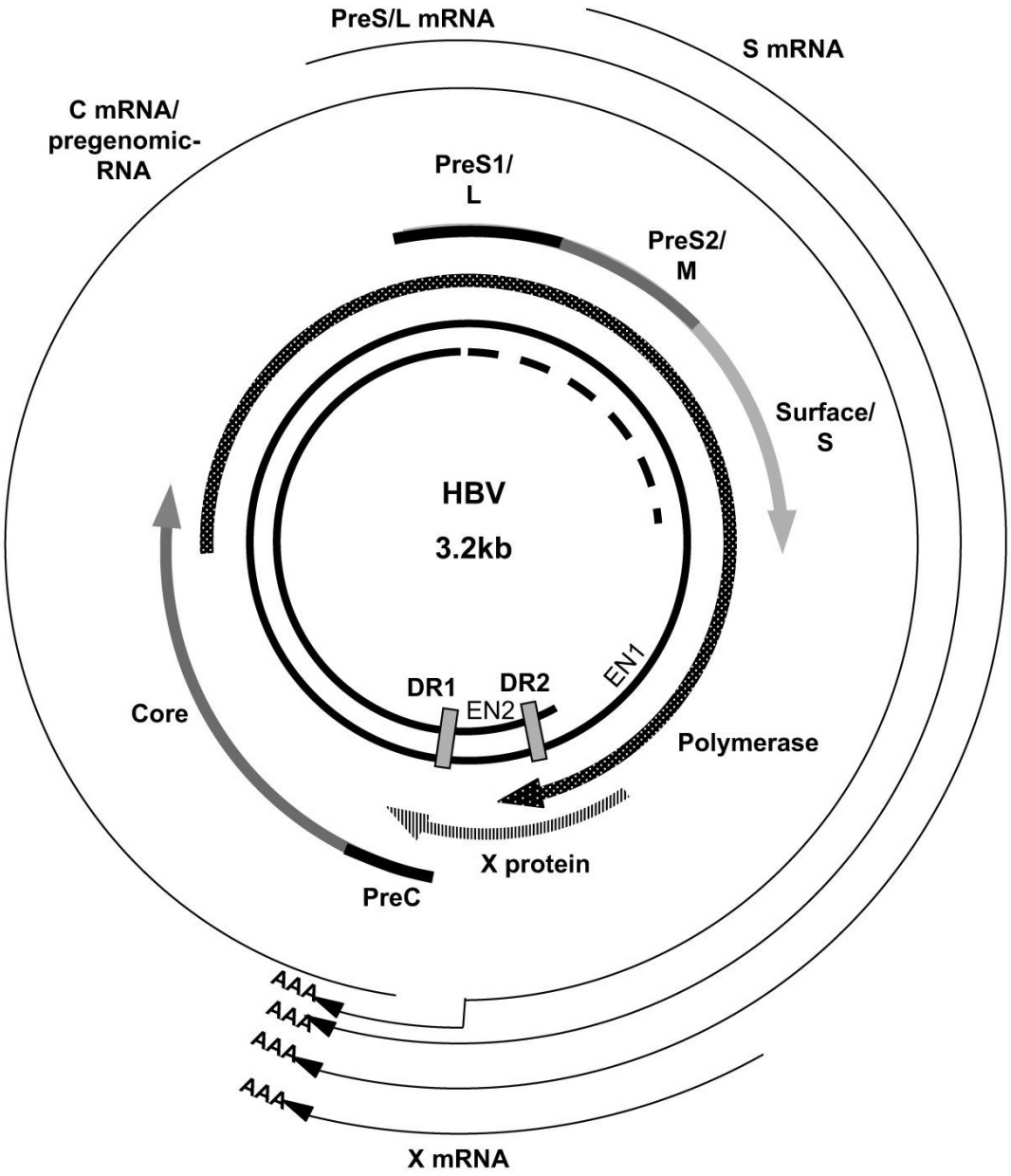

Figure 1. Physical map of the HBV genome. The Figure shows the genomic organization of HBV, showing the partially double-stranded DNA and the positions of the enhancers (EN) 1 and 2, and direct repeats (DR) 1 and 2. The four ORFs encoding for the viral proteins are indicated.

mechanisms that may contribute to the development of HCC. The first is the integration of the viral genome into the host chromosome causing either loss of tumor suppressor functions, or activation of tumor-promoting genes by promoter/enhancer insertions. The second mechanism involves the expression of *trans*-activating factors derived from the HBV genome, which have the potential to influence intracellular signaling and alter host gene expression (4, 5). By disrupting cellular gene expression, viral products may modulate cellular growth, repair and differentiation, thus favoring the transformation of hepatocytes to an oncogenic state.

3. HBV STRUCTURE, GENOME AND TRANSCRIPTS

The HBV genome is a 3.2-kb, circular, partially double-stranded DNA molecule with four partially overlapping open reading frames (ORFs) encoding the envelope (preS/S), core (preC/C), polymerase and X proteins (3) (Figure 1) . Upon attachment of the virion to the hepatocyte, HBV begins its replication cycle when the HBV genome is converted to covalently-closed circular DNA (cccDNA) in the hepatocyte nucleus (Figure 2). This involves entry of the virus's relaxed circular DNA (rcDNA)

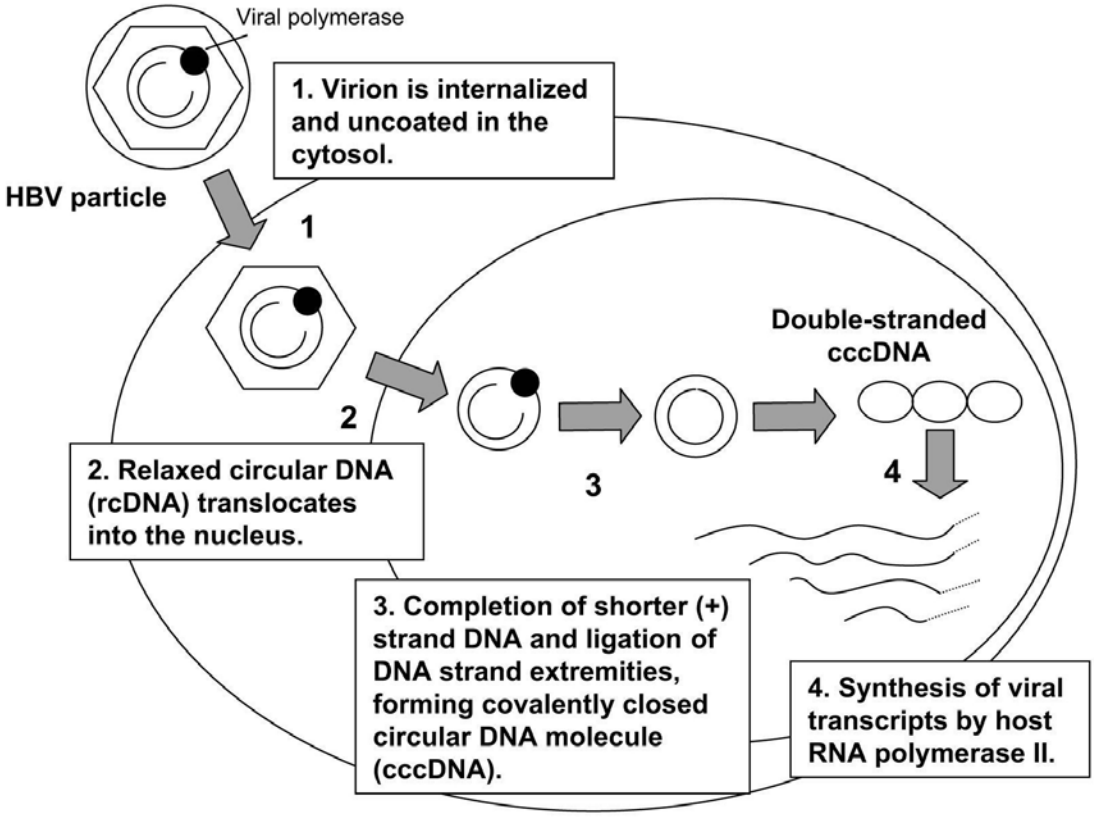

Figure 2. Formation of HBV cccDNA and viral transcripts.

into the nucleus, completion of synthesis for the shorter strand, identified as the plus (+) strand, and ligation of both the DNA ends to form a complete double-stranded DNA (6). The cccDNA serves as a template for transcription by the host RNA polymerase II (pol II), generating the four viral transcripts. The preS/S ORF translates into the hepatitis B surface antigen (HBsAg) polypeptides found on the envelope of the virus comprising the large (L), middle (M), and small (S) surface glycoproteins. The preC/C encodes for a hepatitis B core antigen (HBcAg) polypeptide, which form the nucleocapsid protein. The preC/C also encodes for a larger polypeptide, the hepatitis B e antigen (HBeAg) that is cleaved and secreted into the blood and serves as a marker of viral replication (7-9). The encoded viral polymerase functions as a reverse transcriptase as well as a DNA polymerase. The final viral transcript encodes for the X protein, a mysterious viral product whose function is still being unraveled. Additionally, important *cis*-elements within the genome of the HBV virus are required for the regulation of HBV gene expression and replication. These include viral promoters, enhancers and signal regions. The 5' terminus of both strands contain regions of short (11 nucleotide) direct repeats called DR1 and DR2, essential during replication for priming the synthesis of their respective DNA strands.

4. HBV AND HCC

The HBV is an etiological agent of acute and chronic viral hepatitis. The pathogenesis of HBV infection is highly variable, ranging from subclinical infections to fulminant hepatitis. The majority of these infected adults are asymptomatic and do not develop significant liver disease, but 10-30% develop chronic hepatitis, which may progress to cirrhosis, and finally HCC (4). The limited treatment options available for HCC patients are primarily due to late diagnosis of the disease resulting in poor prognosis. HBV has been described as a 'stealth' virus, as it does not alert the innate immune system to its presence as it spreads throughout the liver (10), nor does it induce the expression of any genes during entry and expansion (11). The HBV virus is able to evade the host's immune surveillance during its most vulnerable early infection phase and spread undetected until the host's immune system respond only weeks after the infection. Most carriers have a high viral load in their blood but are asymptomatic and without liver pathology because HBV is not cytopathic (12). In tissue culture, HBV can even stably replicate without destroying the infected cells (13, 14).

4.1. HBV-related mechanisms in HCC

HBV belongs to the family *Hepadnaviridae*, which includes the hepatitis viruses of the woodchuck, ground squirrel, Peking duck and heron. The highly related woodchuck hepatitis virus (WHV) and the ground squirrel hepatitis virus (GSHV) also cause liver cancer in their hosts (15). Although intensive research has been focused on unraveling the role of HBV in hepatocarcinogenesis for the past three decades, the underlying mechanisms remain unclear, partly due to different viral mechanisms that

contribute in the multistep process of tumorigenesis, including both *cis*- and *trans*-regulation of cellular genes by viral products (16). The HBV DNA either integrates into the host chromosome as a complete genome or rearranged fragments, or it exists episomally in liver cells. This property suggests two major ways in which HBV may contribute to the development of HCC.

4.1.1. *Cis*-effects

The integration of the HBV DNA either completely or as rearranged fragments into the host genome suggests that one of the ways HBV can play a role in hepatocarcinogenesis is through "*cis*-effects" caused by insertional mutagenesis. A *cis*-effect may result from viral regulatory sequences being inserted adjacent to oncogenes and/or tumor-suppressor-encoding genes or when the viral sequences are inserted within these genes causing disruption of the gene's function. Insertion of HBV DNA may cause the separation of upstream regulatory elements of a gene from its coding sequences resulting in the dysregulation of the expression of host genes tethered to the HBV promoter and the dysregulated production of resultant proteins which may be involved in cell proliferation and viability. The complete or partial HBV genome may also integrate within genes causing the disruption of the gene and resulting in perhaps an essential tumor-suppressor protein not being produced or being produced abnormally.

It was reported that in a human HCC sample, the HBV genome was found to be integrated into the human cyclin A gene, an important cell-cycle regulation gene, resulting in a chimeric protein in which the N-terminus of cyclin A is deleted and replaced by viral PreS2/S sequences with transcription being initiated from the viral PreS/S promoter (17, 18). This chimeric protein was found to be undegradable (18) and localizes to the endoplasmic reticulum membrane resulting in cellular transformation (19). The HBV genome has also been reported to be integrated into the retinoic acid receptor (RAR) gene in HCC (20, 21). RAR are members of ligand-regulated transcription factors implicated in the control of cell differentiation and proliferation. It was found that the HBV-RAR chimeric but not wild-type RAR protein was able to transform erythroid progenitor cells (22). In another HCC patient in Shanghai, China, it was found that the HBV genome integrated into chromosome 17p near the p53 gene (23). This region of the 17p was found to be commonly altered, including the loss of one allele of p53, in HBV-positive hepatomas in patients from the same region in China (24). As p53 is an important tumor suppressor gene, the loss of one allele of p53 may contribute to the carcinogenesis process. Utilizing the HBV-Alu PCR strategy, several other cellular genes in which the HBV genome was integrated have been characterized (16, 25, 26). Significantly, it was found that the HBV integrates primarily near or into genes that are key regulators of cell-signaling, cell-proliferation and cell death (16, 25, 26). Although no consensus chromosomal integration site can be identified, the HBV virus was reported to be preferentially integrated into chromosome 3 (P=0.022) (16) or into the human telomerase reverse transcriptase (hTERT) gene, which is important for cell immortalization, in various HCCs and hepatoma derived cell lines (25-28). It was also reported that HBV integration occurs at an early stage during chronic infection and may precede HCC development by a few decades (16, 29). Different sampling of HCC tissues from the same individual revealed the same integration site suggesting clonal expansion of tumor cells (25). The insertion of the HBV genome in or around key cellular genes, whose expression may then be dysregulated or whose function may be altered may provide the affected cells with a selective growth advantage and allow them to expand clonally.

4.1.2. *Trans*-effects

In spite of these interesting data, the majority of integration sites in human HCC are randomly selected (30, 31), prompting researchers to contemplate the possibility that *cis*-acting mechanisms may not contribute significantly to the development of HCC (31). Instead, there is mounting evidence that the major roles in the transformation process are actually played by the viral product(s) themselves. This second model of HBV-associated HCC predicts that expression of transactivating factors derived from the HBV genome results in deregulation of cellular growth controls. PreS2 activators and HBx are the two viral transcriptional activators implicated in this model of hepatocarcinogenesis.

PreS2 activators are derived from the HBV surface gene ORF, which consist of three coding regions, PreS1, PreS2 and S. The PreS1+PreS2+S transcripts encode for the large hepatitis B surface protein (LHBs) while the middle size hepatitis B surface protein (MHBs) is derived from PreS2+S. (32-34). However, only the LHBs and a truncated version of the MHBs called the $MHBs^t$ exhibit transactivation properties. Functional $MHBs^t$ are generated from MHBs following deletion at the 3' end of the HBV surface gene (35, 36) and occurs in one-third of integrated HBV investigated thus far (35, 36). MHBs and its truncated variant protein have different cellular localization, which may account for differences in their attributes. The amino-terminal of the MHBs is oriented towards the lumen of the ER and does not interact with cytosolic proteins (37). In contrast, this domain in $MHBs^t$ activators are oriented towards the cytoplasm, allowing interaction with cytosolic binding partners (38). Cytosolic, non-membrane associated $MHBs^t$ proteins also show similar transactivation activities (38). $MHBs^t$ was found to activate protein kinase C (PKC) and is phosphorylated by PKC at Ser 28, resulting in PKC-dependent activation of c-Raf-1/Erk2 signaling and consequently, the activation of AP-1 and NF-kappaB (39). LHBs proteins were also found to have pleiotropic transcriptional activities. Similar to the $MHBs^t$ activator, AP-1 and NF-kappaB are also activated, and the mechanism of LHBs-dependent transcriptional activation also requires PKC and c-Raf-1 kinase (33). The activation of key players that regulates proliferation suggests that PreS2 activators may deregulate cell proliferation resulting in tumor formation. Transgenic mice that express $MHBs^t$ specifically in the liver showed an increased hepatocyte proliferation rate and increased

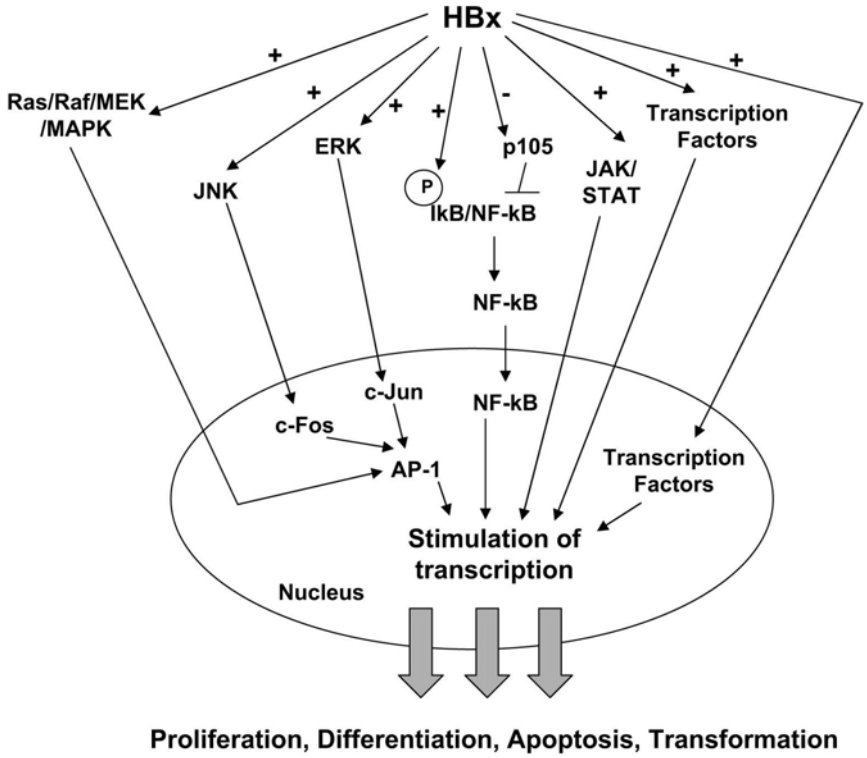

Figure 3. Stimulation of gene transcription by HBx. The Figure shows the putative signal transduction pathways and cellular factors affected by HBx in HBx-related modulation of host cellular signaling pathways. HBx may up-regulate/stimulate (shown by plus sign) or down-regulate/decrease (shown by minus sign) various pathways, resulting in activation of AP-1 or NF-kappaB. HBx may also directly bind and enhance the effects transcription factors (such as TBP, TFIIB, CREB, ATF-2, bZIP, RPB5, p53). The altered patterns of gene expression may result in increased proliferation, cell differentiation, disrupted apoptotic responses and/or malignant transformation.

incidence of liver tumors (39). Interestingly, development of tumors in these mice only occur after one year (39) suggesting that the development of tumors likely results after a certain threshold of cumulative effects is achieved. The roles of these viral products remain inconclusive, but further work on PreS2 activators should yield interesting results as these observations suggest that HBV integrants may give rise to the production of factors that are able to modulate cellular pathways.

Further evidence of this *trans*-effect is derived from the observation that a significant percentage of viral junctions are localized in the carboxy-terminal part of the viral X gene. This results in a fusion of the X ORF to flanking host DNA sequences that might conserve the HBx function (40). HBx but not other viral transcripts are often detected in the tumors of HBV-associated HCC patients (41, 42). In HBV-related HCCs, the integrated HBx often occur as incomplete sequences, but may still retain their functionality as active transactivators (35).

Although the mechanism by which HBV causes transformation of hepatocytes remains incomplete, the HBx protein has emerged as a major suspect. The duck hepatitis B virus (43) and heron hepatitis virus (44) that do not have an X gene do not develop HCC. In animal models, HBx transgenic mice show direct correlation between the level of HBx expression and HCC development (45, 46). However, certain lineages of HBx transgenic mice do not exhibit tumor development unless combined with the induction of *c-myc* (47) or coupled with the exposure to a hepatocarcinogen (48). Additionally, the development of hepatic neoplasia in HBx transgenic mice is dependent on the level of HBx gene expression (49). Recently, we reported that HBx may act as a promoting factor in hepatocarcinogenesis by affecting DNA repair mechanisms in response to a DNA damaging stimuli (50). These observations suggest that HBx may not directly cause cancer but contribute to malignancy as a promoter or co-factor. Due to the possibility of multiple targets, it will be a great challenge to unravel the pleiotropic functions of this viral protein. However, disentangling the cellular mechanisms targeted by HBx may prove to be fruitful and give rise to possible targets for future treatment options.

5. HBX - HBV'S ONE-MAN ARMY?

The above observations are suggestive that HBx may directly contribute to the hepatocarcinogenesis process. What then, are the targets of this oncoprotein? And how does this viral protein modulate the cell's regulatory mechanisms to its own advantage? Evidence collected over the years, suggests that the many phenotypic alterations which consequently contribute to HCC may be caused by alterations in host gene expression induced by HBx. The transforming potential of HBx possibly lies in its promiscuity and its ability to interact with various cellular substrates (Figure 3). The activation of host genes by HBx

is indirect rather than straightforward, acting through various transcription factors such as ATF-2 and CREB (51), the TATA-binding protein (52), bZIP transcription factors (53), RPB5 subunit of polymerases (54), TFIIB (55), components of TFIIH (56), and p53 (57-59). Similar to the PreS2 activators, HBx also increases the DNA binding and activation properties of NF-kappaB and AP-1. NF-kappaB is kept inactive, through its sequestration in the cytoplasm, by its inhibitor IkappaB. HBx was reported to phosphorylate IkappaB which leads to IkappaB degradation by the proteasomes (60, 61). This results in the activation of NF-kappaB which is released from the cytoplasm and translocated to the nucleus to activate other genes. Besides IkappaB, NF-kappaB can also be inhibited by p105, one of its precursors. HBx was also reported to stimulate activation of NF-kappaB by inducing a decrease in the cytoplasmic levels of p105 (61). In addition to stimulating the NF-kappaB pathway, HBx was also found to stimulate the Ras-Raf-mitogen-activated protein kinase (MAP kinase) cascade (62, 63) which is essential for the activation of the AP-1 transcription factor through the activation of the extracellular signal regulated kinases (ERKs) and Jun N-terminal kinases (JNKs) pathways (64). Furthermore, HBx also stimulates the Src-dependent pathway which was shown to be important for HBx activation of AP-1 transcription factor (65) as well as the Janus family tyrosine kinase (JAK) / signal transducer and activator of transcription (STAT) pathways.

Hence, HBx may contribute to the oncogenesis process through modulating these pathways which, in turn, regulate the transcriptional activities of a wide range of transcriptional activators involved in the regulation of cellular growth, differentiation and apoptosis. As the effects of transcriptional activation by HBx is largely via intracytoplasmic modulation of signaling pathways and interaction with nuclear transcription factors, the nucleocytoplasmic distribution of HBx seems to be consistent with the functions of this viral protein (66-68). However, the effects of these interactions remain to be elucidated. What has emerged, however, is the increasing knowledge that HBx may be the responsible viral transforming product, and its modes of action can be as varied as altering the balance between cell proliferation and death, to disrupting cellular repair, consequently leading to HCC.

HBx was also found to modulate apoptotic responses to favor HBV survival either through transctivation mechanisms or direct protein-protein interactions. DNA viruses have been shown to be capable of producing proteins that activate or inactivate apoptosis (5). Inhibition of apoptotic mechanisms may enable viruses to replicate while evading apoptotic defense mechanisms. On the contrary, a pro-apoptotic response can contribute to the spread of the virus and hence ensure its persistence without evoking an immune response (69, 70). The role of HBx in modulating apoptosis remains unclear. HBx was reported to induce spontaneous apoptotic cell death when expressed in mouse fibroblasts (71), Chang liver cells (72), HepG2 cells (73) or the livers of HBx-transgenic mice (74). However, HBx was also reported not to affect cell-cycle or apoptotic profiles (50, 75-78). It is possible that this benign nature of HBx favors HBV survival during the early stages of infection since virus titer during this period may be insufficient for propagation (79). HBx may also alter the host's apoptotic ability by inducing up-regulation of survivin, an inhibitor of apoptosis (IAP) (80). Survivin was found to form a complex with the HBX-interacting protein (HBXIP) (81), a cellular protein originally recognized for its association with HBx (82). Binding of HBx to the survivin-HBXIP complex also inhibits apoptosis by suppressing caspase activation (81). To circumvent the fate of compromised/stressed cells towards death, the HBx protein can also dysregulate p53, the 'Guardian of the genome' (83, 84).

5.1. Disarming the Guardian of the Genome

The p53 tumor suppressor protein plays a major role in hepatocarcinogenesis (85). Dysregulation of p53 has also been implicated in the oncogenic transformation for various tumors (5). Since p53 is a well-known target of HBx (57-59), HBx-p53-dependent mode of malignant transformation has been intensively investigated. HBx was reported to bind to p53 (50, 86-88) and this may affect its tumor suppressor functions. The binding of HBx to p53 can inhibit the sequence-specific DNA binding activity of p53 (59) and affect p53-mediated transactivation of cellular regulatory genes that are involved in cell-cycle or apoptosis (89). This dysregulation of p53 function by HBx would ultimately disrupt the delicate balance between proliferation and cell-death resulting in tumorigenesis. In HBx transgenic mice, tumor development was found to correlate precisely with the binding of HBx to p53 (88).

5.2. Disabling the repair network

By disarming the "Guardian of the Genome", HBx may also disrupt host repair mechanisms (90-92). Genotoxic stress induces post-transcriptional modification and stabilization of p53, resulting in accumulation of p53 levels (93) which, in turn, causes cell cycle arrest for cell repair or apoptosis (83). HBx was found to disrupt cellular repair mechanisms in a p53-dependent manner (94), possibly through binding of the HBx protein to the C-terminal of p53 (95). This region is implicated in the binding of p53 to XPB and XPD (96), components of the TFIIH complex, which are important players in the nucleotide excision repair (NER) pathway. Additionally, HBx may also decrease DNA repair efficiency through interruption of the NER pathway by directly associating with XPB and XPD (56, 97). Nonetheless, an external stimuli that induces DNA-damage was found to be necessary for HBx to affect the NER pathway (50, 75-78).

A disruption in the cell's intricate DNA repair machinery may result in cellular transformation when DNA in the cell is damaged (57-59, 98, 99). While normal hepatocytes usually initiate arrest to enable cellular repair rather than undergo apoptotic cell death (94, 100), in contrast, increased levels of apoptosis was observed in livers of patients with chronic HBV infection (75). The HBx protein has a short half-life of approximately 30 min and is rapidly degraded by the proteasome pathway (101-103). However, *in vitro* studies have shown that in

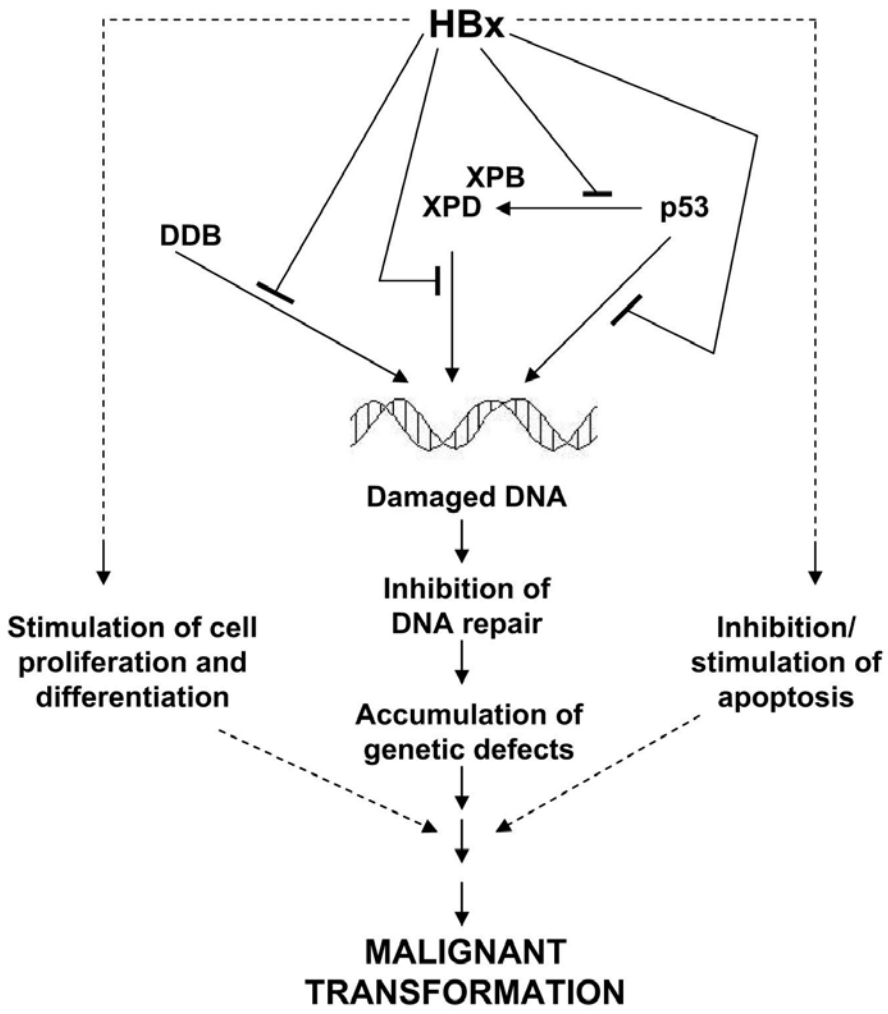

Figure 4. The effect of HBx on DNA repair. The Figure shows the possible effect of HBx on DNA repair. HBx may inhibit DNA repair by binding to various proteins involved in NER (blunt arrows show inhibition by HBx, multiple arrows and broken lines depict the possible multi-step process of hepatocarcinogenesis). The inhibitory effects of HBx on host DNA repair mechanisms give rise to the possibility that genetic defects would accumulate, consequently resulting in mutations favoring malignant transformation. This oncogenic potential of HBx is combined with the other pleiotropic functions of HBx, such as modulation of apoptotic responses and stimulation of cell proliferation, resulting in the phenotypic changes associated with HCC.

response to UV-induced DNA-damage, HBx accumulated in the nucleus in a time- and dose-dependent manner, suggestive of stabilization of the HBx protein (50). These HBx-expressing cells were found to have decreased DNA repair capacity and increased levels of apoptosis (50). Stabilization of the HBx protein may occur when it is bound to DNA-damage binding (DDB) proteins, preventing it from proteasomal degradation (76, 78, 104), and resulting in enhanced nuclear accumulation of HBx (78). The DDB proteins, consisting of DDB1 and DDB2, are implicated in global genomic repair (77, 105, 106), and the binding of HBx to these proteins has been shown to decrease the capacity of the cell to correct genomic lesions (90, 107) and/or promote cell death (79).

Hence, the mounting evidence of HBx's role in DNA repair pathways suggest that this viral protein plays a co-factor or promoting role in the process of hepatocarcinogenesis by disrupting repair mechanisms (Figure 4). A faulty repair system potentially leads to the accumulation of genetic defects that may favor oncogenic transformation.

6. SUMMARY

HCC resulting from HBV infection is one of the most prevalent cancers in the world, and prognosis for this disease is generally poor. However, HBV-associated HCC is still the only malignancy that can be averted by an effective vaccination. Unfortunately, economic and logistical issues often prevent the efficient implementation of immunization programs. Effective treatment of the disease is still a therapeutic challenge, but viable options are increasingly emerging, such as novel drug candidates

targeting chronic HBV infection (108), or gene therapy for the treatment of HCC (109).

Various models for HBV-associated liver oncogenesis are currently being explored, but it still remains unclear if tumorigenesis is caused by the viral infection itself or if viral products cause the transformation of hepatocytes to an oncogenic state. Nonetheless, strong evidence points to the interactions between viral products and the host's cellular regulatory mechanisms as the major contribution to virus-associated hepatocellularcarcinogenesis. HBV, through *cis*- and/or *trans*- mechanisms, effectively alters cellular gene expression and causes deregulation of diverse pathways ranging from cell growth and proliferation, to repair mechanisms and apoptosis. Among the viral-encoded products, the HBx protein has been the subject of intense research. This is mainly due to the plethora of activities displayed by HBx. It has been implicated in the modulation of cellular proliferation and cell death, disruption of DNA repair and influencing transcriptional activation. Given the long latent periods usually observed from the time of initial infection to tumor appearance, it is likely that HBx does not directly cause cancer but plays a role in liver oncogenesis as a co-factor or tumor promoter through its pleotropic functions. Thus, a chronic infection may offer the opportunity for a mutation that favours malignant transformation to occur. This initiating factor, combined with the possibility of clonal expansion, may culminate in the generation of HCC. However, no simple conclusions can be made, as the reported effects of HBx or HBV itself have been greatly diverse, and sometimes even contradictory. These discrepancies may be contributed by differences in experimental set-ups. The elusive X protein still remains mysterious, and the 'stealth' virus, still unconquered. Nonetheless, with new emerging high-throughput technologies that are becoming available, one may soon be able to better understand this enemy.

7. ACKNOWLEDGEMENTS

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Abbreviations: HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HBx: HBV X gene product; ORF: open reading frame; rcDNA: relaxed circular DNA; cccDNA: covalently closed circular DNA; HBsAg: hepatitis B surface antigen; HBcAg: hepatitis B core antigen; HBeAg: hepatitis B e antigen; DR: Direct repeats; EN: enhancer; RAR: retinoic acid receptor; LOH: loss of heterozygosity; hTERT: human telomerase reverse transcriptase; LHBs: large hepatitis B surface protein; MHBs: middle size hepatitis B surface protein; MHBst: truncated middle size hepatitis B surface protein; DDB: DNA-damage binding proteins.

Key Words: Hepatitis B Virus, Transforming viruses, Hepatocellularcarcinogenesis, Hepatocellularcarcinoma, HBx, Review

Send correspondence to: Caroline GL. Lee, Ph.D. Division of Medical Sciences, National Cancer Center, Level 6, Lab 5, 11 Hospital Drive, Singapore 169610, Singapore,Tel: 65-6436-8353. Fax: 65-6372-0161, E-mail: bchleec@nus.edu.sg

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