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The hidden yet threatening link between hepatitis B virus and hepatocellular carcinoma: A Narrative Review

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Abstract

Background: Hepatocellular carcinoma (HCC) is a highly aggressive liver cancer (LC), primarily driven by chronic hepatitis B virus (HBV) infection. Persistent HBV infection causes liver inflammation, dysfunction, and ultimately HCC through mechanisms like viral integration, oncogenic protein expression, and immune disruption. This study explores HBV-related HCC mechanisms and evaluates preventive/therapeutic approaches to reduce the global HCC burden.

Methods: To conduct this comprehensive review, we systematically searched the databases of PubMed, Scopus, Web of Science, and Google Scholar for relevant literature. The search included studies published without a time restriction up to 2025, covering clinical studies, review articles, systematic reviews, and meta-analyses. The following keywords were used to identify pertinent publications: "HBV", "HCC", "Pathogenesis", "Immune response", "LC", "Diagnosis ", "Prevention", and "Treatment".

Results: HBV contributes to HCC through multiple mechanisms, including viral genome integration into the host, oncogenic viral protein expression, genetic mutations, induction of cellular proliferation, inhibition of apoptosis, immune system disruption, and alterations in cellular signaling pathways. Antiviral therapies targeting HBV have shown promise in reducing HCC risk by suppressing viral replication and mitigating liver damage. Early intervention in CHB patients significantly decreases HCC incidence, highlighting the importance of timely diagnosis and treatment.

Conclusion: The strong link between HBV and HCC underscores the need for effective antiviral strategies to prevent and manage HCC. Understanding the molecular mechanisms of HBV-induced hepatocarcinogenesis is crucial for developing targeted therapies. Preventive measures, including vaccination and early antiviral treatment, are essential in reducing the global HCC burden.

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Highlights

What is current knowledge?

HBV enters hepatocytes via NTCP receptors, forming persistent cccDNA that drives viral replication. The HBx protein promotes HCC by inactivating tumor suppressors and inducing oxidative stress. Chronic infection causes liver injury through viral integration and inflammation, with vaccination and antivirals as primary prevention tools.

What is new here?

Recent studies reveal HBV's role in metabolic reprogramming and tumor microenvironment alterations. Emerging therapies target cccDNA with CRISPR and combine antivirals with immunotherapies. This review highlights genotype-specific oncogenic risks and novel biomarkers for improved HCC risk prediction.

Introduction

Globally, liver cancer (LC) is the sixth most common cancer diagnosis and the third leading cause of cancer mortality. This has made LC management and diagnosis one of the significant challenges in global health (1,2). Between 2020 and 2040, the number of people with LC is expected to rise by 55% (3). Among the various types of LC, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) are the most common, accounting for 75-85% and 10-15% of LC cases, respectively (4). Multiple factors can contribute to an increased risk of HCC, including obesity, race, gender (5), age, alcohol and tobacco consumption, diabetes mellitus, liver cirrhosis (6), environmental and genetic factors, exposure to carcinogens such as Aflatoxin B1 (AFB1) (7), metabolic diseases, particularly nonalcoholic fatty liver disease (NAFLD), and viral hepatitis infections (8). The hepatitis B virus (HBV) is recognized as the most common viral carcinogenic agent in the liver (9). Hepatocytes are infected with HBV, which results in a variety of liver disorders such as acute hepatitis B virus (AHB), chronic hepatitis B virus (CHB), liver cirrhosis, and HCC, which accounts for half of all cases of HCC. However, people with CHB have the highest chance of developing HCC (10-12). Various factors play a role in the development of HBV-related HCC, including co-infection with other viruses such as Hepatitis C, Hepatitis D, or human immunodeficiency virus (HIV), virus genotype, the effect of HBV oncoprotein and oncogenic factors, long-term infection, and high viral load (13,14). Given the high prevalence of viral hepatitis and its strong association with HCC occurrence, implementing strategies to prevent

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viral infection, including vaccination and antiviral treatments, is crucial for managing and improving survival rates of patients with HBV-related HCC (15). HBV is one of the most common viral diseases that can have serious consequences, including HCC. However, the molecular mechanisms involved in HBV-related carcinogenesis are not yet fully understood. Additionally, late diagnosis and treatment resistance in HCC patients pose significant challenges, highlighting the need for control and prevention of HBV infection, especially in high-risk populations. This study discusses the relationship between HBV and HCC and to better understand the pathogenic mechanisms involved in this process. Furthermore, this research seeks to evaluate existing and effective preventive strategies and antiviral treatments for the management and treatment of HCC.

Methods

The important connection between HBV and HCC is examined in this thorough narrative review, which focuses on epidemiological patterns, molecular etiology, and preventative measures. We prioritized high-impact clinical studies, reviews, meta-analyses, and recommendations in our systematic literature search throughout PubMed, Scopus, Web of Science, and Google Scholar, with no time limits until 2025. Eighty relevant papers were chosen for in-depth examination from an initial selection. Important facets of HBV-associated hepatocarcinogenesis are examined in this review, including molecular causes, worldwide epidemiological trends, contemporary diagnostic and preventative techniques, and new issues. The narrative method was used to provide both thorough coverage and in-depth analysis of HBV's intricate function in the development of HCC, as well as to integrate existing information, assess current management paradigms, and highlight research needs. This methodology ensures our review integrates the most current, rigorous evidence to clarify HBV-driven hepatocarcinogenesis and its clinical implications, suggesting a foundation for improved prevention and treatment strategies against this lethal cancer.

Results

Structure and genotype of HBV

HBV, as one of the most major human pathogenic viruses, causes serious infectious diseases that lead to a considerable yearly death rate globally. The virus can spread from mother to child (Vertical transmission), through sexual contact, and by contact with bodily fluids, including blood (16-19). A key feature of this virus is its ability to establish lifelong latent infections in cases of CHB, increasing the risk of disease reactivation and necessitating long-term monitoring and treatment. Thus, it remains a major global health challenge (20,21). The 3.2 kb genome of HBV, a partly double-stranded, enveloped DNA virus, is a member of the hepadnaviridae family (22). The compact HBV genome consists of four open reading frames (ORFs): P (Polymerase), Pre-S/S (Surface), Pre-C/C (Core), and X (23). The largest ORF region, P, encodes the viral polymerase (POL), which provides reverse transcriptase (RT), replication, and RNase H activity for the virus (24,25). The three varieties of surface antigens (HBsAg) that include the surface proteins encoded by the S region are small (S-HBs), medium (M-HBs), and large (L-HBs). These three types correspond to the S, Pre-S2 and S, Pre-S1, Pre-S2, and S regions, respectively. The virus may enter the host cell thanks to these proteins, which are found in the viral envelope (26,27). The hepatitis B core protein (HBc), which forms the viral capsid and is necessary for genome packaging and viral replication, is produced in large part by the C region of the viral genome. Hepatitis B virus e antigen (HBeAg) and other core-related proteins are also encoded by the C region (28). The hepatitis B virus regulatory protein X (HBx), encoded by the X region, is responsible for various functions, including DNA transcription control, virus replication, genetic instability induction, DNA damage repair, modulation of cellular signaling pathways, interaction with host cell proteins, apoptosis inhibition, host immune system modulation, and cancer progression (29-31). HBV has ten genotypes, A to J, with their distribution and subgroups dependent on geographical factors, population migrations, and the virus's evolution (32,33). Each HBV genotype has unique clinical outcomes and treatment responses. HCC pathogenesis is often associated with genotypes B and especially C, which are more prevalent in regions where vertical virus transmission is common, such as Asian countries (34,35). Additionally, concurrent infection with various HBV genotypes and viral evolution can result in the creation of recombinant strains, such as HBV C/D, HBV A/G, and HBV D/E, which are highly significant from a clinical standpoint (36,37). Therefore, determining the viral genotype plays a crucial role in selecting appropriate treatment methods and can help reduce symptoms and improve patient outcomes (38).

Molecular mechanisms of HBV pathogenesis and replication and their effect on the development of HCC

Viral entry and receptor interaction

The interaction between the virus and the cell causes conformational changes in the myristoylated N-terminal Pre-S1 region of L-HB. These changes reveal the virus binding site to the sodium taurocholate co-transporting polypeptide receptor (NTCP), leading to virus attachment and entry into the host cell (39). Both the NTCP receptor and the auxiliary epidermal growth factor receptor (EGFR) are bound by HBV, forming an HBV-NTCP-EGFR complex. The HBV-NTCP-EGFR combination enters the cell more easily and co-localizes intracellularly during infection because EGFR functions as a co-receptor for NTCP (40).

Internalization and intracellular transport

Through clathrin-mediated endocytosis (CME), the complex is internalized. After entry, the virus moves through endolysosomes, late endosomes, or early endosomes (41). The endosome carrying the HBV nucleocapsid -followed by the HBV capsid released into the cytoplasm- is transported to the hepatocyte nucleus via the dynein motor complex along the microtubular network (42,43).

Nuclear entry and formation of cccDNA

Nuclear holes made of certain proteins known as the nuclear pore complex (NPC) allow the HBV genome to reach the nucleus, where it disassembles the viral capsid (44). The very stable covalently closed circular DNA (cccDNA) minichromosome is created inside the hepatocyte nucleus from relaxed circular DNA (rcDNA) (45).

Transcription and translation of viral proteins

Pregenomic RNA (pgRNA) and other mRNAs are among the viral RNAs that are produced using cccDNA as a transcription template (46). The pgRNA transcript and other subgenomic transcripts lead to the translation and production of proteins such as viral surface envelope proteins, core proteins, HBx, and viral POL.

Reverse transcription and viral propagation

After transport to the cytoplasm, pgRNA undergoes reverse transcription by viral POL and is converted back to rcDNA. The newly produced rcDNA is encapsidated by HBc. This nucleocapsid can either be expelled from the infected cell, enabling the infection to spread, or it can receive surface envelope polypeptides through the endoplasmic reticulum (ER) and return to the nucleus to refill the cellular cccDNA population (47).

Mechanisms of hepatocarcinogenesis

HBV plays a role in hepatocyte oncogenesis through direct and indirect mechanisms. The integration of newly produced viral DNA via reverse transcription into the host genome and the effect of viral oncoproteins through processes such as chromosomal instability, genetic mutation induction, apoptosis inhibition, cell proliferation induction, and activation of cancer-related genes are among the most important mechanisms contributing to HCC progression (48,49).

Viral mutations and chronic infection

Chronic infection, the virus's unique genome structure, and immune pressure from the host can lead to mutations in HBV genes. These changes support viral persistence and promote HCC development (49,50).

HBV proteins and ER stress

HBV proteins such as HBx, L-HB, and S-HB are involved in signaling pathways and can trigger ER stress, contributing to HCC progression (51). Deletion mutations in the Pre-S1 or Pre-S2 gene regions result in mutant L-HB accumulation in the ER, activating ER stress. HBx modulates this stress response by inhibiting apoptosis and altering the host cell cycle (51,52).

Formation of ground glass hepatocytes

The buildup of viral surface proteins in hepatocytes overloads the ER, leading to the appearance of ground glass hepatocytes (GGH)-cells with a uniform, opaque, glassy appearance (51,53).

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HBx and anti-apoptotic pathways

HBx increases the expression of anti-apoptotic genes (e.g., Bcl-2) and suppresses pro-apoptotic factors (e.g., Bax). It also elevates cytosolic calcium and inactivates caspase-9 and -3, thereby preventing apoptosis and enhancing HBV replication and cytotoxicity (54,55).

Inhibition of tumor suppressors and immune escape

Furthermore, HBx can directly inhibit tumor suppressor genes such as p53, preventing apoptosis and promoting virus replication and spread (56). Furthermore, the accumulation of epitope changes in HBc and HBe over time as a result of immunological pressure from cytotoxic T lymphocytes (CTLs) diminishes the response to the virus, allowing viral immune escape and, ultimately, the advancement of HCC (50) (Figure 1).

Treatment and prevention strategies for HCC associated with the HBV

Management and treatment of HCC depend on various factors, including the patient's age, tumor characteristics and severity, underlying liver dysfunction, comorbidities, access to medical resources, and location (57). Early diagnosis of HCC is crucial for achieving optimal therapeutic outcomes and improving patient survival rates. Therefore, early detection through monitoring and screening in high-risk populations, such as HBV-infected individuals, is essential for implementing preventive strategies and effectively managing HCC (58). Lifestyle modifications, including avoiding alcohol and smoking, engaging in physical activity, maintaining a healthy diet, and utilizing vaccines and antiviral therapies, are well-established strategies for preventing HCC (59). Among these measures, preventing HBV infection is one of the most critical actions to reduce the global incidence of HCC (60). The risk of HBV infection can be minimized by interrupting transmission pathways through blood donor testing, adherence to aseptic principles, screening pregnant women, using human hepatitis B immunoglobulin, and administering vaccines (61). The hepatitis B vaccine, produced from purified viral surface antigens, stimulates the immune system upon injection and leads to antibody production, significantly reducing the risk of HCC (62,63). Since most HBV transmission occurs from mother to child and the likelihood of developing CHB during infancy or early childhood is 90% higher than in adults, vaccinating newborns and infants plays a key role in preventing HBV infection (64,65). Additionally, antiviral therapies for HBV, including interferon-based drugs (Interferons-INF) with immunomodulatory and antiviral effects and nucleotide analogs (Nucleotide Analogs-NAs/NUC), reduce viral DNA levels in CHB patients. These therapies reduce the chance that liver diseases, including HCC, may worsen and recur (62,66). Common NUC drugs include Lamivudine (LAM), Entecavir (ETV), Adefovir (ADV), Telbivudine (LdT), Tenofovir Disoproxil Fumarate (TDF), and Tenofovir Alafenamide (TAF), while Pegylated Interferon (Peg INF) is among interferon-based therapies (67). Although existing antiviral drugs have significantly advanced disease control, challenges such as limited efficacy, numerous side effects, disease recurrence risks, and the emergence of drug-resistant strains highlight the need for developing newer and more effective therapeutic strategies (68) (Table 1). Targeting HBsAg and reducing its levels is considered one of the main goals in the treatment of CHB infection, as this approach is directly associated with improved viral control and a reduction in disease burden. In this regard, in addition to antiviral drugs, new therapies include immunotherapy with immune checkpoint inhibitors (ICIs), particularly drugs targeting the programmed cell death 1(PD-1)/programmed cell death ligand-1(PD-L1) pathway (69,70). Gene and cell therapy, such as chimeric antigen receptor (CAR-T) cells and T cell receptor (TCR-T) cells targeting HBsAg, are also being developed (71,72). Additionally, mucosal-associated invariant T (MAIT) cells (73) and combination therapy are under investigation to enhance treatment efficacy (74,75). Unfortunately, the majority of HCC cases are discovered at an advanced stage, when there are few and ineffective treatment options available, which leads to a far lower patient survival rate (76).

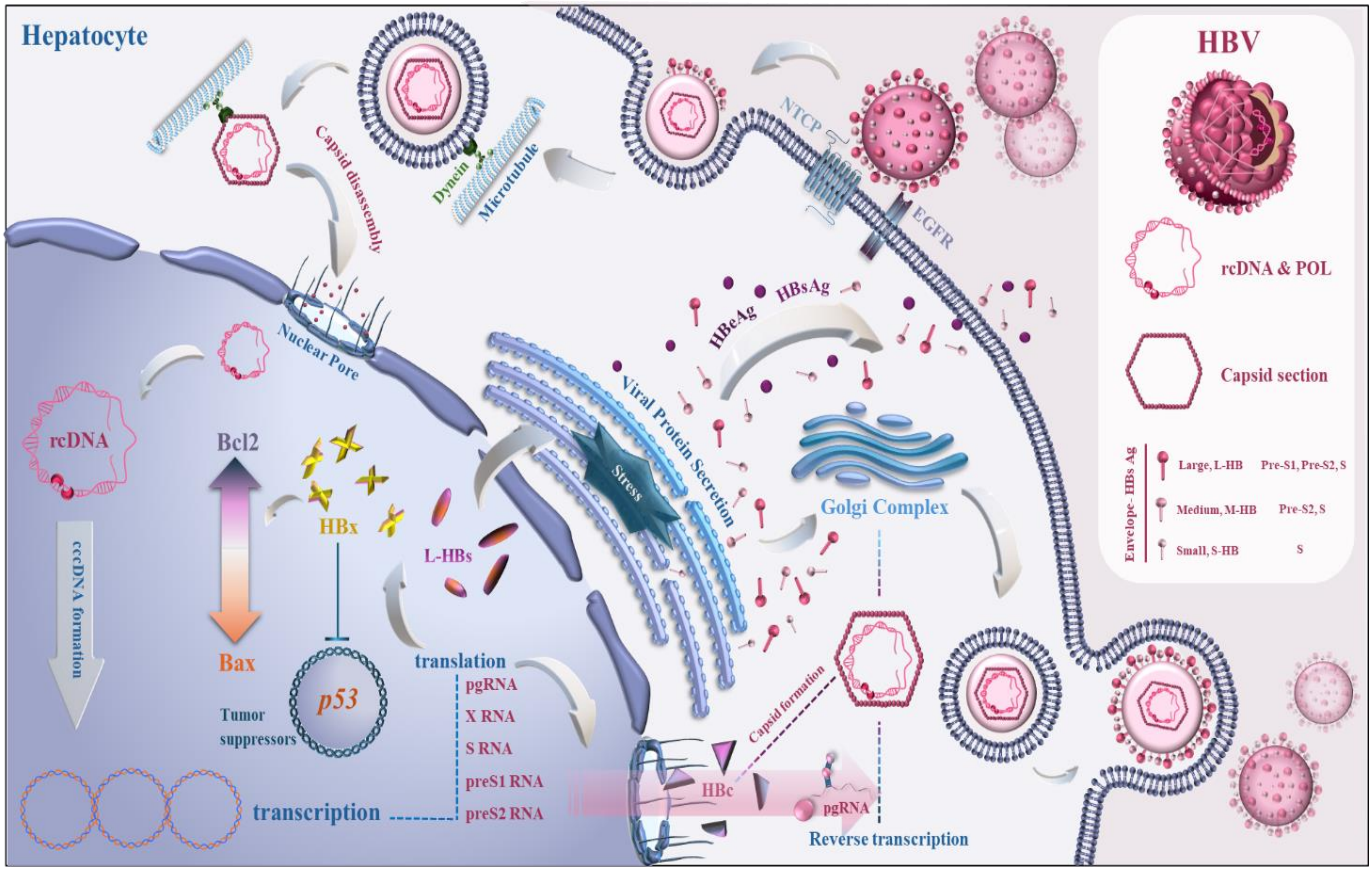

Figure 1. Mechanisms of HBV carcinogenesis and replication, the replication cycle and carcinogenesis of HBV begin with the virus entering hepatocytes through the NTCP receptor and the EGFR co-receptor. After entry, the viral nucleocapsid is transported toward the cell nucleus by the dynein microtubule system, and the viral genome enters the nucleus through the NPC. Inside the nucleus, the viral rcDNA is converted to cccDNA, followed by transcription and translation of viral proteins. Following virus replication, HBV is released from the cell, causing the spread of infection. Factors such as genomic mutations and the effect of viral oncoproteins like HBx and L-HB promote HCC progression by activating ER stress, inhibiting hepatocyte apoptosis, and evading the immune system. HBV: Hepatitis B Virus; NTCP: Sodium Taurocholate Co-transporting Polypeptide receptor; EGFR: Epidermal Growth Factor Receptor; NPC: Nuclear Pore Complex.

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Table 1. Effect of antiviral drugs on HBV

Category / Class	Drugs	Effect on HBV	First-Line	Resistance rate	Side effects	Reference
Interferons	Peg INF-α	Stimulating the immune system leads to suppressing viral replication	No	No	Flu-like symptoms (Fever, Fatigue), Hematological abnormalities (Neutropenia, Thrombocytopenia), and Neuropsychiatric symptoms (Depression, Anxiety)	(77,78)
Nucleotide analogs	LAM	Reverse transcriptase inhibitors result in a reduction in viral replication	No	High. Increase in 3rd year	Few Such as fatigue and mild gastrointestinal discomfort	(77,79,80)
	ETV		Yes	Low (Except lamivudine-pretreated patients increase the rate)	Few and Mild Such as fatigue and nausea	
	ADV		No	High. Increase in 5th year (Cross-resistance with patients with pre-existing lamivudine resistance)	Renal function declines after 2 years of treatment, pharyngitis, headache, abdominal pain, flu-like symptoms and nausea	
	LdT		No	High. Increase in 2nd year	Development of muscle toxicity	
	TDF		Yes	Low	Renal tubular injury in long-term usage (More common in TDF)	
	TAF					

List of Abbreviations

HCC: Hepatocellular Carcinoma; iCCA: Intrahepatic Cholangiocarcinoma, AFB1: Aflatoxin B1, NAFLD: Nonalcoholic Fatty Liver Disease, HBV: Hepatitis B Virus, AHB: Acute Hepatitis B Virus, CHB: Chronic Hepatitis B Virus, ORF: Open Reading Frame; P: Polymerase; S: Surface; C: Core; POL: Polymerase; RT: Reverse Transcriptase; HBsAg: Hepatitis B Virus surface Antigen; S-HB: Small Hepatitis B Surface Protein; M-HB: Medium Hepatitis B Surface Protein; L-HB: Large Hepatitis B Surface Protein; HBeAg: Hepatitis B Virus-e Antigen; HBx: Hepatitis B virus regulatory protein X; NTCP: Sodium Taurocholate Co-Transporting Polypeptide; EGFR: Epidermal Growth Factor Receptor; NPC: Nuclear Pores Complex; rcDNA: Relaxed Circular DNA; cccDNA: Covalently closed circular DNA; pgRNA: Pregenomic RNA; GGH: Ground Glass Hepatocytes; Bcl-2: B-cell leukemia/lymphoma 2; Bax: Bcl-2-associated X protein; CTL: Cytotoxic T Lymphocytes; INF: Interferons; Nas/ NUC: Nucleotide Analogs; LAM: Lamivudine; ETV: Entecavir; ADV: Adefovir; LdT: Telbivudine; TDF: Tenofovir Disoproxil Fumarate; TAF: Tenofovir Alafenamide; Peg INF: Pegylated Interferon; ICIs: Immune Checkpoint Inhibitors; PD-1: Programmed cell Death 1; PD-L1: Programmed cell Death Ligand-1; CAR-T: Chimeric Antigen Receptor T cell; TCR-T: T Cell Receptor cell; MAIT: Mucosal-Associated Invariant T cell; LC: Liver Cancer.

Conclusion

HBV is recognized as a primary etiological factor in LC, particularly HCC. Chronic HBV infection, especially in neonates and infants, can lead to severe hepatic complications, including chronic inflammation, cirrhosis, and ultimately malignant transformations such as HCC. HBV infection disrupts host cellular mechanisms through complex pathways, including genomic integration into host DNA and oncogenic protein activity, which inhibit apoptosis, induce cell proliferation, trigger genetic mutations, and impair immune responses, collectively creating an inflammatory microenvironment conducive to carcinogenesis. Given the strong association between HBV and HCC progression, vaccination and antiviral therapies remain the most effective preventive and therapeutic strategies for controlling HBV infection and reducing HCC risk. However, challenges such as delayed diagnosis, drug resistance emergence, and the need for more targeted therapies persist as critical barriers in this field. Future research should focus on developing curative HBV strategies (e.g., CRISPR-based therapies), personalized antiviral regimens, and integrated screening programs in low- and middle-income countries (LMICs) to enhance early detection and intervention. Addressing these gaps will be essential for advancing novel therapeutic approaches and improving global HCC outcomes.

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Ethical statement

Not applicable.

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

Idea: A.J.S, M.P; Data Collection or Processing: A.J.S, S.M.M, S.K.Z, S.V; Writing-Review & Editing: S.M.M, S.K.Z, S.V; Figure design: S.K.Z, S.V; Supervision: A.J.S, M.P. All authors reviewed the results and approved the final version of the manuscript.

Data availability statement

Data sharing is not applicable.

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