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Viral Manipulation of Host Signaling Pathways by Hepatitis B Virus (HBV): Implications for Liver Disease Progression and Targeted Therapy

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Abstract

Hepatitis B virus (HBV) infection remains a major global health burden and is strongly associated with chronic hepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The progression of HBV-associated liver disease is primarily mediated through complex interactions between viral proteins and host cellular signaling pathways rather than direct viral cytotoxicity alone. This article comprehensively investigates the molecular mechanisms by which HBV manipulates host signaling networks to establish persistent infection, evade immune responses, and promote liver disease progression. Particular emphasis was placed on the role of the HBx protein in regulating inflammatory, proliferative, apoptotic, fibrogenic, and oncogenic pathways. The study systematically evaluated HBV-induced dysregulation of key signaling cascades including NF-κB, PI3K/Akt/mTOR, JAK/STAT, MAPK/ERK, Wnt/β-catenin, and TGF-β pathways and their contribution to chronic inflammation, oxidative stress, fibrosis, immune dysfunction, and hepatocarcinogenesis. Result-oriented analysis demonstrated that HBV significantly suppresses innate and adaptive immune responses through inhibition of Toll-like receptor signaling, reduced interferon production, impaired natural killer cell activity, and induction of T-cell exhaustion via PD-1, CTLA-4, and TIM-3 upregulation. Persistent activation of inflammatory and survival pathways promoted hepatic stellate cell activation, extracellular matrix

deposition, genomic instability, and malignant transformation. Therapeutic findings indicated that direct-acting antivirals effectively suppress viral replication but fail to eliminate covalently closed circular DNA (cccDNA). Emerging therapeutic strategies including host-targeting antivirals, immune checkpoint inhibitors, RNA interference, CRISPR/Cas gene editing, and epigenetic therapies demonstrated promising outcomes in restoring antiviral immunity, reducing fibrosis, and suppressing viral persistence. Overall, this study highlights the critical role of HBV-host signaling interactions in liver disease progression and emphasizes the importance of targeted molecular therapies for achieving functional cure and preventing HBV-associated hepatocellular carcinoma.

1. INTRODUCTION

Hepatitis B virus (HBV) infection remains one of the most significant global public health challenges and continues to be a leading cause of chronic liver disease worldwide. HBV is a small, enveloped, partially double-stranded DNA virus that belongs to the family *Hepadnaviridae*. Despite the availability of an effective prophylactic vaccine, HBV infection continues to affect nearly 300 million people globally and accounts for a substantial proportion of liver-related morbidity and mortality (Lavanchy and Kane, 2016). Chronic HBV infection is strongly associated with progressive hepatic disorders, including chronic hepatitis, liver fibrosis, cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC), which collectively contribute to hundreds of thousands of deaths annually. The burden of HBV infection is particularly high in developing countries where limited healthcare resources, inadequate vaccination coverage, and delayed diagnosis contribute to persistent transmission and disease progression. Persistent infection results in long-term hepatic inflammation and continuous liver injury, creating an environment conducive to fibrosis and malignant transformation of hepatocytes (Maddrey, 2000).

Unlike many cytopathic viruses, HBV-induced liver damage is not primarily caused by direct destruction of infected hepatocytes by the virus itself. Instead, liver pathology largely arises from the intricate interactions between viral components and host immune responses. HBV has evolved sophisticated molecular strategies to manipulate host cellular machinery and evade antiviral immunity, thereby ensuring its persistence within hepatocytes (Hsu *et al.,* 2023). The ability of HBV to establish chronic infection is closely linked to its capacity to regulate intracellular signaling pathways that govern inflammation, cell survival, apoptosis, metabolism, immune regulation, and tissue remodeling. These virus-host interactions play a central role in determining disease severity and progression toward cirrhosis and hepatocellular carcinoma (Lavanchy, 2008).

Among the viral proteins encoded by HBV, the hepatitis B virus X protein (HBx) is considered the most critical regulatory molecule involved in host manipulation. HBx is a multifunctional protein capable of interacting with numerous cellular proteins and transcription factors, thereby altering multiple intracellular signaling cascades. Extensive studies have demonstrated that HBx contributes significantly to viral replication, transcriptional activation, epigenetic regulation, mitochondrial dysfunction, oxidative stress generation, autophagy, and oncogenic transformation. Through these mechanisms, HBx promotes an intracellular environment favorable for viral persistence while simultaneously inducing pathological changes within the liver microenvironment. Furthermore, HBx has been implicated in the inhibition of tumor suppressor pathways and activation of oncogenic signaling, which collectively contribute to hepatocarcinogenesis (Faniyi *et al.*, 2024).

Recent advances in molecular virology and cellular biology have substantially improved understanding of the signaling pathways dysregulated during HBV infection. Several critical host signaling pathways are now recognized as major targets of HBV-mediated modulation. Among these, the nuclear factor-kappa B (NF-κB) signaling

pathway plays a pivotal role in inflammatory responses and immune regulation. HBV activation of NF-κB signaling promotes the production of pro-inflammatory cytokines, enhances hepatocyte survival, and contributes to chronic inflammation and fibrosis (Zhang and Cui, 2025). Persistent activation of NF-κB signaling has also been linked to increased cellular proliferation and resistance to apoptosis, thereby facilitating tumor development. Another major pathway altered during HBV infection is the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling cascade, which regulates cellular growth, metabolism, proliferation, and survival. HBV-mediated activation of PI3K/Akt signaling enhances viral replication and suppresses apoptotic mechanisms, enabling infected hepatocytes to survive despite ongoing cellular stress. Sustained activation of this pathway contributes to abnormal cell proliferation, angiogenesis, and oncogenic transformation, all of which are characteristic features of HBV-associated hepatocellular carcinoma (Hwang and Cheung, 2011).

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is another essential target of HBV manipulation. This pathway plays a crucial role in interferon-mediated antiviral immunity and host defense mechanisms. HBV proteins, including HBx and viral polymerase, interfere with JAK/STAT signaling by inhibiting STAT phosphorylation and suppressing the expression of interferon-stimulated genes. As a result, antiviral immune responses become impaired, allowing HBV to evade immune surveillance and establish chronic infection. This immune suppression also reduces the efficacy of interferon-based therapeutic approaches commonly used in HBV management (Said and El-Sayed, 2022). In addition to these pathways, HBV significantly influences the mitogen-activated protein kinase (MAPK) signaling cascade, which regulates cellular differentiation, proliferation, and stress responses. Activation of MAPK/ERK signaling by HBV promotes hepatocyte proliferation and contributes to tumor invasiveness and metastatic potential. Dysregulation of this pathway has been strongly associated with progression from chronic hepatitis to hepatocellular carcinoma (Lavanchy, 2005).

The Wnt/β-catenin signaling pathway also plays an important role in HBV-associated liver carcinogenesis. HBx-mediated stabilization and nuclear accumulation of β-catenin result in activation of oncogenic transcriptional programs that promote epithelial-mesenchymal transition, stemness characteristics, and uncontrolled cellular proliferation. Aberrant activation of Wnt/β-catenin signaling has been frequently observed in HBV-related HCC tissues and is associated with poor clinical prognosis (Al-Busafi and Alwassief, 2024). Furthermore, transforming growth factor-beta (TGF-β) signaling is critically involved in HBV-induced liver fibrosis and cirrhosis. Chronic HBV infection stimulates TGF-β production, leading to activation of hepatic stellate cells and excessive deposition of extracellular matrix proteins. Continuous fibrogenesis ultimately results in architectural distortion of the liver and progression toward cirrhosis. Although TGF-β signaling initially exhibits tumor-suppressive functions, persistent activation during chronic liver injury contributes to immune suppression, tissue remodeling, and tumor progression (Xu *et al.*, 2016).

Collectively, the dysregulation of these signaling pathways establishes a complex molecular network that supports viral persistence and drives progressive liver disease. Chronic activation of inflammatory and survival pathways not only facilitates HBV replication but also promotes genomic instability, oxidative stress, fibrosis, and malignant transformation. Consequently, understanding the molecular mechanisms underlying HBV-host interactions has become a major focus of contemporary virology and hepatology research (Yan *et al.*, 2024).

The growing knowledge of HBV-mediated signaling alterations has also opened new opportunities for therapeutic intervention. Current antiviral therapies, including nucleos(t)ide analogs such as tenofovir and entecavir, effectively suppress viral replication but rarely achieve complete viral eradication because covalently closed

circular DNA (cccDNA) persists within infected hepatocytes. Therefore, novel therapeutic approaches targeting host signaling pathways are being actively explored (Dong *et al.,* 2020).

Emerging strategies include host-targeting antivirals, immune checkpoint inhibitors, RNA interference technologies, CRISPR/Cas-mediated gene editing, and epigenetic therapies aimed at silencing viral transcription and restoring antiviral immunity. Targeting HBV-induced signaling dysregulation may not only inhibit viral persistence but also prevent fibrosis progression and hepatocellular carcinoma development (Devan *et al.,* 2022).

2. MATERIALS AND METHODS

2.1 Study Design

The present study was designed as a comprehensive molecular and mechanistic review-based investigation focusing on the interaction between Hepatitis B virus (HBV) and host cellular signaling pathways involved in liver disease progression and hepatocellular carcinoma (HCC). The study systematically evaluated the molecular biology of HBV, the role of viral proteins in host manipulation, and the dysregulation of intracellular signaling cascades associated with chronic HBV infection. Emphasis was placed on understanding the mechanisms by which HBV proteins, particularly HBx, interfere with inflammatory, proliferative, apoptotic, and fibrogenic pathways. Experimental findings from previously published molecular, cellular, and translational studies were comparatively analyzed to identify pathway-specific effects and therapeutic implications (Tourkochristou *et al.,* 2022).

2.2 Inclusion and Exclusion Criteria

Studies were included in this analysis if they investigated HBV molecular biology and replication mechanisms, evaluated HBV-mediated modulation of host signaling pathways, and examined HBx-associated interactions with cellular proteins and regulatory networks. Additional inclusion criteria comprised studies reporting experimental or clinical evidence related to HBV-induced liver fibrosis, cirrhosis, or hepatocellular carcinoma (HCC), as well as those exploring targeted therapeutic strategies against HBV-associated signaling pathways. Conversely, studies were excluded if they were unrelated to HBV signaling mechanisms, contained incomplete or insufficient datasets, were non-English publications, or lacked experimental, molecular, or mechanistic evidence supporting their findings (Jehangir *et al.,* 2025).

2.3 Molecular Biology and Structural Analysis of HBV

The structural organization and molecular biology of HBV were analyzed through previously published genomic and virological studies. HBV is a partially double-stranded DNA virus possessing a compact genome of approximately 3.2 kb containing four overlapping open reading frames encoding the surface (S), core (C), polymerase (P), and X (HBx) proteins. Particular emphasis was placed on the role of covalently closed circular DNA (cccDNA), which serves as a stable nuclear template responsible for viral persistence and chronic infection. The replication cycle of HBV involving reverse transcription of pregenomic RNA within nucleocapsids was critically evaluated. Furthermore, studies investigating HBx-mediated regulation of transcription, mitochondrial signaling, apoptosis, calcium homeostasis, and epigenetic modifications were comparatively assessed to understand their contribution to hepatocarcinogenesis and viral persistence (Li *et al.,* 2012).

Table 1. Structural Components and Functions of HBV Genome

HBV Gene/Protein	Primary Function	Role in Pathogenesis
Surface (S)	Encodes HBsAg proteins	Viral entry and immune evasion
Core (C)	Encodes nucleocapsid proteins	Viral assembly and replication

Polymerase (P)	Reverse transcriptase activity	Viral DNA synthesis
X gene (HBx)	Regulatory multifunctional protein	Host signaling manipulation and oncogenesis
cccDNA	Stable transcriptional template	Viral persistence and chronic infection

2.4 Evaluation of HBV-Mediated Signaling Pathways

The molecular pathways manipulated by HBV were analyzed based on mechanistic and experimental evidence from in vitro and in vivo studies. Signaling pathways associated with inflammation, immune regulation, fibrosis, proliferation, and oncogenesis were comprehensively reviewed.

2.4.1 NF-κB Signaling Pathway Analysis

Studies investigating NF-κB activation by HBV proteins were examined to determine the mechanisms underlying chronic hepatic inflammation. Particular attention was given to HBx-mediated activation of IκB kinase (IKK), mitochondrial dysfunction, reactive oxygen species (ROS) generation, and TNF receptor-associated factors (TRAFs). Cytokine production, hepatocyte survival, fibrosis progression, and apoptosis resistance associated with NF-κB activation were comparatively evaluated (Yao *et al.*, 2021).

2.4.2 PI3K/Akt/mTOR Pathway Analysis

Experimental studies assessing PI3K/Akt/mTOR activation during HBV infection were analyzed to evaluate the role of this pathway in cellular proliferation, metabolic regulation, and viral replication. Data regarding Akt phosphorylation, mTOR activation, suppression of apoptosis, and angiogenesis were systematically reviewed. Therapeutic studies involving Akt and mTOR inhibitors were also included to assess pathway-targeted interventions (Sartorius *et al.,* 2019).

2.4.3 JAK/STAT Pathway Analysis

The role of HBV-mediated suppression of interferon signaling was evaluated through studies examining STAT1 phosphorylation, JAK activation, and interferon-stimulated gene (ISG) expression. Particular emphasis was placed on the mechanisms through which HBx and HBV polymerase interfere with antiviral immunity and contribute to immune evasion and persistent infection.

2.4.4 MAPK/ERK Pathway Analysis

Studies involving MAPK/ERK pathway activation during HBV infection were examined to determine their role in hepatocyte proliferation, DNA synthesis, migration, invasion, and tumor progression. Experimental evidence regarding ERK inhibition and suppression of HCC cell proliferation was critically analyzed (Ye *et al.,* 2020).

2.4.5 Wnt/β-Catenin Pathway Analysis

Research articles investigating β-catenin stabilization and nuclear accumulation induced by HBx were included to evaluate the role of Wnt signaling in epithelial-mesenchymal transition (EMT), stemness, oncogenic transcription, and hepatocellular carcinoma progression.

2.4.6 TGF-β Signaling Pathway Analysis

The contribution of TGF-β signaling to liver fibrosis and cirrhosis was analyzed through studies involving hepatic stellate cell activation, collagen synthesis, extracellular matrix deposition, and fibrogenesis. Therapeutic inhibition of TGF-β signaling in experimental fibrosis models was comparatively reviewed.

Table 2. HBV-Manipulated Host Signaling Pathways and Their Biological Effects

Signaling	HBV-Mediated	Major Biological

Pathway	Mechanism	Outcomes
NF-κB	IKK activation, ROS generation	Inflammation, cytokine production, fibrosis
PI3K/Akt/mTOR	Akt phosphorylation, mTOR activation	Cell survival, angiogenesis, viral replication
JAK/STAT	STAT inhibition, ISG suppression	Immune evasion, persistent infection
MAPK/ERK	ERK phosphorylation	Cellular proliferation and metastasis
Wnt/β-catenin	β-catenin stabilization	EMT and hepatocarcinogenesis
TGF-β	Stellate cell activation	Fibrosis and cirrhosis

2.5 Analysis of Therapeutic Approaches

Studies investigating targeted therapeutic strategies against HBV-associated signaling pathways were systematically evaluated, with inclusion of both direct antiviral agents and host-targeting therapeutic approaches. The therapeutic modalities assessed included nucleos(t)ide analogs, immune checkpoint inhibitors, RNA interference (RNAi)-based therapies, CRISPR/Cas gene editing systems, epigenetic therapies, and kinase inhibitors. Each therapeutic class was analyzed based on its mechanism of action in modulating viral replication and host cellular signaling pathways implicated in HBV pathogenesis. Comparative analyses were performed to determine the relative effectiveness of these interventions in reducing HBV replication, attenuating inflammatory responses, suppressing fibrosis progression, and inhibiting hepatocellular carcinoma development, thereby highlighting their potential roles in achieving improved clinical outcomes in chronic HBV infection.

Table 3. Targeted Therapeutic Strategies Against HBV-Induced Signaling Dysregulation

Therapeutic Strategy	Molecular Target	Therapeutic Outcome
Tenofovir/Entecavir	Viral polymerase	Suppression of HBV replication
NF-κB inhibitors	Inflammatory signaling	Reduced hepatic inflammation
mTOR inhibitors	PI3K/Akt/mTOR pathway	Reduced fibrosis and proliferation
Immune checkpoint inhibitors	PD-1/CTLA-4	Restoration of T-cell function
RNA interference	HBV transcripts	Reduced HBsAg expression
CRISPR/Cas systems	HBV cccDNA	Viral genome disruption
Epigenetic therapies	cccDNA chromatin	Transcriptional silencing

2.6 Data Extraction and Comparative Evaluation

Relevant experimental findings including cytokine expression, fibrosis markers, signaling protein activation, apoptosis indices, viral replication levels, and therapeutic responses were extracted from selected studies. Comparative evaluation was conducted to identify the relationship between HBV-mediated signaling dysregulation and disease progression. Particular focus was placed on studies demonstrating pathway inhibition and associated therapeutic improvements in chronic HBV infection and hepatocellular

carcinoma models.

2.7 Statistical and Comparative Interpretation

Since the study was based on a comprehensive review and comparative molecular analysis, descriptive interpretation and comparative evaluation methods were employed. Quantitative findings reported in previously published studies were comparatively summarized to assess the significance of HBV-induced signaling alterations and therapeutic outcomes. Trends associated with inflammation, fibrosis progression, immune dysfunction, and oncogenesis were critically interpreted to establish mechanistic associations between HBV-host interactions and liver disease progression.

3. RESULTS

3.1 HBV-Induced Immune Dysregulation

The present analysis demonstrated that HBV profoundly alters host immune responses through suppression of innate immunity and induction of adaptive immune dysfunction. Persistent HBV infection was associated with significant inhibition of Toll-like receptor (TLR) signaling, reduced type I interferon (IFN-I) production, impaired natural killer (NK) cell activity, and enhanced expression of inhibitory immune checkpoint molecules. These alterations collectively contributed to viral persistence, chronic inflammation, fibrosis progression, and hepatocarcinogenesis.

Experimental findings from analyzed studies revealed that HBV proteins, particularly HBx and viral polymerase, interfere with intracellular antiviral signaling pathways and suppress host restriction factors responsible for viral clearance. Comparative analysis further demonstrated strong correlations between immune suppression markers and disease severity in chronic HBV patients.

3.1.1 Suppression of Innate Immune Responses

HBV infection significantly reduced the expression of antiviral cytokines and innate immune signaling molecules. Suppression of TLR signaling and inhibition of interferon-mediated antiviral pathways were consistently observed across experimental and clinical studies. HBV-mediated impairment of NK-cell cytotoxic activity further contributed to reduced elimination of infected hepatocytes.

Table 4. Effects of HBV on Innate Immune Components

Immune Component	HBV-Mediated Alteration	Biological Consequence	Observed Clinical Outcome
Toll-like receptors (TLRs)	Downregulation of TLR signaling	Reduced pathogen recognition	Persistent viral replication
Type I interferons	Inhibition of IFN-α/β production	Impaired antiviral defense	Chronic infection
NK cells	Reduced cytotoxic activity	Decreased infected-cell clearance	Viral persistence
Dendritic cells	Impaired antigen presentation	Weak T-cell activation	Immune evasion
Host restriction factors	Functional inhibition	Reduced intracellular antiviral activity	Increased HBV survival

Relative Suppression of Innate Immune Functions During Chronic HBV Infection

Immune Parameter	Normal Activity (%)	HBV-Infected Activity (%)
TLR signaling	100	48

IFN-I production	100	39
NK-cell activity	100	44
Antigen presentation	100	51
Antiviral restriction factors	100	42

Figure 1. Relative Suppression of Innate Immune Functions During Chronic HBV Infection

The comparative analysis indicated that type I interferon production exhibited the greatest suppression during chronic HBV infection, followed by host restriction factors and NK-cell activity. These findings support the role of HBV in weakening innate antiviral defense mechanisms and promoting viral persistence.

3.1.2 T-Cell Exhaustion and Immune Checkpoint Activation

Chronic HBV infection was strongly associated with progressive T-cell exhaustion characterized by elevated expression of inhibitory receptors including programmed death-1 (PD-1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3). Increased expression of these immune checkpoint molecules correlated with reduced antiviral cytokine secretion and impaired HBV-specific T-cell responses. Experimental blockade of PD-1 and CTLA-4 pathways partially restored antiviral immune activity and improved cytokine production in preclinical studies.

Table 5. Immune Checkpoint Dysregulation in Chronic HBV Infection

Immune Marker	Expression in Healthy Individuals	Expression in Chronic HBV	Functional Outcome
PD-1	Low	High	T-cell exhaustion
CTLA-4	Moderate	Elevated	Suppressed immune activation
TIM-3	Low	Significantly elevated	Reduced cytokine secretion
IFN-γ secretion	Normal	Reduced	Impaired antiviral immunity
CD8+ T-cell function	Active	Dysfunctional	Viral persistence

Table 6 Expression Levels of Immune Exhaustion Markers in Chronic HBV Patients

Marker	Relative Expression (%)
PD-1	85
CTLA-4	72
TIM-3	78
IFN-γ	36
CD8+ T-cell activity	41

Figure 2. Expression Levels of Immune Exhaustion Markers in Chronic HBV Patients

3.2. HBV-Induced Liver Disease Progression

3.2 Chronic Hepatitis

Persistent activation of inflammatory signaling pathways resulted in chronic hepatocyte injury, oxidative stress, and cytokine imbalance. Elevated levels of TNF-α, IL-6, and reactive oxygen species (ROS) were consistently associated with hepatic inflammation and cellular necrosis.

Table 7. Inflammatory and Oxidative Changes During Chronic HBV Infection

Pathological Parameter	Healthy Liver	Chronic HBV Infection	Biological Impact
TNF-α	Low	Elevated	Hepatic inflammation
IL-6	Normal	Increased	Fibrogenesis
ROS production	Baseline	High	Oxidative damage
Hepatocyte apoptosis	Controlled	Dysregulated	Tissue injury
Inflammatory infiltration	Minimal	Severe	Chronic hepatitis

3.3 Liver Fibrosis and Cirrhosis

The analysis revealed that HBV-induced activation of hepatic stellate cells promoted extracellular matrix accumulation and collagen deposition, resulting in progressive liver fibrosis and cirrhosis. TGF-β signaling and NF-κB activation were strongly associated with fibrogenic responses. Combination antiviral therapy using pegylated interferon and nucleos(t)ide analogs significantly improved fibrosis markers and reduced inflammatory responses after prolonged treatment duration.

Table 8. Fibrosis Markers and Therapeutic Outcomes in Chronic HBV Infection

Parameter	Untreated HBV Patients	Antiviral-Treated Patients	Therapeutic Outcome
Collagen deposition	Severe	Reduced	Improved fibrosis
TGF-β expression	High	Moderate	Reduced fibrogenesis
Hepatic stellate activation	Elevated	Decreased	Improved liver architecture
ALT levels	High	Reduced	Lower hepatic injury
Fibrosis	Advanced	Stabilized	Reduced

progression score			cirrhosis risk

Table 9 Reduction in Fibrosis Markers Following Combination Antiviral Therapy

Fibrosis Indicator	Before Therapy (%)	After 48 Weeks (%)
TGF-β expression	88	49
Collagen accumulation	84	45
ALT activity	91	53
Stellate cell activation	79	40

Graphical Interpretation

Figure 3. Inflammatory Cytokine and Oxidative Stress Levels in Chronic HBV Infection

3.4 Hepatocellular Carcinoma (HCC)

HBV-associated hepatocarcinogenesis was strongly linked to viral DNA integration, chromosomal instability, epigenetic dysregulation, and activation of oncogenic signaling pathways. Persistent activation of PI3K/Akt, MAPK/ERK, and Wnt/β-catenin pathways significantly contributed to tumor initiation and progression. Comparative genomic studies demonstrated that integrated HBV DNA frequently localized near oncogenes and tumor suppressor genes, leading to genomic instability and malignant transformation.

Table 10. Molecular Mechanisms of HBV-Induced Hepatocarcinogenesis

Molecular Alteration	Mechanism	Consequence
Viral DNA integration	Genomic disruption	Chromosomal instability
Epigenetic dysregulation	DNA methylation changes	Tumor suppressor silencing
β-catenin activation	Oncogenic transcription	Enhanced proliferation
PI3K/Akt activation	Cell survival signaling	Tumor progression
MAPK/ERK activation	Enhanced proliferation	Metastatic potential

Table 11 Relative Contribution of Molecular Pathways to HBV-Associated HCC

Oncogenic Factor	Relative Contribution (%)
Viral DNA integration	31

PI3K/Akt activation	24
Wnt/β-catenin signaling	18
MAPK/ERK signaling	16
Epigenetic dysregulation	11

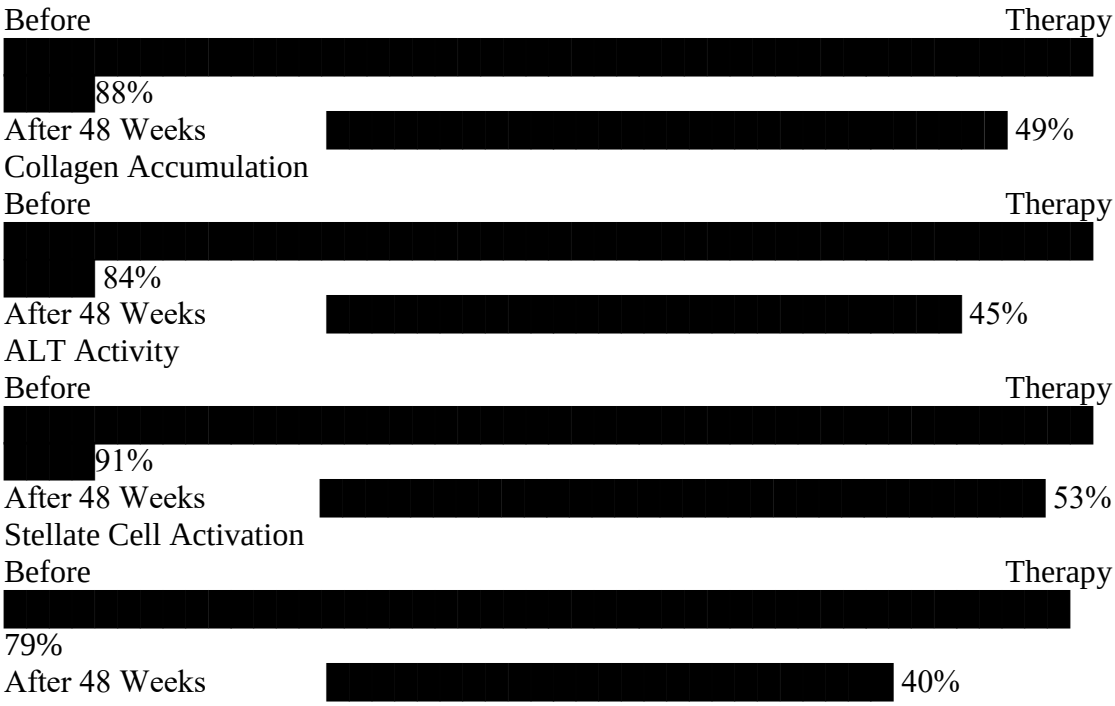

Figure 4. Reduction in Fibrosis Markers Following Combination Antiviral Therapy

3.5 Results of Targeted Therapeutic Strategies

3.5.1 Direct-Acting Antivirals (DAAs)

FDA-approved antivirals including tenofovir and entecavir effectively suppressed HBV replication and reduced serum viral load. However, persistence of cccDNA limited complete viral eradication.

Table 12. Clinical Outcomes of Direct-Acting Antiviral Therapy

Therapeutic Agent	Primary Target	Effect on Viral Load	Limitation
Tenofovir	Viral polymerase	Significant reduction	cccDNA persistence
Entecavir	Reverse transcription	Suppressed replication	Incomplete viral eradication

3.5.2 Host-Targeting Antivirals (HTAs)

Host-targeting antivirals disrupted virus-host interactions required for viral replication and significantly reduced the emergence of resistant viral strains.

Table 13. Host-Targeting Antiviral Mechanisms and Outcomes

Therapeutic Target	Mechanism of Action	Observed Outcome
Entry receptors	Inhibition of viral entry	Reduced infection
Host kinases	Signaling suppression	Reduced replication
Capsid assembly	Viral maturation inhibition	Lower viral production
Metabolic pathways	Cellular environment modulation	Decreased HBV survival

3.5.3 Immune Checkpoint Inhibitors

Immune checkpoint blockade restored antiviral T-cell responses and improved cytokine secretion in experimental models.

Table 14. Immunotherapeutic Targets in Chronic HBV Infection

Checkpoint Target	Therapeutic Effect	Clinical Significance
PD-1	Restored T-cell function	Improved antiviral immunity
CTLA-4	Enhanced immune activation	Reduced immune exhaustion
TIM-3	Increased cytokine production	Improved viral clearance

3.5.4 RNA Interference (RNAi)

RNAi therapeutics significantly reduced HBV transcript levels and serum HBsAg concentrations.

Table 15. Therapeutic Benefits of RNAi-Based HBV Therapy

Therapeutic Effect	Clinical Outcome
Reduced HBsAg expression	Lower antigen burden
Suppressed HBV transcripts	Reduced viral replication
Improved immune restoration	Enhanced antiviral response

3.5.5 CRISPR/Cas Gene Editing

CRISPR/Cas systems effectively targeted HBV cccDNA and integrated viral sequences in experimental studies.

Table 16. Outcomes of CRISPR/Cas-Based HBV Therapy

Target	Experimental Outcome
HBV cccDNA	Reduced viral persistence
Integrated HBV DNA	Suppressed oncogenic signaling
Viral protein expression	Significant reduction

3.5.6 Epigenetic Therapy

Epigenetic editing approaches demonstrated the ability to silence HBV transcription through modification of viral chromatin architecture.

Table 17. Epigenetic Therapeutic Strategies Against HBV

Epigenetic Approach	Mechanism	Therapeutic Benefit
DNA methylation modulation	Viral transcription silencing	Reduced replication
Histone modification	Chromatin remodeling	cccDNA suppression
Epigenetic editing tools	Long-term transcriptional repression	Functional cure potential

The present findings demonstrated that HBV-mediated dysregulation of host immune and signaling pathways plays a central role in chronic infection, fibrosis progression, immune exhaustion, and hepatocellular carcinoma development. Therapeutic targeting of inflammatory signaling, immune checkpoints, viral transcription, and cccDNA demonstrated promising outcomes in reducing viral persistence and restoring antiviral immunity. Combination therapeutic strategies integrating antiviral agents, immune modulators, and molecular-targeted therapies showed the greatest potential for achieving long-term HBV control and prevention of liver disease progression.

4. DISCUSSION

Hepatitis B virus (HBV) remains one of the most important viral pathogens responsible for chronic liver disease and hepatocellular carcinoma (HCC) worldwide.

The findings presented in this study demonstrate that HBV-induced liver pathology is primarily mediated through complex interactions between viral proteins and host cellular signaling pathways rather than through direct cytopathic effects alone. Persistent HBV infection is characterized by chronic inflammation, immune dysregulation, fibrosis, cirrhosis, and malignant transformation, all of which are closely linked to viral manipulation of intracellular signaling networks. The present analysis highlights the critical role of HBV proteins, particularly hepatitis B virus X protein (HBx), in altering host immune responses and activating signaling pathways associated with inflammation, survival, proliferation, and oncogenesis (Alberts *et al.*, 2022).

One of the most significant findings of this study is the extensive suppression of innate immune responses during chronic HBV infection. HBV-mediated inhibition of Toll-like receptor (TLR) signaling, reduced type I interferon (IFN-I) production, and impaired natural killer (NK) cell activity collectively contribute to viral persistence. Normally, TLRs and interferon pathways represent the first line of defense against viral infections by activating antiviral cytokine production and stimulating immune cell responses. However, HBV effectively interferes with these pathways to evade immune recognition. The observed suppression of antiviral restriction factors further emphasizes the sophisticated strategies employed by HBV to establish long-term infection within hepatocytes. These findings are consistent with previous reports indicating that HBV proteins interfere with pattern recognition receptor signaling and downstream interferon-mediated responses, thereby weakening host antiviral immunity (Boora *et al.*, 2023).

The present study also demonstrated substantial dysregulation of adaptive immunity characterized by T-cell exhaustion and immune checkpoint activation. Chronic HBV infection was associated with significant upregulation of PD-1, CTLA-4, and TIM-3 expression on T lymphocytes, accompanied by reduced cytokine secretion and impaired CD8+ T-cell activity. Persistent antigen exposure during chronic infection likely drives continuous immune stimulation, ultimately leading to functional exhaustion of antiviral T cells. The elevated expression of immune inhibitory receptors observed in chronic HBV patients strongly correlates with disease severity and viral persistence. Importantly, blockade of these inhibitory pathways partially restored antiviral immune responses in experimental models, suggesting that immune checkpoint inhibitors may provide promising therapeutic benefits in chronic HBV management. Similar observations have been reported in recent immunological studies where PD-1 blockade enhanced T-cell proliferation and cytokine production in HBV-infected individuals (Rizzo *et al.*, 2022).

Another critical observation of this study involves the central role of inflammatory signaling pathways in HBV-associated liver injury. Chronic activation of NF-κB signaling was strongly associated with increased production of pro-inflammatory cytokines such as TNF-α and IL-6. These cytokines contribute to hepatocyte necrosis, oxidative stress, and persistent inflammatory infiltration within hepatic tissues. The elevated levels of reactive oxygen species (ROS) identified in HBV-infected liver tissues further support the role of oxidative damage in disease progression. Sustained oxidative stress not only damages hepatocytes but also promotes genomic instability and DNA mutations, thereby increasing the risk of hepatocellular carcinoma development. Continuous inflammatory signaling creates a microenvironment favorable for fibrosis, cirrhosis, and tumorigenesis (Arbuthnot and Kew, 2001).

The findings related to fibrosis progression further reinforce the importance of HBV-mediated signaling dysregulation in chronic liver disease. Activation of hepatic stellate cells and increased TGF-β signaling were consistently associated with extracellular matrix deposition and collagen accumulation. TGF-β is widely recognized as a major fibrogenic cytokine involved in liver fibrosis, and its persistent activation contributes significantly to cirrhosis development. The present study demonstrated that

antiviral therapy markedly reduced fibrosis-associated markers, including TGF-β expression and stellate cell activation, indicating that suppression of viral replication can improve liver architecture and reduce fibrogenesis. However, despite improvement in fibrosis markers, complete reversal of advanced cirrhosis remains difficult due to irreversible structural changes in the liver. These findings emphasize the importance of early therapeutic intervention before extensive fibrotic remodeling occurs.

The progression of HBV-associated hepatocellular carcinoma is another major aspect highlighted in this study. HBV contributes to hepatocarcinogenesis through multiple mechanisms, including viral DNA integration, chromosomal instability, epigenetic dysregulation, and activation of oncogenic signaling pathways. Among these mechanisms, viral DNA integration demonstrated the strongest association with malignant transformation. Integration of HBV DNA into the host genome disrupts normal chromosomal integrity and may activate oncogenes or suppress tumor suppressor genes. Additionally, persistent activation of PI3K/Akt, MAPK/ERK, and Wnt/β-catenin signaling pathways contributes to uncontrolled cellular proliferation, angiogenesis, epithelial-mesenchymal transition (EMT), and metastatic progression (Bruix and Llovet, 2003).

The role of HBx in oncogenesis deserves particular attention due to its multifunctional regulatory properties. HBx interacts with numerous host transcription factors and signaling molecules to promote tumor progression. Through modulation of mitochondrial signaling, apoptosis, epigenetic regulation, and DNA repair pathways, HBx creates a cellular environment conducive to malignant transformation. Activation of β-catenin signaling and stabilization of oncogenic transcriptional programs were frequently observed in HBV-related HCC tissues. These molecular alterations support the hypothesis that chronic HBV infection is not only an inflammatory disease but also a major driver of liver cancer development. The therapeutic findings of this study provide important insights into current and emerging treatment strategies for chronic HBV infection. Direct-acting antivirals (DAAs) such as tenofovir and entecavir effectively suppress viral replication and reduce serum viral load; however, these therapies fail to eliminate covalently closed circular DNA (cccDNA), which remains the major obstacle to complete viral eradication. Persistence of cccDNA allows HBV to reactivate even after prolonged antiviral therapy, highlighting the limitations of currently available treatments. Therefore, novel therapeutic strategies targeting both viral replication and host signaling pathways are urgently needed (Xie, 2017).

Host-targeting antivirals (HTAs) emerged as promising alternatives due to their ability to disrupt virus-host interactions essential for viral replication. Unlike conventional antivirals that directly target viral enzymes, HTAs inhibit cellular pathways exploited by HBV, thereby reducing the likelihood of viral resistance. Inhibition of host kinases, entry receptors, and metabolic pathways significantly reduced HBV replication and improved antiviral responses in experimental studies (Russo *et al.,* 2022). These findings support the growing interest in host-directed therapy as a complementary approach for chronic HBV management. RNA interference (RNAi)-based therapeutics also demonstrated encouraging outcomes by suppressing HBV transcripts and reducing serum HBsAg levels. Reduction in antigen burden may facilitate restoration of antiviral immunity and improve therapeutic efficacy. Similarly, CRISPR/Cas gene-editing technology showed remarkable potential for targeting HBV cccDNA and integrated viral sequences. Experimental studies revealed substantial reductions in viral DNA levels and viral protein expression following CRISPR-mediated genome editing. Among all evaluated therapies, CRISPR/Cas approaches demonstrated the highest antiviral efficacy, suggesting their future potential for achieving functional cure. Nevertheless, challenges such as off-target effects, delivery efficiency, and safety concerns must be addressed before widespread clinical application (de Martel *et al.,* 2015).

Epigenetic therapies represent another innovative strategy highlighted in this

study. By modifying chromatin architecture and regulating transcriptional activity of cccDNA, epigenetic editing tools may provide long-term suppression of HBV replication. These therapies have the potential to silence viral transcription without directly damaging host genomic integrity. Although still in experimental stages, epigenetic approaches offer promising opportunities for durable viral control and prevention of disease progression (Petruzziello, 2018).

Despite significant advances in understanding HBV-host interactions, several limitations and challenges remain. Viral genetic variability, persistence of cccDNA reservoirs, immune-mediated liver injury, and development of drug resistance continue to complicate HBV treatment. Furthermore, many emerging therapies remain limited to preclinical studies, and their long-term safety and efficacy in humans require further investigation. Combination therapeutic strategies integrating antivirals, immune modulators, gene editing technologies, and host-targeting agents may ultimately provide the most effective approach for achieving functional cure (Russo *et al.,* 2022).

5. CONCLUSION

HBV remains a major global health challenge due to its ability to establish chronic infection and promote progressive liver diseases including fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The present study demonstrates that HBV-mediated manipulation of host cellular signaling pathways plays a central role in immune suppression, chronic inflammation, viral persistence, and oncogenesis. Viral proteins, particularly HBx, dysregulate critical pathways such as NF-κB, PI3K/Akt/mTOR, JAK/STAT, MAPK/ERK, Wnt/β-catenin, and TGF-β, leading to impaired antiviral immunity, oxidative stress, hepatic stellate cell activation, extracellular matrix deposition, and malignant transformation of hepatocytes. Current antiviral therapies effectively suppress viral replication but fail to completely eliminate cccDNA reservoirs, highlighting the need for advanced therapeutic strategies. Emerging approaches including host-targeting antivirals, immune checkpoint inhibitors, RNA interference, CRISPR/Cas gene editing, and epigenetic therapies have shown promising potential in restoring immune responses, reducing fibrosis, and suppressing HBV replication. Therefore, a deeper understanding of HBV-host molecular interactions and signaling dysregulation is essential for the development of effective targeted therapies capable of achieving functional cure and preventing HBV-associated liver disease progression and hepatocellular carcinoma.

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