Review

Molecular Insights into Hepatitis Virus-Induced Hepatocarcinogenesis

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Abstract

Cancer is a multifactorial disease influenced by genetic, epigenetic, and environmental determinants, including biological agents such as oncogenic viruses. Among these, hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) play pivotal roles in the pathogenesis of hepatocellular carcinoma (HCC)—the predominant form of primary liver cancer and a major contributor to global cancer mortality. Chronic infection with these hepatotropic viruses drives hepatocarcinogenesis through both direct mechanisms, including viral genome integration and oncoprotein expression, and indirect pathways involving persistent inflammation, immune evasion, and oxidative stress. Despite substantial advances in HBV vaccination programs and the development of curative therapies for HCV, the global burden of hepatitis-related liver cancer remains high, driven by underdiagnosis, limited access to care, and the absence of a functional cure for HBV. This review critically examines the molecular and pathogenic mechanisms by which HBV, HCV, and HDV contribute to cancer initiation and progression, and summarizes current therapeutic and preventive strategies. It further highlights emerging research directions and translational challenges that must be addressed to improve prevention, early detection, and treatment of virus-induced hepatocellular carcinoma.

Keywords: carcinogenesis; hepatitis virus; carcinogen; inflammation; metabolic reprogramming

1. Introduction

Cancer represents a heterogeneous group of diseases characterized by uncontrolled cell proliferation, evasion of apoptosis, angiogenesis, and potential to metastasize to distant organs. The process of carcinogenesis is complex and multistep, involving genetic mutations, epigenetic alterations, deregulated cellular signaling, chronic inflammation, and immune evasion. These changes are often triggered or exacerbated by exposure to carcinogens, which can be classified into chemical, physical, and biological agents.

While chemical carcinogens such as tobacco smoke, aflatoxins, and industrial pollutants have historically received the most attention, biological agents have emerged as critical contributors to the global cancer burden. According to the International Agency for Research on Cancer (IARC), approximately 13% of all global cancer cases are attributable to infectious agents, with viruses accounting for the majority of these cases [1,2].

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Among the most important oncogenic viruses are hepatitis B virus (HBV) and hepatitis C virus (HCV), both of which are strongly associated with the development of hepatocellular carcinoma (HCC)—the most prevalent primary liver cancer and a leading cause of cancer-related mortality worldwide. In 2020 alone, liver cancer caused over 830,000 deaths globally, ranking as the third most common cause of cancer death [3]. Chronic infection with HBV or HCV can lead to long-term liver damage, cirrhosis, and, ultimately, malignant transformation of hepatocytes.

Hepatitis B virus (HBV), a DNA virus from the *Hepadnaviridae* family, and hepatitis C virus (HCV), an RNA virus from the *Flaviviridae* family, employ distinct replication strategies and induce liver damage through both direct oncogenic mechanisms (such as viral genome integration and oncoprotein expression) and indirect mechanisms (such as chronic inflammation and oxidative stress) [4,5]. A third agent, hepatitis D virus (HDV), acts as a satellite virus of HBV and has also been linked to an increased risk of liver cancer in co-infected individuals [6].

Despite the availability of effective vaccines for HBV and curative therapies for HCV, millions remain chronically infected worldwide. Barriers such as limited access to healthcare, asymptomatic disease progression, and social stigma contribute to underdiagnosis and undertreatment, especially in low- and middle-income countries [7]. Moreover, the development of antiviral resistance, lack of a functional cure for HBV, and the limited efficacy of therapies in preventing HCC in high-risk individuals underscore the need for further research.

This review aims to critically examine the role of hepatitis viruses—primarily HBV, HCV, and HDV—in the initiation and progression of liver cancer. The discussion will cover the molecular biology of these viruses, mechanisms of carcinogenesis, therapeutic strategies, current research trends, and future directions in prevention and treatment. Understanding these complex interactions is vital for designing effective public health interventions and targeted therapies.

2. Types of Carcinogens with a Focus on Biological Agents

Carcinogens are agents capable of inducing cancer by altering the genetic and epigenetic landscape of cells, leading to uncontrolled proliferation, avoidance of apoptosis, and malignant transformation. The International Agency for Research on Cancer (IARC) classifies carcinogens into five groups based on the strength of evidence supporting their carcinogenicity, with Group 1 including agents that are definitively carcinogenic to humans [8]. Carcinogens are broadly classified into three major categories:

2.1. Chemical Carcinogens

These include a wide array of substances found in the environment, industrial settings, or diet. Prominent examples are polycyclic aromatic hydrocarbons (PAHs) from tobacco smoke and grilled meats, aflatoxins—particularly aflatoxin B1—produced by *Aspergillus flavus* in improperly stored food, and various industrial chemicals such as benzene, arsenic, and vinyl chloride. Chemical carcinogens often induce cancer by forming DNA adducts, generating reactive oxygen species (ROS), and causing mutations in oncogenes or tumor suppressor genes [9].

2.2. Physical Carcinogens

Physical carcinogens include agents that cause cancer through direct physical interaction with cellular components or by inducing chronic damage. Ultraviolet (UV) radiation is a well-known example, capable of inducing DNA damage that can lead to skin cancers. Ionizing radiation, such as X-rays and gamma rays, is associated with an increased risk of various malignancies, including leukemia and thyroid cancers. Additionally, chronic tissue irritation and inflammation—often resulting from repeated physical injury—can contribute to neoplastic transformation over time by promoting a pro-tumorigenic microenvironment.

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2.3. Biological Carcinogens

Biological agents—including viruses, bacteria, and parasites—contribute substantially to the global cancer burden. It is estimated that around 13–15% of all human cancers are attributable to infections, with viruses being the predominant contributors [1,2].

2.3.1. Oncogenic Viruses

Seven human viruses have been classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens, reflecting their well-established role in human oncogenesis [8,10]. These include hepatitis B virus (HBV) and hepatitis C virus (HCV), both of which are strongly associated with hepatocellular carcinoma (HCC); human papillomavirus (HPV), linked to cervical and oropharyngeal cancers; Epstein–Barr virus (EBV), which contributes to nasopharyngeal carcinoma and various lymphomas; human T-cell leukemia virus type 1 (HTLV-1), known to cause adult T-cell leukemia/lymphoma; Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8), implicated in Kaposi's sarcoma and primary effusion lymphoma; and Merkel cell polyomavirus (MCPyV), which is associated with Merkel cell carcinoma.

These oncogenic viruses contribute to cancer development through a variety of molecular mechanisms. Insertional mutagenesis, particularly observed in hepatitis B virus (HBV) infection, can lead to the activation of oncogenes or inactivation of tumor suppressor genes. Many viruses also express viral oncoproteins—such as HBx (HBV), NS5A (HCV), and E6/E7 (HPV)—which interfere with key regulatory pathways controlling the cell cycle, apoptosis, and DNA repair. In addition, persistent viral infection facilitates immune evasion, leading to chronic inflammation, oxidative stress, and sustained DNA damage. Epigenetic alterations, including changes in DNA methylation, histone modification, and dysregulation of non-coding RNAs, further contribute to the malignant transformation of host cells [10,11].

2.3.2. Oncogenic Bacteria and Parasites

In addition to viruses, several non-viral infectious agents have been classified as biological carcinogens. *Helicobacter pylori* is a well-established example, known to induce chronic gastritis and strongly associated with the development of gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. *Schistosoma haematobium*, a parasitic blood fluke, has been linked to squamous cell carcinoma of the urinary bladder, particularly in endemic regions. Furthermore, liver flukes such as *Opisthorchis viverrini* and *Clonorchis sinensis* are associated with cholangiocarcinoma, especially in parts of Southeast Asia where raw freshwater fish consumption is common [12].

2.3.3. Hepatitis Viruses as Major Biological Carcinogens

Among all known oncogenic viruses, HBV and HCV are among the most impactful globally, together accounting for over 80% of hepatocellular carcinoma (HCC) cases [13]. Chronic infection with these viruses leads to liver inflammation, fibrosis, and cirrhosis, creating a microenvironment conducive to malignant transformation. Unlike many other cancer-causing agents, hepatitis viruses are preventable and, in some cases, curable, making them ideal targets for public health intervention.

3. Hepatitis Viruses: Types, Families, Structure, and Replication

Viral hepatitis is a major global health concern, involving inflammation of the liver caused by several distinct viruses. Among them, hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) are the most strongly associated with chronic liver disease and hepatocellular carcinoma (HCC). Though hepatitis A (HAV) and hepatitis E (HEV) viruses also cause hepatitis, they are typically limited to acute, self-limiting infections and show limited oncogenic potential [14].

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3.1. Overview of Hepatitis Viruses

Virus	Genome Type	Family	Envelope	Oncogenic Potential
HBV	DNA (partially ds)	*Hepadnaviridae*	Yes	High
HCV	RNA (+ssRNA)	*Flaviviridae*	Yes	High
HDV	RNA (circular, ss)	*Unassigned* (Satellite)	Yes (requires HBV)	Moderate
HAV	RNA (+ssRNA)	*Picornaviridae*	No	None
HEV	RNA (+ssRNA)	*Hepeviridae*	No	Low (possible in chronic immunosuppression)

3.2. Hepatitis B Virus (HBV)

Hepatitis B virus (HBV) belongs to the family *Hepadnaviridae* and the genus *Orthohepadnavirus*. It possesses a partially double-stranded, relaxed circular DNA genome of approximately 3.2 kilobases in length. The virus is enveloped and characterized by the presence of surface antigens (HBsAg) on its outer coat. HBV encodes several key proteins, including the surface (HBs) and core (HBc) antigens, the e-antigen (HBe), the viral polymerase, and the HBx protein—a multifunctional regulatory protein with a critical role in viral replication and oncogenesis. HBV is transmitted through perinatal routes, sexual contact, and exposure to infected blood, making it a significant global health concern, particularly in regions with limited access to vaccination and screening.

Replication Cycle

The replication cycle of hepatitis B virus (HBV) begins with viral entry into hepatocytes via the sodium taurocholate co-transporting polypeptide (NTCP) receptor. After entry, the viral capsid is uncoated, and the relaxed circular DNA is transported to the nucleus, where it is repaired into covalently closed circular DNA (cccDNA), serving as a stable transcriptional template. The virus then transcribes pregenomic and subgenomic RNAs from the cccDNA. The pregenomic RNA is subsequently reverse-transcribed by the viral polymerase into new DNA genomes. Newly formed nucleocapsids either assemble into complete virions for release from the cell or recycle back to the nucleus to replenish the cccDNA pool, thus maintaining persistent infection. HBV uniquely integrates parts of its genome into host DNA, a key contributor to carcinogenesis [15].

3.3. Hepatitis C Virus (HCV)

Hepatitis C virus (HCV) is classified within the family *Flaviviridae* and the genus *Hepacivirus*. It possesses a linear, positive-sense single-stranded RNA genome approximately 9.6 kilobases in length. The virus is enveloped and displays surface glycoproteins E1 and E2, which play key roles in viral entry and immune evasion. HCV encodes several essential proteins, including structural proteins—core, E1, and E2—and a series of non-structural proteins such as NS2, NS3, NS4A/B, NS5A, and NS5B that are involved in viral replication and assembly. Transmission primarily occurs through bloodborne routes, notably via intravenous drug use and contaminated blood transfusions.

Replication Cycle

The replication cycle of hepatitis C virus (HCV) begins with viral entry into hepatocytes through receptor-mediated endocytosis, involving receptors such as CD81, scavenger receptor class B type 1 (SR-B1), and claudins. Once inside the cell, the viral RNA is translated into a single polyprotein, which is subsequently cleaved by viral and host proteases into individual structural and non-structural proteins. Viral replication occurs on specialized membranous web structures derived from the endoplasmic reticulum, where the viral RNA genome is replicated. Newly assembled virions are then released from the cell through a pathway resembling very-low-density lipoprotein (VLDL) secretion, facilitating viral spread and persistence. Unlike HBV, HCV does not integrate into host

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DNA, but chronic infection induces persistent inflammation, oxidative stress, and metabolic reprogramming, contributing to HCC [16].

3.4. Hepatitis D Virus (HDV)

Hepatitis D virus (HDV) is a unique defective RNA virus that depends on hepatitis B virus (HBV) for its replication and requires HBV surface antigen (HBsAg) for virion assembly. Its genome consists of a circular, single-stranded RNA approximately 1.7 kilobases in length, which possesses intrinsic ribozyme activity crucial for viral replication. HDV encodes two key proteins—the small and large delta antigens—that are essential for RNA replication and viral packaging. Transmission of HDV occurs exclusively through co-infection or superinfection with HBV, making HBV infection a prerequisite for HDV propagation. HDV co-infection dramatically worsens liver disease and increases HCC risk, often accelerating fibrosis and cirrhosis [17].

3.5. Other Hepatitis Viruses (HAV, HEV)

HAV and HEV are primarily associated with acute hepatitis. While generally self-limiting, HEV can persist in immunocompromised individuals (e.g., transplant recipients), and limited evidence suggests it may contribute to liver fibrosis or even cancer under certain conditions [18].

3.6. Geographic Distribution and Burden

Hepatitis B virus (HBV) is highly endemic in regions such as East Asia, Sub-Saharan Africa, and the Pacific Islands, with approximately 296 million people living with chronic infection as of 2021 [7]. Hepatitis C virus (HCV) shows a higher prevalence in countries like Egypt, Central Asia, and Eastern Europe, where an estimated 58 million individuals are chronically infected [7]. Hepatitis D virus (HDV) affects about 5% of those infected with HBV and has notable hotspots in Mongolia, Central Africa, and Eastern Europe [17], contributing to an additional layer of complexity in managing viral hepatitis and its associated disease burden globally.

4. Role of Hepatitis Viruses in Carcinogenesis: Mechanisms and Evidence

Hepatitis B (HBV) and C (HCV) viruses are among the most potent viral carcinogens, primarily driving the development of hepatocellular carcinoma (HCC), which constitutes approximately 80% of primary liver cancers worldwide [13]. The process of viral oncogenesis is multifactorial, involving both direct and indirect mechanisms that promote malignant transformation of hepatocytes.

The complex interplay between hepatitis viral factors and host cell signaling pathways is critical to hepatocarcinogenesis. Table 5 outlines the key molecular pathways altered by hepatitis viruses and their oncogenic consequences.

Table 5. Key Molecular Pathways Altered by Hepatitis Viruses in Hepatocarcinogenesis.

Pathway	Virus	Alteration	Consequence	Reference
p53 Tumor Suppressor	HBV	HBx protein binds and inhibits p53	Reduced apoptosis and DNA repair, increased mutation accumulation	[31,32]
Wnt/β-catenin	HBV, HCV	Activation via HBV DNA integration or viral proteins	Enhanced proliferation, tumor invasion, metastasis	[33,34]
JAK/STAT	HCV	Chronic inflammation induces JAK/STAT activation	Promotes cell survival, immune evasion, and inflammation	[35]
PI3K/Akt	HBV	HBx activates PI3K/Akt signaling	Promotes cell survival, growth, and angiogenesis	[36]

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4.1. Direct Oncogenic Mechanisms

4.1.1. HBV Integration and Genomic Instability

A hallmark of HBV-related carcinogenesis is the integration of HBV DNA into the genome of host hepatocytes. While integration is not required for viral replication, it is observed in up to 85% of HBV-associated hepatocellular carcinomas (HCC) [19]. This viral DNA integration can contribute to cancer development through several mechanisms, including insertional mutagenesis that disrupts tumor suppressor genes or activates oncogenes, and chromosomal instability caused by double-strand DNA breaks. Additionally, the persistent expression of viral proteins, particularly HBx, plays a critical oncogenic role by modulating transcription factors and cell cycle regulators, inhibiting the tumor suppressor activity of p53, interfering with DNA repair processes, and altering pathways involved in apoptosis and autophagy [20,21].

4.1.2. HCV Proteins and Oncogenic Signaling

Unlike HBV, hepatitis C virus (HCV) does not integrate into the host genome but contributes to carcinogenesis primarily through the actions of its viral proteins, notably the core protein, NS3, and NS5A. These proteins disrupt normal cellular processes by dysregulating cell proliferation and apoptosis, activating oncogenic signaling pathways such as Wnt/β-catenin, MAPK, and NF-κB. Additionally, they promote oxidative stress and mitochondrial dysfunction, which further damages hepatocytes. HCV proteins also interfere with the host immune response, facilitating chronic inflammation and enabling immune evasion, thereby creating a microenvironment conducive to malignant transformation [22,23].

4.2. Indirect Oncogenic Mechanisms

4.2.1. Chronic Inflammation and Fibrosis

Both hepatitis B virus (HBV) and hepatitis C virus (HCV) establish persistent infections that lead to chronic liver inflammation, a key driver of hepatocarcinogenesis. This chronic inflammation results in the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), as well as the generation of reactive oxygen and nitrogen species (ROS and RNS) that induce DNA damage. In response, hepatic stellate cells become activated, leading to the deposition of extracellular matrix proteins and the development of fibrosis and cirrhosis. This fibrotic environment fosters a tumor-promoting microenvironment marked by immunosuppression and increased angiogenesis [24,25]. Importantly, cirrhosis itself is a strong independent risk factor for hepatocellular carcinoma development, irrespective of ongoing viral infection.

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4.2.2. Immune Evasion and T-Cell Exhaustion

Hepatitis B virus (HBV) and hepatitis C virus (HCV) evade host immune defenses through mu These oncogenic viruses contribute to cancer development through a variety of molecular mechanisms. Insertional mutagenesis, particularly observed in hepatitis B virus (HBV) infection, can lead to the activation of oncogenes or inactivation of tumor suppressor genes. Many viruses also express viral oncoproteins—such as HBx (HBV), NS5A (HCV), and E6/E7 (HPV)—which interfere with key regulatory pathways controlling the cell cycle, apoptosis, and DNA repair. In addition, persistent viral infection facilitates immune evasion, leading to chronic inflammation, oxidative stress, and sustained DNA damage. Epigenetic alterations, including changes in DNA methylation, histone modification, and dysregulation of non-coding RNAs, further contribute to the malignant transformation of host cells [10,11].ltiple sophisticated mechanisms. They downregulate major histocompatibility complex (MHC) class I molecules, impairing antigen presentation to cytotoxic T cells. Both viruses induce T-cell exhaustion, which results in reduced cytotoxic function and ineffective viral clearance. Additionally, they modulate regulatory T cells and promote the secretion of immunosuppressive cytokines, contributing to immune tolerance. These strategies collectively help establish an immunosuppressive tumor microenvironment that supports viral persistence and favors oncogenesis [26].

4.3. Hepatitis D Virus (HDV) and Hepatocarcinogenesis

Co-infection with hepatitis D virus (HDV) in individuals already infected with hepatitis B virus (HBV) leads to an accelerated progression of liver disease. Although the underlying mechanisms remain incompletely understood, HDV infection is associated with increased hepatic inflammation and fibrosis, which contribute to liver damage. Moreover, patients co-infected with HDV face a higher risk of developing hepatocellular carcinoma compared to those with HBV mono-infection. It is also suggested that HBV and HDV proteins may exert synergistic effects that promote hepatocyte transformation and tumorigenesis [27]. “The multifactorial nature of hepatitis virus-induced carcinogenesis can be categorized into several key mechanisms, as outlined in Table 2, highlighting the viruses involved and their specific molecular and cellular effects.

Table 2. Mechanisms of Hepatitis Virus-Induced Carcinogenesis.

Mechanism	Virus Involved	Description	Key Viral/Host Factors	References
Chronic Inflammation & Fibrosis	HBV, HCV, HDV	Persistent infection causes immune-mediated liver damage, cycles of hepatocyte death and regeneration leading to fibrosis and cirrhosis, setting the stage for HCC	Cytokines (TNF-α, IL-6), ROS, activated stellate cells	[9,10]
Viral DNA Integration	HBV	Integration of HBV DNA into host genome causes genomic instability, insertional mutagenesis, and altered gene expression	HBV DNA, host oncogenes, tumor suppressors	[11,12]
Viral Protein Effects	HBV, HCV	HBx protein modulates transcription, inhibits apoptosis, and interferes with DNA repair; HCV NS5A affects signaling pathways and metabolic reprogramming	HBx, NS5A, core proteins	[13,14]
Epigenetic Modifications	HBV, HCV	Alterations in DNA methylation, microRNA	Host epigenome, viral proteins	[15,16]

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	dysregulation, histone modifications, contributing to gene expression changes favoring oncogenesis

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4.4. Evidence from Epidemiological and Experimental Studies

Epidemiological data firmly establish hepatitis B virus (HBV) and hepatitis C virus (HCV) as major risk factors for hepatocellular carcinoma (HCC), with relative risks varying from 10- to 100-fold depending on factors such as viral load, genotype, and co-exposures like alcohol consumption or aflatoxin exposure [28]. Experimental models, including transgenic mice engineered to express HBx or HCV proteins, develop liver tumors, providing strong evidence of the viruses' oncogenic potential [29]. Furthermore, successful antiviral therapies that effectively reduce viral load have been correlated with a decreased incidence of HCC, underscoring the direct causal relationship between chronic viral infection and liver cancer development [30]. Epidemiological studies reveal significant geographic variation in hepatitis virus prevalence and the corresponding burden of hepatocellular carcinoma (HCC), as summarized in Table 3.

Table 3. Global Epidemiology and Liver Cancer Burden Attributable to Hepatitis Viruses.

Region	HBV Prevalence (%)	HCV Prevalence (%)	HDV Co-infection Rate (%)	Estimated % HCC Cases Attributable to HBV/HCV/HDV	Reference
Sub-Saharan Africa	6-10%	1-3%	Up to 10% among HBV patients	60-80%	[17,18]
East Asia	8-12%	1-2%	5%	70-80%	[19,20]
Europe	<1%	1-5%	<1%	30-40%	[21]
North America	<1%	1-2%	Rare	20-30%	[22]

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5. Prevention, Treatment, and Therapeutics

Given the significant global burden of hepatocellular carcinoma (HCC) attributable to chronic hepatitis virus infections, strategies for prevention and treatment are vital components of cancer control.

5.1. Prevention

5.1.1. Vaccination

The hepatitis B vaccine remains the most effective preventive measure against HBV infection and the subsequent development of hepatocellular carcinoma (HCC). Since its global introduction in the 1980s, universal infant vaccination programs have significantly reduced HBV prevalence and childhood liver cancer incidence in endemic regions [31]. This recombinant subunit vaccine targets the hepatitis B surface antigen (HBsAg) and demonstrates over 95% efficacy in preventing infection. In contrast, no vaccine currently exists for hepatitis C virus (HCV), largely due to its high genetic variability and sophisticated immune evasion strategies, although ongoing research aims to develop effective prophylactic vaccines [32]. For hepatitis D virus (HDV), prevention is indirectly achieved through HBV vaccination, as HDV replication depends on co-infection with HBV [17].

5.1.2. Public Health Measures

Effective public health measures are critical in reducing the transmission of hepatitis viruses. Screening of blood products has significantly decreased transfusion-transmitted infections. Harm reduction strategies, such as needle exchange programs, are essential for preventing virus spread among intravenous drug users. Promoting safe sexual practices and providing antiviral prophylaxis during pregnancy help prevent vertical transmission of HBV and HCV. Additionally, improving sanitation and water quality plays a vital role in reducing the spread of hepatitis A and E viruses.

5.2. Treatment of Chronic Hepatitis Virus Infection

Effective treatment of chronic HBV and HCV infections reduces progression to cirrhosis and HCC.

5.2.1. Hepatitis B Treatment

Treatment of hepatitis B primarily involves nucleos(t)ide analogues (NAs) such as entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), which suppress viral replication by inhibiting the HBV polymerase enzyme. Long-term therapy with these agents effectively reduces HBV DNA levels, improves liver histology, and lowers the risk of hepatocellular carcinoma (HCC). However, NAs do not eliminate the covalently closed circular DNA (cccDNA) reservoir within hepatocytes, which poses challenges for complete viral eradication [33]. Interferon-alpha (IFN-α) offers an alternative treatment option with immunomodulatory properties capable of

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inducing sustained viral suppression in some patients, though its use is limited by side effects and lower overall efficacy.

5.2.2. Hepatitis C Treatment

Direct-acting antivirals (DAAs) have revolutionized hepatitis C virus (HCV) therapy, achieving sustained virologic response (SVR) rates exceeding 95%. These antiviral agents target key viral proteins and include NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. Achieving SVR not only effectively clears the virus but also significantly reduces the risk of hepatocellular carcinoma (HCC). However, ongoing surveillance for liver cancer remains essential, particularly in patients with pre-existing cirrhosis [34].

5.3. Treatment of Hepatocellular Carcinoma

Early diagnosis of hepatocellular carcinoma (HCC) in patients with chronic hepatitis significantly improves prognosis. Curative treatment options for early-stage HCC include surgical resection and liver transplantation. For patients who are not candidates for surgery, locoregional therapies such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) offer effective alternatives. Systemic therapies have advanced with the development of multikinase inhibitors like sorafenib and lenvatinib, which target angiogenesis and tumor proliferation. More recently, immune checkpoint inhibitors, including nivolumab and pembrolizumab, have shown promise by enhancing antitumor immune responses, marking a new era in HCC treatment [35].

5.4. Therapeutics in Pipeline and Future Directions

Emerging therapeutic strategies for hepatitis B virus (HBV) aim to achieve a functional cure by eradicating the persistent covalently closed circular DNA (cccDNA) reservoir, utilizing innovative approaches such as gene editing with CRISPR/Cas9, capsid inhibitors, and therapeutic vaccines [36]. Meanwhile, efforts to develop an effective hepatitis C virus (HCV) vaccine continue, focusing on broadly neutralizing antibodies and T-cell–based immune responses. Advances in biomarker research promise improved tools for early detection of hepatocellular carcinoma (HCC) and monitoring treatment response. Additionally, clinical trials are exploring combination therapies that integrate targeted agents with immunotherapies to overcome drug resistance and enhance therapeutic efficacy. A summary of currently available therapies targeting hepatitis virus infection and hepatitis virus-associated liver cancer, including their mechanisms and limitations, is provided in Table 4.

Table 4. Current Therapeutics for Hepatitis Virus-Associated Liver Disease and HCC.

Treatment Type	Virus Targeted	Drugs / Therapies	Mechanism	Efficacy / Cure Rates	Limitations	Reference
Antiviral	HBV	Tenofovir, Entecavir, Pegylated Interferon	Reverse transcriptase inhibition, immune modulation	Suppression of viral replication; no functional cure due to cccDNA	Persistence of cccDNA, drug resistance	[23,24]
Antiviral	HCV	Direct-acting antivirals (Sofosbuvir, Ledipasvir)	NS3/4A protease, NS5A, NS5B polymerase inhibitors	>95% sustained virological response (SVR)	Cost, limited access in low-income settings	[25,26]
Immunotherapy	HCC	Nivolumab, Pembrolizumab	Immune checkpoint	Objective response	Not universally	[27,28]

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		(checkpoint inhibitors)	blockade (PD-1/PD-L1)	rates ~15-20%	effective, immune-related adverse events	
Surgical / Locoregional	HCC	Resection, Ablation, Transarterial Chemoembolization (TACE)	Tumor removal or local control	Potentially curative in early stages	Limited to early-stage disease, recurrence common	[29,30]

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6. Past and Current Research Status and Future Needs

6.1. Past and Current Research Status

Significant progress has been made in understanding the biology of hepatitis viruses and their critical role in liver carcinogenesis. Early epidemiological studies firmly established the association between hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma (HCC), providing a foundation for molecular research into viral oncogenic mechanisms [13,28]. Advances in genomic technologies, including whole-genome sequencing and integration site mapping, have revealed complex patterns of HBV DNA integration and its oncogenic effects [19]. The introduction of direct-acting antivirals (DAAs) for HCV has revolutionized treatment, showing that viral eradication can substantially reduce the risk of cancer development [34]. Concurrently, immunotherapy trials targeting immune checkpoints have expanded therapeutic options for HCC, reflecting an improved understanding of tumor-immune system interactions [35]. Moreover, novel biomarkers and advanced imaging techniques are enhancing early detection, which is crucial for curative interventions [37]. Despite these advances, significant challenges persist in achieving complete cure of chronic hepatitis infections and fully preventing virus-induced carcinogenesis.

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6.2. Future Needs and Directions

6.2.1. Understanding Viral Persistence and Oncogenesis

A deeper understanding of viral persistence and oncogenesis is essential for advancing hepatitis-related cancer prevention and treatment. In particular, further elucidation of the biology of hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) is critical for developing curative therapies that can eradicate the viral reservoir. Additionally, gaining mechanistic insights into how hepatitis viruses evade the host immune system and shape the tumor microenvironment will be pivotal in guiding the design of more effective immunotherapies

6.2.2. Development of Vaccines and Therapies

The development of effective prophylactic and therapeutic vaccines for hepatitis C virus (HCV) remains a critical unmet need and a top global health priority. Despite significant progress in antiviral treatments, the absence of a vaccine continues to hinder efforts toward HCV elimination. In parallel, research is advancing toward innovative antiviral agents that target both viral components and host cellular pathways. These include epigenetic modulators, gene editing technologies, and host-targeted strategies that may overcome current limitations in viral resistance and persistence, offering new avenues for comprehensive and curative treatment approaches.

6.2.3. Global Public Health and Screening

Addressing the global burden of viral hepatitis and associated liver cancer requires strengthened public health efforts, particularly in low-resource settings. Expanding access to hepatitis B vaccination and scaling up availability of antiviral treatments for both HBV and HCV are essential steps toward reducing infection rates and preventing disease progression. Additionally, implementing cost-effective screening programs targeting high-risk populations will enable earlier diagnosis of hepatocellular carcinoma (HCC), thereby improving the chances of curative treatment and enhancing overall survival outcomes.

6.2.4. Integration of Multi-Omics and Precision Medicine

Advancements in multi-omics technologies—including genomics, transcriptomics, and proteomics—offer powerful tools for identifying novel biomarkers and therapeutic targets in hepatitis-related liver cancer. These approaches enable a more comprehensive understanding of virus-host interactions and disease progression. Furthermore, personalized treatment strategies that consider viral genotype, host genetic factors, and tumor molecular profiles hold significant promise for optimizing therapeutic outcomes, minimizing adverse effects, and improving overall patient prognosis.

7. Conclusion

Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) remain major etiological factors contributing to the global burden of hepatocellular carcinoma (HCC), primarily through multifaceted oncogenic mechanisms involving direct viral effects, chronic inflammation, immune modulation, and integration into the host genome. Advances in molecular virology have significantly enhanced the understanding of viral life cycles, host-pathogen interactions, and the molecular pathways underpinning hepatocarcinogenesis. These insights have facilitated the development of prophylactic HBV vaccines and highly effective direct-acting antiviral (DAA) therapies for HCV, leading to substantial reductions in disease incidence and progression.

Despite these achievements, critical challenges persist, including incomplete viral eradication in HBV-infected individuals, limited access to antiviral therapies in low-resource settings, and residual risk of HCC even after viral suppression or clearance. Therefore, sustained multidisciplinary research efforts, the implementation of comprehensive public health initiatives, and the development of novel

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antiviral and immunotherapeutic strategies are essential to eliminate virus-associated liver cancer and improve long-term clinical outcomes on a global scale.

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