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Hepatitis B-Induced Immunological Remodeling in Hepatocellular Carcinoma

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Abstract: Persistent infection with Hepatitis B virus (HBV) for more than six months can lead to chronic hepatitis B (CHB), which is a major cause of Hepatocellular carcinoma (HCC). Chronic HBV infection continuously damages the liver and promotes the formation of an immunosuppressive and inflammatory hepatic microenvironment, but the mechanisms linking hepatocyte alterations to immune dysfunction during disease progression remain incompletely understood. This review focuses on how chronic HBV infection reprograms hepatocytes and reshapes the hepatic immune microenvironment during the transition from CHB to HCC. We propose that epigenetic alterations and metabolic rewiring are two interconnected mechanisms driving this process. These changes regulate gene expression, signaling pathways, and metabolite production in hepatocytes, thereby influencing cytokine and metabolite release that promotes immune cell dysfunction and immune suppression. Overall, we highlights the mechanistic connection between hepatocyte reprogramming and immune microenvironment remodeling in HBV-related hepatocarcinogenesis, and discusses potential therapeutic targets for HBV-associated HCC.

1. Introduction

Chronic hepatitis B (CHB) caused by persistent hepatitis B virus (HBV) infection remains the leading cause of hepatocellular carcinoma worldwide. It affects approximately 296 million individuals globally and constitutes a major pathogenic factor for liver cirrhosis and HCC. Clinically, HBV infection accounts for 40%–50% of global HCC cases [1]. Given the substantial disease burden, it is imperative to clarify the cellular mechanisms driving the progression from CHB to hepatic carcinogenesis.

CHB infection triggers extensive hepatocyte reprogramming, which involves intricate crosstalk between epigenetic and metabolic processes. Epigenetically, HBV modulates DNA methylation profiles, remodels histone modifications, and regulates ubiquitin-mediated proteolysis, thereby disrupting transcriptional homeostasis and activating oncogenic signaling pathways. Accumulating studies have demonstrated that epigenetic modifications interact with metabolic pathway alterations to form a coordinated regulatory network, which maintains viral persistence and modulates host cellular responses.

Concurrently, HBV induces profound metabolic reprogramming in hepatocytes, covering glucose,

lipid, and amino acid metabolism. These metabolic alterations not only provide biosynthetic substrates and energy for viral replication and hepatocyte survival but also reshape metabolic profiles. The accumulation of metabolites including lactate, lipids, and amino acid intermediates dynamically remodels the liver microenvironment, bridging intracellular hepatocyte changes with extracellular immune regulatory mechanisms.

In this review, the tumor microenvironment (TME) of HCC is defined as a dynamically adaptive physiological structure driven by persistent metabolic alterations. Chronic HBV infection induces sustained immune dysregulation, characterized by aberrant macrophage polarization, impaired functional activities of natural killer (NK) cells and antigen-presenting cells (APCs), and retarded clearance of adaptive immune cells. Such immune dysregulation acts as both a consequence of persistent viral infection and a driving factor for disease pathogenesis. Accordingly, this review systematically explores the CHB–TME–HCC continuum from three dimensions: intrinsic hepatocyte reprogramming, immune cell dysfunction, and their interactive effects on HCC progression.

The remodeled hepatic microenvironment facilitates HCC pathogenesis via an autostimulatory pathological loop. Persistent viral antigen exposure and inhibitory cytokine signaling trigger chronic hepatic inflammation and immune tolerance. Impaired immune surveillance not only fails to eliminate malignant hepatocytes but also activates oncogenic signaling cascades, ultimately accelerating the progression of chronic HBV infection to HCC.

Based on existing research evidence, this review proposes that HBV-induced hepatocyte reprogramming and immune remodeling constitute a tightly coupled pathogenic axis for HCC development.

2. HBV-driven molecular reprogramming in hepatocytes

The progression from CHB to HCC is accompanied by persistent viral infection, which triggers reprogramming of hepatocytes and alters with the TME. Within this process, epigenetic changes and metabolic rewiring serve as two key regulatory layers. They work together to reshape gene expression, cellular behavior, and metabolite profiles, thereby linking hepatocyte dysfunction to immune remodeling and ultimately promoting liver cancer development.

2.1 Regulation of Gene Expression

To clarify the regulatory mechanism of HBV-mediated hepatocyte reprogramming in hepatocarcinogenesis, it is essential to elucidate the alterations in gene expression regulation. Accumulating evidence indicates that chronic HBV infection disrupts multiple layers of gene regulatory networks, including epigenetic modification and metabolic modulation. These combined alterations reshape the transcriptional programs governing cell proliferation, survival, and differentiation, and eventually construct a tumor-permissive microenvironment.

2.1.1 Methylation modification

DNA methylation is a crucial epigenetic mechanism catalyzed by DNA methyltransferases (DNMTs). This enzymatic reaction mediates methylation modification at CpG loci, thereby regulating hepatocytic gene expression and maintaining genomic stability [2]. As a vital epigenetic mediator, hepatitis B virus X protein (HBx) modulates the expression of DNMT family members: it upregulates DNMT1 and DNMT3A while downregulating DNMT3B. This regulatory pattern induces locus-specific hypermethylation of tumor suppressor genes and silences repetitive genomic regions [3].

A growing body of evidence has verified that CHB infection severely disrupts the epigenetic

regulatory system during hepatocarcinogenesis. The transition from chronic inflammation to HCC is accompanied by progressive epigenomic instability, which leads to aberrant DNA methylation patterns, including promoter hypermethylation of tumor suppressor genes and global genomic hypomethylation [4].

Genome-wide methylation analyses further demonstrate that HBV-associated HCC tissues exhibit decreased global methylation levels, with prominent hypomethylation near HBV integration sites. This phenomenon indicates that viral integration directly remodels the host epigenome and facilitates malignant transformation of hepatocytes [5].

In conclusion, methylation modifications silence the transcription of genes related to cell cycle regulation, apoptosis, and cellular differentiation, thereby inducing hepatocyte epigenetic reprogramming and accelerating the progression from CHB to HCC [6].

2.1.2 Acetylation modification

In addition to DNA methylation, histone acetylation serves as another pivotal epigenetic layer governing gene expression. Histone acetylation status is dynamically modulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). These enzymes regulate chromatin compactness and further control gene transcription efficiency in hepatocytes [7].

Distinct alterations in histone acetylation patterns are observed during HBV-associated hepatocarcinogenesis. Dysregulated acetylation at multiple histone loci activates oncogenic genes, thereby promoting excessive proliferation and malignant transformation of hepatocytes [8].

Consistent with the above findings, global epigenomic profiling of HBV-positive HCC samples reveals elevated active acetylation markers. Specifically, H3K27ac is enriched in enhancers associated with oncogenesis, inflammation, and metabolic reprogramming, confirming that HBV induces comprehensive acetylation remodeling of hepatic chromatin [9]. Such epigenetic alterations are primarily driven by HBx. HBx interacts with histone-modifying enzymes such as p300/CBP and HDACs to remodel the acetylation profiles of viral and host gene promoters, which supports viral latency and cellular malignant transformation at the transcriptional level [10].

Collectively, HBx-induced chromatin acetylation abnormalities disrupt the expression of genes controlling cell cycle progression, apoptosis, and immune regulation, thereby promoting the malignant transformation of hepatocytes in CHB-related HCC.

2.1.3 Ubiquitination modification

Apart from chromatin-based epigenetic modifications, post-translational ubiquitination also contributes to the oncogenic microenvironment of HBV-associated HCC. Ubiquitination refers to the covalent binding between ubiquitin and target substrates, which is sequentially catalyzed by three types of enzymes: E1 activating enzymes, E2 conjugating enzymes, and E3 ubiquitin ligases. This modification participates in cellular proteolysis and signal transduction.

Accumulating studies have confirmed that the ubiquitin-proteasome system is severely dysregulated during CHB-related hepatocarcinogenesis. HBV infection alters the expression of numerous E3 ligases and deubiquitinases in hepatocytes, leading to abnormal accumulation or degradation of proteins associated with cell proliferation, apoptosis, and inflammatory responses [11]. Large-scale transcriptomic and proteomic analyses of HBV-related HCC further verify significant perturbations in ubiquitination-related regulatory networks. Oncogenic proteins are abnormally stabilized while tumor suppressor proteins are degraded, which synergistically promotes hepatocyte proliferation and malignant transformation [12].

Molecular mechanistic studies have validated the physical binding between HBx and the host ubiquitin ligase complex. This interaction modulates the ubiquitination level of target proteins and

alters their half-lives in oncogenic signaling pathways. For instance, HBx binds to host E3 ubiquitin ligases to trigger proteasomal degradation of tumor suppressor proteins. These proteins maintain cellular homeostasis and inhibit uncontrolled cell proliferation, and their degradation ultimately facilitates oncogenic progression [13, 14].

In summary, HBV-induced ubiquitination dysregulation disrupts hepatocytic protein homeostasis and intracellular signaling, thereby driving the malignant progression from CHB to HCC.

2.2 Metabolic Regulation

In addition to transcriptional regulation, HBV infection triggers metabolic rewiring in infected hepatocytes. Chronic HBV infection induces persistent immune responses, which further reshape hepatic metabolic patterns and lead to abnormal accumulation of key metabolites.

Metabolite accumulation acts as a critical bridge linking intracellular hepatocyte alterations and extracellular immune microenvironment changes. For example, abnormal accumulation of glucose, lipid, and amino acid metabolites modulates intracellular signaling cascades and immune responses, ultimately causing immune deficiency and tumor-promoting inflammation. Therefore, it is essential to explore metabolic alterations during chronic HBV infection and clarify how hepatic adaptive metabolic changes reshape the surrounding microenvironment to drive HCC progression.

2.2.1 Glucose metabolism

CHB infection significantly disrupts hepatic energy metabolism, and glucose metabolic reprogramming is one of the most prominent metabolic alterations in early hepatocarcinogenesis.

HBV-infected hepatocytes exhibit enhanced glycolysis activity, accompanied by the accumulation of downstream metabolites such as pyruvate and lactate. This metabolic shift towards aerobic glycolysis is consistent with the Warburg effect observed in most malignant tumors [15]. At the molecular level, HBV-derived proteins disrupt hepatic glucose homeostasis and upregulate the transcription of glycolysis-related regulators to mediate metabolic remodeling in HCC [16].

Among viral functional proteins, HBx-mediated activation of the PI3K/AKT signaling axis serves as a core metabolic regulatory pathway in HBV-related hepatocarcinogenesis. This pathway synchronously promotes glycolysis activation, maintains hepatocyte survival, and accelerates tumor progression. It also upregulates the expression of key glycolytic enzymes including HK2, PKM2, and LDHA, thereby elevating the glycolytic rate of hepatocytes [17].

Enhanced glycolysis provides sufficient biosynthetic substrates and energy for the rapid proliferation of hepatocytes. Additionally, it maintains the stemness of cancer stem cells and facilitates the malignant progression of HBV-related liver cancer [18].

2.2.2 Lipid metabolism

Lipid metabolism is another metabolic pathway profoundly disrupted during chronic HBV infection, and its dysregulation plays an essential role in HCC development.

HBV infection breaks hepatic lipid homeostasis, leading to excessive lipid accumulation and increased lipid droplet formation in hepatocytes. This phenomenon indicates abnormal fatty acid synthesis and storage in HBV-infected hepatic cells [19]. HBx is a key viral protein mediating lipid metabolic dysregulation. It activates the SREBP-1-dependent lipogenic signaling pathway and upregulates the expression of lipid synthesis rate-limiting enzymes such as FASN to promote lipogenesis [20].

In addition to lipogenesis promotion, HBx enhances intracellular fatty acid transport and storage capacity. It transcriptionally upregulates FABP1 expression via regulatory factors including HNF3β,

C/EBPα, and PPARα [21].

These lipid metabolic alterations provide membrane components, signaling lipids, and metabolic energy for hepatocyte proliferation, and also sustain the activation of oncogenic signaling pathways during HCC progression.

2.2.3 Amino acid metabolism

Besides glucose and lipid metabolism, amino acid metabolic reprogramming is a critical biological process supporting hepatocyte malignant transformation during chronic HBV infection.

Metabolic analyses have demonstrated that HBV-infected hepatocytes exhibit increased dependence on glutamine and its derivatives, which provide energy for viral replication and ATP synthesis [22]. Mechanistically, HBV infection induces the expression of glutamine transporters and key metabolic enzymes such as GLS. These molecular changes promote glutamine catabolism and convert glutamine into α-ketoglutarate to maintain the stability of the tricarboxylic acid (TCA) cycle [23].

Moreover, viral proteins represented by HBx can activate the oncogenic driver c-Myc. c-Myc further transcriptionally regulates the expression of multiple amino acid transporters and metabolic enzymes [24]. These biological processes accelerate protein catabolism, facilitate nucleotide synthesis, maintain intracellular antioxidant homeostasis, and support the growth, survival, and metabolic adaptation of malignant hepatocytes [25].

In aggregate, these metabolic rewiring events construct a nutrient-rich hepatic microenvironment, enhance the metabolic adaptability of hepatocytes, and promote the pathological progression from CHB to HCC.

3. HBV reprogramming immunology landscape of liver

Hepatocytic epigenetic and metabolic alterations are not independent biological events; instead, they profoundly reshape the hepatic immune microenvironment. HBV-infected hepatocytes continuously secrete cytokines, chemokines, and metabolites, which directly regulate the biological functions of adjacent immune cells. This immune remodeling process drives the transformation of antiviral immune responses into immune tolerance and tumorigenesis.

The remodeled immune microenvironment is characterized by extensive dysfunction of innate and adaptive immunity. Innate immune cells including macrophages, NK cells, and APCs lose antiviral activity and acquire pro-tumorigenic phenotypes. Meanwhile, adaptive immune cells gradually become exhausted or differentiate into regulatory cell subsets, resulting in impaired antitumor immune surveillance.

This section firstly elaborates on the functional alterations of innate immune cells, the primary responders to HBV infection. Subsequently, the dysfunction of adaptive immune cells is systematically summarized. The combined alterations of innate and adaptive immune cells jointly construct an immunosuppressive microenvironment that accelerates the progression from CHB to HCC.

3.1 Innate immune cells

Chronic HBV infection induces persistent hepatic inflammation and progressive immune suppression, which significantly remodels the innate immune landscape of the liver. Macrophages, NK cells, and dendritic cells (DCs) are core innate immune cells responsible for antiviral defense and tumor surveillance. During the CHB – HCC progression, functional abnormalities of these immune cells weaken immune surveillance capacity and facilitate tumor development.

3.1.1 TAM

Macrophages are the most abundant immune cell population in the liver, with high functional plasticity in response to microenvironmental changes. Under physiological conditions, hepatic macrophages eliminate pathogens and mediate antigen presentation to initiate effective antiviral adaptive immune responses. Nevertheless, persistent viral antigen exposure and immunoregulatory signals in CHB patients impair the antigen-presenting capacity of macrophages, reduce the expression of costimulatory molecules, and ultimately suppress antiviral immune responses [26, 27].

Hypoxia, tumor-derived oncogenic factors, and sustained inflammatory signaling further drive macrophage reprogramming and accelerate hepatocarcinogenesis, leading to the accumulation of tumor-associated macrophages (TAMs). In established HCC lesions, TAMs predominantly polarize into the M2 phenotype with immunosuppressive and pro-tumorigenic properties. TAMs secrete multiple cytokines includingIL-6, IL-10, TGF-β, TNF-α, andIL-1β, which remodel the TME and promote tumor immune escape [26, 27].

The phenotypic characteristics and cytokine secretion profiles of TAMs vary among different HCC subtypes. In HBV-related HCC, TAM-derived IL-6 activates the STAT3 signaling pathway to promote tumor cell survival, proliferation, and stemness. Meanwhile, IL-10 and TGF-β inhibit the effector function of T cells and induce immune tolerance [28, 29]. In contrast, non-alcoholic fatty liver disease (NAFLD)-related HCC is driven by metabolic inflammation. Macrophages in this subtype exhibit enhanced inflammasome activation and increased secretion of IL-1 and TNF-α, which sustain chronic inflammatory signaling and facilitate hepatocarcinogenesis [30, 31].

These findings confirm that TAMs are core regulators of hepatic immune remodeling during tumorigenesis. Targeting macrophage polarization or inhibiting TAM-derived cytokine signaling may provide promising therapeutic strategies for HCC treatment.

3.1.2 NK

While macrophages modulate inflammatory signaling in the TME, NK cells serve as the key cytotoxic component of innate immunity, eliminating virus-infected and malignant hepatocytes in the early pathological stage. However, CHB infection induces significant quantitative and functional abnormalities in NK cells, thereby weakening their antiviral and antitumor activities.

Patients with chronic HBV infection exhibit decreased counts of peripheral and intrahepatic NK cells. The remaining NK cells show dysregulated expression of activating and inhibitory receptors. Functionally, these abnormal NK cells secrete reduced levels of effector cytokines, especially IFN-γ andTNF-α, while retaining partial cytotoxic activity. This functional imbalance leads to defective innate immune responses during persistent HBV infection [32, 33].

NK cell dysfunction is closely associated with the immunosuppressive cytokine microenvironment induced by chronic infection. High concentrations of TGF-β and IL-10 downregulate activating receptors and inhibit effector cytokine secretion, thereby impairing the antiviral and antitumor capacity of NK cells [34]. With TME deterioration, NK cells in HCC tissues are further depleted compared with adjacent non-tumor hepatic tissues, accompanied by decreased cytotoxicity and reduced pro-inflammatory cytokine secretion against malignant hepatocytes [35].

Persistent inflammatory signaling and immunosuppressive cytokine networks induce NK cell dysfunction and undermine innate immune surveillance, ultimately promoting the progression of HBV-related HCC.

3.1.3 DC

In addition to macrophages and NK cells, DCs are the primary antigen-presenting cells bridging innate and adaptive immunity. Severe DC dysfunction is observed throughout chronic HBV infection.

DCs isolated from CHB patients exhibit defective antigen presentation, abnormal migration ability, dysregulated cytokine secretion, and decreased expression of key costimulatory molecules including CD80, CD83, CD86, and HLA-DR [36]. These functional defects severely hinder the activation of antiviral T cell responses and impair immune surveillance during persistent viral infection. Furthermore, emerging studies on the HCC immune microenvironment have verified that DC dysfunction exacerbates antitumor immune deficiency and facilitates the formation of a pro-tumorigenic immune microenvironment [37].

Persistent viral antigen exposure further induces immune tolerance in DCs. For example, hepatitis B surface antigen (HBsAg) directly interacts with DCs and inhibits their maturation, thereby reducing IL-12 secretion and impairing the activation of Th1 cells and cytotoxic T cells [38]. Moreover, HBV infection disrupts intracellular metabolic and signaling pathways in DCs, which further suppresses immune activation. Recent studies have indicated that metabolic abnormalities such as intracellular cholesterol accumulation contribute to DC dysfunction in CHB, and cholesterol metabolism modulation can partially reverse DC impairment [39].

In conclusion, DC dysfunction inhibits the initiation of adaptive immune responses and forms an immunosuppressive microenvironment rich in inhibitory mediators such as IL-10. Defective antigen presentation enables HBV to evade immune clearance and accelerates tumor growth, thereby promoting the progression from CHB to HCC.

3.2 Adaptive immune cells

Innate immune cells initiate antiviral responses and construct inflammatory microenvironments, while adaptive immune cells determine the efficiency of tumor immune surveillance. Persistent antigen stimulation and immunosuppressive signaling during chronic HBV infection drive the functional reprogramming of T and B cells. These immune cells gradually differentiate into dysfunctional or regulatory subsets, which facilitate tumor immune escape and carcinogenesis.

3.2.1 $CD8^+$T cell

Virus-specific $CD8^+$T cells are the primary cytotoxic effector cells that eliminate HBV-infected and malignant hepatocytes. During the progression from CHB to HCC, $CD8^+$T cells undergo progressive functional exhaustion, characterized by attenuated cytotoxicity, decreased cytokine secretion, and defective memory cell formation.

Persistent antigen exposure in chronic HBV infection induces $CD8^+$T cell exhaustion. Exhausted $CD8^+$T cells highly express inhibitory receptors such as PD-1, TIM-3, and LAG-3, with reduced secretion of IFN-γ and TNF-α and impaired proliferative capacity [40, 41]. Single-cell RNA sequencing analyses of HBV-related HCC further confirm the enrichment of severely exhausted $CD8^+$T cell subsets in tumor tissues. These cells possess unique transcriptional and epigenetic characteristics, including upregulated expression of the transcription factor TOX. TOX mediates stable epigenetic modification to maintain the exhausted phenotype, which limits the functional recovery of $CD8^+$T cells [42, 43]. This irreversible epigenetic state leads to resistance to immune checkpoint blockade therapy and poor antitumor immune efficacy in HCC patients.

Multiple mechanisms collectively induce $CD8^+$T cell dysfunction. Continuous exposure to viral antigens such as HBsAg and hepatitis B core antigen (HBcAg) activates the NFAT-dependent transcriptional signaling cascade, upregulates TOX expression, and induces exhaustion-associated chromatin remodeling [40]. Additionally, HBx activates the STAT3 signaling pathway and upregulates chemokines including CCL2 and CSF-1. These molecular changes recruit myeloid-derived suppressor cells (MDSCs) and M2-type macrophages to inhibit $CD8^+$T cell activity [43, 44]. Moreover, tumor microenvironmental metabolic stress such as hypoxia and abnormal lipid

metabolism impairs mitochondrial function and cytotoxic granule release, further aggravating $CD8^+$T cell dysfunction during hepatocarcinogenesis [42].

In aggregate, persistent antigenic stimulation, HBx-mediated TME remodeling, and metabolic stress jointly induce quantitative reduction and functional defects of $CD8^+$T cells, thereby weakening tumor immune surveillance and promoting HBV-related HCC progression.

Notably, the exhausted phenotype of HBV-specific $CD8^+$T cells provides a theoretical basis for immune checkpoint blockade therapy. Clinical applications of PD-1 and CTLA-4 inhibitors (e.g., nivolumab, pembrolizumab, tremelimumab) have been proven to partially restore T cell function and enhance antitumor immunity in HBV-related HCC [45].

3.2.2 $CD4^+$T cell

$CD8^+$T cell exhaustion is accompanied by extensive phenotypic and functional alterations of $CD4^+$T cells during chronic HBV infection. Normally, $CD4^+$T cells coordinate antiviral immune responses and assist the activation of cytotoxic T cells. However, chronic HBV infection reverses this antiviral regulatory effect and induces $CD4^+$T cell dysfunction.

In CHB and HBV-associated HCC patients, the proportion of $FOXP3^+$ regulatory T cells (Tregs) increases while HBV-specific Th1 cell subsets decrease. The remaining effector $CD4^+$T cells exhibit reduced IFN-γ and IL-2 secretion, impaired proliferative ability, and upregulated inhibitory receptors such as PD-1 [43]. Tumor-infiltrating $CD4^+$T cells tend to differentiate into regulatory and dysfunctional subsets with weakened auxiliary immune function, which is positively correlated with disease progression and poor clinical prognosis [46].

Mechanistically, long-term HBV antigen exposure and HBx-mediated inflammatory signaling induce persistent immune stimulation and disrupted cytokine homeostasis in the liver. The activated STAT3 signaling pathway and TGF-β-rich microenvironment facilitate Treg differentiation and suppress the activation of effector $CD4^+$T cells [47]. Furthermore, chemokine axes including CCL2/CCR2 and CSF-1 promote the expansion of immunosuppressive myeloid cells, enhance the interaction between Tregs and TAMs, and further exacerbate $CD4^+$T cell dysfunction [48].

In summary, $CD4^+$T cells gradually lose antiviral immune auxiliary function and become an essential component of the immunosuppressive network during CHB–HCC progression, thereby facilitating tumor immune escape and malignant development.

3.2.3 B cell

In addition to T cell dysfunction, accumulating evidence has verified significant functional alterations of B cells during HBV-related hepatocarcinogenesis. In the deteriorative TME, HBV-responsive B cells cease to exert antiviral antibody-secreting functions and differentiate into regulatory subsets to participate in immune suppression.

Phenotypically, HBV-related HCC tissues contain increased proportions of $CD19^+CD24^+CD38^+$ regulatory B cells (Bregs) and $PD\text{-}1^+$ IL-10-producing B cells. These B cell subsets exhibit defective antigen presentation and weakened capacity to assist cytotoxic T cell activation [49, 50]. Additionally, abnormal infiltration of intratumoral B cells disrupts the structural integrity of tertiary lymphoid tissues, leading to dysfunctional humoral immunity, which is closely associated with HCC progression and poor prognosis [43, 51].

Mechanistically, HBV infection remodels B cell signaling pathways and the surrounding cytokine microenvironment via viral proteins such as HBx, thereby driving B cell regulatory differentiation. HBV-induced inflammatory signaling promotes IL-10 secretion and activates immune checkpoint pathways in B cells, which inhibits effector T cell function and induces tumor immune escape [49]. Moreover, upregulated chemokines including CCL2 and CSF-1 mediate the recruitment and

interaction of B cells, monocytes, and macrophages, constructing an immunosuppressive microenvironment conducive to tumor growth [43].

High-dimensional and single-cell sequencing analyses have identified multiple abnormal B cell subpopulations in HBV-related HCC. These B cells possess exhaustion-like transcriptional profiles and regulatory cytokine characteristics, indicating their active involvement in tumor immune remodeling rather than passive accumulation in the TME [52].

In conclusion, B cells undergo functional transformation during CHB–HCC progression. They convert from antiviral effector cells into immunosuppressive regulatory cells, and mediate tumor immune escape via IL-10 secretion, immune checkpoint activation, and chemokine-induced intercellular crosstalk.

4. Summary and Prospect

Persistent HBV infection (over six months) induces integrated epigenetic and metabolic alterations in hepatocytes, constructing a tumor-permissive cellular microenvironment. The progression from CHB to HCC relies on two interconnected pathological mechanisms: epigenetic dysregulation and metabolic rewiring. These two mechanisms synergistically disrupt hepatocytic physiological functions and lay the foundation for tumorigenesis. HBV-induced epigenetic abnormalities, including aberrant DNA methylation, histone modification, and ubiquitination, reshape the transcriptional programs controlling cell proliferation, survival, and immune regulation. Meanwhile, reprogramming of glucose, lipid, and amino acid metabolism provides energy support and generates immunomodulatory metabolites. Intracellular hepatocytic alterations exert distal regulatory effects via continuous cytokine and metabolite secretion, linking cellular dysfunction to systemic immune microenvironment remodeling. Innate immune cells (macrophages, NK cells, DCs) are functionally impaired and polarize into pro-tumorigenic phenotypes. In the adaptive immune system, T cell exhaustion is aggravated, accompanied by the expansion of regulatory T and B cell subsets. The synergistic effect of hepatocyte reprogramming and immune dysregulation forms a self-amplifying pathological loop, which drives immune escape, persistent hepatic inflammation, and eventual HCC occurrence.

Although substantial progress has been made in exploring the molecular mechanism of HBV-related hepatocarcinogenesis, multiple critical scientific issues remain to be resolved. In particular, the specific mechanism by which HBV-induced hepatocyte reprogramming mediates immune cell recruitment and polarization in the hepatic microenvironment requires further clarification. Moreover, the combined effects of persistent viral antigen exposure and chronic inflammatory signaling on long-term immune dysfunction (such as irreversible T cell exhaustion and immune cell subset imbalance) remain unclear. Elucidating these pathological processes will help identify core regulatory nodes for hepatocyte–immune cell crosstalk and tumor-promoting inflammation. In-depth exploration of the above mechanisms will provide novel therapeutic targets for blocking the progression from CHB to HCC and improve the clinical treatment efficacy of HBV-associated liver cancer. s

References

[1] Hsu, Y.C., Huang, D.Q. and Nguyen, M.H. (2023) Global Burden of Hepatitis B Virus: Current Status, Missed Opportunities and a Call for Action. Nature Reviews Gastroenterology & Hepatology, 20, 524-537.

[2] Zheng, Y.F., Lu, X.J., Zhang, X.Y. and Guan, B.G. (2019) The Landscape of DNA Methylation in Hepatocellular Carcinoma. Journal of Cellular Physiology, 234, 2631-2638.

[3] Udali, S., Guarini, P., Ruzzenente, A., Ferrarini, A., Guglielmi, A., Lotto, V., Tononi, P., Pattini, P., Moruzzi, S., Campagnaro, T., Conci, S., Olivieri, O., Corrocher, R., Delledonne, M., Choi, S.W. and Friso, S. (2015) DNA Methylation and Gene Expression Profiles Show Novel Regulatory Pathways in Hepatocellular Carcinoma. Clinical Epigenetics, 7, 13.

[4] Zhang, C., Huang, C.X., Sui, X.B., Zhong, X.Q., Yang, W.J., Hu, X.R. and Li, Y.Q. (2019) Association between Gene Methylation and Hbv Infection in Hepatocellular Carcinoma: A Meta-Analysis. Journal of Cancer, 10, 6457-6465.
[5] Koumbi, L. and Karayiannis, P. (2016) The Epigenetic Control of Hepatitis B Virus Modulates the Outcome of Infection. Frontiers in Microbiology, 6, 9.
[6] Villanueva, A., Portela, A., Sayols, S., Battiston, C., Hoshida, Y., Méndez-González, J., Imbeaud, S., Letouzé, E., Hernandez-Gea, V., Cornella, H., Pinyol, R., Solé, M., Fuster, J., Zucman-Rossi, J., Mazzaferro, V., Esteller, M., Llovet, J.M. and Consortium, H. (2015) DNA Methylation-Based Prognosis and Epidrivers in Hepatocellular Carcinoma. Hepatology, 61, 1945-1956.
[7] Garmpis, N., Damaskos, C., Garmpi, A., Georgakopoulou, V.E., Sarantis, P., Antoniou, E.A., Karamouzis, M.V., Nonni, A., Schizas, D., Diamantis, E., Koustas, E., Farmaki, P., Syllaios, A., Patsouras, A., Kontzoglou, K., Trakas, N. and Dimitroulis, D. (2021) Histone Deacetylase Inhibitors in the Treatment of Hepatocellular Carcinoma: Current Evidence and Future Opportunities. Journal of Personalized Medicine, 11, 15.
[8] Xu, J., Guan, X.Y., Jia, X.D., Li, H.Y., Chen, R.B. and Lu, Y.Y. (2022) In-Depth Profiling and Quantification of the Lysine Acetylome in Hepatocellular Carcinoma with a Trapped Ion Mobility Mass Spectrometer. Molecular & Cellular Proteomics, 21, 19.
[9] Xia, J.K., Qin, X.Q., Zhang, L., Liu, S.J., Shi, X.L. and Ren, H.Z. (2022) Roles and Regulation of Histone Acetylation in Hepatocellular Carcinoma. Frontiers in Genetics, 13, 12.
[10] Xu, Y.Y., Liao, W., Luo, Q., Yang, D.H. and Pan, M.X. (2022) Histone Acetylation Regulator-Mediated Acetylation Patterns Define Tumor Malignant Pathways and Tumor Microenvironment in Hepatocellular Carcinoma. Frontiers in Immunology, 13, 19.
[11] Tian, Z.L., Xu, C., He, W.X., Lin, Z.B., Zhang, W.J., Tao, K.S., Ding, R., Zhang, X. and Dou, K.F. (2023) The Deubiquitinating Enzyme Usp19 Facilitates Hepatocellular Carcinoma Progression through Stabilizing Yap. Cancer Letters, 577, 12.
[12] Ma, M.R., Yi, L., Pei, Y.F., Zhang, Q.M., Tong, C., Zhao, M.Y., Chen, Y.H., Zhu, J.H., Zhang, W.G., Yao, F., Yang, P.Y. and Zhang, P.J. (2024) Usp26 as a Hepatitis B Virus-Induced Deubiquitinase Primes Hepatocellular Carcinogenesis by Epigenetic Remodeling. Nature Communications, 15, 18.
[13] Zhao, J.N., Li, Y.X., Zhu, J., Li, H. and Jin, X.F. (2025) Ubiquitination in Hepatocellular Carcinoma Immunity. Journal of Translational Medicine, 23, 17.
[14] Wang, H.L., Li, Q., Tang, Q.Q., Shi, G., Wu, G., Mao, X.B., Wu, C.K., Zhang, L.X., Liu, J., Li, J.D. and Li, B. (2024) Role and Therapeutic Potential of E3s in the Tumor Microenvironment of Hepatocellular Carcinoma. Frontiers in Immunology, 15, 8.
[15] Zuo, Q.Z., He, J., Zhang, S., Wang, H., Jin, G.Z., Jin, H.J., Cheng, Z.A., Tao, X.M., Yu, C.T., Li, B.T., Yang, C., Wang, S.Y., Lv, Y.Y., Zhao, F.Y., Yao, M., Cong, W.M., Wang, C. and Qin, W.X. (2021) Pparγ Coactivator-1α Suppresses Metastasis of Hepatocellular Carcinoma by Inhibiting Warburg Effect by Pparγ-Dependent Wnt/B-Catenin/Pyruvate Dehydrogenase Kinase Isozyme 1 Axis. Hepatology, 73, 644-660.
[16] Lu, C.Y., Fang, S.J., Weng, Q.Y., Lv, X.L., Meng, M.M., Zhu, J.Y., Zheng, L.Y., Hu, Y.M., Gao, Y., Wu, X.L., Mao, J.T., Tang, B.F., Zhao, Z.W., Huang, L. and Ji, J.S. (2020) Integrated Analysis Reveals Critical Glycolytic Regulators in Hepatocellular Carcinoma. Cell Communication and Signaling, 18, 14.
[17] An, L.B. and Li, Z.F. (2025) Molecular Network of Metabolic Reprogramming and Precision Diagnosis and Treatment of Hepatocellular Carcinoma. Biomarker Research, 13, 32.
[18] Mossenta, M., Busato, D., Dal Bo, M. and Toffoli, G. (2020) Glucose Metabolism and Oxidative Stress in Hepatocellular Carcinoma: Role and Possible Implications in Novel Therapeutic Strategies. Cancers, 12, 30.
[19] Park, S. and Hall, M.N. (2025) Metabolic Reprogramming in Hepatocellular Carcinoma: Mechanisms and Therapeutic Implications. Experimental and Molecular Medicine, 57, 515-523.
[20] Zhou, F.L. and Sun, X.L. (2021) Cholesterol Metabolism: A Double-Edged Sword in Hepatocellular Carcinoma. Frontiers in Cell and Developmental Biology, 9, 10.
[21] Dai, P., Feng, J., Dong, Y.Y., Zhang, S.J., Cao, J.H., Cui, X.P., Qin, X.L., Yang, S.M. and Fan, D.G. (2025) Metabolic Reprogramming in Hepatocellular Carcinoma: An Integrated Omics Study of Lipid Pathways and Their Diagnostic Potential. Journal of Translational Medicine, 23, 17.
[22] Li, Y., Mo, H.Y., Jia, S.Y., Wang, J., Ma, Y., Liu, X. and Tu, K.S. (2022) Comprehensive Analysis of the Amino Acid Metabolism-Related Gene Signature for Prognosis, Tumor Immune Microenvironment, and Candidate Drugs in Hepatocellular Carcinoma. Frontiers in Immunology, 13, 18.
[23] Ye, Y.Y., Yu, B.D., Wang, H. and Yi, F.M. (2023) Glutamine Metabolic Reprogramming in Hepatocellular Carcinoma. Frontiers in Molecular Biosciences, 10, 13.
[24] Gao, B.C., Lu, Y., Lai, X.Y., Xu, X., Gou, S.H., Yang, Z.D., Gong, Y.J. and Yang, H. (2025) Metabolic Reprogramming

in Hepatocellular Carcinoma: Mechanisms of Immune Evasion and Therapeutic Implications. Frontiers in Immunology, 16, 8.
[25] Morine, Y., Utsunomiya, T., Yamanaka-Okumura, H., Saito, Y., Yamada, S., Ikemoto, T., Imura, S., Kinoshita, S., Hirayama, A. and Tanaka, Y. (2022) Essential Amino Acids as Diagnostic Biomarkers of Hepatocellular Carcinoma Based on Metabolic Analysis. Oncotarget, 13, 1286-1298.
[26] Cervantes, A., Daniele, B. and Martinelli, E. (2021) Hepatocellular Carcinoma. Nature Reviews Disease Primers, 7, 1.
[27] Ringelhan, M., Pfister, D., O'Connor, T., Pikarsky, E. and Heikenwalder, M. (2018) The Immunology of Hepatocellular Carcinoma. Nature Immunology, 19, 222-232.
[28] Wan, S.S., Zhao, E.D., Kryczek, I., Vatan, L., Sadovskaya, A., Ludema, G., Simeone, D.M., Zou, W.P. and Welling, T.H. (2014) Tumor-Associated Macrophages Produce Interleukin 6 and Signal Via Stat3 to Promote Expansion of Human Hepatocellular Carcinoma Stem Cells. Gastroenterology, 147, 1393-1404.
[29] Bergmann, J., Müller, M., Baumann, N., Reichert, M., Heneweer, C., Bolik, J., Lücke, K., Gruber, S., Carambia, A., Boretius, S., Leuschner, I., Becker, T., Rabe, B., Herkel, J., Wunderlich, F.T., Mittrücker, H.W., Rose-John, S. and Schmidt-Arras, D. (2017) Il-6 Trans-Signaling Is Essential for the Development of Hepatocellular Carcinoma in Mice. Hepatology, 65, 89-103.
[30] Zhou, M., Yang, H., Learned, R.M., Tian, H. and Ling, L. (2017) Non-Cell-Autonomous Activation of Il-6/Stat3 Signaling Mediates Fgf19-Driven Hepatocarcinogenesis. Nature Communications, 8, 16.
[31] Jiang, J., Wang, G.Z., Wang, Y., Huang, H.Z., Li, W.T. and Qu, X.D. (2018) Hypoxia-Induced Hmgb1 Expression of Hcc Promotes Tumor Invasiveness and Metastasis Via Regulating Macrophage-Derived Il-6. Experimental Cell Research, 367, 81-88.
[32] Sun, C., Sun, H.Y., Zhang, C. and Tian, Z.G. (2015) Nk Cell Receptor Imbalance and Nk Cell Dysfunction in Hbv Infection and Hepatocellular Carcinoma. Cellular & Molecular Immunology, 12, 292-302.
[33] Jin, X.M. and Bi, J.C. (2022) Prospects for Nk-Based Immunotherapy of Chronic Hbv Infection. Frontiers in Immunology, 13, 10.
[34] Sung, P.S. and Jang, J.W. (2018) Natural Killer Cell Dysfunction in Hepatocellular Carcinoma: Pathogenesis and Clinical Implications. International Journal of Molecular Sciences, 19, 23.
[35] Sun, C., Sun, H.Y., Xiao, W.H., Zhang, C. and Tian, Z.G. (2015) Natural Killer Cell Dysfunction in Hepatocellular Carcinoma and Nk Cell-Based Immunotherapy. Acta Pharmacologica Sinica, 36, 1191-1199.
[36] Yonejima, A., Mizukoshi, E., Tamai, T., Nakagawa, H., Kitahara, M., Yamashita, T., Arai, K., Terashima, T., Iida, N., Fushimi, K., Okada, H., Yamashita, T., Sakai, Y., Honda, M. and Kaneko, S. (2019) Characteristics of Impaired Dendritic Cell Function in Patients with Hepatitis B Virus Infection. Hepatology, 70, 25-39.
[37] Li, W.Y., Chen, G.J., Peng, H.L., Zhang, Q.F., Nie, D.Y., Guo, T., Zhu, Y.X., Zhang, Y.H. and Lin, M. (2024) Research Progress on Dendritic Cells in Hepatocellular Carcinoma Immune Microenvironments. Biomolecules, 14, 16.
[38] Ying, S.D., Liu, H.Y., Zhang, Y.L. and Mei, Y. (2025) Harnessing Dendritic Cell Function in Hepatocellular Carcinoma: Advances in Immunotherapy and Therapeutic Strategies. Vaccines, 13, 23.
[39] Zhao, H.J., Yu, Y.T., Wang, Y.C., Zhao, L.H., Yang, A.L., Hu, Y.F., Pan, Z.Y., Wang, Z.X., Yang, J.R., Han, Q.J., Tian, Z.G. and Zhang, J. (2022) Cholesterol Accumulation on Dendritic Cells Reverses Chronic Hepatitis B Virus Infection-Induced Dysfunction. Cellular & Molecular Immunology, 19, 1347-1360.
[40] Cheng, Y., Gunasegaran, B., Singh, H.D., Dutertre, C.A., Loh, C.Y., Lim, J.Q., Crawford, J.C., Lee, H.K., Zhang, X.M., Lee, B., Becht, E., Lim, W.J., Yeong, J., Chan, C.Y., Chung, A., Goh, B.K.P., Chow, P.K.H., Chan, J.K.Y., Ginhoux, F., Tai, D., Chen, J.M., Lim, S.G., Zhai, W., Choo, S.P. and Newell, E.W. (2021) Non-Terminally Exhausted Tumor-Resident Memory Hbv-Specific T Cell Responses Correlate with Relapse-Free Survival in Hepatocellular Carcinoma. Immunity, 54, 1825-1841.
[41] Hao, X.L., Chen, Y.Y., Bai, L., Wei, H.M., Sun, R. and Tian, Z.G. (2021) Hbsag-Specific Cd8+ T Cells as an Indispensable Trigger to Induce Murine Hepatocellular Carcinoma. Cellular & Molecular Immunology, 18, 128-137.
[42] Liu, L.L., Liu, J.W., Li, P., Luo, J.J., Qin, R., Peng, Q., Li, B., Wei, X.Y., Wang, T., Shi, H.Y., Wang, M.D., Li, C., Fang, W.J., Chen, W., Xu, X., Yang, T., Yin, W.W. and Zeng, X. (2023) Single-Cell Analysis Reveals Hbv-Specific Pd-1+Cd8+ Trm Cells in Tumor Borders Are Associated with Hbv-Related Hepatic Damage and Fibrosis in Hcc Patients. Journal of Experimental & Clinical Cancer Research, 42, 17.
[43] Cho, H.J. and Cheong, J.Y. (2021) Role of Immune Cells in Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma. International Journal of Molecular Sciences, 22, 12.
[44] Gao, Y.N., Zhang, Z.X., Huang, X.T., You, M.J., Du, C.Z., Li, N., Hao, Y.J., Wang, K., Ding, X., Yang, F.Q., Cheng, S.Q., Luo, J.J., Chen, R.S. and Yang, P.Y. (2025) Hbv-Associated Hepatocellular Carcinomas Inhibit Antitumor Cd8+ T Cell Via the Long Noncoding Rna Hdac2-As2. Nature Communications, 16, 18.

[45] Zhang, J., Hu, C.W., Xie, X.X., Qi, L.Z., Li, C.Z. and Li, S.Z. (2023) Immune Checkpoint Inhibitors in Hbv-Caused Hepatocellular Carcinoma Therapy. Vaccines, 11, 21.
[46] Broholm, M., Mathiasen, A.S., Apol, A.D. and Weis, N. (2024) The Adaptive Immune Response in Hepatitis B Virus-Associated Hepatocellular Carcinoma Is Characterized by Dysfunctional and Exhausted Hbv-Specific T Cells. Viruses-Basel, 16, 14.
[47] Wang, S., Meng, L.J., Xu, N., Chen, H., Xiao, Z.F., Lu, D., Fan, X.H., Xia, L.M., Chen, J., Zheng, S.S., Wei, Q., Wei, X.Y. and Xu, X. (2024) Hepatocellular Carcinoma-Specific Epigenetic Checkpoints Bidirectionally Regulate the Antitumor Immunity of Cd4+T Cells. Cellular & Molecular Immunology, 21, 1296-1308.
[48] Venzin, V., Beccaria, C.G., Perucchini, C., Delfino, P., Bono, E.B., Giustini, L., Moalli, F., Grillo, M., Fumagalli, V., Laura, C., Di Lucia, P., Reinhard, K., Petschenka, J., Omokoko, T.A., Celant, A., Ottolini, S., Kawashima, K., Rava, M., De Giovanni, M., Inverso, D., Kuka, M., Kennedy, P.T.F., Guilliams, M., Casorati, G., Pedica, F., Ponzoni, M., Sahin, U., Le Bert, N., Bertoletti, A., Vascotto, F., Guidotti, L.G. and Iannacone, M. (2025) Cd4+ T Cells License Kupffer Cells to Reverse Cd8+ T Cell Dysfunction Induced by Hepatocellular Priming. Nature Immunology, 26, 40.
[49] Khlaiphuengsin, A., Chuaypen, N., Sodsai, P., Buranapraditkun, S., Boonpiyathad, T., Hirankarn, N. and Tangkijvanich, P. (2020) Decreased of Baff-R Expression and B Cells Maturation in Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma. World Journal of Gastroenterology, 26, 13.
[50] Zhang, Z., Ma, L.J., Goswami, S., Ma, J.Q., Zheng, B.H., Duan, M., Liu, L.Z., Zhang, L.J., Shi, J.Y., Dong, L.Q., Sun, Y.M., Tian, L.Y., Gao, Q. and Zhang, X.M. (2019) Landscape of Infiltrating B Cells and Their Clinical Significance in Human Hepatocellular Carcinoma. Oncoimmunology, 8, 11.
[51] Garnelo, M., Tan, A., Her, Z.S., Yeong, J., Lim, C.J., Chen, J.M., Lim, K.H., Weber, A., Chow, P., Chung, A., Ooi, L.L.P., Toh, H.C., Heikenwalder, M., Ng, I.O.L., Nardin, A., Chen, Q.F., Abastado, J.P. and Chew, V. (2017) Interaction between Tumour-Infiltrating B Cells and T Cells Controls the Progression of Hepatocellular Carcinoma. Gut, 66, 342-351.
[52] Liu, X., Liu, Z.L., Zhu, C.Z., Kobayashi, T., Lei, P.J., Shi, Y., Yuan, D.D., Wang, J.G., Li, M., Matsui, A., Mafra, K., Ando, T., Kojo, K., Schleinhege, R., Miyazaki, K., Huang, P.G., Kuang, M., Bod, L. and Duda, D.G. (2025) Inhibiting B Cells Enhances the Efficacy of Sting Agonism or Immune Checkpoint Blockade in Hepatocellular Carcinoma. Nature Communications, 16, 17.