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Hot Topic Commentary

Hepatitis B Virus Insertional Mutagenesis and Hepatocellular Carcinoma: Mechanisms and Clinical Significance

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Hepatitis B virus (HBV) infection remains a major global health burden, with an estimated 254 million people living with chronic infection worldwide in 2022.[1] Chronic HBV infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC), accounting for more than half of HCC cases globally.[2] Despite vaccination and antiviral therapy, HBV-related HCC continues to contribute substantially to cancer-related mortality.[3,4] Importantly, HBV infection confers a risk of HCC even in the absence of cirrhosis, suggesting direct virus-associated genomic mechanisms beyond inflammation and fibrosis.[5] Although HBV lacks a viral oncogene, it can promote tumor development through genetic damage, chromosomal instability, and the expression of viral regulatory elements.[3,6]

HBV replicates through reverse transcription of pregenomic RNA, generating relaxed circular DNA, which is converted to covalently closed circular DNA (cccDNA) by host machinery.[4,7] Some viral genomes form double-stranded linear DNA, which cannot produce infectious progeny but can integrate into host chromosomes.[5] These linear molecules resemble cellular DNA breaks and enter host repair pathways, generating integration-competent viral DNA early in infection.[7] HBV integration has been detected as early as 23–49 days after infection, indicating that integration is not merely a late consequence of chronic infection.[6] Integrated HBV DNA can remain transcriptionally active and contribute to circulating hepatitis B surface antigen (HBsAg) levels, thereby promoting immune exhaustion and viral persistence.[4,7]

HBV lacks an integrase and relies on host DNA repair. Double-stranded linear DNA molecules resemble cellular double-strand breaks and are incorporated into host chromosomes primarily through nonhomologous end joining and microhomology-mediated end joining. Because both pathways are error prone, HBV integration generates small insertions, deletions, and complex virus-host junctions that contribute to chromosomal instability.[7,8] Although the initial sites of integration in the host genome are largely random, viral DNA linearization breakpoints occur at specific hotspots (Fig. 1).[3] Hepatocytes harboring oncogenic integrations may undergo clonal expansion.[8] HBV integrations are enriched in regions of high chromatin accessibility, active transcription, early replication, and genomic fragility, and the breakpoint pattern can influence which viral genes remain intact after integration.[3] This commentary reviews the mechanisms of HBV integration, common HBV breakpoints, and their implications for HCC risk and clinical management.

A well-supported mechanism of HBV-driven oncogenesis is enhancer-mediated *cis*-activation of adjacent host genes. HBV enhancer I (HBV-Enh I) and the X region are preferentially preserved in integrated viral sequences, suggesting positive clonal selection of hepatocytes harboring these integrations.[8,9] HBV-Enh I can act in *cis* to drive the expression of nearby oncogenes, such as telomerase reverse transcriptase (*TERT*) and the *MYC* proto-oncogene (*MYC*) (Fig. 2).[10] Ectopic *MYC* overexpression driven by HBV-Enh I integration has been reported to promote HCC cell migration and invasion.[10]

A preferential breakpoint at the 3′ end of hepatitis B virus X protein (HBx) results in C-terminally truncated HBx variants with enhanced oncogenic potential.[9] These 3′-deleted proteins lack regulatory domains involved in p53-dependent transcription, Sp1 binding, and growth suppression, thereby promoting cellular proliferation, transformation, and invasion.[9] C-terminally truncated HBx was detected in up to 79.3% of HBV-associated HCC cases and was associated with venous invasion, increased c-Jun activity, metalloproteinase expression, mitogen-activated protein kinase activation, and cell-cycle dysregulation—features of metastatic potential.[9] The generation of C-terminally truncated HBx proteins is supported by experimental and clinical studies, although its relative contribution to human hepatocarcinogenesis remains under investigation.

Nontumor liver tissue contains a greater diversity of unique HBV integration sites, which are generally low frequency and nonclonal. In contrast, tumor tissue contains fewer unique integration sites but shows substantially greater clonality, indicating the selective expansion of hepatocytes harboring oncogenic integrations.[3,10] Although HBV integration occurs in only approximately 0.1% of infected hepatocytes, integrated HBV DNA has been detected in 85%–90% of HBV-related HCCs, indicating strong biological selection.[10] Integrations in nontumor liver tissue are largely transcriptionally silent, whereas tumor-associated integrations occur

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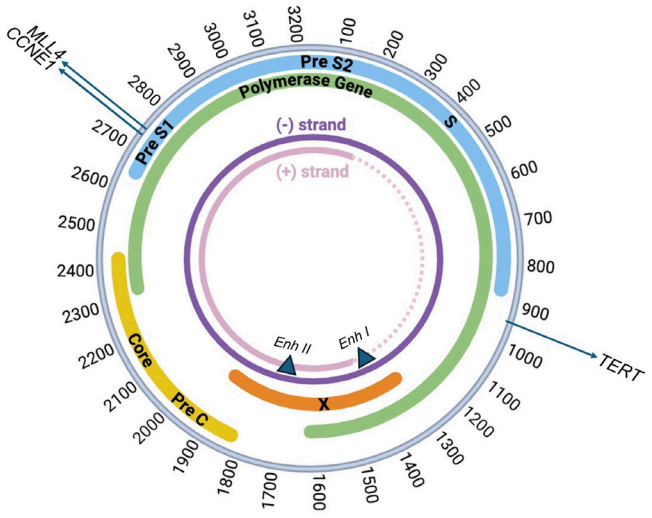


Fig. 1. HBV genomic breakage/linearization hotspots and common integration-receptive host genes. A circular map of the approximately 3.2-kb HBV genome shows the overlapping open reading frames (preS/S, polymerase, core/precore, and X), positive and negative strands, and regulatory elements (enhancer I [Enh I] and enhancer II [Enh II]). Common viral breakpoint regions (green arrows) and associated host integration hotspots, including *TERT*, *KMT2B/MLL4*, and *CCNE1*, are shown. Enrichment is commonly observed within approximately 100 bp of the 5′ and 3′ ends of viral genes, particularly around the HBx and preS/S regions. Core and polymerase regions are more frequently truncated, whereas HBV-Enh I and the X gene region are preferentially preserved. bp, base pairs; *CCNE1*, cyclin E1; Enh, enhancer; HBV, hepatitis B virus; HBx, hepatitis B virus X protein; kb, kilobases; *KMT2B*, lysine methyltransferase 2B; *MLL4*, mixed-lineage leukemia 4; *TERT*, telomerase reverse transcriptase.

near functionally relevant regions.[3,8]

HBV integration events can also promote hepatocarcinogenesis by inactivating tumor suppressor pathways. Tumor suppressor alterations, including mutations and deletions, were identified in up to 48% of HBV-related tumors, compared with 16% of non-HBV-related HCCs.[10] Homozygous deletions of cyclin-dependent kinase inhibitor 2A (*CDKN2A*) occurred in 2%–12%, retinoblastoma 1 (*RB1*) alterations in 3%–8%, and p53 mutations in 41% of HBV-related HCCs.[10] HBV integration-associated telomeric deletions increase the risk of biallelic inactivation of flanking tumor suppressor genes.[11] Truncated HBx can suppress p53-dependent transcriptional activity. Loss of *RB1* promotes uncontrolled S-phase entry and cellular proliferation, whereas *CDKN2A* loss impairs both *RB1* and p53 tumor suppressor activity.[9]

Integrated HBV DNA frequently exists as concatemers that generate unstable virus-host junctions prone to recombination and breakage.[11] These events can cause genomic restructuring, including nonhomologous chromosomal fusions, dicentric chromosomes, and megabase-scale deletions.[10,11] In one genomic analysis, HBV-mediated telomeric deletion events were identified in 8% of HCCs; 40 structural rearrangements resulted in the deletion or inactivation of 244 tumor suppressor genes, including tumor protein p53 (*TP53*) and *RB1*.[11] A 14.9-Mb telomeric deletion encompassing *TP53*, with mutation of the remaining allele, was reported, exemplifying HBV-driven biallelic inactivation.[11] In HBV-associated HCC, p53 dysfunction is consistently associated with more aggressive tumor biology and a poorer prognosis.[10,11] Nevertheless, current evidence suggests that direct disruption of tumor suppressor genes is less common than enhancer-mediated oncogene activation and integration-associated structural rearrangements.

Genome-wide sequencing studies have identified recurrent integration hotspots in HCC involving *TERT* in 20%–50% of cases, lysine methyltransferase 2B/mixed-lineage leukemia 4 (*KMT2B/MLL4*) in 1%–10%, and cyclin E1 (*CCNE1*) in approximately 5%. These frequencies exceed those expected by chance and are associated with clonal expansion and altered gene expression (Table 1).[12]

TERT is the most frequent HBV integration hotspot, with tumor-level frequencies reported as 35.8% (34/95),[13] 23.7% (101/426),[3] and 29.8% (28/94).[14] *TERT* integration has been associated with more aggressive tumor behavior.[13] *TERT* promoter integrations were rare (3%) in nontumor liver tissue, indicating strong positive selection.[13] Insertion of HBV-Enh I into the *TERT* promoter region increases *TERT* transcription through *cis*-activation by recruiting host transcription factors to the chimeric *TERT* promoter, thereby activating telomerase.[13] HBV integration at *TERT* and *TERT* promoter mutations or other alterations are generally mutually exclusive, suggesting distinct but functionally redundant mechanisms of telomerase reactivation.[15]

KMT2B/*MLL4* is the second most consistently reported recurrent hotspot. *KMT2B* and *KMT2C* encode histone H3 lysine 4 (H3K4) methyltransferases involved in chromatin remodeling and transcriptional regulation.[12] Disruption of these genes through HBV integration can lead to dysregulated transcription and aberrant chromatin states. Reported frequencies include 10.5% in a 153-case capture-sequencing series, 7.3% in a 426-case cohort, 10.2% in an 88-case dataset, and 1.7% in a 177-case cohort.[12]

CCNE1 regulates the G1/S cell-cycle transition, and its overexpression can drive uncontrolled cellular proliferation and genomic instability.[12,15] Recurrent *CCNE1* integrations were identified in 4 of 88 (4.5%), 7 of 426 (1.6%), and 4 of 177 (2.3%) HBV-related HCCs.[12] Integration at *CCNE1* can upregulate the gene through the insertion of viral enhancer elements or structural rearrangements; these events were tumor-specific and positively selected.[12,14]

MYC and plasmacytoma variant translocation 1 (*PVT1*) are less frequently recognized HBV integration targets.[12,15] HBV integration can induce focal *MYC* amplification through structural rearrangements or enhancer-mediated activation, thereby promoting proliferation, clonal expansion, and chromosomal instability.[10,15]

Reported frequencies of HBV integration patterns vary substantially among cohorts because of differences in geo-

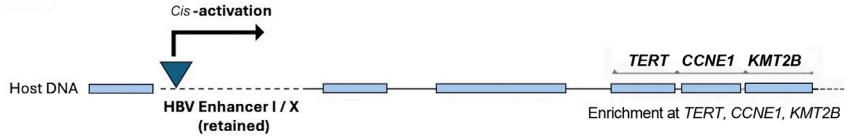


Fig. 2. *Cis*-activation mechanisms of HBV integration-mediated hepatocarcinogenesis. Retention of HBV enhancer I/X regulatory elements at integration sites promotes *cis*-regulatory activation of adjacent host genes. Clonal selection enriches integration events near oncogenic loci, including *TERT*, *CCNE1*, and *KMT2B*, supporting their potential roles as functional drivers of hepatocarcinogenesis. *CCNE1*, cyclin E1; HBV, hepatitis B virus; *KMT2B*, lysine methyltransferase 2B; *TERT*, telomerase reverse transcriptase.

Table 1. Recurrent HBV-host integration-associated structural alterations

Host locus	Key effect	Mechanism	Frequency in HBV-related HCC	Cohort details
TERT	Telomerase activation through *cis*-regulatory enhancer hijacking	Strongest recurrent hotspot; supports early clonal advantage and telomere maintenance	20%–50%	18/88 (20.5%); 101/426 (23.7%); 39/153 (25.5%); 48/177 (27.1%)
KMT2B/MLL4	Histone methyltransferase activity, chromatin remodeling, and epigenetic dysregulation	Recurrent epigenetic driver; promotes tumorigenesis through enhancer/chromatin dysregulation	2%–11% in large series; higher in some small cohorts	9/88 (10.2%); 31/426 (7.3%); 16/153 (10.5%); 3/177 (1.7%); 6/27 (22.2%)
CCNE1	G1/S transition and replication stress	Supports unscheduled cell-cycle entry and genomic instability	1%–5%	4/88 (4.5%); 7/426 (1.6%); 4/177 (2.3%)
CCNA2	Cell-cycle progression	Less frequent but recurrent; suggests broader cell-cycle selection beyond *CCNE1*	2% in one major cohort	8/426 (1.9%)
MYC and *PVT1* region	Oncogene amplification and *cis*-activation	Viral enhancer donation and structural amplification can activate *MYC* programs	Recurrent, but the frequency has not been consistently reported across cohorts	–
TP53	Structural disruption or deletion rather than hotspot integration	Tumor suppressor alteration associated with uncontrolled proliferation	Recurrent, but the frequency has not been consistently reported across cohorts	–

Frequencies are approximate and vary by sequencing method, cohort size, and hotspot. *TERT* is the most reproducible integration hotspot across published HBV-related HCC series, followed by *KMT2B*/*MLL4* and *CCNE1*. *CCNA2*, cyclin A2; *CCNE1*, cyclin E1; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; *KMT2B*, lysine methyltransferase 2B; *MLL4*, mixed-lineage leukemia 4; *MYC*, *MYC* proto-oncogene; *PVT1*, plasmacytoma variant translocation 1; *TERT*, telomerase reverse transcriptase; *TP53*, tumor protein p53.

graphic region, HBV genotype, disease stage, viral replication level, and sequencing methodology. Genotype C has been associated with more HBV integration events, greater clonal expansion, and more frequent integration into cancer-associated genes.[12,15] A meta-analysis of more than 10,000 patients found that HCC developed in 25% of patients with genotype C versus 13% of those with genotype B.[16]

Passenger HBV integrations, typically found in nontumor liver tissue, occur randomly at low clonal frequencies, whereas driver integrations can contribute to oncogenesis by activating proto-oncogenes, inactivating tumor suppressors, or inducing genomic instability, thereby conferring a proliferative advantage and promoting clonal expansion.[3,8,12,17] Only 3%–5% of HBV integration sites overlap between tumor and adjacent nontumor tissue within the same patient, indicating clonal selection.[3,17] Oncogenic integration events may arise early, including in preneoplastic dysplastic nodules, and expand during tumor progression.[6,8]

HBV acts primarily as a regulatory mutagen by donating enhancer activity that activates adjacent oncogenes and as a structural mutagen by inducing chromosomal instability, telomeric deletions, and copy-number alterations.[10,11] Truncated HBx further amplifies oncogenic signaling by suppressing p53-dependent transcription, activating mitogen-activated protein kinase signaling, and dysregulating the cell cycle.[9] Together, these mechanisms may help explain the persistent risk of HCC despite viral suppression and in the absence of cirrhosis.

HBV integration occurs early in infection, including in patients with minimal liver injury, particularly during high-level viral replication.[6,7] The 2025 American Association for the Study of Liver Diseases/Infectious Diseases Society of America guideline suggests antiviral therapy for patients in the immune-tolerant phase who are older than 40 years or have significant hepatic inflammation or fibrosis; for younger patients interested in earlier treatment, it recommends shared decision-making.[18] Because evidence that treatment of otherwise low-risk patients in the immune-tolerant phase reduces HCC risk remains uncertain, the possibility that suppression of high-level HBV replication could reduce insertional mutagenesis and HCC risk warrants prospective evaluation.

Another emerging area of investigation is the interaction between HBV integration and the tumor immune microenvironment. Integrated HBV DNA can remain transcriptionally active and produce viral transcripts and proteins, particularly HBsAg and HBx, even when viral replication is suppressed.[5,17] These persistently expressed viral antigens may influence local hepatic immune responses, with potential downstream effects on antitumor immunity and responses to immune checkpoint inhibitor therapy.[17] This hypothesis warrants evaluation in controlled studies.

Although early studies suggested that circulating chimeric HBV-host DNA might enable earlier detection of residual or recurrent disease, clinical implementation remains limited by the need for highly specialized detection methods, methodological heterogeneity, and the lack of standardized assays.[17,19] Commercial clinical laboratories currently offer serum HBV DNA quantification and related viral biomarkers but do not offer validated integration-site mapping as a standard-of-care assay.[17,19] Detection of recurrent driver integrations involving *TERT*, *KMT2B*, or *CCNE1* may help distinguish random background integrations from tumor-specific events and clarify whether a lesion is linked

to an HBV-driven oncogenic pathway.[12,17] Patient-specific HBV-host junction sequences may serve as molecular fingerprints for monitoring recurrence.[12,19] However, integration profiling has not been validated for routine prognostic decision-making or for guiding surveillance, resectability, or systemic therapy.

HBV integration is an early and intrinsic mechanism of hepatocarcinogenesis that can operate independently of cirrhosis. Although most integrations remain silent, a subset may undergo clonal selection through enhancer-mediated oncogene activation, tumor suppressor disruption, chromosomal instability, and the production of truncated HBx proteins. Thus, integrated HBV DNA can act as both a regulatory and a structural mutagen, potentially helping to explain the persistent risk of HCC in HBV infection despite viral suppression.

The mechanisms of HBV integration provide an additional rationale for early and sustained suppression of viral replication. Although currently available nucleos(t)ide analogues do not eliminate preexisting integrations or cccDNA, antiviral therapy may reduce the formation of new integration events by suppressing viral replication and decreasing the generation of integration-competent double-stranded linear DNA intermediates. Observational data show that antiviral therapy is associated with a lower HCC incidence in broader populations with chronic hepatitis B, but whether treatment during the immune-tolerant phase reduces HCC risk remains uncertain.[18,20] Large, multicenter, long-term controlled studies are needed to test this hypothesis.

Prospective multicenter cohorts are needed to validate associations of specific integration sites—such as *TERT*, *KMT2B*, *CCNE1*, and *MYC*/*PVT1*—and tumor suppressor-disrupting structural events with prognosis, recurrence risk, and vascular invasion. Standardized integration assays are also needed to determine whether serial monitoring of circulating HBV-host junction DNA can reliably identify minimal residual disease or early recurrence and whether integration-site analysis improves risk stratification.

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Conflict of interest

GYW has served as Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. He was not involved in the editorial review of or decision to publish this article. BT has no conflicts of interest related to this publication.

Author contributions

Conceptualization of the commentary (GYW), information collection and drafting of the manuscript (BT), and revision of the manuscript (GYW, BT). Both authors approved the final version of the manuscript.

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