Editorial

Unraveling the Genomic Imprint of HBV in Hepatocarcinogenesis

*Hiroyasu Ito**

* Department of Joint Research Laboratory of Clinical Medicine, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan.
E-mail: hiroyasu.ito@fujita-hu.ac.jp

〔Lab Med Int 2026; 5(1): 1-2〕

See article volume 5(1): 3-19

In this comprehensive review, Dr. Ogata presents a masterful synthesis of four decades of investigation into hepatitis B virus (HBV) integration and its role in hepatocellular carcinoma (HCC) development, a relationship first highlighted in early molecular studies. Advances in sequencing technologies—from Southern blotting and Sanger sequencing to second- and third-generation sequencing—have progressively refined our understanding of how HBV integrates into the human genome, particularly within repetitive genomic regions [1]. One of the most striking contributions detailed in this review is the discovery of HBV integration into centromeric alpha satellite DNA (αSat), first reported by Dr. Ogata. This finding was later reinforced by computational approaches such as SurVirus [2] and long-read sequencing analyses [3], which highlighted the centromere—previously inaccessible due to its repetitive structure—as a key locus where HBV-induced genomic instability may originate. The ability of HBV to integrate into αSat suggests a direct mechanism between viral infection, disruption of centromere function, and aneuploidy, widely observed in HCC. This review also places HBV integration within broader cancer genomics efforts including TCGA and ICGC projects, which revealed that HBV frequently targets major cancer-related genes such as *TERT*, *KMT2B*, and *CCNE1* [1,4]. Structural variations (SVs)—including chromosomal amplifications, deletions, and translocations—were shown to colocalize with HBV integration sites, with some SVs occurring decades before clinical HCC diagnosis [4]. Long-read sequencing has further clarified these events, revealing that HBV can induce not only local but also distant genomic alterations, reshaping the tumor genome in profound ways [3]. Beyond genomic mapping, emerging proteogenomic insights show that although HBV-derived proteins may be detectable in HCC tissues, their expression does not strongly correlate with clinical outcomes [5]. These results suggest that while HBV protein expression may diminish over time, the genomic scars left behind—such as HBV-driven SVs—continue to influence tumor biology. The clinical implications of these findings are likely to be significant. Advances in liquid biopsy technology—including methylated DNA assays and cfDNA-based repeat profiling—have enabled promising new avenues for early HCC detection [6]. Meanwhile, therapeutic strategies targeting telomerase, particularly anti-*TERT* approaches, have gained increasing traction due to the central role of *TERT* activation in HBV-related HCC [7]. Taken together, this review illustrates a cohesive narrative: HBV integration is not a random genomic event but a structured, biologically significant process that interacts with centromeric biology, genomic stability, and cancer evolution. As long-read sequencing and telomere-to-telomere genome assemblies mature, repetitive DNA elements—once viewed as "genetic dark matter"—are emerging as critical components in understanding HBV-mediated hepatocarcinogenesis [8]. This review not only synthesizes past knowledge but also illuminates future directions, urging deeper investigation into HBV integration within repetitive genomic elements and its implications for prevention, early detection, and personalized therapy of HBV-related HCC.

References

1) Totoki Y, Tatsuno K, Covington KR, et al. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes.

Nat Genet. 2014; 46(12): 1267-73.
2) Rajaby R, Zhou Y, Meng Y, et al. SurVirus: a repeat-aware virus integration caller. Nucleic Acids Res. 2021; 49(6): e33.
3) Zhuo Z, Rong W, Li H, et al. Long-read sequencing reveals the structural complexity of genomic integration of HBV DNA in hepatocellular carcinoma. NPJ Genom Med. 2021; 6(1): 84.
4) Qian Z, Liang J, Huang R, et al. HBV integrations reshaping genomic structures promote hepatocellular carcinoma. Gut. 2024; 73(7): 1169-82.
5) Gao Q, Zhu H, Doung L, et al. Integrated proteogenomic characterization of HBV-related hepatocellular carcinoma. Cell. 2019; 179(2): 561-77.
6) Sun J, Sun X, He W, et al. A liquid biopsy approach detects HCC and identifies GJA4 as a potential biomarker for HBV-HCC via plasma cfDNA methylome profiling. Clin Epigenetics. 2025; 17(1): 98.
7) Ningarhari M, Caruso S, Hirsch TZ, et al. Telomere length is key to hepatocellular carcinoma diversity and telomerase addiction is an actionable therapeutic target. J Hepatol. 2021; 74(5): 1155-66.
8) Altemose N, Logsdon GA, Bzikadze AV, et al. Complete genomic and epigenetic maps of human centromeres. Science. 2022; 376(6588): eabl4178.