

New research sheds light on the molecular mechanisms by which a virus contributes to cancer

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer deaths worldwide and is associated with exposure to hepatitis B virus (HBV). Patients carrying the virus have a 100-fold greater risk of developing HCC, but exactly why was unclear until now. Wing Kin Sung

at the A*STAR Genome Institute of Singapore and the National University of Singapore, John Luk at the A*STAR Institute of Molecular and Cell Biology and the National University of Singapore and co-workers have now identified genetic mechanisms by which a virus contributes to this common form of cancer.

To investigate, the researchers obtained samples of liver tumors and adjacent non-cancerous tissues from 88 Chinese HCC patients, and used advanced DNA sequencing technology to analyze their genomes for HBV integration sites. They identified 399 sites at which HBV was integrated into the genome, and found that they were randomly distributed across the whole genome, but that most were clustered within a small number of 'hotspots'. The vast majority of the integration sites (344 out of 399; more than 86%) were found only in the samples obtained from [liver tumors](#).

The researchers analyzed breakpoints in the HBV genome—sites at which the circular genome of the virus breaks before being integrated into the genome of the host cell. They found that about 40% of breakpoints occur within a restricted region where three critical genetic elements are located.

This region, approximately 400 base pairs in length, contains the enhancer, a short regulatory sequence that binds proteins and enhances expression of the viral genes; the X gene, which plays critical roles in infection and replication; and the core gene, which encodes a protein envelope for the viral DNA. The high number of breakpoints in the region may facilitate HBV insertion into the [host genome](#), which in turn may promote [cancer formation](#) by interrupting the coding sequences of [tumor suppressor genes](#).

The researchers also examined the prevalence of HBV insertions in DNA obtained from HCC patients. More than 92% of the patients in the

sample had HBV integrated into their genomes, and the majority of these were found only in DNA from the tumors.

Non-cancerous tissues were also found to contain integrated viral genomes, but DNA isolated from the tumors tended to have more HBV integration sites. Thus, HBV integration patterns differ between cancerous and non-cancerous tissues, and there is a complex relationship between HBV integration and cancer development.

More information: Sung, W. K., Zheng, H., Li, S., Chen, R., Liu, X., et al. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. *Nature Genetics* 44, 765–769 (2012). [Article](#)

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