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Camouflaging of viral DNA could be crucial step in progression of cancers

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An estimated 15% of cancer cases can be linked to a viral infection, however the biological changes that cause some asymptomatic carriers of a virus to develop full-blown tumors are not well understood. In a study published online in *Genome Research*, scientists have mapped a chemical modification of DNA in three oncogenic viruses (Epstein-Barr, human papilloma virus, and hepatitis B virus) and found that the viral genome undergoes critical changes during the progression of disease, with implications for the development of new methods of prevention, diagnosis, and treatment.

Worldwide, most people are already infected with the Epstein-Barr virus, and millions are infected with the human papilloma virus and the hepatitis B virus. Many of these individuals will develop disease, and some will eventually develop a viral-related cancer such as lymphoma, liver cancer, or cervical cancer. Understanding how infections of viruses such as these can progress to cancer in some individuals is essential to the development of new methods to attack the virus and prevent malignancies.

Similarly to cellular organisms, the viral genome is subject to chemical modification. In animals, it is now appreciated that these "epigenetic" properties of genomes are variable in different tissues of the same individual, between identical twins, and in disease states. There are considerable efforts underway to map the landscape of epigenetic marks in the genomes of many organisms, yet it remains technically challenging to resolve the catalog of modifications at every base of DNA. However,

significant clinical importance and a relatively small genome make viruses excellent targets for whole-genome epigenetic mapping.

In this study, an international team of scientists has determined the complete map of DNA methylation, a specific type of chemical modification, for the entire genome of the Epstein-Barr virus, the human papilloma virus, and the hepatitis B virus. Importantly, the researchers compared the DNA "methylomes" of asymptomatic carriers of each virus, patients with active infections, and patients harboring cancerous tumors. "When we move from asymptomatic carriers of the virus to intermediate stages of the disease, and we end with the established associated cancer, the genome of the virus did not change that much," explained Dr. Manel Esteller of the Bellvitge Institute for Biomedical Research (IDIBELL) in Barcelona, senior author of the report. "But its epigenome is completely different." Remarkably, Esteller and colleagues found that the viral genomes become progressively methylated in patients who had developed cancer.

Esteller noted that the viruses use our cell's DNA methylation machinery to modify its own DNA, and could be using methylation to hide itself from the immune system, effectively escaping the body's defense mechanisms in malignant cells. "This a very exciting result that can explain why some of these viruses can survive for such prolonged times in our body."

These findings could lead to several new avenues for the study, diagnosis, and treatment of viral-related disease and cancer. It is likely that the changes observed in the methylomes of these three DNA viruses could extend to other oncogenic viruses, and perhaps even viruses that cause illnesses ranging from the flu to AIDS. Esteller also explained that viral DNA methylation could be used as a biomarker for progression of disease, and furthermore, drugs that remove methylation from DNA could be used against viruses to prevent and erase the camouflaging

employed to evade the immune system.

More information: The dynamic DNA methylomes of double-stranded DNA viruses associated with human cancer. *Genome Res.* doi:10.1101/gr.083550.108. www.genome.org

Source: Cold Spring Harbor Laboratory