Viruses and cancer: DNA sequencing reveals viral components in malignant tumor samples

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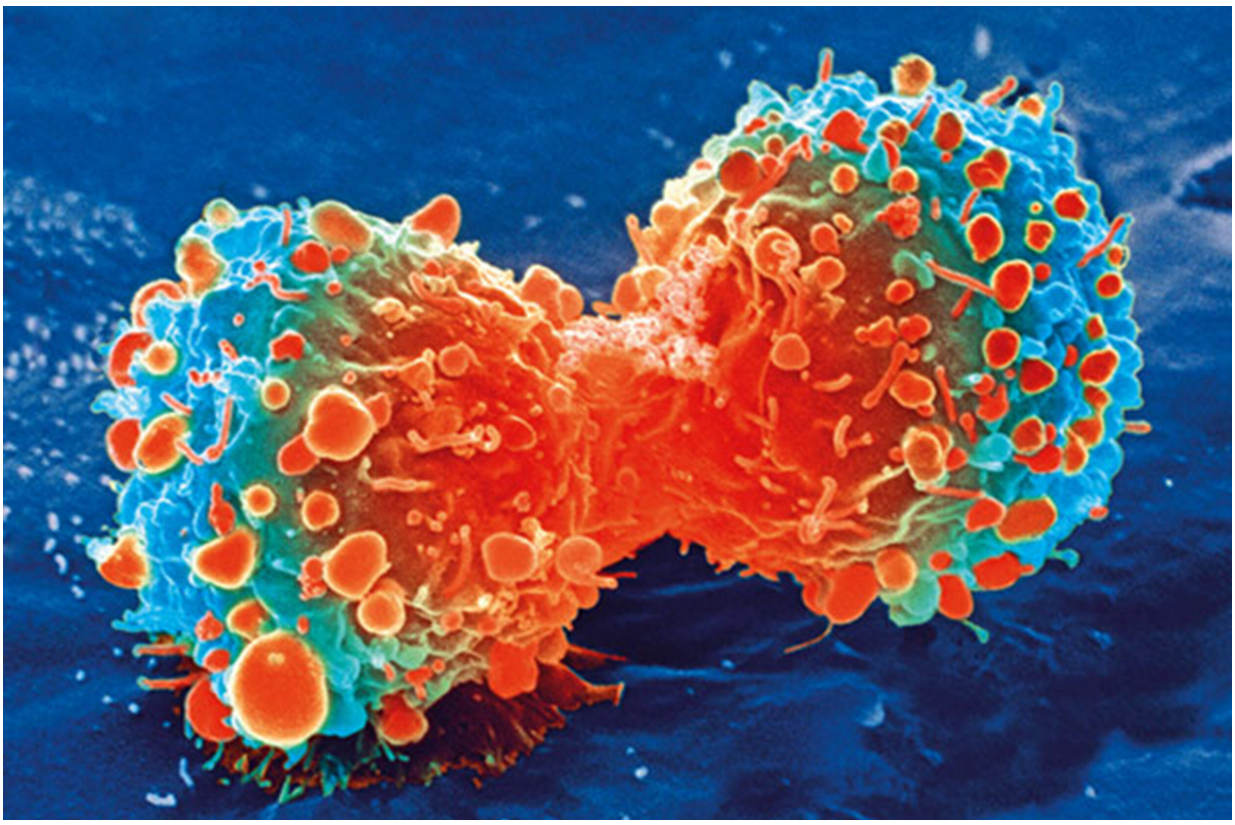

Cancer cell during cell division. Credit: National Institutes of Health

Scientists from the German Cancer Research Center systematically investigated the DNA of more than 2,600 tumor samples from patients

with 38 types of cancer to discover traces of viruses, which they found in 13 percent of the samples studied. The researchers also identified mechanisms that the pathogens use to trigger carcinogenic mutations in the DNA. The work is part of the Pan-Cancer Analysis of Whole Genomes (PCAWG), an initiative launched by the International Cancer Genome Consortium (ICGC).

The World Health Organization (WHO) estimates that more than 15 percent of all cancers are directly or indirectly attributable to infectious pathogens. The International Agency for Research on Cancer (IARC) in Lyon has classified 11 different pathogens—viruses, bacteria, and worms—as carcinogenic agents and estimates that one in ten cancers is linked to viruses. Throughout the world, a total of 640,000 cancers each year are caused by human papillomaviruses (HPV) alone.

A new paper has now been published by an international team of genome researchers led by Peter Lichter from the German Cancer Research Center (DKFZ) to provide a precise overview of which viruses play a role in which cancers. The researchers also looked for viruses that have not previously been associated with carcinogenesis or even ones that were completely unknown.

"The issue of which viruses are linked to cancer is highly relevant in medicine," explained Marc Zapatka from DKFZ, the lead author of the present study. "Because in virus-related cancers, real prevention is possible: If a carcinogenic virus is identified, there is a chance of avoiding infection with a vaccine and hence to prevent cancer developing."

The current work is part of the Pan-Cancer Analysis of Whole Genomes (PCAWG), a consortium of more than 1,300 researchers who have teamed up to establish which genetic mutations or patterns of DNA mutations play a role in several types of tumors. For this meta-analysis,

they carried out a comprehensive bioinformatic analysis of the sequencing data of more than 2,600 tumor genomes from 38 different types of cancer.

The DFKZ team discovered traces of a total of 23 different virus types in 356 cancer patients. As expected, the known viral drivers of tumor initiation and growth were the most common: The genome of Epstein-Barr viruses (EBV), which are known to cause a number of different types of cancer, in particular lymphomas and gastric and nasopharyngeal carcinomas, was found in 5.5 percent of the cancer genomes investigated. Hepatitis B virus (HBV) DNA was found in 62 of the 330 cases of liver cancer.

The researchers primarily found human papillomaviruses, most commonly HPV16, in cervical carcinomas (in 19 of 20 cancer cases investigated) and in head and neck tumors (in 18 of 57 cases).

They were able to rule out a connection with the cancers as highly unlikely for some of the virus types detected. Thus adenoviruses and baculoviruses are often used as research tools in the field of molecular biology, for example, so the sequences found were probably due to contamination.

In a few cases, the team found other viruses already known to cause cancer, such as a retrovirus in kidney carcinoma. Other pathogens were occasionally found in tumors of the tissue type that they normally infect, such as cytomegaloviruses in gastric cancer. Despite thorough bioinformatic analysis, the researchers have not found any completely unknown viruses, however.

In some of the tumors linked to HPV and EBV, the researchers observed that the characteristic driver mutations that the cells of these cancer types normally depend on for growth were missing: The presence of the

virus presumably supports malignant cell degeneration through other factors.

Viral integration into the host genome was found as as the most important mechanism that leads to mutations caused by viruses, particularly HVB and papillomaviruses. "We often observed integration of HPV DNA into the telomerase promoter: This genetic switch steers production of the 'immortality enzyme' telomerase and is mutated in many types of cancer. We have now shown that viral integration can also lead to activation of this genetic switch and can thus immortalize the cells," Marc Zapatka explained.

The DKFZ researchers identified cellular defense against viruses as another key mechanism that leads to mutations in the DNA of infected cells: The cell uses its APOBEC proteins to attack the DNA of dangerous viruses—but this often leads to mutations of the cell's own genome too. As a result, cervical cancer and head and neck tumors may arise following HPV infection, for example.

"When analyzing the whole cancer genome, we discovered traces of viruses in considerably more tumors than in earlier studies that were based on investigating the RNA only. Nevertheless, we were not able to confirm the common speculation that other, as yet unknown viruses are associated with cancer," remarked principal investigator Peter Lichter, summarizing the results of the study. "However, in many cases we now have a clearer idea of how the pathogens cause malignant mutations in cells."

More information: Marc Zapatka, Ivan Borozan, Daniel S. Brewer, Murat Iskar, Adam Grundhoff, Malik Alawi, Nikita Desai, Holger Sültmann, Holger Moch, PCAWG-Pathogens, Colin S. Cooper, Roland Eils, Vincent Ferretti, Peter Lichter, PCAWG Consortium: The landscape of viral associations in human cancers. *Nature Genetics* 2020,

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