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## **Epstein-Barr virus and cancer: new tricks from an old dog**

*Joint press release of the German Cancer Research Center (DKFZ), the German Center for Infection Research (DZIF), and the Institut national de la santé et de la recherche médicale (Inserm)*

**Almost everybody has it: Scientists estimate that approximately 98 percent of adults around the world are infected with the Epstein-Barr virus. In rare cases, an infection with this virus causes cancer. Scientists at the German Cancer Research Center (DKFZ), at the German Center for Infection Research (DZIF), and at the French National Institute of Health and Medical Research (Inserm) have now discovered that a component of the Epstein-Barr virus infectious particle promotes carcinogenesis. This viral protein interferes with cell division and impairs proper distribution of the genetic material to the two daughter cells. This confers a risk of subsequent cancer development.**

After an infection with the Epstein-Barr virus (EBV), the virus persists in the body throughout a person's lifetime, usually without causing any symptoms. About one third of infected teenagers and young adults nevertheless develop infectious mononucleosis, also known as glandular fever or kissing disease, which usually wears off after a few weeks. In rare cases, however, the virus causes cancer, particularly lymphomas and cancers of the stomach and of the nasopharynx.

Scientists have been trying for a long time to elucidate how the viruses reprogram cells into becoming cancer cells. "The contribution of the viral infection to cancer development in patients with a weakened immune system is well understood" says Henri-Jacques Delecluse, a cancer researcher at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg. "But in the majority of cases, it remains unclear how an EBV infection leads to cancer development."

In their present publication, Delecluse, in collaboration with Ingrid Hoffmann, also from the DKFZ, and their respective groups present a new and surprising explanation for this phenomenon. The scientists have shown for the first time that a protein component of the virus itself promotes the development of cancer. When a dividing cell comes in contact with Epstein-Barr viruses, a viral protein present in the infectious particle called BNRF1 frequently leads to the formation of an excessive number of spindle poles (centrosomes). As a result, the chromosomes are no longer divided equally and accurately between the two daughter cells – a known and acknowledged cancer risk factor. By contrast, Epstein-Barr viruses that had been made deficient of BNRF1 did not interfere with chromosome distribution to the daughter cells.

EBV, a member of the herpes virus family, infects B cells of the immune system. The viruses normally remain silent in a few infected cells, but occasionally they reactivate to produce viral offspring that infects nearby cells. As a consequence, these cells come in close contact with the harmful viral protein BNRF1, thus having a greater risk of transforming into cancer cells.

"The novelty of our work is that we have uncovered a component of the viral particle as a cancer driver," Delecluse said. "All human tumors viruses that have been studied so far cause cancer in a completely different manner. Usually, the genetic material of the viruses needs to be permanently present in the infected cell, thus causing the activation of one or several viral

genes that cause cancer development. However, these gene products are not present in the infectious particle itself”.

Delecluse and his colleagues therefore suspect that EBV could cause the development of additional tumors. These tumors might have previously not been linked to the virus because they do not carry the viral genetic material.

For Delecluse, the consequence that follows from his findings is immediate: “We must push forward with the development of a vaccine against EBV infection. This would be the most direct strategy to prevent an infection with the virus. Our latest results show that the first infection could already be a cancer risk and this fits with earlier work that showed an increase in the incidence of Hodgkin’s lymphoma in people who underwent an episode of infectious mononucleosis.”

Experts estimate that an EBV vaccine could prevent two percent of all cancer cases worldwide. Delecluse and his group already developed a vaccine prototype in 2005. It is based on so-called ‘virus-like particles’, or VLPs. These are empty virus shells that mimic an EBV infectious particle, thus prompting the body to mount an immune response.

Henri-Jacques Delecluse is a medical researcher and, since 2012, he has been director of a research unit (Unité Inserm 1074) that was established at the DKFZ by the French ‘Institut National de la Santé et de la Recherche Médicale’ (Inserm). In addition, the DKFZ is a member of the German Center for Infection Research (DZIF), one of six German Centers for Health Research that the German government has established with the goal of fighting major common diseases.

Anatoliy Shumilov, Ming-Han Tsai, Yvonne T. Schlosser, Anne-Sophie Kratz, Katharina Bernhardt, Susanne Fink, Tuba Mizani, Xiaochen Lin, Anna Jauch, Josef Mautner, Annette Kopp-Schneider, Regina Feederle, Ingrid Hoffmann & Henri-Jacques Delecluse:  
Epstein-Barr virus particles induce centrosome amplification and chromosomal instability. Nature Communications 2017, DOI: 10.1038/ncomms14257

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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