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## **How cancer viruses protect their host cells against tumor therapies**

**Certain types of human papillomaviruses (HPV) cause cervical cancer by settling in a body cell and inducing it to divide in an out-of-control process. Scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered a mechanism by which HPV protects cancer cells from undergoing DNA damage and dying as a result of cancer therapies.**

Chemotherapy drugs and irradiation damage the DNA of cancer cells. As a result, a process called programmed cell death is activated, and the cancer cells die. Human papillomaviruses (HPV) that have settled in cells of the cervix protect their hosts from this fate and thereby increase the cells' resistance to cancer therapies. Scientists have suspected for a long time that two genes of the virus, E6 and E7, are involved in this process.

"In order to find out how HPV protects host cells against DNA damage, we blocked the activity of the E6 and E7 genes in HPV-positive tumor cells," says Jenny Leitz, first author of the publication. The result: In the absence of E6 and E7, cells mostly block the production of a protein called LEDGF, which normally protects cancer cells from DNA damage.

Do the two HPV genes activate the production of LEDGF? To pursue this question, the researchers inserted one or both of the viral genes into human skin cells. "Subsequently, levels of LEDGF rose significantly," says Professor Felix Hoppe-Seyler. "The effect was strongest when we introduced both genes into the cells."

In tissue sections of HPV-positive cervical cancer and its precursors, the researchers also found higher levels of LEDGF than in healthy tissue. But does this also mean that higher LEDGF levels protect cancer cells from DNA damage? To find out, the scientists treated HPV-positive cervical cancer cells with DNA-damaging chemical substances or gamma radiation. "When we blocked LEDGF in the cancer cells, there was significantly more DNA damage and the cells divided less frequently," reports Hoppe-Seyler, who led the study. "Based on these experiments, we think that HPV activates the production of LEDGF through the E6 and E7 genes and thereby protects cancer cells from DNA damage."

These findings may be useful in increasing the effectiveness of chemotherapy and radiotherapy when applied to tumors. "To accomplish this, we need to develop LEDGF inhibitors that target cancer cells," says Hoppe-Seyler. "But we still have a long road ahead of us to achieve this goal."

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Leitz J, Reuschenbach M, Lohrey C, Honegger A, Accardi R, Tommasino M, Llano M, von Knebel Doeberitz M, Hoppe-Seyler K, Hoppe-Seyler F. (2014). Oncogenic Human Papillomaviruses Activate the Tumor-Associated Lens Epithelial-Derived Growth Factor (LEDGF) Gene. PLoS Pathog. doi: 10.1371/journal.ppat.1003957

A picture for this press release is available at:  
<http://www.dkfz.de/de/presse/pressemitteilungen/2014/bilder/gebaermutterhalstumor.jpg>

Caption: Tissue section of a cervical tumor. The cancer cells contain high levels of LEDGF protein (brown staining).

Source: Miriam Reuschenbach, Heidelberg University Hospital

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 2,500 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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