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Lack of oxygen turns cancer cells into dangerous “sleeper cells”

For a long time it was considered an established fact that cervical cancer, which is caused by human papillomaviruses (HPV), depends on two specific viral proteins. If they are absent, the cancer cells stop growing permanently. Scientists at the German Cancer Research Center (DKFZ) have now discovered that cancer cells reduce the production of these viral proteins during hypoxia - a condition of oxygen deficiency that is very common in tumors. However, this does not lead to final growth cessation, but instead induces a state of dormancy from which the cancer cells can awaken and start proliferating again and may thus cause the cancer to return.

Human papillomaviruses are considered to be the cause of approximately five percent of all cancers worldwide. They primarily cause cervical cancer but are also responsible for many cancers of the head and neck, the reproductive tract and the anus.

A couple of years ago, researchers were able to uncover the mechanism that the viruses use to turn cells cancerous. Two viral proteins, E6 and E7, disable two crucial cancer brakes in infected cells, thus being responsible for cancer developing.

“E6 and E7 drive cancer growth by preventing senescence, a cell aging process that is associated with irreversible cessation of cell growth,” says Felix Hoppe-Seyler of the German Cancer Research (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg. When E6 and E7 are blocked, the cancer cells stop growing. “However, our knowledge about the functions of E6 and E7 is mostly based on results from cell culture experiments, where oxygen saturation is high,” Hoppe-Seyler explains. “But many tumors have regions where oxygen is deficient because of inadequate supply by blood vessels. So we wanted to know what happens in a state of hypoxia.”

When the scientists lowered the oxygen concentration in the Petri dish to levels commonly found in oxygen-deficient tumor tissue, the cancer cells reduced the production of E6 and E7 and stopped growing. However, they did not induce senescence, but instead entered a dormant state. When oxygen supply was increased again, the dormant cancer cells awakened and promptly resumed cell division.

The sleeper cells that can form in tumor regions with low oxygen levels are more resistant to chemotherapy, which preferably targets dividing cells. Additionally, they escape immune defense because they no longer produce HPV proteins that could be recognized by immune cells.

Until now, E6 and E7 have been regarded as ideal molecular targets for targeted treatment of HPV-induced tumors, which currently is a field of intensive research. However, even these targeted drugs would be ineffective against the dormant cells because they lack the crucial targets.

Hoppe-Seyler said: "For patients with HPV-induced tumors, the sleeper cells are a latent danger. If a tumor shrinks, for example in the wake of successful treatment, and if surviving sleeper cells get reconnected to blood vessels and oxygen supply, they might cause the disease to relapse. Assessing the relevance of the findings, he added: “In our efforts to develop

novel therapies, we cannot solely focus on E6 and E7 as targets. We also need to develop strategies for eliminating the sleeper cells.”

The investigations were supported by the Wilhelm Sander Foundation and German Cancer Aid (Deutsche Krebshilfe).

Karin Hoppe-Seyler, Felicitas Bossler, Claudia Lohrey, Julia Bulkescher, Frank Rösl, Lars Jansen, Arnulf Mayer, Peter Vaupel, Matthias Dürst, and Felix Hoppe-Seyler: Induction of Dormancy in Hypoxic Human Papillomavirus-Positive Cancer Cells.

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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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