

## **Prognostic Marker Found for Oropharyngeal Cancer**

**In cancers of the oropharynx, a specific pattern of chemical tags in tumor cell DNA indicates a favorable prognosis. This so-called “epigenetic signature” predicts disease progression more reliably than previously used prognostic criteria. Patients with a predicted favorable prognosis could be treated less intensively. This was reported by scientists from the German Cancer Research Center (DKFZ) and Heidelberg University Hospital.**

Cancers of the oropharynx are usually so-called squamous cell carcinomas, which originate from cells of the mucous membranes. Known risk factors for this disease include alcohol and cigarettes. However, the incidence is rising, even among people who neither drink nor smoke. “These patients frequently have an infection with cancer-causing types of human papillomaviruses (HPV)”, says Associate Professor (PD) Dr. Jochen Hess, who leads a junior research group at DKFZ and a research group at the Ear, Nose and Throat Hospital of Heidelberg University. “Up to 60 percent of squamous cell carcinomas of the oropharynx are positive for HPV16, the same one which also causes cancer of the cervix.”

Cancer researchers are particularly interested in the group of HPV-associated oropharyngeal tumors, because they take a much more favorable course than cases attributable to the classic risk factors. The majority of HPV-associated oropharyngeal cancers respond particularly well to radiotherapy and chemotherapy, which means that patients have a longer life expectancy. However, even among HPV-associated tumors there are exceptions where the disease progresses unfavorably. The molecular causes for this are unknown.

“Oncologists are therefore very interested in a marker that reliably identifies tumors with a favorable prognosis. These patients could be treated less intensively and side effects could thus be reduced considerably,” Jochen Hess explains. He had the idea that altered epigenetic tags in the tumor DNA might be a possible molecular cause of the varying courses the disease may take. “Tagging with methyl groups, in particular, has an impact on the activity of many genes and hence on a cell’s behavior,” says Hess.

In collaboration with colleagues led by Dr. Efterpi Kostareli and Dr. Dieter Weichenhan from DKFZ, clinicians from Heidelberg University Hospital and Leipzig University Hospital as well as from the University of Chicago, Hess’ team searched for differences in the methylation patterns of oropharyngeal cancer cells with and without HPV involvement. They found out that a very favorable disease progression correlated with a specific pattern of tags: Three specific genes are more active as a result of a mild methylation, while two others are silenced.

This result was first obtained in 100 tumor samples from Heidelberg and subsequently confirmed in tumor tissue of 120 other patients from Leipzig and Chicago. Four of the five affected genes regulate the retinoic acid metabolism, which has an impact on the growth, differentiation and death of cells. The researchers also proved that the epigenetic alterations did in fact have an impact on the biology of cancer cells: The amount of RNA copies of the five genes corresponded to what was expected due to the altered methylation of the respective gene.

The alterations in the epigenetic profile were found particularly often in patients with HPV infection. However, the study also identified HPV-negative tumor patients with the prognostically more favorable methylation pattern. Hence, disease progression can be

predicted with a higher level of exactitude using the signature than by virus detection alone. “The signature can be tested right at first diagnosis and may help physicians differentiate patients who immediately need intensive chemotherapy or radiotherapy from those for whom less aggressive treatment regimens may be sufficient.”

Efterpi Kostareli, Dana Holzinger, Olga Bogatyrova, Thomas Hielscher, Gunnar Wichmann, Michaela Keck, Bernd Lahrmann, Niels Grabe, Christa Flechtenmacher, Christopher R. Schmidt, Tanguy Seiwert, Gerhard Dyckhoff, Andreas Dietz, Daniela Hoefler, Michael Pawlita, Axel Benner, Franz X. Bosch, Peter Plinkert, Christoph Plass, Dieter Weichenhan and Jochen Hess: HPV-related methylation signature predicts survival in oropharyngeal squamous cell carcinomas  
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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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