

A yardstick to measure the malignancy of prostate cancer

A protein that influences the epigenetic characteristics of tumor cells is directly linked to the grade of malignancy of prostate cancer. This key discovery has been made by a team of scientists from the German Cancer Research Center (DKFZ), the University of Zurich, Hamburg-Eppendorf University Hospital, Heidelberg University, and other institutes in a study of 7,700 samples of tumor tissue. The detection of this biomarker may serve as an indicator of the likelihood that the disease may take an aggressive course, and may thus be helpful in choosing an appropriate treatment. The study was part of the “Early Onset Prostate Cancer” project, supported by the Federal Ministry of Education and Research (BMBF) as part of the International Cancer Genome Consortium (ICGC).

When cancer is diagnosed, the grade of its malignancy is a central concern for both patients and their physicians. This value is used to determine how intensively and how radically the cancer must be treated. Particularly in the case of prostate cancer, the disease can take widely varying courses in different patients. Therefore, cancer researchers have been looking for measurable, reliable biomarkers that give clues about the aggressiveness of a tumor in order to choose an appropriate therapy.

In many types of cancer, alterations in a tumor’s genetic material indicate how dangerous the cancer is. Prostate cancer, however, exhibits far fewer of these mutations than other cancer types. “We have therefore suspected that prostate cancer is driven primarily by alterations in epigenetic characteristics, that is, chemical changes in the genetic material that do not affect the sequence of DNA building blocks,” says Prof. Christoph Plass from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), who is one of the project leaders in the current publication.

For a long time, the means by which epigenetic patterns in the DNA of cancer cells undergo changes have remained a mystery. Scientists have discovered specific cellular proteins that can have a major influence on such patterns. A network of researchers from the German Cancer Research Center (DKFZ), the University of Zurich, Hamburg-Eppendorf University Hospital, Heidelberg University, and other institutes have been searching for regulatory proteins that change the epigenetic characteristics of prostate cancer cells and may thus have an impact on the course of the disease.

In a first step, the scientists searched databases containing molecular information on a large number of prostate cancer cases. Using these data, they investigated whether a particular, known epigenetic regulatory protein is expressed in tumor cells at significantly higher or lower levels than in healthy cells from the same patient.

The researchers found the most obvious differences in the expression of a protein called BAZ2A. “The normal known function of this protein is to suppress factories that produce cellular proteins and thus affect the viability of cells,” says Prof. Roland Eils, who leads a research group at both the DKFZ and at Heidelberg University. “But when we turned off BAZ2A in the cell lines of metastasizing prostate cancer, their growth was paradoxically slowed.” Further studies showed that higher levels of BAZ2A increased specific malignant properties of prostate cancer cells, including their mobility and capacity to invade surrounding tissue.

A detailed molecular analysis of prostate cancer cells showed that the overproduction of BAZ2A led to alterations in epigenetic patterns which then inhibited the activity of a number of cancer-suppressing genes. The scientists therefore suspected that the overexpression of BAZ2A might have a direct impact on the malignancy of prostate cancer and thus serve as a predictor for the course of the disease.

The team investigated this hypothesis using nearly 7,700 tissue samples obtained from prostate cancer patients. They discovered that the higher the BAZ2A levels in the tissue were, the more advanced the tumor was at the time of diagnosis, the more frequently it had already spread and formed metastases, and the higher patients' PSA levels were.

"BAZ2A seems to have a direct influence on the aggressiveness of prostate cancer," Plass says. "This suggests that levels of BAZ2A expression may serve as a valuable predictor of disease progression. Of course, this still needs to be clinically confirmed. Particularly in patients whose other clinical results indicate a medium risk, BAZ2A expression may provide important clues for the actual chances of recurrence. This would help physicians and patients choose the most promising treatment.

The study is part of the International Cancer Genome Consortium (ICGC). Collaborators in the project "Early Onset Prostate Cancer" are the Martini-Klinik and Hamburg-Eppendorf University Hospital, EMBL, DKFZ, the National Center for Tumor Diseases (NCT) Heidelberg, and the Max Planck Institute for Molecular Genetics in Berlin. The project coordinators are Prof. Christoph Plass from the DKFZ and Prof. Guido Sauter from Hamburg-Eppendorf University Hospital. The Federal Ministry of Education and Research (BMBF) has provided funds of €7.5 million for the project.

Lei Gu, Sandra C Frommel, Christopher C Oakes, Ronald Simon, Katharina Grupp, Cristina Y Gerig, Dominik Bär, Mark D Robinson, Constance Baer, Melanie Weiss, Zuguang Gu, Matthieu Schapira, Ruprecht Kuner, Holger Sültmann, Maurizio Provenzano, ICGC Project on Early Onset Prostate Cancer, Marie-Laure Yaspo, Benedikt Brors, Jan Korb, Thorsten Schlomm, Guido Sauter, Roland Eils, Christoph Plass und Raffaella Santoro: BAZ2A (TIP5) is involved in epigenetic alterations in prostate cancer and its overexpression predicts disease recurrence.
Nature Genetics 2014, DOI: 10.1038/ng.3165

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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