

No. 25c

June 29, 2016 (Koh)

Misaligned chromosomes give breast cancer cells a selection advantage

If chromosomes are distributed unevenly during cell division, this has a negative effect on the survival of daughter cells. However, in many cancer types, misaligned chromosomes are associated with a negative prognosis, meaning that they appear to benefit the cancer. Scientists at DKFZ have conducted trials with mice to investigate the effect of unevenly misaligned chromosomes on breast cancer. When the scientists triggered aberrant distribution of chromosomes in the mammary gland cells of mice, this delayed the development of breast cancer. However, the developing tumors appeared to have a selection advantage: they continued to grow even when the growth-promoting cancer gene had been switched off.

In most cancer types, the tumor cells show faulty sets of chromosomes. This “chromosome instability” occurs when the set of chromosomes which duplicated before cell division is then not distributed evenly into the two daughter cells. Chromosome instability is an indicator for a negative progression of the disease and for poor therapeutic success.

An apparent contradiction to the cancer-promoting effect of this chromosome misalignment is the fact that chromosome instability is in itself harmful for the cell: Its metabolism gets out of control because proteins are produced in the wrong quantities. As a result, the cells often die due to programmed cell death, i.e. apoptosis. Rocio Sotillo at the German Cancer Research Center has now investigated in breast cancer whether this misalignment does in effect promote or inhibit cancer.

Sotillo and her colleagues activated the cancer gene KRAS in the mammary glands of mice. As a result, a large number of those animals developed breast cancer. When the scientists blocked the growth-promoting KRAS gene, the tumors decreased.

In a second group of mice, in addition to the KRAS gene, the scientists activated the Mad2 gene, which triggers chromosome instability. These animals developed breast cancer later and less frequently. A large number of their mammary gland cells showed interrupted cell division and eventually died through apoptosis. The organism uses this emergency response to protect itself from the adverse effect of misaligned chromosomes.

The initial selection of cells however, appeared to ultimately have tumor-promoting consequences: Just under a quarter of the tumors in these animals continued to grow even after the growth-promoting KRAS gene had been switched off.

Rocio Sotillo and her colleagues concluded that the chromosome instability resulted in a genetic diversity of cancer cells. This encouraged the selection of individual tumor subclones able to continue thriving even without the cancer gene's initial growth stimulus.

Sotillo explains “This also helps us to understand why tumors with chromosome instability show such poor response to therapy: The genetic diversity of tumor cells increases the probability that under the selective pressure caused by cancer treatment, therapy-resistant clones develop and establish themselves.”

Konstantina Rowald, Martina Mantovan, Joana Passos, Christopher Buccitelli, Balca R. Mardin, Jan O. Korb, Martin Jechlinger, Rocio Sotillo: Negative selection and chromosome instability induced by Mad2 overexpression delay breast cancer but facilitate oncogene independent outgrowth.

CELL Reports 2016, DOI 10.1016/j.celrep.2016.05.048

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.

Contact:

Dr. Stefanie Seltmann
Head of Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968
presse@dkfz.de

Dr. Sibylle Kohlstädt
Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2843
F: +49 6221 42 2968
Email: presse@dkfz.de