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 apopotosis. 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. Korbel, 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

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