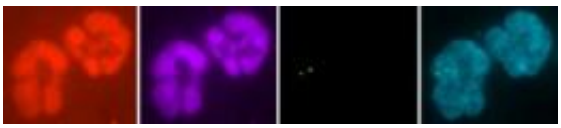
Tumor suppressor p53 prevents cancer progression in cells with missegregated chromosomes

February 1 2010



Thompson and Compton introduced a single fluorescent mark into the genome of a diploid cell line, induced missegregation, and identified the cells that incorrectly carried two or zero marks (green) on their DNA (blue). These cells arrested due to increased levels of the tumor suppressor p53 (purple) and its transcriptional target, the cyclin-dependent kinase inhibitor p21 (red). Credit: Thompson, S.L., and D.A. Compton. 2010. *J. Cell Biol*. doi:10.1083/jcb.200905057.

Cells missegregate a chromosome approximately once every hundred divisions. But don't be too alarmed: new research in the *Journal of Cell Biology* shows that the tumor suppressor p53 limits the growth of cells with incorrect numbers of chromosomes and prevents their progression toward cancer. The study appears online February 1.

Tumor cells tend to missegregate chromosomes at a particularly high frequency (a condition known as chromosomal instability, or CIN), which is probably why they are often aneuploid (i.e., they carry an abnormal number of chromosomes). In 2008, Sarah Thompson and Duane Compton, from Dartmouth Medical School, revealed that most

CIN in tumor cells was caused by incorrect attachments between mitotic spindle microtubules and kinetochores, and that inducing misattachments in normal cells was sufficient to generate high rates of chromosome missegregation. There was a small but significant wrinkle to this story, however: normal, diploid cells stopped proliferating as soon as they gained or lost a chromosome, so they never converted into a cancer-like aneuploid cell line.

To investigate why normal cells stop proliferating when they missegregate their DNA, Thompson and Compton engineered a human cell line to carry a unique fluorescent mark on one of its chromosomes. This allowed them to identify and follow by live microscopy the cells that missegregated a chromosome.

The researchers induced missegregation and then looked for cells that had gained or lost a fluorescent mark within their genome. These cells failed to proliferate, and showed elevated levels of p53 and one of its transcriptional targets, the cell cycle inhibitor p21. Cells lacking p53 became aneuploid after induced missegregation, indicating that the p53 pathway normally serves to limit the propagation of cells with odd numbers of chromosomes.

How is p53 activated by chromosome missegregation? Thompson and Compton think that a change in chromosome number leads to an imbalance in gene expression, resulting in a stress response and cell cycle arrest that is vital to avoid cancer. "By combining loss of p53 with increased missegregation rates, we can convert a diploid cell into something …. that looks like a tumor cell," says Compton. Furthermore, these aneuploid cells develop an inherent genomic instability reminiscent of genuine cancer cells, perhaps because imbalanced gene expression also causes disruptions to mitosis.

A recent study demonstrated that chromosome missegregation initiates

tumorigenesis by causing cells to lose tumor suppressors like p53. "It's like a self-fulfilling prophecy," argues Compton. "If you missegregate a chromosome encoding p53, you make the cells deficient in p53, so they're able to propagate and missegregate more chromosomes."

There are circumstances in which nontumor cells tolerate aneuploidy just fine, but, in most cases, healthy cells keep a tight check on chromosome number. "I think it affects a lot of different pathways," says Compton. "The next question to ask is which pathways are sensitive to aneuploidy, and how do tumor cells overcome those problems?"

More information: Thompson, S.L., and D.A. Compton. 2010. J. Cell Biol. doi:10.1083/jcb. 200905057

Provided by Rockefeller University