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p53 hides a multitude of CIN

Tumor suppressor stops cells from gaining or losing chromosomes.

Cells missegregate a chromosome approximately once every hundred divisions. But don't be too alarmed: Thompson and Compton report that the tumor suppressor p53 limits the growth of cells with incorrect numbers of chromosomes and prevents their progression toward cancer (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, Hanover, NH, 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 (2). 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.

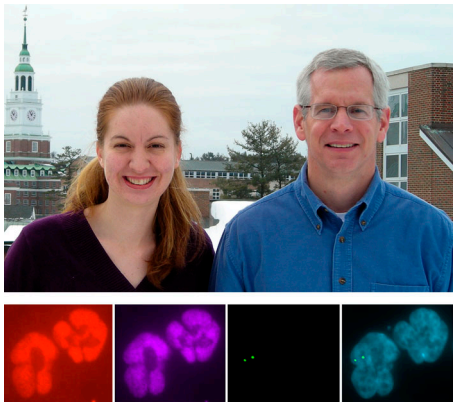
"You can't impose instability on a healthy, diploid cell and get an aneuploid population," says Compton. Aneuploid tumor cells grow well, however, suggesting that they've learned to tolerate changes in chromosome number.

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 us to identify and follow by live microscopy the cells that missegregated a chromosome," explains Compton.

The researchers induced missegregation by either briefly treating the cells with the mitotic inhibitor monastrol or by depleting the mitotic kinesin motor MCAK, and then looked for cells that had gained or lost a fluorescent mark within their genome. These cells failed to proliferate over the course of five days, and showed elevated levels of p53 and one of its transcriptional targets, the cell cycle inhibitor p21. Cells lacking p53 became aneuploid after monastrol treatment or MCAK depletion, 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 with a karyotype that looks like a tumor cell," says Compton. Furthermore, these aneuploid cells develop an inherent genomic instability reminiscent of genuine cancer cells. They are prone to further changes in chromosome number, perhaps because aneuploidy and imbalanced gene expression causes disruptions to mitosis.

> "We can convert a diploid cell into something… that looks like a tumor cell."



Focal Point

Sarah Thompson and Duane Compton investigated why, unlike tumor cells, normal cells don't proliferate once they contain an abnormal number of chromosomes. The researchers 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). The cells could grow and progress toward a cancer-like state if missegregation was combined with a loss of p53.

A recent study demonstrated that chromosome missegregation initiates tumorigenesis by causing cells to lose tumor suppressors like p53 (3). "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."

Compton points out that there may be other pathways that arrest cells after chromosome missegregation but, equally importantly, there are also circumstances in which nontumor cells tolerate aneuploidy just fine. Human brain cells are often aneuploid (4), as are early embryos, where mitotic fidelity may be sacrificed in the name of speed (5). Tissue context therefore seems to affect a cell's response to changes in its chromosome complement.

Nevertheless, in most cases, healthy cells keep a tight check on aneuploidy. "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?"

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3. Baker, D.J., et al. 2009. *Cancer Cell.* 16:475–486.
4. Rehen, S.K., et al. 2005. *J. Neurosci.* 25:2176–2180.
5. Vanneste, E., et al. 2009. *Nat. Med.* 15:577–583.

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