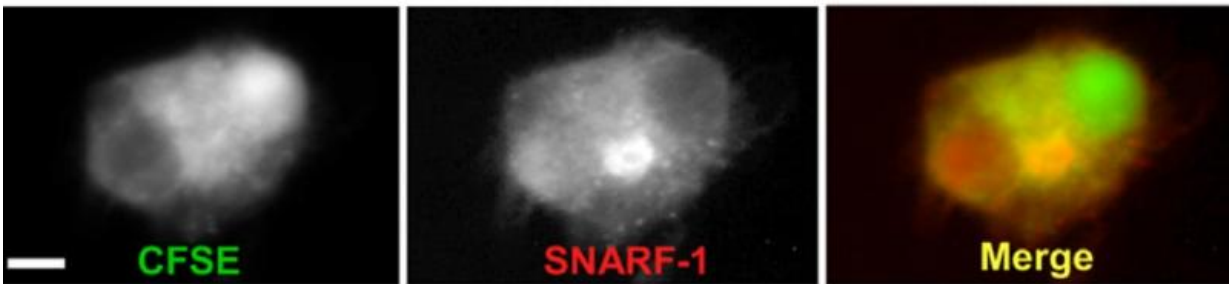


# 'Genomic catastrophe' may cause normal cells to become cancerous

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Typical image of fused cell sorted by FACS and visualized by fluorescence microscopy. The fused cell emits both CFSE (green) and SNARF-1 (red) fluorescence; the image represents at least 50 cells examined per experiment. Scale Bar: 5  $\mu$ m Credit: *American Journal of Pathology*

Although there is no one established universal cause of cancer, genetic changes are central to its development. The accumulation of spontaneous genetic changes, or mutations, that occur when cells divide can be hastened by exposure to carcinogens such as cigarette smoke (lung cancer) and infectious agents such as the papillomavirus (cervical cancer). However, some researchers believe that spontaneous mutations are too infrequent, and the link between carcinogens and genetic changes too uncertain, to fully explain the development of some of the most common cancers. The results of this study may provide an explanation: that fusion of one normal cell with another—as observed in inflammation, infection, and injury from carcinogens—triggers a

'genomic catastrophe' that converts normal cells to cancer cells and enables tumors to form.

Philadelphia, June 8—Cell fusion is a process in which one or more cells combine to form a new cell with more than one nucleus. Cell fusion has been postulated as a possible cause for some cancers because it could explain the occurrence of multiple genetic changes thought to underlie cancer. However, direct evidence that fusion of [normal cells](#) by itself could trigger cancer has not been reported. Now, a new study published in *The American Journal of Pathology* provides the missing link between a single untoward event, cell fusion, and the multiple catastrophic genetic changes that ultimately transform normal cells into [cancerous cells](#). Furthermore, when injected into live animals, these aberrant cells form tumors.

Researchers from the University of Michigan and the Mayo Clinic studied rat IEC-6 [intestinal epithelial cells](#), chosen because they maintain a stable diploid genomic structure (two sets of chromosomes), lack the cellular characteristics of [cancer cells](#), and replicate normally. They also do not form tumors when monitored over many generations. IEC-6 cells were labeled with either red or green fluorescent dyes. The cells were then exposed to 50 percent polyethylene glycol to encourage cell fusion. The fused cells were identified by the presence of both red and green dyes within one cell, whereas nonfused cells displayed only one color. Fused cells were also larger than non-fused cells.

Investigators made several important observations. First, they showed that fused cells could replicate, with 19 percent of fused IEC-6 cells establishing clones and that with replication the chromosomes from the two cells intermixed. They also observed that 41 percent of the clones had abnormal numbers of chromosomes (aneuploidy), 56 percent were near-diploid (40 to 44 chromosomes), and 4 percent were tetraploid (84 chromosomes), whereas the large majority (86 percent) of non-fused

cells were diploid. 'These results indicate that cell fusion generates chromosomal instability,' explained lead investigator Jeffrey L. Platt, M.D., professor of surgery and microbiology and immunology, Departments of Microbiology and Immunology and Surgery, University of Michigan (Ann Arbor). Chromosomal instability refers to changes in the number and appearance of chromosomes in a species.

Because aneuploidy and chromosomal abnormalities are commonly observed in cancer, the researchers looked for evidence of DNA damage in the fused clones. The double-strand DNA break marker phosphorylated H2AX revealed breaks in significantly more fusion-derived clones than in nonfused clones (35 percent to 42 percent versus 4 percent to 9 percent, P genetic changes that underlie cancer. Consistent with that possibility, fused cells often exhibited the same abnormal growth characteristics as cancer cells.

'The frequency of cell fusion events in vivo is not known, although cell fusion is thought to occur under some circumstances such as cell injury, inflammation, and viral infection. Although fusion of normal cells in vitro and in vivo may be a rare event, this study shows that cell fusion between normal cells can have pathological consequences,' commented noted authority and cancer specialist William B. Coleman, Ph.D., of the Department of Pathology and Laboratory Medicine, Program in Translational Medicine at the University of North Carolina Comprehensive Cancer Center (Chapel Hill). 'The results provide evidence for another molecular mechanism driving neoplastic transformation - genomic catastrophe.'

Perhaps the most exciting observation occurred when fused IEC-6 cells were transplanted into immunodeficient mice. Over the course of 12 weeks, these cells generated tumors in 61 percent (11/18) of the hosts whereas no tumors formed from the parental IEC-6 cells or IEC-6 cells that did not fuse. Furthermore, only those fusion-derived IEC-6 cell

clones that had undergone the changes in cellular growth indicative of neoplastic transformation produced tumors in mice. 'We believe one cell fusion event can both initiate malignancy and fuel evolution of the tumor that ensues,' noted lead author Xiaofeng Zhou, Department of Microbiology and Immunology and Surgery and the Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, at the University of Michigan (Ann Arbor).

According to Coleman, most cases of spontaneous cancers in humans are thought to derive from cells that sustained random DNA damage or random errors during DNA replication. 'Zhou et al provide evidence for a different mechanism of spontaneous neoplastic transformation. The observations suggest strongly that genomic catastrophe can produce the required and necessary molecular alterations for neoplastic transformation and tumorigenesis in normal founder [cells](#) in the absence of selective pressures or ongoing genomic evolution.' Coleman added that further research is needed to determine whether [cell fusion](#) events between normal human cell types result in genomic catastrophe and neoplastic transformation.

**More information:** "Cell Fusion Connects Oncogenesis with Tumor Evolution," by Xiaofeng Zhou, Kevin Merchak, Woojin Lee, Joseph P. Grande, Marilia Cascalho, and Jeffrey L. Platt. ( DOI: [dx.doi.org/10.1016/j.ajpath.2015.03.014](https://doi.org/10.1016/j.ajpath.2015.03.014) ). This article appears online ahead of the *American Journal of Pathology*, Volume 185, Issue 7 (July 2015)

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