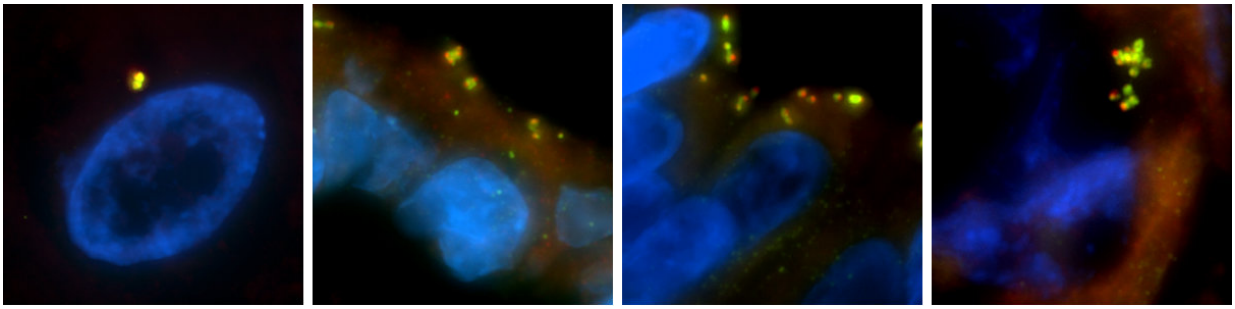
Amplification of key cellular organizer may initiate cancer, study suggests

May 8 2018



Normal esophageal cells (left) have a single centrosome (labeled green and red). But in patients with Barrett's esophagus, centrosome amplification begins during metaplasia (second from left), increases during dysplasia (second from right), and persists in esophageal adenocarcinoma (right). Credit: Lopes et al., 2018

Cells begin to accumulate centrosomes—organelles that play a vital role during cell division—before they transform into cancer cells, according to a new study of patients with Barrett's esophagus condition, which is associated with esophageal cancer. The research, which will be published May 8 in the *Journal of Cell Biology*, suggests that similar cases of centrosome amplification may contribute to the initiation and progression of a variety of human cancers.

Centrosomes play crucial roles in a wide range of cellular processes by organizing the cell's microtubule cytoskeleton. Cells usually contain just

a single centrosome that they carefully duplicate once per cell cycle so that, when the cell divides, they can organize microtubules into a bipolar spindle that allows each daughter cell to inherit an equal number of chromosomes and a single centrosome of its own. Cells with too many centrosomes usually fail to divide properly and die.

Cancer cells often contain excessive numbers of centrosomes, however, and usually survive cell division despite their propensity to form abnormal spindles and missegregate chromosomes. Indeed, the genomic instability created by excess centrosomes may help cancer cells to become more malignant.

"Centrosome amplification is found in human tumors but not in normal cells, so it is an appealing feature to explore for diagnosis, prognosis, and therapy," explains Carla Lopes, from the Instituto Português de Oncologia and Instituto Gulbenkian de Ciência in Portugal. "Despite being a cancer hallmark, however, the timing, mechanisms, and impact of centrosome deregulation in human cancer are poorly understood."

Lopes and colleagues, including co-first author Marta Mesquita and co-senior authors Mónica Bettencourt-Dias and Paula Chaves, investigated the role of centrosome amplification in tumorigenesis by examining samples from patients with the premalignant condition Barrett's esophagus, in which chronic acid reflux causes the epithelial cells lining the esophagus to be replaced by cells usually found only in the stomach and intestine. In a small percentage of patients, these "metaplastic" cells become dysplastic and proliferate abnormally, eventually giving rise to esophageal adenocarcinoma.

Patients with Barrett's esophagus therefore undergo regular biopsy screenings, and any dysplastic tissue is removed. This allowed Lopes, Mesquita, and colleagues to investigate how centrosome numbers change at different stages of the disease.

"We established a method to identify centrosomes at the single-cell level in clinical samples and found that centrosome number abnormalities arise early in Barrett's esophagus progression," Mesquita says.

The researchers never saw excess centrosomes in normal esophageal tissue. Nor did they see centrosome amplification in Barrett's esophagus patients that hadn't progressed to later stages of the disease. But extra centrosomes could occasionally be seen in the premalignant, metaplastic cells of patients that developed dysplasia or adenocarcinoma. The incidence of centrosome amplification increased dramatically during dysplasia, and cells with excess centrosomes persisted throughout adenocarcinoma and metastasis.

The increase in centrosome amplification at the onset of dysplasia coincided with the loss or mutation of the tumor suppressor p53. The most mutated gene in human cancers, p53 is thought to kill cells with too many centrosomes. Lopes, Mesquita, and colleagues found that p53 was activated in metaplastic cells with extra centrosomes and that removing p53 from these cells increased the levels of centrosome amplification.

This suggests that centrosome amplification arises in some cells during metaplasia and that p53 prevents these cells from propagating until it is lost during the transition to dysplasia. Cells with extra centrosomes can then survive and proliferate, giving rise to cells with abnormal numbers of chromosomes that can become malignant cancer cells.

"Given the widespread occurrence of p53 mutations and centrosome amplification in human tumors, our findings on the timing and ordering of these events in Barrett's esophagus tumorigenesis are likely applicable to other cancers as well," Lopes says.

More information: Lopes et al., 2018. *J. Cell Biol.* jcb.rupress.org/cgi/doi/10.1083/jcb.201711191

Provided by Rockefeller University Press