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Link unraveled between chromosomal instability and centrosome defects in cancer cells

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In a new study, Dana-Farber Cancer Institute scientists disprove a century-old theory about why cancer cells often have too many or too few chromosomes, and show that the actual reason may hold the key to a novel approach to cancer therapy.

Since the late 19th century, scientists have attributed the surplus or shortage of intact chromosomes in cancer cells to a kind of fragmentation in cell division: instead of dividing neatly into two identical daughter cells, as normal cells do, cancer cells were thought to frequently split into three or four cells, each with a motley assortment of chromosomes. This explosive division was thought to occur because many cancer cells have extra centrosomes, tiny circular structures that help pairs of chromosomes line up in preparation for cell division.

When study lead author Neil Ganem, PhD, of Dana-Farber used newly developed microscope equipment to watch living cancer cells for a week or more, he found that not only were such abnormal divisions quite rare, but the resulting daughter cells were so discombobulated by their chromosomal quirks, they generally survived for only a few days - far too briefly to deliver abnormal chromosome content to a tumor.

The way that extra centrosomes do cause chromosome instability, Ganem and his colleagues have discovered, is by setting up a tug-of-war for chromosomes that are eventually caught between newly forming

daughter cells of a dividing cancer cell. In normal cells, which have two centrosomes, division occurs as the pairs of chromosomes split neatly apart, like halves of a zipper, each set moving into one of the daughter cells. The extra centrosomes in cancer cells exert an unequal pull on some chromosomes, causing the daughter cells to inherit an irregular number of them - explaining, in part, why tumors are often filled with cells of varying quantities of chromosomes.

Their findings are reported in the journal *Nature* as an advanced online publication.

"Chromosome instability is a hallmark of most cancer cells, arising when chromosomes are missegregated into daughter cells during division," said Ganem, who led the study with senior author David Pellman, MD, and co-author Susana Godinho, PhD, of Dana-Farber. "Such instability may be a double-edged sword. It may confer a survival benefit on cancer cells by enabling them to adapt to a stressful environment in the body or by helping them become resistant to chemotherapy drugs. But it may also have deleterious effects that could make tumor cells susceptible to therapeutic attack."

"Although centrosome defects have been recognized in tumors for a long time," Pellman said, "it has been a tough problem to rigorously study. Neil and Susana have made a significant advance by developing useful methods to create comparable cells that carry or don't carry extra centrosomes."

In the early stages of division, cells make duplicate copies of their chromosomes, enabling their daughter cells to each receive an identical set. The centrosomes' role is to construct the mitotic spindle, the axis along which the chromosome pairs position themselves as division proceeds.

In normal cells, the two centrosomes serve as the polar ends of the spindle, the chromosomes arrayed between them like ranks of twin soldiers. Cells with more than two centrosomes enter a "multipolar" phase with several axes along which division may take place. Under a microscope, such cells look briefly like a sliced pizza ready to be pulled into three or four pieces.

But cancer cells usually avoid this fate by clustering extra centrosomes in a rough line, allowing a single spindle to form and division to proceed somewhat normally. In a study last year, researchers from Pellman's lab used genome-wide approaches to discover how this clustering occurs. In the current study, the investigators found that when cancer cells with extra centrosomes enter "anaphase" - the stage of cell division when chromosomes move toward the poles of the spindle before being drawn into the new daughter cells - a few chromosomes lagged behind the others. As a result, some of those chromosomes became homeless - left out of the daughter cell they were destined for, and marooned in the other daughter cell, where they inhabit a kind of island outside the nucleus where the other chromosomes congregate.

"We showed that even though most cancer cells with extra centrosomes form a single mitotic spindle, they pass through a brief 'multipolar spindle' stage," Ganem said. "The presence of this unique spindle configuration causes a few chromosomes to attach improperly to the eventual two-ended spindle. That, in turn, disrupts the normally orderly process by which chromosomes are pulled into the daughter cells."

According to Pellman, chromosomal instability, it turns out, "is actually a side effect of the cells' ability to cluster their excess centrosomes. From the standpoint of the tumor cell, it is a trade-off: the cell survives because it can correct for the surplus centrosomes, but the correction process creates other problems that result in chromosomal instability."

While the new study demonstrates that extra centrosomes are major actors - but likely not the only ones - in chromosome instability, it is an open question as to what causes some cells to have those extra centrosomes. That will be a future area of research for the Dana-Farber team.

Source: Dana-Farber Cancer Institute