How chromosome imbalances can drive cancer: An analysis of nearly 11,000 human cancers

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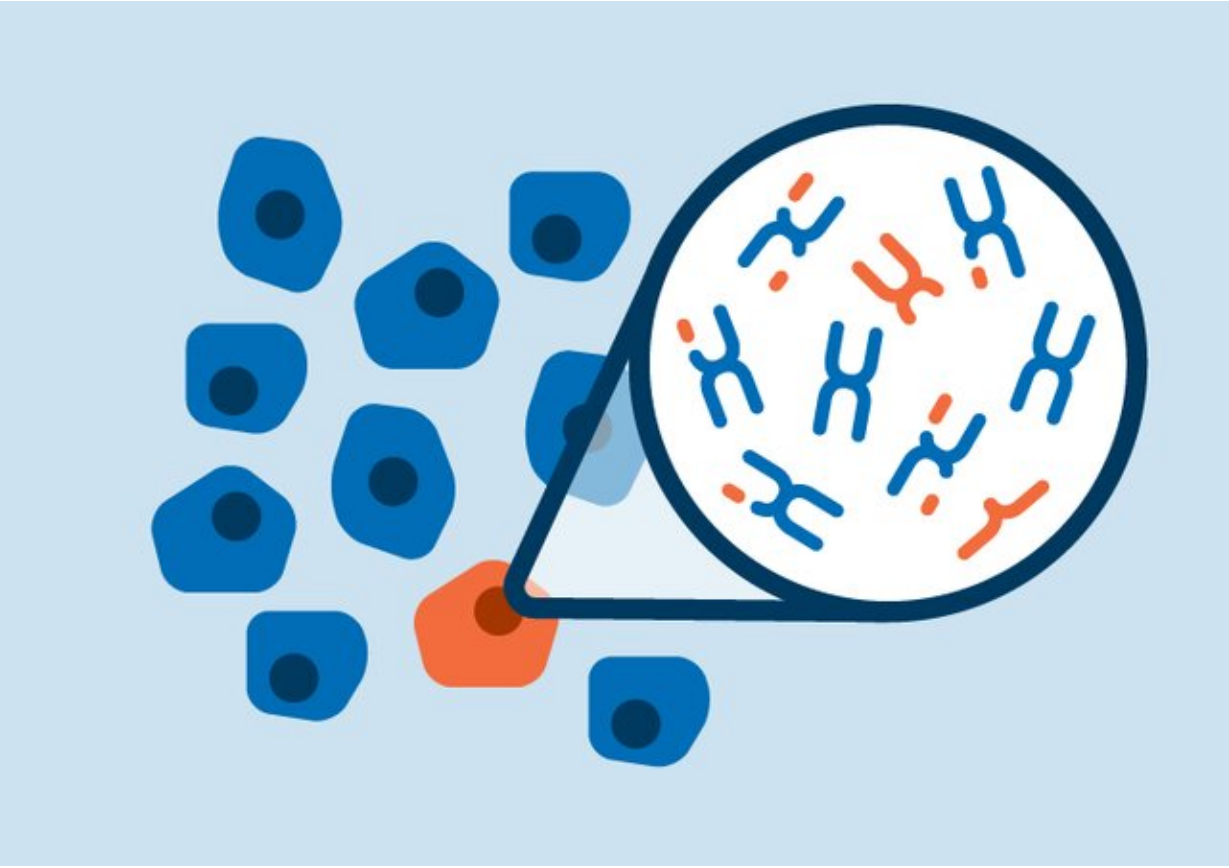

Credit: Ricardo Job-Reese, Broad Communications

The vast majority of cancer cells have too few or too many copies of

some chromosomes, a state known as aneuploidy. But for decades, researchers have debated whether aneuploidy promotes the growth of cancers, or is simply a side effect of cancer cells' fast growth. Such large-scale changes in DNA have been difficult to study.

Now, researchers at the Broad Institute of MIT and Harvard and the Dana-Farber Cancer Institute have found—thanks to a computational tool they developed—that aneuploidy does drive cancer progression. Using that method, the scientists compared large chromosome changes in tumor cells from more than 10,000 cancer patients and identified key chromosome regions that, when duplicated or deleted, were harmful or beneficial to tumor cells. The work also revealed a new role for a known cancer gene called WRN—a result that, the team said, shows how this type of analysis can reveal new insight into cancer biology.

The findings, published today in *Nature*, could lead to new ways of guiding cancer treatment or developing targeted drugs.

"This study provides a computational answer, by directly using tumor samples from patients, to that age-old question of whether these large-scale events are really driving cancer or are just along for the ride," said Rameen Beroukhim, a co-senior author of the study, associate member in the Cancer Program at the Broad, and an oncologist at Harvard Medical School, Dana-Farber Cancer Institute, and Brigham and Women's Hospital. "We found that these aneuploidies are being directly selected for or against depending on their impact on cancer cells."

A common problem

Most human cells contain 23 pairs of chromosomes, but in the late 19th century, scientists noticed that tumors often had cells with abnormal numbers of chromosomes. More recently, studies have shown that aneuploidies—which also include duplications or deletions of entire

arms of chromosomes—are present in almost 90% of human cancers, often appear early in cancer, and are associated with worse clinical outcomes.

Some researchers suspected that aneuploidies appeared because of the severe dysregulation of cancer cells and didn't have any real impact on the cancer. Since the deleted or duplicated DNA regions involved in an aneuploidy can include hundreds or thousands of genes, pinning down any molecular mechanism by which an aneuploidy impacts tumor growth has been difficult.

"We've known for more than a century that these aneuploidies were really prominent in cancer genomes, but we didn't have great methods to study them," said Alison Taylor, a co-senior author of the paper and a former postdoctoral research fellow at the Broad and Dana-Farber Cancer Institute who is now an assistant professor at Columbia University Medical Center.

The long and the short

To study aneuploidy in cancer, Beroukhim and Taylor, in collaboration with first author Juliann Shih and other colleagues, wondered whether they could take advantage of other, shorter types of chromosome changes in cancer cells and tease out what sections of chromosomes might play a role in tumor growth and survival.

"There are large-scale changes that don't quite fit the typical definition of an aneuploidy, but are still impacting a large part of a chromosome arm," said Shih, previously an associate computational biologist at Broad and now an internal medicine resident at the Kirk Kerkorian School of Medicine at the University of Nevada, Las Vegas. "We began to think that these shorter events could give us signals about whether cancer cells were selecting for certain chromosome changes."

The team developed a method, dubbed BISCUT (Breakpoint Identification of Significant Cancer Undiscovered Targets), to analyze where large changes were most likely to begin or end in each chromosome. If the beginning and endpoints were in completely random spots, that would suggest that the aneuploidy had no direct impact on cancer cell survival. However, if a particular region was often included in a large-scale chromosome change, that would hint that the aneuploidy encompassing this area was helping cancer cells survive. Conversely, if a region was often excluded, that would suggest that the aneuploidy encompassing this area killed cancer cells or stunted their growth.

The researchers used BISCUT to analyze 10,872 tumor samples from 33 cancer types, using data from The Cancer Genome Atlas (TCGA). The analysis revealed 193 regions within or near aneuploidies that cancer cells seemed to be selecting for or against. Less than half included known cancer genes.

Beroukhim's group also discovered that the frequencies of aneuploidies on different chromosomes were correlated with the predicted selection pressure on regions within the aneuploidies.

"That was a pretty clear way of showing that selection seems to be the major driver of patterns of aneuploidies, and therefore that aneuploidies are having an impact on cancer cell survival," Beroukhim said.

Toward treatments

In nearly one-third of all cancers in TCGA, one arm of chromosome 8 is missing, but researchers had never been sure why this aneuploidy is so common. The study showed that deletions on chromosome 8 were more likely to include the cancer gene WRN than other areas of DNA, suggesting that it has a particularly large impact.

Certain cancer types are known to rely on WRN and drugs are already under development to block the gene. However, the new study showed a different role in up to a third of cancers, where a partial loss of the gene appears to help cancer cells survive. This observation could lead to new treatment approaches that selectively kill cancer cells harboring WRN loss, and to ways of identifying patients who will most likely benefit from these types of treatments.

This kind of finding is one example of the dozens of insights that Beroukhim, Taylor, and Shih think their dataset will eventually lead to. Separate studies can delve into the mechanism behind each chromosome region identified by BISCUT. Many of the regions, they suspect, will point towards new drug targets or ways of screening cancer patients for the most effective treatment.

"Our ability to address a centuries-old question is an example of how cancer research can make big leaps even in areas where it had seemed hopelessly stymied," Beroukhim said.

More information: Juliann Shih et al, Cancer aneuploidies are shaped primarily by effects on tumour fitness, *Nature* (2023). DOI: 10.1038/s41586-023-06266-3

Provided by Broad Institute of MIT and Harvard

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