Patterns found in cancer's chaos illuminate tumor evolution

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For more than 100 years, researchers have been unable to explain why cancer cells contain abnormal numbers of chromosomes, a phenomenon known as aneuploidy. Many believed aneuploidy was simply a random byproduct of cancer.

Now, a team at Harvard Medical School has devised a way to understand patterns of aneuploidy in tumors and predict which genes in the affected chromosomes are likely to be cancer suppressors or promoters. They propose that aneuploidy is a driver of cancer rather than a result of it.

The study, to be published online in *Cell* on Oct. 31, offers a new theory of cancer development and could open the door for new treatment targets.

"If you look at a cancer cell, it looks like an unholy mess with gene deletions and amplifications, chromosome gains and losses, like someone threw a stick of dynamite into the cell. It seems random, but actually previous work has shown that there is a pattern to which chromosomes and chromosome arms are altered—and that means we can understand that pattern and how or if it drives cancer," said senior author Stephen Elledge, Gregor Mendel professor of Genetics and of Medicine at HMS and professor of medicine at Brigham and Women's Hospital.

"What we have done is to propose a new theory about how this works and then prove it using mathematical analysis," he said.

Mining for answers

For decades since the "oncogene revolution," cancer research has focused on mutations—changes in the DNA code that abnormally activate genes that promote cancer, called oncogenes, or deactivate genes that suppress cancer. The role of aneuploidy—in which entire chromosomes or chromosome arms are added or deleted—has remained largely unstudied.

Elledge and his team, including research fellow and first author Teresa Davoli, suspected that aneuploidy has a significant role to play in cancer because missing or extra chromosomes likely affect genes involved in tumor-related processes such as cell division and DNA repair.

To test their hypothesis, the researchers developed a computer program called TUSON (Tumor Suppressor and Oncogene) Explorer together with Wei Xu and Peter Park at HMS and Brigham and Women's. The program analyzed genome sequence data from more than 8,200 pairs of cancerous and normal tissue samples in three preexisting databases.

They generated a list of suspected oncogenes and tumor suppressor genes based on their mutation patterns—and found many more potential cancer drivers than anticipated. Then they ranked the suspects by how powerful an effect their deletion or duplication was likely to have on cancer development.

Next, the team looked at where the suspects normally appear in chromosomes.

They discovered that the number of tumor suppressor genes or oncogenes in a chromosome correlated with how often the whole chromosome or part of the chromosome was deleted or duplicated in cancers. Where there were concentrations of tumor suppressor genes

alongside fewer oncogenes and fewer genes essential to survival, there was more chromosome deletion. Conversely, concentrations of oncogenes and fewer tumor suppressors coincided with more chromosome duplication.

When the team factored in gene potency, the correlations got even stronger. A cluster of highly potent tumor suppressors was more likely to mean chromosome deletion than a cluster of weak suppressors.

Number matters

Since 1971, the standard tumor suppressor model has held that cancer is caused by a "two-hit" cascade in which first one copy and then the second copy of a gene becomes mutated. Elledge argues that simply losing or gaining one copy of a gene through aneuploidy can influence tumor growth as well.

"The loss or gain of multiple cancer driver genes that individually have low potency can add up to have big effects," he said.

"It's a terrific study," said Angelika Amon, a professor of biology at Massachusetts Institute of Technology who was not involved in the project. "These novel algorithms of identifying tumor suppressors and oncogenes nicely provide an explanation of how aneuploidies evolve in cancer cells, and the realization that subtle changes in the activity of many different genes at the same time can contribute to tumorigenesis is an exciting and intriguing hypothesis."

These findings also may have answered a long-standing question about whether aneuploidy is a cause or effect of cancer, leaving researchers free to pursue the question of how.

"Aneuploidy is driving cancer, not simply a consequence of it," said

Elledge. "Other things also matter, such as gene mutations, rearrangements and changes in expression. We don't know what the weighting is, but now we should be able to figure it out."

Going forward, Elledge and Davoli plan to gather experimental evidence to support their mathematical findings. That will include validating some of the new predicted tumor suppressors and oncogenes as well as "making some deletions and amplifications and seeing if they have the properties we think they do," said Elledge.

Provided by Harvard Medical School