Tethering of shattered chromosomal fragments paves way for new cancer therapies

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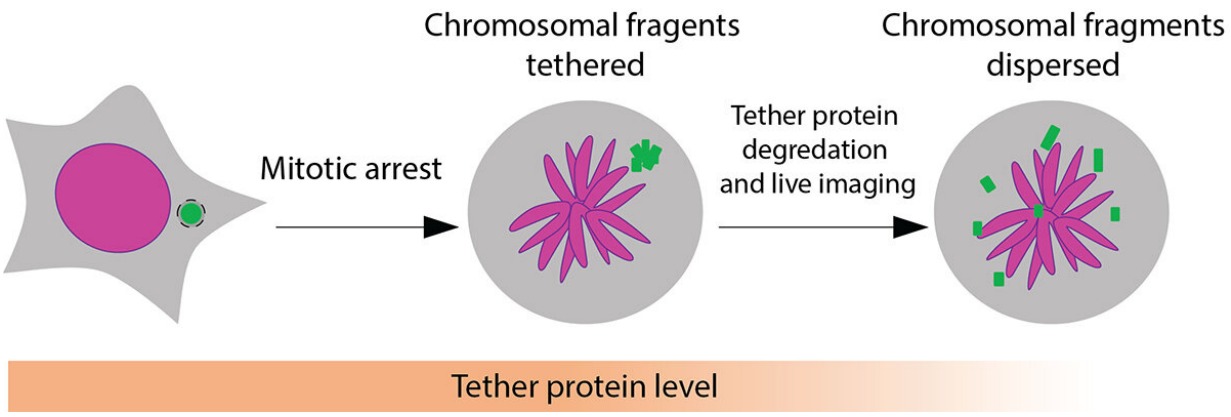

Fragments of micronuclear chromosomal DNA (green) are tethered together in normal conditions (center), but degrading one of the tether proteins prevents this clustering, causing the DNA fragments to disperse (right). Credit: UC San Diego Health Sciences

Healthy cells work hard to maintain the integrity of our DNA, but occasionally, a chromosome can get separated from the others and break apart during cell division. The tiny fragments of DNA then get reassembled in random order in the new cell, sometimes producing cancerous gene mutations.

This chromosomal shattering and rearranging is called "chromothripsis"

and occurs in the majority of human cancers, especially cancers of the bones, brain and fatty tissue. Chromothripsis was first described just over a decade ago, but scientists did not understand how the floating pieces of DNA were able to be put back together.

In a study published in *Nature*, researchers at University of California San Diego have answered this question, discovering that the shattered DNA fragments are actually tethered together. This allows them to travel as one during cell division and be re-encapsulated by one of the new daughter cells, where they are reassembled in a different order.

"It's similar to a smashed car windshield, where the safety glass is designed to keep all of the broken pieces in place," said senior study author Don W. Cleveland, Ph.D., Distinguished Professor and chair of the Department of Cellular and Molecular Medicine at UC San Diego School of Medicine. "What we've done here is find the safety glass and identify several of its core components, which we can now explore as therapeutic targets."

When chromosomes break and rearrange themselves, this can initiate or exacerbate cancer in several ways. For example, if a tumor suppressor gene is broken in the process, the cell will become more vulnerable to tumor formation.

In other cases, genes that aren't usually close to each other on the chromosome can suddenly be stitched together to produce a new oncogenic fusion protein. During chromothripsis, many such changes occur simultaneously, rather than gradually, thus accelerating cancer development or its resistance to therapy.

Now that the researchers had identified an early step in this process—the tethering of shattered DNA fragments—they wondered if they could stop it. By destroying the tether, they might prevent the rearranged

chromosomes from forming, thereby reducing the number of cells potentially carrying cancerous mutations.

To do this, postdoctoral fellow and first author of the study Prasad Trivedi, Ph.D., engineered a modified version of one of the tether proteins so that he could induce its destruction on demand. When he did so, the tether disintegrated, the DNA fragments did not cluster and the resulting cells showed reduced survival.

The authors suggest that the proteins in this tether complex, particularly cellular inhibitor of PP2A (CIP2A), may now be an attractive therapeutic target for chromosomally unstable tumors.

"The process of chromosomal care and repair contributes to cancer in many ways, so the more we understand how it works, the better we can fine-tune it to treat cancer," said Cleveland.

More information: Prasad Trivedi et al, Mitotic tethering enables inheritance of shattered micronuclear chromosomes, *Nature* (2023). DOI: 10.1038/s41586-023-06216-z

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