

Reviving an Old Hypothesis About Chromosomes and Cancer

A Damon Runyon scientist investigates the role of aneuploidy, or abnormal chromosome number, in cancer—and in possible treatments.

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A team of scientists at Yale University School of Medicine, led by former Damon Runyon Innovator Jason M. Sheltzer, PhD, recently cracked a century-old scientific mystery: the role of aneuploidy, or abnormal chromosome number, in driving cancer. As far back as the 19th century, scientists looking under a microscope noticed that when cancer cells divide, the chromosomes sometimes split unequally, resulting in two aneuploid daughter cells. In fact, this was once proposed as a mechanism of cancer development—but was overshadowed in the 20th century by the discovery of individual cancer-causing mutations and genes.

“In 2023, we know that chromosome gains, like oncogenic mutations, are incredibly common across cancer types,” says Dr. Sheltzer. “But, the genetic tools that allow us to study point mutations and individual oncogenes don’t work for chromosome-scale alterations.”

To overcome this, his team developed a new genetic tool using 2023-era technology—a CRISPR-based chromosome engineering technique called ReDACT, short for “Restoring Disomy in Aneuploid cells using CRISPR Targeting.” (Disomy refers to having two of each chromosome.) Using ReDACT, the team created pairs of cancer cells that were genetically identical except for the number of copies of a given chromosome. For example, one cell would have three copies, or a trisomy, of chromosome 7p, while its matched pair had two. With this direct comparison, the researchers could see that eliminating certain trisomies, specifically chromosome 1q, almost completely stopped tumor growth in many cancer types.

How exactly does this third copy of chromosome 1q drive cancer? Digging deeper, the team noticed that cancer cells tended to either have an extra copy of chromosome 1q or a mutation in the tumor suppressor gene p53—but not both. This mutual exclusivity suggested that the extra chromosome 1q somehow inhibits p53, a hypothesis reinforced when the team removed the extra copy and saw p53 reactivated. They were able to trace this p53 suppression to a gene called MDM4, located on chromosome 1q, which can suppress p53 even in disomic cells if it is overexpressed.

Notably, the researchers found that even when they removed the extra copy of chromosome 1q

with ReDACT, cancer cells reacquired a third copy over time, as their evolution favored aneuploid cells. This means, as Dr. Shelter put it: “Aneuploidy isn’t just a ‘bystander’ or a ‘passenger’ in cancer cells. It actually plays a central role in the malignant process. Chemical strategies to target specific aneuploid chromosomes could represent a new therapeutic approach for aggressive tumors.”

In other words, drug that can safely do in patients what ReDACT did in this study may offer a new cancer treatment a hundred years in the making.

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