Biologists discover 1 reason why chromosomes break, often leading to cancer

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In the past ten years, researchers in genome stability have observed that many kinds of cancer are associated with areas where human chromosomes break. They have hypothesized – but never proven – that slow or altered replication led to the chromosomes breaking.

In a Tufts University study published in the Aug. 3 journal *Molecular Cell*, two molecular biologists have used yeast artificial chromosomes to prove the hypothesis. The Tufts researchers have found a highly flexible DNA sequence that increases fragility and stalls replication, which then causes the chromosome to break.

Catherine Freudenreich, associate professor of biology at the School of Arts and Sciences at Tufts University, and doctoral student Haihua Zhang focused on one particular human common fragile site – an area that is a normal part of chromosome structure but is prone to breaking. The site lies in the middle of a tumor suppressor gene and chromosome breakage in this area is highly associated with cancer.

"It is an area that has a tumor suppressor gene – a gene whose absence can cause tumors," explained Freudenreich. "If you delete that gene or delete part of that gene so it doesn't work anymore, that can lead to tumors. The fact that there is fragility in the same region that this gene is located is a bad coincidence."

"Fragility can cause deletions and deletions can cause cancer, so you want to understand the fragility because that might be what's causing

cancer," she continued.

DNA structure leads to fragility

Past research had predicted the flexibility of the DNA helix in this particular common fragile site by calculating the twist angle between consecutive base pairs and found that there were several points of high flexibility, suggesting that the flexibility was connected to the fragility.

Freudenreich and Zhang used yeast artificial chromosomes to test this idea because it allowed them to look at the region in a more detailed way than looking at human chromosomes and to monitor the replication process. They expect the results will be similar when tested in human cells based on previous research using yeast chromosomes.

"What we did was take two of these regions of predicted high flexibility, plus a region near a cancer cell breakpoint and a control region, and test whether any of these regions could cause breakage of a yeast chromosome," Freudenreich said. "We found that one did. This is exciting because it is the first known sequence element within a human common fragile site shown to increase chromosome breakage. What is intriguing is that the sequence that breaks, in addition to being flexible, is predicted to form an abnormal DNA structure."

When replication stalls, chromosomes can break

Next, the researchers had to determine how the chromosomes were breaking. From past studies, they hypothesized that breakage was connected to "replication." As cells divide, the DNA inside those cells must duplicate, which is called replication. The Tufts research showed that the chromosomes were breaking because replication was stalled.

"We found that the fragile sequence actually stops replication," Freudenreich said. "So when replication gets there, it has trouble, it stops, it pauses, it can't go further very easily."

Most of the time, chromosomes break and heal correctly. The problem arises when they do not heal correctly and instead are deleted or rearranged, Freudenreich explained. "Cancer cells almost always have some sort of deletions or rearrangements," she said. "Something is wrong with their chromosomes that then messes up the genes that are in those areas."

The researchers also noticed that this particular sequence was an AT-rich region, where the DNA was composed mostly of the bases adenine (A) and thymine (T), rather than the other bases cytosine (C) or guanine (G). Freudenreich and Zhang found the longer the AT-repeat, the more the replication process was stalled, something they would like to follow up on with further research.

"We think the longer the repeat, the more the abnormal DNA structure forms, and the more fragile your chromosome is, but we haven't completely been able to nail that down," Freudenreich said. "It would be interesting to know, would people with longer repeats be more prone to deleting that tumor suppressor gene and getting cancer as a result" We have made this correlation and we'd like to know if it has a medical consequence."

Source: Tufts University