Researchers describe a 'POT-hole' that protects our chromosome ends

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Researchers have determined a new feature of how the natural ends of our chromosomes are protected from harmful outcomes.

In a new study, University of Michigan researchers looked at how the DNA damage recognition process seems to know the difference between harmful DNA breaks that need repair versus the natural ends of

chromosomes, called telomeres, that need to be left alone.

"If possible, you repair it, and if you can't repair it, then the cell dies. You don't want to keep dividing with broken DNA. That's what happens in a normal cell, and that's a good thing," said Jayakrishnan Nandakumar, a professor of molecular, cellular and developmental biology.

"Except the problem is that the break in the middle of a chromosome and the natural ends of the chromosome are, chemically speaking, the same, but repairing the natural ends could be disastrous, because then our chromosomes would get linked to one another."

Researchers know that a protein complex called shelterin caps the chromosome end and protects telomeres from a DNA damage response. Although shelterin was defined by biologists about 15 to 20 years ago, researchers didn't have the full picture of how it protects telomeres.

Nandakumar and his team, including senior scientist Valerie Tesmer, showed that a shelterin protein called POT1 uses a cavity the researchers call the "POT-hole" to hide the natural end of the chromosome from being recognized as DNA damage by the ATR machinery. The study is published in the journal *Science*.

"We dedicate this to the roads in Michigan—not all POT-holes are bad," Nandakumar said.

Although our chromosomes are mostly double-stranded (ds), one strand ends a little before the other. So the strand that stretches a little further forms a single-stranded (ss) tail at the chromosome end. The region where the ds region meets the ss tail is called the telomeric ds-ss junction. This means that telomeric DNA has three segments: ds, ss, and ds-ss junction segments. The DNA end within the ds-ss junction is called

the five-prime, or 5′, end.

The ATR DNA damage machinery recognizes DNA breaks that have a ds-ss junction and a ss tail. So what prevents ATR from recognizing the ds-ss junction and ss tail of telomeres? It was already known that POT1 protects the telomeric ss tail, but how the telomeric ds-ss junction is protected was not known.

Using a method called X-ray crystallography, the researchers were able to visualize in 3D the union between the POT1 protein and the DNA 5′ end at the ds-ss junction. In particular, the researchers were able to see the cavity into which the chromosome 5' end locks neatly, preventing access to the ATR machinery.

Tesmer was the researcher who clued into this function of POT1. She combed through previous research, focusing on a paper that reported a mysterious POT1 DNA binding site. Tesmer deciphered this DNA site to be the telomeric ds-ss junction, leading to the ultimate discovery that POT1 binds the telomeric ds-ss junction.

Tesmer and fellow co-author Kristen Brenner tested the POT-hole's importance in protecting against a DNA damage response by introducing mutations in the POT-hole that prevent POT1 from uniting with the ds-ss junction. These mutations allowed the DNA damage response machinery to recognize telomeres, showing us why it is important to have an intact POT-hole at our chromosome ends.

"Our discovery that POT1 binds to the (telomeric) ds-ss junction broadens how we think of human POT1 protecting the telomere," Tesmer said.

Along the way, the researchers also solved another major biological mystery. Mice possess two versions of POT1: POT1a and POT1b, but

only POT1a fully protects chromosome ends. Why can't POT1b replace POT1a? The reason is that only POT1a contains the POT-hole and binds the ds-ss junction.

"Our study has shown that even the 5′ ends of our chromosomes are capped by a protein. It's a protein that was previously known to bind the ends of chromosomes. We just didn't know that it physically caps the 5′ end," Nandakumar said. "If we had to revise our textbooks and show what our chromosome ends look like, we should show a cap at the 5′ end, and that cap would be the POT1 protein."

More information: Valerie M. Tesmer et al, Human POT1 protects the telomeric ds-ss DNA junction by capping the 5' end of the chromosome, *Science* (2023). DOI: 10.1126/science.adi2436.

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