Researchers unravel protective properties of telomere t-loops

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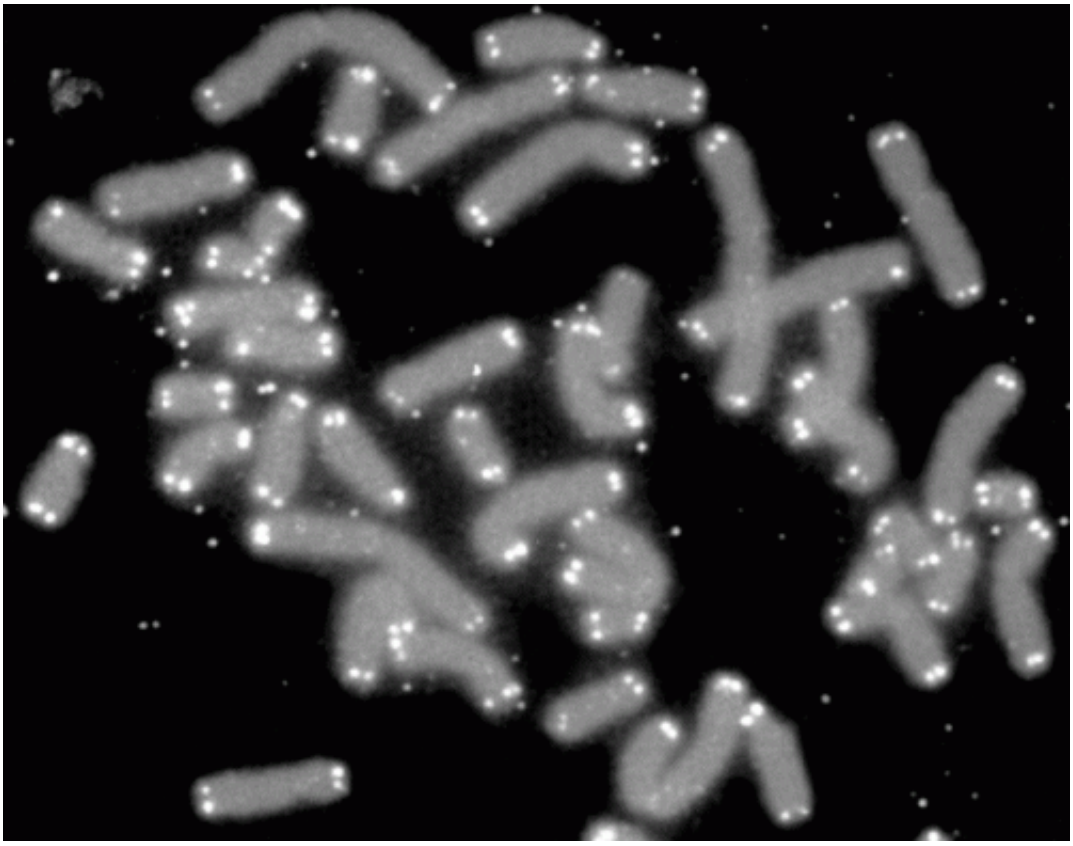

Human chromosomes (grey) capped by telomeres (white). Credit: PD-NASA; PD-USGOV-NASA

Loops at the ends of telomeres play a vital protective role preventing irretrievable damage to chromosomes, according to new research from the Crick.

The study, published in *Nature*, showed how the winding and unwinding of 't-loops' at the end of telomeres prevents chromosomes from being recognised as DNA damage. The study also uncovered how this process is regulated.

A significant challenge for maintaining linear chromosomes is that the DNA end must be prevented from being detected as DNA damage. This problem is solved by telomeres, specialised structures of non-coding DNA that protect the end of chromosomes. One way that telomeres are thought to protect the end of the chromosome is by adopting a lasso-like t-loop structure, which acts to bury the DNA end within the telomere and mask it from being detected as DNA damage. These loops are formed by the telomeres folding back on themselves at the end of the chromosome and can be wound or unwound.

"While telomeres are known to play a vital role in protecting DNA and allowing cells to divide, there has been a cloud of uncertainty surrounding t-loops, their function and importance. This is a question we wanted to resolve with this study," says Panagiotis Kotsantis, paper author and postdoc in the DNA Double Strand Breaks Repair Metabolism Laboratory at the Crick.

The study discovered how important it is for these t-loops to be wound or unwound at the correct stage of the cell cycle.

If DNA replication occurs while the t-loop remains wound up, this creates a problem as the advancing replication fork collides with the t-loop, triggering catastrophic loss of the telomere and damage to the chromosome end.

On the other hand, by manipulating the telomere so that the t-loop is inappropriately unwound throughout all stages of the cell cycle, the researchers discovered that the chromosome ends are now unmasked and

are detected as DNA damage. For the first time, this showed that t-loops are important for protecting the ends of chromosomes.

"Ensuring that these loops are unwound during DNA replication and then re-wound for all other stages in the cell cycle, is essential to stop chromosomes being damaged. It's a really intricate process, and the consequences if it goes wrong can be disastrous for the cell," explains Simon Boulton, paper author and group leader in the DNA Double Strand Breaks Repair Metabolism Laboratory at the Crick.

The researchers also uncovered the mechanism that regulates the winding and unwinding of these t-loops. They found that when a telomere bound protein called TFR2 near the t-loop undergoes a chemical change called de-phosphorylation this attracts another protein, RTEL1. Having been attracted to the t-loop, this second protein can unwind the loop. The study also showed the reverse is true, so when TFR2 is phosphorylated, this repels RTEL1 and so prevents the loop from being unwound outside of the replication stage of the cell cycle.

"Our next step will be to look at how telomeres and t-loops function in stem cells, as these use different protective mechanisms meaning that if you block the loops forming strangely the chromosomes don't fuse—there must be something else at work here," further explains Simon.

More information: CDK phosphorylation of TRF2 controls t-loop dynamics during the cell cycle, *Nature* (2019). DOI: 10.1038/s41586-019-1744-8 , nature.com/articles/s41586-019-1744-8

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