Researchers uncover the unique way stem cells protect their chromosome ends

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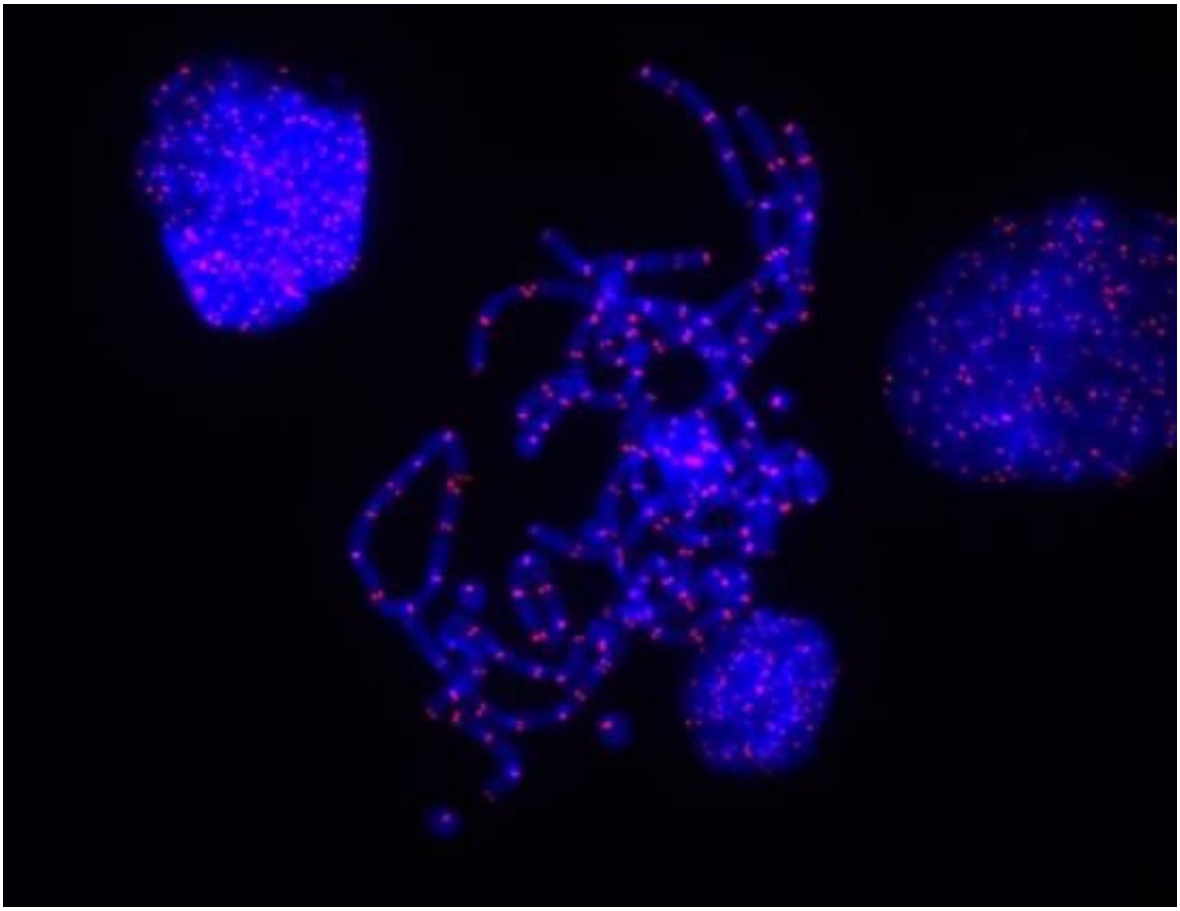

Chromosome fusions in TRF2-knockout MEFs. Credit: The Francis Crick Institute

Telomeres are specialized structures at the end of chromosomes which protect our DNA and ensure healthy division of cells. According to a

new study from researchers at the Francis Crick Institute published in *Nature,* the mechanisms of telomere protection are surprisingly unique in stem cells.

For the last 20 years, researchers have been working to understand how telomeres protect chromosome ends from being incorrectly repaired and joined together because this has important implications for our understanding of cancer and aging.

In healthy cells, this protection is very efficient, but as we age our telomeres get progressively shorter, eventually becoming so short that they lose some of these protective functions. In healthy cells, this contributes to the progressive decline in our health and fitness as we age. Conversely, telomere shortening poses a protective barrier to tumor development, which cancer cells must solve in order to divide indefinitely.

In somatic cells, which are all the cells in the adult body except stem cells and gametes, we know that a protein called TRF2 helps to protect the telomere. It does this by binding to and stabilizing a loop structure, called a t-loop, which masks the end of the chromosome. When the TRF2 protein is removed, these loops do not form and the chromosome ends fuse together, leading to "spaghetti chromosomes" and killing the cell.

However, in this latest study, Crick researchers have found that when the TRF2 protein is removed from mouse embryonic stem cells, t-loops continue to form, chromosome ends remain protected and the cells are largely unaffected.

As embryonic stem cells differentiate into somatic cells, this unique mechanism of end protection is lost and both t-loops and chromosome end protection become reliant on TRF2. This suggests that somatic and

stem cells protect their chromosome ends in fundamentally different ways.

"Now we know that TRF2 isn't needed for t-loop formation in stem cells, we infer there must be some other factor that does the same job or a different mechanism to stabilize t-loops in these cells, and we want to know what it is," says Philip Ruis, first author of the paper and Ph.D. student in the DNA Double Strand Breaks Repair Metabolism Laboratory at the Crick.

"For some reason, stem cells have evolved this distinct mechanism of protecting their chromosomes ends, that differs from somatic cells. Why they have, we have no idea, but it's intriguing. It opens up many questions that will keep us busy for many years to come."

The team have also helped to clarify years of uncertainty about whether the t-loops themselves play a part in protecting the chromosome ends. They found that telomeres in stem cells with t-loops but without TRF2 are still protected, suggesting the t-loop structure itself has a protective role.

"Rather than totally contradicting years of telomere research, our study refines it in a very unique way. Basically, we've shown that stem cells protect their chromosome ends differently to what we previously thought, but this still requires a t-loop," says Simon Boulton, paper author and group leader in the DNA Double Strand Breaks Repair Metabolism Laboratory at the Crick.

"A better understanding of how telomeres work, and how they protect the ends of chromosomes could offer crucial insights into the underlying processes that lead to premature aging and cancer."

The team worked in collaboration with Tony Cesare in Sydney and other

researchers across the Crick, including Kathy Niakan, of the Human Embryo and Stem Cell Laboratory, and James Briscoe, of the Developmental Dynamics Laboratory at the Crick. "This is a prime example of what the Crick was set up to promote. We've been able to really benefit from our collaborator's expertise and the access that was made possible by the Crick's unique facilities," says Simon.

The researchers will continue this work, aiming to understand in detail the mechanisms of telomere protection in somatic and embryonic cells.

More information: Phil Ruis et al. TRF2-independent chromosome end protection during pluripotency, *Nature* (2020). DOI: 10.1038/s41586-020-2960-y

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