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Scientists find mechanisms to avoid telomere instability found in cancer and aging cells

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Researchers from Instituto de Medicina Molecular (iMM) João Lobo Antunes have found that a functional component of telomeres called TERRA has to be kept constantly in check to prevent telomeric and chromosomal instability, one of the underlying anomalies associated with cancer.

Telomeres, the very ends of linear chromosomes, protect the stability of the genome by preventing erosion of genetic material and fusion of independent chromosomes. When telomeres are dysfunctional, severe genomic instability arises, and features of dysfunctional telomeres are often observed in cancer cells as well as in aged cells.

Scientists have tried to understand how telomeres are maintained to better understand the biology of cancer and aging. In this study, the team led by Claus Azzalin wanted to understand whether TERRA could become dangerous if not properly maintained in cells. Combining molecular biology, cellular biology, high-end microscopy and biochemistry, they found a new interplay between three key telomeric molecules—the long, noncoding RNA TERRA and two telomeric proteins, TRF1 and TRF2. While TRF2 is able to promote the formation of RNA-DNA hybrids between TERRA and telomeric DNA, TRF1 prevents this TRF2 associated activity. When this interplay is compromised, the ensuing RNA-DNA hybrid structures lead to loss of telomeres and therefore genome instability.

These results show that telomeres in general and, more specifically

TERRA, need to be regulated to serve their protective functions. Indeed, a lack of such fine regulation leads to the severe telomere and chromosome instability commonly found in cancer and aging cells. "I'm excited at the idea that our work could illuminate novel avenues for therapeutic intervention based on modulation of RNA in cells," said Claus Azzalin.

These discoveries could illuminate the molecular basis of chromosomal instabilities associated with cancer development and age-associated diseases possibly paving the way for new therapeutic approaches. "I expect this study will open a new window on our understanding of genome stability and ultimately help in the development of aging and cancer therapies," said the study's first author Yong Woo Lee.

More information: Yong Woo Lee et al, TRF1 participates in chromosome end protection by averting TRF2-dependent telomeric R loops, *Nature Structural & Molecular Biology* (2018). DOI: 10.1038/s41594-017-0021-5

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