

Why chromosomes never tie their shoelaces

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In the latest issue of the journal *Nature*, Miguel Godinho Ferreira, Principal Investigator at the Instituto Gulbenkian de Ciencia (IGC) in Portugal, lead a team of researchers to shed light on a paradox that has puzzled biologists since the discovery of telomeres, the protective tips of chromosomes: while broken chromosome ends generated by DNA damage (such as radiation or cigarette smoke) are quickly joined together, telomeres are never tied to each other, thus allowing for the correct segregation of the genetic material into all cells in our body.

Since telomeres erode in response to the continuous cell divisions in our body, this protective function fades away as we grow older. Complete loss of telomeres results in sticky chromosome-ends that join to each other creating to genetic chaos - the very initial steps of cancer.

Understanding how the tips of the chromosomes are protected from DNA repair and how the cells respond when they are unprotected will provide insights into the initial stages of tumourgenesis, ageing and future therapeutic interventions.

Cells respond to broken or damaged DNA by arresting their cell cycle while the damage is repaired. If the tips of chromosomes were recognized as broken DNA, cells would be constantly trying to mend the ends of chromosomes, leading to [cell death](#) and mutations in the DNA. Telomeres - the caps made up of protein and DNA at the tips of chromosomes - stop this from happening.

Through a series of meticulous experiments the Portuguese team, in collaboration with researchers at University of Illinois, Chicago, reveal

that the crux lies in the changes of a protein, a Histone modification, located close to the telomeres. Histones are found along the entire length of all [chromosomes](#), helping to package the DNA and also playing a role in regulating gene activity. Using fission yeast (used to make bread and beer) as a model organism, the researchers found that one of the Histones neighbouring the telomeres lacks a chemical signal, thus rendering the DNA damage recognition machinery incapable of arresting the cell cycle.

Says Miguel Godinho Ferreira, 'It's amazing, but it appears to be this single change that underlies the cell's ability to distinguish the end of the chromosome (i.e. a telomere) from a break in the middle. Indeed, along the rest of the genome, these Histones retain the chemical signal, so that when DNA damage does occur in any of these regions, DNA repair is set up and broken ends joined together.'

Telomeres are like the plastic caps on shoelaces: just as a shoelace starts unravelling when the cap is lost, so chromosome ends would become shorter with each cell division were it not for the telomeres. Telomeres are added or elongated by the enzyme telomerase. However, most cells in our body lack telomerase from when we are born, consequently telomeres become shorter and lose protection, sending signals for cells to stop dividing and start ageing. In about 85% of cancers, cells re-activate telomerase, contributing to their ability to divide and proliferate.

Even though DNA repair must be prevented at telomeres, assembly of the [DNA damage](#) recognition machinery is vital for telomerase activation and telomere elongation. Miguel Godinho Ferreira adds, 'Eukaryotic cells have evolved a very specific mechanism whereby telomerase recruitment goes ahead undisturbed, yet the whole [DNA repair](#) process is kept at bay from chromosome ends. Knowing the details of telomere capping is crucial to understanding its relationship to cancer, ageing and several diseases, and the multiple ways in which

telomere manipulation may, potentially, lead to effective treatments".

He continues emphasizing the importance of fundamental basic research: "When Liz Blackburn, Carol Greider and Jack Szostak discovered telomerase and telomeres in the 80s, for which they got last year's Nobel Prize in Physiology or Medicine, they were searching for a solution to the "end-replication problem" and far from imagining the clinical implications these findings are currently developing. They were simply solving an academic puzzle created by the discovery of the double helix and the inability of DNA polymerases to synthesize the ends of linear DNA. Likewise, we are honored and excited to contribute to unravel these mechanisms, but perfectly aware that the direct implications of this work are still many years away".

More information: Tiago Carneiro, Lyne Khair, Clara C. Reis, Vanessa Borges¹, Bettina A. Moser, Toru M. Nakamura & Miguel Godinho Ferreira; 'Telomeres avoid end detection by severing the checkpoint signal transduction pathway'; *Nature*, volume 467, issue 7312, pp 228-232. [DOI:10.1038/nature09353](https://doi.org/10.1038/nature09353)

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