

SHORT TELOMERES IDENTIFIED AS A MAIN SOURCE OF DAMAGE LEADING TO ORGANISMAL AGEING

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Scientists from the Spanish National Cancer Research Centre (CNIO) describe for the first time the genetic and epigenetic alterations through which short telomeres cause organismal ageing. The results of this study are published today in the American journal *P.N.A.S. (Proceedings of The National Academy of Sciences U.S.A.)*.

The accumulation of damage, through the very process of living, on our genetic material (DNA) is the most accepted hypothesis as to why we age. However, the nature of the damage leading to ageing remains the subject of intense scientific debate. Recent research carried out on genetically modified mice suggests that the "free radicals", a popular theory on ageing, do not seem the main culprits of organismal ageing.

Cells, upon division to generate new daughter cells, transmit a DNA that is damaged and incomplete due to the progressive loss of a DNA-protecting structure termed **telomeres**. When telomeres shorten below a minimum length, the cells halt their cell cycle and cease to regenerate the tissues, which results in cell ageing and, consequently, in whole organismal ageing. This notion enjoys a broad experimental support in mice genetically modified for telomerase, the telomeres-synthesising enzyme, as well as in human pathologies of premature ageing caused by an accelerated telomeric shortening.

Are short telomeres a main source of damage leading to organismal ageing?

The recent study led at CNIO by Maria A. Blasco, in which Stefan Schoeftner and Raquel Blanco were the main contributors, shows that the damage produced by short telomeres results in global changes in gene expression consistent with the activation of a cellular stress response involving the AKT and mTOR pathways, coincident with a decrease in both the capability of the cells to divide and to repair the damage in the DNA. Surprisingly, short telomeres also interfere with important epigenetic processes such as X chromosome inactivation in females, which also stops occupying the same nuclear position as the telomeric RNAs, TERRAs (note in the accompanying figure that in the cells with short telomeres the inactive X chromosome -Xist- and TERRAs locate on different positions). Defects on X chromosome inactivation would have fatal consequences on cell and organismal viability.

According to Blasco. "This discovery suggests that progressive shortening of telomeres and accumulation of dysfunctional telomeres constitute a main source of damage, enough on its own to drive global genetic and epigenetic changes that provoke organismal ageing".

Additional info:

The longer the telomeres, the bigger the multiplying capacity of a cell (including the tissue-regenerating stem cells) and, therefore, the organism stays young for a longer time. The relationship between telomeres and ageing is known since 1990 thanks to the research of Carol W. Greider and Calvin Harley. Furthermore, an enzyme exists that contributes to this process by elongating the telomeres: telomerase. Its discovery earned Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak the Nobel Prize in Medicine this year.

Last year, the team of Maria A. Blasco demonstrated that the relationship between telomeres and ageing was also at play in mammals (Tomás-Loba y cols., 2008, *Cell*. 35:609-622). Mice treated with telomerase have a delayed ageing and they live up to 40% longer. But it remained unknown until now the exact inner mechanism by which a cell harbouring short telomeres should age earlier than the rest.

