New insight into how telomeres protect cells from premature senescence

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Researchers at the Institute of Molecular Biology (IMB) and Johannes Gutenberg University Mainz (JGU) have further uncovered the secrets of telomeres, the caps that protect the ends of our chromosomes. They discovered that an RNA molecule called TERRA helps to ensure that very short (or broken) telomeres get fixed again. The work, which was recently published in the journal *Cell*, provides new insights into cellular processes that regulate cell senescence and survival in ageing and cancer.

Telomeres protect the ends of our chromosomes, much like the plastic cap at the end of a shoelace that prevents the lace from unravelling. Over a cell's lifetime, telomeres get gradually shorter with each cell division and therefore the protective cap becomes less and less effective. If they get too short, it is a signal for the cell that its genetic material is compromised and the cell stops dividing. Telomere shortening and reduced cell division are considered a hallmark of ageing and likely contribute to the ageing process. However, telomere shortening is also a defense mechanism against cancer because highly proliferative cells can only divide when their telomeres do not shorten. Therefore, telomere shortening is a double-edged sword and has to be carefully regulated to strike a balance between ageing and cancer prevention. When a telomere accidentally gets cut short early in a cell's lifetime, it needs to be fixed so that the cell doesn't become senescent too early.

"In the life of a cell, you have to find some sort of balance between cancer prevention and ageing. Telomeres are at the nexus between the two, so understanding how they are maintained is really important", said

Brian Luke, Professor at the JGU Institute for Developmental Biology and Neurobiology and Adjunct Director at IMB.

Luke and his lab were interested in understanding how the cell recognizes these shortened and damaged telomeres that have lost their caps. Furthermore, they wanted to determine which factors were important for promoting the repair of short telomeres. This information could help in understanding why cells either commit to senescence or continue to grow.

In their recent paper, published in the prestigious journal *Cell*, Luke and his group have shown that one of the keys to understanding this problem is TERRA. TERRA is an RNA species that accumulates specifically at the ends of critically short telomeres by binding directly to the DNA and signals to the cell that these telomeres should be repaired, allowing the cell to carry on dividing.

"We already knew that short telomeres play a key role in determining the onset of cellular senescence, but we didn't really understand which features of short telomeres were important. What we have found with TERRA is an intricate regulatory system that explains how short telomeres are identified by the cell", said Luke.

The paper is actually the result of two different research projects on telomeres in the Luke lab. Diego Bonetti was looking into the regulation of TERRA in the cell cycle and found that TERRA levels were different at different stages of the cell cycle. Meanwhile, Arianna Lockhart and Marco Graf were investigating the accumulation of TERRA at short telomeres. When they discovered that the pattern of cyclic TERRA accumulation was different between short and long telomeres, they knew they were on to something and joined forces for this project.

Their joint work led them to realize that TERRA actually accumulates at

all telomeres, but at long telomeres it is rapidly removed with the help of proteins Rat1 and RNase H2. These proteins bind preferentially to the long telomeres and ensure that TERRA is removed, but they are not present at the critically short telomeres, which means that TERRA remains for a longer time. This mechanism ensures the subsequent repair of the short telomere, which is crucial for the cell to survive and keep dividing.

Luke's work was carried out in yeast; however, telomeres and TERRA are found across all organisms with linear chromosomes. The researchers expect their work to be applicable to humans as well. Their next step will be to look into these processes in human cells and interrogate their implications for ageing and cancer.

More information: Marco Graf et al, Telomere Length Determines TERRA and R-Loop Regulation through the Cell Cycle, *Cell* (2017). DOI: 10.1016/j.cell.2017.06.006

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