How chromosome ends influence cellular aging

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By studying processes that occur at the ends of chromosomes, a team of Heidelberg researchers has unravelled an important mechanism towards a better understanding of cellular aging. The scientists focused on the length of the chromosome ends, the so-called telomeres, which can be experimentally manipulated. Their research, which was conducted at the Center for Molecular Biology of Heidelberg University (ZMBH), allows for new approaches in the development of therapies for tissue loss and organ failure associated with senescence (cellular aging). The research results may also be significant for cancer treatment. They were recently published in the journal *Nature Structural & Molecular Biology*.

Each cell contains a set of chromosomes in which the vast majority of our genetic information is stored in the form of DNA. This information must be protected to ensure the proper functioning of the cell. To achieve this, the very ends of the chromosomes, the telomeres, play an important role in protecting the chromosomal DNA from being degraded. "We can imagine that telomeres are analogous to the plastic caps at the ends of our shoelaces. Without them, the ends of the laces get frayed and eventually the entire shoelace does not function properly," explains Dr. Brian Luke. His research group at the ZMBH is primarily focused on understanding how telomeres protect DNA.

It is well known in the scientific community that telomeres shorten every time a cell divides and eventually become so short that they can no longer protect the chromosomes. The unprotected chromosome ends send signals that stop the cell from dividing further, a state referred to as

"senescence". Senescent cells occur more frequently as we age, which can contribute to tissue loss and organ failure. "In certain diseases, patients already have very short telomeres at birth and as a result they experience severe tissue loss and organ dysfunction at an early age", says the Heidelberg scientist.

The research group headed by Dr. Luke has now discovered that turning transcription on or off at telomeres can have drastic effects on their length. Transcription is the process of making an RNA molecule from DNA. It has only recently been shown to occur at telomeres, but the functional significance of this discovery has remained a mystery. Molecular biologists Bettina Balk and André Maicher were now able to show that the RNA itself is the key regulator that drives telomere length changes, especially when it sticks to telomeric DNA to make a so-called "RNA-DNA hybrid molecule".

"We experimentally changed the amount of RNA-DNA hybrids at the chromosome ends. We can thus either accelerate or diminish the rate of cellular senescence directly by affecting telomere length," explains Bettina Balk. According to André Maicher, this could be a first step towards telomere-based therapies for tissue loss or organ failure. With respect to diseases, it remains to be determined whether altering transcription rates at telomeres does indeed improve health status. This approach is also significant for cancer cells, which do not senesce and are thus considered immortal. "Transcription-based telomere length control may therefore also be applicable to cancer treatment," Dr. Luke emphasizes.

More information: Balk, B. et al. Telomeric RNA-DNA hybrids affect telomere length dynamics and senescence, *Nat. Struct. Mol. Biol*, 8 September 2013. DOI: 10.1038/nsmb.2662

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