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“Safeguarding the ends of linear chromosomes, known as telomeres, is essential for any animal’s survival. We are trying to understand how cells keep tabs on their telomeres and prevent catastrophic meltdowns to gain a better understanding of the interrelationship of aging and cancer.”

Like slow-burning fuses, telomeres—the protective ends of chromosomes—become shorter each time a cell divides. Eventually they are depleted, and the cell enters a permanently arrested state called senescence. This process has long been correlated to aging, but how cells recognize that their telomeres are getting shorter and how that affects the cell on a genome-wide scale has remained a mystery. Karlseder and his group have recently cracked the case, finding a direct connection between telomere shortening and histones, the protein “spools” that DNA winds around and that control access to DNA. Collectively known as heterochromatin, the histone packaging can be modified by enzymes that leave chemical signals and instructions behind.

In their study, they hypothesized that senescence is an epigenetic adaptation to chronic changes in the chromosomal architecture of telomeres as they shorten over successive cell divisions. To the team’s surprise, the data revealed that a decline in histone biosynthesis is a central feature of cellular aging.

When telomeres become shorter, they start to emit a chronic signal that alerts the DNA damage machinery to the presence of potential problems at the chromosome ends. This signal is not strong enough to induce cell cycle arrest, but it directly affects the synthesis of two core histones, leading to an imbalance in the composition of chromatin. In response, methyl and acetyl groups connected to individual amino acids in histones that monitor cell division and integrity are reshuffled. This redistribution amplifies the signal emitted locally by shortening telomeres and turns it into a nucleus-wide response. The signal amplification cycle continues until a threshold is exceeded, and the cells respond by entering senescence.

This study explains for the first time how a local event at the chromosome ends gets translated into a signal affecting the entire cell. By providing a link between telomere shortening, histone synthesis, and chromatin maintenance, Karlseder’s lab is helping to address a fundamental question: how telomeres determine the lifespan of human cells.

For more information, please visit
salk.edu/faculty/karlseder.html



Left to right:

Front row: Daniel Lackner, Makoto Hayashi, Candy Haggblom, Colleen Naeger, Marcela Raices, and Roddy O’Sullivan

Back row: Anthony Cesare, Liana Oganessian, Jan Karlseder, Pepper Stockton