

Telomere Biology: A Short History

Chromosomes are the thread-like structures containing the twisted helix of DNA that carries genetic information in the form of genes located inside the nucleus of every plant, animal and fungus cell. Each time a cell reproduces, the chromosomes replicate, producing two daughter cells with the same genetic coding. The natural ends of each chromosome are protected from damage by repetitive sequences of non-coding DNA, called telomeres.

Telomeres were first identified in 1938 by Hermann Muller (Nobel Prize in Physiology or Medicine 1933), working with fruit fly (*Drosophila*) cells, and then, in 1940, in corn (*Zea mays*) cells, by Barbara McClintock (Nobel Prize in Physiology or Medicine 1983). Both geneticists found that the ends of natural chromosomes were different from those of broken chromosomes and therefore must be unique structures. They called these structures telomeres. Muller found that telomeres were integral to chromosomal stability, and McClintock further surmised that these caps prevented the ends of chromosomes from fusing together. Thus, telomeres were discovered and their function hypothesized before the double helix structure of DNA was established!

The famous work of James Watson and Francis Crick in 1953 (Nobel Prize in Physiology or Medicine 1962, along with Maurice Wilkins), revealed the double helix structure of DNA, which offered a mechanism for DNA replication that could result in two identical daughter chromosomes. The genetic base-pair alphabet (ACGT) spells out the repetitive sequences of telomeres as well as codons (genes). In 1959, Arthur Kornberg won the Nobel Prize in Physiology or Medicine for his work on DNA polymerases, enzymes crucial to chromosomal replication. This left open the question of how complete and accurate synthesis of the DNA ends was achieved.

In 1961, anatomist Leonard Hayflick showed that populations of normal fetal cells in culture divided only 40-60 times before ceasing division and becoming senescent. This concept (called the Hayflick limit) was controversial at the time, because it flew in the face of the prevailing model of immortal cells in culture propounded by Nobel laureate Alexis Carrel since 1912. Hayflick proposed that this aging of the cell presages the overall physical aging of the body. However, his discovery of cell senescence was not generally accepted for a decade, in part because the connection with telomeres was not yet understood.

These two key concepts: cell senescence and telomere length, began to converge in the 1970s. Alexey Olovnikov, in 1971 (and independently, Watson in 1972) observed that the ends of chromosomes do not replicate completely and hence lose a bit of material with

each replication. After a certain number of replications, when these ends would be worn down to a critically short length, the cell would cease dividing and become senescent. Olonikov pointed out the possible link between chromosome shortening and the Hayflick limit. His research also reinforced the implication that cells used a catalyst enzyme (a polymerase) that could lengthen the chromosomal ends.

In the late 1970s, Elizabeth Blackburn began to search for end sequences of DNA in the unicellular ciliate *Tetrahymena*. In parallel, Jack Szostak was exploring mechanisms of DNA recombination in yeast cells. In 1982, they jointly published work demonstrating that the repeat telomere sequences did indeed stabilize replication in the two species. In 1989, Blackburn and Carol Greider published the first paper elucidating the function of telomerase. Telomerase is a reverse transcriptase, an enzyme used to generate complementary DNA from an RNA primer that adds telomere repeat sequences at the end of telomeres. The Nobel Prize in Physiology or Medicine 2009 was awarded jointly to Blackburn, Greider and Szostak "for the discovery of how chromosomes are protected by telomeres and enzyme telomerase."

Through this research, the connection between cell senescence and whole-body aging with telomere length and telomerase activity was firmly established. To date, several thousand studies have been published on telomeres and telomerase in nearly every area of medical research: wellness and longevity, cardiovascular health, cancer, diabetes, diet and exercise, depression, arthritis, kidney disease, pulmonary disease, etc. Because of their fundamental role in cellular functioning, telomeres continue to be vigorously researched for their role in nearly every known disease state as well as a potential target for therapeutic intervention.

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The information provided by the TeloYears test should not be used to replace medically appropriate screening tests recommended based upon actual age or other risk factors, nor should the information be used to make decisions about diagnosis or treatment of diseases or medical conditions. The Telomere Diagnostics lab is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical testing. The performance characteristics of this test were determined by Telomere Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration.

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