

Telomeres and Telomerase in Cellular Aging (Senescence)

Telomeres are bits of DNA on the ends of chromosomes that protect chromosomes from sticking to each other or tangling, which could cause DNA to abnormally function. As cells replicate, telomeres shorten at the end of chromosomes, and this process correlates to senescence or cellular aging. Integral to this process is telomerase, which is an enzyme that repairs telomeres and is present in various cells in the human body, especially during human growth and development. Telomeres and telomerase are required for normal animal development because they protect DNA as it duplicates copies of itself.

In 1965, Leonard Hayflick's research at the Wistar Institute in Philadelphia, Pennsylvania, showed the limit to which cells duplicate themselves before aging. Hayflick established what became called the Hayflick limit, which states that a cell can divide forty to sixty times before it cannot divide further and begins to age. In the 1970s, scientists researched telomeres. Elizabeth Blackburn studied telomeres while she worked at Yale University in New Haven, Connecticut. Alexey Olovnikov in Russia related telomeres to cellular aging and to the Hayflick Limit. Although Blackburn had helped discover telomeres in 1975, two years before, in 1973, Olovnikov had hypothesized the existence of telomerase, the length of telomeres, and their connections to cellular aging in his study on the Hayflick Limit. Unaware of Olovnikov's research, Blackburn and Joseph G. Gall independently found a repetitive sequence of DNA at the end of chromosomes of the yeast, *Tetrahymena thermophila*. Blackburn and Gall published the results of their research in 1978. In 1982 Blackburn, then at the University of California in Berkeley, California, collaborated with Jack W. Szostak at the Harvard Medical School in Boston, Massachusetts. The pair isolated and cloned telomeres in *Tetrahymena* DNA. Blackburn, with the help of her student Carol Greider, then identified telomerase in 1984 and isolated it from *Tetrahymena* in 1989. Blackburn, Jack Szostak, and Carol Greider received the Nobel Prize in Physiology or Medicine in 2009 for their work to identify and isolate telomeres and telomerase.

Blackburn and others found that cells age when the length of the telomeres in the cells shortens. Each time a cell replicates itself, the end of a strand of DNA or the telomere shrinks in length. The telomeres shrink across replications because the enzyme that replicates DNA, DNA polymerase, only works in one specific direction on the DNA strand. It creates what is called a leading and a lagging strand of duplication. The leading strand receives its name because DNA polymerase constantly moves in one direction and replicates the DNA until it completes the strand of DNA without any breaks. The lagging strand is composed of individual fragments of DNA created by DNA polymerase, called Okazaki fragments, that are later sealed together by the enzyme DNA ligase to create one continuous strand. The name lagging strand derives from the fact that it lags behind the leading strand since lagging or leading strand can take longer to seal together the individual DNA fragments. The DNA polymerase detaches from DNA at the end of a lagging strand and leaves a space that measures a few nucleotides in length. Telomerase normally fills in the gap at the end of the DNA after the polymerase detaches from it.

Telomerase, the enzyme that repairs telomeres, exists in high quantities in developing organisms and in embryonic stem cells. Some cells have higher amounts of telomerase activity than do others. As a human develops and cells replicate with greater frequency, excess telomerase is used and is later replenished only in minute quantities. At the end of the process of DNA replication, without telomerase to fill in the gaps of a new DNA strand, telomeres shorten with each cellular division. According to Blackburn, the Hayflick Limit is a result of decreased telomere length. De-

creased telomere length also leads to chromosomal abnormalities that result in mutations in the genetic code, mutations that can cause cancer and further aging in humans. However, too much telomerase can also lead to cancer by helping cells to become functionally immortal by avoiding the Hayflick Limit. Immortal cells can carry mutations in unrepaired areas of the DNA, and they pass the cancerous mutations to other cells through replication.

Scientists continued researching telomerase, telomere activity, and cellular aging after Blackburn's experiments in the 1980s. Scientists studied how environmental factors could affect the length of telomeres and, consequently, cellular aging. In 2008, Geraldine Aubert and Peter Langsdorp at the Terry Fox Laboratory in Vancouver, Canada, published research showing that cells replicate in response to mutations in the genetic code or in response to stress. Aubert and Langsdorp showed that a cell will replicate to attempt to repair damaged DNA and, in turn, will shorten the telomeres.

In 2012, Blackburn, Jue Lin, and Elissa Epel at the University of California in San Francisco, California, showed the influence of lifestyle on the length of telomeres and cellular aging in humans. They found that stress, nutrition, and personality influence the length of telomeres and telomerase enzyme activity. They defined stress as adverse life events such as death in the family or chronically sick children, and they found that personality also influences how a person perceives stressful events. The authors noted that those who perceived events as less stressful than what the researchers expected had longer telomere lengths compared to individuals who perceived events as more stressful than what researchers expected. Behaviors such as smoking or eating processed meats also correlated with shorter than normal telomere lengths. Also, those who took vitamin C or E supplements had longer than normal telomere lengths. The results of Blackburn and her team's experiment verified that environmental factors affect the length of telomeres.

Some people have criticized telomere research. Harry Rubin, at the University of California in Berkeley argued that researchers who studied telomeres in relation to cancer sometimes produce suspect data. Others argued that scientists pay too much attention on telomere research when they should also study other factors involved in the cell cycle.

Sources

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