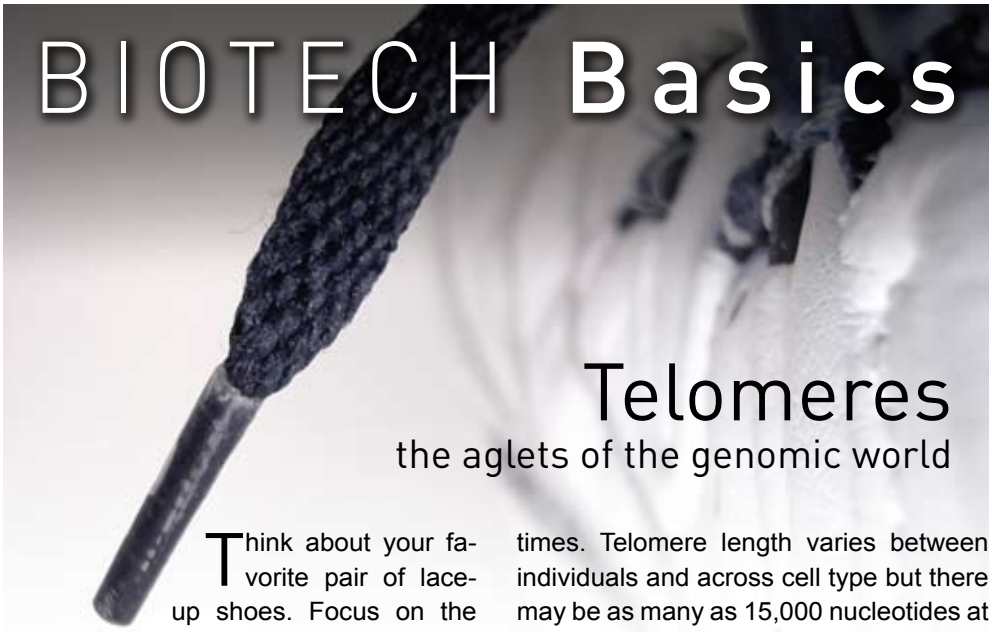
BIOTECH Basics



Telomeres

the aglets of the genomic world

What You Need to Know

- *DNA is organized into small structures known as chromosomes. At the ends of each chromosome are repeating sequences of DNA known as telomeres.*
- *Every time the cell divides and copies its DNA, the very end of the telomere is unable to be copied and the total telomere length is shortened.*
- *Telomeres act as a buffer to protect the genes near the ends of the chromosome from being degraded by the shortening process.*
- *When the telomeres become too short, the cell stops dividing. This is called senescence and is associated with aging.*
- *An enzyme known as telomerase is active in a small number of cells to keep telomeres long. Most adult cells have no telomerase present.*
- *There seems to be a link between long telomeres and longevity. Possibly those individuals who live long lives are producing a very low level of telomerase in their adult cells.*
- *Continually active telomerase is a feature of many types of cancer, as it allows cells to divide indefinitely without reaching senescence. The level of telomerase activity must therefore be balanced between slowing the signs of aging and preventing the growth of tumor cells.*

Think about your favorite pair of lace-up shoes. Focus on the shoelaces from those shoes, specifically on the tips where the small plastic or metal coverings wrap around the lace. Those coverings, known as aglets, protect the ends from damage and keep the fibers of the lace from unraveling. If the aglet wears away, the end becomes frayed and it is time for the shoelace to be replaced.

The image of a genetic aglet, a region at the end of a DNA strand that protects it from damage, serves as an appropriate introduction to this edition of *Biotech Basics*. These regions, found at the tips of chromosomes, are known as telomeres. A critical component of the genome, telomeres have been implicated in both cancer and aging. Recognizing the importance of telomeres, the 2009 Nobel Prize in Physiology or Medicine was awarded to three scientists (Elizabeth Blackburn, Jack Szostak and Carol Greider) for the discovery of telomere structure and identification of how telomeres function and are maintained in cells.

Structure and Function

Telomeres are repeating sequences of DNA found at the ends of each chromosome (figure one). They help prevent chromosomes from fusing into rings or binding haphazardly to each other. Primarily found in plants and animals, telomeres also protect chromosome ends from damage. In humans, telomeres are composed of a six-nucleotide sequence (TTAGGG) that is repeated thousands of times. Telomere length varies between individuals and across cell type but there may be as many as 15,000 nucleotides at the tip of a chromosome.

When a cell divides, the chromosomes are copied by specific enzymes and provide each daughter cell with a complete set of genetic information. Unfortunately, the copying enzymes are unable to completely reproduce the very end of each DNA strand, leading to a slightly shorter copied fragment (for the science buffs reading this article, this occurs at the 5' end of the lagging strand). Damage from molecules known as free radicals also reduces the ends of the DNA in chromosomes. As a result, the copied strand is about 50-200 nucleotides shorter than the original segment. Every time the cell divides, the chromosomes become shorter. Fortunately, the telomeres serve as a buffer region, absorbing the DNA reduction without impacting those genes located near the chromosome tip.

In humans, a small subset of actively dividing cells (such as those from bone marrow, precursor sperm cells or most stem cells) does not undergo telomere shortening. This is due to a remarkable enzyme known as telomerase that functions to extend the telomere after every cell division. Telomerase counteracts the impact of DNA shortening and the telomerase genes are present in every cell. During fetal development, telomerase is active, resulting in long telomeres for all the cells of the growing embryo. During the second trimester of pregnancy, the telomerase genes are silenced across

For more information:

Press release announcing the 2009 Nobel Prize in Physiology of Medicine:
nobelprize.org/nobel_prizes/medicine/laureates/2009/press.html
This Web site has a well-written description of telomeres and telomerase.

Web page from the National Institutes of Health describing the research connecting telomere length with longevity:
www.nih.gov/researchmatters/november2009/11232009longevity.htm

most tissues, so the process of DNA shortening begins. Telomerase remains active at low levels among bone marrow and precursor sperm cells, maintaining long telomeres.

Telomeres and Aging:

As an individual ages and undergoes repeated cell divisions, the telomeres continue to shorten. At some point, the telomeres become so short that the genes at the end of the chromosome are in danger of being deleted. When this critical length is reached, a signal is activated inside the cell to prevent further cell division (figure two). This process, known as senescence, appears to be an important factor in aging. Many scientists believe the physical signs of aging result from an ever-increasing proportion of cells reaching senescence. Because fewer cells are available to reproduce and replenish themselves, maintenance and defense of the body becomes difficult. In support of this theory, a number of premature aging syndromes have been associated with short telomeres, although the precise correlation between telomere length and disease symptoms is still unclear.

Several other studies have confirmed a link between telomere length and long life. When scientists compared lifespan between two groups divided by telomere length, those with the longer telomeres lived five years longer than those with shorter ones. An additional project found that centenarians (individuals 100 years or older) have longer than expected telomeres and have given birth to children with long telomeres. This suggests telomere length may be genetically controlled. When the telomere gene sequences were compared between the centenarians and populations that died at an earlier age, several genetic differences were found. Preliminary findings suggest this genetic variation might allow silenced telomerase genes to "whisper," producing a small amount of telomerase expression. If low levels of telomerase are present in all cells throughout life, the repeated rounds of shortening may be delayed. In the laboratory, telomerase has allowed cultures of human cells to grow and divide far beyond their normal limit. An alternative hypothesis is that long-lived individuals are born with longer telomeres so the symptoms of aging are postponed.

A role in cancer formation

This begs the question: Could achieving long life be as simple as reactivating the telomerase genes? It is not yet known if shorter telomeres are a cause of aging or simply a visible sign of the aging process. Mice, which live only a few years, have longer telomeres than humans, suggesting that telomere length is not the sole regulator of aging. In addition, there is a potential downside to producing telomerase throughout life, as it appears to be a critical player in cancer. Cancer most often results from an accumulation of genetic and environmental changes that slowly convert normal cells into ever-growing tumors (a previous *Biotech Basics* article about cancer can be found online at hudsonalpha.org/education/outreach/basics). A common finding among different types of cancer is the presence of telomerase within the cancer cells. Remember, cancer cells experience cell division at a rapid pace. If telomeres were shortened with each round of division, the signal for senescence would be quickly reached. Tumors would never grow beyond a relatively small size because the cell divisions would be halted. Instead, many cancer cells have acquired mutations that reactivate telomerase production. These cells use telomerase to extend telomere lengths, allowing the tumor to continue its rapid growth. In light of this finding, several research labs are exploring methods to silence telomerase in cancer cells as a potential treatment option.

The awarding of the Nobel Prize based on telomere and telomerase research has brought renewed awareness and interest to this field of study. Telomeres play a critical role: protecting our chromosomes and serving as a molecular "clock" with respect to aging.

A careful balance must be maintained with respect to telomerase activity. If telomerase is silenced too quickly, aging occurs prematurely. If telomerase remains active for too long, there is an increased risk of tumor formation. Research into telomeres and their regulation will be a closely watched field for several years to come.

– Dr. Neil Lamb
director of educational outreach
HudsonAlpha Institute for Biotechnology

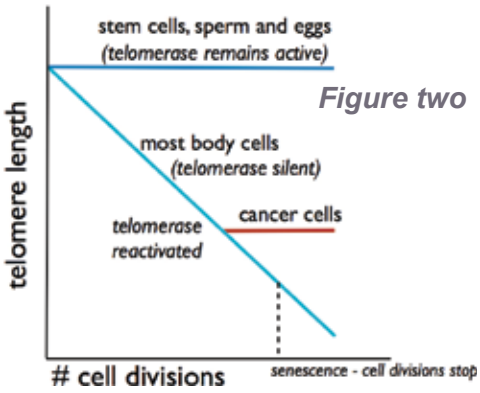
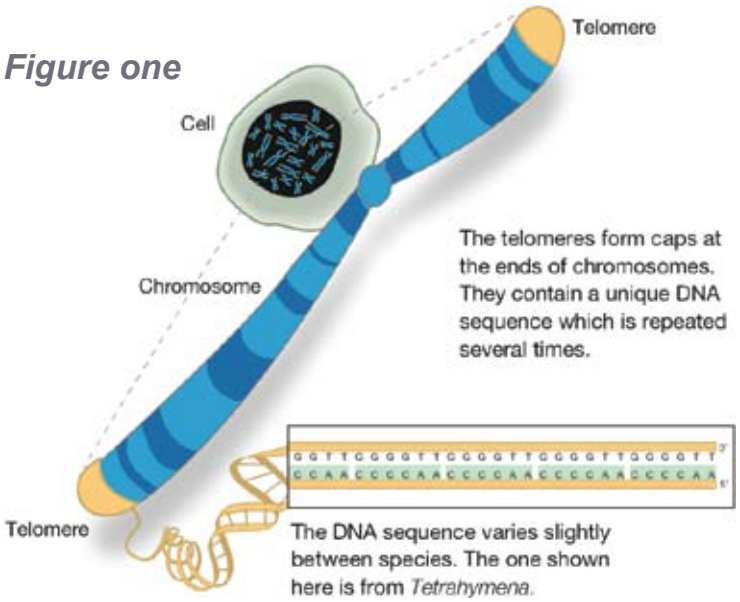


Figure two

The relationship between number of cell divisions, activity of telomerase and telomere length

Figure one



At left: Telomeres. (Credit: © The Nobel Committee for Physiology or Medicine 2009 / Illustration: Annika Röhl)