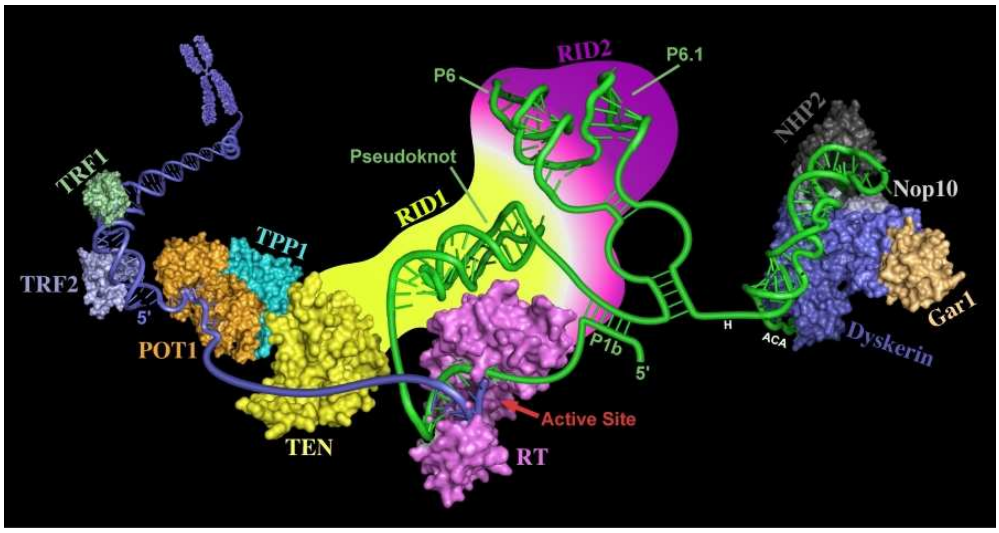
The Telomere, Telomerase and Cancer



The Telomerase Enzyme
Source: Podlevsky, J.D., Bley, C.J., Omana, R.V., Qi, X., Chen, J. (2007) The Telomerase Database. Nucleic Acids Res. 36 D339-D343.

Laurie Larsson
September 24, 2009
BI 103
Danil Hammoudi, M.D.

Introduction

Telomeres, the ends of the double-helix DNA molecule, and telomerase, the enzyme responsible for telomere maintenance, are essential to the processes of cell aging, cell senescence and apoptosis. Ongoing research indicates a probable link among telomere length, telomerase levels, cell immortality and cancer. Defining this relationship in healthy tissue and determining the effects under anomalous conditions may lead to a greater understanding of tumorigenesis and cancer treatment.

Background

Telomeres are regions of repetitive DNA sequences capping the ends of eukaryotic chromosomes. The primary roles of the telomere are to prevent chromosome ends from fusion and recombination and from being recognized as damaged DNA. A telomere can be visualized as an aglet, the plastic tip of a shoestring. Figure 1 highlights the telomeres of human chromosomes.

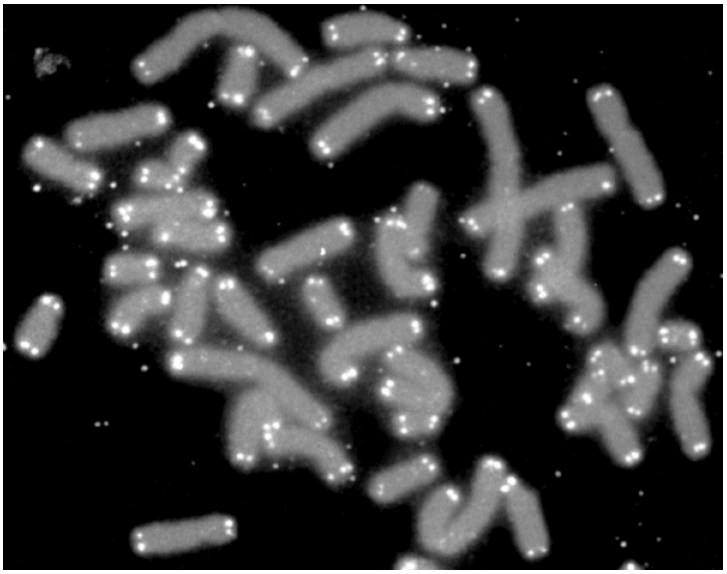


Figure 1. Human Chromosomes (grey) with Telomeres (white).
Source: U.S. Department of Energy Human Genome Program

The telomere was first described in the 1930s by Herman Muller, a geneticist, and Barbara McClintock, a distinguished cytogeneticist. In 1961, Leonard Hayflick refuted the long-standing theory that healthy, normal cells were immortal in culture. His research established the "Hayflick Limit," the maximum number of divisions a differentiated cell can achieve in vitro before entering cell senescence. In the1970s, James D. Watson described the "end-replication problems" of DNA, noting that the extreme 5' ends of the molecule would not be copied. Telomeres would shorten with each DNA replication unless a compensatory mechanism existed. Alexei Olovnikov, a Russian theorist, suggested a relationship between the shortening of the telomere and the Hayflick Limit. This relationship was later substantiated by C. W. Greider and colleagues. The mortality of a cell is programmed by it DNA.

Telomere Structure and Function

The ends of human chromosomes (and those of many other invertebrates) are composed of repetitive 5'-TTAGGG-3' sequences. Elizabeth Blackburn determined the molecular structure of this thymine (T) and guanine (G) rich area of DNA in 1978. In the human chromosome, the telomere is 5 -12 kilobases in length. Along with the repeating 6-base sequence, a telomere has a region termed the 3' overhang which does not have a complementary strand. In humans, the 3' overhang contains between 50 – 100 nucleotides. The classic view of the telomere is the linear structure shown in Figure 2.

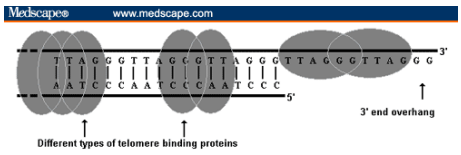


Figure 2. Classic View of the Telomere Sturcture
Source: *Telomeres, Telomerase and Tumorigenesis—A Review*

However, electron microscope studies reveal a double loop structure in which the 3' over hang wraps around and binds with the double-stranded 5' sequence forming a double loop as shown in Figure 3. This looping structure may play a part in the protective role of the telomere.

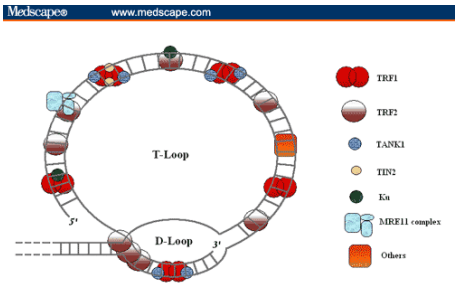


Figure 3. Current View of the Telomere Sturcture
Source: *Telomeres, Telomerase and Tumorigenesis—A Review*

During DNA replication, DNA polymerase can only synthesize in the 3' to 5' direction. After the double-helix is separated into two single strands, DNA primase constructs short RNA primers to act as a starting point for DNA polymerase. DNA polymerase builds the new complementary strand by adding nucleotides and then removing the RNA primers. Removal of the RNA primer leaves a section of un-replicated DNA at the 5' ends. Additionally, exonuclease removes 130 – 210 nucleotides from the 5' end. Figure 4 shows the replication of DNA and the shortening of the telomere.

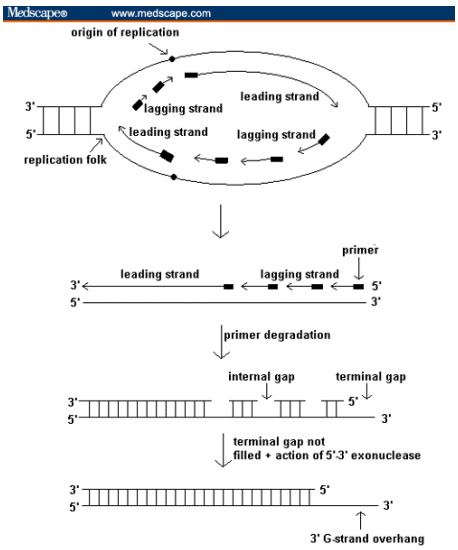


Figure 4. DNA Replication and Telomere Shortening
Source: *Telomeres, Telomerase and Tumorigenesis—A Review*

In normal somatic cells, after a finite number of replications, telomeres shorten to a critical length. Once the critical length checkpoint is reached, cell proliferation is arrested and cells enter senescence. The Hayflick Limit of most differentiated human cells in culture is 40 – 60 divisions. However, germ line cells, stem cells and some regenerative somatic cells bypass the Hayflick Limit and are capable of many more divisions than typical cells. The telomeres of these cells do not shorten. Telomerase, an enzyme isolated in 1984 by Elizabeth Blackburn and colleagues, is the key to telomere maintenance and cell longevity.

Telomerase Structure and Function

Telomerase, the main positive regulator of telomere length, is a ribonucleic protein that acts as a reverse transcriptase (synthesis takes place in the 5'-3' direction). The telomerase enzyme has two main components—a telomere RNA component (TERC) and a telomere reverse transcriptase (TERT). The RNA sequence is complementary to the DNA repeat sequence in the telomere and acts a template. Telomerase binds to the 3'overhang of the telomere and synthesizes the six nucleotide repeat sequence 5'-TTAGGG-3'. Telomerase then moves six nucleotides toward the 3' end and begins another repeat. DNA primase lays an RNA primer on the complementary strand. DNA polymerase follows, completing the complementary strand of the telomere. The process of telomere lengthening prevents the telomere form reaching the critical length checkpoint and entering senescence. Cell division is permitted to continue.

Telomerase activity is nearly nonexistent in normal somatic cells in the human body. However, mitotically active tissue such as skin, lymphocytes and cells of the endometrium exhibits low levels of telomerase activity. The number of cell divisions in these cells is regulated by tissue growth. Stem cells express telomerase throughout their life cycle. Nearly 90% of human cancers express telomerase, making it a promising target for cancer detection and therapies.

Telomere Length, Telomerase and Cancer

Telomere length acts as a biological clock, intrinsic to differentiated cells, regulating their life span. Telomeres naturally limit a cell's ability to replicate. When telomeres reach critical length, a number of pathways are activated to induce senescence (M1). Cell division is arrested and apoptosis is initiated. In normal cells, when the critical length checkpoint is bypassed, telomeres continue to shorten. Extremely short telomeres are recognized as a double-stranded break. DNA-damage proteins are activated. Homologous chromosomes may recombine or nonhomologous chromosome ends may join. Under these conditions, cells enter a crisis phase (M2), become unstable and readily undergo apoptosis.

In tumor cells, bypassing the critical length checkpoint and the crisis phase causes telomeres to continue to shorten. Telomerase is activated and telomeres are stabilized, maintaining a constant length. These cells have overcome the barriers of senescence and crisis and are considered immortal. They may proliferate indefinitely. However, immortality alone is not sufficient to induce malignancy. Additional factors such as the activation of an oncogene or the deactivation of a tumor suppressor gene are required.

Current research indicates that telomerase and telomeres offer potential targets for anticancer therapies. Three areas of research include the inactivation of telomerase in tumor cells, the elimination of telomerase expressing cells tumor cells and the expression of a mutant telomerase RNA template to induce apoptosis in tumors. Research is currently in the experimental stages. A more detailed understanding of the structure and function of the telomere and telomerase and their role in tumorigenesis is necessary to develop clinical applications of these novel therapies.

References

Brooker, R. J., Widmaier, E. P., Graham, L. E., Stiling, P. D. (2008). *Biology* (1st edition). New York, NY. McGraw-Hill.

Greider, C. W. (1999). Telomers Do D-Loop T-Loop. *Cell*, Vol. 97, 419–422,

Wai, Lin Kah. (2004). Telomeres, Telomerase, and Tumorigenesis -- A Review. *MedGenMed*, 6(3):19