

Telomere-Based Cancer Treatment: Emerging Targeted Therapies

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Chemotherapy and radiation therapy are standard care in cancer treatment; however, both have numerous adverse side effects because they affect healthy as well as cancerous cells. The side effects, including decreased white blood cell count, nausea, hair loss, and fatigue, can be severe enough that patients may decide to forgo treatment. Targeted therapies are treatments that focus on specific molecules in cancerous cells and avoid disruption of healthy cells. Telomeres, the ends of chromosomes, are possible targets. In healthy cells, telomeres become shorter with each cell division, limiting the number of divisions that a normal cell can undergo. Many cancer cells have telomerase activity, which rebuilds telomeres after each cell division and confers immortality to cancer cells. Telomerase is an enzyme normally present to a significant degree only in the cells of developing fetuses. Treatments that target the telomerase enzyme itself or the chromosomal telomeres are being developed and tested in early clinical trials. This article focuses on several approaches to telomere-targeted therapy.

Telomeres, the ends of chromosomes, are composed of long, repeating sequences of DNA (see Figure 1). In normal somatic cells, the ends of telomeres cannot be replicated prior to cell division, when the rest of the chromosome is duplicated (Allsopp & Weissman, 2002). Therefore, daughter cells' chromosomes are minutely shorter than those of the parent cell after normal cell division. Cell division results in progressive shortening of each chromosome, such that after a finite number of cell divisions, telomeres become too short and the cell cannot divide further; this state is called senescence (Serrano, 2010). However, an enzyme called telomerase that rebuilds the telomere after each cell division is present in embryonic cells and in most cancer cells. Reports have shown telomerase activity in 80%–90% of cancer cells (Harley, 2008). Because the chromosomal length is maintained, cells with telomerase activity are immortal, meaning they can divide indefinitely. If the telomerase enzyme were prevented from working, cancer cells may undergo senescence and fail to divide further; therefore, the development of therapies that target telomeres or telomerase is an active research area. Figure 2 lists definitions of terms.

Research is focusing on using telomerase activity or telomere length as a prognostic and diagnostic indicator. Analysis of the activity level of telomerase may give insight to the likelihood of recurrence of a particular cancer because higher levels of

At a Glance

- ◆ When telomeres are too short, cells stop dividing, become senescent, and may enter apoptosis or programmed cell death.
- ◆ Telomerase inhibition, active immunotherapy, and telomere-disrupting agents all aim to shorten telomeres and induce senescence in cancer cells.
- ◆ To date, telomere-targeting agents are being tested in clinical trials to determine dosage, toxicity, and effectiveness.

telomerase activity have been correlated to higher chances of tumor recurrence (Tatsumoto et al., 2000). Therefore, knowledge of telomerase activity level or telomere length in patients with cancer may help healthcare providers plan appropriate treatment to combat cancer progression.

Telomeres and Telomerase

Blackburn and Gall (1978) discovered the existence of tandem repeats (5'-CCCAA-3') located at the ends of ribosomal genes in the protozoan *Tetrahymena thermophila*.

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