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Clinical Implications of Basic Research

TELOMERES, TELOMERASE, AND CANCER

WHAT accounts for the ability of cancer cells to proliferate in a manner that is out of control, whereas normal cells die after 40 to 60 cycles of replication? One mechanism that leads to the death of a normal cell is erosion of the structure that caps the ends of chromosomes — the telomere (from the Greek *telos*, meaning end, and *meros*, a component) — each time a cell divides. The clinical relevance of telomeres is that a cancer cell, unlike a normal cell, can repair eroded telomeres. The existence of this repair mechanism suggests a novel target for cancer treatment.

Before any cell can divide, it must first replicate the double-stranded DNA in its chromosomes. But the cell has a problem replicating the DNA at the telomeres, where there are over 1000 short base sequences, TTAGGG, repeated over and over again and a variety of DNA-binding proteins. In a normal cell, the replication machinery cannot copy the last few bases of the telomeres on one of the strands of DNA in the chromosome. As a result, the telomeres shorten with each round of DNA replication.

The telomere, a kind of molecular cap, protects the ends of the chromosome against degradation and prevents ligation of the ends of DNA by DNA-repair enzymes. These functions are crucial to the cell. When repeated during many cell cycles, the wearing away of the telomere with each cell division eventually abrogates its protective function. As a result, the chromosomes become unstable, fused, or lost. Cells with such defects not only are unable to divide, but also may not survive; they may die as a result of apoptosis. Attrition of the telomere thereby limits the life span of many kinds of cells.

There are, however, two distinctive kinds of cells — germ cells and early embryonic cells — that must overcome this problem, because the body cannot afford to lose them. They solve the problem of the truncated telomere by means of a complex of proteins and RNA called telomerase. The RNA component of this complex contains a template sequence on which the TTAGGG repeats at the ends of DNA can be synthesized.

Unlike germ cells and early embryonic cells, most somatic cells switch off the activity of telomerase after birth. By contrast, many kinds of cancer cells — perhaps as many as 90 percent of them — reactivate telomerase. Turning on this complex, which rewinds

the clock on run-down telomeres, contributes to the growth of the malignant clone. Several recent studies have explored the possibility of inhibiting telomerase as a way of arresting the growth of tumor cells.¹⁻³

Part of the telomerase complex is an enzyme called telomerase reverse transcriptase. Using the RNA template in the telomerase complex, this enzyme catalyzes the synthesis of the TTAGGG sequences at the end of the telomere (Fig. 1). Researchers have been able to introduce into cultured cancer cells a mutant gene that causes the cell to produce an inactive telomerase reverse transcriptase, which competes with the active form in the complex. This interference with the active enzyme causes shortening of telomeres, induces many of the chromosomal changes associated with the aging of normal cells, and arrests the growth of the cells, which ultimately undergo apoptosis. These effects were shown to depend on the length of the telomeres in the cancer cells — the shorter the telomere, the more profound the effect of the mutant gene. Even more interesting is the finding that human cancer cells carrying the mutant gene lose their ability to form tumors in immunologically deficient mice.

In other experiments, human cancer cells were treated in vitro with specific 2'-O-methylated RNA and peptide nucleic acid oligomers, compounds that bind to and block the activity of the telomerase complex. Both agents caused considerable inhibition of telomerase, shortening of telomeres, and with repeated treatment, apoptosis of all the cells in the culture.

These results are doubtless interesting and suggest new possibilities for the treatment of cancer. We must, however, remember several points. First, the experiments were conducted in cell lines, and the efficient uptake of inhibitors was ensured by means that are unavailable for in vivo treatment. Second, the inhibitors worked best in cultured tumor cells when telomeres were shortest, but little is known about the length of telomeres in primary human tumors. A recent study found that malignant-lymphoma specimens obtained from patients at the time of diagnosis had shorter telomeres than benign lymphoid tissue. In lymphoma specimens obtained during relapses, however, shortened, unchanged, and elongated telomeres were observed.⁴ Third, up to 20 percent of human tumors do not have telomerase activity and may use other mechanisms to preserve their telomeres. Even though the therapeutic potential of telomerase inhibitors may be limited by these considerations, further investigation of this approach is certainly worthwhile.

Attrition of telomeres may also be a contributing factor in chronic diseases with high rates of cell turnover in specific tissues, such as bone marrow in the case of myeloproliferative diseases or hepatocytes in the case of cirrhosis. In such diseases, the reactivation of telomerase may offer a new treatment. This idea

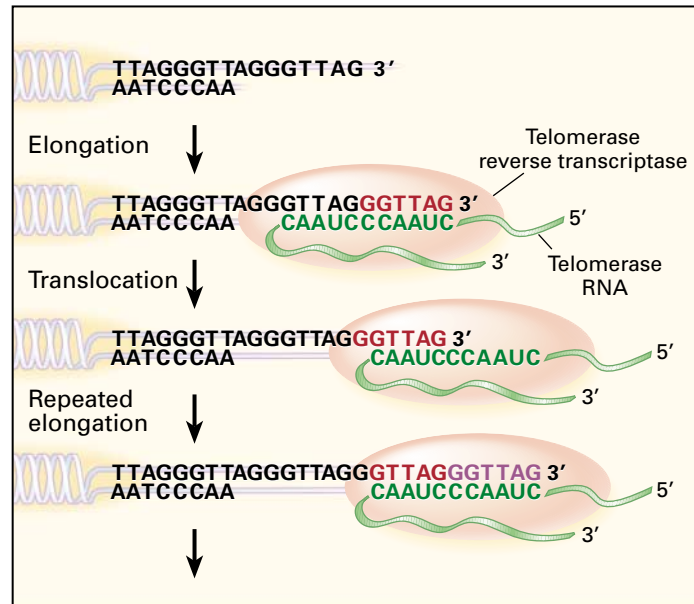


Figure 1. Function of Telomerase.

Telomerase repairs the eroding ends, or telomeres, of chromosomes by adding TTAGGG sequences. At the telomere of a chromosome, the short base sequence TTAGGG occurs repeatedly in the 5'-to-3' strand of DNA (the upper DNA strand). In most types of cells, the chromosome-replication machinery cannot complete the replication of the very end of the 3'-to-5' strand (the lower DNA strand), resulting in a shortening of the telomere with each round of DNA replication that precedes cell division. Germ cells, early embryonic cells, and cancer cells have a special enzyme, telomerase, that adds bases to the 3' end of the DNA strand that serves as the replication template. Telomerase is a complex consisting of an RNA component and several protein components, including a reverse transcriptase. The RNA component contains a template sequence that is complementary to the TTAGGG telomeric repeat sequence. Using this template, telomerase reverse transcriptase catalyzes the addition of nucleotides to the 3' ends of telomeres. Telomerase thus moves along the DNA, elongating the telomere.

is supported by a recent report that the introduction of the gene encoding the RNA component of the telomerase complex into the liver in telomerase-deficient mice with experimentally induced chronic liver injury prevented cirrhosis.⁵ It is clear, however, that any plan to use telomerase gene therapy in humans should take into account the potential risk of tumor induction.

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