Telomeres and Telomerase: Cancer, Immortality, and Mental Retardation

The word telomeres comes from the Greek "telos," which means "end." When applied to chromosomes, it means the end tip of a chromosome. Repetitive DNA sequences (TTAGGG) are located at the end or tip of a chromosome and are called telomeric sequences. Telomeric repeats are highly conserved, with the same sequences found in protozoa, nematodes, lower and higher plants, and vertebrates. Telomeres were first recognized as short repeated sequences at the end of ciliate chromosomes and in lower eukaryotes such as yeast. These repetitive sequences were later recognized and documented in human chromosomes.

Recent evidence has shown that telomeres are involved in a large number of biologic functions. Two among those suggested are very important: (1) protection of the linear chromosome end from degradating, recombining, and ligating to other chromosome ends; and (2) completion of the replication of chromosome DNA sequences at the chromosome ends (Biessman and Mason).

The cloning and characterization of the repetitive sequences that make up human telomeres have greatly benefited from new DNA cloning techniques and have led to interesting observations regarding cancer and aging. For example, the length of a telomere, ie, the number of repetitive sequences, is known to be associated with the number of cell divisions that particular cell has gone through. Telomeres in human germline cells, eg, sperm and egg, are known to be longer than those seen in somatic tissue cells, such as in blood. The telomeres of the human chromosomes shorten with each cell division. Shortened telomeres (in comparison with those of adjacent nontumor mucosa) have been documented in Wilms' tumors and colorectal carcinomas. The telomeric hypothesis (originally called the marginotomy theory) stated that the gradual loss of chromosome ends leads to cell arrest. This theory was based on progressive telomeric shortening with aging and on the observation that if a telomere became too short, cell growth would arrest.

The enzyme that synthesizes the telomeric sequences is a ribonucleoprotein enzyme called telomerase. Telomerase has been shown to be abnormally increased in some cancer cells. The gene for telomerase in humans has not been mapped. Telomerase expression is directly related to telomeric conservation. Excessive expression of telomerase has the potential to stop or delay the normal shortening of the telomeres and, consequently, delay cell cycle arrest. Aberrant telomerase expression has been suggested as a mechanism for producing the "immortality" of cancer cells.

The shortening of telomeres of human chromosomes with each cell division has been thought to serve as some sort of mitotic clock that can be used as a direct marker for the number of times a cell has divided. The exact role shortened telomeres play in aging is still unclear; however, telomeric loss with a successful series of cell divisions has been referred to as a "genetic time bomb" (Harley), since it will eventually lead to cell death.

An abnormality of telomeres also has been associated with mental retardation. In a recent report, Flint et al studied the subtelomeric regions of 99 mentally retarded individuals. They hypothesized that since the telomeric end of the chromosome is an area of active recombination, it would be expected to be at risk for small deletions. To detect chromosomal abnormalities within the subtelomeric region, they used hypervariable DNA polymorphism probes. They compared the DNA of both parents with the mentally retarded offspring. They found that 3 of 99 patients had abnormalities. One arose from an interstitial or terminal deletion and 2 from the de novo derivative translocation of 2 chromosomes. They suggest that at least 6% of all unexplained mental retardation may be the result of these small telomeric abnormalities.

***Editor's comment**: Telomeres have been studied for many years but only lately have we become aware that they are involved in much more than just making up the ends of a chromosome. Telomerase expression may provide the means for diagnosing cancer or identifying the presence of malignant cells. Downregulating telomerase as a molecular therapeutic intervention may be applicable to a wide range of cancers. The findings of Flint et al address a different aspect of telomeres. The suggestion that as many as 6% of cases of idiopathic mental retardation can be explained by a telomeric loss provides a new and important diagnostic tool in mental retardation for families with previously unexplained mental retardation who are concerned about the risk of recurrence. Looking for telomere abnormalities may allow a definitive diagnosis with a low recurrence risk for the parent but with as much as a 50% risk to the offspring of the affected individual. It will now be necessary to counsel families that a search for telomeric loss may be appropriate in nonspecific mental retardation.*

Judith G. Hall, MD

Biessmann H, Mason JM. *Adv Genet* 1994;30:185-249.
Flint J, et al. *Nature* 1995;9:132-138.
Harley CB. *Mutation Res* 1991;256:271-282.

***2nd Editor's comment:** Daniel Haber discussed the topic of telomeres, cancer, and immortality in a brief commentary in the* New England Journal of Medicine *(April 6, 1995). He states that, among other things, the progressive shortening of telomeres correlates with the absence of expression of telomerase and that continuing expression of telomerase correlates with the presence of cancer cells. In humans, germ cells express telomerase and maintain their ability to divide throughout life. In other cells, an estimated 15 to 40 nucleotides are lost each year. Kim et al (*Science *1994;266:2011) demonstrated that 90 of 101 specimens from primary tumors representing 12 different types of cancer contained telomerase activity, in contrast to none of 50 normal tissues. The extreme sensitivity of the polymerase chain reaction–based enzymatic assay allows the detection of 1 cancer cell expressing telomerase among 4,000 normal cells. Haber points out that an effective inhibitor of telomerase might induce prompt senescence in rapidly dividing tumors. Whether clinical applications will be forthcoming in the near future is unknown at this time. You, the reader are urged to learn more about telomeres and telomerase. Haber's commentary is a good place to start. The references listed above are excellent as follow-ups. Dr. Hall has done her usual proficient job in calling these phenomena to our attention.*

Robert M. Blizzard, MD