

CHROMOSOME TELOMERES: THE AGING CLOCK

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A human life span is the length of time which a normal individual will live, without being afflicted with a major disease or accident. The life span of a given population may vary between 75 and 100 years and is determined, to a great extent, by genetic and environmental factors. The medical health system of a country also has a major impact on the life span of its population. The life span of humans has three phases: young (up to 25 years), middle (around 40 years), and old age (>60 years), the final phase of growth and development. Scientists have long been puzzled by this transition from youth to old age, a process generally called aging. One of the hallmarks of an aging cell is the presence of chromosomal abnormalities such as aneuploidy—a deviation from the normal 46 chromosomes present in a cell. Accumulation of lipofuscin in nerve, kidney, liver and muscle cells, resulting in cell dysfunction, is yet another important aspect of aging.

In the early 1960s, Hayflick¹ demonstrated by *in vitro* culture methods differences in the replication doublings between embryonic fibroblast and fibroblast cultures established from mature individuals. The embryonic cells were shown to divide approximately 50 times in culture, whereas the mature cells exhibited significantly reduced numbers of cell division. The morphological features of cells approaching the end of their span were shown to be characteristic of “aging cells.”² These interesting results led to the theory of a biological clock in every cell which determines its life span.

Telomeres were implicated in the aging process for the first time by Watson in 1972.³ The tips of the human chromosome arms (Figure 1), known as telomeres, consist of DNA repeats TTAGGG synthesized by an RNA-dependent DNA polymerase enzyme known as telomerase. The presence or absence of active transcription of telomerase correlates with the size of TTAGGG. Telomerase is active in germ cells, with a size of about 15 kilobase (kb), whereas in most somatic tissues telomerase is not transcribed and the telomere length is significantly decreased.

Watson showed indirectly that a portion of telomere is masked from the action of DNA polymerase, thereby defying the tips from replication with each successive cell division. In other words, the length of the telomeres decreases with each replication cycle. Telomere shortening

in the aging process remained a hypothesis until 1990, when it was strengthened by additional evidence.⁴⁻⁷

Experimental proof directly implicating telomeres in the aging mechanism came from the works of Bodner et al.⁸ and Vaziri and Benchimol.⁹ Bodner et al. showed that by transfecting normal human somatic cells with a subunit of telomerase enzyme (which is absent in normal somatic cells), the length of the telomeres were increased. As a result, the replicative life span of these cells were dramatically extended beyond their usual limit of 50 population doublings. Similarly, Vaziri and Benchimol independently confirmed the role of telomeres in replicative senescence of cells. Both of these studies showed that telomeres become shortened as the cells age. Furthermore, it was also shown that relengthening the telomeres reverses the aging process, activates gene expression, and changes the morphology of cells to young-looking cells. These unique features of telomeres undoubtedly establishes them as the biological clock of aging.

The possibilities for clinical exploitation of telomeres and telomerase-dependent aging phenomenon is enormous. For example, certain genetic conditions characterized by premature aging, such as Werner syndrome, can be treated by restoring the cells' telomere length to normal levels either *in vivo* or *in vitro*, followed by transplantation. Similarly, the life span of aging tissues or cells, which gives rise to conditions such as arteriosclerosis, dementia and immunosuppression, can be reset by telomere extension so that these cells can become normal and cure the disease. These innovative therapies will be the focus in the next millennium.

The role of telomeres in malignancies has also been investigated. Malignant cells which escape their life span have been shown to have longer telomeres, with increased telomerase activity, than their normal counterparts.¹⁰⁻¹¹ Theoretically, it should be possible to end the life span of a cancer cell by inhibiting its telomerase activity and shortening its telomeres. More importantly, the impact of such an approach will be greater in genetic conditions with a high risk of malignancy, such as Fanconi anemia. But the relationship between high telomerase activity and malignancy raises an important question. By resetting the aging clock in non-malignant cells, is there a risk of



FIGURE 1. Human metaphase chromosomes hybridized with digoxigenin-labeled All Human Telomeres Probe (Cat #P5097-DG.5, Oncor Inc., Gaithersburg, MD, USA). The tips of the chromosomes or telomeres appear as bright red. The chromosomes are counterstained with DAPI. Methodology used was as recommended by the manufacturer (Edition 6.95, Oncor Inc.).

initiating malignancy? So far, the evidence about telomerase enzyme has been encouraging. By increasing telomerase expression in a non-malignant aging cell to reset its life span, no deleterious effect have been observed, in fact, these cells appeared and replicated as normal cells.⁸

The understanding of the aging phenomenon has come a long way and has started to unfold. Telomere research opens up an important area in this field. There may be many more mechanisms by which aging can occur,

however, telomere and telomerase research currently occupy the central position. It remains to be seen whether telomere research will eventually increase the human life span from its current level, or if it may totally eliminate the final phase of life—old age.

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References

1. Hayflick L, Moorhead PS. The limited in vitro lifetime of human diploid cell strains. *Exp Aging Res* 1961;25:585-621.
2. Hayflick L. The cell biology of human aging. *Sci Am* 1980;242:58-66.
3. Watson JD. Origin of concatameric T7 DNA. *Nat New Biol* 1972;239:197-201.
4. Harley CB, Futcher AB, Greider CW. Telomeres shorten during aging of human fibroblasts. *Nature* 1990;345:458-60.
5. Hastie ND, Dempster M, Dunlop MG, Thompson AM, Green DK, Allshire RC. Telomere reduction in human colorectal carcinoma and with aging. *Nature* 1990;346:866-8.
6. Allsopp R, Vaziri H, Patterson C, et al. Telomere length predicts replicative capacity of human fibroblasts. *Proc Natl Acad Sci USA* 1992;89:10114-8.
7. Allsopp RC, Harley CB. Evidence for a critical telomere length in senescent human fibroblasts. *Exp Cell Res* 1995;219:130-6.
8. Bodner AG, Ouellette M, Frolkis M, et al. Extension of life span by introduction of telomerase into normal human cells. *Science* 1998;179:349-52.
9. Vaziri H, Benchimol S. Reconstitution of telomerase activity in normal cells leads to elongation of telomeres and extended replicative life span. *Curr Biol* 1998;8:279-82.
10. Shay JW, Gazdar AF. Telomerase in the early detection of cancer. *J Clin Pathol* 1997;50:106-9.
11. Shay JW, Bacchetti S. A survey of telomerase in human cancer. *Eur J Cancer* 1997;33:787-91.