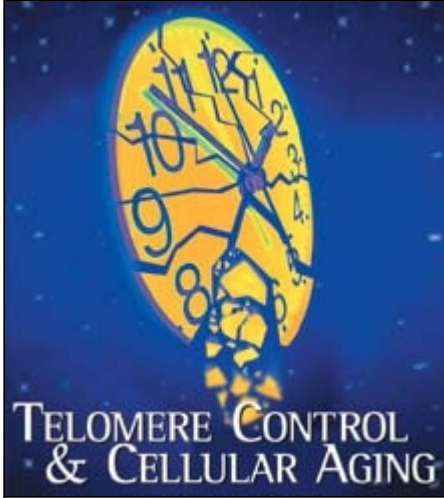


REPORT

Telomere Control & Cellular Aging



Aging cells may not be clueless about their life span: Recent studies show they have a "clock" that reminds them of passing time so that they can achieve essential goals before it is too late. Normal human cells replicate a limited number of times before they reach "replicative senescence" and stop dividing. At this point the cells are still alive, breathing and metabolizing food, sometimes for months, until they die. The "molecular clock" that informs the cell of its limited life span is the telomere, a structure at the end of each chromosome that shortens with each cell division. Research shows the mechanism by which a human cell keeps track of its division, by the length of bits of DNA at the end of the chromosome, and their proximity to specific genes.

by Carmia Borek, Ph.D.

A study reported in Science magazine found that in human cells, as in yeast cells, there exists a "telomere position effect" (TPE). TPE is dependent on telomere length and the position of the gene in relation to the telomere. It enables a cell to keep track of its number of divisions, and provides a way to modify gene expression during the lifetime of the cell. According to Dr. Woodring Wright, a senior co-author of the study with Dr. Jerry

Shay and colleagues, the telomere position effect suggests that it can "let a cell know how old it is so that it could change its behavior before it became senescent."

Telomeres, telomerase and aging

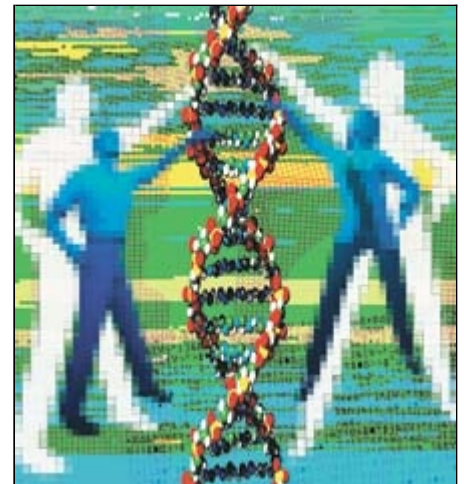
The hallmark of aging is a gradual loss of functioning cells in the body. But not all cells age at the same rate, even in the same organ. When tested for their ability to divide, normal cells taken from a particular organ, such as the skin, are happily dividing. Others are incrementally slowing and dividing at a more gradual pace. And then there are those that have reached cell senescence ("old age") and no longer divide or function. On the whole, as tested in cell culture, normal human cells reach senescence after dividing around 60 to 80 times.

The telomere, p53 and senescence

The telomere is a kind of molecular cap, made of DNA, that protects the ends of the chromosome from damage. Telomere DNA has over 1000 bases (building blocks), with the sequence TTAGG, that repeats over and over. In order to divide, a normal cell has to replicate all the DNA in its chromosomes. But normal cells have difficulty in copying the last few bases on the telomere. As a result, the telomere shortens with each round of DNA replication and cell division. As a cell ages, the telomere keeps shortening until it reaches a finite length. At that point cells stop dividing. This halt in growth is triggered by a gene called p53 that is activated in response to DNA damage. A telomere that has become too short no longer protects the chromosome from DNA damage. When the damage takes place, p53 responds by stopping cell replication and forcing it into senescence. As a telomere gets too short, the finite cell growth prevents DNA-damaged cell growth that could lead to abnormal cells and to cancer.

Telomerase and longevity

As there are 46 chromosomes in each cell, each with double strands, there are 92 telomeres that dictate its life span. Cells in most growing human tissues and organs gradually slow in growth, in proportion to the shortening of their telomeres. Studies have shown that normal cells from old people lose their ability to divide at a faster rate than cells from the young, and that senescent cells increase in the body, with age.



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most growing human tissues and organs gradually slow in growth, in proportion to the shortening of their telomeres.

While telomere shortening provides replicative history—a clock that reminds a cell how many times it has divided and how long it yet has to live—elongation of the telomere adds longevity to a cell. This occurs naturally in cancer cells, where a complex protein called telomerase, which has an enzyme component, helps build up and elongate the telomere with each cell division. This allows the cells to continue growing and become effectively "immortal," the hallmark of cancer cells. If one blocks the action of telomerase in a cancer cell by genetic manipulation, the telomere will begin to shorten with each division, as in normal cells, and the cancer cells will stop dividing and die.

In normal cells that are not germ cells, telomerase is switched off at an early stage of development. Telomeres do not elongate and cells must yield to a fate of a limited number of divisions. If one introduces a telomerase gene into normal cells by genetic manipulation, the cell can extend its life span. This has been shown in several studies, including experiments by a team that included Drs. Wright and Shay.

In these experiments telomerase was introduced into telomerase-negative human retina and foreskin cells. The cells began to express telomerase, as actively as cancer cells. Their telomere elongated, and the cells divided vigorously and did not express a cell marker for senescence (beta galactosidase). Furthermore, the cells showed an increased number of cell divisions and a longer life span, compared to the cells that were not treated with telomerase, whose telomere shortened with each division, leading to senescence. Another important observation was that the introduction of telomerase into the cells and their continuous rapid division and longer life span did not make them cancerous. They remained with a normal appearance and normal number of chromosomes.

Telomere position effect and gene silencing

Position effect is a term used to describe an event in which a gene's behavior is affected by its location on the chromosome. The changes in behavior can be expressed in various ways, such as differences in the appearance and functions of cells (phenotype), relay of instructions from the gene, and in doubling time of the dividing cells. Position effects have been reported in insects, plants, yeast and mice, and more recently in human cells.

TPE in yeast cells

In 1990, Gottschling and colleagues showed in yeast cells that by inserting a gene next to a telomere, it was silenced. The experiments used marker gene ADE2 that produces changes in the color of colonies, depending on whether the gene is expressed (white colonies) or silenced (red colonies). Insertion of ADE2 next to the telomere produced red colonies, (silenced gene). But the red cell colonies had sectors of white colonies, showing the gene was switched back on. Within the white sectors, in the largely red colonies, red sectors appeared. This shows gene reversal; the ADE2 gene was first silenced (red colony), then switched on (white sector), and then silenced again (red within white). The switches may be due in part to neighboring genes influencing the ADE2 gene. This means that while silencing depends on the gene's proximity to the telomere, competing regulatory factors produced by neighboring genes may modify a gene's behavior.

TPE in human cells

The findings that TPE exists in human cells is novel; they show a similarity between TPE in human cells and yeast, and offer clues to cellular aging. In the experiments reported in *Science*, investigators used a human cancer cell line called HeLa to investigate TPE and the relation between gene activity and telomere length. HeLa cells, which are "immortal," contain telomerase that lengthens the telomere, enabling the cells to keep dividing.

In the experiments, investigators introduced into the cell a gene called luciferase (the gene that makes fire flies glow), linked to DNA. Luciferase, called a reporter gene whose location is identified in the cell by its luminescence, was inserted near a telomere. Its luminescence compared to that of the reporter inserted at internal sites of the chromosome. To test if telomere length influences gene silencing, the investigators then elongated the telomere by telomerase, and examined telomere positional effect on luciferase.

The results showed that luciferase near the telomere produced 10 times less luminescence than luciferase located at internal sites in the chromosome. Increasing the length of the telomere further increased TPE, resulting in an additional two- to 10-fold decrease in luminescence. These experiments showed that the proximity of a telomere to a gene silences the gene: when the telomere is lengthened, and the gene is located further away from the critical end of the telomere, it is silenced even more.

Telomere position effects and cellular aging

Telomere position effect sheds light on the role of telomere in cellular aging. According to a simple and older telomere hypothesis of cellular aging, senescent cells have lost an essential gene that allows them to divide. By contrast, immortal cells, including cancer cells, have avoided this loss because they have regained telomerase activity. They continue to maintain their telomeres and press on with cell division.



The existence of telomere positioning effect in human cells offers a different scenario, where there is no need for the loss of a gene to push cells into senescence. It is speculated that, for example, when the cell is young and the telomere long, TPE silences "aging genes" that are located near the telomere, but far away from its end. As the cell divides and the telomere shortens, an "aging gene" would be more affected by its position on the telomere, as it increases its proximity to the end of the telomere. In an old cell where the telomere has shortened to its final length, the "aging genes" are no longer repressed. Silencing is switched off and the "aging genes" activated.

According to Drs. Shay, Woodring and their colleagues, J. Bauer and Dr. Ying Zou, once TPE has been discovered in human cells, there will be a challenge: to identify genes on chromosomes "whose expression is influenced by telomere length, in order to determine whether TPE actually influences the physiology of aging or cancer."

It is known that certain proteins (gene products), affect cell behavior in different ways, depending on the age of the cell. The genes that regulate these proteins may be important for programming pre-senescence changes in a cell, before telomeres reach their final length.

Take, for example, a cell that needs to alter its energy metabolism to allow for changes in old age. TPE, which keeps track of the "aging gene" in relation to telomere length, will cause mobilization of regulatory genes to help make the needed change before the telomere is too short.

Telomere, telomerase and age related disease

Cellular aging contributes to many conditions in the elderly. The skin wrinkles through loss of collagen production by skin cells that have lost function, partly through free radical damage to DNA (sun damage), and senescence. Atherosclerosis is caused by a loss of division-capacity in cells that line blood vessels (endothelial cells). This, in turn, results in overloading of cell factors that increase the risk of atherosclerotic plaques and blood clots. Active cell division is also important in response to injury. For instance, a damaged liver resulting from excess alcohol intake can lead to liver cirrhosis. In this condition, rapid cell division of the normal healthy liver cells, in response to the injury, could replace damaged tissue by supplying functioning liver cells. The shortening of telomeres, however, would limit liver cell replication and prevent tissue renewal. Introducing telomerase into the dividing liver cells, to elongate the telomere, would exert TPE and a silencing of the "aging gene," allowing continuous division that may offer treatment. This was shown experimentally, in a mouse model of chronic liver injury, where inserting the telomerase gene into the injured liver of the mouse prevented cirrhosis.

Possible therapies

It is thought that in normal human organs with a capacity for cell replacement, the telomere clock allows enough divisions for normal growth, repair and maintenance. This setting point is not enough, however, to enable additional cell replications needed during chronic disease. Under these conditions, a potential remedy may be found by increasing the life span of tissue cells, by telomerase. Another possibility may involve taking cells from an individual, extending the life span of the cells in vitro by telomerase, and then re-introducing the cells into the organ that requires help. The discovery of TPE in human cells provides a mechanism to silence critical genes and change the pattern of cell behavior. This finding may lead to further research that uncovers the secrets of cellular aging.

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