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The Role of Telomeres in Aging and Carcinogenesis: A Brief Overview

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Abstract

Telomeres and telomerases have been shown to be involved in the control of cell proliferation, the aging process and the unlimited proliferation ability of malignant cells. Usually during mitosis one part of the end of chromosome is lost and this short telomere is found in most dividing somatic cells leading to cell senescence. In contrast, some somatic cells undergo epigenetic mechanisms that leaving the telomerase active, preventing the telomeric shortening and participates that carcinogenesis process.

Keywords: Aging; Telomere length; Telomerase; Carcinogenesis

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Introduction

Aging is a biological process of a universal, dynamic and progressive feature, in which morphological, functional, biochemical and psychological changes occur that reduce the human ability to adapt to the environment. This phenomenon determines the longevity of the individual affecting its integrity and making it susceptible to chronic diseases that impact the quality of life [1].

Biological aging results of several cellular changes mainly in its structure and physiological scope. The impact of these cellular changes on their behavior remains uncertain. However, it is known that the cells become phenotypically senescent after the end of the replicative phase and inhibit its metabolization. The accumulation of molecular damages during cell cycles that compromise cellular function occur through the interaction of genetic and epigenetic factors and are influenced by hereditary, environmental and stochastic coefficients [2].

The process of cell division (mitosis) is commanded by the cell nucleus based on duplication of the genetic material, including the chromosomes, which are passed on to new cells formed. Chromosomes have structures essential for cell function, as well as those responsible for genetic modeling: centromeres and telomeres. During mitosis one part of the telomeres is lost and according to the telomeric senescence hypothesis, this progressive loss acts as a biological clock for the cellular divisions, thus triggering the end of cell division. When this phenomenon happens the process of cellular aging is triggered. This process is called the Hayflick limit [3].

In addition to loss of replication capacity, senescence is determined by the absence of telomerase (reverse transcriptase) activity, resulting in telomeres with limited size and increased oxidative stress and free radical accumulation. At the end of the senescence period, cell death is triggered by cellular apoptosis mechanism [4].

Distinctly somatic cells, the tumor cells have an infinite multiplication capacity due to changes occurring throughout their cell divisions. This is because even while being senescence, they can reactivate telomerase, losing control over their cell cycle and ensuring immortality. Typically, these cells have short telomeres and gradually accumulate mutations in their chromosomes, which triggers instability in their genetic material. In addition, the accumulation of free radicals which is a common characteristic of cells in senescence, compromises cellular functioning, causing the process of carcinogenesis [5,6].

Molecular Nature of Telomeres

Telomeres at chromosome ends are nucleoprotein structures consisting of tandem TTAGGG repeats and a complex of proteins termed shelterin that serve as protective caps. At each division cycle the chromosomes become smaller by loss of part of the telomeric region. Over time telomers are totally lost and deletions happen. This shortening of the chromosomes is considered one of the factors that limits the continuous cell division and is probably associated with the normal aging process [7,8].

With the loss of the telomeres and decrease of the terminal segment DNA polymerase can not replicate the helix effectively. Thus, there will be no DNA template to allow binding with a new primer after the last Okasaki fragment has the RNA primer removed. This region will only be replicated when the enzyme telomerase is present [7].

Telomerase recognizes the end of the telomer sequence, binds to the DNA and extends the template ribbon in the 5 'to 3' direction, adding a new TTAGGG repeat at a time [8].

Genetic Features of Aging

Aging is a global event that affects all humans in the post-reproductive phase determined by their own genetic characteristics. Primarily, aging does not depend on environmental influences or the presence of diseases. It happens gradually and progressively and it has a cumulative effect on the body [7].

Currentely several theories have been proposed to explain such a process, such as cellular aging theory, neuroendocrine theory, immunological theory, and, finally, the theory of telomeres.

Hayflick and Morread [9] have shown that human cells have a finite ability for genetically predetermined cell duplication. Thus, cell death was not occur due to causes that involve the culture medium, but due to cellular alterations caused by its own genetic material, such phenomenon was denominated cellular aging theory. During their experiments, the authors demonstrated two types of cells: normal cells that are diploid and mortal and cancerous cells that are heteroploid and immortal. The first ones with finite ability of duplication while in the second this capacity is infinite. Therefore, they concluded that longevity is genetically determined once the cell has its predefined proliferation capacity [3,10].

The neuroendocrine theory proposes that the level of aging results from the decline of hormones of the hypothalamic-pituitary-adrenal axis that control the reproductive system, basal metabolism and other aspects of the organism. This axis is controlled primarily by the hypothalamus that coordinates the release of neuropeptides and neurotransmitters through the expression of specific genes. During the senescence process, these genes are suppressed or hypoexpressed, decreasing the ability to regulate the hypothalamus and impairing the functioning of the entire hormonal axis. Thus, the age-related physiological disability of the organism can be explained on the basis of the hormonal alteration triggered by the change in gene expression [10,11].

Immunological changes are also related to the aging process. With advancing age, there is a decline in the immune response of a T-cell triggered individual, as well as reduced resistance to infectious processes, decreased production of interleukins, and alteration in the human leukocyte antigen (HLA) system. All these changes contribute to accumulation of cellular damage, immunosuppression and accentuation of the secondary aging process [11].

In addition to all these genetic alterations of aging, normal cells lose part of the chromosome (telomeres) after cell division, so when this loss is very significant the telomer decreases in size and the cell loses the capacity for cell division. Telomeres are specialized structures, being composed of DNA repeat sequences and the protein complex, which protect chromosome ends and preserve genome integrit [4,12]. Physiologically, to maintain the ability of cell multiplication, the enzyme telomerase with reverse transcription function produces a segment of telomeric DNA and adds to the chromosome avoiding its shortening. However, with human development the activity of this enzyme declines and most somatic cells can not synthesize it again, leading to the genetic process of cell death by senescence. In fact, telomere damage is a key factor in cellular senescence [4].

Carcinogenesis

Telomeres are DNA complex present at the end of chromosomes, which has as main function to protect them from any injury, thereby promoting the integrity of the genetic material making up such structures. They have a loop-shaped structure that is essential to their stability, activity, and prevents degradation by the action of DNAse [13].

Chromosomal endings have several proteins, among which the main ones are: TRF1 and TRF2. The first is a protein responsible for regulating telomere size while the second protein assists in chromosomal stability and prevents the repair of the cell [13].

According to telomeres theory on the cellular aging process, the cell loses DNA bases after cell division, resulting in a chromosome shortening. When these terminals reach a minimum size, called the Hayflick limit, signaling stops the cell divisions. As the cells reach their predetermined boundary of division, the shortened telomeres are worn out, making them more vulnerable to DNA damage. In the face of increasing DNA damage, an activation of p53 gene prevents cell division by ordering them to remain at rest or to be destroyed. This signaling is mediated by protein p53 and results in the formation of a control point between the G1 and S phase of the cell cycle, in which cell remains until apoptosis [13]. At this stage the cell keeps the metabolism preserved, but without the replicative capacity, that is, after a certain period of reproduction, the somatic cells have a limited number of generations, then the growth stops, becomes senescent and it dies.

Before the senescence phase, the cells maintain telomere length stable through the action of the telomerase enzyme, a reverse transcriptase (RT) that generate complementary DNA, that is, adds DNA repeats to the 3 'end of the chromosome after the cell division. This enzyme is found in germ cells and some somatic cells, such as hematopoietic and skin stem cells (basal cells of the epidermis) that keep it active throughout life. However, most somatic cells do not express telomerase. The enzyme is composed of two subunits, the catalytic subunit hTERT (human Telomerase Reverse Transcriptase) and the nuclear RNA subunit hTR (human Telomerase RNA), produced by the TERC gene (Telomerase RNA Component). The hTERT subunit functions as reverse transcriptase and hTERC serves as a template for the telomeric synthesis of DNA that serves as the template

for telomere extension during de novo addition of TTAGGG repeats onto chromosome ends [14,15]. Some mechanims as methylation and histone modifications of this gene can suppress the telomerase activity favoring the telomere shortening [16].

The proliferative capacity of the cells is related to the activity of the enzyme telomerase. When normal somatic cells reach the Hayflick limit they stabilize the cell cycle until they undergo apoptosis while somatic cells that begin to divide infinitely will exhibit high telomerase activity with loss of cellular control. As a consequence of genomic instability occurs the activation of the cellular repair that is normally inhibited by TRF2. The cell repair interprets that the DNA is damaged and begins to repair these damages favoring the fusion of the chromosomal terminals. The association of these effects determines the onset of oncogenesis in certain types of tumors [13]. Besides solid tumors, development telomere dysfunction has been implicated in bone marrow failure syndromes and leukemia.

In most cancers (85-90%), it is observed that the cells regained the active telomerase wrongly, enabling suffering many cell divisions in a disorganized and uncontrolled manner. Moreover, with the inactivation of the tumor suppressor gene, cell immortality ensures a capacity which is an important step in the formation of tumors. It is also argued that the aggressiveness of the tumor is directly related to the levels of this enzyme [17,18].

Conclusion

Carcinogenesis mechanism usually happens slowly and may take years to formation a visible tumor. This process goes through several stages before it reaches the tumor. Many cancer are sporadic and occurs by epigenetic changes, that is, the durable changes affecting the genome of an individual during development and aging, but which are not from the genome of previous generations. Telomeres and telomerases have been shown to be involved of this epigenetic changes.

Telomere shortening has been found in most dividing somatic cells, leading to cell senescence when overly short chromosome ends reached. They preserve genome stability, proliferation on a cellular level, and prevent degenerative diseases and cancer on an organism level. In contrast, most of malignant tumors demonstrate high telomerase activity which makes stable telomere length allowing the unlimited proliferative ability and immortality of tumor cells.

As it is an important epigenetic alteration in carcinogenesis, the mechanism of telomerase and telomere length regulation should be extensively investigated in order to discover new strategies to prevent or reverse the oncogenesis process.

Conflict of Interest

The authors declare that they have no conflict of interest.

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