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Brief approach to the relationship between aging and telomeres

Abstract

Aging is not a stage of life, but a biological process that starts from the intrauterine life; and it is due to the interaction of individuality with the environment. Telomeres are essential functional elements of human chromosomes located at their ends, which play an important role in carcinogenesis and cell aging; its functions are of great importance for the maintenance of the structure of the chromosome, as well as for cellular life in general. With age, the speed of telomeric shortening increases. Among the factors that can accelerate the reduction of the size of them are psychological stress, obesity, smoking or socioeconomic status; so, lifestyles play an important role in the aging process. Telomere wear during the course of cell cycles prevents its protective function of the chromosome. There are human diseases in which premature aging occurs due to genetic alterations that increase the erosion of telomeres and inhibit the normal repair of DNA. In this brief communication, we intend to explain the relationship between these structures and the aging process.

Keywords: aging, telomeres, individuality

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Introduction

Aging is not a stage of life, but a biological process that starts from the intrauterine life; and it is due to the interaction of individuality with the environment. Individuality is understood as the uniqueness of each individual; reached by genetic variation, which originates new nucleotide sequences, which can change the function of the proteins involved or remain apparently "silent"; and by the modifications of the epigenetic pattern, which are currently very important as a cause of diversity.

Genetic variation ensures that it is practically impossible for two individuals in a population to have the same genotype at all loci. It is often asserted that individuals of the human species have 99% of their genes equal and that only 1% varies. As members of the species, we share the genes that guarantee our own characteristics, as well as those that guarantee our vital functions; however, the siblings share 50% of the genes with each other, but with a random combination, which guarantees the variability between them. If we refer to the particular case of monozygotic twins, 100% of their genes are the same and, apparently at birth, they are identical, but after a time differences begin to appear, often subtle or not distinguishable to the human eye, because they can be at a biochemical, physiological, psychic or other level. These differences are always attributable to the effect of the environment on gene expression, and this effect exists for all individuals of the species; hence, each individual is unique and unrepeatable. This genetic variation is determined by several factors such as: mutations, genetic recombination, migrations, genetic drift and natural selection.[1–3]

On the other hand, the DNA molecule is related to others and to chemical groups, which form what is called the epigenetic pattern. In addition to histones, there are methyl groups (CH3) and RNA micromolecules, which are associated with DNA and modify its expression without modifying its base sequence, which is why they are said to regulate the functioning of genes. Therefore, this pattern works like a code, beyond the genetic code; which expands the possibilities of variation in gene expression and contributes to individuality. Epigenetic changes are transmitted between generations of cells and individuals, which makes them of great importance for Medicine, since they have been related to pathological conditions such as cancer, some metabolic diseases, aging and the capacity of pathogenic microorganisms to acquire heritable resistance to medicines.[4,5]

In this way, we can say that the biochemical individuality, a concept first exposed by Archibald Garrod in the last century, is retaken today, because each individual of the human species has its own biochemical individuality determined by the variations explained above, manifested in a different protein composition as a final expression of the genes according to the interaction with their specific environment, determining their health/disease state. This explains why each individual responds uniquely to environmental influences, to different diets and medications.

Modern molecular research has revealed that telomeres play an important role in carcinogenesis and cell aging.[6,7] The fundamental biological role of this part of human chromosomes was identified in 1930 by Hermann Muller and Barbara McClintock. In this brief communication, we intend to explain the relationship between these structures and the aging process.

Development

Telomeres are essential functional elements of human chromosomes located at their ends. They are made up of DNA and proteins (Figure 1). The DNA of this region is highly repetitive, and the sequence 5 'TTAGGG 3' is repeated up to 2000 times. Its length and structure are functionally linked to the mechanisms of response to DNA damage, in the cellular response to stress and the organization of chromatin. Several proteins called telomere binding proteins are associated with telomeres, which are of great importance for elongation, replication and function.[6–8]

The functions of the telomeres are of great importance for the maintenance of the structure of the chromosome, as well as for cellular life in general.[7–9] Following is a reference to each of them:

i. **Stability of the chromosome and protection of its ends:**Tthe telomeres protect the chromosomes from the action of the cellular exonucleases, protect them against the union of non-homologous ends, allow the cells to differentiate between the natural ends of the chromosomes and the DNA damaged and maintain the integrity of the chromosomes allowing replication without losing coding sequences.

ii. **Recorders of the number of cell divisions**: These structures keep a record of the number of cell divisions and determine the cellular life and the time of occurrence of replicative senescence, which is why they have been called "cell biological clocks".

iii. **They provide the mechanism to replicate the ends of the DNA:** The discontinuous replication in the delayed strand requires the participation of the Okazaki fragments. Telomerase adds repeats of hexamers to the 3 'ends, allowing the DNA polymerase to complete the synthesis of the opposite strand.

For the initiation of the replication of this chromosomal region, the polymerase enzyme requires an RNA primer, which is subsequently removed and the resulting holes are filled with deoxynucleotides, provided that the corresponding polymerase can be anchored on both sides of the gap. This double anchoring is not possible at the 5 'end of the new chain, so the primer segment can´t be repaired. In each replication, a segment (single-stranded) is lost from the end of the chromosome, that is, from the telomere, which has important repercussions for the cell, which we will explain later.[6–8]

Telomere wear during the course of cell cycles prevents its protective function of the chromosome, making it unstable, which causes it to fuse or be lost. Cells with these defects can´t be duplicated and are no longer viable, so apoptosis is activated. The shortening of telomeric length affects the telomere separation during mitosis, leading to the formation of telomeric associations (tas).[7] All this justifies that the cells, at all costs, try to maintain the telomere length, which achieved by several mechanisms:

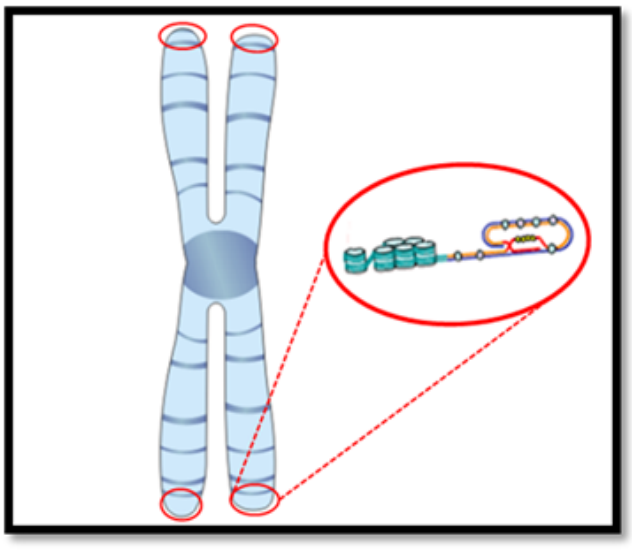

Figure 1 Telomeres.

The telomerase enzyme

Telomerase is an enzyme DNA polymerase that uses RNA as a template and whose function is to lengthen the telomeres. It is active in the germ cells and during embryonic development. It is inhibited in mature somatic cells after birth, and in this way telomeric shortening occurs after each cell division. This enzyme acts by lengthening the eroded ends of the chromosomes at the expense of an RNA component that contains a domain complementary to the telomeric DNA sequence. This domain allows the alignment of the enzyme with the substrate and the de novo addition of deoxynucleotides to the telomeric sequences. Telomerase produces a DNA copy of its own copy of RNA by retrotranscription, which is fused to the 3 'end of the telomere. The telomere lengthening by telomerase is necessary to reach the normal contraction that occurs after each DNA replication. Telomerase activity has been detected in the G1, S and G2 phases of the cell cycle, with repression observed when cells enter G0 due to the lack of growth factors, contact inhibition of cell division, the induction of senescence by reversion in an immortalized cell line or by differentiation. It has been observed that premature aging in mice without telomerase can be rescued reactivating the expression of said enzyme. By recovering its expression, the telomere length is prevented from decreasing below a critical threshold and the stability of the chromosomes is recovered, slowing aging and cell death.[10–13]

Alternative lengthening of the telomeres/telomere-independent (ALT, alternative lengthening of telomeres)

The length of the telomeres synthesized by ALT is heterogeneous. In the ALT mechanism, homologous recombination between telomeres is likely to be involved; the sequences are copied from one telomere to another by complementary pairing to form a new telomeric DNA.[6,7]

Epigenetic modifications in the telomeric and subtelomeric regions

It influences the organization of telomeres in chromatin domains, controlling their length and functions.[14]

Influence of non-coding telomeric RNAs

they also participate in the organization of telomeres in chromatin domains, as well as in the control of their functions and their length.[15]

Several factors have been associated with telomeric shortening

In addition to age and sex, the action of nucleases is related to the increase of reactive oxygen species (EROS), psychological stress, obesity, smoking or socioeconomic status; so that, as can be seen, lifestyles play an important role in the aging process.[7] The connection between environmental factors and this phenomenon can be explained by the modifications that the epigenetic pattern of each individual undergoes during life, that are changing the expression of the genome without altering its sequence.

In 2011, Estringer and colleagues published that young individuals subjected to stress during intrauterine life had significantly short telomeres; this finding is very important because it shows that prenatal stress can increase the susceptibility of individuals to suffer diseases related to aging.[16]

The relationship of sex with the process of telomeric shortening is given by the fact that it is more accelerated in men than in women, which justifies the higher mortality and reproductive variability in the former. This behavior has been explained by the influence of estrogens, which have an antioxidant effect and are able to stimulate the expression of telomerase.[7]

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With age, the speed of telomeric shortening is increased, due to the wear and tear of cell division cycles, as previously explained.[8,17] However, there are human diseases in which premature aging appears due to genetic alterations, which involve the gene of telomerase and increase the erosion of telomeres and other genes related to normal DNA repair. These diseases show a high predisposition to cancer.[18–22] Following are some of them:

1. Werner syndrome (shows accelerated destruction of telomeres).
2. Bloom syndrome (BLM DNA helicase eliminates inappropriate recombination, binds to TRF2 in ALT (+) cells, allows telomere amplification mediated by recombination).
3. Ataxia-telangiectasia (shows accelerated loss of telomeres due to alteration of the ATM protein, which causes the appearance of alterations in DNA repair and alterations in the control of the cell cycle).
4. Congenital dyskeratosis (in which there is a defective telomerase and very short telomeres).[15]

Many studies have referred to the association between life expectancy of humans and the length of telomeres; referring that the individuals with mutations in the telomerase gene, are born with smaller telomeres and live less. This reduction in longevity is attributed to the early loss of tissue regeneration capacity, showing a relationship between the length of the telomeres and the appearance of hematological, intestinal or neuronal alterations; since the progressive telomeric shortening, resulting from the absence of telomerase prevents the regeneration of tissues by the stem cells, causing degenerative diseases. On the other hand, it has been observed that the length of telomeres acts in a predictive way in mortality due to the diseases most frequently associated with the aging process; such as cardiovascular, infectious, diabetes, Alzheimer's and Parkinson's and others.[6,18,20]

Commentary

As can be seen, the role of telomeres in aging is of the utmost importance; but as it is evidenced, its functioning can be regulated by the genome and the epigenome, which function adequately or not according to their individual characteristics, responding to environmental factors by means of a "cascade" of signals that are sent by the external growth factors and stop or stimulate cell division in response to these factors and the needs of cells at any time, precipitating or slowing down the aging process.

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Conflict of interest

Author declares that there is no conflict of interest.

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