

Importance of Telomeres in Their Potential Scope for Determining Aging

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ABSTRACT

Aging has had and will have a considerable relevance in the population for millions of years. Various ways have been explored to prevent or prolong it, since aging is often accompanied by chronic degenerative diseases. Although not much information has been discovered about this, the participation of telomeres in aging has been studied. Telomeres are the ends of DNA that protect and prevent its degradation, however, the relationship of the presence of long telomeres to a long life has been contemplated in conjunction with the reduction of chronic degenerative diseases, so that these individuals have a more desirable quality of life than individuals who have shortened telomeres.

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INTRODUCTION

Aging is an irreversible multifactorial process that eventually occurs in all living organisms, in which genetics and the environment are usually involved, and can also be defined as deterioration in structure and function; alteration of support and repair systems; increased susceptibility to disease and death, as well as reduced productive and reproductive capacity (14). The phenotypic components of aging include structural and functional transformations that are divided into primary aging changes (sarcopenia, gray hair, oxidative stress, increased peripheral vascular resistance) or age-related disease (dementia, osteoporosis, arthritis, insulin resistance, hypertension).

It has been found that many cellular processes occur in the aging process, certain theories have been proposed such as the theory of oxidative stress and free radicals, which basically talks about how oxidants resulting from the synthesis of ATP to accumulate over time cause chain reactions that cause damage to cells, It also talks about altered gene expression, epigenetics and micro RNA in which it talks about how the expression of genes and proteins changes during aging, it also talks about how the environment interacts in these expressions thus accelerating aging. (15)

The theory of altered autophagy describes that intracellular degradation is performed by the lysosomal and proteomic ubiquitin systems. Both are altered with aging, allowing the accumulation of waste products that alter cellular functions. Finally, one of the most studied theories lately and the one we will discuss in this research is how telomeres interact with aging.

Telomeres are specific DNA structures that are part of chromosomes and are found at the ends of chromosomes, it is stipulated that they may be related to certain cellular functions, especially the function in controlling the life span of cells. Telomeres preserve genetic information and protect against genomic instability. However, with natural aging, telomeric DNA is lost with each round of cell division (3).

Telomeres were identified by H.J. Muller during the 1930's. Hermann J. Müller was working at the Institute of Animal Genetics in Edinburgh (UK) with flies of the species *Drosophila melanogaster* exposed to X-rays, he noticed that the chromosomes have a protective cap at the ends, which he first called terminal gene, and later changed the name to telomere. (16) Since then, the knowledge of these structures has deepened extraordinarily.

Aging is one of the leading causes of death in the world today, although death certificates write causes of death such as myocardial infarction, cancer, pneumonia or respiratory failure, there is no doubt that these pathologies are related to the biological changes of aging. (2) It is said that the population of 80 years and older will triple by 2050 as life expectancy is increasing due to the progress of years without the rise of diseases, as the understanding of chronic diseases in the elderly. (6) The prevalence of chronic diseases has been increasing as the population has a long life and this leads to live more years with a disability. (5)

Aging occurs in most species and there are several theories about aging, such as the argument that there must be a programmed internal clock that dictates to the organism when to age and die. (2) Likewise, there is the theory that aging is an accumulation of damage that is the cause of the decrease

Importance of Telomeres in Their Potential Scope for Determining Aging

in the functions of cells and the organism that inevitably leads to death. (2) Although it is unlikely that aging is programmed since its purpose as such is the decline and eventual death of individuals. Aging involves complex biological mechanisms involving DNA damage and mitochondrial mutation (including telomeres), oxidative damage, protein aggregation, immune dysfunction, and dysfunction of epigenetic mechanisms (2).

The concept of telomeres was born in the 1930s when McClintock and Muller inferred the existence of a unique structure at the ends of chromosomes in "*Zea mays* and *Drosophila melanogaster*" and hypothesized that it was critical for the prevention of terminal chromosome fusion. (12) Muller coined the term "telomere" from the Greek telos, meaning "end", and meros, meaning "part", emphasizing "end part". (12)

Telomeres have been a mainstay of disease and aging research since their discovery. (7) They are located at the end of chromosomes and are specialized structures that in humans consist primarily of nucleotide repeats and are specialized to maintain the integrity of genomes and prevent their degradation. (1) This function of telomeres which mitigates damage to genes when chromosome replication occurs, DNA polymerase is unable to replicate the ends of chromosomes, this by the nature of DNA replication. (7) Telomeres act as a buffer zone, thus prevent the gradual degradation of genes, however, throughout life, telomeres are shortening and once they shorten to a critical length will contain a deterioration. (7)

The degree of telomere shortening behavior can be accelerated by various factors and stimuli such as oxidative stress, inflammation, and hormones, such as genetic variants. (1) Also, it has been observed that shortened telomere as well as decreased telomerase activity may be associated with psychological stress and life stress in many studies, which may influence telomere dynamics. These findings were discovered in a study that was conducted with mothers carrying a baby with a serious illness, along with mothers carrying healthy infants. (5)

Several chronic inflammatory diseases have been associated with telomere shortening, including cardiovascular and metabolic diseases, such as substance abuse, autoimmune diseases, and infectious diseases. (1) Telomere size is genetically determined and this size along with the rate of shortening varies between species, for example, humans have a shorter telomere than mice, however, mouse telomeres shorten 100 times faster than that of humans. (4) It was described in a study that mice with telomerase deficiency, telomere dysfunction, showed a release of pro-inflammatory cytokines in the absence of external stimuli. (1)

Similarly, in a study with mice, it was observed that mice with larger telomere size were thinner, had a greater number of telomeres and had a greater number of telomeres. improved glucose metabolism than mice with shortened telomeres and it was observed that mice with longer telomere

size lived longer and, in this, developed fewer tumors associated with aging. (4) This study demonstrated that lengthened telomeres demonstrate a great benefit in mice, delaying their metabolic aging and the development of cancer, resulting in a longer life span. (4)

Telomere dynamics in long-lived people have been extensively linked to the fact that according to some studies, people who have lived more than 100 years who have generally escaped major age-related diseases have longer telomeres as well as better telomere length maintenance. (5) Therefore, variations or polymorphisms in the human telomerase gene that are associated with better telomere length maintenance may confer healthy aging and exceptional longevity in humans. (5)

Telomeres possess clear biological plausibility as a candidate biomarker of aging, reflecting oxidative stress, inflammation, replicative history, and cellular senescence. (6) There are variable associations between accelerated telomere shortening and age-related diseases such as: cardiovascular disease, cancer, stroke, diabetes, dementia, chronic obstructive pulmonary disease, and skin disorders. (6) The function of the elderly is related to the decline in physical activity. In fact, physical inactivity is a major contributor to aging, decreased strength and muscle mass. Sarcopenia with age is mainly related to the decline of physical activity with age, but also nutritional and hormonal factors. (3) Scientific evidence mentions and concludes that exercise helps to prevent telomere shortening, making it a good option to prevent this process.

Telomerase is the specialized polymerase that synthesizes new telomere repeats, compensating for the shortening that normally occurs with cell division. Telomerase has two essential core components, telomerase reverse transcriptase (TERT) and telomerase RNAase (TR). In human cells, telomerase is the primary mechanism by which telomeric DNA is synthesized de novo. (10)

As with any gene or protein within a biological system, telomeres and telomerase are affected by a few different genes. Modifications of these genes often induce changes associated with cancer and aging, one of the genes is nuclear assembly factor 1 (NAF1). (7) Within CRISPR-induced mouse and cellular models' mutations of the NAF1 gene result in a loss of approximately half of the cellular TERT activity. This disease is likely to progress to disrupt telomere homeostasis, a process that many elderly and cancer-associated genes also influence. (7) Alternatively, lifespan predictions can be made using both initial telomere length and telomere shortening rate. (8)

Genetics, lifestyle, and aging are key factors that affect telomere length and the rate at which telomeres shorten. Thus, it is these factors that are implicated in a wide range of telomere-related diseases. Genetics contributes to 30-80% of the variability in telomere length, leaving 20-70% to unknown factors, probably external factors, including environmental and lifestyle factors. Genetically inherited

Importance of Telomeres in Their Potential Scope for Determining Aging

diseases have been termed telomeropathies. (13) Among these diseases are pulmonary fibrosis, bone marrow failure (associated with dyskeratosis congenita), dyskeratosis congenita, Hoyeraal-Hreidarsson syndrome, Revesz syndrome, RECQ helicase mutations (Werner syndrome and Bloom syndrome). (13)

A study in mice showed that telomere shortening with aging can trigger a series of secondary reactions, phenomena that favor aging, such as increased DNA damage and genomic instability, cellular senescence and/or apoptosis, altered capacity of stem cells to regenerate tissues, etc., and is therefore considered one of the main characteristics of aging organisms. (4) In turn, telomere maintenance in the adult organism focused on telomerase overexpression and gene therapy strategies have been shown to delay aging and age-associated pathologies, as well as to increase life expectancy in mice (4).

Some pathologies have been related to telomere shortening, as is the case of chronic obstructive pulmonary disease. It has been suggested that this pathology presents accelerated aging, so it has been proposed to measure telomere length as a marker of aging. In a review of an article on the subject, it shows that COPD patients experienced an accelerated process of telomere shortening compared to smokers without COPD. (9) The study also confirms that COPD patients have shorter telomeres than smokers without COPD. However, there were no associations between telomere length and clinical and pulmonary function parameters at baseline or between changes in telomere length and change in those parameters over time. (9) It is important that we are aware of the current evidence to be able to apply these types of studies, assessing telomere length against other pathologies and circumstances. It is important to mention that in addition to COPD and other chronic diseases that are related to telomere shortening, malignancies are no exception. According to one of the articles reviewed, it mentions that clinical observations have been made in patients with "telomere syndrome," shedding light on the role of telomeres in cancer, which until recently has been studied mainly in cell culture and animal models. Like other DNA repair disorders, telomere disorders were seen to be prone to cancer; however, the overall incidence is relatively low. (10)

Cancer-related mortality in patients with "telomere syndrome" is so far unknown, and clinical observations make it clear that although patients with telomere syndrome have a significantly increased risk of developing cancer, an important example being degenerative disease, which accounts for most of the morbidity and mortality in at least 90% of cases (10).

Most articles point to a causal link between inflammation and oxidative stress as determinants of telomere integrity. (11) However, there is information that is so far unknown that animal models of aging are needed to support the idea that

aging involves the interaction between inflammation and telomere dysfunction. The studies discussed in this review suggest the possibility of therapeutic interventions to slow cellular aging and thus reduce the incidence of age-associated diseases. (11)

Abnormal cell types appear to respond to antioxidant and anti-inflammatory agents in the opposite manner to normal tissues; consumption of these exogenous materials appears to exclusively benefit cells of non-pathological origin. While the reasons underlying this important difference are not well understood, the application of micronutrients in the diet is one of the safest approaches to achieve optimal aging and increased longevity. This could include antioxidant and anti-inflammatory agents, including specific dietary modifications or scientifically engineered mixtures. (11)

DISCUSSION

Since aging is an irreversible and inevitable process and that it is one of the first causes of death in the world, we consider that it is important to know what a telomere is, what it is and how its alteration affects us as humans. This with the objective of showing its importance and impact on aging and to be able to understand more about some pathologies that can occur due to the morphological change of the telomere and its possible consequence as in the case of COPD and some cardiovascular and metabolic diseases. We also consider that it is important to know the

normal morphology of telomeres and their normal process in order to better understand what happens in each pathology, in which the telomeres are morphologically affected either by a shortening or by a bad integrity of the genomes and thus be able to understand how we are affected, how this can lead to an affectation of a certain organ or tissue and that as a consequence can produce some pathology as those mentioned above.

Understanding these changes, we can also clarify how life expectancy has been increasing, this with a better control of chronic degenerative diseases thanks to drugs that have been able to control or slow down the degenerative process of some pathologies and thus be able to have a better quality of life and life expectancy. The information obtained from each of the articles used in this work helped us to know more about aging and to understand more about its process and the cause of certain pathologies that are directly related to telomeres and to understand how the life expectancy of humans has increased and has increased.

CONCLUSION

Talking about aging involves absolutely all living beings; despite being a heterogeneous process, it is inevitable that every organism ages and dies. For the physician and any health professional, knowing the mechanisms by which aging probably occurs is very important, since this will allow us to establish preventive measures, which, although probably not to prolong or avoid aging, will be aimed at achieving a

Importance of Telomeres in Their Potential Scope for Determining Aging

successful aging. There is probably a lack of studies and conclusive results about the role played by telomere shortening and the telomerase enzyme in aging, especially in humans, however, with the information we have so far and according to the articles included in this research we can conclude that, there may be several mechanisms and triggering factors that lead to the shortening of important parts of the chromosomes such as telomeres, and therefore accelerate aging. Therefore, it is our responsibility to know the importance of avoid any type of risk factor that is modifiable, mainly psychological stress and lack of physical activity.

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