Opinion Paper

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How can I protect my telomeres and slow aging?

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Abstract: Recently, short telomeres have become a widely accepted cellular hallmark of aging. Telomere lengths in a single cell are heterogeneous and it is believed that the shortest telomere in a cell drives the induction of senescence. Hence, measuring the shortest telomere lengths (not just average) can provide more information about aging, cancer progression and telomere related diseases. Chronic exposure to DNA damaging agents, oxidative stress, inflammation, smoking, alcohol, exposure to acute and chronic stress promote telomere shortening and earlier onset of cell aging. Healthy life style including Mediterranean diet, moderate exercise, managing stress (breathing, meditation, yoga), spending time with loved ones and lots of laughter will help us to keep our telomeres long and safe.

Keywords: Aging; Cancer; Telomerase; Telomere; TA-65.

Introduction

Aging is associated with tissue degeneration and decreased tissue regenerative capacity. This can be caused by stem cell failure, mitochondrial dysfunction, genotoxic stress, epigenetic changes and telomere shortening. Recently, short telomeres are accepted as cellular hallmark of aging. Although telomere shortening is most likely involved in biological aging, no major determinants of telomere length are known besides inheritance, age, sex, paternal age at conception. In humans, telomere length are heterogeneous among different chromosomes, accelerated telomere shortening is associated with early onset of age-related health problems, including coronary heart disease, diabetes, increased cancer risk, and osteoporosis [1, 2].

Why telomeres are getting shorter by aging?

Telomeres are repetitive nucleotide sequences (TTAGGG) at each end of eukaryotic chromosomes, which protect chromosomes against genomic instability by capping the chromosome ends. Telomeres shorten approximately 60 base pairs with each cell division due to the inability of DNA polymerase to fully replicate the chromosome end, which is referred to as the end-replication problem. As cells acquire critically short telomeres, replicative senescence occurs. The mechanism by which short telomeres induce replicative senescence is unknown. In this process, if critically short telomeres are recognized as DNA double-strand breaks, they will induce cell cycle arrest. This response is a mechanism that protects cells from tumor formation. Cells which bypass replicative senescence by acquiring oncogenic changes continue to divide until they undergo crisis. Rare cells escape crisis by activating or upregulating telomerase, maintain their telomere lengths and thus become immortal with unlimited proliferation [3, 4].

The rate of telomere shortening is affected by a combination of factors including donor age, genetic and epigenetic factors, environmental, social and economic status, exercise, body weight, and smoking.

What is the role of telomerase in malignant transformation?

Telomerase is a reverse transcriptase enzyme that elongates chromosomes by adding TTAGGG sequences to the end of chromosomes; it binds to telomeric DNA by the hTR subunit (telomerase RNA component, also known hTERC) and hTERT (telomerase reverse transcriptase), the catalytic subunit [5].

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Telomerase is found in fetal tissues, adult germs cells and ~90% of tumor cells. It is particularly active during development, but has almost undetectable activity in somatic cells. Therefore it is a highly attractive, almost universal, target for anti-cancer therapy [6].

Multiple mechanisms have been proposed to explain how telomerase is activated. However, somatic mutations in the proximal promoter of the hTERT gene are now considered the most common non-coding mutations in cancer [7].

**How can we measure telomere length? Are the methods frequently used for measuring telomere length accurate?**

Several methods are established to measure telomere length, such as terminal restriction fragment (TRF) analysis [8], in situ Q-FISH [9], flow-FISH [10], Q-PCR [11], chromosome-specific single telomere length analysis-STELA [12], universal STELA [13] and telomere shortest length assay (TeSLA) [14]. However, comparison of telomere length measurements by using qPCR, TRF and STELA across a wide group of laboratories showed that reproducibility is still a major issue [15]. Inter-laboratory coefficients of variation (CVs) averaged about 10% for TRF and STELA and more than 20% for qPCR. The samples with the shortest telomere length ratios caused the largest differences in inter-laboratory CVs between qPCR and gel-based techniques such as TRF and STELA.

Telomere lengths in a single cell are heterogeneous and it is believed that the shortest telomere in a cell drives the induction of senescence [14]. Therefore, measuring the shortest telomere lengths (not just the average) with sensitive methods such as Q-FISH and TeSLA provide more information about aging, cancer progression and telomere related diseases. TeSLA is an improved novel technique which detects telomeres from all chromosome ends (<1 to 18 kb) and shows high specificity and efficiency of telomere length measurements in individual cells [14].

**Which environmental factors cause telomere shortening?**

Chronic exposure to DNA damaging agents (e.g. UV), oxidative stress, and inflammation result in a sudden telomere loss [18]. Significantly shorter telomere lengths in peripheral blood lymphocytes (PBLs) were observed in alcohol users compared to non-alcohol users, indicating that decreased telomere length is correlated with increased alcohol consumption [19].

Increased body mass and smoking including prenatal tobacco exposure are also associated with shortened telomere length [20]. It has been shown that children who exposed prenatal tobacco had significantly shorter telomere length than those who did not expose [21].

**How can we prevent telomeric shortening?**

Several studies have shown that continuous exercise is associated with telomere length maintenance and slows cellular aging by reducing the rate of telomere shortening. It has been shown that active individuals have longer telomeres than sedentary individuals [22]. Healthy lifestyle factors such as lower BMI, tobacco abstinence and a diet high in fruit and vegetables are associated with longer telomere length [23].

Recently, the influence of environmental factors on telomere length were investigated in a group of older men such as psychological stress counseling, dietary modification, increased physical activity, and social support groups. Following 5-year followup, longer telomere length was observed in the lifestyle intervention group compared to controls [24].
What is the teloprotective effect of TA-65?

TA-65 is a telomerase activator derived from an extract of a Chinese plant, *Astragalus membranaceus*. Primary chemical constituent is cycloastragenol (CAG). Blasco et al. [25] have shown that TA-65 dietary supplementation in mice elongated critically short telomeres in a telomerase-dependent manner. In addition, TA-65 improved glucose tolerance, osteoporosis and skin fitness without significantly increasing cancer incidence. TA-65 has been studied in humans as a dietary supplement and it has been found that it significantly reduces the percentage of short telomeres and leads to a decline in both senescent and natural killer cells [26].

Unfortunately, the long-term effects of TA-65 in humans are still unknown. Ginkgo biloba, Silymarin, Purslane and Maltese mushroom are natural compounds scientifically proven to activate telomerase, but tested only on mice. Such telomerase activators, either synthetically produced or in the herbal supplements may be dangerous as they can convert precancerous lesions to malignant diseases. Instead, understanding the importance of adopting/maintaining a healthy life style and managing stress (breathing, meditation, relaxation techniques such as yoga, group sports, walking), following the Mediterranean diet (fish, fruits and vegetables), spending time with loved ones and lots of laughter will help us to keep our telomeres long and safe. However, it should be noted that the effect sizes of the suggested telomere protecting lifestyle factors are typically small compared to the impact of general inheritance, age, sex, etc. Nevertheless, many small bits together add up to something that may have an impact in telomere protection.

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