Consequence and Role of Telomeres on Cell-Division Rates and Life-Spans

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Abstract

There has been growing evidence that lifestyle factors may affect the health and lifespan of an individual by affecting telomere length. Telomeres are unique protein–DNA structures that comprise the termini of eukaryotic linear chromosomes. Telomere length shortens with age. Progressive shortening of telomeres leads to senescence, apoptosis, or oncogenic transformation of somatic cells, affecting the health and lifespan of an individual. We planned to focus the significance of telomeres in human health and aging and to summarize possible lifestyle factors that may affect health and longevity by altering the rate of telomere shortening.

1 Introduction

Telomeres, the DNA–protein complexes at chromosome ends, protect genome from degradation and interchromosomal fusion. Telomeres have been compared with the plastic tips on shoelaces, because they keep chromosome ends from fraying and sticking to each other, which would destroy or scramble an organism's genetic information. A telomere is a length of DNA that is made up of a repeating sequence of six nucleotide bases (TTAGGG). This sequence of TTAGGG is repeated approximately 2,500 times in humans. During chromosome replication, Small numbers of these terminal TTAGGG sequences are lost from the tips of the chromosomes, but the addition of TTAGGG repeats by the enzyme telomerase, prevents their shortening.

Telomerase have the ability to add telomeric repeats to the chromosome ends, is present in germline, hematopoietic, stem, and certain other rapidly renewing cells but extremely low or absent in most normal somatic cells. Transgenic induction of a telomerase gene in normal human cells extends their lifespan.

Length of telomere shortens with age. Cawthon *et al* showed that individuals with shorter telomeres had significantly poor survival due to higher mortality rate caused by heart and infectious diseases[1]. Progressive shortening of telomeres leads to senescence, apoptosis,

or oncogenic transformation of somatic cells which affecting the health and lifespan of an individual. Shorter telomeres have been associated with increased incidence of diseases and poor survival. People older than 60 with short telomeres have three and eight times increased risk to die from heart and infectious diseases, respectively[2]. Rate of telomere shortening is therefore critical to an individual's health and pace of aging. Telomere length may therefore serve as a biological clock to determine the lifespan of a cell. Telomere shortens in the absence of telomerase in non-ALT cells.

The rate of telomere shortening can be either increased or decreased by specific lifestyle factors. Better choice of diet and activities has great potential to reduce the rate of telomere shortening or at least prevent excessive telomere attrition, leading to delayed onset of age-associated diseases and increased lifespan. To preserve telomeres and pace of aging, we may consider to eat less (include antioxidants, fiber, soy protein and healthy fats in our diet), and stay lean, active, healthy, and stress-free through regular exercise and meditation.

2 Telomere

The term "telomere" was coined by Muller (1962) from the Greek for "end" (telos) and "part" (meros).

Telomeres are distinctive DNA–protein structures found at the ends of our chromosomes which protect the end of the chromosome from deterioration or from fusion with neighboring chromosomes and maintain chromosome stability. The telomenc DNA consists of noncoding tandemly repeated sequences, with the exact repeat sequence varying from one species to the other. In humans and other vertebrates, the repeat unit is the hexanucleotide 5'TTAGGG3' [3].

TRF1 was the first telomere-binding protein identified[4], followed by TRF2[5], a distantly related homolog of TRF1. Both proteins have a single myb repeat at the carboxyl terminus and an internally located dimerization domam. They form homodimers and bind very specifically to double-stranded telomeric sequence.

3 Telomerase

The complete replication of telomeric DNA requires telomerase, a specialized cellular ribonucleoprotein RNP reverse transcriptase (RT). It has a RNA component (hTR), which acts as a template for synthesis of telomeric repeats onto the chromosome ends. It also consists of a catalytic unit (hTERT) with reverse transcriptase activity, which adds the telomeric repeats on the chromosome ends. By copying a short template sequence within its intrinsic RNA moiety, telomerase synthesizes the telomeric DNA strand running 5′ to 3′ toward the distal end of the chromosome, thereby extending it. Regulated extension of the chromosomal DNA termini occurs to compensate for shortening that results from nuclease action and incomplete terminal DNA replication.

Telomerase activity is found to be repressed or inactivated in the majority of human tissues except some tissues like fetal and adult testes, ovarian follicles, etc. In contrast, telomerase activity is detectable in most tumors[6]. Activation of telomerase is one of the major mechanisms adapted by most of the cancer cells to overcome the phase of senescence

4 Structure and function of Telomere

Telomeres are composed of a DNA component and multiple protein components[7].

The telomeric DNA consists of noncoding repeated sequences (rich in guanine (G)). Repeat sequences can vary from one species to the other, with hexanucleotide repeat TTAGGG followed by terminal 3′ G-rich single-stranded overhangs being characteristic for humans (TTAGGG; 5′→3′ direction) and other vertebrates. Telomere DNA is thought to adopt the T-loop structure, where the telomere end folds back on itself and the 3′ G strand overhang invades into the double-stranded DNA (the so-called D-loop)[8] (Fig-1).

Because of its enriched G content, the single-stranded telomere G overhangs can form G-quadruplexes, where each G base serves as both donor and acceptor for hydrogen bond formation. In human, telomeric G-quadruplex structures have been implicated in telomere protection, suppression of recombination, and inhibition of telomerase-dependent telomere extension[9].
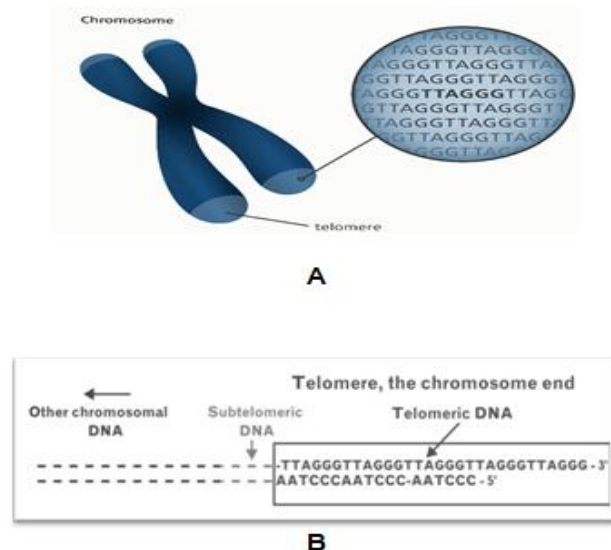

Fig: - A. position of Telomere; B. structure of Telomere

A myriad of proteins are directly or indirectly associated with telomeric DNA. Some of these proteins (most notably TIN2, TRF1, TRF2, TPP1, and POT1) are found in telomeres at any time, even though there is a highly dynamic exchange between proteins that are telomere-bound and unbound.

All chromosomes lose a small amount of telomeric DNA during each cell division and if telomere length reaches below a critical limit, this leads to chromosomal degradation and cell death[10].

Although telomeres are generally considered to be localized structures at the ends of chromosomes, such sequences are also being identified at internal positions in chromosomes[11]. The length of telomeres also varies among different species. Humans have telomeres 8–14 kilobasepairs (kbp) long[12]. In human chromosomes, telomeres are adjoined centromerically by a subtelomeric region consisting of degenerated telomeric DNA sequences and unique repeats.

Telomere-associated proteins include some that are central to the repair of broken chromosomes and to the cell cycle checkpointing that prevents cells with nonviable broken chromosomes from propagating.

Telomeres compensate for incomplete semi-conservative DNA replication at chromosomal ends. A protein complex known as shelterin serves as protection against double-strand break (DSB) repair by homologous recombination (HR) and non-homologous end joining (NHEJ)[13].

Telomeric DNA is associated with telomere binding proteins and a loop structure mediated by TRF2, which protects the ends of human chromosomes against exonucleolytic degradation[14].

In most organisms, telomere repeats are maintained by the enzyme, telomerase, which replaces the few terminal nucleotides that are lost at each cycle of DNA replication, as well as nucleotides lost to enzymatic degradation. Lost sequences are replaced by copying from the enzyme's RNA component. While replicating DNA, DNA replication enzymes cannot replicate the sequences present at the ends of the chromosomes. Hence, these sequences and the information they carry may get lost. This is the reason telomeres are so important in context of successful cell division: They "cap" the end-sequences and themselves get lost in the process of DNA replication. But the cell has an enzyme called telomerase, which carries out the task of adding repetitive nucleotide sequences to the ends of the DNA.

Telomere and telomerase activities are varied and important in many aspects of the control of cellular replication.

Telomeres prevent the cell from treating chromosome ends as broken chromosomes.

Telomeres also appear to play a role in the correct pairing and movement of chromosomes at meioses. They serve as the attachment points to the nuclear matrix.

They help to ensure equal distribution of genetic material into each gamete at meiosis.

They are involved in regulating the expression of highly variable subtelomeric genes in response to environmental changes.

Telomerase also shows important roles in stem cell proliferation, as well as reprogramming of induced pluripotent stem cells.

5 Effect on Telomeres during cell-division

Telomeres provide a reservoir against the loss of few base pairs taking place at every cell replication cycle due to the end replication problem. This shortening of telomeres at every cell cycle represents a genetic mitotic clock, which counts the number of cell divisions rather than chronological or metabolic age. When telomeres shorten critically, the cells are signaled to pull out of the cell cycle pool and enter into the senescence phase.

Telomeres shorten as a function of proliferative age. Human diploid fibroblasts have a mean TRF length of 7-9kb in the adults, which falls to around 5-7kb by the time the cells reach the senescence limit described by Hayflick[15-17]. When the telomere length is reduced to a critical point, a signal is given to stop further cell division, which is the hallmark of cellular senescence[18].

Normal diploid cells lose telomeres with each cell division and therefore have a limited lifespan in culture. Human liver tissues have been reported to lose 55 base pairs of telomeric DNA per year[19]. The expression of stathmin and EF-1a, the biomarkers for telomeric dysfunction and DNA damage in a cell, increases with age and age-related diseases in humans. Telomere length negatively correlates with age whereas the expression of p16, which increases in aging cells, positively correlates with age[20, 21].

Cells in culture are thought to stop dividing because of activation of an antiproliferative mechanism termed "mortality stage 1" (MI). The stimulus for the induction of MI may be DNA-damage signals from the altered expression of subtelomeric regulatory genes or from a critically shortened telomere. p21, pl6, p53 and pRb are believed to be involved in the execution of MI. If these cell cycle regulators are activated or mutated/blocked, the cells continue to divide and thus the telomeres continue to shorten. The telomere function appears to be critically diminished when mean telomere length falls to around 1-2 kb, although this possibly reflects the near total loss of telomeres from a subset of chromosomes, due to the second independent block in proliferation called the "mortality stage 2" (M2) or "crisis". This stage is punctuated by another surge of cell death.

6 Telomere shortening may increase the pace of aging

Telomeres shorten with age and rate of telomere shortening may indicate the pace of aging. As a normal cellular process, telomere length decreases with age. Telomere length in humans seems to decrease at a rate of 24.8–27.7 base pairs per year. Telomere length, shorter than the average telomere length for a specific age group, has been associated with increased incidence of age-related diseases and/or decreased lifespan in humans. Telomere length is affected by a combination of factors including donor age, genetic, epigenetic make-up and environment, social and economic status, exercise, body weight, and smoking[22-26].

Smoking, obesity, lack of exercise, and consumption of unhealthy diet can increase the pace of telomere shortening, leading to illness or premature death. Excessive telomere shortening can affect health and lifespan at multiple levels. Accelerated telomere shortening is associated with early onset of many age-associated health problems, including coronary heart disease, heart failure, diabetes, increased cancer risk, and osteoporosis[27, 28]. The individuals whose leukocyte telomeres are shorter than the corresponding average telomere length have three-fold higher risk to develop myocardial infarction. Shorter telomeres can also induce genomic instability by mediating interchromosomal fusion and may contribute to telomere stabilization and development of cancer. Certain individuals may also be born with shorter telomeres or may have genetic disorder leading to shorter telomeres. Such individuals are at a greater risk to develop premature coronary heart disease and premature aging.

7 Dietary restrictions reduces the pace of aging

Dietary restriction or eating less has an extremely positive impact on health and longevity. Reducing food intake in animals leads to reduced growth rate, reduced oxidative burden and reduced damage to DNA, and therefore keeps the animals in a biologically younger state and can increase their lifespan by up to 66%. It has been shown that dietary restriction in rodents delays the onset of age-associated diseases and increases the lifespan. Rats subjected to a protein-restricted diet early in life displayed a long-term suppression of appetite, reduced growth rate, and increased lifespan. The increased lifespan in such animals was associated with significantly longer telomeres in kidney. Because oxidative stress can substantially accelerate telomere shortening, the reduction in oxidative stress by dietary restriction is expected to preserve telomeres and other cellular components[29].

8 Exercise may preserve telomeres and reduce the pace of aging

Song et al [21] have demonstrated that duration of exercise inversely correlates with biomarkers for damage to DNA and telomeres and with p16 expression, a biomarker for aging human cell. Exercise can reduce harmful fat and help mobilize waste products for faster elimination, leading to reduced oxidative stress and preservation of DNA and telomeres. Werner et al showed that exercise was associated with elevated telomerase activity and suppression of several apoptosis proteins, including p53 and p16, in mice. Consistently, in humans the leukocytes derived from athletes had elevated telomerase activity and reduced telomere shortening, relative to nonathletes. Exercise seems to be associated with reduced oxidative stress and elevated expression of telomere stabilizing proteins and may therefore reduce the pace of aging and age-associated diseases.

9 Conflict of interests

None

10 Authors contributions

SS carried out literature review and draft the manuscript. MP participated in collection of data. All authors read and approved the final manuscript.

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