Telomerase, ageing and Lifestyle

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Abstract—*Telomeres are repetitive, non-coding sequences that cap the ends of linear chromosomes. They consist of hexameric nucleotide sequences (TTAGGG in humans) repeated hundreds to thousands of times. Telomeres protect the protein-coding sequences of DNA on the chromosome, and telomeres shortening during sequential cell divisions is believed to dictate a cell's life span. Telomerase activity is required to maintain telomeres. One consequence of telomere dysfunction is cellular senescence, a permanent growth arrest state. Telomere length shortens with age. Progressive shortening of telomeres leads to apoptosis, or oncogenic transformation of somatic cells, affecting the health and lifespan of an individual. Shorter telomeres have been associated with increased incidence of diseases and poor survival. 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. This review highlights the role of telomeres in aging and describes the lifestyle factors which may affect telomeres, human health, and aging.*

Keywords*: Nucleotide, apoptosis, somaticcells, senescence.*

1. INTRODUCTION

Telomeres, the specific DNA–protein structures found at both ends of each chromosome, protect genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion. Telomeres therefore play a vital role in preserving the information in our genome. As a normal cellular process, a small portion of telomere DNA is lost with each cell division. When telomere length reaches a critical limit, the cell undergoes senescence and/or apoptosis. Telomere length may therefore serve as a biological clock to determine the lifespan of a cell and an organism.Recent research points to the crucial roles of telomeres and telomerase in cellular ageing and potentially in disease. Ageing is a process associated with progressive changes, ultimately leading to death, and the mechanisms involved in ageing are still far from well understood. The search for ageing and longevity genes has long been a focus in biomedical research. Since telomeres shorten as a function of age in vivo and telomerase antagonizes the process of telomere shortening, whether or not telomereshortening serves, as a timer with different settings in different species to control the onset of cell senescence, and thus life span, has been the subject of intense debate[1]Accelerated telomere shortening in genetic disorder dyskeratosis congenital is associated with an early onset of several age-associated disorders and reduced lifespan. Telomerase activity, 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 [2]. Cawthon *et al.* [3] showed that individuals with shorter telomeres had significantly poor survival due to higher mortality rate caused by heart and infectious diseases. Progressive shortening of telomeres leads to senescence, apoptotic cell death, or oncogenic transformation of somatic cells in various tissues. Telomere length, which can be affected by various lifestyle factors, may determine overall health, lifespan, and the rate at which an individual is aging. As a normal cellular process, telomere length decreases with age [4, 5]. Telomere length in humans seems to decrease at a rate of 24.8–27.7 base pairs per year [4,5]. 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 [6, 7]. Telomere length is affected by a combination of factors including donor age [8], genetic, epigenetic make-up and environment [9–12], social and economic status [13,14], exercise, body weight [15], and smoking [16]. Gender does not seem to have any significant effect on the rate of telomere loss. When telomere length reaches below a critical limit, the cells undergo senescence and/or apoptosis [17, 18].

2. STRUCTURE OF TELOMERES

Telomeres, the DNA–protein complexes at chromosome ends, protect genome from degradation and interchromosomal fusion. Telomeric DNA is associated with telomere-binding proteins and a loop structure mediated by TRF2 protects the ends of human chromosomes against exonucleolytic degradation [19], and may also prime telomeric DNA synthesis by a mechanism similar to 'gap filling' in homologous recombination [20]. As shown in telomere shortening occurs at each DNA replication, and if continued leads to chromosomal degradation and cell death [21]. Telomerase activity, the ability to extend telomeres, is present in germline and certain hematopoietic cells, whereas somatic cells have low or undetectable levels of this activity and their

telomeres undergo a progressive shortening with replication . Telomerases are reactivated in most cancers and immortalized cells. However, a subset of cancer/immortalized cells lack telomerase activity and maintain telomere length by alternative mechanisms, probably involving genetic (homologous) recombination [22], which is elevated in most immortal/cancer cell lines [23].

2.1 Telomere lengthening

Telomere shortening can be reversed by the action of the enzyme telomerase (TERT), a reverse transcriptase that uses an RNA template called TERC to extend the ends of chromosomes by adding additional telomeric repeats .This can allow cells to live longer by counteracting the normal cell "aging" process of telomere shortening. Other less well-understood pathways can also extend telomeric DNA, such as the alternative pathway (ALT), which uses recombination between chromosomes to maintain telomere length. Sometimes telomeres are extended under normal conditions, such as those of stem cells and many cells of the immune system that need to divide regularly. Other times, however, telomerase can act out of turn, resulting in excessive proliferation of cells that can lead to cancer.

3. TELOMERES AND AGEING

Recent research points to the crucial roles of telomeres and telomerase in cellular ageing and potentially in disease. Ageing is a process associated with progressive changes, ultimately leading to death, and the mechanisms involved in ageing are still far from well understood. The search for ageing and longevity genes has long been a focus in biomedical research. Since telomeres shorten as a function of age in vivo and telomerase antagonizes the process of telomere shortening, whether or not telomereshortening serves, as a timer with different settings in different species to control the onset of cell senescence, and thus life span, has been the subject of intense debate[24]

A well established model for the analysis of ageing at the cellular level is in vitro cultivation of human diploid cells that divide a limited number of times before undergoing a state called "cellular senescence". This limit has been named "the Hayflick limit". Such cells are irreversibly blocked in G1 phase of the cell cycle and become unresponsive to mutagenic stimuli yet can remain viable and metabolically active. The senescent phenotype is accompanied by dramatic changes in morphology, nuclear structure, gene expression, protein processing and metabolism. An increased fraction of these cells positively stained for senescence-associated b-galactosidase and tumour suppressors such as p53, p21 and p16 is up regulated. This cellular senescence thus, represents a tumour suppressor mechanism[25]. Early studies in mice bearing a germ line knockout of the MTR gene and thus null telomerase activity show that short telomeres trigger multiple ageing related processes including cell growth arrest, apoptosis and decreased capacity in response to stresses in highly proliferative organs, demonstrating a critical role for telomere length in genomic stability, cell replicative life span and ageing5. The consequences of telomere ablation at the organismal level have been rigorously assessed in TERC-deficient mice[26] which undergo progressive telomere shortening with each generation and lose viability when they reach critically short telomeres (typically after 3 to 5 generations).

3.1 Stress increases the pace of telomere shortening and aging

The stress is associated with release of glucocorticoid hormones by the adrenal gland. These hormones have been shown to reduce the levels of antioxidant proteins [27] and may therefore cause increased oxidative damage to DNA [28] and accelerated telomere shortening [29]. Consistently, the women, exposed to stress in their daily life, had evidence of increased oxidative pressure, reduced telomerase activity, and shorter telomeres in peripheral blood mononuclear cells, relative to the women in the control group [30]. Importantly, the difference in telomere length in these two groups of women was equivalent to 10 years of life, indicating that the women under stress were at a risk for early onset of age-related health problems. Because telomere length may indicate an individual's biological age, the stress would adversely affect health and longevity.

4. IMPACT OF DIET AND EXERCISE ON TELOMERES AND AGING

Impact of fiber, fat, and protein on telomeres

Cassidy *et al*. studied the association of leukocyte telomere length with various lifestyle factors in a relatively large group of women. Telomere length positively correlated with dietary intake of fiber and negatively associated with waist circumference and dietary intake of polyunsaturated fatty acids, especially linoleic acid. Reduction in protein intake of food also seems to increase longevity. Reduction in the protein content of food by 40%, led to a 15% increase in the lifespan of rats. The rats subjected to a protein-restricted diet early in life displayed a long-term suppression of appetite, reduced growth rate, and increased lifespan [31], and the increased lifespan in such animals was associated with significantly longer telomeres in kidney [32]. Consistently, the highest life expectancy of Japanese is associated with low protein and high-carbohydrate intake in diet. The source of protein also seems to be an important factor as replacing casein with the soy protein in rats, is associated with delayed incidence of chronic nephropathies and increased lifespan.

Exercise may preserve telomeres and reduce the pace of aging

Song *et al.* 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.

5. CONCLUSION

Telomeres shorten with age and progressive telomere shortening leads to senescence and/or apoptosis. Shorter telomeres have also been implicated in genomic instability and oncogenes. Older people with shorter telomeres have three and eight times increased risk to die from heart and infectious diseases, respectively. Telomeres, the specific DNA–protein structures found at both ends of each chromosome, protect genome from nucleolytic degradation, unnecessary recombination, repair, and inter chromosomal fusion. Telomeres therefore play a vital role in preserving the information in our genome. As a normal cellular process, a small portion of telomere DNA is lost with each cell division. When telomere length reaches a critical limit, the cell undergoes senescence and/or apoptosis. Telomere length may therefore serve as a biological clock to determine the lifespan of a cell and an organism. The search for ageing and longevity genes has long been a focus in biomedical research. Since telomeres shorten as a function of age in vivo and telomerase antagonizes the process of telomere shortening, whether or not telomere shortening serves, as a timer with different settings in different species to control the onset of cell senescence, and thus life span, has been the subject of intense debate.T he stress is associated with release of glucocorticoid hormones by the adrenal gland. These hormones have been shown to reduce the levels of antioxidant proteins and may therefore cause increased oxidative damage to DNA and accelerated telomere shortening .Telomere is one of the reasons of ageing and lifestyle is big factor which influence this shortening of telomere.

REFERENCE

[1] Liu JP. Studies of the molecular mechanisms in the regulation of telomerase activity. FASEB J 1999; 13: 2091104.

[2] Bonnard AG, Ouellette M, Frolkis M, et al. Extension of life-span by introduction of telomerase into normal human cells. Science.1998; 279:349–352.

[3] Cawthon RM, Smith KR, O'Brien E, et al. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet.2003; 361:393–395.

[4] Valdes AM, Andrew T, Gardner JP, et al. Obesity, cigarette smoking, and telomere length in women. Lancet.2005; 366:662–664.

[5] Brouilette S, Singh RK, Thompson JR, et al. White cell telomere length and risk of premature myocardial infarction. Arterioscler Thromb Vasc Biol. 2003; 23:842–846.

[6] Farzaneh-Far R, Cawthon RM, Na B, et al. Prognostic value of leukocyte telomere length in patients with stable coronary artery disease: data from the Heart and Soul Study. Arterioscler Thromb Vasc Biol. 2008; 28:1379–1384.

[7] Yang Z, Huang X, Jiang H, et al. Short telomeres and prognosis of hypertension in a Chinese population. Hypertension.2009; 53:639–645.

[8] Frenck RW, Jr, Blackburn EH, Shannon KM. The rate of telomere sequence loss in human leukocytes varies with age. Proc Natl Acad Sci U S A. 1998; 95:5607–5610.

[9] Steinert S, Shay JW, Wright WE. Modification of subtelomeric DNA.Mol Cell Biol. 2004; 24:4571–4580.

[10] Munoz P, Blanco R, Flores JM, Blasco MA. XPF nuclease-dependent telomere loss and increased DNA damage in mice overexpressing TRF2 result in premature aging and cancer. Nat Genet. 2005; 37:1063–1071.

[11] Celli GB, de Lange T. DNA processing is not required for ATM mediated telomere damage response after TRF2 deletion. Nat Cell Biol. 2005;7:712–718.

[12]Benetti R, Garcia-Cao M, Blasco MA. Telomere length regulates the epigenetic status of mammalian telomeres and subtelomeres. Nat Genet. 2007;39:243–250.

[13] Cherkas LF, Hunkin JL, Kato BS, et al. The association between physical activity in leisure time and leukocyte telomere length. Arch Intern Med. 2008; 168:154–158.

[14] Adams J, Martin-Ruiz C, Pearce MS, et al. No association between socioeconomic status and white blood cell telomere length. Aging Cell. 2007; 6:125–128.

[15]Nordfjall K, Eliasson M, Stegmayr B, et al. Telomere length is associated with obesity parameters but with a gender difference. Obesity (Silver Spring) 2008;16:2682–2689.

[16] Nawrot TS, Staessen JA, Gardner JP, Aviv A. Telomere length and possible link to X chromosome. Lancet.2004; 363:507–510.

[17] Gong JG, Costanzo A, Yang HQ, et al. The tyrosine kinase c-Abl regulates p73 in apoptotic response to cisplatin-induced DNA damage. Nature.1999; 399:806–809.

[18] Stiewe T, Putzer BM. p73 in apoptosis. Apoptosis.2001; 6:447–452.

[19]Van Steensel B, Smogorzewska A, de Lange T. TRF2 protects human telomeres from end-to-end fusions. Cell.1998;92:401–413.

[20]. Griffith JD, Comeau L, Rosenfield S, et al. Mammalian telomeres end in a large duplex loop. Cell.1999; 97:503–514.

[21] Shin JS, Hong A, Solomon MJ, Lee CS. The role of telomeres and telomerase in the pathology of human cancer and aging.Pathology.2006; 38:103–113.

[22] Dunham MA, Neumann AA, Fasching CL, Reddel RR. Telomere maintenance by recombination in human cells.Nat Genet. 2000; 26:447–450.

[23] Shammas MA, Shmookler Reis RJ, Koley H, et al. Dysfunctional homologous recombination mediates genomic instability and progression in myeloma. Blood.2009; 113:2290–2297.
[24] Liu JP. Studies of the molecular mechanisms in the regulation of telomerase activity. FASEB J 1999; 13 : 2091104.
[25] Von Zglinicki T, Martin-Ruiz CM.Telomeres as biomarkers for ageing and age-related diseases.Curr Mol Med 2005; 5 : 197-203.
[26] Wong KK, Maser RS, Bachoo RM, Menon J, Carrasco DR, Gu Y, et al. Telomere dysfunction and Atm deficiency compromises organ homeostasis and accelerates ageing. Nature 2003; 421: 643-8.
[27] Patel R, McIntosh L, McLaughlin J, et al. Disruptive effects of glucocorticoids on glutathione peroxidase biochemistry in hippocampal cultures. J Neurochem.2002; 82:118–125.
[28] Irie M, Asami S, Ikeda M, Kasai H. Depressive state relates to female oxidative DNA damage via neutrophil activation. BiochemBiophys Res Commun.2003; 311:1014–1018.
[29] Von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci. 2002; 27:339–344.
[30] Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A. 2004; 101:17312–17315.
[31] Jennings BJ, Ozanne SE, Dorling MW, Hales CN. Early growth determines longevity in male rats and may be related to telomere shortening in the kidney. FEBS Lett.1999; 448:4–8.
[32] Jennings BJ, Ozanne SE, Hales CN. Nutrition, oxidative damage, telomere shortening, and cellular senescence: individual or connected agents of aging? Mol Genet Metab.2000; 71:32–42.