British Journal of Medicine & Medical Research
4(1): 57-67, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Telomeres and Oxidative Stress

Nurul Fatihah Mohamad Nasir[1], Thirumulu Ponnuraj Kannan[1,2*], Siti Amrah Sulaiman[3], Shaharum Shamsuddin[4], Azlina Ahmad[1] and Stefan Stangaciu[5]

[1]School of Dental Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[2]Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[3]Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia,16150 Kubang Kerian, Kelantan, Malaysia.
[4]School of Health Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[5]Apitherapy Consulting and Trading International SRL, Sat Mereni, str. Principala nr. 106A, Comuna Contesti, Dambovita district, Postal code 137133, Romania.

Authors' contributions

All the authors have appropriately contributed to this review article. All authors read and approved the final manuscript.

Review Article

Received 26th June 2013
Accepted 25th August 2013
Published 14th September 2013

ABSTRACT

Telomeres are long repetitive DNA sequences of TTAGGG located at the end of the linear chromosomes and bound by shelterin proteins. Shelterin proteins function as the protection for the loop structure of telomere, which prevents the chromosome ends uncapped; resemble a DNA break and activates DNA repair mechanism. Telomere length is maintained by an enzyme called telomerase. There are several factors that can shorten the telomeres which include telomere attrition during cell division, deficiency of Rad 54, which is involved in DNA repair and the methylation of histones H3 and histones H4, which can diminish telomerase activity. Three major mechanisms which influence the telomere length are the end-replication problem, the action of C-strand-specific exonuclease and oxidative DNA damage induced by environmental risk factors. However, oxidative stress has been shown to be the major mechanism which can influence the telomere length. This review explores the association between telomere length and

**Corresponding author: Email: tpkannan@kb.usm.my;*

oxidative stress.

Keywords: Telomere; oxidative stress; telomerase; 8-oxodG.

1. INTRODUCTION

Early research on the mechanism of DNA replication revealed a surprising fact. In each round of cell division, the ends of chromosomal DNA are slightly shortened, which if left unhindered would eventually lead to the loss of crucial genetic material [1]. This 'end replication problem' is solved by telomeres - structures at the ends of chromosomes that contain a series of non-coding DNA repeats. Although telomeres shorten with every cell division but they protect the coding regions from damage [2].

The discovery that telomeres shorten with every cell division in somatic human cells but not in immortal tumour cell cultures [2] has led to the suggestion that telomere might act as a mitotic clock, counting the number of cell divisions and eventually activating replicative senescence as an ultimate DNA damage checkpoint [1]. Moreover, it is also suggested that the telomere loss is the molecular clock that drives aging [2-5].

Based on the analysis of cultured human fibroblasts and lymphocytes, the rate of loss of telomeres is 50-100 bp per cell division [5]. However, the rate of telomere loss can be accelerated by chronic mild oxidative stress [6,7]. Interestingly, telomeres have been found to be preferential targets for acute oxidative damage [8]. This review will explore the association between the oxidative stress and telomere shortening.

2. WHAT IS TELOMERE?

Telomeres are the long repetitive DNA sequence of TTAGGG located at the end of the linear chromosomes [9,10] and bound by shelterin proteins. The best known shelterin proteins in human cells are telomere repeat binding factors 1 (TRF1) and telomere repeat binding factor 2 (TRF2). TRF1 and TRF2 are both the negative regulators of the telomeric length [11]. Other shelterin proteins include protection of telomeres 1 (POT1), tripeptidyl peptidase 1 (TPP1), tripeptidyl peptidase 2 (TIN2) and repressor activator protein 1 (RAP1). Shelterin proteins function as the protection for the loop structure of telomere, which prevents the chromosome ends uncapped; resemble a DNA break and activates DNA repair mechanism [11] The telomeric repeat does not encode for protein [12]. However, it consists of G-rich hexanucleotide repeats which enable the single-stranded telomere G overhangs to form G-quadraplexes. The G-quadraplexes structure of telomeres is believed to be involved in telomere protection, suppression of recombination and inhibition of telomerase-dependent telomere extension [13]. It is thought that telomeres' structure can switch between a closed, protected state and an open, extendable state, which allows the DNA terminus to undergo replication. The protected state is necessary for safeguarding the integrity of genomic material, whereas the extendable state allows the enzyme telomerase to extend short telomeres [14]. The length of telomeric repeats varies between chromosomes and between species. In human chromosomes, the telomeric repeats length is between 0.5 and 15 kilobase (kb) pairs. In addition, the length of these repeats is dependent on the type of tissue, the age of the donor and the replicative history of the cells. For example, the average telomere length declines significantly with increasing age in human nucleated blood cells [15].

Telomeres are the linear chromosomes' solution in protecting their ends from breaking down and degradation and avoid recognition and processing as double-strand breaks [16]. Studies carried out in yeast and other single organisms have showed that the functions of the telomeres include protection from the chromosomal recombination, end-to-end fusion, recognition as damaged DNA, the determination of chromosomal localization within the nucleus and to regulate the cell capacity for replication [12].

3. THE HOMEOSTASIS OF TELOMERE LENGTH

Telomerase is an enzyme that maintains telomere length. It is a ribonucleoprotein complex composed of RNA and protein components [17]. The major components of the active telomerase complex are telomerase reverse transcriptase (TERT), a telomerase RNA component (TERC) and dyskerin. Dyskerin is a protein that binds to TERT and TERC which increases the stability of the complex [18,19]. Telomerase elongates the telomere sequence in mammals and yeast by binding to the open ends of the G-strand. It is highly expressed in highly proliferative cells such as progenitor cells, lymphocytes, skin keratinocytes, cancer cells [17] and embryonic stem cells [20].

There are many factors that can shorten the telomeres; telomere attrition during cell division [23], deficiency of DNA repair proteins such as Mre11/Rad50/NBS, Ku, DNA PKcs, BLM/WRN ERCC1/XPC [21-23] and Rad 54 and the methylation of histones H3 and histones H4 which can diminish telomerase activity [24]. This review however, will elaborate more on the three major mechanisms which influence the telomere length; the end-replication problem, the action of C-strand-specific exonuclease and oxidative DNA damage induced by environmental risk factors [25].

Telomeres shorten with every successive cell division due to the intrinsic ability of the replication machinery to copy the linear DNA [26]. This happens because the synthesis of the lagging strand occurs non-continuously unlike the leading strand. In lagging strand, the DNA synthesis occurs via a multitude of Okazaki fragments primed by short RNAs, which are about 8 to 12 nucleotides long. The gap between the two Okazaki fragments is filled in and ligated later, but the gap left by removal of the most distal primer remains, resulting in G-rich overhang on one of the chromosome ends and finally in the shortening of the telomere by at least one quarter of the primer length [27].

The action of C-strand-specific exonuclease was suggested because human telomeres contains G-rich overhangs about 100-200 nucleotides in length [28]. The exonuclease degrades the RNA primer necessary for the DNA synthesis of the lagging strand. Degradation of the RNA primer leads to the inhibition of formation of Okazaki fragments and leaves the DNA single stranded and exposed to the risks of DNA damage, the risk of fusion of chromosome extremities [29] and the activation p53-dependent responses to DNA damage [30].This action of exonuclease shortens each telomere by half the overhang length per round of replication [28].

Telomere shortening due to the end-replication problem is relatively small and constant in each cell, irrespective of telomere length, whereas, telomere shortening induced by oxidative stress is proportional to telomere length, as longer telomeres are larger targets for free radicals [31-33]. In fact, the results from the exposure of human fibroblast cells in culture to oxidative stress have shown that the telomere shortening rate is accelerated [32]. Studies also showed that the chronic oxidative stress compromised the telomere integrity and

accelerates the onset of senescence in human endothelial cells [34]. Further details on the oxidative stress and telomere length will be discussed below.

4. OXIDATIVE STRESS

Oxidative stress is defined as an increase in the intracellular concentration of reactive oxygen species (ROS). The ROS include superoxide anions, hydroxyl radicals and hydrogen peroxide. ROS are generated during regular metabolism because of incomplete oxygen reduction in the mitochondrial electron transport chain; a one-electron reduction of oxygen forms superoxide (0_2^-), a two-electron reduction forms hydrogen peroxide (H_2O_2), and a three-electron reduction forms the hydroxyl radical ($^{\cdot}OH$). Many other ROS species can be derived from superoxide and hydrogen peroxide [35-38].

These various radical species can be generated exogenously or produced intracellularly from different sources. The exogenous sources of ROS include ultraviolet light, ionizing radiation, chemotherapeutics, inflammatory cytokines and environmental toxins. The endogenous sources of ROS include mitochondria, peroxisomes, lipoxygenases, NADPH oxidase and Cytochrome P450 [39]. However, many researchers suggest that the majority of ROS produced intracellularly comes from mitochondria. There are two distinct points involved in the generation of ROS in mitochondria during the electron transport chain which are complex I (NADH dehydrogenase) and at complex III (ubiquinone-cytochrome c reductase). The complex III is the main site of ROS production under normal metabolic production [40]. The free radical semiquinone anion species ($^{\cdot}Q^-$) is formed as an intermediate in the regeneration of coenzyme Q. This $^{\cdot}Q^-$ can readily and non-enzymatically transfer electrons to molecular oxygen with the subsequent generation of superoxide radical. The generation of superoxide can be enzymatically dismutated by SOD to form hydrogen peroxide that in turn is metabolized by enzymes such as catalase (CAT) and gluthatione reductase (GPx) regenerating water and molecular oxygen. Therefore, higher the rate of metabolism, greater is the production of ROS [39].

It is interesting to note that mitochondrial DNA is more sensitive than nuclear damage to oxidative damage. Increasing damage to mitochondrial DNA inevitably leads to compromised mitochondrial function and integrity. It is thought that damaged mitochondria release more ROS and set in motion a vicious cycle of increasing DNA damage leading to increased ROS production that in turn leads to more DNA damage [39].

5. HOW DOES OXIDATIVE STRESS CAUSE TELOMERE SHORTENING?

Oxidative stress causes damage to telomeric DNA by increasing the level of 8-oxodG (8-oxo-7,8-dihydro-2-deoxyguanosine). Progressive increases in 8-oxodG has been shown to be associated with decreasing telomere length [36]. Besides that, ROS, especially the hydroxyl radical, induce breaks in DNA and deteriorate DNA base repair [41]. Telomeres seem to be unable to repair DNA breaks in single-strand DNA as compared to the rest of the genome [42]. This is because the binding of TRF2 on telomere prevent the DNA repair enzymes from reaching the site [43]. Moreover, the interaction between TRF2 and polymerase beta has negative effect on the repair of DNA damage [43]. Next, TRF2 also inhibits the initiation process of DNA repair by inhibiting ataxia telangiectasia muted kinase phosphorylation [44].

Other than that, increased production of ROS can lead to the development of inflammatory process [45]. The proinflammatory cytokines can cause telomere shortening directly. Several studies have shown that the increasing levels of tumour necrosis factor alpha can decrease the telomerase activity by negatively regulate the expression level of human TERT [46].

Telomeres are sensitive to damage by oxidative stress due to their high guanine (-GGG) content. Guanine is the most easily oxidised DNA base because the oxidation potential is lower than the other three bases which are adenine, cytosine and thymine. Other than that, it is easily oxidised because the highest occupied molecular orbital that accommodates electrons with the greatest energy is located on the 5'-G of the GG sequence [36].

Besides that, study showed that oxidative stress efficiently induced DNA damage at the 5' site of 5'-GGG-3' in telomere sequence. H_20_2 plus Cu(II) caused predominant DNA cleavage at the 5' site of 5'-GGG-3' in the telomere sequence region in DNA fragment [5'-(TAGTAG)4(TTAGGG)4-3']. SIN-1, which leads to simultaneous generation of both NO and O_2^- and NO-generating agent plus O_2^- generating system efficiently caused base alteration at 5' site of 5'-GGG-3' sequence in telomere sequence [36].

Furthermore, oxidative stress can function as a common trigger for activation of the senescence program. The GGG-specific DNA damage in telomere sequence induced by oxidative stress may play an important role in increasing of the rate of telomere shortening [47-48]. Telomere shortening might impact on the regenerative capacity of human tissues during aging and chronic disease. A schematic diagram on how the increased production of ROS causes telomere shortening is shown in Fig. 1.

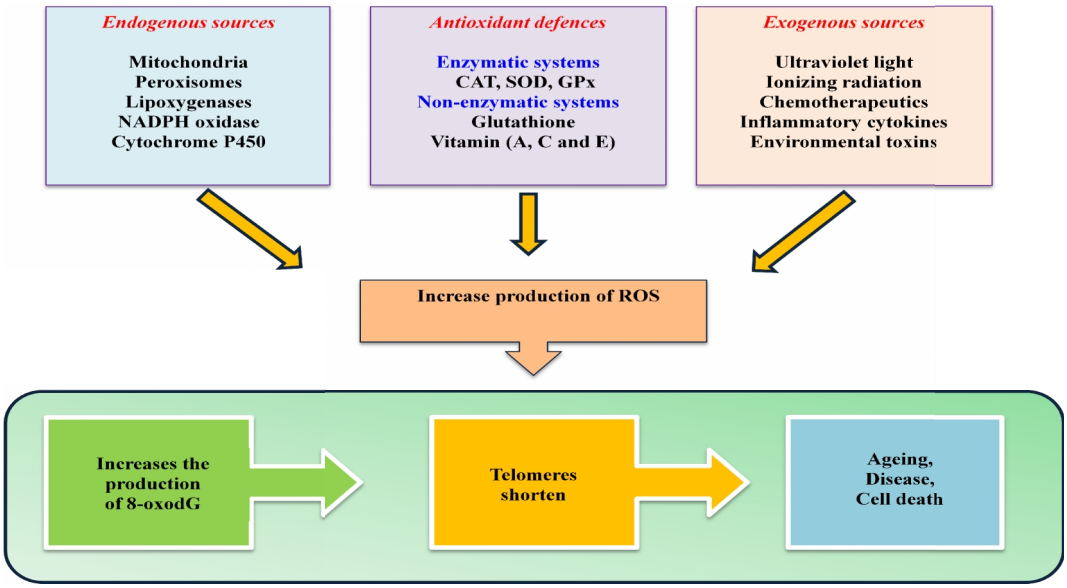

Fig 1. Schematic diagram showing the shortening of telomere through increased production of ROS

6. TELOMERE SHORTENING AND EXAMPLES OF DISEASES

A study conducted by Ma et al. showed that shorter telomere length and increased oxidative stress were observed in both type 1 and type 2 diabetes. In addition, older people with central obesity, hyperglycemia, insulin resistance and severe antioxidant status tended to have shorter telomere length [49]. Several cross-sectional clinical studies have demonstrated an association between shorter telomere length and type 2 diabetes [50-52]. The studies suggest that the severity of the telomere shortening is in gradation. Patients with impaired glucose tolerance have been reported to have shorter telomere length as compared to controls and those with diabetes with even shorter lengths. However, the shortest telomere lengths were noted in patients with the combination of pre-diabetes/diabetes and atherosclerotic vascular disease compared to those with diabetes or cardiovascular disease alone [53].

In Alzheimer disease (AD), oxidative stress is proposed to be an early event that aids in progressive neurodegeneration and subsequent cognitive impairment [54-55]. One of the contributing factors that are common to many neurodegenerative diseases involving oxidative stress pathways is mitochondrial dysfunction which has been reported to cause an increase of ROS production [56-57]. A study that characterizes telomere integrity and telomerase activity in the brains of AD patients has shown that the neuronal telomeres were significantly shorter in hippocampal neurons of AD patients compared with that in control subjects. They also found that there is a loss of nuclear localization of TERT in the pyramidal neurons of AD patients as compared to controls [58].

7. COMBATING AGENTs AGAINST TELOMERE SHORTENING

Studies have shown that antioxidants are able to reverse the accelerated telomere shortening induced by increased oxidative stress [59-60]. In addition, treatment of human endothelial cells and fibroblasts with either ascorbic acid 2-O-phosphate [61] or with free-radical scavenger α-phenyl-t-butylnitrone [62] prolonged the replicative life span and decreased the rate of telomere shortening compared to cells under standard culture conditions.

Interestingly, a study conducted by Sheng et al. has shown that Epigallocatechingallate (EGCG), quercetin and carvedilol with potent antioxidant effect, may inhibit cardiac myocyte apoptosis by preventing telomere shortening and telomere repeat-binding factor 2 (TRF2) loss [63]. It was also found that EGCG suppresses oxidative stress-induced H9c2 cardiomyoblast apoptosis through inhibiting telomere dependent apoptotic pathway [64].

In yet another study, it has been shown that Interleukin 8 (IL-8) exerted protective effects against endothelial senescence, which may be related to the activation of telomerase. The results showed that IL-8 attenuated the oxidative stress induced high-expression of cell cycle regulation protein and inhibited the activation of p38 and NF-κB pathway. IL-8 also increased telomerase activity which was accompanied with an upregulation of the catalytic subunit, TERT [65].

8. CONCLUSION AND FUTURE PERSPECTIVES

In summary, oxidative stress plays an important role in contributing to telomere shortening. Damage towards the telomeric DNA is achieved by progressive increases in 8-oxodG. Since

the damage is hard to repair, the proinflammatory response is induced, thus, activating the senescence program. Combating agents against telomere shortening such as antioxidants seem to promise an alternative to slow down the telomere shortening. Therefore, they might provide a new approach for combating the age-related diseases and ageing. However, further exploration of these combating agents is deemed important which could provide us a better understanding of their underlying properties especially in terms of their absorption and distribution in the tissues. Further insights into the role of oxidative stress in telomere shortening are crucial as they might provide a better understanding of the age-related diseases and longevity in humans.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

ACKNOWLEDGEMENTS

This review was supported by the Universiti Sains Malaysia Short Term Grant (304/PPSG/61312032).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Olovnikov AM. A theory of marginotomy: the incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon. J Theor Biol. 1973;41(1):181-90.
2. Harley CB, Futcher AB, Greider CW. Telomeres shorten during aging of human fibroblasts. Nature. 1990;345:458-60.
3. Hastie ND, Dempster M, Dunlop MG, Thompson AM, Green DK, Allshire RC. Telomere reduction in human colorectal carcinoma and with ageing. Nature. 1990;346:866-68.
4. Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mut Res. 1991;256(2-6):271-82.
5. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, et al. Telomere length predicts replicative capacity of human fibroblasts. PNAS. 1992;89(21):10114-18.
6. von Zglinicki T, Saretzki G, Döcke W, Lotze C. Mild hyperoxia shortens telomeres and inhibits proliferation of fibroblasts: a model for senescence? Exp Cell Res. 1995;220(1):186-93.
7. Vaziri H, West MD, Allsopp RC, Davison TS, Wu YS, Arrowsmith CH, et al. ATM-dependent telomere loss in aging human diploid fibroblasts and dna damage lead to the post-translational activation of p53 protein involving poly(adp-ribose) polymerase. EMBO J. 1997;16:6018-33.

8. Henle ES, Han Z, Tang N, Rai P, Luo Y, Linn S. Sequence-specific DNA cleavage by Fe2+-mediated fenton reactions has possible biological implications. JBC, 1999;274(2):962-71.
9. Blackburn EH. Structure and function of telomeres. Nature. 1991;350:569-73.
10. Zakian VA. Telomerase: Beginning to understand the end. Science. 1995;270:1601-7.
11. Gomez DE, Armando RG, Farina HG, Menna PL, Cerrudo CS, Ghiringhelli PD, et al. Telomere structure and telomerase in health and disease. Int J Oncol. 2012;41:1561-69.
12. Hodes RJ. Telomere length, aging, and somatic cell turnover. J Exp Med. 1999;190:153-56.
13. Lipps HJ Rhodes D. G-quadruplex structures: in vivo evidence and function. Trends Cell Bio. 2009;19:414-22.
14. Stewart JA, Chaiken MF, Wang F and Price CM. Maintaining the end: role of telomere proteins in end-protection, telomere replication and length regulation. Mut Res. 2012;730:12-19.
15. Aubert GA, Landsdorp PM. Telomeres and aging. Physiol Rev. 2008;88:557-79.
16. Kobryn KA, Chaconas G. The circle is broken: telomere resolution in linear replicons. CurrOpinMcrobiol. 2001;4:558-64.
17. Flores I, Benetti RA, Blasco MA. Telomerase regulation and stem cell behaviour. CurrOpin Cell Biol. 2006;18:254-60.
18. Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in tetrahymena extracts. Cell. 1985;43:405-13.
19. Cohen SB, Graham ME, Lovrecz GO, Bache N, Robinson PJ, Reddel RR. Protein composition of catalytically active human telomerase from immortal cells. Science. 2007;315:1850-53.
20. Hiyama E, Hiyama K. Telomere and telomerase in stem cells. Br J Cancer. 2007;96:1020-24.
21. de Lange T. Shelterin: the protein complex that shapes and safeguards human telomeres. Genes Dev. 2005;19:2100-10.
22. Meier A, Fiegler H, Munoz P, Ellis P, Rigler D, Langford C, etal. Spreading of mammalian DNA-damage response factors studied by ChIP-chip at damaged telomeres. EMBO J. 2007;26:2707-18.
23. Verdun RE, Karlseder J. The DNA damage machinery and homologous recombination pathway act consecutively to protect human telomeres. Cell. 2006;127:709-20.
24. Khan S, Chuturgoon AA Naidoo DP. Telomeres and atherosclerosis. Cardiovasc J Afr. 2012;23:563-71.
25. VonZqlinicki T. Role of oxidative stress in telomere length regulation and replicative senescence. Ann N Y Acad Sci. 2006;908(1):99-110.
26. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet. 2005;6:611-22.
27. Olovnikov AM. Principle of marginotomy in template synthesis of polynucleotides. DoklAkdNauk SSSR. 1971;201:1496-99.
28. Makarov VL, Hirose Y, Langmore JP. Long G tails at both ends of human chromosomes suggest a C strand degradation mechanism for telomere shortening. Cell. 1997;88:657-66.
29. vanSteensel B, Smogorzewska A, de Lange T. TRF2 protects human telomeres from end-to-end fusions. Cell. 1998;92(3):401-13.

30. Karlseder J, Broccoli D, Dai Y, Hardy S, de Lange T. P53- and ATM-dependent apoptosis induced by telomeres lacking TRF2. Science. 1999;283(5406):1321-25.
31. Chen W, Gardner JP, Kimura M, Brimacombe M, Cao X, Srinivasan SR, et al. Leukocyte telomere length is associated with hdl cholesterol levels: the bogalusa heart study. Atherosclerosis. 2009;205(2):620-25.
32. vonZglinicki T. Oxidative stress shortens telomeres. Trends BiochemSci. 2002;27(7):339-44.
33. De Meyer T, Rietzschel ER, De Buyzere ML, Langlois MR, De Bacquer D, Segers P, et al. . Systemic telomere length and preclinical atherosclerosis: the asklepios study. Eur Heart J. 2009;30(24):3074-81.
34. Kurz DJ, Decary S, Hong Y, Trivier E, Akhmedov A, Erusalimsky JD. Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells. J Cell Sci. 2004;117:2417-26.
35. Von Zglinicki T, Bürkle A. Kirkwood TB. Stress, DNA damage and ageing - an integrative approach. Exp Gerontol. 2001;36(7):1049-62.
36. Kawanishi S, Oikawa S. Mechanism of telomere shortening by oxidative stress. Ann N Y Acad Sci. 2004;1019(1):278-84.
37. Heinecke JW. Oxidants and antioxidants in the pathogenesis of atherosclerosis: implications for the oxidized low density lipoprotein hypothesis. Atherosclerosis. 1998;141(1):1-15.
38. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res. 2000;87(10):840-44.
39. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408(6809):239-47.
40. Turrens JF. Superoxide production by the mitochondrial respiratory chain. Biosc Rep.1997;17:3-8.
41. Fotiadou PO, Henegariu, Sweasy, JB. DNA polymerase β interacts with trf2 and induces telomere dysfunction in a murine mammary cell line. Cancer Res. 2004;64(11):3830-37.
42. Petersen S, Saretzki G, von Zglinicki, T. Preferential accumulation of single-stranded regions in telomeres of human fibroblasts. Exp Cell Res. 1998;239(1):152-60.
43. Richter T, Saretzki G, Nelson G, Melcher M, Olijslagers S, von Zglinicki T. TRF2 over expression diminishes repair of telomeric single-strand breaks and accelerates telomere shortening in human fibroblasts. Mech Ageing Dev. 2007;128(4):340-45.
44. Karlseder J, Hoke K, Mirzoeva OK, Bakkenist C, Kastan MB, Petrini JH, et al. The telomeric protein TRF2 binds the ATM kinase and can inhibit the ATM-dependent dna damage response. Plos Biol. 2004;2:E240.
45. Floyd RA, Hensley K, Jaffery F, Maidt L, Robinson K, Pye Q, et al. Increased oxidative stress brought on by pro-inflammatory cytokines in neurodegenerative processes and the protective role of nitrone-based free radical traps. Life Sci. 1999;65(18-19):1893-99.
46. Beyne-Rauzy O, Prade-Houdellier N, Demur C, Recher C, Ayel J, Laurent G, et al. Tumor necrosis factor-α inhibits htert gene expression in human myeloid normal and leukemic cells. Blood. 2005;106(9):3200-5.
47. Oikawa S, Tada-Oikawa S, Kawanishi S. Site-specific DNA damage at the GGG sequence by UVA involves acceleration of telomere shortening. Biochemistry. 2001;40(15):4763-68.

48. Oikawa S, Kawanishi S. Site-specific DNA Damage at GGG sequence by oxidative stress may accelerate telomere shortening. FEBS Lett. 1999;453(3):365-68.
49. Ma D, Zhu W, Hu S, Yu X, Yang Y. Association between oxidative stress and telomere length in type 1 and type 2 diabetic patients. J Endocrinol Invest. 2013;[Epub ahead of print].
50. Salpea KD, Talmud PJ, Cooper JA, Maubaret CG, Stephens JW, Abelak K, Humphries SE. Association of telomere length with type 2 diabetes, oxidative stress and UCP2 gene variation. Atherosclerosis. 2010;209(1):42-50.
51. Zee RY, Castonguay AJ, Barton NS, Germer S, Martin M. Mean leukocyte telomere length shortening and type 2 diabetes mellitus: a case-control study. Transl Res. 2010;155(4):166-9.
52. Satoh M, Ishikawa Y, Takahashi Y, Itoh T, Minami Y, Nakamura M. Association between oxidative DNA damage and telomere shortening in circulating endothelial progenitor cells obtained from metabolic syndrome patients with coronary artery disease. Atherosclerosis. 2008;198(2):347-53.
53. Salpea KD, Humphries SE. Telomere length in atherosclerosis and diabetes. Atherosclerosis. 2010;209(1):35–38.
54. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol. 2001;60(8):759-67.
55. Zhu X, Lee HG, Casadesus G, Avila J, Drew K, Perry G, et al. Oxidative imbalance in Alzheimer's disease. Mol Neurobiol. 2005;31(1-3):205-17.
56. Sheng B, Wang X, Su B, Lee HG, Casadesus G, Perry G, Zhu X. Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. J Neurochem. 2012;120(3):419-29.
57. Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis. J Alzheimers Dis. 2010;20Suppl 2:S265-79.
58. Franco S, Blasco MA, Siedlak SL, Harris PL, Moreira PI, Perry G, Smith MA. Telomeres and telomerase in Alzheimer's disease: epiphenomena or a new focus for therapeutic strategy?.Alzheimers Dement. 2006;2(3):164-8.
59. Xu D, Neville R, Finkel T. Homocysteine accelerates endothelial cell senescence. FEBS Lett. 2000;470:20-24.
60. Bar-Or D, Thomas GW, Rael LT, Lau EP, Winkler JV. Asp-Ala-His-Lys (DAHK) inhibits copper-induced oxidative DNA double strand breaks and telomere shortening. BiochemBiophy Res Commun. 2001;282:356-60.
61. Furumuto K, Inoue E, Nagao N, Hiyama E, Miwa N. Age-dependant telomere shortening is slowed down by enrichment of intracellular vitamin C via suppression of oxidative stress. Life Sci. 1998;63:935-48.
62. vonZglinicki T, Pilger R, Sitte N. Accumulation of single-strand breaks is the major cause of telomere shortening in human fibroblast. Free RadicBiol Med. 2000;28:64-74.
63. Sheng R, Gu ZL, Xie ML. Epigallocatechin gallate, the major component of polyphenols in green tea, inhibits telomere attrition mediated cardiomyocyte apoptosis in cardiac hypertrophy. Int J Cardiol. 2013;162(3):199–209.
64. Sheng R, Gu ZL, Xie ML, Zhou WX, Guo CY. Epigallocatechin gallate protects H9c2 cardiomyoblasts against hydrogen dioxides- induced apoptosis and telomere attrition. Eur J Pharmacol. 2010;641(2-3):199-206.

65. Shen XH, Xu SJ, Jin CY, Ding F, Zhou YC, Fu GS. Interleukin-8 prevents oxidative stress-induced human endothelial cell senescence via telomerase activation. Int Immunopharmacol. 2013;16(2):261-67.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=215&id=12&aid=2000