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Review

Telomere shortening during aging: Attenuation by antioxidants and anti-inflammatory agents

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ABSTRACT

Telomeres are a repeated sequence -of bases found at the ends of chromosomes. In humans, this sequence is TTAGGG, which is repeated over 2000 times. Telomeres protect the ends chromosomes from fusion with nearby chromosomes, and allow effective replication of DNA. Each time a cell divides, 25–200 base pairs are lost from the terminal sequence of chromosomes. By becoming truncated during cell division, telomeres protect essential genes from being shortened and thus inactivated. In addition, telomeres are sensitive to inflammation and oxidative stress, which can further promote telomere shortening. Reduction in the length of telomeres leads to the cessation of cell division and thus cellular senescence and apoptosis. This review discusses evidence for the role of oxidative stress and inflammation in regulating the length of telomeres in mammalian cells during senescence. Evidence is presented suggesting that antioxidants and anti-inflammatories can reduce the pace of shortening of telomere length during aging. The distinctive properties of transformed cells suggest that treatment with such materials will have a deleterious rather than a protective effect on such abnormal cells.

1. Introduction

Ageing can be defined as a gradual deterioration of organ function toward the end of the life span. Environmental-, dietary-, lifestyle-related factors, and heritable gene mutation can all contribute to the individual rate of aging. Levels of oxidative stress, inflammation, mitochondrial dysfunction, antioxidants, shortening of telomeres and gene mutations are all likely to play a role in determining the pace of cellular aging. There is considerable evidence to show that reduction in the length of telomeres is associated with failure of cell division and senescence of normal cells, and that oxidative stress and inflammation can contribute to the rate of attrition of telomere length. These studies are discussed in this manuscript together with some suggestions as to how aging events may be beneficially influenced by exogenous factors.

Telomeres consist of a repetitive sequences of TTAGGG located at the end of chromosome needed for the replication of DNA. Telomerase reverse transcriptase (TRT) is the catalytic subunit of telomerase enzyme that is responsible for maintaining telomere length by adding telomere repeats TTAGGG at the end. On the other hand, telomeric repeat-binding factor-2 (TRF-2) is needed for the telomere maintenance, cell cycle progression, and protection of the ends to avoid chromosomal fusion (Hanaoka et al., 2005; Kim et al., 2009).

One of the widely held hypotheses is that aging of mammalian cells is due to shortening of telomere length (Mikhelson and Gamaley, 2012). This is supported by the fact that point mutations within the telomere cause accelerated attrition of telomere length and also lead to premature aging (Fyhrquist and Saijonmaa, 2012). There is substantial evidence to show that increased oxidative stress and inflammation play a central role in shortening the length of telomeres possibly by decreasing the activity of telomerase and/or TRF-2 level.

The length of telomeres is maintained in cancer cells despite increased oxidative stress and inflammation (Ennour-Idrissi et al., 2016; Bertorelle et al., 2014; Rode et al., 2016). Telomerase is expressed in over 95% of cancer types, at a much higher levels than in normal adult tissues. This is due to the reactivation of the gene hTERT, which is generally silent in adult tissues, leading to production of telomerase reverse transcriptase, TERT (Bermudez et al., 2007), and reappearance of active telomerase ribonucleoprotein. Inhibition of oxidative stress protects telomerase activity in normal cells but inhibits that in tumor cells. This apparent contradiction has been accounted for by the higher redox homeostasis threshold that exists in cancer cells causing them to have a high demand for reactive oxygen species (ROS), (Li et al., 2016a).

This review discusses the role of oxidative stress and inflammation

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in regulating the length of telomeres in mammalian cells. In addition, it presents evidence to show that antioxidant and anti-inflammatory agents may reduce the pace aging by curtailing the rate of shortening of telomere length. It should be emphasized that, in view of the large overlap between oxidant and inflammatory events the distinction between protective agents acting on either, is rather arbitrary.

2. Effects of oxidative stress on telomere length

Evidence from a variety of human studies that show oxidative status and telomere length are closely related. These studies are enumerated here.

2.1. Clinical reports

Several clinical reports illustrate the link between pro-oxidant events and telomere status.

2.1.1. Periodontitis

Increased oxidative stress and inflammation is associated with reduced leukocyte telomere length in patients with periodontitis (Masi et al., 2011).

2.1.2. Parkinson's disease

Enhanced oxidative stress is found in patients with Parkinson's disease and that shortened length of telomeres in the blood cells is associated with this disease (Watfa et al., 2011).

2.1.3. Depression

Gene expression of oxidative defense enzymes superoxide dismutases (SOD1 and SOD2), catalase (CAT) and glutathione peroxidase (GPX1) were significantly lower in oligodendrocytes derived post-mortem from patients suffering from major depressive disorders. This was accompanied by a reduction of both telomeric length and levels of TERT in oligodendrocytes but not astrocytes (Szebeni et al., 2014).

2.1.4. Diabetes

Increased oxidative stress together with shortened length of leukocyte telomeres is found in type 1 and type 2 diabetes. In addition, older people with central obesity, hyperglycemia, insulin resistance and lower antioxidant levels had shorter leukocyte telomere length (Ma et al., 2013). The monocyte telomere shortening observed in type 2 diabetes could be due to increased oxidative DNA damage to monocyte precursors during cell division (Sampson et al., 2006).

2.1.5. Aging

Elderly men living in Greece have lower indices of oxidative stress and higher antioxidant levels, than a corresponding population of elderly Dutch men, living in a more stressful urban setting and a diet less rich in antioxidant nutrients. The length of telomeres in leukocytes was significantly greater in the Greek relative to the Dutch population (De Vos-Houben et al., 2012). This suggests causal relationship between increased oxidative stress and shortening of the telomere length during aging.

2.1.6. Twin study

In a metabolomics study of over 300 adult twins, there was a relation between indices of oxidative stress, decline in organ function and reduced leukocyte telomere length (Zierer et al., 2016). While this does not imply causality, such a correlation supports findings from studies involving more defined studies using in vitro systems

2.1.7. Dyskeratosis congenita

Dyskeratosis congenita (DC) is a multi-system disorder characterized by defects of the skin, nails, and mucous membrane. Most cases are also associated with bone marrow dysfunction. This disease exhibits severe telomere abnormalities attributable to defects in six genes coding for those proteins, such as TERC and TERT responsible for maintaining telomere length (Kirwan and Dokal, 2009).

2.2. Isolated systems

Findings directly paralleling the human studies described above have also been obtained in isolated cell systems. Some examples:

Increased oxidative stress induced by treatment with H2O2 shortened the length of telomeres isolated in mouse skeletal muscle fibers (Ludlow et al., 2014).

Enhanced oxidative stress induced by treatment with *tert*-butyl hydroperoxide or L-buthionine-(S, R)-sulphoximine shortened the length of telomeres and caused senescence in human endothelial cells (Kurz et al., 2004).

Mild hyperoxia reduced the length of telomeres and induced senescence in human fibroblasts (von Zglinicki et al., 1995).

While it is clear that oxidative events can lead to telomere shortening, it is not fully established whether this is due to inhibition of TERT and/or TRF2. Additional studies on effects of ROS donors on telomere length in normal cell models as well as animal models of aging are needed to identify the mechanisms underlying such events.

2.3. Immune system

The cells of the immune system are very sensitive to shortening of telomere length, since the competency of immune system depends upon cell renewal and clonal expansion of T-and B-lymphocytes. These cells can increase the activity of telomerase and thereby limit telomere attrition in cells undergoing active proliferation. Oxidative stress is one of the factors that induce senescence in immune cells (Kaszubowska, 2008). In many cell types from patients with coronary heart disease (leukocytes, CD34+ peripheral blood stem cells and progenitor cells, monocytes, granulocytes, B-lymphocytes, and CD4+ T lymphocytes), the length of telomeres was shorter than in their age-matched control subjects. Shortening of telomere length was the most pronounced in cytotoxic CD8 T lymphocytes (Spyridopoulos et al., 2009). The same study reported that cytomegalovirus infection in CD8+CD28 (−) T cells caused further shortening of telomere length. T cell senescence occurs prematurely in patients with rheumatoid arthritis. The low levels of the DNA double-strand break repair nuclease MRE11A caused damage to telomeres and induced senescence in rheumatoid arthritis t-lymphocytes. Inhibition of the activity of MRE11A in healthy T cells induced senescence, whereas overexpression of MRE11A in T cells from patients with rheumatoid arthritis reversed these cells to normal phenotypes (Li et al., 2016b). Thus the length of telomeres in T cells depends upon the activity of MRE11A. In the CD3+T-cells from patients with myelodysplastic syndrome (MDS), the high rate of attrition of telomere length occurs because of lower telomerase activity as well as reduced expression of telomere reverse transcriptase mRNA (Yang et al., 2013).

3. Effects of inflammation on telomere length

Some examples of the intimate relation between inflammatory events and telomeric length are listed:

3.1. Obesity

Obesity is associated with enhanced oxidative stress and inflammation (Hulsegge et al., 2016; Zhao et al., 2016). Weight gain during adulthood and obesity contribute to shorter leukocyte telomere length in adults younger than 60 years of age (Muezzinler et al., 2016). Higher Body Mass Index (BMI) and obesity at the age of 25 can lead to a reduced length of leukocyte telomeres (Wulaningsih et al., 2016).