

THE EFFECTS OF OXIDATIVE STRESS ON TELOMERES AND CELL LIFE SPAN

WPŁYW STRESU OKSYDACYJNEGO NA TELOMERY I DŁUGOŚĆ ŻYCIA KOMÓREK

ANNA PAŃCZYSZYN^{1 E,F}

EWA BONIEWSKA-BERNACKA^{1 E,F}

¹ Independent Department of Biotechnology and Molecular
Biology, University of Opole

A – przygotowanie projektu badania | study design, **B** – zbieranie danych | data collection, **C** – analiza statystyczna | statistical analysis, **D** – interpretacja danych | interpretation of data, **E** – przygotowanie maszynopisu | manuscript preparation, **F** – opracowanie piśmiennictwa | literature review, **G** – pozyskanie funduszy | sourcing of funding

SUMMARY

Oxidative stress is associated with excessive amounts of reactive oxygen species (ROS) in the body. The sources of ROS constitute the respiratory chain, immune system cells and external factors, e.g. smoking. ROS may cause damage and faster shortening of nucleoprotein structures called telomeres, which protect chromosome ends. The consequence of faster shortening of telomeres is aging and death of cells. The aim of this paper was to present the impact of ROS on the rate of telomere shortening and cell life span. It is common knowledge that shorter telomeres are associated with higher risk of cardiovascular diseases and tumors. An antioxidant-rich diet, avoiding stress, and physical activity contribute to lower levels of oxidative stress, slower telomere shortening, and longer and healthier life.

KEYWORDS: oxidative stress, telomeres

STRESZCZENIE

Stres oksydacyjny związany jest ze zbyt dużą ilością reaktywnych związków tlenowych (ROS) w organizmie. Źródłem ROS jest łańcuch oddechowy, komórki odpornościowe oraz czynniki zewnętrzne, np. palenie tytoniu. W wyniku aktywności ROS uszkodzeniu mogą ulegać telomery, nukleoproteinowe struktury chroniące końce chromosomów, co prowadzi do nadmiernego ich skracania się. W konsekwencji komórki posiadające krótsze telomery szybciej starzeją się i ulegają śmierci. W pracy przedstawiono wpływ ROS na tempo skracania się telomerów i długość życia komórek. Jak wiadomo, krótsze telomery związane są z ryzykiem wystąpienia chorób układu krążenia i nowotworów. Dieta bogata w przeciwutleniacze, unikanie stresu oraz aktywność fizyczna przyczyniają się do obniżenia poziomu stresu oksydacyjnego i tempa skracania się telomerów w komórkach, czego konsekwencją może być dłuższe i zdrowsze życie.

SŁOWA KLUCZOWE: stres oksydacyjny, telomery

BACKGROUND

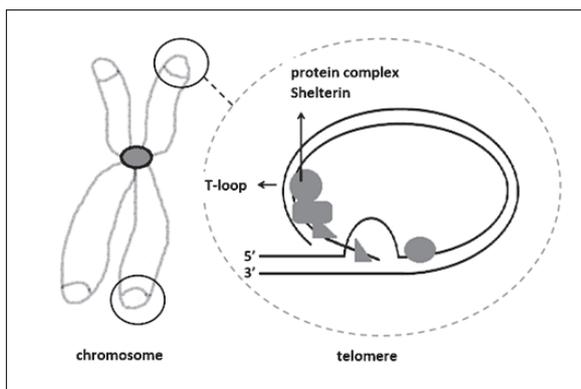
Oxidative stress is defined as excessive amount of reactive oxygen species (ROS) in the body. Reactive oxygen species include such free radicals as: superoxide anion (O_2^-), hydroxyl radical (OH^\cdot), hydroperoxyl radical (HO_2^\cdot) and their precursors (hypochlorous acid, hydrogen peroxide, peroxyxynitrite, singlet oxygen). The majority of ROS are formed during metabolic processes, as a result of incomplete reduction of oxygen in the mitochondrial respiratory chain, which consists of the following protein complexes: I – NADH dehydrogenase, III

– ubiquinol-cytochrome-c reductase, IV – cytochrome-c oxidoreductase. The main source of ROS is complex III and ubiquinol. During the transfer of an even number of electrons and hydrogens to the oxygen, sometimes the oxygen is reduced in a one-electron reaction and the result is a superoxide anion, which is the precursor of other reactive oxygen species. Other sources of ROS in the organism constitute cells of the immune system, especially neutrophils and macrophages, which engulf pathogens through phagocytosis and destroy them, inter alia by releasing toxic ROS in a process known as respiratory burst [1]. Increased amounts of

ROS are also formed in the body due to external factors, such as: ultraviolet and ionising radiation, chemotherapeutics, smoking tobacco, drinking alcohol [2–3]. Because free radicals have the capacity to enter chemical reactions with different cell components, they can cause various types of damage: oxidative modification of nucleic acids, protein and fats [4]. In physiological conditions, excess of free radicals is neutralised by antioxidants, which constitute so-called radical catchers (ascorbic acid, α -tocopherol, vitamin and provitamin A, flavonoids) and specialised enzymes: superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (Gpx). Chronic oxidative stress in the body is caused by a lack of effective defence mechanisms, lower antioxidant count and lower enzyme (CAT, SOD and Gpx) activity, and can lead to severe effects, such as cardiovascular diseases, neoplastic diseases, neurodegenerative diseases, and faster aging of the body resulting from excessive shortening of telomeres [5].

TELOMERES, ROS AND CELL LIFE SPAN

Telomeres are structures securing the termini of chromosomes in eukaryotic cells. In human cells they are built from repeating nucleotide sequences (5'-TTAGGG-3')_n, connected with a protein complex known as Shelterin (Figure 1). Telomere sequences are located in a double-stranded, cytosine-rich DNA string (dsDNA) 10–20 kbp (kilo base pairs) long and single-stranded guanine-rich DNA string (ssDNA). The single-stranded DNA string constitutes a part of the so-called overhang that invades the dsDNA and forms a T-loop, which is tasked with protecting the chromosome from external factors. Telomeres prevent chromosomes from breaking, fusing and ensure the stability of the genome. Telomeres are shortened with each cell division, which stems from the way they multiply via DNA polymerase. Telomeres are referred to as “molecular clocks of the cell”, because they indicate the limit of cell division. If the telomeres reach critical length (< 100 repetitions), it is a signal for the cell to stop dividing and to begin the process of aging [6]. Telomeres can lengthen as a result of the activity of a specialised enzyme – telomerase, however its activity is limited only to cells which can divide: embryo cells, stem cells, haematopoietic progenitor cells, and skin cells. High telomerase activity is also reported in neoplastic cells [7].



Source: Own study.

Figure 1. Chromosome and telomere structure

Telomere length is an individual feature, similarly as the pace of shortening. The most exemplary cells for measuring telomere length are lymphocyte cells, because they are continuously formed in the body and the pace of shortening of their telomeres is similar to that in other cells [8]. Different studies have proven that measuring lymphocyte telomeres is useful for assessing the risk of developing some diseases, including cardiovascular diseases, oesophageal cancer, and diabetes [9–11]. In the future, monitoring telomere length will help assess the risk of developing a particular disease, before first symptoms even appear. A number of external factors affect the speed of telomere shortening. These include smoking tobacco, lack of physical activity, vegetable and fruit-poor diet, and stressful life-style [12]. Reactive oxygen species also facilitate telomere shortening and subsequent faster aging of cells. Due to high volumes of guanine telomeres are sensitive to the activity of reactive oxygen species, especially the hydroxyl radical, which reacts with guanine to form 8-oxo-2'-deoxyguanosine. Furthermore, reactive oxygen species induce telomeres to break [13–14]. Damage to telomeres is not effectively repaired, due to difficult access to telomere DNA, which is connected with the Shelterin protein complex. Oxidative stress can facilitate the development of inflammation. Pro-inflammatory cytokines released by cells of the immune system can lower telomerase activity and promote inflammation, during which ROS production increases. Cumulation of telomere damage leads to a halt in cell division, aging and eventually death, and, moreover, to carcinogenesis [15]. Studies conducted *in vitro* in human endothelial cells showed that in oxidative stress conditions their telomeres shorten twice as fast, in comparison with cells free from oxidative stress. Furthermore, the endothelial cells entered the aging stage after 36 divisions, while the cells from the control group began aging after 46 divisions [16]. Shortened telomeres were observed among patients with lung, bladder, renal, stomach, neck and head, and ovarian cancer [17–19]. The results of multiple studies show that the faster the telomere shortening, the higher the risk of developing severe diseases and premature death. In an average person, telomeres shorten by 26 base pairs per year. Significant shortening of lymphocyte telomeres was observed in people with inherent predispositions for atherosclerosis or obesity. The cell age was assessed based on telomere length, cells of subjects with atherosclerosis and obesity were older by 11 and 9 years, respectively, in comparison of their healthy peers [20–21].

So is it possible to slow down telomere shortening and lengthen life span? Studies show that healthy life-style has positive effect on slowing down telomere shortening. Eating anti-oxidant-rich fruit and vegetables can help decrease ROS levels. *In vitro* studies on human endothelial cells showed that ascorbic acid slowed down telomere shortening by 52–62% and as a result cells divided slower and took longer to enter the aging stage [22]. Moreover, study by Farzaneh-Far et al. [23] showed that an unsaturated fatty acids-rich diet slowed down telomere shortening. In a population of over 600 subjects, who ingested omega-3 acids during the period of 5 years, the authors observed that telomere shortening slowed down by 32%, in comparison with the other study group, whose diet was poor in unsaturated fatty acids. Moderate and regular physical activity has posi-

tive effect on maintaining telomere length by lowering oxidative stress and increasing expression of telomere-stabilising proteins [24]. Avoiding stressful situations seems to be as important as a healthy diet. Stress releases glucocorticosteroid hormones, which reduce the levels of antioxidative proteins and can thus facilitate the increase of ROS levels and, as a result, telomere damage. A study on a group of women living under pressure showed that their lymphocyte telomeres were significantly shorter than those of the control group, and their length corresponded to that of people 10 years older than the study subjects [12]. On the other hand, oxidative stress was notably lower and telomeres longer among people doing yoga [25].

CONCLUSIONS

Telomeres become shorter with age and their sped up shortening leads to premature aging and death of cells. Short telomeres are connected with increased risk of damage to genetic material and neoplastic disease. In an older population, whose telomeres are short, the risk of developing cardiovascular diseases and premature death is 3 to 8 times higher. Smoking tobacco, lack of physical activity, unhealthy diet increase ROS levels in body, which facilitates oxidative-based damage of telomeres [26–27]. Changing the life-style, low-protein diet rich with fruit and vegetables, and sea fish [28], avoiding stress and doing sports have positive effecting on slowing down telomere shortening and can limit the risk of developing some diseases and extend life span.

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Correspondence address:

Anna Pańczyszyn
Independent Department of Biotechnology
and Molecular Biology
University of Opole
Kominka str. 6 a
45-032 Opole
phone: +48 77 401 6050
e-mail: apanczyszyn@uni.opole.pl

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