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Journal of Aging Science

Research Article

Telomerase Level: A Useful Tool to Predict Longevity

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ABSTRACT

In the context of the global elderly population increase, due to the rise of average life span, many researches try to explain the molecular bases of ageing and age-related diseases. In the headlines, there are the telomere-telomerase based studies, which support the idea that telomere length dynamics and telomerase activity level are involved in cellular senescence, immortalization and tumorigenesis. Here, no statistical difference is shown between hTERT content in the plasma of young and elderly groups, Nevertheless the higher level of telomerase increases with age in the older age group. A good balance between telomerase level and telomere shortening seems to be a useful machinery to maintain health and prolong lifespan. In this scientific concept, further progress has to be made in order to explain the origin of increasing life span and the lack of pathology during ageing.

Keywords: Ageing; Telomere; hTERT; Centenarian

INTRODUCTION

Although the lifespan has constantly increased during the last centuries, the quality of life has not kept the pace. The hopes of solving this are strongly linked to telomeres and telomerase. Telomeres are nucleoprotein structures at the end of eukaryotic chromosomes that consist of an array of tandemly repeated TTAGGG sequences [1]. Due to the unidirectional and semi-conservative nature of DNA replication, in normal somatic tissues the telomeres shorten with each round of replication, thus the telomeres of old cells are shorter than those of young cells. By contrast, in immortal cells, like stem and cancer cells, telomeres are maintained by the ribonucleoprotein complex of telomerase, a specialized reverse transcriptase, which synthesizes de novo TTAGGG repetitions on their own RNA template [2]. There is another known path with a lower occurrence that slows down the telomere shortening through the alternative lengthening of telomeres or ALT, which is probably a recombination using a telomerase-independent mechanism [3].

The triggers for cellular senescence and ageing, clinically translated in age-related pathology and finally death include gene expression and epigenetic changes in every cell, telomere shortening in replicative cells, and ROS and DNA damage accumulation in non-replicative ones.Given that the bone marrow cellularity declines over the years [4] and even the stem cells age, the highly differentiated cells will not renew at the pace needed to maintain the functionality of tissues or organs. Moreover, they will continue to "wear and tear", which leads to tissue degeneration and eventually organ failure.

Telomeres carry out several essential roles for ensuring the function and structural integrity of cells. Together with associated proteins, telomeres: 1) cap the chromosome ends, ensuring the stability of the genome [5], and thus preventing chromosomal fusions which lead to dicentric chromosomes [6]; 2) associate with the nuclear matrix leading to the maintenance of the nuclear architecture [7]; and 3) protect the ends from enzymatic degradation and incomplete replication of linear DNA [8].

Although telomerase is expressed in 85%-90% of malign tumors [9], there are many other healthy cells such as germ cells, activated lymphocytes or proliferative cells of renewal tissues which contain it as well. Catalytic subunit of telomerase or TERT activity varies between both species and specific tissues. In this regard, telomerase is considered a marker of immortality, not one of malignant transformation [10]. In the absence of any other hallmarks of cancer [11], a higher level of telomerase activity may just be a good prognostic marker for longevity.

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Received: March 31, 2021; **Accepted**: April 14, 2021; **Published**: April 21, 2021

Citation: Hertzog RG, Popescu DM, Calborean O (2021) Telomerase Level: A Useful Tool to Predict Longevity. J Aging Sci. 9:251.

Through its role in maintaining the telomeres (irrespective of their length) [12], telomerase ensures the maintenance of the genetic (in) stability requested for continuing the cell division.

In our study based on the telomerase level assessment of two groups with an age difference of almost 60 years, we show that hTERT activity resurgence is an underlying mechanism present in very elderly people with a good health.

MATERIALS AND METHODS

A total of 16 healthy women volunteers were enrolled in this study. Eight of them were 30 to 40 years of age (the young group). The other eight (the elderly group) were older than 90. From each person, informed consent has been obtained. Plasma hTERT concentrations were determined with ELISA kit (Abbexa Ltd., Cambridge, UK) according to the manufacturer's protocol.

Whole blood samples have been collected on EDTA and centrifuged at ~3,000 rpm for 20 minutes within 1 hour after blood sampling. The plasma samples were stored at -40 °C for up to 2 months. After thawing, the samples were diluted 10 times. hTERT levels were quantified by reading the O.D. absorbencies at 450 nm in a microplate reader and interpolated from a standard curve. The standard curve was generated using the free computer software CurveExpert 1.4. The blank value was subtracted from each value, including the standards. The final values read from the standard curve were multiplied by dilution factor. For statistical analysis, we used the R software to perform the unpaired (one-tailed) Student's test.

RESULTS AND DISCUSSION

The purpose of this study was to compare hTERT plasmatic level between two healthy, but different age groups. Each young individual had no known diseases. The people from the elderly group had no significant illnesses at the moment of the test, as well as throughout their life. The young group expressed an hTERT mean of 243.94 ± 43.49 pg/mL, unlike the elderly, whose mean was 173.29 ± 80.82 pg/mL (Figure 1). The results showed no statistical differences between hTERT values of the young group and the elderly one ($p>0.05$). The results are consistent with those obtained by other authors, considering the hTERT cut-off value of 500 pg/mL for healthy control groups [13].

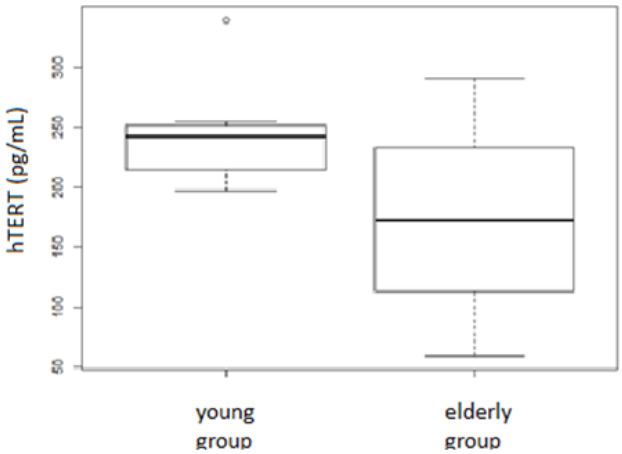

Figure 1: Comparison of plasma telomerase concentrations (pg/mL) between the young and elderly groups (n=8), with standard deviations represented as bars. We can see that the average values of young group are higher, but the difference is not statistically significant.

Many pathologies are linked to cellular senescence, which is a consequence of redox imbalance, telomere shortening or/and telomerase up/down regulation, limited proliferative capacity, etc. Thus, being associated with age, the coronary heart diseases, stroke, diabetes, cancer and neurodegenerative diseases are the leading causes of illness and death. Every age-related disease starts with morphological and functional tissue changes and, sooner or later, organ dysfunctions will happen, due to an accelerated or regular senescence of affected cellular components. Each of them is related to telomere shortening or/and telomerase up/down regulation. In diabetes mellitus, increased ROS production and glucose auto-oxidation lead to telomere shortening in pancreatic β-cells and, subsequently, in loss of capacity to insulin secretion [14]. Cardiovascular diseases are mainly the consequences of endothelial and vascular smooth muscle cells senescence [15].The senescent tissue suffering from telomere attrition a highly probable location where atherosclerosis might appear and develop through oxidative stress and inflammatory processes [16].In addition, arterial telomere uncapping is under the influence of sex hormones as seen in pre- and post-menopausal women [17].

Actually, cellular senescence is an interlinked process, mediated by regulators of both telomere biology and inflammation [18]. By contrast, for centenarians inflammation is no longer a risk, and might even be a good predictor of functional health spans [19]. Although the studies regarding the relationship between telomere length and neurodegenerative conditions are controversial, it should not be surprising that Alzheimer's and Parkinson's diseases have been associated with shorter telomeres in peripheral blood cells [20]. Nevertheless, CNS ageing and related diseases are induced by telomere dysfunction *via* stress induced premature senescence or metabolism-driven process rather than the telomere erosion based replicative senescence per se [21].

Telomere length and telomerase activity have a pivotal role in progressing ageing toward healthy or ill status, such as cancer or atherosclerosis, consistent with an undergoing evolutionary

human health trade-off [22]. Other long living mammals, such as the elephant and bowhead whale, have developed TP53-based tumor suppressor mechanisms to maintain lower cancer prevalence [23]. Recently, in a different species study, it has been proven that telomere shortening rate could be a good predictor of life span [24]. Telomere length has been positively associated with a good immune response to influenza [25]. In the same way, telomere length is inversely correlated with infection risks [26]. In a population study, the shortest telomeres have been associated with a higher risk of developing cancer [27]. In fact, in order to further its proliferative life, a cell with short telomeres does not require much telomerase activity [23]. All these data show the importance of telomere – telomerase ensemble to protect the health during ageing and prolong the life of elderly people towards and beyond the 100 year threshold. It is interesting to notice that the majority of centenarians never had significant illnesses throughout their life, except for typical childhood or traumatic ones. Actually, super centenarians show a biomarkers profile typical for young people (Figure 2) [19].

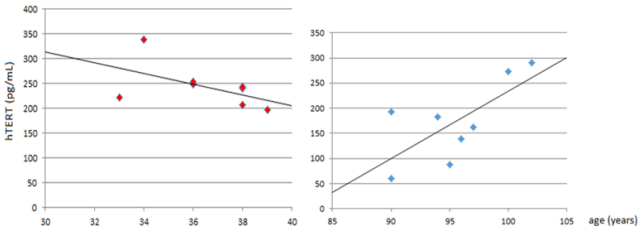

Figure 2: Telomerase level decreases with age in the younger group (left side, R= -0.533, R Squared=0.284) but increases with age in the elderly group during super-ageing (right side, R=0.713, R-Squared=0.509). Each spot represents an individual plasma telomerase concentration.

The older age may be positively associated with hTERT level. Besides longer telomeres [28], the presence of telomerase in healthy centenarians seems to be needed to delay replicative senescence of the cells. Likewise, the telomeres might not be long enough to form a loop and to keep silent telomerase gene by TPE-OLD [29]. Our study suggests that older healthy people express more telomerase, which can be considered a booster of longevity. This is consistent with the outcome of a study on a large cohort of centenarians that showed slow telomeres increasing rate after the age of 100 years [19].

Telomere length decreases with age, as we indirectly shown through the decreasing hTERT level. Although the mean telomerase in elderly was globally below the value of the younger group, the hTERT levels of the two centenarians included in our study were above average, despite the effects of ageing.

As age increases, and perhaps correlated with telomere shortening, the telomerase should be at a higher level to compensate for telomere attrition. Elderly people with telomeres long enough to stabilize nuclear envelope and cell architecture do not need a high hTERT level. On the other hand, a shorter telomere associated with a much higher hTERT activity is the suitable combination to promote cells towards proliferation and malignant transformation in Figure 2.

CONCLUSION

We determined that healthy people over 90 have an increasing level of hTERT, unlike young people whose hTERT decreases with ageing hTERT is a prerequisite to maintain telomere length at a level that helps people to become the next healthy centenarians. How could we be getting old and reaching 100 without any significant pathology? Achieving successful ageing depends on the stem cell reservoir, the cell division and telomere shortening speeds, DNA repair capacity, the mitotic rates and also the hTERT level and activity. The longevity of an organism might be the cumulative expression of the replicative and non-replicative lifetime of all cell lines that make it. How fast or slow do cells divide in order to replace some damaged tissue or, respectively, to delay telomere shortening? In order to get the right answer, we have to ask centenarians the suitable molecular questions.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

FUNDING

This study had financial support from Romanian Society of Telemicroscopy.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki decla-ration and its later amendments.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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