Telomeres and telomerase: source of eternal youth?

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Abstract

Telomeres of normal human somatic cells became shorter with each cell division as a result of end replication problem, so that they possess a limited replicative potential. Critically short telomeres can trigger a persistent DNA damage response that leads to the cell enters senescence and eventually apoptosis. This situation causes an accelerated-aging phenotype and decreased lifespan due to premature depletion of stem cells and subsequent organ/tissue failure. The rate of telomere shortening associated with normal aging can be modified by risk factors, such as psychological and oxidative stress, obesity and sedentary life-style, smoking, excess alcohol intake and cognitive impairment, that induce diseases and premature death.

Keywords: aging, leukocyte telomere length, lifespan, cell senescence, risk factors

Objective

Nowadays aging is one of the problems that more concern us. Hence, the aim of this work is to report on the factors that increase the rate of shortening telomere length and causes a premature-aging phenotype. Thus, we will can delay the telomere-based replicative senescence, and ultimately the onset of age-related diseases.

Methodology

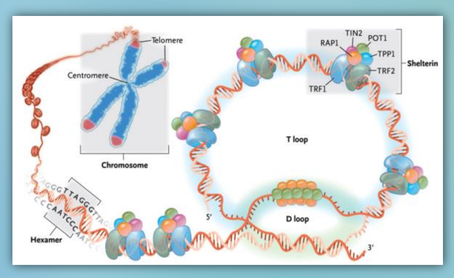
The materials required for the memory have been books, articles and reviews from Pubmed, articles whose corresponding author sent me, and videos. To choose them I considered the most outstanding authors in this field.

Results

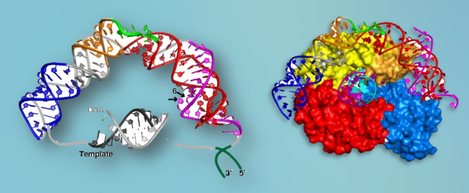
1. TELOMERES AND TELOMERASE

In mammals, telomeres are capped with shelterin complex. Some of these six core proteins influence the T-loop formation, which protects chromosome ends from degradation.

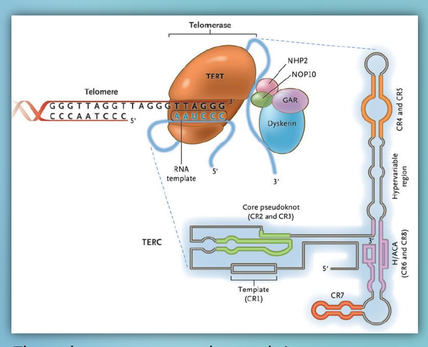
Telomere length is maintained by a balance between processes that lengthen telomeres, such as the activity of the telomerase, and processes that shorten them, as the end-replication problem.



Telomere structure with associated shelterin. From: Calado R, et al. (2009) N Engl J Med. **361**:2353-2365.



hTR core domain including a DNA primer bound to the template (left) and interaction with *T. castaneum* TERT-telomeric RNA/DNA complex. Modified from: Zhang Q, et al. (2011) Proc Natl Acad Sci USA **108**(51):20325-20332

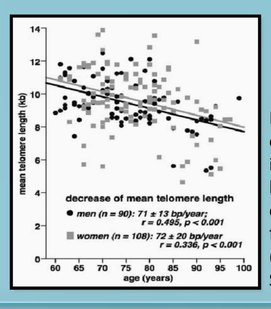


The telomerase complex and its components. From: Calado R, et al. (2009) N Engl J Med. **361**:2353-2365.

2. TELOMERE LENGTH MEASUREMENTS

2.1. Telomere shortening

Telomeres are 15–20 kb but shorten gradually throughout the life[2].



Effect of age and gender on telomere length (left) in peripheral blood lymphocytes from elderly people. Modified from: Canela A, et al. (2007) Proc. Natl. Acad. Sci. **104**, 5300–5305

2.2. Telomere length as a biomarker

- **Biological ageing**
- **General health status and health span**
- **Chronic disease risk**
- **Progression and premature mortality for people aged >60 years**

3. REPLICATIVE SENESCENCE PROMOTES AGING

Critical telomere shortening & loss of function of sheltering components → **Single- and double-strand DNA breaks** → **Constitutive p53 maintains cellular senescence for years[1]** → **Somatic mutations** → **Telomere shortening or Rb/p16/p53 inactive** → **Genomic instability** → **Cellular crisis** → **Reactivation of hTERT** → **Immortal growth state**

Stewart SA, Weinberg RA. (2006) Annu. Rev. Cell. Dev. Biol. **22**:531-57

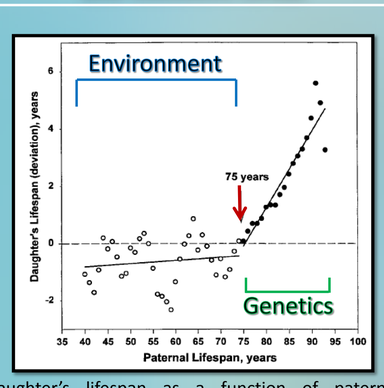
4. LENGTH TELOMERE-RELATED DISEASES

Age-related diseases[3]	Germline mutations in the Terc and Tert telomerase	Mutations in sheltering components
Type 2 diabetes	Dyskeratosis congenital	
Cardiovascular diseases	Aplastic anaemia and leukaemia	
Vascular dementia or Alzheimer	Idiopathic pulmonary fibrosis	Cancer

5. FACTORS THAT MODULATE AGING

5.1. Genetics vs environment factors

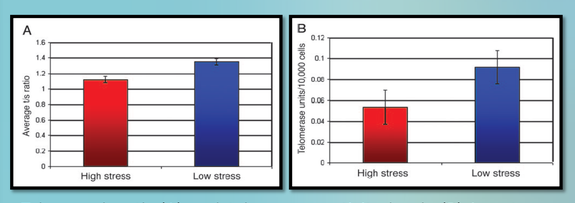
Environment factors (healthy lifestyle behaviours) modulate inflammation and oxidative stress



Daughter's lifespan as a function of paternal lifespan. Modified from: Gavrilova N. and Gavrilov L. (2001) Journal of Anti-Aging Medicine **4**:2, 115-124

5.2. Psychological stress

Difference in "biological age" between high- and low-stress groups: 9-17 years.

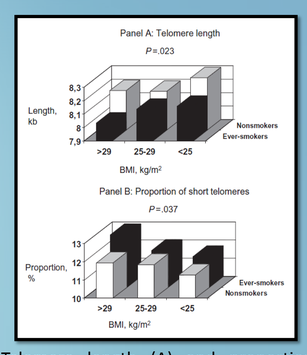


Telomere length (A) and telomerase activity levels (B) in extreme high- and low-stress women groups. From: Epel E.S, et al. (2004) PNAS **101**:17312-17315

5.3. Physical activity, diet and body weight

Anti-aging effects[4]	Pro-aging effects
Anti-oxidative dietary components	Long duration of obesity
Physical activity	
Low LDL cholesterol	

5.4. Smoking



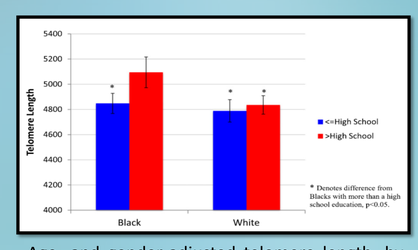
Telomere length (A) and proportion of short telomeres (B) in old age according to body mas index (BMI) and smoking in midlife. From: Strandberg T.E, et al. (2011) J Gerontol A Biol Sci Med Sci. **66A**(7):815-820

5.5. Alcohol intake

The difference in leukocyte telomeres length at old age between alcohol abstainers and heavy drinkers corresponds to a difference in ''biological age'' of 10 years.

5.6. Socio-economic status/education

Relative status reduces risk for multiple diseases of aging[4] and better health.



Age- and gender-adjusted telomere length, by race and education. From: Adler N, et al. (2012) Brain Behav. Immun. **27**:15-21

Conclusions

1. **Aging is dependent on number of cell divisions, not necessarily by chronological time, due to the end-replication problem provides a limited proliferative capacity.**
2. **Telomere shortening in lymphocytes becomes faster in people >50 years of age. In the elderly, telomere shortening is strongly associated with age-related diseases and higher mortality rates.**
3. **The production of immortalized cells, using telomerase activators, may treat chronic and aged-related diseases that are due to telomere-based replicative senescence.**
4. **We have to adopt a healthy lifestyle, especially after age 30, when the low-risk factors most influence telomere length.**

References

1. Stewart SA, Weinberg RA. (2006) Telomeres: cancer to human aging. Annu. Rev. Cell. Dev. Biol. **22**:531-57
2. Shay JW, Wright WE. (2007) Hallmarks of telomeres in ageing research. J Pathol. **211**:114-123
3. Sun Q, et al. (2012) Healthy lifestyle and leukocyte telomere length in U.S. women. PLoS ONE **7**:e38374
4. Tiainen A-MK, et al. (2012) Leukocyte telomere length and its relation to food and nutrient intake in an elderly population. Eur J Clin Nutr **66**:1290-1295