Research Perspective

# Nutrition and lifestyle in healthy aging: the telomerase challenge

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**Abstract: Nutrition and lifestyle, known to modulate aging process and age-related diseases, might also affect telomerase activity. Short and dysfunctional telomeres rather than average telomere length are associated with longevity in animal models, and their rescue by telomerase maybe sufficient to restore cell and organismal viability. Improving telomerase activation in stem cells and potentially in other cells by diet and lifestyle interventions may represent an intriguing way to promote health-span in humans.**

Aging is defined as the progressive decline in physiological functions which leads to increased vulnerability to diseases and death [1]. This is a universal process underlying by many mechanisms and different pathways, whose burden rises to three different phenotypes: normal aging, accelerated aging and successful aging [2]. Despite variability among definitions, "successful aging" is as a multidimensional process encompassing major chronic diseases, major impairments in cognitive, in physical function and sustained engagement in social and productive activities [2,3]. However, reaching old age in good health is not just a "fate effect" but the result of a complex interweaving between environmental and genetic factors [4]. Studies conducted in twins have estimated that approximately 20-30% of an individual's lifespan is related to genetics, while the rest is due to individual behaviors and environmental factors [5,6]. In this contest, nutrition and lifestyle are the most important contributors to longevity and healthy aging [7-11]. Follow a diet rich in vegetables, fruits, nuts, olive oil, fish, a small amount of red wine and exercise at least 20 minutes a day three times a week, avoiding obesity, smoke and alcohol, represents the working recipe for long and healthy life. Many mechanisms and pathways underlie nutrition, lifestyle and longevity including telomere length modulation [12-15].

Telomeres are long sequences of nucleotides at the end of our chromosomes, forming with specific proteins complex, an "end caps" which preserve genome stability and lead a cell to correctly divide [16-18]. Telomeres have been compared with the plastic tips on shoelaces, since they are able to keep chromosome ends from fraying and fusion to each other, which would destroy or interfere genetic information. At each cell division or replication event, telomeres lose some of their length and when they get too short, the cell is no longer able to divide becoming "senescent" [19]. This shortening process triggers a sustaining damage response scrambling with cell health leading to disease risk and cell death [20]. In 1962, Leonard Hayflick revolutionized cell biology when he developed a telomere theory known as the "Hayflick limit", which places the maximum potential lifespan of humans at 120 years, the time at which too many cells with extremely short telomeres can no longer replicate and divide [21,22]. Fifty years later, new science came out opening the door to maximizing our genetic potential. In fact, published data suggested that extremely short or dys-

functional telomeres can be repaired by the enzyme "*telomerase",* which working as a reverse transcriptase, adds nucleotides at the end of each chromosome promoting its stability [22,23]. In 2009, Blackburn, Greider and Szostak received the Nobel Prize for the discovery of "how chromosomes are protected by telomeres and the enzyme telomerase". These discoveries had a great impact within the scientific community, supporting that aging can be potentially delayed by telomerase activation and telomere erosion rate reduction.

In contrast to stem cells which constitutively express low levels of telomerase, normal somatic human cells repress its expression immediately after birth [24-27]. Thus, for a long time, telomere length has been considered as an indicator of cellular senescence, and a potential biomarker of human aging, but studies supporting this role are still contradictory and inconclusive [22,28,29] . More recent genetic studies in animal models have demonstrated that short telomeres rather than average telomere length are associated with age-related diseases and, their rescue by telomerase is sufficient to restore cell and organismal viability [30,31]. In humans, circulating telomerase activity rather than telomeres length is inversely associated with the major cardiovascular disease risk factors [32]. Thus, another concept is coming up, the "telomere stability", a quite different concept from telomere length. For example, patients with Alzheimer's disease do not invariably have shorter telomeres, but their telomeres have significant signs of dysfunction [33-38]. Improving the activity of telomerase enzyme -that can add length back to shorter telomeres, and, in the meantime, protect longer telomeres to ensure stability- seems a way to actually turn back the biological clock. Telomerase has also extra-telomeric functions influencing various essential cellular processes, such as gene expression, signaling pathways, mitochondrial function as well as cell survival and stress resistance [40,41]. Therefore, the presence of active telomerase in stem cells, and potentially in all cells, may be helpful for longevity and good health.

Lifestyle factors known to modulate aging and age-related diseases might also affect telomerase activity. Obesity [42], insulin resistance [43,44], and cardio-vascular disease processes [45,46], which are related to oxidative stress and inflammation, have all been linked to shorter telomeres. Smoking, exposure to pollution, lower physical activity, psychological stress, and unhealthy diet significantly increase the oxidative burden and the rate of telomere shortening [47-53]. So, what a better way to counteract the "biological clock" by reactivating telomerase trough diet and lifestyle interventions? There is a recent paper showing that with intensive lifestyle modification, with a low fat diet, regular physical activity, and mental stress reduction (by yoga and meditation), telomerase activity increases significantly in peripheral blood mononuclear cell (PBMC) [54]. Again, people living in the Mediterranean countries have longer and healthier life as compared with people living in other industrialized countries, and we previously demonstrated that they have also claim longer telomeres and higher telomerase activity in PBMC [55]. It is still unclear if there is a single nutrient or a factor responsible of Mediterranean diet anti-aging properties or the whole, single ingredient foods and lifestyle are the key to "healthspan".

Today, researchers are struggling to find a compound or an "elixir" for long life, while common people are taking dietary supplements with the intent to preserve mental, physical, and emotional health into old age. Most dietary supplement programs include combinations of vitamins, antioxidants, and other constituents, some of which have been shown to have significant health benefits in controlled clinical studies. Specific nutrients provide all the necessary building blocks to support telomere health and extend lifespan. This is the case of folate [56,57], vitamins (B, D, E, C) [58] zinc [59] and polyphenol compounds such as resveratrol [60], grape seed extract and curcumin [61]. Several foods -such as tuna, salmon, herring, mackerel, halibut, anchovies, cat-fish, grouper, flounder, flax seeds, sesame seeds, kiwi, black raspberries, green tea, broccoli, sprouts, red grapes, tomatoes, olive fruit- are a good source of antioxidants. These, combined with a Mediterranean type of diet containing fruits, vegetables and whole grains would help protect our chromosome ends [62-70].

In conclusion, what we eat, how we eat and how much we eat, together with lifestyle significantly, can affect our telomerase/telomere system with a great impact on healthspan. "*Similes cum similibus curantur*" and in nature is still hidden the secret of healthy and long life whereas telomerase could represent the distinctive target.

## Conflict of interest statement

The authors have no conflict of interests to declare.

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