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Review

Telomerase activation: A potential key modulator for human healthspan and longevity

Virginia Boccardi, Giuseppe Paolisso*

Department of Internal Medicine, Surgical, Neurological, Metabolic Disease and Geriatric Medicine, VI Division of Internal Medicine, Second University of Naples, P.zza Miraglia 2, Naples 80138, Italy

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ABSTRACT

The elderly population is increasing progressively. Along with this increase the number of age related diseases, such as cardiovascular, neurodegenerative diseases, metabolic impairment and cancer, is also on the rise thereby negatively impacting the burden on health care systems. Telomere shortening and dysfunction results in cellular senescence, an irreversible proliferative arrest that has been suggested to promote organismal aging and disabling age-related diseases. Given that telomerase, the enzyme responsible for maintaining telomere lengths, is not expressed at levels sufficient to prevent telomere shortening in most of our cells, telomeres progressively erode with advancing age. Telomerase activation, therefore, might serve as a viable therapeutic strategy to delay the onset of cellular senescence, tissue dysfunction and organismal decline. Here we analyze the more recent findings in telomerase activation as a potential key modulator for human healthspan and longevity.

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1. Introduction

Ageing is a natural process characterized by a gradual decline in the function of organs and organ systems ultimately leading to an increased risk of diseases and death. Many mechanisms have been proposed to contribute to aging process. A stress response called cellular senescence, has been hypothesized to be a primary contributing factor to age-associated tissue dysfunction, reduced regenerative capacity and diseases (Hayflick, 1976; Collado et al., 2007). In fact, senescent cells have been found to increase in mice (Baker et al., 2011), primates, humans organs and tissues with increasing age, while suppressing this accumulation it has been shown to improve healthspan in mice, supporting this hypothesis (Collado et al., 2007; Herbig et al., 2006; Jeyapalan et al., 2007).

During the last 20 years, mounting evidences suggest that the progressive loss of telomeric repeats of chromosomes may function as an important timing mechanism during the aging process in various species (Campisi et al., 2001; López-Otín et al., 2013). Numerous epidemiological studies show that shorter telomeres in humans are associated with many age related diseases such as cancer, cardiovascular diseases (atherosclerosis, hypertension, myocardial infarction), cognitive decline, diabetes and overall mortality (Armanios, 2013; Fyhrquist and Saijonmaa, 2012; Epel et al., 2009).

Strikingly, patients affected by dyskeratosis congenital and idiopathic pulmonary fibrosis, display chromosomal instability and accelerated cellular senescence, particularly in tissues at high

* Corresponding author. Tel.: +39 0815665135; fax: +39 0815665303.
E-mail address: giuseppe.paolisso@unina2.it (G. Paolisso).

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proliferative activity (Garcia et al., 2007). These hereditary diseases are caused by mutations in telomerase, a special ribonucleoprotein reverse transcriptase critical for telomere length maintenance and stability (Mason et al., 2005). While telomerase in human tissues is active only in stem and germinal cells, also a somatic cell without a functional telomerase expression shows accelerated telomere shortening and dysfunction (Hayflick and Moorhead, 1961; Harley et al., 1990).

Partial or complete loss of telomerase function dramatically accelerates aging in mice andit is associated with age-related disorders in humans (Garcia et al., 2007). Thus, it has been hypothesized that the re-activation of telomerase may represent a promising mechanism to reverse or at least delay cellular senescence, potentially leading to healthspan extension.

2. Cellular senescence and telomeric aging

Cellular senescence was first described by Hayflick and Moorfield in 1961 who observed that adult and differentiated cells in cultures do not have the ability to proliferate indefinitely, but instead arrest irreversibly following a limited number of cellular divisions (reviewed in Campisi and d'Adda di Fagagna, 2007). Senescence may contribute to *in vivo* organismal aging phenotypes; in fact, as in culture, senescent cells accumulate with increasing population doublings in organism normal tissues (Herbig and Sedivy, 2006; Jeyapalan et al., 2007). For example, greater than 15% of dermal fibroblasts in very old baboons show senescent phenotypes as determined by the presence of damaged telomeres and increased expression of other senescence biomarkers (Herbig et al., 2006; Jeyapalan et al., 2007).

Telomeres are specialized structures localized at very ends of eukaryotic chromosomes whose primary functions are to prevent a cell from sensing linear chromosome ends as breaks in the DNA. In vertebrates, telomeres are composed of tandem repeats of TTAGGG which together with specialized proteins, form a cap like structure thereby suppressing the activation of DNA damage response (DDR). However with every cell division cycle, telomeres progressively erode which eventually causes one or more telomeres to become dysfunctional and, as a result, initiate a permanent DDR. Telomere shortening thus has been proposed to function as a "mitotic clock" that measures how many times a cell has divided (Sfeir et al., 2005; de Lange, 2002).

Because of this progressive and cell division dependent telomere erosion, telomeres length is frequently being used as a marker of somatic cells replicative history. In general telomeres length reflects the balance between additions and losses of TTAGGG repeats (de Lange, 2002). While telomere loss is typically attributed to "the end replication problem" and it is clearly accelerated by many other factors, such as oxidative stress, replication stress and inflammation (von Zglinicki, 2002). Epidemiologists measured telomere length in cohort studies and investigated its association with demographics, behaviors, indicators of health, and other molecular markers. Based on these studies it has been suggested that measurement of telomere length in white blood cells (LTL) can be used as a surrogate marker for relative telomere length in many other tissues (Blackburn, 2000). LTL associations have only been found for age, gender, and race, whereas association to most other phenotypes, such as smoking, alcohol consumption, physical activity, diets, socioeconomic status and education, body mass index, lipid levels, markers of glucose metabolism, and blood pressure was inconsistent across studies (Sanders and Newman, 2013). Thus, whether telomere length may be considered as a biomarker of aging and age related diseases is still not clear (Sanders and Newman, 2013); however shorter telomeres have been found in many age-related diseases such as, diabetes, cardiovascular disorders, and neurodegenerative diseases, while its role in predicting longevity and lifespan is still contradictory (von Zglinicki and Martin-Ruiz, 2005; Mather et al., 2011). Interestingly, although mice have very long telomeres compared with humans (Gomes et al., 2011; Wright and Shay, 2000), they have a much shorter maximal lifespan (5 years in mice) (Brown-Borg and Bartke, 2012) compared to us (the oldest confirmed recorded age for any human is 122 years). Thus telomere length *per se* does not predict lifespan, although it has been suggested that the telomere rate of telomere erosion does (Haussmann et al., 2003). Telomere shortening rates are apparently not constant but instead are influenced by a competing set of positive and negative regulators of telomere length. In the elderly (>60), telomere attrition is significantly associated with higher mortality rates, both from infectious and cardiovascular diseases (Cawthon et al., 2003). Indeed, more recently, based on studies in mice, it has been suggested that the rate of increase of short telomeres, rather than average telomere length, predicts longevity in mammals. (Vera et al., 2012).

3. Telomerase and aging

Telomerase is a multiprotein complex containing a reverse transcriptase catalytic subunit (TERT) and an associated telomerase RNA template (TERC). As a reverse transcriptase, telomerase adds DNA repeats to chromosome ends, counteracting telomere shortening associated with replication and degrading activities (Blackburn, 2001). Human TERC (hTERC) is ubiquitously expressed in germ line cells and stem cells (Feng et al., 1995), while human TERT (hTERT) is expressed only in telomerase-positive cells (Wright et al., 1996; Shay and Bacchetti, 1997). This is because, telomerase activity is repressed in most normal human somatic tissues shortly before birth (Kim et al., 1994). Telomerase activity, however, is detectable in highly proliferative cells such as primary germ line cells (Wright et al., 1996; Chiu et al., 1996), activated lymphocytes, smooth muscle cells, and fibroblasts (Bayne and Liu, 2005). Even if telomere length is heritable (Slagboom et al., 1994), changes in telomerase activity may regulate telomeres shortening rate, telomere stability and potentially lifespan. Starting from these assumptions, hTERT has been overexpressed in several differentiated cell types with the aim to maintain their mitotic competence. Through hTERT over-expression, immortalized retinal pigment epithelial cells, dermal fibroblasts, endothelial cells, osteoblasts, stromal cells, myometrial cells and neuronal progenitors, have been generated. Over-expressing hTERT in telomerase-negative cells, telomerase activity was reconstituted to prevent excessive telomere shortening and to keep cell proliferation going almost indefinitely (Masutomi et al., 2003). Thus, it has been hypothesized that telomerase, mainly acting on short telomeres can slow down inescapable telomere shortening and consequently delay senescence (Stewart et al., 2003).

Subsequent to the *in vitro* observations, investigators attempted to translate these promising finding also in *in vivo* models. Studies demonstrated that TERT or TERC knockout mice with critically short telomeres were characterized by an increased incidence of age-related diseases and premature tissue degeneration, affecting tissues with higher cellular turnover (Blasco, 2003). Telomerase knockout mice displayed a decrease in mean telomere length and a higher percentage of short telomeres in several organs which correlated with an incapacity of tissues to regenerate. (Hao et al., 2005; Armanios et al., 2009; Strong et al., 2011).

In humans, mutations in the hTERC gene are associated with autosomal dominant dyskeratosis congenital (Vulliamy et al., 2001). Patients with this syndrome display premature ageing traits including grey hair, dental loss, bone marrow failure, cirrhosis, lung disease and skin cancer. In addition, heterozygous mutations in the