Florea: Jurnal Biologi dan Pembelajarannya
Vol. 11, No. 2, November 2024, pp. 54~61
ISSN 2355-6102; e-ISSN 2502-0404 DOI: 10.25273/florea.v11i2.21771

A Systematic Review of Telomere Biology & Telomerase as a Novel Therapeutic Tool for Ageing & Cancer

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Article Info

Article history:

Received August 11, 2024
Revised September 23, 2024
Accepted November 30,2024

Keywords:

Telomere
Telomerase
Oxidative Stress
Telomerase activators
Aging

ABSTRACT

Advances in medical science has lead to increase in life expectancy of human beings all over the world. Deterioration of physiological functions is typically associated with ageing process.This often manifests as various diseases which eventually creates a burden on health infrastructure.Telomere attrition is a phenomenon which involves shortening of telomeres with each cycle of cell division.The phenomenon of “Telomere Attrition” is a “Bi edged sword” as while being a protective shield for the genome on one hand, it also is the cause of many senility related degenerative disorders. As the role of telomere biology is well established in ageing,current research therefore aims to develop means to reduce telomere attrition,thereby reducing ageing & age related diseases.This review will focus on summarising the role of telomere biology in ageing & age related diseases while highlighting the recent advances in research aiming towards enhanced longevity & healthy ageing.This review will further emphasize on telomere targetted therapeutics such as telomerase activators & tankyrase inhibitors while also highlighting the role of antioxidative & antiinflammatory agents alongwith indirectly related approaches such as statins.

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1. INTRODUCTION

Globally the population of individuals above the age of 60 years is expected to reach around 2.1 billion by 2050. This is primarily attributed to the increase in average life expectancy in almost all the developed countries of the world [1]. Increased life expectancy in turn is causing a demographic shift which in turn is causing an increased burden on our healthcare system [2]. Process of aging leads to an overall functional decline leading to cancer, neurodegenerative diseases, diabetes mellitus & cardiovascular diseases [3],[4],[5]. After the age of 60 years for every 5 years increase in age ,the incidence of such degenerative diseases double. Moreover advancing age has been designated as an independent risk factor for major life threatening disorders by WHO, for example advancing age is considered an equally significant risk factor as smoking when it comes to cardiovascular disease [6].

It is therefore of utmost importance to develop strategies to mitigate risk of developing age related degenerative conditions.This in turn will help in promoting healthy aging patterns, thereby promoting quality of life of individuals alongwith increased lifespan [7]. The ultimate goal of all such efforts should be to increase healthspan (period of life spent free from age related degenerative diseases) alongwith lifespan [8]. A significant disparity has been observed over the the past few decades between the rate at which life expectancy has increased & healthspan has increased. Healthspan has not increased as fast as life expectancy of the population in most developed countries. This is an extreme cause of concern,considering the fact that most developed countries in the world have a significant population in the geriatric age group.It therefore poses a significant challenge to prioritize & ensure healthy life span for this population in [9].

The aging process has been attributed to 9 variables which are believed to be the primary contributors to the process[10]. These are:

1. Genomic instability.
2. Telomere shortening.
3. Mitochondrial dysfunction.
4. Deregulated nutrient sensing.
5. Changes in epigenetic regulation.
6. Loss of proteostasis.
7. Cellular Senescence.
8. Stem cell exhaustion.
9. Altered intercellular communication.

Each cycle of cell division contributes to diminution of the protective ends of chromosomes called telomeres. Over the past few years the phenomenon of “Telomere Attrition” has garnered significant attention in gerontological research. This phenomenon is a highly regulated cluster of events & as the telomeres reach a”critical length”,it signals the cell to undergo senescence & apoptosis,thereby safeguarding the individual against any kind of genetic abnormalities or irregularities [11]. Although this has a protective side but on the contrary it also accelerates tissue degradation thereby causing age related disorders. As reported by several researchers, counteractive strategies to reduce telomere attrition are being targetted for devising therapeutic techniques that can mitigate occurrence of age related degenerative diseases [12], [9], [13]. Telomere dynamics targetted therapies can therefore be a promising avenue of research in gerontology [14].

2. METHOD

For this review, we systematically searched for published articles on Telomere biology with emphasis on its utilisation as a therapeutic intervention for ageing & cancer.. This was done by taking into account the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and by following the steps “identification”, “screening”, “eligibility” and “inclusion”.Accordingly, we considered the current PRISMA recommendations and checklist in the design and conduct of this review. The literature search was executed using the PubMed database.For identification of relevant papers, we wanted the search to be sensitive and potentially over-inclusive so that no relevant articles are missed.Therefore, only terms, “telomerase , “telomere*”, “ageing” & “therapeutic target” combined using the Boolean operator and, were entered in the respective search interfaces.The asterisk wildcard symbol (*) was used for search term truncation. All articles were evaluated in full length in a standardized manner.The criteria for study selection were defined previously. We included studies that were written in English only and that appeared either in a scholarly journal or in an open access preprint repository.

3. RESULTS AND DISCUSSION

3.1 Telomere Shortening:Kingpin of Cellular Aging

Telomeres are thymine & guanine rich six nucleotide repeat sequence at the ends of chromosomes in the form of a cap like structure [15] which protect the chromosomes & prevent the cell from initiating a DNA damage response. DNA polymerase has its own inherent limitations as a result of which telomeric DNA cannot be replicated completely.This phenomenon in turn leads to shortening of the telomeres with each cycle of cell division [16]. This progressive shortening of the telomeres lead to a point where the telomeres reach a length called”critical length”. At this critical length the telomeres cannot shorten further & therefore it causes genomic instability & therefore it triggers asenescence & apoptosis for the cell [17]. DNA replication is unidirectional extending from 5’ to 3’ direction. This process requires an RNA primer without which DNA replication cannot occur. But DNA polymerase while replicating DNA is unable to replicate completely replicate the 3’ ends

of the chromosome. This phenomenon is known as the “end replication problem” (Levy et al., 1992). The answer to the “end replication” problem remained a mystery until 1985 when Greider & Blackburn discovered “Telomerase” which is considered as milestone in telomeric research. Telomerase or “Telomere terminal tranferase” is a ribonucleoprotein that elongates the 3’ end of the chromosomes with TTAGGG repeat sequences facilitating extension of telomere length (Greider and Blackburn, 1985). Experiments conducted by certain researchers have revealed that in late generation specimens of successive generations of mice,spermatogenesis was impaired alongwith a reduced proliferative capacity in bone marrow & spleen . The cause of these deficits was found to be due to significant chromosomal aberrations and telomeric attrition which in turn highlighted the importance of telomerase & telomeres in protecting genomic integrity in organ systems with a high turnover rate of replication (Lee et al., 1998). Martinez & Blasco reported that telomerase is most active in stem cells & a few progenitor cells,whereas in somatic cells the activity of telomerase is practically negligible [12]. Lack of telomerase in somatic cells therefore leads to telomere shortening over time with each successive cell division,thereby acting as a “Biological Clock” as the number of cell divisions are capped & is possible until the telomere reaches a critical length. The maximum number of times that a cell can undergo division as limited by the telomeric critical length is known as the “Hayflick Limit” [15]. Lack of telomerase in somatic cells is also considered a boon in disguise as it has been found to be a barrier for uncontrolled cell division leading to numerous varieties of cancer [18]. About 85% of cancer types have been found to reactivate telomerase, allowing cancer cells to maintain their telomeres and thus enabling them to proliferate indefinitely [10].

3.2 Mechanisms By Which Telomeres Influence Cellular Ageing.

3.2.1 Telomere Mitochondrial Axis

Telomere shortening can disrupt normal cellular function and is implicated in the increased production of ROS, which further contribute to mitochondrial dysfunction and cell aging [12]. On the other hand, mitochondria are the primary producers as well as targets of ROS. An excessive accumulation of ROS can lead to damaged mitochondrial DNA (mtDNA), which in turn may induce further mitochondrial dysfunction. This dysfunction can exacerbate ROS production, creating a detrimental feedback loop that significantly contributes to cell aging and age-related pathologies [19]. One proposed mechanism involves the tumor suppressor protein p53. Dysfunctional telomeres can trigger the activation of p53, which in turn may inhibit the transcription of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), which is the primary regulator of mitochondrial biogenesis and function. Reduced PGC-1α levels can lead to mitochondrial dysfunction and increased ROS production [15]. Cells with critically short telomeres can undergo senescence, which is often accompanied by a pro-inflammatory senescence associated secretory phenotype (SASP). SASP can exacerbate mitochondrial dysfunction and further increase oxidative stress [7]. In short, the telomere-mitochondrial axis captures the dynamic crosstalk between telomeres and mitochondria, both vital to cellular aging.

3.2.2 The Sheltrin Complex

The sheltrin complex plays a very important role in telomere dynamics. It is a complex of several proteins that bind specifically to telomeric DNA & prevents it from being identified as DNA breaks & also a false positive DNA damage response from being triggered [19]. Recombination,end to end fusions & aberrations in chromosomes,telomere uncapping have been observed in the event of dysfunction of sheltrin complex leading to gross genomic instability [20]. TRF 1 & TRF 2 are two factors which are essential for functioning of the sheltrin complex. TRF 2 in particular plays an important role in inhibiting the ATM kinase signalling pathway which is considered as the first responder for DNA breaks [8]. POT 1 is another crucial component which inhibits the ATR kinase mediated DNA damage response. This constant interplay between telomerase activity, telomere length & the sheltrin complex activity maintains a fine balance of cellular stability,which in turn is essential for the sustainance of life. The understanding of this interplay has also offered us with therapeutic targets, which are being explored as a possible cure for cancer.

3.2.3 Oxidative Stress & Telomeres

The “Free Radical Theory of Aging,” introduced in the 1950s by Denham Harman, suggests that the aging process in organisms is due to the cumulative cellular damage caused by free radicals over time. Free radicals, especially reactive oxygen species (ROS), can inflict damage to

various cellular macromolecules, with DNA being a prime target [20]. This influential approach laid the foundation for subsequent research on aging. Over time, it has been refined and adapted according to emerging insights.Oxidative stress, emerging from an imbalance between the production of ROS and the cell's antioxidative defense mechanisms, is significantly detrimental to telomeric regions. Telomeres, with their guanine-rich sequences, are particularly prone to oxidative modifications due to the raised susceptibility of guanine to oxidative damage [21]. One notable outcome of this vulnerability is the formation of 8-oxo-guanine (8- oxoG) lesions, which is a prevalent DNA damage type caused by ROS. A study by Fouquerel et al. demonstrated that 8-oxoG in the telomeric region has a dual role, either hindering telomerase mediated elongation when incorporated as 8-oxodGTP or promoting telomerase activity by destabilizing G-quadruplex structures when preexisting in telomere DNA. This dual impact of 8-oxoG on telomere function is a key factor in determining whether a cell will experience telomere-related dysfunction or maintain its genomic stability [9].

3.2.4 Telomeres & Chronic Inflammation

Over the past decade, the complex interplay between telomere dynamics and chronic inflammation has gained further attention. Evidence suggests that telomere length is closely tied to chronic inflammatory states. Specifically, elevated levels of proinflammatory cytokines, such as IL-6 and TNF-α, seem to trigger accelerated telomere shortening [14],[16]. One proposed mechanism suggests that chronic inflammation directly affects telomerase activity. Elevated cytokine levels might suppress telomerase activity, thereby limiting the enzyme's ability to counteract telomere shortening and leading to cellular senescence [20]. This senescence can further enhance inflammation by releasing senescence-associated secretory phenotype (SASP) factors, which induces a feedback loop between inflammation and telomere attrition [21] Jurk et al. demonstrated in mice that chronic inflammation, induced by the knockout of the nfkb1 subunit of the NF-κB transcription factor, exacerbates telomere dysfunction and cell senescence through a feedback loop involving NF-κB, COX-2, and ROS, thereby leading to premature aging and reduced tissue regeneration in liver and gut [22]. These findings underline the importance of managing chronic inflammation to preserve telomere integrity, potentially delaying the onset of age-related diseases.

3.3 Telomere Targetted Therapeutics

3.3.1 Telomerase Activators

Telomerase activation has gained prominence as a potential therapeutic approach for extending telomere length and subsequently, cellular healthspan. As Telomerase catalyzes the addition of TTAGGG Tankyrase inhibitors are molecules designed to inhibit the function of tankyrases (Tankyrase 1 and Tankyrase 2), which are enzymes in the poly (ADP-ribose) polymerase (PARP) family (Smith et al., 1998; Smith and de Lange, 2000). A fundamental work in this field was conducted by Huang et al. showing that tankyrases regulate the stability of axin, which is a key component of the β-catenin destruction complex. By using a small-molecule inhibitor of tankyrase, XAV939, they showed stabilization of axin and downregulation of Wnt signaling (Huang et al., 2009). The Wnt pathway is indirectly connected to telomere biology through its regulation of adult stem cell function. Essential for stem cell selfrenewal and maintenance, Wnt signaling indirectly contributes to telomere length preservation during stem cell divisions. Consequently, any dysregulation in Wnt signaling can affect these regenerative processes, potentially destabilizing telomeres and thereby impacting aging and the onset of age-related diseases [23].

Nucleotide repeats to chromosome ends, it counteracts telomere attrition resulting of cellular divisions (Greider and Blackburn, 1985; Tsoukalas et al., 2019). Few telomerase activators of interest are

a) TA-65

A prominent agent of telomerase activators is TA-65, a compound derived from the Chinese herb *Astragalus membranaceus*. Studies suggest that TA-65 might activate telomerase, potentially leading to telomere extension [24],[25]. In a randomized, double-blinded, placebo-controlled trial, involving 117 cytomegalovirus-positive adults, supplementation with a low dose (250 U) of the telomerase activator TA-65 led to a significant increase in telomere length over 1 year, while the placebo group experienced a significant reduction in telomere length. A higher dose (1000 U) of TA-65 showed a non-significant trend toward telomere lengthening [26].

b) Cycloastragenol

Another postulated telomerase activator is Cycloastragenol (CAG), which is also a compound derived from the *Astragalus membranaceus* plant. Idrees et al. examined the role of CAG in activating telomerase and its impact on the Klb (β-Klotho) gene in mouse ovaries, a key factor in female fertility and aging. Molecular simulations confirmed CAG's binding to the hTERT model, and its subsequent application rejuvenated telomerase activity, restoring ovarian health in age-induced and Doxorubicin-induced damage models. These findings highlight CAG's potential in addressing female infertility via TERT-dependent β-Klotho regulation [27]. However, while preliminary findings seem promising, comprehensive clinical trials are essential to ascertain the efficacy and safety in promoting telomere elongation and the associated health benefits.

3.3.2. Telomerase gene therapy

Telomerase gene therapy is an emerging approach that seeks to address cellular aging by directly modulating telomerase activity in cells. In an in vivo study conducted in mice, telomerase gene therapy using an adeno-associated virus to express TERT led to significant health improvements and reduced aging markers without elevating cancer incidence. Remarkably, the treatment extended the median lifespan by 24% in 1-year-old mice and 13% in 2-year-old subjects, underscoring the potential of TERT-focused interventions in aging mitigation [27].Certainly, direct telomerase gene therapy has not been tested in humans due to safety and ethical concerns, unknown long-term effects, and the technically challenging delivering mechanism. Nevertheless, abandoning the telomerase gene therapy approach may be premature given its potential to revolutionize aging and disease treatment.

3.3.3.Tankyrase Inhibitors

3.3.4. Antioxidants

Oxidative stress and chronic inflammation are significant contributors to cellular aging; there is growing evidence linking both to accelerated telomere attrition [7], [28]. Antioxidants neutralize free radicals, which can inflict damage on cellular structures [19], including DNA and telomeres. This protective effect can be essential in countering telomere shortening, and thereby possibly delaying cellular aging [23] Some potent antioxidants are

a) Vitamin C

Vitamin C, a potent water-soluble antioxidant, scavenges free radicals in the aqueous cellular environment, preventing damage to critical biomolecules. Notably, it can also augment the enzymatic action of telomerase, potentially supporting telomere elongation (Furumoto et al., 1998). Recent studies underscore its capability to enhance telomerase activity, elucidating its integral role in telomere preservation.

b) **Vitamin E**

Vitamin E is a lipid-soluble antioxidant, primarily located in cell membranes, with its primary role to protect polyunsaturated fatty acids (PUFAs) from lipid peroxidation, which is a significant source of DNA damage, including telomeres [29]. In the CORDIOPREV study, involving 1.002 cardiovascular disease patients, dietary intake of vitamin E was found to significantly influence leukocyte telomere length, a biomarker for cellular aging. Patients with inadequate vitamin E intake exhibited shorter telomere length compared to those with sufficient intake [29].

c) Polyphenols

Polyphenols, widely present in sources such as fruits, vegetables, or tea, exert antioxidant effects by neutralizing oxidizing species. Resveratrol, a polyphenol found highly concentrated in berries, nuts, grapes, and red vine, exerts antioxidant and anti-inflammatory effects [24], [21].The anti-inflammatory effect is potentially facilitated through the action of cyclooxygenase, AP1, and NF-κB, although the precise mechanisms remain to be elucidated. The antioxidant effects occur via activating the SIRT1 pathway [11], also a recognized positive regulator of telomere length [30]. it supports cellular defense mechanisms against oxidative and metabolic stress and enhances DNA repair [30].

3.3.5.Antiinflammatory agents

Prolonged inflammatory responses can increase oxidative stress and DNA damage, potentially accelerating telomere attrition. Several studies have been investigated anti-inflammatory agents and its influence on telomere biology, being discussed in the following section

a) Omega-3 fatty acids

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential polyunsaturatedfatty acids (PUFAs) recognized for their anti-inflammatory properties. Emerging research indicates a potential role for these fatty acids in telomere biology [31], [21]. A prospective cohort study by Farzaneh-Far et al., examining 608 patients with stable coronary artery disease found that individuals with higher blood levels of EPA and DHA had reduced rates of telomere shortening over a 5-year period, suggesting a protective effect of omega-3 fatty acids on telomeres. The proposed mechanisms underlying these observations include the ability of omega-3s to reduce oxidative stress and systemic inflammation. Moreover, omega-3 fatty acids might modulate the activity of telomerase, and thereby extending telomeric DNA [6]. O'Callaghan et al. investigated the potential of omega-3 fatty acid supplementation to attenuate telomere shortening in elderly individuals with mild cognitive impairment. The findings suggest that omega-3s might play a role in telomere maintenance, which could have implications for aging and neurodegenerative diseases. While the study emphasizes the connection between telomere length, cognitive decline, and omega-3 supplementation, it adds to the growing body of evidence on the potential benefits of omega-3s in cellular aging [32].

b) Statins

Statins are a class of drugs commonly prescribed to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase [11], thereby reducing the risk of cardiovascular diseases [33]. The relationship between statins and telomere length has been an area of interest, but the evidence is not entirely conclusive. However, there is the assumption that they might influence telomere length through anti-inflammatory and antioxidative effects or by increasing the activity of telomerase, the enzyme responsible for maintaining telomere length. Some observational studies have suggested that statin users tend to have longer telomeres compared to non-users, which could imply a potential protective effect of statins on cellular aging [33]. In a cross-sectional study analyzing 3.496 adults, no significant difference in leukocyte telomere length between statin users and nonusers was observed. A non-statistically significant trend indicated longer telomeres with prolonged statin use, but potential biases could not be out [27].

c) **Spermidine:-** Spermidine is a polyamine implicated in cellular autophagy and anti-inflammatory pathways [26], has been demonstrated to influence telomere stability and elongation. Further, spermidine is associated with its cardio-protective effects. An in vivo study showed that spermidine intake in mice enhances cardiac autophagy, mitophagy, and mitochondrial respiration, and reduces cardiac hypertrophy and systemic inflammation, which are closely linked to age-related cardiovascular disease [13]. Also, a prospective cohort study emphasized the potential cardioprotective effect, which might be mediated by its influence on oxidative stress markers, although the exact mechanism was not totally comprehended [15].

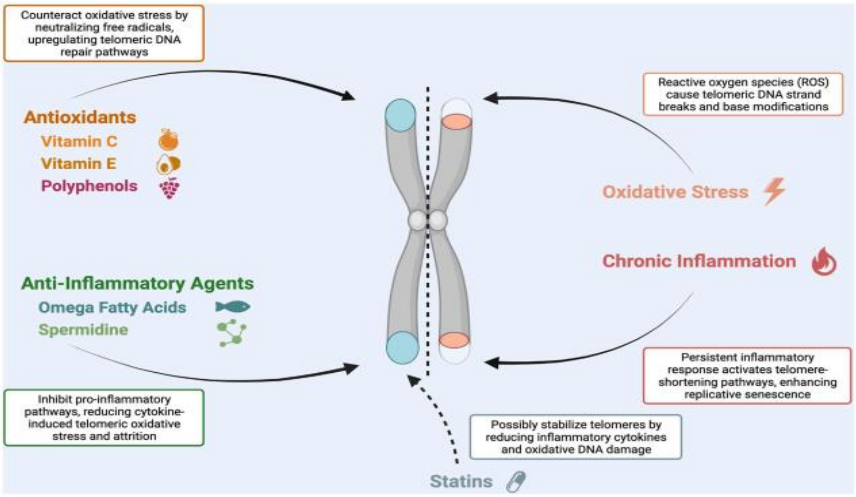

Figure 1. Role of antioxidants & anti-inflammatory agents in preventing telomere attrition.

4. CONCLUSION

Over the past decades, medicine has already undergone a notably transformation, shifting from a “sick care” approach, which centered mainly on the treatment of diseases after manifestation, to a “healthcare” paradigm that proactively identifies and mitigates specific risk factors to prevent the manifestation of diseases. Nevertheless, considering the demographic shift towards a progressively aging population worldwide, an even more health-focused approach must be pursued to not only prevent a collapse of the healthcare system but also other socioeconomic structures. A deep understanding of the mechanisms and pathological processes involved in aging is crucial not only for refining therapies for age related diseases but also for positively influencing the aging process, thereby extending the prospect of a longer, active lifespan. In this context, the telomere complex seems to have a pivotal role. Consequently, unraveling the complexities of telomere biology could unlock potential strategies for tackling age-associated diseases and modulating the aging process itself. Although the described therapeutic approaches and interventions targeting telomere dynamics show some promise, further high-quality human studies and detailed investigations are needed to substantiate any recommendations.

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