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Function of telomeres in aging and anti-aging

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Abstract

Telomeres play a important role in the aging process. Telomeres normally shorten would lead to cellular senescence and the decline of various bodily functions in human. Application of interventions could reduce the rate of aging.

In this review paper, we hope to the find ways in preserving telomere length and function roles of telomeres in aging and anti-aging programs.

Keywords: Telomere; Telomerase; Anti-Aging; P53 Protein; Proteostasis; Stem cell

1. Introduction

Telomeres, the protective caps at the ends of our chromosomes, play a critical role in the aging process (Shammas, 2011). As human age, telomeres naturally shorten, eventually leading to cellular senescence and the decline of various bodily functions (Zhu, *et al*., 2019). However, recent scientific advancements have shed light on the potential of telomeres as targets for anti-aging interventions (Semeraro, *et al*., 2020). We explore the role of telomeres in aging and the emerging field of anti-aging programs aimed at preserving telomere length and function.

In the early 1930s, a scientist named Hermann Muller proposed the concept of telomeres, which he referred to as "terminal genes" (Muller, 1930). However, it wasn't until the 1970s and 1980s that the true nature and significance of telomeres were elucidated (Chuaire, 2006). In 1971, Elizabeth Blackburn and Joseph Gall made a critical observation while studying the chromosomes of a single-celled organism called *Tetrahymena thermophila (T. thermophila)* (Blackburn & Gall, 1978). They noticed that the ends of the chromosomes had unique repetitive DNA sequences that were conserved across species. These repetitive sequences were distinct from the genes present in the body of the chromosome (Blackburn & Gall, 1978). . Building on this initial observation, Blackburn, along with her graduate student Carol Greider, conducted further investigations in the early 1980s. They focused on a specific organism, Tetrahymena, which had large and easily detectable telomeres (Greider & Blackburn, 1987).

By DNA sequencing, Blackburn and Greider determined the precise sequence of the repetitive DNA at the ends of *T. thermophila* chromosomes. They found that the sequence consisted of tandem repeats of a short DNA motif. Telomeres are specialized structures located at the ends of chromosomes, which consist of repetitive DNA sequences and associated proteins that protect the integrity of the chromosomes. Telomeric DNA consists of tandem repeat sequences, with the terminus ending in a single-stranded guanine nucleotides rich 3' overhang. The tandem repeat sequences are varies from species to species and are "TTAGGG" in vertebrates. Telomeres play an important part in eukaryotic cells; they are important in maintaining the stability of the genome and ensuring the accurate replication of DNA during cell division. The concept of telomeres was first introduced by McClintock and Muller in 1930's inferred the unique end

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structure of chromosomes play a crucial role in preventing chromosome end fusion. In fact, telomeres maintain the integrity of chromosomes and stop chromosome ends behaving as random breaks, otherwise they will activate the DNA damage checkpoints and generate inter-chromosomal fusions.

Specialized structures were adopted in telomeres, the 3'overhang folds back on itself to form the T-loop and with one strand displaced to form the D-loop (Griffith et al., 1999) and telomeres are capped at least 6 proteins subunits (TRF1, TRF2, TPP1, POT1, TIN2, and RAP1), collectively known as Shelterin, that physically shield the DNA, inhibit DNA damage signaling from the telomere ends and prevent DNA repair programs from fusing end via recombination or classical/alternatives non-homologous end joining, and regulate the access and activity of telomerase at the termini (de Lange, 2018).

2. Function of telomerase

In the early 1980s, after the discovery of telomeres, Blackburn and Greider sought to understand the mechanism by which telomeres are maintained and prevent their shortening. They hypothesized the existence of an enzyme that could replenish telomeric DNA, compensating for the loss during replication. In 1984, Greider, working in Blackburn's laboratory, isolated an enzyme from *T. thermophila* that had the ability to add repeated DNA sequences to the ends of chromosomes. This enzyme was later named telomerase.

Telomerase is a ribonucleoprotein that acts on the 3' overhang of telomeres, it encompasses a highly conserved reverse transcriptase (TERT) and a template RNA component (TERC). Using the 3'overhang of telomeres as a primer to align with TERC sequences, TERT adds telomeric repeats to chromosome ends, thus lengthening the telomeres. The major function of telomerase is to compensate for the "end replication problem" of conventional DNA polymerase to replicate chromosome. During DNA replication, the conventional DNA polymerases are unable to fully replicate the ends of chromosomes, resulting in the progressive shortening of telomeres with each cell division. This shortening is a natural consequence of the "end replication problem". By extending the telomeres, telomerase helps to prevent the loss of genetic information and allows cells to continue dividing. This is particularly important for cells with high proliferative capacity or cells that need to be constantly replenished, such as stem cells and certain immune cells. Telomerase activity is tightly regulated, with most somatic cells in the body having low or no telomerase expression, which contributes to the limited replicative lifespan of these cells, which also known as "Hayflick limit". "Hayflick limit" refers to the finite number of times (around 50 cell divisions on average) a normal human cell population can divide before undergoing cellular senescence. This limit is associated with telomere shortening and represents a fundamental aspect of cellular aging and lifespan. On the other hand, telomerase was found to be highly active in germ cells, stem cells, and most cancer cells. The reactivation of telomerase in cancer cells allows them to overcome the Hayflick limit and continue proliferating indefinitely, contributing to the immortality and uncontrolled growth characteristic of cancer.

2.1. Roles of telomere in Aging

Aging is a complex biological process accompanied by a gradual decline in physiological functions and an increased susceptibility to age-related diseases. Telomeres, the protective caps at the ends of chromosomes, have emerged as crucial players in cellular senescence and aging. Throughout the years, scientists have been intrigued by the factors contributing to aging and have discovered that telomeres play a crucial role in this intricate phenomenon.

During each round of DNA replication, telomeres undergo gradual shortening due to the end replication problem, where the DNA polymerase cannot fully replicate the very ends of the linear chromosomes. Telomeres, which are limited in nature, act as a barrier to cellular immortality. However, when telomere function is compromised, it coincides with a decline in fitness associated with aging and the development of genome instability that can lead to cancer. In fact, telomere attrition is considered one of the nine cellular and molecular hallmarks of aging (López-Otín et al., 2013). Besides, telomere attrition, the other eight of the nine hallmarks of aging includes genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

The TERC and TERT knockout mouse models have played a crucial role in studying the roles of telomere and telomerase in aging. These models have provided significant insights into the molecular biology of telomeres and their impact on health and disease.

The TERC and TERT knockout mouse models have confirmed the essential role of telomeres in aging. They have shown that telomere dysfunction accelerates signs of aging, including shortened life expectancy, an aged appearance, declining

tissue stem cell reserves, organ atrophy, and reduced ability to cope with stress, injury, and regenerative demands (Lee et al., 1998; Rudolph et al., 1999).

2.2. Telomere dysfunction with p53 protein

Transcriptomics analyses of late-generation TERC$^{-/-}$ mice have revealed the p53-PGC pathway of aging. In high-turnover tissues, the malfunctioning of telomeres triggers cellular growth arrest, senescence, and apoptosis through the activation of p53. This process leads to a gradual decline in tissue function and atrophy. p53 protein is a well-known tumor suppressor that plays a crucial role in regulating cell cycle arrest, DNA repair, and apoptosis in response to various forms of cellular stress. In the context of the p53-PGC pathway of aging, it has been found that telomere dysfunction and the resulting genotoxic stress activate the p53 pathway. When telomeres become critically short or dysfunctional, it triggers a DNA damage response, leading to the activation of p53. This activation of p53 initiates a series of downstream events. One of the significant outcomes is the suppression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha and beta (PGC-1α and PGC-1β), leading to a decrease in mitochondrial biogenesis and function, as well as metabolic alterations. These changes closely resemble the effects observed when PGC-1α and PGC-1β are simultaneously reduced *in vitro* or eliminated *in vivo*. The repression of the PGC network, induced by telomere dysfunction, along with the resulting mitochondrial dysfunction and metabolic changes, combined with telomere-induced apoptotic and proliferative checkpoints, collectively contribute to the decline in multiple systems' functionality in the presence of telomere dysfunction (Sahin et al, 2011). The significance of the p53-PGC pathway of aging lies in its integration of multiple aging theories and its comprehensive approach to understanding the mechanisms underlying aging. By linking telomere dysfunction, genotoxic stress, oxidative damage, mitochondrial decline, and the activation of p53 and repression of PGC-1α and PGC-1β, this pathway provides a more complete understanding of the molecular processes involved in aging.

2.3. Stem cell exhaustion and telomere attrition

The progressive depletion of stem cells is a significant contributing factor to the aging process, with implications for tissue regeneration and overall health. As cells undergo replication over time, the telomeric DNA, which serves as protective caps at the ends of chromosomes, gradually diminishes. This erosion of telomeres eventually triggers a cellular response known as replicative senescence, leading to irreversible growth arrest and preventing cells from further dividing and replenishing tissues. Consequently, senescent cells accumulate in aging tissues, contributing to the impairment of replicative potential not only in tissue stem cells but also in immune cells, a phenomenon known as immunosenescence. In the context of hematopoiesis, the process of forming blood cells, studies conducted on aged mice have demonstrated a decline in the cell-cycle activity of hematopoietic stem cells. Comparatively, older hematopoietic stem cells undergo fewer cell divisions than their younger counterparts (Rossi et al., 2007). This reduction in the replicative capacity of hematopoietic stem cells with age leads to a decline in hematopoiesis, resulting in a diminished production of adaptive immune cells. Consequently, the immune system becomes less efficient in mounting an effective immune response, making individuals more susceptible to infections and diseases. Additionally, the decrease in hematopoietic stem cells with age is associated with an increased incidence of anemia and myeloid malignancies, such as certain types of leukemia (Shaw et al., 2010).

The consequences of stem cell exhaustion and telomere attrition extend beyond the hematopoietic system. In various tissues, the decline in the number and function of stem cells contributes to diminished regenerative capacity and tissue maintenance. This impairment in tissue regeneration affects organs such as the skin, muscles, and nervous system, leading to functional decline and age-related diseases.

Moreover, the accumulation of senescent cells in aging tissues further exacerbates the detrimental effects of stem cell exhaustion. One of the mechanisms is the acquisition of a senescence-associated secretory phenotype (SASP) leading to the release of pro-inflammatory factors, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a), by senescent cells (Coppé et al., 2010) causing chronic inflammation and tissue dysfunction. This chronic inflammation, known as inflammaging, creates an unfavorable microenvironment for stem cells and further impairs their regenerative potential.

The consequences of inflammaging are extensive. The persistent activation of inflammatory pathways can lead to tissue damage and impair the normal process of tissue repair and regeneration. One of the major consequences of chronic inflammation is its contribution to the development and progression of age-related diseases. Cardiovascular disease, including conditions like atherosclerosis and hypertension, is closely linked to chronic inflammation. Inflammation can promote the formation of plaques within blood vessels, leading to reduced blood flow and increased risk of heart attacks and strokes (Libby et al., 2011). Moreover, neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, have also been associated with chronic inflammation. Inflammation in the brain can contribute to the

accumulation of abnormal protein aggregates and the activation of immune cells, leading to progressive neuronal damage and cognitive decline (Heneka et al., 2015)

Besides, chronic inflammation plays a role in the development of metabolic syndrome, a cluster of conditions including obesity, high blood pressure, elevated blood sugar levels, and abnormal cholesterol levels. Inflammatory signaling molecules can interfere with insulin signaling, promoting insulin resistance, and contributing to the development of type 2 diabetes. Additionally, chronic inflammation in adipose tissue can disrupt its normal function and contribute to the release of pro-inflammatory factors, further exacerbating metabolic dysfunction. Inflammatory cytokines interfere with insulin signaling and contribute to metabolic dysfunction (Hotamisligil et al., 2006).

2.4. Loss of proteostasis

Telomere dysfunction and the subsequent repression of SIRT1 expression, mediated by the p53 pathway, play a role in the age-related loss of proteostasis. Proteostasis refers to the maintenance of proper protein folding and functionality within cells. A decline in the activity of chaperone proteins responsible for facilitating correct protein folding can lead to proteostasis disruption. Studies on mutant mice lacking the co-chaperone CHIP have shown accelerated aging phenotypes, further emphasizing the importance of chaperone networks in maintaining proteostasis. In mammalian cells, SIRT1, a protein involved in regulating cellular processes, including aging, plays a role in the deacetylation of heat shock factor-1 (HSF-1). This deacetylation process enhances the transcriptional activation of heat shock genes like HSP70, which are responsible for protecting cells from stress-induced damage. Therefore, it is plausible that telomere dysfunction-induced repression of SIRT1 and subsequent reduction in HSP70 levels impair protein homeostasis and the ability of cells to respond to stress (Westerheide et al., 2009).

Proper protein folding is particularly crucial for maintaining neuronal homeostasis, as post-mitotic long-lived neurons are unable to dilute misfolded proteins through cell division (Muchowski et al., 2005). Neurological diseases associated with aging, such as Alzheimer's disease and Parkinson's disease, are characterized by the accumulation of misfolded proteins, including β-amyloid peptide and α-synuclein, respectively. This accumulation leads to progressive neuronal death and cognitive impairment.

2.5. Telomerase activity and cancer

Telomerase and its role in cancer have been subjects of extensive research. Telomeres are protective structures at the ends of chromosomes, which prevent them from eliciting a DNA damage response (DDR). When telomeres become critically short, cells enter a state of replicative senescence or undergo programmed cell death to prevent the propagation of damaged cells. However, some cancer cells could bypass this limitation through the activation of telomerase. In most normal human somatic cells, telomerase activity is low or absent, leading to gradual telomere shortening with each cell division. However, in most cancer cells, telomerase is reactivated, allowing them to maintain or even lengthen their telomeres indefinitely. Almost all human cancers present activation of telomerase as a hallmark, most likely as a mechanism to enable unlimited cell proliferation of tumor cells (Shay et al., 1997). This enables cancer cells to bypass senescence and continue dividing, contributing to their immortalization and uncontrolled growth. Telomerase activation can occur through several mechanisms in cancer cells, such as some oncogenes that act as transcriptional regulators of telomerase. Other mechanisms of telomerase activation have been identified, including alternative splicing and epigenetic modifications. These additional pathways contribute to the activation of telomerase and have been observed in certain contexts (Kyo et al., 2002). Another mechanism involves the upregulation of TERT expression, which can be driven by various genetic and epigenetic alterations. For example, mutations in the promoter region of the TERT gene or alterations in the signaling pathways that regulate TERT expression can lead to increased telomerase activity in cancer cells. Multiple research investigations have emphasized the significant occurrence of recurring mutations in the TERT promoter in melanoma. These mutations have been demonstrated to enhance the activity of the TERT promoter in functional studies, indicating their functional relevance in melanoma development and progression (Horn et al., 2013; Huang et al., 2013). The role of telomerase in cancer extends beyond telomere maintenance. Telomerase has been found to have additional functions that can promote tumor growth and progression. It can influence gene expression, cellular proliferation, resistance to cell death, and genomic stability (Begus-Nahrmann et al., 2012). Telomerase can also interact with various signaling pathways involved in cancer development, including those related to cell cycle regulation, DNA damage response, and cellular senescence.

Targeting telomerase has emerged as a promising strategy for cancer therapy. Therapeutic approaches aim to inhibit telomerase activity in cancer cells to induce telomere shortening and trigger cell death or senescence. Several telomerase inhibitors and telomerase-targeted immunotherapies are being investigated in preclinical and clinical studies as potential anti-cancer treatments. It is worth noting that while telomerase activation is a common mechanism for telomere maintenance in cancer cells, not all cancer cells rely on telomerase. An alternative pathway known as the

alternative lengthening of telomeres (ALT) can be utilized by a subset of cancer cells to elongate their telomeres (Henson et al., 2002). ALT involves recombination-based mechanisms to maintain telomere length and is frequently observed in specific types of tumors, including osteosarcoma and glioblastoma. In the ALT pathway, cancer cells utilize homologous recombination and DNA repair mechanisms to elongate their telomeres without the reliance on telomerase activity. This process involves the exchange of telomeric DNA sequences between different chromosomes, resulting in the lengthening of telomeres. ALT-positive cancer cells exhibit distinct characteristics, such as the presence of ALT-associated promyelocytic leukemia (PML) bodies, specialized structures within the nucleus that are involved in telomere maintenance (Henson et al., 2010).

2.6. Telomere and anti-aging interventions

The association between impaired telomere function and the characteristic features of aging, including age-related diseases and the onset of inherited and acquired degenerative conditions, has sparked considerable interest in the use of telomerase restoration therapy as a potential strategy for combating the aging process. The extensive research conducted using the TERC and TERT knockout mouse models has significantly contributed to our understanding of telomeres and their role in aging and disease. These findings have shed light on the molecular mechanisms underlying the aging process and hold potential for developing interventions to delaying aging processes.

In fact, the potential of telomerase as an anti-aging therapy has been demonstrated in various studies. One notable research involved an telomerase-deficient mouse model, to study the adverse cellular and organismal consequences of wide-spread endogenous DNA damage signaling activation in vivo. By using knock-in allele encoding a inducible telomerase reserve transcriptase-oestrogen receptor under transcriptional control of the endogenous TERT promoter, the reactivation of endogenous telomerase reversed advanced premature aging in mice (Jaskelioff et al., 2011). The research demonstrated the capability of telomerase activation to reverse age-related phenotypes. The researchers utilized an inducible system to reactivate telomerase in adult mice with critically short telomeres. The results were remarkable, as the reactivation of telomerase led to reduced DNA damage signaling and associated cellular checkpoint responses, resumption of proliferation in quiescent cultures, and eliminate degenerative phenotypes across multiple organs including testes, spleens, and intestines as well as reserved neurodegeneration. This study provides strong evidence for the potential of telomerase activation as an anti-aging intervention.

Furthermore, studies employing adenoviral delivery of telomerase in aged mice have demonstrated a wide range of positive outcomes. For instance, the research involved gene therapy by TERT interventions based on adeno-associated vectors in adult and old mice by re-activating telomerase activity in a wide-range of tissues. Their findings revealed significant improvements in epithelial barrier fitness, improved metabolic function, improved neuromuscular coordination, delayed osteoporosis, and extended lifespan life expectancy without an increase in cancer incidence. These results highlight the potential of telomerase-based therapies and anti-aging gene therapy (de Jesus, 2012).

2.7. Application of telomerase therapy and future perspectives

Several compounds have been discovered as potential activators of telomerase. One of which being extensively studied is TA-65, it is a natural compound derived from an extract of a plant commonly used in traditional Chinese medicine, Astragalus membranaceous. Although the exact mechanisms of action for these compounds are not fully understood, ongoing human trials of TA-65 have reported positive outcomes, such as improved macular function, reduced levels of high-density lipoprotein, enhances immunity and reduces inflammation.

Furthermore, hormonal agents like danazol (an antiestrogenic and antiprogestogenic) and 5a-dihydrotestosterone (an androgen) have been investigated for their ability to increase telomerase levels in individuals with telomeropathies (Calado et al., 2009; Townsley et al., 2016). Study using a mouse model of telomere dysfunction also demonstrated that treatment with male hormones resulted in hematologic improvement and elongation of telomeres (Bär et al., 2015). These agents are currently undergoing testing to explore their potential in treating telomere-related disorders.

In addition to small molecules and hormonal agents, recent advancements have been made in targeting TERC stability, providing new therapeutic options for telomeropathies. Specifically, the enzyme PAPD5 plays a role in degrading TERC through oligoadenylation, leading to its subsequent destruction by the RNA exosome. Mutations in PARN, which is involved in TERC de-adenylation and maturation, have been linked to diseases like dyskeratosis congenita. A small-molecule inhibitor of PAPD5 has shown promise in increasing telomere length in induced pluripotent stem cells derived from individuals with dyskeratosis congenita. Moreover, this inhibitor has been well tolerated in mice over an extended period (Nagpal et al., 2020).

These findings highlight various compounds and therapeutic approaches that have shown potential in modulating telomerase activity and telomere length. While further research is necessary to fully understand their mechanisms of action and evaluate their efficacy in humans, these studies pave the way for the development of novel treatments for telomeropathies and age-related diseases.

3. Conclusion

To maintain telomerase activity in a normal level may keep cells and organs in a healthy condition, as the result, it may slow the rate of aging.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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