Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU31815

Telomere Dynamics and Telomerase Regulation in Cellular Senescence and Aging: A Review Synthesis

Zhengju Zhang

School of Biological Sciences, The University of Hong Kong, Hong Kong, China
u3613593@connect.hku.hk

Abstract. In an era of increasing life expectancy and rising age-related diseases, assessing the intertwined roles of telomeres and telomerase as molecular drivers of cellular senescence promises transformative advances in extending human healthspan and developing anti-aging solutions. This literature review synthesizes key advancements in understanding telomere and telomerase's role in aging, spanning from foundational mitotic clock hypotheses to contemporary models of cellular and systemic decline. It examines telomerase-mediated telomere elongation as a countermeasure to replicative shortening, highlighting its impact on proliferative capacity across stem and somatic cells. Additionally, the review explores the perspectives on telomerase functions in preventing cellular senescence that extend beyond mere length maintenance, and instead participate in a dynamic model which also considers the state of telomere structures. Drawing from seminal works and empirical evidence over the past thirty years, this synthesis bridges historical discoveries with modern implications, elucidating how telomere and telomerase participate in shaping cell senescence, aging, and tissue regeneration

Keywords: Telomere Dynamics, Telomerase Regulation, Cellular Senescence, Cellular Aging

1. Introduction

The intricate interplay between telomeres and telomerase has long captivated researchers in the fields of longevity studies, offering profound insights into the mechanisms underpinning aging and regenerative potential. Pioneering observations by Hayflick in 1961 [1] and the theory foundation laid by Olovnikov in 1971 [2] collectively posited that incomplete replication of chromosome ends could serve as a molecular timer for cellular lifespan, a concept that has evolved into a cornerstone of modern aging theories. Works in the subsequent decades have illuminated telomerase's critical role as an enzyme essential for telomere maintenance and elongation, with its presence implicated in a spectrum of aging phenotypes [3]. While mounting evidence suggests telomerase expression can reverse this mitotic clock and delay or avoid cellular senescence, the narrative of aging has yet to expand beyond simple replicative attrition of telomere length. Current understanding emphasizes that telomere dysfunction, whether driven by the end-replication problem or internal or external stress, precipitates a persistent DNA damage response (DDR) that enforces cellular arrest pathways. This process is tightly modulated by the telomere structure, and, though debatable, is affected by

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.AU31815

telomerase expression. Over the implication of telomerase-regulated telomere elongation in avoiding cellular senescence, this essay also highlights the emerging debates that challenge the sufficiency of telomere length alone as a predictor of cell fate, pointing instead to the structural integrity of chromosome ends and the persistence of irreparable damage as the true drivers of physiological decline. By integrating foundational theories with recent empirical findings on telomere dynamics and telomerase functions, this review aims to offer a consolidated perspective that supports ongoing efforts

2. Telomerase modulates telomere

2.1. The telomere

Telomeres are specialized nucleoprotein structures that cap the ends of linear chromosomes and preserve genome stability. In mammals, telomeric DNA consisting of a conserved tandem of 5'-TTAGGG-3' repeats is observed. The telomere of mammals is bound by the shelterin complex. Shelterin contains several core subunits, including TRF1 [4], TRF2 [5], POT1, TIN2, TPP1 , and RAP1 [6], that together promote the formation of higher-order configurations such as the t loop, in which the 3' overhang invades the double-stranded telomeric tract. This lariat masks chromosome termini from DNA damage surveillance pathways and prevents activation of DNA damage reactions (DDR) [7] and chromosome fusion.

The concept that cells possess a finite proliferative capacity was first established by Hayflick and his colleagues, who observed that in vitro cultured human fibroblast cells undergo replicative senescence after 40–60 population doublings despite favorable culture conditions for continued proliferation [8]. This phenomenon, known as the Hayflick limit, gave rise to the mitotic clock hypothesis of replicative aging, which proposes that an intrinsic molecular counter tracks cumulative cell divisions and eventually enforces growth arrest [1,9]. Subsequent work associated this proliferative limit with the progressive telomere shortening of cells, which arises primarily from the end replication problem. In eukaryotic DNA replication, DNA polymerases cannot fully replicate the lagging strand at linear chromosome ends, and the gap generated by degradation of the terminal RNA primer is not filled, leading to the loss of a short DNA segment at the 5′ end of the lagging strand [10]. As a result, each S phase produces a small but cumulative shortening of telomeres in the absence of compensatory mechanisms. In vitro, cultured human cells lose approximately 50–250 bp of telomeric DNA per mitotic division [11] . In addition to the end replication problem, oxidative damage has been found to contribute to the reduction of telomeric DNA, which is particularly susceptible due to its guanine-rich sequence [12]. At a mechanistic level, this gradual erosion leads to an increasing proportion of telomeres that fall below a critical length threshold, losing shelterin coverage and becoming uncapped. The short or uncapped telomeres are recognized as DNA damage sites, triggering DDR and pathways such as ATM and ATR signaling. The cascades lead to the recruitment of DDR proteins such as γH2AX and 53BP1 [13] as well as the activation of p53, promoting the expression of cyclin-dependent kinase inhibitors p21, eventually driving a durable cell cycle arrest [14]. Another DDR-associated signal pathway is the p16-pRB pathway, which blocks the phosphorylation of pRB, also leading to cell cycle stagnation. However, studies in mouse models reveal that inhibition of p16 alone does not prevent cell-cycle arrest. This suggests that p16, at least in certain types of cells, plausibly functions as a secondary barrier, such that cell proliferation is effectively halted only when both p53 and p16 are suppressed [15].

Advances in the past few decades supported the mitotic clock hypothesis, with telomere length now understood to function as a key component: once a critical number of telomeres possess

DOI: 10.54254/2753-8818/2026.AU31815

telomeric length below a critical threshold, checkpoint pathways enforce cell senescence. In the meantime, this framework provided insight that genome integrity and cell immortality can be achieved by means of sustaining telomere length.

2.2. Telomerase as the telomere-modulating enzyme

Telomerase is the enzyme that counteracts the end replication problem by adding telomeric repeats to chromosome ends. It is a ribonucleoprotein reverse transcriptase composed of a catalytic protein subunit, telomerase reverse transcriptase (TERT), and an RNA component (TERC), which serves as the template for TTAGGG repeat synthesis. TERT uses the template sequence to extend the 3' overhang through a cycle of template alignment, reverse transcription, and translocation. For human telomerase, once assembled, the reverse transcriptase subunit (hTERT) remains stably bound to its RNA template subunit (hTR) throughout the lifecycle of the holoenzyme. Telomere recognition and extension are mediated through interactions with the template region of hTR, after which the enzyme translocates to the next position suitable for hTR engagement [16]. Additional factors, including dyskerin and associated H/ACA ribonucleoproteins subunits, bind and stabilize TERC, while the shelterin subunit TPP1 and other telomere-associated proteins facilitate recruitment of telomerase to telomeres and regulate its processivity [12,17].

In mammals, telomerase activity is controlled predominantly at the level of TERT expression. Early embryonic cells and germ cells express high levels of TERT and show robust telomerase activity. Adult stem cells also retain observable telomerase expression, slowing down telomere length erosion and enabling extensive self-renewal capacity [18,19]. However, telomerase levels in these adult stem cells are not sufficient to counteract the telomere shortening driven by continuous tissue renewal. Thus, stem cells still exhibit a progressive decline in telomere length, which is observed in both human and animal models [20,21]. In contrast, most somatic cells downregulate TERT transcription shortly after birth and exhibit little or no telomerase activity, leading to progressive telomere shortening with each cell division. The strict regulation of TERT at the transcriptional, post-translational, and epigenetic levels [10,22-24] results in a tightly controlled pattern of telomerase activity that grants embryonic stem cells [25] profound proliferation potential, while limiting telomere maintenance in both adult stem cells and somatic cells, thereby constraining the latter's proliferative capacity and life spans across various tissues. TERT expression has consequently emerged as a critical and potent target in aging research, given the robust association between telomere length and cellular senescence.

3. Telomerase, telomere length and aging

3.1. Aging hypotheses and phenotype

Aging represents a complex, multifactorial process characterized by the gradual deterioration of physiological functions, heightened susceptibility to diseases, and diminished resilience to stress. This process encompasses interconnected hallmarks such as genomic instability, epigenetic modifications, cellular senescence, and exhaustion of stem cells. Although recent advances have provided a more detailed understanding of the mechanisms and signal pathways involved in aging, qualified biomarkers that are capable of quantifying aging progress across different tissues and cell types remain to be found due to the complexity and diversity of tissue-specific and cell-specific phenotype presentations [18]. From evolutionary perspectives, aging is portrayed as a non-adaptive consequence [25]. For instance, the disposable soma theory proposes that organisms prioritize

DOI: 10.54254/2753-8818/2026.AU31815

resources toward reproduction rather than somatic maintenance, tolerating the accumulated damage over time [26]. Similarly, the antagonistic pleiotropy theory suggests that genes advantageous in early life may exert detrimental effects later [27]. An intriguing concept that aligns with this theory is that replicative senescence due to telomere erosion serves as a tumor-suppressing barriers that enhance early-stage survival and reproduction, with replicative aging representing the late-life costs [28,29].

Telomere length attrition has been considered as a fundamental hallmark of aging since the proposal of the Hayflick limit and the mitotic clock hypothesis, connecting replicative constraints to broader, systemic deterioration. Extending beyond earlier examinations of telomere shortening and its role in inducing replicative senescence of cells, telomere attrition is also associated with widespread influences at the intercellular level. Studies have proven that senescence cells release paracrinally a complex mixture of pro-inflammatory factors, and such phenotypes of the senescence cells are addressed as the senescence-associated secretory phenotype (SASP). In recent advances, it has been suggested that senescence can be transmitted to normal cells by cells demonstrating SASP [29], reinforcing age-related conditions, including cardiovascular disorders and neurodegenerative diseases [3]. Meanwhile, research further confirms that telomerase-regulated telomere maintenance governs stem cell fate decisions between regeneration, senescence, and transformation [30,31], closely linked to the aging phenotype of diminished proliferative responses and abnormal differentiation in tissue-resident stem cells, which arguably underlies key aspects of age-related physiological deteriorations [3,32]. With studies over the past three decades proving telomere shortening serves as both a biomarker and a mechanistic driver of aging, approaches aimed at preserving telomere length through telomerase expression hold potential to combat aging by sustaining cellular division potential and limiting the spread of damage.

3.2. Telomerase-modulated telomere length increase prevents cellular senescence

Substantial experimental evidence from animal models demonstrates that boosting telomerase activity to elongate or sustain telomere length can elevate cells' proliferative life span. In the human model, it had been reported that induced expression of the human TERT (hTERT) in hTERT-negative human cells (retinal pigment epithelial cells and foreskin fibroblasts) effectively elongated telomeres and circumvented replicative senescence, extended cells' proliferative lifespan by at least 20 population doublings beyond the Hayflick limit. Induced hTERT expression is found to maintain cells at a phenotypically youthful state with reduced senescence-associated β-galactosidase level, thereby establishing a direct link between telomere maintenance and the prevention of in vitro cellular aging [33]. Similarly, ectopic introduction of hTERT into both human hepatic stellate cells and human bone marrow stromal cells promotes the elongation and maintenance of telomere length [34,35], with a concomitant increase in replicative capacity and life span compared to the hTERT-negative controls. Telomerase introduction in animal models also exhibited compelling results, where a foundational study in mice achieved cellular immortalization by overexpressing mouse telomerase reverse transcriptase (mTERT) in primary cortical collecting duct principal cells [36]. Intriguingly, in both human and animal in vitro models, the telomere length is maintained, and senescence is prevented. TERT expression preserves cells' differentiated characteristics, and does not alter cellular karyotype nor provoke tumorigenic transformation, aligning with the established knowledge that TERT is not an oncogene. Collectively, telomerase modulation of telomere length plausibly underscores the therapeutic promise for countering cell senescence across diverse tissues.

DOI: 10.54254/2753-8818/2026.AU31815

3.3. Telomere elongation via telomerase mitigates systematic aging

Building on the therapeutic potential of telomerase modulation to combat cellular senescence in isolated tissues, emerging evidence from animal models further illustrates how telomere elongation through telomerase reactivation can reverse broader, systemic aging phenotypes. Recent studies demonstrated that induced activation of the mouse TERT (mTERT) in telomerase-deficient adult mice demonstrated the capacity to reverse multi-system degenerative processes. mTERT-/- adult mice presented severe aging phenotypes, including tissue atrophy and stem cell depletion. Telomerase activation in mice is found to facilitate telomere elongation, attenuate DNA damage signaling, and restore proliferative capacity in quiescent cell populations. Consequently, systematic ameliorations were observed, encompassing normalization of spleen dimensions, enhancement of neural progenitor activity with concomitant improvement in olfactory function, as well as a 30% extension in median lifespan without an elevated risk of oncogenesis [37]. Similarly, gut-specific expression of the TERT gene in telomerase-deficient zebrafish abrogates local telomere attrition and senescence, preserving tissue morphology within the intestine. This localized intervention also conferred systemic benefits, alleviating age-dependent deficits including diminished adipocyte size in visceral adipose tissue, reduced muscle fiber thickness, and decreased retinal pigment epithelium width, along with an average 40% prolongation of lifespan of TERT -positive fish compared to TERT-negative group [38]. Nonetheless, while these findings highlight the promise of ectopic telomerase expression for systemic rejuvenation, safety risks arising from current gene modification methods, such as potential off-target effects and insertional mutagenesis [39], as well as ethical concerns regarding genome modifications and long-term impacts [40,41], have led to very limited information on whether ectopic telomerase expression can effectively induce systemic reverse aging in humans. Still, data from animal models offer a convincing rationale for such therapeutic outcomes, justifying cautious further exploration in translational research in the future.

3.4. Aging beyond telomere length

Although telomere length remains pivotal in cellular aging, emerging evidence indicates that it is not the sole determinant of senescence. While replicative stress-induced shortening triggers DNA damage responses, multiple studies demonstrate that senescence can occur independently of telomere length. For instance, a previous study has documented that introducing hTERT to virus-transformed human fibroblasts prevents growth crisis and immortalizes cells even as telomeres shorten below senescent levels, suggesting an alternative potential telomerase-associated mechanism distinct from elongation that stabilizes telomere structure and prevents abnormal chromosome formations [42]. Similarly, the senescence of human melanocytes is associated with telomere dysfunction and the pro-inflammatory secretory phenotype (SASP), with no measurable attrition concomitantly occurring [43]. Telomere length decrease arises primarily from the end replication problem, meaning the senescence of cells that possess limited replicative capacity is not explicitly explained. In post-mitotic tissues such as the heart, aging cells exhibit senescence markers without detectable telomere shortening [44]. Collectively, such evidence demonstrates that while short telomeres are an important trigger of senescence, the doctrine to explain senescence solely based on telomere length can be limiting.

Over the past twenty years, models have arisen to conceptualize telomeres as dynamic structures in which length acts as one variable among several influencing outcomes. For example, the progressive erosion of telomeres is portrayed as an overall transition from capped, protected states to uncapped, deprotected states [45-47], which triggers sentence. Such models consider the overall

DOI: 10.54254/2753-8818/2026.AU31815

telomere structure (including its length, shelterin content, and topology) as causes of telomere dysfunction that trigger senescence pathways, providing more comprehensive insights than interpretations based solely on telomere length. Aligning with this framework, researchers increasingly posit telomere dysfunction and consequent persistent DDR foci as a central hallmark of aging that bridges cellular senescence with systemic aging signatures, such as genomic instability, mitochondrial dysfunction, and chronic inflammation [48]. The conceptual shift views telomeres not merely as passive "replicameters" but as active sensors of cellular stress [49]. Associated telomere-length-independent factors have been explored, with oxidative stress being a representative one. Recent evidence has suggested that reactive oxygen species (ROS) induce DDR foci at the telomeric region, independent of telomere length [44,50]. Intriguingly, the effect of telomerase on telomere-associated foci remains debatable. Studies in telomerase-deficient mice revealed that telomerase activation elongates telomeres, concomitant with the reduction in DDR foci, and reverses tissue degeneration in organs like the brain and intestines [37]. Conversely, studies on in vitro human fibroblasts show telomerase expression does not reduce stress-induced telomeric DDR foci. Despite hTERT fibroblasts demonstrating elevated replicative life span and sustained telomere length, telomeric DDR foci eventually lead to stress-induced senescence [51]. Similarly, in mouse models, telomeric DNA damage from exogenous agents is shown to be irreparable, leading to persistent DDR foci despite expression of the telomerase [47,51,52]. Thus, the significance of telomerase in modulating telomere-associated foci, along with other potential mechanisms involved, warrants further investigation.

4. Conclusion

In summary, this review synthesizes the evolving understanding of telomere and telomerase biology in aging, transitioning from static length-based models to dynamic frameworks centering on overall structural integrity and DNA damage responses. While telomerase activation demonstrates therapeutic potential in reversing systemic degeneration, its efficacy in resolving cellular sentence due to stress-induced telomeric damage remains a subject of debate. Notably, this article falls short in providing a credible resolution to ongoing controversies surrounding telomerase's potential non-elongation functions across cell types, such as its affiliated roles in telomere foci repair or stress response modulation. Overall, this synthesis provides new insights into the multifaceted drivers of senescence and highlights the importance of dynamic telomere frameworks for advancing anti-aging interventions.

References

[1] Hayflick, L., & Moorhead, P. S. (1961). The serial cultivation of human diploid cell strains. Experimental Cell Research, 25(3), 585–621. https: //doi.org/10.1016/0014-4827(61)90192-6

[2] Olovnikov, A. M. (1971). Principle of marginotomy in template synthesis of polynucleotides. PubMed, 201(6), 1496-1499.

[3] Jones-Weinert, C., Mainz, L., & Karlseder, J. (2024). Telomere function and regulation from mouse models to human ageing and disease. Nature Reviews Molecular Cell Biology, 26, 297-313. https: //doi.org/10.1038/s41580-024-00800-5(Review_Telo and function)

[4] Chong, L., van Steensel, B., Broccoli, D., Erdjument-Bromage, H., Hanish, J., Tempst, P., & de Lange, T. (1995). A Human Telomeric Protein. Science, 270(5242), 1663-1667. https: //doi.org/10.1126/science.270.5242.1663

[5] Bilaud, T., Brun, C., Ancelin, K., Koering, C. E., Laroche, T., & Gilson, E. (1997). Telomeric localization of TRF2, a novel human telobox protein. Nature Genetics, 17(2), 236-239. https: //doi.org/10.1038/ng1097-236

[6] Shay, J. W., & Wright, W. E. (2019). Telomeres and telomerase: three decades of progress. Nature Reviews Genetics, 20(5), 299-309. https: //doi.org/10.1038/s41576-019-0099-1

DOI: 10.54254/2753-8818/2026.AU31815

[7] Takai, Kaori K., Kibe, T., Donigian, Jill R., Frescas, D., & de Lange, T. (2011). Telomere Protection by TPP1/POT1 Requires Tethering to TIN2. Molecular Cell, 44(4), 647-659. https: //doi.org/10.1016/j.molcel.2011.08.043
[8] Huang, W., Hickson, L. J., Eirin, A., Kirkland, J. L., & Lerman, L. O. (2022). Cellular senescence: the good, the bad and the unknown. Nature Reviews Nephrology, 18(10). https: //doi.org/10.1038/s41581-022-00601-z (When bad things happens)
[9] Harley, C. B. (1991). Telomere loss: mitotic clock or genetic time bomb? Mutation Research/DNAging, 256(2-6), 271-282. https: //doi.org/10.1016/0921-8734(91)90018-7(mitotic clock)
[10] Srinivas, N., Rachakonda, S., & Kumar, R. (2020). Telomeres and Telomere Length: A General Overview. Cancers, 12(3), 558. https: //doi.org/10.3390/cancers12030558
[11] Heidenreich, B., & Kumar, R. (2017). TERT promoter mutations in telomere biology. Mutation Research/Reviews in Mutation Research, 771(1383-5742), 15–31. https: //doi.org/10.1016/j.mrrev.2016.11.002
[12] Petersen, S., Saretzki, G., & Zglinicki, T. von. (1998). Preferential Accumulation of Single-Stranded Regions in Telomeres of Human Fibroblasts. Experimental Cell Research, 239(1), 152-160. https: //doi.org/10.1006/excr.1997.3893
[13] Takai, H., Smogorzewska, A., & de Lange, T. (2003). DNA Damage Foci at Dysfunctional Telomeres. Current Biology, 13(17), 1549-1556. https: //doi.org/10.1016/s0960-9822(03)00542-6
[14] Karlseder, J. (1999). p53- and ATM-Dependent Apoptosis Induced by Telomeres Lacking TRF2. Science, 283(5406), 1321-1325. https: //doi.org/10.1126/science.283.5406.1321
[15] Jacobs, J. J. L., & de Lange, T. (2004). Significant Role for p16INK4a in p53-Independent Telomere-Directed Senescence. Current Biology, 14(24), 2302-2308. https: //doi.org/10.1016/j.cub.2004.12.025
[16] Cong, Y.-S. ., Wright, W. E., & Shay, J. W. (2002). Human Telomerase and Its Regulation. Microbiology and Molecular Biology Reviews, 66(3), 407–425. https: //doi.org/10.1128/mmbr.66.3.407-425.2002
[17] D Aisner. (2002). Telomerase regulation: not just flipping the switch. Current Opinion in Genetics & Development, 12(1), 80–85. https: //doi.org/10.1016/s0959-437x(01)00268-4
[18] Sahin, E., & DePinho, R. A. (2010). Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature, 464(7288), 520–528. https: //doi.org/10.1038/nature08982(review1)
[19] Hiyama, E., & Hiyama, K. (2007). Telomere and telomerase in stem cells. British Journal of Cancer, 96(7), 1020–1024. https: //doi.org/10.1038/sj.bjc.6603671
[20] Vaziri, H., Dragowska, W., Allsopp, R. C., Thomas, T. E., Harley, C. B., & Lansdorp, P. M. (1994). Evidence for a mitotic clock in human hematopoietic stem cells: loss of telomeric DNA with age. Proceedings of the National Academy of Sciences, 91(21), 9857–9860. https: //doi.org/10.1073/pnas.91.21.9857
[21] Allsopp, R. C., Cheshier, S., & Weissman, I. L. (2001). Telomere Shortening Accompanies Increased Cell Cycle Activity during Serial Transplantation of Hematopoietic Stem Cells. Journal of Experimental Medicine, 193(8), 917–924. https: //doi.org/10.1084/jem.193.8.917
[22] Arndt, G. M., & MacKenzie, K. L. (2016). New prospects for targeting telomerase beyond the telomere. Nature Reviews Cancer, 16(8), 508–524. https: //doi.org/10.1038/nrc.2016.55
[23] Lee, D. D., Komosa, M., Nunes, N. M., & Tabori, U. (2020). DNA methylation of the TERT promoter and its impact on human cancer. Current Opinion in Genetics & Development, 60(ISSN 0959-437X), 17–24. https: //doi.org/10.1016/j.gde.2020.02.003
[24] Thomson, J. A. (1998). Embryonic Stem Cell Lines Derived from Human Blastocysts. Science, 282(5391), 1145–1147. https: //pubmed.ncbi.nlm.nih.gov/9804556/
[25] Mc, M. T. (2024). The evolution of ageing: classic theories and emerging ideas. Biogerontology, 26(1). https: //doi.org/10.1007/s10522-024-10143-5
[26] Shefferson, R. P., Jones, O. R., & Salguero-Gómez, R. (2017). The Evolution of Senescence in the Tree of Life. Cambridge University Press.
[27] Mitteldorf, J. (2019). What Is Antagonistic Pleiotropy? Biochemistry (Moscow), 84(12-13), 1458–1468. https: //doi.org/10.1134/s0006297919120058
[28] Nassour, J., & Karlseder, J. (2025). Telomere Crisis Shapes Cancer Evolution. Cold Spring Harbor Perspectives in Biology, a041688. https: //doi.org/10.1101/cshperspect.a041688
[29] Shay, J. W. (2016). Role of Telomeres and Telomerase in Aging and Cancer. Cancer Discovery, 6(6), 584–593. https: //doi.org/10.1158/2159-8290.cd-16-0062
[30] Allsopp, R. C., Vaziri, H., Patterson, C., Goldstein, S., Younglai, E. V., Futcher, A. B., Greider, C. W., & Harley, C. B. (1992). Telomere length predicts replicative capacity of human fibroblasts. Proceedings of the National Academy of Sciences, 89(21), 10114–10118. https: //doi.org/10.1073/pnas.89.21.10114
[31] López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The Hallmarks of Aging. Cell, 153(6), 1194–1217. https: //doi.org/10.1016/j.cell.2013.05.039

DOI: 10.54254/2753-8818/2026.AU31815

[32] Jiang, Y., Zhou, Y., Wang, Y., Li, Z., Ashraf, G. M., & Guo, L. (2025). Telomerase dynamics in stem cells: Unraveling the molecular nexus of cellular aging and regeneration. Ageing Research Reviews, 112(1568-1637), 102853. https: //doi.org/10.1016/j.arr.2025.102853
[33] Bodnar, A. G. (1998). Extension of Life-Span by Introduction of Telomerase into Normal Human Cells. Science, 279(5349), 349–352. https: //doi.org/10.1126/science.279.5349.349
[34] Simonsen, J. L., Rosada, C., Serakinci, N., Justesen, J., Stenderup, K., Rattan, S. I. S., Jensen, T. G., & Kassem, M. (2002). Telomerase expression extends the proliferative life-span and maintains the osteogenic potential of human bone marrow stromal cells. Nature Biotechnology, 20(6), 592–596. https: //doi.org/10.1038/nbt0602-592
[35] Schnabl, B., Choi, Y. H., Olsen, J. C., Hagedorn, C. H., & Brenner, D. A. (2002). Immortal Activated Human Hepatic Stellate Cells Generated by Ectopic Telomerase Expression. Laboratory Investigation, 82(3), 323–333. https: //doi.org/10.1038/labinvest.3780426
[36] Steele, S. L., Wu, Y., Kolb, R. J., Gooz, M., Haycraft, C. J., Keyser, K. T., Guay-Woodford, L., Yao, H., & Bell, P. D. (2010). Telomerase immortalization of principal cells from mouse collecting duct. American Journal of Physiology-Renal Physiology, 299(6), F1507–F1514. https: //doi.org/10.1152/ajprenal.00183.2010
[37] Jaskelioff, M., Muller, F. L., Paik, J.-H., Thomas, E., Jiang, S., Adams, A. C., Sahin, E., Kost-Alimova, M., Protopopov, A., Cadiñanos, J., Horner, J. W., Maratos-Flier, E., & DePinho, R. A. (2010). Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature, 469(7328), 102–106. https: //doi.org/10.1038/nature09603
[38] El Maï, M., Bird, M., Allouche, A., Targen, S., Şerifoğlu, N., Lopes-Bastos, B., Guigonis, J.-M., Kang, D., Pourcher, T., Yue, J.-X., & Ferreira, M. G. (2023). Gut-specific telomerase expression counteracts systemic aging in telomerase-deficient zebrafish. Nature Aging, 3(5), 567–584. https: //doi.org/10.1038/s43587-023-00401-5
[39] Wang, D. C., & Wang, X. (2019). Off-target genome editing: A new discipline of gene science and a new class of medicine. Cell Biology and Toxicology, 35(3), 179–183. https: //doi.org/10.1007/s10565-019-09475-7
[40] Macpherson, I., Roqué, M. V., & Segarra, I. (2019). Ethical Challenges of Germline Genetic Enhancement. Frontiers in Genetics, 10(767). https: //doi.org/10.3389/fgene.2019.00767
[41] Evans, J. H. (2021). Setting ethical limits on human gene editing after the fall of the somatic/germline barrier. Proceedings of the National Academy of Sciences, 118(22). https: //doi.org/10.1073/pnas.2004837117
[42] Zhu, J., Wang, H., Bishop, J. M., & Blackburn, E. H. (1999). Telomerase extends the lifespan of virus-transformed human cells without net telomere lengthening. Proceedings of the National Academy of Sciences, 96(7), 3723–3728. https: //doi.org/10.1073/pnas.96.7.3723
[43] Victorelli, S., Lagnado, A., Halim, J., Moore, W., Talbot, D., Barrett, K., Chapman, J., Birch, J., Ogrodnik, M., Meves, A., Pawlikowski, J. S., Jurk, D., Adams, P. D., Heemst, D., Beekman, M., Slagboom, P. E., Gunn, D. A., & Passos, J. F. (2019c). Senescent human melanocytes drive skin ageing via paracrine telomere dysfunction. The EMBO Journal, 38(23). https: //doi.org/10.15252/embj.2019101982
[44] Anderson, R., Lagnado, A., Maggiorani, D., Walaszczyk, A., Dookun, E., Chapman, J., Birch, J., Salmonowicz, H., Ogrodnik, M., Jurk, D., Proctor, C., Correia-Melo, C., Victorelli, S., Fielder, E., Berlinguer-Palmini, R., Owens, A., Greaves, L. C., Kolsky, K. L., Parini, A., & Douin-Echinard, V. (2019). Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. The EMBO Journal, 38(5). https: //doi.org/10.15252/embj.2018100492
[45] Blackburn, E. H. (2000). Telomere states and cell fates. Nature, 408(6808), 53–56. https: //doi.org/10.1038/35040500
[46] von Zglinicki, T. (2001). Telomeres and replicative senescence: is it only length that counts? Cancer Letters, 168(2), 111-116. https: //doi.org/10.1016/s0304-3835(01)00546-8
[47] Cesare, A. J., & Karlseder, J. (2012). A three-state model of telomere control over human proliferative boundaries. Current Opinion in Cell Biology, 24(6), 731–738. https: //doi.org/10.1016/j.ceb.2012.08.007
[48] Eppard, M., Passos, J. F., & Victorelli, S. (2023). Telomeres, cellular senescence, and aging: past and future. Biogerontology, 25(2). https: //doi.org/10.1007/s10522-023-10085-4
[49] Victorelli, S., & Passos, J. F. (2017). Telomeres and Cell Senescence - Size Matters Not. EBioMedicine, 21(14-20), 14–20. https: //doi.org/10.1016/j.ebiom.2017.03.027
[50] Barnes, R. P., de Rosa, M., Thosar, S. A., Detwiler, A. C., Roginskaya, V., Van Houten, B., Bruchez, M. P., Stewart-Ornstein, J., & Opresko, P. L. (2022). Telomeric 8-oxo-guanine drives rapid premature senescence in the absence of telomere shortening. Nature Structural & Molecular Biology, 29(7), 639–652. https: //doi.org/10.1038/s41594-022-00790-y
[51] Hewitt, G., Jurk, D., Marques, F. D. M., Correia-Melo, C., Hardy, T., Gackowska, A., Anderson, R., Taschuk, M., Mann, J., & Passos, J. F. (2012). Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. Nature Communications, 3(1), 1–9. https: //doi.org/10.1038/ncomms1708

DOI: 10.54254/2753-8818/2026.AU31815

[52] Fumagalli, M., Rossiello, F., Clerici, M., Barozzi, S., Cittaro, D., Kaplunov, J. M., Bucci, G., Dobreva, M., Matti, V., Beausejour, C. M., Herbig, U., Longhese, M. P., & d'Adda di Fagagna, F. (2012). Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. Nature Cell Biology, 14(4), 355–365. https://doi.org/10.1038/ncb2466