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# Telomerase at the intersection of cancer and aging

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## Abstract

Although cancer and aging have been studied as independent diseases, mounting evidence suggest that cancer is an aging-associated disease and that cancer and aging share many molecular pathways. In particular, recent studies validated telomerase activation as a potential therapeutic target for age-related diseases, and at the same time, abnormal telomerase expression and telomerase mutations have been associated with many different types of human tumors. Here, we revisit the connection of telomerase to cancer and aging in light of recent findings supporting a role for telomerase not only in telomere elongation, but also in metabolic fitness and Wnt activation. Understanding the physiological impact of telomerase regulation is fundamental considering the therapeutic strategies that are being developed involving telomerase modulation.

### Keywords

Telomerase; aging; cancer

## Telomerase defects may lead to aging and cancer

Telomeres are repetitive DNA sequences at chromosome ends that are bound by a protective protein complex known as shelterin, which prevents them from eliciting a DNA damage response (DDR) [1, 2]. Seminal studies have shown that telomeres shorten with each cell division due in part to the end-replication problem, an inability of the DNA replication machinery to fully replicate DNA ends [3-6]. This is paralleled by the silencing of telomerase, a reverse-transcriptase responsible for *de novo* telomere extension in most adult tissues. Some adult cell types, such as adult stem cells, have the ability to activate telomerase, particularly in the transient amplifying compartments [6]. Nevertheless, telomerase expression in stem cells is not sufficient to prevent progressive telomere shortening associated with increasing age [7].

The first connection linking telomere length to the aging process came from the observation that human primary fibroblasts had shorter telomeres with increasing donor age and that when telomeres reached a critically short length they resulted in loss of proliferative ability, a terminal condition for cells known as replicative-senescence [8]. It is now thought that senescence, either triggered by telomere shortening or by other non-telomere related pathways, is a key cellular outcome which may contribute to the aging process, as well as act as a barrier for tumor progression [9]. In particular, telomere shortening and increased numbers of senescent cells have been found to occur in both proliferative and non-proliferative tissues as they age [10-12]. The importance of cellular senescence in the aging

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process was recently demonstrated by depletion of senescent cells in the context of an adult organism, the BubR1 progeroid mouse model, which rescued tissue dysfunction and increased organismal health-span (of note, BubR1 mice present an unusually high level of senescent cells and so may not be completely reflective of the natural aging process) [13]. In a similar manner, telomerase activation strategies have been recently shown to prevent telomere shortening associated with aging, delay organismal aging, and increase both healthspan and longevity [14, 15].

The anti-aging role of telomerase has been demonstrated to be largely mediated by its canonical role in elongating telomeres, which prevents the accumulation of critically short telomeres and loss of tissue homeostasis [14, 15]. In particular, telomere shortening in the context of adult stem cell compartments, has been previously demonstrated to cause severe impairment of stem cell mobilization and a subsequent defect in the ability to regenerate tissues [16], a situation that is similar to that of the so-called human telomere syndromes [17, 18]. This is because short/unprotected chromosome ends are recognized as persistent/non-repairable DNA breaks triggering persistent DDR [18-20], as well as cellular senescence or apoptosis mediated by the p53 pathway.

Short telomeres, and subsequent DDR activation, could occur both in cancer and aging (Fig. 1). On one hand, increased abundance of short telomeres correlates with higher genomic instability and decreased longevity in various organisms, including mice, zebrafish, and yeast [21-24]. In particular, mice deficient for telomerase or for telomere binding proteins are characterized by accelerated age-related defects [14, 16, 18, 19, 21, 22, 25-32] with the load of telomere dysfunction correlating with the lifespan of mice [33]. In humans, short telomeres are considered good indicators of an individual's health status and correlate with both genetic and environmental factors [18, 34-37]. Although recent findings strongly support the idea that short telomeres drive several age-related diseases [38] we cannot exclude the possibility that in some situations short telomeres may be a consequence of the disease itself.

Although tumors may arise from cells with short telomeres and chromosomal instability, telomerase activation and telomere maintenance are requisites for the progression of most human tumor types [39-49]. Further linking TERT (telomerase reverse transcriptase, the human telomerase) to cancer are GWAS results showing correlations between particular SNP variants on the 5p15.33 bin (which includes TERT) and a higher cancer risk [21, 50-58]. In particular, genetic variants in telomerase-associated genes and in the TERT-CLPTM1L locus are associated with different cancer types [50, 59-65]. Although the mechanism by which these variants interfere with telomerase levels/activity is mostly unknown, there are indications that the variants may lead to an increase in the gradual shortening of telomeres over time [52, 59], but these results still need to be confirmed [66]. On the other hand, two recent studies linked melanoma risk to promoter mutations in the TERT gene associated with increased transcriptional activity of the TERT promoter [67, 68], demonstrating the importance of tightly controlled telomerase expression.

Like cancer, aging encompasses a spectrum of cellular and molecular changes, but in the case of aging, these eventually result in loss of regenerative capacity and tissue dysfunction, either through loss of functional cells or through the accumulation of surviving aberrantly damaged cells, which could result in the appearance of neoplasias. In this review we focus on aging associated with telomere shortening, and on how telomerase could be an important therapeutic target for this process. To support the dual role of telomerase in aging and cancer we highlight recent studies that have demonstrated that expression of telomerase in aged organisms is a valuable tool to counteract tissue degeneration through the protection of short telomeres [69], envisioning that controlled telomerase activation under particular settings may delay age-related tumorigenesis.

## Telomerase as a key factor that regulates aging

Evolution has developed different barriers against cancer amongst different species. These barriers are related to the ability to cope with DNA damage and the prevention of the accumulation of damaged cells and tissues. Irrespective of its source, damage acts as the basis for the development of dysfunctional tissues, which are a hallmark of age decline as well as the basis for cancer [69, 70].

Patients carrying mutations in genes crucial for telomere maintenance show accelerated aging phenotypes. Such is the case for patients carrying mutations in *TERT*, *TERC* or other telomere maintenance genes, which lead to an accelerated aging syndrome known as dyskeratosis congenita (DC) [71]. DC encompasses a spectrum of pathologies including abnormal skin pigmentation, nail dystrophy, leukoplakia and pancytopenia [72]. In patients carrying mutations in *TERT* and *TERC*, the severity of pathologies correlates with the abundance of short telomeres, so the onset of disease is anticipated with increasing generations (a phenomenon known as "genetic anticipation") [73]. Interestingly, human telomere syndromes closely recapitulate the phenotypes of previously generated mouse models for telomerase deficiency. In particular, mice genetically deficient for telomerase or some of the telomere-binding proteins present a plethora of pathologies generally characterized by the loss of tissue regeneration and organ function [32, 74]. In addition to the defects in the highly proliferative tissues such as the bone marrow or the skin, mice and humans with telomerase deficiency also present pathologies in more quiescent tissues, such as cardiomyopathy, insulin resistance, and lung and liver fibrosis [75, 76]. To date it remains unknown how telomerase deficiency also leads to short telomeres in tissues with a lower proliferative potential [77, 78]. In this regard, mitochondrial dysfunction has been recently reported in quiescent tissues (such as the heart and liver) in the context of telomerase deficiency in mice. Several reports described that mt-TERT (TERT that localizes at mitochondria) improves mitochondrial function and protects from oxidative stress [79-81]. In particular, telomerase deficient mice that have been bred for several generations and have an increased abundance of short telomeres present a marked mitochondrial compromise triggered by the suppression of the peroxisome proliferator-activated receptor gamma, coactivator 1 alpha and beta (PGC1α and PGC1β) networks which control, amongst other processes, mitochondrial function and oxidative defense [82]. Interestingly, this connection between telomere dysfunction and mitochondrial dysfunction is mediated by p53, a common checkpoint to telomere syndromes [83]. Additionally, mitochondrial dysfunction in quiescent tissues of telomerase-deficient mice could be initiated by pathways independent of p53 [83]. Of note, mitochondrial defects have been described in the first generation of TERT KO mice (G1) [82], when telomere length is still conserved, demonstrating that mitochondrial dysfunction could, at least partially, precede or parallel telomere shortening. It has also been recently demonstrated that mitochondrial dysfunction is associated with physiological mouse aging, and reverted by telomerase activation [15, 82].

With the aim of dissecting the role of telomerase activity and telomere length in cancer and aging, various mouse models for telomerase over-expression have been generated (table 1). Transgenic mice that carry the mouse *TERT* gene under the control of the keratin 5 promoter (*K5-mTERT* referred hereafter as *TgTERT*) show increased tissue fitness, however, owing to an increased incidence of spontaneous tumors, these mice do not show an extended median lifespan [84]. To unmask the potential anti-aging role of telomerase, TgTERT mice were crossed with mice carrying extra copies of the tumor suppressors p53, p16 and Arf (Sp16/SArf/Sp53 mice), which were previously reported to be cancer resistant [14]. In this context, TgTERT/Sp16/SArf/Sp53 showed improved health span and a 40% increase in median longevity compared to wild-type controls, or 26% comparing with the long-lived and healthy Sp16/SArf/Sp53 mice, demonstrating the anti-aging activity of telomerase. A similar

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scenario occurred when telomerase overexpression was combined with other cancer-protective conditions, such as by subjecting mice to caloric restriction (CR). In this setting, telomerase overexpression synergized with CR to significantly extend mouse lifespan [85]. This synergy between telomerase and tumor resistance in extending organismal longevity seems to be a naturally occurring strategy, such as in the case of the mole rat or other small animals that are positive for telomerase, present higher tumor suppressor barriers [86, 87] and have an unusually increased longevity for their species. Although this synergy could be a strategy in some situations, there are exceptions (such as the American beaver, another long-lived rodent, which has no detectable telomerase activity [88]), highlighting the complexity of aging.

More recently, two independent studies demonstrated that telomerase activation either in a mouse model of accelerated-aging (late generation TERT-ER mouse model) or in natural-aged mice (1 and 2 year old wild-type mice) is sufficient to delay aging without increasing cancer incidence [15, 89]. These studies support the idea that telomere shortening is one of the molecular mechanisms of cellular aging and lifespan modulation, and more notably, they demonstrate that telomerase reactivation in adult (or aged) organisms has a positive impact in delaying aging, which can be separated from its role in cancer when its aberrantly expressed. Future work should focus on understanding the molecular mechanisms by which telomerase delays aging and disease in different organs and tissues. Below we discuss novel pathways and telomerase partners which could be also involved in these processes.

## Telomerase regulation in cancer

The role of telomerase in cancer has been extensively studied. Almost all human cancers present activation of telomerase as a hallmark, most likely as a mechanism to allow unlimited cell proliferation of tumor cells [90]. Although telomerase activation can be an early event in cancer, it is not necessary for cancer initiation [91]. However, telomerase can stimulate tumor progression by ensuring maintenance of telomeres above a critically short length, thus preventing induction of cellular senescence or apoptosis. Several mechanisms have been reported to activate telomerase in cancer, such as different oncogenes including Myc and Wnt [92-94] which act as transcriptional regulators of telomerase. Additional telomerase activation mechanisms involving alternative splicing or epigenetic alterations have also been described [95]. Recently, mutations increasing transcriptional activity of the TERT promoter from generation of *de novo* consensus binding motifs for E-twenty-six (ETS) transcription factors have been described in human melanomas [67, 68]. In addition to the canonical role of telomerase in maintaining telomeres above a critical length, telomerase has also been proposed to regulate other pathways, which could have an impact on cancer growth, such as regulation of Wnt targets and metabolism ([82, 96]). Getting rid of telomerase can also be problematic; the lack of telomerase could lead to increased chromosomal instability, which in turn could be at the basis for cancer initiation when tumor suppressor barriers are bypassed [97]. Indeed, recent evidence demonstrated that short telomeres alone could lead to genomic instability and cancer [98]. Thus, the current view is that telomerase deficiency may contribute to the early steps of cancer development by fueling chromosomal instability, while subsequent activation of telomerase may be necessary to allow tumor growth and tumor progression towards more malignant states [99].

Loss of function and gain of function mouse models for telomerase have been instrumental in understanding the role of telomerase in cancer. On one hand, telomerase deficient mice ($mTR^{-/-}$) are resistant to both induced and spontaneous tumorigenesis [100], except when telomerase deficient mice were crossed with $p53^{+/-}$ or $p53^{-/-}$ [101, 102]. In this scenario a switch to epithelial carcinogenesis was observed, consistent with the role of telomere shortening in the pathophysiology of human cancers [103]. Short telomeres could be recognized as DNA double strand (dsDNA) breaks, a deleterious DNA aberration that results in a strong activation of DNA damage repair (DDR) pathways. With an intact DDR and active checkpoints, cells with dsDNA breaks activate a multitude of signaling cascades which conclude in p53 and tumor suppressor activation. This cascade of events culminates in activation of anti-proliferation signals. On the other hand, if tumor suppressors or p53 are bypassed, a common characteristic of tumors, chromosome fusions and genomic instability could converge to give rise to cancer. This potential of telomerase to sustain the growth of tumor cells illustrates the importance of telomerase regulation in adult tissues, and probably explains why most adult cells silence telomerase expression.

Given the importance of telomerase to sustain cancer growth, telomerase inhibitors were considered as potential therapies against tumor malignancy. Recent evidence demonstrates, however, that tumors in which telomerase are lost may well activate different pathways to overcome this situation, such as alternative telomere lengthening [104-106].

In addition to the canonical role of telomerase in maintaining telomeres, telomerase overexpression has also been shown to influence the regulation of the Wnt pathway, although the physiological relevance and mechanism of this regulation is still debated [15, 93, 94, 96, 107]. Nevertheless, given that telomerase activity is aberrantly overexpressed in some cancers, it is possible that Wnt modulation through higher levels of telomerase could contribute to the phenotype of some neoplasias [108].

Metabolic defects are an important link between cancer and aging. Interestingly, metabolically relevant genes that have been shown to be down-regulated in the presence of short telomeres, such as *PGC1α/β*, and potentially activated by telomerase re-expression, are also linked to tumor progression [109, 110]. Thus, telomerase activation in tumors may also alter cellular metabolism. Further work will be required to refine these complex relationships been telomeres, telomerase and metabolism.

In this regard, transgenic mouse models (e.g., TgTERT mice [14]) have shown that constitutive telomerase over-expression throughout mouse development results in a slightly higher incidence of cancer. Interestingly, telomerase over-expression to similar levels but in the context of the adult organism using a gene therapy strategy, showed beneficial effects delaying aging and extending longevity without increased cancer incidence [15]. This could be related to the fact that the gene-therapy vectors employed (AAV) lead to a loss of TERT expression in highly proliferating cells or tissues. Another explanation could be that AAV preferentially targets post-mitotic cells, which are potentially more resistant to cancer initiation. Alternatively, although the TgTERT mice are the product of single germline integration, they constitutively express telomerase, independently of the replicative potential of a tissue, most likely facilitating proliferation and expansion of cells carrying pathogenic mutations.

## Telomerase in stem cells

Stem cells play an important role in the aging process. Stem cell depletion seems to be at the basis of some diseases and could account for accelerated aging syndromes [111-115]. Moreover, conditions that trigger premature aging, such as telomere shortening, also impair the ability of stem cells to regenerate tissues [16]. Indeed, cells with the longest telomeres are enriched at adult stem cell niches both in mice and humans, most likely owing to the fact that these cells have the ability to activate telomerase [7, 116]. However, physiological telomerase activation in stem cell compartments is not sufficient to maintain overall telomere length with aging, and telomere shortening and DNA damage accumulation is also a characteristic of aged stem cells [117].

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Tumors are thought to be sustained by a subpopulation of cells with stem cell-like properties, the so called cancer initiating cells [118, 119]. It will be of interest to address whether these cancer-initiating populations also have the ability to maintain telomeres and activate telomerase activity.

## Therapies based on telomerase: therapeutic value and future perspectives

As discussed above, telomerase activation is a potential therapeutic strategy for the treatment of age-related diseases [14, 120]. In particular, telomerase activation in adult or old mice by means of a gene therapy strategy was shown to be sufficient to improve metabolic fitness, neuromuscular capacity, and prevent bone loss, as well as significantly increase both median and maximum longevity, without increased cancer incidence. The finding that this strategy of telomerase activation does not lead to cancer could be due to the fact that the vectors used (AAV)9[121] are non-integrative, thus preventing the expansion of clones with telomerase overexpression [122]. Similarly, telomerase expression in an accelerated model of ageing owing to telomere loss ($G4^{TERT\text{-}ER}$ model) rescued several age phenotypes [89], and although higher genomic instability was detected, it did not lead to an increase in tumorigenesis. These studies suggest that telomerase expression could be considered a feasible approach to reverse tissue dysfunction and extend healthy lifespan without increasing cancer incidence. Dedicated studies should be performed in the future, using mice at different ages and comparisons at the same age, to assess the safety potential of these strategies. The actual value of these new therapies will reside in their safety, and a detailed understanding of the telomeric and non-telomeric roles of telomerase in tissue-specific healing and cancer will be crucial for considering telomerase for anti-aging therapies.

Whether these promising results could be translated to humans is unknown. It seems hazardous to use the lack of tumorigenesis in mice as evidence for the safety of pro-telomerase therapies in humans, as it is known that telomerase is differentially regulated in these organisms [123, 124]. The fact that human longevity is much longer than that of mice could increase the probability of cancer formation favored by an external telomerase treatment. The opposite argument can be made, however, in that humans are much more resistant to cancer than mice and therefore it is less likely that telomerase activation could lead to cancer in humans compared to mice. Even though the peak of telomerase activity in humans occurs at early stages, as it does in mice,, humans almost completely lose telomerase activity from somatic tissues in the adulthood, contrary to mice where telomerase is found in some somatic tissues [125, 126]. As a starting point for translating these findings to the clinic, telomerase activation is likely to be first tested for treatment of the so-called telomere syndromes [17]. In this scenario the use of tissue specific gene-therapy vectors expressing telomerase could be envisaged as a potential solution. Based on those outcomes, it will be easier to assess the feasibility of expanding telomerase activation as a strategy for combating cancer.

## Concluding Remarks

The finding that telomerase plays roles in distinct and complementary circuitries have helped reveal its function in cancer and aging. Indeed, a change of paradigm seems to be occurring in telomerase biology, with a switch from viewing telomerase as fueling cancer to reversing aging. Telomerase expression in a background of high levels of tumor suppressors or in aged organisms seems to prevent its expected pro-cancer activity and yet it still functions as an anti-aging factor. Supporting this notion are novel telomerase activators [120, 127, 128], some of which are commercially available, used as anti-aging supplements. Although much of the recent work provides only proof-of-principle that telomerase works for tissue healing, we cannot dismiss that in the future telomerase expression could be used as a safe approach for certain telomere-diseases [17] or other accelerated aging syndromes.

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## References

1. McClintock B. The Behavior in Successive Nuclear Divisions of a Chromosome Broken at Meiosis. Proc Natl Acad Sci U S A. 1939; 25:405–416. [PubMed: 16577924]
2. Muller HJ. The remaking of chromosomes. The Collecting Net. 1938; 8:182–195.
3. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961; 25:585–621. [PubMed: 13905658]
4. Levy MZ, et al. Telomere end-replication problem and cell aging. J Mol Biol. 1992; 225:951–960. [PubMed: 1613801]
5. Olovnikov AM. Telomeres, telomerase, and aging: origin of the theory. Exp Gerontol. 1996; 31:443–448. [PubMed: 9415101]
6. Blasco MA. Telomere length, stem cells and aging. Nat Chem Biol. 2007; 3:640–649. [PubMed: 17876321]
7. Flores I, et al. The longest telomeres: a general signature of adult stem cell compartments. Genes Dev. 2008; 22:654–667. [PubMed: 18283121]
8. de Jesus BB, Blasco MA. Assessing cell and organ senescence biomarkers. Circ Res. 2012; 111:97–109. [PubMed: 22723221]
9. Collado M, Serrano M. The power and the promise of oncogene-induced senescence markers. Nat Rev Cancer. 2006; 6:472–476. [PubMed: 16723993]
10. Jiang H, et al. Telomere shortening and ageing. Z Gerontol Geriatr. 2007; 40:314–324. [PubMed: 17943234]
11. Epel ES, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A. 2004; 101:17312–17315. [PubMed: 15574496]
12. Canela A, et al. High-throughput telomere length quantification by FISH and its application to human population studies. Proc Natl Acad Sci U S A. 2007; 104:5300–5305. [PubMed: 17369361]
13. Baker DJ, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature. 2011; 479:232–236. [PubMed: 22048312]
14. Tomas-Loba A, et al. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell. 2008; 135:609–622. [PubMed: 19013273]
15. Bernardes de Jesus B, et al. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. EMBO Mol Med. 2012; 4:1–14. [PubMed: 22180285]
16. Flores I, et al. Effects of telomerase and telomere length on epidermal stem cell behavior. Science. 2005; 309:1253–1256. [PubMed: 16037417]
17. Armanios M, Blackburn EH. The telomere syndromes. Nat Rev Genet. 2012; 13:693–704. [PubMed: 22965356]
18. Armanios M, et al. Short telomeres are sufficient to cause the degenerative defects associated with aging. Am J Hum Genet. 2009; 85:823–832. [PubMed: 19944403]
19. Hao LY, et al. Short telomeres, even in the presence of telomerase, limit tissue renewal capacity. Cell. 2005; 123:1121–1131. [PubMed: 16360040]
20. Morrish TA, Greider CW. Short telomeres initiate telomere recombination in primary and tumor cells. PLoS Genet. 2009; 5:e1000357. [PubMed: 19180191]
21. Blasco MA, et al. Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. Cell. 1997; 91:25–34. [PubMed: 9335332]

22. Hemann MT, et al. The shortest telomere, not average telomere length, is critical for cell viability and chromosome stability. Cell. 2001; 107:67–77. [PubMed: 11595186]
23. Lundblad V, Szostak JW. A mutant with a defect in telomere elongation leads to senescence in yeast. Cell. 1989; 57:633–643. [PubMed: 2655926]
24. Henriques CM, et al. Telomerase is required for zebrafish lifespan. PLoS Genet. 2013; 9:e1003214. [PubMed: 23349637]
25. Gonzalez-Suarez E, et al. Increased epidermal tumors and increased skin wound healing in transgenic mice overexpressing the catalytic subunit of telomerase, mTERT, in basal keratinocytes. EMBO J. 2001; 20:2619–2630. [PubMed: 11387197]
26. Martinez P, Blasco MA. Role of shelterin in cancer and aging. Aging Cell. 2010; 9:653–666. [PubMed: 20569239]
27. Armanios MY, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007; 356:1317–1326. [PubMed: 17392301]
28. Mitchell JR, et al. A telomerase component is defective in the human disease dyskeratosis congenita. Nature. 1999; 402:551–555. [PubMed: 10591218]
29. Tsakiri KD, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A. 2007; 104:7552–7557. [PubMed: 17460043]
30. Vulliamy T, et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature. 2001; 413:432–435. [PubMed: 11574891]
31. Yamaguchi H, et al. Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. N Engl J Med. 2005; 352:1413–1424. [PubMed: 15814878]
32. Martinez P, Blasco MA. Telomeric and extra-telomeric roles for telomerase and the telomere-binding proteins. Nat Rev Cancer. 2011; 11:161–176. [PubMed: 21346783]
33. Vera E, et al. The rate of increase of short telomeres predicts longevity in mammals. Cell Rep. 2012; 2:732–737. [PubMed: 23022483]
34. Alder JK, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A. 2008; 105:13051–13056. [PubMed: 18753630]
35. Benetos A, et al. Short telomeres are associated with increased carotid atherosclerosis in hypertensive subjects. Hypertension. 2004; 43:182–185. [PubMed: 14732735]
36. Cipriano C, et al. Accumulation of cells with short telomeres is associated with impaired zinc homeostasis and inflammation in old hypertensive participants. J Gerontol A Biol Sci Med Sci. 2009; 64:745–751. [PubMed: 19359441]
37. Elvsashagen T, et al. The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder. J Affect Disord. 2011; 135:43–50. [PubMed: 21880373]
38. Codd V, et al. Identification of seven loci affecting mean telomere length and their association with disease. Nat Genet. 2013; 45:422–427. 427e421–422. [PubMed: 23535734]
39. Chadeneau C, et al. Telomerase activity associated with acquisition of malignancy in human colorectal cancer. Cancer Res. 1995; 55:2533–2536. [PubMed: 7780964]
40. Tang R, et al. Close correlation between telomerase expression and adenomatous polyp progression in multistep colorectal carcinogenesis. Cancer Res. 1998; 58:4052–4054. [PubMed: 9751608]
41. Fang DC, et al. Telomere erosion is independent of microsatellite instability but related to loss of heterozygosity in gastric cancer. World J Gastroenterol. 2001; 7:522–526. [PubMed: 11819821]
42. Engelhardt M, et al. Telomerase and telomere length in the development and progression of premalignant lesions to colorectal cancer. Clin Cancer Res. 1997; 3:1931–1941. [PubMed: 9815582]
43. Maruyama Y, et al. Telomere length and telomerase activity in carcinogenesis of the stomach. Jpn J Clin Oncol. 1997; 27:216–220. [PubMed: 9379506]
44. Lantuejoul S, et al. Telomere shortening and telomerase reverse transcriptase expression in preinvasive bronchial lesions. Clin Cancer Res. 2005; 11:2074–2082. [PubMed: 15756034]
45. Meeker AK, et al. Telomere shortening occurs in subsets of normal breast epithelium as well as in situ and invasive carcinoma. Am J Pathol. 2004; 164:925–935. [PubMed: 14982846]

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46. van Heek NT, et al. Telomere shortening is nearly universal in pancreatic intraepithelial neoplasia. Am J Pathol. 2002; 161:1541–1547. [PubMed: 12414502]

47. Meeker AK, et al. Telomere shortening is an early somatic DNA alteration in human prostate tumorigenesis. Cancer Res. 2002; 62:6405–6409. [PubMed: 12438224]

48. Finley JC, et al. Chromosomal instability in Barrett's esophagus is related to telomere shortening. Cancer Epidemiol Biomarkers Prev. 2006; 15:1451–1457. [PubMed: 16896031]

49. Zheng YL, et al. Telomere attrition in cancer cells and telomere length in tumor stroma cells predict chromosome instability in esophageal squamous cell carcinoma: a genome-wide analysis. Cancer Res. 2009; 69:1604–1614. [PubMed: 19190333]

50. McKay JD, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet. 2008; 40:1404–1406. [PubMed: 18978790]

51. Wang Y, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet. 2008; 40:1407–1409. [PubMed: 18978787]

52. Hills M, Lansdorp PM. Short telomeres resulting from heritable mutations in the telomerase reverse transcriptase gene predispose for a variety of malignancies. Ann N Y Acad Sci. 2009; 1176:178–190. [PubMed: 19796246]

53. Willeit P, et al. Telomere length and risk of incident cancer and cancer mortality. JAMA. 2010; 304:69–75. [PubMed: 20606151]

54. Londono-Vallejo JA. Telomere length heterogeneity and chromosome instability. Cancer Lett. 2004; 212:135–144. [PubMed: 15341022]

55. Meeker AK, et al. Telomere length abnormalities occur early in the initiation of epithelial carcinogenesis. Clin Cancer Res. 2004; 10:3317–3326. [PubMed: 15161685]

56. Calado RT, Chen J. Telomerase: not just for the elongation of telomeres. Bioessays. 2006; 28:109–112. [PubMed: 16435298]

57. Hosgood HD 3rd, et al. Genetic variation in telomere maintenance genes, telomere length, and lung cancer susceptibility. Lung Cancer. 2009; 66:157–161. [PubMed: 19285750]

58. Van Dyke AL, et al. Chromosome 5p Region SNPs Are Associated with Risk of NSCLC among Women. J Cancer Epidemiol. 2009; 2009:242151. [PubMed: 20445798]

59. Rafnar T, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet. 2009; 41:221–227. [PubMed: 19151717]

60. Shete S, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet. 2009; 41:899–904. [PubMed: 19578367]

61. Wrensch M, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nat Genet. 2009; 41:905–908. [PubMed: 19578366]

62. Jin G, et al. Common genetic variants on 5p15.33 contribute to risk of lung adenocarcinoma in a Chinese population. Carcinogenesis. 2009; 30:987–990. [PubMed: 19369581]

63. Landi MT, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet. 2009; 85:679–691. [PubMed: 19836008]

64. Petersen GM, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet. 2010; 42:224–228. [PubMed: 20101243]

65. Hofer P, et al. MNS16A tandem repeats minisatellite of human telomerase gene: a risk factor for colorectal cancer. Carcinogenesis. 2011; 32:866–871. [PubMed: 21422235]

66. Pooley KA, et al. No association between TERT-CLPTM1L single nucleotide polymorphism rs401681 and mean telomere length or cancer risk. Cancer Epidemiol Biomarkers Prev. 2010; 19:1862–1865. [PubMed: 20570912]

67. Huang FW, et al. Highly recurrent TERT promoter mutations in human melanoma. Science. 2013; 339:957–959. [PubMed: 23348506]

68. Horn S, et al. TERT promoter mutations in familial and sporadic melanoma. Science. 2013; 339:959–961. [PubMed: 23348503]

69. de Jesus BB, Blasco MA. Potential of telomerase activation in extending health span and longevity. Curr Opin Cell Biol. 2012

Europe PMC Funders Author Manuscripts


70. Serrano M, Blasco MA. Cancer and ageing: convergent and divergent mechanisms. Nat Rev Mol Cell Biol. 2007; 8:715–722. [PubMed: 17717516]

71. Calado RT, Young NS. Telomere diseases. N Engl J Med. 2009; 361:2353–2365. [PubMed: 20007561]

72. Dokal I. Dyskeratosis congenita. Hematology Am Soc Hematol Educ Program. 2011; 2011:480–486. [PubMed: 22160078]

73. Armanios M. Syndromes of telomere shortening. Annu Rev Genomics Hum Genet. 2009; 10:45–61. [PubMed: 19405848]

74. Beier F, Foronda M, Martinez P, Blasco MA. Conditional TRF1 knockout in the hematopoietic compartment leads to bone marrow failure and recapitulates clinical features of Dyskeratosis congenita. Blood. 2012; 120:2990–3000. [PubMed: 22932806]

75. Leri A, et al. Ablation of telomerase and telomere loss leads to cardiac dilatation and heart failure associated with p53 upregulation. EMBO J. 2003; 22:131–139. [PubMed: 12505991]

76. Basel-Vanagaite L, et al. Expanding the clinical phenotype of autosomal dominant dyskeratosis congenita caused by TERT mutations. Haematologica. 2008; 93:943–944. [PubMed: 18460650]

77. Aikata H, et al. Telomere reduction in human liver tissues with age and chronic inflammation. Exp Cell Res. 2000; 256:578–582. [PubMed: 10772830]

78. Chimenti C, et al. Senescence and death of primitive cells and myocytes lead to premature cardiac aging and heart failure. Circ Res. 2003; 93:604–613. [PubMed: 12958145]

79. Chiodi I, Mondello C. Telomere-independent functions of telomerase in nuclei, cytoplasm, and mitochondria. Front Oncol. 2012; 2:133. [PubMed: 23061047]

80. Saretzki G. Telomerase, mitochondria and oxidative stress. Exp Gerontol. 2009; 44:485–492. [PubMed: 19457450]

81. Gordon DM, Santos JH. The emerging role of telomerase reverse transcriptase in mitochondrial DNA metabolism. J Nucleic Acids. 2010; 2010

82. Sahin E, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature. 2011; 470:359–365. [PubMed: 21307849]

83. Sahin E, DePinho RA. Axis of ageing: telomeres, p53 and mitochondria. Nat Rev Mol Cell Biol. 2012; 13:397–404. [PubMed: 22588366]

84. Gonzalez-Suarez E, et al. Antagonistic effects of telomerase on cancer and aging in K5-mTert transgenic mice. Oncogene. 2005; 24:2256–2270. [PubMed: 15688016]

85. Vera E, et al. Telomerase Reverse Transcriptase Synergizes with Calorie Restriction to Increase Health Span and Extend Mouse Longevity. PLoS ONE. 2013; 8:e53760. doi: 53710.51371/journal.pone.0053760. [PubMed: 23349740]

86. Gorbunova V, Seluanov A. Coevolution of telomerase activity and body mass in mammals: from mice to beavers. Mech Ageing Dev. 2009; 130:3–9. [PubMed: 18387652]

87. Seluanov A, et al. Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat. Proc Natl Acad Sci U S A. 2009; 106:19352–19357. [PubMed: 19858485]

88. Gorbunova V, Bozzella MJ, Seluanov A. Rodents for comparative aging studies: from mice to beavers. Age. 2008; 30:111–119. [PubMed: 19424861]

89. Jaskelioff M, et al. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. Nature. 2011; 469:102–106. [PubMed: 21113150]

90. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. Eur J Cancer. 1997; 33:787–791. [PubMed: 9282118]

91. Hackett JA, Greider CW. Balancing instability: dual roles for telomerase and telomere dysfunction in tumorigenesis. Oncogene. 2002; 21:619–626. [PubMed: 11850787]

92. Wu KJ, et al. Direct activation of TERT transcription by c-MYC. Nat Genet. 1999; 21:220–224. [PubMed: 9988278]

93. Hoffmeyer K, et al. Wnt/beta-catenin signaling regulates telomerase in stem cells and cancer cells. Science. 2012; 336:1549–1554. [PubMed: 22723415]

94. Greider CW. Molecular biology. Wnt regulates TERT--putting the horse before the cart. Science. 2012; 336:1519–1520. [PubMed: 22723405]

95. Kyo S, Inoue M. Complex regulatory mechanisms of telomerase activity in normal and cancer cells: how can we apply them for cancer therapy? Oncogene. 2002; 21:688–697. [PubMed: 11850797]

96. Park JI, et al. Telomerase modulates Wnt signalling by association with target gene chromatin. Nature. 2009; 460:66–72. [PubMed: 19571879]

97. Feldser DM, Greider CW. Short telomeres limit tumor progression in vivo by inducing senescence. Cancer Cell. 2007; 11:461–469. [PubMed: 17433785]

98. Begus-Nahrmann Y, et al. Transient telomere dysfunction induces chromosomal instability and promotes carcinogenesis. J Clin Invest. 2012; 122:2283–2288. [PubMed: 22622037]

99. Ding Z, et al. Telomerase reactivation following telomere dysfunction yields murine prostate tumors with bone metastases. Cell. 2012; 148:896–907. [PubMed: 22341455]

100. Gonzalez-Suarez E, et al. Telomerase-deficient mice with short telomeres are resistant to skin tumorigenesis. Nat Genet. 2000; 26:114–117. [PubMed: 10973262]

101. Chin L, et al. p53 deficiency rescues the adverse effects of telomere loss and cooperates with telomere dysfunction to accelerate carcinogenesis. Cell. 1999; 97:527–538. [PubMed: 10338216]

102. Artandi SE, et al. Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. Nature. 2000; 406:641–645. [PubMed: 10949306]

103. Chang S, et al. Modeling chromosomal instability and epithelial carcinogenesis in the telomerase-deficient mouse. Semin Cancer Biol. 2001; 11:227–239. [PubMed: 11407947]

104. Hu J, et al. Antitelomerase therapy provokes ALT and mitochondrial adaptive mechanisms in cancer. Cell. 2012; 148:651–663. [PubMed: 22341440]

105. Sachsinger J, et al. Telomerase inhibition in RenCa, a murine tumor cell line with short telomeres, by overexpression of a dominant negative mTERT mutant, reveals fundamental differences in telomerase regulation between human and murine cells. Cancer Res. 2001; 61:5580–5586. [PubMed: 11454711]

106. Herrera E, et al. Impaired germinal center reaction in mice with short telomeres. EMBO J. 2000; 19:472–481. [PubMed: 10654945]

107. Strong MA, et al. Phenotypes in mTERT+/− and mTERT−/− Mice Are Due to Short Telomeres, Not Telomere-Independent Functions of Telomerase Reverse Transcriptase. Mol Cell Biol. 2011; 31:2369–2379. [PubMed: 21464209]

108. Liang Y, et al. Stem-like cancer cells are inducible by increasing genomic instability in cancer cells. J Biol Chem. 2010; 285:4931–4940. [PubMed: 20007324]

109. Zhu Y, et al. Amplification and overexpression of peroxisome proliferator-activated receptor binding protein (PBP/PPARBP) gene in breast cancer. Proc Natl Acad Sci U S A. 1999; 96:10848–10853. [PubMed: 10485914]

110. Bhalla K, et al. PGC1alpha promotes tumor growth by inducing gene expression programs supporting lipogenesis. Cancer Res. 2011; 71:6888–6898. [PubMed: 21914785]

111. Rosengardten Y, et al. Stem cell depletion in Hutchinson-Gilford progeria syndrome. Aging Cell. 2011; 10:1011–1020. [PubMed: 21902803]

112. Schlessinger D, Van Zant G. Does functional depletion of stem cells drive aging? Mech Ageing Dev. 2001; 122:1537–1553. [PubMed: 11511395]

113. Ruzankina Y, et al. Deletion of the developmentally essential gene ATR in adult mice leads to age-related phenotypes and stem cell loss. Cell Stem Cell. 2007; 1:113–126. [PubMed: 18371340]

114. Rossi DJ, et al. Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature. 2007; 447:725–729. [PubMed: 17554309]

115. Rando TA. Stem cells, ageing and the quest for immortality. Nature. 2006; 441:1080–1086. [PubMed: 16810243]

116. Jung P, et al. Isolation and in vitro expansion of human colonic stem cells. Nat Med. 2011; 17:1225–1227. [PubMed: 21892181]

117. Sperka T, et al. DNA damage checkpoints in stem cells, ageing and cancer. Nat Rev Mol Cell Biol. 2012; 13:579–590. [PubMed: 22914294]

118. Jordan CT, et al. Cancer stem cells. N Engl J Med. 2006; 355:1253–1261. [PubMed: 16990388]

119. Reya T, et al. Stem cells, cancer, and cancer stem cells. Nature. 2001; 414:105–111. [PubMed: 11689955]
120. de Jesus BB, et al. The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. Aging Cell. 2011; 10:604–621. [PubMed: 21426483]
121. Kaplitt MG, et al. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet. 2007; 369:2097–2105. [PubMed: 17586305]
122. Buning H, et al. Recent developments in adeno-associated virus vector technology. J Gene Med. 2008; 10:717–733. [PubMed: 18452237]
123. Fujiki T, et al. Regulatory mechanisms of human and mouse telomerase reverse transcriptase gene transcription: distinct dependency on c-Myc. Cytotechnology. 2010; 62:333–339. [PubMed: 20454928]
124. Weise JM, Gunes C. Differential regulation of human and mouse telomerase reverse transcriptase (TERT) promoter activity during testis development. Mol Reprod Dev. 2009; 76:309–317. [PubMed: 18729084]
125. Collins K, Mitchell JR. Telomerase in the human organism. Oncogene. 2002; 21:564–579. [PubMed: 11850781]
126. Prowse KR, Greider CW. Developmental and tissue-specific regulation of mouse telomerase and telomere length. Proc Natl Acad Sci U S A. 1995; 92:4818–4822. [PubMed: 7761406]
127. Harley CB, et al. A natural product telomerase activator as part of a health maintenance program. Rejuvenation Res. 2011; 14:45–56. [PubMed: 20822369]
128. Eitan E, et al. Novel telomerase-increasing compound in mouse brain delays the onset of amyotrophic lateral sclerosis. EMBO Mol Med. 2012; 4:313–329. [PubMed: 22351600]
129. Artandi SE, et al. Constitutive telomerase expression promotes mammary carcinomas in aging mice. Proc Natl Acad Sci U S A. 2002; 99:8191–8196. [PubMed: 12034875]
130. Gonzalez-Suarez E, et al. Cooperation between p53 mutation and high telomerase transgenic expression in spontaneous cancer development. Mol Cell Biol. 2002; 22:7291–7301. [PubMed: 12242304]
131. Canela A, et al. Constitutive expression of tert in thymocytes leads to increased incidence and dissemination of T-cell lymphoma in Lck-Tert mice. Mol Cell Biol. 2004; 24:4275–4293. [PubMed: 15121848]
132. Sarin KY, et al. Conditional telomerase induction causes proliferation of hair follicle stem cells. Nature. 2005; 436:1048–1052. [PubMed: 16107853]
133. Fauce SR, et al. Telomerase-based pharmacologic enhancement of antiviral function of human CD8+ T lymphocytes. J Immunol. 2008; 181:7400–7406. [PubMed: 18981163]
134. Zhou QG, et al. Hippocampal telomerase is involved in the modulation of depressive behaviors. J Neurosci. 2011; 31:12258–12269. [PubMed: 21865469]

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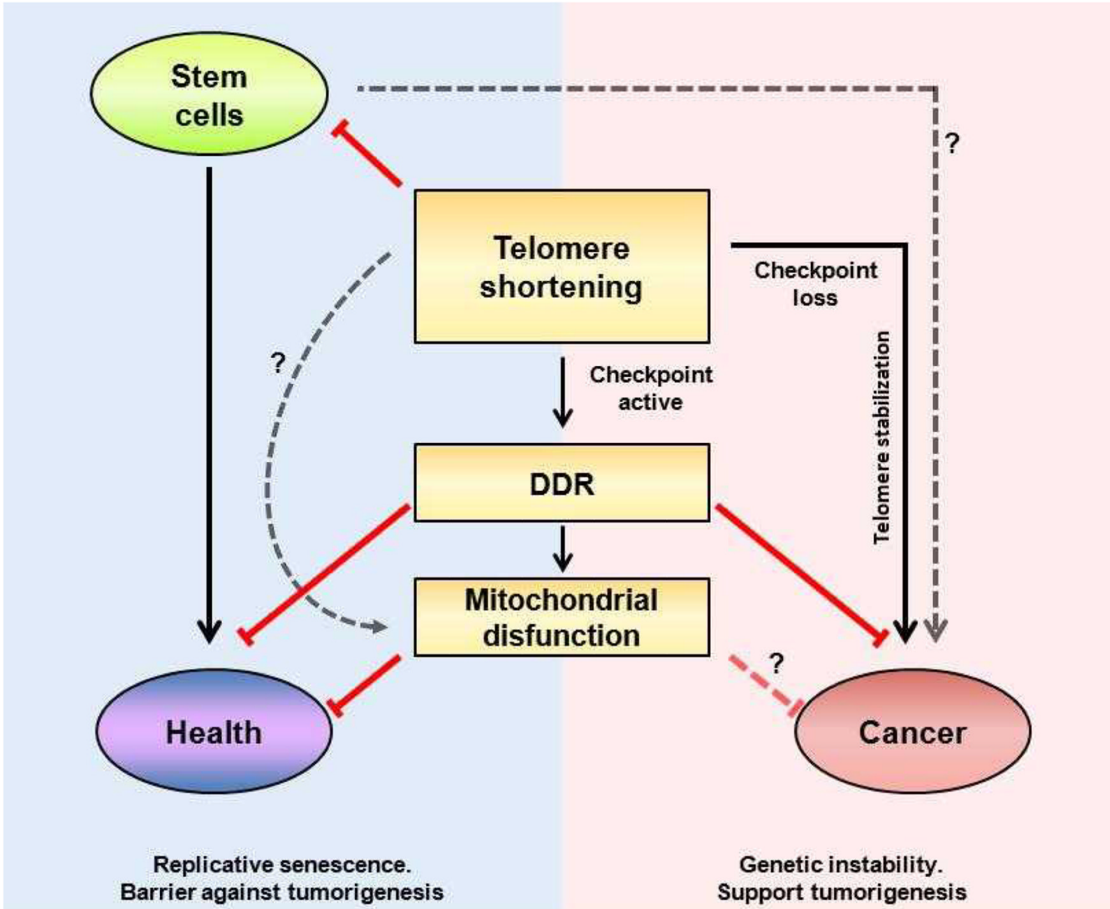


**Figure 1. Short telomeres in aging and cancer.**

Major pathways affected by short telomeres and their impact on aging or cancer. DNA damage and tumor suppressor activity have been shown to impact tissue decline and aging. When DNA damage checkpoints are bypassed, cells with short telomeres could potentially progress to cancer. The role of stem cells with short telomeres in cancer and whether short telomeres could modulate other pathways independently of p53 (such as mitochondrial dysfunction) remains unknown.

## Table 1
**Outcomes of enforced expression of telomerase in mice.**

| Ref | Model / Telomerase activation | Cancer | Aging | Comments |
|---|---|---|---|---|
| 25 | • C57Bl/6<br>• Germline<br>• K5-mTERT | Stratified epithelia histologically normal More tumors after DMBA+TPA treatment. Skin more sensitive to esters. | Increased wound-healing | High levels of telomerase activity in stratified epithelia do not alter the normal epithelium structure and are not associated with changes in p53, Ras or c-Myc levels. |
| 129 | • FVB/n strain<br>• Germline<br>• CAG promoter | Higher incidence of breast carcinoma in all but 1 female of founder A. No differences in males. | *n.d.* | No susceptibility to spontaneous or DMBA-induced papillomas in mTERT Tg mice. Enforced mTERT expression did not alter the high rate of spontaneous tumor formation in Ink4a/Arf-deficient mice. |
| 130 | • C57Bl/6<br>• Germline<br>• K5-mTERT and K5-mTERT/p53$^{-/-}$ | Higher tumor incidence (spontaneous pre- neoplastic and neoplastic lesions in stratified and non- stratified epithelia) | Lower lifespan in both k5-mTERT or k5-mTERT/p53$^{-/-}$ | Loss of p53 results in a dramatic decrease in the life span of these mice, concomitantly with an increased incidence of tumors, in particular lymphomas. |
| 131 | • C57Bl/6<br>• Germline<br>• Lck-TERT mice | Higher incidence of spontaneous lymphoma. | *n.d.* | Lck-Tert thymocytes show greater spontaneous and IR-induced chromosomal instability. |
| 84 | • C57Bl/6<br>• Germline<br>• K5-mTERT | More hyperproliferative lesions | Increased maximal lifespan<br>Decreased degenerative lesions (kidney, male germ line) | |
| 132 | • FVB/n strain<br>• CMV enhancer/β-actin promoter | *n.d.* | Enhancing of hair growth through stem cell mobilization (independently of the TERC component) | |
| 14 | • C57Bl/6<br>• Germline<br>• K5-mTERT/Sp53 and K5-mTERT/Sp53/SArf/Sp16 | Higher tumor incidence (mainly lymphomas) and similar lifespan (K5-mTERT/Sp53 *vs* K5-mTERT) | Lower tumor incidence and higher lifespan and health-span in K5-mTERT/Sp53/SArf/Sp16 *vs* K5-mTERT/Sp53 or WT controls | |
| 89 | • G4$^{TERT\text{-}ER}$ mice (30–35 week old C57Bl/6)<br>• 4-OHT activation late in life | Telomerase activation was not sufficient to promote tumorigenesis. | Extended life and health span | Chromosomal instability was referred. |

| Ref | Model / Telomerase activation | Cancer | Aging | Comments |
|---|---|---|---|---|
| 120 | • C57Bl/6 (1yr and 2 yrs old)<br>• TA-65 | No increase in tumor incidence | Extended health. No differences in lifespan | Activation of telomerase is not direct<br>Other studies have described similar telomerase activators in mice and humans (see references: [127, 133]) |
| 82 | • G4 TERT$^{-/-}$ (WW6/C57BL/6)<br>• Ad-mTERT (specifically to the liver) | *n.d.* | Ad-mTERT injection partial rescue PGC-1α/β, Glc-6-P and Pepck expression, accompanied by a 30% increase in glucose levels relative to Ad-GFP controls, in G4-TERT$^{-/-}$ mice | |
| 134 | • C57Bl/6 (18 to 22 g., males and females)<br>• Ad-mTERT-GFP (microinjection into the bilateral Dg of mice) | *n.d.* | Ad-mTERT-GFP led to neurogenesis upregulation, produced antidepressant-like behaviors, and prevented the CMS-induced behavioral modifications | |
| 128 | • CD1 (9–11 weeks old)<br>• AGS-499 | *n.d.* | Extended health (neuroprotective effects in NMDA-injected CD-1 mice) | No mechanism of telomerase activation |
| 15 | • C57Bl/6 (1yr and 2 yrs old)<br>• AAV9-mTERT | No increased tumor incidence | Extended life and health span | |