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Potential of telomerase activation in extending health span and longevity

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Abstract

The progressive increase in the elderly population worldwide has resulted in higher numbers of individuals affected by age-associated diseases, such as neurodegenerative and heart diseases, metabolic impairment, or cancer, with the subsequent burden for national health systems. Therapeutic interventions aimed to increase the quality of life at advanced age are visualized as important demands for the future, both at the level of individuals and society. Novel advances in telomerase function from several independent laboratories have resulted in potential new therapeutic strategies which appear as promising new venues to prevent cellular and tissue dysfunction and organismal decline, thereby increasing the so-called “health span”. Here, we analyze these recent advances.

Ageing as the cause of disease

Ageing, previously though has an unmodifiable trait, is nowadays viewed as a dynamic process. Furthermore, aging is currently seen as a causative factor for tissue dysfunction and increased risk for developing various age-associated diseases, including cancer. This highlights the importance of understanding the molecular and genetic causes of aging for the developed world, which is experiencing a dramatic increase in the elderly population [1]. In particular, a better understanding of how ageing results in tissue dysfunction and/or cancer and how we can circumvent ageing-associated decline are important questions at the present time. It has been demonstrated that ageing could be modulated and respond to several biological pathways [2]. A number of these pathways are conserved in different species, demonstrating that ageing can involve common cellular processes, which are conserved over evolution. In particular, pathways involved in genome stability, nutrient sensing, oxidative damage balance, and growth, seem to be central in ageing modulation [2,3]. In this review, we will focus on the relatively recent notion that aging is produced by accumulation of DNA damage associated to cell division. In particular, we will discuss recent advances for health improvement in mammals (in particular laboratory mice), based on prevention of the accumulation of critically short telomeres, a particularly deleterious type of DNA damage which induces a persistent DNA damage response (DDR), leading to cell death and senescence at the cellular level, and to loss of regenerative capacity of tissues at the organismal level [4-6]. This review will examine what is known on the historical role of telomerase in ageing, paying special attention to recent works which undoubtedly demonstrate that ageing can be actually reversed (and not only retarded) through telomerase re-expression.

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Telomerase, DNA damage, and ageing

Tissue degeneration occurs in long-lived organisms. The accumulation of dysfunctional cells, together with a limited regenerative capacity of tissues, is thought to determine the age-related decline of body organs [7,8] and, in some situations, settle a basis for cancer progression [9]. Dysfunctional cells, usually characterized by the presence of short telomeres, are a barrier for tumor progression when presenting an intact DNA damage response which directs cells for senescence or cell death [8,10,11], although recent evidence demonstrated that transient telomere dysfunction *per se* could promote chromosomal instability and carcinogenesis in telomerase-proficient mice [12]. If DNA damage response barriers are bypassed (for instance through deletion of p53 [11]) short telomere cells resume and accelerate transformation phenotypes. In this scenario, re-activation of telomerase further enables full malignancy [13].

Therapies that prevent the appearance or that decrease the number of damaged cells are therefore viewed as potentially effective in slowing the ageing progression. In this regard, increased gene dose of tumor suppressor genes that eliminate damage cells from the organism through apoptosis and senescence such as p53 and p16 are known to increase life span [14,15] furthermore, clearance of senescent cells from already-adult organisms also delays aging, thus confirming the involvement of damaged cells in tissue dysfunction [16]. Similarly, prevention of metabolic damage also increases health span, as recently shown for SIRT1 and PTEN gain of function mouse models [17-19]. Interestingly, a link between telomeres and mitochondrial function has been also proposed [20,21]. In particular, aging provoked by telomere-dysfunction leads to changes in key metabolic genes that involve a functional p53 and are characterized by a repression of PGC-1α. In turn, telomerase re-activation in old wild-type mice, results in increased PGC-1α levels [21]. These metabolic changes associated to telomere dysfunction could potentially synergize with the DNA damage response triggered by short telomeres and contribute to senescence and/or apoptosis, and the eventual organismal failure associated to the aging process. Here we will focus in strategies aimed to decrease the accumulation of persistent DNA damage associated to short/dysfunctional telomeres by using telomerase reactivation strategies, which has been extensively linked to organismal aging [4,22,23].

Telomerase phenotypes

Telomerase is a multiprotein complex encompassing a reverse transcriptase catalytic subunit (Tert) and an associated RNA component (Terc) [24]. Telomerase adds DNA repeats (TTAGGG in mammals) to chromosome ends, thereby counteracting telomere shortening associated to DNA replication (the so-called end-replication problem) or to DNA degrading activities [25-28]. Animal models with mutations in telomerase or telomere-associated proteins (shelterin) have been instrumental to unveil the role of telomeres in cancer and ageing [4-6,22,23,29-33]. In particular, knockout mice for Tert or Terc with critically short telomeres are characterized by an increased incidence of age-related diseases and premature tissue degeneration which mostly, but not only, affects tissues with elevated cellular turnover such as the bone marrow or the gastrointestinal system [34]. In this regard, a role for telomerase and telomere integrity in stem cell functionality has been shown for different adult stem cell niches, including the skin and the bone marrow [29,35-38]. In particular, some adult stem cell compartments are telomerase positive and present longer telomeres than the surrounding tissues [37, 39, 40]. Further supporting a role for stem cells in tissue functionality, mice with mutations directly affecting the pools of stem cells are characterized by accelerated aging [41]. Late generation Tert or Terc knockout mice present a decrease in mean telomere length and a higher percentage of short telomeres in several organs (including the pools of stem cells), which correlate with an incapacity of tissues to

regenerate and result, ultimately, in an accelerated tissue degeneration and a concomitant decrease of the lifespan [5,6,42]. These seminal studies characterizing telomerase deficient mice have placed telomeres and telomerase as key elements for organismal aging. Further supporting it, there is recent evidence demonstrating that telomere size measured early in life is a *bona fide* predictor of lifespan in birds [43], and telomere dynamics seems to similarly correlate with the lifespan of laboratory mice (Vera E.; Bernardes de Jesus B.; Foronda M.; Blasco MA.; Cell Reports, *In Press*, [2012]).

Anti-ageing role of telomerase

Telomerase constitutive expression by using mouse transgenesis in adult tissues has pinpointed a role for telomerase in tissue fitness and prevention of aging, although at the expense of an slightly increased incidence of cancer [22,44,45], Importantly, when cancelling the increased cancer incidence associated to constitutive transgenic telomerase expression by generating telomerase transgenic mice in a cancer resistant background owing to increase gene dosage of tumors suppressor genes [*p16, Arf and p53*], this resulted in an improved extension of lifespan of 43% when comparing to the corresponding WT mice [22].

The cancer promoting activity of telomerase observed in the transgenic mouse models, however, is not apparent when telomerase is re-activated late in life. In particular, we have recently shown by using a gene therapy strategy with non-integrative adeno associated virus (AAV), that re-activation of telomerase in adult or old mice results in delayed aging and significant lifespan extension in the absence of increased cancer susceptibility [21]. A single telomerase (TERT) treatment of WT mice with these vectors was sufficient to rescue the age-dependent decline and to delay normal mouse physiological aging (Fig. 1). In this experimental setting, median lifespan was extended by up to 24% in 1-year-old mice, and by 13% in animals of 2 years of age. This study confirms that telomerase expression, by means of a gene therapy, could be considered a feasible approach to extend lifespan without increasing cancer incidence. Old mice treated with TERT showed a better skin and metabolic fitness and less bone loss after treatment, which are well characterized indicators of ageing progression. Moreover, TERT-treated mice showed an improved age-related impairment of balance and coordination and interestingly, a tendency for memory improvement. Telomerase has been proposed to have telomere-independent roles (independent of its catalytic activity) as a cofactor on the promoter of Wnt targeted genes [46], although questions have been raised about the relevance of this activation [42,47]. In this regard, when mice were treated with a catalytically dead TERT (TERT-DN [48]) the beneficial effects of TERT could not be reproduced and longevity was not increased, demonstrating that healthspan amelioration requires telomerase reverse transcriptase activity [21].

Importantly, the safety of this type of strategy is illustrated by the fact that adult mice expressing TERT did not develop more cancer. This could be related to the fact that AAV vectors are non-integrative, leading to a loss of TERT expression in highly proliferating cells or tissues, such as cancer cells. Other explanation, could be the fact that AAV preferentially targets post-mitotic cells from peripheral tissues (of adult mice in that case), which are considered more refractory to cancer than the highly proliferative tissues. In this regard, telomerase re-introduction in an accelerated model of ageing involving accelerated telomerase loss ($G4^{TERT\text{-}ER}$ model) rescues the “ageing-phenotype” [49] without increasing cancer incidence. This could be related to the fact that cells lacking telomerase are resistant to cancer initiation [50], mimicking the tumor suppressor situation and, somehow, can preserve this characteristic after a telomerase pulse, even in the presence of a higher genomic instability [49]. These studies validate that telomerase could play important roles in tissue regeneration of adult organisms and are a proof-of-principle that ageing can be

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reversed and retarded. Moreover, normal aging comprises similar changes to those observed in aging produced by accelerated telomere shortening further linking telomere biology to the aging process. Novel therapeutic strategies involving telomerase expression could unveil potential mechanisms against tissue deterioration.

Chemical activators of telomerase are promising strategies nowadays. Some telomerase activators were assessed in the literature. TA-65, a single chemical compound extracted from *Astragalus Membranaceus*, was shown to activate telomerase *in vitro* and *in vivo* [51,52]. Adult mice supplemented with this compound presented an improved healthspan, in particular at the metabolic level. Previously (to the study in mice), data in humans demonstrated a better dynamics of the immune system (CD8+ T lymphocytes) from HIV-infected humans [51] and a similar increase in health-span of aged healthy costumers [53]. Recently, new compounds activators of telomerase have been described, for instance a novel telomerase activator (AGS-499) was demonstrated to play neuroprotective effects after NMDA treatment in mice and delayed the progression of amyotrophic lateral sclerosis (ALS) in SOD1 transgenic mice increasing their survival, further supporting a role for telomerase in tissue functionality [54].

These new findings open a new door in ageing research and degenerative healing. The modulation of telomerase and/or its associated “ageing-network” [55] in adult tissues establishes an important basis for ageing research and demonstrates that age-associated degeneration is a potential target of biomedical intervention. Further studies; in particular long-term follow ups, should be carried to assess adverse effects and to discriminate changes at the tissue-level.

Perspectives for a healthy life

The increase in the worldwide life expectancy was accompanied by intensification in age-associated diseases. Characterization of biomarkers and modulation of different pathways are candidates for a faster characterization of disease and discovery of novel therapeutics, respectively. In this aspect telomerase has been recently scrutinized as an anti-ageing factor. Several independent works demonstrated that telomerase expression through genetic modifications, viral delivery or chemical activation result in a significant rescue of age-related pathologies. These new results are exciting however additional efforts will be needed to translate these findings into actual therapies. This opens an unprecedented door for anti-aging research.

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authors describe that a small-molecule activator of telomerase (TA-65) is capable of increasing average telomere length and decreasing the percentage of critically short telomeres and of DNA damage *in vitro* and *in vivo*. TA-65 supplementation result in an improvement of certain health-span indicators. This study, together with references 21, 48 and 53 support the development of regenerative strategies designed to restore telomere integrity.

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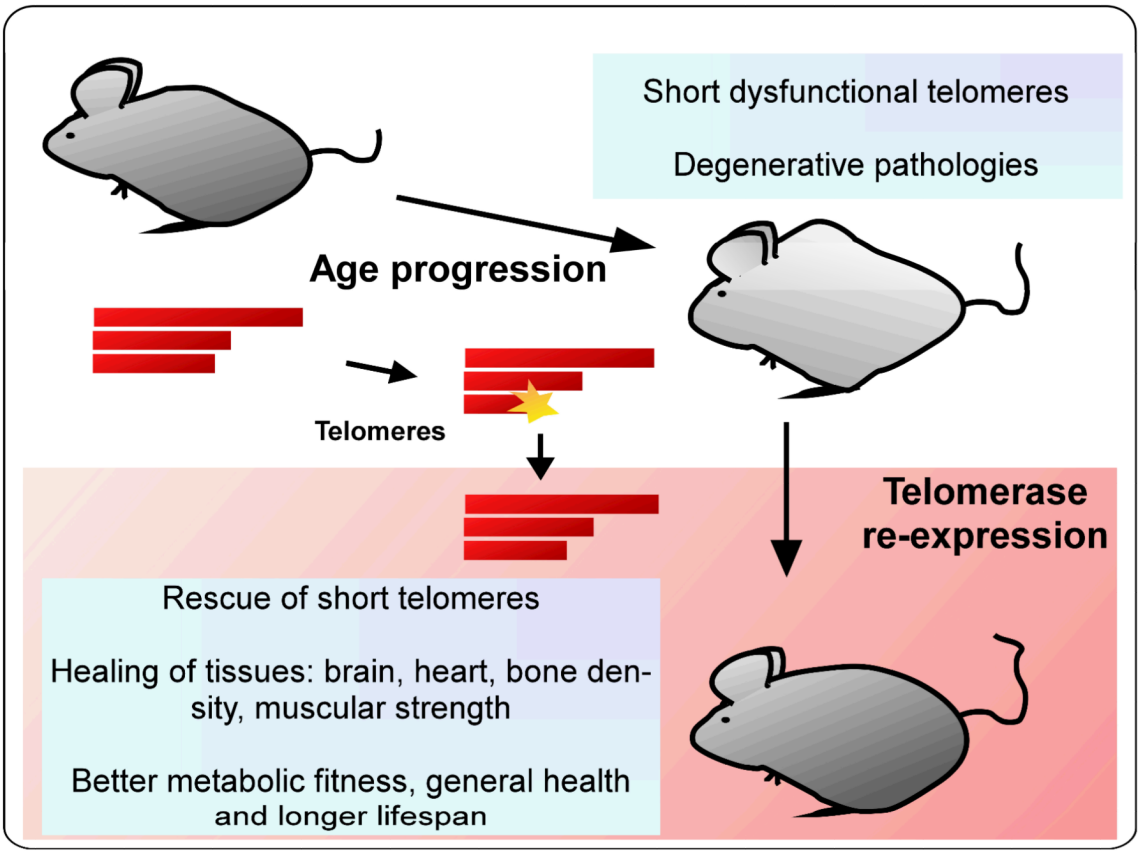

Fig.1. Rescue of age-dependent tissue degeneration in adult mice.

Therapies involving telomerase expression in adult tissues have demonstrated a potential impact in rescuing of age-associated degenerative pathologies [21,49]. Extension of short telomeres is one of the outcomes, but we cannot dismiss novel roles for telomerase in distinct networks [55].