Telomere biology in healthy aging and disease

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Abstract Aging is a biological process that affects most cells, organisms and species. Telomeres have been postulated as a universal biological clock that shortens in parallel with aging in cells. Telomeres are located at the end of the chromosomes and consist of an evolutionary conserved repetitive nucleotide sequence ranging in length from a few hundred base pairs in yeast till several kilo base pairs in vertebrates. Telomeres associate with shelterin proteins and form a complex protecting the chromosomal deoxyribonucleic acid (DNA) from recognition by the DNA damage-repair system. Due to the “end-replication problem” telomeres shorten with each mitotic cycle resulting in cumulative telomere attrition during aging. When telomeres reach a critical length the cell will not further undergo cell divisions and become senescent or otherwise dysfunctional. Telomere shortening has not only been linked to aging but also to several age associated diseases, including tumorigenesis, coronary artery disease, and heart failure. In the current review, we will discuss the role of telomere biology in relation to aging and aging associated diseases.

Keywords Aging · Tumor · Heart · Apoptosis · Cell death

“Death takes place because a worn-out tissue cannot forever renew itself, and because a capacity for increase by means of cell division is not everlasting but finite”

A. Weismann. Clarendon, Oxford 1881

A brief historical perspective

Telomeres are special deoxyribonucleic acid (DNA) structures that “cap” the ends of our chromosomes in conjunction with specialized proteins, the telomere-shelterin complex. This complex protects the chromosomes from erosion and end-to-end fusion. The term telomere originates from the Greek telos, which means “end” and meros which means “part”. The existence of these end-parts of the chromosomes was first suggested in 1938 by Muller [60]. In 1961, Hayflick undermined a major paradigm of his time by providing convincing evidence that primary cells were not immortal, but could undergo only a limited number of cell divisions. This phenomenon, currently being referred to as the Hayflick limit [38], predicts the existence of an internal counting mechanism within the cell. Olovnikov, a Russian researcher, was the first who linked the end of the chromosomes to the cell cycle arrest described by Leonard Hayflick [66]. The term “end-replication problem” describes the effect that linear chromosomes cannot replicate their terminal ends of the chromosome and consequently shorten at each mitotic cycle. The first identification of the sequence of the terminal end of the chromosome (the telomere) in the Tetrahymena was discovered by Elizabeth Blackburn and Joseph Gal in 1978 [6]. Ten years later, Robert Moyazis and colleagues revealed that the sequence of the human telomere consists of TTAGGG repeats [59]. Up to date, the sequence of many species and organisms have been established and we can conclude that the telomeres are an evolutionary well-conserved sequence [55] (Table 1). The next major breakthrough in telomere biology was the discovery of the reverse transcriptase telomerase by Carol Greider working as a postdoctoral student at the laboratory of Elizabeth Blackburn in 1985 [31]. In contrast to DNA-polymerase, telomerase is capable of elongating the telomeres. Bypassing the end-replication problem for germ cells is essential to maintain
telomere length for offspring. In 1997 Maria Blasco in the lab of Carol Greider created a telomerase deficient mouse, which had inactive telomerase and consequently reduced telomere length in each following generation [8]. The most striking characteristic of the telomeres in somatic cells is the shortening with age and in cell culture the telomere length is directly linked to the replicative capacity. In this review, we will discuss the function of the telomeres and will focus on the importance of telomere biology in normal aging and in pathology.

### Telomere; structure and T-loop

In vertebrates, the end of the chromosome, a G-rich strand, ends in a single strand extension of 75–200 bp, the G-tail (Fig. 1). In the nonmitotic phase of the cell cycle this G-tail is shielded by a crucial so-called telomere shelterin complex in which the telomere binds internally by forming two internal loops, the D-loop and the T-loop [33]. The telomere shelterin complex is designed to protect the chromosomal ends from erosion and end-to-end fusion [21] and is formed by different proteins associated with the telomeres, such as telomeric repeat binding factor 1 (TRF1) and 2 (TRF2) that can bind to double stranded telomere DNA. Another telomere associated protein, protein protection of telomeres 1 (POT1), can bind directly to single stranded DNA, and it is suggested that POT1 binding to the 3’overhang is important for forming the D-loop. Other proteins involved in the shelterin complex that are recruited

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**Table 1** Telomere length and telomere sequence in different species

| Species          | Telomere length | Telomere sequence | Reference |
|------------------|-----------------|-------------------|-----------|
| Ciliates         |                 |                   |           |
| Protozoan (T. thermophila) | 120–420 bp | T₂G₄ | [6] |
| Yeast            |                 |                   |           |
| Baker’s yeast (S. cerevisiae) | 200–300 bp | T𝐆₂₋₃(T𝐆)₁₋₆ | [76] |
| Vertebrates      |                 |                   |           |
| Humans           | 5–15 kb         | T₂A🇬₃            | [59] |
| Mice             | Up to 150 kb    | T₂Agratis        | [39] |
| Rats             | 20–100 kb       | T₂A gratis        | [17] |
| Birds            | 5–20 kb         | T₂A gratis        | [37] |
| Invertebrate     |                 |                   |           |
| Ants             | 9–13 kb         | T₂A gratis        | [50] |
| Plants           | 2–5 kb          | T₃A gratis        | [68] |
| Thale cress (A. thaliana) | 2–5 kb | T₃A gratis        | [68] |

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Fig. 1 Telomeres are located at the very final ends of the linear chromosomes and consists of TTAGGG repeats in vertebrates. Reproduced with permission [42]
by TRF1 and TRF2 are repressor activator protein 1 (Rap1), TPP1, and TRF1-interacting nuclear factor 2 (TIN2) [21] (Fig. 2). Telomere shortening will result in destabilization of the chromosomes and an inability to recruit the proteins of the shelterin complex. As a result, the T-loop cannot be formed as easily and the chromosome ends will be left uncapped. This is a situation that resembles double stranded DNA breaks, and presents a highly unstable cellular state that may lead to activation of the p53 or p16ink4a pathway and eventually can result in senescence or apoptosis [20].

Telomere length and aging

In contrast to the similarity of the sequence, the telomere length is highly variable among species, within species, within an organism, and even between chromosomes. In a study that evaluated telomere length in different organs from humans of different age, telomere length varied between 8 and 15 kbp and was highly variable between organs from one subject [82]. This may be explained by variable telomere attrition rate—in humans it is estimated that telomere length shortens 30–150 bp per replication cycle in fibroblasts and lymphocytes [35, 97]. There is a high amount of variance in telomere length in humans. Already at birth, remarkable differences in telomere length are observed. In addition, females have longer telomeres than men and in African Americans telomeres generally are longer than in White Americans [41]. As there is no gender difference at birth, it is most likely due to differences in environmental factors such as differences in estrogens levels [48]. Strikingly, macaques have approximately the same life span as humans but have longer telomeres in addition to a longer subtelomeric region [29]. Telomere attrition rate is not stable for each chromosome, in human cells the chromosomes 17p, 13p, and 19p have been identified as being shorter compared to the other chromosomes [30, 52].

In humans, telomere length is measured extensively in leukocytes in relation to aging and various pathologies. Leukocyte telomere length obviously has the advantage of being relatively easily obtained and processing is a relatively simple process. Telomere length in leukocytes is highly variable among individuals and decreases throughout life. Especially large differences develop the first few years after birth [70] after which telomere length are relatively stable throughout childhood, preadolescent, and adolescent years. Eventually, telomere length attrition increases at very old age (Fig. 3). An important aging hypothesis is that telomere attrition increases at the onset of disease. Therefore, telomere length of the leukocytes could be a good marker for disease. Telomere length in different aging diseases is discussed later in the review. The major disadvantage of using leukocyte telomere length is that it is a measure of the activity state of the immune system and one might argue that leukocyte telomere length is rather a representation of increased inflammation than of aging.

Most animal research on telomeres has been performed in rodents, especially on inbred mice and rat species that have highly variable telomere lengths. Laboratory rats have relatively long telomeres that vary between 20 and 100 kb and telomere length in mice is even more variable and can extend up to 150 kb (of the C57BL/6 mice) [17, 39]. In contrast, the outbred (wild type) mice strain Mus spretus has telomere length that is comparable to human cells. Comparing multiple mice strains showed that most mouse species do not have long telomeres, and long telomeres in mice strains originate from excessive breeding [39]. In rats, telomere length shortens with aging in several organs like kidney, liver, pancreas, and lungs. Research into telomere

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Fig. 2 Schematic representation of the telomere shelterin complex and its associated proteins; TRF1, TRF2, POT1, Rap1, TIN2, and TPP1

Fig. 3 Telomere length in lymphocytes and granulocytes during human lifespan. Reproduced with permission from [4]
length from blood derived cells from multiple bird species with different life expectancies shows that telomere attrition rate is a better predictor of life expectancy than the age of the animal [37]. One remarkable animal is the Leach’s storm-petrel, a long lived bird species with a maximum observed lifespan of 36 years. Instead of telomere attrition, it is suggested that the telomere length increases during aging in this species [37]. The Leach’s storm-petrel has increased levels of telomerase activity in their bone marrow cells compared to other birds [36]. It is tempting to speculate that these animals have managed to increase their lifespan by dealing with telomere erosion. However, the assumption that absolute telomere length has an effect on life span is still elusive. For example, mice strains with longer telomeres do not seem to have an increased lifespan compared to mice strains with shorter telomeres. How these differences in telomere length affect lifespan are still unknown, the most accepted hypothesis is that the shortest telomeres are contributing most to the expected lifespan [40].

**Quantifying telomere length**

The most commonly used techniques to measure telomere length are Southern blot, polymerase-chain reaction (PCR) based techniques and in situ hybridization. Southern blotting or telomere restriction fragment analysis (TRF) is the traditional method and still considered the gold standard [22]. The telomeres are represented as smears, and the weight of the smear is representative for the average telomere length. The main disadvantage of this technique is the relatively high amounts of DNA which is required. This technique is therefore not feasible for determining telomere length in single cells, or for different chromosomes, or when DNA availability is limited. The real-time PCR-based method is relatively fast and only requires small amounts of genomic DNA. This technique is based on modified PCR primers to avoid primer-dimer amplification as much as possible [13]. The final measure will be a ratio telomere quantity divided by a reference gene quantity (T/S ratio) which is a relative measure, perfectly valid within a given population (as it will correctly rank subjects) but more difficult to compare between populations. The most recent advantage is the development of a multiplex assay in which both the telomere and the reference gene is targeted in a single well [14]. The PCR technique suffers the same disadvantage as the TRF method when considering single cell or specific chromosome analysis. The quantitative PCR technique has been widely used and accepted to estimate telomere length in large cohort studies [10, 15, 86, 93]. A specific modification of the previous techniques is single telomere length analysis, which uses Southern blotting techniques to separate PCR-amplified products, by combining specific primers and probes for the telomeres and the subtelomeric regions to measure telomere length per chromosome [5]. This technique is at the moment thought to be the most accurate telomere measurement, but it is a labor-intensive and technically challenging technique that can only be used for chromosomes from which the subtelomeric region is known. In situ hybridization techniques make it possible to visualize the telomeres in single cells. Quantitative fluorescence in situ hybridization (Q-FISH) uses a (CCCTAA), peptide nucleic acid probe to visualize the telomeres. In metaphase spreads, the telomeres are visible at the end of the chromosomes and they can be quantified also in single chromosomes [52]. An important variation on this technique is the flow fluorescence in situ hybridization, or Flow-FISH. By combining Q-FISH hybridization and flow cytometry analysis, it is possible to measure average telomere length in interphase cells in combination with standard flow cytometry antibodies to select the cell population of interest [71].

**Telomere maintenance**

Telomerase, a ribonucleoprotein complex that is composed of RNA and protein components, can elongate the telomere sequence in mammals and yeast by binding to the open end of the G-strand. Telomerase is highly expressed during embryonic development but its expression is suppressed within a few weeks after birth in most somatic cells. Highly proliferative cells maintain high levels of telomerase, like stem cells, progenitor cells, lymphocytes, skin keratinocytes, and cancer cells [27]. The major components of the active telomerase complex are telomerase reverse transcriptase (TERT), a telomerase RNA component (TERC, that is complementary to the telomere sequence) and dyskerin, which is a protein that binds to both TERT and TERC and increases stability of the complex [19, 32]. Elongation of the telomeres in mammals and yeast not depending on telomerase is called alternative lengthening of telomeres (ALT). In human tumors, it was discovered that cells negative for telomerase could also elongate their telomeres by a recombination mechanism [12]. Recombination takes place by binding of the ALT-associated promyelocytic leukemia bodies to the telomeres. Telomere elongation occurs heterozygous in these cells and ALT can best be recognized by the presence of both short and long telomeres.

The TERC /− mouse has increased our knowledge on the importance of telomerase in aging and in the potential role of telomerase and telomere shortening in the different diseases [101]. As always, it is difficult to translate data...
from knockout models directly to human pathology, but especially in premature aging diseases the TERC-/- mice show great overlap with human disease [7].

Telomere biology and cellular senescence

Primary cells in culture are not immortal. As Hayflick demonstrated in 1961, cells stop dividing after a certain number of passages and become sedative [38], a phenotype also known as replicative senescence. The senescent phenotype is accompanied by changes in morphology, gene expression, and proteins. Beta galactosidase staining is frequently used to identify senescent cells and is associated with changes in p53, p16, and p21 expression [26, 62, 78]. There are multiple stimuli that can induce senescence; telomere shortening, DNA damage, and induction of oncogenic or tumor suppressor signals [16, 47, 79]. Induction of cellular senescence is an important suppressor of tumorigenesis [79, 103]. Although telomere attrition might not be primarily involved in the acute induction of senescence [16], the cumulative burden of oxidative stress and the cumulative telomere attrition might increase to likelihood of a cell to enter senescence [47]. Telomere attrition through replication and accumulation of DNA damage can result in an increase of senescent cells in different tissues and organs eventually resulting in decreased function and pathology. Telomere shortening has been implicated as one of the major mechanisms of replicative senescence [97]. The end-replication problem accounts for a loss of ~100 bp telomere length at each population doubling. On average cells are estimated to reach senescence after ~50 population doublings. This is a bit earlier than predicted by the end-replication problem alone. It is likely that the state of the telomere and the presence of the proteins involved in forming the shelterin complex are important cofactors associated with the induction of senescence [46]. For example, there is ample evidence that disruption of the telomere binding proteins results in early senescence. In primary human fibroblasts, TRF2 inhibition induces a p53- and retinoblastoma-dependent senescent phenotype [46, 94]. Likewise, inhibiting POT1 by RNA interference led to the disappearance of the telomer shortening single-stranded overhangs and induced apoptosis, chromosomal instability, and senescence [104].

Telomere biology in stem cells

Stem cells and progenitor cells have an important role in maintaining tissue homeostasis by replenishing (senescent, apoptotic) cells and repairing damage that occurs throughout life. Exhaustion of the stem cell or progenitor cell pool has been considered an important factor in the aging process of an organism [67]. One of the hallmarks of stem cells is their telomerase activity and stable length of their telomeres [63, 87]. Stem cells reside in different compartments throughout the body. In mice it has been shown that there exists a large difference in telomere length among the different compartments. The longest telomeres have been observed in skin, small intestine, cornea, testis, and brain compartments [28]. Although it seems that stem cells have stable telomeres by its increased telomerase activity, it does not make them invulnerable to telomere erosion. Clonal expansion after damage or in a disease state could induce telomere erosion that ultimately could induce senescence and an exhaustion of the stem cell pool. This hypothesis is supported by data from bone marrow-derived cells exhibiting a decreased migratory capacity and significant telomere shortening in patients with coronary artery disease [80]. The best characterized stem cells are the hematopoietic stem cells (HSC) which continuously replenish the hematopoietic cell lineages. HSC have been reported to have shorter telomeres compared to fetal liver and cord blood derived cells [96]. Recent data have also suggested a reduction of telomere length of HSC during aging [99].

Telomere biology and premature aging

Some human disorders associated with shorter telomere length originate from defective telomerase function or mutations in the DNA repair system. For example, Dyskeratosis congenita (DC) is a human premature aging syndrome linked to mutations in the telomerase complex resulting in decreased telomerase stability and shorter telomeres [57]. Patients with DC develop numerous different pathologies, including short stature, hypogonadism, infertility, bone marrow failure, skin defects, hematopoietic defects, and premature death. In addition, these patients have an increased susceptibility to develop malignancies. Another human disease example that involves a telomerase mutation is aplastic anemia. Subjects with aplastic anemia experience accelerated telomere shortening and die young [51]. Some diseases originating from mutations in genes of the DNA repair system also result in a phenotype characterized by accelerated telomere shortening and premature aging. Example genes include the Ataxia telangiectasia (ATM), Werner syndrome, Bloom syndrome, and Fanconi anemia genes. Most of these DNA repair genes also have a role in telomere biology. Mouse knockout models for these proteins do not always result in the same characteristics as the human disease. It has been suggested that the remarkable longer telomere length in mice might provide an explanation for these discrepancies. Combining DNA repair KO mice for Werner, Bloom, and ATM syndrome with the TERC -/- mice.
Indeed resulted into a phenotype with characteristics that more closely resembled the expected pathology in humans [7].

Telomeres and aging associated diseases

The debate on how telomere biology affects life span is ongoing, but a link between telomere length and mortality has been established. In addition, numerous associations between aging-associated diseases and telomere length have been reported [15]. Telomere length could be considered as a biological parameter that intertwines replicative history and exposure to environmental stress. Human life span is highly dependent on the development of aging associated diseases especially cancer and cardiovascular disease.

Cancer

Tumorigenesis is a major factor influencing life expectancy in long-lived species. Shorter telomere length is also a risk factor for the development of cancer [102]. Progressive shortening of the telomeres will lead to activation of the DNA damage response [34, 102]. In the normal situation this will result in activation of ataxia telangiectasia mutated (ATM) and ataxia telangiectasia- and Rad3-related (ATR), and the associated downstream factors including CHK1, CHK2, and phosphorylation of p53. In the setting of a competent p53 pathway, senescence or apoptosis will be initiated and tumorigenesis inhibited [25]. However, when the p53 pathway is inadequate tumorigenesis is no longer inhibited in the presence of telomere dysfunction [25, 34, 69]. In addition, 80 to 90% of all tumors express telomerase or have a form of alternative telomere lengthening [77]. Clinical data revealed that telomere length (measured in lymphocytes) is shorter in subjects with different types of cancer, including cancers of the head and neck, breast, bladder, prostate, lung, and kidney [102].

Cardiovascular risk factors

Next to cancer, cardiovascular disease and its risk factors are the major contributors to the population’s disease burden during aging. For example, the presence of diabetes has been linked to reduced telomere length [1, 44, 75]. In the Framingham Heart Study, even a subclinical presence of insulin resistance was associated with reduced telomere length [24]. Hypertension and the responsiveness to angiotensin are related to outcome in humans [88, 92]. The number of genetic variants influencing the development of hypertension is only small [61]. However, a role for telomeres has been suggested, normotensive persons with short telomeres were more susceptible to develop hypertension and hypertensive subjects with short telomeres were more susceptible to develop atherosclerosis [105]. Interestingly, even subclinical activation of the renin-angiotensin system (RAS) has been associated with shorter telomeres [24, 95]. A final example is cigarette smoking, a strong risk factor for the development of coronary heart disease [2]. Smoking negatively affects telomere length [54, 58, 84], possibly due to mechanisms involving oxidative stress [98].

Atherosclerosis

Endothelial dysfunction is recognized as one of the earliest events of atherogenesis [3] and is associated with classical risk factors or risk markers including cholesterol and inflammatory markers [85, 91], which can be modified by pharmacological treatment [92]. The endothelial and smooth muscle cells in the vessel, which are most susceptible to develop atherosclerosis are highly proliferative and are subjected to stress by increasing mean arterial pressure, increased cholesterol, and increased oxidative stress. This results in an increased susceptibility for senescence [45, 53]. Indeed senescent-positive endothelial cells can be found in almost any atherosclerotic plaque [56] and an association with shorter telomeres in atherosclerotic plaques has been established [64]. The first clinical study linking coronary artery disease to telomere length dates back to 2001 [72]. This groundbreaking study suggested telomeres of circulating white blood cells to be approximately 300 bp shorter in patients with coronary artery disease compared to controls. The authors estimated that this telomere differences resembles an age difference of almost 9 years [72]. Further and larger scale studies confirmed these findings and extended it to premature atherosclerosis and ischemic heart failure [9, 10, 15, 93]. For example, the West of Scotland Primary Prevention Study (WOSCOPS) observed that subjects in the middle or lower tertile of telomere length were at greater risk to experience a clinical manifestation of coronary heart disease than persons with longer telomeres [10]. The WOSCOPS data also suggested that the use of statins was more beneficial for the patients with the shortest telomeres [10]. Apparently patients that are protected by longer telomeres addition of statin treatment did not result in additional protection. Interestingly, telomeres of offspring from subjects with coronary artery disease already have shorter telomeres compared to offspring from parents without atherosclerosis [11]. This might explain part of the heritability of coronary artery disease next to other genetic factors [73, 83].

Heart failure

Chronic heart failure (CHF) is the main cardiovascular discharge diagnosis in the United States [23]. In particular,
after the necessity of hospital admission, CHF is associated with a high mortality rate [43]. Recent clinical trials have not added much to the prognosis, and the search for new strategies is intensive [49, 89, 90, 100]. Although in general, the incidence and prevalence of CHF steeply increases with aging, there exists a striking variability in the susceptibility, age of onset and pace of progression. This variability cannot completely be attributed to the presence of conventional risk factors and recent evidence is suggesting a role for telomere biology [74]. Endomyocardial biopsies from patients with heart failure have demonstrated that diseased hearts are characterized by shorter telomeres, increased cellular senescence, and cell death [18]. It has been estimated that telomere length is reduced by as much as 25% in failing hearts compared to nonfailing hearts [65]. Also, the telomere length in leukocytes of subjects with heart failure are significantly shorter compared to age and gender balanced controls [86]. In this study, the severity of heart failure symptoms was also associated with the degree of telomere shortening. Furthermore, cardiac function as measured by ejection fraction in general has been associated with telomere length [81]. One standard deviation of longer telomere length was associated with a 5% higher left ventricular ejection fraction. In these elderly subjects, telomere length alone accounted for 12% in the observed variability of ejection fraction. Renal function impairment relates to even worse outcome in patients with CHF. Shorter telomere length in CHF is also associated with decreased renal function, possibly due to drop-out of functional nephrons [93].

Conclurene and future perspectives

Telomere biology is involved in biological aging and disease processes. Experimental evidence suggests that telomere shortening, uncapping, and cellular senescence results in an “aging” phenotype [46]. The exhaustion of progenitor cells and the cumulating of senescent cells might explain the decline in organ function associated with aging. Shorter telomere length has been associated with several age associated diseases, including cancer, diabetes, atherosclerosis, and heart failure. To gain more insights in the role of telomere biology in the aging process of humans, we are still in need of large population based cohorts with telomere length and telomerase activity measurements at multiple time-points. If telomere biology can be proven to be causally involved in the development and progression of these age-associated diseases, it will pave the way for new therapeutic or preventive strategies. For example, telomerase or telomere length could be targeted in the emerging stem cell therapies for organ dysfunctions.

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