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REVIEW ARTICLE

The role of telomere dysfunction in genomic instability and age-related diseases

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Abstract

Telomeres are specialized structures located at the ends of chromosomes that are critical for maintaining genomic integrity. Telomeres are shortened during each cycle of cell division because chromosomes are not able to completely replicate, a phenomenon known as the end-replication problem. Telomere shortening or dysfunction causes genome instability and is implicated in a variety of diseases, including cancer, cardiovascular disease and neurodegenerative disorders. Here, we discuss recent advances in basic and clinical research into telomere regulation and maintenance, and highlight how dysfunctional telomeres influence aging and age-related diseases.

Keywords Telomere · Genome stability · Aging · Age-related diseases

Introduction

Telomeres are specialized structures located at the ends of chromosomes. Structurally, telomeres are composed of tandem-repeat sequences (TTAGGG) in vertebrates and are terminated by a single-stranded overhang of the G-rich strand (Fig. 1). Telomeres protect the end of chromosome from degradation and DNA repair activities (de Lange, 2009). Because of a phenomenon known as the 'end-replication problem', which was introduced by Olovnikov and Watson about 50 years ago (Olovnikov, 1973; Watson, 1972), DNA polymerase cannot replicate sequences at 3' ends and telomeres lose TTAGGG repeats with each cell division. Once telomere shortening reaches a critical length, referred to as the "Hayflick limit" (Harley et al., 1990), cells undergo growth arrest and become senescent. Therefore, the length of the telomere is highly correlated to the number of cell division, and telomeres are regarded as the 'molecular clock' of cellular aging. Telomeres have many other important functions, including the regulation of gene expression by the telomere position effect (Gottschling et al., 1990). Telomere chromatin contains telomeric repeat-containing RNA (TERRA), which has been implicated in telomerase regulation, organization of heterochromatin at telomeres and in the regulation of gene expression (Porro et al., 2014). Moreover, telomeres are critical to ensure proper chromosome separation during mitosis (Canudas & Smith, 2009).

Telomere dysfunction causes chromosomal instability, which is associated with many age-related diseases. In highly proliferating tissues such as the skin, gastrointestinal tract and hematopoietic system, progressive telomere attrition, due to the low level of telomerase and the continuous renewal of the tissues, trigger DNA damage responses, whereas ROS-induced damage of telomere sequences causes attrition and uncapping of telomere in lowly proliferative tissue such as heart, brain, and liver (Chakravarti et al., 2021). Telomere dysfunction not only causes genome instability, but also contributes to inflammatory responses in aging-related diseases including atherosclerosis (Hagg, 2018), type 2 diabetes (Cheng et al., 2020), osteoarthritis (Bekaert et al., 2005), and Parkinson's (Chen & Zhan, 2021) and Alzheimer's diseases (Lukens et al., 2009).

In this review, we provide an overview of current telomere research. We will describe the structure of telomeres, then introduce the mechanisms of telomere maintenance and lengthening and finally highlight the role of telomere dysfunction in cardiovascular disease, neurological disorder and cancer.

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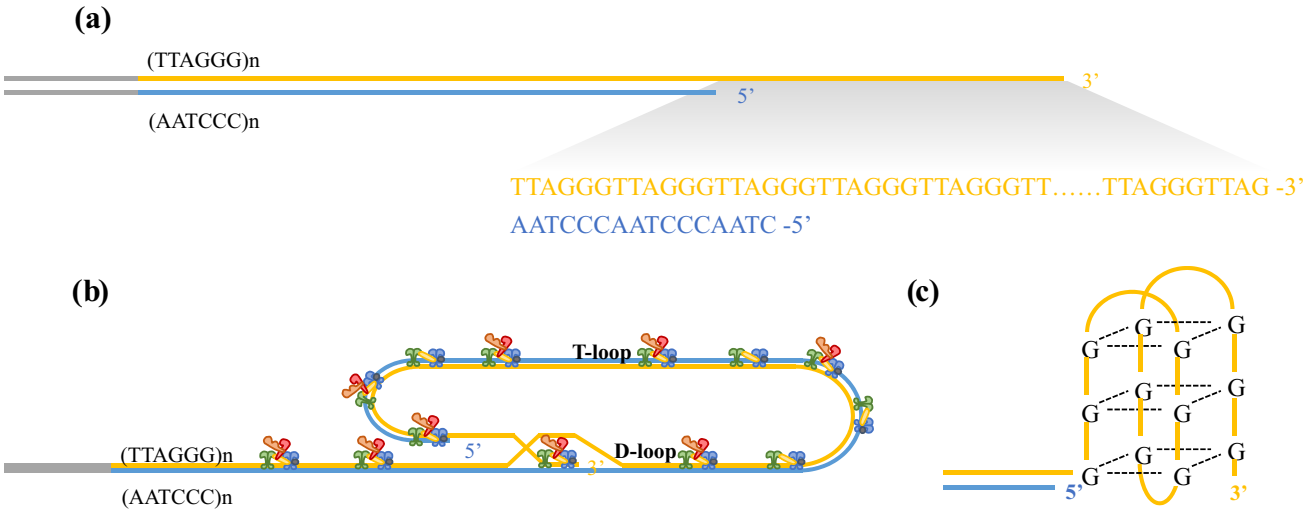

Fig. 1 Telomere structure. **A** Telomeres are composed of tandem-repeat sequences (TTAGGG). Telomeric DNA is largely double-stranded, but ends in a short single-stranded G-rich 3' overhang. **B** The ends of telomeres are protected by invasion of the terminal single-stranded DNA overhang into duplex TTAGGG repeats to form the T-loop and D-loop. The shelterin complex (TRF1, green; TRF2, blue; TPP1, red; POT1, orange; TIN2, yellow and RAP1, gray) prevents the ends of telomeres from being recognized as damaged DNA and activation of DNA damage response. **C** Structure of the telomere G quadruplex

Telomere structure and maintenance

The average length of telomere DNA varies by species. In humans, telomeres are typically 10–15 kb in length and in mice are about 25–40 kb in length (Blackburn, 2001; Blasco, 2005; Moyzis et al., 1988). The telomere is covered by the shelterin complex (de Lange, 2005, 2018), a multimer composed of six protein subunits: TRF1, TRF2, TPP1, POT1, TIN2, and RAP1 (Fig. 1A, B). TRF1 and TRF2 directly bind to duplex TTAGGG repeats, and TRF2 forms a heterodimer with RAP1 (de Lange, 2018; Janouskova et al., 2015). POT1 recognizes single-strand TTAGGG overhangs and binds to TPP1 (Wu et al., 2012). TIN2 connects POT1–TPP1 to TRF1 and TRF2 to form a large complex (Hu et al., 2017). Shelterin interacts with both double-stranded and single-stranded telomeric DNA and is sufficiently abundant to bind all telomeric DNA (Takai et al., 2010). This higher-order structure can fold back and form a T-loop (Griffith et al., 1999). When the guanine-rich single chain folds back to invade the double-stranded region, the two chains of the double-stranded region are separated, and the three chains form a D-loop structure (Fig. 1B). Telomeres can also form another specialized structure, in which the four adjacent TTAGGG repeats can form a four-stranded structure, known as a guanine quadruplex (G quadruplex) (Burge et al., 2006). A square plane is formed by the four guanine residues of the telomere quadruplex; each guanine residue is a hydrogen bond donor and acceptor, meaning that Hoogsteen hydrogen bond pairing occurs between guanine residues (Fig. 1C). It has been proposed that G-quadruplexes can sequester the 3' end of the telomere and prevent it from being extended by telomerase (Rhodes & Lipps, 2015).

Telomeres are susceptible to the actions of DNA damage response pathways (de Lange, 2018). The shelterin complex has fundamental roles in the regulation of telomere length and telomere maintenance. This complex is composed of six core proteins including TRF1, TRF2, TPP1, POT1, TIN2, and RAP1 (de Lange, 2018). TRF1 negatively regulates telomere length and participates in telomere DNA replication (Sfeir et al., 2009; Steensel & Lange, 1997). TRF2 and POT1 control the formation of the 3' overhang at telomeres, which is critical for T-loop formation and telomere protection (Doksani et al., 2013; Griffith et al., 1999; Wu et al., 2012). The T-loop protects chromosome ends from degradation and deleterious effects of DNA damage responses to contribute to normal telomere function (Griffith et al., 1999). POT1 binds to single-stranded DNA with high specificity and affinity, thereby inhibiting the ATR damage signal and inhibiting homologous recombination (Denchi & Lange, 2007). The POT1–TPP1 complex increases the affinity of POT1 binding to single-stranded DNA, which stabilizes chromosome ends (Wang et al., 2007; Xin et al., 2007). When telomeres are in an open state, such as during replication or extension, POT1–TPP1 recruits telomerase to accelerate the process of telomere extension (Xin et al., 2007). TIN2 acts as a bridge connecting the POT1–TPP1 complex with TRF1 and TRF2, and stabilizes binding between TRF1 and TRF2 and double-stranded DNA. The RAP1–TRF2

complex inhibits non-homologous end joining of telomeres (Sfeir et al., 2010). The dysfunction of shelterin complex due to critically shortened telomeres and/or mutations in shelterin components triggers DNA damage response (DDR) at chromosome ends.

Mechanisms of telomere lengthening

In normal human somatic cells, telomeres are shortened 50–200 bases every cell cycle. However, in tumor cells, the telomere length can be maintained usually by telomerase. Telomerase is a reverse transcriptase that synthesizes telomeric DNA and is composed of the telomerase RNA component (TERC) and the telomerase reverse transcriptase (TERT) (Schmidt & Cech, 2015). Telomerase activity is usually absent in normal human somatic cells due to transcriptional repression of hTERT gene during embryonic differentiation, except in some high proliferative tissues, such as male germ cells, stem cell populations and activated lymphocytes, the enzyme remains active. However, during the cellular immortalization and transformation process, telomerase is reactivated by diverse and complex mechanisms (Cong et al., 2002). Recent studies demonstrated that TERT promoter mutations are the most common non-coding mutations in human cancer (Fredriksson et al., 2014; Rheinbay et al., 2020). Re-activation telomerase plays a critical role in the initiation and development cancer by maintaining telomere length and replicative capacity of cancer cells (Bodnar et al., 1998; Yuan et al., 2019).

The alternative lengthening of telomeres (ALT) is another mechanism of telomere maintenance and is observed in ~ 10–15% of cancer cells (Cesare & Reddel, 2010). ALT telomeres are characterized by chronic replication stress and are susceptible to double-strand breaks (DSBs) (Cesare & Reddel, 2010), which can result in a break-induced telomere synthesis through break-induced replication (BIR) mechanism, a type of homology-directed repair (Kramara et al., 2018; McEachern and Haber, 2006). ALT is naturally present in tumors and many immortal cell lines without reactivating telomerase, but it can also be induced by inhibiting telomere replication or by depleting several factors needed for telomere integrity like the shelterin complex (Bryan et al., 1995; Epum & Haber, 2021). ALT-associated replication defects trigger RAD52-dependent mitotic DNA synthesis (MiDAS) (Min et al., 2017). Cancer cells that rely on the ALT mechanism have a very variable and rapidly changing telomere length. For example, 61% of human pancreatic neuroendocrine tumors have variable telomeres and display characteristics of ALT (Heaphy et al., 2011). In addition to maintaining telomere length in telomerase-deficient mammalian cells, ALT has several additional characteristics. The C-circle, which is an extrachromosomal circle with an intact CCCTAA (C-rich) strand, is ALT specific (Epum & Haber, 2021; Nabetani & Ishikawa, 2009). ALT is often associated with promyelocytic leukemia (PML) body, referred to as ALT-associated PML body (APB) (Yeager et al., 1999). APB contains PML protein, telomeric DNA, and the telomere-specific binding proteins hTRF1 and hTRF2 (Yeager et al., 1999). Immunostaining showed that some proteins involved in DNA synthesis and recombination have been found in APBs, including replication factor A, RAD51, and RAD52 (Yeager et al., 1999). Furthermore, both ATRX and DAXX gene mutations are significantly correlated with ALT positivity (Heaphy et al., 2011). Studies have shown that ATRX affects telomeric double-strand break (DSB) repair through telomere cohesion and a DAXX-dependent pathway (Lovejoy et al., 2020).

TERRA (telomeric repeat-containing RNA) is a long non-coding RNA that is transcribed from subtelomere and telomere-derived sequences and contains (UUAGGG)n repeat sequences (Azzalin et al., 2007). Recent studies have shown that all eukaryotic cells examined express TERRA (Azzalin et al., 2007; Luke et al., 2008; Schoeftner & Blasco, 2008). The length of TERRA ranges from 100 bp to more than 9 kb in mammals (Azzalin et al., 2007). Since TERRA has a unique G-rich (UUAGGG)n sequence, it has the potential to generate TERRA–telomere DNA hybrids that create R-loop structures (Aguilera & Garcia-Muse, 2012; Graf et al., 2017). The shortening of telomeres induces TERRA expression and TERRA R-loops formation, which in turn activates the DNA damage response (DDR) and homology directed repair (HDR) at critically short telomeres (Graf et al., 2017). In addition, TERRA might also fold into G quadruplexes (Xu et al., 2008, 2010), which has been shown to inhibit telomerase activity (Mei et al., 2021; Rocca et al., 2017).

Telomere crisis and genome instability

Critically shortened telomeres or dysfunctional telomeres can be recognized as a double-stranded DNA break and trigger a permanent growth arrest known as cellular senescence (Maciejowski et al., 2017). In the absence of tumor suppressor pathways such as the p53 and/or Rb pathways that prevent cell cycle arrest induced by telomere shortening, cells continue to divide with further telomere loss, which ultimately leads to the genome instability. This causes the cells to enter into a period called telomere crisis (Maciejowski & Lange, 2017; Shay & Wright, 2005). Telomere crisis occurs during the early stages of tumorigenesis (Dewhurst, 2020). During telomere crisis, unprotected chromosome ends generate end-to-end fusions and dicentric chromosomes, resulting in breakage–fusion–bridge cycles, aneuploidy and tetraploidization, translocations, and amplifications

(Hayashi et al., 2015). These processes eventually lead to various forms of genome instability through kataegis (localized hypermutations) and chromothripsis (clustered chromosomal rearrangements) during mitosis (Artandi & DePinho, 2010; Maciejowski & Lange, 2017; Maciejowski et al., 2015) (Fig. 2).

The breakage–fusion–bridge cycle occurs when a bicentric chromosome (including a chromosome formed by telomere fusion) breaks, followed by a secondary fusion of the broken ends in the daughter cells (Eisfeldt et al., 2019; Tang et al., 2018). The fusion between sister chromatids can also lead to end deletions or inverted end repeats, which can be amplified in subsequent breakage–fusion–bridge cycles (Maciejowski & Lange, 2017). Many studies indicate that the breakage–fusion–bridge cycle is closely related to cancer outcomes such as loss of heterozygosity, translocation, and gene amplification (Maciejowski et al., 2015).

Recently, it has been shown that chromothripsis occurs as a result of telomere crisis. Chromothripsis describes a pattern of genome rearrangement in which fragmented or broken chromosomes are randomly reconnected to the derived chromosome arrangement (Cleal & Baird, 2020; Stephens et al., 2011). Thus, chromothripsis could promote tumorgenesis in a variety of ways. Chromothriptic breakpoints are frequently associated with kataegis mutation clusters (Maciejowski & Lange, 2017)—hypermutated patterns of clustered C > T and C > G changes at TpC dinucleotides associated with APOBEC-mediated mutagenesis (Maciejowski et al., 2015). Whole-genome sequence analysis revealed that kataegis occurs at the break sites of chromothriptic rearrangements (Maciejowski et al., 2015).

Dysfunctional telomeres in age-related diseases

The special properties of telomeres not only protect the ends of linear chromosomes from degradation and repair activities to ensure genome stability, but are also critically involved in a number of cellular processes contributing to the pathology of aging and cancer. Telomeres are protected and maintained by the shelterin complex; therefore, deficiency of any shelterin component may result in telomere dysfunction, which triggers DNA damage response. Recent studies using mouse models suggest that the deficiency of shelterin complex has been implicated in cancer susceptibility and aging-related pathologies (Martinez & Blasco, 2017).

Numerous studies have implicated telomere dysfunction as a major driver of age-related diseases, such as dyskeratosis congenita (DC), aplastic anemia (AA), and idiopathic pulmonary fibrosis (IPF) (Armanios, 2013). DC is associated with germline mutations in genes involved in telomere biology (Mitchell et al., 1999). *DKC1* encodes the nuclear protein dyskerin, which is as an essential component of the telomerase holoenzyme, and is the first gene found mutated in DC (Holme et al., 2012; Mitchell et al., 1999). The classic phenotype of DC consists of the mucocutaneous triad of dysplastic finger and toenails, oral leukoplakia, and lacy,

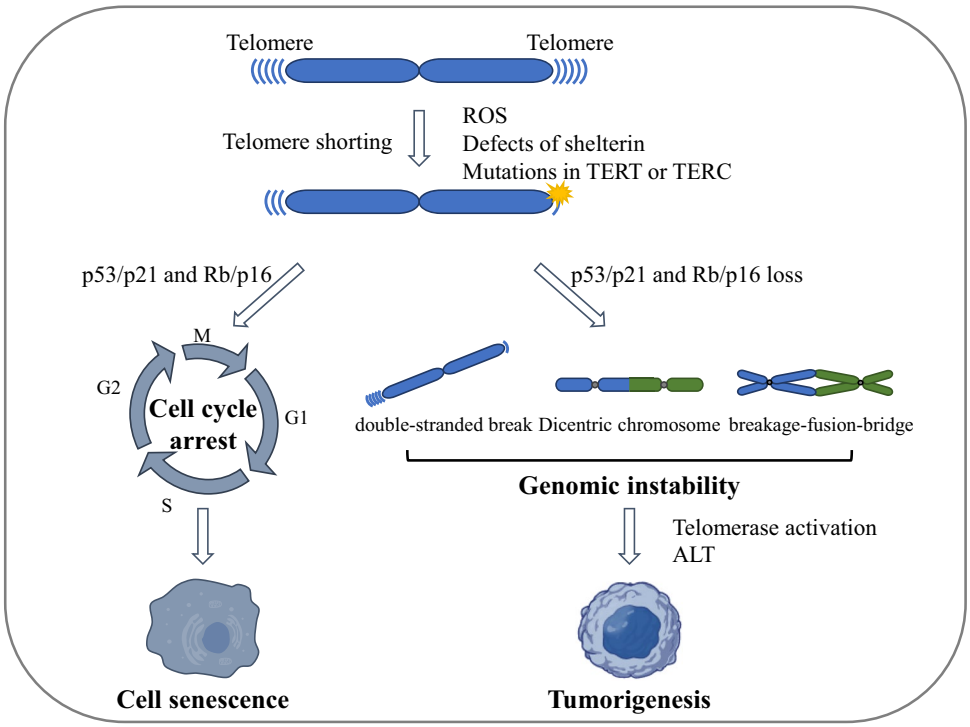

Fig. 2 Telomere crisis and genome instability. In the presence of tumor suppressor pathways (such as p53/p21 and/or Rb/p16 pathways), critically shortened or dysfunctional telomeres induce leads to cellular senescence, whereas in the absence of tumor suppressor pathways, unprotected chromosome ends can generate end-to-end fusions and dicentric chromosomes. These dicentric chromosomes generate anaphase bridges with subsequent chromosome breakage and the breakage–fusion–bridge (BFB) cycle, which promote genome instability and eventually tumorigenesis. *ROS* reactive oxygen species, *ALT* alternative lengthening of telomeres

reticular skin pigmentation (Niewisch & Savage, 2019). AA is a common complication in DC patients, and was later characterized as an independent telomere biology disorder (Savage & Bertuch, 2010). About 10–20% of patients with acquired AA have short telomeres (Dolberg & Levy, 2014). Moreover, IPF is considered the most prevalent manifestation of telomere disorders (Armanios, 2012). Studies have shown that mutations in TERT or TERC confer a dramatic increase in susceptibility to adult-onset IPF (Tsakiri et al., 2007). These findings provide strong evidences that telomere length is a determinant or a predictor for some of specific diseases.

A recent study highlighted that there is a strong correlation between whole-blood telomere length and the telomere length of various tissues, and showed that the telomere length of blood cells is a biomarker of human aging and disease (Demanelis et al., 2020). The researchers collected 6391 tissue samples across more than 20 tissue types from 952 individuals, and characterized the variability of telomere length of each tissue sample. Generally, telomere length differs across human tissue types, but is correlated among tissue types. Whole blood telomere length was positively correlated with tissue-specific telomere length measurements, and leukocyte blood telomere length is used as a proxy for telomere length in many tissue types (Demanelis et al., 2020). The positive correlations of telomere length among tissue types are likely due to the fact that the initial telomere length in the zygote affects telomere length in all adult tissues through mitotic inheritance. This finding provides support for the validity of epidemiological studies based on blood telomere length. Shortened telomeres are associated with an increased risk of cardiovascular disease, type 2 diabetes, neurodegenerative disorders, and cancer (Table 1).

Cardiovascular disease is the leading cause of death worldwide. Several studies indicate that telomere dysfunction is associated with coronary heart disease, atherosclerosis, myocardial infarction, heart failure and stroke (Willeit et al., 2010). Compared with age-matched healthy controls, individuals with early myocardial infarction have shorter leukocyte telomere length (Brouilette et al., 2003). Telomeres are shorter in leukocytes from patients with severe heart failure (van der Harst et al., 2007), and there is a significant independent association between shorter telomeres and cardiovascular risk (Brouilette et al., 2007; D'Mello et al., 2016).

Similarly, telomere shortening is associated with the development of type 2 diabetes and related clinical conditions such as insulin resistance, impaired glucose tolerance, obesity and inflammation. A study conducted over 5 years indicated that diabetic patients have significantly shorter leukocyte telomere length (Zhao et al., 2014). Patients with type 2 diabetes also had shorter telomeres in peripheral monocytes and endothelial cells (Sampson et al., 2006). Meanwhile, two GWAS studies have indicated that type 2 diabetes is strongly linked to telomere shortening (Liu et al., 2014; Saxena et al., 2014).

Alzheimer's disease is one of the most common neurodegenerative diseases. Defects in telomere maintenance accelerate aging in mice and humans (Blasco et al., 1997; Herrera et al., 1999; Lopez-Otin et al., 2013). Many studies have showed that leukocyte telomere length is shorter in patients with Alzheimer's disease than in control individuals (Forero et al., 2016), and that telomere length in peripheral blood mononuclear cells may help predict disease progression (Tedone et al., 2015). Telomere

Table 1 Association of telomere length and age-related diseases

Disease	Sample size	Study type	Method	References
Cardiovascular disease				
Coronary heart disease	566	Observational	QPCR	Hammadah et. al. (2017)
Atherosclerosis	259	Observational	Southern blot	Hagg (2018)
Myocardial infarction	203	Observational	Southern blot	Brouilette et al. (2003)
Stroke	419	Observational	Southern blot	Fitzpatrick et. al. (2006)
Type 2 diabetes	17 cohorts	Metaanalysis	N/A	Cheng et al. (2020)
Neurodegenerative diseases				
Alzheimer's disease	30	Observational	qPCR	Lukens et. al. (2009)
Parkinson's disease	37,688	Mendelian randomization	N/A	Chen and Zhan (2021)
Cancer				
Breast cancer	70	Observational	Slot blot	Fordyce et al. (2006)
Lung cancer	1385	Observational	qPCR	Sanchez-Espiridion et al. (2014)
Colon cancer	124	Observational	Southern blot	Nakamura et al. (2000)
Prostate cancer	128	Observational	Slot blot	Heaphy et al. (2010)
Osteoporosis	110	Observational	Southern blot	Bekaert et al. (2005)

shortening is also involved in the pathogenesis of the neurological disorder Parkinson's disease (Eitan et al., 2014).

A number of studies have explored the relationship between telomere length and cancer risk or prognosis (Aviv et al., 2017). Telomeres in breast, colon, and prostate tumor tissues are shorter than those in adjacent tissue from the same patient (Fasching, 2018). Furthermore, in telomerase-positive tumors, short telomeres are usually associated with cancer progression and reduced survival rate (Fordyce et al., 2006; Valls et al., 2011). However, in lung cancer, patients with adenocarcinoma have longer telomeres than controls, while patients with squamous cell carcinoma have shorter telomeres than controls (Sanchez-Espiridion et al., 2014). Whether telomere length can be used to predict cancer risk prediction requires further investigation.

Telomeres in osteoblasts and mesenchymal stem cells are shortened with age. The first large-scale epidemiology study by Valdes et al. showed that there is a significant correlation between leukocyte telomere length and the bone mineral density of the spine and forearm (Boccardi et al., 2013). In a prospective study of elderly population (age range 71–86 years), shorter leukocyte telomere length was associated with bone loss in several distal forearm locations (Bekaert et al., 2005). Experiments in mice showed that the replicative senescence of osteoblast precursors promotes bone loss and senile osteoporosis (Saeed et al., 2011). A recent study suggests that short and dysfunctional telomeres contribute to age-associated renal fibrosis by influencing the epithelial-to-mesenchymal transition program (Saraswati et al., 2021).

Telomeres and the external environment

Telomere length serves as a 'molecular clock' for human aging. Strong evidence indicates that telomere length in parental germ cells affects telomere length in offspring cells (Delgado et al., 2019). Besides genetic factors, lifestyle factors (diet, physical activity, cigarette smoking) and environmental exposures (including radiation) also affect telomere length (Chakravarti et al., 2021; Fasching, 2018). A meta-analysis showed a positive correlation between adherence to the Mediterranean diet and maintenance of telomere length (Canudas et al., 2020). A study conducted on 5309 adults from the USA with no history of diabetes or cardiovascular disease showed that people who consumed sugar-sweetened beverages had a shorter leukocyte telomere length (Leung et al., 2014). Telomere length correlates with body mass index; obese individuals have shorter telomeres and weight loss positively correlates with telomere length (Wulaningsih et al., 2018). Increased physical activity positively correlates with telomere length, and people who engage in higher levels of physical activity have longer telomeres than sedentary individuals (Ludlow et al., 2008). The NASA Twins Study, in which one twin went to the International Space Station for 340 days while the other identical twin remained on Earth, observed the effects of the Earth and space environments on physiological functions (Garrett-Bakelman et al., 2019). Both twins had similar telomere lengths at the start of the study. The telomere length of the twin on Earth remained relatively stable, whereas telomere length increased significantly in the other twin during the space flight and then shortened rapidly upon return to Earth. Interestingly, within 6 months after return to Earth, telomere length stabilized to near preflight averages, but increased numbers of short telomeres were observed. Together, these studies strongly support the notion that telomere length is carefully regulated and is subject to changes in lifestyle and environment factors.

Conclusions and future perspectives

In conclusion, telomeres have a crucial role in maintaining genome stability. Detailed understanding of the mechanisms of telomere maintenance and regulations will provide insights into the role of telomere attrition in disease development and progression, and opportunities for prognosis and therapeutic intervention. Basic and clinical research showed that telomere length can be used as an indicator of aging and age-related diseases. The telomerase repair therapy has been explored as a potential anti-aging or anti-tumor strategies. Several small molecules such as TA-65 and the histone deacetylase inhibitors targeting TERT have been identified (Bernardes de Jesus et al., 2011; Yu et al., 2018). Jesus et al. show that TA-65 is capable of increasing average telomere length and decreasing the percentage of critically short telomeres in haploinsufficient mouse embryonic fibroblasts (Bernardes de Jesus et al., 2011). Won et al. suggest that the HDAC complex plays an important role in the regulation of hTERT in various proliferation conditions such as normal cycling, senescent, and tumor cells (Won et al., 2004). Future research will reveal the complex biological mechanisms between telomere function and diseases. This research may be translated into more accurate predictors of age-related disease risks and more effective treatment strategies that may ultimately be useful in monitoring and intervening in the aging process.

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