

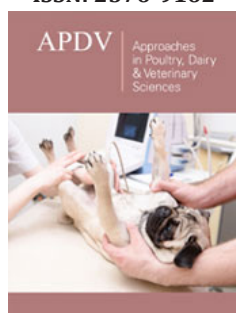
Research Status and Prospects of Telomeres in Disease Research

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Abstract

Telomeres, protective structures composed of TTAGGG repeat sequences and proteins at chromosome ends, play a pivotal role in cell cycle regulation and aging. Studies show that telomere shortening during cell division to a critical length triggers cellular senescence, tightly linked to the development of aging-related diseases like cancer, cardiovascular disorders, and osteoporosis. Current telomere research has achieved dual breakthroughs in technology and application. Detection methods have evolved from traditional quantitative PCR and Fluorescence in Situ Hybridization (FISH) to Next-Generation Sequencing (NGS), digital PCR and nanogold labelling techniques. Telomerase has demonstrated significant potential in delaying aging and combating cellular senescence, with technologies targeting telomerase showing promise in reversing cell senescence and treating aging-related diseases. In therapeutic strategies, telomerase inhibitors (e.g., oligonucleotides, nucleoside reverse transcriptase inhibitors, non-nucleoside small-molecule inhibitors) combat tumor cells by suppressing telomerase activity, while telomerase activators delay cellular senescence by activating telomerase. These strategies targeting telomerase genes provide new therapeutic pathways for cancer treatment and aging intervention. Future research will focus on interdisciplinary innovation: decoding the regulatory network between telomeres and gene expression through multi-omics integration, optimizing clinical interpretation of detection data with artificial intelligence and achieving precise delivery of telomere-targeted drugs via nanocarriers. These explorations not only promote the clinical use of telomere length as an aging biomarker but also hold promise for intervening in cellular senescence by regulating telomere dynamics, opening an interdisciplinary paradigm for early warning and prevention of aging-related diseases.

Keywords: Telomere; Biomarker; Therapeutic target; Precision medicine

Introduction

With the intensification of the global aging trend, the number of elderly people in countries such as China has increased significantly. It is projected that the population aged 65 and above will rise substantially by 2050. This phenomenon not only exerts far-reaching impacts on the economy and society, but also poses severe challenges associated with aging and diseases. For instance, chronic conditions including cardiovascular diseases, diabetes, neurodegenerative disorders (such as Alzheimer's disease and Parkinson's disease) and cancer have a high incidence rate among the elderly population, which seriously impairs the quality of life of senior citizens. Therefore, investigating the molecular mechanisms of aging and the intervention strategies for aging-related diseases is of profound scientific and social significance in addressing the challenges brought by an aging society.

Telomeres are specialized DNA-protein complexes located at the ends of eukaryotic chromosomes, consisting of tandem hexanucleotide repeats (TTAGGG) and associated proteins. Their primary function is to protect chromosome ends from nuclease degradation,

abnormal end-to-end fusion and chromosomal recombination [1]. During cell division, telomeres, as specialized DNA-protein complexes at chromosome termini, undergo progressive shortening. This is because telomeric DNA cannot be fully replicated with each round of cell division, resulting in gradual telomere attrition—a phenomenon known as the cellular “mitotic clock”, which reflects the replication history and potential replicative capacity of cells. When telomeres shorten to a critical length, cells enter a state of replicative senescence, a process regarded as one of the key hallmarks of organismal aging [2].

In-depth investigations into the functions of telomeres and telomerase have led to a growing recognition that telomeres are not only molecular markers of cellular replicative senescence, but also potential biomarkers for predicting the risk of various diseases [3]. This insight has elevated the pivotal role of telomere research in both basic science and clinical applications. Remarkable progress has been achieved in telomere studies spanning the fields of molecular biology, medicine and bioengineering, which has opened up novel avenues for the prevention and treatment of aging-related diseases and laid a theoretical foundation for personalized therapy and health management.

Current Research Status of Telomeres

Telomere shortening is recognized as one of the core mechanisms underlying biological aging, and it is also closely associated with a variety of aging-related diseases, including cancer, osteoporosis, cardiovascular diseases and neurodegenerative disorders [4].

Research on the mechanisms underlying the effects of telomeres on aging

Studies have demonstrated that telomere length can reflect the biological age of an organism and exhibits a certain correlation with chronological age, with telomere shortening serving as a key hallmark of cellular senescence [5]. During each round of cell division, DNA polymerase is unable to fully replicate the base sequences at chromosome ends, causing telomeres to shorten progressively. Once telomeres are shortened to a critical length, cells enter a state of replicative senescence and cease mitotic division [6]. The number of cell divisions is directly limited by telomere length, a phenomenon known as the Hayflick limit [7]. In healthy individuals, telomere length gradually shortens with age, which underscores the hallmark role of telomeres in the process of cellular aging. Studies have indicated a significant correlation between telomere length and age, with mean telomere length showing a gradual decline as age advances [8]. In addition, telomere shortening can affect cellular functions through multiple mechanisms. For example, research conducted by the College of Medicine, Chang Gung University has revealed that telomere shortening is significantly associated with PM2.5 exposure. This association impairs the protective function of chromosome ends, elevating the risk of chromosome breakage, rearrangement and nuclease degradation, thereby compromising genomic stability [9]. Furthermore, telomere shortening may be linked to the accumulation of TERRA and R-loops; these non-coding RNAs play critical roles in telomere repair and contribute to the delay of cellular senescence. Telomere shortening can also activate

key cell cycle regulatory genes such as p53 and p16, triggering irreversible cell cycle arrest [10]. Moreover, telomere shortening can induce DNA damage responses, which in turn activate pro-inflammatory signalling pathways, leading to the development of a chronic inflammatory state [11]. Collectively, telomere length is closely correlated with the functional decline of multiple organs in the body [12].

Research on telomerase and telomere lengthening mechanisms

Telomerase is a key enzyme for maintaining telomere length, consisting of human Telomerase Reverse Transcriptase (hTERT), human telomerase RNA template (hTR) and a variety of associated proteins [13]. Through a reverse transcription mechanism, telomerase adds telomeric repeat sequences (TTAGGG) to the ends of chromosomes, thereby slowing down the process of telomere shortening [14]. In specific cell types such as embryonic stem cells, hematopoietic stem cells and tumor cells, telomerase activity is relatively high, which can maintain telomere length to a certain extent and support the continuous proliferative capacity of these cells [15]. In addition to the telomerase-dependent lengthening mechanism (telomerase-dependent, TA pathway), cells can also maintain telomere length via the Alternative Lengthening of Telomeres mechanism (ALT pathway) [16]. The ALT mechanism usually occurs in the absence of telomerase activity, and replenishes telomere length by utilizing telomeric fragments from another chromosome through homologous recombination [17]. This mechanism plays an important role in protecting genomic stability and preventing uncontrolled cell proliferation (e.g., tumorigenesis) [18].

Research on telomeres in the field of tumor therapy

The relationship between telomeres and tumors constitutes one of the key topics in the field of telomere research. In most somatic cells, telomerase activity is tightly repressed, and telomere shortening limits the number of cell divisions, thus preventing the unlimited proliferation of cells with genomic instability. However, tumor cells overcome this limitation and acquire the capacity for unlimited proliferation by activating telomerase or the Alternative Lengthening of Telomeres (ALT) mechanism, which represents a crucial mechanism underlying carcinogenesis [19].

Aberrant activation of telomerase: Aberrant activation of telomerase is recognized as a vital mechanism enabling the unlimited proliferation of tumor cells, whereas the decline of telomerase activity in normal somatic cells accelerates telomere shortening and cellular senescence [20]. Therefore, regulating telomerase activity has become one of the important research directions in studies on aging and tumors. Telomerase is reactivated in 85% to 90% of tumors [21]. Overexpression of the hTERT gene, which encodes the catalytic subunit of telomerase, endows tumor cells with the characteristic of “immortalization” by extending telomere length [22]. In addition, mutations in the hTERT gene promoter are widely regarded as one of the key mechanisms driving the occurrence and progression of various cancers. For example, such mutations significantly enhance telomerase expression and promote tumor

development in melanoma, liver cancer and bladder cancer [23].

Alternative lengthening of telomeres (ALT) mechanism: In some tumors lacking telomerase activity (e.g., glioma and osteosarcoma), tumor cells maintain telomere length via the ALT mechanism [24]. ALT relies on homologous recombination between telomeres and extends telomeres through DNA replication and repair pathways [25]. This mechanism not only sustains the proliferation of tumor cells, but also may lead to high heterogeneity in telomere length—a feature that can serve as a diagnostic marker for ALT-associated tumors [26].

Dual roles of telomere length: The relationship between telomere length and tumorigenesis exhibits a double-edged sword effect [27]. In the early stages of tumorigenesis, telomere shortening induces genomic instability, thereby increasing the risk of cellular malignant transformation [28]. Conversely, excessively long telomeres provide tumor cells with the capacity for unlimited proliferation, facilitating tumor progression [29]. Therefore, regulating telomere length has become one of the important directions in anti-tumor research.

Strategies for telomere-targeted therapy: Telomere-targeted therapies mainly include telomerase inhibitors and small-molecule drugs. Telomerase inhibitors primarily suppress the unlimited proliferation of tumor cells by inhibiting the activity or expression of telomerase, thus preventing telomere elongation in tumor cells [30]. Currently, there are two classic inhibitors: Imetelstat (GRN163L) and BIBR1532. GRN163L is an antisense oligonucleotide-based telomerase inhibitor that blocks the reverse transcription function of telomerase by targeting the telomerase RNA (hTR) sequence [31]. Clinical trials have demonstrated that this drug exhibits favourable efficacy in certain cancer types (e.g., myelofibrosis and acute myeloid leukaemia) [32]. BIBR1532 is a small-molecule inhibitor that suppresses telomerase activity by directly binding to its catalytic subunit [33]. Studies have indicated that BIBR1532 can significantly reduce telomerase activity in tumor cells and restrict tumor cell growth. Meanwhile, targeted therapies against TERT gene mutations have shown promising outcomes in clinical trials [34].

Research on telomeres in the field of cardiovascular diseases

Cardio Vascular Diseases (CVDs) are among the leading causes of death worldwide and are closely associated with telomere shortening [35]. Telomere shortening is not only an important biological marker for the onset of cardiovascular diseases, but may also play a causal role in disease progression [36]. First, telomere shortening in arterial endothelial cells and smooth muscle cells can trigger cellular dysfunction, which in turn impairs the vascular endothelial barrier and elevates the risk of Low-Density Lipoprotein (LDL) oxidation and inflammatory factor infiltration [37]. By activating cellular apoptotic signalling pathways, telomere shortening further accelerates the progression of atherosclerotic lesions [38]. Second, there is a negative correlation between telomere length and blood pressure levels [39]. Among hypertensive patients, individuals with shorter telomeres face a

higher risk of complications such as myocardial hypertrophy and heart failure [40]. Studies have shown that telomere shortening may promote vascular damage and dysfunction through oxidative stress and chronic inflammatory pathways [41]. Third, a large-scale study published in *JAMA Internal Medicine*, a top medical journal, revealed the association between telomere length and cardiovascular diseases. The study found that individuals with shorter telomere length had a significantly higher all-cause mortality rate than those with longer telomere length, with the all-cause mortality rate in the shortest telomere length group being 76% higher than that in the longest telomere length group [42]. In addition, shortened telomere length is significantly correlated with increased cardiovascular disease mortality, which provides an important basis for the application of telomere length in the prevention and early diagnosis of cardiovascular diseases [43].

Telomeres and osteoporosis

Osteoporosis is one of the diseases closely associated with aging, characterized by decreased bone mineral density and degradation of bone tissue structure, which leads to an increased risk of fractures [44]. Studies have shown that telomere shortening plays an important role in the occurrence and progression of osteoporosis [45]. First, telomere shortening plays a pivotal role in the senescence of bone cells. In bone tissue, the dynamic balance between osteoblasts (which promote bone formation) and osteoclasts (which promote bone resorption) is essential for maintaining bone mineral density [46]. Senescence of osteoblasts induced by telomere shortening results in the decline of their proliferative capacity and differentiation potential, thereby reducing bone formation [47].

In contrast, osteoclasts exhibit hyperactivity due to the activation of telomere-related signalling pathways, which in turn exacerbates bone resorption [48]. This phenomenon constitutes a key link in the pathogenesis of osteoporosis. Second, during cellular senescence, telomere shortening can trigger the release of the Senescence-Associated Secretory Phenotype (SASP), including pro-inflammatory cytokines (e.g., IL-6, TNF- α) and chemokines, thereby inducing a persistent inflammatory state [49]. This inflammatory microenvironment further impairs the structural integrity of the bone tissue niche, compromises osteoblast function and accelerates the process of bone loss [50]. There is a close epidemiological correlation between telomere length and bone mineral density. Multiple studies have found that individuals with shorter telomeres are more prone to decreased bone mineral density and elevated fracture risk [51]. For example, in a cohort study involving elderly women, the incidence of fractures was significantly higher in individuals with shorter telomeres than in those with longer telomeres [52]. These findings indicate that telomere length can serve as a biomarker for assessing the risk of osteoporosis.

Telomeres and metabolic diseases

The development of metabolic diseases such as metabolic syndrome and diabetes is also closely associated with telomere length [53]. Studies have shown that short telomeres may increase the risk of insulin resistance and diabetes [54]. Telomere

characteristics in diabetic patient's diabetic patients generally have shorter telomeres, a feature that may provide a basis for the early warning of the disease and thus enable effective intervention in its progression [55].

Methods for Detection and Evaluation of Telomere Length

Traditional telomere detection technologies

The detection of telomere length is the basis of telomere research, and its accuracy and reliability directly affect the credibility of research results. Traditional telomere detection methods mainly include quantitative PCR, Southern blotting and Fluorescence in Situ Hybridization (FISH), which have provided valuable tools for telomere research [56]. Quantitative PCR (qPCR) is one of the most commonly used methods for telomere length detection at present [57]. This method involves amplifying telomeric repeat sequences and Single-Copy Gene (SCG) sequences, and then estimating telomere length by calculating the amplification ratio of the two (namely the T/S ratio). It features simple operation procedures and relatively low cost. However, it can only provide an estimation of relative telomere length instead of absolute length. Moreover, the detection results are susceptible to DNA quality and PCR reaction conditions, with poor reproducibility [58]. Southern blotting is a classic method for telomere length detection. It involves digesting chromosomal DNA with restriction endonucleases, followed by hybridization detection using telomere-specific probes and finally obtaining a telomere length distribution profile [59]. This method is capable of measuring absolute telomere length, but has a long experimental cycle and low detection sensitivity, making it difficult to detect extremely short telomeres [60]. Fluorescence in Situ Hybridization (FISH) realizes telomere length assessment by hybridizing fluorescence-labelled telomere-specific probes to chromosome ends and observing the fluorescence signal intensity under a fluorescence microscope [61]. It allows simultaneous observation of telomere length and spatial distribution of multiple chromosomes. Nevertheless, it faces the challenge of data quantification when detecting telomere length at the single-cell level, and the results are usually presented in a semi-quantitative form [62].

Emerging telomere detection technologies

With the advancement of technologies, telomere detection methods are constantly updated, and a variety of new techniques have emerged in recent years. These novel technologies exhibit outstanding performance in terms of sensitivity, accuracy and high throughput, opening up brand-new directions for telomere research [63]. Next-Generation Sequencing (NGS) is a telomere length detection method centered on DNA sequencing [64]. By sequencing telomeric repeat sequences, it enables accurate measurement of telomere length. This technology can directly sequence the telomeric sequences at chromosome ends and provide absolute length data. Its data processing relies on bioinformatics analysis, making it suitable for large-scale research. NGS offers

a new perspective for investigating the relationship between telomeres and genetic variations. In the field of personalized medicine, this technology can be applied to assess disease risks and aging status [65]. The telomere detection technology based on gold nanoparticle-labelled probes is a rapidly developed novel method in recent years [66]. This approach utilizes single-stranded DNA probes labelled with gold nanoparticles to hybridize with telomeric sequences, and detects telomere length by measuring changes in light scattering signals. It features high detection sensitivity, which allows for accurate identification of short telomeres. Moreover, it has low requirements for detection equipment, making it suitable for application in primary laboratories. This technology holds extensive application potential in the fields of rapid screening and on-site detection, and shows promising prospects for the early diagnosis of aging-related diseases [67]. Digital PCR (dPCR) is a high-precision telomere detection method based on droplet technology [68]. DNA is dispersed into thousands of droplets and each droplet undergoes independent PCR amplification and fluorescence signal detection, thereby achieving accurate quantitative analysis of telomere length. This method has high precision, is suitable for the detection of small sample sizes, and realizes absolute quantification of data, which enhances the comparability of results. It also has high sensitivity and is applicable for telomere detection in low-concentration or degraded samples. dPCR has great application potential in fields such as tumor monitoring, organ transplantation and gene therapy [69].

Future Research Directions and Challenges

Prospects of telomeres as biomarkers

Telomere length can serve as an effective biomarker for predicting disease risk [70]. Monitoring of telomere length provides a basis for individualized disease management. The mechanism underlying the role of telomeres in aging-related diseases is intricate and complex. Regulating telomere length and its related signalling pathways may offer novel insights for the early diagnosis and treatment of diseases [71].

Future development directions of telomere detection

The evolution of telomere length detection technologies from traditional methods to emerging techniques has provided a diverse array of tools for telomere research. Different technologies exhibit distinct advantages in terms of sensitivity, resolution and application scenarios and the optimal approach should be selected according to specific research requirements [72]. In the future, with continuous optimization and integration of technologies, telomere detection techniques will play an increasingly important role in the research, diagnosis and treatment of aging-related diseases, thereby providing robust support for the advancement of precision medicine [73].

Critical roles of telomeres in tumors, osteoporosis and cardiovascular diseases: Telomeres are not only core molecules for understanding the mechanisms of aging, but also important targets for disease prevention and treatment [74]. Future research

should focus on the optimization of telomere length detection technologies, exploration of multi-dimensional telomere regulatory mechanisms and development of telomere-related therapeutic strategies. These efforts will facilitate the translation of telomere research findings into clinical applications and benefit more patients [75].

Integration of multi-omics technologies with telomere detection: Combining telomere length detection with genomics, transcriptomics and epigenomics to investigate the relationship between telomere dynamic changes and gene expression as well as epigenetic modifications will provide more comprehensive data support for mechanistic research on aging-related diseases [76].

Potential of telomerase-targeted therapy

Telomerase plays a pivotal role in maintaining the unlimited proliferation of cells and delaying aging, which renders it a potential target for the treatment of aging-related diseases and cancers. In recent years, drug development strategies such as telomerase inhibitors, telomere protectants and telomerase activators have become research hotspots, among which telomerase inhibitors have shown potential in tumor therapy in clinical trials [77].

Telomerase inhibitors: In recent years, targeted drug development strategies against telomerase gene promoter mutations (e.g., TERT promoter mutations) have gradually emerged. This progress benefits from researchers' in-depth understanding of the specific expression regulatory role of the hTERT promoter in tumor cells, as well as advances in studies on the high frequency and relevance of TERT promoter mutations in urinary system tumors [78]. Such mutations are common in various cancers including melanoma and liver cancer, and related drugs are currently under exploration [79].

Telomere protectants: Telomere protectants are designed to slow down telomere shortening and delay the progression of aging and associated chronic diseases [80]. Telomeric regions contain abundant G-quadruplex structures, which are highly sensitive to Reactive Oxygen Species (ROS). Accumulation of ROS can induce oxidative damage to telomeres and accelerate their shortening [81]. The DNA damage response triggered by telomere shortening can further activate cell cycle arrest signalling pathways and impair normal cellular functions [82]. Antioxidants (e.g., vitamin C, vitamin E, lipoic acid) have potential telomere-protective effects by scavenging ROS to reduce telomere damage [83]. Small-molecule activators refer to certain small-molecule compounds such as TA-65, which extend telomeres and improve cellular functions by activating telomerase activity [84]. The application potential of such compounds in healthy aging and chronic disease treatment is currently under investigation.

Gene therapy: Gene therapy provides novel insights for telomere length regulation through direct intervention in the telomerase gene or related regulatory pathways [85]. The CRISPR/Cas9 gene-editing technology has demonstrated potential in cancer

therapy in clinical trials by targeting and regulating the expression of the telomerase gene (hTERT), for instance, through engineering T cells to enhance their tumor-killing capacity [86]. In gene delivery systems, viral vectors are used to deliver the telomerase gene to specific cells, thereby enhancing telomerase activity for tissue repair and functional restoration [87].

Potential of interdisciplinary research

The integration of telomere research with genetics, epigenetics and molecular biology offers new perspectives for uncovering the fundamental mechanisms of aging-related diseases [88]. For example, regulating telomerase gene expression by combining gene-editing technologies (e.g., CRISPR/Cas9) is expected to enable precision medicine and disease intervention [89]. The development of Artificial Intelligence (AI) and machine learning technologies has enabled in-depth analysis of telomere detection data [90]. Intelligent monitoring devices, such as portable telomere detectors, can achieve real-time monitoring and personalized data analysis. In-depth mining of telomere detection data using AI and machine learning technologies can improve analysis efficiency and result accuracy, providing a more powerful tool for research on the association between telomeres and diseases [91]. Multi-target combination therapy strategies are emerging as a research hotspot. Multi-target drug therapies that integrate telomerase inhibitors, immunotherapies and antioxidant therapies are expected to yield more efficient treatment regimens. The advantage of multi-target drug therapies lies in their ability to act on multiple biomolecular targets simultaneously, producing potent therapeutic effects, reducing drug resistance and improving drug tolerance, thus enhancing the long-term efficacy and stability of treatment. For example, in tumor therapy, telomerase inhibitors can be combined with PD-1 inhibitors to enhance therapeutic efficacy through the dual mechanisms of inhibiting tumor cell proliferation and activating immune responses [92].

The combination of nanotechnology and drug delivery systems provides a new avenue for telomere-targeted therapy [93]. Targeted delivery of telomerase inhibitors or activators using nanoparticles can improve the targeting ability and bioavailability of drugs while reducing systemic toxicity [93]. For example, liposome-based nanocarriers can encapsulate telomerase antisense oligonucleotides to exert specific effects on tumor cells [93]. The integration of microfluidic technology with telomere detection has promoted the development of portable diagnostic devices [94]. Miniaturized PCR systems or Point-Of-Care Testing (POCT) devices based on chip technology can rapidly measure telomere length on-site, making them well-suited for screening in primary medical institutions and large-scale population studies [94].

Precision health management and longevity research

Precision health management: By comprehensively considering telomere length, genomic data and personal lifestyle information, we can tailor personalized health management plans for individuals. For example, for individuals with shorter

telomeres, antioxidant-rich diets, exercise interventions and stress management strategies can be recommended to slow down the aging process [95].

Longevity research: Telomere length is often regarded as a key indicator for measuring biological age in long-lived populations [96]. Studies on telomere regulatory mechanisms in centenarians have revealed that specific mutations exist in their telomere maintenance-related genes (e.g., TERT, TERC), which provide clues for unravelling the mechanisms underlying longevity [96].

Limitations of current telomere research

The regulatory mechanisms of telomeres involve multiple levels including DNA-protein interactions, cell cycle checkpoints and epigenetic modifications. However, the causal relationship between their dynamic changes and diseases has not been fully elucidated so far. The bidirectional regulatory relationship between telomere shortening and chronic inflammation increases the difficulty of etiological research.

Conclusion

Telomere research has gradually advanced from basic biological mechanisms to clinical applications, demonstrating significant potential as both a disease biomarker and a therapeutic target. In the future, we will leverage technological innovations-such as high-precision telomere detection technologies and gene-editing tools-while promoting in-depth interdisciplinary integration (e.g., the cross-application of artificial intelligence and molecular biology) and implementing personalized intervention strategies, with the aim of breaking through current research bottlenecks. These initiatives will effectively drive the translational application of telomere research in the field of precision medicine, opening up novel pathways and paradigms for the prevention and treatment of aging-related diseases.

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