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Telomeres: The Promise of New Cancer Therapies

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Abstract

Telomeres have been a subject of genetic research since the 1930s. They play a crucial role in cancer biology, as they influence both cellular senescence and genomic stability. In cancer cells, dysfunctional telomeres can lead to chromosomal fusions and, through deregulation of telomerase, allow replication of mutated chromosomes that might otherwise lead to apoptosis. Research is now focused on improving telomere-based cancer cell detection and developing potential therapies that inhibit telomerase activity in cancerous cells. Telomere research is crucial in understanding the molecular mechanisms influencing tumor growth and invasiveness because of the central role played by telomeres in various cancer types. Several telomerase inhibitors and immunotherapy treatments are in pre-clinical or clinical development. Research on the role of telomeres in oncogenesis has made significant strides, but obstacles remain, including a lack of high-resolution structural understanding, inadequate preclinical models, and concern over potential side effects. Even so, the current path of telomere research holds promise.

Keywords

Telomere, Telomerase Inhibition, Cancer Detection, Cancer Treatment, Immunotherapy

1. Introduction: The Discovery of Telomeres

From their initial discovery to their study in the clinical trials of today, telomeres have been at the forefront of genetic research, transforming our understanding of cellular biology and potential therapeutic interventions. The concept of telomeres was first posited in the 1930s by Barbara McClintock and Herman Muller. Herman Muller worked at the Edinburgh Animal Genetics Institute in the United Kingdom

and found the unique structure at the ends of chromosomes in fruit flies [1], while Barbara McClintock used X-rays to induce chromosome fragmentation in the Cold Spring Harbor Laboratory in New York and found them in corn [2]. In 1961, Leonard Hayflick and Paul Moorhead proved, contrary to the established belief of the time, that human fetal cells have a limited ability to replicate, with a maximum of 50 to 60 doublings before cell death would occur [3]. This phenomenon was later termed "replicative senescence" or the "Hayflick limit," but its underlying mechanism was not immediately understood. A key insight emerged in the 1970s, when Alexei Olovnikov and James Watson described the "end replication problem," where the ends of linear deoxyribonucleic acid (DNA) were determined to not be completely replicated during lagging strand DNA synthesis [4]. Later, in 1985, Elizabeth Blackburn, along with Carol Greider and Jack Szostak, identified telomerase, the enzyme responsible for extending telomeric sequences [5].

In 1996, further understanding of telomerase structure was gained when it was shown that the enzyme is a ribonucleoprotein that specifically targets a 3' double-stranded DNA overhang. Subsequently, the process of cloning human telomerase reverse transcriptase (hTERT) and the human telomerase RNA component (hTERC), two of the key components of the telomerase complex, followed in 1997 [6]. The first mouse genetically engineered to lack the TERC gene ("TERC knockout mouse") was generated in the same year. In the years that followed, TERC and TERT knockout mice, either alone or in mice also suffering from progeria (a genetic condition that causes rapid aging) or having oncogenes, demonstrated that telomere disruption is a major cause of degenerative illnesses, cancer, and premature aging. These mice allowed researchers to demonstrate that intact telomeres help to maintain genome stability, tissue stem cell reserves, organ system homeostasis, and normal lifespan [4]. In 1999, a collaboration among Jack Griffith, Lubomir Tomáška, and Jozef Nosek discovered T-loops, a folding of the DNA that is thought to hide telomeres from being detected as DNA damage and thus protecting the ends from double-stranded break repair enzymes. Since then, research has expanded to explore telomeres in various organisms and their implications for aging and disease prevention [7].

This article will discuss the relationship between telomeres and cancer and how ongoing research is aimed at developing potential therapies that block telomerase in cancerous cells and improving telomere-based cancer cell detection.

2. The Role of Telomeres in Cancer

Telomeres play a crucial role in cancer biology, primarily through their involvement in cellular senescence and genomic stability. Since telomeres shorten with each cell division due to the incomplete replication of DNA ends, telomeres serve as a biological clock that limits the number of times a cell can divide, acting as a tumor suppressor mechanism and helping to explain the Hayflick limit. However, in cancer cells, this process is often bypassed through upregulation of telomerase, which allows for indefinite cell division—a hallmark of cancer. Telomeres that are

too short cannot provide protection for chromosomes, leading to chromosomal fusions. This occurs after replication when an exposed end of a chromosome that has lost a telomere due to a breakage event joins with either another broken chromatid or its sister chromatid to form a dicentric chromosome, *i.e.*, a chromosome having two centromeres. Such mutations can be oncogenic, contributing to cancer initiation [8]. Telomerase activity and telomere dysfunction are therefore critical in understanding cancer development and provide a potential target for therapeutic intervention.

3. Telomeres as Cancer Diagnostics

Since the discovery that telomere shortening is related to serious health conditions, the measurement of telomere length has emerged as a promising tool in both diagnostics and prognostics. In cancer cells, telomere shortening can vary significantly from normal cells due to alterations in telomere maintenance mechanisms [9]. Shortened telomeres have been linked to increased cancer susceptibility and poorer prognosis in various cancers, including breast, prostate, and lung cancers [10]. Telomere lengthening can also contribute to some cancers through upregulated telomerase activity, which is associated with aggressive tumor behavior and resistance to therapies [11]. Assessment of telomere length, often through techniques like quantitative polymerase chain reaction (qPCR), quantitative fluorescence *in situ* hybridization (Q-FISH), and terminal restriction fragmentation (TRF), can provide insights into cancer risk.

TRF analysis was the first method to be developed for telomere length determination, and it is frequently referred to as the "gold standard" method. This process involves the use of restriction enzymes that cleave DNA sequences not found within the telomeric repeats (5'-TTAGGG-3'), followed by Southern blotting [12]. A disadvantage of using this method is that if DNA samples are not properly maintained in the laboratory, degradation could lead to inaccuracies in telomere length assessments, producing a bias toward shorter lengths. This can happen from repeated thawing and freezing of DNA, prolonged exposure to room temperature, and residual nucleases resulting from inadequate purification. Nonetheless, TRF provides a reliable method for comparing telomere length across studies, and does not require costly, specialized equipment [13].

In 1996, Peter Lansdorp and colleagues developed the Q-FISH method in which telomeres are visualized by hybridization using laboratory-synthesized fluorescent peptide nucleic acids that probe sequences in chromosomal DNA with the remaining chromatin on the chromosome being visualized by a nonspecific DNA stain. The ability to estimate sizes for each of the 92 distinct telomeres in humans (four chromosome "ends" for each of the 23 chromosome pairs)—rather than being restricted to an average or just small telomeres—is one benefit of employing the Q-FISH method. Moreover, this evaluation technique is the only one that can identify DNA sequences that are entirely lacking telomeres. However, its greatest weakness may be that it cannot be used to measure telomeres in cells that are not

mitotically active (such as terminally senescent cells) and those with a low proliferation rate [13].

In 2002, quantitative PCR telomere length measurement was reported by Richard Cawthon. In this process, DNA is isolated from a patient's blood sample, then amplified, and the amount of repetitive DNA sequences is measured. qPCR requires high-quality DNA that is not compromised by degradation but does not require large initial amounts of DNA. Due to its relatively low cost, amenability for high-throughput testing, and high accessibility of the necessary equipment used in the assay, qPCR is a popular method for estimating telomere length.

4. Emerging Therapies and Theoretical Approaches Using Telomeres

The targeting of telomeres offers promise for new cancer therapies, which can be aimed at disrupting the mechanisms that maintain telomere integrity and length. Some have suggested that cancers are less likely to develop resistance to telomerase-based therapies than to other cancer medicines [14], but this remains to be determined.

Alternative lengthening of telomeres (ALT) is a telomerase-independent pathway observed in some cancers that involves homologous recombination to elongate telomeres, suggesting one potential means by which cancers could circumvent telomerase-based therapies. Targeting ALT-specific mechanisms, such as DNA repair pathways involved in telomere maintenance, may therefore represent a potential strategy for novel therapies. ALT can be detected in 10% to 15% of cancers and is particularly prevalent in tumors of mesenchymal origin (soft tissue tumors, also known as connective tissue tumors or sarcomas) [15]. A study by Lee Zou and his team found that cancer cell lines using the ALT pathway often carry mutations in the ATRX gene, which leads replication protein A to promote recombination and the activation of the ALT pathway, thus allowing the cancer to continue to grow rapidly [16]. They found that these cells died rapidly after testing ATRX inhibitors on ALT-positive osteosarcoma and glioblastoma cancer cells *in vitro* [17], which suggests that patient survival could be improved if therapies for ALT elimination could be developed [18].

Telomerase is composed of two major subunits, hTERT and TERC, as noted previously. The reverse transcription protein component, hTERT, adds nucleotides to chromosome ends by reverse-transcribing RNA, while the RNA component, TERC, provides the template that is transcribed into the repeated sequence of DNA that is added to the end of chromosomes [19]. By increasing telomerase activity and TERT expression, cancers can evade replicative senescence, and both appear to be widespread. Elevated telomerase activity has been reported in approximately 90% of cancers and TERT expression detected in about 75% of tumor samples. TERC levels have been found to be upregulated in certain cancer types, such as carcinomas of the cervix, ovary, head and neck, and lung [20].

Approaches to targeting telomerase range from immunotherapies that recog-

nize TERT tumor-associated antigens, to small molecule inhibitors or oligonucleotides that directly bind telomerase and suppress telomere extension [20]. Numerous TERT peptide vaccines have progressed to early-stage clinical trials, typically eliciting few adverse events. Unfortunately, early results have also shown that these vaccines offer limited clinical efficacy, though it is hoped that they may work better on those whose tumors exhibit high TERT expression [20]. Outside of the oncology context, more than a dozen oligonucleotides have been approved as medications, and several potential candidates are progressing through clinical trials, creating optimism that antisense nucleic acids could eventually be a viable option for the clinical development of telomerase-based cancer therapies [5].

Although telomerase possesses many desirable properties as a cancer target, development of successful clinical therapies has been slowed by significant challenges such as the difficulty of optimizing telomere length, given that both shortened and lengthened telomeres appear able to contribute to malignancies [21]. Nevertheless, the constant flow of continued research findings will likely open avenues for new innovative treatments.

5. Research with Different Types of Cancer and Telomeres

Telomere research has been conducted across various cancer types. The 5-year relative survival rates range from 3% to 14% for advanced-stage cancers, such as lung, colorectal, liver, and pancreatic, even after maximal surgical excision, radiation, chemotherapy, and hormone, immune, and targeted therapies [22]. Thus, no current treatment can completely cure most patients at an advanced stage of cancer, continuing a long-term trend of substantial technical advancement that has not translated into large improvements in patient outcomes [23] [24]. Nevertheless, there is still optimism that increased knowledge of the molecular mechanisms influencing tumor growth and invasiveness could lead to novel and effective therapies to improve the poor prognoses of late-stage cancers.

Telomerase is active in over 90% of breast cancer. Most research on breast cancer focuses on antisense oligonucleotides, dominant negative mutant hTERT, and reverse transcriptase inhibitors. The most used reverse transcriptase inhibitor in studies of breast cancer is 3'-azido-3'-deoxythymidine (AZT), the drug famously launched in 1987 as the first FDA-approved treatment for the Human Immunodeficiency Virus (HIV). AZT has been shown to inhibit the growth and telomerase activity of human ovarian cancer HO-8910 cells *in vitro*, creating hope that these laboratory results could be translated to clinical settings [25]. Melana *et al*. found that AZT inhibited telomerase activity and the growth of breast cancer cells at lower concentrations than in normal breast cells [26]. However, the short half-life of the AZT in the body is a potential challenge [26]. In another study, AZT was shown to efficiently inhibit the growth and telomerase activity of human ovarian cancer HO-8910 cells *in vitro*, which suggests that AZT may be utilized in the treatment of ovarian cancer in clinical settings [25]. Unlike studies with AZT, those conducted with antisense oligonucleotides and dominant negative mutant

hTERT have shown these treatments can effectively inhibit telomerase in breast epithelial and carcinoma cells *in vitro*.

Lung cancer studies reveal that high telomerase activity is associated with aggressive tumor behavior and poor prognosis. According to several studies utilizing non-small cell lung cancer (NSCLC) tissues from both humans and animals, lung cancer cells overexpress TERT mRNA and TERT protein in comparison to normal lung tissues [27]. Studies conducted on mice with a mutated version of their telomerase subunit (mTERC) with telomere dysfunction and active p53 (a tumor suppressor gene) showed increased lung epithelial cell death and delayed tumor formation. After testing GRN163L, a telomerase antagonist, in animal models and *in vitro*, it was used in clinical trials in combination with standard chemotherapy and showed efficacy [28] [29]. Other studies used synthetic TERT peptides to induce antigen-presenting cells to produce an immune response against cancer cells expressing TERT [14].

Liver cancer research has shown that telomere dysfunction can promote cirrhosis and hepatocellular carcinoma (HCC). A case-control study found that people with long telomeres were more likely to develop HCC and other liver diseases [30]. Telomerase knockout mice have also been used to study hepatocarcinogenesis, with studies suggesting that a stable telomere-telomerase system plays a role in suppressing HCC formation. Most studies have sought to identify a relationship between telomerase and liver cancers, but few have tested telomerase inhibitors in humans as a possible treatment. Telomerase inhibitors that have been used in preclinical and clinical trials include an antisense oligonucleotide (Rytelo, imetelstat) that was FDA approved on June 6, 2024 for the treatment of myelodysplastic syndromes, a small-molecule inhibitor (BIBR1532), as well as G-quadruplex stabilizers (BRACO, RHPS4, telomestatin) [31].

Pre-clinical research on pediatric cancers such as neuroblastoma, a cancer that develops from immature nerve cells found in several areas of the body, has involved compounds that could inhibit telomerase and ALT activities. Compounds such as imetelstat, BIBR1532, and sodium meta-arsenite target telomerase activity but testing was stopped due to toxicity [15]. Telomestatin has been shown to inhibit telomerase activity but is not yet in clinical development. 6-thio-2'-deoxyguanosine, although having mixed results, has shown pre-clinical efficacy in melanoma, non-small cell lung cancer, and pediatric brain tumor models [15]. This compound is also thought to be less toxic than traditional telomerase inhibitors, suggesting promise for further development in neuroblastoma.

6. Conclusion

Research on telomeres and cancer has advanced our understanding of how these genetic nucleotide structures can be used to promote human health. Despite advances, several limitations and challenges remain, including limited clinical efficacy studies and questions about the potential development of resistance. The potential for harmful side effects, given that telomerase is also active in healthy cells,

presents an additional challenge. Looking forward, future research should focus on better understanding the mechanisms of telomerase and ALT dysfunction in different cancer contexts, as well as identifying biomarkers that can predict response to telomere-targeted therapies. Advances in gene editing technologies, such as CRISPR-Cas9, could provide new ways for selectively targeting telomerase in cancer cells while sparing normal cells. Moreover, exploring the interactions between telomerase, the immune system, and the tumor microenvironment could unveil new approaches for enhancing the efficacy of cancer immunotherapies.

Despite tremendous progress in understanding the function of telomeres in cancer, much remains to be discovered. Future cancer therapy may be greatly impacted by the creation of novel, telomere-based diagnostic and therapeutic strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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