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Mechanisms of telomere dysfunction in cancer from genomic instability to therapy: A review

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Abstract

Telomeres are critical nucleoprotein structures that safeguard chromosome ends from degradation and fusion, thereby ensuring genomic stability. Without proper maintenance, telomeres progressively shorten with each cell division, leading to dysfunction and triggering chromosomal instability. This dysfunction is a significant driver of tumorigenesis, primarily by facilitating genetic alterations such as aneuploidy, gene amplifications, and chromosomal rearrangements. Cancer cells bypass cellular aging by activating mechanisms like telomerase reactivation or the Alternative Lengthening of Telomeres (ALT) pathway to maintain telomere length. This review explores the mechanisms by which telomere dysfunction contributes to genomic instability and cancer progression, including telomere shortening, breakage-fusion-bridge (B/F/B) cycles, and the ALT pathway. Additionally, it addresses the therapeutic potential of targeting telomere maintenance, highlighting current strategies like telomerase and ALT inhibitors. However, developing telomere-based therapies presents challenges, including resistance mechanisms, off-target effects, and potential impacts on normal stem cells. Emerging research areas such as the development of biomarkers and combination therapies offer promising directions for overcoming these challenges. Understanding telomere dynamics provides novel opportunities to exploit cancer cell vulnerabilities and advance treatment strategies.

Keywords: Telomere dysfunction; Genomic instability; Cancer progression; Alternative Lengthening of Telomeres (ALT); Breakage-fusion-bridge cycles; Therapeutic resistance

1. Introduction

Telomere dysfunction is increasingly recognized as a pivotal mechanism contributing to genomic instability, a hallmark of cancer progression. Telomeres, the protective caps of chromosomes, prevent unwanted chromosomal end-to-end fusions and protect against DNA damage responses. However, when telomeres shorten or become dysfunctional, as occurs in many cancer cells, they initiate chromosomal instability through breakage-fusion-bridge (B/F/B) cycles, amplifying oncogenic regions or causing large-scale deletions [1–3]. This process promotes tumor initiation and progression by facilitating continuous genetic rearrangements.

Cancer cells must overcome the detrimental effects of telomere dysfunction to proliferate indefinitely. Most achieve this through reactivation of telomerase or the alternative lengthening of telomeres (ALT) pathway, both of which stabilize chromosomal ends by elongating telomeres [1,4]. The dual role of telomeres in both inhibiting and promoting cancer underscores the complexity of targeting telomere maintenance as a therapeutic strategy. While therapies aimed at inhibiting telomerase show promise, challenges such as resistance mechanisms and off-target effects persist [2].

Recent evidence has highlighted the intricacies of how transient telomere dysfunction leads to chromosome instability, initiating B/F/B cycles and driving cancer evolution. Specifically, studies have demonstrated that both transient and

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chronic telomere dysfunction accelerate tumorigenesis in telomerase-proficient backgrounds by promoting chromosomal fusions and amplifications [1,2]. These findings underscore the therapeutic potential of targeting telomere maintenance mechanisms and the importance of understanding the distinct pathways cancer cells use to maintain telomere integrity.

This review will focus on the mechanisms by which telomere dysfunction promotes genomic instability and cancer progression. We will explore the role of telomere shortening, telomerase reactivation, and the ALT pathway in facilitating oncogenesis. Additionally, the review will examine current therapeutic strategies targeting telomere maintenance, their limitations, and future directions for overcoming these challenges.

2. Telomere Structure and Function

Telomeres are specialized nucleoprotein structures located at the ends of eukaryotic chromosomes, essential for maintaining chromosomal integrity and preventing degradation or fusion with neighboring chromosomes. These structures consist of repetitive DNA sequences and associated proteins, which together form a protective cap. In humans, telomeric DNA is made up of tandem repeats of the sequence TTAGGG, extending over several kilobases [5,6].

The primary role of telomeres is to prevent the ends of chromosomes from being recognized as double-strand DNA breaks. Without these protective structures, chromosomes would be susceptible to degradation, recombination, or end-to-end fusion, which can lead to genomic instability [7]. The structure of telomeres includes a single-stranded G-rich overhang, which plays a key role in forming higher-order structures such as the telomeric loop (T-loop). The T-loop forms when the single-stranded overhang folds back and invades the double-stranded region of the telomere, creating a displacement loop (D-loop). This loop structure effectively hides the telomere end, preventing inappropriate DNA damage responses [6,7].

Telomere maintenance is facilitated by a group of six core proteins collectively known as the **shelterin complex**. This complex includes TRF1, TRF2, POT1, TIN2, TPP1, and RAP1, which together bind to the telomeric DNA and ensure the stability of telomeres. TRF1 and TRF2 bind the double-stranded regions of the telomere, while POT1 binds the single-stranded G-rich overhang [5,6]. These proteins work to regulate telomere length, protect telomeres from degradation, and prevent the activation of DNA damage pathways [8].

Telomerase, a ribonucleoprotein reverse transcriptase, is another critical component in telomere biology. It adds repetitive nucleotide sequences to the ends of chromosomes, counteracting the natural shortening that occurs with each cell division due to the end-replication problem [6]. In somatic cells, telomerase is typically inactive, leading to gradual telomere shortening, which eventually results in cellular senescence. However, in germ cells, stem cells, and most cancer cells, telomerase activity is maintained, allowing these cells to proliferate indefinitely [7,8].

In summary, telomeres are vital for preserving genomic stability, with their structure and associated proteins providing the necessary functions for end protection, regulation of length, and prevention of inappropriate DNA repair mechanisms. Without proper telomere maintenance, cells face increased risks of genomic instability, a hallmark of cancer and other age-related diseases.

3. Telomere Dysfunction: Mechanisms Leading to Instability

Telomeres are critical in maintaining chromosomal integrity, and their dysfunction can lead to significant genomic instability. This instability occurs through mechanisms such as telomere shortening, erosion, or loss of protective capping. When telomeres fail to protect chromosome ends, they become prone to chromosomal fusions, triggering a series of catastrophic genetic rearrangements that drive cancer progression. Below are the key mechanisms that lead to telomere-induced instability:

3.1. Telomere Shortening and Crisis

Telomeres naturally shorten with each cell division due to the end-replication problem, a process where DNA polymerase cannot fully replicate the terminal end of linear DNA [4,9]. Over time, this gradual shortening leads to the loss of critical telomeric sequences. When telomeres become critically short, they lose their ability to cap chromosome ends effectively, and the cell enters a state of crisis. During this stage, the DNA damage response (DDR) is activated, and p53-dependent pathways initiate cell-cycle arrest or apoptosis [1,4].In the absence of functional p53 or other checkpoint proteins, cells evade apoptosis and continue dividing, despite dysfunctional telomeres. This opens the door

for chromosomal instability as uncapped chromosome ends are vulnerable to fusion events, leading to the formation of dicentric chromosomes, which initiate breakage-fusion-bridge (B/F/B) cycles [1,9].

3.2. Breakage-Fusion-Bridge (B/F/B) Cycles

When telomeres become critically short or dysfunctional, chromosome ends may fuse, leading to the formation of dicentric chromosomes. These fused chromosomes are pulled apart during anaphase in mitosis, forming chromatin bridges between the separating daughter cells. The mechanical tension in these bridges can cause them to break, producing chromosome fragments with unstable ends [3,4]. These fragments may fuse again, initiating a new cycle of breakage, fusion, and bridge formation. This repetitive process, known as the Breakage-Fusion-Bridge (B/F/B) cycle, leads to significant chromosomal instability by causing duplications, deletions, and amplifications of genetic material [3,9]. Over successive cycles, this instability can result in large-scale chromosomal rearrangements, which are common in cancer cells and contribute to tumorigenesis by promoting genetic diversity and facilitating the acquisition of oncogenic mutations [4][10–13].

3.3. ALT and its Role in Chromosomal Instability

In some cancer cells, particularly those that lack telomerase, an alternative mechanism called **Alternative Lengthening of Telomeres (ALT)** is activated to maintain telomere length. ALT relies on homologous recombination to elongate telomeres [3,4]. While this mechanism prevents immediate telomere shortening and crisis, it introduces its own form of instability. The ALT pathway often results in heterogeneous telomere lengths, and some telomeres may become critically short while others are excessively long [4]. This imbalance, coupled with the recombination events inherent in ALT, leads to additional chromosomal instability. Cells using ALT also display an elevated frequency of telomere-telomere fusions and complex karyotypic alterations [3,4].

In summary, telomere dysfunction through shortening, B/F/B cycles, or ALT pathways plays a critical role in driving genomic instability in cancer cells. By enabling chromosomal fusions and rearrangements, telomere dysfunction contributes to tumor progression and provides cancer cells with a mechanism to evade normal cellular aging and death.

4. Consequences of Telomere Dysfunction: Chromosomal Instability in Cancer

Telomere dysfunction is a critical driver of chromosomal instability, which plays a central role in cancer progression. Dysfunctional telomeres lead to a series of genomic alterations, including aneuploidy, gene amplification, and loss of heterozygosity (LOH). These alterations fuel tumorigenesis by promoting cancer cell survival, tumor heterogeneity, and resistance to therapy.

4.1. Aneuploidy and Genetic Diversity

Telomere shortening and loss of function can trigger aneuploidy, a condition characterized by an abnormal number of chromosomes in cells. Telomere shortening activates the DNA damage response, leading to chromosomal fusions and mis-segregation during cell division [14]. As a result, aneuploidy increases genetic diversity within tumors, which provides a pool of mutations that may confer selective advantages to cancer cells under various microenvironmental pressures. The presence of aneuploidy has been associated with poor prognosis in multiple cancer types, including hepatocellular carcinoma (HCC) [15].

4.2. Breakage-Fusion-Bridge Cycles and Their Impact on Chromosomal Rearrangement

Telomere dysfunction often leads to breakage-fusion-bridge (B/F/B) cycles, a mechanism by which chromosomes without proper telomeric caps fuse, break, and fuse again during cell division. These cycles contribute to massive chromosomal rearrangements, including amplifications, deletions, and translocations, which further drive genomic instability [16]. In cancers such as hepatocellular carcinoma and colorectal cancers, this process has been observed to result in the formation of complex chromosomal aberrations that contribute to tumor progression [15,17].

4.3. Gene Amplifications and Tumorigenesis

Telomere dysfunction is closely associated with regional amplifications and deletions at specific loci within the genome, often targeting oncogenes and tumor suppressor genes. For example, in mouse models with telomere dysfunction, amplifications in chromosomal regions analogous to human cancer hotspots have been observed [16]. These gene amplifications can result in the overexpression of oncogenes, promoting tumorigenesis. This mechanism is significant in cancers where telomere dysfunction leads to nonreciprocal translocations and complex chromosomal abnormalities

[18]. Amplified regions often contain genes that provide cancer cells with enhanced survival, growth, and metastatic potential.

5. Interplay Between Telomere Dysfunction and DNA Repair Pathways

Telomere dysfunction can lead to genomic instability, a hallmark of cancer, by triggering inappropriate activation of DNA repair pathways. In healthy cells, telomeres are protected by the shelterin complex, which prevents the DNA damage response (DDR) from recognizing chromosome ends as double-stranded breaks (DSBs). However, when telomeres become critically short or dysfunctional, DDR pathways like non-homologous end joining (NHEJ) and homologous recombination (HR) are activated, leading to chromosomal fusions and rearrangements [19,20]. The following section explores how telomere dysfunction interacts with these DNA repair pathways.

5.1. DNA Damage Response and Repair at Telomeres

Telomere dysfunction is closely linked to the activation of DNA damage response proteins. Shelterin components like TRF2 and POT1 play a central role in inhibiting the DDR at telomeres. TRF2 is essential in repressing the activation of the ataxia-telangiectasia mutated (ATM) kinase, which senses double-strand breaks. In the absence of TRF2, telomeres are processed as DSBs, leading to ATM activation and the fusion of chromosome ends by NHEJ [21,22].

Similarly, POT1, part of the shelterin complex, inhibits the ATR (ATM and Rad3-related) kinase pathway, which is typically activated by the presence of single-stranded DNA. POT1 binds to single-stranded telomeric DNA, preventing replication protein A (RPA) from binding and activating ATR [19,21]. The interplay between these shelterin components and DDR pathways highlights the delicate balance required to maintain telomere stability and prevent inappropriate DNA repair activation.

In the context of telomere dysfunction, the DDR is activated due to loss of telomere protection, causing recruitment of repair proteins like MDC1, 53BP1, and the MRN complex to dysfunctional telomeres. These proteins recognize damaged telomeres as DSBs, leading to chromosomal instability [23]. Additionally, proteins involved in both HR and NHEJ, such as BRCA1, Ku70/80, and DNA-PK, are recruited to dysfunctional telomeres, further exacerbating chromosomal instability through misregulated repair [22,24].

The failure of telomeres to properly interact with DNA repair mechanisms results in detrimental outcomes like end-to-end chromosomal fusions, genomic instability, and cancer progression. Understanding these interactions provides insights into the complex role of telomere dysfunction in cancer development.

5.2. Role of p53 and Other Tumor Suppressors in Telomere Maintenance

The tumor suppressor protein p53 plays a crucial role in maintaining telomere stability by inducing cell cycle arrest, apoptosis, or senescence in response to telomere dysfunction [25,26]. When telomeres become critically short or lose their protective capping, p53 activates DNA damage checkpoints, such as ATM and ATR, which initiate repair or, if the damage is irreparable, lead to programmed cell death or senescence [25].

p53, often termed the "guardian of the genome," is crucial in ensuring that cells with dysfunctional telomeres do not continue to divide, preventing the accumulation of mutations that drive cancer progression [27]. In cells with compromised p53 function, such as in many cancer types, dysfunctional telomeres are not adequately managed, leading to increased chromosomal instability and tumorigenesis [28].

Other tumor suppressors, including BRCA1 and DNA-PK, also play vital roles in telomere maintenance. BRCA1 is involved in the homologous recombination repair of DSBs, including those at dysfunctional telomeres, while DNA-PK is critical for NHEJ repair. The loss of these proteins further exacerbates the instability of telomeres, promoting cancer development [27–29].

In summary, the interplay between telomere dysfunction and DNA repair pathways is a critical determinant of genomic stability. Tumor suppressors like p53, BRCA1, and DNA-PK are essential in regulating these interactions, ensuring that dysfunctional telomeres are either repaired or eliminated to prevent the onset of cancer.

6. Therapeutic Implications of Targeting Telomere Dysfunction in Cancer

Telomere dysfunction presents a promising therapeutic target in cancer treatment due to its central role in enabling the unlimited proliferation of cancer cells. Most human cancers maintain their telomeres through the activation of telomerase, while others utilize the Alternative Lengthening of Telomeres (ALT) pathway. Targeting these mechanisms offers novel therapeutic avenues aimed at either inhibiting telomerase activity or disrupting telomere maintenance. This section outlines the current strategies aimed at exploiting telomere dysfunction in cancer therapy, focusing on telomerase inhibitors, ALT pathway inhibitors, and the heightened sensitivity of telomere-dysfunctional cancer cells to DNA damage and cell cycle arrest.

6.1. Telomerase Inhibitors

Telomerase is reactivated in approximately 85-90% of human cancers, making it an attractive target for cancer therapy [30,31]. Several inhibitors targeting the telomerase enzyme have been developed, with Imetelstat (GRN163L) being one of the most advanced. Imetelstat is a lipid-modified oligonucleotide that binds the RNA template region of telomerase, preventing it from extending telomeres. Preclinical studies have shown that imetelstat effectively inhibits telomerase activity, induces telomere shortening, and causes growth arrest in cancer cells [30,32]. Clinical trials have demonstrated encouraging results in hematologic malignancies such as myelofibrosis and essential thrombocythemia, with some patients achieving durable responses [31,32].

Another notable telomerase inhibitor is BIBR1532, a small molecule that selectively inhibits the catalytic subunit of telomerase (hTERT). BIBR1532 impairs telomere elongation and induces apoptosis in cancer cells after progressive telomere shortening [31,33]. However, one challenge with telomerase inhibitors is the delayed therapeutic effect due to the time required for telomeres to reach a critically short length. This lag can be mitigated by combining telomerase inhibitors with DNA-damaging agents, which accelerate telomere dysfunction [30,31].

6.2. ALT Inhibitors

In approximately 10-15% of cancers, telomere length is maintained by the ALT pathway, which relies on homologous recombination between telomeric repeats [30]. ALT-positive tumors are typically found in sarcomas and gliomas, and targeting the ALT mechanism is an emerging area of research. ALT inhibitors focus on disrupting key proteins involved in the recombination process, such as ATR (ataxia-telangiectasia and Rad3-related protein) and RAD51. Inhibitors like VE-822 and NVP-BEZ235 have shown promise in preclinical studies by selectively targeting ALT-positive cells, leading to telomere dysfunction and apoptosis [30,31].

Another strategy is the use of G-quadruplex stabilizers, which induce the formation of four-stranded DNA structures at the telomeric overhang, thereby preventing telomere elongation. Drugs such as RHPS4 and BRACO19 have been shown to induce DNA damage in both telomerase-positive and ALT-positive cancer cells by disrupting telomere capping and initiating a DNA damage response [30,33].

6.3. Exploiting Telomere Dysfunction for DNA Damage Sensitization

Cancer cells with dysfunctional telomeres are highly sensitive to DNA damage due to impaired telomere capping and the activation of DNA damage response pathways such as ATM (ataxia-telangiectasia mutated) and ATR [33,34]. This vulnerability can be exploited by combining telomere-targeting agents with DNA-damaging therapies, such as chemotherapy or radiation. For instance, telomerase inhibitors like imetelstat have been shown to sensitize cancer cells to radiation, leading to enhanced cell death [31].

Similarly, cancer cells undergoing breakage-fusion-bridge (B/F/B) cycles due to telomere dysfunction are prone to genomic instability, making them more susceptible to DNA damage response inhibitors such as PARP inhibitors. This combination approach has the potential to selectively kill cancer cells while sparing normal cells with intact telomeres [31,35].

7. Future Directions and Challenges

Research on telomere dysfunction has advanced significantly, yet numerous challenges persist in translating these findings into effective cancer therapies. Targeting telomere maintenance offers promising strategies for halting cancer progression, but there are several critical obstacles to overcome.

7.1. Challenges in Targeting Telomere Dysfunction

One of the primary challenges in targeting telomere dysfunction is the potential for off-target effects on normal stem cells and other highly proliferative tissues. Telomerase is not exclusive to cancer cells; it plays a crucial role in maintaining the telomeres of normal stem cells, particularly in tissues such as the bone marrow, skin, and gastrointestinal tract [15,36,37]. Inhibiting telomerase across all cell types could lead to unwanted consequences, including tissue degeneration, immunosuppression, and accelerated aging. For example, Werner Syndrome, a telomere dysfunction disorder, is characterized by premature aging and cancer, illustrating the delicate balance of telomerase activity in normal and malignant cells [38].

Another challenge lies in resistance mechanisms that cancer cells may develop. While telomerase inhibition has shown potential, some cancer cells evade this strategy by switching to the Alternative Lengthening of Telomeres (ALT) pathway. ALT is a telomerase-independent mechanism that uses homologous recombination to maintain telomere length. This process is particularly common in certain cancers like osteosarcomas and gliomas [7,39,40]. As a result, future therapies need to address both telomerase-dependent and ALT-driven mechanisms to prevent therapeutic resistance.

7.2. Emerging Research Areas

- **Biomarkers for Telomere Dysfunction**: A critical area of emerging research involves the identification of **biomarkers** to detect telomere dysfunction in cancer early and non-invasively. Techniques such as measuring telomere length in circulating tumor cells or through liquid biopsies could help monitor the progression of cancer and evaluate responses to telomere-targeting therapies [17,18]. These biomarkers could also guide personalized treatment, ensuring that therapies targeting telomere dysfunction are applied to patients who would benefit most.
- **New Therapeutic Approaches**: Researchers are exploring novel drugs aimed at disrupting the telomere maintenance machinery selectively in cancer cells. One promising approach is the development of telomerase inhibitors like imetelstat, which has shown potential in clinical trials. In addition, ALT inhibitors are an area of growing interest. ALT-targeted therapies focus on disrupting the proteins involved in homologous recombination, such as ATR, to prevent cancer cells from compensating for telomerase inhibition [18,41]. Furthermore, the combination of telomere-targeting therapies with other strategies, such as DNA-damage response inhibitors, may enhance their efficacy by exploiting the inherent vulnerabilities of cancer cells with dysfunctional telomeres.
- **Combination Therapies**: Combining telomere-targeting therapies with other cancer treatments is a key area of exploration. Research is increasingly focusing on combining telomerase inhibitors with immunotherapies or conventional chemotherapies to induce greater cancer cell death. Cancer cells with telomere dysfunction are more vulnerable to DNA-damage response inhibitors, creating an opportunity to enhance the efficacy of traditional treatments [42,43]. For instance, in cancers where ALT is active, combining ALT pathway inhibitors with DNA repair inhibitors may offer a more comprehensive approach to therapy.
- **Addressing Resistance and Adaptive Mechanisms**: Tackling resistance mechanisms is essential to the future of telomere-targeting therapies. As mentioned, the ALT pathway serves as a key bypass mechanism for telomerase inhibition [44]. Research into dual-target therapies—those that inhibit both telomerase and ALT—holds promise for overcoming this adaptive resistance. Moreover, some studies suggest that telomere dysfunction may also cause complex genomic rearrangements, such as amplifications and deletions, that contribute to therapeutic resistance [4,45,46]. Thus, future therapies need to account for the genomic instability driven by telomere dysfunction.

8. Conclusions

Telomere dysfunction plays a central role in driving genomic instability, which is a key factor in cancer progression. Mechanisms such as telomere shortening, breakage-fusion-bridge cycles, and the activation of the Alternative Lengthening of Telomeres (ALT) pathway contribute to the uncontrolled proliferation of cancer cells. These processes not only enable tumor growth but also fuel genetic diversity, which supports tumor heterogeneity and therapeutic resistance.

Therapeutically, targeting telomere maintenance offers promising strategies for halting cancer progression. Telomerase inhibitors like imetelstat, ALT inhibitors, and G-quadruplex stabilizers are currently being explored to disrupt the telomere maintenance machinery in cancer cells. Despite these advances, challenges remain, particularly in overcoming resistance mechanisms and minimizing off-target effects on normal stem cells. The combination of telomere-targeting

agents with DNA-damaging therapies presents a compelling approach to enhancing treatment efficacy, as cancer cells with dysfunctional telomeres are particularly sensitive to DNA damage.

As research progresses, the development of biomarkers for early detection of telomere dysfunction and the design of combination therapies will be crucial in optimizing treatment outcomes. With a deeper understanding of telomere biology and its role in cancer, telomere-targeting therapies hold significant potential to improve cancer treatment strategies and patient survival.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The authors state that the research was conducted according to ethical standards.

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