

The telomere connection between aging and cancer: The burden of replication stress and dysfunction

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ABSTRACT

Aging is a complex process that affects individuals at the molecular, cellular, tissue, and systemic levels, arising from the cumulative effects of damage and reduced repair mechanisms. This process leads to the onset of age-related diseases, including cancer, which exhibits increased incidence with age. Telomeres, the protective caps at chromosome ends, play a crucial role in genome stability and are closely connected with aging and age-related disorders. Both excessively short and long telomere lengths may contribute to cancer development when their balance is disrupted. Fragile telomeres, characterized by abnormalities and replication stress, may provide novel insights into the connection between aging and cancer. The accumulation of fragile telomeres, possibly due to intense replicative stress, may represent a key factor. Given the dynamic nature of telomeres, large longitudinal studies are essential for understanding their role in aging and cancer susceptibility, which is crucial for developing effective strategies to promote healthy aging and mitigate cancer risk.

1. Introduction

As life expectancy increases, the prevalence of age-related diseases, including cancer, also rises, posing significant challenges for public health systems worldwide. Cancer is predominantly a disease of aging, with the majority of cancer cases diagnosed in individuals aged 65 and older (Pilleron and Bastiaannet, 2024). Aging is a multifaceted phenomenon impacting individuals across molecular, cellular, tissue, and systemic levels (Guo et al., 2022). It arises from the cumulative effects of damage and diminishing repair mechanisms collectively contributing to the onset of age-related diseases (López-Otín et al., 2023). Interestingly, as individuals age, various physiological changes occur at the cellular and molecular levels, contributing to an increased susceptibility to cancer (Berben et al., 2021). Cancer, together with age-related degenerative diseases, increases in incidence with nearly exponential kinetics beginning at approximately the mid-point of the lifespan (in subjects with predisposition), thus not differing from other diseases of aging (Campisi, 2013). Along with aging, the body undergoes numerous biological and physiological changes that can accelerate aging, initiate tumor formation, and aid in cancer progression. This interplay between aging and cancer is influenced by various factors, including mutations,

cellular senescence, and systemic inflammation (Laconi et al., 2020). Predominant among the cancer types are prostate cancer in men, breast cancer in women, and lung and colorectal cancer in both genders (Sung et al., 2021). The challenge of cancer in aging is a multifaceted and pressing issue that arises due to the complex interplay between the processes of aging and the development of cancerous conditions (Berben et al., 2021). Importantly, the link between aging and cancer is deeply rooted in telomere biology (Chakravarti et al., 2021). Telomeres, the protective sequences at the ends of chromosomes, gradually shorten with each cell division, eventually triggering cellular senescence or apoptosis to prevent uncontrolled proliferation—a key feature of aging (Srinivas et al., 2020). However, this same mechanism that limits cellular lifespan can fail in cancer, where cells acquire the ability to maintain or extend their telomeres through mechanisms such as telomerase activation or the alternative lengthening of telomeres (ALT). This enables unlimited replication, a hallmark of cancer (López-Otín et al., 2023). Thus, telomeres act as a critical interface between aging and cancer, where their natural erosion contributes to aging, while their artificial maintenance fuels tumorigenesis. Understanding this complex balance offers opportunities to address both age-related diseases and cancer through targeted therapeutic strategies. Improving human

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healthspan and reducing cancer risk in an increasingly aging population is in the modern world crucial. This mini-review will explore the complex relationship between aging and cancer through the lens of telomere biology. We will discuss how telomere shortening and replication stress contribute to cellular dysfunction in aging, while also highlighting the paradoxical role of telomere maintenance in supporting cancer progression. Understanding this telomere connection offers critical insights into the shared molecular pathways underlying aging and cancer, and presents potential avenues for therapeutic intervention.

2. Exploring aging-cancer connections

The biological connection between aging and cancer is rooted in various molecular and cellular processes that occur over time. As individuals age, the body's ability to maintain homeostasis and repair damage declines, leading to an increased risk of cancer (López-Otín et al., 2023). As we age, the accumulation of genetic mutations increases due to both endogenous factors (e.g., reactive oxygen species) and exogenous factors (e.g., UV radiation). Aging is associated with widespread changes in DNA methylation, histone modification, and chromatin remodeling. These epigenetic alterations can lead to the dysregulation of gene expression, contributing to the development and progression of cancer. Again, the immune system's ability to detect and eliminate cancer cells declines with age. This immunosenescence reduces the efficacy of immune surveillance, allowing cancer cells to evade detection and grow unchecked (Fulop et al., 2021). Aging is also accompanied by chronic low-grade inflammation, known as "inflammaging" (Furman et al., 2019). Chronic inflammation can promote all stages of tumor development, including initiation, promotion, and progression, by inducing genetic mutations, promoting cellular proliferation, and inhibiting apoptosis (Fulop et al., 2021). Other common mechanisms shared by aging and cancer include cellular senescence, disruptions in proteostasis, microbiota imbalances (decreased beneficial bacteria and increased harmful bacteria), extensive immunosenescence, abnormal energy metabolism, altered material metabolism, endocrine disorders (Shen et al., 2022). Cellular senescence is considered a central hallmark of aging as well as of cancer (Di Micco et al., 2020). Cellular senescence is a state in which cells permanently stop dividing but do not die. This phenomenon occurs when cells experience various forms of stress, such as critically short telomeres, DNA damage, oxidative stress, or oncogenic signals. While senescent cells stop to proliferate, they remain metabolically active and secrete inflammatory cytokines, growth factors, and proteases, a phenomenon known as the senescence-associated secretory phenotype (SASP) (Campisi, 2013; Di Micco et al., 2020). As we age, the number of senescent cells in tissues increases. These cells contribute to the aging process by promoting tissue dysfunction and chronic inflammation. The accumulation of senescent cells reduces the regenerative capacity of tissues, impairs organ function, and creates a pro-inflammatory environment that further accelerates the aging process. Cellular senescence, in turns, acts as a tumor suppressor mechanism by preventing damaged or stressed cells from continuing to divide and potentially forming tumors (Campisi, 2013; Di Micco et al., 2020; Schmitt et al., 2022). However, the SASP can have paradoxical effects; while it can reinforce growth arrest and immune surveillance, it can also create a pro-tumorigenic environment by promoting inflammation, altering tissue structure, and enhancing the growth and invasiveness of nearby pre-malignant or malignant cells. Senescence, driven by telomere shortening and dysfunction, links aging and cancer by halting cell division, thus contributing to tissue degeneration (Schmitt et al., 2022).

3. Aging and cancer: the telomere/telomerase connection

Telomeres are complex structures located at the ends of chromosomes, serving as protective caps that prevent the degradation and fusion of chromosomes during cell division. They consist of the DNA

sequence "TTAGGG" repeated thousands of times and are bound by a complex of specialized proteins known as the shelterin complex (Blasco, 2005). Telomeres, working as protective caps at the ends of chromosomes, play a critical role in maintaining genomic stability by preventing chromosome ends from being mistaken for DNA damage. However, telomeres shorten with each cell division due to the "end-replication problem." This phenomenon occurs because DNA polymerase, the enzyme responsible for DNA replication, cannot fully replicate the ends of linear chromosomes (Liao et al., 2023). Consequently, a small portion of the telomere is lost during each round of DNA replication. Several factors contribute to telomere shortening over time including DNA replication, genetic factors, lifestyle factors, oxidative stress as well as cellular stress and inflammation. During DNA replication, the enzyme DNA polymerase requires a primer to start synthesis. This leads to the inability to replicate the very end of the chromosome, resulting in gradual telomere shortening with each cell division (Li and Durbin, 2024). Variations in genes involved in telomere maintenance can influence the rate of telomere shortening. For example, mutations in the telomerase gene can lead to faster telomere erosion and related disorders (Martínez and Blasco, 2017). Environmental and lifestyle factors such as smoking, poor diet, lack of exercise, and psychological stress have been associated with accelerated telomere shortening. These factors increase oxidative stress and inflammation, contributing to telomere erosion (Gürel et al., 2024). Reactive oxygen species (ROS) generated during cellular metabolism can cause damage to telomeric DNA, accelerating telomere shortening. Telomeric regions are particularly susceptible to oxidative damage due to their high guanine content (Barnes et al., 2019). Chronic inflammation and cellular stress can increase the rate of telomere attrition. In turn, DNA damage-induced senescence can induce cytokines as part of the SASP (Lin and Epel, 2022). Collectively, this shortening is a hallmark of cellular aging and has profound implications for both aging and cancer (Liao et al., 2023). As telomeres reach a critically short length, they trigger a persistent DNA damage response, resulting in cellular senescence or apoptosis. This process, known as replicative senescence, acts as a tumor suppressor by limiting cell proliferation, thereby preventing the uncontrolled growth characteristic of cancer (Blasco, 2005). In stem cells, higher telomerase activity (an enzyme that adds repetitive nucleotide sequences to the ends of chromosomes) helps maintain telomere length, allowing for continued division and tissue regeneration (Brazvan et al., 2018; Lupatov and Yarygin, 2022). Over time, however, telomere shortening in stem cells reduces their regenerative capacity, contributing to aging and age-related diseases (Liao et al., 2023; López-Otín et al., 2023). In premalignant lesions, critically short telomeres lead to genomic instability, promoting mutations and chromosomal rearrangements that drive tumorigenesis by increasing the likelihood of oncogene activation and tumor suppressor gene inactivation. Many cancer cells reactivate telomerase enabling limitless replicative potential (Maciejowski and De Lange, 2017). In detail, telomerase is a ribonucleoprotein enzyme complex that adds repetitive nucleotide sequences to the ends of chromosomes, specifically to the telomeres, which protect the chromosome from deterioration or fusion with neighboring chromosomes (Mason et al., 2011). The primary components of telomerase are the telomerase reverse transcriptase (TERT) protein and the telomerase RNA component (TERC) which serves as a template for the synthesis of telomeric DNA. The main function of telomerase is to elongate telomeres, thereby maintaining their length and ensuring the stability and integrity of chromosomes during cell division (Zvereva et al., 2010). This is crucial in stem cells, germ cells, and certain white blood cells where rapid cell division is necessary. In most other human somatic cells, telomerase activity is low or absent, leading to progressive telomere shortening with each cell division, eventually triggering cellular senescence or apoptosis (reviewed in (Boccardi and Paolisso, 2014)). In cancer cells, telomerase activity is often reactivated, which allows these cells to bypass the normal limits on cell division (Dratwa et al., 2020). This reactivation provides a mechanism for indefinite replication, a hallmark of cancer

known as cellular immortality (Dratwa et al., 2020; Yuan et al., 2019). Cancer cells upregulate telomerase to maintain telomere length, thereby avoiding the senescence or apoptosis that would normally occur due to critically short telomeres. By maintaining telomere length, telomerase helps prevent chromosomal instability, which can lead to aneuploidy and further mutations that drive cancer progression (Robinson and Schieman, 2022). The continued division and proliferation of cancer cells supported by telomerase allow tumors to grow and metastasize. Telomerase activity level, in many types of cancers, is associated with poor prognosis. It is critical that telomerase stabilizes and protects telomeres independently of their length, especially since many cancer cells exhibit very short telomere lengths (TL)—sometimes even shorter than the critically minimal TL that would typically induce senescence or apoptosis in normal cells with intact tumor suppressor pathways such as p53 and p21. In cases where these tumor suppressors are inactivated, cancer cells can continue to proliferate despite critically short telomeres. This proliferation persists until the cells reach a "crisis" phase, characterized by extensive cell death due to critically short telomeres, except for those cells that manage to activate a telomere maintenance mechanism (TMM), such as telomerase activity or ALT pathway, allowing them to survive and progress into immortalized cell lines (Shay and Wright, 2005). During this crisis phase, key events in tumorigenesis occur, including the activation of oncogenes and the inactivation of tumor suppressor genes, often due to increased genomic instability. This stage is crucial for understanding how cancer progresses, as the genetic alterations that drive malignancy often accumulate during this phase. Moreover, metastasis involves multiple factors beyond telomerase activity, including the non-telomeric functions of the catalytic subunit hTERT, which can influence cellular processes such as gene expression, cellular signaling, and interactions with the tumor microenvironment (Liu et al., 2024; Rasouli et al., 2024). For example, recent studies have highlighted how hTERT contributes to metastasis by modulating pathways that influence the tumor microenvironment and support tumor cell invasiveness (Liu et al., 2020). Recognizing these multifaceted roles of hTERT provides a more comprehensive understanding of cancer progression beyond simple telomere length maintenance. Thus, given its critical role in cancer cell survival, telomerase is considered a promising target for cancer therapy. Therapeutically, targeting telomerase activity offers a promising strategy for cancer treatment (Lansdorp, 2022; López-Otín et al., 2023). Telomerase inhibitors can selectively affect cancer cells with high telomerase activity, potentially limiting their growth and inducing apoptosis. Unfortunately, telomerase inhibitors in vivo also compromise stem cells and lymphocytes and thus have serious side-effects, making any specific direct therapy difficult.

Indeed, telomeric repeat-containing RNA (TERRA) plays a significant role in telomere maintenance by forming RNA:DNA hybrids, known as TERRA R-loops (Wang et al., 2023). These structures are particularly relevant in human cancer cells that rely on homologous recombination-mediated alternative lengthening of telomeres (ALT) for telomere maintenance (Fernandes and Lingner, 2023). Emerging evidence underscores the importance of TERRA R-loops in telomere maintenance, as they contribute to the regulation of telomere dynamics and stability. However, excessive TERRA R-loops can have detrimental effects, such as interfering with DNA replication, inducing replication stress, and increasing chromosomal fragility or rearrangements. These disruptions may ultimately lead to telomere loss, highlighting the necessity for precise regulation of TERRA and its associated R-loops to preserve genomic stability and prevent telomere-related dysfunction (Fernandes et al., 2021).

4. Telomere, cancer and aging: the short and the long of it

Telomere length plays a complex role in cancer susceptibility, with both extremely short and unusually long telomeres contributing to cancer risk under different circumstances. Critically short telomeres during crisis and before telomerase is induced, can lead to chromosomal

instability, a hallmark of cancer (Li and Durbin, 2024; O'Sullivan and Karlseder, 2010). When telomeres become too short, they lose their protective function, resulting in end-to-end chromosome fusions, aneuploidy, and other genomic aberrations that promote cancer initiation and progression (Li and Durbin, 2024). Short telomeres can induce cellular senescence or apoptosis, acting as a barrier to uncontrolled cell proliferation and thereby serving as a tumor suppressor mechanism. During the crisis phase, the most crucial genomic aberrations that drive tumorigenesis include the activation of oncogenes and the deactivation of tumor suppressor genes. These changes significantly contribute to the transformation of cells into a malignant state. The activation of oncogenes, such as MYC and RAS, leads to increased cell proliferation, survival, and invasiveness, providing a growth advantage to the cancer cells (Dhanasekaran et al., 2021). Simultaneously, the loss of function of key tumor suppressor genes, such as p53, RB, and p21, removes essential regulatory checkpoints that normally prevent uncontrolled cell division and genomic instability (Engeland, 2022). This combination of increased oncogenic signaling and the loss of tumor suppressive control enables cells to bypass growth arrest and evade apoptosis, allowing for the survival and expansion of genetically unstable cell populations. The accumulation of these genomic aberrations is a pivotal event during the crisis phase, setting the stage for the progression to advanced malignancy as cells acquire the ability to maintain telomere length through mechanisms like telomerase activation or ALT, thus avoiding senescence and achieving immortalization (Okabe and Kaneda, 2021). In contrast, unusually long telomeres can provide cancer cells with the ability to divide indefinitely (Finkel et al., 2007). Interestingly, some cancers, especially those of mesenchymal origin, maintain their telomeres through a telomerase-independent mechanism known as alternative lengthening of telomeres (ALT) (Dilley and Greenberg, 2015). This mechanism involves homologous recombination and can lead to very long telomeres, supporting cellular immortality and tumor progression. However, ALT-maintained telomeres are not only partially very long, more important is that they are very heterogenous in length—from rather short to very long. Recent evidence from "space" is showing that telomere length changes over time and in astronauts during long-duration spaceflight aboard the International Space Station (ISS) (Mason et al., 2024). Longer telomeres have been detected during spaceflight compared to pre-flight and post-flight measures (Garrett-Bakelman et al., 2019). However, upon returning to Earth, telomere length shortened rapidly, resulting in an overall decrease in average telomere length post-flight. Additionally, there was an increase in the number of short telomeres after spaceflight compared to before (Garrett-Bakelman et al., 2019; Luxton et al., 2020). Off the planet, astronauts seem to experience an "accelerated aging syndrome," which includes mitochondrial dysfunction and immunological defects associated with increased oxidative stress and inflammation. On one hand, recent research indicates that both short and long telomeres are associated with increased disease risk, with quantitative estimates suggesting similar degrees of risk elevation (Haycock et al., 2017; Protsenko et al., 2020). On the other hand, contradictory findings exist, emphasizing the need for a deeper understanding of how telomere length and sequence variations affect human health and aging trajectories. A recent study has shown that as individuals age, telomeres begin to accumulate abnormal structures associated with replication stress (Boccardi et al., 2018). Interestingly, especially in cancer cells, telomeres are hot spots for replication stress, which can result in a visible phenotype in metaphase cells termed "telomere fragility" (Barnes et al., 2023). Telomere fragility is characterized by the presence of multiple telomeric DNA foci at the end of a chromatid, as revealed by telomere PNA fluorescence in situ hybridization staining (FISH). It's believed that these sites indicate regions of telomeric chromatin that have become de-condensed due to stalled DNA replication forks and indicative of telomere instability (Ojima et al., 2004). The concept of fragile telomeres was first introduced by the group of Titia de Lange (Sfeir et al., 2009), highlighting regions of telomeres prone to replication stress and structural

abnormalities. Subsequent studies further elucidated the mechanisms underlying fragile telomere formation, demonstrating that replication stress can lead to their generation (Bonnell et al., 2021; Herr et al., 2024). Beyond this, multiple research groups, have demonstrated that telomeres can induce cellular senescence in vivo without undergoing detectable shortening, suggesting that telomere dysfunction and structural changes play a role in aging independent of length reduction (Fumagalli et al., 2012; Victorelli and Passos, 2017).

Cells displaying traits of telomere instability, such as those found in Werner syndrome, have been documented to exhibit increased levels of abnormal telomere fluorescence in situ hybridization (FISH) signals (Ariyoshi et al., 2007). While the precise molecular role of this remains incompletely understood, accumulating evidence highlights its involvement in pathways that respond to replication stress and preserve genome integrity, particularly in telomeric regions (Orren and Machwe, 2024). Increased telomere fragility led to degenerative pathologies and increased cancer in mice as well as such telomere abnormality is sufficient to produce severe telomeric damage in the absence of telomere shortening, resulting in premature tissue degeneration and development of neoplastic lesions (Martínez et al., 2009). This implies that issues with telomeric replication might influence the evolving status of telomeres in humans as they age, potentially affecting the trajectory of aging as well as cancer susceptibility. Collectively, fragile telomeres may appear as telomeric elongation when assessed by available methods to measure the telomere length. Significant telomeric replication stress can be experienced during space travel. The accumulation of fragile telomeres during spaceflight might be associated with intense replicative stress, making telomeres appear longer during the stay. Thus, fragile telomeres, which per se exhibit mobilized upon telomeric replication stress and DNA damage (Lamm et al., 2021), may represent a paradigm for emerging connections between aging and cancer. Since telomere

maintenance is a critical feature of cancer, understanding the indicators and mechanisms of replication stress at telomeres is crucial for developing effective cancer treatments (Hou et al., 2012). Fig. 1 shows the hypothetical impact of burden of telomere shortening, dysfunction, and alternative lengthening in healthy and cancer cells.

5. The burden of replicative stress and fragile sites

Fragile telomeres, characterized by structural abnormalities and increased susceptibility to breakage, represent critical points of vulnerability in chromosome stability. They are typically observed as gaps or constrictions in metaphase chromosomes, indicating regions of underlying replication stress (Barnes et al., 2023). This stress often arises when replication forks stall, which can be caused by the formation of secondary DNA structures, such as G-quadruplexes, or from DNA damage that hampers the smooth progression of replication machinery through telomeric regions (Protsenko et al., 2020). Such disruptions can overwhelm cellular repair mechanisms, especially when telomere maintenance is compromised. Key factors contributing to telomere fragility include inadequate telomerase activity or dysfunction in shelterin complex components—proteins that protect telomeres and regulate their maintenance. Telomerase, by elongating telomeres, counteracts the natural shortening that occurs during replication, while the shelterin complex prevents inappropriate activation of DNA damage responses at telomeres (Victorelli and Passos, 2017). Insufficient telomerase or defects in shelterin components like TRF1 or TRF2 can leave telomeres vulnerable to degradation and improper repair, resulting in fragile sites that trigger DNA damage signaling pathways (Harman and Bryan, 2024). These fragile telomeres contribute significantly to cellular senescence, a state of permanent cell cycle arrest, as cells attempt to cope with persistent DNA damage signals (Barnes et al., 2023). This

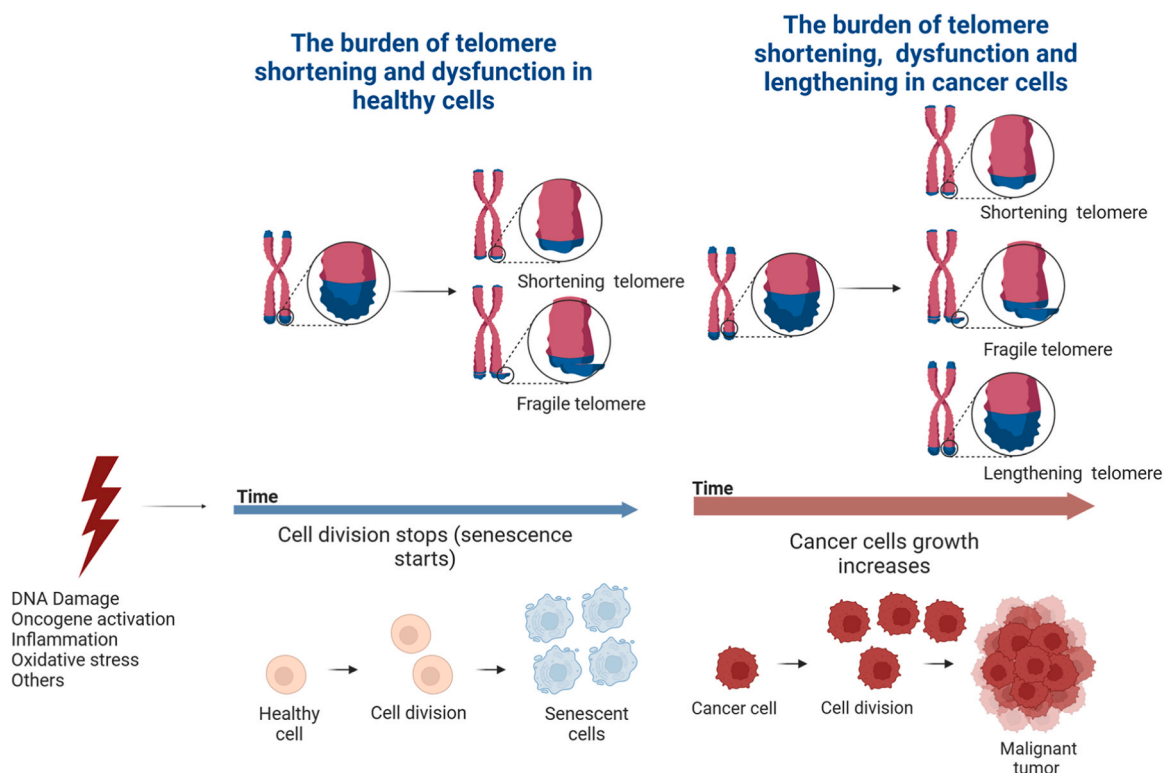


Fig. 1. The hypothetical impact of burden of telomere shortening, dysfunction, and lengthening in healthy and cancer cells. Telomeres are protective caps at the ends of chromosomes that prevent DNA damage during cell division. Telomere shortening and dysfunction occur naturally with each cell division, eventually leading to cell senescence. The burden of telomere shortening, dysfunction (such as aberrant fragile site accumulation), or lengthening (through telomerase reactivation or other mechanisms) induced by replication stress (e.g., DNA damage, oncogene activation, inflammation, oxidative stress) can lead to chromosomal instability and contribute to cancer development. Created with BioRender.

increased senescence impairs tissue regeneration, leading to a decline in the regenerative capacity of various tissues and contributing to the aging process. In the context of cancer, however, the impact of telomere fragility takes a different trajectory. Here, fragile telomeres can drive genomic instability through mechanisms such as chromosomal fusions and breakage-fusion-bridge cycles-events that perpetuate cycles of chromosomal rearrangement and amplification, fostering the genetic diversity that allows tumor cells to evolve and adapt to therapeutic pressures (Bhargava et al., 2020). Given their dual role in aging and cancer, fragile telomeres present a potential target for novel therapeutic strategies. By focusing on pathways that modulate telomere stability, such as enhancing telomerase function or stabilizing shelterin interactions, it might be possible to mitigate the harmful effects of telomere fragility. This could be particularly valuable in treating cancers characterized by high levels of telomere dysfunction, where targeted interventions could reduce chromosomal instability and slow tumor progression. Furthermore, developing sensitive methods to detect telomere fragility could provide a diagnostic tool for early identification of at-risk cells, offering a chance to intervene before genomic instability leads to full-blown malignancy. Accordingly, very recently it has developed and validated Topotools (Ghilain et al., 2024), a novel set of instruments to study DNA topology within cells. Unlike existing tools such as Trioxsalen and GapR, this method allows the visualization of both negative and positive writhe in DNA, representing supercoiled structures such as catenanes (interlinked DNA loops) and plectonemes (twisted DNA strands). Utilizing these tools, authors examined the topology of telomeres and the FRA3B fragile site in human cancer cells, uncovering significant topological changes induced by replicative stress (Ghilain et al., 2024). Overall, a better understanding of the factors that drive telomere fragility, as well as the downstream consequences of fragile telomeres, is essential for devising strategies that balance their dual role in cellular aging and tumorigenesis. This research could pave the way for treatments that address both the degenerative aspects of aging and the proliferative potential of cancer cells.

6. Perspective and final remarks

Telomeres play a pivotal role in the complex interplay between aging and cancer, serving as both biomarkers and active participants in cellular stability and dysfunction. Table 1 provides a comparison of how telomere dynamics influence aging and cancer, emphasizing their dual roles and the opportunities for targeted interventions. While substantial progress has been made in understanding telomere biology, their dynamic nature presents both opportunities and challenges for advancing knowledge in this field. The dual role of telomeres in promoting genomic stability during aging and facilitating cancer progression through telomerase reactivation or ALT pathways underscores their importance as therapeutic targets. However, as highlighted in this review, telomere maintenance is not solely about length; replication stress, telomere fragility, and structural abnormalities are equally critical in determining cellular outcomes. These nuances complicate efforts to translate basic telomere biology into clinical applications. Despite significant advances, several open questions remain. How do short and long telomeres contribute to disease risk in different contexts? Why do some cancer cells maintain critically short telomeres while others rely on unusually long telomeres? What specific mechanisms underlie telomere fragility, and how can they be exploited for therapeutic benefit? Additionally, the relationship between telomeres and systemic factors, such as inflammation, metabolism, and the microbiome, remains incompletely understood.

Conflicting evidence, such as the paradoxical roles of telomere shortening and elongation in cancer risk, highlights the need for more critical examination. For example, the observed telomere dynamics during spaceflight demonstrate that environmental and physiological stressors can induce rapid and reversible changes in telomere length, complicating interpretations of their static measurements. These

Table 1
Dual roles of telomeres in aging and cancer: a comparative overview.

| Aspect | Aging | Cancer |
|------------------------------|---|--|
| Telomere shortening | <ul style="list-style-type: none"> - Limits cellular lifespan through replicative senescence. - Acts as a tumor suppressor by preventing uncontrolled cell proliferation. | <ul style="list-style-type: none"> - Leads to genomic instability, driving mutations and chromosomal rearrangements. - Promotes oncogene activation and tumor suppressor loss. |
| Telomere lengthening | <ul style="list-style-type: none"> - Minimal role in normal somatic cells. - Maintains regenerative capacity in stem and germ cells. | <ul style="list-style-type: none"> - Reactivation of telomerase or ALT enables immortalization of cancer cells. - Supports tumor progression and metastasis. |
| Replication stress | <ul style="list-style-type: none"> - Accumulates with age, leading to fragile telomeres and senescence. - Contributes to tissue degeneration and functional decline. | <ul style="list-style-type: none"> - Drives genomic instability via breakage-fusion-bridge cycles. - Facilitates tumor evolution and adaptation under therapeutic pressure. |
| Fragile telomeres | <ul style="list-style-type: none"> - Induce cellular senescence without shortening. - Linked to degenerative diseases. | <ul style="list-style-type: none"> - Enhance chromosomal rearrangements and genetic diversity. - Contribute to cancer progression and resistance to therapy. |
| Telomere dynamics | <ul style="list-style-type: none"> - Influenced by lifestyle, oxidative stress, and systemic inflammation. - Show variability under stress (e.g., during spaceflight). | <ul style="list-style-type: none"> - Exhibit heterogeneity, particularly in ALT-dependent cancers. - Dynamic changes correlate with tumor aggressiveness and therapeutic outcomes. |
| Therapeutic potential | <ul style="list-style-type: none"> - Strategies targeting senescence to improve tissue regeneration. - Addressing replication stress to delay aging-related dysfunction. | <ul style="list-style-type: none"> - Telomerase inhibitors and ALT-targeting therapies to prevent cancer progression. - Balancing treatments to avoid side effects on healthy cells. |

ALT: Alternative lengthening of telomeres.

findings underscore the necessity of studying telomeres as dynamic entities rather than fixed structures. Given the dynamic nature of telomeres, large-scale longitudinal studies are essential to capture their temporal behaviour and to identify causal relationships between telomere dynamics, aging, and cancer susceptibility. Integrating advanced tools with molecular and imaging technologies will enable more precise characterization of telomere structure, replication stress, and fragility. Moreover, incorporating multi-omics approaches—spanning genomics, epigenomics, proteomics, and metabolomics—can help unravel the complex networks that influence telomere function. Developing effective strategies to promote healthy aging and mitigate cancer risk will require a deeper understanding of the interplay between telomeres and broader cellular and systemic processes. Therapeutic interventions targeting telomerase, replication stress, and telomere-associated pathways must balance the dual roles of telomeres in aging and cancer, minimizing adverse effects on healthy tissues while selectively targeting disease mechanisms.

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Declaration of Competing Interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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