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Inflammation and Oxidative Stress in Telomere Attrition: Mechanisms and Therapeutic Opportunities

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ABSTRACT

Telomeres, the protective caps at the ends of chromosomes, progressively shorten with each cell division, serving as a fundamental marker of cellular aging. Emerging evidence implicates chronic inflammation and oxidative stress as pivotal accelerators of telomere attrition, thereby exacerbating biological aging and predisposing to a spectrum of age-related diseases. This review synthesizes the current understanding of the mechanistic interplay between inflammation and oxidative damage in promoting telomere shortening. Proinflammatory cytokines such as interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha induce reactive oxygen species (ROS) production, which directly damages the guanine-rich telomeric DNA. The cumulative oxidative lesions, compounded by inefficient DNA repair within telomeres, amplify telomere erosion beyond replication-dependent loss. Additionally, inflammatory signaling pathways negatively regulate telomerase enzyme activity, further compromising telomere maintenance. This self-perpetuating cycle of inflammation and oxidative stress establishes a feedback loop that accelerates cellular senescence, apoptosis, and genomic instability, underpinning disorders ranging from cardiovascular diseases to neurodegeneration. The review explores emerging therapeutic interventions aimed at breaking this cycle, including telomerase activators, antioxidants, anti-inflammatory agents, and lifestyle modifications proven to attenuate inflammation and oxidative damage. Furthermore, it addresses the challenges and research gaps in translating mechanistic insights into clinical applications and the potential for personalized medicine based on telomere biology. Overall, this comprehensive synthesis underscores the importance of integrated approaches to preserve telomere integrity, offering promising avenues to mitigate aging processes and improve healthspan. Understanding these pathways provides critical insights into novel diagnostic and therapeutic strategies to combat inflammation-driven telomere shortening and associated age-related diseases..

Keywords: Inflammation, oxidative stress, cytokines, DNA, age-related diseases, neurodegeneration.

INTRODUCTION

Telomeres are specialized DNA-protein structures located at the ends of linear chromosomes. Composed of repetitive TTAGGG nucleotide sequences and associated shelterin proteins, telomeres function as protective caps that preserve genomic stability by preventing chromosomal end-to-end fusions and degradation.

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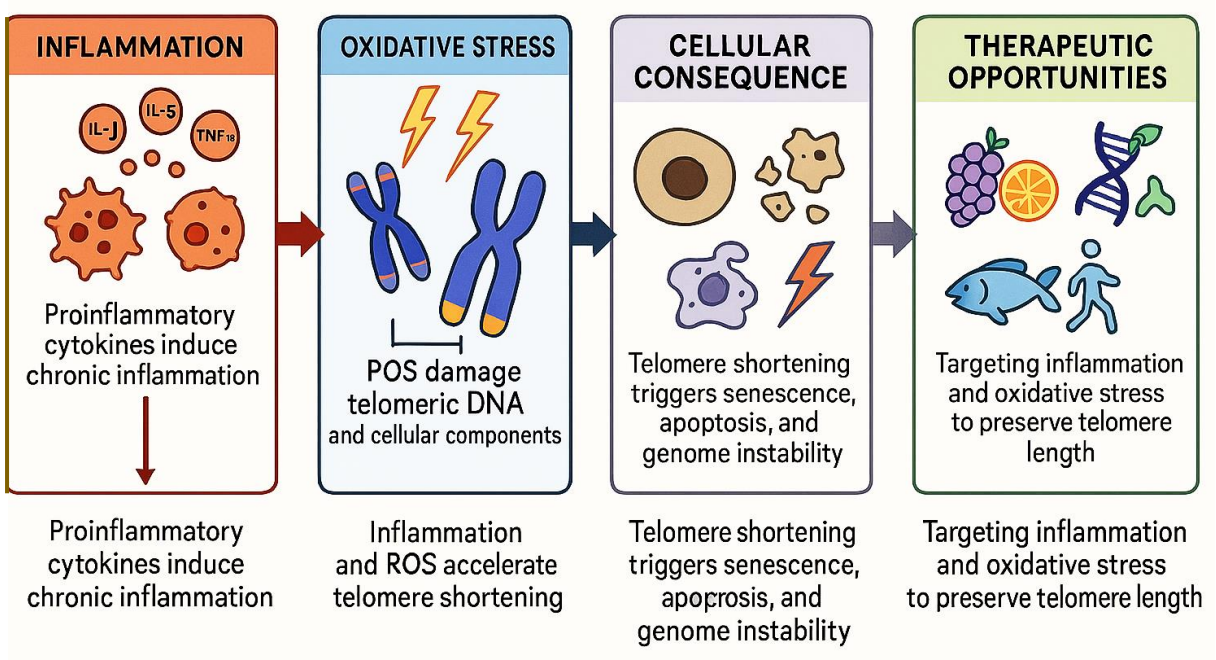
Graphical Abstract



During each round of DNA replication, due to the end-replication problem, a portion of the telomeric sequence is lost, resulting in gradual shortening of telomeres over time. This attrition acts as a biological clock, limiting the replicative capacity of somatic cells and serving as a critical determinant of cellular aging and senescence (Blackburn, 2022). The integrity of telomeres is thus essential for maintaining chromosomal stability and organismal health.

Significance of Telomere Attrition in Aging and Age-Related Diseases

Progressive shortening of telomeres is a hallmark of cellular aging and is intricately linked with increased vulnerability to age-associated pathologies including cardiovascular diseases, diabetes, neurodegeneration, and various cancers. Critically short telomeres trigger DNA damage response pathways, inducing cellular senescence or apoptosis, thereby limiting tissue regeneration and function (Jaskelioff et al., 2017). Beyond chronological aging, external stressors such as chronic inflammation and oxidative stress accelerate telomere attrition, exacerbating biological aging and disease progression. Understanding mechanisms that contribute to telomere shortening and strategies to counteract this process has emerged as a vital area for aging and therapeutic research.

Scope and Objectives of the Review

This review synthesizes current knowledge on the dual roles of inflammation and oxidative stress in driving telomere attrition, highlighting molecular pathways involved and their clinical implications in aging and disease. Further, it explores therapeutic opportunities aiming to mitigate inflammation-driven telomere shortening through pharmacological, dietary, and lifestyle interventions. This comprehensive overview aims to inform future research directions and the development of targeted therapies to preserve telomere function and promote healthy aging.

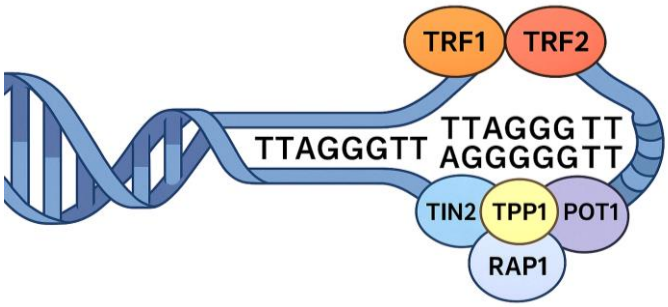


Fig 1. Telomere Structure

Telomere Structure and Function

Telomeric DNA consists of tandem hexameric repeats (TTAGGG) that extend for several kilobases in humans, forming a specialized chromatin structure that caps chromosome ends. These repeats are bound by the shelterin complex, composed of six

core proteins—TRF1, TRF2, POT1, TIN2, TPP1, and RAP1—that collectively protect telomeres from being recognized as DNA double-strand breaks (de Lange, 2018). Shelterin regulates telomere length, prevents inappropriate activation of DNA damage repair pathways, and orchestrates telomere replication (Fig 1). Disruption of shelterin components leads to telomere uncapping and genomic instability, underscoring their indispensable role.

Role of Telomerase Enzyme in Telomere Maintenance

Telomerase is a ribonucleoprotein reverse transcriptase complex that counteracts telomere shortening by adding telomeric repeats de novo to chromosome ends. Its catalytic subunit, TERT, uses an RNA template to elongate telomeres, predominantly active in germline, stem cells, and certain immune cells (Greider & Blackburn, 1985). In most somatic cells, telomerase activity is low or absent, contributing to progressive telomere attrition with cell divisions (Fig 2). Reactivation or enhancement of telomerase has been proposed as a potential intervention to maintain telomere length and extend cellular lifespan.

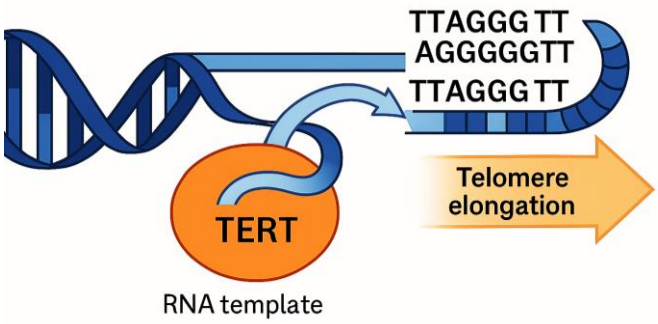


Fig 2. Role of Telomerase Enzyme in Telomere Maintenance

Mechanisms of Telomere Shortening

Telomere length is influenced by intrinsic replication-associated loss of terminal sequences and by extrinsic factors including oxidative damage, genotoxic stress, and inflammation. The end-replication problem leads to loss of up to 50–200 base pairs per division due to incomplete lagging strand synthesis (Olovnikov, 1973). Additionally, nucleolytic degradation and inefficient repair of oxidative lesions at telomeres contribute to accelerated shortening (von Zglinicki, 2002). Without replenishment by telomerase or alternative lengthening mechanisms, gradual telomere attrition ultimately triggers replicative senescence or apoptosis, limiting tissue regenerative capacity.

Inflammation and Its Role in Telomere Attrition

Inflammation is a complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants. It involves the activation of immune cells and the release of proinflammatory cytokines, which are signaling proteins that regulate the intensity and duration of the inflammatory response. Key proinflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) play pivotal roles in mediating inflammatory processes. While acute inflammation is protective and resolves after pathogen eradication, chronic inflammation leads to sustained cytokine production that can induce tissue damage and alter cellular functions (Medzhitov, 2021). Chronic low-grade inflammation, often termed "inflammaging," is now recognized as a major driver of cellular aging and age-related diseases, particularly through its impact on telomere integrity.

Impact of Chronic Inflammation on Cellular Aging

Chronic inflammation accelerates cellular aging by promoting persistent cellular stress and damage, which increases the rate of telomere attrition beyond normal replicative shortening. Sustained exposure to proinflammatory cytokines induces oxidative stress through the generation of reactive oxygen species (ROS), which can directly damage telomeric DNA due to its high guanine content. This damage often overwhelms the cell's repair mechanisms, leading to the accumulation of critically short telomeres that trigger DNA damage responses. Additionally, inflammatory cytokines stimulate immune cells to undergo repeated cell divisions during immune activation, further accelerating telomere loss. These effects result in premature cellular senescence or apoptosis, impairing tissue homeostasis and regenerative capacity (Furman et al., 2019; Ridker et al., 2020).

Molecular Pathways Linking Inflammation to Accelerated Telomere Shortening

At the molecular level, inflammatory signaling pathways such as NF-κB and STAT3 are activated by proinflammatory cytokines and contribute to telomere dysfunction by modulating gene expression involved in telomere maintenance and cellular stress responses. For example, TNF-α signaling can downregulate telomerase reverse transcriptase (TERT) expression and activity, reducing the cell's ability to elongate telomeres (Fig.3). Furthermore, chronic inflammation is linked with increased expression of senescence-associated secretory phenotype (SASP) factors, which propagate inflammatory signals and reinforce telomere shortening and cellular aging in neighboring cells via paracrine effects. This creates a vicious cycle exacerbating tissue aging and damage (Chung et al., 2019; Salminen et al., 2020).

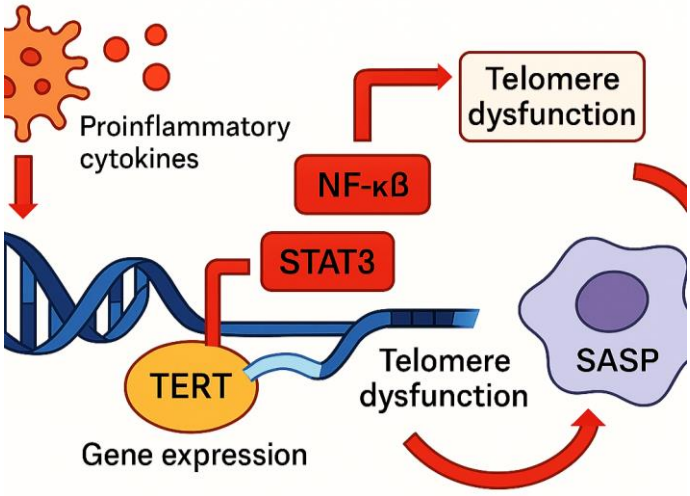


Fig.3. Molecular Pathways Linking Inflammation to Accelerated Telomere Shortening

Role of Inflammatory Cytokines (e.g., IL-1β, IL-6, TNF-α) in Telomere Dynamics

IL-1β, IL-6, and TNF-α are central mediators of the inflammatory response implicated in telomere dynamics. IL-1β is known to induce ROS production and promote inflammatory cascades that enhance telomere damage. IL-6 exhibits dual roles; while high chronic levels contribute to telomere shortening by fostering oxidative stress and senescence, transient IL-6 exposure can enhance telomerase activity in certain progenitor cells, highlighting complexity in telomere regulation (Ulanowska et al., 2021) (Fig.4). TNF-α contributes to mitochondrial dysfunction and oxidative stress, accelerating telomere attrition and cellular senescence. The interplay among these cytokines governs the balance between telomere preservation and attrition in inflammatory microenvironments (Weng et al., 2023).

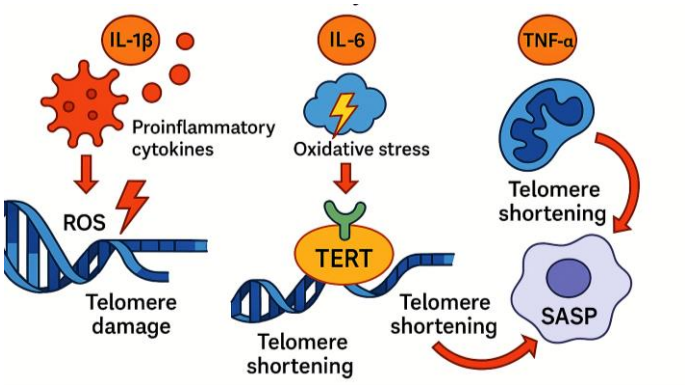


Fig.4. Role of Inflammatory Cytokines (e.g., IL-1β, IL-6, TNF-α) in Telomere Dynamics

Oxidative Stress and Telomere Shortening

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen, including superoxide anions, hydrogen peroxide, and hydroxyl radicals. They arise as natural by-products of cellular metabolism, especially oxidative phosphorylation in mitochondria, and are also generated in response to environmental stressors such as UV radiation, pollution, and toxins. While ROS are involved in cellular signaling and immune defense, excessive ROS production overwhelms antioxidant defenses, resulting in oxidative stress that damages cellular components including DNA, proteins, and lipids (Sies et al., 2022). The telomeric region of chromosomes is particularly vulnerable due to its high guanine content, which is easily oxidized, making telomeres hotspots for ROS-induced damage (von Zglinicki, 2002).

Susceptibility of Telomeric DNA to Oxidative Damage

Telomeric DNA is highly susceptible to oxidative damage for several reasons. Guanine bases within telomeric repeats are prone to oxidation, forming 8-oxoguanine lesions that cause mutagenesis and destabilize the DNA helix. Unlike other genomic regions, telomeres have relatively inefficient mechanisms for repairing oxidative damage, resulting in an accumulation of lesions. This damage compromises the binding of protective shelterin proteins and interferes with proper telomere replication. Oxidative DNA damage at telomeres induces replication fork stalling and single-strand breaks, which exacerbate telomere loss during

cellular division (Saretzki & von Zglinicki, 2002; Opresko et al., 2014). These factors collectively accelerate telomere shortening beyond the basal rate driven by the replication process.

Mechanisms of ROS-Induced Telomere Attrition and DNA Damage

Several mechanisms underlie ROS-induced telomere attrition. ROS can directly induce single-strand breaks in telomeric DNA or generate base modifications that impair DNA replication fidelity. These lesions lead to replication fork collapse and loss of telomeric sequences during S phase (Fig.5). Additionally, oxidative stress impairs the recruitment and function of DNA repair proteins and shelterin components required for telomere stability. The inability to fully repair oxidative damage results in persistent DNA damage signals and accelerates cellular senescence. This phenomenon is observed in mitochondrial dysfunction-linked aging where heightened ROS continuously damages telomeres, further compromising cell viability (Passos et al., 2022; Sbodio et al., 2021).

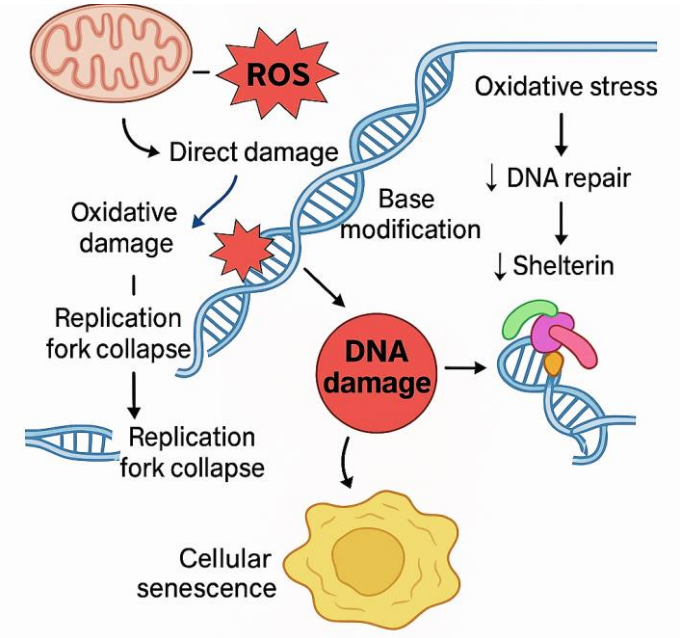


Fig.5. Mechanisms of ROS-Induced Telomere Attrition and DNA Damage

Interplay Between Oxidative Stress and DNA Repair at Telomeres

DNA repair pathways normally resolve oxidative damage; however, telomeres exhibit uniquely low efficacy of base excision and nucleotide excision repair mechanisms, leading to prolonged presence of lesions. Moreover, chronic oxidative stress depletes cellular energy and reduces the efficiency of DNA repair enzymes (Fig. 6). As oxidative lesions accumulate, telomeric chromatin undergoes structural changes that further hinder repair protein access. This impaired repair contributes to the generation of fragile telomeres characterized by increased DNA breaks and replication stress, culminating in accelerated attrition and genomic instability. Understanding these interactions provides critical insights into therapeutic interventions to enhance telomere repair capacity (Fouquerel et al., 2021; Opresko & Shay, 2021).

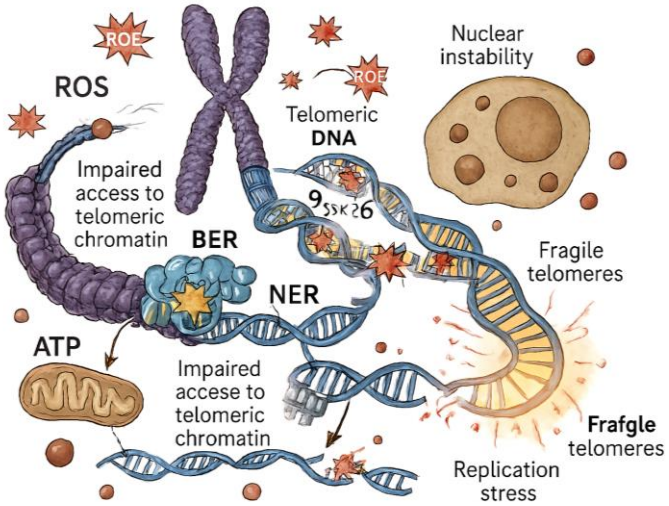


Fig.6. Interplay Between Oxidative Stress and DNA Repair at Telomeres

Interaction Between Inflammation and Oxidative Stress in Telomere Dynamics

Inflammation and oxidative stress are intricately linked in a bidirectional relationship that amplifies cellular damage and accelerates telomere attrition. Chronic inflammation leads to the activation of immune cells such as macrophages and neutrophils that produce excessive reactive oxygen species (ROS) as part of the antimicrobial response (Fig.7). This increased ROS generation causes oxidative damage to telomeric DNA, proteins, and lipids. Conversely, oxidative stress activates redox-sensitive transcription factors such as NF-κB, which promote the expression of proinflammatory cytokines, further intensifying inflammation (Morgan & Liu, 2011). This positive feedback loop creates a self-sustaining cycle of damage, resulting in accelerated telomere shortening and cellular senescence. The interplay is particularly detrimental in aging tissues where the

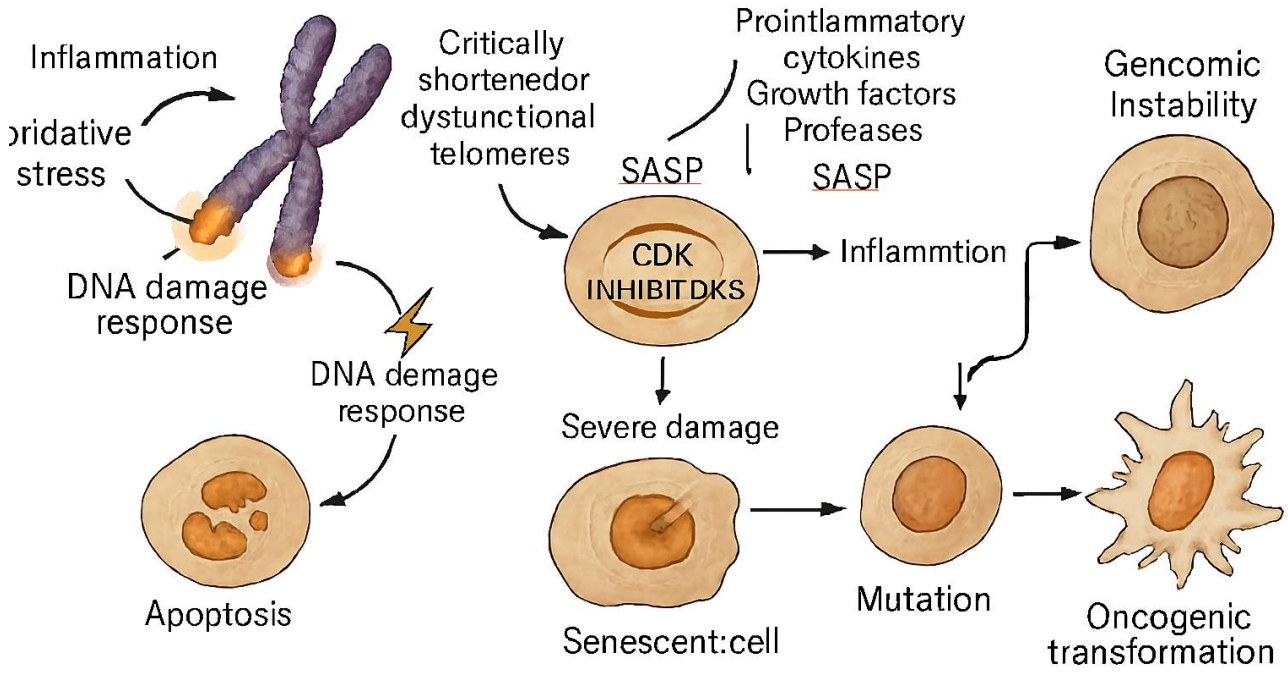


Fig.7. Cellular Consequences: Senescence, Apoptosis and Genomic Instability

balance between ROS production and antioxidant defenses is already compromised, thus driving a state of "inflammaging" (Franceschi & Campisi, 2014: Daipule et al., 2020)).

Feedback Loops Amplifying Telomere Damage

Several molecular feedback mechanisms contribute to the amplification of telomere damage in the presence of inflammation and oxidative stress. One such loop involves the telomere-associated shelterin protein RAP1, which modulates NF-κB signaling. Telomere dysfunction triggers RAP1 translocation from telomeres to the cytoplasm, where it promotes NF-κB-mediated inflammatory gene expression, exacerbating systemic inflammation (Teo et al., 2010). Additionally, DNA damage responses activated by shortened telomeres stimulate further production of inflammatory mediators and ROS, creating a vicious cycle that sustains cellular stress. These feedback loops not only magnify telomere attrition but also contribute to tissue dysfunction and promote the progression of age-related diseases (Anderson et al., 2023).

Cellular Consequences: Senescence, Apoptosis, and Genomic Instability

The combined effect of inflammation and oxidative stress at telomeres leads to irreversible cellular outcomes, including senescence and apoptosis. Critically shortened or dysfunctional telomeres activate the DNA damage response (DDR), triggering cell cycle arrest—known as replicative senescence—to prevent propagation of damaged DNA. Senescent cells secrete proinflammatory cytokines, growth factors, and proteases within the senescence-associated secretory phenotype (SASP), which perpetuates inflammation and nearby tissue damage (Coppe et al., 2010). If damage is severe and irreparable, cells may undergo apoptosis, leading to loss of functional tissue cells. Moreover, telomere dysfunction compromises chromosomal stability, increasing the risk of mutations and oncogenic transformations. These cellular outcomes underpin the pathogenesis of several chronic and degenerative diseases linked to aging (Munoz-Espin & Serrano, 2014).

Clinical Implications of Inflammation-Driven Telomere Attrition - Associations with Age-Related Diseases

Telomere shortening driven by chronic inflammation and oxidative stress correlates strongly with the onset and progression of a wide array of age-associated diseases. In cardiovascular disease, shortened telomeres in vascular endothelial cells contribute to impaired repair capacity and increased atherosclerosis risk (Fuster et al., 2020; Sucharitha et al., 2013. In metabolic disorders such as type 2 diabetes, telomere attrition exacerbates pancreatic

beta-cell dysfunction and systemic insulin resistance, often mediated by inflammatory cytokines (Salpea et al., 2010). Furthermore, neurodegenerative diseases including Alzheimer's and Parkinson's disease also display markers of accelerated telomere loss linked to neuroinflammation and oxidative stress, which contribute to neuronal death and cognitive decline (Milaneschi et al., 2019). Collectively, telomere length serves as a predictive biomarker of biological aging and disease susceptibility.

Biomarkers Involving Telomere Length and Inflammatory Status

Measurement of leukocyte telomere length (LTL) has emerged as a non-invasive biomarker for systemic telomere attrition linked with chronic inflammation. Elevated circulating levels of proinflammatory cytokines such as IL-6 and TNF-α often inversely correlate with LTL, providing insight into a patient's inflammaging status (Ridout et al., 2019). In clinical settings, combined assessment of telomere length and inflammatory markers has shown predictive value for disease progression, treatment response, and mortality risk in conditions ranging from cancer to autoimmune diseases. Advances in high-throughput techniques now allow more accurate and routine screening of these biomarkers to guide personalized medicine approaches aimed at mitigating inflammation-induced cellular aging (Franceschi et al., 2018).

Prognostic and Diagnostic Relevance

Beyond serving as markers, telomere length and associated inflammatory signatures hold prognostic and diagnostic potential. Short telomeres identify individuals at higher risk for rapid disease progression and poor outcomes in chronic inflammatory conditions. For example, shortened telomeres have been linked with poorer survival in cancer and cardiovascular patients, highlighting their utility in risk stratification (Kordinas et al., 2016). In autoimmune diseases such as rheumatoid arthritis and lupus, telomere attrition correlates with disease activity, informing therapeutic interventions (Cross et al., 2021). Hence, telomere dynamics provide clinicians with valuable tools to refine diagnoses and optimize treatments tailored to the patient's biological aging profile.

Therapeutic Strategies to Prevent Inflammation and Oxidative Stress-Induced Telomere Shortening

Therapeutic approaches targeting telomerase activation show promise in counteracting telomere attrition driven by chronic inflammation and oxidative stress. Telomerase activators such as TA-65, derived from the Astragalus plant, have demonstrated the capacity to lengthen telomeres and improve immune function in clinical studies without increasing cancer risk when used at appropriate doses (Harley et al., 2011). Gene therapy strategies introducing the TERT gene into somatic cells also hold potential to restore telomerase activity and promote tissue regeneration, as shown in preclinical models. However, tight regulation is imperative to avoid uncontrolled cell proliferation. These interventions offer hope for reversing aging-related telomere shortening and reducing inflammation-mediated tissue dysfunction (Bernardes de Jesus et al., 2012; Janakiramulu et al., 2025).

Anti-Inflammatory Agents and Lifestyle Interventions

Reducing systemic inflammation through pharmacological and lifestyle measures can mitigate telomere erosion. Anti-inflammatory medications, including omega-3 fatty acid supplements and non-steroidal anti-inflammatory drugs (NSAIDs), normalize cytokine levels and reduce oxidative stress, thereby preserving telomere length (Barbaresko et al., 2019). Lifestyle modifications such as adopting a Mediterranean diet rich in antioxidants, engaging in regular moderate exercise, practicing stress reduction techniques, and obtaining sufficient sleep have been shown to decrease inflammatory biomarkers and slow telomere shortening. Mind-body interventions like yoga and meditation also reduce psychological stress-mediated inflammation, further supporting telomere maintenance in healthy aging populations (Ornish et al., 2013; Mamidala et al., 2022).

Antioxidants and Mitochondrial-Targeted Therapies

Targeting oxidative stress directly with antioxidants helps protect telomeric DNA from ROS-mediated damage. Vitamins C and E, polyphenols found in fruits and vegetables, and synthetic antioxidants improve cellular redox balance and reduce telomere attrition (Richards et al., 2021; Luthra et al., 2017). Recent advances focus on

mitochondrial-targeted antioxidants that specifically decrease ROS production at the source, improving mitochondrial function, and cellular energy metabolism. Compounds such as MitoQ and SkQ1 have shown efficacy in reducing oxidative damage, inflammation, and preserving telomere length in experimental models, suggesting a promising avenue for therapeutic development against aging and inflammatory diseases (Smith & Murphy, 2022).

Emerging Molecular Targets and Inhibitors of Inflammatory Signaling

Novel therapies are emerging that target key molecular regulators of inflammation-telomere crosstalk. Inhibitors of NF-κB and JAK-STAT pathways reduce proinflammatory cytokine production and signaling, curbing telomere dysfunction. Small molecules and biologics targeting senescence-associated secretory phenotype (SASP) factors prevent the propagation of inflammatory signals that accelerate telomere shortening. Additionally, YAP1 inhibitors have been shown to attenuate inflammation-driven tissue degeneration linked to telomere dysfunction in preclinical studies. These cutting-edge interventions signify the potential for precision medicine approaches aimed at the molecular nexus of inflammation and telomere biology for improved healthspan (Anderson et al., 2023; Salminen et al., 2020; Davella et al., 2021).

Challenges and Future Directions

Despite advances, significant gaps remain in delineating the precise mechanisms by which inflammation and oxidative stress accelerate telomere shortening across different cell types and disease contexts. Variability in telomere measurement techniques and lack of longitudinal data hinder consensus on causality versus correlation. Moreover, the dual roles of certain inflammatory mediators complicate therapeutic targeting without unintended side effects. The interplay between genetic predisposition, environmental factors, and telomere regulation needs further investigation to develop personalized interventions.

Potential of Personalized Medicine Based on Telomere Biology

Tailoring therapies based on individual telomere dynamics and inflammatory profiles represents a promising frontier. Integration of genomic, epigenomic, and biomarker data can identify populations at risk for inflammation-induced telomere erosion and guide preventive and therapeutic strategies. Advances in single-cell sequencing and imaging technologies offer improved resolution to monitor telomere and inflammation status in vivo. Personalized lifestyle, pharmacological, and regenerative medicine interventions hold potential to optimize aging trajectories and reduce disease burden.

Innovative Therapeutic Development Opportunities

Emerging technologies such as CRISPR-based gene editing, senolytics, and telomere extension approaches provide exciting avenues for combating inflammation-associated telomere attrition. Innovations in drug delivery systems and nanomedicine may enhance specificity and reduce toxicity of anti-inflammatory and antioxidant agents. Collaborative research integrating molecular biology, clinical studies, and computational modeling is essential to translate these discoveries into safe and effective therapies. The convergence of multiple disciplines promises breakthroughs in mitigating aging and chronic inflammatory diseases via telomere preservation.

CONCLUSION

Inflammation and oxidative stress are principal drivers of accelerated telomere attrition, contributing to cellular aging and multiple age-related disease processes. The complex molecular interplay involves proinflammatory cytokines inducing ROS production, telomeric DNA damage, and activation of senescence pathways. Understanding these mechanisms has facilitated identification of therapeutic targets and strategies aimed at preserving telomere length and cellular function. Effective interventions require a multifaceted approach combining telomerase activation, inflammation reduction, and antioxidant therapy alongside lifestyle modifications. Such integrated strategies have the potential to slow biological aging, improve tissue homeostasis, and reduce the burden of chronic diseases associated with telomere dysfunction. Ongoing advancements in molecular biology and therapeutics hold promise for novel interventions to protect telomeres from inflammation and oxidative damage. Personalized

medicine approaches and emerging biotechnologies offer hope for extending healthspan and combating age-related diseases by targeting the fundamental mechanisms underlying telomere attrition. Continued research into telomere biology will be pivotal in unlocking new avenues for promoting longevity and healthy aging.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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