J. Phytomol. Pharmacol., 3(2), 57-72, 2024
https://doi.org/10.56717/jpp.2024.v03i02.027
ISSN (Print): 2957-5818, ISSN (Online): 2958-6224

Journal of Phytomolecules & Pharmacology

Review Article

The role of telomerase in cellular senescence and skin aging: A molecular perspective

Mariana Najara Rosa Rodrigues[1, 3] and **Rodrigo Cé**[2, 3*]

1. Discente do Curso de Biomedicina do Centro Universitário Avantis – UNIAVAN - Av. Marginal Leste, 3600, Estados, Balneário Camboriú–SC, CEP: 88339125, Brazil.
2. Coordenador e Professor do Curso de Biomedicina do Centro Universitário Avantis – UNIAVAN - Av. Marginal Leste, 3600, Estados, Balneário Camboriú – SC, CEP: 88339125, Brazil.
3. Department of Biomedical Sciences, Centro Universitário Avantis – UNIAVAN - Av. Marginal Leste, 3600, Estados, Balneário Camboriú – SC, CEP: 88339125, Brazil.

Abstract

Telomeres are essential structures located at the ends of eukaryotic chromosomes, composed of G-rich repeats, which play a crucial role in protecting chromosomal ends. Telomere shortening is associated with genetic instability and cellular senescence. This review study aims to investigate the role of telomerase in cellular senescence and skin aging. The methodology involved a qualitative exploratory literature review, with research conducted in databases such as PubMed, Web of Science, and Google Scholar. Telomeres protect the ends of eukaryotic chromosomes, and their dysfunction leads to cellular senescence. Telomerase, a ribonucleoprotein, regulates telomere length and is crucial for cellular longevity. However, dysregulated telomerase expression may be associated with pathologies such as cancer. Oxidative stress accelerates telomere shortening and contributes to cellular aging. The analysis revealed a growing trend of publications related to telomeres and telomerase, with peaks in 2020 and 2017, respectively. Cellular senescence showed consistent growth, and exogenous telomerase expression demonstrated therapeutic potential, albeit with associated risks. Telomeres and telomerase play essential roles in regulating cell division and longevity. Telomerase is crucial for preserving cellular function, but its dysregulated expression can lead to pathologies. Oxidative stress accelerates cellular senescence, and research on exogenous telomerase expression highlights both potential and challenges for anti-aging therapies. Understanding these mechanisms is essential for developing effective strategies to promote cellular health and treat age-related diseases.

Article Information
Received: 28 October 2024
Revised: 21 November 2024
Accepted: 21 November 2024
Published: 30 November 2024

Academic Editor
Prof. Dr. Marcello Iriti

Corresponding Author
Prof. Dr. Rodrigo Cé
E-mail:
rodrigoce@uniavan.edu.br
rodrigoce@hotmail.com,
Tel: +55 51 981409716

Keywords
Telomeres, telomerase, cellular senescence, skin aging, oxidative stress.

1. Introduction

Skin aging is a multifactorial biological process characterized by a series of structural, molecular, and functional changes over time, influenced by various intrinsic and extrinsic factors. Similar to the aging of other organs, the skin gradually loses functionality and regenerative capacity [1]. However, what makes skin aging unique is its strong susceptibility to external factors such as lifestyle and exposure to harmful environmental agents [2]. Ultraviolet radiation, primarily from sunlight, emerges as a major driver of premature skin aging. This radiation can cause DNA damage and trigger oxidative processes in

skin cells, thus contributing to cellular aging and senescence [3].

Cellular senescence is a key phenomenon in the study of skin aging and other tissues. Prior to this discovery, it was believed that all cells were essentially immortal and could replicate indefinitely [4]. Cellular senescence is a state in which cells enter an irreversible cell cycle arrest in response to various stress factors, such as DNA damage, oxidative stress, and environmental influences. The accumulation of dysfunctional and senescent cells in aging tissues has detrimental effects, impairing their repair and regeneration capacity [5]. In the context of the skin, cellular senescence is associated with a range of changes and alterations [6].

Telomeres are essential structures located at the ends of eukaryotic chromosomes, composed of multiple G-rich repeats. In mammals, the repetitive telomeric sequence is TTAGGG, repeated thousands of times [7]. These structures play a vital role in protecting chromosomal ends from degradation and being identified as double-strand breaks. In the absence of telomeres, chromosomes can fuse, resulting in genetic instability [8]. Telomere shortening, damage to them, or the expression of mutant proteins that bind to telomeres can compromise the protective complex, triggering a DNA damage response and leading to cellular senescence [9].

Due to the inability of standard DNA polymerases to fully replicate linear DNA models in the absence of telomerase, an independent DNA polymerase model, and due to nucleolytic processing, DNA replication results in the formation of chromosomes with progressively shorter telomeres [10]. When telomeres reach a critical length, they can no longer bind to telomeric covering proteins in sufficient quantity, being detected as exposed DNA ends. This activates DNA damage response pathways, which, through the induction of cell cycle inhibitors such as p21 and p16, halt cell proliferation [9, 11]. Telomere shortening is widely recognized as an indicator of cellular aging and replicative senescence, marking the limit of cell replication and the aging process [12].

This literature review aims to investigate the role of telomerase, an enzyme responsible for maintaining telomeres, in cellular senescence and skin aging, seeking to address the following research question: What are the cellular senescence processes and factors that best explain skin aging? Providing molecular insights that may aid in developing strategies to combat skin aging.

2. Materials and methods

The methodology of this study is a qualitative, exploratory literature review focused on investigating aspects of cellular senescence. The search used specific keywords: telomeres, telomere shortening, telomerase, cellular senescence, skin, and skin aging. These keywords were searched in the U.S. National Library of Medicine (PubMed), Web of Science, and Google Scholar databases. Publications from the past 10 years were prioritized, although relevant older studies were also considered. The study selection process was carried out in four stages: First, article titles were assessed for relevance to the research topic. Second, abstracts were analyzed according to predefined inclusion and exclusion criteria to select the most relevant articles. Third, full-text articles were reviewed to ensure alignment with the study's objectives. Finally, a total of 185 articles were identified, with 136 selected for inclusion in the final database. Inclusion criteria required that articles be published in English, available in the selected databases, and accessible for free. Exclusion criteria involved the exclusion of articles published outside the last 10 years and those that did not address the research objectives. The final analysis synthesized key findings, offering insights into cellular senescence, particularly in relation to skin aging.

3. Theoretical framework

3.1 Telomeres and telomerase

The term "telomere" originates from the Greek words "telos" (end) and "meros" (part). Telomeres are structures typical of eukaryotic cells found at the ends of linear chromosomes [13]. They play a fundamental role in genome stability by protecting the ends of linear eukaryotic chromosomes, preventing their manipulation and recognition by modified DNA enzymes [14]. Additionally, they function to identify damaged chromosome ends, preserving DNA integrity during repair and recombination processes [15], and protecting against oxidative damage [16].

The function of telomeres can vary between species

https://doi.org/10.56717/jpp.2024.v03i02.027

[16]. They serve as markers of aging, with telomeres being shortened by an average of 50 to 200 base pairs with each cell division [17]. Maintaining telomere length homeostasis is crucial for cell survival, as short telomeres can cause DNA damage, leading to cellular senescence and apoptosis [18]. Several factors are essential for ensuring telomere stability [18], including an enzymatic complex responsible for their components, known as telomerase, in which the (Telomerase Reverse Transcriptase) TERT proteins, dyskerin, and the RNA component TR are fundamental [19].

Telomerase is a human ribonucleoprotein that regulates telomere balance and chromosomal integrity, being the primary regulator of telomere length in cells [20]. Most somatic cells lack sufficient telomerase, resulting in telomere shortening with each cell division [21]. Telomerase is recruited to chromosomal ends via a specific complex [22]. Among the telomerase components, the level of expression of the catalytic component, TERT, seems to correlate well with enzyme activity [23].

Although some adult somatic cells express telomerase, this is not common, especially in human cells. For example, activated human cells may express a transient form. Regardless of telomerase activity, these cells continue to lose telomeric DNA with each cell division, eventually leading to senescence. Thus, in some cases, the presence of telomerase is insufficient to prevent telomere erosion and senescence resulting from DNA replication. On the other hand, ectopic expression of telomerase may prevent telomere shortening and replicative senescence in some human cells, such as fibroblasts and epithelial cells [24, 25].

The specific components of the telomerase enzymatic complex are TERT (Telomerase Reverse Transcriptase) and TERC (Telomerase RNA Component). TERT is a catalytic subunit of telomerase that performs its reverse transcription role by adding repetitive sequences to telomeric DNA using telomerase RNA as a template, being essential for nucleotide addition at telomere ends. TERC is a structured molecule with the ability to fold, serving as a template for telomeric DNA synthesis and aiding in the correct positioning of nucleotide addition at telomere ends. Additionally, associated proteins such as Dyskerin help incorporate RNA into the telomerase complex and ensure TERC binds to TERT correctly, while other proteins like Nop10 and Gar1 are crucial for the stability and assembly of the telomerase complex, assisting in the formation of the ribonucleoprotein complex. These components regulate telomere homeostasis through structural interaction between TERT and TERC [133].

3.2 Telomerase in human skin

According to published data, telomerase is expressed in situ in the skin, especially in the epidermis, regardless of the individual's age [26]. Exposure of the skin to factors such as UV rays and other agents results in telomere shortening, interfering with telomerase activity and causing genetic alterations in melanocytes [27]. Telomerase activity has been associated with melanoma-related lesions, providing insights into its function and clinical relevance in this context [28].

Telomerase plays an essential role in maintaining telomere integrity and has a direct impact on skin health and aging [29]. Its activity in the skin is considered one of the main characteristics of cellular aging [30]. In proliferative and germinative cells, telomerase remains active, renewing tissues [31], and in human tissues and cells, it is closely linked to the skin's capacity for renewal and regeneration over time [32].

Numerous studies in the field have explored anti-aging strategies based on natural chemical molecules as potential telomerase activators, due to their fundamental role in skin aging and skin health [33, 34]. Therefore, the search for therapies that preserve telomere integrity and identify strong telomerase activators is of special interest [35]. To develop strategies for preventing and treating skin aging and skin-related diseases, it is essential to understand the molecular mechanisms underlying telomerase regulation in the skin [36, 37].

3.3 Interaction between telomeres and oxidative stress

The interaction between telomeres and oxidative stress plays a crucial role in cellular aging. Cellular damage caused by oxidative stress results in genomic instability [38, 39], leading to cellular senescence due to telomere shortening [40]. Studies show that oxidative stress can trigger cellular responses that lead to senescence by disrupting the cell cycle [41, 42].

https://doi.org/10.56717/jpp.2024.v03i02.027

One of the main outcomes of oxidative stress is DNA oxidation [43]. Recent research suggests that oxidative stress accelerates telomere shortening through DNA precursor molecules, and this DNA oxidation can inhibit telomerase activity, becoming a potential focus for cancer treatments [44].

Oxidative stress involvement in telomeres is associated with the progression of aging-related conditions, such as metabolic syndrome [45], and also with the activation of inflammatory pathways that affect cellular senescence [46], as well as certain pathological conditions like male infertility [47]. Some studies suggest that oxidative damage may directly influence telomerase, impeding its function.

Oxidative stress resulting in excessive production of reactive oxygen species (ROS) can alter cellular signaling pathways that control telomerase expression, leading to reduced enzymatic activity in adverse ways. This can cause direct damage to telomeric DNA, promoting degradation and accelerating telomere shortening [40, 131]. Telomerase activity can be affected by ROS in various ways, but mainly through damage to TERT, impairing its ability to interact with RNA and preventing the addition of new DNA repeats to the telomeres [132].

Understanding the interaction between telomeres and oxidative stress is fundamental for developing therapeutic interventions aimed at mitigating the effects of cellular aging. Research indicates that antioxidants and modulators of oxidative stress may counteract oxidative damage to telomeres [48], reducing chronic inflammation related to oxidative stress and contributing to the preservation of telomere integrity, thereby delaying cellular aging [49]. Understanding the underlying mechanisms of this interaction can expand the possibilities for non-pharmacological interventions, promoting cellular health [50].

3.4 Exogenous telomerase expression to correct telomere defects

Exogenous expression of telomerase has shown promise for correcting telomeric defects [51]. Studies demonstrate that introducing telomerase into human cells helps restore telomere length [52], associating with effective telomere management and reprogramming of stem cells [51-54], providing an efficient means to preserve chromosomal integrity [43]. However, despite the potential benefits, overexpression of this enzyme has been linked to various pathological conditions, such as cancer and progeria [55, 56].

In cultures of normal human fibroblasts, exogenous expression of TERT maintains these cells viable in vitro [23]. Therefore, it is crucial to consider the possible adverse effects of this exogenous telomerase expression [57]. Studies suggest that indiscriminate activation of telomerase may increase the risk of malignant transformation, tumorigenesis, genomic instability, and chromosomal rearrangements [58], as well as contribute to the progression of aging-related diseases [59].

Exogenous telomerase expression has emerged as a promising strategy for cellular rejuvenation therapies and may be used to restore the proliferative capacity of cells and reduce signs of cellular senescence [134]. However, this application also raises concerns about potential carcinogenesis risks, as longer telomeres may allow uncontrolled proliferation of cells with mutations [135]. Additionally, it may lead to genomic instability, compromising genome integrity and significantly affecting cell functionality in the long term [136].

Various therapeutic approaches are being developed to modulate telomerase activity, providing potential treatments for aging-related pathologies and telomeric disorders [60]. With advances in gene editing technology, specific compounds capable of modulating telomerase activity have been identified, offering new perspectives for correcting telomeric defects through direct manipulation of its expression [61]. These approaches, combined with progress in gene editing technology, allow precise manipulation of telomerase expression, opening new therapeutic possibilities for correcting telomeric defects [51].

3.5 Telomere dysfunction during aging

Telomere dysfunction during the aging process occurs intrinsically and complexly, triggering a series of molecular and cellular changes [62]. Over time, telomeres undergo gradual shortening, becoming chromosomally unstable and compromising cellular functions [63, 64]. This telomeric shortening is directly linked to the replicative capacity of cells, leading to

https://doi.org/10.56717/jpp.2024.v03i02.027

cellular senescence and depletion of cellular reserves over time [65, 66]. Consequently, telomere dysfunction affects tissue and organ regeneration capacity, contributing to the development of age-related diseases [67, 68].

In addition to reduced telomere length, dysfunction during aging is also associated with the activation of cellular stress signaling pathways and chronic inflammation [69, 70]. This results in DNA damage that contributes to aging through genomic alterations and impairment of cellular functions [71, 72]. Telomere dysfunction is one of the mechanisms that can lead cells to senescence. While telomere shortening is a significant factor in this process, recent studies have found that telomeric dysfunction can occur independently of telomere length [65].

3.6 Histology of the skin and types of skin cells

The skin is the largest organ of the human body and histologically [73], it exhibits a complex organization of specific layers. The outermost layer of the skin is the epidermis, which is predominantly composed of stratified squamous epithelium [74]. Keratinocytes, the predominant cells in the epidermis, form a physical barrier that prevents transepidermal water loss and protects the body against external agents [75]. Additionally, the epidermis houses other specialized cells, such as melanocytes, which are responsible for producing melanin, giving color to the skin and protecting against ultraviolet radiation damage [76], and Langerhans cells, which are involved in the skin's immune response by detecting and presenting antigens [77, 78].

The dermis, located below the epidermis, is the thickest layer of the skin, composed of dense connective tissue [75]. It is divided into two layers: the papillary dermis, made up of loose connective tissue, and the reticular dermis, the deeper layer composed of dense connective tissue [76]. In the dermis, fibroblasts are responsible for the synthesis and maintenance of extracellular matrix components, such as collagen and elastin fibers, playing a crucial role in wound healing [76]. Mast cells, part of the immune system, are also present in the dermis, performing functions related to inflammatory and allergic responses [75, 78]. Furthermore, the dermis is characterized by abundant and compact protective keratin, lamellar or Vater-Pacini corpuscles, Meissner's corpuscles, specialized arteriovenous communications, and eccrine sweat glands [79, 80].

The hypodermis, located below the dermis, is known as subcutaneous tissue and is primarily composed of adipose tissue [74]. It contains adipocytes, specialized cells for fat storage and temperature regulation, as well as blood vessels and nerves responsible for tissue vascularization [76]. Other important skin structures include hair follicles and sebaceous and sweat glands, which play essential roles in temperature regulation and skin lubrication [81, 82]. Hair follicles consist of different types of cells, including stem cells, matrix cells, and hair pressure cells, which are responsible for hair growth and regeneration [75].

3.7 Cellular senescence

Cellular senescence represents the loss of the capacity for cellular replication, where the cell cycle is permanently halted. Various stressors can induce cellular senescence, including oxidative stress, telomere alterations, mitochondrial dysfunctions, ribosomal stress, epigenetic modifiers, irradiation, drugs, and oncogenic stress [83]. This disadvantage is manifested by the interruption of post-mitotic cell division in response to some type of damage, with telomere shortening being one of the main factors. However, subsequent studies have revealed other pathways initiated by stimuli through which cells can enter senescence and cease to proliferate, regardless of the number of duplications [84].

Different types of senescence include replicative, stress-induced, oncogene-induced, and developmental senescence. Replicative senescence is characterized by short telomeres and is influenced by the activation of the CDKN2A locus, which encodes the tumor suppressor p16, responsible for inhibiting CDK4 and CDK6 [85]. Stress-induced senescence is related to high intracellular levels of reactive oxygen species (ROS) and results from the RAS-RAF-MEK-ERK cascade, which activates p38 MAPK and leads to increased transcriptional activity of p53 and positive regulation of p21 [86]. Oncogene-induced senescence is marked by the activation of the CDKN2A15 locus, leading to abnormal DNA replication. Developmental senescence is normal and necessary for the formation of certain human organs, such as neural tube closure

https://doi.org/10.56717/jpp.2024.v03i02.027

and gallbladder formation during embryonic development [85].

Recent discoveries are shifting the perspective on cellular senescence, viewing it as a stimulus for tissue alteration processes and also as a mechanism for eliminating unwanted cells following tissue damage. Senescent cells eliminate their deficiencies and recruit immune cells, promoting tissue renewal. If these senescence phases do not occur effectively, it can result in the accumulation of senescent cells in the organism [87].

3.8 Cellular senescence of various skin cell types

Senescent cells exhibit four interdependent aspects, as described by the International Cellular Aging Society (ICSA): permanent cell cycle arrest, Senescence-Associated Secretory Phenotype (SASP), macromolecular damage, and dysregulated metabolism [83]. Senescent cells have been observed in various types of skin cells [69]. Over time, senescent cells accumulate in the skin, with histochemical detection of beta-galactosidase expression in senescent fibroblasts and keratinocytes [88]. This accumulation is considered a reliable biomarker of aging, contributing to age-related skin changes, expanding the basal layer of the epidermis, and affecting its regeneration and structure [89].

Studies have shown that in human skin in vivo, during melanocyte senescence, these cells express a succession of senescence markers, such as increased p16 INK4A levels over the years [90]. It has also been found that in aged melanocytes, there is a much higher occurrence of dysfunctional telomeres, although without telomere shortening, suggesting that the primary cause of telomere dysfunction in aged melanocytes is not telomere shortening [65].

3.9 Skin stem cells and their relevance to skin aging

Stem cells can be classified as totipotent, pluripotent, and multipotent, with these cells varying in capability depending on the organs they derive from, facilitating tissue regeneration [91]. Researchers have identified and categorized stem cells into two broad groups: embryonic and adult [92]. The skin is a tissue in constant self-renewal, and to maintain homeostasis, there are niches with stem cells responsible for addressing natural cellular losses or those caused by injuries [93]. In its outermost compartment, the epidermis, there are indications of epidermal stem cells. These quiescent cells are located in the most basal layer of the interfollicular epidermis, attached to the basement membrane through integrin-class proteins. As these cells migrate to the upper layers, they undergo differentiation until they reach the skin surface as non-scaly corneocytes [93].

Stem cells have been linked to the aging process, with oxidative stress caused by reactive oxygen species being the primary effector in the skin. This phenomenon has been more extensively studied in hematopoietic stem cell models, where it was implicated in the activation of the INK4a/ARF locus transcription, leading to the activation of the senescence program. Despite its relevance, the relationship between these pathways and skin stem cell aging remains largely unexplored [93]. Another important stem cell niche is hair. Dermal mesenchymal stem cells are capable of differentiating into adipocytes, chondrocytes, and osteocytes, typically derived from mesodermal precursors [93]. In many tissues, stem cells also progressively lose telomerase activity and, consequently, the ability to maintain tissue renewal, which is one of the main causes of aging [19].

3.10 Cellular senescence and organismal aging

Researchers assert that the terms senescence and aging are used interchangeably, as both refer to cellular transformations that occur in organs and tissues related to the passage of time and biological processes. These processes impair the physiology of the organism, leading to functional effects that make it vulnerable to pathologies [94].

Senescent cells do not die immediately; most remain viable and metabolically active for extended periods in culture, indicating that senescence occurs not only during aging but also naturally throughout the life of organisms [95]. These cells exhibit morphological changes, both in vivo and in vitro, such as increased size with a flattened appearance and numerous vacuoles, the presence of DNA damage “scars,” and alterations in heterochromatin [96].

Senescent cells are distinct from other non-dividing cells, such as quiescent cells, characterized by the absence of proliferative markers like Ki67, as well as other markers like p16, p21, and p27 [97].

https://doi.org/10.56717/jpp.2024.v03i02.027

Additionally, ß-galactosidase activity associated with senescence is observed, reflecting the expression of tumor suppressors and cell cycle inhibitors. Although none of these markers are completely specific or universal for all types of senescence, senescent cells express most of them [98].

3.11 Cellular senescence and telomeres

Cellular senescence refers to the response of mitotically competent cells, which are not terminally differentiated and thus capable of division, to stimuli that have the potential to cause neoplastic transformations, resulting in, among other aspects, growth arrest [99]. Cellular senescence is not only expressed through a halt in cell growth but also involves functional alterations that, together, define the senescent phenotype. Due to mutated RAS, telomerase cannot prevent senescence in human fibroblasts, indicating that cells can manifest a senescent phenotype independently of specific telomeres [100,101].

When discussing cellular senescence, it is closely associated with telomeres, which are structures containing a short, repetitive DNA sequence (5'TTAGGG3') located at the chromosomal ends of cells with the function of preserving genetic information and bases [102]. Telomeres serve as cellular markers, functioning as an intrinsic counter to protect the organism from uncontrolled cell divisions, undergoing shortening with each division until they lose their function and enter a state of cellular senescence [103].

3.12 Why is cellular senescence important?

Cellular senescence is significant because it represents a permanent proliferative halt in response to various stressors and acts as a tumor-suppressing mechanism. However, it also entails a loss of repair and tissue regeneration capacity due to cell cycle interruption [104]. Cellular senescence plays a crucial endogenous role as an antitumoral mechanism and is related to the activity of antitumoral drugs [105]. Conceptual advancements have been made regarding the role of senescent cells, highlighting the importance of understanding that senescence is not limited to the loss of proliferative capacity but also involves gene expression, epigenome, metabolism, and especially the SASP [106]. Evidence suggests that the senescence response evolved to suppress tumorigenesis, acting as a safety mechanism to prevent cells at risk of undergoing neoplastic transformations. Thus, normal cells undergo senescent arrest when exposed to various stimuli capable of inducing or promoting neoplastic changes [101].

3.13 What are telomeres and how do they signal senescence?

Initial records about telomeres emerged in the 1930s by McClintock and Muller studying the ends of chromosomes in *Zea mays* and *Drosophila melanogaster*. However, it was not until 1961 that Hayflick and Moorhead observed that human fetal cells had a replication capacity of 50 to 60 times, establishing the "Hayflick limit" known as replicative senescence. This was a landmark in scientific history, paving the way for numerous new studies in the field [107].

Telomeres act as protective structures at the chromosomal ends, being highly vulnerable to intrinsic and extrinsic stress factors, affecting cellular health [65]. During DNA replication, telomeres lose genetic material—about 50 to 100 base pairs—leading to their shortening. Both this shortening and the specific proteins associated with it signal the cessation of the cell cycle. Cell death then occurs through chromosomal instability resulting from telomere shortening [108].

Senescence signaling can occur through two pathways: ATR-Chk1 and ATM-Chk2. These pathways phosphorylate Chk1 and Chk2, blocking cell development during the G1/S and G2/M phases by inhibiting CDC25 and suppressing CDK activation. Thus, ATM and ATR promote p53 activation, inhibiting further cell cycle progression [109]. The p53 transcription factor, in its specific sequence, directs the expression of target genes that respond to cellular stress and damage [110].

Senescent cells also produce molecules that are pro-inflammatory and degradative to the extracellular matrix, known as the SASP. SASP is primarily initiated by inflammatory cascades mediated mainly by NF-κB and p38 MAPK signaling and is autocrinely inhibited [104]. One of the main functions of SASP is to recruit the immune system to eliminate senescent and tumor cells, but SASP also induces cellular plasticity and tissue regeneration [111].

https://doi.org/10.56717/jpp.2024.v03i02.027

3.14 Telomere dysfunction can occur independently of length

Additionally, not only the reduction in telomere length but also changes in their structure and function can result in cellular senescence or apoptosis, leading to organ dysfunctions [112]. Telomere damage unrelated to length has been recently proposed as a mechanism of slow or post-mitotic cellular senescence, showing low proliferative potential in vivo and harboring dysfunctional telomeres without significant shortening [69].

Therefore, telomeric length can be considered an important biomarker of aging or even a mitotic clock partially responsible for this process, with telomere shortening and consequent dysfunction being related to the development of various chronic diseases [113,114]. An increased population of senescent cells in specific tissues, resulting from telomere shortening or dysfunction, has been associated with various aging-related phenotypes, including cardiovascular and metabolic diseases and changes in cognitive performance [115]. Shortened telomeres are associated with a 3.2-fold increase in cardiovascular disease mortality and an 8.5-fold increase in infectious disease mortality [116].

3.15 Skin aging

Aging occurs gradually, affecting all organs, with the skin being no exception. Skin aging can be classified as chronological, also known as intrinsic aging, which is influenced by genetic factors and occurs with age, or extrinsic aging, which results from external factors [117]. Extrinsic factors include environmental elements that damage skin health, such as UV radiation, the primary and most significant factor contributing up to 80% to skin aging, along with other factors such as smoking, alcohol consumption, and poor diet [109].

Intrinsic factors related to skin aging are characterized by genetic and/or metabolic changes that lead to collagen loss and even tissue degeneration. This intrinsic skin aging is marked by the atrophy of structural components, with decreased dermal density, reduced vascularization, changes in the dermal-epidermal junction, and a reduction in the number and size of epithelial cells [118]. Various intrinsic factors, such as genetically programmed lifespan, or extrinsic factors like the accumulation of radiation damage, result in gradual phenotypic and functional changes in cells. These changes lead to senescence, characterized by prolonged and sometimes irreversible cell cycle arrest [119].

Aging brings biochemical changes that cause clinical manifestations in the skin, such as increased thickness, pigmentation, and wrinkles. Some of these changes involve alterations in immune system functions, skin appendages, DNA components, and the balance between oxidative and antioxidant species, often resulting from oxidative stress [117].

3.16 Genetic diseases and skin aging

Genetic diseases are caused by mutations in genes that encode telomerase complex proteins or are involved in other telomere maintenance processes [120]. Gene expression also changes with age, influencing matter production. Additionally, telomeres shorten, and external factors can impact the aging process [121]. Oxidative stress causes mutations, leading to telomere shortening, lipid alterations through lipid peroxidation, and oxidative damage to DNA and proteins. Another factor to consider is free radicals, which can damage DNA by increasing genetic damage and reducing telomere repair [48]. Cellular damage associated with aging includes distorted nuclei and Golgi complexes, as well as inefficient mitochondria. Over a lifetime, cellular degeneration increases, and mitochondrial functionality, responsible for cellular respiration, diminishes ATP production with aging [121].

Aging in humans and most species is also associated with genetic variants. A group of European scientists is analyzing over 500,000 genetic variations. According to Nilesh Samani, a cardiology professor and one of the study coordinators, biological aging can cause cells to appear younger or older than the actual age of the individual [122]. Telomeres can be seen as protective caps at the ends of shoelaces; when this protection is damaged, the shoelace threads begin to fray. This analogy explains the importance of preserving telomeres for chromosome stability. Thus, repetitive DNA sequences (at the end of chromosome) known as telomeres, wear down, leaving the genetic material unprotected, and significant cell renewal does not occur [121].

https://doi.org/10.56717/jpp.2024.v03i02.027

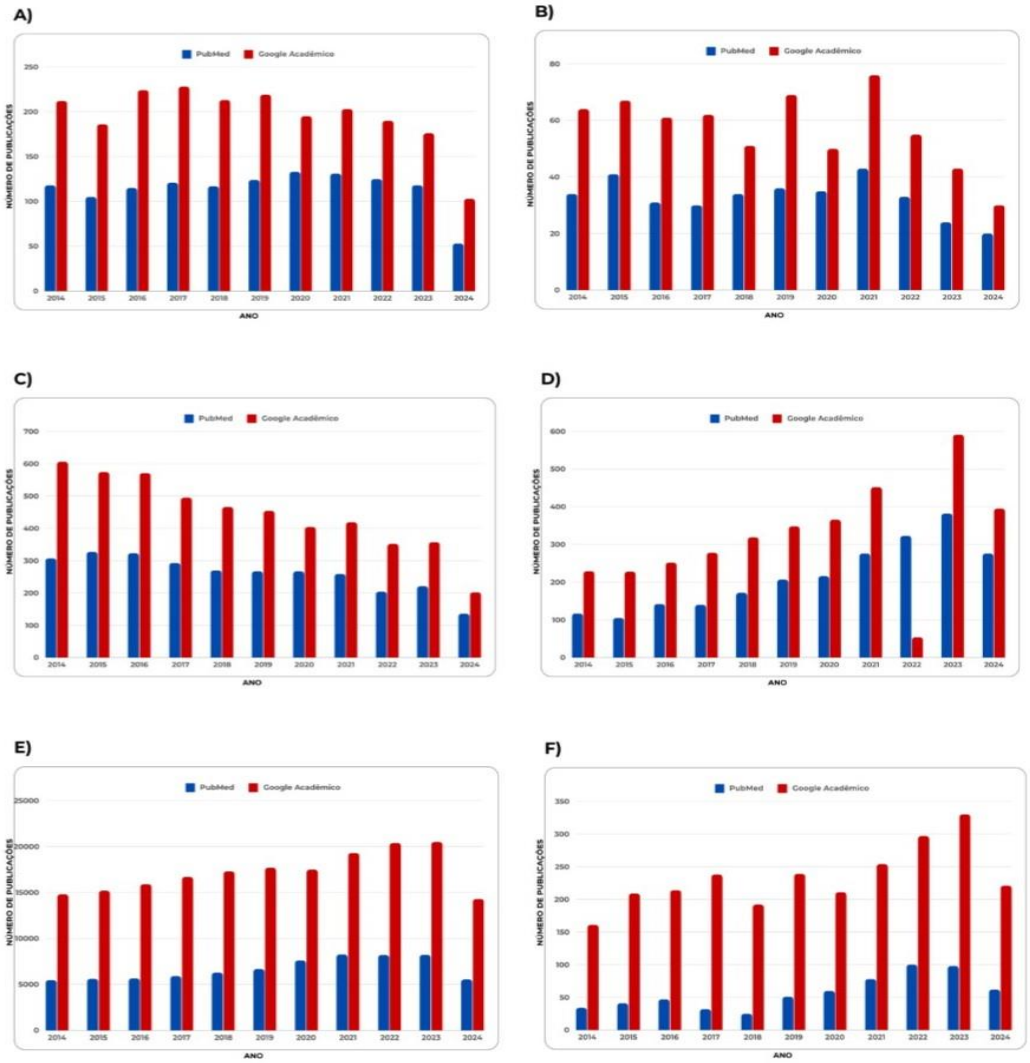

Figure 1. Representation of the research results, with keywords found in PubMed and Google Scholar, comparing the publication year and the number of publications: A) Telomeres, B) Telomere shortening, C) Telomerase, D) Cellular senescence, E) Skin, and F) Skin aging.

4. Results and discussion

Based on the results obtained from the search using keywords such as telomeres, telomere shortening, telomerase, cellular senescence, skin, and skin aging, available in the PubMed and Google Scholar databases, a notable trend was observed in the number of articles published over the past ten years. This trend is illustrated in the following comparative analysis, represented in graphs (Fig. 1). The graphs (Fig. 1) reveal a significant variation in the number of documents published across the two databases. For telomerase, there was an initial growth in the first years, visible in both databases, with a peak in 2020 on PubMed (133 publications) and in 2017 on Google Scholar (228 publications) (Fig. 1). After these peaks, the numbers stabilized and began to decrease from 2021 onward. Regarding telomere shortening, there was a reduced number of publications. Initially, there was fluctuation in the early years, with a significant increase in 2021 in both databases (43 articles in PubMed and 76 in Google Scholar) (Fig. 1). Since then, there has been a gradual reduction, with a more pronounced decline on PubMed compared to Google Scholar. For telomerase, the analysis shows a significant initial increase (Fig. 1), reaching 327 publications on PubMed and 574 on Google Scholar in 2015, followed by a progressive decline in both cases in recent years.

https://doi.org/10.56717/jpp.2024.v03i02.027

For cellular senescence, there was consistent growth over the decade, with a notable peak in 2023 (382 publications on PubMed and 591 on Google Scholar), followed by a slight reduction in 2024, with a few months still pending publication (Fig. 1). Concerning skin, there were many publications with a clear trend of expansion in academic production. PubMed recorded a peak of 8,265 publications, while Google Scholar reached a remarkable total of 20,500 publications in 2023 (Fig. 1). For skin aging, the numbers were relatively low, especially on PubMed, which peaked at 100 publications in 2022, while Google Scholar reached 330 publications the following year, suggesting a slight expansion compared to earlier years (Fig. 1). The data indicate a general trend of growth in the number of scientific articles published in both databases over the past ten years, highlighting an increase in research activity. Google Scholar demonstrated a broader coverage, resulting in a higher number of publications compared to PubMed, which is more focused on medical and health sciences literature. However, both databases show efficacy in the reliability of their publications and reflect their respective emphases and scopes.

Skin aging is a complex phenomenon caused by a variety of intrinsic and extrinsic factors, resulting in significant functional and structural changes in the skin. One of the main aspects of this process is cellular senescence, characterized by permanent cell cycle arrest, directly related to telomere shortening. Located at the ends of chromosomes, telomeres primarily function to protect chromosomes, preventing their degradation and ensuring genetic stability. With each cell division, telomeres progressively shorten due to the inability of DNA polymerases to fully replicate this region. This gradual shortening leads to a point where the cell enters senescence, halting its ability to divide and proliferate [10, 123, 124].

The enzyme responsible for maintaining telomeres is telomerase, which adds repetitive sequences to telomeres, helping to ensure their integrity and prevent cellular senescence. However, telomerase activity is typically low in mature somatic cells, limiting tissue renewal capacity and contributing to skin aging. Studies suggest that reactivation of telomerase may influence the reversal of aspects of cellular senescence and promote tissue regeneration [24,125,126].

Extrinsic factors, such as UV radiation exposure, accelerate skin aging by causing oxidative stress and DNA damage, accelerating telomere shortening, and contributing to cellular senescence. UV radiation also promotes the production of reactive oxygen species (ROS), which elevate oxidative stress and stimulate aging. Thus, environmental stress and intrinsic aging mechanisms, such as telomere shortening, lead to the deterioration of skin function and structure. The combination of extrinsic stress with intrinsic mechanisms results in telomere shortening and skin aging [127,128].

Understanding the role of telomerase in cellular senescence and its impact on skin aging is crucial for developing new interventions aimed at increasing telomerase activity, inhibiting cellular senescence, and potentially slowing skin aging while improving its condition. Recent studies suggest that modulation of telomerase activity through genetic or pharmacological therapies may offer new approaches in combating skin aging and conditions related to cellular senescence [33,129,130].

5. Conclusions and future directions

The detailed analysis of telomeres, telomerase, and their roles in cellular senescence and skin aging underscores their pivotal role in maintaining cellular stability and longevity. Telomeres protect chromosomal ends and regulate cellular division, while telomerase activity is vital for preserving telomere length and cellular function. Dysregulation of telomerase expression, however, can lead to diseases such as cancer. The role of oxidative stress in accelerating telomere shortening and cellular senescence further emphasizes the importance of antioxidant strategies to safeguard telomere integrity. Additionally, telomeric dysfunction, although central to aging, is part of a broader and more complex mechanism of cellular senescence. Research into exogenous telomerase expression holds promise for therapeutic interventions, yet challenges remain in safely manipulating these pathways for anti-aging purposes. Looking ahead, future research should focus on exploring more precise methods to regulate telomere length and telomerase activity without

https://doi.org/10.56717/jpp.2024.v03i02.027

triggering unwanted side effects, such as tumorigenesis. Further studies into the interactions between oxidative stress and telomere dynamics could lead to innovative antioxidant therapies. Additionally, a deeper understanding of the molecular mechanisms underlying cellular senescence could reveal new targets for combating age-related diseases. Ultimately, developing effective strategies to modulate telomere biology will be essential for advancing therapeutic interventions aimed at promoting cellular health and mitigating the effects of aging.

Authors' contributions

Investigation, conceptualization, methodology and writing - original draft, M.N.R.R; Conceptualization, formal analysis, writing-reviewing, editing, supervision and validation, R.C.

Acknowledgements

The authors don't have anything to acknowledge.

Funding

We would like to thank UNIAVAN for its financial support.

Availability of data and materials

All data will be made available on request according to the journal policy.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Rittie, L.; Fisher, G.J. Natural and sun-induced aging of human skin. Cold Spring Harb. Perspect. Med. 2015, 5(1), a015370, https://doi.org/10.1101/cshperspect.a015370
2. Gruber, F.; Kremslehner, C.; Eckhart, L.; Tschachler, E. Cell aging and cellular senescence in skin aging - Recent advances in fibroblast and keratinocyte biology. Exp. Gerontolog. 2020, 130, 110780. https://doi.org/10.1016/j.exger.2019.110780
3. Cavinato, M.; Jansen-Dürr, P. Molecular mechanisms of UVB-induced senescence of dermal fibroblasts and its relevance for photoaging of the human skin. Exp. Gerontolog. 2017, 94, 78-82. https://doi.org/10.1016/j.exger.2017.01.009
4. Bulbiankova, D.; Díaz-Puertas, R.; Álvarez-Martínez, F.J.; Herranz-López, M.; Barrajón-Catalán, E.; Micol, V. Hallmarks and biomarkers of skin senescence: an updated review of skin senotherapeutics. Antioxidants, 2023, 12(2), 444. https://doi.org/10.3390/antiox12020444
5. Ho, C.Y.; Dreesen, O. Faces of cellular senescence in skin aging. Mech. Ageing Dev. 2021, 198, 111525, https://doi.org/10.1016/j.mad.2021.111525
6. Csekes, E.; Račková, L. Skin aging, cellular senescence and natural polyphenols. Int. J. Mol. Sci. 2021. 22(23) 12641. https://doi.org/10.3390/ijms222312641
7. Moyzis, R.K.; et al. A highly conserved repetitive DNA sequence, (TTAGGG)n, present at the telomeres of human chromosomes. Proceedings of the National Academy of Sciences of the United States of America, 1988, 85(18), 6622-6626. https://doi.org/10.1073/pnas.85.18.6622
8. O'sullivan, R.J.; Karlseder, J. Telomeres: protecting chromosomes against genome instability. Nat. Rev. Mol. Cell Biol. 2010, 11(3), 171-181. https://doi.org/10.1038/nrm2848
9. D'adda Di, F.F.; et al. A DNA damage checkpoint response in telomere-initiated senescence. Nature. 2003, 426 (6963), 194-198. https://doi.org/10.1038/nature02118
10. Harley, C.B.; Futcher, A.B.; Greider, C.W. Telomeres shorten during ageing of human fibroblasts. Nature, 1990, 345 (6274), 458-460. https://doi.org/10.1038/345458a0
11. Herbig, U.; et al. Telomere shortening triggers senescence of human cells through a pathway involving ATM, p53, and p21CIP1, but not p16INK4a. Mol. Cell. 2004, 14, 501-513. https://doi.org/10.1016/s1097-2765(04)00256-4
12. D'avila, J. Da C.; et al. Mecanismos moleculares do envelhecimento: revisão da literatura. Revista Brasileira de Ciências do Envelhecimento Humano. 2020, 17, 1. https://doi.org/10.5335/rbceh.v17i1.10543
13. Félix, Nathália Quaiatto. Papel da obesidade, do estilo de vida e dos fatores imunológicos no comprimento dos telômeros em crianças e adolescentes. 2024.
14. Wood, A.M.; et al. A beginning of the end: new insights into the functional organization of telomeres. Nucleus. 2015, 6(3), 172-178. https://doi.org/10.1080/19491034.2015.1048407
15. Bryan, T.M. G-Quadruplexes at telomeres: friend or foe? Molecules. 2020, 25(16), 3686. https://doi.org/10.3390/molecules25163686
16. Olsson, M.; Wapstra, E.; Friesen, C.R. Evolutionary ecology of telomeres: a review. Ann. New York Acad. Sci. 2018, 1422, 5-28. https://doi.org/10.1111/nyas.

https://doi.org/10.56717/jpp.2024.v03i02.027

13443
17. Grill, S.; Nandakumar, J. Molecular mechanisms of telomere biology disorders. J. Biol. Chem. 2021. 296, 100064. https://doi.org/10.1074/jbc.REV120.014017
18. Greider, C.W. Regulating telomere length from the inside out: the replication fork model. Gen. Dev. 2016, 30(13), 1483-1491. https://doi.org/10.1101/gad.280578.116
19. Perona, R. et al. Molecular diagnosis and precision therapeutic approaches for telomere biology disorders. In: Larramendy, M.; Soloneski, S. (Ed.). Telomeres: a complex end of the chromosome. 2015. https://doi.org/10.5772/65353
20. Schmidt, J. C.; Cech, T.R. Human telomerase: biogenesis, trafficking, recruitment, and activation. Gen. Dev. 2015, 29(11), 1095-1105. https://doi.org/10.1101/gad.263863.115
21. Bernardes D.J.B.; Blasco, M.A. Telomerase at the intersection of cancer and aging. Trend. Gen. 2016, 32(8), 442-450. https://doi.org/10.1016/j.tig.2013.06.007
22. Bernal, A.; Tusell, L. Telomeres: implications for cancer development. Int. J. Mol. Sci. 2018, 19(1) 294. https://doi.org/10.3390/ijms19010294
23. Baek, S.; et al. Telomerase induction in astrocytes of Sprague-Dawley rat after ischemic brain injury. Neurosci. Lett. 2015, 610, 54-59. https://doi.org/10.1016/j.neulet.2004.03.059
24. Shay, J.W.; Wright, W.E. Telomeres and telomerase: implications for cancer and aging. Rad. Res. 2015, 183(2), 129-142. https://doi.org/10.1667/0033-7587(2001)155[0188:TATIFC]2.0.CO;2
25. Leung, K.; Pereira-Smith, O.M. Identification of genes involved in cell senescence and immortalization: potential implication for tissue aging. Novart. Found. Symp. 2015, 344, 205-217. https://doi.org/10.1002/0470868694.ch10
26. Babizhayev, M.A. Treatment of skin aging and photoaging with innovative oral dosage forms of nonhydrolized carnosine and carcinine. Int. J. Clin. Dermatol. Res. 2017, 5(5), 116-143, https://doi.org/10.19070/2332-2977-1700031
27. De, S.S.C.P.; et al. Azidotimidina (AZT) na expressão gênica e na síntese proteíca da telomerase em células de melanoma metastático humano / Azidothymidine (AZT) in gene expression and protein synthesis of telomerase in human metastatic melanoma cells. Braz. J. Dev. 2022, 8(5), 40646-40661. https://doi.org/10.34117/bjdv8n5-415
28. Carvalho, L.M.Y. Atividade de telomerase nas lesões melanocíticas e na pele: correlação com aspectos histopatológicos do melanoma. 2000.
29. Shay, J.W. Role of telomeres and telomerase in aging and cancer. Cancer Discover. 2016, 6(6), 584-593. https://doi.org/10.1158/2159-8290.CD-16-0062
30. López-Otín, C.; et al. The hallmarks of aging. Cell. 2013, 153(6), 1194-1217. https://doi.org/10.1016/j.cell.2022.11.001
31. Heidenreich, B.; Kumar, R. Tert promoter mutations in telomere biology. Rev. Mut. Res. 2017, 771, 15-31. https://doi.org/10.1016/j.mrrev.2016.11.002
32. Chiu, C.P.; et al. Telomerase expression in human cells and tissues. Aging Clin. Exp. Res. 1995, 7, 460-461. https://doi.org/10.1007/BF03324363
33. Jacczak, B.; Rubiś, B.; Totoń, E. Potential of naturally derived compounds in telomerase and telomere modulation in skin senescence and aging. Int. J. Mol. Sci. 2021, 22(12), 6381. https://doi.org/10.3390/ijms22126381
34. Cé, R.; et al. Estratégias antienvelhecimento baseadas em moléculas químicas naturais como potentes ativadores de telomerase. Arq. ciências saúde UNIPAR. 2022. 1229-1247.
35. Tsoukalas, D.; et al. Discovery of potent telomerase activators: unfolding new therapeutic and anti-aging perspectives. Mol. Med. Rep. 2019, 20(4), 3701-3708. https://doi.org/10.3892/mmr.2019.10614
36. Veverka, P.; Janovič, T.; Hofr, C. Quantitative biology of human shelterin and telomerase: searching for the weakest point. Int. J. Mol. Sci. 2019, 20(13), 3186. https://doi.org/10.3390/ijms20133186
37. Castro, I.A. de. p53 protein expression in skin with different levels of photoaging. Photodermatol. Photoimmunol. Photomed. 2009, 25(2), 106-108. https://doi.org/10.1111/j.1600-0781.2009.00400.x
38. Boonekamp, J.J. et al. Does oxidative stress shorten telomeres? Biol. Lett. 2017, 13(5), 20170164. https://doi.org/10.1098/rsbl.2017.0164
39. Armstrong, E.; Boonekamp, J. Does oxidative stress shorten telomeres in vivo? A meta-analysis. Ageing Res. Rev. 2023, 85, 101854. https://doi.org/10.1016/j.arr.2023.101854
40. Berra, C.M.; Menck, C.F.M.; Di Mascio, P. Estresse oxidativo, lesões no genoma e processos de sinalização no controle do ciclo celular. Quím. Nova. 2006, 29, 1340-1344. https://doi.org/10.1590/S0100-40422006000600032
41. Nasir, N.F.M.; et al. Telomeres and oxidative stress. British J. Med. Med. Res. 2014. 4(1), 57. https://doi.org/10.9734/BJMMR/2014/5548
42. Lin, J.; Epel, E.; Stress and telomere shortening: insights from cellular mechanisms. Ageing Res. Rev. 2022, 73, 101507. https://doi.org/10.1016/j.arr.2021.101507
43. Coluzzi, E.; Leone, S.; Sgura, A. Oxidative stress

induces telomere dysfunction and senescence by replication fork arrest. Cells. 2019, 8(1), 19. https://doi.org/10.3390/cells8010019

44. Fouquerel, E.; et al. Oxidative guanine base damage regulates human telomerase activity. Nat. Struct. Mol. Biol. 2016. 23(12),1092-1100. https://doi.org/10.1038/nsmb.3319
45. Gavia-García, G.; et al. Telomere length and oxidative stress and its relation with metabolic syndrome components in the aging. Biology. 2021, 10(4), 253. https://doi.org/10.3390/biology10040253
46. Correia-Melo, C.; Hewitt, G.; Passos, J.F. Telomeres, oxidative stress and inflammatory factors: partners in cellular senescence? Long. Health. 2014, 3, 1-9, https://doi.org/10.1186/2046-2395-3-1
47. Berby, B.; et al. Oxidative stress is associated with telomere interaction impairment and chromatin condensation defects in spermatozoa of infertile males. Antioxidants, 2021, 10(4), 593. https://doi.org/10.3390/antiox10040593
48. Borson, L.A.M.G.; Romano, L.H. Revisão: o processo genético de envelhecimento e os caminhos para a longevidade. Revista Saúde em Foco. 2020, 12, 239-244.
49. Casalicchio, A.B.R.; Leonardo, H.A.; D.E.S.; Gabriella, S. Actions of telomerase enzyme against physical exercise and aging: studies of the behavior of telomerase in specific actions imposed. Braz. J. Health Rev. 2022, 5(1), 843-858. https://doi.org/10.34119/bjhrv5n1-073
50. Erusalimsky, Jorge, D. Oxidative stress, telomeres and cellular senescence: what non-drug interventions might break the link? Free Rad. Biol. Med. 2020, 150, 87-95. https://doi.org/10.1016/j.freeradbiomed.2020.02.008
51. Ravindranathan, A.; et al. Preliminary development of an assay for detection of TERT expression, telomere length, and telomere elongation in single cells. PLoS One. 2018. 13(12), e0206525. https://doi.org/10.1371/journal.pone.0206525
52. Hidema, S.; et al. Transgenic expression of Telomerase reverse transcriptase (Tert). PLoS One. 2016, 38,19, e96659. https://doi.org/10.1080/09168451.2016.1191330
53. Rubtsova, M.; et al. Telomere lengthening and other functions of telomerase. Acta Nat. 2012, 2(13), 44-61,
54. Grolimund, L.; et al. A quantitative telomeric chromatin isolation protocol identifies different telomeric states. Nat. Commun. 2013, 4(1), 2848, https://doi.org/10.1038/ncomms3848
55. Chołjnowski, A. et al. Progerin reduces LAP2α-telomere association in Hutchinson-Gilford progeria. eLife, 2015, 4, e07759. https://doi.org/10.7554/eLife.07759
56. Mukherjee, J.; et al. Mutant IDH1 cooperates with ATRX loss to drive the alternative lengthening of telomere phenotype in glioma. Cancer Res. 2018, 78(11), 2966-2977. https://doi.org/10.1158/0008-5472.CAN-17-2269
57. Rossiello, F.; et al. Irreparable telomeric DNA damage and persistent DDR signalling as a shared causative mechanism of cellular senescence and ageing. Curr. Opin. Gen. Dev. 2014, 26, 89-95. https://doi.org/10.1016/j.gde.2014.06.009
58. Lee, M.; et al. Telomere extension by telomerase and ALT generates variant repeats by mechanistically distinct processes. Nucleic Acids Res. 2014, 42(3), 1733-1746. https://doi.org/10.1093/nar/gkt1117
59. Li, F.; et al. ATRX loss induces telomere dysfunction and necessitates induction of alternative lengthening of telomeres during human cell immortalization. EMBO J. 2019. 38(19), e96659. https://doi.org/10.15252/embj.201796659
60. Clynes, D.; et al. Suppression of the alternative lengthening of telomere pathway by the chromatin remodelling factor ATRX. Nat. Commun. 2015, 6(1), 7538. https://doi.org/ 10.1038/ncomms8538
61. Roake, C.M.; Artandi, S.E. Regulation of human telomerase in homeostasis and disease. Nat. Rev. Mol. Cell Biol. 2020, 21(7), 384-397. https://doi.org/ 10.1038/s41580-020-0234-z
62. Aguado, J.; et al. Telomere transcription in ageing. Ageing Res. Rev. 2020, 62, 101115, https://doi.org/10.1016/j.arr.2020.101115
63. Rossiello, F.; et al. Telomere dysfunction in ageing and age-related diseases. *Nat. Cell Biol.* 2022, 24(2),135-147. https://doi.org/ 10.1038/s41556-022-00842-x
64. Aubert, G.; Lansdorp, P.M. Telomeres and aging. Physiol. Rev. 2008, 88(2), 557-579. https://doi.org/10.1152/physrev.00026.2007
65. Victorelli, S.; et al. Senescent human melanocytes drive skin ageing via paracrine telomere dysfunction. EMBO J. 2019, 38, 23, e101982. https://doi.org/10.15252/embj.2019101982
66. Ishikawa, N.; et al. Changes of telomere status with aging: an update. Geriatr. Gerontol. Int. 2016, 16, 30-42. https://doi.org/10.1111/ggi.12772
67. Opresko, P.L.; Shay, J.W. Telomere-associated aging disorders. Ageing Res. Rev. 2017, 33, 52-66. https://doi.org/10.1016/j.arr.2016.05.009
68. Razdan, N.; Vasilopoulos, T.; Herbig, U. Telomere dysfunction promotes transdifferentiation of human fibroblasts into myofibroblasts. Aging Cell. 2018, 17(6), e12838. https://doi.org/10.1111/acel.12838
69. Victorelli, S.; Passos, J.F. Telomeres: beacons of autocrine and paracrine DNA damage during skin

https://doi.org/10.56717/jpp.2024.v03i02.027

aging. Cell Cycle. 2020, 19(5), 532-540. https://doi.org/10.1111/acel.12838
70. Li, S.; et al. Links between telomere dysfunction and hallmarks of aging. Mut. Res.: Gen. Toxicol. Environ. Mutagen. 2023, 888, 503617. https://doi.org/10.1016/j.mrgentox.2023.503617
71. Kalmykova, A. Telomere checkpoint in development and aging. Int. J. Mol. Sci. 2023, 24(21), 15979. https://doi.org/10.3390/ijms242115979
72. Sengupta, D.; Sengupta, K. Lamin A and telomere maintenance in aging: Two to tango. Mut. Res.: Fundament. Mol. Mech. Mut. 2022, 825, 111788. https://doi.org/10.1016/j.mrfmmm.2022.111788
73. Eroschenko, V.P.; Di, F.M.S.H. Difiore's Atlas of Histology With Functional Correlations. 11. Edn. Philadelphia: Lippincott Williams and Wilkins, 2014. https://doi.org/10.1111/j.1469-7580.2008.00956.x
74. Yousef, H.; Alhajj, M.; Sharma, S. Anatomy, Skin (Integument), Epidermis. 14 nov. 2022. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024.
75. Arda, O.; Göksügür, N.; Tüzün, Y. Basic histological structure and functions of facial skin. Clin. Dermatol. 32(1), 3-13. 2014. https://doi.org/10.1016/j.clindermatol.2013.05.021
76. Prost-Squarcioni, C.; et al. Functional histology of dermis. In: Ann. Dermatol. Vénéréol. 2008. 135(1 Pt 2), 1S, 5-20. https://doi.org/10.1016/s0151-9638(08)70206-0
77. Ishida-Yamamoto, A.; et al. Lessons from disorders of epidermal differentiation-associated keratins. Histol. Histopathol. 2002, 17, 815-822. https://doi.org/10.14670/HH-17.331
78. Khavkin, J.; Ellis, D.A.; Aging skin: histology, physiology, and pathology. Facial Plastic Surgery Clinics of North America, 2011, 19(2), 229-234. https://doi.org/10.1016/j.fsc.2011.04.003
79. Ross, M.H.; Pawlina, W. Histologia: Texto e Atlas Color com Biologia Celular e Molecular. 5. edn. Buenos Aires: Médica Panamericana, 2015.
80. Gartner, L.P.; Hiatt, J.L. Texto Atlas de Histología. 3. Edn. Cidade do México: McGraw-Hill, 2015.
81. Agarwal, S.; Krishnamurthy, K. Histology, Skin. 1 maio 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. https://doi.org/10.7282/t3-kvx1-5747
82. Prost-Squarcioni, C. Histologie de la peau et des follicules pileux. Méd. Sci. 2006. 22(2), 131-137, https://doi.org/10.1051/medsci/2006222131
83. Gorgoulis, V.; et al. Cellular senescence: defining a path forward. Cell. 2019, 179(4), 813-827. https://doi.org/10.1016/j.cell.2019.10.005
84. González-Puertos, V.Y.; et al. Participación del fenotipo secretor de las células senescentes en el desarrollo del cáncer, el envejecimiento y las enfermedades asociadas a la edad. Gac. Méd. México. 2015, 151(4), 491-500.
85. Muñoz-Espín, D.; Serrano, M. Cellular senescence: from physiology to pathology. Nat. Rev. Mol. Cell Biol. 2014, 15(7), 482-496. https://doi.org/10.1038/nrm3823
86. De Magalhães, S.; Pedro, E. The impact of MAO-A in cellular senescence. 2014. Tese (Doutorado) – Universidade de Coimbra, Coimbra, Portugal, 2014.
87. Burton, D.G.A.; Krizhanovsky, V. Physiological and pathological consequences of cellular senescence. Cell. Mol. Life Sci. 2014, 71, 4373-4386. https://doi.org/10.1007/s00018-014-1691-3
88. Dimri, G.P.; et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proceed. Nat. Acad. Sci. 92(20), 1995, 9363-9367. https://doi.org/10.1073/pnas.92.20.9363
89. Adamus, J.; et al. p16INK4A influences the aging phenotype in the living skin equivalent. J. Investigat. Dermatol. 2014, 134(4), 1131-1138. https://doi.org/10.1038/jid.2013.468
90. Waaijer, M.E.C. et al. The number of p16INK4a positive cells in human skin reflects biological age. Aging Cell. 2012, 11(4), 722-725. https://doi.org/10.1111/j.1474-9726.2012.00837.x
91. Oliveira, D.; Félix, P.; et al. Tecnologia para a qualidade de vida: a pele e as células-tronco. ID on line: Revista de Psicologia. 2013, 7(19), 103-108. https://doi.org/10.14295/idonline.v7i19.228
92. Zorzanelli, R.T.; et al. Stem cell research in Brazil: the production of a new field of science. História, Ciências, Saúde-Manguinhos. 2017, 24(1), 129-144. https://doi.org/10.1590/S0104-59702016005000026
93. Forni, M.F.D. Bases moleculares da depleção de glutationa sobre a pontencialidade, diferenciação e envelhecimento de células-tronco de pele. Tese de Doutorado. Universidade de São Paulo. Universidade de São Paulo, 2013. https://doi.org/10.11606/T.46.2013.tde-10062013-111755
94. Teixeira, I.N.D.; Guariento, M.E. Biologia do envelhecimento: teorias, mecanismos e perspectivas. Ciência & Saúde Coletiva. 2010, 15, 2845-2857. DOI: 10.1590/S1413-81232010000600022
95. Campisi, J. Aging, cellular senescence, and cancer. Ann. Rev. Physiol. 2015, 77, 1-28. https://doi.org/10.1146/annurev-fisiol-030212-183653
96. Rodier, F.; Campisi, J. Four faces of cellular senescence. J. Cell Biol. 2015, 205(5), 635-644. https://doi.org/10.1083/jcb.201009094
97. Serafim, A.L.; Silva, K.S.O.; Bozzi, A. Senescência das células-tronco mesenquimais para proposta

terapêutica. Rev. Brasil. Edu. Saúde Bem-estar. 2022, 1(2), 1-15. https://doi.org/10.29327/2335218.1.2-9

98. Guadix, J.A.; Zugaza, J.L.; Gálvez-Martín, P. Characteristics, applications and prospects of mesenchymal stem cells in cell therapy. Med. Clín. (English Edition), 2017, 148, (9), 408-414. https://doi.org/10.1016/j.medcle.2017.04.018
99. Campisi, J. Cancer, aging and cellular senescence. In Vivo. 2014, 28(6), 941-951. https://doi.org/10.1146/annurev-physiol-030212-183653
100. Kim, S.H.; Kaminker, P.; Campisi, J. Telomeres, aging and cancer: in search of a happy ending. Oncogene. 2015, 34(25), 3126-3134. https://doi.org/10.1038/sj.onc.1205077
101. Campisi, J. From cells to organisms: can we learn about aging from cells in culture? Exp. Gerontol. 2001, 36(4–6), 607-618. https://doi.org/10.1016/s0531-5565(00)00230-8.
102. Alberts, B. et al. Biologia Molecular da Célula. 6. ed. Porto Alegre: Artmed, 2017. ISBN 9780815344322.
103. Amaral, C.P. Amaral, E.P.; Reuter, C.P. Metabolismo celular, genética e estilo de vida. VI Seven International Multidisciplinary Congress, 2024. https://doi.org/10.56238/sevenVImulti2024-107
104. Childs, B.G.; et al. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nat. Med. 2015, 21(12), 1424-1435. https://doi.org/10.1038/nm.4000
105. Suhre, T. Senescência celular induzida pelo tratamento combinado de resveratrol e quercetina com butirato de sódio em glioblastomas. 2012. Dissertação (Mestrado) – Universidade Federal de São Paulo, São Paulo, 2012. https://doi.org/10183/63720
106. Coppé, J.P.; et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008, 6(12), e301. https://doi.org/10.1371/journal.pbio.0060301
107. Chakravarti, D.; Labella, K.A.; Depinho, R.A. Telomeres: history, health, and hallmarks of aging. Cell. 2021, 184(2), 306-322. https://doi.org/10.1016/j.cell.2020.12.028
108. Santos, D., Tersariol, I.L. Bases moleculares da longevidade humana: possibilidade de terapias não medicamentosas na promoção da longevidade. 2021. Tese (Doutorado) – Universidade Fernando Pessoa, Porto, Portugal, 2021.
109. Ferreira, C.P.; et al. Modelagem lógica de senescência celular humana. 2012. Dissertação (Mestrado) – Universidade Federal de São Paulo, São Paulo, 2012.
110. Hasty, P., Christy, B.A. p53 as an intervention target for cancer and aging. Pathobiol. Aging Age Relat. Dis. 2013, *3*(1), 22702. https://doi.org/10.3402/pba.v3i0.22702
111. Ritschka, B.; et al. The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. Gen. Dev. 2017, 31(2), 172-183. https://doi.org/10.1101/gad.290635.116
112. Autexier, C.; Lue, N.F. The structure and function of telomerase reverse transcriptase. Ann. Rev. Biochem. 2015, 84, 1-31. https://doi.org/10.1146/annurev.biochem.75.103004.142412
113. Martínez, P.; Blasco, M.A. Role of shelterin in cancer and aging. Aging Cell. 2015, 14(5), 749-755. https://doi.org/10.1111/j.1474-9726.2010.00596.x
114. Saretzki, G. Telomerase, mitochondria and oxidative stress. Exp. Gerontol. 2015, 71, 4-8. https://doi.org/10.1016/j.exger.2009.05.004
115. Valdes, A.M.; et al. Leukocyte telomere length is associated with cognitive performance in healthy women. Neurobiol. Aging, 2016, 41, 32-39. https://doi.org/10.1016/j.neurobiolaging.2008.07.012
116. Cawthon, R.M.; et al. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet. 2003, 361(9355), 393-395. https://doi.org/10.1016/S0140-6736(03)12384-7
117. Ruivo, A.P. Envelhecimento cutâneo: fatores influentes, ingredientes ativos e estratégias de veiculação. Tese (Doutorado) – Universidade Fernando Pessoa, Porto, Portugal, 2014.
118. Cunha, A.F.; et al. Pele: alterações anatômicas e fisiológicas do nascimento à maturidade. Rev. Saúde em Foco. 2019, 11, 15-30.
119. Bajek, A.; et al. Does aging of mesenchymal stem cells limit their potential application in clinical practice? Aging Clin. Exp. Res. 2015, 24(5), 404-411. https://doi.org/10.1007/BF03654824
120. Pintado B.L.; et al. GSE4 peptide suppresses oxidative and telomere deficiencies in ataxia telangiectasia patient cells. Cell Death Diff. 2019, 26(4), 745-761. https://doi.org/10.1038/s41418-018-0272-7
121. Silva, W.J. Martins, D.F.; Bucalen, C.K. Metabolismo mitocondrial, radicais livres e envelhecimento. Rev. Brasil. Geriat. Gerontol. 2015, 14(3), 441-451. https://doi.org/10.1590/S1809-98232011000300005
122. Codd, V. Common variants near TERC are associated with mean telomere length. Nat. Gen. 2015, 42(3), 197. https://doi.org/10.1038/ng.532.
123. Blackburn, E.H.; Epel, E.S.; Lin, J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. Science. 2015, 350 (6265), 1193-1198. https://doi.org/10.1126/science.aab3389
124. Campisi, J.; D'adda, D.F.F. Cellular senescence: when bad things happen to good cells. Nat. Rev. Mol. Cell

Biol. 2007, 8(9), 729-740. https://doi.org/10.1038/nrm2233

125. De Lange, T. Telomere-related genome instability in cancer. Cold Spring Harbor Symp. Quant. Biol. 2005, 70, 197-204. https://doi.org/10.1101/sqb.2005.70.032
126. Wright, W.E.; Shay, J.W. Telomere dynamics in cancer progression and prevention: fundamental differences in human and mouse telomere biology. Nat. Med. 2000, 6, 849-851. https://doi.org/10.1038/78592
127. Panich, U.; et al. Ultraviolet radiation-induced skin aging: the role of DNA damage and oxidative stress in epidermal stem cell damage mediated skin aging. Stem Cells Intern. 2016, 1, 7370642. https://doi.org/10.1155/2016/7370642
128. Jennings, B.J.; Ozanne, S.E.; Hales, C.N. Nutrition, oxidative damage, telomere shortening, and cellular senescence: individual or connected agents of aging? Mol. Gen. Metabol. 2000, 71(1-2), 32-42. https://doi.org/10.1006/mgme.2000.3077
129. Baur, J.A.; Sinclair, D.A. Therapeutic potential of resveratrol: the *in vivo* evidence. Nat. Rev. Drug Dis. 2006, 5(6), 493-506. https://doi.org/10.1038/nrd2060
130. Zhang, S.; Duan, E. Fighting against skin aging: the way from bench to bedside. Cell Tran. 2018, 27(5), 729-738. https://doi.org/10.1177/0963689717725755
131. Pereira, C.A.C.; et al. Mecanismos fisiopatológicos do envelhecimento. 2015. Dissertação de Mestrado.
132. Smith, S. Telomerase can't handle the stress. Gen Dev. 2018, 32, 597-599. https://doi.org/10.316/30643 10.1101/gad.316042.118
133. Wang, Y., Sušac, L., Feigon, J. Structural Biology of Telomerase. Cold Spring Harbor Persp. Biol. 2018, 11(12), a032383. https://doi.org/10.316/3064310.1101/cshperspect.a032383
134. Sahin, E., Colla, S., Liesa, M.; et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature, 2011, 470 (7334), 359-365. https://doi.org/10.316/3064310.1038/nature09787
135. Maciejowski, J.; De, L.T. Telomeres in cancer: tumour suppression and genome instability. Nat. Rev. Mol. Cell Biol. 2017, 18(3), 175-186. https://doi.org/10.316/3064310.1038/nrm.2016.171
136. Deng, Y.; Chang, S. Role of telomeres and telomerase in genomic instability, senescence and cancer. Lab. Invest. 2007, 87, 11, 1071-1076. https://doi.org/10.1038/labinvest.3700673

https://doi.org/10.56717/jpp.2024.v03i02.027