Cellular Senescence, Aging, and Cancer: Molecular Pathways and Emerging Therapeutic Interventions

[1]Emmanuel Olanrewaju Adebayo., [1]Blessing Adeola Fadola., [2]Oluwadayomi Adedeji., [3]Imoleayo Moses Olorunyolemi

[1]Federal University of Technology Akure, Nigeria

[2]Africa Research Institute of Technology Osun State, Nigeria

[3]North Carolina Agricultural and Technical State University, Greensboro USA

DOI: https://doi.org/10.51584/IJRIAS.2025.10050020

Received: 02 May 2025; Accepted: 09 May 2025; Published: 31 May 2025

ABSTRACT

The global biological process of aging is marked by a slow deterioration in physiological and cellular processes, which makes people more vulnerable to degenerative diseases, including cancer. Scientists are growing more interested in the molecular pathways that connect aging and carcinogenesis as life expectancy increases worldwide, and aging-related malignancies become more common. Cellular senescence, a stress-induced, irreversible growth arrest condition, is a key element of this connection. Senescent cells are initially beneficial because they stop damaged cells from proliferating, but with time, they build up and create a pro-inflammatory environment called the senescence-associated secretory phenotype (SASP), which encourages tissue malfunction and cancer in older people. According to López-Otín et al. (2013), aging is driven by nine interconnected hallmarks: genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion, cellular senescence, and altered intercellular communication. These hallmarks disrupt cellular homeostasis, fostering an environment conducive for tumor growth and development. However, over time, small interventions have emerged, resolving some of these issues, developing new avenues for solutions, or modifying the ones that already exist. This journal delves further into these aging processes, emphasizing how they contribute to the development and spread of aging related diseases with a major look at cancer. It also examines new treatments that target these pathways to postpone aging-related illnesses, such as lifestyle changes and senolytic medications which prevent senescence expression. In the end, the study promotes a multidisciplinary strategy to prolong life expectancy and lessen the impact of age-related malignancies.

Keywords: Aging, Age-related diseases, Cancer, senescence and interventions.

INTRODUCTION

Many questions have surrounded the term aging, although we age every day, there has been reason for people to believe that certain diseases come with aging, research has shown that different types of diseases always accompany aging. (Guo et al. 2022).

Aging is a fundamental biological process that affects all living organisms, characterized by a progressive decline in cellular and systemic functions. This decline is often accompanied by an increased susceptibility to chronic diseases, including cancer, cardiovascular diseases, and neurodegenerative conditions (Guo et al., 2022). As life expectancy continues to increase globally, the prevalence of aging-related cancers has surged, placing immense pressure on healthcare systems and spurring scientific interest in understanding the mechanisms that underpin the relationship between aging and cancer.

Central to this relationship is the concept of cellular senescence, a state of irreversible cell cycle arrest triggered by stressors such as DNA damage, telomere shortening, oxidative stress, and oncogene activation

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

(McHugh & Gil, 2018). While senescence serves as a natural tumor-suppressive mechanism by preventing the proliferation of damaged cells, its chronic accumulation in tissues contributes to a pro-inflammatory environment known as the senescence-associated secretory phenotype (SASP). This environment fosters tissue dysfunction and promotes tumorigenesis, particularly in older individuals (Wyld et al., 2020).

From a molecular perspective, the aging process is governed by several interconnected mechanisms, often referred to as the hallmarks of aging (López-Otín et al., 2013). These include genomic instability, telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion, and altered intercellular communication. Each of these hallmarks contributes to cellular dysfunction, creating conditions that facilitate the initiation and progression of cancer. For example, telomere shortening limits the replicative capacity of cells, leading to cellular senescence, while genomic instability increases the likelihood of mutations that drive tumorigenesis (McHugh & Gil, 2018).

In recent years, significant progress has been made in identifying interventions that target the aging process to mitigate cancer risks. senolytic therapies, which selectively eliminate senescent cells, have emerged as a promising approach for reducing age-related inflammation and improving tissue function (Wyld et al., 2020). Additionally, lifestyle interventions such as caloric restriction, antioxidant supplementation, and exercise have been shown to delay the onset of aging-related diseases, including cancer (Guo et al., 2022).

Despite these advances, many challenges remain. The complex interplay between aging, senescence, and cancer requires a multidisciplinary approach that integrates insights from molecular biology, oncology, geriatrics, and epidemiology. This paper aims to look at major senescence pathway, possible alteration to sensescence, Key interventions and progress, which end goal will be to prevent aging related diseases to increase human life span.

Senescence and Aging

Cellular senescence is a complex biological process that serves as both a protective and pathological mechanism. It involves a stable cell cycle arrest in response to various forms of stress, such as DNA damage, oxidative stress, or oncogene activation, preventing damaged cells from proliferating. However, as organisms age, senescent cells begin to accumulate, primarily because of impaired clearance mechanisms. This buildup becomes detrimental, as these cells secrete pro-inflammatory factors known as the senescence-associated secretory phenotype (SASP), which drive chronic inflammation, disrupt tissue structure, and contribute to age-related diseases and functional decline.

McHugh and Gil (2018) emphasize that the most effective window for targeting senescence lies in midlife (approximately ages 40–60), when the body still retains enough regenerative capacity to recover from intervention. This period provides an opportunity to remove harmful senescent cells or modulate their activity before irreversible damage occurs, without disrupting the protective roles senescence plays in younger individuals, such as guarding against cancer.

If targeted too early, senescence interventions could undermine the body's natural tumor-suppressive functions. On the other hand, delaying treatment until old age may allow the accumulation of senescent cells to inflict irreversible harm. Thus, precise timing is crucial. As highlighted by Baker et al. (2016), monitoring biomarkers such as p16^INK4A, p21^CIP1, and specific SASP components offers a practical means of assessing senescent cell burden. These molecular indicators help clinicians identify not only who would benefit from senescence-targeting therapies like senolytics (which eliminate senescent cells) or senomorphics (which suppress their harmful effects), but also when to administer them for maximum benefit.

By tailoring therapeutic interventions to an individual's biological state rather than relying solely on chronological age, it becomes possible to mitigate age-related degeneration, enhance tissue repair, and preserve the beneficial roles of senescence in processes such as wound healing and cancer prevention.

Mechanism of Aging

According to López-Otín et al. (2013), aging can be defined by nine interrelated hallmarks that contribute to the progressive deterioration of cellular homeostasis and functionality. These includes; genomic instability,

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

telomere attrition, epigenetic alterations, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion, cellular senescence, and altered intercellular communication all interact to drive the aging process as this are also major trigger element of senescence. Understanding these mechanisms provides insight into how senescence and aging predisposes individuals to diseases, particularly cancer.

Genomic Instability

One of the defining features of aging is the accumulation of DNA damage over time, a phenomenon referred to as genomic instability. In both somatic and germ cells, endogenous factors such as oxidative stress and exogenous factors such as ultraviolet (UV) radiation and chemical mutagens cause breaks in DNA strands and mutations (Guo et al., 2022). The accumulation of unrepaired DNA damage compromises genomic integrity, leading to cellular dysfunction and increased susceptibility to cancer.

Studies have shown that key DNA damage response (DDR) pathways, such as those involving p53 and ATM/ATR, become less efficient with age (McHugh & Gil, 2018). Persistent DNA damage activates these pathways, triggering apoptosis or senescence to prevent the proliferation of damaged cells. However, the chronic activation of senescence also promotes inflammation and tissue degeneration.

Telomere Attrition

Telomeres, composed of repetitive nucleotide sequences, cap the termini of chromosomes to preserve genomic stability by preventing enzymatic degradation and aberrant chromosomal fusions. With each cell division, telomeres shorten due to the inability of DNA polymerase to fully replicate the ends of linear DNA strands, a phenomenon known as the end-replication problem (McHugh & Gil, 2018).

In young, healthy cells, telomerase, an enzyme that extends telomeres, counteracts this shortening. However, telomerase activity declines in most somatic cells with age, leading to progressive telomere attrition (Guo et al., 2022). Critically shortened telomeres elicit a DNA damage response that promotes cellular senescence or initiates apoptotic pathways. This is a protective mechanism against uncontrolled proliferation, such as in the case of cancer.

Telomere attrition is a key driver of both aging and cancer. For example, shortened telomeres have been observed in patients with age-related diseases, including idiopathic pulmonary fibrosis and liver cirrhosis (McHugh & Gil, 2018). In contrast, the reactivation of telomerase in cancer cells enables them to bypass senescence and achieve unlimited replication.

Epigenetic Alterations

Epigenetics encompasses heritable modifications in gene expression that occur independently of alterations to the DNA sequence. These changes, which include DNA methylation, histone modification, and chromatin remodeling, play a crucial role in regulating cellular processes such as differentiation, proliferation, and DNA repair (Guo et al., 2022).

As cells age, they undergo epigenetic drift, characterized by global DNA hypomethylation and site-specific hypermethylation at promoter regions. Such disruption impairs the expression of genes critical for cell cycle regulation, DNA repair mechanisms, and apoptotic processes.

For instance, the silencing of tumor suppressor genes through hypermethylation has been implicated in the development of several cancers (Wyld et al., 2020).

Additionally, aging is associated with alterations in histone acetylation and methylation patterns. These changes affect chromatin structure, leading to the loss of heterochromatin and genomic instability. Recent studies have shown that interventions such as caloric restriction and histone deacetylase inhibitors can reverse some of these epigenetic changes, highlighting their potential as anti-aging therapies.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

Mitochondrial Dysfunction

Mitochondria, the powerhouse of the cell, are central to energy production through oxidative phosphorylation. However, mitochondrial function declines with age due to the accumulation of mutations in mitochondrial DNA (mtDNA) and oxidative damage caused by reactive oxygen species (ROS) (McHugh & Gil, 2018).

Reactive oxygen species (ROS), generated as byproducts of mitochondrial respiration, can induce damage to lipids, proteins, and DNA within the cell. While low levels of ROS play a role in signaling and homeostasis, excessive ROS production contributes to aging and age-related diseases (Guo et al., 2022). Mitochondrial dysfunction not only reduces cellular energy production,also exacerbates oxidative stress, creating a vicious cycle that accelerates aging. Research has identified several interventions that target mitochondrial health, such as antioxidants and mitochondrial-targeted drugs. For example, the administration of coenzyme Q10 and NAD+ precursors has shown promise in restoring mitochondrial function and delaying aging in preclinical models.

This decline in mitochondrial function and the resulting increase in oxidative stress do not only affect aging tissues but also contribute significantly to the tumor microenvironment (TME), particularly in cancers like breast cancer.

Case study: breast cancer

Breast cancer is one of the most common malignancies in women, with incidence rates significantly increasing after the age of 50. Studies show that aging-associated changes in the tumor microenvironment (TME) play a critical role in breast cancer progression.

In a clinical analysis of breast cancer patients over the age of 65, high levels of p16INK4A, a marker of cellular senescence, were detected in the tumor microenvironment. This accumulation of senescent fibroblasts was found to secrete pro-inflammatory cytokines such as IL-6 and IL-8, contributing to chronic inflammation and tumor growth (Guo et al., 2022). Additionally, the senescence-associated secretory phenotype (SASP) altered the extracellular matrix, facilitating cancer cell invasion and metastasis.

The study also revealed that aging-related immunosenescence reduced the ability of T cells to target tumor cells effectively, further worsening prognosis. These findings highlight the need for therapies that target senescence-associated inflammation, such as senostatics, to improve outcomes for older breast cancer patients.

Case Study: Lung Cancer

In one case study, an 80-year-old male lung cancer patient underwent radiation therapy, leading to initial tumor remission. However, within two years, the patient experienced tumor recurrence with more aggressive phenotypes. Post-mortem analysis revealed high levels of senescence markers, including p16INK4A and p21, in the recurrent tumor tissue. The presence of SASP-associated cytokines, such as IL-6 and TNF-α, contributed to an inflammatory tumor microenvironment that facilitated relapse (McHugh & Gil, 2018).

Cellular Senescence

Cellular senescence is a stable state of cell cycle arrest that occurs in response to various intrinsic and extrinsic stressors. Initially identified as a mechanism to limit the replicative capacity of normal cells via telomere shortening (Shay & Wright, 2005), senescence is now recognized as a multifaceted process involved in tumor suppression, tissue remodeling, and aging. Key triggers include DNA damage, oxidative stress, oncogene activation, and mitochondrial dysfunction (d'Adda di Fagagna, 2008; Wiley et al., 2016). Senescent cells exhibit distinct features such as chromatin remodeling, metabolic reprogramming, and the secretion of pro-inflammatory cytokines known as the senescence-associated secretory phenotype (SASP) (Coppe et al., 2010). Central to the regulation of this process are the p53/p21^CIP1 and p16^INK4a/Rb pathways, which mediate growth arrest and reinforce the senescent phenotype (Campisi & d'Adda di Fagagna, 2007). Beyond its role in physiological aging, cellular senescence contributes to the depletion of regenerative capacity in tissues through

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

stem cell exhaustion and disrupted intercellular signaling. Furthermore, its paradoxical roles in cancer suppression and progression underscore its relevance in both health and disease contexts.

Stem Cell Exhaustion and Intercellular Communication

Stem cells are fundamental to tissue homeostasis and the facilitation of repair mechanisms. Hematopoietic stem cells (HSCs) in the bone marrow lose their ability to regenerate the blood system, leading to immunosenescence and anemia (McHugh & Gil, 2018). Similarly, mesenchymal stem cells and neural stem cells show reduced functionality with age, contributing to tissue degeneration.

Inflammaging, driven by SASP factors such as IL-6 and TNF-α, disrupts intercellular communication and promotes chronic inflammation, contributing to tissue dysfunction and age-related diseases (Wyld et al., 2020).

Senescent cells retain metabolic activity and undergo notable phenotypic alterations, including chromatin remodeling, metabolic reprogramming, and the secretion of inflammatory cytokines, growth factors, and proteolytic enzymes. This secretion collectively form the senescence-associated secretory phenotype (SASP), which plays a paradoxical role in cancer development (Wyld et al., 2020).

Although senescence contributes to aging and inflammation, it also plays critical roles in cancer biology. Notably, it has both tumor-suppressive and therapy-related implications, as explored below

Tumor-Suppressive Role of Senescence

Senescence serves as a natural barrier to tumorigenesis by halting the proliferation of cells that have acquired oncogenic mutations. For instance, activation of tumor suppressor pathways such as p53/p21 and p16INK4A/Rb enforces senescence in response to DNA damage, preventing the replication of damaged cells (Guo et al., 2022).

Senescence is particularly critical during early cancer development, where it acts as a checkpoint to suppress malignant transformation. Studies indicated that the loss of senescence-inducing pathways, such as p53 mutations, is a hallmark of advanced cancers (McHugh & Gil, 2018).

Benefits and Challenges of the Tumor-Suppressive Role of Senescence

Senescence acts as a critical tumor-suppressive mechanism by halting the proliferation of damaged or mutated cells, thereby preventing cancer initiation. This is mediated through tumor suppressor pathways like p53/p21 and p16^INK4a/Rb (Campisi & d'Adda di Fagagna, 2007). However, while senescent cells prevent tumor growth initially, their accumulation can contribute to chronic inflammation through the senescence-associated secretory phenotype (SASP), which may promote cancer progression and metastasis (Wyld et al., 2020). Additionally, the evasion of senescence, particularly in cases of p53 mutations, is a key factor in cancer development and progression (McHugh & Gil, 2018).

Therapy-Induced Senescence (Tis)

While cellular senescence is primarily associated with aging, it can also be induced by cancer treatments such as chemotherapy, radiotherapy, and targeted therapies. This phenomenon, referred to as therapy-induced senescence (TIS), presents a dual role in the field of oncology.

Benefits of TIS

TIS is beneficial in the short term, as it halts the proliferation of cancer cells by inducing a state of growth arrest. Studies have shown that drugs such as doxorubicin and etoposide induce senescence in cancer cells by activating DDR pathways and triggering p53-mediated growth arrest (McHugh & Gil, 2018).

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

Challenges of TIS

However, the persistence of senescent cells following therapy poses significant challenges. Senescent cancer cells may escape growth arrest, leading to tumor relapse or the emergence of more aggressive cancer phenotypes. Additionally, the SASP secreted by therapy-induced senescent cells can promote inflammation, immunosuppression, and resistance to subsequent therapies (Wyld et al., 2020).

For instance, a case study involving lung cancer patients treated with radiotherapy showed tumor remission followed by recurrence within two years. Analysis revealed high levels of senescence markers such as p16INK4A, suggesting that TIS contributed to relapse (Guo et al., 2022).

Senescence-Associated Secretory Phenotype (SASP)

The SASP is a defining feature of senescent cells and plays a critical role in the interaction between aging, senescence, and cancer. The SASP consists of a diverse array of secreted factors, including:

Pro-inflammatory cytokines: IL-6, IL-8, and TNF-α

Growth factors: VEGF and HGF, which promote angiogenesis and tumor growth.

Proteases: MMPs that degrade the extracellular matrix and facilitate cancer cell invasion.

Case Study: Prostate Cancer and the Role of SASP

Prostate cancer is another malignancy strongly associated with aging. Older men exhibit higher levels of chronic inflammation, driven in part by the SASP secreted by senescent cells in the prostate tissue.

A longitudinal study involving prostate cancer patients aged 60 and above found that senescent stromal cells in the tumor microenvironment secreted growth factors such as VEGF and HGF, which promoted angiogenesis and tumor proliferation (Wyld et al., 2020). Furthermore, matrix metalloproteinases (MMPs) released by senescent fibroblasts degraded the extracellular matrix, enabling cancer cell migration and invasion.

These findings emphasize the importance of senolytic therapies, such as dasatinib and quercetin, to selectively eliminate senescent cells and reduce tumor progression in older patients.

Interventions Targeting Senescence

Senescence, a critical driver of aging and age-related diseases, can be modulated through various interventions aimed at either eliminating senescent cells or modulating their harmful effects. Emerging research focuses on two major strategies for manipulating senescent cells: senolytics and senostatics:

Senolytics

Senolytics are drugs that selectively target and eliminate senescent cells, potentially reducing the harmful effects they have on tissues and organs. Notable senolytic agents include:

- **Quercetin and Fisetin** – Natural flavonoids that selectively induce apoptosis in senescent cells.
- **Navitoclax (ABT-263)** – A Bcl-2 inhibitor that promotes the clearance of senescent cells.
- **Dasatinib + Quercetin (D+Q)** – A combination therapy targeting senescent fibroblasts.

In preclinical models, senolytic drugs such as **dasatinib** and **quercetin** have been shown to improve tissue function, extend lifespan, and reduce age-related inflammation (Wyld et al., 2020).

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

Senostatics

Unlike senolytics, **senostatics** do not eliminate senescent cells but instead modulate the **senescence-associated secretory phenotype (SASP)** to mitigate its inflammatory and tumor-promoting effects. These include:

- **Metformin** – A widely used anti-diabetic drug that reduces SASP-related inflammation.
- **Rapamycin** – An mTOR inhibitor that enhances autophagy and delays aging-related diseases.

By targeting the inflammatory components of the SASP, senostatics offer a safer alternative, especially for aging populations where extensive senescent cell clearance could be detrimental.

Integration with Cancer Treatments

Senolytic therapy has potential in cancer treatments. Wyld et al. (2020) suggested integrating senolytic drugs with existing cancer therapies to reduce the risk of therapy-induced senescence and tumor relapse. These therapies offer new hope in modulating cancer progression and improving therapeutic outcomes.

Nutritional and Lifestyle Interventions

In addition to pharmacological interventions, lifestyle modifications and dietary interventions have also been shown to delay senescence and reduce cancer risk, further enhancing overall health.

Caloric Restriction (CR)

Caloric restriction, defined as a reduction in caloric intake without malnutrition, has been extensively studied for its ability to:

- Reduce oxidative stress and inflammation.
- Enhance autophagy and DNA repair mechanisms.
- Delay the onset of age-related diseases, including cancer (Guo et al., 2022).

Studies in rodent models have demonstrated that CR not only extends lifespan but also reduces the incidence of spontaneous tumors by up to 40% (Wyld et al., 2020).

Polyphenols and Antioxidants

Several dietary components, such as polyphenols (resveratrol, curcumin, EGCG) and antioxidants (Vitamin C, E, selenium), protect cells from oxidative stress and reduce inflammation, helping to extend cellular lifespan and prevent cancer. These compounds exhibit anti-inflammatory and anti-cancer properties, promoting overall health and longevity (Guo et al., 2022).

Exercise and Physical Activity

Regular physical activity contributes to healthy aging by improving cardiovascular health, reducing inflammation, and enhancing immune function. It also positively affects the tumor microenvironment (TME), improving tissue oxygenation and reducing insulin resistance, which in turn inhibits cancer progression (McHugh & Gil, 2018).

Experimental Interventions and Emerging Therapies

Experimental approaches are also being explored to target senescence and improve health outcomes. For example:

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

- **Fecal Microbiota Transplantation (FMT)** is being studied for its potential to reduce systemic inflammation by modulating the gut microbiome (Bajaj et al., 2017).

- **Senescence Vaccines**, aimed at targeting senescent cell antigens, are being developed to enhance immune clearance of senescent cells (Kim et al., 2022).

These experimental therapies highlight the growing range of potential strategies to mitigate senescence's effects, particularly in aging populations at risk for cancer and other age-related diseases.

Implications for Precision Medicine

As our understanding of senescence and its role in aging and cancer deepens, precision medicine can play a critical role in tailoring treatments for aging populations. By integrating senescence-targeting therapies, lifestyle interventions, and biomarker-based screening, personalized treatment approaches can be developed to optimize outcomes for older patients at risk of cancer. Recent studies have shown that senolytic drugs like dasatinib and quercetin are effective in improving tissue function and reducing systemic inflammation in aging animal models, offering promise for future clinical trials (Zhu et al., 2015).

Additionally, senomorphic compounds, which modulate the SASP without eliminating senescent cells, provide an alternative to senolytics. These compounds, including metformin and rapamycin, reduce inflammation and enhance autophagy, reducing the pathologies driven by senescence (Childs et al., 2017).

Lifestyle interventions such as caloric restriction, intermittent fasting, and regular physical activity also remain essential in reducing the burden of senescent cells and supporting overall metabolic health (Lopez-Otin et al., 2016).

Key Molecular Regulators to Senescence and Aging

Several molecular pathways have been recognized as major drivers of senescence and aging. These pathways present promising opportunities for developing drug and gene therapies to promote healthier aging.

1. The p53 Tumor Suppressor Pathway

The p53 pathway plays a crucial role in how cells respond to stress, helping to maintain a balance between preventing cancer and influencing aging. Under healthy conditions, p53 halts the growth of damaged cells by triggering cell cycle arrest or apoptosis. However, when DNA damage persists, continuous activation of p53 can push cells into a state of senescence, contributing to tissue breakdown and age-related decline. (Levine & Oren, 2009)

Modulating p53 activity presents a promising approach to delaying senescence while minimizing oncogenic risk. Recent studies have explored p53 isoforms such as p53β and p53γ, which may regulate senescence differently than the canonical p53 pathway (Fujita et al., 2009). MDM2 inhibitors, which enhance p53 stability, are being evaluated for their dual role in cancer prevention and longevity extension. (Andreeff et al., 2016).

2. The mTOR Pathway and Longevity

The mechanistic target of rapamycin (mTOR) pathway, which controls cellular growth and metabolism, has emerged as a crucial determinant of lifespan. mTORC1 hyperactivation has been linked to accelerated aging, whereas its inhibition via compounds like rapamycin has been shown to extend lifespan in yeast, worms, flies, and mice. (Johnson et al., 2013)

Pharmacological inhibition of mTOR, particularly through rapamycin and everolimus, reduces cellular stress, enhances autophagy, and improves metabolic efficiency (Lamming et al., 2013). These findings have led to clinical trials investigating the potential of rapalogs (rapamycin analogs) in delaying human aging and treating age-related diseases such as Alzheimer's and cardiovascular disorders. (Kraig et al., 2018).

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

3. Sirtuins and Epigenetic Control of Aging

Sirtuins, a family of NAD+-dependent deacetylases, play a pivotal role in regulating genomic stability, mitochondrial function, and stress resistance (Guarente, 2011). The activation of SIRT1 has been associated with increased lifespan in multiple organisms, with studies showing that NAD+ supplementation via precursors like nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) restores mitochondrial function and enhances cellular resilience. (Gomes et al., 2013)

Emerging research suggests that SIRT6 activation may be particularly beneficial in combating aging and cancer. SIRT6 regulates DNA repair, telomere maintenance, and inflammation, making it a key target for longevity interventions (Tasselli et al., 2017). Small-molecule SIRT6 activators, such as MDL-800, have been identified as potential therapeutics for delaying age-related diseases. (Pan et al., 2021).

Substantial Progress in the Field

Several critical pathways have contributed to the progress in understanding and managing senescence and aging. Although significant strides have been made, ongoing research continues to refine these approaches to achieve a balance between lifespan extension and the preservation of cellular integrity. The major contributing pathways include:

CRISPR-based Senescence Clearance: Gene-editing technologies are being explored to selectively remove senescent cells by targeting senescence-associated markers such as p16INK4A and p21. These approaches hold promise for precise senescence modulation and have been demonstrated in preclinical models (Xie et al., 2021). Recent innovations in CRISPR/Cas9 and gene-targeting systems are enabling targeted clearance of senescent cells without harming normal tissue (Zhu et al., 2022).

Senescence-Associated Biomarkers for Early Detection: The identification of circulating senescence biomarkers, such as GDF15, SA-β-gal, and inflammatory cytokines, enables early diagnosis of aging-related diseases and personalized interventions (Kirkland et al., 2017). These markers are being studied in the context of both systemic inflammation and localized tissue aging, improving risk stratification and monitoring of therapeutic responses (Wiley et al., 2016).

Artificial Intelligence in Aging Research: AI-driven drug discovery platforms are accelerating the identification of novel senolytic and senomorphic compounds (Zhavoronkov et al., 2019), improving drug repurposing strategies for age-related diseases. (Chen et al., 2021).

Microbiome and Aging: Studies suggest that gut microbiota composition influences aging and immune function. Probiotic and prebiotic interventions targeting microbiome dysbiosis may help mitigate senescence-associated inflammation (O'Toole & Jeffery, 2015). Experimental models show that microbial metabolites like short-chain fatty acids can modulate aging pathways (Thevaranjan et al., 2017).

3D Organoids for Senescence Research – The development of 3D organoid models mimicking aging tissues allows for better screening of anti-senescence compounds and understanding tissue-specific aging mechanisms. (Horvath et al., 2022).

CONCLUSION

The interplay between cellular senescence and cancer has emerged as a transformative axis in modern biomedical research. Therapeutic strategies now target senescent cells either by eliminating them (senolytics), modulating their harmful secretions (senostatics), or enhancing immune clearance through immunotherapy. The integration of novel technologies, such as CRISPR gene-editing, senescence biomarkers, microbiome interventions, and AI-driven drug discovery is accelerating progress in early diagnosis and treatment.

Research on the relationship between aging, senescence, and cancer is advancing rapidly. Some of the key areas of exploration include:

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

1. Targeting SASP to Reduce Cancer Risk

Developing drugs that block the pro-inflammatory secretions of senescent cells without affecting their tumor-suppressive functions.

2. Senescence-Based Cancer Therapies

Using controlled senescence induction to halt tumor progression while preventing therapy-induced relapse.

3. Genetic and Epigenetic Interventions

CRISPR-based approaches to modify senescence-related genes and restore youthful cell function.

4. Personalized Anti-Aging and Cancer Prevention Plans

Biomarker-based screening to predict and delay age-related cancers through lifestyle and pharmacological interventions.

The development of senescence-targeting interventions—ranging from pharmacological treatments to lifestyle modifications—offers promising avenues to combat aging and cancer. Combining these strategies could significantly enhance the quality of life and extend healthy aging, particularly when personalized within the framework of precision medicine. Future directions will involve fine-tuning these interventions to avoid adverse effects and tailoring therapies for individual patient profiles. Furthermore, expanding our understanding of tissue-specific senescence and its role in tumor microenvironments will be crucial in advancing precision oncology.

REFERENCES

1. Andreeff, M., Kelly, K. R., Yee, K., et al. (2016). Results of the phase I trial of RG7112, a small-molecule MDM2 antagonist in leukemia. Clinical Cancer Research, 22(4), 868–876.
2. Baker, D. J., Childs, B. G., Durik, M., Wijers, M. E., Sieben, C. J., Zhong, J., ... & van Deursen, J. M. (2016). Naturally occurring p16^Ink4a-positive cells shorten healthy lifespan. Nature, 530(7589), 184–189.
3. Bajaj, J. S., Kassam, Z., Fagan, A., Gavis, E. A., Liu, E., & Fuchs, M. (2017). Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology, 66(6), 1727–1738. https://doi.org/10.1002/hep.29306
4. Belsky, D. W., Caspi, A., Arseneault, L., Baccarelli, A., Corcoran, D. L., Gao, X., ... & Moffitt, T. E. (2020). Quantification of biological aging in young adults. Proceedings of the National Academy of Sciences, 117(15), 8491–8497.
5. Bhatt, V., & Tiwari, A. K. (2022). Sirtuins, a key regulator of ageing and age-related neurodegenerative diseases. International Journal of Neuroscience, 1–26. https://doi.org/10.1080/00207454.2022.2057849
6. Campisi, J., & d'Adda di Fagagna, F. (2007). Cellular senescence: When bad things happen to good cells. Nature Reviews Molecular Cell Biology, 8(9), 729–740.
7. Chang, A. R., Ferrer, C. M., & Mostoslavsky, R. (2020). SIRT6, a mammalian deacylase with multitasking abilities. Physiological Reviews, 100(1), 145–169. https://doi.org/10.1152/physrev.00030.2018
8. Chen, Q., Liu, K., Robinson, A. R., et al. (2019). DNA damage drives accelerated aging through NF-κB-mediated transcriptional activation of senescence markers. Aging Cell, 18(1), e12828.
9. Childs, B. G., Gluscevic, M., Baker, D. J., Laberge, R. M., Marquess, D., Dananberg, J., & van Deursen, J. M. (2015). Senescent cells: An emerging target for diseases of ageing. Nature Reviews Drug Discovery, 14(10), 719–735.
10. Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. New England Journal of Medicine, 372(9), 793–795. https://doi.org/10.1056/NEJMp1500523

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue V May 2025

11. Coppe, J. P., Patil, C. K., Rodier, F., et al. (2010). A human-like senescence-associated secretory phenotype is conserved in mouse cells dependent on physiological oxygen. PLoS ONE, 5(2), e9188. https://doi.org/10.1371/journal.pone.0009188
12. d'Adda di Fagagna, F. (2008). Living on a break: Cellular senescence as a DNA-damage response. Nature Reviews Cancer, 8(7), 512–522. https://doi.org/10.1038/nrc2440
13. Dutta, D., Heo, I., & Clevers, H. (2020). Organoid culture systems to study host–pathogen interactions. Current Opinion in Immunology, 66, 41–49.
14. Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. The Journals of Gerontology: Series A, 59(3), M255–M263.
15. Fujita, K., Mondal, A. M., Horikawa, I., et al. (2009). p53 isoforms Delta133p53 and p53β are endogenous regulators of replicative cellular senescence. Nature Cell Biology, 11(9), 1135–1142. https://doi.org/10.1038/ncb1928
16. Gomes, A. P., Price, N. L., Ling, A. J. Y., et al. (2013). Declining NAD+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell, 155(7), 1624–1638.
17. Guarente, L. (2011). Sirtuins, aging, and medicine. New England Journal of Medicine, 364(23), 2235–2244.
18. Guo, J., Li, J., Chen, H., et al. (2022). Aging and aging-related diseases: From molecular mechanisms to interventions and treatments. Signal Transduction and Targeted Therapy, 7, 391.
19. Harrison, D. E., Strong, R., Sharp, Z. D., et al. (2009). Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature, 460(7253), 392–395.
20. Horvath, S. (2013). DNA methylation age of human tissues and cell types. Genome Biology, 14(10), R115.
21. Imai, S., & Guarente, L. (2016). It takes two to tango: NAD+ and sirtuins in aging and disease. Trends in Cell Biology, 26(8), 576–586.
22. Johnson, S. C., Rabinovitch, P. S., & Kaeberlein, M. (2013). mTOR is a key modulator of ageing and age-related disease. Nature, 493(7432), 338–345.
23. Justice, J. N., Nambiar, A. M., Tchkonia, T., et al. (2018). Senolytics in aging: A new therapeutic opportunity. Translational Medicine of Aging, 2, 1–11.
24. Kang, C. (2019). Senolytics and senostatics: A two-pronged approach to target cellular senescence for delaying aging and age-related diseases. Molecules and Cells, 42(12), 821–827. https://doi.org/10.14348/molcells.2019.0298
25. Kim, K. M., Noh, J. H., Bodogai, M., Martindale, J. L., Yang, X., Indig, F. E., ... & Campisi, J. (2022). Aged senescent cells reprogram their secretory phenotype via PGE2 signaling to promote age-related pathology and suppress immune clearance. Nature Aging, 2, 382–398. https://doi.org/10.1038/s43587-022-00202-3.
26. Kirkland, J. L., & Tchkonia, T. (2020). Senolytic drugs: from discovery to translation. Journal of Internal Medicine, 288(5), 518–536
27. Kraig, E., Linehan, L. A., Liang, H., et al. (2018). A randomized study of the effects of rapamycin on cognitive and physical function in older adults. The Journals of Gerontology: Series A, 73(7), 964–971.
28. Kritchevsky D. Caloric restriction and cancer. J. Nutr. Sci. Vitaminol. 2001;47:13–19. doi: 10.3177/jnsv.47.13.
29. Lamming, D. W., et al. (2013). Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. Science, 339(6116), 812–815.
30. Levine, A. J., & Oren, M. (2009). The first 30 years of p53: growing ever more complex. Nature Reviews Cancer, 9(10), 749–758.
31. Lopez-Otin, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2016). The hallmarks of aging: an expanding universe. Cell, 166(4), 802–821.
32. McHugh, D., & Gil, J. (2018). Senescence and aging: Causes, consequences, and therapeutic avenues. Journal of Cell Biology, 217(1), 65–77.
33. Mattson, M. P., (2017). Intermittent metabolic switching, neuroplasticity and brain health. Nature Reviews Neuroscience, 18(2), 63–74.
34. Mattison, J. A., Roth, G. S., Beasley, T. M., et al. (2017). Caloric restriction improves health and survival of rhesus monkeys. Nature Communications, 8, 14063.

35. Mercier BD, Tizpa E, Philip EJ, Feng Q, Huang Z, Thomas RM, Pal SK, Dorff TB, Li YR. Dietary Interventions in Cancer Treatment and Response: A Comprehensive Review. Cancers (Basel). 2022 Oct 20;14(20):5149. doi: 10.3390/cancers14205149
36. Moiseeva, O., Deschenes-Simard, X., St-Germain, E., et al. (2013). Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κB activation. Aging Cell, 12(3), 489–498.
37. O'Toole, P. W., & Jeffery, I. B. (2015). Gut microbiota and aging. Science, 350(6265), 1214–1215.
38. Pan, H., Guan, D., Liu, X., et al. (2021). SIRT6 safeguards human mesenchymal stem cells from oxidative stress by regulating the NRF2 pathway. Redox Biology, 38, 101813
39. Rayburn ER, Ezell SJ, Zhang R. Anti-Inflammatory Agents for Cancer Therapy. Mol Cell Pharmacol. 2009;1(1):29-43. doi: 10.4255/mcpharmacol.09.0
40. Schmitt CA, Wang B, Demaria M. Senescence and cancer - role and therapeutic opportunities. Nat Rev Clin Oncol. 2022 Oct;19(10):619-636. doi: 10.1038/s41571-022-00668-4. Epub 2022 Aug 31. PMID: 36045302
41. Shay, J. W., & Wright, W. E. (2005). Senescence and immortalization: Role of telomeres and telomerase. Carcinogenesis, 26(5), 867–874. https://doi.org/10.1093/carcin/bgh296
42. Sona Ciernikova, Aneta Sevcikova, Lubos Drgona, Michal Mego. Modulating the gut microbiota by probiotics, prebiotics, postbiotics, and fecal microbiota transplantation: An emerging trend in cancer patient care, Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, Volume 1878, Issue 6,2023,188990, ISSN 0304-419X. https://doi.org/10.1016/j.bbcan.2023.188990.5
43. Tasselli, L., Zheng, W., & Chua, K. F. (2017). SIRT6: Novel mechanisms and links to aging and disease. Trends in Endocrinology & Metabolism, 28(3), 168–185.
44. Thevaranjan, N., Puchta, A., Schulz, C., et al. (2017). Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host & Microbe, 21(4), 455–466.
45. Van Deursen, J. M. (2014). The role of senescent cells in ageing. Nature, 509(7501), 439–446.
46. Wiley, C. D., Velarde, M. C., Lecot, P., et al. (2016). Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. Cell Metabolism, 23(2), 303–314.
47. Wilkinson, J. E., Burmeister, L., Brooks, S. V., et al. (2012). Rapamycin slows aging in mice. Aging Cell, 11(4), 675–682.
48. Wyld L, Bellantuono I, Tchkonia T, Morgan J, Turner O, Foss F, George J, Danson S, Kirkland JL. Senescence and Cancer: A Review of Clinical Implications of Senescence and Senotherapies. Cancers (Basel). 2020 Jul 31;12(8):2134. doi: 10.3390/cancers12082134.
49. Xie, W., Ma, X., Liu, Y., et al. (2021). Targeted removal of senescent cells by CRISPR/Cas9 for aging intervention. Nature Communications, 12, 4196.
50. Xu, M., et al. (2018). Senolytics improve physical function and increase lifespan in old age. Nature Medicine, 24(8), 1246–1256.
51. Yousefzadeh, M. J., Zhu, Y., McGowan, S. J., et al. (2018). Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine, 36, 18–28. https://doi.org/10.1016/j.ebiom.2018.09.015
52. Zhu, Y., et al. (2015). The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell, 14(4), 644–658.
53. Zhavoronkov, A. (2021). Deep aging clocks: the emergence of AI-driven biomarkers of aging and longevity. Ageing Research Reviews, 67, 101260.