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Hallmarks of Aging 2.0: Decoding the Molecular Drivers of Human Longevity – Senolytics Vs. Senomorphics as Strategies to Eliminate Senescent "Zombie" Cells

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Abstract:
The process of aging is a complicated biological phenomenon that is marked by a loss of functionalities and high susceptibility to illness. Recent developments in geroscience have narrowed down the classical paradigm of aging processes into the so-called Hallmarks of Aging 2.0 where molecular pathways including genomic instability, epigenetic changes, mitochondrial dysfunction, chronic inflammation, and cellular senescence are connected. The buildup of senescent cells also known as the zombie cells has come out as one of the major causes of tissue degeneration during the aging process. These cells are metabolically active and irreversibly differentiate but continue to secrete pro-inflammatory factors referred to as senescence-associated secretory phenotype (SASP). There are two key therapeutic approaches that have been optimized to combat cellular senescence; senolytics, which are specific to eliminate senescent cells, and senomorphics, which inhibit the pathogenic secretory phenotype of senescent cells, but do not kill them. The current review presents an overview of the current results of animal-based experimental research on the molecular hallmark of aging and compares the relative efficacy of senolytic and senomorphic treatment in regulating aging pathways. The article identifies the most important experimental models, mechanisms of action, therapeutic potential and limitations of the existing approaches. The knowledge of these strategies offers an insightful critical view of longevity science and can lead to new possibilities in creating anti-aging interventions to work on basic biological processes.

Keywords: Aging; Hallmarks of Aging 2.0; Senolytics; Senomorphics; Senescence-Associated Secretory Phenotype (SASP); Longevity; Geroscience.

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1. INTRODUCTION

Aging refers to a natural biological process where bodies become more and more unhappy in their physiological activities and more vulnerable to chronic illnesses[1]. This is initiated by a set

of genetic, environmental, and metabolic influences that develop with time and destabilize the cells of the body. In the last ten years, there has been the use of the framework of Hallmarks of Aging in aging research, which is the identification of the basic molecular and cellular processes that cause biological aging. More recently, developments in molecular biology and experimental gerontology have broadened this concept into the Hallmarks of Aging 2.0 which focuses on the system-wide interrelationships of aging processes and their system-wide effects.

1.1. Background of the study

In the recent decade, the field of aging studies has been shaped by the so-called Hallmarks of Aging paradigm that defines the molecular and cellular processes that lead to biological aging[2]. These characteristics are genomic instability, loss of telomeres, epigenetic changes, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, as well as chronic inflammation. These mechanisms are interlinked and as a result they lead to the progressive decrease in cellular functions seen with aging.

New developments in molecular biology, genetics and experimental gerontology have extended this model to the Hallmarks of Aging 2.0 concept. This recent view focuses on the dynamicity and interrelationship of the aging pathways with much attention being paid to the interaction of multiple biological processes in determining lifespan and healthspan. Newer causes of aging are also identified in the updated framework which includes chronic inflammation, disrupted intercellular communication and dysfunctional cellular repair processes which have offered a more holistic view of the aging process.

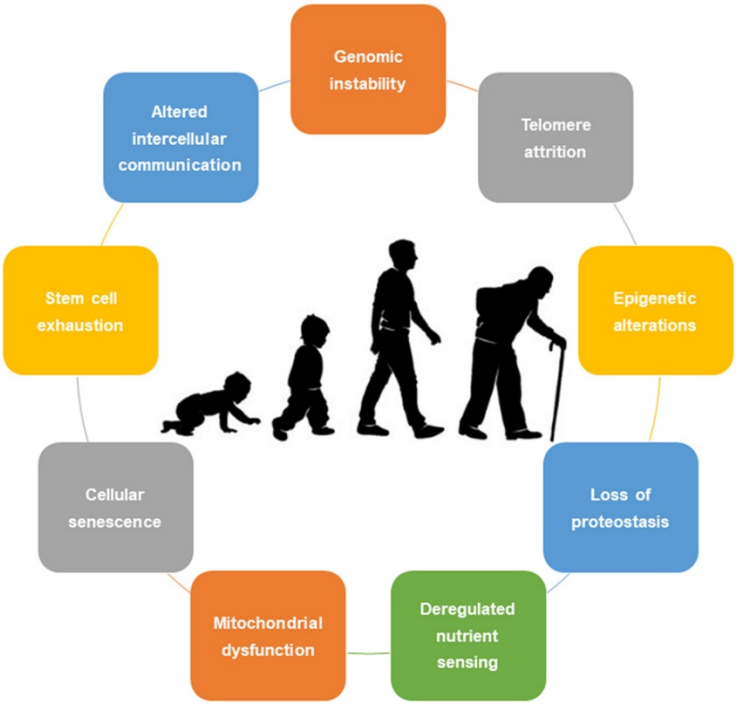

Figure 1: Hallmarks of Aging

Cellular senescence is one of the many aging hallmarks that have received specific focus in the context of the extreme linkage to dysfunction of tissues in the elderly. Cellular senescence is a permanent cell-cycle arrest, which is triggered by stresses like DNA damages, oxidative stress,

mitochondrial impairments and telomere shortening. Although senescence may be a defense strategy to avert the growth of damaged or even malignant cells in the first place, senescence cells may lead to adverse outcomes in tissue homeostasis and physiological processes in the long run. Senescent cells both survive and are metabolically active and release numerous pro-inflammatory cytokines, chemokines, proteases, and growth factors, which are known as the senescence-associated secretory phenotype (SASP). The chronic secretion of these factors is associated with chronic inflammation, remodeling of tissues and the development of various diseases that occur as a result of aging.

1.2. Objectives of the Review

The main objectives of this review are:

- To examine the molecular mechanisms involved in the Hallmarks of Aging 2.0 framework.
- To evaluate the role of cellular senescence in the aging process.
- To compare the therapeutic strategies of senolytics and senomorphics based on animal-based experimental studies.
- To identify research gaps and future directions for senescence-targeted anti-aging therapies.

1.3. Importance of the Topic

The aging and senescence-targeting therapies are of interest to study due to a number of reasons:

- Aging is a significant risk factor to many chronic diseases, such as neurodegenerative, cardiovascular and metabolic diseases.
- Knowledge of molecular pathways of aging can be used to determine ways of increasing healthy lifespan and quality of life.
- Senescent cells build up to play a major role in dysfunction of the tissues and chronic inflammation.
- Senolytics and senomorphics are therapeutic plans that provide new methods of delaying aging and averting age-associated illnesses.
- Animal experimental research: The experimental researches involving animals would be useful in finding out the working mechanisms, safety, and the possible effectiveness of senescence-targeting treatment.

2. HALLMARKS OF AGING 2.0: MOLECULAR DRIVERS OF LONGEVITY

The mechanisms that cause aging represent a complicated set of molecular and cellular changes, which ultimately affect physiological processes and hinder the capacity of the organism to be at homeostasis[3]. In order to further elucidate these biological processes, the researchers have developed the concept of the Hallmarks of Aging 2.0, which builds the previous idea of aging hallmarks to highlight the complexity of a combination of various cellular pathways that participate in aging. This revised model emphasizes the interaction of various biological

processes and the overall accumulation of these processes to cause failure of functions, tissue destruction, and the development of age-related conditions. The signs involve genomic instability, telomeres degradation, epigenetic modifications, mitochondrial impairment, chronic inflammation, and cellular senescence processes that are vital in the regulation of longevity and organism wellbeing.

2.1. Genomic Instability

Genomic instability is regarded as one of the basic molecular cause of aging, and it can be defined as the gradual increase in the number of damage in the genetic material of cells with age. The genome is constantly subjected to different internal and external stress which may lead to a break down of DNA. Internal causes are mistakes during the process of DNA replication, metabolic by-products like reactive oxygen species (ROS) and spontaneous chemical reactions in the cell. Environmental stressors (ultraviolet radiation, ionizing radiation, toxins and chemical pollutants) fall under the external factors. These are capable of inducing various forms of DNA damage such as single strand breakage, double strand breakage, base damage, rearrangement of the chromosomes, and mutations and all these have the effect of impairing normal cell functionality.

In a healthy condition the cells have complex DNA repair systems, which ensure stability of the genome. The repair systems are base excision repair, nucleotide excision repair, mismatch repair and double strand break repair pathways that collaborate to repair or detect DNA damage. Nevertheless, as age advances, the efficiency of these repair mechanisms decreases slowly and there is accretion of unrepaired lesions in the DNA. This build-up is able to interfere with gene expression, impair cellular metabolism, and promote cellular dysfunction which will eventually lead to aging and age related diseases.

Experimental studies in animals have a lot of evidence to prove that genomic instability plays a big role in ageing. Specifically, the aging phenotype has been shown to be accelerated in genetically modified mice with faulty DNA repair mechanisms. Individually, the mice with mutations in genes that are important in nucleotide excision repair, i.e., UV-induced DNA damage repair, have characteristics of premature aging such as hair loss, bone loss, poor tissue repair, immune defects, and shortened life span. Equally, genetic alterations of DNA repair mechanisms have been associated with neurodegenerative and metabolic syndrome vulnerability in animal models.

2.2. Telomere Attrition

The other hallmark of aging that is fundamental is the telomere attrition which is vital in the regulation of cell lifespan and genomic stability. Telomeres are often repeated sequences of nucleotides that are present at the ends of the chromosomes, which serve to act as protective caps to ensure that the chromosomes do not undergo degradation, fusion, or abnormal fusion during cell division. Such sophisticated DNA -protein assemblies guarantee the integrity of genetic material since vital coding regions of DNA are not lost during replication. Nevertheless, the very nature of DNA replication puts a limit on the number of times a cell may divide and as such, telomeres progressively become shorter with each division, a process known as telomere attrition[4].

With time, telomeres gradually shorten and eventually reach a critical length where they can no longer be able to confer adequate protection to the end of chromosomes. At this threshold, cells trigger a DNA damage response resulting in cellular senescence or apoptosis thus inhibiting additional cell division. Even though such mechanism serves as a defensive mechanism against uncontrolled proliferation of cells and the formation of tumors, excessive shrinkage of telomeres also leads to aging as it suppresses the ability of tissues to regenerate. Specifically, the ability of stem cells and highly proliferative tissues (e.g. skin, blood, and intestinal lining) to mitigate the consequences of age-associated tissue deterioration relies heavily on the telomere erosion that diminishes homeostatic mechanisms and damages the tissue (Makar et al. 23).

Animal studies that have been carried out experimentally have given solid support to the fact that telomere attrition contributes to aging. The study on telomerase deficient mice which do not have the enzyme that maintains the length of the telome has demonstrated that these mice are early aging phenotypes. Such phenotypes encompass defect dysfunction of the stem cells, diminished tissue repair, organ degeneration, infertility, and reduced life span. The fact that in these models, telomeres become shorter and shorter as cells proliferate is a source of genomic instability and poor cell proliferation that eventually results in the symptoms of early aging.

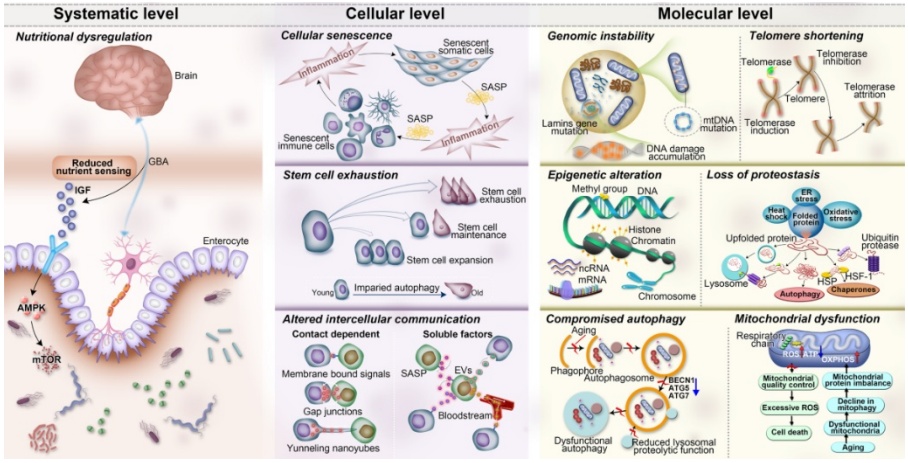

Figure 2: Multi-Level Representation of the Hallmarks of Aging and Their Role in Age-Related Cellular and Molecular Changes

2.3. Epigenetic Alterations

Another significant aging hallmark is epigenetic alterations, which are heritable modifications in the gene expression without altering the underlying sequence of DNA. They are the changes that help to control the activation or silencing of genes and play an important role in the control of cellular development, differentiation, and physiological functions[5]. The key epigenetic events are DNA methylation, histone modifications, and chromatin remodelling, which together can affect the accessibility of genetic information and control the transcriptional activity of the cell. Normal epigenetic regulation properly keeps the genes active at the appropriate time and quantity so as to keep the cells functioning normally.

Epigenetic patterns alter slowly as a person ages resulting in such phenomenon as epigenetic drift. The process includes the changes in the DNA methylation patterns, abnormal histone changes, and the distortion of the chromatin structure. These alterations may cause the disorder

of genes that are associated with the most important biological functions like metabolism, immune responses, inflammation and cell repair. Consequently, epigenetic modifications with age increase the vulnerability to stress, diminish cellular efficiency and cause multiple age related diseases.

Experimental studies (animal) have yielded quality information regarding the correlation between epigenetic regulation and aging. Studies in mouse models have shown that the accumulation of epigenetic changes in old age has biological effects on the biomarkers of aging. To give an example, epigenetic clocks have been created using age-related variations in DNA methylation and are used to estimate biological age by using certain methylation patterns in the genome. These clocks have been ample aids in the study of the pace of aging and the efficacy of anti aging interventions in model studies.

2.4. Mitochondrial Dysfunction

The mitochondrion is a very important cell organelle that produces energy in the form of adenosine triphosphate (ATP) during oxidative phosphorylation. Mitochondria are also vital in control of cellular metabolism, calcium homeostasis, apoptosis, and synthesis of signaling molecules besides generation of energy. Since mitochondrial integrity is central to cellular homeostasis, this integrity is essential to the preservation of tissue health and physiological homeostasis. But in the aging process, the efficiency of mitochondria is slowly decreased, which causes a reduced energy production and cell stress[6].

Overproduction of reactive oxygen species (ROS) is one of the significant effects of mitochondrial dysfunction in old age. ROS are extremely reactive molecules that are generated as by-products of the mitochondrial respiration. Although low concentrations of ROS are vital signaling molecules, the overbuilding of ROS may lead to cellular damages on DNA, proteins, and lipids. This oxidative injury can interfere with the normal cellular mechanisms and this can lead to the gradual degradation of tissues as we age. Also, mitochondrial DNA (mtDNA) is especially susceptible to oxidative damage due to its exposure to oxidants that do not bind to nuclear DNA and a low repair capacity.

Animal based experimental studies, especially on rodent models have provided evidence of a close relationship between aging-related diseases and mitochondrial dysfunction. The proof of this has been demonstrated in experiments of mice when mutations in mitochondrial DNA or in mitochondrial maintenance pathways occur which have accelerated aging phenotypes. These animals usually display some of these symptoms; muscle weakness, lack of endurance, neurodegeneration, metabolic imbalance, and malfunction of the organism, which demonstrates the paramount importance of mitochondria in the preservation of physiological health.

2.5. Chronic Inflammation (Inflammaging)

A major characteristic of aging is chronic low-grade inflammation also known as inflammaging which helps to explain the overall decline of physiological functions with age. In contrast to acute inflammation, which is a temporary protective reaction to disease or injury, inflammaging is typified by long-term and systemic inflammatory pathology that accumulates with age. This sustained inflammatory process causes a disturbance in the normal tissue homeostasis and it

interferes with the capacity of the body to maintain cellular homeostasis, leading to the aging process and predisposing a person to a number of chronic illnesses.

Several biological aspects have a role in the development of inflammaging such as the build up of cellular damage, deregulation of the immune system, dysfunction of the mitochondria, and the presence of senescence cells[7]. With age, the immune system becomes less efficient in controlling inflammatory activities and results in sustained production of pro-inflammatory molecules, including cytokines, chemokines as well as inflammatory mediators. These inflammatory signals disrupt normal cell communication and may end up destroying the tissues in the immediate area in the long term.

The use of animal models especially rodents in experimental studies has shown good evidence in the role of chronic inflammation in aging. It has been found that the production of inflammatory cytokines like interleukins (IL-6, IL- 1b) and tumor necrosis factor-alpha (TNF- 0) rises with age in different tissues. These molecules have been linked to the development of age related conditions such as cardiovascular diseases, neurodegenerative diseases, metabolic syndromes with relation to their elevated levels. Persistent inflammatory signaling in animal models has also been associated with compromised tissue regeneration and augmented detrimental cell injuries.

2.6. Cellular Senescence

Cellular senescence is a severe biological phenomenon that is related to aging and is defined by an irreversible cell-cycle arrest, during which cells cease to divide but retain their metabolic activity. Senescence normally results as a reaction to a range of cellular stress which includes DNA damage, oxidative stress, shortening of telomes, mitochondrial dysfunction, and oncogenic signaling. At first, cellular senescence is a protective process that avoids the increase in the number of damaged or even cancer cells. The body can inhibit cell division and thereby decrease the probability of tumor growth and preserve genomic integrity. Nevertheless, despite the favorable effect of senescence during early stages, expanding the number of senescent cells in old age is harmful to the health and functionality of the tissue.

Senescent cells are distinct to normal cells in a number of ways. They become abnormally expressing the genes and secrete a broad spectrum of inflammatory molecules, growth factors, proteases and cytokines even though they are metabolically active. A combination of these released factors constitutes the senescence-associated secretory phenotype (SASP). The SASP has the potential to affect surrounding cells and their tissue environment through its ability to induce chronic inflammation, extracellular matrix breakdown, and cellular atypical signaling. In the long-term, the continuous release of such inflammatory molecules can lead to the dysfunction of the tissues, inhibition of regeneration and the development of age-related diseases[8].

Although experimental studies with animal models have also given substantial evidence to support the linkage of cellular senescence with aging and degenerative diseases, the use of animal models, most notably genetically engineered mice, has been used. It has been observed that senescent cells accumulate in several tissues such as adipose tissue, liver, skeletal muscle, and the vascular system during old age. This build up has been linked to reduced tissue healing

ability, metabolic impairment and heightened vulnerability to illnesses including heart diseases, brain deterioration and metabolic illness.

Table 2. Review of Literature on Senescence-Targeted Therapies and Molecular Drivers of Aging

Author Name	Topic Covered	Research Study Title
Shafiq, B. (2025)[9]	Molecular and genetic mechanisms involved in cardiac aging, including genomic instability, mitochondrial dysfunction, and inflammatory responses affecting cardiovascular health	Decoding Cardiac Aging: Integrative Genetic, Cellular, and Molecular Insights Through a Data-Driven Perspective
Alum, E. U., Izah, S. C., Uti, D. E., Ugwu, O. P. C., Betiang, P. A., Basajja, M., & Ejemot-Nwadiaro, R. I. (2025)[10]	Therapeutic strategies targeting cellular senescence, focusing on the development and mechanisms of senolytics and senomorphics for healthy aging	Targeting Cellular Senescence for Healthy Aging: Advances in Senolytics and Senomorphics
López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023)[11]	Expanded conceptual framework of aging mechanisms and the interconnected biological hallmarks driving the aging process	Hallmarks of Aging: An Expanding Universe
Keshavarz, M., & Ehninger, D. (2025)[12]	Re-evaluation of traditional aging frameworks and the need for improved biological age measurement and biomarkers	Beyond the Hallmarks of Aging: Rethinking What Aging Is and How We Measure It
Guerville, F., Barreto, P. D. S., Ader, I., Andrieu, S., Casteilla, L., Dray, C., & Vellas, B. (2020)[13]	Identification of biomarkers linked with aging processes such as inflammation, mitochondrial dysfunction, and cellular senescence	Revisiting the Hallmarks of Aging to Identify Markers of Biological Age

3. Senolytics: Targeting and Eliminating Senescent Cells

Senesolytics Senesolytic compounds are selective induction of senescent cells using their survival pathways. The anti-apoptotic signaling networks that enable senescence cells to be resistant to normal cell death processes are referred to as senescence-associated anti-apoptotic pathways (SCAPs). Senesolytic medication interferes with them and causes selective destruction of senescent cells.

3.1. Experimental Senolytic Compounds

A variety of senolytic compounds have been explored in detail in animal-based experimental research on their capacity to selectively destroy senescent cells and mitigate their harmful activities on tissues. Senolytics work by inhibiting the survival mechanisms enabling senescent cells to survive programmed cell death. Senesolytic agents interfere with these pathways and induce selective apoptosis of senescent cells but do not induce apoptosis in normal, healthy cells. Some of the best and most researched senolytic compounds in animal models include dasatinib, quercetin, fisetin, and navitoclax, all of which have been shown to have differing efficacy levels in the reduction of senescent cell buildup and enhancement of physiological processes linked with aging.

Dasatinib and quercetin (D+Q) are considered one of the most extensively studied senolytic combinations. Dasatinib is a tyrosine kinase inhibitor, whereas quercetin is an antioxidant and an anti-inflammatory natural flavonoid[14]. These compounds when used in combination with each other have been demonstrated to selectively kill senescent cells within various tissues. The D+Q combination has been shown to remarkably decrease the number of senescent cells in adipose tissue and enhances various points of physical fitness, including assessment mobility, muscle activity, and systemic inflammation in mouse models conducted experimentally. These observations indicate that senolytic therapy may help to achieve better healthspan that is the lifespan that is lived in good health.

Fisetin is another promising senolytic compound; this is a flavonoid, a naturally occurring flavonoid that has been discovered in a range of fruits and vegetables. A study made on the aging mice indicated the treatment with fisetin has the potential to reverse indicators of cellular senescence and inflammation. The use of fisetin as the drug in these animal experiments led to a reduced number of pro-inflammatory cytokines and the amelioration of tissue functionality. Moreover, it is also observed that long-term fisetin administration in old mice was correlated with the median lifemajority, indicating it should be considered a longevity-promoting substance.

Another senolytic agent is navitoclax, which acts by inhibiting anti-apoptotic proteins of the BCL-2 family which is usually increased in the senescent cell to evade the programmed cell death. Navitoclax selectively eliminates the senescent cells by preventing these survival signals. Rodent models have demonstrated that navigation using navitoclax can be effective to lower senescence cell population and enhance tissue recovery and physiology[15].

3.2. Mechanisms of Action

Senolytic agents work by inducing apoptosis (programmed cell death) selectively in senescent cells via its molecular pathways that enable the survival of such cells despite the high levels of cellular damage. The senescence-associated anti-apoptotic pathways (SCAPs) are commonly set of survival networks which senescence cells use to become resistant to apoptotic. These pathways aid the survival of senescent cells in tissues avoiding natural cell death processes and leading to chronic inflammation as well as tissue dysfunction. Senolytic pharmaceuticals are aimed at disrupting such protective signaling pathways and enhancing the selective removal of senescent cells and reducing the destruction of normal and healthy cells.

The BCL-2 family of anti-apoptotic proteins is also one of the primary targets of senolytic agents. These proteins are significant in terms of homeostatic cell survival in that they inhibit the activation of apoptotic pathways in cells. The BCL-2 proteins are also highly expressed in senescent cells, and they are therefore resistant to apoptotic pathways. The use of senolytic compounds like navitoclax which prevent the BCL-2 proteins will eliminate this survival advantage and induce programmed cell death in senescent cells only[16].

The other crucial pathway that senolytics are targeted to is PI3K/AKT signaling pathway that controls cellular growth, metabolism, and survival. This pathway is often hyperactivated in senescent cells and enables them to survive even with extreme molecular damage. Senesolytic agents block survival signals of PI3K/AKT, exposing their senescence to apoptosis.

Interaction with p53-mediated stress response pathways are also important in senolytics interaction, which are important in the regulation of cell cycle arrest, DNA repair, and apoptosis. The p53 protein is a cellular stress sensor and it reacts to the damage of DNA and other cellular stresses. Senescent cells are associated with a possible change in the control of p53 signal, which permits the survival of damaged cells. Some senolytic substances reinstate or amplify p53-dependent apoptotic signaling and consequently stimulate the targeted eradication of senescent cells.

Through accessing these critical molecular signatures of BCL-2 anti-apoptotic, PI3K/AKT survival, and p53-mediated stress responses an effective mechanism of senolytic action of apoptosis in senescent cells is achieved by targeting these pathways. This selective ablation suppresses dysfunctional cell accretion, decreases the inflammatory signaling related to the senescence-associated secretory phenotype (SASP), and is useful in restoring unperturbed tissue homeostasis. Therefore, senolytic therapies are now actively being explored in animal model systems as a promising intervention to enhance healthspan and postpone the age-associated physiologic deterioration[17].

3.3. Strengths and Limitations

Experimental studies on animals have reported noticeable enhancement of various parameters of the physiological state of animals after senolytic treatment. Senescent cells are selectively killed by senolytic compounds, which decreases the number of dysfunctional cells that cause tissue degeneration and chronic inflammation. Consequentially, there have been reports of significant change in healthspan, which is defined as the duration of life that an organism is healthy and functional, as a result of experimental studies in rodent models. Senolytic therapies have also been linked with the increase of physical mobility, better metabolism and tissue regeneration, especially in skeletal muscle, fat tissue and the cardiovascular system. The ablation of senescent cells has been observed to reverse the impairment of the stem cell activity, inflammatory indicators and physiological performance in old mice.

Even though there are these encouraging results, there are also some limitations and challenges to senolytic therapies that should be looked into keenly[18]. Off-target toxicity is one of the possible issues since not all senolytic compounds can target only cancer cells or disrupt the necessary cellular processes causing a side effect. Moreover, the senescent cells are extremely varying and may differ immensely across different tissues and physiological states. This

heterogeneity causes one senolytic drug to have a hard time destroying all senescent cell populations[19].

The other weakness is that there may be partial clearance of senescent cells. Although senolytic therapies are capable of decreasing the load of senescent cells in the body, they do not necessarily remove all senescent cells in the body. Senescent cells which remain may keep producing inflammatory factors and cause tissue dysfunction as time goes by. Moreover, after treatment, senescent cells may reaccumulate because of the continuous cell stress and damage related to age.

4. SENOMORPHICS: MODULATING THE HARMFUL EFFECTS OF SENESCENT CELLS

As opposed to senolytics, which operate by specifically killing senescent cells, senomorphic compounds modify the behavior and activity, but do not destroy these cells. The main focus of senomorphics is the negative biological consequences of aging cells, specifically, the senescence-associated secretory phenotype (SASP). The SASP is a complex of pro-inflammatory cytokines, chemokines, growth factors, and proteolytic enzymes that are released by senescent cells. Such molecules interfere with the normal tissue structure, stimulate chronic inflammation and lead to the development of different age-related disorders[20].

The goal of senomorphic agents is to inhibit or alter the generation and release of SASP factors to decrease inflammation and limit the harmful effect of senescent cells on the tissues around them. These compounds assist in ensuring tissue homeostasis by balancing the inflammatory signaling pathways and cellular stress responses enabling senescent cells to stay in a metabolically dormant status. This method would be able to restrict tissue loss and enhance physiological activity without causing extensive cell death[21].

Experimental experiments, involving animals, have demonstrated that senomorphic compounds have the potential to lower inflammatory signaling, oxidative stress, and metabolic impairment in relation to the aging process. The senomorphics prevent the propagation of inflammatory signals to the surrounding cells as well as diminish the total number of age-related tissue damages by regulating the detrimental secretory activity of the senescent cells. This approach can also be used to retain the positive features of cellular senescence, including its ability to counter such things as an uncontrolled increase in the number of damaged or even cancerous cells[22].

4.1. Common Senomorphic Agents

A number of pharmacological and naturally occurring compounds have undergone experimental research in animals with respect to their possible senomorphic action[23]. Senescent cells are removed by senolytics unlike senomorphic agents that can regulate cell signaling pathways that regulate inflammation, metabolism, and stress responses. Such compounds prevent the pathological effects of the senescence-associated secretory phenotype (SASP) and thus decrease the chronic inflammation and tissue damage in aging. Rapamycin, metformin, resveratrol and Janus kinase (JAK) inhibitors are some of the most popular senomorphic agents studied in animal models[24].

Rapamycin: is a widely researched senomorphic compound and is the primary inhibitor of the mechanistic rapamycin (mTOR) signaling pathway that is critical in cell growth, metabolism, and protein synthesis regulation[25]. Rapamycin has been demonstrated to inhibit the production of SASP, to reduce inflammation and to increase the lifespan of mice in animal studies. Rapamycin also enhances cellular resistance to stress and metabolic homeostasis, through panentheism of mTOR signaling[26].

Metformin: a senomorphic animal study has also proven senomorphic with a well-known metabolic regulator. It mostly stimulates the AMP-activated protein kinase (AMPK) cascade, promoting cellular energy homeostasis and decreasing oxidative stress. Metformin treatment in rodent models has been linked to the reduction of inflammatory signaling, an enhancement of metabolic activity and the slowing of the development of some age-associated pathologies.

Resveratrol: Another compound that shows senomorphic activity is a naturally occurring polyphenol grape-derived and some plant-derived, called ellagic acid[27]. Resveratrol stimulates sirtuin signaling pathways, especially SIRT1, which can be used to control cellular stresses, mitochondrial processes, and metabolic integrity. Research done on animal models has indicated that resveratrol is able to decrease the inflammatory markers, increase the efficiency of the mitochondria, as well as the general wellbeing of the cell.

Janus kinase (JAK) inhibitors: which are inflammatory signaling pathways associated with the production of SASP. These compounds have the capability of suppressing the synthesis of pro-inflammatory cytokines that are produced by senescent cells significantly by blocking the JAK/STAT pathway. There is evidence in the animal models that JAK inhibitors are capable of suppressing chronic inflammation, enhancing the functionality of tissues, and mitigating age-related degenerative symptoms[28].

4.2. Mechanisms of Action

Senomorphic agents affect their actions by tuning the major cellular signaling pathways that control inflammation, metabolism and stress response related to cellular senescence. Instead of killing the senescent cells themselves, the main objective of these compounds is to inhibit the senescence-associated secretory phenotype (SASP) of the senescent cells, consequently lowering the damaging inflammatory state of senescent cells[29]. Senomorphics can restore cellular homeostasis by modulating certain molecular pathways to prevent excessive damage of tissues due to prolonged inflammatory process in old age.

The mechanistic target of rapamycin (mTOR) signaling pathway is one of the most important pathways that senomorphic compounds target and which is critical in the regulation of cell growth and formation, protein synthesis, and metabolism[30]. The mTOR pathway has been linked to overactivation which has been linked with aging and augmented SASP production. Senomorphic drugs like rapamycin can suppress mTOR and, therefore, minimize inflammatory signaling, as well as decelerate the aging process in cells. Rapamycin has been reported to inhibit the production of SASP in animal models, reduce the systemic inflammation, and prolong the life span of mouse models.

The other significant pathway that takes part in senomorphic activity is the nuclear factor kappa B (NF-kB) signaling pathway that controls the expression of many inflammatory genes. NF-KB is specifically involved with the production of SASP factors like the pro-inflammatory cytokines and chemokines. NF- -blockers such as senomorphic molecules can lower the production of these inflammatory products and, as a result, chronic inflammation can be limited and the surrounding tissue spared the destruction[31].

The AMP-activated protein kinase (AMPK) pathway is also a senomorphic agent that regulates cellular energy balance and metabolic homeostasis. AMPK activation increases mitochondrial function, cellular stress resistance, and oxidative stress. Metformin and other compounds are known to induce AMPK signal and suppress aging-related inflammatory processes. This action brings about better metabolic control and less cell damage through the actions of senomorphic agents.

The experimental evidence on the effectiveness of senomorphic compounds in regulating these pathways is supported by experimental evidence in animal models, especially in mice. An example of this is the rapamycin therapy in mouse models which has been shown to inhibit SASP, decrease systemic inflammation, enhance metabolic activity, and greatly increase lifespan[32]. The findings demonstrate senomorphic agents as possible therapeutic agents to reduce the adverse consequences of cellular senescence and enhance a healthy aging process.

4.3. Advantages and Challenges

Senomorphic therapies have been regarded as potentially safer in the long term approach to cellular senescence since they do not kill senescence. They instead act by regulating the destructive secretory behavior of these cells, especially senescence-associated secretory phenotype (SASP)[33]. The senomorphic compounds are helpful in minimizing tissue damage and preserving cellular homeostasis by blocking inflammatory signaling and decreasing the secretion of harmful cytokines, chemokines, and proteases. This could minimize the risk of side effects that might occur due to the mass destruction of the cells and senomorphics can be more appropriate to be used in extended treatment[34].

The other benefit of senomorphic agents is that the senescent cells can be kept in a dormant state of growth without any harm to their structure or to the entire body, which saves the positive aspect of senescence in controlling the unregulated growth of mutilated or even cancerous cells. Senomorphic compounds like rapamycin, metformin, and resveratrol in animal studies have already proven to have anti-inflammatory effects, ability to regulate metabolism and overall tissue functionality with minimal cell loss[35].

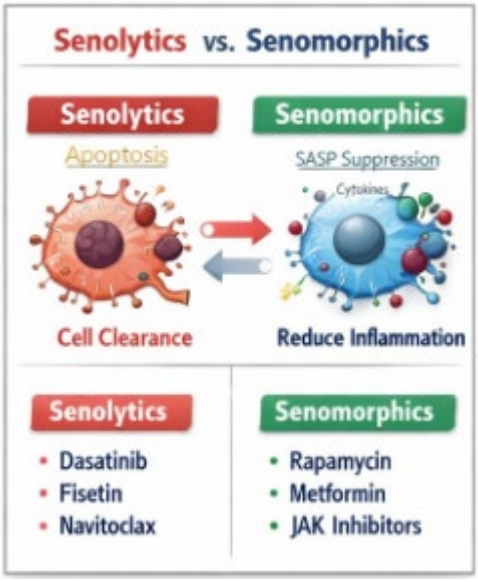

Figure 3: Comparison between senolytic and senomorphic therapeutic strategies

5. DISCUSSION

Recent reporting of new developments in geroscience have now made the biological mechanisms of aging much better understood, including the contribution of cellular senescence states to functional age-related deterioration[36]. The experimental studies done with animal models have shown that the targeting of senescent cells may result in an increase in physiological activities, decrease of chronic inflammation, and the improvement of tissue regeneration[37]. Senescent cells accumulation has been proven to cause harmful effects, but two important therapeutic modalities have become attractive as potential solutions to the problem, namely senolytics and senomorphics[38]. Whereas the senolytics kill senescent cells, senomorphics control their secretory phenotype and decrease inflammatory signaling. The next sections will cover the major findings of the experimental studies, the general implications of these methods, and the future research perspectives of senescence-targeted therapies.

5.1. Findings

The key discoveries in the experimental research on senescence-targeted therapies performed on animals involve the following:

- Senescent cells are known to accumulate in aged tissues, making them significant contributors to chronic inflammation, tissue degeneration and age-related illnesses.
- Senesolytic agents like dasatinib, quercetin, fisetin and navitoclax have shown the capacity to selectively destroy senescence cells in animals.
- Deletion of senescent cells of experimental animals has been linked to health span, physical mobility, metabolic activity, and tissue rejuvenation.
- Senomorphic agents Rapamycin, metformin, resveratrol, and JAK inhibitors inhibit the senescence-associated secretory phenotype (SASP) and decrease inflammatory signaling.

- Senesomorphic therapies are also used to stabilize the cellular environment and enhance metabolic regulation without killing senescent cells.

5.2. Implications and Significance

The aging research and healthcare are relevant to the development of senescence-targeting therapies:

- Senescent cell therapy is a new approach that can be used to enhance healthspan and not just to increase the lifespan.
- Senolytic therapy can assist in alleviating the burden of age diseases including cardiovascular disorders, neurodegeneration, and metabolic dysfunction.
- Senomorphic agents offer a safer long-term solution to the problem by regulating inflammatory signalling without causing widespread loss of cells.
- The addition of senolytics and senomorphics to combination therapies can be a more comprehensive anti-aging intervention.

5.3. Future Directions

Despite the positive developments, there are still a number of research challenges that still need to be researched further:

- Beyond senolytic compounds: development of more selective compounds with limited off-target toxicity.
- Determination of good biomarkers to identify and follow senescent cell in experimental models.
- The safety and efficacy of senescence-targeted therapies in the long term.
- Overcoming the fact that senescent cells are heterogeneous in various tissues, hence difficult to develop universal therapies.
- Researching synergistic approaches to therapies that also combine to address many aging hallmarks.
- Other experimental studies on animals to improve the treatment regimens and assess the long-term effects.

Such future research directions will be necessary in enhancing senescence-targeted therapy and strategies that are designed to enhance healthy aging and longevity.

6. CONCLUSION

The understanding of complex molecular and cellular mechanisms which lead to aging and longevity in the body is supported by the concept of Hallmarks of Aging 2.0. This model points out the bio-linked mechanisms that affect the gradual deterioration of physiological activities as the body ages[39]. One of these processes has turned out to be cellular senescence as one of the most important sources of age-related human degradation through the accumulation of metabolically active yet dysfunctional cells in different tissues. The effects of the targeted

approach to senescent cells in animal models have been proven to be significantly effective in the regard of extending health span, tissue regeneration and age-related degenerative processes by senolytic/senomorphic methods[40].

6.1.Importance of the Review

The significance of this review is the fact that it offers an in-depth investigation of the molecular determinants of aging in the Hallmarks of Aging 2.0 framework, specifically, in regard to the role of cellular senescence. The review can reveal the possibilities of senolytic and senomorphic therapies to modulate the aging pathways and enhance the physiological outcomes, by synthetizing the results of experimental studies that are performed on animals. Knowledge of such mechanisms will help in the ever-expanding science of geroscience to not only treat distinct age-related diseases, but also to tackle the biological factors underlying aging that lead to age-related diseases. The paper also highlights how senescence-targeted therapies have the potential to enhance healthspan and decrease the global burden of age-related chronic conditions.

6.2.Recommendations

To some extent, the present findings of experimental research allow making several recommendations in relation to the future study:

- The first recommendation is that additional animal-based experimental research should be carried out to gain a clearer insight into the long-term safety and efficacy of senolytic and senomorphic treatment.
- Research needs to be done on the creation of more selective senolytic agents which are able to kill senescence cells without triggering off-target toxicity.
- It is necessary to detect useful biomarkers to detect and track cellular senescence to enhance the assessment of therapeutic interventions.
- Future research must look into combination treatment therapies that would look at both senolytics and senomorphics in order to produce more holistic anti-aging activities.
- Further research is also needed on the effects of interventions to address senescence on other aging hallmarks, including mitochondrial dysfunction and epigenetic changes.

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