

Review Article

Molecular Mechanisms of Cellular Senescence and Immuno-Senescence: Insights from Model Organisms and Emerging Pathways

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Abstract

Cellular senescence and immunosenescence encompass critical molecular pathways that govern aging and age-related pathologies. Central to cellular senescence are DNA damage response activation, telomere attrition, chromatin remodeling, metabolic reprogramming, and cytoplasmic DNA sensing via cGAS-STING signaling, which collectively drive cell cycle arrest and the pro-inflammatory senescence-associated secretory phenotype (SASP). Immunosenescence involves progressive deterioration of immune cell function characterized by depleted naive lymphocytes, accumulation of dysfunctional senescent immune cells, and chronic inflammation (inflammaging), creating a feedback loop that exacerbates tissue degeneration and systemic aging. Model organisms such as mice and killifish have been indispensable for unraveling these mechanisms, enabling genetic and functional studies that illuminate senescence dynamics and immune clearance processes. Future research, empowered by multi-omics, single cell sequencing, and artificial intelligence, promises deeper dissection of senescence heterogeneity and tissue-specific pathways, offering biomarkers and therapeutic targets with unprecedented precision. Therapeutic strategies aiming to selectively eliminate or modulate senescent cells through senolytics, senomorphics, and immunomodulatory approaches hold promise to extend health span and ameliorate chronic diseases. However, challenges including senescent cell heterogeneity, context-dependent functions, and biomarker limitations necessitate individualized and careful translation of findings into clinical therapies. Continued interdisciplinary efforts integrating molecular biology, systems medicine, and clinical research will be pivotal in harnessing the full potential of senescence targeting for healthy aging and transformative disease management. This review was conducted to comprehensively compile and discuss the intricate molecular mechanisms underlying cellular senescence and immunosenescence, which are critical processes involved in aging and age-related diseases. The aim of this review article is to comprehensively elucidate the molecular mechanisms underlying cellular senescence and immunosenescence, integrating insights gained from model organism research and emerging signaling pathways.

Keywords

Cellular Senescence, Immunosenescence, Senescence-Associated Secretory Phenotype, DNA Damage Response, Senolytic Therapies

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1. Introduction

Cellular senescence and immunosenescence are fundamental aging processes that contribute significantly to the decline in physiological functions and the onset of various age-related pathologies [1, 2]. Cellular senescence is characterized by a stable and essentially irreversible arrest in cell proliferation, accompanied by metabolic activity and a distinctive secretory phenotype that influences tissue microenvironments [3]. This process can be triggered by factors such as DNA damage, telomere shortening, oxidative stress, and oncogene activation, playing roles in tumor suppression, tissue repair, and aging-related degenerative changes [4].

Immunosenescence refers to the age-related deterioration of the immune system, involving thymic involution, reduced diversity and function of adaptive immune cells, accumulation of memory T cells, and chronic low-grade inflammation, rendering elderly individuals more susceptible to infections, cancer, and autoimmune diseases [5]. It is characterized by thymic involution, reduced naïve T-cell production, accumulation of memory T cells, diminished response to new antigens, and chronic low-grade inflammation known as inflammaging [6]. These changes lead to impaired immune responses, increased infection risk, cancer incidence, and autoimmune disorders. Senescent immune cells also develop proinflammatory SASP, exacerbating immune dysfunction, and chronic viral infections further accelerate immunosenescence [7]. Both processes are interconnected; impaired immune clearance of senescent cells increases their accumulation, promoting systemic inflammation and aging-related pathologies [7]. Understanding molecular pathways governing cellular senescence and immunosenescence is crucial for developing strategies to extend healthspan and treat age-related diseases.

A molecular understanding of cellular senescence and immunosenescence is critical for unraveling the complex biological pathways that drive organismal aging and the development of age-related diseases [8]. Cellular senescence involves mechanisms such as DNA damage response, telomere attrition, oncogene activation, epigenetic alterations, mitochondrial dysfunction, and the senescence-associated secretory phenotype (SASP), which collectively disrupt tissue homeostasis, promote chronic inflammation, and impair regenerative capacity [9]. These molecular changes contribute directly to the pathogenesis of many chronic diseases including cardiovascular disease, neurodegenerative disorders (e.g., Alzheimer's and Parkinson's), metabolic syndrome, and cancer [10].

Similarly, molecular insights into immunosenescence reveal alterations in immune cell signaling, thymic involution, and chronic inflammation (inflammaging) that impair immune surveillance and response, increasing vulnerability to infections, cancer, and autoimmunity in aged individuals [11]. Clarifying these molecular pathways enables the identification of biomarkers for aging and disease risk as well as the

opportunity to design targeted interventions such as senolytic drugs to remove senescent cells or therapies that modulate immune function [12, 13].

A detailed molecular understanding of these processes is crucial for deciphering the cellular and molecular pathways that drive organismal aging and the etiology of age-associated diseases, thereby informing potential therapeutic interventions [4, 14]. Model organisms like *Drosophila*, *Caenorhabditis elegans*, and mice have been invaluable in aging research, allowing the exploration of conserved molecular mechanisms and the identification of new targets, given their genetic tractability, shorter lifespans, and similarity in fundamental aging pathways [15, 16].

This review aims to present an integrative overview of cellular senescence and immunosenescence as central pillars of aging biology. It will address the molecular hallmarks and signaling pathways implicated, discuss their contributions to age-related pathologies, and highlight the critical insights gained from model organism studies. The scope will cover emerging mechanisms and therapeutic perspectives targeting these aging processes, advancing understanding toward improving health span and longevity.

2. Cellular Senescence: Molecular Hallmarks and Pathways

Cellular senescence is a complex cellular program characterized by a stable and essentially irreversible arrest of cell proliferation in response to various intrinsic and extrinsic stressors, including DNA damage, telomere attrition, oxidative stress, and oncogenic signals [3, 4]. This arrest is primarily governed by the activation of two critical tumor suppressor pathways: the p53/p21 WAF1/CIP1 pathway and the p16 INK4A/pRB pathway [17]. These pathways function by inhibiting cyclin-dependent kinases, which halts the cell cycle and maintains the growth arrest state, preventing potentially damaged cells from proliferating. The activation of p53, often referred to as the guardian of the genome, is triggered by DNA damage and involves multiple post-translational modifications that stabilize and activate the protein to regulate transcription of genes involved in cell cycle arrest [18].

2.1. DNA Damage Response and Persistent DNA Lesions Driving Senescence

The DNA damage response (DDR) is a critical driver of cellular senescence, a process by which cells permanently lose their ability to proliferate while remaining metabolically active [19]. DDR is activated when cells detect DNA lesions caused by various factors such as oxidative stress, telomere shortening, oncogene activation, or external insults like ultraviolet radiation and chemotherapy. Persistent or irreparable

DNA damage triggers a chronic DDR that engages a signaling cascade involving key proteins such as ATM and ATR kinases, which phosphorylate downstream effectors including checkpoint kinases CHK1 and CHK2 [20]. These signals stabilize and activate the tumor suppressor protein p53, often called the guardian of the genome, preventing its degradation. Activated p53 then translocates to the nucleus where it functions as a transcription factor to upregulate target genes like p21, leading to cell cycle arrest primarily at the G1/S or G2/M checkpoints [21].

2.2. Key Cell Cycle Regulators

The p53-p21 and p16 INK4a-RB pathways are key cell cycle regulatory mechanisms that govern the establishment and maintenance of cellular senescence [4]. The p53-p21 pathway is activated primarily in response to DNA damage and other cellular stresses. Activated p53, a tumor suppressor transcription factor, induces the expression of p21 WAF1/CIP1, a cyclin-dependent kinase inhibitor (CDKI) [18]. p21 inhibits cyclin-CDK complexes, particularly Cyclin E-CDK2, preventing phosphorylation of the retinoblastoma protein (RB). Hypo phosphorylated RB remains active and binds to E2F transcription factors, repressing genes required for S-phase entry, thus eliciting a stable G1 cell cycle arrest. Prolonged activation of this pathway leads to irreversible growth arrest, a hallmark of cellular senescence [18].

The p16 INK4a-RB pathway functions somewhat independently but converges on RB regulation. p16 INK4a is another CDKI that inhibits Cyclin D-CDK4/6 complexes, maintaining RB in its growth-suppressive hypo phosphorylated state [4]. This reinforces cell cycle arrest by preventing E2F-mediated transcription of proliferation genes. The expression of p16 INK4a is often upregulated during stress responses and aging, serving as a robust biomarker of senescent cells [22].

2.3. Telomere Shortening and Dysfunction-Induced Senescence

Telomere shortening is a crucial mechanism driving cellular senescence, specifically a form known as replicative senescence or telomere dysfunction-induced senescence (TIS) [23]. Telomeres are protective repetitive DNA sequences located at the ends of linear chromosomes that safeguard genome integrity by preventing chromosomal ends from being recognized as DNA breaks. However, due to the end-replication problem during cell division, telomeres progressively shorten with each round of replication. When telomeres reach a critically short length, their protective structure, including the shelterin protein complex, is compromised. This leads to exposure of chromosome ends, which are recognized by the DNA damage response (DDR) machinery as DNA double-strand breaks [24].

Activation of the DDR at dysfunctional telomeres triggers

signaling pathways involving key proteins such as ATM kinase, which leads to phosphorylation and activation of p53 [25]. This in turn induces downstream effectors such as p21, enforcing cell cycle arrest and establishing the senescent phenotype. Thus, telomere shortening acts as a biological clock limiting the replicative capacity of somatic cells a phenomenon first described as the Hayflick limit. Notably, telomerase, an enzyme capable of extending telomeres, can bypass this arrest, underscoring the causal role of telomere length in senescence [26].

2.4. Chromatin Remodeling and Formation of Senescence-Associated Heterochromatin Foci

Chromatin remodeling during cellular senescence involves dramatic reorganization of the genome's three-dimensional structure, prominently characterized by the formation of senescence-associated heterochromatin foci (SAHF) [4]. SAHFs are dense, punctate foci of heterochromatin that appear in the nuclei of senescent cells due to condensation and spatial clustering of chromatin regions. These structures are enriched in classical heterochromatin markers, such as trimethylation of histone H3 on lysine 9 (H3K9me3) and heterochromatin protein 1 (HP1), as well as histone variants like macroH2A and HMGA proteins, which contribute to chromatin compaction [27].

SAHF formation is a multi-step dynamic process rather than a static endpoint. Initially, individual chromosomes undergo condensation detectable by DNA staining methods (e.g., DAPI) [27]. Subsequently, these condensed regions acquire heterochromatic marks like H3K9me3 and recruit HP1 proteins and other chromatin-binding factors that stabilize and maintain the compact state. Notably, the formation of SAHF is accompanied by a reduction of nuclear lamina components such as lamin B1, leading to the release of perinuclear heterochromatin, which contributes to genome reorganization within the nucleus. This reorganization correlates with a loss of the usual radial distribution of chromatin and is associated with altered nuclear pore density [28].

2.5. Senescence-Associated Secretory Phenotype and Its Regulation

The senescence-associated secretory phenotype (SASP) is a complex and dynamic phenotype exhibited by senescent cells characterized by the secretion of a broad spectrum of bioactive molecules including pro-inflammatory cytokines, chemokines, growth factors, and proteases [29]. These secreted factors modulate the tissue microenvironment by influencing immune responses, extracellular matrix remodeling, and paracrine signaling to neighboring cells, which can induce senescence or alter their function [30]. Key cytokines in the SASP include interleukins such as IL-1 α , IL-1 β , IL-6, and IL-8, which play significant roles in promoting inflammation

and reinforcing cell cycle arrest. Chemokines like CXCL1, CXCL2, and CCL2 are involved in recruiting immune cells to sites of senescent cell accumulation, contributing to immune surveillance or chronic inflammation [31]. Growth factors secreted as part of SASP participate in tissue repair and angiogenesis but may also contribute to fibrosis and tumor progression depending on context.

SASP composition is heterogeneous and influenced by the senescence inducer, cell type, and the stage of senescence [32]. Initially, SASP tends to have immunosuppressive and profibrotic profiles dominated by TGF- β isoforms, progressing later to a proinflammatory, fibrolytic profile dominated by IL-1 β , IL-6, and IL-8. Senescent neurons and post-mitotic cells can also exhibit SASP with unique molecular profiles linked to neuroinflammation and aging-related neurodegenerative conditions [4].

The regulation of SASP involves several pathways, including persistent DNA damage response signaling, activation of NF- κ B transcription factors, and cGAS-STING cytosolic DNA sensing pathways [33]. Epigenetic and metabolic changes further fine-tune SASP gene expression. Importantly, SASP not only perpetuates senescence in an autocrine and paracrine manner but also modulates the immune system's ability to clear senescent cells, influencing tissue homeostasis and the progression of age-related diseases [34].

2.6. Epigenetic Regulation of Senescence

Epigenetic regulation plays a crucial role in orchestrating cellular senescence by modulating gene expression without altering the DNA sequence [35]. This regulation encompasses diverse mechanisms including histone modifications, DNA methylation, chromatin remodeling, non-coding RNA activity, and super-enhancer dynamics. During senescence, the chromatin landscape undergoes profound changes such as global histone loss, altered histone modification patterns, and the redistribution of histone variants, which collectively impact chromatin accessibility and gene transcription [27].

Histone modifications such as methylation (e.g., H3K9me3, H3K27me3) and acetylation dynamically regulate the expression of senescence-associated genes [34]. These modifications contribute to the formation of heterochromatin regions that silence proliferation-promoting genes and regulate the senescence-associated secretory phenotype (SASP) [36, 37]. Super-enhancers, which are large clusters of enhancers that drive high expression of key genes, have been implicated in SASP regulation. Proteins like BRD4, a bromo-domain-containing epigenetic reader, recognize acetylated histones and are essential for maintaining super-enhancer activity that promotes SASP gene expression [38].

DNA methylation patterns also shift during senescence, with overall genome hypomethylation but locus-specific hypermethylation changes, affecting gene silencing or activation [39]. Reduced activity of DNA methyltransferases and altered function of demethylases contribute to these changes,

influencing inflammatory and senescence-related gene networks. These epigenetic modifications collectively establish and sustain the senescent state by tightly controlling cell cycle arrest, inflammatory signaling, and tissue remodeling. Given their reversible nature, epigenetic regulators represent promising therapeutic targets to modulate senescence and extend healthy aging [34]. Modulating key players such as BRD4 with inhibitors has shown potential in dampening SASP and alleviating detrimental effects of senescence.

3. Immunosenescence: Molecular Features and Cellular Impact

Immunosenescence is defined as the progressive deterioration and remodeling of the immune system associated with aging, which leads to impaired immune responses and increased vulnerability to infections, cancer, autoimmune diseases, and poorer vaccine efficacy [5]. This complex process involves changes at the cellular, molecular, and organ levels, critically impacting both innate and adaptive immunity [8].

The hallmarks of immunosenescence include thymic involution, which results in reduced output of naïve T cells and an imbalanced ratio of naïve to memory T cells. Hematopoietic stem cell dysfunction contributes to impaired renewal and differentiation of immune cells [6]. A key feature is the accumulation of late-differentiated or senescent memory T cells, often characterized by loss of co-stimulatory molecules like CD28 and expression of senescence markers such as p16 INK4a and p21 CIP1 [40]. Another hallmark is chronic low-grade systemic inflammation, termed inflammaging, marked by persistently elevated pro-inflammatory cytokines. This state can drive tissue damage and exacerbate age-related pathologies [41].

3.1. Senescence of Innate Immune Cells: Macrophages

Senescence of innate immune cells, particularly macrophages and natural killer cells, contributes significantly to age-related immune dysfunction [1, 42]. Macrophages in aged individuals exhibit altered polarization and functional changes that impair their ability to clear pathogens and senescent cells effectively. Aging macrophages show dysregulated cytokine production with increased pro-inflammatory mediators, contributing to chronic inflammation or inflammaging. Additionally, macrophage phagocytic capacity and efferocytosis (clearance of apoptotic cells) decline, undermining tissue homeostasis and immune surveillance [43].

Natural killer (NK) cells are critical for the early immune response against tumors and infected or stressed cells, including senescent cells [44]. NK cell senescence is characterized by reduced cytotoxic activity due to impaired degranulation and diminished expression of key cytolytic proteins like perforin and granzyme B. Aging also leads to

altered receptor expression on NK cells, affecting their activation and capacity to recognize targets. Furthermore, NK cells produce fewer cytokines such as interferon-gamma (IFN- γ), weakening their ability to orchestrate immune responses [45]. Senescent NK cells additionally experience metabolic dysfunction, including mitochondrial impairments that reduce energy production and increase reactive oxygen species, which further compromise function [46].

The accumulation of senescent macrophages and NK cells not only diminishes innate immunity but also exacerbates tissue inflammation and pathology through secretion of senescence-associated secretory phenotype (SASP) factors [47]. Importantly, the decline in NK cell-mediated clearance of senescent and damaged cells allows their accumulation, which can drive age-related diseases and cancer progression [48].

3.2. T and B Cell Senescence and Their Altered Signaling Pathways

T and B cell senescence is a key aspect of immunosenescence, characterized by progressive functional decline and altered signaling pathways that impair adaptive immune responses [49]. In T cells, senescence involves several mechanisms including chronic antigen stimulation, telomere shortening, mitochondrial dysfunction, and activation of age-related signaling pathways [50]. Key molecular pathways driving T cell senescence include p38 MAPK and ERK1/2 signaling, which induce cell cycle arrest by activating cell cycle inhibitors like p53, p21, and p16 [51]. Sestrin proteins (SESN1/2/3) promote senescence through modulation of mTOR and activation of AMP-activated protein kinase (AMPK), which in turn activate p38 MAPK and other stress kinase pathways [52]. Senescent T cells show decreased proliferative capacity, altered metabolic profiles with changes in oxidative phosphorylation and glycolysis, and reduced cytokine production [53]. They also accumulate markers of senescence like p16 INK4a, lose co-stimulatory molecules (e.g., CD28), and show restricted T cell receptor (TCR) diversity, leading to impaired immune surveillance and response to new antigens [22].

B cell senescence similarly involves a decline in early progenitors and a shift from a naïve to more activated, pro-inflammatory phenotype termed age-associated B cells (ABCs) [54]. ABCs express markers like CD11c and T-bet, produce higher levels of inflammatory cytokines and autoantibodies, and contribute to chronic inflammation (inflammaging) and impaired humoral immunity, such as reduced vaccine responsiveness [55]. B cells interact closely with T cells, influencing T cell senescence by modulating T cell differentiation, exhaustion, and clonal diversity through cytokine signaling pathways like TNF α , IFN γ , IL-2, and TGF β . This crosstalk exacerbates overall adaptive immune dysfunction with age [54].

3.3. Chronic Low-Grade Inflammation and SASP Factors in Immune Aging

Chronic low-grade inflammation, termed as inflammaging, is a hallmark feature of immune aging and is closely linked to the accumulation of senescent cells and their senescence-associated secretory phenotype (SASP) [56]. Senescent cells secrete a diverse array of SASP factors including pro-inflammatory cytokines (such as IL-6, IL-1 β , TNF- α), chemokines, growth factors, proteases, and matrix remodeling enzymes. These factors act in an autocrine and paracrine manner to sustain a tissue environment of persistent inflammation, which contributes to the gradual deterioration of immune function and the development of age-related diseases [57].

The primary physiological role of SASP is to activate immune responses, particularly recruitment and activation of macrophages and other immune cells to eliminate senescent cells [56]. However, with aging, the efficiency of immune clearance declines due to impaired phagocytosis, causing accumulation of senescent cells and chronic SASP secretion [57]. This persistent SASP-driven inflammation exacerbates tissue damage, promotes immune dysregulation, and disrupts lymphoid organ integrity, which further impairs immune cell development and function [58].

3.4. Interplay Between Cellular Senescence and Immune Function Decline

The interplay between cellular senescence and immune function decline is a central feature of aging and contributes to multiple age-related diseases. Senescent cells accumulate in various tissues with age and acquire a senescence-associated secretory phenotype (SASP), characterized by the secretion of pro-inflammatory cytokines, chemokines, growth factors, and proteases [1, 59]. While low levels of SASP may aid in tissue repair and immune surveillance, chronic excess SASP disrupts tissue homeostasis by maintaining a persistent pro-inflammatory environment, impairing intercellular communication, and promoting further cellular damage [60].

This chronic inflammatory milieu, termed inflammaging, undermines immune system function. Senescent immune cells such as T cells exhibit features like overexpression of cell cycle inhibitors p16 and p21, altered surface markers, and reduced proliferative capacity, leading to impaired responses to infections and vaccines [59]. SASP factors further exacerbate immune dysfunction by contributing to thymic involution, reduced naïve T cell generation, altered naïve/memory cell ratios, and impaired antigen presentation by dendritic cells and macrophages [1].

4. Model Organisms in Senescence Research

Model organisms play a pivotal role in senescence research by providing tractable systems to investigate the complex molecular and cellular mechanisms underpinning aging and age-related diseases [61]. These organisms allow detailed genetic, cellular, and physiological studies that are often not feasible in humans due to lifespan and ethical constraints. These model organisms include Yeast, *C. elegans*, *Drosophila melanogaster*, and Mouse provide insights into conserved and species-specific mechanisms of senescence, enabling discoveries with translational potential to human health span extension [62].

4.1. Yeast as a Model for Replicative Aging and Molecular Pathways

Yeast, particularly the budding yeast *Saccharomyces cerevisiae*, serves as a powerful model organism for studying replicative aging and the molecular pathways involved [62]. Aging in yeast is primarily investigated through two paradigms: replicative lifespan (RLS) and chronological lifespan (CLS). The replicative lifespan measures the number of daughter cells a mother yeast cell can produce before senescence, modeling aging of dividing cells such as stem cells in higher eukaryotes. Chronological lifespan, on the other hand, measures the survival time of non-dividing yeast cells in a stationary phase, analogous to aging of post-mitotic cells like neurons [63].

Budding yeast cells age asymmetrically, with mother cells retaining damaged cytoplasmic components including oxidatively damaged proteins and dysfunctional mitochondria, which accumulate over successive divisions leading to senescence [64]. Hallmarks of yeast aging include a buildup of reactive oxygen species (ROS), loss of mitochondrial function, DNA damage, chromatin alterations, apoptotic cell death features, and decline in cellular homeostasis, mirroring key aspects of human cellular aging [65].

At the molecular level, several conserved pathways regulate yeast aging. The target of rapamycin (TOR) pathway, nutrient-sensing kinases such as Sch9 and protein kinase A (PKA), and sirtuins (Sir2) coordinate cellular responses to nutrients and stress, influencing longevity [64]. Caloric restriction, achieved by reducing glucose and amino acid availability, extends lifespan in yeast by modulating these pathways, demonstrating evolutionary conservation of nutrient signaling in aging [66].

Due to its short lifespan, genetic tractability, and thoroughly characterized aging phenotypes, yeast remains an essential system for identifying anti-aging compounds, dissecting longevity genes, and understanding fundamental aging mechanisms that are relevant to more complex organisms [67]. Yeast, particularly *Saccharomyces cerevisiae*, is a widely used model organism for studying replicative aging

and the molecular pathways involved. Yeast aging is studied mainly through replicative lifespan (RLS) the number of daughter cells a mother cell can produce before senescence and chronological lifespan (CLS), which measures survival time in a nondividing state [68]. RLS in yeast mimics aging of dividing cells such as stem cells, while CLS models aging of post-mitotic cells like neurons.

4.2. *Caenorhabditis Elegans* for Genetic Dissection of Senescence and Immune Aging

Caenorhabditis elegans (*C. elegans*) is a widely used genetic model organism for dissecting the molecular and cellular mechanisms of senescence and immune aging [69]. This nematode offers several advantages including a short lifespan of approximately three weeks, a fully sequenced and well-annotated genome with high conservation of key aging-related genes, and powerful genetic manipulation tools such as RNA interference (RNAi), CRISPR, and transgenics [70]. These features enable detailed examination of longevity pathways, stress responses, and age-related physiological decline in an experimentally tractable system.

C. elegans aging is characterized by progressive functional deterioration of tissues such as its nervous system, muscle, and intestine, influenced by the interplay of genetic pathways and environmental factors [70]. Central aging regulatory pathways elucidated in *C. elegans* include the insulin/IGF-1 signaling (IIS) pathway, where mutations in the *daf-2* gene (insulin/IGF-1 receptor homolog) extend lifespan by activating the downstream transcription factor DAF-16/FOXO, which promotes stress resistance and longevity genes [71]. Additional pathways important in *C. elegans* longevity and senescence include the mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuin pathways, which coordinate nutrient sensing, metabolism, and autophagy.

4.3. *Drosophila Melanogaster* in Metabolic and Systemic Aging Studies

Drosophila melanogaster, the common fruit fly, serves as a valuable model for studying metabolic and systemic aging due to its well-characterized genetics, relatively short lifespan, and conserved metabolic pathways relevant to humans [72, 73]. Research integrating metabolomic profiling with experimental evolution has revealed that aging in *Drosophila* involves extensive metabolic remodeling affecting carbohydrates, amino acids, and the tricarboxylic acid (TCA) cycle. These metabolomic changes correlate with life history traits such as accelerated aging induced by selection for early reproduction [74].

Metabolic aging in *Drosophila* is associated with alterations in pathways like oxidative phosphorylation, mitochondrial function, and nutrient sensing pathways including insulin/IGF

signaling and mTOR [72]. Age-related decline in mitochondrial efficiency and shifts in energy metabolism are key contributors to systemic aging and functional deterioration observed in the fly [74].

Metabolomic clocks constructed from *Drosophila* data have demonstrated that metabolite profiles can serve as reliable biomarkers of biological age, predicting mortality risk and lifespan [73]. Metabolites such as kynurenine, putrescine, choline, lysine, and glucose show significant associations with aging phenotypes, some of which are evolutionarily conserved across species like *C. elegans* and mice [72].

4.4. Mouse Models Elucidating Tissue-Specific Senescence and Immune Aging Mechanisms

Recent research utilizing mouse models has elucidated various aspects of tissue-specific senescence and immune aging mechanisms. These models have shown that senescence in immune cells, such as T cells (CD4⁺ and CD8⁺), B cells, NK cells, and monocytes/macrophages, accumulates with age due to DNA damage and leads to secretion of senescence-associated secretory phenotype (SASP) factors that can induce secondary senescence in non-immune tissues like liver, kidney, muscle, and intervertebral discs [61, 75]. For example, mice with hematopoietic cell-specific deletion of DNA repair gene *Ercc1* showed systemic tissue degeneration and aging phenotypes driven by senescent immune cells, confirming a non-autonomous mechanism where immune senescence promotes tissue-wide aging [76]. Conversely, adoptive transfer of young immune cells can reduce senescent cell burden in multiple tissues, highlighting immune surveillance roles in senescence clearance.

Additionally, mouse models have illuminated molecular pathways regulating immune aging such as increased expression of CISH in aged T cells, impairing lysosomal degradation and leading to excessive inflammation (inflammaging), and IL-33 driven thymic involution that causes naive T cell aging and immunosuppression during severe infections [75]. These studies emphasize the tissue-specific immune senescence processes and their impact on systemic aging and age-related diseases.

5. Emerging Molecular Pathways and Novel Insights

Emerging molecular pathways and novel insights in immune aging highlight several key mechanisms and therapeutic targets with recent advances focused on aging biomarkers, immune cell functions, and signaling pathways [77]. One main area of progress is the development of immunological aging clocks such as the inflammatory aging clock (iAge), which uses deep learning to quantify systemic chronic inflammation and identify biomarkers like CXCL9 that promote vascular and endothelial cell senescence [78]. This biomarker

approach allows prediction of multimorbidity and frailty and provides potential targets for reversing aging phenotypes by silencing key inflammatory mediators. Single-cell RNA sequencing (scRNA-seq) further reveals shifts in naive and memory T cell subsets as indicators of biological age and immune resilience, seen even in supercentenarians, highlighting immune cell heterogeneity and functional changes with age [79].

5.1. Role of Retrotransposons and Cytoplasmic DNA in Senescence Signaling

The role of retrotransposons, especially LINE-1 (L1), in senescence signaling has gained substantial attention as an emerging mechanism that links genomic instability to cellular aging. LINE-1 elements are autonomous retrotransposons that can become transcriptionally derepressed during cellular senescence due to epigenetic changes such as DNA hypomethylation [80]. This leads to increased expression and retrotranscription of LINE-1 RNA into cytoplasmic DNA, which can accumulate and act as damage-associated molecular patterns (DAMPs) [6].

Cytoplasmic DNA derived from retrotranscribed LINE-1 sequences triggers innate immune responses primarily through the cGAS-STING pathway [80]. Activation of this pathway induces type I interferon responses and a senescence-associated secretory phenotype (SASP), characterized by secretion of pro-inflammatory cytokines (e.g., IL-1 β , IL-6) that reinforce senescence both cell-autonomously and in surrounding tissues [80]. For instance, in senescent human endothelial and fibroblast cells, increased LINE-1 and Alu RNA expression accompanies elevated cytoplasmic DNA copies from retrotransposons, contributing to chronic inflammation signaling and sustained senescence [6].

5.2. RNA Modifications

RNA modifications, particularly N6-methyladenosine (m6A) methylation, play a crucial regulatory role in gene expression programs controlling cellular senescence [81]. This epigenetic modification affects mRNA stability, splicing, transport, storage, translation, and decay, ultimately influencing the levels and activity of key senescence-associated genes [79].

In senescent cells, altered m6A methylation has been observed in processes linked to oxidative stress, DNA damage response, telomere maintenance, and the senescence-associated secretory phenotype (SASP) [82]. For example, methyltransferases such as METTL3 and METTL14 catalyze m6A addition leading to enhanced mRNA stability and translation of genes involved in DNA repair (e.g., recruitment of RAD51 and BRCA1), antioxidant defense (e.g., superoxide dismutase, catalase), and SASP regulation through inflammatory cytokines [83]. Conversely, m6A demethylases such as FTO and ALKBH5 remove these marks impacting

mRNA turnover and modulating cellular stress responses and telomerase expression [82].

Specifically, METTL3-mediated m6A methylation reduces pro-inflammatory cytokines like TNF while promoting IL-17 expression via IGF2BP2 in some cell types, showing dynamic regulation of inflammatory signaling during senescence [84]. m6A also influences oxidative stress by regulating antioxidant enzyme expression and formation of stress granules, balancing cell survival and senescence [85]. These modulations of m6A on senescence-associated transcripts form an important layer of posttranscriptional gene regulation that determines cell fate decisions related to aging, chronic inflammation, and tissue dysfunction. Targeting m6A writers, erasers, and readers represents a promising therapeutic strategy to modulate aging and senescence pathologies at the RNA level [86].

5.3. Metabolic Reprogramming During Senescence and Immune Aging

Metabolic reprogramming is a hallmark of cellular senescence and immune aging that sustains the bioenergetic and biosynthetic demands of senescent cells and senescent immune cells, thereby shaping their phenotype and function [87]. Senescent cells undergo profound metabolic shifts, characterized by increased glycolysis and extracellular acidification to compensate for mitochondrial dysfunction, which is a common feature in aged cells [5]. Additionally, there is remodeling of fatty acid oxidation and lipid metabolism supporting the production of the senescence-associated secretory phenotype (SASP), which contributes to chronic inflammation and tissue dysfunction. Mitochondrial regulation is tightly linked to these metabolic changes, with non-coding RNAs such as senescence-induced lncRNAs interacting with mitochondrial enzymes to maintain cellular homeostasis and prevent excessive damage [88].

In the immune system, metabolic reprogramming occurs in T cells, macrophages, and other immune subsets during aging, marked by mitochondrial decline, increased reliance on glycolysis, and altered fatty acid oxidation [89]. These alterations lead to diminished immune surveillance, immunosenescence, and a heightened inflammatory state termed inflammaging [90]. The metabolic state influences immune cell differentiation and function, thereby impacting responses to infections and vaccination efficacy. Restoration of mitochondrial function and modulation of metabolic pathways have emerged as promising strategies to rejuvenate immune cells and mitigate age-related immune dysfunction [91]. Overall, the interplay between metabolic reprogramming and cellular senescence critically governs tissue homeostasis and systemic aging, offering potential targets for therapeutic intervention to promote healthy aging and delay age-associated diseases [90].

5.4. Multi-Omics and Single-Cell Approaches Revealing Senescence Heterogeneity

Multi-omics and single-cell approaches have profoundly advanced the understanding of cellular senescence heterogeneity by capturing the complexity and diversity of senescent states at multiple molecular layers [92]. Integrated multi-omics studies combining ATAC-seq, RNA-seq, and ChIP-seq have revealed dynamic changes in chromatin accessibility, histone modifications, and gene expression that define unique regulatory networks in different types of senescence, such as replicative and oncogene-induced senescence. These analyses uncovered key regulatory genes including NAT1, PBX1, and RRM2 that exhibit coordinated regulation at the epigenetic and transcriptional levels and may serve as biomarkers for senescence and aging-related diseases [92]. The chromatin landscape alterations, such as loss or gain of accessibility correlated with histone marks, illustrate distinct nuclear architecture remodeling between senescent subtypes, contributing to transcriptional noise and gene expression variability [27].

At the single-cell level, multi-omics technologies enable resolution of cellular senescence heterogeneity by simultaneously profiling transcriptomes, epigenomes, and proteomes within individual cells [93]. This allows identification of senescent cell subpopulations with distinct functional states, metabolic profiles, and inflammatory phenotypes. Single-cell RNA sequencing combined with epigenetic profiling has revealed that senescent cells are not uniform but comprise diverse subsets that differ in their secretory profiles, immune evasion capabilities, and susceptibility to clearance [27]. This heterogeneity underlines the challenges and opportunities for designing precise senolytic and senomorphic therapies targeting specific senescent subtypes.

5.5. Immune Surveillance of Senescent Cells and Strategies for Senolytic Therapies

Immune surveillance of senescent cells is a critical mechanism by which the immune system identifies and eliminates these cells to maintain tissue homeostasis and prevent age-related pathologies [94]. Senescent cells are highly immunogenic due to their senescence-associated secretory phenotype (SASP), which includes chemokines, cytokines, and adhesion molecules that recruit and activate innate and adaptive immune cells such as natural killer (NK) cells, macrophages, and T cells [95]. These immune cells recognize senescent cells through upregulated surface ligands and respond by deploying cytotoxic mechanisms, notably perforin-granzyme mediated apoptosis, essential for clearing senescent cells. Impaired surveillance, such as loss of perforin function, leads to accumulation of senescent cells, exacerbating tissue dysfunction and aging [4].

Senescent cells also engage innate immune pattern recognition receptors (PRRs) via damage-associated molecular

patterns (DAMPs) like HMGB1 and cytoplasmic chromosomal DNA fragments, activating cGAS-STING signaling that amplifies inflammatory SASP and attracts immune effectors [96]. Interestingly, some senescent cells can evade immune clearance by modulating these signals or expressing immune checkpoint molecules, contributing to chronic senescent cell accumulation, especially in aging tissues [97].

Senolytic therapies aim to harness or enhance immune-mediated clearance by targeting senescent cell anti-apoptotic pathways (SCAPs) that confer resistance to cell death [98]. Approaches include pharmacological agents to sensitize senescent cells to immune attack, chimeric antigen receptor (CAR) T cells engineered against senescence markers, and boosting NK cell activity. Enhancing immune surveillance through cytokine modulation or checkpoint blockade also represents a promising intervention to promote senescent cell removal and ameliorate age-associated diseases [99].

6. Experimental Techniques and Advances

Recent advances in experimental techniques have significantly enhanced the capacity to study cellular senescence, providing deeper insights into its mechanisms, heterogeneity, and biological impact [87]. Traditional methods for senescence detection, such as senescence-associated β -galactosidase staining and analysis of cell cycle regulators (p16, p21), have been complemented by more sophisticated molecular and omics-based approaches [100]. Multi-omics strategies integrating genomics, transcriptomics, proteomics, metabolomics, and lipidomics now enable comprehensive profiling of senescent cells at multiple biological layers, unraveling complex regulatory networks and metabolic reprogramming associated with senescence [101].

6.1. Genetic Manipulation Tools in Model Organisms

Genetic manipulation tools such as CRISPR/Cas9 and RNA interference (RNAi) are indispensable for investigating cellular senescence and aging in model organisms [102]. CRISPR/Cas9 technology enables precise genome editing by creating targeted double-strand breaks and facilitating gene knockout, knockin, or base editing. This has been applied extensively in organisms like mice, zebrafish, *C. elegans*, and the African turquoise killifish, the latter offering a compressed lifespan ideal for aging studies [103]. For example, CRISPR-mediated knockout of the telomerase gene (TERT) in killifish accelerated aging phenotypes, illustrating the model's utility for dissecting genetic contributions to senescence [102]. Similarly, in mice, CRISPR has been used to target genes like LMNA for progeria models, advancing the understanding of premature aging mechanisms.

RNAi complements CRISPR by enabling selective gene

silencing via degradation of target mRNA, allowing functional studies of senescence-related genes across various organisms [103]. While RNAi libraries are mainly developed for human, mouse, and rat cells, they continue to provide a robust platform for rapid gene knockdown and high-throughput screening [102].

Advances in CRISPR-based functional screens revealed novel senescence modulators, including histone variants like H2AZ1 whose reduction ameliorated senescence in human stem cells [39, 103]. These genetic tools facilitate dissecting molecular pathways, validating therapeutic targets, and developing interventions for age-associated diseases. Together, CRISPR and RNAi offer powerful, complementary approaches for elucidating senescence biology in vivo and in vitro across diverse model organisms, accelerating translation of findings to human health [103].

6.2. Omics Technologies

Omics technologies, encompassing transcriptomics, epigenomics, proteomics, and metabolomics, have revolutionized the study of cellular senescence by providing comprehensive molecular profiles that reveal the mechanistic underpinnings of aging and senescence-associated diseases [92]. Transcriptomics, through RNA sequencing (RNA-seq), allows high-resolution mapping of gene expression changes during senescence, identifying key pathways such as cell cycle arrest, DNA damage response, and the senescence-associated secretory phenotype (SASP) [104]. Epigenomics techniques, including ATAC-seq and ChIP-seq, uncover alterations in chromatin accessibility and histone modifications that regulate gene transcription in senescent cells, revealing distinctive patterns like senescence-associated heterochromatin foci and remodeling of nucleosome landscapes [92]. These epigenetic changes contribute to elevated transcriptional noise and altered regulatory networks.

Proteomics and metabolomics complement transcriptomic and epigenomic data by quantifying protein abundance, post-translational modifications, and metabolic shifts characteristic of senescence [105]. Proteomic profiling captures changes in SASP components and identifies senescence biomarkers, while metabolomics reveals reprogramming of energy metabolism, amino acid turnover, and lipid remodeling that sustain senescent cell function and inflammation [106]. Importantly, integrative multi-omics approaches combining these datasets provide a systems-level understanding of senescence dynamics, revealing coordinated regulatory elements and pathways that drive senescence phenotypes. These methodologies have been successfully applied in various tissues including cardiovascular, skeletal muscle, and skin, fostering discovery of novel therapeutic targets and biomarkers for age-related diseases [107]. Overall, omics technologies represent powerful tools to dissect the heterogeneity and complexity of cellular senescence and enable precision medicine strategies targeting aging and its associated pathologies.

6.3. Live-Cell Imaging and Single-Cell Sequencing in Senescence Research

Live-cell imaging and single-cell sequencing have become indispensable techniques in senescence research, offering unique insights into the dynamics and heterogeneity of senescent cells [108]. Live-cell imaging methods, including advanced fluorescence microscopy and imaging flow cytometry, enable real-time monitoring of senescence markers such as senescence-associated β -galactosidase (SA- β -Gal) activity, morphological changes, and autofluorescence in individual cells without disrupting their viability [109]. Techniques like the Fully-Automated Senescence Test (FAST) utilize high-content imaging combined with machine learning to provide high-throughput, quantitative assessment of senescence at single-cell resolution, reducing false positives and allowing detailed temporal analyses [108]. Additionally, novel probes for positron emission tomography (PET) facilitate non-invasive in vivo detection and quantification of senescent cells, expanding the translational impact of live imaging [109].

Single-cell sequencing technologies complement imaging by enabling comprehensive molecular profiling of individual senescent cells [93]. Single-cell RNA sequencing (scRNA-seq) deciphers transcriptional heterogeneity, identifying diverse senescent cell subpopulations with distinct gene expression patterns and SASP phenotypes. Integrating single-cell transcriptomics with epigenomic and proteomic data further elucidates regulatory networks governing senescence, immune evasion, and tissue-specific functions [110]. Together, live-cell imaging and single-cell sequencing provide a holistic approach to characterize senescence, advancing understanding of its complexity and informing development of targeted senolytic and senomorphic therapies.

6.4. Biomarkers and Assays for Detecting Senescence and Immunosenescence

Biomarkers and assays for detecting cellular senescence and immunosenescence rely on a combination of morphological, biochemical, molecular, and functional indicators due to the heterogeneity and complexity of senescent states [111]. The classical hallmark of senescent cells is increased lysosomal senescence-associated β -galactosidase (SA- β -gal) activity, detectable by enzymatic staining with substrates like X-gal. Morphologically, senescent cells are enlarged and flattened, which can be assessed by microscopy or flow cytometry [112]. DNA damage response (DDR) markers such as γ H2AX, 53BP1, and telomere-associated foci indicate persistent DNA damage characteristic of senescent cells. Key cell cycle regulators p16 INK4a, p21, and p53 are elevated, with detection methods including immunohistochemistry, western blotting, and immunofluorescence. Additional markers include reduced lamin B1 levels, formation of senescence-associated heterochromatin foci (SAHF), and accumulation of lipofuscin, a

pigment detectable by microscopy [111].

Immunosenescence is characterized by altered expression of surface markers on immune cells, increased pro-inflammatory cytokine secretion (inflammaging), and functional impairments that can be assessed by multiplex cytokine assays, flow cytometry, and functional immune assays [112]. Due to no single marker being definitive, multiparametric approaches combining senescence-associated secretory phenotype (SASP) profiling, cell cycle arrest markers, DNA damage indicators, and morphological assessments are commonly employed for accurate detection. Emerging assays include reporter systems for senescence gene promoters, high-content imaging, and single-cell resolution techniques that allow precise quantification and characterization of senescent and senescent-like immune cells in various tissues and experimental models [111]. These biomarkers and detection methods are fundamental for advancing senescence research and developing targeted senolytic and senomorphic therapies.

7. Clinical and Therapeutic Implications

Cellular senescence plays a pivotal and dual role in various chronic diseases including cancer, fibrosis, and inflammatory disorders. In cancer, senescence acts as an early tumor-suppressive mechanism by enforcing irreversible growth arrest in damaged or precancerous cells, preventing malignant transformation [113]. However, the senescence-associated secretory phenotype (SASP) paradoxically promotes tumor progression by creating a pro-inflammatory microenvironment that facilitates cancer cell plasticity, epithelial-mesenchymal transition, and immune evasion [114]. Senescent stromal cells and tumor-associated senescent cells release cytokines such as IL-6 and IL-8, which enhance invasiveness and metastatic potential of neighboring tumor cells [113]. Moreover, therapy-induced senescence in tumors can drive relapse by promoting stem-like traits in residual cancer cells. In fibrosis, persistent senescent cells contribute to aberrant tissue remodeling and chronic inflammation via SASP factors, exacerbating organ dysfunction. Similarly, in chronic inflammatory diseases, senescent cells sustain low-grade inflammation driving tissue degeneration and impaired regeneration [114].

Therapeutically, senolytics and senomorphics have emerged as promising interventions targeting senescent cells [114]. Senolytics are drugs designed to selectively induce apoptosis in senescent cells by inhibiting their survival pathways, thereby reducing SASP burden and associated tissue damage. Examples include dasatinib, quercetin, and BCL-2 inhibitors, which have shown efficacy in preclinical models of fibrosis, metabolic syndrome, and osteoarthritis [98]. Senomorphics, on the other hand, modulate the SASP without killing cells to suppress chronic inflammation and improve tissue homeostasis. Immunomodulatory strategies targeting immunosenescence focus on rejuvenating immune

function, enhancing senescent cell clearance by boosting natural killer cells, T cells, or macrophage activity, and using immune checkpoint inhibitors to reverse immune dysfunction in aging and cancer [113].

Despite encouraging preclinical successes, translating senescence-targeted therapies into clinical practice faces several challenges. Senescence heterogeneity, tissue-specific roles, and the dynamic balance between protective and deleterious aspects complicate patient selection and treatment regimens [113]. Additionally, current biomarkers lack universal specificity, making monitoring and targeting senescent cells difficult. Moreover, off-target effects and immunosuppression risk require careful evaluation [98]. Nevertheless, ongoing advances in molecular profiling, drug delivery systems, and immunotherapy hold promise for overcoming these hurdles and harnessing senescence modulation to improve outcomes in cancer, fibrosis, and chronic inflammatory diseases [75].

8. Challenges and Future Directions

The complex molecular interplay between cellular senescence and immunosenescence is increasingly recognized as a key driver of aging and age-related diseases [2]. Senescent cells secrete pro-inflammatory factors known as the senescence-associated secretory phenotype (SASP), which induce chronic inflammation (inflammaging) that impairs immune function and promotes immunosenescence a decline in immune cell number and function, including reduced naive T and B cells and increased dysfunctional memory cells [115]. This creates a vicious cycle where senescent immune cells fail to clear senescent cells effectively, further exacerbating tissue degeneration and systemic aging. Pathways such as cGAS-STING, TORC1-S6K-Syx13, and regulatory proteins like CISH in T cells have emerged as critical molecular mediators linking senescence to immune dysfunction and chronic inflammation [7].

Despite advances, significant gaps remain in fully understanding tissue-specific senescence dynamics due to heterogeneity in senescent cell types, differential SASP composition, and varied immune response profiles across organs [115]. Integrated multi-omics approaches, including single-cell transcriptomics, epigenomics, proteomics, and metabolomics, combined with artificial intelligence and machine learning tools, hold great potential to decode these complex networks [92]. These technologies can identify novel biomarkers, regulatory circuits, and therapeutic targets with unprecedented resolution, enabling dissection of cellular crosstalk and senescence heterogeneity in diverse tissues [29, 115].

Looking forward, personalized anti-aging interventions targeting senescence are on the horizon. Strategies may involve tailored senolytic and senomorphic therapies guided by individual molecular and immune profiling, combined with immune rejuvenation approaches to enhance senescent cell clearance [116]. Advances in gene editing, epigenetic modulation, and AI-driven drug discovery will further refine these

therapies. Overcoming challenges of senescence heterogeneity, tissue specificity, and ensuring safety during senolytic treatment will be critical to translating findings into effective, personalized clinical applications aimed at improving healthspan and lifespan.

9. Conclusion

Cellular senescence and immunosenescence represent interconnected aging phenomena characterized by irreversible cell cycle arrest and functional decline in both somatic and immune cells. Key molecular mechanisms governing cellular senescence involve activation of DNA damage response pathways, persistent telomere attrition, metabolic reprogramming, and engagement of innate immune sensors such as the cGAS-STING pathway that promotes inflammatory SASP secretion and systemic inflammation. Immunosenescence, the aging of the immune system, features diminished naive T and B cell pools, increased senescent and exhausted immune cells, and chronic inflammation (inflammaging), partly driven by senescent immune cells failing to clear damaged tissue and other senescent cells. Regulatory pathways such as TORC1-S6K and proteins like CISH have recently been identified as critical to the development of immunosenescence and age-related inflammatory dysfunction. Model organism research, encompassing mice, fruit flies, and killifish, has been instrumental in elucidating these complex molecular pathways. Animal models with genetic alterations in DNA repair, telomerase, and immune regulation genes reveal how senescence accumulation leads to tissue degeneration and aging phenotypes at systemic levels. Moreover, adoptive transfer experiments with young immune cells demonstrate the ability to mitigate systemic senescence, underscoring immune clearance as a therapeutic target.

Looking ahead, integrated multi-omics and single-cell technologies combined with artificial intelligence-driven analyses promise unprecedented mechanistic insights into senescence heterogeneity, tissue specificity, and crosstalk with immunity. Such advances pave the way for personalized anti-aging interventions, including targeted senolytics, senomorphics, and immunomodulatory therapies designed to selectively eliminate or reprogram senescent cells while boosting immune rejuvenation. Addressing challenges related to senescence complexity, biomarker specificity, and translational hurdles will be critical to fully realize the therapeutic potential of senescence targeting in aging biology and age-related disease treatment.

Abbreviations

ABCs	Age-Associated B Cells
AMPK	Activated Protein Kinase
CDKI	Cyclin-Dependent Kinase Inhibitor
CLS	Chronological Lifespan

DAMPs	Damage-Associated Molecular Patterns
DDR	DNA Damage Response
FAST	Fully-Automated Senescence Test
NK	Natural Killer
PET	Positron Emission Tomography
RLS	Replicative Lifespan
RNAi	RNA Interference
SAHF	Senescence-Associated Heterochromatin Foci
SASP	Senescence-Associated Secretory Phenotype
SCAPs	Senescent Cell Anti-Apoptotic Pathways
scRNA-seq	Single-Cell RNA Sequencing
TCA	Tricarboxylic Acid
TCR	T Cell Receptor
TIS	Telomere Dysfunction-Induced Senescence
TOR	Target of Rapamycin

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