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REVIEW ARTICLE

Physiological Mechanisms of Paracrine Signaling in Tissue Aging and Repair

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Abstract: Cellular senescence is a fundamental physiological mechanism characterized by stable cell cycle arrest coupled with a hyperactive secretory metabolism. While historically viewed merely as a mechanism to prevent tumorigenesis, the accumulation of senescent cells acts as a primary driver of organismal aging and tissue dysfunction. The Senescence-Associated Secretory Phenotype (SASP) constitutes the functional output of these cells, mediating autocrine and paracrine signaling through a complex secretome of cytokines, chemokines, growth factors, and matrix metalloproteinases. The physiological cascade initiating the SASP requires the integration of nuclear DNA damage signals and mitochondrial metabolic perturbations, culminating in the activation of cytosolic DNA sensing pathways such as cGAS-STING. Functionally, these paracrine signals exhibit antagonistic pleiotropy: acute expression facilitates wound healing, tissue remodeling, and tumor suppression, whereas chronic persistence fundamentally disrupts the tissue microenvironment. This pathological shift drives chronic low-grade inflammation, induces secondary senescence in neighboring cells via the bystander effect, and overwhelms immune clearance mechanisms. The molecular regulation of the SASP provides the mechanistic basis for age-related physiological decline and emphasizes the secretome as a critical target for therapeutic intervention to extend healthspan.

Keywords: Cellular Senescence; SASP; Inflammaging; Paracrine Signaling; Tissue Repair.

1. Introduction

The biological conceptualization of aging has undergone a profound transformation since the seminal discovery of the "Hayflick Limit," which first delineated the finite replicative capacity of somatic cells in culture [1]. Initially, cellular senescence was interpreted through a narrow lens as a static endpoint a cell-autonomous mechanism evolved primarily to arrest the proliferation of damaged or potentially oncogenic cells. Early research, therefore, concentrated heavily on the intracellular molecular brakes governing this arrest, mapping the canonical tumor suppressor pathways involving p53/p21CIP1 and p16INK4a/Rb. While these pathways remain critical for the establishment of the senescent state, contemporary inquiry has fundamentally shifted its focus from the arrested cell itself to its dynamic influence on the surrounding tissue microenvironment. It is now understood that senescent cells are far from being metabolically inert "zombie cells" simply occupying space within a tissue. Instead, they remain highly metabolically active, characterized by enlarged morphology, resistance to apoptosis, and, most importantly, robust protein synthesis and secretion [2].

This hyperactive secretory state, termed the Senescence-Associated Secretory Phenotype (SASP), represents a complex form of intercellular communication. Through the SASP, senescent cells release a potent cocktail of bioactive molecules including pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodeling proteases enabling them to signal physiological distress to the local tissue architecture and the systemic immune system. This paracrine signaling capability reframes senescence not merely as a halt in replication, but as a mechanism of tissue-level regulation and remodeling.

The physiological relevance of the SASP is governed by the evolutionary principle of antagonistic pleiotropy, where a biological process may be beneficial early in life but detrimental in later stages. In acute physiological settings, the SASP serves an essential, adaptive function. During embryonic development, wound healing, and tissue regeneration, the transient presence of senescent cells is critical. The paracrine signals they emit, such as Platelet-Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF), recruit immune actors (specifically Natural Killer cells and macrophages) to clear cellular debris and facilitate matrix remodeling. In this "acute" phase, the program operates as a self-limiting loop: senescent cells orchestrate the repair and are subsequently cleared by the very immune cells they recruited [3].

However, the trajectory of this signaling shifts dramatically with organismal aging. The efficiency of immune system in clearing senescent cells decreases as the immune system undergoes age-related functional decline (immunosenescence). This failure leads to

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a persistent, rather than transient, accumulation of senescent cells within tissues. Under these chronic conditions, the SASP ceases to be a repair signal and becomes a driver of pathology. The continuous, low-level secretion of pro-inflammatory factors such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) from these uncleared cells fuels "inflammaging" a state of sterile, chronic, low-grade inflammation that underpins frailty and a spectrum of age-related diseases, including atherosclerosis, osteoarthritis, and neurodegeneration [4]. Decoding the precise signaling cascades that regulate the tipping point between beneficial repair mechanisms and deleterious tissue degeneration has become a central challenge in modern geroscience.

2. Molecular Mechanisms Initiating the Secretory Phenotype

The establishment of the SASP is not an immediate consequence of cell cycle arrest but rather a distinct, temporally regulated program requiring persistent signaling. The initiation of this secretory profile relies on the integration of nuclear DNA damage signals and mitochondrial metabolic perturbations.

2.1. Genomic Instability and the DNA Damage Response (DDR)

The primary trigger for the SASP in many tissue contexts is the detection of unrepairable DNA damage, which activates the DNA Damage Response (DDR) machinery. Telomere attrition, oxidative stress, and oncogene activation all converge on double-strand breaks that recruit sensor proteins such as the MRE11-RAD50-NBS1 (MRN) complex [5]. This recruitment facilitates the activation of the ataxia-telangiectasia mutated (ATM) and Ataxia Telangiectasia and Rad3-related (ATR) kinases.

Table 1. Transcription Factors Regulating the SASP

Transcription Factor	Regulation Mechanism	Target Genes	Role in SASP
NF-κB (p65/p50)	Activated by DDR (via GATA4), p38 MAPK, and cGAS-STING.	IL-6, IL-8, CXCL1, ICAM-1	Master Regulator: Drives the bulk of the pro-inflammatory secretome.
C/EBP-β	Upregulated during senescence; works cooperatively with NF-κB.	IL-6, IL-8, GROα	Amplifies the inflammatory signal; critical for oncogene-induced SASP.
GATA4	Stabilized by inhibition of p62-mediated autophagy.	TRAF3IP2, IL-1A	Connects DNA damage to NF-κB activation; independent of p53.
mTORC1	Senses nutrient/energy status; regulates translation.	IL-1A, MAPKAPK2	Enhances translation of SASP mRNAs; 4EBP1-dependent regulation.

These kinases initiate a phosphorylation cascade that stabilizes p53, leading to the transcription of the Cyclin-Dependent Kinase (CDK) inhibitor *CDKN1A* (p21), which enforces cell cycle arrest. However, for the SASP to manifest, the DDR signaling must persist beyond the initial arrest. Persistent DNA damage foci maintain high levels of GATA4, a transcription factor that is normally degraded by autophagy. In senescent cells, the inhibition of p62-mediated autophagy stabilizes GATA4, allowing it to activate the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) [6]. NF-κB serves as the master transcriptional regulator of the SASP, driving the expression of key pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Interleukin-8 (IL-8). This pathway illustrates a critical physiological link between genomic instability and the induction of an inflammatory tissue state.

Table 2. Molecular Initiators of the Secretory Phenotype

Initiation Pathway	Primary Trigger	Sensors & Mediators	Mechanism of SASP Activation
DNA Damage Response (DDR)	Double-strand breaks (DSBs), Telomere dysfunction	ATM, ATR, Chk1/Chk2, p53	Persistent DDR foci stabilize GATA4 (via autophagy inhibition), enabling NF-κB activation.
Mitochondrial Dysfunction	Electron transport chain inefficiency	ROS (Reactive Oxygen Species)	ROS create a feedback loop reinforcing DDR; oxidation of signaling molecules.
Cytosolic DNA Sensing	Cytoplasmic Chromatin Fragments (CCFs), leaked mtDNA	cGAS, STING, TBK1	cGAS binds cytosolic DNA, producing cGAMP to activate STING, driving Type I Interferon and NF-κB responses.
Oncogene Activation	Ras/Raf hyperactivation	p38 MAPK, ERK	Direct phosphorylation of SASP-regulating transcription factors.

2.2. Mitochondrial Dysfunction and Cytosolic DNA Sensing

While nuclear DNA damage provides the initial trigger, mitochondrial dysfunction acts as an essential amplifier and sustainer of the paracrine phenotype. Senescent cells typically exhibit an increase in mitochondrial mass but a decrease in membrane potential, leading to the inefficient coupling of the electron transport chain and significant production of Reactive Oxygen Species (ROS) [7]. Elevated ROS levels create a feedback loop that induces further DNA damage, thereby perpetuating the DDR signaling described previously.

Moreover, a distinct mechanism linking mitochondrial distress to inflammation involves the mislocalization of DNA. Mitochondrial membrane permeabilization allows mitochondrial DNA (mtDNA) to leak into the cytosol. Additionally, persistent nuclear genomic instability can result in the formation of Cytoplasmic Chromatin Fragments (CCFs). These cytosolic DNA species are recognized as "non-self" or danger signals by the cyclic GMP-AMP synthase (cGAS) [8]. Upon binding DNA, cGAS produces the secondary messenger cGAMP, which activates the Stimulator of Interferon Genes (STING). The cGAS-STING pathway subsequently triggers the phosphorylation of IRF3 and NF-κB, launching a type I interferon response and reinforcing the production of SASP factors. This physiological sensing mechanism explains how metabolic deregulation and genomic instability synergize to create a robust inflammatory microenvironment.

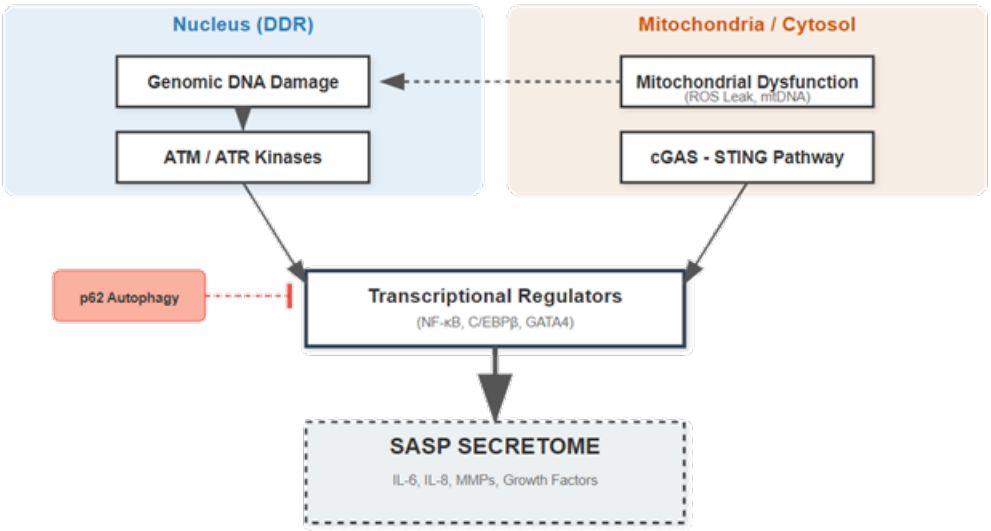

Figure 1. Molecular Initiation of the SASP

3. Physiological Classification of the SASP Secretome

The SASP is not a single, uniform program; its composition varies based on the cell type and the senescence-inducing stressor. However, a core "canonical" secretome exists, comprising several distinct classes of bioactive molecules that remodel the extracellular matrix (ECM) and modulate immune behavior.

3.1. Pro-inflammatory Cytokines and Chemokines

The most prominent feature of the SASP is the secretion of pro-inflammatory cytokines, with IL-6 and IL-8 (CXCL8) acting as reliable biomarkers. IL-6 functions in an autocrine manner to reinforce the senescence arrest via the STAT3 pathway, while simultaneously acting in a paracrine manner to alert the immune system [9]. Chemokines such as CXCL1 (GROα) and CXCL10 (IP-10) are critical for establishing chemotactic gradients that recruit Natural Killer (NK) cells, macrophages, and T cells to the site of damage. Under physiological conditions, this recruitment ensures the removal of damaged cells. However, in pathological aging, the high concentration of these factors contributes to a "cytokine storm"-like state within the tissue microenvironment, disrupting the function of adjacent healthy progenitor cells.

3.2. Proteases and Extracellular Matrix Remodeling

Beyond inflammation, senescent cells fundamentally alter tissue architecture through the secretion of proteases, specifically Matrix Metalloproteinases (MMPs) such as MMP-1, MMP-3, and MMP-10, as well as Serine Protease Inhibitors (SERPINs) [10].

Physiologically, the degradation of the ECM is necessary during wound healing to allow cell migration and the deposition of new matrix components. However, the constitutive secretion of MMPs by accumulated senescent cells in aging tissues leads to the degradation of collagen and elastin fibers, contributing to the loss of tissue structural integrity observed in skin aging and vascular stiffening. Moreover, MMPs can cleave membrane-bound receptors and latent growth factors trapped in the ECM, inadvertently increasing the bioavailability of proliferative signals to nearby cells, which can ironically promote tumorigenesis in the aging niche

Table 3. Classification and Physiological Functions of Major SASP Components

Category	Factors	Physiological Function	Pathological Consequence (Chronic)
Pro-inflammatory Cytokines	IL-6, IL-1β, IL-1α	Autocrine reinforcement of senescence arrest; recruitment of immune cells.	Chronic low-grade inflammation (Inflammaging); tissue damage.
Chemokines	IL-8 (CXCL8), CXCL1 (GROα), CXCL10 (IP-10), CCL2 (MCP-1)	Chemoattraction of NK cells, monocytes/macrophages, and T cells to sites of damage.	Persistent immune infiltration; "Cytokine storm"-like microenvironment.
Growth Factors	TGF-β, VEGF, PDGF-AA, EGF	Stimulation of angiogenesis; fibroblast activation for wound closure; epithelial proliferation.	Fibrosis (excessive collagen); promotion of tumor growth and metastasis.
Proteases & Modulators	MMP-1, MMP-3, MMP-10, TIMPs, PAI-1	Degradation of ECM to facilitate cell migration during repair; shedding of membrane receptors.	Loss of tissue structural integrity (e.g., skin wrinkling); rupture of atherosclerotic plaques.
Insoluble Factors/ECM	Fibronectin, Laminin	Remodeling of the immediate cellular niche.	Altered tissue stiffness and mechanotransduction signaling.

4. Paracrine and Systemic Effects

The physiological consequences of the Senescence-Associated Secretory Phenotype (SASP) extend far beyond the immediate vicinity of the senescent cell. While the initial arrest is a cell-autonomous tumor suppressor mechanism, the secretome mediates significant alterations in the tissue microenvironment and systemic physiology. This paracrine signaling operates on a temporal spectrum, shifting from beneficial regenerative processes in acute phases to deleterious degenerative remodeling during chronic persistence.

4.1. The Bystander Effect and Secondary Senescence

One of the most profound impacts of the SASP is the propagation of the senescent state to neighboring, healthy cells a phenomenon termed the "bystander effect." This paracrine mechanism effectively amplifies the senescence burden within a tissue, even if the initial damage was restricted to a small population of cells. The transmission of this phenotype is mediated primarily through the secretion of Transforming Growth Factor-beta (TGF-β) family ligands and the generation of reactive oxygen species (ROS) [11]. TGF-β signaling in adjacent cells triggers the production of ROS, which subsequently induces DNA damage and activates the p21/p53 axis, locking previously healthy cells into a state of secondary senescence.

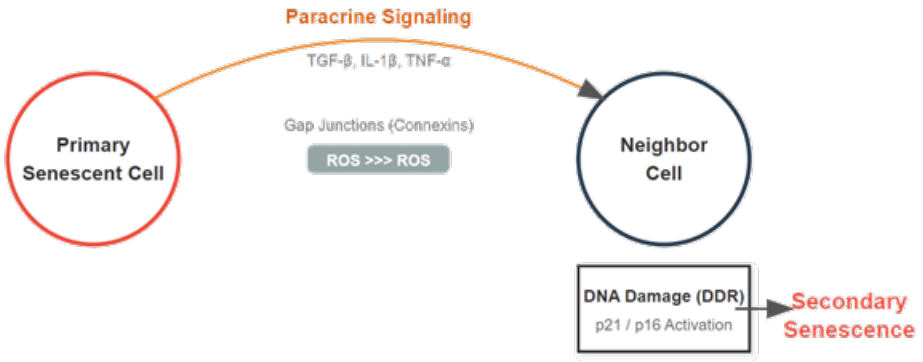

Figure 2. Propagation via the Bystander Effect. Senescence is transmitted from a primary senescent cell to a healthy neighbor via two routes: 1) **Paracrine:** Secretion of TGF-β and pro-inflammatory cytokines activates ROS generation in the neighbor. 2) **Juxtacrine:** Direct transfer of ROS and calcium through Gap Junctions. Both pathways converge to induce DNA damage and activate cell cycle inhibitors (p21/p16) in the neighbor, driving "Secondary Senescence."

Moreover, direct intercellular communication via gap junctions plays a critical role in this propagation. Connexin channels allow the transfer of ROS and inflammatory mediators directly from senescent cells to their neighbors, bypassing the extracellular space [12]. This contagious nature of senescence suggests that the SASP functions physiologically not just as a distress signal, but as a mechanism to coordinate tissue-level responses to stress. However, in the context of aging, this amplification loop contributes significantly to organ dysfunction by depleting the pool of functional progenitor cells and expanding the footprint of damaged tissue

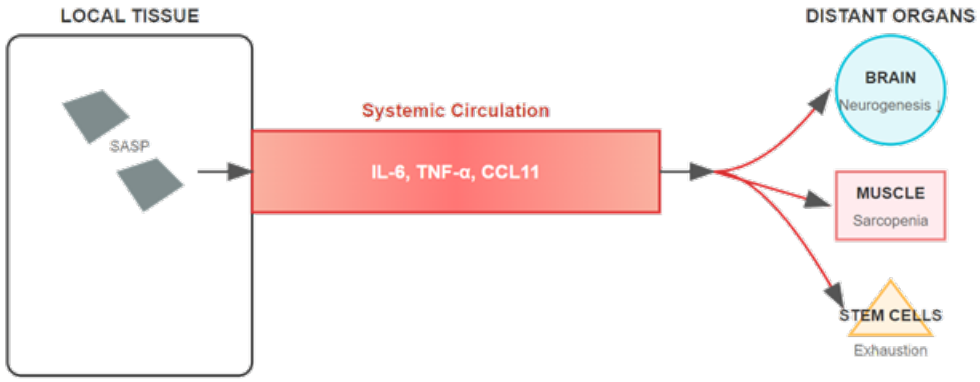

Figure 3. From Local Senescence to Systemic Inflammaging. Persistent SASP factors secreted from local tissues leak into the systemic circulation. This elevates the basal level of inflammatory cytokines (IL-6, TNF-α) and aging factors (CCL11/Eotaxin) in the blood. These factors travel to distant organs, impairing neurogenesis in the brain (cognitive decline), inducing muscle wasting (sarcopenia), and exhausting stem cell reserves, thereby driving organismal frailty.

Table 4. The Physiological Dichotomy of Paracrine Signaling

Context	Duration	Physiological Outcome	Paracrine Mediators	Biological Goal
Acute Senescence	Transient (Days to Weeks)	Tissue Repair / Regeneration	PDGF-AA, VEGF, MMPs	Recruit immune cells to clear debris; stimulate myofibroblasts to close wounds; limit fibrosis.
Developmental Senescence	Transient (Embryonic stages)	Morphogenesis	TGF-β, IL-1	Remodel embryonic structures (e.g., regression of interdigital webs); structural fine-tuning.
Chronic Senescence	Persistent (Months to Years)	Tissue Degeneration / Aging	IL-6, IL-8, MMPs, TGF-β	Induce bystander senescence; disrupt stem cell niches; degrade collagen/elastin.
Pathological Fibrosis	Persistent	Scarring / Organ Failure	TGF-β, CTGF, PAI-1	Excessive fibroblast proliferation and matrix deposition replacing functional tissue.

4.2. Divergent Roles in Wound Healing and Fibrosis

The physiological utility of the SASP is best exemplified in the context of tissue repair, where it plays a paradoxical role defined by temporal dynamics. In acute injury responses, such as cutaneous wound healing, the transient induction of senescent cells is essential. These cells secrete Platelet-Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF), which stimulate myofibroblast differentiation and angiogenesis, facilitating wound closure [13]. Once the tissue is repaired, these senescent cells are typically cleared by the immune system, resolving the inflammation.

Pathology arises when this "acute" SASP transitions into a "chronic" state due to persistent damage or uncleared senescent cells. In this scenario, the continuous secretion of pro-fibrotic factors, particularly TGF-β and connective tissue growth factor (CTGF), leads to the excessive activation of fibroblasts and aberrant collagen deposition. This mechanism is central to the pathogenesis of idiopathic pulmonary fibrosis and liver cirrhosis, where the SASP drives the replacement of functional parenchymal tissue with non-functional scar tissue [14]. Thus, the transition from physiological repair to pathological fibrosis is determined by the duration and persistence of the paracrine signal.

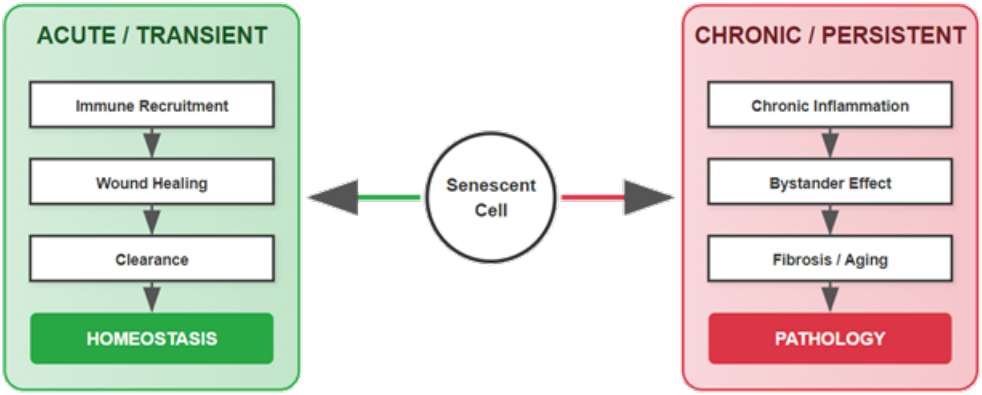

Figure 4. Physiological Dichotomy of Paracrine Signaling

4.3. Inflammaging and Frailty

The effects of the SASP are not confined to the local tissue microenvironment; soluble SASP factors can leak into the circulation, contributing to systemic physiological decline. This phenomenon provides the molecular basis for "inflammaging" the chronic, sterile, low-grade inflammation observed in the elderly [15]. Elevated serum levels of SASP components, such as IL-6, TNF-α, and C-reactive protein (CRP), act as predictors of frailty and multimorbidity.

Systemically, these circulating factors can impair the function of distant stem cell niches. For example, circulating eotaxin (CCL11) and Beta-2 Microglobulin (B2M) have been shown to cross the blood-brain barrier and inhibit neurogenesis in the hippocampus, linking peripheral cellular senescence to cognitive decline [16]. Similarly, the systemic burden of SASP factors correlates with skeletal muscle wasting (sarcopenia) and metabolic dysregulation, illustrating how local cellular defects translate into organismal aging.

5. Immune Surveillance and Clearance Failure

The accumulation of senescent cells in aging tissues is not solely a result of increased generation, but also a failure of physiological clearance mechanisms. Under homeostatic conditions, the immune system acts as a "senolytic" agent, recognizing and eliminating senescent cells to restore tissue integrity.

5.1. Mechanisms of Physiological Clearance

The immune clearance of senescent cells is orchestrated primarily by the innate immune system, involving Natural Killer (NK) cells and macrophages. The SASP paradoxically facilitates this clearance by upregulating ligands for the NKG2D receptor, such as MICA and MICB (MHC class I polypeptide-related sequence A/B), on the surface of senescent cells [17]. The binding of these ligands to NKG2D receptors on NK cells triggers cytotoxicity and the subsequent removal of the senescent cell. Macrophages are also recruited via CCL2 and other chemokines to engulf these cells through phagocytosis. This "senescence-surveillance" mechanism is crucial for preventing the accumulation of damaged cells and resolving the fibrotic response after tissue injury.

Table 5. Immune Surveillance Mechanisms and Evasion

Immune Cell Type	Clearance Mechanism	Interaction/Receptor	Senescent Cell Evasion
Natural Killer (NK) Cells	Granule Exocytosis (Perforin/Granzyme)	NKG2D Receptor binds to ligands MICA/B and ULBP1-6 on senescent cells.	Ligand Shedding: Proteolytic cleavage of MICA/B by MMPs creates soluble decoys that block NKG2D without triggering killing.
Macrophages	Phagocytosis	Chemotaxis via CCL2; recognition of "eat me" signals.	Inhibitory Signaling: Upregulation of HLA-E to bind inhibitory receptor NKG2A ("Don't eat me" signal).
CD4+ T Cells	Cytokine Regulation	Th1 response supporting cytotoxicity.	Immuno-senescence: General decline in T-cell repertoire and responsiveness in the aged host.

5.2. Immuno-senescence and Evasion

During aging, the efficiency of this surveillance system declines due to two converging factors: the functional deterioration of the immune system (immuno-senescence) and the development of evasion strategies by senescent cells. NK cells and macrophages exhibit reduced cytotoxic activity and impaired chemotaxis as the immune system ages, rendering them less effective at clearing target cells [18].

Figure 5. Mechanisms of Immune Evasion. (Left) Physiologically, NK cells recognize senescent cells via the interaction between NKG2D receptors and surface ligands (MICA/B), triggering apoptosis. **(Right)** Pathologically, senescent cells upregulate MMPs which proteolytically shed MICA/B ligands. These soluble decoys bind NKG2D remotely, blocking recognition. Additionally, upregulation of HLA-E sends an inhibitory signal via NKG2A, preventing clearance.

Simultaneously, senescent cells adapt to evade detection. The main mechanism involves the proteolytic shedding of NKG2D ligands (MICA/B) from the cell surface, mediated by the upregulation of metalloproteinases like MMPs and ADAMs within the SASP itself [19]. This shedding generates soluble decoy ligands that bind to NKG2D receptors on immune cells, blocking them without triggering cytotoxicity, effectively cloaking the senescent cell from immune view. Moreover, senescent cells may upregulate the non-classical MHC molecule HLA-E, which interacts with the inhibitory receptor NKG2A on NK cells, sending a "don't eat me" signal [20]. This immune evasion, coupled with a weakened immune response, creates a permissive environment for the exponential accumulation of senescent cells and the perpetuation of the deleterious SASP.

6. Conclusion

The physiological mechanisms of paracrine signaling in tissue aging and repair reveal a complex landscape where cellular senescence functions as a potent regulator of tissue homeostasis. What initiates as a protective, anti-tumorigenic DNA damage response evolves into a hyperactive secretory phenotype that can fundamentally alter the tissue microenvironment. The SASP is a master regulator of this transition, coordinating beneficial wound healing processes in the acute phase while driving chronic inflammation, fibrosis, and secondary senescence when persistent. The dichotomy of the SASP essential for repair yet detrimental in aging highlights the importance of temporal regulation in paracrine signaling. The failure of the immune system to clear these cells, exacerbated by the active evasion strategies of the senescent secretome, marks a critical tipping point in the aging process. Consequently, therapeutic techniques aiming to target senescence must navigate this complexity carefully. The goal of emerging senolytic and senomorphic therapies is not the total ablation of senescence, but the restoration of the physiological balance: enabling the beneficial repair functions while abrogating the chronic, maladaptive signaling that drives organismal frailty.

References

[1] Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961;25(3):585-621.

[2] Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010;5:99-118.

[3] Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol. 2014;15(7):482-496.

[4] Franceschi C, Bonafe M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244-254.

[5] d'Adda di Fagagna F. Living on a break: cellular senescence as a DNA-damage response. Nat Rev Cancer. 2008;8(7):512-522.

[6] Kang C, Xu Q, Martin TD, et al. The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4. Science. 2015;349(6255):aaa5612.

[7] Passos JF, Nelson G, Wang C, et al. Feedback between p21 and reactive oxygen production is necessary for cell senescence. Mol Syst Biol. 2010;6:347.

[8] Dou Z, Ghosh K, Vizioli MG, et al. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature. 2017;550(7676):402-406.

[9] Kuilman T, Michaloglou C, Vredeveld LC, et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. Cell. 2008;133(6):1019-1031.

[10] Acosta JC, Banito A, Wuestefeld T, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat Cell Biol. 2013;15(8):978-990.

[11] Hubackova S, Krejcikova K, Bartek J, Hodny Z. IL1- and TGFβ-Nox4 signaling, oxidative stress and DNA damage response are shared features of replicative, oncogene-induced, and drug-induced paracrine 'bystander senescence'. Aging (Albany NY). 2012;4(12):932-951.

[12] Nelson G, Wordsworth J, Wang C, et al. A senescence-bystander effect: senescence-induced senescence. Aging Cell. 2012;11(2):345-349.

[13] Demaria M, Ohtani N, Youssef SA, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell. 2014;31(6):722-733.

[14] Schafer MJ, White TA, Iijima K, et al. Cellular senescence mediates fibrotic pulmonary disease. Nat Commun. 2017;8:14532.

[15] Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69(Suppl 1):S4-S9.

[16] Villeda SA, Luo J, Mosher KI, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature. 2011;477(7362):90-94.

[17] Sagiv A, Biran A, Yon M, et al. Granule exocytosis mediates immune surveillance of senescent cells. Oncogene. 2013;32(15):1971-1977.

[18] Ovadya Y, Landsberger T, Leor J, et al. Impaired immune surveillance accelerates accumulation of senescent cells and aging. Nat Commun. 2018;9(1):5435.

[19] Munoz DP, Yannone SM, Daemen A, et al. Targetable mechanisms driving immunoevasion of persistent senescent cells link chemotherapy-resistant cancer to aging. JCI Insight. 2019;4(12):e124716.

[20] Pereira BI, Devine OP, Vukmanovic-Stejic M, et al. Senescent cells evade immune clearance via HLA-E-mediated NK and CD8+ T cell inhibition. Nature. 2019;570(7759):94-98.