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SENOLYTICS – A DISCOVERY THAT COULD TRANSFORM THE COURSE OF AGING AND CHRONIC DISEASES

Kamil Kania *(Corresponding Author, Email: kania.kamil.lek@gmail.com)*
Department of Human Anatomy, Faculty of Medicine, Medical University of Silesia, Medyków 18, 40–762 Katowice, Poland
ORCID ID: 0000-0002-7660-2505

Marcel Bobiński
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0007-8351-5884

Zuzanna Wieczorek
Multi-specialty Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0005-9952-780X

Wiktoria Skowron
Independent Public Healthcare Facility of the Ministry of Interior and Administration named after Sergeant Grzegorz Załoga in Katowice, Katowice, Poland
ORCID ID: 0009-0008-2494-837X

Justyna Bartol
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0007-8635-9418

Aleksandra Sosińska
Multi-specialty Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0006-8364-0055

Justyna Rajczyk
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0003-1307-931X

Monika Wiczuk–Wiczewska
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0000-0002-4558-6549

Adam Szymczak
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0007-4822-845X

Tomasz Lepich
Department of Human Anatomy, Faculty of Medicine, Medical University of Silesia, Katowice, Poland
ORCID ID: 0000-0001-8443-4014

ABSTRACT

Senescent cells play a pivotal role in the progression of age-related diseases by promoting chronic inflammation and disrupting tissue function through the secretion of senescence-associated secretory phenotype (SASP) factors. Senolytics, a novel class of therapeutic agents, enable the selective elimination of these cells or the attenuation of their deleterious effects, offering a potential avenue to enhance healthspan. Preclinical studies and early clinical trials indicate that senolytics can improve cardiovascular function, metabolism, and physical performance, while demonstrating an acceptable safety profile. This review presents the mechanisms of action of senolytics, the current state of research, and their potential applications in metabolic, neurodegenerative, and cardiovascular diseases.

KEYWORDS

Senolytics, Cellular Senescence, SASP (Senescence-Associated Secretory Phenotype), Aging, Chronic Diseases

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Introduction

Aging processes are natural yet complex phenomena in which cells, tissues, and organs gradually lose their functional capacity. Over time, the risk of chronic diseases, such as atherosclerosis, diabetes, and neurodegenerative disorders, increases. A central mechanism underlying these changes is the accumulation of senescent cells—cells that have ceased to divide but remain metabolically active and secrete factors that induce chronic inflammation and impair organ function.

In recent years, increasing attention has been directed toward senolytics—drugs capable of selectively eliminating senescent cells or mitigating their deleterious effects. Preliminary studies suggest that these agents may enhance cardiovascular function, metabolism, tissue regeneration, and physical performance. This presents promising prospects for the treatment of age-related diseases and the promotion of healthy aging.

Definition of Cellular Senescence

The concomitant biological processes underlying organismal aging constitute a significant pathogenic factor in numerous diseases and dysfunctions. A fundamental mechanism in this context is cellular senescence, defined as a stable cell cycle arrest induced by diverse damaging stimuli. Senescent cells can accumulate throughout life, and their persistent presence leads to tissue dysfunction, primarily through the secretion of proinflammatory and proteolytic components of the senescence-associated secretory phenotype (SASP) [1]. Data from preclinical models clearly indicate that targeted elimination of senescent cell populations responsible for chronic microdamage and disruption of tissue homeostasis can delay, mitigate, or entirely prevent the development of many age-related pathologies [2]. In this context, the introduction of small-molecule senolytics—pharmacological agents that selectively induce apoptosis in senescent cells—has opened new therapeutic avenues for the prevention and treatment of age-associated diseases [3].

Molecular Determinants and Markers of Cellular Senescence

Cellular senescence represents a specific functional state of the cell, primarily viewed as a stress response. Unlike other forms of non-proliferative cellular states, such as reversible quiescence, which requires mitogenic stimulation to re-enter the cell cycle, or terminal differentiation, in which cells mature within defined lineages and permanently arrest the cell cycle through various regulatory mechanisms, cellular senescence is characterized by an irreversible cessation of cell division [4]. In response to intrinsic or extrinsic factors, such

as telomere shortening or ionizing radiation, the signalling pathways initiating cell cycle arrest during senescence predominantly converge on the p53/CDKN1A (p21) axis and the retinoblastoma (RB)/CDKN2A (p16) pathway [5]. Elevated levels of cyclin-dependent kinase inhibitors, p21 and p16, constitute a critical mechanism for inhibiting the G1/S transition in the cell cycle. This process results from the suppression of cyclin–CDK complex formation and the maintenance of active RB protein, leading to the repression of transcription of genes essential for further cell cycle progression [6].

Biology of Cellular Senescence – Mechanisms Leading to Senescence

DDR (DNA Damage Response)

DNA Damage Response (DDR) represents a key molecular pathway activated by cells in response to DNA damage. Failure of repair mechanisms leads to the accumulation of mutations in transcriptional and translational processes, destabilizing cellular function and promoting aging as well as pathological conditions, including cancer [7]. The most deleterious form of DNA damage is double-strand breaks (DSBs), which, if not efficiently repaired, can trigger senescence in proliferative cells [8]. Repair of such breaks occurs primarily via two mechanisms: homologous recombination (HR) and non-homologous end joining (NHEJ) [9]. HR uses the sister chromatid for relatively error-free DSB repair, but it is active only when chromatids are present, mainly during S and G2 phases [10]. NHEJ does not require a homologous sequence, although the DNA ends may possess short microhomologies (<10 bp) [11]. Canonical NHEJ (C-NHEJ) is the dominant repair mechanism in G1 phase, and studies indicate it is also the most frequently employed in S and G2 phases [10]. C-NHEJ is ineffective at telomeres, whereas alternative NHEJ (alt-NHEJ), which relies on microhomology, can repair DSBs at telomeres but is error-prone and may lead to chromosomal fusions [12,13]. The DDR pathway involves numerous proteins. The MRN complex (MRE11, RAD50, NBS1) detects DSBs, while the kinases ATM and ATR phosphorylate H2AX, facilitating the recruitment of checkpoint and repair proteins (53BP1, MDC1/NFBD1, NBS1). γH2AX activates the kinases Chk1 and Chk2, which transmit signals to p53/p21 [14]. If DNA repair is successful, DDR foci typically resolve within 24 hours, allowing the cell to resume proliferation. When repair is not possible, persistent DDR foci remain, characteristic of the senescent phenotype and capable of initiating cellular senescence [15,16]. Alternatively, the cell may undergo apoptosis [9]. Properly functioning DDR safeguards the cellular genome, prevents the transmission of damaged information to progeny, and reduces the risk of oncogenic transformation [15].

Telomere Shortening

Telomeres are nucleoprotein complexes located at the ends of linear chromosomes [15,16]. Their DNA component consists of repetitive TTAGGG sequences, characteristic of all vertebrates, and a 3’ single-stranded guanine-rich overhang. Telomeres form a unique structure known as the t-loop, in which the 3’ end of the strand inserts between the two strands of the double helix. This configuration, together with protective protein components, prevents chromosome fusions and inappropriate activation of DSB repair mechanisms [17]. Telomere protection is provided by the shelterin protein complex, composed of TRF1, TRF2, TIN2, RAP1, TPP1, and POT1, as well as by telomerase [16]. TRF2 is responsible for t-loop formation, and individual shelterin proteins bind to both double-stranded and single-stranded DNA: TRF1, TRF2, TIN2, and RAP1 bind double-stranded regions, whereas the POT1/TPP1 heterodimer binds the single-stranded overhang [12–14]. Experimental tethering of TRF2 to internal DSBs in mouse fibroblasts blocked repair of these breaks [18], while inhibition of TRF2 in human lung fibroblasts caused chromosomal end fusions and premature senescence resembling replicative aging [19].

The Role of Senescent Cells in the Development of Chronic Diseases

Senescent cells gradually accumulate in tissues in response to DNA damage and cellular stress. They arrest the cell cycle and release proinflammatory cytokines, chemokines, and metalloproteinases, forming the characteristic SASP phenotype. This phenotype promotes chronic inflammation and disrupts organ homeostasis, increasing the risk of age-related chronic diseases [20]. In adipose tissue, the presence of senescent cells is associated with insulin resistance and a higher risk of type 2 diabetes, highlighting their role in the pathogenesis of metabolic disorders. Additionally, these cells modulate systemic metabolic functions through the secretion of proinflammatory factors, which can lead to tissue imbalance [21]. In chronic kidney diseases, increased senescent cell accumulation in the renal interstitium correlates with decreased organ function and disease progression. Animal model studies have shown that removal of these cells improves renal function, suggesting their direct involvement in the pathogenesis of chronic kidney disorders. The presence of

senescent cells in tissues fosters a persistent, microinflammatory environment that accelerates degeneration and limits regenerative capacity [22]. Their excess increases susceptibility to cardiovascular and metabolic diseases through enhanced release of proinflammatory factors [23]. Prolonged senescent cell persistence sustains inflammation and tissue degeneration, representing a common pathogenic mechanism in chronic diseases [24].

Senolytics

Definition and Mechanism of Action

Senolytics are a class of chemical compounds capable of selectively inducing apoptosis in senescent cells, which have lost proliferative capacity but retain secretory activity of proinflammatory cytokines, chemokines, and metalloproteinases (SASP phenotype), contributing to chronic inflammation and tissue dysfunction [25]. By eliminating these cells, senolytics mitigate their negative impact on the tissue microenvironment, potentially delaying the progression of age-related diseases [26]. The mechanism of action of senolytics is based on the inhibition of senescent cell anti-apoptotic pathways (SCAPs), which include BCL-2 family proteins, PI3K/AKT kinases, p53/p21 proteins, and receptor tyrosine kinases, responsible for maintaining the survival of senescent cells despite accumulated DNA damage and oxidative stress [25,27]. Inhibition of these pathways disrupts the resistance of senescent cells to pro-apoptotic signals, enabling their selective elimination [26]. The combination of dasatinib, a tyrosine kinase inhibitor, and quercetin, an antioxidant polyphenol, simultaneously blocks multiple SCAPs, including PI3K/AKT and BCL-2, resulting in apoptosis induction and SASP reduction [28,29]. Dasatinib attenuates receptor kinase signaling, modulating PI3K/AKT activity, whereas quercetin targets anti-apoptotic BCL-2 proteins and PI3K kinases, enhancing senescent cell clearance [30]. Navitoclax (ABT-263) is another senolytic that selectively targets BCL-2 proteins, rendering senescent cells susceptible to apoptosis induction [31]. This strategy exploits the dependency of senescent cells on overexpressed survival pathways, reflecting their specific vulnerability due to SCAP overexpression, and allows selective removal of these cells. Consequently, SASP mediators are reduced, leading to decreased chronic inflammation and partial restoration of tissue function [32].

The literature also describes intermittent, “hit-and-run” senolytic administration, allowing brief drug exposure that results in sustained elimination of senescent cells for weeks while minimizing potential adverse effects [33]. This approach may be particularly relevant in treating chronic age-related diseases, where control of inflammation and tissue microenvironment is critical [34]. Importantly, senolytics do not require daily administration. “Hit-and-run” strategies allow short-term treatment, after which senescent cell clearance persists for weeks, reducing the risk of side effects while providing long-term health benefits [26].

Classes of Senolytics

Table 1. Classes of senolytics, their molecular targets, examples, mechanisms of action, and advantages and limitations – own elaboration [based on 35–40]. SnC – Senescent Cells

Class of Senolytics	Main Molecular Targets / SCAPs or Other Mechanisms	Example Compounds / Therapies	Mechanism of Action	Advantages	Limitations
BCL-2 Inhibitors (BH3-mimetics)	BCL-2, BCL-xL, BCL-w	Navitoclax (ABT-263), ABT-737, A1331852, A1155463	Inhibition of anti-apoptotic proteins → induction of apoptosis in senescent cells	Highly effective across multiple SnC types	Toxicity (e.g., thrombocytopenia), limited selectivity among SnC types
Tyrosine Kinase Inhibitors	Receptor tyrosine kinases, PI3K/AKT	Dasatinib	Inhibition of signaling kinases → attenuation of SCAP survival signals → apoptosis	Well-studied oncologic drug, broad activity	Potential for severe side effects, specificity depends on SnC type

Class of Senolytics	Main Molecular Targets / SCAPs or Other Mechanisms	Example Compounds / Therapies	Mechanism of Action	Advantages	Limitations
Polyphenols / Flavonoids	PI3K/AKT, NF-κB, BCL-2 and other survival pathways	Quercetin, Fisetin, Resveratrol	Modulation of survival signaling, induction of cellular stress, promotion of apoptosis	Natural compounds, relatively low toxicity, oral potential	Lower potency than synthetics, limited bioavailability
FOXO4-p53 Disruptors (Peptide-based)	FOXO4–p53 complex	FOXO4-DRI	Disrupts FOXO4–p53 interaction, "releases" p53 → apoptosis in SnC	Highly selective – minimal damage to healthy cells	Peptide delivery challenges, preclinical stage
MDM2 Inhibitors / p53 Modulators	MDM2–p53	UBX0101, other MDM2 inhibitors	Stabilization of p53 → SnC apoptosis	Potential for precise SnC elimination	Risk of affecting proliferating healthy cells, still experimental
HSP90 Inhibitors	HSP90 (chaperone protein)	17-AAG (tanespimycin), 17-DMAG	Disrupts HSP90 function → weakens SnC survival → apoptosis or senolysis	Novel, alternative mechanism	Potential toxicity, dosing optimization needed
Cardiac Glycosides	Na+/K+ ATPase pump, cellular metabolic signaling	Digoxin, Ouabain, Digitoxin	Inhibition of Na+/K+ ATPase → ionic homeostasis disruption → selective SnC death	Clinically used compounds, potential rapid clinical translation	Risk of cardiotoxicity, variable selectivity
Senolytic Immunotherapy	SnC surface markers (e.g., uPAR), specific epitopes	Senolytic CAR-T cells, antibody-drug conjugates (ADC), vaccines against SnC	Directs immune system to SnC → elimination	Very high specificity, potential for long-term therapy	Challenges in identifying specific markers, risk of autoimmunity
Targeted Therapy-based Senolytics (ADC – Antibody Drug Conjugates)	SnC surface markers	Antibody + cytotoxin	Combines specific antibody with cytotoxic drug → selective delivery and killing of SnC	Potentially highly selective, reduced side effects vs systemic drugs	Still experimental, complex production, safety requirements

Clinical Studies

Recent Insights from Human Trials

In recent years, clinical studies assessing the potential of dasatinib and quercetin (D+Q) as senolytic therapy in humans have received particular attention. One of the most significant projects was the randomized trial by Justice et al., which evaluated the safety of D+Q administration, their impact on pharmacodynamic markers of senescent cell clearance, and preliminary clinical benefits in patients with idiopathic pulmonary fibrosis (IPF). The employed "hit-and-run" regimen, involving short-term, intermittent drug administration, was well tolerated, with no severe dose-limiting adverse events. During therapy, reductions in senescence markers, such as p16^Ink4a, were observed in peripheral blood cells, alongside improvements in functional tests, including the 6-minute walk distance. These findings confirmed that senolytics exhibit measurable biological activity in humans, serving as a foundation for further clinical investigations [41].

Another key step in translating senolytic research to clinical practice was the study by Hickson et al., which assessed D+Q administration in patients with chronic kidney disease (CKD) stages 3–4. In this pilot interventional trial, even short-term exposure to senolytic drugs led to reductions in SASP markers, such as IL-6, MCP-1, and

MMP-12, confirming their capacity to eliminate dysfunctional cells. The therapeutic regimen was well tolerated, did not cause significant adverse events or deterioration of renal filtration, and was associated with improvements in skeletal muscle function and selected physical performance metrics. These results suggest that senolytic interventions can modulate inflammatory and degenerative processes in patients with chronic age-related diseases, although larger randomized trials are needed to confirm clinical efficacy [42].

Both studies highlight that short-term D+Q therapy cycles are well tolerated and effectively influence various biological markers of cellular senescence. It should be noted, however, that these trials remain in early clinical phases, and the findings are preliminary, paving the way for larger, more comprehensive studies to evaluate the effects of senolytic therapy on hard endpoints such as disease progression, organ function, or mortality. Despite these limitations, they currently represent the most robust clinical evidence supporting the potential of senolytic interventions in humans.

STAMINA — Senolytics for Improving Cognitive and Motor Function in Older Adults

The STAMINA (Senolytics To Alleviate Mobility Issues and Neurological Impairments in Aging) clinical trial was designed as a pilot study to assess feasibility, safety, and preliminary functional and biological effects of the senolytic combination Dasatinib + Quercetin (DQ) in older adults exhibiting features of advanced age (slow gait) and mild cognitive impairment (MCI) [43]. STAMINA was a 12-week study using an intermittent dosing regimen: participants ≥65 years old, with gait speed <1.0 m/s and MCI, received 100 mg Dasatinib + 1250 mg Quercetin for two consecutive days every two weeks over six cycles (total of 12 doses) [44]. The study included 12 participants, the target sample size for feasibility assessment [44]. Evaluations were conducted before treatment, at mid-study, and post-intervention, and included cognitive tests (e.g., Montreal Cognitive Assessment – MoCA), gait parameters (stride length, speed), and a set of biological markers (cytokines, SASP markers) in blood and urine [43,44]. Analysis published in 2025 indicated that DQ therapy was feasible and well tolerated, with no serious intervention-related adverse events. Out of 332 individuals screened via phone, only 12 completed the study (~10%). Participants adhered to the dosing protocol with ≥99% compliance [43]. Functional outcomes showed a mean change in MoCA score of +1.0 points (95% CI −0.7 to 2.7), which was not statistically significant across the full cohort [43]. However, in the subgroup with the lowest baseline scores (MoCA 18–25), a significant improvement of +2.0 points (95% CI 0.1–4.0) was observed. Gait parameters, such as stride length, also improved (mean change +0.031 m, 95% CI −0.003 to 0.066), though this change did not reach significance for the whole group [45]. Among biological senescence/inflammatory markers, TNF-α levels decreased (mean change −3.0%, 95% CI −13.0 to 7.1), and TNF-α reduction was significantly correlated with MoCA improvement ($r = -0.65$; $p = 0.02$) [45]. This suggests that the intervention may modulate SASP, which corresponded with cognitive improvement, consistent with the hypothesis that SnC clearance reduces inflammation and neurodegeneration [43]. The authors interpret these results as preliminary and hypothesis-generating: DQ appears safe and feasible in older adults with MCI and impaired mobility; trends toward cognitive improvement and correlations with inflammatory markers indicate a biological senolytic signal; however, due to the small sample size, lack of randomization, and absence of a control group, interpretation must consider study limitations [43,44]. STAMINA represents a pioneering step in gerontology and geroscience, demonstrating that senolytics can be administered in older adults with MCI and mobility impairment—a key population for dementia and fall prevention. The results provide evidence of feasibility and preliminary efficacy, justifying further, larger, randomized trials. Significant limitations remain: absence of a control group, small sample size, short follow-up, and selective participant inclusion (gait and MCI criteria), indicating the need for broader studies to determine whether observed effects generalize to the wider older adult population. Additionally, SnC measurement relied on SASP markers (e.g., TNF-α), which are indirect and may be influenced by other factors (e.g., infections, medications, lifestyle). Long-term impacts on dementia risk, falls, hospitalization, or mortality were not assessed.

STAMINA provides the latest published (2025) clinical data supporting the feasibility of senolytic therapy in humans, with a promising safety profile and preliminary signals of functional benefit (cognitive and motor). These findings require confirmation in larger, controlled, long-term studies and represent a foundation for novel medical intervention strategies in aging, dementia, and geriatrics [43–45].

Navitoclax in Cardiovascular Diseases — Current Knowledge and Perspectives from Preclinical Studies

Cardiovascular aging is associated with the accumulation of senescent cells in the myocardium, vasculature, and extracellular matrix. These dysfunctional cells are not merely "passive" — on the contrary, through SASP secretion, they contribute to chronic inflammation, fibrosis, and structural and functional impairments of the heart and vessels. Consequently, the risk of heart failure, arrhythmias, atherosclerosis, and premature mortality increases [46]. In response, the concept of pharmacological "clearing" of senescent cells has emerged as a potential strategy to slow or modify the course of cardiovascular diseases. Among available senolytics, navitoclax, an inhibitor of anti-apoptotic proteins from the BCL-2 family (BCL-2, BCL-xL, BCL-W), has shown particular promise, effectively eliminating senescent cells and improving cardiovascular parameters in preclinical studies [46,47]. In mouse models of heart failure induced by chronic angiotensin II infusion, navitoclax administration led to noticeable improvements in left ventricular ejection fraction (LVEF), reduction of myocardial fibrosis and hypertrophy, decreased inflammation, and improved electrical conduction — translating into lower arrhythmia susceptibility [46]. In these models, the drug selectively eliminated senescent cardiomyocytes and cardiac fibroblasts via apoptosis (p16+, p21+) [46]. In aged mice subjected to acute myocardial infarction, pharmacological clearance of senescent cells improved survival, limited cardiac remodeling, reduced fibrosis, and supported regeneration of damaged tissue, suggesting that senolysis may facilitate post-ischemic repair [47]. Similarly, in models of chemotherapy-induced cardiotoxicity (e.g., doxorubicin), navitoclax decreased the number of senescent cardiomyocytes, reduced injury markers, and restored cardiac function [48]. At the level of blood vessels and vascular tissues, senescent cell clearance with navitoclax was associated with improved arterial elasticity, endothelial function, and reduced SnC burden in the vascular wall — theoretically slowing atherosclerosis progression and mitigating vascular complications [49].

Literature reviews consistently indicate that senescent cells, via SASP and disrupted tissue homeostasis, play a central role in cardiovascular disease development — from atherosclerosis, hypertension, and myocardial hypertrophy to heart failure and ischemic heart disease [50]. In this context, pharmacological tissue "clearing" of SnC, for example with navitoclax, is considered a novel potential therapeutic strategy. However, with this potential comes several challenges. Removal of SnC in structural tissues, such as atherosclerotic plaques, the aortic wall, or myocardium, may lead to tissue destabilization — structural weakening, plaque rupture, aneurysm formation, or hemostatic disturbances. Additionally, in oncology studies, navitoclax-related adverse effects, such as neutropenia and thrombocytopenia, have been observed [50,51]. Despite promising animal data, clinical translation requires caution, appropriate patient selection, and confirmation of safety in human trials [49,50,52]. As of 2025, no clinical studies have evaluated navitoclax as a senolytic in human cardiovascular diseases — including heart failure, post-myocardial infarction, atherosclerosis, or hypertension [50,52]. The drug remains used exclusively in oncology, and its toxicity, mainly thrombocytopenia, limits its application in geriatric or cardiology patients [51].

Navitoclax remains one of the most promising senolytic candidates for therapy or prevention of cardiovascular diseases. To enable safe use in humans, phase I/II clinical trials assessing tolerability, safety, and biomarkers of senescence and cardiac and vascular remodeling are needed [50]. Patient selection with high senescent cell burden, cautious "hit-and-run" pulsatile dosing, long-term monitoring of functional outcomes, and hard endpoints — including hospitalizations, myocardial infarction, heart failure, bleeding events, or arrhythmias — are also critical considerations [51,52].

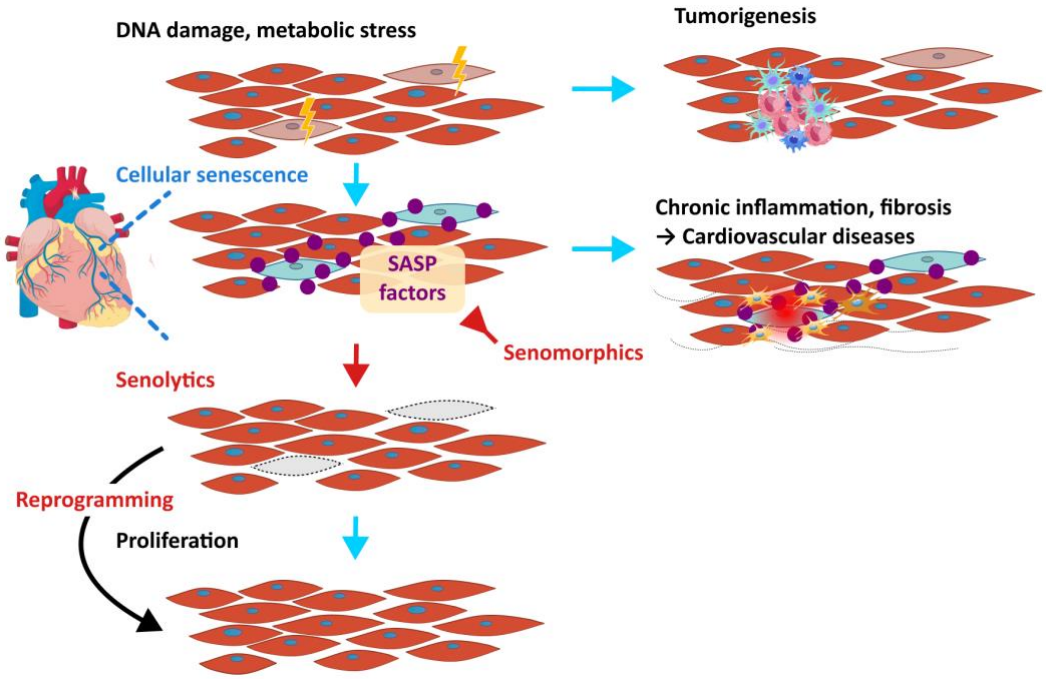

Fig. 1 - The figure illustrates the role of senescent cells in the development of cardiovascular diseases, highlighting their accumulation with aging and in response to various stressors. Although cell cycle arrest initially serves a protective function, the persistent presence of senescent cells leads to the secretion of pro-inflammatory senescence-associated secretory phenotype (SASP) factors, which exacerbate tissue damage and promote chronic inflammation within the cardiovascular system. The figure also presents therapeutic strategies aimed at mitigating these adverse effects, including the selective elimination of senescent cells (senolytics), epigenetic reprogramming (OSKM), and suppression of SASP signaling through senomorphic agents [46-51]. Own elaboration.

Therapeutic Potential of Senolytics in Other Organs and Systems

Neurodegenerative Diseases (e.g., Alzheimer's, Parkinson's)

Brain aging is associated with an increasing number of SnC in glial, endothelial, support, and neuronal cells; these cells secrete SASP factors, promote neuroinflammation, disrupt the microenvironment, and contribute to degeneration. Preclinical studies demonstrate that SnC removal can restore microenvironmental balance, reduce inflammation, and support the survival and function of neurons and support cells [53, 54]. In animal models, senolytic treatment with various compounds improved cognitive function, spatial memory, and learning abilities, while reducing neuropathological features (inflammation, microglial activation, barrier dysfunction), indicating a real potential for neurodegenerative diseases. However, effects depended on cell type, disease stage, and age of the animals; widespread elimination of SnC in the brain without adequate regeneration may disrupt homeostasis or accelerate degeneration [53, 55, 56].

Given the lack of long-term clinical data in humans, senolysis in Alzheimer's or Parkinson's disease currently remains a promising but experimental therapeutic strategy.

Metabolic Diseases (Diabetes, Obesity, Metabolic Syndrome)

In aged mice, senolytic treatment with Dasatinib + Quercetin (D+Q) reduced the number of SnC in white adipose tissue, decreased inflammation, lowered expression of proinflammatory cytokines (TNF-α, MCP-1, IL-6), and limited infiltration by immune cells (macrophages, lymphocytes). This modulation of the adipocyte environment translated into improved metabolic homeostasis, including enhanced glucose tolerance, insulin sensitivity, and reduced fat accumulation [57]. In models of diabetes and nephropathy, D+Q treatment improved renal function, reduced fibrosis, decreased proteinuria, and restored normal expression of genes involved in fatty acid metabolism (PPARα activation) and autophagy in renal tubular cells [55,58]. These findings indicate that senolysis may protect against metabolic complications by improving metabolism and reducing oxidative stress [54].

Osteoarthritis and Orthopedic Disorders

Studies have shown that D+Q selectively eliminate SnC in human chondrocytes, restoring the chondrogenic phenotype—upregulating COL2A1, ACAN, SOX9, increasing type II collagen and glycosaminoglycan synthesis, and reducing SASP factors (IL-6, CXCL1). In animal models of OA (e.g., mechanically overloaded mice), SnC clearance reduced joint inflammation, slowed matrix degradation, and supported joint homeostasis, suggesting that senolytics could serve as disease-modifying agents in degenerative joint diseases [59].

Nephropathies and Organ Fibrosis

In models of diabetic nephropathy, D+Q administration over several weeks improved renal function, lowering creatinine, BUN, proteinuria, and interstitial fibrosis, while reducing ECM deposits. Mechanisms involved activation of autophagy, improved podocyte function, and removal of harmful metabolites via PPARα modulation [59,60]. In fibrosis models of other organs (lung, liver), senolytics decreased SnC numbers, reduced expression of fibrogenic factors (TGF-β, MMP, TIMP), limited inflammation, and promoted tissue regeneration [60].

Immunosenescence

Senescence also affects immune cells (lymphocytes, hematopoietic cells, endothelial cells in lymphoid organs), leading to immunosenescence, reduced hematopoietic renewal, impaired responses to infections and vaccines, and chronic inflammation [57]. Preclinical studies using senolytics (BCL-2/BCL-xL inhibitors, D+Q cocktails) rejuvenated hematopoietic stem cell pools, improved tissue and muscle regeneration, decreased SnC in immune and vascular cells, enhanced immune responses, and reduced age-associated tissue damage [57,58].

Overall Anti-Aging Effects – Impact on Healthspan

Animal studies indicate that senolytics, by clearing accumulated SnC, can extend healthspan: improving physical function, lowering incidence of age-related diseases, supporting tissue regeneration, and reducing mortality [53,61]. Senolysis mitigates chronic inflammation, enhances metabolic homeostasis, and reduces oxidative damage, slowing multiple aging processes, making it a promising geroprotective strategy [54,56-59,61]. Translational long-term studies in humans are required to evaluate the efficacy and safety of senolytics as geroprotective therapies [61].

Conclusions

In the coming years, research on senolytics should focus on the development of second-generation drugs that are even more selective for senescent cells while minimizing the risk of adverse effects [1, 3, 4, 13]. Simultaneously, organ-targeted therapies are gaining increasing importance, allowing senolytics to act on specific tissues or organs. This approach not only enhances treatment efficacy but also reduces potential damage to healthy structures [2, 5–12].

Another important direction is combining senolytics with anti-inflammatory therapies, which may amplify clinical benefits by mitigating the chronic inflammation induced by senescent cells [9–11]. In recent years, interest has also grown in immunosenolytics, including CAR-T cell and natural killer (NK) cell-based therapies, which enable targeted elimination of senescent cells by the patient's own immune system [4–6].

Equally important is the development of senescence biomarkers, which allow monitoring of therapeutic efficacy and precise identification of patients who are most likely to benefit from treatment [1, 8, 13, 14]. Finally, future strategies will increasingly be personalized, taking into account individual differences in the rate of aging, the type and location of senescent cells, and comorbid conditions [1, 8, 13, 14].

Summary

Senolytics represent a promising class of drugs that enable the removal of senescent cells—key drivers of chronic inflammation, metabolic dysregulation, and age-related organ dysfunction [1,3,6,20]. By inhibiting or eliminating these cells, it is possible to reduce their detrimental effects mediated through SASP, the pro-inflammatory and tissue-degrading secretory phenotype of senescent cells [8–10, 14, 21].

Clinical studies to date, including pilot trials with dasatinib and quercetin, suggest that senolytics can improve vascular function, metabolism, and physical performance in older adults and patients with chronic conditions, with a relatively favorable safety profile [41–43]. Nevertheless, further research is needed to

determine optimal dosing, the most effective administration schedules—including “hit-and-run” strategies—and to minimize the risk of adverse effects during long-term use [25,26,28,33].

The future of senolytic therapy includes the development of second-generation drugs, organ-targeted therapies, immunosenolytics, and combination approaches with anti-inflammatory and metabolic agents [1,4,5,35–37]. At the same time, the importance of senescence biomarkers and personalized treatment strategies is growing, allowing better tailoring of therapy to individual patient needs and monitoring of its efficacy [1,8,13,14].

In conclusion, senolytics offer a tangible opportunity to extend healthspan and represent a promising strategy for treating age-related diseases, opening new avenues in geroprotection.

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