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REVIEW

Cellular Senescence in the Cardiovascular System: Molecular Mechanisms, Pathophysiology, and Senotherapeutic Interventions

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ABSTRACT: Cellular senescence and the Senescence-Associated Secretory Phenotype (SASP) play both physiological and pathological roles in the cardiovascular system. While transient senescence aids regeneration, chronic accumulation of senescent cells promotes endothelial dysfunction, arterial stiffening, and maladaptive cardiac remodeling. This review elucidates the pivotal role of the immune system in senescent cell clearance and explores how immunosenescence drives systemic low-grade inflammation. Significant emphasis is placed on emerging pharmacological strategies, specifically senolytics and senomorphics, assessing their capacity to restore cardiac function and attenuate atherosclerosis. Additionally, the utility of molecular biomarkers and diverse *in vitro* and *in vivo* models is analyzed in the context of therapeutic efficacy. Ultimately, this article asserts that a comprehensive understanding of senescent-immune interactions is fundamental to the development of targeted, personalized interventions for age-related cardiovascular pathologies.

KEYWORDS: Cellular senescence; cardiovascular aging; senolytics; senomorphics; cardiovascular system; heart failure; atherosclerosis; endothelial dysfunction

1 Introduction

Aging induces progressive structural and functional changes in the cardiovascular system, even in individuals without hypertension or overt cardiovascular disease. These changes reduce cardiac reserve and impair the heart's ability to respond to stress [1]. Cardiac aging is characterized by loss of cardiomyocytes, mild compensatory hypertrophy, decreased responsiveness to sympathetic stimulation, and impaired contractility. At the same time, large arteries become thicker, stiffer, and less elastic due to collagen and calcium deposition and elastin fiber fragmentation, contributing to left ventricular hypertrophy, chronic heart failure, and atrial fibrillation [2]. Chronological age is a major risk factor for cardiovascular disease, lowering the threshold for clinical symptoms [3]. Aging can also be examined at the cellular and molecular level. In cardiology, cellular senescence arises in response to stressors such as telomere shortening, deoxyribonucleic acid (DNA) damage, oxidative stress, hypoxia, and mitochondrial dysfunction [4]. Senescent cells exhibit cell cycle arrest in G1 or G2, macromolecular damage, metabolic and morphological alterations, resistance to apoptosis, and acquire a senescence-associated secretory phenotype (SASP). Post-mitotic cellular senescence (PoMiCS) also plays an important role in cardiovascular health and disease [5]. Molecular markers of cellular aging include tumor protein p53 (p53), protein p21 (p21), cyclin-dependent kinase inhibitor 2A (p16Ink4a), p38 mitogen-activated protein kinase and phosphorylated H2A histone family member X (γH2AX). These are often accompanied by telomere shortening, telomere-associated foci (TAF), and increased activity of senescence-associated β-galactosidase (SA-β-gal), which collectively contribute to pathologies like mitral valve-associated heart failure and sudden arrhythmic death syndrome (Fig. 1). Pharmacological and genetic treatments that target senescent cells can reverse signs of aging and lessen the impact of chronic disease [6]. The aim of this work is to provide a timely and critical update by integrating a comprehensive analysis of the role of cellular senescence in the cardiovascular system with emerging data on therapeutic strategies. The study focuses particularly on molecular mechanisms, physiological functions, and pathological consequences, and synthesizes novel findings regarding the heterogeneity of the SASP and the crucial interactions with immunosenescence. Furthermore, it reviews available therapeutic strategies, including senolytics and senomorphics, and the research tools used to study cardiovascular aging and evaluate the efficacy of potential interventions.

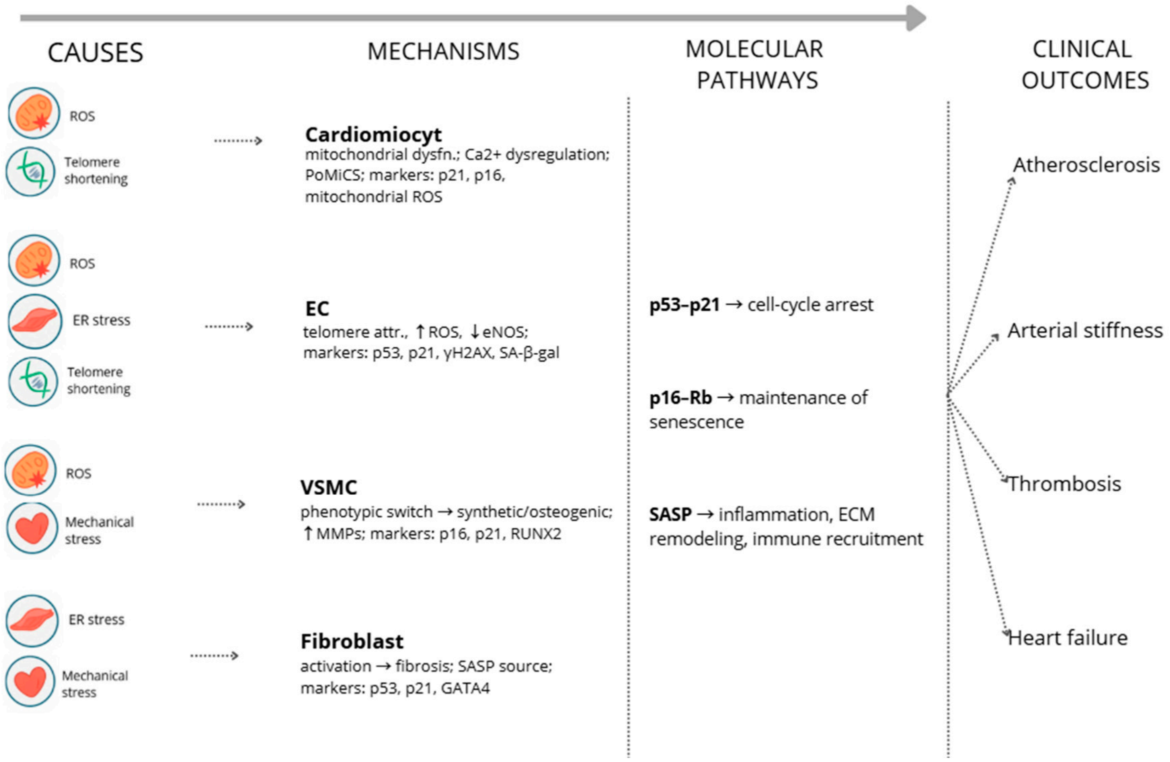

Figure 1: Schematic overview linking stressors, cell-type responses, senescence pathways, and clinical outcomes in the cardiovascular system. SASP, Senescence-associated secretory phenotype; PoMiCS, Post-mitotic cellular senescence; SA-β-gal, Senescence-associated β-galactosidase; γH2AX, Phosphorylated H2A histone family member X; IL-6, Interleukin-6; IL-1β, Interleukin-1β; MCP-1, Monocyte chemoattractant protein-1; MMPs, Matrix metalloproteinases; EC, Endothelial cell; VSMC, Vascular smooth muscle cell; ROS, Reactive oxygen species; ER, Endoplasmic reticulum; UPR, Unfolded protein response; PRb, Retinoblastoma protein; p53, Protein 53; p21, Protein 21; CDKN1A, Cyclin-dependent kinase inhibitor 1A; p16, Protein 16; "↑" indicates an increase; "↓" indicates a decrease. Figure created using Canva Free (Canva.com, accessed on 1 November 2025). All icons used are free elements available under Canva's Free Content License (https://www.canva.com/policies/content-license-agreement/).

2 Molecular Mechanisms of Senescence in the Main Cell Fractions of the Cardiovascular System

Cellular senescence is a durable stress-response state marked by persistent DNA-damage signaling, stable cell-cycle arrest, and a specific secretory phenotype that can reshape surrounding tissue [4]. In the cardiovascular system, senescence accumulates across endothelial cells, vascular smooth muscle cells, fibroblasts, and cardiomyocytes, interfacing with broader aging hallmarks such as genomic/telomeric damage, mitochondrial dysfunction, impaired autophagy, and altered intercellular communication [4,7]. These molecular programs rarely act in isolation: paracrine networks induced by senescence amplify inflammation, oxidative stress, extracellular-matrix remodeling and functional decline that underlie vascular stiffening, atherogenesis, fibrosis, and electrical instability [7,8]. Importantly, senescence is context-dependent—transient senescent states can support repair processes, whereas persistence of senescent cells promotes chronic pathology [4,7,8]. The main mechanisms driving progression of senescence in diverse cell fractions of the cardiovascular system and resulting features of the senescent phenotype have been summarized in Table 1 and Fig. 2.

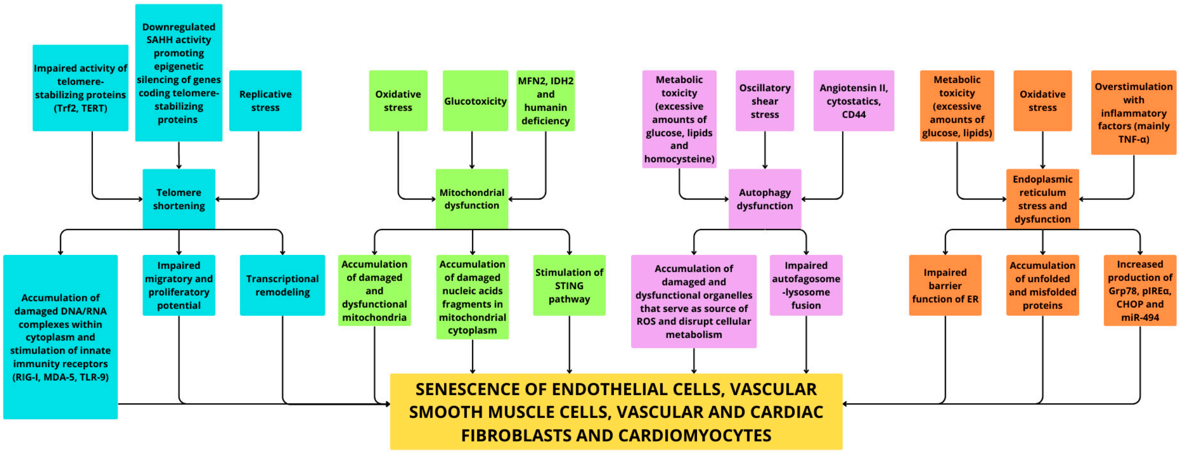

Figure 2: Summarized molecular mechanisms of senescence in endothelial cells. (Figure created with Canva Free [Canva.com accessed on 3 January 2026]). CD44, cluster of differentiation 44; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; Grp78, glucose-regulated protein 78; IDH2, isocitrate dehydrogenase 2; MDA-5, melanoma differentiation-associated protein 5; MFN2, mitofusin 2; miR-494, microRNA 494; pIRE-α, phosphorylated inositol-requiring enzyme α; RIG-I, retinoic acid-inducible gene I; ROS, reactive oxygen species; STING, stimulator of interferon genes; TERT, telomerase reverse transcriptase; TLR-9, toll-like receptor 9; TNF-α, tumor necrosis factor α; Trf2, telomeric repeat-binding factor 2.

2.1 Overview of the Cardiovascular System's Main Cell Fractions

2.1.1 Overview of Endothelial Cells' (ECs) Role and Function

ECs form the innermost layer of lymphatic and blood vessels. Histologically, they are classified as single-layered, squamous epithelial cells and display a relatively simple structure [9]. However, their complex functionality contrasts with their morphological simplicity as they serve as important regulators of vascular homeostasis. Among the numerous processes they control, hemostasis, permeability, vascular tone and formation of new vessels emerge as the most essential [9–11]. Such a broad spectrum of different functions is mediated through various cytokines and other signaling compounds they secrete, including interleukins, growth factors, coagulation factors, platelet activators and nitric oxide (NO) [12,13]. Together with endothelin, NO represents the most notable regulators of vascular tone and permeability [12,13].

As the most superficial layer, lining the inside of the blood vessels, ECs are exposed to a diverse set of harmful agents that may cause irreversible damage and significantly alter their functionality [13,14]. Exposure to environmental toxins, oxidants, dyslipidemia and mechanical stress can negatively affect ECs' structure, proliferation and secretory activity. By disrupting numerous molecular signaling pathways and other homeostatic mechanisms, such factors contribute substantially to endothelial senescence and the progressive decline of cardiovascular health [14]. Acceleration of endothelial aging leads, among others, to the development of atherosclerotic plaques, which represent a crucial risk factor for acute coronary events and other disorders arising from impaired blood flow [14,15].

2.1.2 Overview of Vascular Smooth Muscle Cells (VSMCs) Role and Function

VSMCs constitute the predominant cellular component of the tunica media of arteries and veins and are typically arranged in concentric layers around the vessel lumen [16,17]. In contrast to the morphologically uniform endothelial monolayer, VSMCs display a pronounced functional plasticity that enables them to act as central regulators of vascular structure and tone [16,17]. Under physiological conditions, they maintain a contractile phenotype characterized by abundant cytoskeletal contractile machinery and a primary role in controlling vasoconstriction and vasodilation, thereby contributing to blood pressure regulation and blood flow distribution [16,17]. This function is coordinated through signaling pathways triggered by vasoactive mediators such as angiotensin II, catecholamines, endothelin, and nitric oxide, as well as local calcium-dependent mechanisms [16,17]. Importantly, VSMCs can switch toward non-contractile phenotypes in response to injury or inflammatory stimuli, acquiring increased proliferative and migratory capacity and producing extracellular matrix proteins, cytokines, and proteases that remodel the vessel wall [16–19]. While this phenotypic transition is essential for repair, chronic exposure to oxidative stress, dyslipidemia, mechanical strain, and inflammatory cues promote VSMC senescence and maladaptive remodeling, contributing to arterial stiffening, vascular calcification, and atherosclerotic plaque progression and instability [19–21].

2.1.3 Overview of Fibroblasts Role and Function

Fibroblasts represent a major non-myocyte cell population in the myocardium and are also abundant within the vascular adventitia, where they serve as key architects of tissue structure by synthesizing and maintaining the extracellular matrix [22–24]. Histologically, fibroblasts are spindle-shaped mesenchymal cells with extensive secretory activity, reflecting their central role in regulating collagen and elastin turnover and preserving the mechanical integrity of the heart and vessel wall [22–24]. Beyond structural support, fibroblasts actively shape local signaling networks through the secretion of growth factors, cytokines, and matrix-remodeling enzymes, including transforming growth factor β TGF-β, interleukins, connective tissue growth factor (CTGF), and matrix metalloproteinases (MMPs), thereby influencing inflammation, angiogenesis, and cardiomyocyte function [22–24]. Upon stress or injury, fibroblasts can differentiate into myofibroblasts, characterized by enhanced contractility and markedly increased production of extracellular matrix components, which is essential for wound closure and scar formation, particularly after myocardial infarction [22,24]. However, persistent neurohormonal stimulation, chronic low-grade inflammation, and reactive oxygen species can drive fibroblast dysfunction and senescence, leading to excessive fibrosis and extracellular matrix remodeling that elevate myocardial and vascular stiffness, impair electrical conduction, and promote heart failure progression as well as age-related vascular dysfunction [25–27].

2.1.4 Overview of Cardiomyocytes Role and Function

Cardiomyocytes form the contractile core of the myocardium and are highly specialized striated muscle cells optimized for continuous rhythmic work throughout life [28]. Their morphology is defined by organized sarcomeres, abundant mitochondria, and an intricate excitation–contraction coupling apparatus that translates electrical depolarization into calcium-dependent contraction and relaxation [28]. Functionally, cardiomyocytes ensure cardiac output by generating force and synchronizing contraction through tightly regulated ion channel activity and calcium handling systems [28]. In addition to mechanical work, cardiomyocytes contribute to endocrine and paracrine signaling by producing natriuretic peptides, which influence vascular tone and systemic volume regulation [29]. As terminally differentiated cells with limited regenerative capacity, cardiomyocytes are particularly vulnerable to cumulative damage induced by mitochondrial dysfunction, oxidative stress, impaired proteostasis, and metabolic shifts [30–32]. These stressors promote cellular hypertrophy, altered electrophysiological properties, and contractile decline, ultimately contributing to age-associated diastolic dysfunction, increased arrhythmia susceptibility, and reduced cardiac reserve under stress conditions [31,33,34].

2.2 Telomere Dysfunction and DNA Damage

Telomeres are repetitive structures, composed of DNA and protein complexes, at chromosome ends that protect the genome by preventing chromosome termini from being recognized as DNA breaks [35,36]. Across multiple cardiovascular-relevant cell types, progressive telomere shortening (from replicative aging and stress) and telomere "uncapping" (loss of shelterin integrity) converge with non-telomeric genomic injury (oxidative lesions, replication stress, strand breaks) to activate a persistent DNA damage response (DDR) and enforce long-term growth arrest accompanied by SASP [36]. In the vasculature, aging is associated with a measurable rise in both general DNA damage and telomere dysfunction, with particularly strong effects in ECs and in atheroprone regions [36,37].

2.2.1 Telomere Dysfunction and DNA Damage in ECs

In ECs, *in vivo* and *ex vivo* data show that advanced age increases the abundance of dysfunctional telomeres marked by DDR signaling at telomeric DNA, supporting the concept that telomere damage is not merely a marker but a mechanistic driver of endothelial aging [36]. Consistently, endothelial reduction of the shelterin telomeric repeat-binding factor 2 (Trf2) in young mice is sufficient to induce telomere dysfunction–linked senescence, accompanied by increased inflammatory and oxidative signaling as well as impaired endothelial function [38]. Telomere-driven ECs senescence is further reinforced by epigenetic and metabolic control of telomerase. Notably, S-adenosylhomocysteine hydrolase (SAHH) inhibition can downregulate human telomerase reverse transcriptase (hTERT) via reduced activation at the hTERT promoter, inducing endothelial senescence, providing a direct link between methylation chemistry, telomerase suppression, and ECs aging [39]. Beyond telomeres, ECs senescence is increasingly recognized to involve accumulation of aberrant nucleic acids and innate immune activation, which can originate downstream of DNA damage and replication stress [40]. In human endothelial cells, replicative senescence and high glucose caused accrual of self-derived cytosolic nucleic acids, linking dysmetabolism to nucleic acid stress and inflammatory signaling in senescent ECs [40]. Independently, transcriptomic work has shown that endothelial senescence can feature self-RNA accumulation and upregulation of RNA sensing pathways like retinoic acid-inducible gene I (RIG-I), providing a mechanistic bridge between nucleic acid dysregulation and inflammatory senescence phenotypes [41]. *In vivo*, a complementary axis was demonstrated in diabetic retinopathy models where activation of cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS–STING) signaling promoted retinal endothelial senescence and vascular pathology, while STING loss-of-function attenuated senescence progression and vascular degeneration [42]. Therapeutically, nucleic acid–based telomerase restoration has shown reversal of ECs aging phenotypes in progeroid contexts. Telomerase mRNA therapy reduced vascular senescence and improved outcomes in progeria models, supporting telomere maintenance as an actionable anti-senescence strategy in vascular tissues [43]. More recently, TERT circRNA was shown to extend telomerase expression more effectively than linear mRNA and reverse hallmarks of endothelial senescence in Hutchinson–Gilford progeroid syndrome (HGPS)-derived endothelial cells, including improved telomere measures and functional rescue [44].

2.2.2 Telomere Dysfunction and DNA Damage in VSMCs

In VSMCs, both telomere dysfunction and general DNA damage promote senescence programs that can directly shape vascular remodeling. In a clonal-tracking injury model it was demonstrated that persistent telomere damage in VSMCs (via Trf2 perturbation) increased neointima formation, senescence, and inflammatory cell accumulation [45]. Complementing this, DNA damage is also sufficient to accelerate VSMC senescence. Ionizing radiation induced VSMC senescence and engaged a mechanistic pathway involving nuclear factor kappa B (NF-κB)/CCCTC-binding factor (CTCF)/p16, linking exogenous DNA damage to stable senescence enforcement in the vascular wall [46]. Importantly, aging-associated mapping studies indicate that DNA damage and telomere dysfunction are detectable across different vascular cell types [36]. However, ECs often show stronger signals than VSMCs in aged arteries and atheroprone regions, highlighting both shared and cell-type-biased susceptibility to molecular mechanisms that promote and drive development of senescence-associated phenotype [36].

2.2.3 Telomere Dysfunction and DNA Damage in Fibroblasts

Fibroblast aging in cardiovascular and cardiopulmonary tissues is also shaped by telomere integrity and DDR activation. Conditional loss of the shelterin component telomeric repeat binding factor 1 (Trf1) in lung fibroblasts induced telomeric damage, proliferative defects, cell-cycle arrest, and apoptosis, demonstrating that direct telomere dysfunction is sufficient to trigger a robust DDR-linked alterations in fibroblasts [47]. Separately, fibroblast senescence can be driven by telomere-independent DNA damage mechanisms. Fibroblast-specific deletion of Lmna gene (encoding lamin A and lamic C proteins responsible for reinforcement of cellular nucleus structure and DNA replication) caused double-strand break signaling and activation of senescence pathways with SASP induction, implicating nuclear-envelope instability and DDR as potent upstream causes of fibroblast senescence with downstream cardiac consequences [48].

2.2.4 Telomere Dysfunction and DNA Damage in Cardiomyocytes

Although cardiomyocytes are largely post-mitotic, telomere erosion and telomere-associated chromatin changes remain relevant to myocardial aging and failure. In human heart failure cardiomyocytes and experimental systems, telomere shortening was linked to proximal telomeric decompaction and a forkhead box C1 (FoxC1)-dependent transcriptional program that promoted cardiomyocyte senescence and mitochondrial dysfunction, supporting telomere state as an active regulator of cardiomyocyte aging phenotypes [49]. Moreover, cardiac telomerase modulation intersects with DNA damage control. In cardiomyocytes, TERT overexpression increased telomere length, while simultaneously reducing ROS-associated DNA damage, and improved repair outcomes after myocardial infarction (MI) [50]. These findings link telomere maintenance with attenuation of DDR–driven dysfunction in the injured heart [50].

2.3 Mitochondrial Dysfunction and Oxidative Stress

Mitochondria are the central hub of aerobic energy metabolism, and their dysfunction, together with sustained oxidative stress, has emerged as a convergent driver of cellular senescence in different cell fractions of the cardiovascular system [36,51,52]. Across these cell types, a common sequence is frequently observed: metabolic or environmental stress perturb mitochondrial dynamics and bioenergetics, elevates mitochondrial reactive oxygen species (ROS). It also triggers persistent redox-sensitive stress signaling, often coupled to DDR and inflammatory amplification, culminating in stable growth arrest and acquisition of a senescence-associated phenotype [36,51,52].

2.3.1 Mitochondrial Dysfunction and Oxidative Stress in ECs

In ECs, hyperglycemia is a well-documented inducer of mitochondrial dysfunction and premature senescence [53]. Comparative analyses of primary human umbilical vein endothelial cells (HUVECs) versus immortalized ECs cultures showed that high glucose robustly activates senescence programs alongside a stronger DNA damage response in primary ECs, consistent with mitochondrial ROS-driven stress signaling in a diabetic-like milieu [53]. In retinal microvascular ECs, long-term high-glucose exposure similarly provokes premature senescence, supporting the concept that chronic metabolic overload imprints a stable, pro-senescent endothelial state [54]. A comparable manifestation of glycemic memory has been described *in vitro* in endothelial cells exposed transiently to high glucose, where a short hyperglycemic insult followed by return to normoglycemia elicited persistent endothelial senescence. This long-lasting phenotype was mediated by sustained suppression of SIRT1 and reciprocal activation of p300, leading to prolonged acetylation of p53 and induction of p21. Notably, these signaling alterations were accompanied by durable mitochondrial abnormalities, including increased mitochondrial ROS production, impaired mitochondrial dynamics, and reduced bioenergetic efficiency, which persisted despite glucose normalization. Together, these findings support a SIRT1/p300/p53/p21–dependent metabolic memory program in which enduring mitochondrial and redox remodeling maintains endothelial dysfunction after withdrawal from the hyperglycemic environment [55]. Beyond glucose, mitochondrial structure–function control is causally linked to endothelial aging. For example, angiotensin II-driven ECs senescence is potentiated by loss of mitofusin-2, which promotes mitochondrial structural abnormalities, increased ROS, and impaired respiration. Restoration of mitofusin-2 alleviates these effects, directly tying mitochondrial fusion control to senescence suppression [56]. Complementing this, mitochondria-derived protective signals can counteract hyperglycemic endothelial aging. Humanin reduces high-glucose–induced endothelial senescence and dysfunction, implicating mitochondria-to-nucleus protective signaling as a modulator of senescence severity [57].

2.3.2 Mitochondrial Dysfunction and Oxidative Stress in VSMCs

In VSMCs, mitochondrial dysfunction and oxidative stress similarly act as proximal mechanisms accelerating senescence and pathological remodeling. Primary VSMCs isolated from human abdominal aortic aneurysm tissue exhibit persistent mitochondrial dysfunction characterized by increased superoxide production and impaired redox buffering resulting from altered NADPH metabolism. These findings are accompanied by enhanced γ-H2AX-defined DNA damage, and earlier growth arrest consistent with accelerated senescence [58]. Diabetes-linked vascular pathology provides another mechanistic example. Activation of STING1, with DNA leaked from mitochondria damaged by Nε-carboxymethyl-lysine, has been implicated to contribute to progression of VSMCs calcification and premature senescence. This phenomenon supports mitochondria–innate immunity coupling as a driver of VSMC aging in metabolic diseases [59]. Therapeutically, interventions that improve mitochondrial performance can blunt senescence outputs in VSMCs. Simvastatin was reported to ameliorate senescence-induced mitochondrial dysfunction, reduce oxidative stress, and modulate SASP-associated outputs in senescent VSMCs, linking mitochondrial rescue to functional "anti-senescent" benefit [60].

2.3.3 Mitochondrial Dysfunction and Oxidative Stress in Fibroblasts

Fibroblasts (including vascular-associated and cardiac stromal fibroblasts) are likewise highly sensitive to mitochondrial quality-control failure. Primary human fibroblasts maintain active basal mitophagy initiated by mitochondrial superoxide signaling [61]. However, suppression of PTEN Induced Kinase 1 (PINK1)/Parkin/p62-dependent mitophagy is sufficient to trigger senescence phenotypes in these cell fractions [62]. Oxidant-driven fibroblast senescence is also experimentally well supported [63]. Exposure to hydrogen peroxide in human dermal fibroblasts induces senescence programs with distinct secretory outputs, consistent with oxidative stress acting as a primary upstream senescence trigger [63]. More recently, pharmacologic enhancement of mitochondrial quality has been shown to mitigate fibroblast senescence. Pterostilbene reduced SA-β-gal activity (senescence marker) and p16/p21 expression while simultaneously restoring mitochondrial morphology, membrane potential, respiration and lowering mitochondrial ROS generation in senescent dermal fibroblasts. These alterations were accompanied by concomitant improvement in mitophagy markers [64].

2.3.4 Mitochondrial Dysfunction and Oxidative Stress in Cardiomyocytes

In cardiomyocytes, which are exceptionally mitochondria-rich, multiple independent lines of evidence link mitochondrial metabolic disruption and mitochondrial ROS generation to senescence progression and age-related functional decline. Chronic arsenite exposure disrupts mitochondrial tricarboxylic acid (TCA)-cycle and electron transport chain (ETC) components and induces cardiomyocyte senescence reflected by cyclin-dependent kinase 1A (CDKN1A) upregulation in human cardiomyocytes. Conversely, interventions focused on improving mitochondrial functionality (nicotinamide mononucleotide [NMN] supplementation) mitigate senescence-associated phenotypes and improve cardiomyocytes' functional readout [52]. Chemotherapy-associated cardiotoxicity further supports mitochondrial ROS as a causal lever of senescence progression. Doxorubicin elevates mitochondrial ROS alongside senescence markers in cardiomyocytes while targeted mitochondrial antioxidants (mitoquinol [MitoQ]) reduce the senescence burden in experimental cardiomyocyte models [51,65]. In cardiomyopathy models, mitochondrial fragmentation is mechanistically tied to cardiomyocyte aging as it leads to excessive release of mtDNA, ROS and accumulation of defective organelles which impair functioning of other cellular structures and activate innate immunity receptors that stabilize senescent state [66,67].

2.4 Autophagy Dysfunction

Autophagy is a natural mechanism that provides measures of neutralizing and removing damaged or degenerated intracellular organelles. It helps maintain the high functionality of different tissues and provides alternative energy sources under unfavorable environmental conditions [68,69]. Defects in autophagy lead to the accumulation of dysfunctional organelles that may act as sources of ROS or impair physiological mechanisms that maintain cellular homeostasis, therefore accelerating the aging process [68,69].

2.4.1 Autophagy Dysfunction in ECs

In vascular ECs, several recent studies directly link impaired autophagy to senescence. Homocysteine exposure induced HUVECs senescence, and pharmacologic activation of autophagy with rapamycin alleviated SA-β-gal positivity and oxidative stress, whereas autophagy inhibition exacerbated the phenotype [70]. An age-associated, mechanistic brake on endothelial autophagy was identified in the cluster of differentiation 44 (CD44) signal transducer and activator of transcription 3 (STAT3)-phosphatidylinositol 3-kinase (PtdIns3K) axis. The CD44 intracellular domain reduced PIK3R4/PIK3C3 signaling, suppressed autophagy, and promoted vascular endothelial aging signatures *in vitro* and *in vivo* [71]. Mechanical stress can drive a similar outcome. Oscillatory shear stress increased integrin β3 (ITGB3), blocked autophagic flux (impaired autophagosome–lysosome coupling), and promoted endothelial senescence markers such as p16 and p21 in human aortic ECs [72]. Metabolic lipotoxicity also intersects with autophagy control as palmitic acid was shown to decrease autophagic flux and as a result accelerate senescence in ECs [73].

2.4.2 Autophagy Dysfunction in VSMCs

In VSMCs, disruption of autophagic homeostasis likewise promotes senescence and contributes to pro-atherogenic remodeling. Genetic or stress-induced suppression of autophagy in VSMCs leads to accumulation of p62-Sequestosome 1 (SQSTM1), activation of cell-cycle arrest pathways, and acquisition of senescence hallmarks, ultimately accelerating neointimal formation and atherosclerotic lesion development. Conversely, pharmacological or genetic restoration of autophagic activity mitigates senescence-associated phenotypes, reduces inflammatory and extracellular-matrix-remodeling programs, and preserves VSMC functional capacity. These findings support a central role for intact autophagic flux in restraining VSMC senescence and maintaining vascular wall integrity during aging and disease [74–76]. Complementary mechanistic work showed that PPAR-γ activation inhibits H_2O_2-induced VSMC senescence by relieving suppression of forkhead box O3a (FoxO3a)-autophagy signaling [77]. More recently, activating transcription factor 3 (ATF3) was positioned as an endogenous anti-senescence safeguard in VSMCs by orchestrating autophagy through an ATF3-autophagy related 7 (ATG7) amplification loop, with ATF3 deficiency aggravating ageing-associated atherosclerosis [78].

2.4.3 Autophagy Dysfunction in Fibroblasts and Cardiomyocytes

Beyond the vessel wall, autophagy decline is a robust driver of senescence in stromal and cardiac compartments. In human dermal fibroblasts, SIRT1 activation reduced senescence and inflammatory cytokine output while increasing autophagy markers (light chain 3-II [LC3-II], Beclin-1), linking autophagy reinforcement to suppression of SASP-like programs [79]. A mechanistic framework connecting selective autophagy to cellular aging was further strengthened by evidence that suppression of basal PINK1/Parkin/p62-dependent mitophagy is sufficient to trigger senescence, whereas reactivation of mitophagy is required for anti-senescence effects of interventions such as NAD precursors or rapamycin [62]. In cardiomyocytes, causality has been demonstrated using cardiac ATG7 loss-of-function approaches. Suppression of general autophagy induced accumulation of senescent cardiomyocytes and contributed to myocardial dysfunction, while autophagy reactivation mitigated these changes [80]. Consistently, pro-autophagy signaling (SIRT1/AMP-activated protein kinase [AMPK]/mammalian target of rapamycin [mTOR] modulation) attenuated D-galactose-induced cardiomyocyte senescence *in vitro*, supporting the concept that maintaining autophagic competence counteracts cardiac aging programs [81].

2.5 Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) is a membrane network that coordinates biosynthesis of proteins and lipids as well as homeostasis of Ca^{2+} and oxidoreductive balance [82–84]. When ER function is chronically challenged by hyperglycemia, oxidized lipids, inflammation or mechanical overload cells activate the unfolded protein response (UPR). The main effector elements of this axis encompass protein kinase R-like endoplasmic reticulum kinase (PERK), eukaryotic initiation factor 2 α subunit (eIF2α), activating transcription factor 4 (ATF4), activating transcription factor 6 (ATF6), inositol-requiring enzyme 1α (IRE1α) and spliced X-box binding protein 1 (XBP1s) [82–84]. Although the UPR is initially adaptive, sustained ER stress can become maladaptive and amplify oxidative stress, disturb Ca^{2+} handling, impair mitochondria–ER crosstalk and engage DNA-damage. Such alterations may promote stable growth arrest and a pro-inflammatory senescence program across multiple cardiovascular cell types [82–84].

2.5.1 Endoplasmic Reticulum Stress in ECs

In vascular ECs metabolic and lipotoxic stimuli directly connect ER stress to senescence-like remodeling. ECs derived from human coronary artery, exposed to high glucose or oxidized LDL, display UPR activation (including XBP1 splicing and ATF6 activation) accompanied by upregulated expression of canonical senescence regulators (p16/p21/p53) and deterioration of endothelial barrier function [84]. ER stress also induces microRNA programs that modify endothelial stress responses. miR-494 is robustly induced in ECs by pharmacologic ER stressors and hyperglycemia, which leads to modulation of UPR marker expression (DNA Damage Inducible Transcript 3 [DDIT3], C/EBP homologous protein [CHOP], XBP1s), indicating tight coupling between ER stress signaling and endothelial cell-fate control [85]. *In vivo*, chronic vascular inflammation can synergize with ER stress to accelerate microvascular dysfunction. In studies assessing diabetic tie2-TNF mice it was shown that ER-stress-linked pathways contribute to retinal vascular leakage and visual impairment, while treatment with the chemical chaperone (tauroursodeoxycholic acid [TUDCA] alleviates ER-stress signatures alongside functional readouts [86].

2.5.2 Endoplasmic Reticulum Stress in VSMCs

In VSMCs ER-stress and resulting UPR activation are not merely bystanders but mechanistic drivers of senescence phenotypes. Cholesterol loading can promote VSMC senescence through ER stress and ROS coupling. Reduced activity of the ER-associated degradation (ERAD) component HMG-CoA reductase degradation protein 1 (HRD1) increases ER stress, elevates mitochondrial dysfunction and ROS generation and as a result accelerates senescence. Conversely, restoring HRD1 or dampening ER stress or ROS activity partially reverses these outcomes [87]. Complementing this, a recent study by Jiao et al. demonstrated that VSMC senescence is accompanied by increased ER-stress markers (Grp78, CHOP) and activation of IRE1/XBP1, PERK/eIF2α/ATF4 and ATF6 axes [88]. Mechanical cues also converge on ER dysfunction. Excessive matrix stiffness (relevant to aneurysm biology) promotes VSMC senescence together with disrupted mitochondria and ER function, with lipid stress exacerbating these effects. These findings implicate ER stress as part of a mechano-metabolic senescence axis in the vascular wall [82].

2.5.3 Endoplasmic Reticulum Stress in Fibroblasts

Beyond ECs and VSMCs, ER stress and UPR signaling also reshape the phenotype of fibroblasts residing in the vascular wall and myocardium, thereby contributing to age-associated vascular remodeling and cardiac dysfunction. In vascular adventitial fibroblasts, the importance of proteostasis is highlighted in a study by Cicalese et al. showing that the chemical chaperone 3-hydroxy-2-naphthoic acid (3HNA) prevented induction of UPR markers in adventitial fibroblasts and attenuated angiotensin 2–driven fibrosis and vascular remodeling, linking fibroblast ER stress to hypertensive vascular pathology [89]. In human cardiac fibroblasts pharmacological induction of ER stress with tunicamycin activated canonical UPR arms, including IRE1α/XBP1 and ATF4/CHOP, and promoted a CHOP-dependent inflammatory program, with increased NF-κB signaling, IL-6 release, and collagen I expression. Importantly, these responses were blunted by the by ER-stress inhibition with TUDCA, supporting the concept that limiting ER stress in cardiac fibroblasts can restrain inflammation and matrix remodeling, features that commonly accompany fibroblast aging in the diseased heart [90]. Consistently, in a metabolic stress setting, paracrine crosstalk between cardiomyocytes and cardiac fibroblasts mediated by extracellular vesicles provides an additional conduit for ER-stress-linked senescence and fibrotic remodelling. In models of diabetic cardiomyopathy, cardiomyocytes under lipid overload secreted small extracellular vesicles with altered miRNA/protein cargo that were taken up by fibroblasts, promoting activation of pro-fibrotic signalling and fibroblast-to-myofibroblast conversion with upregulation of TGF-β pathways and extracellular matrix gene expression. These maladaptive responses were accompanied by enhanced ER-stress signalling and disturbances in autophagy regulation in recipient fibroblasts, contributing to persistent fibrotic phenotypes. Importantly, restoring specific cardiomyocyte EV cargo (e.g., miR-194-3p) or inhibiting stress pathways mitigated fibroblast activation and reduced fibrotic outcomes, supporting a stress-dependent EV-mediated mechanism of intercellular remodelling between cardiomyocytes and fibroblasts under lipid overload [91].

2.5.4 Endoplasmic Reticulum Stress in Cardiomyocytes

In cardiomyocytes, original studies support ER-stress–driven senescence as a contributor to cardiac aging. Proprotein convertase subtilisin/kexin type 6 (PCSK6) deficiency in cardiomyocytes increases senescence hallmarks (p16/p21, SA-β-gal, ROS) and is mechanistically associated with ER-stress signaling via upregulation of DDIT3/CHOP linking maladaptive UPR activation to aging progression [92]. Consistently, an H_2S-donor strategy in a cardiac-aging context attenuated senescence-associated phenotypes while suppressing IRE1α/XBP1s pathway activity, supporting the concept that targeting specific UPR branches can mitigate cardiomyocyte senescence and cardiac functional decline [93].

2.6 Fibroblasts and Cardiomyocytes

Fibroblast senescence can be regarded as a major factor contributing to cardiac fibrosis. They are crucial for supporting myocytes structurally, as well as producing the main components of ECM [94]. Their correct function is thus necessary for cells' functions and responses. Most importantly, fibroblast activation is crucial for the response to injury—they migrate to the injured region, produce growth factors and inflammatory cytokines, and differentiate from pro-inflammatory to pro-fibrotic phenotype [26,95].

Diseases of the cardiovascular system can cause local fibroblasts to become senescent. The exact mechanism is not yet fully understood; similarly to smooth muscle cells' senescence, it has been shown to involve a transcription factor, GATA Binding Protein 4 (GATA4) [96]. In mice, the deletion of GATA4 in cardiac fibroblasts was shown to increase senescence. Moreover, the expression of GATA4 has been proven to decrease with aging. The senescence of cardiac fibroblasts can also be triggered by mechanical stressors [97] and oxidative stress. This is mainly in response to DNA damage and the increase in the p53/p21 and p16 accordingly. As was previously explained, SASP factors, secreted by other senescent cells, can also likely trigger the senescence of surrounding fibroblasts.

In mice post-MI, p53-mediated fibroblast senescence is known to be associated with decreased cardiac collagen production [98]. Senescent cells, which are likely fibroblast-derived, were also proven to accumulate in the heart after an MI episode. This may explain the altered uptake of mediators and the decrease in regenerative fibrosis after MI [26].

Direct reprogramming of ischemia-activated fibroblasts seems like a potential therapeutic target [99]. Reprogramming fibroblasts into cardiomyocyte-like cells is currently based on three transcription factors—GATA4, Myocyte Enhancer Factor 2 (MEF2) and T-Box Transcription Factor 5 (TBX5) [100]—collectively known as GATA4, MEF2C, TBX5 (GMT). The clinical potential of direct reprogramming is yet to be shown; nonetheless, great hopes are currently associated with it. To be useful, the GMT gene sequence must be shortened. The way to do so was previously shown by Honda et al. [100], who also suggested and showcased the effectiveness of the deletion of effector domains in MEF2C and GATA4. Recently, it has been suggested that the reprogramming may further be stimulated by epigenetic factors such as the histone reader PHF7 [101]. Most importantly, PHF7 has been shown to improve survival, function, and fibrosis up to 16 weeks after infarction in a murine model. This is likely due to its ability to increase chromatin accessibility [102]. The use of epigenetic factors has the chance to overcome the previous obstacles associated with the use of GMT.

Table 1: Summarized senescence-driving mechanisms and main alterations associated with the senescent phenotype in different cell fractions of the cardiovascular system.

Cell Type	Main Senescence-Driving Mechanisms	Molecular Background	Cell-Specific Senescence Features	References
Endothelial cells	Telomere shortening and DNA damage	↑ accumulation of dysfunctional telomeres ↑ DDR signaling in telomere regions of the chromosomes ↓ shelterin and Trf2 function ↓ activity of the hTERT promoter ↑ accumulation of self-derived cytosolic nucleic acids and activation of innate immunity receptors (RIG-I, MDA5, TLR9, cGAS-STING)	Reduced vasodilator capacity: diminished NO bioavailability and impaired endothelium-dependent relaxation; disturbed flow-mediated dilation physiology Barrier dysfunction: higher permeability, tight-junction/cytoskeletal junction remodeling, greater tissue edema susceptibility and inflammatory infiltration Pro-inflammatory and pro-thrombotic shift: enhanced leukocyte adhesion and transmigration, impaired anticoagulant surface, and increased propensity for platelet–endothelium interactions Impaired angiogenic repair competence: reduced regenerative capacity and defective adaptive remodeling after injury or stress	[36,38–42, 44,53–57,70, 72,73,82,87, 88,103–106]
	Mitochondrial dysfunction and oxidative stress	↑ generation of cellular peroxides and mitochondrial superoxides ↓ mitochondrial inner membrane potential ↓ SIRT1 activity ↓ efficacy of mitochondrial antioxidant response ↓ humanin and MFN2 activity		
	Autophagy dysfunction	↑ susceptibility to homocysteine-driven senescence ↓ autophagic flux caused by OSS-dependent ITGB3 overexpression ↑ CD44-driven PIK3R4 and PIK3C3 downregulation ↓ impaired autophagosome-lysosome fusion		
	Endoplasmic Reticulum Stress	↑ UPR activation (XBP1 splicing, ATF6, DDIT3, CHOP) ↑ expression of miR-494		

Table 1: *Cont.*

Cell Type	Main Senescence-Driving Mechanisms	Molecular Background	Cell-Specific Senescence Features	References
Vascular smooth muscle cells	Telomere shortening and DNA damage	↑ DDR signaling in telomere regions of the chromosomes ↓ shelterin and Trf2 function ↓ HMGB2 activity ↑ formation of senescence-induced CTCF clusters	Loss of contractile homeostasis: reduced ability to maintain tone and vasomotor adaptability; increased functional rigidity of the vascular wall Arterial stiffening trajectory: senescence-associated ECM remodeling, accompanied by biomechanical changes contribute to reduced compliance and higher pulse wave velocity risk Pro-calcific remodeling: enhanced osteogenic differentiation programs and mineral deposition Fibrous-cap repair impairment: reduced reparative capacity, compromising stable plaque architecture, and increasing vulnerability features	[36,45,46, 58–60,77,78, 82,87,88, 107–110]
	Mitochondrial dysfunction and oxidative stress	↑ generation of superoxides ↓ redox buffering (resulting from altered NADPH metabolism) ↑ release of mitochondrial DNA and subsequent activation of STING1		
	Autophagy dysfunction	↓ autophagic flux and autophagosome/lysosome fusion via LAMP1 downregulation ↑ suppression of PTEN and FoxO3a ↓ ATF3 activity		
	Endoplasmic Reticulum Stress	↑ accumulation of cholesterol ↓ ERAD-HRD1 activity ↑ activation of IRE1/XBP1 axis ↑ activation of PERK/eIF2α/ATF4 and ATF6 axis		
Fibroblasts	Telomere shortening and DNA damage	↑ DDR signaling in telomere regions of the chromosomes ↓ shelterin and Trf1 function ↓ expression of lamin A and C ↑ instability of the cellular nucleus	Fibrosis pattern changes over time: fibroblast senescence can limit excessive early scar expansion, but persistent senescence supports chronic fibrotic remodeling through sustained SASP and ECM imbalance ECM quality deterioration: maladaptive collagen organization and crosslinking, accompanied by protease imbalance, lead to increased myocardial stiffness and impaired relaxation (diastolic dysfunction propensity) Arrhythmogenic remodeling: senescent myofibroblasts can promote pro-arrhythmic myocyte changes (cell–cell interactions and paracrine signaling), contributing to conduction heterogeneity	[47,48,62, 63,79,89,90, 104–106, 111]
	Mitochondrial dysfunction and oxidative stress	↓ mitophagy (dysfunctional mitochondria act as sources of ROS and nucleic acids, stimulating innate immunity receptors) ↓ mitochondrial inner membrane potential		
	Autophagy dysfunction	↓ LC3-II and Beclin 1 activity ↓ PINK1/Parkin/p62-dependent mitophagy		
	Endoplasmic Reticulum Stress	↑ activation of IRE1α/XBP1 axis ↑ activation of ATF4/CHOP ↑ stimulation with tropomyosin 1		

Table 1: *Cont.*

Cell Type	Main Senescence-Driving Mechanisms	Molecular Background	Cell-Specific Senescence Features	References
Cardiomyocytes	Telomere shortening and DNA damage	↑ accumulation of dysfunctional telomeres ↑ DDR signaling in telomere regions of the chromosomes ↑ expression of FoxO1 ↓ activity of TERT	Reduced contractile performance and reserve: depressed systolic function under stress, slower recovery, and impaired β-adrenergic responsiveness Calcium handling deterioration: excitation–contraction coupling inefficiency (slower Ca^{2+} cycling, impaired relaxation), systolic/diastolic dysfunction Arrhythmia susceptibility: remodeling of atrial and ventricular ion currents and conduction barriers caused by the progression of ECM fibrosis	[49–52,66, 67,80,81,93, 112–116]
	Mitochondrial dysfunction and oxidative stress	↓ activity of the TCA cycle ↓ activity of ETC components ↑ mitochondrial fragmentation (damaged mitochondria act as sources of ROS and nucleic acids that activate innate immunity receptors		
	Autophagy dysfunction	↓ activity of ATG7 ↑ mTOR phosphorylation ↓ SIRT1 expression		
	Endoplasmic Reticulum Stress	↓ PCSK6 activity ↑ activity of DDIT3/CHOP axis ↑ activity of IRE1α/XBP1s axis		

Note: ATF3, activating transcription factor 3; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; ATG7, autophagy related 7; CD44, cluster of differentiation 44; cGAS–STING, cyclic GMP-AMP synthase–stimulator of interferon genes; CHOP, CCAAT/enhancer-binding protein homologous protein; CTCF, CCCTC-binding factor; DDIT3, DNA damage inducible transcript 3; DDR, DNA damage response; ECM, extracellular matrix; eIF2α, eukaryotic initiation factor 2 α subunit; ERAD-HRD1, endoplasmic reticulum–associated degradation-HMG-CoA reductase degradation 1 homolog; ETC, electron transport chain; FoxO3a, forkhead box O3a; hTERT, human telomerase reverse transcriptase; HMGB2, high mobility group box 2; IRE1α, inositol-requiring enzyme 1α; LAMP1, lysosomal-associated membrane protein 1; LC3-II, microtubule-associated protein 1A/1B-light chain 3; MDA5, melanoma differentiation-associated protein 5; MFN2, mitofusin 2; miR-494, microRNA-494; mTOR, mechanistic target of rapamycin; NADPH, reduced nicotinamide adenine dinucleotide phosphate; PCSK6, proprotein convertase subtilisin/kexin type 6; PERK, protein kinase R-like endoplasmic reticulum kinase; PIK3C3, phosphatidylinositol 3-kinase catalytic subunit type 3; PIK3R4, phosphoinositide-3-kinase regulatory subunit 4; PINK1, PTEN-induced kinase 1; PTEN, phosphatase and tensin homolog; RIG-I, retinoic acid–inducible gene I; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SIRT1, sirtuin 1; TCA, tricarboxylic acid cycle; TLR9, toll-like receptor 9; Trf1, telomeric repeat-binding factor 1; Trf2, telomeric repeat-binding factor 2; XBP1, X-box binding protein 1. ↑ indicates increase/activation/upregulation, ↓ indicates decrease/inhibition/downregulation.

3 Cellular Senescence in the Physiology and Homeostasis of the Cardiovascular System

Cellular senescence has traditionally been associated with organismal aging and permanent cell-cycle arrest [105], but increasing evidence indicates that it is a dynamic, context-dependent process that may support tissue repair when activated transiently. After acute tissue injury (e.g., skin wounding, partial hepatectomy), in multiple cell types—fibroblasts, endothelial cells, and some parenchymal cells—a wave of stress-induced senescence is triggered, and these cells adopt a distinct SASP containing cytokines, chemokines, growth factors, and ECM-remodeling enzymes, which coordinate inflammation resolution, immune recruitment, and ECM reorganization, collectively supporting effective repair rather than chronic scarring [104,105].

Evidence from murine skin and liver regeneration models shows that transient senescent fibroblasts accelerate ECM deposition and epithelial closure, whereas timely removal of these cells by the immune system is necessary to avoid later fibrosis and persistent inflammation. Experimental manipulations that block early senescence impair optimal wound closure, while premature elimination of senescent cells can also delay repair—this biphasic requirement underscores the need for temporal precision in senescence-targeted therapies in regenerative medicine [106].

3.1 Senescence in Remodeling after Myocardial Infarction

MI triggers a coordinated sequence of inflammatory clearance, scar deposition, and structural remodeling; cellular senescence is increasingly recognized as a key regulator of these stages. After ischemic injury, cardiomyocytes, cardiac fibroblasts, and vascular cells express markers of stress-induced senescence (e.g., p16INK4, p21, SA-β-gal) and produce SASP factors that recruit immune cells and modulate fibroblast behavior [111].

In the early post-MI period, senescence may be adaptive: by restraining excessive fibroblast proliferation, it limits fibrosis, and SASP-derived growth factors (e.g., from the Vascular Endothelial Growth Factor [VEGF] family) may transiently support angiogenesis in the border zone, improving perfusion of salvaged myocardium [111]. However, mounting evidence highlights the darker side of persistent post-MI senescence: long-lived senescent fibroblasts and endothelial cells maintain a pro-inflammatory, matrix-degrading SASP (e.g., IL-1β, TNF-α, MCP-1, MMPs) that sustains maladaptive remodeling—chamber dilation, scar thinning, and progressive contractile dysfunction [107,111]. Senescent cardiomyocytes show mitochondrial dysfunction, disrupted calcium regulation, and reduced contractility; their presence correlates with impaired functional recovery and development of heart failure phenotypes [107,111].

Animal studies demonstrate that pathological persistence of senescent cells in the heart is associated with worse outcomes after ischemic injury, although it remains unclear which cell populations contribute most to these deleterious effects [108]. In preclinical MI models, senolytic approaches have been tested: pharmacologic elimination of senescent cells (e.g., B-Cell Lymphoma 2 (BCL-2) inhibitors such as navitoclax, or dasatinib + quercetin combinations) reduced inflammation and fibrosis and improved cardiac function when administered after the reparative phase. Yet, the timing of drug administration is critical, and adverse effects (e.g., thrombocytopenia with navitoclax) complicate clinical translation [109]. Some studies report mixed or even harmful effects of senolytics when applied without temporal control, emphasizing the need for deeper mechanistic clarity before human trials in post-MI settings [108–110].

3.2 Beneficial Effects of Senescent Cells in the Cardiovascular System

When properly induced and cleared, senescent cells perform protective and regenerative roles in the cardiovascular system. Key mechanisms include: (1) restricting excessive proliferation of damaged cells (tumor suppressive/antifibrotic checkpoint), (2) secreting SASP factors that support repair, coordinate immune recruitment, and remodel ECM, and (3) transiently enhancing angiogenesis via paracrine secretion of VEGF and related factors by senescent endothelial or perivascular cells. In the context of acute ischemia or mechanical injury, these functions support formation of structurally competent scar tissue and limit maladaptive hypertrophy [108,117].

Additionally, SASP components can actively polarize infiltrating immune cells toward pro-resolving phenotypes (e.g., M2 macrophages) and secrete mediators that dampen excessive inflammation at later phases. An emerging view portrays transient senescence as a biological “brake”, coordinating arrest of proliferation and the shift from inflammatory clearance to reparative remodeling. This suggests that wholesale elimination of senescence signals may be detrimental in acute cardiovascular injury unless alternative repair pathways are secured [117,118].

3.3 Detrimental Effects of Senescent Cells in Cardiovascular Tissues

Chronic accumulation of senescent cells in the vasculature and myocardium is a major contributor to age-related cardiovascular pathology. In vessels, senescent endothelial cells exhibit impaired NO production, increased expression of adhesion molecules and procoagulant factors, and a SASP that promotes leukocyte recruitment and local inflammation—early events in atherogenesis and arterial stiffening [119,120]. Senescent vascular smooth muscle cells lose contractile phenotype markers and secrete ECM-remodeling enzymes, destabilizing atherosclerotic plaques and increasing rupture risk [119,120].

In addition to plaque destabilization, senescent VSMCs actively contribute to medial vascular calcification (MVC), a key determinant of arterial stiffness. Senescence is associated with phenotypic switching of VSMCs from a contractile to an osteogenic-like state, driven in part by senescence-associated inflammatory and osteoinductive signaling, and characterized by upregulation of bone-related transcription factors and deposition of calcium–phosphate minerals, primarily hydroxyapatite, within the tunica media. Progressive mineral accumulation disrupts the organization and mechanical properties of elastin and collagen fibers, leading to loss of arterial compliance.

Increased arterial stiffness elevates systolic blood pressure and cardiac afterload, thereby promoting hypertension and exacerbating conditions such as heart failure, particularly heart failure with preserved ejection fraction. Moreover, stiffened arteries impair normal pulsatile hemodynamics and limit the buffering capacity of large vessels, further increasing peripheral vascular resistance. Mechanistically, calcification-associated damage to the elastic lamina compromises the ability of the vessel wall to accommodate cyclic strain, ultimately contributing to global vascular dysfunction and age-related cardiovascular disease progression [112].

In the cardiac muscle, prolonged SASP induces paracrine deterioration: persistent inflammatory cytokines and MMPs degrade ECM, favor fibrotic replacement, and impair mechanical coupling. Mitochondrial dysfunction and elevated ROS in senescent cardiomyocytes exacerbate energetic deficits, disrupt calcium cycling, and drive further senescence in a vicious feedback loop [113,120].

Importantly, the ability of the immune system to clear senescent cells declines with age (immunosenescence), permitting their numerical and functional expansion. This correlates with hypertension, heart failure with preserved ejection fraction (HFpEF), and worse outcomes after ischemic episodes [113,120]. Epidemiologic and experimental evidence link senescent cell burden both to disease initiation (e.g., atherosclerosis) and progression (e.g., chronic heart failure), making senescence a tempting but complex therapeutic target [113].

3.4 Balancing Protective and Detrimental Roles of Senescence

Maintaining the balance between beneficial and harmful effects of senescence requires tight spatiotemporal control over its induction, SASP composition, and immune-mediated clearance. Multiple regulatory layers contribute to this equilibrium: external triggers (DNA damage, telomere shortening, oxidative stress), intracellular effectors (p53–p21 and p16–Rb axes), and extracellular modulators (immune cells and local niche factors that decide whether to amplify or resolve SASP). Crucially, distinct senescence programs may yield different SASP profiles—implying that not all senescent cells are functionally equivalent. This heterogeneity opens the possibility for selective modulation (senomorphic strategies) that suppress harmful SASP elements while preserving reparative signals [114,118].

4 Senescence in Cardiovascular Disease Pathogenesis

4.1 Atherosclerosis

Atherosclerosis, which leads to conditions such as ischemic heart disease (IHD), peripheral artery disease (PAD), or ischemic stroke [115], is the major cause of death globally [116]. The disease is a result of inflammation and lipid build-up, leading to narrowing of the arterial lumen [121]. Pathophysiology of atherosclerosis involves numerous mechanisms and is continuously researched [122]. Considering that the disease is strongly age-related, cellular senescence is one of the factors contributing to its development [123]. Multiple ways in which cellular senescence contributes to atherosclerosis have been identified. One of them, stemming from the accumulation of senescent cells, is called "inflammaging", which manifests as constant low-grade inflammation [124]. The pro-inflammatory SASP associated with cellular senescence is responsible for generating pro-inflammatory particles, including interleukins (such as Interleukin-1 alpha [IL-1α], IL-1β, IL-6, IL-8, Interleukin-18 [IL-18], C-C motif chemokine ligand 2 [CCL-2]), metalloproteinases, and TNF-α, leading to persistent inflammation linked to atherogenesis [125]. Another senescence–related contributor to atherosclerosis is foam macrophages. A study by Childs et al. has shown that the senescent intimal foam cells affect not only plaque formation, but also maturation and contribute to the plaque's instability. Moreover, in the research expression of proatherogenic factors such as MMP3, MMP12, matrix metalloproteinase 3 (MMP13), MCP1, Vascular Cell Adhesion Molecule 1 (VCAM1), and mentioned earlier IL1-α and TNF-α have been found on senescent cells [126]. In addition, the senescence of endothelial cells, immune cells, and vascular smooth muscle cells significantly affects the pathogenesis of atherosclerosis [127].

4.2 Hypertension

Hypertension, which significantly contributes to premature mortality worldwide [128], is an age-related disease [129]. Age-related changes in vessels that contribute to high blood pressure include hypercontractility, remodelling, stiffening, and inflammation. Moreover, cellular senescence is a common finding in patients affected by hypertension [130]. Senescence of endothelial cells leads to endothelial dysfunction, closely related to the development of hypertension [131]. In rats, the detrimental effects of endothelial cells' senescence were prevented by targeting mitochondria with the antioxidant MitoQ. MitoQ administration was shown to reduce systolic blood pressure highlighting the role of ROS production in hypertension [132]. In a 2023 study, Clayton et al. demonstrated that cellular senescence is a mediator in endothelial dysfunction, and senolytic therapy shows a restorative effect. In addition, the study links senescence to alterations in aortic wall stiffness as well as collagen deposition, elastin degradation, and enhanced presence of AGEs (advanced glycation end products) [133]. Aortic stiffness has been linked to a higher risk of hypertension [134].

Another senescence-related contributors to hypertension include eNOS dysfunction, vascular redox imbalance, and increased levels of ROS [135]. Research by Long et al. revealed that a decrease in expression of the natriuretic peptide receptor A (NPRA) gene is associated with endothelial senescence and hypertension. Age-related down-regulation of NPRA leads to disruption in ANP-mediated signaling-NPRA/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) axis, which is crucial to maintain blood pressure [136]. It is also worth noting that cellular senescence is not only the cause of hypertension, but might result from it [137].

4.3 Heart Failure

Senescent cells, such as endothelial cells, VSMCs, cardiac progenitor cells (CPCs), cardiomyocytes, myofibroblasts, and immune cells, are involved in the development of chronic heart failure [138]. Cardiac progenitor cells have the ability to differentiate into vascular cells or myocytes in case of heart damage [139]. In 2019, Lewis-McDougall et al. demonstrated on a mouse model that senescent CPCs have impaired differentiation, growth ability, and regeneration capacity [140], which influences fibrotic remodeling and myocardial hypertrophy, contributing to chronic heart failure [138]. Moreover, these cells present SASP [140]. In a study by Bian et al., high expression of CDKN1A, heat shock protein family A member 1B (HSPA1B) in senescent cardiomyocytes was strongly associated with increased risk of heart failure. CDKN1A is speculated to modulate numerous mechanisms leading to heart failure [141]. The results of another study, conducted on mice, indicate that senescent cardiomyocytes induce myocardial remodeling after a heart attack, contributing to the development of heart failure. As aforementioned, excessive mitochondrial ROS production seen in heart failure further promotes premature senescence through DNA-damage in the genome or the telomeres [142]. Indeed, transplantation of exogenous mitochondria derived from mesenchymal stem cells was shown to alleviate MI-induced endothelial senescence further highlighting the role of mitochondrial dysfunction in the process [143]. Another mitochondrial process driving myocardial remodeling is the accumulation of toxic byproducts. Spreading senescence to other kinds of cells, as an earlier proposed mechanism leading to remodeling, has also been confirmed [142]. Similarly, remodeling in the heart was shown to further disrupt the functioning of cardiac mitochondria [144]. The role of SASP in fibrosis and scar formation has been highlighted as well [108].

4.4 Inflammaging and Cardiovascular Diseases

Inflammaging, a state of chronic low-grade inflammation with high levels of pro-inflammatory particles, predisposes to cardiovascular diseases and might be an underlying mechanism in the pathology of those diseases as well [145]. There are several mechanisms of inflammaging involved in the pathogenesis of cardiovascular diseases. One of them is the replacement of C-C chemokine receptor type 2 (CCR2-) macrophages, which participate in reducing inflammation following myocardial damage, with pro-inflammatory CCR2+ macrophages. This process may cause constant inflammation in the myocardial tissue [146]. Another mechanism is mitochondrial dysfunction, which leads to the accumulation of ROS, causing oxidative stress in the vascular endothelium. Aging enhances this phenomenon via the sirtuin 2-mitochondria-oxidative damage axis [147]. This results in dysfunction of the endothelium, which contributes to the initiation and progression of atherosclerosis [148]. Moreover, inflammation has a crucial influence on the pathogenesis of acute and chronic heart failure due to, inter alia, an increase in oxidative stress, cardiac remodeling, and inflammatory response in other organs, which also affects the heart [149].

5 Interaction between Senescence and the Immune System

Cellular senescence, characterized by irreversible cell-cycle arrest and acquisition of a SASP, has emerged as a central process in both physiological tissue repair and pathological aging [150–152]. The immune system plays a decisive role in regulating the balance between beneficial and detrimental consequences of senescence [153–155]. On one hand, immune surveillance clears senescent cells, preventing their accumulation and maintaining tissue homeostasis [156,157]. On the other hand, with advancing age, immune function itself undergoes remodeling and decline, a process termed immunosenescence, leading to impaired senescent cell clearance, chronic inflammation, and accelerated tissue dysfunction [156,158,159]. In the cardiovascular system, this interplay between cellular senescence and immune aging contributes to vascular stiffening, endothelial dysfunction, myocardial remodeling, and heightened susceptibility to disease [4,108,157,160].

5.1 Immune Clearance of Senescent Cells

5.1.1 Natural Killer (NK) Cells

NK cells are important effectors involved in the elimination of senescent cells [151,161]. Senescent cells upregulate ligands for activating NK receptors, such as MHC class I polypeptide-related sequence A/B (MICA/B) and UL16-binding protein 2 (ULBP2) in response to stress and DNA damage, which trigger cytotoxic responses [162]. Through the release of perforin, granzymes, and pro-inflammatory cytokines, NK cells eliminate senescent cells and prevent their pathological accumulation [158]. However, aging is associated with reduced NK cell cytotoxicity, impaired cytokine production, and altered receptor expression, ultimately compromising their surveillance capacity [107]. The decline in NK function is associated withincreased senescent cell burden in tissues, including the cardiovascular system [150,160].

5.1.2 Macrophages

Macrophages contribute to the clearance of senescent cells through phagocytosis and efferocytosis, as well as by orchestrating tissue repair [154,155,161]. In young organisms, macrophages efficiently recognize and engulf senescent cells, thereby preventing excessive SASP-driven inflammation [154,155]. Aging alters macrophage numbers, subsets, and phenotypes: there is a shift toward pro-inflammatory M1-like states, impaired phagocytic capacity, mitochondrial dysfunction, and reduced metabolic adaptability [154,159,163]. Senescent macrophages themselves can accumulate, amplifying inflammatory circuits [154,164]. Recent studies have identified molecular pathways such as interleukin-4 (IL-4)/STAT6 signaling, which protect macrophages from senescence [157], and chromatin regulators such as bromodomain-containing protein 4 (BRD4), which drive macrophage senescence in atherosclerosis [158].

5.1.3 Immune Evasion by Senescent Cells

Senescent cells deploy multiple strategies to evade immune surveillance [151]. These include shedding or downregulation of NK-activating ligands such as MICA/B and ULBP2, often mediated by a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10)-dependent proteolysis and exosomal release, which reduces recognition by NK cells [165]. They also upregulate "don't eat me" signals, including cluster of differentiation 47 (CD47) and cluster of differentiation 24 (CD24), suppressing macrophage efferocytosis and promoting persistence [163]. In parallel, senescent cells secrete immunosuppressive SASP factors that blunt local immune function [166] and transcriptionally remodel ECM, increasing expression of matrisome regulators such as collagens, laminins, and lysyl oxidase-like 1 (LOXL1), while upregulating molecules like cluster of differentiation 200 (CD200) that suppress immune access [165]. Such evasion strategies become increasingly effective with aging, enabling senescent cells to accumulate and drive chronic, low-grade inflammation known as inflammaging [163]. Notably, recent work shows that senescence-associated upregulation of NKG2D ligands can be therapeutically exploited, as natural killer group 2 member D (NKG2D)-chimeric antigen receptor T (CAR T) cells successfully cleared senescent cells *in vivo*, improving function in aged mice and primates [166].

Despite substantial progress, most data on immune surveillance of senescent cells originate from animal models, and their translational relevance to human cardiovascular aging remains uncertain [152,155,157,161]. The relative contribution of NK cells, macrophages, and adaptive immune subsets to senescent cell clearance likely differs between tissues and disease contexts and is insufficiently characterized in humans [150,152,167].

Moreover, chronic SASP exposure may simultaneously promote immune recruitment and induce immune exhaustion, complicating therapeutic targeting of immune–senescence interactions [156,160,167].

5.2 Immunosenescence and Cardiovascular Aging

5.2.1 Effects on the Heart

The aging heart undergoes structural and functional remodeling, driven in part by immune dysfunction [4]. Cardiac resident macrophages (CRMs) are critical for electrical conduction, tissue repair, and homeostasis [168]. With age, CRM subsets are depleted or adopt pro-inflammatory phenotypes, contributing to fibrosis and electrical dysfunction [169]. Activation of mineralocorticoid receptor pathways in aging macrophages promotes pro-fibrotic remodeling, whereas its deletion attenuates cardiac inflammation and fibrosis [164]. Impaired immune clearance of senescent cardiomyocytes and fibroblasts exacerbates tissue stiffening and maladaptive remodeling following injury [108,164].

5.2.2 Effects on the Vasculature

Immunosenescence accelerates vascular aging by impairing endothelial function, promoting arterial stiffening, and facilitating atherosclerosis [170]. Senescent endothelial cells and vascular smooth muscle cells secrete pro-inflammatory SASP mediators, recruiting dysfunctional immune cells [126]. Senescent macrophages within vascular lesions exhibit enhanced lipid uptake, impaired clearance functions, and contribute to plaque instability [154]. Furthermore, adaptive immune alterations-including loss of naïve T cells, accumulation of exhausted T cell subsets, and impaired regulatory T cell function-further drive vascular inflammation [167,171]. Together, these processes amplify cardiovascular risk in the elderly.

6 Senotherapeutics in Cardiovascular Aging

6.1 Senolytics and Senomorphics: Mechanisms and Cardiovascular Implications

Senotherapeutics are small-molecule interventions designed to counteract the adverse effects of cellular senescence. They work by either eliminating senescent cells or modulating their pathological activity. These strategies can be divided into two principal groups: senolytics, which selectively induce apoptosis in senescent cells, and senomorphics, which suppress the pro-inflammatory SASP to reduce tissue damage. Together, these approaches aim to restore cellular balance and delay age-related degeneration.

While aging typically impairs the body's ability to clear senescent cells, senotherapeutic agents can enhance immune-mediated removal mechanisms to mitigate tissue dysfunction. Senolytics are designed to selectively trigger cell death pathways in senescent cells by targeting antiapoptotic and survival mechanisms such as those mediated by p53 and p21. By reducing the overall "burden" of these cells, senolytics help restore tissue health and may even reverse signs of aging. Many senolytic compounds are repurposed chemotherapeutic agents administered in lower, intermittent doses—examples include dasatinib and navitoclax. Experimental studies have demonstrated that senolytic treatment decreases the number of naturally occurring senescent human cells *in vitro*, while in aged animal models, it improves physical performance and extends lifespan.

In contrast, senomorphics do not kill the senescent cells but instead modify their behavior to lessen their detrimental systemic impact. These compounds downregulate components of the SASP and act through molecular targets such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF−κB), Mechanistic Target of Rapamycin (mTOR), and interleukin-1α. Representative senomorphic agents include rapamycin, everolimus, apigenin, and metformin [172,173].

Cardiovascular aging is driven by cellular senescence (CS)—a state where cells permanently stop dividing but remain metabolically active. This arrest is triggered by various stressors, including oxidative stress, DNA damage, and mitochondrial dysfunction. Senescent cardiovascular cells, such as endothelial, smooth muscle, fibroblast, cardiomyocyte, and immune cells, accumulate in vascular and myocardial tissues. Their presence contributes to the development and progression of cardiovascular diseases like atherosclerosis, valvular disease, arrhythmias, and cardiomyopathies [174]. In cardiovascular diseases, the accumulation of senescent cells (SCs) and their secretome, particularly the SASP, exacerbates existing pathological conditions. SASP exerts potent paracrine and autocrine activities on SCs, displaying both beneficial and harmful effects depending on the cellular context. It is, at least partially, responsible for reshaping the microenvironment of aging tissues, contributing to their structural and functional deterioration and to the process of inflamm-ageing. In the extracellular environment, specific SASP components alter the ECM, leading to dysfunctions typical of senescent cells. These alterations include the upregulation of metalloproteases, which promote matrix degradation, and modifications in the expression of ECM components such as collagen, fibronectin, and proteoglycans. Inflamm-ageing plays a central role in age-related diseases (ARDs), including cardiovascular disturbances. As aging progresses, the combination of inflamm-ageing and immunosenescence establishes an immunosuppressive environment that hinders the effective inflammatory response in older individuals. The persistent activity of SASP further amplifies chronic inflammation, thereby aggravating the impact of cellular senescence on the onset and progression of cardiovascular pathologies.

Senotherapeutic strategies—specifically senolytic agents that target senescent cells and reduce SASP levels—have shown significant benefits. Research indicates that senolytics improve health in conditions like diabetes and cardiovascular disorders, highlighting their potential to reduce the harmful effects of cellular senescence in the heart and vessels [175]. Evidence shows that senescent cells accumulate in aging hearts and within atherosclerotic vascular lesions. Virtually all cardiac cell types—including cardiomyocytes, endothelial cells, fibroblasts, progenitor cells, and immune cells—can undergo senescence during aging or under cardiovascular stress. In cardiomyocytes, which are terminally differentiated, senescence may develop in response to inflammation, oxidative damage, or ischemia–reperfusion injury, resulting in increased expression of Cyclin-dependent kinase inhibitor 1A (p21Cip1), p16Ink4a, and SASP factors that promote fibrosis and hypertrophy. Similarly, endothelial and smooth muscle cells in aged vessels exhibit "senescent features", such as cell-cycle arrest and a drop in nitric oxide signaling. Inside atherosclerotic plaques, these senescent cells amplify inflammation through SASP signaling, which makes the plaques more likely to rupture. By targeting these specific cells, senotherapeutics could reduce vascular inflammation and slow the progression of atherosclerosis [110,175,176].

Experimental and genetic studies indicate that removing senescent cells can improve cardiac function, reduce fibrosis, and limit atherosclerotic progression in various animal models. Senolytic drugs such as dasatinib, quercetin, and navitoclax have shown beneficial effects on myocardial remodeling, vascular function, and overall survival. However, emerging evidence also reveals potential adverse outcomes. In certain conditions, these treatments may impair tissue repair, destabilize atherosclerotic plaques, or even increase mortality. These observations highlight the need for careful evaluation of senotherapeutic interventions in cardiovascular disease, as their efficacy and safety likely depend on disease stage, senescent cell type, and treatment context [110].

6.2 Senolytics and Their Cardiovascular Effects

The cardiac glycoside digoxin has recently gained attention for its potential senolytic activity. Traditionally used to treat heart failure and atrial fibrillation, digoxin has been shown to selectively eliminate senescent human cells without harming healthy ones. Furthermore, subsequent studies confirmed its senolytic action across various human cell types through shared survival pathways [177]. An ongoing clinical trial (NCT06240403) is evaluating its effects on adipose tissue homeostasis and endothelial function in patients with heart failure and type 2 diabetes, underscoring its translational potential in cardiovascular aging. Altogether, the convergence of its classical cardiotonic role with emerging senolytic properties positions digoxin as a promising bridge between traditional cardiovascular therapy and geroscience [177].

Among the most extensively investigated senolytic strategies is the combination of dasatinib (D) and quercetin (Q). These two compounds work synergistically to eliminate senescent cells. Dasatinib, a tyrosine-kinase inhibitor used in leukemia therapy, induces apoptosis through inhibition of survival pathways such as Phosphoinositide 3-Kinase (PI3K)/Akt, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), and Mitogen-Activated Protein Kinase (MAPK)/extracellular signal-regulated kinase (ERK). While high doses can cause cardiotoxicity by disrupting mitochondrial function, lower and intermittent doses are effective as a senolytic.

Quercetin is a plant-derived flavonol with antioxidant and anti-inflammatory properties. It works primarily by inhibiting PI3K and modulating signaling through NF-κB, AMPK, and Nuclear factor erythroid 2–related factor 2 (Nrf2). The D + Q combination targets multiple pro-survival networks, thereby reducing senescent-cell burden and improving tissue homeostasis in both aged and disease models.

Preclinical findings show that intermittent D + Q treatment in aged mice restores cardiac function, reduces fibrosis, and increases progenitor-cell activity. In diabetic models, the treatment decreases the release of the SASP, prevents cardiomyocyte senescence, and improves heart structure. Moreover, studies in female mice after myocardial infarction showed improved repair and renewed cardiomyogenic potential following D + Q exposure. Collectively, preclinical findings support the D + Q combination as one of the most promising and widely investigated senolytic interventions with demonstrable benefits for age- and diabetes-related cardiovascular dysfunction [178].

Another notable senolytic agent is navitoclax (ABT-263)—a small-molecule inhibitor that targets the BCL-2 family of pro-survival proteins, specifically BCL-2, BCL-xL, and BCL-w. It acts as a senolytic in certain cell types, effectively reducing the viability of senescent endothelial, lung fibroblast, and murine embryonic fibroblast cells, while sparing non-senescent cells such as preadipocytes. This selectivity reflects cell-type-specific dependence on BCL-2 family proteins, similar to the way cancers respond to navitoclax. Overall, navitoclax eliminates senescent cells by disrupting their survival pathways, thereby extending the catalog of senolytic agents first identified through the dasatinib-quercetin discovery approach [179]. In cardiovascular models, navitoclax has shown significant efficacy. In aged mice or those recovering from a heart attack, it targets senescent cardiomyocytes, reduces the expression of fibrotic proteins, and improves heart structure and diastolic function. When administered after oxygen deprivation (ischemia–reperfusion injury), it limits tissue damage, decreases scar formation, and enhances overall heart performance. In addition, navitoclax has demonstrated potential in limiting vascular restenosis following stent implantation by suppressing excessive smooth-muscle proliferation. Consistently, in atherosclerotic mouse models, navitoclax reduced lesion size and plaque instability markers, suggesting benefits that may extend beyond direct senolytic activity. Although these findings highlight its therapeutic promise in cardiovascular aging and injury, the exact cellular targets and mechanisms underlying its senolytic effects remain to be fully elucidated. This lack of mechanistic specificity contributes to significant hurdles in clinical translation;

most notably, navitoclax is hindered by off-target toxicities such as dose-limiting thrombocytopenia, which necessitates careful monitoring and intermittent dosing strategies [180].

Among naturally derived compounds, fisetin—a flavonoid found in plants, fruits, and vegetables—has recently attracted attention as a senotherapeutic agent for treating age-related chronic diseases. It targets senescent cells that accumulate with aging and disease, which contribute to chronic inflammation and tissue dysfunction through their SASP [181]. Experimental evidence indicates that fisetin confers cardioprotective effects by reducing myocardial infarction–induced injury, lowering IL-6 and TNF-α levels, and improving left ventricular function in animal models. Moreover, it can modulate key signaling pathways, including suppression of receptor for advanced glycation end products (RAGE)/NF-κB activation and enhancement of the insulin-like growth factor 1 receptor (IGF-1R)/PI3K/Akt survival cascade, supporting its potential role in protecting cardiac tissue from ischemic damage [182]. Similarly, the second natural senolytic, curcumin, is a polyphenolic compound derived from turmeric that exhibits significant anti-inflammatory and antioxidant effects. It has been shown to inhibit NF-κB signaling and suppress SASP expression, thereby reducing vascular inflammation, endothelial dysfunction, and smooth-muscle cell proliferation associated with cardiovascular aging [182].

6.3 Senomorphics and Their Cardiovascular Effects

In recent years, researchers have identified pharmacological approaches capable of modulating vascular aging, with SGLT2 inhibitors gaining particular attention. These compounds have been reported to reduce the burden of senescent cells and systemic inflammation, exhibiting senomorphic activity that may confer protective effects in age-associated cardiovascular conditions. Consequently, SGLT2 inhibitors are being explored as potential senotherapeutic agents relevant to both diabetic and non-diabetic cardiovascular disease [183].

Given that the accumulation of senescent cells in the heart and vasculature contributes to structural and functional deterioration with age. Experimental studies show that clearing these cells, either genetically or pharmacologically, improves cardiac performance and reduces fibrosis. SGLT2 inhibitors have emerged as a promising tool in this area due to their ability to restore calcium balance and improve both mitochondrial and endothelial function. In preclinical models, these agents alleviated cardiac remodeling, atherosclerosis progression, and arterial stiffening, suggesting protective effects against cardiovascular aging. Moreover, their use has shown benefits in counteracting drug-induced cardiotoxicity and hypertension-related vascular dysfunction. While several mechanisms have been proposed—including the modulation of oxidative stress, autophagy, and STAT3 signaling—the exact pathways are still being defined. Taken together, SGLT2 inhibitors represent a promising class of pharmacological senotherapeutics with potential to ameliorate both metabolic and age-related cardiovascular decline [183]. While these agents are well-tolerated, their long-term use as senotherapeutics requires further investigation to ensure that chronic modulation of cellular pathways does not interfere with physiological stress responses or tissue regeneration.

Beyond SGLT2 inhibitors, several other agents—including resveratrol, rapamycin, and metformin—have shown promise in slowing cardiovascular decline. These compounds work through senomorphic mechanisms that suppress the SASP and restore tissue balance. For example, resveratrol reduces oxidative stress through its antioxidant and anti-inflammatory effects, while rapamycin blocks the Akt–mTOR pathway to decrease inflammation in heart muscle cells. Likewise, metformin activates AMPK, improving endothelial function and inhibiting profibrotic signaling. Together, these agents represent complementary strategies aimed at suppressing the SASP and restoring cardiovascular homeostasis [184].

Metformin, traditionally used for diabetes, is a cornerstone of senomorphic research. It counteracts cardiovascular aging by reducing vascular inflammation, oxidative stress, and endothelial dysfunction. Through AMPK activation and suppression of SASP-related signaling, it enhances mitochondrial efficiency and improves vascular smooth muscle cell function, thereby supporting cardiovascular protection and longevity. Although not possessing direct senolytic properties, metformin effectively suppresses cellular senescence and SASP activity across tissues affected by age-related cardiovascular deterioration. Its pharmacokinetic behavior depends on multiple organic cation transporters that regulate its intestinal absorption, tissue distribution, and renal elimination, influencing its availability and overall therapeutic activity within cardiovascular tissues. Among different pharmacologic interventions, metformin exerts broad anti-senescence effects within the cardiovascular system. It is done by ameliorating VSMC senescence, restoring autophagic flux, and preserving endothelial and mitochondrial function. Through activation of AMPK and upregulation of sirtuin 3 (SIRT3), metformin enhances mitochondrial biogenesis and energy balance, reduces oxidative stress, and delays vascular aging. Moreover, it suppresses VSMC proliferation, inflammation, and calcification, thereby attenuating atherosclerotic plaque formation and promoting vascular homeostasis. In this manner, metformin acts through both AMPK-dependent and AMPK-independent pathways to inhibit fibrotic remodeling, improve contractile efficiency, and maintain cardiometabolic resilience during aging [185].

Resveratrol is a natural phenolic compound found in plants such as grapes, peanuts, and Veratrum grandiflorum, known for its potent antioxidant and anti-inflammatory properties. It acts primarily as an activator of SIRT1, a key anti-aging regulator involved in DNA repair and cellular stress responses, and exerts anti-inflammatory effects through inhibition of NF-κB signaling. In cardiovascular research, resveratrol has been shown to protect endothelial and myocardial cells, reduce oxidative stress, and suppress SASP-related cytokines such as TNF-α and IL-1β. Clinical studies in post-infarction and cardiovascular patients suggest that short-term resveratrol supplementation can improve endothelial function and reduce inflammatory markers. While resveratrol shows promise, its therapeutic efficacy remains limited by poor systemic bioavailability and rapid metabolism; these factors contribute to the inconsistent outcomes observed in small-scale human trials and currently prevent definitive conclusions regarding its clinical use in cardiovascular disease [182,186].

In parallel with resveratrol's effects, rapamycin is another well-characterized senomorphic agent with documented anti-aging and cardiovascular protective actions. As a potent mTOR inhibitor, numerous studies have demonstrated that rapamycin reduces cellular senescence and inhibits the secretion of SASP markers across various cell lines, thereby extending lifespan. Its derivatives, collectively known as rapalogs (including rapamycin, everolimus, and tacrolimus), are widely used in cardiovascular medicine as components of drug-eluting stents, where they prevent in-stent restenosis through local anti-proliferative and immunosuppressive effects mediated by mTOR inhibition. Within senescent cells, mTOR blockade mitigates NF-κB signaling and downregulates IL-1A expression, reducing inflammatory activity. Experimental models have shown that systemic rapamycin therapy ameliorates cardiac hypertrophy and stiffness and improves longevity in aged mice. Nevertheless, despite these promising effects, broader cardiovascular application remains constrained by its potential immunosuppressive and hyperlipidemic side effects [182,186].

Altogether, senotherapeutic interventions represent a rapidly evolving field. However, translating these findings to human clinical practice requires overcoming significant challenges, including low bioavailability, off-target toxicities, and the need for long-term safety data to ensure that therapeutic benefits outweigh the risks of systemic intervention.

6.4 Critical Perspectives and Clinical Hurdles in Senotherapy

The clinical translation of senotherapeutics—encompassing both senolytic and senomorphic agents—is currently constrained by several complex biological and pharmacological barriers. While preclinical evidence suggests significant potential for mitigating age-related pathologies, the transition to human application requires a nuanced understanding of the risks associated with the systemic modulation of senescence. These hurdles are particularly pronounced in the context of CVD, where patients often present with multi-morbidity and complex polypharmacy.

6.4.1 Biological Heterogeneity and Cell-Type Specificity

A primary challenge in senotherapy is the inherent heterogeneity of the senescent phenotype. Senescence is not a singular, uniform state; it is a context-dependent program influenced by the cell type of origin, the specific senescence-inducing stimulus, and the surrounding tissue microenvironment. This diversity complicates the development of "universal" agents, as senescent cells exhibit varying dependencies on survival pathways and divergent sensitivities to pharmacological intervention [187]. Recent studies on the Dasatinib and Quercetin (D + Q) cocktail underscore this complexity, revealing that its effects on chromatin structure can be diametrically opposed in young versus senescent cells. Furthermore, while D + Q may "rejuvenate" the chromatin of senescent cells, it has been observed to induce transient features typical of senescence in young, proliferating cells, raising significant concerns regarding long-term tissue homeostasis and the lack of precise cell-type specificity [188].

6.4.2 Pharmacological Limitations and Off-Target Toxicity

The pharmacokinetics and safety profiles of existing senotherapeutics present substantial hurdles to clinical implementation. Natural compounds such as Quercetin are limited by low bioavailability, stemming from poor aqueous solubility, limited stability, and extensive systemic metabolism. Overcoming these limitations requires advanced delivery systems, such as pH-responsive or mucus-penetrating carriers, which are still largely in the early stages of development [189]. Conversely, synthetic senolytics such as Navitoclax are hindered by significant off-target toxicities. Specifically, Navitoclax induces dose-limiting thrombocytopenia due to its inhibition of BCL-xL in platelets [180]. In aging populations where platelet function and vascular integrity are already compromised, such adverse effects necessitate rigorous monitoring and intermittent dosing strategies, complicating the therapeutic regimen [177].

6.4.3 The Biomarker Gap and Clinical Quantification

The absence of specific, non-invasive biomarkers remains a critical bottleneck for clinical trials. While experimental markers like p16INK4a and SA-β-gal are useful in laboratory settings, they are not exclusive to senescence and are difficult to quantify *in vivo*. Without validated biomarkers to assess systemic senescent cell burden, it is challenging for clinicians to identify appropriate candidates for therapy, monitor real-time therapeutic response, or optimize dosing [5,187]. This is further exacerbated by the contextual role of senescence in human physiology; the process is essential for embryogenesis, wound repair, and tumor suppression. Indiscriminate clearance of senescent cells carries the risk of impairing these regenerative responses or disrupting tissue repair, particularly in the liver and skin [5,187].

6.4.4 Regulatory Frameworks and Patient Heterogeneity

From a translational perspective, the regulatory path for senotherapeutics is largely undefined. Unlike traditional therapies designed to treat acute pathology, senolytics are often proposed as preventative interventions to delay age-related decline. This shift requires a re-evaluation of clinical trial design, including the selection of biologically meaningful surrogate endpoints such as biological age or functional resilience [187]. Moreover, patient heterogeneity—driven by sex differences, comorbidities, and varying disease stages—demands a personalized approach to therapy [177]. For example, recent research into SGLT2 inhibitors has highlighted a significant bias toward male subjects in preclinical studies, leaving questions regarding the generalizability of anti-senescence effects in females [183]. Addressing these gaps will require interdisciplinary collaboration, the integration of multi-omics and computational modeling, and a rigorous approach to evaluating the long-term safety of these novel interventions [5].

7 Biomarkers and Research Models

7.1 Molecular Biomarkers

Accurate detection of cellular senescence in the cardiovascular system requires marker panels, not single assays. In practice, three domains should be profiled together: durable cell-cycle arrest (p16INK4a, p21Cip1), the DDR (e.g., γH2AX with Tumor suppressor p53-binding protein 1 (53BP1)/, Ataxia Telangiectasia Mutated (ATM)/, Checkpoint Kinase 2 (CHK2), and the pro-inflammatory SASP. It is advisable to use at least two independent markers plus one functional readout, and to include explicit negatives for proliferation (e.g., kiel-67 antigen Ki-67, 5-ethynyl-2′-deoxyuridine (EdU)) to avoid false positives in mixed tissues [190–192]. Because acute stress can raise p21 without stable arrest, time-course sampling and co-staining with proliferation indices can be helpful. In vessels, TAF supports persistent DDR typical of senescent EC and VSMC; reporting counting criteria and image-acquisition settings is recommended for reproducibility [191,193]. The senescence-associated β-galactosidase (SA-β-gal; pH 6.0) is supportive but non-specific and is generally not used alone. Given that SASP factors can arise from immune activation, it is helpful to specify cell-identity markers and pre-analytics (processing delay, storage) to limit confounding. A concise reporting checklist—assays, controls, thresholds for positivity, and planned analyses—improves comparability across cohorts [191].

7.2 Circulating Biomarkers

Blood-based readouts enable repeated, minimally invasive assessment of organism-level senescence burden. Three complementary classes dominate: leukocyte telomere length (LTL), extracellular vesicles (EVs), and circulating microRNAs (miRNAs). Shorter LTL associates with higher cardiovascular risk; translation requires harmonized assays (qPCR vs. Southern), control for leukocyte subsets, and use of internal calibrators when pooling data [194,195]. For EVs, diagnostic value improves when origin and cargo are characterized together under Minimal Information for Studies of Extracellular Vesicles 2023 (MISEV2023) guidance [196] with transparent reporting of quantification methods (e.g., nanoparticle tracking, small-particle flow cytometry), EV markers (tetraspanins cluster of differentiation 9/63/81, CD9/CD63/CD81), and controls for co-isolates (apolipoprotein A1 [ApoA1], albumin). Pre-analytics (anticoagulant, processing delay, freeze–thaw cycles) markedly affect EV particle counts and size distributions; it is advisable to include size-reference beads and swarm-detection checks to prevent event overestimation, and authors should state the thresholds and maximum event rates used during acquisition [196,197]. miRNA panels can aid risk stratification and treatment monitoring if normalization is explicit and hemolysis is controlled (e.g., microRNA-451/microRNA-23a ratio), noting that platform choice (qPCR panels vs. small-RNA sequencing) shifts detectability and fold-change estimates [198]. Panels combining LTL + EV features + miRNA dynamics may outperform single markers, but will require validation in external cohorts with prespecified minimal clinically important differences (MCIDs) and quality-control failure criteria to reduce analytic flexibility [176,194,196]. Integrating circulating readouts into interventional studies (exercise, diet, senotherapeutics) strengthens the mechanism from biomarker to outcome chain [199].

7.3 In Vitro and In Vivo Models

7.3.1 In Vitro

In vitro, senescence can be induced by long-term passaging or stressors hydrogen peroxide, ionizing radiation, and anthracyclines). Readouts typically combine p16/p21, γH2AX/53BP1, SASP, proliferation indices, and cell-type functions (e.g., NO/eNOS in endothelium, calcification in VSMC). 3D constructs—engineered heart tissues (EHT) and cardiac organoids—better capture biomechanics when loading, pacing, and maturation are standardized; washout and rescue assays can help distinguish transient toxicity from stable senescence [200,201].

7.3.2 In Vivo

In vivo, telomerase-deficient (Terc−/−) mice link telomere damage to cardiovascular dysfunction, while NK-Linked Apoptosis Through Targeted Activation of Caspase (INK-ATTAC) and p21-Linked Apoptosis Through Targeted Activation of Caspase (p21-ATTAC) systems enable selective clearance of senescent cells to test effects on arterial stiffness, remodeling, and function in atherosclerosis, angiotensin II (AngII)–induced hypertension, and anthracycline cardiotoxicity [202,203]. Core endpoints to report include echocardiographic parameters, pulse-wave velocity, and key histology, with randomization, sex-balanced cohorts, blinded analysis, and standardized anesthesia to limit bias [199,204].

Across platforms, align molecular readouts with functional and imaging endpoints under harmonized terminology (marker panels, quantification methods, processing delays). Claims of superiority are best made cautiously until findings are replicated independently; the *in vitro* mechanism to *in vivo* validation pathway supports rigorous translation of senescence-targeted interventions [176].

8 Conclusions

Cellular senescence is a context-dependent andheterogeneous biological program that exerts dual effects within the cardiovascular system. Transient senescence facilitates tissue repair after acute injury, whereas the persistent accumulation of senescent endothelial cells, vascular smooth muscle cells, fibroblasts, and cardiomyocytes contributes to vascular and myocardial dysfunction.

Mechanistically, senescence is triggered by telomere attrition, DNA-damage responses, mitochondrial dysfunction, impaired autophagy, and ER stress. These pathways converge on the p53–p21 and p16–Rb axes, resulting in the secretion of a pro-inflammatory SASP. Collectively, these processes drive endothelial dysfunction, arterial stiffening and calcification, plaque destabilization, profibrotic remodeling, and impaired post-infarct recovery, thereby linking cellular aging to atherosclerosis, hypertension, and heart failure.

Therapeutically, both senolytics and senomorphics show promise in improving cardiac and vascular outcomes in experimental models. However, most efficacy data remain preclinical, and clinical evidence is limited to small early-phase trials. Future optimization of safety profiles, cell-type selectivity, dosing schedules, and timing will be crucial to preserve beneficial transient senescence while minimizing potential adverse effects.

Priority research directions include: (1) validating standardized, multimodal biomarker panels (cellular markers, telomere metrics, EV/miRNA signatures) for patient stratification and response monitoring; (2) optimizing dosing regimens and selectivity of senolytics/senomorphics in age- and disease-stage-stratified studies; (3) conducting biomarker-guided, randomized trials integrating functional cardiovascular endpoints. These steps will be essential to establish the therapeutic index and enable personalized senotherapeutic strategies for cardiovascular aging.

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Abbreviations

ABT-263	A Bcl-2 Family Inhibitor Compound 263
ADAM10	A Disintegrin and Metalloproteinase Domain-Containing Protein 10
AMPK	AMP-Activated Protein Kinase
AngII	Angiotensin II
ApoA1	Apolipoprotein A1
ARD	Age-Related Disease
ATM	Ataxia Telangiectasia Mutated
ATF6α	Cleaved Activating Transcription Factor 6 Alpha
BMPs	Bone Morphogenetic Proteins
BCL-2	B-Cell Lymphoma 2
BRD4	Bromodomain-Containing Protein 4
CAR T	Chimeric Antigen Receptor T
CCL-2	C–C Motif Chemokine Ligand 2
CDKN1A	Cyclin-Dependent Kinase Inhibitor 1A
CDKN2A	Cyclin-Dependent Kinase Inhibitor 2A
CDKN2B	Cyclin-Dependent Kinase Inhibitor 2B
CDKN2D	Cyclin-Dependent Kinase Inhibitor 2D
CD44	Cluster of Differentiation 44
CD9	Cluster of Differentiation 9
CD24	Cluster of Differentiation 24
CD47	Cluster of Differentiation 47
CD63	Cluster of Differentiation 63
CD81	Cluster of Differentiation 81
CD200	Cluster of Differentiation 200

CHEK2	Checkpoint Kinase 2
CHOP	C/EBP Homologous Protein
COL4A1	Collagen Type IV Alpha 1 Chain
CPCs	Cardiac Progenitor Cells
CS	Cellular Senescence
cGMP	Cyclic Guanosine Monophosphate
CXCL2	Chemokine (C–X–C Motif) Ligand 2
CCR2	C–C Chemokine Receptor Type 2
CRM	Cardiac Resident Macrophage
DDR	DNA Damage Response
DNA	Deoxyribonucleic Acid
EdU	5-Ethynyl-2′-Deoxyuridine
EC	Endothelial Cell
ECM	Extracellular Matrix
EHT	Engineered Heart Tissues
ER	Endoplasmic Reticulum
ERK	Extracellular Signal-Regulated Kinase
ET-1	Endothelin 1
EPCs	Endothelial Progenitor Cells
eNOS	Endothelial Nitric Oxide Synthase
FBN2	Fibrillin 2
GATA4	GATA Binding Protein 4
GMT	GATA4, MEF2C, TBX5
GDF15	Growth Differentiation Factor 15
Grp78	Glucose-Regulated Protein 78
HCAECs	Human Coronary Artery Endothelial Cells
HGPS	Hutchinson–Gilford Progeroid Syndrome
HFpEF	Heart Failure with Preserved Ejection Fraction
HMGB2	High Mobility Group Protein 2
HSPA1B	Heat Shock Protein Family A Member 1B
HUVECs	Human Umbilical Vein Endothelial Cells
IHD	Ischemic Heart Disease
IDH2	Isocitrate Dehydrogenase 2
IFN-1	Interferon 1
IGF-1R	Insulin-Like Growth Factor 1 Receptor
IL-1α	Interleukin-1 Alpha
IL-1β	Interleukin-1 Beta
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-15	Interleukin-15
IL-18	Interleukin-18
INK-ATTAC	INK-Linked Apoptosis through Targeted Activation of Caspase
JAK	Janus Kinase
Ki-67	Kiel-67 Antigen
KLF4	Krüppel-Like Factor 4
LDL	Low-Density Lipoprotein
LTL	Leukocyte Telomere Length
LOXL1	Lysyl Oxidase-Like 1
LC3-II	Light Chain 3-II
lncRNA	Long Non-Coding RNA
MDA-5	Melanoma Differentiation-Associated Protein 5
MAPK	Mitogen-Activated Protein Kinase
MCP-1	Monocyte Chemoattractant Protein 1
MEF2C	Myocyte Enhancer Factor 2C

MEG3	Maternally Expressed 3
MMP-2	Matrix Metalloproteinase 2
MMP-3	Matrix Metalloproteinase 3
MMP-9	Matrix Metalloproteinase 9
MMPs	Matrix Metalloproteinases
MFN2	Mitofusin-2
miRNA	MicroRNA
miR-21	MicroRNA-21
miR-92	MicroRNA-92
miR-126	MicroRNA-126
miR-125b	MicroRNA-125b
miR-214	MicroRNA-214
miR-221	MicroRNA-221
miR-222	MicroRNA-222
miR-494	MicroRNA-494
MI	Myocardial Infarction
MICA/B	MHC Class I Polypeptide-Related Sequence A/B
MRE11	Meiotic Recombination 11
MRN	MRE11–RAD50–NBS1 Complex
MISEV2023	Minimal Information for Studies of Extracellular Vesicles 2023
mTOR	Mechanistic Target of Rapamycin
MVC	Medial Vascular Calcification
NK	Natural Killer
NKG2D	Natural Killer Group 2 Member D
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
Nrf2	Nuclear Factor Erythroid 2–Related Factor 2
NPRA	Natriuretic Peptide Receptor A
NO	Nitric Oxide
NBS1	Nibrin 1
OSS	Oscillatory Shear Stress
OPN	Osteopontin
PAD	Peripheral Artery Disease
PI3K	Phosphoinositide 3-Kinase
PIK3C3	Phosphatidylinositol 3-Kinase Catalytic Subunit Type 3
PKG	Protein Kinase G
PINK1	Phosphatase and Tensin Homolog-Induced Kinase 1
PtdIns3K	Phosphatidylinositol 3-Kinase
PoMiCS	Post-Mitotic Cellular Senescence
PRb	Retinoblastoma Protein
p16	Protein 16
p16INK4a	Cyclin-Dependent Kinase Inhibitor 2A
p21	Protein 21
p21ˆCip1	Cyclin-Dependent Kinase Inhibitor 1A
p21-ATTAC	p21-Linked Apoptosis through Targeted Activation of Caspase
p53	Tumor Protein p53
PIK3R4	Phosphoinositide 3-Kinase Regulatory Subunit
RAGE	Receptor for Advanced Glycation End Products
RIG-I	Retinoic Acid-Inducible Gene I
ROS	Reactive Oxygen Species
RUNX2	Runt-Related Transcription Factor 2
SA-β-Gal	Senescence-Associated β-Galactosidase
SASP	Senescence-Associated Secretory Phenotype
SAHH	S-Adenosylhomocysteine Hydrolase
SIRT1	Sirtuin 1
SIRT3	Sirtuin 3

SIRT6	Sirtuin 6
SC	Senescent Cell
SM-MHC	Smooth Muscle Myosin Heavy Chain
SM22α	Smooth Muscle 22 Alpha
STAT	Signal Transducer and Activator of Transcription
STAT3	Signal Transducer and Activator of Transcription 3
STING	Stimulator of Interferon Genes
sXBP1	Spliced X-Box Binding Protein 1
TBX5	T-Box Transcription Factor 5
TAF	Telomere-Associated Foci
TERC	Telomerase-Deficient
TERT	Telomerase Reverse Transcriptase
TGF-β	Transforming Growth Factor Beta
TNF-α	Tumor Necrosis Factor α
TNFR1	Tumor Necrosis Factor Receptor 1
TRF2	Telomeric Repeat-Binding Factor 2
TLR-9	Toll-Like Receptor 9
TWIST1	Twist Family BHLH Transcription Factor 1
ULBP2	UL16-Binding Protein 2
UPR	Unfolded Protein Response
VSMC	Vascular Smooth Muscle Cell
VCAM-1	Vascular Cell Adhesion Molecule 1
VEGF	Vascular Endothelial Growth Factor
WNT	Wingless-Related Integration Site
γH2AX	Phosphorylated H2A Histone Family Member X
53BP1	Tumor Suppressor p53-Binding Protein 1

References

1. Fleg JL, Strait J. Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. Heart Fail Rev. 2012;17(4–5):545–54. [CrossRef].
2. Jakovljevic DG. Physical activity and cardiovascular aging: physiological and molecular insights. Exp Gerontol. 2018;109:67–74. [CrossRef].
3. Castelli R, Gidaro A, Casu G, Merella P, Profili NI, Donadoni M, et al. Aging of the arterial system. Int J Mol Sci. 2023;24(8):6910. [CrossRef].
4. Evangelou K, Vasileiou PVS, Papaspyropoulos A, Hazapis O, Petty R, Demaria M, et al. Cellular senescence and cardiovascular diseases: moving to the “heart” of the problem. Physiol Rev. 2023;103(1):609–47. [CrossRef].
5. Muthamil S, Kim HY, Jang HJ, Lyu JH, Shin UC, Go Y, et al. Biomarkers of cellular senescence and aging: current state-of-the-art, challenges and future perspectives. Adv Biol. 2024;8(9):e2400079. [CrossRef].
6. Shimizu I, Minamino T. Cellular senescence in cardiac diseases. J Cardiol. 2019;74(4):313–9. [CrossRef].
7. Nunkoo VS, Cristian A, Jurcau A, Diaconu RG, Jurcau MC. The quest for eternal youth: hallmarks of aging and rejuvenating therapeutic strategies. Biomedicines. 2024;12(11):2540. [CrossRef].
8. Shvedova M, Samdavid Thanapaul RJR, Thompson EL, Niedernhofer LJ, Roh DS. Cellular senescence in aging, tissue repair, and regeneration. Plast Reconstr Surg. 2022;150:4S–11S. [CrossRef].
9. Trimm E, Red-Horse K. Vascular endothelial cell development and diversity. Nat Rev Cardiol. 2023;20(3):197–210. [CrossRef].
10. Augustin HG, Koh GY. A systems view of the vascular endothelium in health and disease. Cell. 2024;187(18):4833–58. [CrossRef].
11. Sturtzel C. Endothelial cells. Adv Exp Med Biol. 2017;1003:71–91. [CrossRef]
12. Cyr AR, Huckaby LV, Shiva SS, Zuckerbraun BS. Nitric oxide and endothelial dysfunction. Crit Care Clin. 2020;36(2):307–21. [CrossRef].
13. Krüger-Genge A, Blocki A, Franke RP, Jung F. Vascular endothelial cell biology: an update. Int J Mol Sci. 2019;20(18):4411. [CrossRef].

14. Bloom SI, Islam MT, Lesniewski LA, Donato AJ. Mechanisms and consequences of endothelial cell senescence. Nat Rev Cardiol. 2023;20(1):38–51. [CrossRef].
15. Fan J, Watanabe T. Atherosclerosis: known and unknown. Pathol Int. 2022;72(3):151–60. [CrossRef].
16. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev. 2004;84(3):767–801. [CrossRef].
17. Lacolley P, Regnault V, Segers P, Laurent S. Vascular smooth muscle cells and arterial stiffening: relevance in development, aging, and disease. Physiol Rev. 2017;97(4):1555–617. [CrossRef].
18. Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis. Cardiovasc Res. 2012;95(2):156–64. [CrossRef].
19. Chen R, McVey DG, Shen D, Huang X, Ye S. Phenotypic switching of vascular smooth muscle cells in atherosclerosis. J Am Heart Assoc. 2023;12(20):e031121. [CrossRef].
20. Zha Y, Zhuang W, Yang Y, Zhou Y, Li H, Liang J. Senescence in vascular smooth muscle cells and atherosclerosis. Front Cardiovasc Med. 2022;9:910580. [CrossRef].
21. Chi C, Li DJ, Jiang YJ, Tong J, Fu H, Wu YH, et al. Vascular smooth muscle cell senescence and age-related diseases: state of the art. Biochim Biophys Acta Mol Basis Dis. 2019;1865(7):1810–21. [CrossRef].
22. Tallquist MD, Molkentin JD. Redefining the identity of cardiac fibroblasts. Nat Rev Cardiol. 2017;14(8):484–91. [CrossRef].
23. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac fibrosis: the fibroblast awakens. Circ Res. 2016;118(6):1021–40. [CrossRef].
24. Ivey MJ, Tallquist MD. Defining the cardiac fibroblast. Circ J. 2016;80(11):2269–76. [CrossRef].
25. Biernacka A, Frangogiannis NG. Aging and cardiac fibrosis. Aging Dis. 2011;2(2):158–73.
26. Osorio JM, Espinoza-Pérez C, Rimassa-Taré C, Machuca V, Bustos JO, Vallejos M, et al. Senescent cardiac fibroblasts: a key role in cardiac fibrosis. Biochim Biophys Acta Mol Basis Dis. 2023;1869(4):166642. [CrossRef].
27. Trial J, Cieslik KA. Changes in cardiac resident fibroblast physiology and phenotype in aging. Am J Physiol Heart Circ Physiol. 2018;315(4):H745–55. [CrossRef].
28. Bers DM. Cardiac excitation-contraction coupling. Nature. 2002;415(6868):198–205. [CrossRef].
29. Nakagawa Y, Nishikimi T, Kuwahara K. Atrial and brain natriuretic peptides: hormones secreted from the heart. Peptides. 2019;111:18–25. [CrossRef].
30. Chang D, Wang J, Zhu S, Shentu Y, Wang Y, Zhu P, et al. Cellular senescence and cell therapy in cardiovascular diseases. Stem Cell Res Ther. 2025;16(1):613. [CrossRef].
31. Grootaert MOJ. Cell senescence in cardiometabolic diseases. npj Aging. 2024;10(1):46. [CrossRef].
32. Peoples JN, Saraf A, Ghazal N, Pham TT, Kwong JQ. Mitochondrial dysfunction and oxidative stress in heart disease. Exp Mol Med. 2019;51(12):162. [CrossRef].
33. Li X, Pang X, Sun H, Zhang B, Wang H, Wu N, et al. Cardiac aging: molecular mechanisms and therapeutic interventions. Pharmacol Res. 2025;221:107954. [CrossRef].
34. Lozhkin A, Vendrov AE, Ramos-Mondragón R, Canugovi C, Stevenson MD, Herron TJ, et al. Mitochondrial oxidative stress contributes to diastolic dysfunction through impaired mitochondrial dynamics. Redox Biol. 2022;57:102474. [CrossRef].
35. Liu Y, Bloom SI, Donato AJ. The role of senescence, telomere dysfunction and shelterin in vascular aging. Microcirculation. 2019;26(2):e12487. [CrossRef].
36. Bloom SI, Tucker JR, Lim J, Thomas TG, Stoddard GJ, Lesniewski LA, et al. Aging results in DNA damage and telomere dysfunction that is greater in endothelial versus vascular smooth muscle cells and is exacerbated in atheroprone regions. Geroscience. 2022;44(6):2741–55. [CrossRef].
37. Lim J, Kim J, Abdeahad H, Hall SA, Lesniewski LA, Donato AJ. Late-life aerobic exercise attenuates DNA damage and telomere dysfunction in non-atheroprone but not in atheroprone aortic regions. Aging Cell. 2025;24(10):e70196. [CrossRef].
38. Bloom SI, Liu Y, Tucker JR, Islam MT, Machin DR, Abdeahad H, et al. Endothelial cell telomere dysfunction induces senescence and results in vascular and metabolic impairments. Aging Cell. 2023;22(8):e13875. [CrossRef].
39. You Y, Sun X, Xiao J, Chen Y, Chen X, Pang J, et al. Inhibition of S-adenosylhomocysteine hydrolase induces endothelial senescence via hTERT downregulation. Atherosclerosis. 2022;353:1–10. [CrossRef].

40. Ramini D, Giuliani A, Kwiatkowska KM, Guescini M, Storci G, Mensà E, et al. Replicative senescence and high glucose induce the accrual of self-derived cytosolic nucleic acids in human endothelial cells. Cell Death Discov. 2024;10(1):184. [CrossRef].
41. Guduric-Fuchs J, Pedrini E, Bertelli PM, McDonnell S, Pathak V, McLoughlin K, et al. A new gene signature for endothelial senescence identifies self-RNA sensing by retinoic acid-inducible gene I as a molecular facilitator of vascular aging. Aging Cell. 2024;23(9):e14240. [CrossRef].
42. Liu H, Ghosh S, Vaidya T, Bammidi S, Huang C, Shang P, et al. Activated cGAS/STING signaling elicits endothelial cell senescence in early diabetic retinopathy. JCI Insight. 2023;8(12):e168945. [CrossRef].
43. Mojiri A, Walther BK, Jiang C, Matrone G, Holgate R, Xu Q, et al. Telomerase therapy reverses vascular senescence and extends lifespan in progeria mice. Eur Heart J. 2021;42(42):4352–69. [CrossRef].
44. Qin W, Castillo KD, Li H, Nguyen TKC, Kiss DL, Cooke JP, et al. Circular RNA telomerase reverses endothelial senescence in progeria. Aging Cell. 2025;24(6):e70021. [CrossRef].
45. Uryga AK, Grootaert MOJ, Garrido AM, Oc S, Foote K, Chappell J, et al. Telomere damage promotes vascular smooth muscle cell senescence and immune cell recruitment after vessel injury. Commun Biol. 2021;4(1):611. [CrossRef].
46. Zheng X, Liu Z, Bin Y, Wang J, Rao X, Wu G, et al. Ionizing radiation induces vascular smooth muscle cell senescence through activating NF-κB/CTCF/p16 pathway. Biochim Biophys Acta Mol Basis Dis. 2024;1870(4):166994. [CrossRef].
47. Piñeiro-Hermida S, Martínez P, Bosso G, Flores JM, Saraswati S, Connor J, et al. Consequences of telomere dysfunction in fibroblasts, club and basal cells for lung fibrosis development. Nat Commun. 2022;13(1):5656. [CrossRef].
48. Rouhi L, Auguste G, Zhou Q, Lombardi R, Olcum M, Pourebrahim K, et al. Deletion of the Lmna gene in fibroblasts causes senescence-associated dilated cardiomyopathy by activating the double-stranded DNA damage response and induction of senescence-associated secretory phenotype. J Cardiovasc Aging. 2022;2(3):30. [CrossRef].
49. Li B, Xiong W, Zuo W, Shi Y, Wang T, Chang L, et al. Proximal telomeric decompaction due to telomere shortening drives FOXC1-dependent myocardial senescence. Nucleic Acids Res. 2024;52(11):6269–84. [CrossRef].
50. Wei X, Zhou Y, Shao E, Shi X, Han Y, Zhang Y, et al. Tert promotes cardiac regenerative repair after MI through alleviating ROS-induced DNA damage response in cardiomyocyte. Cell Death Discov. 2024;10(1):381. [CrossRef].
51. Abdeahad H, Moreno DG, Bloom SI, Norman L, Lesniewski LA, Donato AJ. MitoQ reduces senescence burden in doxorubicin-treated endothelial cells by reducing mitochondrial ROS and DNA damage. Am J Physiol Heart Circ Physiol. 2025;329(5):H1154–61. [CrossRef].
52. Wāng Y, Han Y, Xu DX. Mitochondrial metabolism reprogramming-mediated cardiomyocyte senescence involved in arsenic stress-evoked heart failure. Environ Int. 2025;202:109686. [CrossRef].
53. Uruski P, Mikuła-Pietrasik J, Drzewiecki M, Budkiewicz S, Gładki M, Kurmanalina G, et al. Diverse functional responses to high glucose by primary and permanent hybrid endothelial cells *in vitro*. J Mol Cell Cardiol. 2021;156:1–6. [CrossRef].
54. Bertelli PM, Pedrini E, Hughes D, McDonnell S, Pathak V, Peixoto E, et al. Long term high glucose exposure induces premature senescence in retinal endothelial cells. Front Physiol. 2022;13:929118. [CrossRef].
55. Zhang E, Guo Q, Gao H, Xu R, Teng S, Wu Y. Metformin and resveratrol inhibited high glucose-induced metabolic memory of endothelial senescence through SIRT1/p300/p53/p21 pathway. PLoS One. 2015;10(12):e0143814. [CrossRef].
56. Li J, Yang Z, Song H, Yang L, Na K, Mei Z, et al. The role of mitofusin 2 in regulating endothelial cell senescence: implications for vascular aging. iScience. 2024;27(9):110809. [CrossRef].
57. Li M, Liu Z, Cao X, Xiao W, Wang S, Zhao C, et al. [Gly14]-humanin ameliorates high glucose-induced endothelial senescence via SIRT6. Sci Rep. 2024;14(1):30924. [CrossRef].
58. Tavris BS, Peters AS, Böckler D, Dihlmann S. Mitochondrial dysfunction and increased DNA damage in vascular smooth muscle cells of abdominal aortic aneurysm (AAA-SMC). Oxid Med Cell Longev. 2023;2023:6237960. [CrossRef].
59. Chen Z, Li X, Sun X, Xiao S, Chen T, Ren L, et al. STING1-accelerated vascular smooth muscle cell senescence-associated vascular calcification in diabetes is ameliorated by oleoylethanolamide via improved mitochondrial DNA oxidative damage. Free Radic Biol Med. 2024;222:437–55. [CrossRef].

60. Rossi C, Macchi C, D’Alonzo C, Venturin M, Ruscica M, Corsini A, et al. Simvastatin ameliorates senescence-induced mitochondrial dysfunction in vascular smooth muscle cells. Atherosclerosis. 2025;403:119176. [CrossRef].
61. Soh JEC, Shimizu A, Molla MR, Zankov DP, Nguyen LKC, Khan MR, et al. RhoA rescues cardiac senescence by regulating Parkin-mediated mitophagy. J Biol Chem. 2023;299(3):102993. [CrossRef].
62. Kelly G, Kataura T, Panek J, Ma G, Salmonowicz H, Davis A, et al. Suppressed basal mitophagy drives cellular aging phenotypes that can be reversed by a p62-targeting small molecule. Dev Cell. 2024;59(15):1924–39. [CrossRef].
63. McCarty TY, Kearney CJ. Human dermal fibroblast senescence in response to single and recurring oxidative stress. Front Aging. 2025;6:1504977. [CrossRef].
64. Zhou X, Wang N, Wei J, Li G, Lue Z, Liu C, et al. Pterostilbene mitigates the senescence of human dermal fibroblast cells by enhancing mitochondrial quality. Front Pharmacol. 2025;16:1732154. [CrossRef].
65. Xiong W, Li B, Pan J, Li D, Yuan H, Wan X, et al. Mitochondrial amount determines doxorubicin-induced cardiotoxicity in cardiomyocytes. Adv Sci. 2025;12(12):2412017. [CrossRef].
66. Li Y, Cui J, Liu L, Hambright WS, Gan Y, Zhang Y, et al. mtDNA release promotes cGAS-STING activation and accelerated aging of postmitotic muscle cells. Cell Death Dis. 2024;15(7):523. [CrossRef].
67. Yang B, Li T, Wang Z, Zhu Y, Niu K, Hu S, et al. Ruxolitinib-based senomorphic therapy mitigates cardiomyocyte senescence in septic cardiomyopathy by inhibiting the JAK2/STAT3 signaling pathway. Int J Biol Sci. 2024;20(11):4314–40. [CrossRef].
68. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell. 2011;147(4):728–41. [CrossRef].
69. Liu S, Yao S, Yang H, Liu S, Wang Y. Autophagy: regulator of cell death. Cell Death Dis. 2023;14(10):648. [CrossRef].
70. Zhang Y, Ouyang J, Zhan L, Li Y, Li S, He Y, et al. Autophagy in homocysteine-induced HUVEC senescence. Exp Ther Med. 2023;26(1):354. [CrossRef].
71. Zhang L, Yang P, Chen J, Chen Z, Liu Z, Feng G, et al. CD44 connects autophagy decline and ageing in the vascular endothelium. Nat Commun. 2023;14(1):5524. [CrossRef].
72. Li S, Jiang X, Huang W, Meng Q, Pu L, Sun B, et al. Oscillatory shear stress activates integrin β3, blocking autophagic flux in endothelial cells and promoting endothelial cells senescence. Biochim Biophys Acta Mol Cell Res. 2025;1872(7):119991. [CrossRef].
73. Lee J, Yoo JH, Kim HS, Cho YK, La Lee Y, Lee WJ, et al. C1q/TNF-related protein-9 attenuates palmitic acid-induced endothelial cell senescence via increasing autophagy. Mol Cell Endocrinol. 2021;521:111114. [CrossRef].
74. Grootaert MO, da Costa Martins PA, Bitsch N, Pintelon I, De Meyer GR, Martinet W, et al. Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neointima formation and atherogenesis. Autophagy. 2015;11(11):2014–32. [CrossRef].
75. Yan W, Cao Y, Zhen P, Ji D, Chai J, Xue K, et al. Decreased autophagy of vascular smooth muscle cells was involved in hyperhomocysteinemia-induced vascular ageing. Clin Exp Pharmacol Physiol. 2021;48(4):524–33. [CrossRef].
76. Salazar G, Cullen A, Huang J, Zhao Y, Serino A, Hilenski L, et al. SQSTM1/p62 and PPARGC1A/PGC-1alpha at the interface of autophagy and vascular senescence. Autophagy. 2020;16(6):1092–110. [CrossRef].
77. Kim SG, Sung JY, Kang YJ, Choi HC. PPARγ activation by fisetin mitigates vascular smooth muscle cell senescence via the mTORC2-FoxO3a-autophagy signaling pathway. Biochem Pharmacol. 2023;218:115892. [CrossRef].
78. Nie H, Ji T, Wan Z, Huang J, Li H, Zou L, et al. ATF3 deficiency exacerbates ageing-induced atherosclerosis and clinical intervention strategy. Adv Sci. 2025;12(37):e02249. [CrossRef].
79. Sung JY, Kim SG, Kim JR, Choi HC. SIRT1 suppresses cellular senescence and inflammatory cytokine release in human dermal fibroblasts by promoting the deacetylation of NF-κB and activating autophagy. Exp Gerontol. 2021;150:111394. [CrossRef].
80. Zhai P, Sung EA, Shiheido-Watanabe Y, Takayama K, Tian Y, Sadoshima J. Suppression of autophagy induces senescence in the heart. J Mol Cell Cardiol. 2024;195:83–96. [CrossRef].
81. Yang L, Shi J, Wang X, Zhang R. Curcumin alleviates D-galactose-induced cardiomyocyte senescence by promoting autophagy via the SIRT1/AMPK/mTOR pathway. Evid Based Complement Alternat Med. 2022;2022:2990843. [CrossRef].
82. He H, Zeng B, Wu X, Hou J, Wang Y, Wang Y, et al. Higher matrix stiffness promotes VSMC senescence by affecting mitochondria-ER contact sites and mitochondria/ER dysfunction. FASEB J. 2023;37(12):e23318. [CrossRef].

83. Ngassie MLK, Drake LY, Roos BB, Koenig-Kappes A, Pabelick CM, Gosens R, et al. Endoplasmic reticulum stress-induced senescence in human lung fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2024;327(1):L126–39. [CrossRef].
84. Fatima S, Ambreen S, Mathew A, Elwakiel A, Gupta A, Singh K, et al. ER-stress and senescence coordinately promote endothelial barrier dysfunction in diabetes-induced atherosclerosis. Nutrients. 2022;14(14):2786. [CrossRef].
85. Chatterjee N, Fraile-Bethencourt E, Baris A, Espinosa-Diez C, Anand S. microRNA-494 regulates endoplasmic reticulum stress in endothelial cells. Front Cell Dev Biol. 2021;9:671461. [CrossRef].
86. Lenin R, Jha KA, Gentry J, Shrestha A, Culp EV, Vaithianathan T, et al. Tauroursodeoxycholic acid alleviates endoplasmic reticulum stress-mediated visual deficits in diabetic tie2-TNF transgenic mice via TGR5 signaling. J Ocul Pharmacol Ther. 2023;39(2):159–74. [CrossRef].
87. Wang L, Wang M, Niu H, Zhi Y, Li S, He X, et al. Cholesterol-induced HRD1 reduction accelerates vascular smooth muscle cell senescence via stimulation of endoplasmic reticulum stress-induced reactive oxygen species. J Mol Cell Cardiol. 2024;187:51–64. [CrossRef].
88. Jiao L, Yan Q, Yang J, Wu R, Wei Z, Ruan J, et al. Hydrogen sulfide alleviates vascular smooth muscle cell senescence by inhibiting endoplasmic reticulum stress. Cell Signal. 2025;135:112075. [CrossRef].
89. Cicalese S, Torimoto K, Okuno K, Elliott KJ, Rizzo V, Hashimoto T, et al. Endoplasmic reticulum chemical chaperone 3-hydroxy-2-naphthoic acid reduces angiotensin II-induced vascular remodeling and hypertension *in vivo* and protein synthesis *in vitro*. J Am Heart Assoc. 2022;11(23):e028201. [CrossRef].
90. Suhail H, Peng H, Matrougui K, Rhaleb NE. Ac-SDKP attenuates ER stress-stimulated collagen production in cardiac fibroblasts by inhibiting CHOP-mediated NF-κB expression. Front Pharmacol. 2024;15:1352222. [CrossRef].
91. Li Y, Du Y, Liu Y, Chen X, Li X, Duan Y, et al. Cardiomyocyte-derived small extracellular vesicle: a new mechanism driving diabetic cardiac fibrosis and cardiomyopathy. Theranostics. 2024;14(15):5926–44. [CrossRef].
92. Zhan W, Chen L, Liu H, Long C, Liu J, Ding S, et al. Pcsk6 deficiency promotes cardiomyocyte senescence by modulating Ddit3-mediated ER stress. Genes. 2022;13(4):711. [CrossRef].
93. Li S, Li Q, Xiang H, Wang C, Zhu Q, Ruan D, et al. H_2S donor SPRC ameliorates cardiac aging by suppression of JMJD3, a histone demethylase. Antioxid Redox Signal. 2025;42(7–9):301–20. [CrossRef].
94. DeLeon-Pennell KY, Barker TH, Lindsey ML. Fibroblasts: the arbiters of extracellular matrix remodeling. Matrix Biol. 2020;91–92:1–7. [CrossRef].
95. Doppler SA, Carvalho C, Lahm H, Deutsch MA, Dreßen M, Puluca N, et al. Cardiac fibroblasts: more than mechanical support. J Thorac Dis. 2017;9(Suppl 1):S36–51. [CrossRef].
96. Zhang Z, Shayani G, Xu Y, Kim A, Hong Y, Feng H, et al. Induction of senescence by loss of Gata4 in cardiac fibroblasts. Cells. 2023;12(12):1652. [CrossRef].
97. Schneider SE, Scott AK, Gallagher KM, Miller EY, Ghosh S, Neu CP. Mechanical stress triggers premature senescence in cardiac fibroblasts. Adv Sci. 2025;12(47):e13314. [CrossRef].
98. Zhu F, Li Y, Zhang J, Piao C, Liu T, Li HH, et al. Senescent cardiac fibroblast is critical for cardiac fibrosis after myocardial infarction. PLoS One. 2013;8(9):e74535. [CrossRef].
99. Abe Y, Tani H, Sadahiro T, Yamada Y, Akiyama T, Nakano K, et al. Cardiac reprogramming reduces inflammatory macrophages and improves cardiac function in chronic myocardial infarction. Biochem Biophys Res Commun. 2024;690:149272. [CrossRef].
100. Honda S, Sadahiro T, Abe Y, Yamada Y, Akiyama T, Nakano K, et al. Shortening and optimization of MEF2C and GATA4 promote cardiac reprogramming. Biochem Biophys Res Commun. 2025;781:152511. [CrossRef].
101. Bann GG, Dos Santos M, Chen K, Tan W, Bezprozvannaya S, Gan P, et al. Cellular reprogramming by PHF7 enhances cardiac function following myocardial infarction. Circulation. 2025;152(9):616–29. [CrossRef].
102. Garry GA, Bezprozvannaya S, Chen K, Zhou H, Hashimoto H, Morales MG, et al. The histone reader PHF7 cooperates with the SWI/SNF complex at cardiac super enhancers to promote direct reprogramming. Nat Cell Biol. 2021;23(5):467–75. [CrossRef].
103. Chen Y, Liu Z, Chen H, Huang X, Huang X, Lei Y, et al. p53 SUMOylation mediates AOPP-induced endothelial senescence and apoptosis evasion. Front Cardiovasc Med. 2022;8:795747. [CrossRef].

104. Wilkinson HN, Hardman MJ. Senescence in wound repair: emerging strategies to target chronic healing wounds. Front Cell Dev Biol. 2020;8:773. [CrossRef].

105. Wilkinson HN, Hardman MJ. Cellular senescence in acute and chronic wound repair. Cold Spring Harb Perspect Biol. 2022;14(11):a041221. [CrossRef].

106. Samdavid Thanapaul RJR, Shvedova M, Shin GH, Crouch J, Roh DS. Elevated skin senescence in young mice causes delayed wound healing. Geroscience. 2022;44(3):1871–8. [CrossRef].

107. Owens WA, Walaszczyk A, Spyridopoulos I, Dookun E, Richardson GD. Senescence and senolytics in cardiovascular disease: promise and potential pitfalls. Mech Ageing Dev. 2021;198:111540. [CrossRef].

108. Redgrave RE, Dookun E, Booth LK, Camacho Encina M, Folaranmi O, Tual-Chalot S, et al. Senescent cardiomyocytes contribute to cardiac dysfunction following myocardial infarction. npj Aging. 2023;9(1):15. [CrossRef].

109. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020;288(5):518–36. [CrossRef].

110. Yang Z, Potenza DM, Ming XF. Is senolytic therapy in cardiovascular diseases ready for translation to clinics? Biomolecules. 2025;15(4):545. [CrossRef].

111. Hu C, Zhang X, Teng T, Ma ZG, Tang QZ. Cellular senescence in cardiovascular diseases: a systematic review. Aging Dis. 2022;13(1):103–28. [CrossRef].

112. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovasc Res. 2018;114(4):590–600. [CrossRef].

113. Li D, Li Y, Ding H, Wang Y, Xie Y, Zhang X. Cellular senescence in cardiovascular diseases: from pathogenesis to therapeutic challenges. J Cardiovasc Dev Dis. 2023;10(10):439. [CrossRef].

114. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol. 2021;22(2):75–95. [CrossRef].

115. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res. 2016;118(4):535–46. [CrossRef].

116. Perrotta I. Atherosclerosis: from molecular biology to therapeutic perspective. Int J Mol Sci. 2022;23(7):3444. [CrossRef].

117. Schafer MJ, Zhang X, Kumar A, Atkinson EJ, Zhu Y, Jachim S, et al. The senescence-associated secretome as an indicator of age and medical risk. JCI Insight. 2020;5(12):e133668. [CrossRef].

118. Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. Nat Rev Nephrol. 2022;18(10):611–27. [CrossRef].

119. Han Y, Kim SY. Endothelial senescence in vascular diseases: current understanding and future opportunities in senotherapeutics. Exp Mol Med. 2023;55(1):1–12. [CrossRef].

120. Mahoney SA, Bloom SI, Seals DR, Donato AJ, Rossman MJ, Clayton ZS. Mechanisms of cellular senescence-induced vascular aging: evidence of senotherapeutic strategies. J Cardiovasc Aging. 2025;5(2):6. [CrossRef].

121. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. Eur Heart J Acute Cardiovasc Care. 2012;1(1):60–74. [CrossRef].

122. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, et al. Pathophysiology of atherosclerosis. Int J Mol Sci. 2022;23(6):3346. [CrossRef].

123. Machado-Oliveira G, Ramos C, Marques ARA, Vieira OV. Cell senescence, multiple organelle dysfunction and atherosclerosis. Cells. 2020;9(10):2146. [CrossRef].

124. El Hadri K, Smith R, Duplus E, El Amri C. Inflammation, oxidative stress, senescence in atherosclerosis: thioredoxine-1 as an emerging therapeutic target. Int J Mol Sci. 2021;23(1):77. [CrossRef].

125. Stojanović SD, Fiedler J, Bauersachs J, Thum T, Sedding DG. Senescence-induced inflammation: an important player and key therapeutic target in atherosclerosis. Eur Heart J. 2020;41(31):2983–96. [CrossRef].

126. Childs BG, Baker DJ, Wijshake T, Conover CA, Campisi J, van Deursen JM. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. Science. 2016;354(6311):472–7. [CrossRef].

127. Molnár AÁ, Pásztor DT, Tarcza Z, Merkely B. Cells in atherosclerosis: focus on cellular senescence from basic science to clinical practice. Int J Mol Sci. 2023;24(24):17129. [CrossRef].
128. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16(4):223–37. [CrossRef].
129. Cheng W, Du Y, Zhang Q, Wang X, He C, He J, et al. Age-related changes in the risk of high blood pressure. Front Cardiovasc Med. 2022;9:939103. [CrossRef].
130. McCarthy CG, Wenceslau CF, Webb RC, Joe B. Novel contributors and mechanisms of cellular senescence in hypertension-associated premature vascular aging. Am J Hypertens. 2019;32(8):709–19. [CrossRef].
131. Kyi P, Hendee K, Hunyenyiwa T, Matus K, Mammoto T, Mammoto A. Endothelial senescence mediates hypoxia-induced vascular remodeling by modulating PDGFB expression. Front Med. 2022;9:908639. [CrossRef].
132. Graham D, Huynh NN, Hamilton CA, Beattie E, Smith RAJ, Cochemé HM, et al. Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy. Hypertension. 2009;54(2):322–8. [CrossRef].
133. Clayton ZS, Rossman MJ, Mahoney SA, Venkatasubramanian R, Maurer GS, Hutton DA, et al. Cellular senescence contributes to large elastic artery stiffening and endothelial dysfunction with aging: amelioration with senolytic treatment. Hypertension. 2023;80(10):2072–87. [CrossRef].
134. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012;308(9):875–81. [CrossRef].
135. Das KC, Kundumani-Sridharan V, Subramani J. Role of thioredoxin in age-related hypertension. Curr Hypertens Rep. 2018;20(1):6. [CrossRef].
136. Long C, Liu H, Zhan W, Chen L, Yu Z, Tian S, et al. Chronological attenuation of NPRA/PKG/AMPK signaling promotes vascular aging and elevates blood pressure. Aging Cell. 2022;21(9):e13699. [CrossRef].
137. Somsura R, Kamkajon K, Chaimongkolnukul K, Chantip S, Teerapornpuntakit J, Wongdee K, et al. Tissue-specific expression of senescence biomarkers in spontaneously hypertensive rats: evidence of premature aging in hypertension. PeerJ. 2023;11:e16300. [CrossRef].
138. Zhao S, Zhang Y, Zhao Y, Lu X. Cellular senescence as a key player in chronic heart failure pathogenesis: unraveling mechanisms and therapeutic opportunities. Prog Biophys Mol Biol. 2025;196:8–18. [CrossRef].
139. Le T, Chong J. Cardiac progenitor cells for heart repair. Cell Death Discov. 2016;2(1):16052. [CrossRef].
140. Lewis-McDougall FC, Ruchaya PJ, Domenjo-Vila E, Shin Teoh T, Prata L, Cottle BJ, et al. Aged-senescent cells contribute to impaired heart regeneration. Aging Cell. 2019;18(3):e12931. [CrossRef].
141. Bian R, Zhang L, Li D, Xu X. CDKN1A as a target of senescence in heart failure: insights from a multiomics study. Front Pharmacol. 2024;15:1446300. [CrossRef].
142. Camacho-Encina M, Booth LK, Redgrave RE, Folaranmi O, Spyridopoulos I, Richardson GD. Cellular senescence, mitochondrial dysfunction, and their link to cardiovascular disease. Cells. 2024;13(4):353. [CrossRef].
143. Liang X, Zhang Y, Lin F, Li M, Li X, Chen Y, et al. Direct administration of mesenchymal stem cell-derived mitochondria improves cardiac function after infarction via ameliorating endothelial senescence. Bioeng Transl Med. 2022;8(1):e10365. [CrossRef].
144. Gao S, Li G, Shao Y, Wei Z, Huang S, Qi F, et al. FABP5 deficiency impairs mitochondrial function and aggravates pathological cardiac remodeling and dysfunction. Cardiovasc Toxicol. 2021;21(8):619–29. [CrossRef].
145. Barcena ML, Aslam M, Pozdniakova S, Norman K, Ladilov Y. Cardiovascular inflammaging: mechanisms and translational aspects. Cells. 2022;11(6):1010. [CrossRef].
146. Spray L, Richardson G, Haendeler J, Altschmied J, Rumampouw V, Wallis SB, et al. Cardiovascular inflammaging: mechanisms, consequences, and therapeutic perspectives. Cell Rep Med. 2025;6(9):102264. [CrossRef].
147. Zhang Y, Wang X, Li XK, Lv SJ, Wang HP, Liu Y, et al. Sirtuin 2 deficiency aggravates ageing-induced vascular remodelling in humans and mice. Eur Heart J. 2023;44(29):2746–59. [CrossRef].
148. Müller L, Di Benedetto S. Inflammaging, immunosenescence, and cardiovascular aging: insights into long COVID implications. Front Cardiovasc Med. 2024;11:1384996. [CrossRef].
149. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(11):1324–40. [CrossRef].

150. Esfahani NS, Wu Q, Kumar N, Ganesan LP, Lafuse WP, Rajaram MVS. Aging influences the cardiac macrophage phenotype and function during steady state and during inflammation. Aging Cell. 2021;20(8):e13438. [CrossRef].
151. Hou C, Wang Z, Lu X. Impact of immunosenescence and inflammaging on the effects of immune checkpoint inhibitors. Cancer Pathog Ther. 2023;2(1):24–30. [CrossRef].
152. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nat Rev Mol Cell Biol. 2007;8(9):729–40. [CrossRef].
153. Zhou Z, Yao J, Wu D, Huang X, Wang Y, Li X, et al. Type 2 cytokine signaling in macrophages protects from cellular senescence and organismal aging. Immunity. 2024;57(3):513–27. [CrossRef].
154. Wang L, Hong W, Zhu H, He Q, Yang B, Wang J, et al. Macrophage senescence in health and diseases. Acta Pharm Sin B. 2024;14(4):1508–24. [CrossRef].
155. Antonangeli F, Zingoni A, Soriani A, Santoni A. Senescent cells: living or dying is a matter of NK cells. J Leukoc Biol. 2019;105(6):1275–83. [CrossRef].
156. Muñoz DP, Yannone SM, Daemen A, Sun Y, Vakar-Lopez F, Kawahara M, et al. Targetable mechanisms driving immunoevasion of persistent senescent cells link chemotherapy-resistant cancer to aging. JCI Insight. 2019;5(14):e124716. [CrossRef].
157. Fulop T, Larbi A, Hirokawa K, Cohen AA, Witkowski JM. Immunosenescence is both functional/adaptive and dysfunctional/maladaptive. Semin Immunopathol. 2020;42(5):521–36. [CrossRef].
158. Kale A, Sharma A, Stolzing A, Desprez PY, Campisi J. Role of immune cells in the removal of deleterious senescent cells. Immun Ageing. 2020;17:16. [CrossRef].
159. Zhang Y, Hu R, Xi B, Nie D, Xu H, Liu A. Mechanisms of senescence-related NKG2D ligands release and immune escape induced by chemotherapy in neuroblastoma cells. Front Cell Dev Biol. 2022;10:829404. [CrossRef].
160. Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J, et al. An update on inflamm-aging: mechanisms, prevention, and treatment. J Immunol Res. 2016;2016:8426874. [CrossRef].
161. Song P, An J, Zou MH. Immune clearance of senescent cells to combat ageing and chronic diseases. Cells. 2020;9(3):671. [CrossRef].
162. Gasser S, Orsulic S, Brown EJ, Raulet DH. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. Nature. 2005;436(7054):1186–90. [CrossRef].
163. Schloesser D, Lindenthal L, Sauer J, Chung KJ, Chavakis T, Griesser E, et al. Senescent cells suppress macrophage-mediated corpse removal via upregulation of the CD47-QPCT/L axis. J Cell Biol. 2022;222(2):e202207097. [CrossRef].
164. Fraccarollo D, Geffers R, Galuppo P, Bauersachs J. Mineralocorticoid receptor promotes cardiac macrophage inflammaging. Basic Res Cardiol. 2024;119(2):243–60. [CrossRef].
165. Zingoni A, Vulpis E, Loconte L, Santoni A. NKG2D ligand shedding in response to stress: role of ADAM10. Front Immunol. 2020;11:447. [CrossRef].
166. Yang D, Sun B, Li S, Wei W, Liu X, Cui X, et al. NKG2D-CAR T cells eliminate senescent cells in aged mice and nonhuman primates. Sci Transl Med. 2023;15(709):eadd1951. [CrossRef].
167. Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol. 2018;8:1960. [CrossRef].
168. Hulsmans M, Clauss S, Xiao L, Aguirre AD, King KR, Hanley A, et al. Macrophages facilitate electrical conduction in the heart. Cell. 2017;169(3):510–22. [CrossRef].
169. Epelman S, Lavine KJ, Beaudin AE, Sojka DK, Carrero JA, Calderon B, et al. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. Immunity. 2014;40(1):91–104. [CrossRef].
170. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. Circ Res. 2018;123(7):825–48. [CrossRef].
171. Goronzy JJ, Weyand CM. Successful and maladaptive T cell aging. Immunity. 2017;46(3):364–78. [CrossRef].
172. Raffaele M, Vinciguerra M. The costs and benefits of senotherapeutics for human health. Lancet Healthy Longev. 2022;3(1):e67–77. [CrossRef].

173. Alam MT, Mansoor MAM, Ashiqueali SA, Golusinski P, Golusinska-Kardach E, Strzelczyk JK, et al. The impact of senescence-associated secretory phenotype (SASP) on head and neck cancers: from biology to therapy. Cancers. 2025;17(24):4024. [CrossRef].
174. Pal A. Cellular senescence and senotherapeutics in cardiovascular diseases. Adv Pharmacol. 2025;104:313–49. [CrossRef].
175. Calabrò A, Accardi G, Aiello A, Caruso C, Galimberti D, Candore G. Senotherapeutics to counteract senescent cells are prominent topics in the context of anti-ageing strategies. Int J Mol Sci. 2024;25(3):1792. [CrossRef].
176. Suda M, Paul KH, Minamino T, Miller JD, Lerman A, Ellison-Hughes GM, et al. Senescent cells: a therapeutic target in cardiovascular diseases. Cells. 2023;12(9):1296. [CrossRef].
177. Atlante S, Gottardi Zamperla M, Cis L, Farsetti A, Gaetano C. Senolytic therapies for cardiovascular aging: tackling fibrosis and metabolic dysfunction. Eur J Intern Med. 2025;140:106413. [CrossRef].
178. Nieto M, Konigsberg M, Silva-Palacios A. Quercetin and dasatinib, two powerful senolytics in age-related cardiovascular disease. Biogerontology. 2024;25(1):71–82. [CrossRef].
179. Zhu Y, Tchkonia T, Fuhrmann-Stroissnigg H, Dai HM, Ling YY, Stout MB, et al. Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. Aging Cell. 2016;15(3):428–35. [CrossRef].
180. Kumar M, Yan P, Kuchel GA, Xu M. Cellular senescence as a targetable risk factor for cardiovascular diseases: therapeutic implications: JACC family series. JACC Basic Transl Sci. 2024;9(4):522–34. [CrossRef].
181. Tavenier J, Nehlin JO, Houlind MB, Rasmussen LJ, Tchkonia T, Kirkland JL, et al. Fisetin as a senotherapeutic agent: evidence and perspectives for age-related diseases. Mech Ageing Dev. 2024;222:111995. [CrossRef].
182. Tang H, Zhang X, Hu S, Song Y, Jin W, Zou J, et al. Natural products acting as senolytics and senomorphics alleviate cardiovascular diseases by targeting senescent cells. Targets. 2025;3(3):23. [CrossRef].
183. Yesilyurt-Dirican ZE, Qi C, Wang YC, Simm A, Deelen L, Hafiz Abbas Gasim A, et al. SGLT2 inhibitors as a novel senotherapeutic approach. npj Aging. 2025;11(1):35. [CrossRef].
184. Fuentes-Mendoza JM, Concepción-Zavaleta MJ, Muñoz-Moreno J, Concepción-Urteaga L, Ibarra JP, Garza-Boullosa R, et al. Cardiovascular aging: from molecular mechanisms to targeted therapies. Mol Diagn Ther. 2025;29(6):759–72. [CrossRef].
185. Turgut Ş, Atasever E, Cebe T, Andican G, Çakatay U. Senotherapeutic repurposing of metformin for age-related diseases and their signaling pathways. Mol Biol Rep. 2025;52(1):410. [CrossRef].
186. Stojanović SD, Thum T, Bauersachs J. Anti-senescence therapies: a new concept to address cardiovascular disease. Cardiovasc Res. 2025;121(5):730–47. [CrossRef].
187. Saliev T, Singh PB. Targeting senescence: a review of senolytics and senomorphics in anti-aging interventions. Biomolecules. 2025;15(6):860. [CrossRef].
188. Gadecka A, Nowak N, Bulanda E, Janiszewska D, Dudkowska M, Sikora E, et al. The senolytic cocktail, dasatinib and quercetin, impacts the chromatin structure of both young and senescent vascular smooth muscle cells. GeroScience. 2025;47(3):3907–25. [CrossRef].
189. Bai C, Hu X, Lu S, Xu B, Ma T, Song Y. Recent advances and application challenges of quercetin-loaded delivery systems: from material selection to bioavailability. J Future Foods. 2025:1–37. [CrossRef].
190. Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. Cellular senescence: defining a path forward. Cell. 2019;179(4):813–27. [CrossRef].
191. Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of cellular senescence. Trends Cell Biol. 2018;28(6):436–53. [CrossRef].
192. Kang E, Kang C, Lee YS, Lee SV. Brief guide to senescence assays using cultured mammalian cells. Mol Cells. 2024;47(9):100102. [CrossRef].
193. Hewitt G, Jurk D, Marques FDM, Correia-Melo C, Hardy T, Gackowska A, et al. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. Nat Commun. 2012;3:708. [CrossRef].
194. Deng Y, Li Q, Zhou F, Li G, Liu J, Lv J, et al. Telomere length and the risk of cardiovascular diseases: a Mendelian randomization study. Front Cardiovasc Med. 2022;9:1012615. [CrossRef].
195. Aung N, Wang Q, van Duijvenboden S, Burns R, Stoma S, Raisi-Estabragh Z, et al. Association of longer leukocyte telomere length with cardiac size, function, and heart failure. JAMA Cardiol. 2023;8(9):808–15. [CrossRef].

196. Welsh JA, Goberdhan DCI, O'Driscoll L, Buzas EI, Blenkiron C, Bussolati B, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. J Extracell Vesicles. 2024;13(2):e12404. [CrossRef].
197. Buntsma NC, Shahsavari M, Gąsecka A, Nieuwland R, van Leeuwen TG, van der Pol E. Preventing swarm detection in extracellular vesicle flow cytometry: a clinically applicable procedure. Res Pract Thromb Haemost. 2023;7(4):100171. [CrossRef].
198. Searles CD. microRNAs and cardiovascular disease risk. Curr Cardiol Rep. 2024;26(2):51–60. [CrossRef].
199. Englund DA, Sakamoto AE, Fritsche CM, Heeren AA, Zhang X, Kotajarvi BR, et al. Exercise reduces circulating biomarkers of cellular senescence in humans. Aging Cell. 2021;20(7):e13415. [CrossRef].
200. Cho J, Lee H, Rah W, Chang HJ, Yoon YS. From engineered heart tissue to cardiac organoid. Theranostics. 2022;12(6):2758–72. [CrossRef].
201. Tani H, Tohyama S. Human engineered heart tissue models for disease modeling and drug discovery. Front Cell Dev Biol. 2022;10:855763. [CrossRef].
202. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature. 2016;530(7589):184–9. [CrossRef].
203. Chandra A, Lagnado AB, Farr JN, Doolittle M, Tchkonia T, Kirkland JL, et al. Targeted clearance of p21- but not p16-positive senescent cells prevents radiation-induced osteoporosis and increased marrow adiposity. Aging Cell. 2022;21(5):e13602. [CrossRef].
204. Childs BG, Li H, van Deursen JM. Senescent cells: a therapeutic target for cardiovascular disease. J Clin Investig. 2018;128(4):1217–28. [CrossRef].