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STATE-OF-THE-ART REVIEW

JACC FAMILY SERIES

Cellular Senescence as a Targetable Risk Factor for Cardiovascular Diseases

Therapeutic Implications: *JACC* Family Series

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HIGHLIGHTS

- **Aging is a prominent risk factor in the development of cardiovascular diseases, and cellular senescence plays a pivotal role in this process.**
- **Cellular senescence contributes to the onset and progression of various cardiovascular diseases, as indicated by several animal studies targeting senescent cells.**
- **Senolytic drugs effectively remove senescent cells in the cardiac and vascular systems, offering a potential avenue for alleviating cardiovascular diseases in animal models.**
- **It is imperative to conduct preclinical investigations and clinical trials to assess the safety and efficacy of senolytic treatments.**

SUMMARY

The prevalence of cardiovascular diseases markedly rises with age. Cellular senescence, a hallmark of aging, is characterized by irreversible cell cycle arrest and the manifestation of a senescence-associated secretory phenotype, which has emerged as a significant contributor to aging, mortality, and a spectrum of chronic ailments. An increasing body of preclinical and clinical research has established connections between senescence, senescence-associated secretory phenotype, and age-related cardiac and vascular pathologies. This review comprehensively outlines studies delving into the detrimental impact of senescence on various cardiovascular diseases, encompassing systemic atherosclerosis (including coronary artery disease, stroke, and peripheral arterial disease), as well as conditions such as hypertension, congestive heart failure, arrhythmias, and valvular heart diseases. In addition, we have preclinical studies demonstrating the beneficial effects of senolytics—a class of drugs designed to eliminate senescent cells selectively across diverse cardiovascular disease scenarios. Finally, we address knowledge gaps on the influence of senescence on cardiovascular systems and discuss the future trajectory of strategies targeting senescence for cardiovascular diseases. (J Am Coll Cardiol Basic Trans Science 2024;9:522–534) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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With more individuals reaching advanced age, the prevalence of clinical and subclinical cardiovascular disease (CVD) is on the rise both in the United States and worldwide.[1] CVD, especially in older adults, remains one of the leading causes of morbidity and mortality despite recent emergences in medicine and technology.[2] Throughout life, the cardiovascular system is exposed to constant mechanical, hemodynamic, and metabolic stressors, challenging the capacity of compensatory mechanisms to maintain normal function. With aging, such homeostatic capacities get gradually eroded, resulting in molecular, cellular, structural, and functional changes in the cardiovascular system that contribute to the development of numerous diseases such as hypertension; coronary heart disease; heart failure; valvular, arterial, and cardiac skeleton calcification; amyloidosis; and cerebrovascular and peripheral arterial disease.[3,4] Chronological aging, based on time since birth, accounts for most of the risk for developing varied chronic diseases, including CVD.[2] Nonetheless, the risk of developing CVD varies considerably between individuals of the same chronological age due to variations in biological aging.

Biological aging is a universal, multifaceted, and ultimately malleable process driven by varied molecular, cellular, and organ-level processes, collectively termed the biological hallmarks of aging.[5] These include genomic instability, telomere attrition, loss of proteostasis, inflammation, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, gut dysbiosis, chronic inflammation, and altered intercellular communication.[5] Biological aging occurring via these distinct yet highly interconnected hallmarks of aging drive the phenotypic expression of age-related physical and functional degenerative changes in the cardiovascular and almost every organ system.

Among the aging hallmarks mentioned previously, cellular senescence (**Central Illustration**) has emerged as one of the risk factors for aging and various aging-associated organ dysfunctions, including cardiovascular systems. A stable proliferative cell cycle arrest characterizes cellular senescence and is accompanied by a secretome called the senescence-associated secretory phenotype (SASP).[6,7] In response to internal or external stressors, such as telomere shortening or DNA damaging regents, p53-CDKN1A (p21) and CDKN2A (p16) pathways are activated. Elevated levels of cyclin-dependent kinase inhibitors p21 or p16 induce G1/S cell cycle blockade by inhibiting the formation of cyclin-cyclin-dependent kinase complexes and preventing the inactivation of retinoblastoma, thus suppressing the expression of S-phase genes by binding to and sequestering the transcription factors such as E2F family. Concurrent with the halt in proliferation, senescent cells release a diverse array of SASP factors comprising cytokines, matrix metalloproteinases, microRNAs, chemokines, growth factors, and small molecule metabolites, either directly secreted or packaged in exosomes. SASP can potentiate further senescent cell accumulation, and elicit a chronic inflammatory environment and additional senescence-inducing stressors, thereby establishing a self-perpetuating cycle of senescent cell accumulation.[7] Accordingly, SASP is a crucial contributor to the combined physiologic and pathologic roles of senescent cells. Senescent cells are apoptosis resistant and display distinct characteristics compared with normal cells. Generally, it is consensus that senescent cells exhibit enlarged size, increased granularity, and heightened senescence-associated β galactosidase (SA-β-gal) activity. Furthermore, they tend to accumulate lipofuscin in lysosomes and cytosolic DNA, activate anti-apoptotic pathways (senescent cell anti-apoptotic pathways), and manifest various nuclear alterations, including loss of Lamin B1, telomere shortening, the formation of senescence-associated heterochromatin foci, and DNA damage in telomeres (termed telomere-associated foci).[6] Recently, several groups reported that senescent cells exhibit elevated expression of molecular markers, including cell surface protein urokinase-type plasminogen activator receptor (uPAR), transmembrane glycoprotein nonmetastatic melanoma protein B (GPNMB), and glutamine metabolism enzyme glutaminase 1 (GLS1). Relying on the preceding hallmarks, several p16- and p21-based mice models,[8-12] uPAR, GPNMB, and GLS1-based senolysis are used to explore the role of senescent cells in various aging-related diseases, including cardiovascular diseases.[13-15] To date, senescent cells have been proven to have detrimental effects on a wide range of conditions, including morbidity, death, and health care burdens such as CVD, cancers, and diabetes.[7-11,16]

Interventions aimed at targeting the harmful effect of senescent cells have shown a beneficial effect on improving tissue function encompassing various organ systems (**Figure 1**). The current senolytic class originates from work demonstrating senescent cell-specific clearance with the combination of the Src

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AS = aortic stenosis

CAD = coronary artery disease

CVD = cardiovascular disease

D&Q = dasatinib and the flavonoid quercetin

EC = endothelial cell

GLS1 = glutaminase 1

GPNMB = glycoprotein nonmetastatic melanoma protein B

HFpEF = heart failure with preserved ejection fraction

IRI = ischemia-reperfusion injury

LVEF = left ventricular ejection fraction

MI = myocardial infarction

SA-β-gal = senescence-associated β galactosidase

SASP = senescence-associated secretory phenotype

uPAR = urokinase-type plasminogen activator receptor

VSMC = vascular smooth muscle cell

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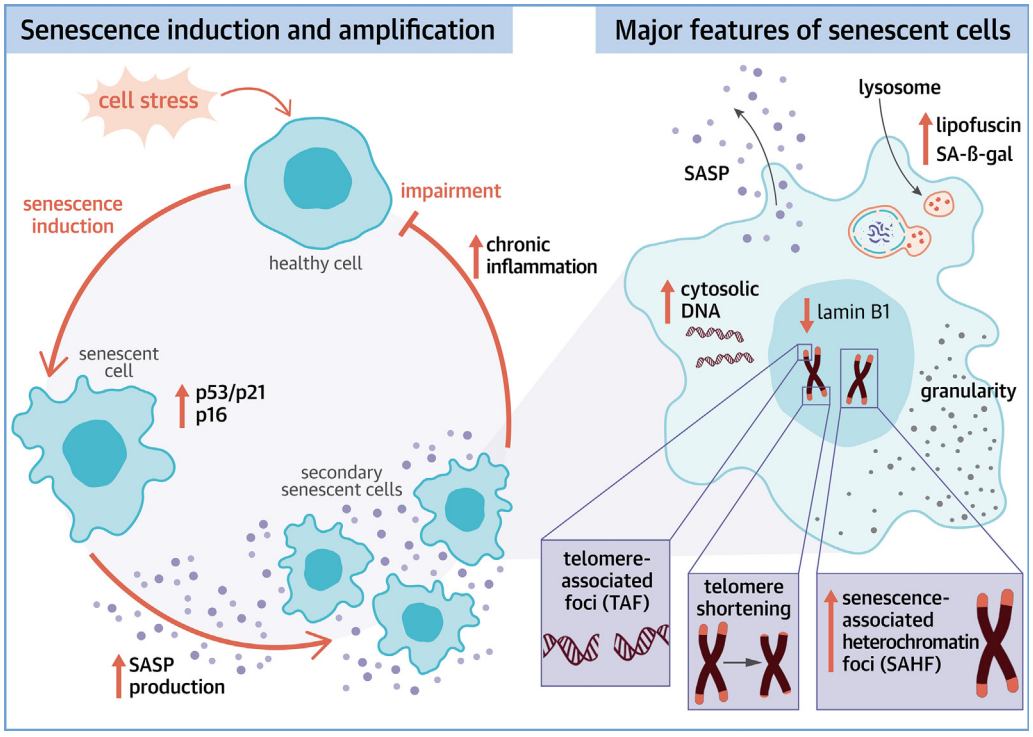
CENTRAL ILLUSTRATION **Induction, Amplification, and Features of Senescent Cells**



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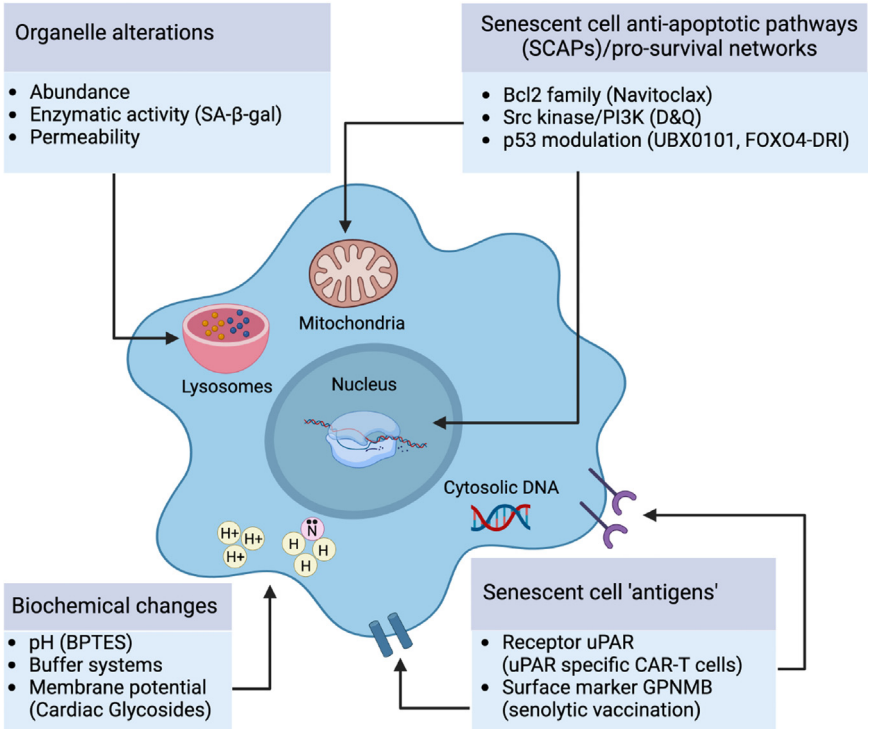
When exposed to initial stress, healthy cells upregulate the cyclin-dependent kinase inhibitors p53/p21 and p16, leading to cell cycle arrest and entry into a state of senescence. The primary senescent cells release a complex mix of factors known as the senescence-associated secretory phenotype (SASP), contributing to the generation of secondary senescent cells. These senescent cells establish a chronic inflammatory environment, adversely affecting neighboring healthy cells and thus induce organism dysfunction. In addition to these characteristics, senescent cells exhibit increased cell size and granularity, accumulated cytosolic DNA and lipofuscin, heightened senescence-associated β galactosidase (SA-β-gal) activity, telomere shortening, formation of telomere-associated foci and senescence-associated heterochromatin foci, and reduced expression of Lamin B1. The figure is adapted from reviews by Cohn et al[6] and Gasek et al[7] and created by BioRender.com.

kinase inhibitor dasatinib and the flavonoid quercetin (D&Q)[17] and subsequently, BCL-2 family inhibitor navitoclax (also termed ABT-263).[18,19] These drugs suppress prosurvival pathways prominently activated in senescent cells. These pathways are crucial for shielding senescent cells from cell death triggered by the toxic microenvironment around them. In addition to disrupting senescent cell anti-apoptotic pathways and other prosurvival networks (eg, p53 modulation by modified FOXO4/p53 interfering peptide FOXO4-DRI or MDM2/p53 inhibitor UBX0101),[20,21] the senolytic class has expanded to take advantage of other senescence features including organelle alterations, biochemical changes like pH,[15] and senescent cell "antigens" including surface marker GPNMB or receptor uPAR.[13,14,22] Some of these senolytic approaches have shown beneficial effects on age-associated cardiovascular diseases. In the following sections, we outline the rationale and current evidence for senescent cells being a therapeutic target and summarize the implications of senescence-targeting strategies in various aging-related cardiovascular disorders.

SYSTEMIC ATHEROSCLEROSIS: CORONARY ARTERY DISEASE, STROKE, AND PERIPHERAL ARTERIAL DISEASE

Atherosclerosis refers to stenosis of the coronary arteries due to plaque formed primarily of lipid and macrophage foam cells. Cellular senescence has been implicated in the pathogenesis of systemic

FIGURE 1 **Senescent Cell Features Targeted by Senolytics**



Selective features of senescent cells have been targeted to reduce their abundance, generally comprising the following 4 categories. 1) Senescent cell anti-apoptotic pathways (SCAPs) and other prosurvival networks. Senolytics designed to inhibit SCAPs encompasses Bcl2 family inhibitor navitoclax, Src kinases inhibitor dasatinib, and PI3K inhibitor quercetin (D&Q). Senolytics that target prosurvival networks modulate p53-dependent apoptotic activity, such as MDM2-p53 interaction inhibitor UBX0101, modified FOXO4/p53 interfering peptide FOXO4-DRI. 2) Organelle alterations. Cytotoxic drugs specifically target senescent cells by using the advantage of their high senescence-associated β galactosidase (SA-β-gal) activity, either by loading cytotoxic chemicals into galactose-polymer–coated nanoparticles that can be preferentially released into senescent cells or by synthesizing senescence-specific killing compound 1 (SSK1) that is cleaved and activated by S-gal. 3) Biochemical changes. Senolytics are designed to modulate cellular pH, either by disturbing the pH neutralization system within senescent cells (BPTES, an inhibitor of glutaminase 1) or by targeting the Na+/K+ ATPase pump, causing an imbalanced electrochemical gradient, thus leading to depolarization and acidification (Cardiac Glycosides). 4) Senescent cell antigens. Senolytics target specific senescent cell antigens, including CAR T cells recognizing receptor uPAR and senolytic vaccination against the surface marker GPNMB. The figure is adapted from the review by Gasek et al[7] and created by BioRender.com.

atherosclerosis. Atherosclerotic lesions have a high burden of senescent endothelial cells (ECs) based on the evidence of heightened SA-β-gal activity, elevated p16 and p21 expression, and shortened telomeres. Such accumulation of senescent cells has been attributed to reduced telomerase activity, telomere shortening, and oxidative stress.[23,24] Moreover, in population studies, leucocyte telomere length is inversely associated with the incidence of ischemic heart disease independent of risk factors.[25]

Furthermore, individuals with genetic premature aging disorders (eg, Hutchinson-Gilford progeria syndrome) manifest typical pathological signs of vascular aging early in life, making them more susceptible to atherosclerosis.[26,27] All of these clinical observations have raised the possibility of a direct connection between senescent vascular cells and the development of atherosclerosis. In a study using atherosclerotic low-density lipoprotein receptor-deficient (Ldlr KO) mice subjected to a high-fat diet, Childs et al.[9] demonstrated the accumulation of all 3 types of senescent cells (foamy-like ECs, vascular smooth muscle cells [VSMCs], and macrophages) within plaques. Remarkably, removing p16Ink4a+ foamy macrophages using INK-ATTAC and p16-3MR mice led to significant lesion regression and

reinforced the stability of deteriorated fibrous caps in advanced lesions.[9,28] These 2 proof-of-concept mechanistic animal model studies offer compelling evidence for the likely detrimental role of senescent cells in atherosclerosis.

ECs form the innermost luminal layer of arteries that act as sensors and transducers of biologically active substances in the blood to other vascular cell layers. The first step in the initiation of atherosclerosis involves EC dysfunction. ECs are constantly exposed to hemodynamic stressors within blood vessels, such as toxic traditional atherosclerotic risk factors associated with dyslipidemia, diabetes mellitus, and shear stress. Several senescence stressors mediate endothelial cell senescence, including replicative and oxidative stress, oncogenic activation, telomere attrition, DNA damage, and mitochondrial dysfunction.[26,29] EC senescence is associated with numerous abnormalities, such as reduced nitric oxide production and increased inflammatory cytokines and adhesion molecules.[30]

EC dysfunction is followed by infiltration and retention of low-density lipoproteins and leucocytes, especially monocytes.[31] Monocytes differentiate into macrophages and release proinflammatory cytokines, reactive oxygen species, and other chemokines to promote monocyte recruitment and escalation of the inflammatory response.[32] This promotes foam cell accumulation, progression of atherosclerotic plaque, and plaque rupture, leading to ischemia in vascular territories supplied by the vessel. Senescent VSMCs are not directly involved in plaque formation but contribute to increased plaque size.[33] Moreover, senescent VSMCs also lead to increased release of proinflammatory cytokines.[34]

CORONARY ARTERY DISEASE. Age is one of the most substantial independent risk factors for coronary atherosclerosis, along with traditional cardiovascular risk factors.[1,2,4] Coronary artery disease (CAD) contributes substantially to the overall CVD burden and remains the leading cause of mortality in adults >65 years of age.[1] The prevalence of CAD rises with age, with unique differences mediated by gender and race. Throughout their lifetime, male (as compared with female) and Black (as compared with White) individuals have higher incidence and prevalence of CAD. CAD affects 30.6% of men older than 80 years as compared with 20.6% of women. Similarly, Black individuals have a higher risk of fatal CAD and a lower risk of nonfatal CAD as compared with White male and female individuals.[1] The prevalence of asymptomatic coronary atherosclerosis, as measured by coronary artery calcium score, shows a similar pattern and rises with age, affecting more than 50% of adults >75 years of age.[35] In older adults, the presentation of CAD ranges from subclinical atherosclerosis to chronic stable CAD to acute arterial occlusion caused by plaque rupture and thrombus formation leading to myocardial infarction (MI). The incidence of MI has a similar trend of increasing with age, with the highest incidence in Black men (15.9%) aged 75 to 85 years.[1] Older adults do not present with characteristic precordial pain and often present with atypical symptoms depending on age and other comorbidities. Approximately one-third of all MIs in older people are silent or unrecognized, especially in those with advanced age, such as those older than 80.[36] CAD at older age is characterized by high anatomic burden and complexity of disease manifesting as extensive multivessel disease including left main stenosis, heavy calcification, vessel tortuosity, and ostial lesions.[37]

Cardiomyocytes are terminally differentiated cells with limited regeneration and repair capacity due to the accumulation of senescent cardiac progenitor cells. Typically, cardiac progenitor cells comprise 2% of the cardiomyocytes and have myogenic potential, which may be helpful in repair following MI. However, as these cardiac progenitor cells become senescent with aging, they lose the ability to maintain homeostasis, repair, or regenerate following ischemic injury.[38-40] Therefore, patients who suffer acute myocardial ischemic events are at increased risk of morbidity and mortality. Dasatinib and quercetin (D&Q) are 2 senolytic drugs that, when used together, permit the clearance of many different senescent cells, resulting in the activation of 10% of these progenitor cells in aged mice and may thus be able to enhance the regenerative capacity of aged myocardial tissues.[38] Other studies in mouse models have suggested improved heart function and survival on clearance of senescent cells following MI.[41-45]

In particular, another senolytic drug, navitoclax, has shown promise in eliminating senescent cardiomyocytes and reducing fibrotic protein expression in aged mice.[42] Administering navitoclax into mice following MI resulted in improved myocardial remodeling, enhanced diastolic function, and an overall increase in survival rate.[42] In addition, D&Q has demonstrated efficacy in enhancing global left ventricle function and myocardial performance after MI.[44] Timely reperfusion remains the critical intervention for rescuing ischemic myocardium from MI[46]; however, restoring perfusion can sometimes induce reperfusion injury in myocardial tissue due to heightened reactive oxygen species production. A

study using a cardiac ischemia-reperfusion injury (IRI) mouse model revealed the role of senescent cardiomyocytes and interstitial cell population in reperfusion injury. Treatment with navitoclax after reperfusion attenuated reperfusion injury with subsequent improvement in left ventricular function and reduced fibrotic scar size.[41] Importantly, this study showed the potential of senolytics in mitigating various aspects of reperfusion injury. Although systemic administration of navitoclax has shown promise in the preceding mice studies, it does present risks of systemic toxicity in clinical cancer trials.[47] To reduce the toxicity, Lee et al[43] used a biodegradable poly (lactic-co-glycolic acid) nanoparticle-based local delivery of yet another senolytic drug (ABT263-PLGA) to successfully eliminate senescent cells in the IRI rat hearts and restore cardiac functions without systemic toxicity.

After acute MI treatment using stents to open coronary arteries, patients can have recurrent long-term events due to stent restenosis attributed to neo-intimal hyperplasia due to excessive VSMC proliferation and atherosclerosis. This complication has an extremely high mortality rate, yet, in recent years, the incidence has been reduced with drug-coated stents.[48] Navitoclax also showed promise in attenuating stenosis restenosis in rabbits treated with a high-cholesterol diet and may further reduce the incidence over what is seen in the current era.[49]

Despite the encouraging findings from these studies regarding the potential of senolytics in MI and IRI, several pivotal questions remain to be clarified. First, the exact cell types targeted by senolytics like navitoclax after MI and IRI remain unknown. Fibrotic tissues accumulate and extend into noninfarcted regions during left ventricular remodeling, alter cardiac structure, and impair heart function. Although senolytics showed the ability to reduce fibrosis and improve heart function, the specific cell types affected, such as fibroblasts, remain unidentified. Furthermore, the precise mechanism through which senescence hinders the recovery process after MI and IRI remains unclear. This knowledge gap poses a significant barrier to exploring alternative approaches, such as strategies using senomorphic drugs that can attenuate the damaging effects of senescent cells by inhibiting the actions of molecules secreted by senescent cells via the SASP. Second, it has also become clear that, as in other systems, cellular senescence may, in certain contexts, be nonharmful and even beneficial following MI. For example, Cui et al[50] found that premature myocardial senescence in ischemic hearts improves postinfarction heart function through the GATA4-CCN1 pathway. Therefore, it is essential to conduct further studies to thoroughly assess the impact of senescence on the outcomes of both MI and IRI before advancing to clinical trials.

STROKE. Atherosclerosis involving intracranial and extracranial vessels can cause cerebral ischemia and stroke. Prevalence of stroke increases with advancing age in both male and female individuals. Of all the strokes, 87% are ischemic, and the rest are hemorrhagic.[1] Stroke affects 6.2% to 8.9% of adults older than 65 years and remains one of the leading causes of substantial disability, morbidity, and mortality. The prevalence of silent cerebrovascular disease, as evidenced by silent infarcts, white matter hyperintensity, and cerebral microbleeds, is seen in 6% to 28%, 20% to 94%, and 38% of adults older than 80.[51] Older patients with stroke have high mortality and morbidity and worse functional recovery than younger patients.[52]

Ischemic stroke causes neuronal dysfunction and death in the ischemic region of the brain. Restoration of cerebral blood flow using tissue plasminogen activator or mechanical thrombectomy is used frequently depending on the severity of symptoms and time elapsed since onset. With the restoration of blood flow, tissue hypoxia is mitigated, although neuronal injury may be exacerbated because of IRI, which could be fatal.[53] Cellular senescence has been thought to be one of the key drivers involved in the pathogenesis of cerebral IRI.[54,55] Navitoclax has shown promise in eliminating senescent cells following cerebral IRI, reducing infarct volume, and improving neurological function in rats.[54,56] Also, chronic neuroinflammation mediated by senescent cells may exist following brain injury, especially traumatic. Senolytic therapy with intermittent D&Q was shown to be neuroprotective by reduction of SASP and subsequent attenuation of depressive symptoms and improved cognition.[57]

PERIPHERAL ARTERIAL DISEASE. Peripheral arterial disease is a manifestation of atherosclerosis affecting limb vasculature, such as the superficial femoral or popliteal artery. Clinical presentation ranges from asymptomatic to claudication pain to acute or chronic limb ischemia. The prevalence of peripheral arterial disease increases with age and ranges from 16.8% to 29.0% in adults older than 65 years.[1] Risk factors parallel to those of atherosclerosis in other vascular beds.

Navitoclax was proven to effectively deplete senescent cells, reduce plaque burden, and prevent thinning of fibrous caps in atherosclerotic Ldlr KO mice. This is accompanied by suppression of key

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factors in the SASP, inflammatory processes, and inhibiting metalloprotease activity and proteolysis. In an alternative atherosclerotic apolipoprotein E knockout (ApoE KO) mice model, senolytic vaccines against GPNMB[14] and an inhibitor of GLS1 BPTES (bis-2-[5-phenylacetamido-1,3,4-thiadiazol-2-yl] ethyl sulfide)[15] also proved to reduce atherosclerotic burden. A recent study reported that navitoclax treatment in ApoE KO mice reduced atherosclerotic lesions and absolute core size, albeit without affecting the expression of p16 or a range of SASP cytokine mRNA in the vessel wall. This raises the possibility that the effect of navitoclax may not solely rely on sonolysis.[58] Furthermore, in the same study, the authors demonstrated that genetically removing p16-positive cells globally or selectively in vessel and bone-marrow-derived cells had no significant effect on the extent of atherosclerosis. Conversely, inflammation levels were elevated. Another senolytic, D&Q, was also found to have no discernible effect on reducing senescent cell burden in established intimal atherosclerotic plaques, as well as plaque size. However, it reduces markers of osteogenesis and plaque calcification in advanced intimal plaques.[59]

These conflicting studies suggest that the specific effects of different senolytics may require further investigation, because they may not be as specific as genetically eliminating senescent cells. Even though some senolytics show promise in treating atherosclerosis, their effects may be attributed to systemic influences such as reducing circulating monocytes and serum interleukin-6 levels. Second, traditional senescence markers like p16 may have limitations in identifying and eliminating senescent cells in various atherosclerosis contexts. The new senolytics being explored for atherosclerosis may necessitate more specific markers restricted to particular lineages.

HYPERTENSION

The incidence and prevalence of hypertension increases linearly with age.[1,60] Nearly 80% of adults older than 75 years have hypertension.[1] Biological aging is accompanied by generalized endothelial dysfunction and arterial stiffening due to a loss of elastin, an increase in collagen, and calcification.[61,62] These changes are accentuated by age-induced chronic low-grade inflammation, accumulation of reactive oxygen species, and metabolic syndrome.[3,63] Arterial stiffness, especially of large vessels, causes diminished baroreflex sensitivity, leading to neurohormonal dysregulation and sympathetic activation.[64] Loss of distensibility of major central vessels, increased vascular resistance, reduced arterial reservoir capacity, and altered blood flow dynamics lead to low diastolic pressure, elevated pulse pressure, and pulse wave velocity.[3,62] This causes isolated systolic hypertension and is the predominant form of hypertension in older adults.[3] Additional contributions to age-related increase in blood pressure include a decline in renal function, increased salt sensitivity and upregulation of epithelial sodium channels, reduced nitric oxide bioavailability and increased endothelin 1, and reduced levels of aldosterone and renin.[65-68] Environmental and lifestyle factors, including low physical activity, poor diet, salt intake, and weight gain, further contribute to elevated blood pressure. Common comorbidities, such as obstructive sleep apnea, renal dysfunction, and thyroid disorders, may also contribute as secondary causes of hypertension, increasing the likelihood of treatment-resistant hypertension.

Typical senescence markers are also observed in humans and animals with hypertension. Arterial telomere uncapping (serine 139 phosphorylated histone γ-H2A.X localized to telomeres) and p53/p21-induced senescence (p53 bound to p21 gene promoter) were 2-fold higher in hypertensive patients vs aged-matched normotensive individuals.[69] Elevated blood pressure has been shown to induce p16 expression in rat kidneys, hearts, and human kidneys.[70] In addition, pro-hypertension factors also show senescence-inducing effects. For example, angiotensin II is reported to induce VSMC senescence.[71] Deoxycorticosterone acetate salt-induced elevated blood pressure induces p16 upregulation in rat kidneys and hearts.

Conversely, antihypertensive therapy (hydrochlorothiazide, hydralazine, and reserpine), losartan, and spironolactone all attenuate p16 expression.[70] These studies show a bidirectional relationship between cellular senescence and hypertension. Nonetheless, there is still limited evidence investigating the effect of the removal of senescent cells on systemic hypertension. Further research is imperative to elucidate how senescence affects hypertension at the molecular and cellular levels.

CONGESTIVE HEART FAILURE

Heart failure is a global burden and is considered an epidemic worldwide. In the United States, 2.4% of the population has heart failure, and this number is projected to increase to 3% by 2030.[35] Heart failure is a disease of aging and affects more than 6.6% of men aged 60 to 79 years and 10.6% of men older than 80 years. The prevalence in women has a similar trend, with a steeper increase as compared with men from

the age of 66 to 79 years (4.8%) to more than 80 years (13.5%).[72] Higher prevalence during later years of life is attributed to the presence of multiple traditional cardiovascular risk factors such as CAD, diabetes, and hypertension, along with age-related changes in the structure and function of the heart.[72] Based on left ventricular ejection fraction (LVEF), heart failure is categorized into 3 different groups: LVEF <40% as heart failure with reduced ejection fraction (HFrEF); LVEF >50% as heart failure with preserved ejection fraction (HFpEF); and LVEF 40% to 50% as heart failure with mid-range ejection fraction. In older adults, HFpEF predominates, and in adults older than 90 years, HFpEF is almost exclusively the cause of heart failure.[1,72,73] Older adults with HFpEF have a high multimorbidity burden, higher mortality, rehospitalization, and poor quality of life as compared with patients with HFrEF.[74]

HFpEF occurs due to cumulative effects of various cardiovascular and noncardiovascular risk factors that, in combination, cause increased myocardial stiffness and impaired relaxation with subsequent increases in filling pressures and clinical syndrome of heart failure.[73] As an individual ages, several structural changes such as reduced myocyte number, increased myocyte size, and increased nonmyocyte matrix occur.[75] These changes promote diastolic stiffness and act as a substrate for the development of HFpEF. Moreover, increasing age is characterized by changes in body composition, leading to reduced muscle mass and an increase in adiposity.[76] This increase in adiposity is accompanied by ectopic site fat deposition in viscera, such as epicardial and intermuscular fat.[77,78] This epicardial fat, along with diabetes, induces inflammation and causes inflammatory and fibrotic atrial and ventricular myopathy.[79] As a result, metabolic disorders promote the rapid development and progression of HFpEF.[73] HFpEF and diastolic dysfunction are often interchangeable; however, they are not synonymous. Myocardial stiffness increases with age and manifests as impaired relaxation identified by reduced longitudinal myocardial diastolic velocity on echocardiogram.[80]

Age-related changes, myocardial hypertrophy, and fibrosis attributed to senescent cell accumulation in cardiac structure culminating in impaired diastolic function are also seen in normal-aged mice.[81] Cardiomyocytes isolated from wild-type aged mice exhibit higher telomere-associated foci frequencies and typical senescence markers, including p16, p21, and SA-β-gal. Treatment with navitoclax significantly cleared senescent cells and reduced hypertrophy and fibrosis in aged mice.[82] Similarly, Baker et al[10] found that eliminating p16-positive senescent cells reduced cardiac fibrosis and extended life span in a p16-ATACC mouse model. At the same time, it is uncertain whether the safeguarding impact of senescence clearance on the heart arises from the removal of cardiac cells or those in other organs. Of note, navitoclax treatment has been shown to induce the elimination of presumably senescent largest cardiomyocites (CMs) with the appearance of a "new" population of small CMs previously associated with CM regeneration. Although all the evidence suggests that senescence contributes to age-related myocardial remodeling in mice, genetic removal of p16 high cells or navitoclax does not affect systolic function.[82] In other studies, D&Q significantly improved LVEF and left ventricular fractional shortening in 24-month-old mice.[17] This improved heart function was suggested to develop as the result of restoration of vascular endothelial function. These studies indicate that achieving a positive effect on various cardiac functional indices may hinge on eliminating distinct cardiac and vascular cell types.

The effect of senolytics on heart failure, including HFpEF, remains to be further studied for clarification. Current evidence revealed the complexity of various senolytics on heart function. The mechanism through which specific types of senescent cardiovascular cells contribute to age-related heart failure remains to be elucidated. Second, the most significant limitation of clinical potential is whether loss of senescent cells may be detrimental to the heart. At least until now, the removal of senescent cells has not adversely altered cardiac function in mice,[10,59,82] which might be attributed to compensatory CM regeneration.[10,82]

ARRHYTHMIAS

Atrial fibrillation (AF) is primarily a disease of aging, with prevalence rising from 10% in adults older than 70 years to >28% in those 85 years and older.[83] Aging is characterized by cardiomyocyte hypertrophy and interstitial and perivascular space fibrosis. This increased fibrosis, especially in atria, forms the substrate for AF development, maintenance, and progression.[84] In addition to aging, hypertension is the most potent risk factor among many associated with AF.[85] AF increases the risk of stroke, heart failure, and overall mortality. Rate or rhythm control and stroke prevention with systemic anticoagulation are the mainstays of management.

Researchers have demonstrated a correlation between cellular senescence and AF in older

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individuals. In patients with AF, the right /left atrial appendage had elevated senescence biomarkers p16, p53, and p21, and heightened levels of prothrombotic and inflammatory proteins like MMP9.[86,87] Moreover, blood cells from adults with AF had shorter telomeres than those in normal sinus rhythm.[88] Furthermore, p16, p21, and p53 correlate with AF severity, indicating that senescence markers increase as AF progresses from sinus rhythm to paroxysmal and persistent AF.[87]

There has been considerable interest in using senolytics to clear atrial senescent cells and improve AF outcomes. Quercetin and fisetin, used as antifibrotic agents, have shown efficacy in reducing atrial fibrosis and subsequent development of AF in rodents. Quercetin alleviates AF by inhibiting fibrosis of atrial tissues by inhibiting the transforming growth factor-β/Smads pathway via promoting miR-135b expression.[89] Similarly, post MI, fisetin improved left atrium expansion, inflammation, and fibrosis by regulating AMPK/NF-κB p65 and p38MAPK/smad3 signaling pathways.[45] Also, 2 months of D&Q treatment in old mice (18-20 months old) reduced vulnerability to arrhythmia due to age-related reversal of ventricular neural innervation, although AF was not explicitly studied.[90] Cardiac glycosides, digoxin, and digitoxin have been commonly used to manage AF for many years. At the same time, these drugs have also been shown to possess senolytic activity, which might thus contribute to their clinical efficacy.[91,92]

Although the current studies hold promise, further research is essential to establish the direct interactions between senescence and AF. In addition, more animal and preclinical studies are required to validate the efficacy and safety of senolytics, even if the drug is already approved. For instance, although current guidelines endorse the use of digoxin in patients with AF, there remain debates regarding its safety because some studies already linked digoxin with an increased relative risk of mortality.[93,94]

VALVULAR HEART DISEASES

Valvular heart disease, especially calcific aortic stenosis (AS) and mitral annular calcification occurs primarily due to advancing age. AS is one of the most common CVDs seen in the elderly population and affects 12.4% of patients older than 75 years, with 3.4% of older adults having severe AS.[95] AS occurs via complex pathophysiologic processes: endothelial injury and dysfunction, immune cell infiltration, chronic inflammation, myofibroblastic/osteoblastic differentiation, and calcification.[96] Moreover, AS pathology shares similar risk factors as vascular atherosclerosis, such as age, smoking, hyperlipidemia, obesity, diabetes, elevated creatinine, and calcium.[97-99] Untreated symptomatic AS has a high mortality rate of 50%, and surgical or percutaneous valvular replacement is the mainstay of treatment.[100] Despite the recent revolution and advancement in the surgical and percutaneous technique of valve replacement, mortality remains substantially high at 8.4%, primarily due to coexisting multiple comorbidities.[100,101] The presence of multimorbidity in patients with AS is substantial and affects the clinical course, the therapeutic approach, and eventual outcomes.

Valvular heart diseases, including aortic calcification, degeneration, and sclerosis, are generally caused by repetitive mechanical stress that leads to endothelial injury over time.[102] Mechanical stress is increased with aging and induces endothelial denudation. The focally damaged endothelium is mainly repaired by the adhesion of circulating endothelial progenitor cells to the broken site. However, normal aging reduces the regenerative capacity of endothelial progenitor cells because the release of these cells from the bone marrow decreases with aging.[103] In addition, senescent endothelial progenitor cells increase with aging, reducing the number of available regenerative cells as they cannot improve. Mechanical stress leads to the accumulation of pathologic senescent ECs, mainly on the aortic side of the valve where the blood flow is oscillatory. These senescent cells secrete SASP factors, leading to extracellular matrix remodeling and increasing leaflet stiffness, which is needed to develop sclerosis and stenosis. As supporting evidence, senescent cell marker p16 was found to be ubiquitously expressed in calcified aortic valves and correlated with the severity of tissue remodeling in patients with valvular calcification.[104] Other aging-associated factors, such as metabolic stress like high blood pressure and cholesterol, are demonstrated to induce the senescence markers, including elevated SA-β-gal activity, and increased expression of p53/p21 and p16 in aortic valvular cusps of pigs.[105]

CONCLUSIONS AND FUTURE DIRECTIONS

The current advancements in senescence-targeting strategies for cardiovascular diseases, as outlined in **Table 1**, are generating excitement, particularly evidenced by a growing body of preclinical animal studies. However, currently, there are few clinical trials investigating senolytics specifically for

TABLE 1 Animal Studies Testing the Role of Senolytics for Cardiovascular Diseases

Senolytics	Animal Model	Results	Ref. #
Coronary artery disease			
Navitoclax after IRI	IRI in young mice	Improved LV function and reduced fibrotic scar size	42
Navitoclax before MI	MI in aged mice (104 wk old)	Improved myocardial remodeling, enhanced diastolic function, and an overall increase in survival rates	43
ABT263-PLGA during IRI	IRI in young rat	Ameliorate inflammatory responses, restore cardiac function	44
D&Q after MI	MI in aged mice (20-24 mo old)	Enhanced global LV function and myocardial performance	45
Atherosclerosis			
Navitoclax after 12 wk of HFD	Ldlr KO mice with HFD	Reinforced fully deteriorated fibrous caps in highly advanced lesions	28
Navitoclax during HFD	Ldlr KO mice with HFD	Reduced fatty steaks burden in aortic arch	9
Navitoclax during HFD	ApoE KO mice with HFD	Reduced senescent VSMCs in culture and attenuated atherogenesis, did not reduce senescence markers in vivo	59
Vaccine against GPNMB	ApoE KO mice with HFD	Reduced atherosclerotic burden	14
GLS1 inhibitor BPTES during HFD	ApoE KO mice with HFD	Reduce atherosclerotic plaque formation	15
D&Q after HFD	ApoE KO mice with HFD	No effect on reducing senescent cells burden and plaque size. Reduced markers of osteogenesis and plaque calcification in advanced intimal plaques	60
Congestive heart failure			
Navitoclax	Aged mice (100 wk old)	Reduced hypertrophy and fibrosis. No effect on cardiac function, LV mass and ventricle wall rigidity	83
D&Q	Aged mice (24 mo old)	Improved LV ejection fraction and fractional shortening	17
Arrythmias			
D&Q	Aged mice (18 mo old)	Restored their characteristic day-night rhythm and reduced vulnerability to arrhythmia	92

ApoE KO = apolipoprotein E knockout; D&Q = dasatinib and the flavonoid quercetin; GLS1 BPTES = bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl) ethyl sulfide; GPNMB = glycoprotein nonmetastatic melanoma protein B; HFD = high-fat diet; IRI = ischemia-reperfusion injury; Ldlr KO = low-density lipoprotein receptor-deficient; LV = left ventricular; MI = myocardial infarction; VSMC = vascular smooth muscle cell.

cardiovascular diseases, despite many ongoing clinical trials exploring senolytics in other conditions, such as those in diabetic and chronic kidney diseases (see review by Gasek et al[7]). It is suggested that clinical trials assessing the safety of established senolytics in the context of cardiovascular systems be prioritized. Encouragingly, a recent phase 1 trial conducted in mild Alzheimer's disease demonstrated the safety, tolerability, and feasibility of the senolytic D&Q.[106]

Additional efforts are required to improve the efficacy and specificity of senolytics, which can be achieved through: 1) the identification of the specific types of senescent cells induced and accumulated during the progression of cardiovascular diseases; and 2) the discovery of additional unique biomarkers for senescent cardiac and vascular cells, enabling the design of specific targeting and delivery strategies by researchers. In addition to the relatively abundant research on systemic atherosclerosis and heart failure, the impact of senescence on other diseases, such as hypertension, arrhythmias, and valvular heart diseases, remains poorly understood. There is a crucial need to elucidate the intricate interplay between senescence and these diseases. Although this field is relatively new and much remains to be explored, targeting senescent cells holds promise for enhancing the quality of life for patients with cardiovascular diseases.

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