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Review

Immunosenescence: Driver of Cardiac Aging

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ABSTRACT: Immunity is essential for host's survival, and aging of immune system (immunosenescence) may compromise host immunity, leading to chronic, low-grade inflammation, consequently contributing to aging and age-related diseases, like cardiovascular diseases, neurodegenerative diseases. Although with a strong reserve capacity, hearts of the elderly manifest structural and functional changes, including left ventricular hypertrophy, left ventricular enlargement, interstitial fibrosis and diastolic dysfunction. The senescent immune cells undergo decline in antigen processing and presentation capacity, reduced phagocytosis, increased inflammatory phenotype (SASP), and limited specificity. Through autocrine and paracrine style, these senescent cells lead to cardiac aging and cardiac diseases, including atherosclerosis, cardiomyopathy and heart failure. Senotherapeutics development on eliminating or modulating senescent immune cells to alleviate cardiac aging and cardiovascular diseases is also covered in this review.

Key words: immune cells, cellular senescence, aging, inflammaging/chronic inflammation

Introduction

Currently, our society is undergoing a rapid aging process, with the population over 60 years doubled (2.1 billion) and that of over 80 years tripled by 2050 (426 million), according to World Health Organization (WHO; www.who.int/news-room/fact-sheets/detail/ageing-and-health). Driven by environmental and genetic factors, aging exhibit an array of hallmarks, such as cellular senescence, chronic inflammation, mitochondrial dysfunction, genomic instability, consequently manifested by age-related diseases, including cancers, neurodegenerative diseases, metabolic disorders, and cardiovascular diseases [1]. These age-related diseases contribute to morbidity and mortality of senior population [2].

Multiple studies have demonstrated that the elderly displayed an active state of systemic inflammation, featured by increased circulating levels of proinflammatory cytokines, such as TNF-α and IL-6, and localized tissue inflammation [3]. This kind of low-grade inflammation correlates with aging (inflammaging) and usually leads to tissue and organ injury [4]. Meanwhile, the older individuals also more likely show a presence of autoantibodies [5]. Naturally, age-related diseases, such as cardiovascular diseases and degenerative diseases, have clearly shown evidence of systemic or tissue inflammation [6].

During aging, virtually all cells and organs undergo progressive functional impairment and homeostasis disorder. Undoubtedly, immune system has no exception, with numerous and profound changes with aging (immunosenescence) [7]. As a surveillance system, the immune system ceaselessly monitors the presence of exogenous and endogenous threats, such as pathogen-associated molecular patterns (PAMP), damage-associated molecular patterns (DAMP), and aims to eliminate the stresses and maintain homeostasis [8]. While immunosenescence diminishes the responses against pathogen invasion, autoimmunity, as well as chronic disorders, such as degenerative and cardiovascular diseases [9].

As the leading cause of mortality in senior population, cardiovascular diseases are commonly regarded as age-

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related disorders. A growing body of evidence has linked immunosenescence with cardiac aging and cardiovascular dysfunction [10]. Indeed, cardiac aging usually comes along with persistent low-grade inflammation, commonly termed as 'cardiac inflammaging'. The causal role of inflammation for cardiovascular disease was substantiated by the CANTOS trial (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), in which the risk of cardiovascular events was largely reduced by IL-1β inhibition, particularly in participants with elevated IL-6 levels [11-13].

In the current review, we first describe the cellular and molecular changes during immunosenescence, then discuss the implications of immunoscence in diverse cardiovascular pathological processes and lastly explicate how regulation of immunosenescence processes could be captalized on therapeutic intervention of cardiovascular pathologies.

Immunosenescence

Being responsible for host defense to pathogens, supervision on cellular aberration, and homeostasis maintenance, immune system plays paramount role during organism development, growth, and health. As most immune cells are derived from hematopoietic stem cells (HSC) in bone marrow, the differentiation capability of HSC is critical for host immunity [10]. During the aging process, self-renew potential of HSC is considerably reduced, and the differentiation balance between myeloid and lymphoid lineage is also impaired, with a bias towards the myeloid lineage. This bias could be due to massive clonal expansion and persistence of antigen-selected cells for decades, which impose enormous proliferative pressure on immune cells, making the immune system highly susceptible to the aging process [14-16]. With this progressive deterioration of protective immunity, the older individuals become more vulnerable to infection, malignancies, autoimmune diseases, and many other age-related diseases, such as cardiovascular diseases [17]. This phenomenon in which the immune system gradually declines with age is immunosenescence [18]. With impaired immune surveillance, more inflammatory response and less efficient resolution of inflammation, immunosenescence is coupled with amplifying chronic inflammatory state associated with inflammaging [15]. Inflammaging, featured by chronic systemic inflammation, impairs immune function additionally, and plays a vital role in host aging process.

Adaptive immune system senescence

Lymphocytes, derived from common lymphoid progenitor cells, are more susceptible to change with aging, compared with myeloid cells. Upon aging, production of naïve T cells is reduced, and the cytotoxic $CD8^+$ T cells exhibit a drastic decrease in the elderly, while $CD4^+$ T cells are less affected [19]. However, the $CD4^+$ T cells acquire cytotoxic phenotype and more pro-inflammatory in senior population [20], releasing various pro-inflammatory cytokines, such as interleukins and tumor necrosis factor (TNF) [21]. In addition, the Treg subpopulation in $CD4^+$ T cells are not only considerably less, but also with compromised suppressive capabilities in elderly [22]. While activated $CD8^+$ T cells from aged individuals display features of cellular senescence with differentiated memory phenotype [23]. Aging T cells possess less antigen specificity, especially for $CD8^+$ cells, which worked in an antigen-independent style, instead of a typical TCR-mediated activity [24]. Currently, there are no commonly accepted biomarkers to characterize senescent T cells, although $CD81^+CD28^-$ T cells were regarded as senescent lymphocytes. Increased expression of CD57 or CD153 and reduced CD27 have been also proposed as biomarkers of senescent-like T cells [25, 26].

Also derived from common lymphoid progenitor cells, B lymphocytes, especially those expressing CD28, decrease significantly with aging [27-29]. Two age-related B cell subsets have been identified [30, 31]: Aged-associated B cells (ABC) in spleen and bone marrow, and adipose B cells (AAB) in fat associated lymphoid clusters. Another lymphoid lineage cells, natural killer (NK) cells, also increase in the peripheral blood with healthy aging [32].

Innate immune system senescence

Innate immune cells, such as neutrophils, macrophages, and dendritic cells (DC), are derived from myeloid lineage. Most innate immune cells are increased in the elderly, with prominent dysfunction, such as decline in antigen processing and presentation capacity, reduced macrophage chemotaxis and phagocytosis, increased peroxide and cytokine/chemokines production, especially pro-inflammatory cytokines [33-36], contributing to systemic and microenvironmental aging, e.g. "inflammaging". The aging-related proinflammatory state is closely associated with increased levels of proinflammatory mediators, such as IL-6, TNF-α, IL-1α, CRP, interferons (IFN-β1 and α), which were termed senescence-associated secretory phenotype (SASP). Ranging from cytokines, chemokines, growth factors and extracellular matrix (ECM) proteases, SASP is highly heterogeneous [37-40], and are widely used as readouts to assess aging/inflammaging. Notably, inflammatory SASP-producing senescent cells can cause substantial

pathological damage and lead to aging-related phenotypes [41].

Senescent macrophages are the main cells with high levels of SA-β-Gal staining and SASP production [42], and play a critical role in maintaining chronic low-grade inflammation in age-related diseases [43, 44]. These highly senescent macrophages could promote itself senescence (autocrine) and the senescence of the surrounding cells (paracrine) [45-47], thus propagating extensive inflammation [48]. Cardiac macrophages from aged mice display impaired phagocytosis and the resolution of inflammation [49, 50], probably resulting from reduced expression of TIM-4 receptor, which is responsible for phagocytosis [51]. The impaired phagocytosis also aggravates senescence due to the accumulation of senescent cells [52]. Combined with reduced production of specialized pro-resolving mediators (SPM) [53], senescent macrophages could release more SASP and induce more neutrophile infiltration [54], leading to increased generation of the SASP and exacerbated inflammation.

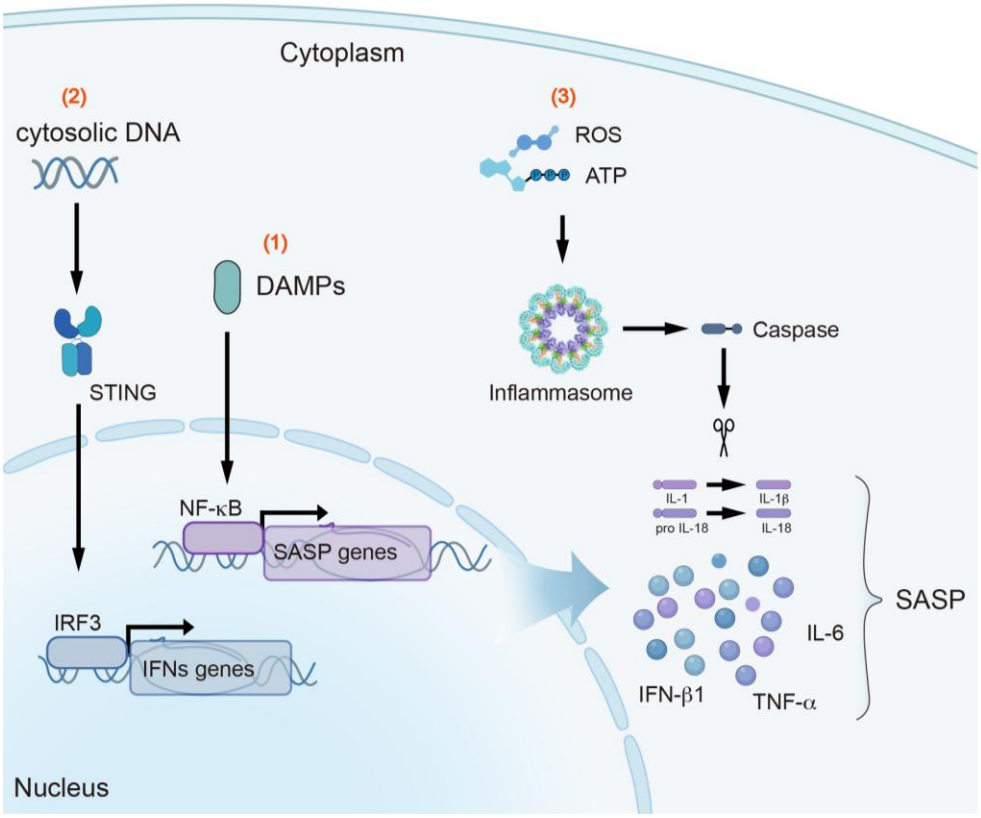

Figure 1. Regulation of SASP. As a dynamic process during aging, initiation and production of senescence-associated secretory phenotype (SASP) is fine-tuned. With aging, (1) intracellular and extracellular damage-associated molecular patterns (DAMP), such as high mobility group box 1 (HMGB1), S100 proteins, and heat shock proteins (HSP), induce SASP genes via nuclear factor-κB (NF-κB) activation. (2) Meanwhile, DNA sensor cyclic GMP–AMP synthase (cGAS) and the adaptor stimulator of interferon genes (STING) were also activated by cytosolic DNA leaked from mitochondria and nuclear, inducing SASP genes via interferon regulatory factor (IRF) 3 pathways. In addition, (3) inflammasome was also activated by ROS and ATP, leading to production of IL-1β and IL-18. These activated SASP genes contribute to production and releasing of many core SASP, such as proinflammatory tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), interferon b (IFN-β). The SASP works in a paracrine and autocrine style during aging process.

Core Inflammatory Pathways in Immunosenescence

Suppressed autophagy/mitophagy, increased ROS production, and downregulated DNases, resulted in cytosolic accumulation of nuclear and mitochondria DNA in senescent immune cells, activating chronic sterile inflammation. The leaked nuclear and mitochondria DNA stimulates DNA sensor cGAS and the adaptor protein STING, which activate NF-κB and IRF-3 pathway, leading to SASP initiation and execution (Fig. 1) [55, 56]. The activation of cGAS−STING pathway is critical for SASP production, as cGAS−STING deficiency leads to

less proinflammatory SASP production and mitigates immunosurveillance on senescence *in vivo*. Loss-of-function mutations in the STING gene (R293Q) could antagonize aging-related diseases, especially in subjects of chronic lung diseases [57], while gain-of-function mutations are associated with severe inflammation [58]. The mammalian target of rapamycin (mTOR) pathway is also vital for promoting SASP production, through stimulating NF-κB pathway, IL-1α production, and the serine/threonine kinase MK2 [59]. Meanwhile, released DAMP (nuclear and mitochondria DNA, et al) and ROS in senescent cells due to aberrant autophagy and mitophagy activate NLRP3 inflammasome, leading to production of IL-1β and IL-18, which play critical role in aging and age-related diseases, such as atherosclerosis and metabolic syndrome. For example, NLRP3 inflammasome activation plays critical roles in cardiovascular aging through controlling the release some critical SASP components [60-62]. And *Nlrp3* deficiency or inhibition alleviates cardiac inflammaging, myocardial remodeling and HF development, improves cardiac function, and atrial fibrillation shortening in aged mice by suppressing inflammation and cytokine production, such as IL-1β and IL-18 [60, 63-66]. IL-1β could lead to TGFB1/TGF-β1 pathway in LV, and induces excessive collagen I deposition, thus favoring cardiac remodeling, LV hypertrophy, interstitial fibrosis, while CASP1-mediated cell death in cardiomyocytes [65, 67-69]. Furtherly, a recent study found that somatic NAP1L1 mutation (D349E) destabilizes nucleosome formation, causing DNA leaking into the cytoplasm and activating cGAS-STING pathway, which promotes the release of inflammatory mediators and leads to cardiac hypertrophy [70]. In addition, STING pathway activation also promotes the phosphorylation of STAT1 and the expression of NALP3, causing more production of pro-inflammatory cytokines, involving in vascular calcification of multiple cardiac disorders [71].

Multiple transcriptomics and proteomics datasets based on diverse senescence models also support the strong correlation between the senescence and the overexpression of various complement components [72, 73], and our analysis based on RNA-seq also showed boosted intracellular complement activation in senescent macrophages [49]. While the pathophysiological mechanisms remain to be revealed and is interesting to explore further.

Recent studies supported that immunosenescence act as a primary driver for systemic senescence and age-related diseases. Deficiency of ERCC1, a crucial DNA repair protein, in hematopoietic cells, leads to DNA damage and cellular senescence in multiple immune cell populations, including follicular T helper cells and NK cells. The mice with ERCC1 deletion demonstrate generally accelerated aging, such as the increased expression of p16 and p21 in non-lymphoid organs [74]. Similarly, deletion of TFAM, a key regulator of induction of mtDNA replication and transcription, in T lymphocytes leads to premature $CD4^+$ T cell aging, resulting accumulation of circulating proinflammatory cytokines, which resembles the chronic inflammation typically associated with aging. This type of immunosenescence instigates various aging-related features, including cardiovascular, cognitive, metabolic, physical, and cardiovascular alterations, which together result in premature death [35].

To make the situation more complicated, immunosenescence may have beneficial effect on some age-related disorders. For example, higher levels of IFN-γ from NK or monocytes in blood plasma have protective effect against cognitive deterioration in elderly populations [75]. Natural IgM derived from aged B1 cells shows somewhat protective effects for infection, such as *Streptococcus pneumoniae* infection [76].

Cardiac Aging

Mechanisms of cardiac aging

With a strong reserve capacity, human hearts are rather resistant to aging and typically show no severe dysfunction among the healthy senior population. However, even in healthy elderly, age-related alterations could be easily detected, such as left ventricular hypertrophy, left ventricular enlargement, even interstitial fibrosis with some diastolic dysfunction. Compared with 4-month old mice, the hearts from aged mice (18-month old) showed elevated SA-β-galactosidase activity, a major marker of cell senescence, as well as cardiomyocyte hypertrophy and fibrosis [77]. Indeed, there is evident correlation between aging and increased risk of cardiovascular diseases, including heart failure with preserved ejection fraction (HFpEF), and electrical conduction system disorders, with distinct differences between male and female subjects [78].

Cardiac macrophages in cardiac aging

Heart is a high energy-demanding organ, predominantly relying on mitochondrial oxidative phosphorylation for ATP production [79], and that is maybe why mitochondria compromise nearly one-third of the volume of adult cardiomyocytes [80]. Mitochondrial function declines with aging [9, 81], and this dysfunction has been shown to be a major cause of cardiac disease [82], especially for cardiomyocytes. Aging-related accumulation of damaged mitochondria and excessive mitochondrial ROS production result in DNA damage and telomere

dysregulation, which trigger cellular senescence in cardiomyocytes independent of telomere length [81, 83, 84]. During the process, immune cells have been shown to play critical roles (Fig. 2), although the immunological senescent profiling for myocardium and vasculature is distinct (Table 1). Macrophages, especially cardiac resident macrophages, are the predominant immune cell population in the heart physiologically [85-90]. These cardiac macrophages are embryonically derived and are indispensable to heart development. Additionally, the cardiac macrophages also maintanin homeostasis, prevent fibrosis and stimulate angiogenesis in response to pressure overload [91, 92], probably by eliminating damaged mitochondria to ensure mitochondrial and cardiomyocyte fitness. Either cardiac macrophage depletion or Mertk, a phagocytic receptor, deficiency led to defective elimination of mitochondria from the myocardial tissue, impaired autophagy, accumulation of anomalous mitochondria in cardiomyocytes, metabolic alterations, activation of the inflammasome and ventricular dysfunction during aging [93].

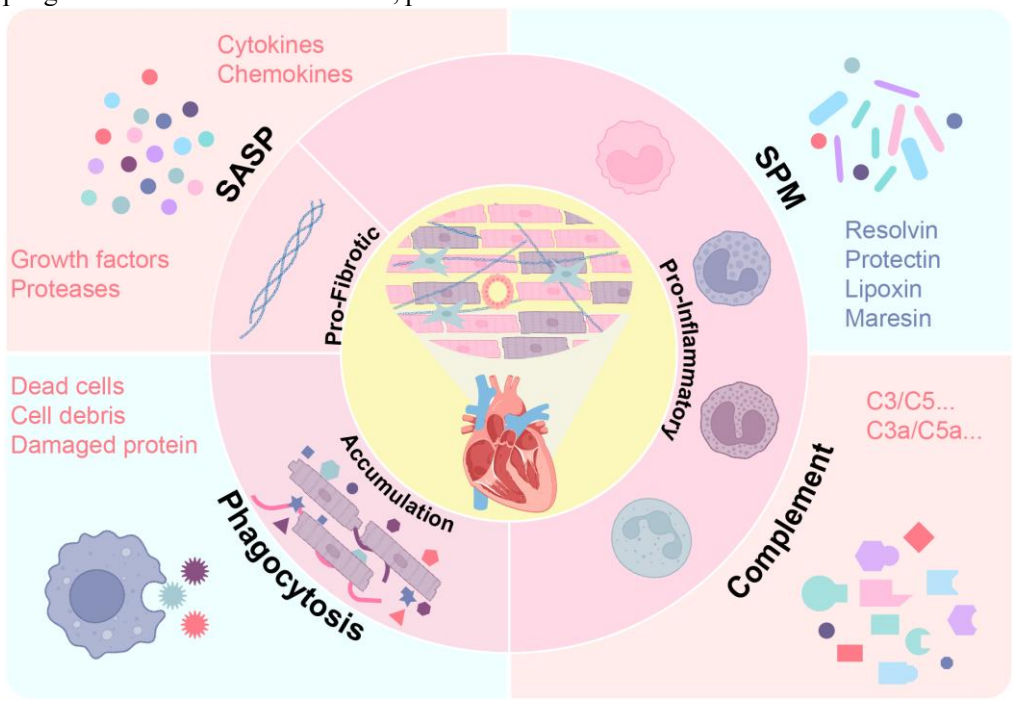

Figure 2. Effect of immunosenescence on cardiac aging. Immunosenescence leads to dysfunction of immune cells, such as increased inflammatory phenotype and SASP production, inappropriate activation of complement cascade, and reduced phagocytosis. Pro-inflammatory phenotype (mainly cytokines and chemokines) in most immune cells is manifested with chronic low-grade inflammation (inflammaging), resulted from excessively activated inflammation and impaired production of specialized pro-resolving mediators (SPM), is prominently present in aging hosts, and actively involved in aging process. Some SASP, especially matrix metalloproteinases (MMP), is pro-fibrotic, and contribute to fibrosis, leading to structural and function decline of cardiac aging. While limited phagocytosis, especially in macrophages, leads to accumulation of dead cells and cell debris, releasing multiple DAMP, which are usually both pro-inflammatory and pro-fibrotic.

Upon aging, resident macrophages are progressively replaced by recruited monocyte-derived macrophages [94]. Distinct from embryonically derived cardiac macrophages, the recruited monocytes/macrophages express CCR2, and might cause cardiovascular damage under malignant stimuli, such as ischemic injury, hypertension, and hyperlipidemia [92]. With aging, the reduced phagocytosis of these macrophages contributes to increased generation of the SASP, promoting inflammation and the development of age-related diseases [44, 95]. The SASP from senescent cardiac macrophages include various pro-inflammatory and pro-fibrotic cytokines, which impair the heart's contractile and diastolic functions, and conduce to the remodeling of left ventricle [96], ultimately leading to various forms of heart failure. Additionally, these SASP also lead to endothelial damage, vascular remodeling, and contribute to atherosclerosis [97, 98]. We also observed evident increase in pro-inflammatory and pro-fibrotic mediators, such as TGF-β in senescent cardiac macrophages, with a significant upregulation of TGF-β–TGFβR1 crosstalk between CRMs and fibroblasts, which potentially

promotes age-related cardiac fibrosis and remodeling in aged mice [49]. Additionally, senescent macrophages can contribute to other processes that are known to contribute to HFpEF, such as oxidative stress, fibrosis, and vascular stiffening [99]. In aged C57BL/6 mice (both sexes), SASP components, including TNF-α, MIP-1α, eotaxin, TNF-α, IL-1β, and IL-6, were found to be increased, and associated with altered function and structure of the heart and frailty [100], while anti-inflammatory implement has protective effect for cardiac aging.

Table 1. Senescent profiling for myocardium and vasculature.

	Myocardium	vasculature	Ref
Gender bias	Female	Male	
Inflicting cells	Cardiomyocyte, fibroblast	Endothelial cell, VSMC	[78, 171]
Immune cells	Resident cardiac macrophages	Adipose tissue, Recruiting cells: Perivascular infiltrating monocytes and macrophages, $CD4^+$ T, $CD8^+$ T, ABC	[172-176]
SASP	IL-6, IL-1β, TNF-α, CRP, IFN-γ, TGF-β, ROS	IL-1, TNF-α, IFN-γ, Adipokines, TGF-β, RNS, ROS, RSS	[177-179]
Signaling pathways	NF-κB, cGAS-STING	NF-κB, Inflammasome	
Manifestation	Cardiomyocyte hypertrophy, Cardiac fibrosis	Vascular diameter↑, Thickening of arterial wall	[5, 49, 126]

Abbreviation: VSMC, Vascular smooth muscle cell; ABC, Age-associated B cell; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reaction protein; IFN, interferon; TGF, transforming growth factor; ROS, reactive oxygen species; RNS, reactive nitrogen species; RSS, reactive sulfur species; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cell; cGAS-STING, cyclic GMP-AMP synthase - stimulator of interferon genes.

Cardiac resident macrophages are critical to maintain cardiac impulse conduction by connexin 43, which facilitate myocardial intercellular communication through gap junctions, while connexin 43 deletion in macrophages or congenital lack of macrophages leads to prolonged atrioventricular conduction and contributes to cardiomyocyte senescence [101, 102]. Channels such as Kv1.3, Kv1.5, and Kir2.1 may contribute to ion currents [103]. And amphiregulin produced by cardiac macrophages is essential to control connexin 43 phosphorylation and translocation in cardiomyocytes [104]. While the conductive microenvironment can promote the expression of Connexin 43 in $CCR2^-$ CRMs to regulate paracrine signaling for MI repair [105].

Our analysis based on RNA sequencing of cardiac macrophages from aged mice (20 months old) revealed multiple genes associated with cardiomyopathy and fibrosis increased considerably [49, 106], highlighting the crucial role of macrophages for cardiomyocyte senescence and cardiac diseases. Besides macrophages, mast cells also play essential roles for cardiomyocyte hypertrophy and senescence [107], and depletion of mast cells reduces cardiomyocyte contractility and impaires post-ischemia cardiac function [108].

Lymphocytes in cardiac aging

With aging, the heart-draining lymph node and myocardial T cells underwent clonal expansion and up-regulated pro-inflammatory transcription signature, marked by an increased interferon-g (IFN-γ) production [109]. Among them, more $CD4^+CD44^{high}CD62^{low}$ T cells (activated or effector-memory) were observed, with pronounced Treg:Tcov ratio shift in aged mice, suggesting a dynamic change of T cell populations in age-related cardiac inflammation and dysfunction [110], and adoptive transfer of T cells from old to young mice could induce mild cardiac dysfunction [110], as well as cardiac inflammation typically observed at an old age [111]. Even transfer of adult T cells to neonates also induces local inflammation and impair cardiac regenerative capacity [112]. Deletion of TFAM, a mitochondrial transcription factor responsible for mtDNA stabilization and replication, induces T cell senescence, with prominent chronic inflammation and cardiac aging [35]. How these T cells were primed during the cardiac aging process remain elusive, with a reasonably speculation that cardiomyocyte components could be served as auto-antigens and results in an autoreactive immune response [22, 110], consistent to the study that $MHCII^+$ resident macrophages could present CM components to T cells and results in priming them in the absence of injury [113].

Cardiovascular Diseases

Atherosclersosis is the major pathological processes of age-associated cardiovascular diseases and can lead to most ischemia disorders, and heart failure. Abundant studies have illustrated that atherosclerosis is primarily associated with immunosenescence and inflammation [114]. Immunosenescence and the pro-inflammatory SASP are found in the elderly and in atherosclerotic subjects [98]. Immune cells ditectly interact with endothelial cells, which expose them to senescence-induced stimuli, and play prominent roles in atherosclerosis, while fibroblasts are essential for fibrosis,

which is a hallmark in cardiovascular aging and various cardiovascular diseases. Several SASP factors, such TGF-β2 and Growth differentiation factor (GDF)15 were identified in human and murine cardiomyocytes senescence [115], probably through activating fibroblasts and its senescence. There are another two TGF-β family members, Activin and Growth differentiation factor (GDF)-11, have been found to play essential roles during cardiac aging and cardiovascular diseases [116, 117]. For example, activin is positively correlated with cardiac aging and heart failure [116], and forced expression of activin A promotes degradation of SERCA2a and lead to contractile dysfunction and heart failure [116], while deletion of type II receptors for activin improved cardiac function in aged mice [116]. Replenishing circulating GDF-11 attenuates cardiac hypertrophy in aged mice [117], highlighting the critical roles of SASP in age-related cardiac dysfunction.

Atherosclerosis

As the fundamental pathology of cardiovascular diseases, atherosclerosis has been commonly regarded as an inflammatory disorder. Atherosclerosis could be seen in youth and earlier, and manifests progressively upon aging [69]. During the process, macrophages infiltrate into subintima and phagocytose modified lipid, leading to development of foam cells, which contribute to plaque formation and vascular remodeling. During the development, hallmarks of chronic inflammation, such as IL-6, TNF-α, and multiple chemokines are strongly associated with the pathology. Circulating biomarkers of inflammation serve as prognostic indicators for the progression of atherosclerosis with its cardiovascular complications, and inflammation evidently further drives secondary events of disease progression [118]. CANTOS has shown that targeting inflammation has significant therapeutic effect on atherosclerotic diseases [11].

Growing evidence showed that cellular senescence is critical for atherosclerosis. Multiple senescence biomarkers, such as P16/INK4A, P53, P21, and increased activity of SA-β-Gal, have been found in multiple stages of atherosclerotic plaques, and relate to the severity of atherosclerosis [119-122]. In LDL receptor deficient (*Ldlr*$^{-/-}$) mice, high amount of SA-b-Gal- and p16-positive endothelial cells, vascular smooth muscle cells and macrophages have been accumulated in atherosclerotic plaques, while depletion of p16-positive cells in both p16-3MR and INK-ATTAC transgenic mice could reduce plaque formation and progression [119].

Transmission electron microscopy analysis of the early atherosclerotic lesion revealed a high accumulation of senescent macrophages in the fatty-streak lesions, while the elastic fibers remained intact [123], and these senescent foamy macrophages express high level of chemokines and adhesion molecules, such as VCAM1 and MCP1, resulting more release of SASP, such as IL-1α and TNF-α, and matrix metalloproteinases (MMP)-3 and MMP-13 [42]. These SASP components from macrophages work on endothelial cells and smooth muscle cells to accelerate the atherosclerotic process probably through a paracrine mechanism [42, 124]. The induced endothelial dysfunction, a hallmarker of vascular aging, hinders vasodilation and the repair capacity of the vasculature [125], increasing vascular stiffness and remodeling, luminal dilation[126-128].

Meanwhile, impairment of the vascular endothelium results in more macrophage diapedesis and deposition of low-density lipoprotein (LDL) particles, favoring LDL oxidization and an inflammation storm [129]. To make things worse, senescent macrophages express I ncreased arachidonate 15-lipoxygenase (ALOX15), which promotes production of SPM such as 9/13-HODE and suppresses inflammation resolution [130]. Besides pro-inflammatory cytokines, the senescent macrophages release more MMP, such as MMP9 and MMP7, degrading the matrix, and making the atherosclerotic plaques unstable, thus promoting atherosclerosis development [42, 131, 132]. Atherosclerotic mice model based on aged *Ldlr*$^{-/-}$ mice showed upregulated *Mmp*2 and *Mmp*9 expression and activity in atherosclerotic lesions, which promote macrophage infiltration [133], highlighting the critical role of SASP from macrophages for plaque instability and atherosclerosis development.

Cardiomyopathy and heart failure

As a hallmark for cardiac aging, cardiomyocyte hypertrophy and consequent cardiomyopathy, especially dilated cardiomyopathy, are very common among senior people [134]. Heart failure with preserved ejection fraction (HFpEF) is another clinical syndrome associated with aging process, and gradually rises with age, up to around 20% in adults over 75 [135]. HFpEF is more strongly associated with aging, and systemic inflammatory comorbidities relative to HF with reduced ejection fraction (HFrEF). Wealthy evidence has demonstrated the critical role of immune dysfunction and inflammaging for these disorders.

Diastolic dysfunction due to LV and arterial stiffening serve as a predominant characteristic of HFpEF, and both diastolic dysfunction and ventricular-arterial stiffening have been identified as potential results from chronic low-grade pro-inflammatory state [136], while there exist much lower circulating inflammatory cytokines, such as IL1RL1 and CRP, in HFrEF patients [137]. A featured systemic chronic inflammation characterized by elevated oxidative stress has been found

to be commonly present in elderly HFpEF and cardiomyopathy patients [138]. The oxidative stress-induced inflammation contributes to interstitial fibrosis and cardiac myocyte stiffening, which appears to be an underlying mechanism for heart failure. Diverse inflammatory signaling pathways, such as NF-κB, inflammasome, and cGAS-STING, are involved in the pathogenesis of cardiomyopathy and HFpEF. Transgenic mice with cardiomyocyte-specific constitutively active IKK2 (IKKβ, a catalytic component of NF-κB) were more susceptible to inflammatory dilated cardiomyopathy and heart failure, while dominant-negative IkB transgenic mice were resistant to the development of disease [139, 140]. Similarly, cardiac-specific overexpression of TNF-α induces dilated cardiomyopathy in even young mice [141], while NLRP3 inflammasome deficiency protected mice from age-related cardiac structural and functional alterations, including dilated cardiomyopathy [63]. In addition, inhibition of NLRP3 inflammasome activation attenuated the development of cardiac dysfunction [11, 142]. NAP1L1, a nucleosome assembly protein, has been found to be a predictive biomarker for age-related disorders, such as Alzheimer's disease [143]. These studies highlight the excessive inflammatory response for the development of cardiomyopathy and heart failure.

IL-17A, predominately secreted by activated Th17 cells, drives cardiomyocyte apoptosis following cardiac ischemia/reperfusion [144], probably through stimulating CCL2 expression in cardiomyocyte [145], while inhibiting T-cell activation could prevent pressure overload induced cardiomyocyte apoptosis and hypertrophic growth and heart failure [146]. Th17/Treg balance in heart was also critical for cardiac homeostasis, and adoptive transfer of $CD4^+CD25^+$ regulatory T (Treg) cells led improved Ang II-induced cardiac injury and fibrosis [147].

Senolytics and Senotherapeutics

Cellular senescence can be beneficial or detrimental for organism health [148]. However, senotherapeutics has been widely developed for aging and age-related disorders, including cardiac aging and age-related cardiovascular diseases. Senotherapeutics mainly include senolytic and senomorphic methods. Senolytics aim to eliminate senescent cells, whereas senomorphics modulate the properties of senescent cells without eliminating them [149]. Both senolytics (elimination of senescent cells) and senomorphics (modulation of properties of senescent cells) are largely regarded as beneficial and no long-term negative consequences have been observed. For example, eliminating $p16^{Ink4a}$ senescent cells with AP20187 attenuated the phenotype of cardiac aging [77]. ABT263, a senolytic drug, could alleviate telomere dysfunction in cardiomyocytes and reduced hypertrophy as well as fibrosis in the hearts [150]. These studies highlight the critical role of cellular senescence for cardiac aging.

Mechanisms of senotherapeutics

Immunosurveillance decline (such as phagocytosis), chronic low-grade inflammation and SASP secretion are main outcomes of immunosencescence and lead to senescent cell accumulation and proinflammatory phenotypes, greatly contributing to cardiac aging and age-related cardiovascular diseases. Therefore, mitigating inflammation, and restoring/boosting the ability of the immune system as an intrinsic senolytic system could specifically eliminate senescent cells from tissues, serving as a new therapeutic strategy to inhibit the occurrence of age-associated diseases [17]. Poly(I:C), a simulator of viral infection, has been used to stimulate innate immune response to improve senescent cell clearance. And efforts focusing on combining different approches, including anti-inflammatory drugs and immune checkpoint inhibitors, could optimally block inflammation [151].

Senomorphics is mainly targeted to modulate core attributes of senescence, particularly suppressing SASP production and secretion, interfering with the proinflammatory nature of senescent cells and potentially delaying key aspects of aging and aging-associated disease. Modulators of NF-κB signaling, including metformin, apigenin, kaempferol and BAY 11-7082, have been shown to effectively reduce SASP production [152-154]. NLRP3 inflammasome has been shown to be another potential target to suppress SASP for multiple cardiovascular diseases [45, 155]. Colchicine is an inhibitor for tubulin polymerization and the assembly of NLRP3 inflammasome, and could reduce major cardiovascular events (MACE) in patients with chronic stable coronary artery disease [156, 157] as well as those with recent myocardial infarction [158]. In addition, physical exercise could lower inflammation probably by dampening the methylation of the apoptosis-associated protein caspase gene (ASC) and the downstream NLRP3 inflammasome [159]. As an age-related epigenetic regulator, SIRT (Sirtuin) family has been shown to be crucial for macrophage polarization and differentiation. Generally, SIRT1-3 and SIRT6 inhibit the M1 and promote M2 polarization of macrophages, while SIRT4 exerts the opposite effect [160]. As Sirt1/2 activator, resveratrol has been shown to reverse immune aging and inflammation in old mice [161] to improve left ventricular diastolic function, and alleviate cardiac fibrosis [162]. Further research on Sirt-activating compounds/reagents potentially shed more light to treat age-related

cardiovascular disease through modulating macrophage senescence.

Monoclonal antibodies have been developed to against some SASP component to alleviate cardiac aging and related diseases in clinical trial [11-13]. For example, canakinumab, a monoclonal antibody against IL-1β, could significantly reduce the risk of MACE in patients with a history of myocardial infarction and elevated levels of high-sensitivity C-reactive protein (hs-CRP) [11, 163]. This CANTOS trial found that canakinumab administration led to a 25% reduction in inflammatory markers, and a 16% reduction in MACE [11].

Nonpharmacological approaches using CAR T or CAR NK cells that target senescent cells are demonstrating promise in pre-clinical and early clinical studies [164]. Meanwhile, immune checkpoint inhibitors, such as inhibitory molecules and monoclonal antibodies against PD1, PD-L1, and cytotoxic T lymphocyte-associated protein 4 (CTLA4), also represent promising strategies for enhancing immunosurveillance [165]. Such approaches depend on the recognition of specific membrane markers on senescent cells. Recent work has foretold a premising potential application of senolytic CAR T cell on attenuating senescence-associated diseases [166]. A CAR-T cell therapy has been developed to deliver modified messenger RNA (mRNA) in T cell–targeted lipid nanoparticles (LNPs) and displayed effect to reduce cardiac fibrosis after injury [167]. However, more efforts are needed to minimize the cardiovascular toxicities associated with this CAR T therapy [168].

Cell transplantation, especially bone marrow transplantation, has been widely used to reestablish immune system in cancer, immune deficiency, and autoimmune disease patients. Although stem cell transplantation aiming to regenerate cardiomyocytes seems to have made no great progress, recent cardiomyocyte-committed iPSC transplantation leaves some hope for heart failure patients [169]. Allow for the critical role of macrophages, especially cardiac macrophages, for cardiac aging, it will be interesting to further investigate whether bone marrow or even differentiated macrophages transplantation works for alleviating cardiac aging.

Limitations of senotherapeutics

Currently, application of immune-targeted seno-therapeutics for cardiac aging or cardiovascular diseases is just in its incipient stage, probably due to some concerns: As aging is long process, the change for immune cells during this process is hardly synchronous, so it is difficult to identify definite senescent markers for immune cells, even for individual population of immune cells. This heterogeneity of senescent immune cells provides huge hinderances for cell-specific senotherapeutics for cardiac aging. Meanwhile, immune cells are usually distributed ubiquitously in the body, so it is hard to implement senolytics and senomorphics tissue-specifically. Another concern is the immune compromised condition due to lack of specificity of senolytic and senomorphic methods from unintentional killing of immune cells. Additionally, inadvertent activation of immune cells by senotherapeutics, especially senomorphics, may lead to tissue or organ damage.

Knowledge Gaps and Future Directions

Until recently, most studies on senotherapeutics targeting immunosenescence were based on model animals. Some knowledge gaps have to be filled before its feasible application for alleviating cardiac aging, including (1) The heterogeneity and context-specific roles of senescent immune cells in cardiac tissue; (2) Translational challenges in applying immunosenescence data from murine models to human cardiovascular disease; (3) The current lack of validated biomarkers for immune aging in cardiovascular contexts. For example, growth differentiation factor 11 could reverses age-related cardiac hypertrophy [117], while the role of it for clinical intervention remains to be confirmed. As most immune cells are derived from hematopoietic stem cells (HSC) in bone marrow, so bone marrow transplantation or more precisely, adoptive transfer of induced pluripotent stem cell (iPSC) with commited differentiation to specific immune cells deserves to be explored for cardiac aging. Alternatively, plasmapheresis with young plasma has rejuvenating effects, probably by suppressing the levels of circulating SASP, such as pro-inflammatory and other pro-aging molecules [170]. More investigation on the effect of plasmapheresis for cardiac aging is also interesting, especially to further analyze the precise mediator associated with immunosenescence.

Conclusion

Despite of the estabilsed role of inflammation in cardiac aging, some key questions remain unsolved: which patient population will benefit from anti-inflammatory therapies and whether simultaneous targeting of several cell types (such as macrophages and T lymphocytes), intracellular pathways (such as the cGAS–STING, NF-κB and inflammasome pathways) or pro-inflammatory effector molecules (such as type I interferons, TNF and IL-1β) might constitute an effective combination strategy for postponing or halting cardiovascular ageing remains to be determined.

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Author Contributions

All authors contributed to the writing and final approval of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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