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Cellular Senescence as a Key Player in Chronic Heart Failure Pathogenesis: Unraveling Mechanisms and Therapeutic Opportunities

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Abstract

Chronic Heart Failure (CHF) is the final stage of heart disease and can be caused by a variety of factors in clinical practice. Unfortunately, CHF has a poor prognosis and a high mortality rate. Recent studies have found that aging is a significant risk factor for developing CHF and that cellular senescence plays a vital role in its development. Therefore, this article reviews the role and therapeutic progress of cellular senescence in CHF from different types of cellular senescence, mitochondrial dysfunction in senescent cells, autophagy in senescent cells, and Senescence-Associated Secretory Phenotype (SASP), to provide perspectives on the research and treatment of CHF.

Keywords: Chronic heart failure; Senescence-associated secretory phenotype; Mitochondrial dysfunction; 2'-deoxyadenosine

Introduction

Chronic Heart Failure (CHF) is a clinical condition characterized by typical symptoms swelling, and fatigue often accompanied by signs caused by structural or functional cardiac abnormalities, such as elevated jugular neck venous pressures, lung rales, and extremity edema [1]. These symptoms can worsen as the disease progresses, often accompanied by signs of structural or functional abnormalities in the heart [2]. It is estimated that over 64 million people worldwide suffer from CHF [3]. The clinical features of the disease become more typical with age, and the mortality rate is higher, resulting in increased healthcare costs and a greater socioeconomic burden [4]. Currently, CHF is mainly treated by reducing cardiac load and regulating the neuroendocrine system to relieve symptoms, but they have limited long-term efficacy [5]. Therefore, it is crucial to thoroughly investigate the pathogenesis of CHF and develop more relevant therapeutic approaches. Cells typically go through several stages, including differentiation, growth, maturation, senescence, and death. In 1961, Hayflick et al., first described cellular senescence as a progressive and irreversible state of loss of proliferative potential in human somatic cells based on the irreversible replication in human fibroblasts in culture [6].

According to the different manifestations of cellular senescence at different stages, cellular senescence is categorized into acute cellular senescence and chronic cellular senescence. Acute cellular senescence is characterized by a clear senescence triggering mechanism, short-term senescent cells, and rapid clearance of senescent cells, which is a physiological process beneficial to the human body, with a short cell cycle stagnation time; Chronic cellular senescence is a variety of sustained stress factors acting on tissues and organs, which makes it impossible for senescent cells to be efficiently eliminated, and more and more senescent cells are accumulated and induced to senesce more severely through autocrine or paracrine secretion of SASP ultimately leading to dysfunction of the heart and other organs. Therefore, there may be a certain pathophysiologic relationship between cellular senescence and CHF. This review summarizes the relationship between different types of cellular senescence and CHF, and the roles of mitochondrial dysfunction, senescent cell autophagy, and SASP in the pathogenesis of CHF, potentially opening new avenues for the targets in the treatment of CHF (Figure 1).

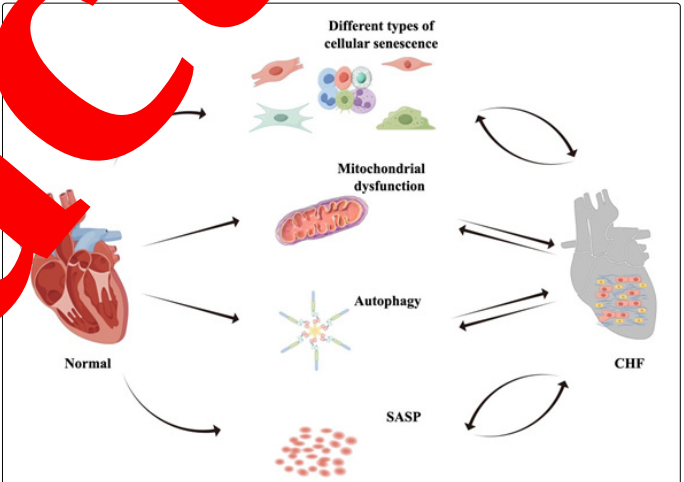

Figure 1: Cellular senescence's involvement in the mechanism of action of CHF: Different types of cellular senescence, mitochondrial dysfunction in senescent cells, autophagy in senescent cells, and Senescence-Associated Secretory Phenotype (SASP).

Literature Review

Different types of cellular senescence and CHF

The pathophysiology of CHF is closely related to the process of senescence in various cell types , including cardiomyocytes, endothelial cells, Vascular Smooth Muscle Cells (VSMC), fibroblasts/

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myofibroblasts, and immune cells. Studies have revealed that these cells share similar senescence drivers, such as oxidative stress, mitochondrial dysfunction, telomere shortening, and DNA damage [7,8]. However, there are significant differences in the regulatory mechanisms. In the following sections, we will describe the roles and mechanisms of different types of cellular senescence in the development of CHF.

Cardiomyocyte senescence and CHF

The percentage of senescent cardiomyocytes increases with age, leading to a decrease in the renewal rate of cardiomyocytes, which ultimately causes CHF. Studies have shown that Rb1 and Meis homology box 2, which act as cell cycle inhibitors, can accelerate cardiomyocyte senescence. However, inhibiting both can significantly enhance the proliferation capacity of adult rat cardiomyocytes, reduce the infarct area after myocardial infarction, and alleviate the large-scale loss of cardiomyocytes and CHF [9]. Diabetes can cause an increase in the production of Reactive Oxygen Species (ROS), which promotes cardiomyocyte senescence and can lead to CHF [10]. These findings provide valuable insights into the repair mechanism of cardiomyocyte senescence and CHF, and also suggest potential therapeutic interventions. Anderson et al., quantified *mRNA* encoding the cyclin-dependent kinase inhibitors $p^{16INK4a}$ and p^{21CIP} in cardiomyocyte populations from 3 and 20-month-old animals [11].

They found that senescent cardiomyocytes activate the senescence pathway of p^{21CIP} and $p^{16INK4a}$, leading to atypical SASP compared to normal cardiomyocytes. These SASP may cause pro-fibrotic and pro-hypertrophic effects on the heart under pathological stress, which can eventually lead to cardiac hypertrophy. Cardiac hypertrophy is characterized by several changes, including the proliferation of myofibroblasts, an increase in cardiomyocyte size, interstitial and perivascular fibrosis, and an increase in protein synthesis. If these alterations are not resolved within a short period, they progressively worsen and ultimately result in CHF [12]. Cardiac hypertrophy leading to CHF leads to the death of cardiomyocytes, hypertrophy of the remaining cardiomyocytes, and fibrosis [13]. This process worsens the damage caused by cardiomyocyte senescence, which is a key factor in the development of CHF in the elderly. Therefore, inhibiting cardiomyocyte senescence at the cardiac level is a promising treatment for CHF.

Endothelial cell senescence and CHF

Endothelial cells are the most critical barriers for the formation of the closed vascular duct system. Senescent endothelial cells have flat and enlarged structures with polyploid nuclei in contrast to normal endothelial cells [14]. Vascular endothelial cell senescence is a significant contributor to CHF. CHF is a condition where the heart can't pump enough blood to meet the body's needs. IL-17A is a cytokine produced by T lymphocytes. Zhang et al., discovered that IL-17A induces endothelial senescence through the NF-κB/p53/Rb pathway in mice of different ages through *in vitro* assays [15]. They also found that IL-17A inhibits the expression of SERCA2α and Cav1.2, which contributes to the development of CHF [16]. Clinical manifestations of CHF include increased infarct size, deterioration of cardiac function, increased myocardial fibrosis, and cardiomyocyte apoptosis.

These factors further exacerbate CHF. Therefore, it is clear that endothelial cellular senescence plays a crucial role in the initiation and progression of CHF, particularly in vascular aging [17]. Furthermore, in a mouse model of senescence, endothelial cell inflammation was induced by a high-fat or high-salt diet. As a result, the mice developed typical symptoms of CHF, including left atrial dilatation, left ventricular hypertrophy, and fibrosis. These findings suggest that there may be a connection between endothelial cell senescence and CHF [18]. In conclusion, senescent endothelial cells contribute to changes in vascular structure and function, exacerbating inflammation, thrombosis, and atherosclerosis. This can lead to cardiac circulatory dysfunction syndromes and ultimately the development of CHF.

Vascular smooth muscle cell senescence and CHF

Vascular Smooth Muscle Cell Senescence (VSMC) produces an extracellular matrix, which is responsible for arterial constriction and is involved in arterial repair and aging [19]. Compared with normal cells, senescent VSMC has a flattened and hypertrophied cell morphology, reduced proliferation level, increased P16 and P21 expression levels, and increased Senescence-Associated Beta-Galactosidase (SA-β-gal) activity [20]. These findings suggest that senescence has a significant impact on the production of VSMC in various aspects. Senescent VSMC secrete a variety of SASP mediators (e.g., IL6, IL8, MCP1), reduce the expression of anti-inflammatory molecules (e.g., Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) and Interleukin 1 Receptor Type II (IL1R2), and degrade the extracellular matrix [21].

The SASP factor secreted by senescent VSMC cells promotes chemotaxis of surrounding monocytes and macrophages, which enables further cytokine release and the expression of adhesion molecules by non-senescent VSMC and Endothelial Cell Senescence (ECs). Furthermore, the VSMC is the main source of collagen production in the fibrous cap, and senescent VSMC leads to plaque fibrous cap thinning, necrotic transformation, and calcification; senescent VSMC also drives plaque inflammation through the release of Extracellular Signal-Regulated Kinase (ERK) and interleukins [22]. Through a combination of these pathways, senescent VSMC exacerbates arterial plaque instability, and sudden rupture of vulnerable plaques can lead to acute ischemic cardiovascular events in moderately stenotic vascular occlusion, and is more likely to result in adverse clinical events such as malignant heart failure. Compared with cardiomyocytes and endothelial cells, smooth muscle cell senescence can lead to cardiovascular and cerebrovascular diseases such as atherosclerotic vulnerable plaques, but the specific mechanisms of action and effects in heart disease have been reported less, and further studies are still needed.

Fibroblast senescence and CHF

Cardiac fibroblasts play a central role in both normal cardiac physiology and cardiovascular disease [23]. Studies have shown that fibroblasts constantly alter the microenvironment by degrading and depositing extracellular matrix proteins. In elderly patients and senescent mice, senescent fibroblasts are responsible for the gradual deposition of Extracellular Matrix (ECM) in the heart, leading to cardiac fibrosis and dysfunction. Persistent fibrosis can ultimately result in CHF [23,24]. High Temperature Requirement A3 (HTRA3) is a crucial regulator of cardiac fibrosis and CHF. According to Ko et al., mild stress experiments involving Transverse Aortic Arch Constriction (TAC) showed that overloaded pressure reduces the expression of HTRA3 in cardiac fibroblasts and activates Transforming Growth Factor-Beta (TGF-β) signaling, inducing cardiac fibrosis and ultimately leading to CHF. Overexpression of HTRA3 in the heart inhibits TGF-β signaling, attenuates cardiac fibrosis, and improves cardiac dysfunction after pressure overload [25]. The findings mentioned above indicate that slowing down CHF can also be achieved by improving cardiac fibrosis.

Immune cell senescence and CHF

In human cardiac tissue, various types of immune cells regulate inflammatory responses, and cardiomyocyte senescence and contribute to CHF to varying degrees [26,27]. The innate immune system is

made up of several types of cells, including neutrophils, monocytes, macrophages, and Natural Killer (NK) cells. Senescent neutrophils produce ROS in response to mitochondrial oxidative stress, leading to telomere dysfunction and abnormal release of Neutrophil Extracellular Traps (NETs) [28]. Simultaneously, the content of 7-ketocholesterol increases the lipid deposition in blood vessels and reduces blood flow in the internal environment. This ultimately increases the risk of hyperlipidemia, hypercholesterolemia, and atherosclerosis in senescent individuals. Aging monocytes-macrophages produce a variety of pro-inflammatory factors and macrophages can release the inflammatory factors IL-4 and IL-13 by promoting Signal Transducer and Activator of Transcription 3 (STAT3) phosphorylation, leading to cardiomyocyte hypertrophy.

Persistent myocardial hypertrophy leads to maladaptive ventricular remodeling, which is thought to be the main cause of CHF27; NK cells are central players in the immunological detection of senescent cells and increase in number with age. Senescent NK cells cause decreased cytotoxicity and cytokine secretion in the immune system, increasing the risk of infection and inflammation in the body [29]. All these unfavorable factors are closely related to CHF. In addition, by studying NK cells from healthy volunteers and patients with Coronary Heart Disease (CHD), Hak et al., found that compared with healthy volunteers, NK cytotoxic activity was lower in CHD patients, and the percentages of CD3-CD56 bright regulatory NK sub-populations and CD3-CD56^{+} IFN-γ^{+} cells had a decreased trend [30]. Thus, it is clear that impaired NK cell function is also an important factor affecting coronary heart disease and even CHF. The adaptive immune system comprises T cells and B cells. Senescent CD4^{+} T [illegible]ecrete significant amounts of Interferon-gamma (IFN-γ), wh[illegible]es the heart, leading to myocardial inflammation and stre[illegible] respo[illegible]

This infiltration may also erode car[illegible]rial plaque[illegible]as been observed that senescent T cells are presen[illegible]nts with Coronary Artery Disease (CHD), which can worsen [illegible]ression of the disease and lead to a decline i[illegible]cular fu[illegible] [32]. Patients with CHF show an increas[illegible]n hyp[illegible]entiate[illegible] CD4^{+} T cells in advanced stages, indicating [illegible]orrelatio[illegible]ween T cells and CHF [33]. This su[illegible] a correlat[illegible]ween T c[illegible]and CHF. Additionally, *miR-181c* expression was foun[illegible]decrea[illegible]d and circulating B cells were reduced in C[illegible]tients, [illegible]reduced immune function [34]. However, the e[illegible]enescent B cells on CHF requires further investiga[illegible]n. The resea[illegible]sts that senescent immune cells may increase [illegible]k factors for [illegible]rough various pathways. However, further s[illegible] needed to [illegible]engthen these findings. The current research findi[illegible]e role[illegible]f different types of cellular senescence in CH[illegible]ummar[illegible]e 1.

Cell Type	Pathway	Mechanism	Clinical [illegible]sentation	References
Cardiomyocytes	p^{21CIP}/$p16^{INK4a}$	1. Senescent cardiomyocytes acti[illegible]e the s[illegible] pathway of p^{21CIP} and $p^{16INK4a}$, lead[illegible] to atypi[illegible] ultimately resulting in CHF.	The activation of myofibroblasts; An increase in cardiomyocyte size; Interstitial and perivascular fibrosis; An increase in protein synthesis	[12]
	ROS	2. ROS promotes cardiom[illegible]cyte senesce[illegible]an lead to CHF		
Endothelial cells	IL-17A	1. IL-1[illegible]es endothel[illegible]ence through the NF-κB/[illegible]pathway.	Increased infarct size;	[15-17]
	NF-κB/p53/Rb SERCA2α/Cav1.2	2. IL-17A inhibit[illegible]n of SERCA2α and Cav1.2, [illegible]ributes t[illegible]lopment of CHF.	Deterioration of cardiac function; Increased myocardial fibrosis; Cardiomyocyte apoptosis	
VS[illegible]	p16/p21/SA-β-g[illegible]	[illegible]escent VSM[illegible] increased P16 and P21 expression [illegible]and incr[illegible]ed SA-β- gal activity.	Plaque fibrous cap thinning, necrotic core formation, and calcification;	[20-22]
	SAS[illegible]	2. Senescent VSMC secrete a variety of SASP mediators, reduc[illegible] the expression of anti-inflammatory molecules [illegible]RANTES and IL1R2), and degrades the extracellular [illegible]trix.	Arterial plaque instability; Sudden rupture of vulnerable plaques;	
	E[illegible]kins	3. Release of ERK and interleukins to drive plaque inflammation.	Adverse clinical events such as malignant heart failure.	
Fibroblasts	ECM	1. The gradual deposition of ECM in the heart, leads to cardiac fibrosis and dysfunction. Persistent fibrosis can ultimately result in CHF.	Cardiac fibrosis and dysfunction.	[23-25]
	TGF-β	2. Activation of TGF-β signaling induces cardiac fibrosis, ultimately leading to CHF.	-	

Immune cells	Oxidative-stress	1. Senescent neutrophils produce ROS in response to mitochondrial oxidative stress, leading to telomere dysfunction and abnormal release of NETs, ultimately increasing the risk of hyperlipidemia, hypercholesterolemia, and atherosclerosis in aging individuals.	Hyperlipidemia, hypercholesterolemia, and atherosclerosis;	[27-34]
	STAT3	2. Senescent monocyte-macrophages activate phosphorylation of STAT3 thereby leading to cardiomyocyte hypertrophy. Persistent myocardial hypertrophy leads to chronic heart failure.	Cardiomyocyte hypertrophy Infe mation;	
	CD3-CD56^{bright}	3. CD3-CD56^{bright} Regulatory NK subpopulations and CD3-CD56+ IFN-γ+ cells are on the decline. NK cell function was impaired.	Myocardial inflam stress re	
	IFN-γ	4. Senescent CD4+ T cells secrete significant amounts of IFN-γ, which infiltrates the heart, leading to myocardial inflammation.	Decreased le ar func n.	

Table 1: Summary of the mechanisms of different types of cellular senescence in CHF.

Mitochondrial dysfunction in senescent cells and CHF

Cellular senescence is characterized by a decrease in the level cellular repair capacity, which is dependent on mitochondrial ene y conversion. Senescent cells exhibit decreased mitochondrial respira y capacity and reduced Mitochondrial Membrane Potential (MMP), which contribute to arterial aging in mice [35]. These changes lead t ased or decreased respiratory delay and accelerated changes asso ted with aging. However, the decrease in mitochondrial au y during aging typically increases the number of mitochondr lt, this increase in the number of dysfunctional itoch dria ca lly compensate for the loss of mitochondrial f n. Cigarette S (CS) can induce senescence by disrupting ndrial autop y and increasing the number of damaged mitoch ung fibroblasts and small airway epithelial cells. Additionally, CS th the movement of Parkin to mitochondr g the a iation of cytoplasmic p53, which then inter s with kin [36].

Research has demonstrate antioxid ts specific to mitochondria can ellular sen Thes ndings suggest a close relations mitochond nction and cellular senescence. idative s and increased levels of Reactive Oxygen Species ( ) in the my rdium are im ortant molecular markers of CHF yocyte s damage to mitochondrial DNA (*mtD* eased le ROS [37]. High levels of ROS and mitochon unction cause oxidation of cardiac lipids and proteins, exacerba iomyocyte damage and potentially leading to late-stage CHF. This ocyte damage, in turn, leads to further *mtDNA* damage, accele telomere shortening, and accelerated cellular senescence. Stud s have also shown that arterial collagen accumulation, elastin fracture, vessel wall thickening, and other risk factors for inducing CHF also occur in aged mice. The *RNA*-binding protein LARP7 plays a protective role in heart muscle function and can prevent the onset of CHF by regulating mitochondrial biosynthesis and energy metabolism [38]. Therefore, mitochondrial dysfunction is an important factor contributing to cellular senescence and is closely related to CHF (Figure 2).

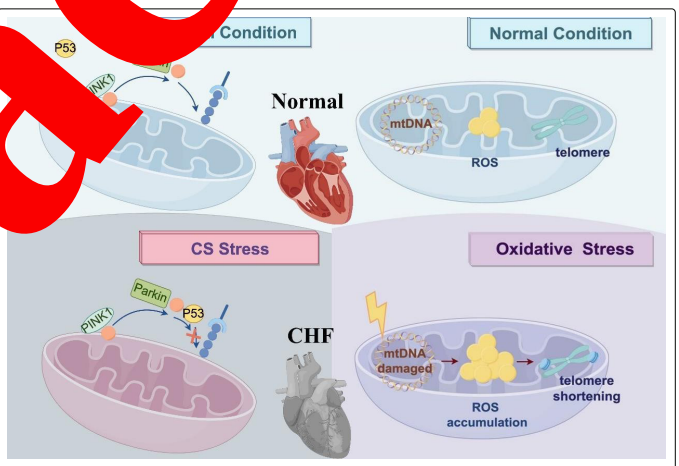

Figure 2: CS induces cellular senescence by inducing p^{53} interaction with Parkin. Cardiac oxidative stress leads to *mtDNA* damage and elevated Reactive Oxygen Species (ROS), ultimately leading to Congestive Heart Failure (CHF). Thus, mitochondrial dysfunction is an important factor contributing to cellular senescence, which is closely related to CHF.

Autophagy and CHF in senescent cells

Autophagy is the process by which cells degrade their cytoplasmic proteins and damaged organelles *via* lysosomes, regulated by autophagy-related genes [39]. Studies have shown that autophagy is closely related to aging and has a protective effect on the failing heart. Jun et al., research conducted on aged mice indicated that autophagy can prevent pathological changes caused by cardiac aging by inhibiting Phosphatidylinositol 3-Kinase (PI3K) and its downstream signaling target Protein kinase B (Akt). Additionally, it significantly reduces the expression levels of p^{16}, p^{21}, and p^{53}, as well as the senescence marker Sirtuin 1 (SIRT1) [40]. Reduced autophagy impairs the accumulation of intracellular components, including protein aggregates, and ultimately accelerates cellular senescence. Increasing autophagy can slow down ventricular remodeling, contraction defects, and CHF. Chen et al., found that activating selective autophagy in aging cardiomyocytes

by promoting the binding of *Bmi-1-RING1B* to *GATA4* and the ubiquitination of *GATA4* can prevent CHF [41]. SIRT6 deficiency leads to autophagy impairment, and senescent SIRT6 KO mice exacerbate the development of CHF [42]. Taken together, these experiments suggest that activating the autophagic capacity of senescent cells may be a potential therapeutic approach for CHF (Figure 3).

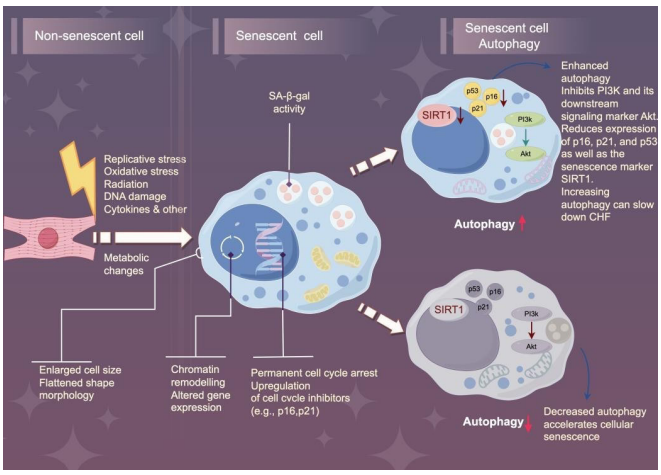

Figure 3: In senescent cells, autophagy prevents pathological changes induced by cardiac senescence by inhibiting phosphatidylinositol 3-kinase (PI3K) and its downstream signaling target protein kinase B (Akt). In addition, autophagy significantly reduced the expression levels of p^{16}, p^{21}, and p^{53}, as well as the senescence marker SIRT1. Therefore, autophagy is closely related to aging and has a protective effect on CHF.

SASP and CHF

Cellular senescence is a process that leads to the release of bioactive molecules, such as pro-inflammatory cytokines, chemokines, growth factors, and proteases, known as Senescence-Associated Secretory Phenotype (SASP) [43]. SASP-based therapeutic approaches are emerging as alternatives to traditional treatments for aging-related diseases. Several studies have shown that the metabolic state of cells and tissues greatly affects senescence and SASP, which in turn results in phenotypes associated with metabolic dysfunction, a condition closely linked to CHF. Cellular senescence is a process where cells release SASP, which triggers an inflammatory signaling loop that involves pathways such as NF-κB, TGF-β, IL-1α, and IL-6 [44]. This response to senescence affects other cells with paracrine effects, induces inflammation, promotes atherosclerosis, causes cardiac circulatory disturbances, and increases risk factors for CHF [45]. Therefore, inhibiting pro-inflammatory molecular mechanisms or addressing associated inflammatory development promptly can slow down the process of aging and age-related diseases, such as CHF.

Additionally, research has found that SASP can induce organismal weakness, and frailty is an independent risk factor for CHF in the elderly [46]. Adriamycin (Doxorubicin, DOX) is a known cause of delayed-onset severe CHF due to its cardiotoxic effects. DOX induces the cellular secretion of the acute proinflammatory factor IL-6 *via* ROS-mediated activation of p53. This results in increased expression of SASP, which is a contributing factor to CHF [47]. Alternatively, downregulation of the *GATA4* protein reduces SASP production, as noted by Chen. In a recent study, it was found that ubiquitination could promote the binding of *GATA4* to *Bmi-1-RING1B*, which could help to form autophagosomes and degrade them, preventing CHF. Additionally, the analysis of SASP using Artificial Intelligence Electrocardiography (AIECG) showed that SASP expression was closely related to telomerase activity, severity of inflammation, and CHF [48].

These results suggest a mechanism linking SASP and CHF. There is a certain level of understanding of senescence factors and CHF, and the development of targeted therapeutic agents has become possible. However, researchers still face great challenges, such as a lack of relevant *in vivo* experiments required for signaling pathway studies, an incomplete understanding of the secretion mechanism of senescence factors, and difficulty in identifying precise targets. Exploring and investigating new targets for CHF prevention and treatment based on cellular senescence is significant in ameliorating diseases related to cellular senescence and providing new directions for the treatment of CHF (Figure 4).

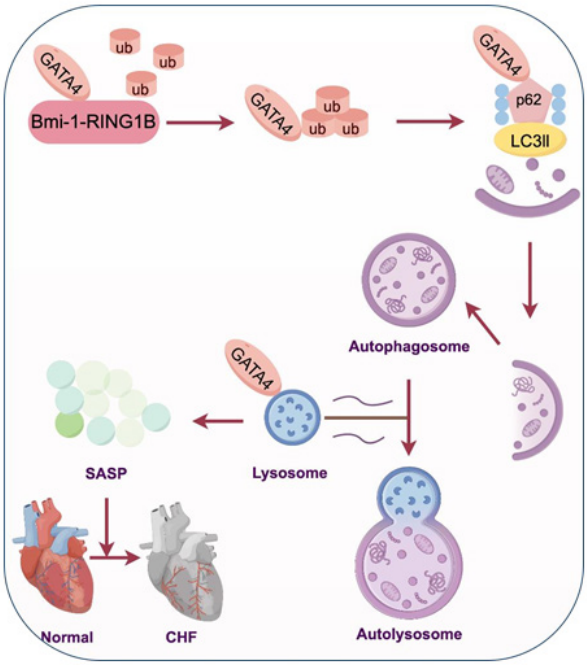

Figure 4: *GATA4* is ubiquitinated upon binding *to Bmi-1-RING1B*, then recognized by p62, translocated to autophagosomes to form autophagic lysosomes, and degraded. Downregulation of *GATA4* alleviates CHF by reducing *GATA4*-dependent hypertrophy and SASP-related molecules.

Discussion

New targets for CHF control based on cellular senescence

Lee et al., discovered that anthocyanins can inhibit oxidative stress and redox pathways during cellular senescence by treating aged rats with anthocyanin-rich mulberry extracts. A recent study found that anthocyanin intake is negatively correlated with the development of CHF [49]. Therefore, anthocyanins have significant potential for clinical application in CHF treatment, although further research is needed to investigate the correlation between the two. A Toll-like Receptor (TLR4), belonging to the immunoglobulin superfamily, is involved in several aspects of CHF. According to Ping et al., TLR4, including the promotion of the release of inflammatory mediators such as TNF-α, IL-1β, and IL-6, and the affecting of mitochondrial function as well as the endoplasmic reticulum stress pathway [50].

Therefore, studying TLR4's biological function and mechanism of action is of great significance for finding effective therapeutic approaches for CHF. Resveratrol may have an anti-cellular senescence effect by regulating the Akt/Bad/Bcl-2 pathway, which can improve the pathological changes associated with CHF [51]. Knockout of IL-

17 improved cardiac function and attenuated hypertrophic growth of the failing heart, suggesting that IL-17 is a promising therapeutic target for treating CHF. Navitoclax, a Bcl-2 family inhibitor, can eliminate senescent cells by inducing apoptosis, improving the contractile function of the left ventricle in senescent mice, and reducing cardiac fibrosis, hypertrophy, and inflammation in CHF mice [52,53]. Pharmacologic removal of senescent cells may be a potential treatment for CHF with reduced ejection fraction.

Conclusion

The following are some of the new targets that have been identified for CHF therapy based on cellular senescence. Ongoing research on the mechanism of cellular senescence in CHF will continue to explore key molecules related to cellular senescence. This will help accelerate the process of drug discovery and development in CHF, providing more therapeutic choices for CHF patients. Cellular senescence plays a crucial role in several pathophysiological processes in CHF, and CHF itself accelerates the process of cellular senescence. This interconnectedness is particularly evident in mitochondrial dysfunction, autophagy, and SASP. However, it is worth noting that normal cellular senescence has positive implications for the human body, such as contributing to wound healing, tissue repair, and regeneration when present at sites of tissue injury. Currently, the contribution of cellular senescence to the development of CHF has not been fully recognized due to inadequate research. Both cellular senescence and CHF are complex physiological processes, requiring further research to develop effective strategies for preventing and treating CHF by targeting cellular senescence.

Author contributions

Shuqing Zhao wrote the first draft of the manuscript. Yu Zh g contributed to the revision of the manuscript. Ying Z nd Xia Lu contributed to the writing and revision of the manus pt. All aut contributed to the manuscript revision, and read d approved the submitted version.

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Declaratio ting interest

The authors de e that we have no competing financial interests or personal relatio ips that could be perceived to have influenced the work reported in this paper.

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