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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

conclusion, senescent endothelial cells contribute to changes in vascular structure and function, exacerbating in ammation, thrombosis, and atherosclerosis. is can lead to cardiac circulatory dysfunction syndromes and ultimately the development of CHF.

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 ow in the internal environment. is ultimately increases the risk of hyperlipidemia, hypercholesterolemia, and atherosclerosis in senescent individuals. Aging monocytes-macrophages produce a variety of pro-in ammatory factors and macrophages can release the in ammatory 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 in ammation 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]. us, it is clear that impaired NK cell function is also an important factor a ecting coronary heart disease and even CHF. e adaptive immune system comprises T cells and B cells. Senescent CD4^{+} T cells secrete signi cant amounts of Interferon-gamma (IFN-γ), which in ltrates the heart, leading to myocardial in ammation and stress response [31].

is in ltration may also erode cardiac arterial plaque. It has been observed that senescent T cells are present in patients with Coronary Artery Disease (CHD), which can worsen the progression of the disease and lead to a decline in le ventricular function [32]. Patients with CHF show an increase in hyper-di erentiated CD4^{+} T cells in advanced stages, indicating a correlation between T cells and CHF [33]. is suggests a correlation between T cells and CHF. Additionally, *-1 1* expression was found to be decreased and circulating B cells were reduced in CHF patients, indicating reduced immune function [34]. However, the e ect of senescent B cells on CHF requires further investigation. e research suggests that senescent immune cells may increase the risk factors for CHF through various pathways. However, further studies are needed to strengthen these ndings. e current research ndings on the role of di erent types of cellular senescence in CHF are summarized in Table 1.

Cell Type	Pathway	Mechanism	Clinical presentation	References

[illegible] [illegible] [illegible] CHF

Cellular senescence is characterized by a decrease in the level of cellular repair capacity, which is dependent on mitochondrial energy conversion. Senescent cells exhibit decreased mitochondrial respiratory capacity and reduced Mitochondrial Membrane Potential (MMP), which contribute to arterial aging in mice [35]. ese changes lead to increased or decreased respiratory delay and accelerated changes associated with aging. However, the decrease in mitochondrial autophagy during aging typically increases the number of mitochondria. As a result, this

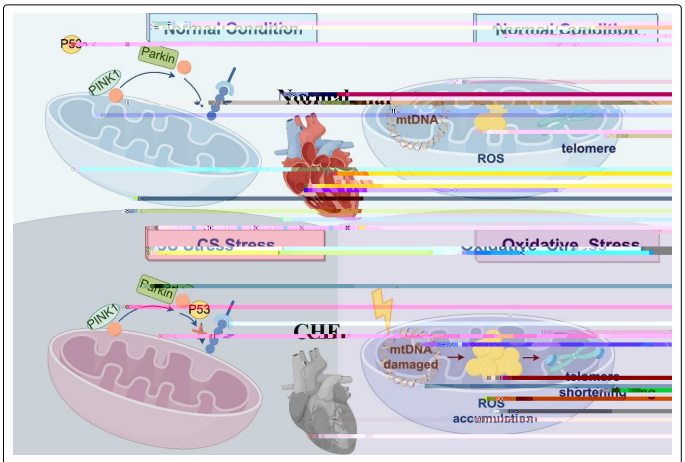

Figure 2: CS induces cellular senescence by inducing p^{53} interaction with Parkin. Cardiac oxidative stress leads to *mtDNA* damage and elevated Reactive Oxygen Species (ROS), ultimately leading to Congestive Heart Failure (CHF). Thus, mitochondrial dysfunction is an important factor contributing to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

A [illegible] CHF [illegible]

Autophagy is the process by which cells degrade their cytoplasmic proteins and damaged organelles , lysosomes, regulated by autophagy-related genes [39]. Studies have shown that autophagy is closely related to aging and has a protective e ect 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 signi cantly 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

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