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The Mechanism of Action of MSCs and iPSCs in Cardiovascular Aging-Targeting Cardiomyocytes and Endothelial Cells

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Abstract. The aging of the cardiovascular system is an important contributor to heart failure and other cardiovascular diseases, which specifically manifests in the decline of myocardial cell function, endothelial cell injury and regeneration ability. These changes not only affect the structural integrity of the heart and blood vessels, but also disrupt their normal function, ultimately leading to an imbalance in cardiovascular homeostasis and an increase in disease susceptibility. In recent years, mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) have shown great potential in cardiovascular regenerative medicine. MSCs can delay myocardial and vascular aging by secreting exosomes, regulating immunity, and improving the microenvironment. iPSCs can differentiate into cardiomyocyte-like cells and endothelial-like cells, which can be used for tissue repair and functional reconstruction. This article mainly focuses on the targeted mechanisms of MSC and iPSC on cardiomyocytes and endothelial cells, exploring their potential applications in cardiovascular aging intervention.

Keywords: Mesenchymal stem cells, Induced pluripotent stem cells, cardiovascular aging, cardiomyocytes, endothelial cells

1. Introduction

Cardiovascular aging is an important risk factor for various diseases such as heart failure, atherosclerosis and hypertension [1]. With the increase of age, cardiomyocytes gradually show changes such as mitochondrial dysfunction, enhanced oxidative stress and increased apoptosis [2].

Mesenchymal stromal cells (MSCs) are considered to be able to improve the tissue microenvironment, regulate immune response and promote wound repair due to their ability to secrete a variety of bioactive factors and extracellular vesicles [3, 4]. Induced pluripotent stem cells (iPSCs) can differentiate into cardiomyocyte-like cells (iPSC-CMs) and endothelial-like cells (iPSC-ECs), demonstrating great potential in cell replacement therapy.

Previous studies have suggested that regulating SIRT1-related signaling and inhibiting the TGF-β/Smad pathway can reduce oxidative stress, inflammatory response and fibrosis processes, and then have a certain protective effect on cell aging [5]. However, the specific role of these mechanisms in cardiomyocytes and vascular endothelial cells remains to be systematically elucidated. In addition,

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studies that combine the paracrine regulatory effects of MSCs with the regenerative potential of iPSC-derived cells are currently still relatively limited.

This article mainly reviews the mechanism of MSC and its extracellular vesicles in the regulation of cardiovascular aging, as well as the application progress of iPSC-derived cells in cardiovascular regeneration, which is of great significance for exploring potential combined intervention strategies. This review aims to summarize the related research progress, analyze the possible synergistic mechanisms, and provide reference for future research directions.

2. The relationship between stem cells and cardiovascular system

2.1. Biological characteristics and rules of action of MSCs and iPSCs

Mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) represent two different but complementary modes of action in cardiovascular regenerative medicine. MSCs are adult stem cells from a wide range of sources, which can be obtained from bone marrow, adipose tissue and umbilical cord. They possess self-renewal capacity and multilineage differentiation potential, and are generally considered to have relatively low immunogenicity and a favorable safety profile [6]. However, immune responses may still occur under certain conditions, including allogeneic transplantation, inflammatory cardiovascular microenvironments, repeated administration, or phenotypic changes during in vitro expansion and differentiation.

VEGF, HGF, IL-10 and extracellular vesicles (EVs) secreted by MSCs are thought to contribute to anti-inflammatory, antioxidant, anti-apoptotic and anti-fibrotic effects, partly through modulation of SIRT1/AMPK, Nrf2 and TGF-β/SMAD signaling pathways. These mechanisms may help support the damaged myocardial microenvironment and support angiogenesis [7].

Clinically, MSCs have been investigated for acute myocardial infarction and chronic heart failure. However, compared with bone marrow-derived mononuclear cells (BMCs), which have been more extensively studied in trials such as REPAIR-AMI, evidence supporting MSC therapy remains limited [8].

Current studies suggest MSC therapy may confer modest or variable support in left ventricular function and ventricular remodeling. However, these findings are not consistently observed across trials and follow-up periods. Moreover, several intrinsic limitations of MSCs, including restricted differentiation capacity, limited in vivo survival and engraftment, and substantial heterogeneity across cell sources and preparation protocols, may constrain their long-term efficacy and reproducibility.

In contrast, induced pluripotent stem cells (iPSCs) can differentiate into cardiomyocytes and endothelial cells, promoting cardiac repair through partial tissue regeneration rather than complete replacement. iPSCs also support vascular reconstruction and are widely used in disease modeling and drug screening for cardiovascular research [9, 10]. Nevertheless, important challenges remain, including immature cell phenotypes resembling fetal cardiomyocytes, potential tumorigenicity, inadequate electrical integration leading to arrhythmias, and high manufacturing costs, all of which limit clinical translation.

Overall, MSCs mainly regulate the cardiac microenvironment through paracrine mechanisms and may be more suitable for early therapeutic intervention, whereas iPSCs offer greater potential for structural regeneration and precision medicine. Their complementary biological properties provide a promising foundation for developing more effective and sustainable strategies for cardiovascular regeneration.

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2.2. Application of MSCs and iPSCs in cardiovascular diseases

MSCs and iPSCs have shown important application potential in the treatment of cardiovascular diseases and aging intervention, but pathways of action are significantly different [11, 12]. MSCs mainly regulate the injured microenvironment through paracrine mechanisms [13]. MSCs promote cardiac repair by secreting growth factors and EVs that enhance angiogenesis and reduce inflammation. Although widely studied in clinical trials, including DREAM-HF, MSCs have not yet become a standard therapy [14, 15]. While some analyses suggested potential signals of benefit, particularly in patients with higher levels of inflammation, the overall findings remain heterogeneous, and consistent improvements in left ventricular ejection fraction (LVEF) have not been robustly demonstrated across studies [16].

However, EV-based therapies remain in the early research stage, with efficacy influenced by cell source and preparation methods [17]. In contrast, iPSCs focus on structural repair by generating cardiomyocytes and vascular cells and are widely used for disease modeling and drug screening [18]. Early clinical studies suggest potential benefits, but challenges remain, including immature cells, poor electrical integration, and uncertain long-term safety [19].

In general, MSCs represent one of the most extensively studied stem cell populations in cardiovascular clinical research, mainly used for microenvironment regulation and functional support, while iPSCs have greater potential in achieving myocardial regeneration but are still in the exploration stage. In recent years, the collaborative application of MSCs and iPSCs has gradually become a research hotspot: MSCs may help create a more favorable microenvironment that could support the survival and integration of iPSC-derived cells, while iPSCs may provide structural repair to form a more promising comprehensive regeneration strategy.

2.3. Prospects and challenges of MSC and iPSC applications

Mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) have important prospects in cardiovascular regeneration, but their clinical transformation is still limited by a series of specific technical and application problems.

MSCs have a wide range of sources (bone marrow, fat, and umbilical cord) and relatively low immunogenicity, which have been used in clinical studies of heart failure and myocardial infarction [20]. However, the instability of the therapeutic effect is mainly due to the functional heterogeneity caused by donor differences (age, underlying diseases) and tissue sources. In addition, the function of cells is prone to decline during in vitro expansion (such as the decline of paracrine ability and the increase of aging markers), which affects the therapeutic effect [21, 22]. Administration methods (such as coronary artery injection and intramyocardial injection) also affect the cell retention rate, and the cell survival rate is usually low [23]. Therefore, the current focus is to establish standardized preparation processes (such as GMP-conditioned culture), screen high-functional cell populations, and develop MSC-derived EVs to replace the cells themselves so as to support the stability and safety [24, 25].

In contrast, iPSCs can theoretically provide an unlimited source of cardiomyocytes for tissue replacement, but major challenges remain. iPSC-derived cardiomyocytes are immature, integrate poorly with host myocardium, and may increase arrhythmia and tumor risks [26]. Current studies are improving cell maturity through long-term culture, electrical stimulation, 3D myocardial tissue engineering and other methods [27], while gene editing or immune regulation strategies are used to reduce immune rejection [28]. On the other hand, the long preparation cycle and high cost of iPSC also limit its large-scale clinical application.

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Future strategies can combine MSCs and iPSCs to improve therapeutic outcomes. Meanwhile, biomaterials such as hydrogels, scaffolds, and 3D-printed cardiac patches can enhance cell retention, survival, integration, and overall regenerative efficacy after transplantation [29].

In general, the main challenge of MSCs is stability and standardization, while the core issue of iPSCs is maturity and safety. In the future, only by optimizing the quality control of cells, improving the functional integration ability and combining with engineering methods, stem cell therapy is expected to realize the transformation from experimental research to large-scale clinical application.

3. Intervention mechanism of stem cells on cardiomyocytes

3.1. Aging mechanism of cardiomyocytes

The regeneration ability of adult hearts is limited, so the damaged myocardium is mainly replaced by fibrosis scars after myocardial infarction. Although a scar can help maintain structural integrity, it can increase myocardial stiffness, weaken diastolic filling and systolic function, induce ventricular remodeling and eventually progress to heart failure [30, 31]. At the same time, coronary artery perfusion damage is not only the cause of myocardial dysfunction, but also further aggravates ischemia in the process of remodeling, forming a vicious circle [32].

With aging and continuous pathological stress, the myocardium can undergo fetal-like metabolic reprogramming, which is manifested as decreased fatty acid oxidation and relatively increased glucose uptake and glycolysis. This change may have a compensatory significance in the early stage, but in the long run, the decrease of metabolic flexibility, the uncoupling of glucose oxidation and glycolysis, and the impairment of mitochondrial oxidation capacity will further aggravate the myocardial energy deficiency [33]. In addition, endothelial cells, fibroblasts and immune cells jointly create a harmful microenvironment through inflammatory mediators, extracellular vesicles and SASP, and form amplified pathological crosstalk with cardiomyocytes.

At the molecular level, increased mechanical load and ROS accumulation can cause DNA damage and telomere shortening, activate p53/p21 and p16/Rb pathways, and lead to cell cycle arrest and hypertrophy. Mitochondrial dysfunction and impaired autophagy further aggravate ATP deficiency and oxidative stress, while decreased SERCA2a and abnormal RyR2 calcium leakage lead to calcium homeostasis imbalance, affecting diastolic function and increasing the risk of arrhythmia [34]. Meanwhile, NAD^+ depletion, weakened SIRT1/AMPK signaling and abnormal activation of mTOR aggravate metabolic imbalance [35]. NF-κB and NLRP3-mediated chronic inflammation and TGF-β/SMAD-driven fibrosis may jointly promote the deterioration of myocardial structure and function [36, 37].

In general, these mechanisms are continuously amplified through a positive feedback loop of stress-metabolic imbalance-inflammation-intercellular crosstalk, which eventually manifests as impaired diastolic function, decreased systolic reserve and unstable electrical conduction, which constitute an important basis for cardiac aging and heart failure (Figure 1).

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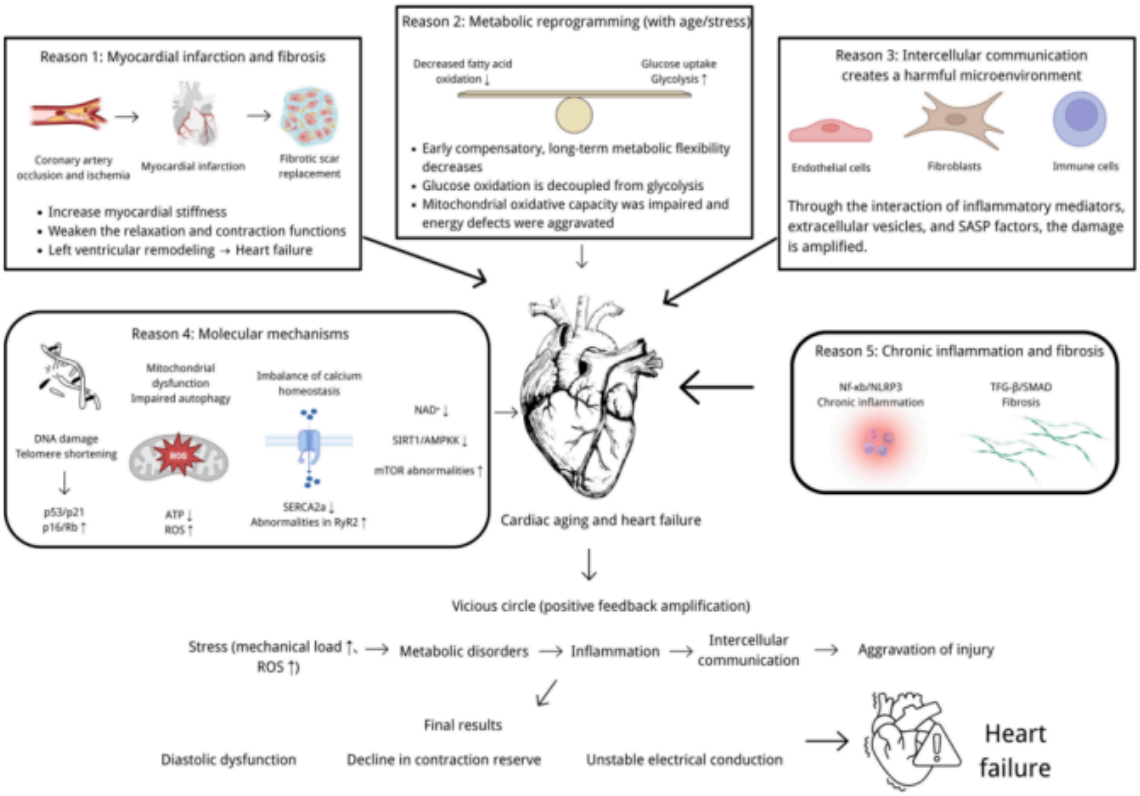


Figure 1. Integrated mechanisms of cardiomyocyte aging and metabolic remodeling

3.2. Regulation and environmental support of cardiomyocytes by MSCs and iPSCs

MSCs are thought to regulate cardiomyocytes and modulate the damaged microenvironment through paracrine mechanisms. They secrete VEGF, HGF, IGF-1, IL-10 and TSG-6, and release EVs rich in miR-21, miR-126, miR-29b and miR-210. MSC-derived factors have been reported to exert anti-inflammatory, antioxidant and anti-apoptotic effects, potentially through modulation of pathways, such as SIRT1/AMPK and Nrf2 pathways, which may contribute to attenuation of fibrotic remodeling and support angiogenesis and perfusion recovery [38].

At the cellular level, experimental studies have shown that MSC paracrine factors may indirectly improve Ca^{2+} homeostasis in injured cardiomyocytes by alleviating oxidative stress and energy deficit. At the same time, MSC-derived exosomes are also thought to be able to affect mitochondrial function and energy metabolism, enhance ATP production and support metabolic activity. In addition to paracrine effects, in vitro studies have found that MSCs can transport mitochondria to damaged cells through cell fusion or tunneling nanotubes, and this process may improve the energy metabolism and survival ability of recipient cells [39, 40]. But the actual role of this process in vivo remains unclear. Therefore, MSCs are more suitable to be regarded as cells that regulate the microenvironment and indirectly promote myocardial repair by reducing inflammation, oxidative stress, and fibrosis [41].

In contrast, induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) have the advantage of providing new contractile cardiomyocytes. Animal studies showed that transplanted iPSC-CMs could form new tissue in the injured myocardium and establish a certain electromechanical connection with the host. However, insufficient cell maturity, uneven coupling and arrhythmia are still major challenges [42, 43]. Induced pluripotent stem cell-derived endothelial

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cells (iPSC-ECs) have the ability to form vascular structures and produce NO, and may participate in microvascular reconstruction, but their long-term stability still needs to be verified [44].

MSCs and iPSC-derived cells are complementary: MSCs improve the cardiac microenvironment, while iPSC-derived cells provide structural repair. Preclinical studies suggest combined therapy enhances angiogenesis, reduces scar formation, and improves cell survival, although the underlying mechanisms and clinical efficacy require further investigation [45].

4. Regulation of endothelial cells by stem cells

4.1. Aging mechanism and manifestations of endothelial cells

Endothelial cells maintain vascular homeostasis by regulating vasodilation, anti-inflammation, anti-thrombosis and maintaining barrier function, while aging and pathological stress can lead to endothelial dysfunction, which further promotes atherosclerosis and cardiovascular diseases [46]. It is also closely related to diabetes and hypertension [47].

Endothelial cell aging also affects myocardial function through paracrine mechanisms. The normal coronary microvascular endothelium can release NO and NRG1, which directly regulate the survival, relaxation and stress response of cardiomyocytes. At the same time, endothelium-derived PDGF-B indirectly supports myocardial tissue homeostasis mainly by recruiting pericytes and maintaining microvascular stability [48]. However, in the process of aging or remodeling, its secretion profile shifts to pro-inflammatory factors such as ET-1, TGF-β and IL-6, and releases exosomes with potentially deleterious biological effects [49, 50], which may enhance inflammatory signaling, impair autophagy and promote cardiomyocyte injury, forming a significant cardio-endothelial crosstalk (Figure 2).

At the molecular level, oxidative stress and mitochondrial dysfunction lead to ROS accumulation, causing DNA damage and activation of p53/p21 and p16INK4a pathways, leading to cell cycle arrest. Nf-κb-mediated SASP continuously releases inflammatory factors and adhesion molecules, which aggravates vascular inflammation [51]. At the same time, the decrease of eNOS activity leads to the decrease of NO, which weakens the vasodilation and antithrombotic function, while the increase of ET-1 may further promote vasoconstriction [52, 53]. In addition, the weakened LKB1/AMPK and SIRT1 signaling aggravates metabolic imbalance and reduces antioxidant capacity [54].

In terms of functional performance, aged endothelial cells showed impaired vasodilation, decreased barrier function, increased inflammation and coagulation activity, accompanied by cell hypertrophy and reduced regeneration capacity. These changes together are associated with vascular stiffness, increased blood pressure, and impaired angiogenesis, which further aggravate myocardial decline through persistent inflammation and metabolic abnormalities.

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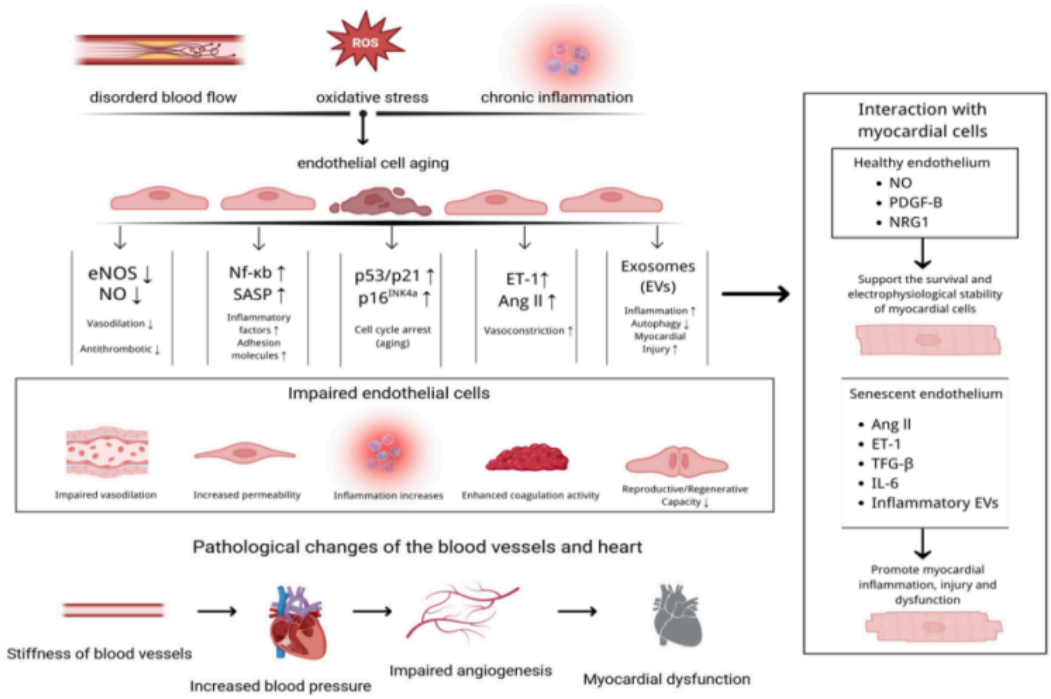


Figure 2. Mechanisms of endothelial cell aging and dysfunction

4.2. Regulation and activation of endothelial progenitor cells by stem cells

Endothelial progenitor cells (EPCs) are important cell sources for maintaining vascular endothelial integrity and promoting angiogenesis in ischemic tissues [55]. With aging and the progression of cardiovascular disease, the number and function of circulating EPCs gradually decline, which is manifested as weakened recruitment, migration, proliferation and tube formation, thereby weakening the ability of endothelial repair and angiogenesis [56]. Therefore, increasing the number of EPCs or restoring their functions is regarded as an important strategy for delaying vascular aging and promoting the repair of ischemic tissues.

Mesenchymal stromal cells (MSCs) regulate EPC function mainly through paracrine and extracellular vesicles. VEGF and HGF secreted by MSCs can promote the recruitment, migration and homing of EPCs [57]. miR-126 in MSC-derived extracellular vesicles can enhance the survival, migration and angiogenesis of EPCs through PI3K/Akt/eNOS signaling [58]. At the same time, MSC can improve the microenvironment of EPC by reducing oxidative stress and inflammatory response, thereby partially restoring its repair function.

In contrast, iPSCs support vascular repair by generating endothelial or ECFC-like cells and releasing angiogenic factors [59, 60]. MSCs mainly activate endogenous EPCs, whereas iPSCs provide new endothelial cells. Their complementary effects may promote vascular regeneration and delay vascular aging, although clinical benefits require further validation.

5. Limitations

Stem cell therapies show great promise, but most remain in early-stage research, with efficacy and safety still under evaluation [61]. Current stem cell therapies face several important limitations. Different stem cell types have distinct mechanisms and therapeutic effects. Mesenchymal stem cells (MSCs) mainly act through paracrine signaling and have limited ability to regenerate myocardium

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[62]. iPSC-derived cardiomyocytes can replace damaged tissue, but remain immature and may carry a risk of tumor formation [63]. Bone marrow-derived cells have shown modest functional benefits but limited evidence of true cardiac regeneration. In addition, technical challenges such as cell heterogeneity, lack of standardized manufacturing and differentiation protocols, poor reproducibility, and limited cell survival reduce treatment consistency and long-term efficacy. Future research should improve cell maturation, delivery methods, and quality control, while extracellular vesicle (EV)-based cell-free therapies may provide a safer and more effective alternative.

6. Ethical concern

Stem cell research must undergo strict ethical review and safety evaluation before moving from laboratory studies to clinical applications [64]. Participants should provide informed consent and clearly understand the purpose, benefits, and potential risks of the research. It is also important to distinguish experimental therapies from established clinical treatments.

In addition, researchers should respect cultural and religious differences and comply with international ethical guidelines and clinical regulations. These measures help ensure patient safety, improve research credibility, and support the safe and responsible translation of stem cell therapies into clinical practice.

7. Conclusion

This article focuses on the mechanism of cardiomyocytes and endothelial cells in the aging of the cardiovascular system, and explores the potential roles of MSCs and iPSCs in delaying cardiovascular aging. Current evidence suggests that MSCs secrete exosomes and anti-inflammatory factors through paracrine pathways. This pathway can improve the metabolic status of aging cardiomyocytes, slow down oxidative stress, and restore mitochondrial function. Meanwhile, it has a positive effect on promoting NO production and alleviating endothelial dysfunction in endothelial cells. iPSCs have high differentiation potential, which can induce the generation of cardiomyocyte-like cells and endothelial-like cells. iPSC also can participate in tissue repair and functional reconstruction. Preclinical evidence suggests that MSCs and iPSC-derived cells may exert complementary effects by combining microenvironmental modulation with structural regeneration. However, direct evidence that they synergistically regulate specific aging pathways, such as p21 signaling, remains limited.

Although this article shows some of the mechanisms of stem cells in cardiovascular aging, there are still some limitations. For example, the differences between in vitro experiments and in vivo microenvironments, and further optimization of stem cell differentiation efficiency and safety issues are needed. Future research can focus on the synergistic mechanism between MSCs and iPSCs, providing a theoretical basis and technical support for constructing precise and effective stem cell therapy plans.

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