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Review

Application and challenges of stem cells in cardiovascular aging

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ABSTRACT

With the rapid development of society and the economy, population aging has become a common challenge faced by many countries in the world today. Structural and functional changes in the cardiovascular system can occur with age, increasing the incidence and severity of cardiovascular diseases in older adults. Due to the limited regenerative capacity of myocardial cells, myocardial infarction and its resulting heart failure and congenital heart disease have become the number one killer of human health. At present, the treatment of cardiovascular diseases includes drug therapy and nondrug therapy. Nondrug therapy mainly includes minimally invasive interventional therapy, surgical diagnosis and treatment, and cell therapy. Long-term drug treatment may cause headache due to vasodilation, lower blood pressure, digestive system dysfunction and other side effects. Surgical treatment is traumatic, difficult to treat, and expensive. In recent years, stem cell therapy has exhibited broad application prospects in basic and clinical research on cardiovascular disease because of its plasticity, self-renewal and multidirectional differentiation potential. Therefore, this paper looks at stem cell therapy for diseases, reviews recent advances in the mechanism and clinical transformation of cardiovascular aging and related diseases in China, and briefly discusses the development trend and future prospects of cardiovascular aging research.

Contents

Abbreviations: ADSCs, Adipose-derived mesenchymal stem cells; ASCs, Adult stem cells; BM, Bone marrow; BMSCs, Bone marrow mesenchymal stem cells; BM-MSC therapy, Bone marrow-mesenchymal stem cell therapy; CSCs, cardiac stem cells; CVD, cardiovascular disease; DNMT1, DNA methyltransferase 1; ESCs, Embryonic stem cells; hiPSC, human induced pluripotent stem cell; iPSCs, induced pluripotent stem cells; MI, myocardial infarction; MSCs, mesenchymal stem cells; NKx2-5, NK2 homeobox 5; Oct, octamer binding transcription factor; SCs, Stem cells; Sox, sex determining region Y box protein; UC, Umbilical cord; UCMSCs, Umbilical cord mesenchymal stem cells.

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1. Introduction

Cardiovascular aging is the most important factor leading to cardiovascular diseases, and the incidence and severity of cardiovascular events tend to increase with age. According to the China Cardiovascular Health and Disease Report 2021, cardiovascular diseases are the leading cause of death for Chinese residents [1]. In 2019, rural and urban center cardiovascular disease (CVD) accounted for 46.74 % and 44.26 % of the causes of death, respectively. China is facing the double pressure of population aging and the continued prevalence of metabolic risk factors, and the number of CVDs will continue to increase [2]. This not only increases the burden on patients and their families but also poses a huge challenge to the health care system. Therefore, it is important to find effective treatments for cardiovascular disease. At present, treatment schemes including drug therapy and surgical treatment are typical strategies for treating these diseases [3]. However, the use of some drugs may lead to side effects and adverse reactions. In addition, surgery can cause recurrence of some complications and diseases [4], so the prevalence of cardiovascular diseases is gradually increasing every year. In recent years, stem cell therapy as a treatment for cardiovascular disease has developed rapidly. Many animal experiments and clinical studies have shown that stem cells are safe and effective in treating cardiovascular diseases [5], which brings new hope to patients with cardiovascular disease and their families. The ideal stem cells must be able to successfully differentiate into cardiomyocytes, vascular endothelial cells and smooth muscle cells or to exert effects through paracrine action, they must be easily extracted and separated, and the transplantation must be safe and effective. This review summarizes and discusses the application of different types of stem cells in cardiovascular diseases and future challenges and examines the development trend and prospects of cardiovascular aging research on this basis. To further elucidate the molecular and cellular regulatory network of cardiovascular aging and related diseases (Fig. 1), we searched for coping strategies for cardiovascular aging and related diseases to provide a reference for the application of stem cells in the treatment of cardiovascular diseases and to promote the in-depth development and clinical transformation of cardiovascular aging and related disease research.

2. Materials and methods

2.1. Data sources

The authors used “cardiovascular disease, embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, retrospective study, cohort study, case study, clinical trial, meta-analysis” as the search term to search the China National Knowledge Network (CNKI), Wanfang Medical Database, PubMed, WHO, USFDA, and Clinical Trials.Gov to retrieve related reviews and studies published in the past 10 years.

2.2. Inclusion criteria

The inclusion criteria were as follows: ① articles on the classification of stem cells and the mechanism of action in the treatment of cardiovascular diseases; ② related experiments and clinical studies on the application of exosomes from different stem cells in the treatment of cardiovascular diseases; and ③ documents that strictly explain facts and ideas.

2.3. Exclusion criteria

The exclusion criteria were: ① repeated studies ② stale paper.

2.4. Data extraction and literature quality evaluation

The titles and abstracts were read to screen and exclude duplicate reports and Chinese and English literature irrelevant to the inclusion criteria. The full texts were checked, 75 articles were retained, and each dedication, introduction and summary were studied.

3. Overview of stem cells

Stem cells (SCs) are cells with self-renewal and multidirectional differentiation potential. Under certain conditions, they have the functional potential of regenerating into various cells, tissues, organs and human bodies [6](Fig. 2). According to their stage of development, they can be divided into embryonic stem cells and

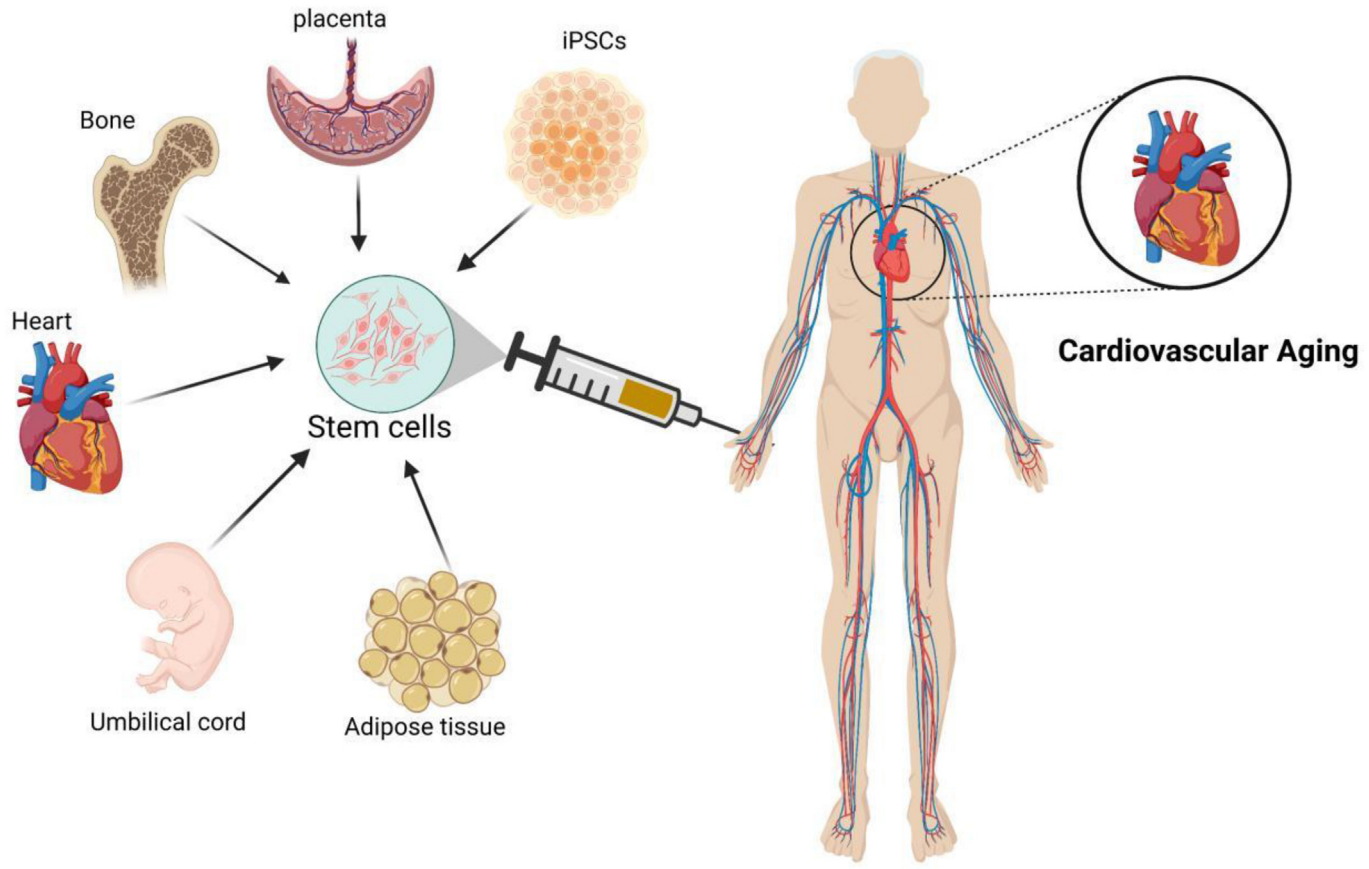

Fig. 1. Different types of stem cells in cardiovascular aging.

adult stem cells (Fig. 2). Embryonic stem cells (ESCs) are undifferentiated cells with high differentiation potential in the cell mass of the blastocyst that can differentiate into any type of cell, tissue, and organ needed in the body and finally develop into complete individuals, which make them totipotent stem cells. Adult stem cells (ASCs) can be separated from bone marrow, adipose tissue, placental cord blood and other human tissues and organs. ASCs have lower differentiation potential than ESCs and can only differentiate into several or one kind of cell, including pluripotent stem cells and multipotent stem cells [7](Fig. 2). Stem cell therapy involves transplanting healthy stem cells into patients to repair diseased cells or rebuild normal cells and tissues. In recent years, stem cell therapy for cardiovascular disease has become a promising frontier of scientific research. For the effective treatment of CVD, it is very important to improve the treatment efficiency based on SCs. At present, stem cells used to treat cardiovascular diseases mainly include induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), cardiac stem cells (CSCs) and embryonic stem cells (ESCs) (Fig. 2).

4. Application of stem cells in cardiovascular disease

Cardiovascular disease is a serious threat to human life and health and not only has a high mortality rate in the acute phase but also has a poor long-term prognosis. At the same time, any serious loss of myocardial cells (such as myocardial injury) is irreversible, which leads to the decline in cardiac function and the progressive heart failure worsens. Cardiovascular diseases cause a series of cellular and molecular disorders, leading to apoptosis, necrosis and hypertrophy of myocardial cells; damage to new blood vessels; myocardial fibrosis and inflammatory reactions; decreased contractility; and subsequent pathological remodeling. Therefore, regeneration and repair therapy play a crucial role in cardiovascular diseases. Scientists are eager to use stem cells to replace damaged heart cells and fundamentally repair the function of the heart, that is, to introduce new cells into the heart, induce cells to proliferate in situ, or allow cells to settle in the heart so that they can be converted into muscle cells with myocardial function. Stem cells provide the body with new cells as it grows and replace damaged or lost specialized cells. They have the same properties (for example; They can divide repeatedly to produce new cells, and after division, they can transform into other types of cells that make up the body and show immunosuppressive abilities). Stem cells are undifferentiated or partially differentiated in nature. But they have the ability to produce undifferentiated cells. They can multiply and produce more and more stem cells. Scientists are eager to use stem cells to replace damaged heart cells and fundamentally repair the heart's function, introduce new cells into the heart, induce cell in-situ proliferation, or allow cells to settle in the heart so that they can be converted into myocardial muscle cells. In recent years, SCs have attracted extensive attention in the field of cardiovascular disease repair and regeneration. After years of exploration, scientists have made remarkable achievements in the treatment of cardiovascular diseases with stem cells. At present, stem cell therapy is considered a promising method to treat cardiovascular diseases. A large number of reports have shown that a variety of stem cells, including embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells and cardiac stem cells, can be used to treat coronary artery disease, myocardial infarction and heart failure through intravenous or intramyocardial injection; promote the

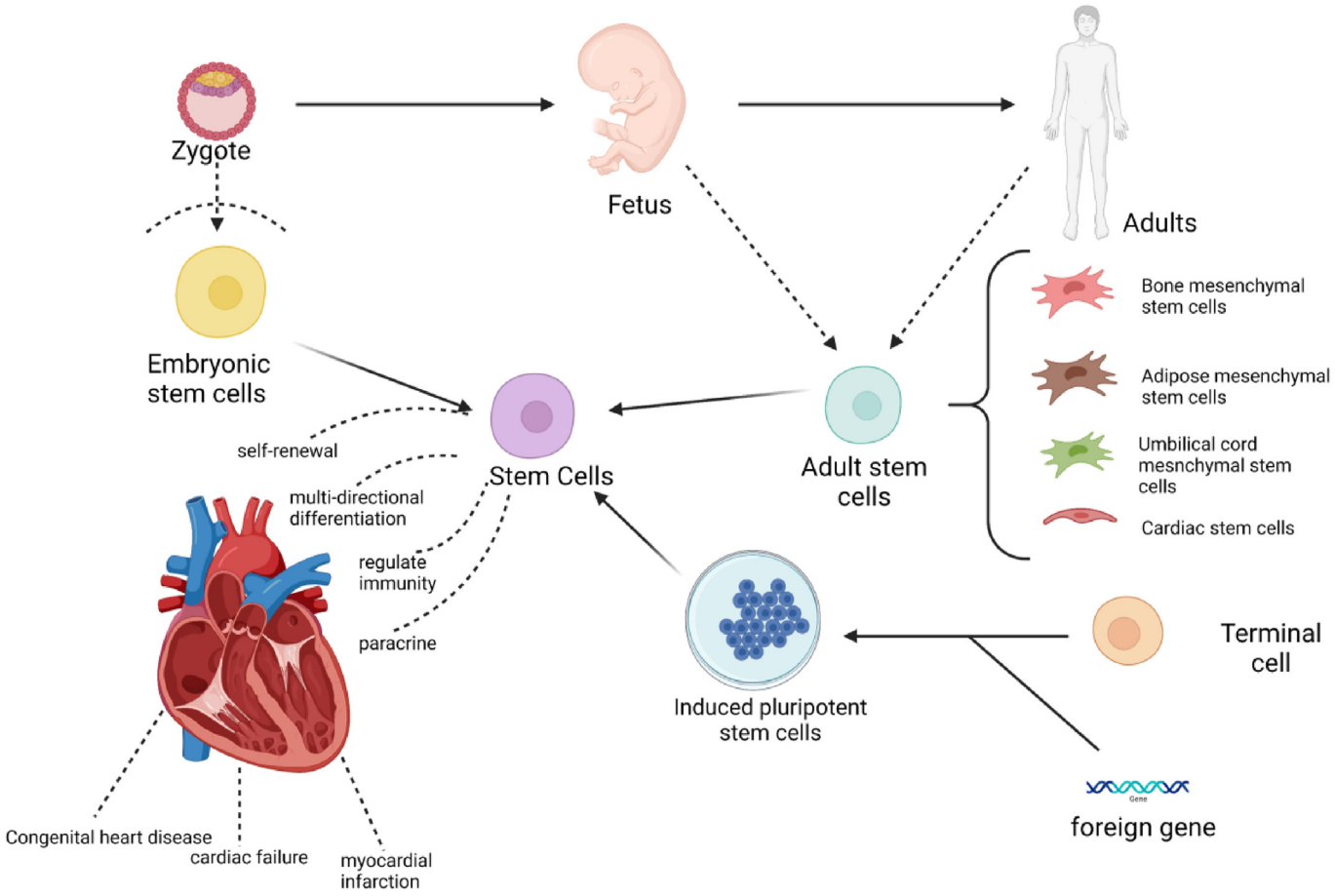

Fig. 2. Principle of stem cell therapy for cardiovascular diseases. Stem cells from a variety of sources (bone marrow mesenchymal stem cells, adipose mesenchymal stem cells, umbilical cord blood mesenchymal stem cells, cardiac stem cells, induced pluripotent stem cells, and embryonic stem cells) have self-renewal, multidirectional differentiation, immune regulation, paracrine and other effects and can have therapeutic effects on cardiovascular diseases such as congenital heart disease, heart failure, and myocardial infarction.

repair and regeneration of myocardial cells; and improve myocardial contractile function [8].

4.1. Embryonic stem cells

ESCs are pluripotent cells that can remain undifferentiated when cultured in vitro and have the potential to differentiate into specific somatic cells, including cardiomyocytes. ESCs can provide a large number of differentiated myocardial cells for the treatment and regeneration of damaged myocardial layers. ESCs are mainly derived from early developing embryos and have totipotency and the ability to differentiate into three types of embryonic cells: ectoderm, endoderm and mesoderm. In 1998, Thomson and colleagues first isolated and cultured them from human blastocysts [9], and ESCs exhibit several advantages over adult stem cells, including pluripotent differentiation potential, which is virtually unlimited in vitro due to their self-renewal capacity, and they can generate CMs similar in structure and function [10]. ESCs have been observed to have the ability to differentiate into functional heart, neuronal, and pancreatic cells [11]. ESCs-differentiated cardiomyocytes have cell morphology and physiology similar to adult cardiomyocytes. Currently, due to ethical concerns, application to large non-human primates has been reported less, but it has still been reported. Studies have found that models of ESCs transplanted in vivo can muscularized substantial amounts of the infarcted monkey heart and global left ventricular ejection fraction improved [12,13]. Another Study found lack of Remuscularization Following Transplantation of human ESC-derived Cardiovascular Progenitor Cells in cynomolgus monkeys [14]. In addition to large non-human primate trials, a trial in small animals has also demonstrated the efficacy of ESCs in the treatment of cardiovascular diseases. Johannes Bargehr et al. tested the ability of human ESC-derived epicardium to augment the structure and function of engineered heart tissue in vitro and to improve efficacy of human ESC-cardiomyocyte grafts in infarcted athymic rat hearts. Importantly, cross transplantation improved systolic function compared with hearts receiving either cardiomyocytes alone, epicardial cells alone or vehicle [15]. Qiang Wu et al. found extracellular vesicles from human ESC-derived cardiovascular progenitor cells promote cardiac infarct healing through reducing cardiomyocyte death and promoting angiogenesis [16]. ESCs are very promising for the treatment of CVD, and their isolation and purification are relatively easy to carry out, but because the origin is mostly from embryos or aborted fetal embryos, especially very early embryos such as mulberry embryos, there is controversy in medical ethics, and the possibility of forming teratomas and immune rejection in the human body, which limits its clinical application [17] (Table 1).

4.2. Adult stem cells

4.2.1. Bone marrow mesenchymal stem cells

MSCs are a heterogeneous population of adherent, fibroblast-like multipotent cells, which can differentiate into several cell types of the mesodermal lineage, such as osteoblasts, adipocytes,

Table 1
Advantages and disadvantages of stem cell types used for cardiovascular diseases.

Stem cell type	Methods of stem cell therapy for cardiovascular diseases	Advantages	Shortcomings
ESCs	Expression of a variety of heart-specific genes and transcription factors; react to drugs through cardiac cell-specific receptors	Clear source and easy purification; multifunctional differentiation and self-renewal; easy to produce cell lines; electromagnetic binding to host myocardium	Immune rejection; ethical issues are only allogeneic; teratoma formation; genomic instability; lack of availability
BM-MSCs	Upregulate nuclear membrane proteins and transcription factors, and finally activate downstream signaling pathways, such as Notch1 and WNT	Less ethical considerations, less tumorigenic risk and lower immunogenicity	No obvious shortcomings and have been applied in clinical practice
UCMSCs	Secrete growth factors, cytokines and chemokines to improve different cell repair mechanisms	More primitive than adult stem cells	Ethical problems arising from human umbilical cord
AMSCs	The paracrine activation of AMSCs on fibroblasts can regenerate damaged cardiomyocytes by directly transforming endogenous cardiac fibroblasts into induced cardiomyocyte-like cells to restore cardiac function	Wide range of sources and is easy to prepare; can be maintained and expanded in culture for a long time without losing differentiation ability	No obvious shortcomings and have been applied in clinical practice
iPSCs	Adult cells (such as fibroblasts) can differentiate into cardiomyocytes by reprogramming transcription factors (such as octamer binding transcription factor Oct4, sex determining region Y box protein Sox2, nuclear transcription factor Klf4 and proto-oncogene c-Myc)	Multifunctional differentiation and self-renewal; minimal ethical issues; easily accessible source organization; strong cardiac muscle generating ability	Teratoma formation; immune rejection; limited genome editing technology; possible genomic instability; not tested in the clinical environment
CSCs	Parasecretory effect can promote the migration, proliferation, differentiation and angiogenesis of cardiac endogenous stem cells; promote the recruitment of endogenous CSCs; inhibit the apoptosis of infarct cells; and resist myocardial remodeling, thus improving cardiac function	Autotransplantation; multipotential; practicability in clinical trials; low tumorigenic risk; a short culture period is required to produce CMs (weeks)	The cost of in vitro proliferation before transplantation is high; the number of cells is limited; obtained from invasive myocardial biopsy; cell characteristics are not sufficient; the stem cell pool seems to experience aging

and chondrocytes, due to their immunomodulatory and anti-inflammatory properties, MSCs have been the most studied stem cells for the treatment of cardiac injury [18]. Apart from their direct effect on cardiac tissue repair and regeneration [19], MSCs may also play important roles through the secretion of trophic factors [18], which improve cardiac function by tissue injury reduction, inhibition of fibrotic remodeling, angiogenesis, activation of host tissue stem cells niches, and reducing inflammation. Cells isolated from bone marrow are called bone marrow mesenchymal stem cells. Bone marrow mesenchymal stem cells (BMSCs) are subtypes of nonhematopoietic stem cells that are localized in the bone marrow. Although they only account for 0.001%—0.01 % of the total number of monocytes in bone marrow, they can be amplified 1 million times or for 6 generations in vitro [20]. Friedenstein et al. established the first method for isolating bone marrow mesenchymal stem cells [21]. In 2002, Shake et al. first observed the beneficial effect of bone marrow stromal stem cell transplantation in a pig model of myocardial infarction (MI), and they found that the wall thickness at the end of diastole/systole was significantly increased after autologous bone marrow mesenchymal stem cell transplantation [22]. In 2004, Chen et al. randomly divided 69 patients with acute ST segment elevation myocardial infarction within 12 h of onset into two groups [23]. The patients were injected with either autologous bone marrow MSCs or normal saline into the coronary artery. The follow-up for 6 months showed that the myocardial function of the patients in the stem cell therapy group was improved compared with that of the control group. Since then, BM-MSC therapy has been widely discussed for the treatment of a wide range of cardiovascular diseases [24,25]. In 1999, a research team at Keio University successfully produced cardiomyocytes from bone marrow stromal cells through in vitro treatment with 5-azacytidine (5-aza) [26]. At present, several methods have been established to induce BM-MSCs to differentiate into cardiomyocyte-like cells in vitro. These methods include coculture of aggregates, treatment with demethylating agents, incubation with growth factors and treatment with oligosaccharides [27,28]. In addition, several research teams reported that BM-MSCs differentiated into heart cells that express various cardiac markers in vivo, such as desmin, β-MHC and β-actin. The levels of actin, CTn-T and phosphoprotein are almost the same as those of endogenous myocardial cells [29]. The molecular mechanisms of this differentiation include upregulation of nuclear membrane proteins and transcription factors and ultimately activation of downstream signaling pathways, such as Notch1 and WNT [30—33]. A multicenter randomized clinical trial of bone marrow MSCs in the treatment of acute myocardial infarction showed that the treatment of acute myocardial infarction with bone marrow MSCs via coronary artery transplantation could improve the myocardial blood flow perfusion and left ventricular ejection fraction of patients, that the feasibility and safety of treatment were high, and that no related ventricular arrhythmia or other major adverse cardiac events occurred [34]. In 2023, Li H et al. reported that $CD133^{+}$/Lin^{-}/$CD45^{-}$ cells derived from swine bone marrow were successfully isolated and amplified, laying a good foundation for further research on this promising therapeutic cell. The effect of exosomes may be a promising potential treatment strategy for cardiac fibrosis [35]. Zhou P et al., suggest that bone marrow-derived c-$kit^{+}$$VEGFR\text{-}2^{+}$ MSCs have the potential to differentiate toward cardiovascular cells. The cells can effectively repair the infarcted myocardium after transplantation [36]. These cells show great potential and prospects in the treatment of cardiovascular diseases (Table 1). Despite the potential of MSCs, clinical trials have shown conflicting results on

their effect in the treatment of CVDs [37](Table 1). These differences can be due to several causes, including the protocols used for the manipulation of the MSCs, which might influence the viability and therapeutic potential of the cells, the administration route used to transplant them, as well as the intrinsic differences in functional cardiac parameters and severity among participants.

4.2.2. Adipose-derived mesenchymal stem cells

ADSCs are isolated from adipose tissue. Recently, direct cardiac reprogramming has become a new technology that can regenerate damaged cardiomyocytes by directly transforming endogenous cardiac fibroblasts into induced cardiomyocyte-like cells to restore cardiac function. Fibroblasts replace dead cardiomyocytes, leading to the formation of fibrosis and myocardial remodeling. There are studies on the interaction between ADSCs and fibroblasts. ADSC-conditioned medium promoted the proliferation of fibroblasts, which indicated that ADSCs activated the paracrine secretion of fibroblasts. It was found that the same fibroblasts cultured in ADSC-conditioned medium secreted increased type I collagen. These findings suggest that these interactions may play an important role in myocardial protection. On the other hand, ADSCs may be of great interest in cardiovascular research, and these cells have been studied in many clinical trials in the past decade. ADSCs were directly injected into the myocardial tissue of MI or ischemic heart failure patients without related events, and ADSCs were used to improve cardiac function safely and effectively [37,38]. In animal models, ADSCs have demonstrated efficacy regardless of whether they are administered by intracoronary, intracardiac, intramyocardial, or intravenous methods [39](Table 1). One recent study suggested that ADSC-to-cardiomyocyte mitochondrial transfer occurs both in vitro and in vivo, thereby contributing to the recovery of early cardiac function after ADSC transplantation in ischemic cardiomyopathy. Thus, enhancement of the mechanisms of mitochondrial transfer is proposed to enhance the efficacy of cell therapy [40]. In 2023, one study was novel in the role of exosomes from adipose-derived stem cells and related microRNAs in Atherosclerotic cardiovascular disease (ASCVD). Therapeutic potentials of adipose-derived stem cell exosomes in terms of their impact on macrophage polarization, endothelial effect, anti-apoptosis intervention, and angiogenesis. Adipose tissue now tops the list of stem cell sources in terms of its availability, abundance and less painful collection process compared to other sources [41] (Table 1). It contains AMSCs that can be maintained and expanded over long periods of time in culture without losing their ability to differentiate, leading to the increasing use of large numbers of AMSCs for cell therapeutic purposes.

4.2.3. Umbilical cord mesenchymal stem cells

Umbilical cord mesenchymal stem cells (UCMSCs) are separated from umbilical cord blood. These cells can be separated from different parts of the UC, including the Wharton's jelly, umbilical cord lining and perivascular areas. However, almost all studies used bone marrow mesenchymal stem cells from cord blood and Wharton's jelly [42,43]. Compared with BM, the frequency of MSCs in UCB is reduced [44], while their versatility is maintained for a longer time [45]. The expression of the aging markers p53, p21 and p16 in UCMSCs was significantly decreased. They are slightly positive for the markers Oct4, Nanog, Sox2 and KLF4 of embryonic stem cells, indicating that these cells are more primitive than adult stem cells [46]. (Table 1) A recent discovery showed that MSCs isolated from Wharton's jelly of male origin show higher gene expression levels of Oct4 and DNA methyltransferase 1 (DNMT1), thus correlating stem cell characteristics with sex differences [47]. Their ability to differentiate into three mesodermal lineages (adipocytes, chondrocytes and osteocytes) is controversial [44,48]; however, they have shown the maximum proliferation rate and clonogenic activity, as well as high cartilage differentiation ability [45,49]. Similar to their counterparts, UCMSCs are known to secrete growth factors, cytokines and chemokines to improve different cell repair mechanisms [44]. However, they are widely used, especially due to their low expression of MHCII antigens; inhibition of the proliferation of T cells, B cells and NK cells; and inactivation of monocytes and dendritic cells [50,51]. When transplanted into animal models, these cells can also differentiate into spinal cord tissue with an increasing number of GAP43+ fibers and more residual gray matter in a dose-dependent and repeated manner [52]. Parkinson's disease, myocardial infarction and diabetes also benefit from the differentiation ability of these cells [53–55]. A promising clinical report showed that the muscular activity of patients with muscular dystrophy after infusion of UCMSCs was improved [56,57]. However, the paracrine activity of these MSCs is more likely to improve cardiac function by enhancing angiogenesis and anti-apoptosis, rather than directly differentiating into cardiomyocytes [58,59]. As the source of umbilical cord mesenchymal stem cells is more primitive than adult stem cells, they are more capable of differentiating into fully functional heart cells and have broad prospects in the treatment of diseases by stem cells. However, their clinical application is limited due to the medical ethical problems caused by their origin from the human umbilical cord. Despite the potential of mesenchymal stem cells, clinical trials have shown conflicting results for their efficacy in treating cardiovascular disease (Table 1). These differences may be caused by some uncertain parameters such as route of administration, optimal timing, stem cell source, and necessary dose, which may affect cell viability and therapeutic potential, limiting the routine use of mesenchymal stem cell therapy in clinical practice [37].

4.2.4. Cardiac stem cells

The adult heart was once considered a terminally differentiated organ that was unable to regenerate after myocardial infarction Cardiomyocytes (CMs) are thought to be post-mitotic cells and therefore exhibit very limited regenerative capacity after birth. It wasn't until 2009 that Bergmann and his colleagues discovered that CMs did update, but with low turnover. In fact, they showed that approximately 50 % of CMs are exchanged throughout life, thus supporting the existence of CMs reproduction over a lifetime [60]. The origin of CSCs remains unknown, but there are many different types including CKIT + cells, Isl 1+ cells, cardio sphere-derived cells (CDCs) and epicardium-derived cells, lateral population cells, etc. CSCs can be extracted from the cardiac appendages of adults, and in vitro these cells are more efficient at expressing cardiovascular markers than bone marrow MSCs. In vivo, CSCs are injected into the rat myocardium after myocardial infarction, and CSCs can differentiate into cardiomyocytes more efficiently. In another study comparing subcutaneous adipose tissue-derived MSCs with pericardium-derived CSCs, pericardium-derived CSCs were better at expressing intrinsic transcription factors that contribute to cardiomyocyte differentiation [61]. Animal studies have shown that CSCs have a greater ability to differentiate into cardiac cells and can more efficiently acquire structural properties of cardiomyocytes and blood vessels [62]. Some studies have used CDCs to treat myocardial infarction. Trans endocardial myocardial needle biopsy obtains tissue, cultures cardioglobulocytes in culture medium, and proliferates in vitro to produce more CDCs prior to transplantation. In 2022, Ángel Arenal et al. evaluated the effect of cardio sphere-derived cells (CDC) on ventricular tachycardia (VT) substrates in a post-infarction monomorphic VT pig model. They investigated the effect of CDC on the electrophysiological properties and histological structure of dense scars and heterogeneous tissues (HT). Allogeneic

CDC in the early post-myocardial infarction alters the structure and electrophysiology of post-infarction scars. These findings suggest that the CDC has a new therapeutic role. Therefore, CSCs are ideal for the treatment of cardiovascular diseases in the future, and the disadvantage of CSCs is the high cost of in vitro proliferation before transplantation [63] (Table 1). How to improve its ability to divide into cardiomyocytes, replace necrotic cardiomyocytes to play a role, because there is still a very slow cell division ability in adult cardiomyocytes, after the appearance of myocardial ischemia, how to improve its ability to divide into cardiomyocytes, replace necrotic cardiomyocytes to play a role, improve cardiac function, or will be a hot spot in future research.

4.3. Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are produced by adult cells (such as fibroblasts) through reprogramming transcription factors (such as octamer binding transcription factor Oct4, sex determining region Y box protein Sox2, nuclear transcription factor Klf4 and proto-oncogene c-Myc) and can differentiate into various human cell types [64] (Table 1). iPSCs and ESCs have similar morphology, surface markers, gene expression, teratoma formation and other characteristics in vivo, and have the same cell culture conditions as ESCs (Table 1) (Fig. 2). Some researchers have effectively reprogrammed other somatic cells such as keratinocytes, peripheral blood mononuclear cells, or squamous epithelial cells collected from urine [65]. Therefore, iPSCs are considered an alternative resource for CVD cell therapy. The advantage of iPSCs over adult stem cells and ESCs is that they are easy to generate and avoid ethical and immune rejection issues associated with the use of ESCs. In addition, similar to ESCs, iPSCs can differentiate into three germ layer cells, including (cardiomyocytes)CMs, and due to their self-renewal ability, they represent an unlimited source of CMs. IPSCs may develop into teratomas and malignancies during differentiation, reprogrammed cells may retain epigenetic characteristics of their somatic cells of origin, and accumulation of chromosomes and/or mutations may exhibit genomic instability [66]. Therefore, the main research direction on iPSCs is how to improve reprogramming techniques to detumor cellulatization during induction (Table 1). Since iPSC-derived cardiomyocytes have successfully treated heart failure in animals such as monkeys. One study data demonstrate that allogeneic iPSC-CM transplantation is sufficient to regenerate the cynomolgus monkey heart researchers are excited about human clinical studies of such innovative therapies [67]. Recently, the top international academic journal Nature reported on a clinical treatment study by Wang Dongjin's team at Nanjing Gulou Hospital, in which two Chinese men received experimental heart disease treatment based on “reprogramming” stem cells and successfully recovered a year later. It is reported that this is the world's first known clinical application of iPSC technology for the treatment of damaged hearts [68]. Clinical trials using human iPS cell-derive cardiac tissue sheets have been also conducted in Japan [69]. In combination with an efficient and simultaneous differentiation of various cardiac lineages from hiPSCs and cell sheet technology, they generated clinical-sized large cardiac tissue sheets (L-CTSs) and to evaluate the therapeutic potential in porcine infarct heart. Japan's Ministry of Health approved a clinical research project at Keio University that transplants cardiomyocytes made from iPSCs into heart patients that Improves cardiac function and reverses fibrosis in chronic myocardial infarction [70]. At the same time, In Chain, Beijing – Nanjing Alp Regenerative Medicine Technology Co., Ltd. announced that the new drug clinical trial (IND) of the company's self-developed heart failure cell therapy product “human iPSC-derived cardiomyocyte injection” has been granted implied clinical trial authorization by the Center for Drug Evaluation (NMPA) of the National Medical Products Administration (ClinicalTrails.gov:NCT03763136). A study called Treating Congestive Heart Failure Patients With Human iPSC-derived Cardiomyocytes Through Catheter-based Endocardial Injection has entered phase I clinical trials (ClinicalTrails.gov: NCT04982081). Although iPSCs have been initially effective in the treatment of cardiovascular diseases, it is still necessary to continuously develop new programming schemes and new technical methods to minimize potential risks and improve efficiency, so as to ensure the safe and effective application of iPSCs technology in clinical practice [71].

5. Conclusion

Cardiac aging is a risk factor for cardiovascular diseases and the pathological basis of cardiovascular diseases such as heart failure and atrial fibrillation. In recent years, with the in-depth study of cardiovascular diseases, various treatment methods have emerged, but most methods can only control the development of the disease, and there are some drawbacks. The advantages of stem cell therapy have attracted increasing attention from the scientific and medical communities and may provide a good technical platform for gene therapy, tissue and organ transplantation, and even cell replacement therapy. The clinical application of stem cell therapy is still at the exploratory stage. How to effectively harvest a large number of purified cells and ensure their stability and safety in the process of transplantation therapy remains to be studied in the future. In summary, although there are many experiments, preclinical trials and follow-up data indicating that stem cells have good clinical application prospects in the treatment of cardiovascular diseases, there is still a lack of sufficient and reliable clinical evidence for their tumorigenicity, safety and effectiveness, which requires further in-depth research. The limitations of immune rejection, tumorigenicity and infusion toxicity should not be ignored. In addition, we need to continue to study the pathogenesis of cardiovascular aging and related diseases and the mechanism of stem cell transplantation driving injury to provide more evidence and scientific support for stem cell therapy. At present, a preliminary understanding of the biological characteristics of stem cells has been obtained, which provides a solid foundation for their further clinical application. However, the research field of cardiovascular aging and related diseases still faces a series of challenges in strengthening the transformation and application of basic cardiovascular research and promoting the prevention and treatment of cardiovascular diseases through scientific research.

Ethical approval and consent to participate

Not applicable.

Consent for publication

All authors have read and approved the content, and agree to submit for consideration for publication.

Availability of data and material

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Authors' contributions

X.-Q.Z. and H.-L.Y. conceptualize the content and wrote the paper. All authors (X.-Q.Z., H.-L.Y., L.C., W.-W.F., X.L., Q.L., C.T., J.Z., Z.-A.L., and X.-H.P) made substantial contributions to the conception of the project and provided critical review of the final document.

Declaration of competing interest

This paper has not been published elsewhere in whole or in part. All authors have read and approved the content, and agree to submit for consideration for publication in the journal. There are no any ethical/legal conflicts involved in the article. Your consideration for this manuscript is highly appreciated.

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