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The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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EDITORIAL

Living biodrugs and how tissue source influences mesenchymal stem cell therapeutics for heart failure

Siddharth Shah, Huzaifa Sabir Nawaz, Muhammad Saeed Qazi, Hritvik Jain, Brandon Lucke-Wold

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Abstract

In this editorial we comment on the article by Safwan M *et al*. We especially focused on the cardiac function restoration by the use of mesenchymal stem cells (MSCs) therapy for heart failure (HF), which has emerged as a new treatment approach as "Living Biodrugs". HF remains a significant clinical challenge due to the heart's inability to pump blood effectively, despite advancements in medical and device-based therapies. MSCs have emerged as a promising therapeutic approach, offering benefits beyond traditional treatments through their ability to modulate inflammation, reduce fibrosis, and promote endogenous tissue regeneration. MSCs can be derived from various tissues, including bone marrow and umbilical cord. Umbilical cord-derived MSCs exhibit superior expansion capabilities, making them an attractive option for HF therapy. Conversely, bone marrow-derived MSCs have been extensively studied for their potential to improve cardiac function but face challenges related to cell retention and delivery. Future research is focusing on optimizing MSC sources, enhancing differentiation and immune modulation, and improving delivery methods to overcome current limitations.

Key Words: Mesenchymal stem cells; Heart failure; Umbilical cord-derived mesenchymal stem cells; Bone marrow-derived mesenchymal stem cells; Therapeutics for heart failure;

Biodrugs; Tissue source

Core Tip: Mesenchymal stem cells (MSCs) offer a novel regenerative approach to treating heart failure (HF), especially ischemic HF, by modulating inflammation, reducing fibrosis, and promoting tissue repair. Sources like bone marrow and umbilical cord each provide distinct benefits. Umbilical cord-derived MSCs are particularly promising due to their superior growth capacity and reduced senescence. However, challenges in cell retention and delivery persist. Current research focuses on refining MSC sources, enhancing differentiation, and improving delivery methods, paving the way for MSCs to become a pivotal therapy in HF management.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by the heart's inability to pump blood effectively, leading to insufficient blood flow to meet the body's needs. Ischemic heart disease, particularly ischemic cardiomyopathy, is a leading cause of HF[1]. This form of HF, referred to as ischemic HF, arises from chronic ischemic injury to the myocardium, such as that caused by coronary artery disease or a prior myocardial infarction[2]. The prognosis of ischemic HF remains poor despite advancements in medical therapies, cardiac rehabilitation, and device-based interventions like left ventricular assist devices (LVADs). These devices have shown survival and quality of life benefits in patients with advanced HF, serving as a bridge to heart transplantation or as long-term therapy for those not eligible for transplantation[3,4]. However, while LVADs can induce partial reverse remodeling of the left ventricle[5], this improvement is rarely sufficient to allow device removal, highlighting the need for adjunctive therapies[6]. Cell therapy has emerged as a promising approach to treating ischemic HF in the last 2 decades[7]. The potential of cell therapy lies in its ability to improve cardiac function through mechanisms beyond simple regeneration of cardiomyocytes. Mesenchymal stem cells (MSCs), in particular, have garnered significant attention due to their low immunogenic potential and ability to be isolated from various adult tissues, including bone marrow, adipose tissue, and umbilical cord tissue[8]. MSCs are multipotent cells capable of self-renewal and multilineage differentiation[9]. Their therapeutic potential in HF is attributed not only to their capacity to differentiate into various cell types but also to their paracrine effects, which include antifibrotic, anti-apoptotic, anti-inflammatory, and pro-angiogenic actions[10]. Unlike whole organ transplantation or many other allogeneic cell transplants, MSC transplants do not cause rejection and may even induce tolerance to the donor, making them an attractive candidate for cell-based therapies in HF[11].

Clinical trials have shown that MSCs can improve cardiac performance in patients with chronic ischemic HF. For instance, studies involving the transendocardial injection of bone marrow-derived MSCs (BM-MSCs) have demonstrated improvements in left ventricular function and reductions in scar size[12]. However, while these findings are promising, the clinical efficacy of MSC therapy in HF remains a topic of debate, with some studies showing significant benefits and others reporting more modest outcomes.

The niche of origin of MSCs plays a crucial role in determining their therapeutic efficacy. The properties of MSCs can be highly influenced by the microenvironment from which they are harvested, making the tissue source an essential factor in evaluating the potential of these cells as living biodrugs. Figure 1 depicts different sources for MSC. The purpose of writing an editorial article on "Living Biodrugs and How Tissue Source Influences MSC Therapeutics for HF" is to shed light on the evolving field of (MSC therapies and highlight how the tissue origin of MSCs significantly impacts their therapeutic potential in HF. The article aims to explore how MSCs derived from different sources (such as bone marrow, adipose tissue, or umbilical cord) exhibit varying bioactive properties and paracrine effects, influencing outcomes in cardiac repair.

DIVERSE MSC MODALITIES

MSCs have emerged as a promising therapeutic modality for HF, particularly in the context of ischemic heart disease. MSCs, characterized by their multipotent differentiation capacity and unique immunomodulatory properties, have been extensively studied for their potential to mitigate the pathophysiological consequences of HF[13]. Originally isolated from bone marrow by Friedenstein *et al*[14], MSCs have since been identified in a variety of tissues including adipose tissue, umbilical cord, and peripheral blood, offering a diverse range of sources for therapeutic application[15].

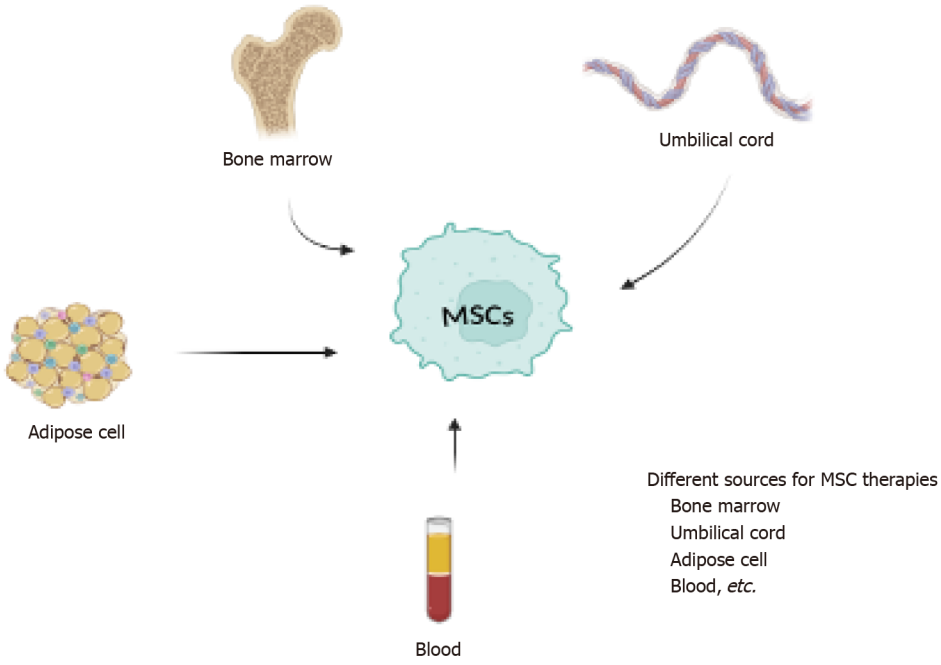

Figure 1 Different sources for mesenchymal stem cell. MSCs: Mesenchymal stem cells.

The therapeutic efficacy of MSCs in HF is attributed to their ability to modulate inflammatory responses, reduce fibrosis, and promote endogenous tissue regeneration. In particular, MSCs have been shown to exert paracrine effects that may contribute to cardiac repair and functional improvement, even in the face of limited direct engraftment and cell survival within the myocardial tissue[16]. Recent advancements in MSC therapy include the development of clinical-grade allogeneic MSC products, such as those derived from adipose tissue, which offer several advantages over autologous sources[17].

UMBILICAL CORD-DERIVED MSCS

Umbilical cord-derived MSCs (UC-MSCs), particularly those sourced from Wharton's jelly, offer notable advantages for HF therapy due to their accessibility, reduced cellular senescence, and absence of ethical concerns[18,19]. UC-MSCs can be readily isolated and expanded in vitro, demonstrating superior expansion capacity and faster growth rates compared to BM-MSCs[20]. These cells have been shown to express cardiac-specific markers such as troponin I and connexin-43 and possess the ability to differentiate into cardiomyocyte-like and endothelial cells under controlled conditions. Additionally, UC-MSCs exert significant paracrine effects that enhance vascular regeneration and provide cardiomyocyte protection, mechanisms implicated in the observed improvements in cardiac function in preclinical models of chronic ischemic cardiomyopathy and dilated cardiomyopathy[21]. The process of isolating UC-MSCs involves aseptic collection of umbilical cords from full-term placentas *via* caesarean section, followed by washing and culturing of Wharton's jelly fragments in a defined medium supplemented with fetal bovine serum and antibiotics. Cells are subsequently characterized based on International Society for Cellular Therapy guidelines and cryopreserved for clinical applications[22]. UC-MSCs, in our opinion, have significant promise for HF treatment due to their distinct advantages over other MSC sources. These cells are highly proliferative, immunoprivileged, and easily accessible, without the ethical problems associated with other stem cell sources. UC-MSCs have strong anti-inflammatory, anti-apoptotic, and pro-angiogenic capabilities, making them ideal for mending injured heart tissue in ischemia circumstances. Furthermore, their non-invasive collecting method makes them a more accessible and scalable choice for clinical applications. Given these characteristics, UC-MSCs might play a critical role in developing cell-based therapeutics for HF, providing an effective and ethical approach to cardiac regeneration.

BM-MSCS

BM-MSCs have been extensively investigated for the treatment of HF, demonstrating their potential to improve cardiac function and reduce adverse remodeling. BM-MSCs, although only representing approximately 0.01% of nucleated cells in bone marrow, exhibit robust *in vitro* expansion capabilities, maintaining their stem cell properties and multipotency [23]. Preclinical and clinical studies have shown that BM-MSCs can differentiate into cardiomyocyte-like cells, secrete a range of growth factors, cytokines, and microRNAs, and exert paracrine effects that support cardiomyocyte regeneration and reduce inflammation and fibrosis[24]. For instance, BM-MSCs have been utilized in clinical trials such as the phase III

study by Celyad SA, which tested autologous BM-MSCs with a "cardiopoietic" phenotype for chronic advanced ischemic HF[25]. This trial sought to capitalize on the benefits of autologous cells, mitigating immune incompatibility, and involved administering 600 million MSCs in multiple endoventricular injections. Despite initial promising results from earlier studies, the phase III trial did not show significant improvement in primary endpoints between MSC and placebo groups, suggesting that factors such as cell dosing and delivery methods may influence outcomes[26]. Specifically, the challenge of delivering multiple injections across a heterogeneous myocardial landscape could lead to variability in treatment efficacy and potential myocardial damage.

BM-MSCs have long been regarded as a useful alternative for HF treatment due to their well-established regeneration potential. These cells have been widely investigated and are renowned for their strong ability to control immune responses, decrease inflammation, and promote tissue repair *via* paracrine communication. However, one disadvantage of BM-MSCs is the invasive approach of extracting them, which may restrict their scalability when compared to alternative sources such as UC-MSCs. Furthermore, their therapeutic potency may reduce as donors age, impacting treatment consistency. Despite these issues, BM-MSCs remain a promising possibility for cardiac repair, particularly when derived from younger donors or improved using modern procedures.

FUTURE DIRECTIONS IN MSC THERAPY FOR HF

The future of MSC therapy for HF holds great promise as researchers explore alternative MSC sources, refine differentiation pathways, and enhance immune modulation. Novel sources such as adipose tissue, umbilical cord blood, and menstrual blood offer accessible and ethically sound alternatives to BM-MSCs, with the potential for superior therapeutic outcomes. Advances in understanding the factors that influence MSC differentiation and immune response are critical to improving their clinical efficacy. Moreover, the challenge of low MSC retention in target tissues is being addressed through innovations in delivery methods, including genetic modification, biomaterials, and pre-conditioning techniques [27]. These approaches aim to improve MSC survival, promote tissue regeneration, and ultimately enhance the therapeutic impact of MSCs in HF. As research progresses, MSC-based therapies are poised to become a key treatment option for patients with HF, offering new avenues for effective, long-term care.

CLINICAL IMPLICATION

The clinical implications of MSC therapy in HF are profound, given the cells' accessibility from various sources such as peripheral blood, adipose tissue, and bone marrow, facilitating autologous transplantation. This is particularly crucial in circumventing the immunogenic challenges often associated with allogeneic cardiac cell transfer. Additionally, emerging evidence underscores the paracrine mechanisms of MSCs, particularly through the secretion of exosomes. These 50 to 100 nm vesicles have been shown to exert cardioprotective effects, as demonstrated by Lai *et al*[28], who reported a significant reduction in myocardial infarction in an *ex vivo* murine model of ischemia-reperfusion injury.

MSC-derived extracellular vesicles (EVs) have substantial therapeutic promise in ischemic HF, due to their natural capacity to develop into diverse cell types as well as their strong paracrine actions[9]. These EVs carry a variety of bioactive chemicals that exert antifibrotic, anti-apoptotic, anti-inflammatory, and pro-angiogenic effects, all of which are necessary for heart tissue healing. They aid in retaining cardiac shape and prevent heart tissue stiffening by lowering fibrosis, while their anti-apoptotic actions protect cardiac cells from ischemia-induced death. Their anti-inflammatory characteristics reduce damaging immune responses, preventing further injury to cardiac tissue[29]. MSC-derived EVs also promote angiogenesis, which encourages the development of new blood vessels, boosting oxygen flow to ischemic areas and overall heart function. Collectively, these features make MSC-EVs a potential cell-free treatment for treating ischemic HF[30]. Adipose-derived stem cells (ADSCs) and induced pluripotent stem cells (iPSCs) are two alternative sources of MSCs with promising therapeutic applications in ischemic HF. ADSCs derived from adipose tissue are plentiful and have significant anti-inflammatory, pro-angiogenic, and antifibrotic properties, supporting heart repair by increasing blood flow and decreasing tissue damage. iPSCs, which are created by reprogramming adult cells to a pluripotent state, may develop into a variety of cell types, including cardiac cells, providing a personalized approach to rebuilding damaged heart tissue. ADSCs and iPSCs increase myocardial recovery through paracrine signaling, encouraging healing, minimizing scar tissue development, and enhancing heart function, making them valuable options for HF therapies[31].

Clinical research on MSC treatment for ischemic HF are now yielding encouraging but conflicting outcomes. Many studies have shown that MSCs derived from bone marrow, adipose tissue, and the umbilical cord can improve heart function, minimize scar tissue, and improve patient outcomes by exhibiting anti-inflammatory, anti-apoptotic, and pro-angiogenic properties. However, the variety in research designs, cell sources, administration techniques, and patient demographics has resulted in conflicting results in certain circumstances. While MSC therapy is typically safe and well tolerated, larger, standardized clinical studies are required to refine treatment procedures and thoroughly establish its efficacy. The current research is improving MSC-based treatments, bringing them closer to routine clinical use for ischemic HF. Table 1 summarizes the advantages and disadvantages of MSC Therapy.

Table 1 Advantages and disadvantages of mesenchymal stem cell therapy

MSC therapies	Comparison
Advantages	MSCs can be sourced from various tissues, including bone marrow, adipose tissue, and umbilical cord, providing multiple options for therapy
	MSCs have immunomodulatory properties, which can reduce inflammation and fibrosis, promoting tissue regeneration
	UC-MSCs are easily accessible, have reduced cellular senescence, and do not raise ethical concerns
	MSCs exhibit paracrine effects that contribute to cardiac repair and functional improvement, even without direct differentiation into cardiomyocytes
Disadvantages	The therapeutic efficacy may be limited by low cell engraftment and survival within myocardial tissue
	Clinical trials, such as those using BM-MSCs, have shown variable outcomes, with some failing to achieve significant improvements in heart failure patients
	Delivery methods, such as multiple intraventricular injections, can pose challenges and may lead to inconsistent results or myocardial damage
	Factors like cell dosing, delivery techniques, and heterogeneous myocardial environments can affect the overall success of the therapy

MSC: Mesenchymal stem cell.

CONCLUSION

In conclusion, MSCs represent a viable and potent option for HF therapy, offering advantages in terms of accessibility, proliferative capacity, and regenerative potential. Continued research and clinical trials will be essential in determining their role in the evolving landscape of HF treatment. By addressing the current limitations and refining the therapeutic strategies, MSCs have the potential to become a cornerstone of regenerative medicine for HF.

FOOTNOTES

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