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The Secretome of Mesenchymal Stem Cells: A Promising Cell-Free Option for Heart Regeneration

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Abstract
One of the most common causes of global death is cardiovascular disease (CVD). Using mesenchymal stem cell (MSC) therapy for treating CVDs is revolutionizing regenerative medicine. Some challenges that have limited MSC therapy's practical application include cell harvesting difficulty, ectopic transplantation, spontaneous differentiation to cartilage and bone, and possible immune responses following transplantation. MSCs release extracellular vesicles and biologically active molecules such as growth factors, chemokines, and cytokines, collectively called the secretome. Recent studies have shown that secretome administration could replace MSC transplantation. The secretome of MSCs plays a crucial role in controlling inflammatory reactions, enhancing tissue reperfusion by stimulating angiogenesis and vasculogenesis, preventing apoptosis and fibrosis development, and fostering the proliferation and differentiation of cardiac stem cells. This review discusses the current knowledge of MSC secretome application in cardiac regenerative medicine. It introduces possible approaches to improve cardiac recovery outcomes by utilizing the secretome in the clinic.
Keywords: Cardiomyocytes, Mesenchymal stem cells, Secretome, Cell therapy, Regenerative medicine

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Introduction

Approximately 30% of global deaths are attributed to cardiovascular diseases (CVDs), and CVD-related mortality is expected to increase by 2030 (1-3). Among CVDs, myocardial infarction (MI) is the primary cause of death, defined as myocardial cell death resulting from reduced blood supply in the coronary arteries (4,5). The proliferative potential of cardiomyocytes and resident cardiac stem cells (CSCs) is minimal; therefore, the scar tissue formation following the fibroblast infiltration and collagen deposition could result in myocardial fibrosis and, eventually, heart failure (1,6,7).

Although recently suggested pharmacological interventions and advanced techniques have improved patients' quality of life, mortality and morbidity rates have not significantly decreased yet (8).

Heart transplantation is considered the most optimal course of treatment for individuals with advanced heart failure. Nonetheless, the low availability of heart donors, the considerable expenses associated with the procedure, and the probability of transplant rejection have resulted in limited accessibility. As a consequence, numerous patients with heart ailments succumb to their condition during the prolonged wait for a suitable organ transplant (9-12).

Stem cell technology and therapy have experienced significant advancements, offering considerable promise as therapeutic approaches for cardiac diseases (13). The application of stem cell-based therapies has demonstrated the ability to mitigate the formation of scars effectively, and they have also been recently used to inhibit inflammatory

responses of myocardial tissue and reduce myocardial cell apoptosis; myocardial perfusion can be enhanced by promoting the growth of new blood vessels, thereby improving metabolic pathways and electromechanical disorders (14). Stem cells, including embryonic and mesenchymal stem cells (MSCs), are increasingly utilized in heart regeneration due to their notable capacity for self-renewal and proliferation (1,15). There are concerns regarding the ethical issues and the oncogenic potential of embryonic stem cells. At the same time, MSCs have successfully passed preclinical and clinical trials and are now among the readily accessible stem cells for clinical purposes (16,17). Introducing either a person's stem cells or stem cells from a donor, particularly MSCs, in a transplantation procedure into the injured heart environment has attracted increasing interest recently. Even though several investigations argue that heart function improves following MSC therapy, many challenges still need to be resolved. Cell therapy strategies encounter constraints due to limited cell engraftment and survival rates.

Nevertheless, stem cell therapy faces significant challenges due to inadequate cell migration and transplanted cell mortality rates. According to research findings, MSCs demonstrate a limited lifespan, whereby less than 1% of the administered cells can migrate and survive beyond four days. Optimal cell type, dose, and the transplantation route are other obstacles to cell therapy. Many studies have reported that single-dose cell transplantation may not improve cardiac function. Cultivating therapeutically qualified cells in substantial quantities is imperative when using in-vitro expansion techniques to conduct repeated cell transplantation. The significance of emphasizing the commitment of transplanted cells to their lineage is demonstrated by recently documented cases of immune rejection of allogeneic cells, further highlighting a notable restriction in this context (18).

Scientific evidence demonstrates that the therapeutic benefits of MSCs result from the paracrine effects of the factors they secrete. MSCs secrete different substances, mainly growth factors, chemokines, cytokines, and extracellular vesicles (19,20) (Figure 1), which we will discuss in the second section.

Methods

Data were gathered from multiple reputable databases, including Web of Science, PubMed, Scopus, Google Scholar, Cochrane Library, and Medline. The focus was sourcing original and review articles from 2000 to 2023. Specific keywords such as "mesenchymal stem cells," "mesenchymal stem cells secretome," "mesenchymal stem cells conditioned media," "cardiovascular diseases," and "heart failure" were utilized in the search process. A total of 192 articles met the criteria for inclusion.

These articles were selected based on their publication year, title, study outcomes, and whether they involved preclinical or clinical investigations. Studies such as case reviews, those with inadequate sample sizes, articles not in English, historical pieces, editorials, letters, and commentaries were excluded from consideration. The studies encompassed in this analysis focused on the insights provided by authors regarding the importance of the MSC secretome in facilitating cardiac regeneration after damage to the heart. The evaluation process involved two authors reviewing the titles and full texts of the identified articles to ensure they adhered to the defined inclusion and exclusion criteria. Data extracted from the chosen articles were categorized and analyzed to assess the secretome's impact on heart regeneration after injury.

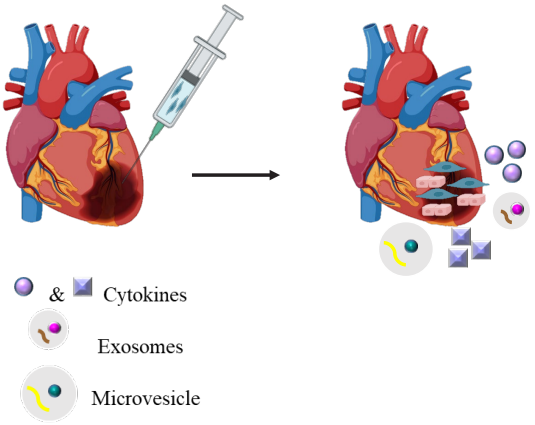

Figure 1. Paracrine factors of mesenchymal stem cells regenerate cardiac injury

Result and Discussion

The MSC secretome offers numerous benefits compared to direct stem cell-based therapy. These advantages include enhanced safety due to immunocompatibility and reduced risk of tumorigenicity associated with stem cells. Additionally, the secretome enables off-the-shelf production and dosage evaluation akin to traditional pharmaceutical agents. It allows for long-term storage without potency loss, eliminates the need for invasive cell collection procedures, and ensures high availability while reducing time and cost requirements (21,22). Even though limited, differentiation of MSCs into cardiomyocytes for cardiac regeneration is suggested to result from the paracrine factors and extracellular MSC vesicles. While this highlights the importance of the secretome, the clinical outcomes of using the secretome broadly vary based on the MSC tissue source (23), study environment (24), and secretome components (25). Several approaches are provided in the following and in (Tables 1 and 2) (26-37) to promote the secretome, especially for the treatment of heart diseases.

Secretome content

Cytokines

Cytokines are a significant part of the MSC secretome

Table 1. Enriched secretions of human mesenchymal stem cells and their impact on cardiovascular repair

Tissue cell source	Study procedure	Methodology for secretome optimization		Modified factor under preconditioning	Outcome	Year reference
Human adipose-derived adherent stromal cells	in-vitro study	Hypoxia	CM under hypoxic condition	Angiogenin, FGF-19, MIF.	Expression of cardiomyogenic factors induction	(26) 2019
Human umbilical cord mesenchymal stem cell	Rat myocardial infarction model	Exosomes release from PGN hydrogel mixture Or transplantation of Exo-PGN hydrogel into infarcted rat myocardium	Encapsulated exosomes	Enhancement of exosome retention and stability	Myocardial function improvement	(27) 2019
Human umbilical cord mesenchymal stem cells	Rat acute myocardial infarction model	overexpression of AKT	Engineered exosomes adenovirus transfection system	PDGF-D	Cardiac regeneration improvement and angiogenesis promotion	(28) 2016
Human umbilical cord blood mononuclear cell		Hypoxia	CM under hypoxic condition	Angiopoietin, hepatocyte growth factor, interleukin-4, insulin-like growth factor, placental growth factor, vascular endothelial cell growth factor, angiogenin, and stem cell factor	Limit apoptosis in endothelial cells and cardiac myocytes	(29) 2013
Human BMDMSC		Overexpression of VEGF	CM	SDF-1	CSC migration promotion	(30) 2011
Human BMDMSC	In-vitro study	Enrichment for STRO-1	CM conditioned medium from STRO-1- MPC	CXCL12 and HGF	Increased expression of cardiovascular-relevant cytokines and enhanced trophic activity	(31) 2010

CM: condition media, Exo-PGN: exosome-PGN-hydrogel, AKT: protein kinase B, BMDMSC: bone marrow-derived mesenchymal stem cells, VEGF: vascular endothelial growth factor, CSC: cardiac stem cell, STRO-1: stromal precursor antigen-1, FGF-19: fibroblast growth factor-19, MIF: macrophage inhibitory factor, PDGF-D: platelet-derived growth factor D, MPCs: mesenchymal precursor cells.

Table 2. Enriched animal mesenchymal stem cell secretome and its effects on cardiovascular repair

Tissue cell source	Study procedure	Methodology for secretome optimization		Modified factor under preconditioning	Outcome	Reference/ Year
Mice BM-MSCs	In-vitro study	MSC seeding density	CM	No result	Generating functional conditioned medium	(32) 2018
Mice BM-MSCs	Mouse MI model	Overexpression of Lamp2b by IMTP plasmid	Engineered exosomes	No result	Improvement of therapeutic effects of exosomes on acute myocardial infarction	(33) 2018
Mice BM-MSCs	In-vitro study	miR-132-Electroporated Exosomes	Exosomes	No result	Induction of tube formation of endothelial cells	(34) 2018
Mice BMDMSC	Mice MI model	Depletion of nuclear casein kinase and cyclin-dependent kinase substrate 1 Hypoxia	BM-MSCs secretion	VEGF	cardioprotective effects against MI	(35) 2017
Rat BM-MSCs	Rat MI model	Overexpression of calcium/CAMKK1	CM	No result	Improved cardiac function following vascular density increase and scar formation decrease	(36) 2017
Rat BM-MSCs	In-vitro study	Hypoxia	CM	No result	Promote cardiac regeneration	(37) 2014

MSC: mesenchymal stem cell, CM: condition media, MI: myocardial ischemia, BM-MSCs: bone marrow-mesenchymal stem cells; CAMKK1: calmodulin-dependent protein kinase kinase-1; VEGF: vascular endothelial growth factor; BMDMSC: bone marrow-derived mesenchymal stem cells.

(32); their types, properties, and therapeutic mechanisms are reviewed below.

Insulin-like growth factor-1

Insulin-like growth factor-1 (IGF-1) is an essential regulator of proliferation, migration, and apoptosis at the cellular scale. The anti-apoptotic and vasculogenetic properties of IGF-1 are ideal for restoring cardiac function after MI. IGF-1 inhibits hypoxia-induced apoptosis, promotes CSC differentiation and myocardial regeneration, and enhances overall tissue survival (38,39). It has been previously reported that a week of IGF-1 administration (100 μg/kg) could ameliorate heart failure by promoting CSC survival, proliferation, and differentiation (40,41).

Insulin gene enhancer binding protein ISL-1

In cardiac development and cardiomyocyte differentiation, insulin gene enhancer binding protein ISL-1 (Islet-1) plays a considerable role as a regulator, a role which is also essential to cardiac function. Regarding stem cells, this factor plays a central role in cardiomyocyte differentiation through epigenetic modifications, such as the acetylation of histones and methylation of DNA strands (23-25). It has been shown that overexpression of Islet-1 in MSC with lentiviruses could facilitate MSC differentiation to cardiomyocytes (42). Therefore, Islet-1 gene induction may improve the MSC secretome in cardiac regeneration.

Primary fibroblast growth factor (bFGF)

Previous data showed that bFGF can increase the migratory activity of MSCs after transplantation. It also enhances the engraftment and therapeutic influence of MSCs, increasing MSC differentiation into cardiomyocytes. bFGF can improve the ischemic environment after MI by promoting new capillary formation by triggering the release of vascular endothelial growth factor and hepatocyte growth factor (HGF), meaning that bFGF can improve ventricular function by promoting angiogenesis and vasculogenesis (43-47). Liguori et al reported that fibroblast growth factor-2 (FGF2) decreases myofibroblast differentiation and fibrotic tissue formation (48).

Interleukins

Interleukins (ILs) are various cytokines that regulate cardiac development, function, and pathogenesis. Previous studies have discussed the beneficial effect of using IL-1β in mediating neovascularization post-myocardial ischemia and promoting cardiac tissue development (49).

Recent data has shown that the MSC secretome modulates immune response via IL-10 as an anti-inflammatory cytokine. Also, the secretome contains IL-6, which mediates the immunomodulatory effect of MSC secretions (50). Exposure to hypoxic conditions triggers the upregulation of IL-11 in MSCs. The enhanced expression of IL-11 promotes angiogenesis, leading to notably longer tubular structures and increased presence of connections and tubules compared to the normoxic control medium (51).

Widowati et al reported that the amounts of IL-1α, IL-6, and IL-8 increased with hypoxia and high cell passage number in the MSC secretome (52).

Transforming growth factor β family

Transforming growth factor β1 (TGF-β1)

TGF-β1, a member of the TGF-β family, makes a well-known contribution to embryonic heart development. Following the administration of TGF-β1, it has been observed that stem cells exhibit the activation of markers specific to the cardiac system. This factor can modulate survival, proliferation, differentiation, and migration in various cells. Therefore, TGF-β1 could improve the curative potency of differentiated cardiomyocytes in clinical use (53-56). The anti-inflammatory and fibroblast-activating effect of TGF-β1 has been implicated in regulating cardiac regeneration (57).

Bone morphogenic protein-2

Bone morphogenetic proteins (BMPs), particularly BMP-2, are other notable members of the TGF-β family. Many studies have illustrated the therapeutic potential of BMP-2 in MI. Studies have shown that BMP-2 promotes the contractility of cardiomyocytes and prevents cell death after MI. Other BMP sub-types are significant; BMP-4 promotes cardiac differentiation, and BMP-10 plays an essential role in embryonic cardiogenesis. In addition, the BMP signaling pathway regulates the reproduction, differentiation, and viability of cardiac progenitor cells (7,58).

Hepatocyte growth factor

There are various cellular responses that the HGF signaling pathway governs during embryogenesis and tissue homeostasis. Extensive research has been conducted on the physiological impacts of HGF1 during the initial stages of cardiac development. They are recognized for enhancing the activation of transcription factors and genes related to cardiac function, playing a crucial role during the initial stages of cardiac development. Moreover, HGF1 effectively restrains the generation of reactive oxygen species (ROS) while simultaneously suppressing cardiomyocyte apoptosis. As a result, HGF1 holds potential as a valuable therapeutic element for treating heart failure (59-64).

Platelet-derived growth factor

Current studies suggest that platelet-derived growth factor (PDGF) has cardioprotective effects in ischemic conditions. PDGF facilitates the generation of cardiac-specific markers in both stem cells and cardiac progenitor cells. Moreover, the release of PDGF initiates the proliferation, migration, differentiation, and cell cycle progression of cardiac progenitor cells. These findings suggest that the secretion of PDGF leads to the inhibition of cellular injury and death in cardiomyocytes after ischemia (64-66). Furthermore, priming MSCs with PDGF improves the therapeutic effect of the MSC secretome for cardiac ischemia (66).

Stromal-derived growth factor-1

Cardiomyocytes secrete stromal-derived growth factor-1 (SDF-1) in response to myocardial ischemia, resulting in a significant mobilization and migration of stem cells, primarily mesenchymal and CSCs, towards the ischemic site. The promotion of stem cell homing is followed by a reduction of the infarcted heart tissue size, and

consequently, an improvement in cardiac function can be expected after administrating SDF-1 (30,67-71).

Vascular endothelial growth factor

Numerous studies have consistently indicated that the primary mechanism by which stem cells mediate cardioprotection following ischemia is through the action of vascular endothelial growth factor (VEGF). VEGF plays a crucial role in stimulating the mobilization of stem cells from the bone marrow and their subsequent recruitment and differentiation into cardiomyocytes and endothelial cells. Consequently, VEGF promotes both myogenesis and angiogenesis, thereby facilitating the process of post-ischemic cardiac repair. Moreover, VEGF possesses anti-fibrotic and anti-inflammatory properties, contributing to its diverse clinical applications (72-74).

Extracellular vesicles

Exosomes

Exosomes are small vesicles attached to the endoplasmic membrane, measuring between 30 and 150 nm in diameter. These vesicles, found outside cells, contain components such as proteins, lipids, and RNA, particularly microRNA and mRNA. They originate within cells and are actively secreted by various cell types. Exosomes facilitate cell communication at intercellular and tissue levels by releasing bioactive molecules to transport cargo. Recent research suggests that exosomes derived from MSCs can potentially be used in cell-free therapeutic approaches for cardiac repair. This is due to their ability to enhance cell survival, promote cell proliferation, and stimulate vasculogenesis by mitigating inflammatory reactions in cases of heart infarction (19,75).

Microvesicles

Microvesicles (MVs) are extracellular vesicles originating from different cell types ranging in size from 100 nm to 1 μm. These MVs play a pivotal role in cellular interaction at the ischemic site. By secreting MVs, cells facilitate proliferation induction and apoptosis suppression. Consequently, MVs are recognized as a significant regenerative mechanism and a fundamental factor contributing to the efficacy of MSC therapy (76-79).

Facilitating an optimal environment for enhanced cell-to-cell communication is beneficial for differentiating CSCs and maintaining existing cells in cardiac pathologies. The MVs derived from stem cells serve as potent mediators of cellular communication, exerting both activating and inhibiting effects on various biological processes while mitigating the detrimental effects of CVDs (78,80,81).

MVs fulfill various functions, including transmitting genetic information, immunomodulation, and promoting angiogenesis (82). These MVs comprise genetic material, proteins (e.g., transcription factors, cytokines, and growth factors), transmembrane proteins, and cellular receptors from their source cells. Furthermore, MVs transport genetic material such as mRNA, microRNA, and DNA from source to recipient cells (83).

Recent investigations have revealed that MVs derived from stem cells contain genetic information and bioactive factors. These components influence signaling pathways, facilitating the ischemia/reperfusion process during the restitution of acute injuries (84).

This genetic transfer optimizes the capabilities of stem cells and enhances cellular differentiation and phenotypic modulation (85). This particularly applies to cardiac tissue, suggesting a potential intervention to enhance cardiomyocyte function after cardiac damage (86).

An example is miR-31, which explicitly targets HIF-1α to promote angiogenesis. Recent data has shown that preconditioning adipose-derived mesenchymal stem cells (ASCs) in endothelial differentiation medium amplifies miR-31 secretion and facilitates angiogenesis. Conversely, miR-129-5p has been demonstrated to downregulate ROS production and inhibit apoptosis in response to oxidative stress (87).

HIF-1α overexpression yields miR-15, miR-16, miR-17, miR-31, miR-126, miR-145, miR-221, miR-222, miR-320a, and miR-424, which can also be extracted to a greater extent from MSC-derived MVs (86). MSC-derived MVs have the potential to act as immunomodulators through the secretion of cytokines and RNA, making MV treatment a viable option for addressing inflammatory responses following a heart attack (88).

The process of angiogenesis is vital for maintaining and enhancing the circulation of blood flow, absorption of nutrients, and exchange of respiratory gases. The mentioned functions are often affected in cases of ischemic injury or congestive heart failure. Due to cellular communication and enhanced signal transduction, the ability of MVs to promote and induce angiogenesis has been widely acknowledged (89).

MSC-derived MVs demonstrate enhanced efficacy in facilitating the restoration of blood circulation and decreasing the size of tissue damage caused by ischemic injury. This remarkable ability stems from their ability to initiate blood vessel development (90).

MSC-derived MVs from the bone marrow have demonstrated the ability to induce angiogenesis by activating protein kinase B (AKT), STAT3, and ERK signaling pathways. These signaling factors enhance the expression of crucial mediators such as VEGF, bFGF, and TGF-β, all contributing to angiogenesis (89).

Likewise, MVs derived from ASCs have facilitated angiogenesis both in vitro and in vivo. The increased presence of proliferative cyclin molecules, namely cyclin D1 and cyclin A1, as well as the secretion of growth factors like VEGF, PDGF, fibroblast growth factor (FGF), and epidermal growth factor (EGF), contribute to the angiogenic potential of ASC-derived MVs. Furthermore,

by delivering RNA and miRNA, MVs stimulate angiogenesis, and their administration to the peri-wound area has proven to enhance wound healing primarily by promoting angiogenesis (91).

Figure 2 provides an overview of the secretome's beneficial effects on supporting cardiac regeneration in ischemic heart conditions.

Optimization of the mesenchymal stem cell secretome

Recent studies have recommended the optimization of MSC cultures to produce an enriched secretome with sufficient efficacy for therapeutic purposes. Consequently, a significant body of literature has been devoted to investigating various parameters that may influence the quality of the secretome. Some of these parameters are presented in Tables 1 and 2. Figure 3 provides an overview of the methods used to enrich a conditioned media with the MSC secretome (32).

The donor source and the cell source are two primary factors that can affect the variability in secretome

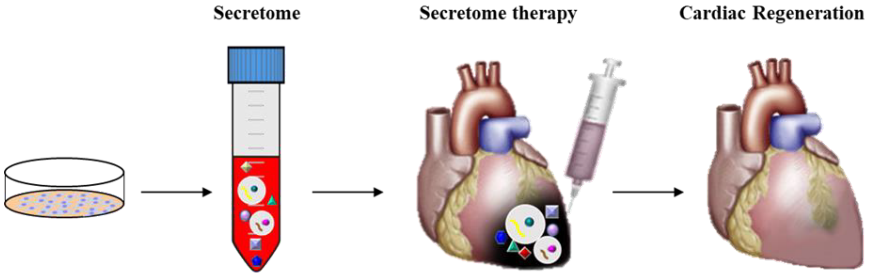

Figure 2. Summary of the beneficial effects of the secretome in promoting cardiac regeneration in the ischemic heart

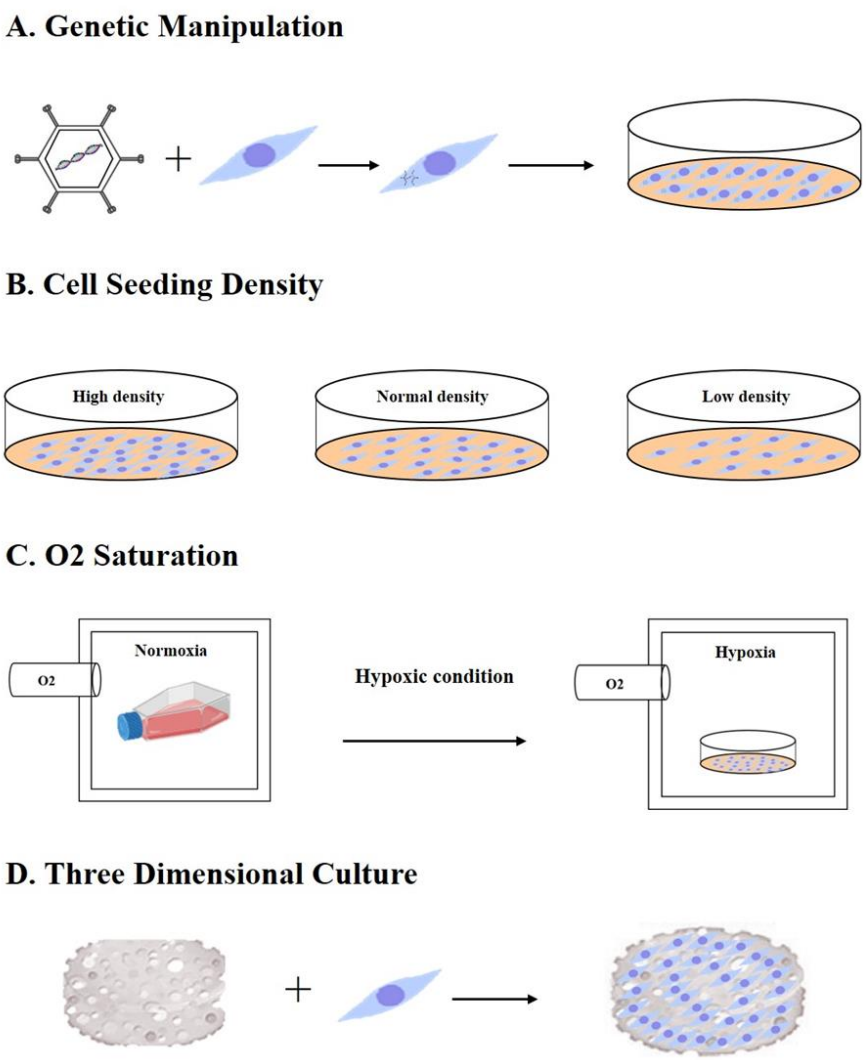

Figure 3. Depicts different approaches to mesenchymal stem cell secretome enrichment: A. genetic manipulation; B. cell seeding density; C. O2 saturation; D. three-dimensional culture

composition. Preconditioning strategies have been widely utilized to modify the original secretome. These strategies include physiological preconditioning, molecular preconditioning using proteins, genetic manipulation, pharmacological preconditioning, and cell stress induced by serum, glucose deprivation, and hypoxia. Additionally, physical preconditioning through three-dimensional cultures stimulates MSCs to enhance the secretion of the secretome into the culture medium (49,50). Tables 1 and 2 showcase the secreted factors influenced by different preconditioning methods.

Various factors, such as the origin of the donor, the source of tissue cells, and strategies employed for preconditioning, can impact the stem cells' secretion capabilities. Consequently, these factors may impact the therapeutic effect of the secretome. Recent data have demonstrated that the therapeutic effect of the secretome acquired from fetal-derived MSCs (placenta and Wharton jelly) surpasses that of adult-derived MSCs (adipose tissue and bone marrow). Microenvironmental cues significantly influence the features of the secretome. Therefore, conducting in vitro experiments under equal conditions using similar MSC isolation and expansion methods and a standardized secretome isolation protocol is essential to facilitate a meaningful comparison between the secretome acquired from cells of different sources. Furthermore, a hypoxic condition may enhance the angiogenic effect of the MSC secretome.

Conclusion

Recent research indicates that the favorable results observed following MSC engraftment can be attributed to the paracrine impact of MSCs. The secretions of MSCs promote angiogenesis, inhibit inflammatory responses, and reduce fibrosis and infarction size. Moreover, this paracrine effect mitigates myocardial damage and improves ventricular remodeling, ultimately facilitating the recovery of cardiac function. However, no universally accepted method for optimizing the MSC secretome exists, and viewpoints differ. Future studies should investigate the factors that regulate and enhance the functions of the MSC secretome.

Authors' Contribution

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Project administration: Mona Saheli.
Resources: Mona Saheli, Shahriar Dabiri.
Software: Kayvan Khoramipour.
Supervision: Mona Saheli, Masoumeh Baghalishahi.
Validation: Mona Saheli, Masoumeh Baghalishahi, Shahriar Dabiri.
Visualization: Shahrzad Sadat Eftekharvaghefi, Shahriar Dabiri.
Writing–original draft: Mona Saheli, Masoumeh Baghalishahi.

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

Not applicable.

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