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■ REVIEW ARTICLE

Emerging Novel Stem Cell Therapies for Cardiovascular Diseases

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ABSTRACT: Cardiovascular diseases (CVDs), including atherosclerosis, ischemia/reperfusion (I/R), and heart failure (HF), present a difficult problem with a high mortality rate. One method of treating various cardiovascular diseases (CVDs) could involve using Mesenchymal stem cells (MSCs), which are multipotent non-hematopoietic cells and their exosomes that are being researched as a promising tool for tissue regeneration. This review explores how MSCs work and their role in cardiac repair, with a focus on key challenges that include the survival rate of cells after transplantation, incomplete differentiation, biosafety concerns, and the complexity of the effective application of these therapies *in vivo*. Additionally, we go over cardiovascular diseases such as heart failure (HF) and peripheral arterial disease (PAD) and discuss the potential of MSCs, MSCs-derived exosomes, or hPSCs to treat these conditions, highlighting the latest breakthroughs in heart tissue reparative therapies. Finally, the paper will address the most relevant issues involving this technology and current efforts to form solutions.

KEYWORDS: Biomaterials and Regenerative medicine, Cell and tissue engineering, Cardiovascular diseases (CVDs), Mesenchymal stem cells (MSCs), exosomes.

■ Introduction

Cardiovascular diseases (CVDs), which include heart disease and heart stroke, are one of the leading causes of death worldwide, contributing to approximately 17.9 million deaths annually and affecting over 500 million lives yearly.[1,2] Traditional treatments such as heart transplantation, revascularization interventions, and pharmacotherapy deliver positive results, including better quality of life and progression management. However, these therapeutic interventions often focus on alleviating symptoms, rather than the root cause of the issue. One challenge in addressing the root cause of CVDs is the heart's limited ability to regenerate. This has led fields like regenerative medicine, tissue engineering, and cell-based therapies to shed some hope in improving the recovery of damaged tissues.

Stem cells are undifferentiated cells that appear in human tissues and organs. These cells give rise to differentiated cells that are the foundation of biological structures and are characterized by capabilities such as extensive proliferation (self-renew), clonality (arising from a single cell), and differentiation into other cell subtypes.[3] They can be derived from different sources and have contrasting differentiation potential. For instance, embryonic stem cells (ESCs) are pluripotent stem cells that naturally are found in the inner cell mass of the human blastocyst and can generate cell types from all three germ layers: mesoderm, ectoderm, and endoderm. Somatic stem cells are found in most human tissues and are multipotent, meaning they can differentiate into cell types from a single germ layer.[4] Mesenchymal stem cells (MSCs) are somatic cells that have been recognized in stem-cell therapy for their ability to differentiate into bone, cartilage, muscle, neural, skin, and corneal cells. This versatility has allowed MSCs to demonstrate therapeutic promise in numerous studies about neurodegenerative disorders, autoimmune as well as cardiovascular diseases (CVDs).[5] Induced pluripotent stem cells (iPSCs) are derived from adult somatic cells that had been genetically reprogrammed to resemble ESC cells.[2] iPSCs have revolutionized regenerative medicine because they resemble ESCs, without the need to use human embryos, making their utilization ethical and providing opportunities for disease modeling. Furthermore, these cells have shown potential in treating blood, cardiovascular, and degenerative disorders.[6]

First, this paper will go over CVDs, and discuss in detail heart failure (HF), and peripheral arterial disease (PAD), because these diseases result in cardiomyocyte death and damaged tissue. Additionally, the review aims to uncover the current evidence on the workings of MSCs and iPSCs as well as explain the role of these cells in cardiac tissue engineering and regenerative medicine. Finally, we will uncover the main issues revolving around stem cells, because, despite the potential of these cells, there are still a plethora of problems in using them *in vivo*.

■ Discussion

Cardiovascular diseases, risk factors, and characteristics:

Cardiovascular diseases (CVDs), despite their decline, remain the leading cause of mortality and morbidity worldwide, affecting over 500 million people's lives yearly.[7] CVDs occur for a plethora of reasons including modifiable risk factors such as an unhealthy diet, inactivity, tobacco use, and alcohol consumption, as well as non-modifiable including age, sex, family history, and ethnicity. These behaviors are associated with conditions namely diabetes, obesity, hypercholesterolemia, hypertriglyceridemia, and hypertension, that are linked to various CVDs. Approximately all cardiovascular disease

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progression and pathology are of atherosclerotic origin, which leads to coronary artery disease (CAD), venous thromboembolism, cerebrovascular disease, and peripheral vascular disease.[8] Eventually, these diseases are linked to stroke, myocardial infarction, and heart failure. In this paper, we will focus on the potential to treat issues that result from CVDs such as cardiomyocyte apoptosis and cardiac fibrosis with stem cells. These conditions have been studied extensively in relation to cell-based therapy and have demonstrated positive results in cardiac regeneration.[9,10]

Heart Failure (HF):

Heart Failure is a heterogeneous clinical syndrome that usually results from underlying diseases such as hypertension, cardiomyopathy, coronary artery disease, and valvular heart disease that cause abnormal heart structure or function. Common symptoms include breathlessness, swelling of body parts, wheezing, and coughing. Medical specialists can identify further symptoms like elevated jugular venous pressure, pulmonary crackles, and peripheral edema.[11] If the diagnosis is unclear elevated levels of natriuretic peptides in the blood and evidence of pulmonary or systematic congestion are a sure sign of HF.[12] HF is classified into acute and chronic syndromes. Chronic heart failure (CHF) is a long-standing condition when the heart gradually weakens and pumps blood less efficiently. It is assessed by a system, that emphasizes the left ventricular ejection fraction (LVEF) which is classified into three groups: a reduced ejection fraction LVEF ≤ 40%); a mildly reduced ejection fraction (LVEF 41–49%); and a preserved ejection fraction (LVEF ≥ 50%).[12] Acute heart failure (AHF) is typically described as a sudden worsening of heart failure symptoms from events such as myocardial infarction, severe valve dysfunction, or hypertensive crises that often lead to hospitalization. In this review paper, we will focus on CHF, because cell-based treatments aim to slowly regenerate the damaged heart tissue and potentially reverse the progression of HF. In contrast, AHF typically demands urgent interventions like revascularization or mechanical support.

Current treatments for HF:

Currently, HF has four classified pharmacological treatments depending on the LVEF (Table 1). First, there are renin-angiotensin-aldosterone system inhibitors (RAASi). These include angiotensin receptor/neprilysin inhibitors (ARNI), ACE inhibitors (ACE-I), and angiotensin receptor blockers (ARB). The rest are beta blockers, including mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).[13] Other treatments may include diuretics, device therapy, oxygen therapy, lifestyle changes, and for patients with end-stage heart failure, heart transplantation, and revascularization interventions. Even though the morbidity and mortality of patients with HF have reduced, during the last decade the success rate of drug-development programs and clinical studies has been low, with a few exceptions. While pharmacotherapy alleviates symptoms and manages to stop progression, it often fails to achieve long-term recovery because the origin of problems like muscle fibrosis and the death of cardiomyocytes is not addressed. The only treatment for patients with heart failure remains heart transplantation, however, we have to acknowledge the donor organ scarcity and the high costs that come with it. This is why researching new methods, like cellular-based therapies to treat HF that focus on reducing the level of inflammation, promoting the differentiation of myocardial cells and inhibiting fibrosis is crucial.

Table 1: This table describes the current treatments for heart failure.

Medication Class	Example Drugs	Mechanism of Action	Therapeutic Effects
ACE Inhibitors (ACE-I)	Lisinopril, Enalapril, Ramipril	Prevents the conversion of Angiotensin I to Angiotensin II, which decreases aldosterone secretion and vasoconstriction.[14]	Manages hypertension, reduces workload on the heart, manages disease progression and symptoms
Angiotensin II Receptor Blockers (ARBs)	Losartan, Valsartan, Candesartan	Blocks the action of Angiotensin II by targeting an enzyme, which prevents vasoconstriction.[15]	Similarly to (ACE-I), ARBs lower blood pressure and prevent damage to the heart, and are often used when ACE inhibitors are not tolerated.
Beta-Blockers	Metoprolol, Carvedilol, Bisoprolol	Blocks the action of adrenaline by targeting beta-adrenergic receptors, causing the heart to beat more slowly.[16]	Lowers heart rate, helps treat angina, prevents arrhythmias, reduces oxygen demand
Mineralocorticoid Receptor Antagonists (MRAs)	Spirinolactone, Eplerenone	MRAs block receptors that bind aldosterone, which reduces sodium retention and myocardial fibrosis.[17]	Manages disease progression, decreases body fluid and lowers blood pressure
Diuretics	Furosemide, Bumetanide, Torsemide	Promotes the excretion of sodium, chloride and potassium, which reduces blood volume.[18]	Helps achieve the state of euvolemia, gets rid of symptoms such as pulmonary congestion and edema.
Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)	Sacubitril/Valsartan (Entresto)	Blocks the receptors to which angiotensin II typically attaches, inhibits neprilysin, and in result increases levels of natriuretic peptides which promotes vasodilation.[19]	Widens blood vessels, which improves blood flow and reduces workload on the heart.
SGLT2 Inhibitors	Dapagliflozin,	Block the SGLT2 amount of reabsorbed glucose and sodium in the blood.[20]	Can decrease risk diabetic and non-diabetic HF patients.
Ivabradine	Ivabradine	Inhibits the cardiac pacemaker current (I_f), which reduces heart rate without affecting contractility .[21]	Reduces heart rate in patients with HF.
Digoxin	Digoxin	Inhibits the sodium-potassium ATPase pump, which enchances myocardial contractility.[22]	Manages symptoms of HF, helps control arrhythmias. Also used in atrial fibrillation.
Vasodilators	Hydralazine, Isosorbide Dinitrate (combination)	Decreases systematic vascular resistance (SVR), and increases blood flow.[23]	Lowers blood pressure and improves symptoms of HF patients.

Peripheral Arterial Disease (PAD):

PAD is a common condition defined by abnormal narrowing of the peripheral arteries that supply blood into the limbs and the periphery. The major cause of PAD is the build-up of plaques in arteries, known as atherosclerosis. Less common causes include embolism, blood vessel inflammation, and injury. Typically, PAD affects the legs, but other arteries may also be involved, such as those of the arms, neck, or kidneys.[24]

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Major risk factors for this disease include tobacco use, diabetes mellitus, hypertension, HIV, hypercholesterolemia, age, obesity, family history, and elevated levels of homocysteine. The general symptom of PDA is intermittent claudication, an intense muscle pain that occurs during exercise and is localized to the thigh, hip, buttock, and calf muscles.[25] Other symptoms can range from asymptomatic, in which patients do not exhibit any noticeable symptoms, to chronic limb-threatening ischemia (CLTI), a severe stage of PAD that is defined by an inadequate supply of blood to a limb to allow it to function normally and includes manifestations such as lower-limb rest pain, gangrene, ulceration, stroke, or myocardial infarction (MI).[26,27] Acute limb ischemia is another manifestation of PAD, that can result in a loss of a limb. It typically occurs of a sudden block of blood flow due to an embolism or thrombosis.[28]

Current treatments of PAD:

Current treatments are based on age, risk factors, illness severity, and functional status (Table 2). The therapies are divided into two broad categories focused on improving symptoms and progress management. For early-stage PAD patients, the primary approach is to reduce the risk factors of all CVDs and make lifestyle changes, including diet, exercise, and elimination of tobacco and alcohol. Pharmacotherapy for PAD involves antiplatelet agents such as aspirin, clopidogrel, ticagrelor, and vorapaxar. Furthermore, direct OAC medication like rivaroxaban, antihypertensive therapies that use angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and statin therapy can help manage the progress of PAD, usually alongside lifestyle changes and, when necessary, surgery.[26]

Advanced-stage patients, specifically with Chronic Limb ischemia (CLI) or Chronic Limb-Threatening ischemia (CLTI) are candidates for revascularization therapy, including endovascular, surgical, or combined endovascular and surgical intervention, that aims to reduce the damage of tissue, relieve symptoms, and prevent further complications such as limb loss or myocardial infarction.[24] While pharmacotherapy and revascularization interventions offer some benefits, they do not provide long-term solutions. Additionally, they have been related to side effects like abdominal pain, bleeding, flatulence, headaches, and limitations such as restenosis, complications from surgery, and limited effectiveness. Lately, researchers have been focused on finding more permanent solutions involving novel strategies such as cell-based treatments, regenerative medicine, and gene therapy that provide fast recovery, the growth of new healthy tissues, and fewer adverse reactions.[26]

Table 2: This table describes the current treatments of PAD.

Treatment type	Specific Treatments	Explanation
Lifestyle Modifications	Smoking cessation, Exercise, Heart-healthy diet	Quitting smoking reduces arterial damage. Regular exercise improves circulation and reduces the risk for all CVDs. A healthy diet can manage weight, lower cholesterol, balance blood sugar, and improve overall quality of life.
Medications	Antiplatelet agents (e.g., Aspirin, Clopidogrel), Statins, Cilostazol, Pentoxifylline	Antiplatelet agents prevent blood clots from forming by stopping the platelets from sticking together.[29] Statins prevent plaque buildup in arteries by lowering cholesterol, specifically low-density lipoprotein (LDL) cholesterol.[29] Cilostazol widens blood vessels, improves blood flow, and reduces symptoms of claudication. [30] Pentoxifylline improves blood flow by reducing blood viscosity and making red blood cells more flexible.
Advanced modifications	Rivaroxaban, Vorapaxar	Rivaroxaban is an anticoagulant that reduces the risk of blood clots by inhibiting a protein involved in clot formation.[31] Vorapaxar is a protease-activated receptor-1 antagonist that decreases the risk of cardiovascular events in PAD patients by inhibiting thrombin-related platelet aggregation.[32]
Surgical and Minimally Invasive Procedures	Angioplasty, Stenting, Bypass surgery, Cryoplasty, Drug-coated balloons	Angioplasty opens blocked coronary arteries and involves using a balloon to widen the narrowed artery.[33] Stenting is a small tube placed in passages, such as narrowed blood vessels to provide the heart with oxygen-rich blood.[34] Bypass surgery creates a new path for blood to flow to the heart around a blocked artery using a graft.[35] Cryoplasty typically involves opening up narrowed or clogged arteries in the legs. Drug-coated balloons and stent work mechanically open the blocked artery, release medication to prevent scar tissue formation and keep the artery open longer.[36]

Stem cells:

Stem cells have been researched since 1950, and had their first breakthrough in 1956 when the first successful bone marrow transplant was performed by Dr. E Donnal Thomas in Cooperstown, New York.[37] They are undifferentiated cells that can specialize into any cell type of an organism and make up all biological materials of our body. Stem cells are characterized by remarkable traits such as extensive proliferation (self-renew), clonality (arising from a single cell), and differentiation into other cell subtypes[3] and can be found both in embryos and adult cells.[4] They all could be characterized into five groups based on their differentiation potential: totipotent or omnipotent, pluripotent, multipotent, oligopotent, and unipotent as well as based on their origin: ESCs, iPSCs, adult or somatic, and fetal stem cells.[3] Totipotent stem cells are found in the early stages of embryonic development and have the highest differentiation potential because they can divide into any adult cell including both embryo and extra-embryonic structures. Pluripotent stem cells originally arise from the inner cell mass of a human blastocyst and can differentiate into cells of all three germ layers: mesoderm, ectoderm, and endoderm. Multipotent stem cells are more specialized and can differentiate into cells of the same lineage. Oligopotent stem cells have little differentiation potential and can only differentiate into cell subtypes of a specific tissue. Unipotent stem cells have the lowest development potential and are only able to form and divide into one specific cell type.[7,38] This unique

ability to differentiate makes these types of cells crucial in the research and progress of regenerative medicine. In the next paragraph, we will evaluate the stem cells that are the most appropriate for cardiac repair.

Stem cells for cardiac repair:

Stem cell therapy holds significant potential for cardiac reparative therapy, with various stem cell types demonstrating certain advantages and drawbacks. ESCs and iPSCs are pluripotent, which allows them to develop into cardiomyocytes, endothelial cells, and smooth muscle cells. This makes them suitable for generating personalized therapies because of their ability to differentiate into a wide array of cell types (Figure 1). However, the transplantation of ESCs or ESC-derived cells is plagued by several formidable problems that involve graft rejection, arrhythmias, and the potential risk of teratomas. ESCs can develop into mature, contracting myocytes *in vitro*, which provides potential for the regeneration of dead myocardium.[39,40] However, there is a great possibility that ESCs might form teratomas in the host cell, which paves the way for a wide array of issues that include potential tumorigenicity, ethical concerns, the need for long-term immunosuppression, and pro-arrhythmic actions.[41] In contrast, iPSCs offer pluripotency similar to ESCs, not requiring lifelong immunosuppression. However, preclinical studies indicate an increased risk for arrhythmogenesis and possibly tumor formation.[42] MSCs are favored due to their secretion of bioactive molecules and microvesicles that activate tissue repair processes, immunomodulatory properties, ability to differentiate into cardiac-relevant lineages, and ease of isolation. They are easily accessible from abundant sources such as bone marrow and adipose tissue and show no evidence of tumorigenic or arrhythmogenic risk, making them favorable candidates for cardiac repair.[43, 44] CSCs require access to adult cardiac tissue, and it is still unknown whether there is a need for immunosuppression. Nonetheless, they are capable of stimulating endogenous repair by paracrine signaling (growth factors and microvesicles) and are not tumorigenic or arrhythmogenic. Furthermore, they have a more focused role in cardiac repair, without concerning ethical issues. HSCs offer potential benefits, contributing indirectly by generating immune cells that modulate inflammatory responses and tissue repair. HSCs are often derived from bone marrow and do not raise concerns about immune rejection. Furthermore, they can promote angiogenesis, which can improve heart function. However, there are certain disadvantages, such as limited differentiation range into cardiomyocytes or vascular cells. Overall, while iPSCs and ESCs offer extensive differentiation, MSCs, CSCs and HSCs provide more practical advantages for cardiac repair therapies.

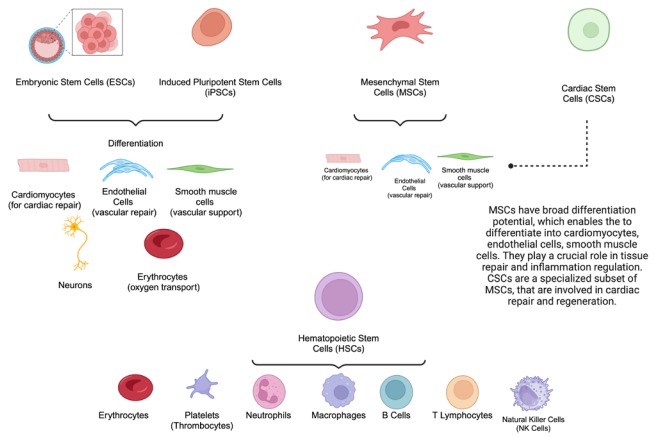

Figure 1: The figure demonstrates the differentiation potential of embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, cardiac stem cells, and hematopoietic stem cells for cardiac repair. Created in https://BioRender.com.

Mesenchymal stem cells:

MSCs represent a vast number of multipotent somatic stem cells that are found in almost all existing tissues and have been a target of research for their versatility to differentiate into a wide array of cell types. MSCs can differentiate into adipocytes, chondrocytes, osteoblasts, myocytes, and neurons. Additionally, they are greatly involved in physiological and pathological processes such as cellular homeostasis maintenance, tissue damage, tissue replacement, aging, and inflammatory diseases. Morphologically MSCs have a similar shape to fibroblasts and are usually located near blood vessels.[45] They can be derived from various tissues and have specific qualities based on their origin. For instance, bone marrow-derived mesenchymal stem cells (BM-MSCs) have shown high regenerative and immunomodulatory properties and have been used in many clinical trials that highlighted their safety and effectiveness. The dental pulp is also a source of MSCs with neurotropic properties since they originate from the neural crest. Adipose tissue-derived MSCs (AD-MSCs) can be obtained from abundant adipose tissue, with a minimally invasive procedure, compared to (BM-MSCs), and result in a great number of cells.[46] The unbiblical cord (UC-MSCs), placenta, amniotic fluid, and amniotic membrane are also sources of mesenchymal fetal cells.[7] Synovial fluid-derived MSCs (SF-MSCs) can be useful for joint repair and cartilage repair and also exhibit anti-inflammatory properties.[47] Similarly, periosteum-derived MSCs (P-MSCs) have potential in cartilage and joint repair, however, they are more oriented towards bone formation.[48] These stem cells can also be obtained from the skin (S-MSCs) and aid in wound-healing properties.[49] Overall, MSCs can be characterized by two important functions that make them the main objectives in regenerative medicine. Immunosuppression, tissue repair, and the paracrine action of MSCs give rise to cytokines, chemokines, and growth factors to promote tissue repair.

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Induced pluripotent stem cells (iPSCs):

iPSCs are adult somatic cells that were reprogrammed to resemble ESC.[3] This was first discovered in 2006 by Takahashi and Yamanaka and since then scientists managed to reprogram various somatic cells including skin fibroblasts, hair keratinocytes, mononuclear cells, and urine cells. However, even though there are successful cases of reprogramming somatic cells to iPSCs, the differentiation is still often inefficient, with only a few cells differentiating into specific cell lineages. Furthermore, the process is still not well understood and highly depends on the age and type of somatic cells used.[50] Overall, iPSCs offer a great number of valuable factors that make them attractive for in vitro disease modeling, individualized medicine, and regenerative medicine. Additionally, they helped overcome the ethical limitations that are associated with human embryonic stem cells, because iPSCs are derived from adult somatic cells that come from plentiful sources such as blood, skin, and urine.

Stem cells and CVDs:

There are many problems including cardiomyocyte apoptosis, and cardiac fibrosis, that are still unaddressed by current treatments of CVDs. This is why we aim to address issues that might develop from CVDs and provide solutions using stem cell-based therapies in the next part of this paper.

Heart Failure, MSC-derived exosomes, cardiomyocyte apoptosis, and cell survival:

Acute and chronic heart failure patients, including those with PAD, can suffer significantly from damaged muscle tissue, especially after a myocardial infarction (MI). This is especially critical for PAD patients because the impaired blood flow further worsens the condition and makes it harder for the heart to regenerate. The problem occurs after MI when adult heart cells fail to restore due to ischemia which leads to the irreparable loss of cardiomyocytes. The current treatment is reperfusion, however, it is often linked to the worsening of cardiomyocyte function and tissue damage, a process called ischemia/reperfusion injury. This is why there is a crucial need for novel treatments that help lower oxidative stress and apoptosis after intense therapies.[51]

MSCs are appealing for the treatment of heart disease because they promote angiogenesis and aid in the recovery of ischemic tissue. They can be derived from many sources, however, BM-MSCs are particularly attractive because they are characterized by multidirectional differentiation, weak immunogenicity, high transplantability, and successful clinical trials. Furthermore, the exosomes from BM-MSCs can reduce cardiac injury and achieve positive therapeutic effects on joint action with regulatory RNAs that may help heal tissue injury following MI.[52] The inhibition of cardiomyocyte death with BM-MSCs and their secreted exosomes is a complex task involving microRNAs (miRNAs) found in the exosomes that can influence the process through various pathways.[9]

Current studies of miRNAs in exosomes have provided some positive results by targeting specific pro-apoptotic genes. These studies are focused mainly on finding miRNAs that could potentially suppress genes, such as PTEN or P53, that regulate the cell cycle and apoptosis. When the miRNA suppresses those genes, it prevents cell death and creates a more favorable environment for the survival of cardiomyocytes. For instance, when rat models with ischemia/reperfusion were treated with miR-183-5p, it inhibited FOXO1, a protein that promotes oxidative stress and apoptosis.[53] MiR-183-5p was another miRNA that helped decrease cardiomyocyte death and targeted a protein called Bax, which is proapoptotic.[53] MiR-21a-5p can successfully downregulate the expression of pro-apoptotic genes PTEN, Peli1, and FasL in the heart muscle tissue. Additionally, MiR-25-3p reduces the expression of FasL and Pten, both genes that promote cardiomyocyte death.[54] Other genes that encourage cell death are P53 and Bak1. They were targeted by miRNA miR-125b found in BM-MSCs, which inhibited apoptosis and helped regulate heart function.[55]

However, despite the potential of these therapies, there are still a plethora of challenges that occur while translating this approach into clinical practice. One significant issue is ensuring the long-term survival and integration of the transplanted cells within the heart tissue. MSCs have been shown to improve cardiac function after MI in pigs[56], improve lower limb ischemia in mice,[57] and lower limb movement after spinal cord ischemia in rats.[58] However, after transplantation, most MSCs experience low retention rates and are characterized by cell death due to the stressful environment, which results from ischemia, oxidative stress, and inflammation.[59] Research has shown that only 1-10% of transplanted cells survive a few weeks after injection into the heart.[60] One method that may prolong the survival of MSCs is the encapsulation of MSCs in alginate microcapsules. The goal of this technique is to enhance the therapeutic efficacy of MSCs by prolonging the local presence of MSCs and their secreted factors at a desired location. A study done by researchers showed that the encapsulation of MSCs in alginate, a material used for the protection of MSCs, can prolong the survival rate of these cells in a challenging environment. This approach was tested in rats with osteoarthritis which showed that the encapsulated MSCs stayed alive and active for at least 8 weeks.[59] Another promising approach is the use of bioactive scaffolds, like hydrogels, that have been shown to promote tissue repair and reverse heart damage. For instance, hydrogels can improve retention rates of MSCs at the injection site because they provide a supporting matrix that prevents the cell from being flushed out or migrating away from the target area.[61] Furthermore, hydrogels can deliver growth factors and oxygen to the cells, resulting in longer survival rates and improved integration.[59] A study on live animals showed that the hydrogel is an excellent retention platform for MSCs and might improve the paracrine effect of the transplanted MSCs, contributing to better heart function. Additionally, interstitial fibrosis was decreased significantly in the left ventricle, which may inhibit the remodeling process of the left ventricle. This shows the important role hydrogel-based MSC transplantations could have in cardiac repair. Nevertheless, while they provide benefits, the gels fail to alleviate the harsh microenvironment in the damaged myocardium, which could affect the long-term survival of MSCs. Hence, the hydrogel method still requires further research.[61]

Overall, the ongoing studies of MSC-derived exosomes for treating cardiomyocyte apoptosis are making significant improvements. Recent research done on mice shows that the mi-RNA found in the BM-MSCs can decrease the apoptosis of cardiomyocytes and aid in the process of heart regeneration by targeting proteins and genes that increase the death of these cells. Additionally, using exosomes provides a great delivery approach because they can be engineered to carry specific miRNAs. Nonetheless, translating these approaches into clinical practice presents challenges. Guaranteeing the survival and retention rates of the transplanted cells remains a significant issue due to the harsh environment in the ischemic myocardium, which leads to cell apoptosis and low retention rates. However, techniques like alginate microcapsules and bioactive scaffolds such as hydrogels provide hope of improving the therapeutic efficacy of stem cell therapies. Moreover, it is worth mentioning that while these methods work, they still require further research to optimize their effects, particularly inhibiting inflammation and ensuring the long-term survival of transplanted cells.

Cardiac fibrosis, transplanted cell integration:

Cardiac fibrosis usually occurs from MI, when a great number of cardiomyocytes die, or hypertension. This triggers the activation of myofibroblasts that produce collagen and other extracellular matrix (ECM) proteins that create a scar in the damaged area. The myofibroblast on the muscle becomes stiff from excess deposition of ECM, resulting in disrupted cardiac function that causes reduced ejection fraction or the impairment of electric conductance of the heart which can lead to HF or even death.[62,63]

Stem cell therapies have been researched widely to find new treatments that could reduce cardiac fibrosis and its consequences. Both hPSCs and MSCs have been widely researched, however, judging from the clinical trials in this case hPSCs provided more success. hPSCs are highly expandable and can differentiate into cardiomyocytes (hPSC-CM), therefore serve as a promising treatment for cardiac fibrosis by reducing the scar and increasing vascular density. Furthermore, hPSCs secrete growth factors, cytokines, and other molecules that enhance cardiac tissue regeneration. Nevertheless, when directly injected into the myocardium, the cell transplantation rate is less than 10%.[64] Therefore, there has been extensive research done on how to improve cell retention rates during cell transplantation. For instance, a successful study by Ye Laboratories has reported that using thymosin β4 (Tβ4) in combination with hPSCs-CM promotes angiogenesis, implantation success, and proliferation of endogenous cells in a pig model of myocardial infarction.[65] A study by Zhao *et. al* described that the overexpression of Cyclin D2 in hPSC-CMs decreases the apoptosis of cardiomyocytes, increases heart function, and reduces fibrotic scar tissue damage.[66] In addition, other new ways have emerged that focus on cell transplantation efficiency in the field of cardio TE. 3D bioprinting is a technique that has a lot of potential for fabricating biomimetic scaffolds because it gives a supportive framework for cell proliferation and differentiation. In a recent study core-shell scaffolds were created with electrospun nanofiber yarns (NFYs) as the core and hydrogel as the shell. This provided a three-dimensional structure that mimics the ECM that formed a suitable environment for cellular nutrient exchange and mechanical protection. Additionally, it induced cell alignment and elongation. Unfortunately, this technique of making traditional scaffolds increases the complexity of cell culture, and the precise organization of 3D cell printing is limited. However, 3D printing by computers has shown great promise in fabricating 3D complex structure scaffolds that overcome these limitations. Progression of HF leads to the formation of non-elastic scar tissue that affects heart contraction. 3DBP can potentially develop heart patches that may be able to promote functional CMs migration for repairing the cardium, instead of scar formation. For instance, Bejleri *et al*.[67] developed heart patches using a combination of gelatin methacryloyl (GelMA), and cardiac ECM hydrogel scaffolds with human cardiac progenitor cells (hCPCs). As a result, during cell culture hCPCs showed high viability and exhibited transcriptor factors that regulate the formation of heart cells and a protein troponin T, which is crucial for muscle contraction. Ajdary *et al*.[68] developed a 3D-printed curcumin-releasing heart patch using nanofibrilated cellulose, polyglycerol sebacate (PGS), and polypyrrole (PPy) that helped form structural support, elasticity, and electrical conductivity for cardiac repair. In addition, the slow degradation of cardiac patches made the heart patch suitable for long-term drug release. Nevertheless, this novel technology still has some unresolved challenges that include printing resolution, controlled vascularization, and the limited ability to print soft materials, therefore, further research is needed. For more details on the advancements of 3DBP, please refer to the research by Wang *et al*. which reviews 3D bioprinting in cardiac tissue engineering.[69]

It is important to mention that while stem cell therapy for heart tissue repair has a promising future, it does have certain limitations. While stem cells, including MSCs, hPSCs can aid in cardiac repair by reducing inflammation and supporting angiogenesis, evidence of whether the cells fully integrate and contract in sync with native heart tissue is mixed. One promising method is using bioactive scaffolds, which improve cell retention rates and alignment with native cardiomyocytes, however, ensuring consistent contraction strength and synchronization remains difficult. There are ongoing studies that explore genetic modification, and bioengineering techniques that may amplify MSC differentiation and make these cells more responsive to the cardiac electrical signaling that is required for synchronized contraction.[70] For instance, a promising genetic approach is to engineer MSCs to express cardiac pacemaker ion channels, such as HCN2, which may help MCSs create electrical impulses compatible with cardiomyocyte function. Recent research suggests that MSCs engineered to express the pacemaker "funny" current (If) can generate electrical impulses similar to the cardiac rhythm. HCN2-MSCs transferred into the cardiac tissue can electrically couple with surrounding cardiomyocytes, resulting in the creation of biological pacemakers.[71] This method provides an alternative approach for patients with heart rhythmic disorders as well as could help integrate the engineered MSCs with the

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surrounding cardiomyocytes, leading toward more stable heart contractions.

In summary, cell-based therapy is an advancing technology that holds a lot of promise for developing novel treatments for cardiac fibrosis. Continuous research and technology development are making new treatment strategies that shed hope for better recovery after events like cardiac fibrosis. Nevertheless, many issues related to this field still need to be conquered, such as biosafety concerns, the selection of the right stem cell sources, and ensuring the successful survival of transplanted cells. Furthermore, limitations such as the integration of the transplanted cells and correct synchronization with the native heart tissue are yet to be solved. However, bioengineering techniques such as bioactive scaffolds and genetic modification that engineer MSCs to express cardiac pacemaker ion channels provide hope that the transplanted cells will be able to integrate with the native heart tissue.

The future of stem-cell therapy research:

The field of cardiac tissue repair is mainly focused on improving techniques for improved cell retention, enhanced cell specialization, and the optimization of cell integration with native heart tissue. The first approach that holds great promise is the use of hydrogels. Hydrogels are characterized by biocompatibility, biodegradability, and bioactivity, which can help restore heart function after MI. They are great agent delivery systems for cardiac implants due to their qualities, such as binding, swelling, and absorption. Furthermore, hydrogels have also been shown to be great at enhancing electrical conductivity, resulting in better contraction. They can be injected or applied in hydrogel-based cardiac patches, which can work as mechanically supportive biomaterials. However, to be used clinically, certain challenges must be overcome.[72] Furthermore, researchers have been exploring different stem cell types- particularly MSCs and hiPSCs, that may aid in cardiac regeneration. hiPSCs are great candidates for cardiovascular regeneration. Efforts have been made towards optimizing methods of hiPSC differentiation into vascular cells like endothelial (EC) and smooth muscle cells (SMC). Studies on animal models show that hiPSCs-derived ECs have great potential for promoting neovascularization, which is the formation of new blood vessels.[73] This is crucial in treating various CVDs including PAD and HF, because it restores blood to the ischemic, oxygen-derived tissues, resulting in an improved heart's ability to pump blood effectively and reduce damage from ischemia.[74] Additionally, genetic engineering is another key strategy that helps modify cells for improved responses to cardiac signaling and functional integration. For instance, iPSCs engineered with specific gene modifications are showing promising results in enhancing electrical and mechanical coupling with host cardiomyocytes.[75] In summary, future directions for cardiac repair involve advances in hydrogels, hiPSCs-derived vascular cells, and genetic engineering. While these approaches show great promise additional research is essential to address clinical challenges and optimize these methods for safe and effective patient use.

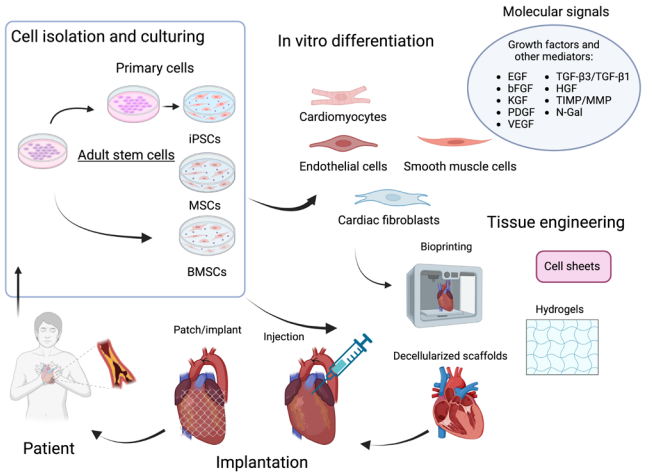

Figure 2: Novel stem cell therapies for cardiac repair using BM-MSCs, MSCs, and iPSCs. Adapted from.[76] Stem cell-based approaches in cardiac tissue engineering: Controlling the microenvironment for autologous cells. Licensed under CC BY 4.0. Created in https://BioRender.com.

Conclusion

In conclusion, the potential of cell-based therapies particularly involving MSCs, hPSCs, and iPSCs provides promise in treating cardiovascular diseases, such as heart failure. These therapies aim to address the root cause of CVDs by focusing on cardiomyocyte apoptosis, ischemia, cardiac fibrosis, and muscle regeneration. While current treatments focus primarily on decreasing disease progression and alleviating symptoms, stem cells provide more targeted strategies for treating CVDs with the potential to repair the myocardium. Nevertheless, despite the progress of research related to cell-based therapies, there are still issues that need to be addressed. Those challenges include the survival rate of cells after transplantation, incomplete differentiation, cell integration and the complex problems of the effective application of these therapies in vivo. Nonetheless, recent research on MSC-derived exosomes for threatening cardiomyocyte apoptosis, and the genetic manipulation of hPSCs for better transplantation potential show significant progress in the field of cardiac TE. Furthermore, new methods of cell application with 3D patches offer exciting potential in healing the injured cardiac muscle and regenerating the damaged tissue. These innovations still require a lot of research and clinical trials to overcome existing challenges, however, they hold significant promise for better and novel treatments that ultimately improve outcomes for patients with cardiovascular diseases.

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