An updated review on the therapeutic potential of stem cells for treating cardiovascular disorders

Abstract:

Despite significant progress in the field of medicine, cardiovascular illnesses continue to be the primary cause of mortality on a global scale. The increasing prevalence of cardiovascular illnesses necessitates the exploration of novel and potential therapeutic strategies to address the escalating risk associated with CVDs. Stem cell therapy has emerged as the central focus of regenerative cardiovascular medicine, surpassing all other treatments and therapies. Multiple clinical trials and studies have demonstrated that stem cell therapy, particularly mesenchymal stem cells, is the most appealing approach for treating cardiac disorders due to their significant therapeutic potential. Recent research have shown that mesenchymal stem cells have a positive impact on several cardiac muscle diseases, such as heart failure, problems with blood vessel lining, damage caused by lack of blood flow, and high blood pressure in the lungs. This study specifically examines the potential, preconditioning techniques, methods of administration, and mechanisms of mesenchymal stem cell (MSC) therapy for the treatment of cardiovascular diseases (CVDs).

Key word:mesenchymal stem cell, cardiovascular disease, cardiogenic myopathies, infusional toxicity, ectopic tissue formation

1. Introduction:

With more than 17 million deaths in 2016, cardiovascular diseases (CVDs) remain a prevalent cause of high mortality worldwide [1] and are projected to cross 25 million annual deaths till 2030 [2]. Generation of a large number of free radicals (ROS) leading to oxidative stress in the area of ischemic necrosis in ischemic heart failure [3] exacerbates cardiac myopathies due to anincrease in apoptotic/necrotic death of cardiomyocytes [4].Developed countries reportedly have lower CVDs than developing Asiatic regions, including Pakistan, which poses a threat to their economies with increased pressure on human resources and health budgets[5, 6]. This situation demands novel therapeutic approaches for decreasing the CVD epidemic. The most

promising emerging therapies include artificial heart transplant and cardiovascular regeneration (biological hearts) approaches which have an advantage over currently used palliative strategies [7, 8]. Now, stem cell therapy is a major focus in regenerative cardiovascular medicine. Except for embryonic-derived stem cells, others are isolated from patients with the same phenotypic and genotypic characteristicsuseful in transplant rejection studies and for developing effective patient-specific therapies [9].

Recent studies have demonstrated the beneficial use of stem cell therapy in various cardiogenic myopathies, including heart failure [10], pulmonary hypertension [11], endothelial dysfunction [12], atherosclerosis [13], and peripheral artery disease [14]. Based on origin, stem cells are classified as adult stem cells and embryonic stem cells [15]. Adult stem cells are further divided into tissue-specific and bone marrow-specific cells (BMCs). BMCs have endothelial progenitor cells, mesenchymal stem cells,andhematopoietic stem cells [16]. Transplantation of progenitor stem cells through infusion or intra-myocardial injection is currently used for treating CVDs as it positively influences cardiac regeneration and improves heart function [17]. Despite this, several shortcomings stills exist, including high costs, immune rejection, infusional toxicity, ectopic tissue formation, safety challenges, ethical concerns of the community in clinical practice, poor survival and differentiation [18, 19]. The cardioprotective effect of stem cells is usually achieved by paracrine interaction between donor and recipient stem cells. (Paracrine mechanisms in adult stem cell signaling and therapy Massimiliano Gnecchi1).

Mesenchymal stem cells (MSCs), first isolated in 1970 [20], are pluripotent progenitor stem cells with the ability of self-renewing as defined by the International Society for Cellular Therapy and can be differentiated into various mesodermal origin cell types like chondrocytes, osteocytes, and adipocytes [21]. They are also named as signaling cells, stromal stem cells, and adult progenitor multipotent cells [22]. Under optimum culture conditions, MSCs demonstrate plastic adherence capability with the expression of CD105, CD90, CD73 surface molecules in absence of HLA-DR, CD79a, CD45, CD34, CD19, and CD14 [23, 24]. MSCs have been isolated from amniotic fluid [25], placenta [26], umbilical cord blood [27], human urine [28], the dental pulp [29], adipose tissue [30], and synovial fluid [31]. MSCs of multiple origins show variations in organ morphology, isolation protocols, and growth conditions on cell culture [32]. They have been investigated as an alternative therapeutic substance in different injury and disease models such as Alzheimer's disease, myocardial infarction, acute renal failure, hepatic injuries, orthopedic

injuries, acute lung injury, autoimmune diseases, corneal damage, cerebral ischemia, and cardiovascular diseases [33-37].The use ofMSCs in medical therapies have several advantages over other stem cells including their encouraging anti-inflammatory properties, low immunogenicity, easy *in vitro* cultivation and expansion [38]. MSCs are strong mediators of cardiogenic tissue regeneration in damaged heart and effects fibrosis, cardiac remodeling, and proliferation of cardiogenic stem cells. Moreover, ease of systemic administration of MSCs through IV injections (intramayocardial) without heart catheterization and their ability to differentiate in to smooth muscle cells,cardiomyocytes, and endothelial cells make them a promising candidate in heart regeneration therapies since their first use incardiomyoplasty by Tomita and co-workers in 1999 [39, 40].

2. Pathophysiology of Cardiovascular diseases (CVDs):

CVDs has a wide range of clinical manifestations such as restenosis, cardiomyopathy, aortic aneurysms, valvular heart disease, coronary heart disease and hypertensive heart failure [41, 42]. CVDs has multiple pathogeneses such as natriuretic peptide ligand-receptor complex- guanylyl cyclase (cGMP) [43], endothelial senescence mediated production of altered extracellular vesicles [44], defective redox status with enhanced superoxide stress leading to atherosclerosi, hypertension [45], altered microRNAs associated with defective proteolysis, lipid metabolism, cell mitosis, and dysregulated inflammatory mediators generation [46], low concentrations of Adiponectin [47] and cell injury associated with inappropriate activation of mineralocorticoid receptors through Rac1-signaling pathways [48]. Recently reported risk factors of CVDs in humans to include age, gender, alcohol consumption, physical inactivity, familial prevalence, depression, nutrient deficiency, hypertension, obesity, diet, and high blood pressure [49-54]. Congenital-based secondary hypertension increases the risk of myocardial infarction (MI), stroke, and heart failure [55]. Similarly, Vitamin D deficiency leads to derangements in cardiac myocyte contraction, abnormal cardiac relaxation with ultimate heart failure [56, 57]. Among cardiovascular disorders, ischemic heart disease is the most common type and is the leading cause of death worldwide with estimated 9 million deaths in 2016 [58]. The Problem in cardiovascular diseases is related to severally limited repair capacity after injury. Heart transplantation is the only ultimate approach to cope with end-stage cardiac failure. But it has limitations of being costly and there are limited organs for transplantation [59]. Therefore, researchers look forward to determining the best and minimally invasive cure for CVDs. For this

purpose, stem cells gained special interest due to their unique self-renewal properties, varied potency, and ability to differentiate into multilineage[60].

3. Interaction with Immune system:

Human MSCs lack expression of MHC-II and costimulatory molecules such as CD40 ligand and B7 [61, 62]. Immunogenic tolerance of MSCs is attributed to their specific immunophenotype and strong immunosuppressive properties [63]. They positively influence both humoral and cell-mediated immune responses. However, their interaction with cells of the immune system is under investigation. From 2001 to 2014, PubMed and ScienceDirect data showed 149 and 495 peer-reviewed research publications based on animal models to study MSCs directed immune-modulation with promising results [64]. MSCs interact with adaptive (dendritic cells, T & B lymphocytes) and innate (natural killer cells) immune components. Cells of innate immunity (natural killer cells, mast cells, neutrophils, eosinophils, macrophages, and dendritic cells) modulate the nonspecific immune response to infections and most of these cells are suppressed by MSCs. Neutrophils are the first line of defense against microbial infections with the production of respiratory bursts[65]. MSCs release IL-6 which suppress respiratory burst [66]. Reversible inhibition of monocytes differentiation into dendritic cells (DCs) with upregulation of HLA-DR, CD86, CD80, CD40, and CD1a surface molecules cause suppression of their antigen-presenting ability [67-69]. PD-L1/PD-1 mediated contact between B-lymphocytes and MSCs causes inhibition of B-cell proliferation, largely depending on culture conditions [70, 71]. Differentiation activity of MSCs is mainly controlled by the TGF-β superfamily and Wnt canonical pathways [72].

They cause immunoregulation through cellular contacts via the PD-1 pathway [73] and secretion of various chemokines [74], cytokines [75], growth factors [76], and biologically active agents [77]. They contribute to immune response homeostasis by creating a tolerogenic environment and preventing untimely T-lymphocytes activation, especially during wound repair or healing [78]. T-cell activation is characterized by secretion and expression of surface molecules such as tumor necrosis factor (TNFα), CD69, CD25, CD38, IL2, HLA-DR, and CTLA-4 [79]. Some studies reported inhibition of CD69 and CD25 expression by bone marrow-derived MSCs in T-lymphocytes treated with phytohemagglutinin[80], while some revealed no direct effect on theexpression of surface molecules [81]. This contraindication may be due to thedifference in the T-lymphocytes population studied in each experiment. Some studies revealed that activated T-

cells can reduce [82] or increase [79]IFNγ secretion in the presence of MSCs; however, this effect depends on the source of the T-cells population under investigation [83]. CD3/CD28 mediated activation of $CD3^+$ T-cells in MSCs presence from adipocytes stimulatesIFNγ secretion. MSCs interfere with the antigen-presenting property of T-cells by suppressing $CD34^+$ progenitor cells[84].

Recent studies have demonstrated that MSCs can survive and differentiate in immunocompatibility- mismatchedxenogeneic or allogeneic transplant recipients [85] with reported ability to induce immunological tolerance in immunocompetent xenotransplant or allotransplant recipients [86]. This uniqueimmunotolerance mechanism is under intensive research and three possible interrelated mechanisms have been proposed. MSCs evade host immune defense by (a) immunosuppression of local environment, (b) modulating T- cell phenotype, and (c) being immune privileged (hypoimmunogenic) [87]. Being hypoimmunogenic enables transplantation of mesenchymal stem cells across histocompatibility barriers and devising therapeutic approaches based on MSCs growth in culture [88].

4. MSCs in Cardiovascular regenerative therapy:

Recently, stem cell therapy gave new insights into cardiovascular disease treatment and clinical operations. MSCs are now considered an attractive candidate for MI treatment; because MSCs can transdifferentiate into cardiomyocytes with complete replacement of damaged cardiomyocytes [89]. Various studies have demonstrated MSCs differentiation into cardiomyocytes and engrafting to host tissue after directly injecting into the myocardium (Mesenchymal Stem Cell-Based Therapy for Cardiovascular Disease: Progress and Challenges LuizaBagno). *In vitro* and *in vivo* treatment of MSCs with 5-azacytidine stimulate their differentiation into beating cardiomyocytes. Directly injected MSCs into infarcted heart induce myocardial regeneration and improve cardiac function. The cardiac function improvement in the rat model of DCM through MSC transplantation was due to myogenesis or angiogenesis and inhibition of myocardial fibrosis. The clinically beneficial effect of MSCs might not be due to their differentiation into cardiomyocytes but also due to their ability to provide a large number of angiogenic, anti-apoptotic, and mitogenic factors [90]. In a study, Konstantinos and coworkers concluded that MSC derived from bone marrow (BM-MSCs) facilitates substantial cardiac recovery and engraftment and differentiation when injected into the porcine heart. Differentiation actually occurs after transplantation [91].

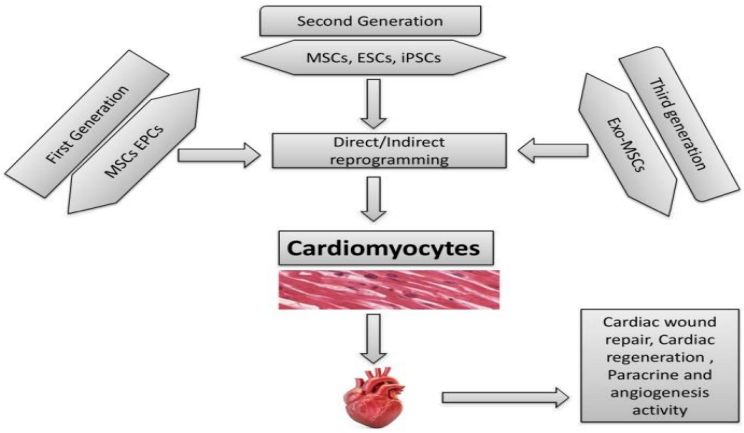

Figure 1Direct reprogramming of cells into cardiomyctes

Preconditioning of MSCs:

Convenient isolation and ex-vivo expansion, along with the greater potential of differentiation into myocardial cells with low rejection rates, have made bone marrow-derived stem cells (BMSCs) a preferred choice for cardiac regenerative therapy [92, 93]. Despite of initial hype and promising results, stem cell therapy is of little clinical usage due to low retention, differentiation, and survival of transplanted MSCs in hostile tissue surroundings. In diseased myocardium, low pH, overexpression of inflammatory mediators, deprivation of oxygen and nutrients cause poor post-transplant survival of MSCs. Aggregation of macrophages and neutrophils in response to myocardial insult leads to reactive oxygen species (ROS) and cytokines, which intensify cell death. This emphasizes the importance of identifying new methods for improving post-transplantation survival and differentiation of MSCs. Optimizing, pre-treating, reprogramming, or preconditioning stem cells by genetic manipulation, pharmacological, environmental/physical, or using cytokines can help transplanted cells to withstand the hostile microenvironment of injured tissue. [94, 95]. Preconditioning of stem and progenitor cells before transplantation with various preconditioning triggers is an emerging research area with established promising results. Preconditioning of MSCs results in increased cell survival by reducing immune responses, enhanced homing to target tissue, and improved neuronal differentiation [96].

Heat shock treatment is one of the several physical preconditioning treatments. Thermal exposure of cardiomyocytes to high temperature (39°C-45°C) triggers HSP70 expression, protecting MSCs from *in vivo* and *in vitro* oxidant stress [97]. Thermal treatment of MSCs to

43°C results in HSP70 and HSP27 secretion, which are associated with increased cell survival [98]. Oxygen tension is crucial for stem cell survival and differentiation in both *in vivo* and *ex vivo* environments. *In vivo*, hypoxia can cause apoptosis, but it can be reduced with MSCs hypoxic preconditioning and overexpression of some important pro-survival genes like Akt. In cell culture, hypoxia can enhance proliferation and differentiation of stem cell lineages by modulating their paracrine activity, resulting in upregulation of IL-6 and angiogenic factors. Hypoxia-induced overexpression of stromalcell–derived factor-1 plays an important role in homing of MSCs [99, 100]. Autophagy is promoted in BMSCs after hypoxic preconditioning and it serves as a protector for MSCs apoptosis under H/SD [101]. Transplantation of hypoxic preconditioned stem cells shows the improved expression of angiopoietin-1, hypoxia-inducible factor 1, and vascular endothelial growth factors along with its receptors i.eBcl-xL, Flk-1, Bcl-2, and erythropoietin. Preconditioned stem cells also show decreased caspase-3 activation and increased angiogenesis after myocardial infarction (MI) [102]. The protective effect of hypoxic preconditioning on cultured cells remains approximately for six days [103].

Pharmacologically active substances also cause increased cell survival. Conditioning mimetics triggers the release of cytokines and growth factors (IGF, VEGF, HGF, Ang-1, and SDF-1α) with angiogenic effects [104]. Priming stem cells with Pitocin (a synthetic analog of Oxytocin) enhances differentiation into vascular cells and cardiomyocytes with increased protection against oxidative stress [105, 106]. Oxytocin treatment cause upregulation of HSP70, HSP27, VEGF, MMPs, TIMPs, and HSP32 with cardiac anti-apoptotic and anti-remodeling properties [107]. In recent years, the protective role of hydrogen sulfide signaling in cardiac myopathies in mammals is under investigation[108]. H_2S plays a critical role in vasorelaxation, angiogenesis, cardioprotection, atherosclerosis inhibition, and lowering of blood pressure [109, 110]. Transplantation of H_2S-treated MSCs improves left ventricular heart function (LVHF), reduces the infarct size, and enhanced cell survival 4-days post-transplantation in themyocardium of MI patient [111]. Nitric oxide is an essential factor of chemical signaling for cardiovascular homeostasis. NO can be generated from a family NO synthase (NOS). The endothelial NOS (e-NOS) produces nitric oxide from L-arginine amino acid. A study showed that overexpression of NOS could improve the therapeutic potential of MSCs in cardiac repair [112].

MSCs regenerative therapy can be made more effective by genetic modifications. There are four main strategies adopted for genetic modification, including gene editing (CRISPR/Cas9), gene

silencing (RNAi), protein overexpression through DNA delivery, and miRNA-based modifications [113]. Currently, viral transduction is a widely used method for DNA delivery. However, it has several reported safety issues like tumorigenesis and mutagenesis[114]. CRISPR/Cas9 gene-editing tool is a novel technique for the precise insertion of required genes without activation of an oncogene [115].CRISPER/CAS9 technology derives from the adaptive immunity of bacteria and archaea against invading nucleic acids by using CRISPER RNAs which guides the silencing of invading nucleic acids [116].CAS 9 is an enzyme produced in bacteria naturally which initiates anti-phage activity by combining with CRISPER loci which are short repetitive sequences of about 30 to 40bp. These loci are transcribed into long RNAs, which are broken down into small CRISPER RNA(crRNA) by the activity of CRISPR-associated nucleases. Cas-RNA complex is formed by these crRNAs, which helps recognize invading nucleic acids and cleaves them. The crisper cas9 technology is applied to develop mouse models of cardiomyopathy in a shorter time than traditional techniques [117, 118]. CRISPER technology helps to generate the genetically modified cells and model organisms to study CVDs more efficiently [119]. Some gene modifications are reported till now which includes AkT and Bcl-2 (apoptosis-regulating protein) modifications. Bcl-2 gene is involved in apoptosis. It reduces apoptosis and promotes cardiac regeneration. A study showed the effect of exosomes derived from Akt on MSC's role in CVDs. They use human umbilical cord stem cells and AKt genes were transfected into hucMSCs and extracted exosomes from control (hucMSCs) and Akt(hucMSC). They studied the effect in MI rat model and demonstrated that platelet-derived growth factor D was upregulated in Akt-exo which increased cardiac repair [120, 121].

5. Modes of MSCs delivery to cardiac tissues:

Different methods are used to successfully implant mesenchymal stem cells to the infected or injured area. Following are some methods which are commonly used nowadays.

5.1 Direct surgical inframyocardial (IM) injection:

This procedure is the most precise, direct, and authentic approach for injecting mesenchymal stem cells into damaged/infracted regions of the heart [122]. It can be done either during thoracotomies for open-heart surgeries or as a separate method without cardiac arrest [123, 124].Infra-myocardial infraction involves the injection of therapeutic agents directly into the myocardium into LV either directly or by using a catheter-based approach [125]. The location

for IM method can be identified by using RCG or nuclear imaging. It offers an extra advantage of targeting localized myocardium without perturbing neighboring tissues [126]. Wang et al performed experiments in which Mesenchymal stem cell sheet fragments injected by direct IM method shows increased vascular density, more cell retention in infected zone and increased graft/host cell communication, thus improving left ventricle functions [127]. Such direct IM techniques of stem cells have been used when trans-vascular cell delivery becomes limited due to occluded coronary artery in cardiomyopathy patients[128].

5.2 Intracoronary Delivery:

This approach includes the infusion of MSCs inside the coronary artery. In this procedure, cells can be injected while maintaining coronary flow or following flow interruption with balloon occlusion to minimize rapid cell washout. An intracoronary approach allows for selective delivery of cells to the myocardial area of interest and theoretically limits risks of systemic administration [128].This procedure has some advantages in that there is no need for special equipments for injecting cells and the injected cells are uniformly distributed in the infracted region. Some disadvantages are also associated with this technique and among them, the most important is the low immediate retention of cells which may cause microvascular occlusion [129, 130].

5.3 Mechanism of action:

For the development and improvement of MSC therapy, it is utterly important to know the mechanism of action of MSC in cardiac tissue regeneration and repair. MSCs follow two main mechanisms known as Direct and Indirect/paracrine. Numerous *in-vitro/in-vivo* studies showed that paracrine signaling is the major and fundamental mechanism of action of MSCs [131].

5.3.1 Direct Pathway (direct trans-differentiation of MSCs into cardiac cells):

Despite the fact that MSCs can differentiate into different cell types e.gcardiomyocytes and endothelial cells, it is not the primary mechanism of action of cardiovascular regeneration [132]. Direct trans-differentiation of MSCs into cardiac tissue is still a major controversy in cardiac regeneration. Some studies suggest that MSCs transdifferentiate into functional cardiomyocytes and some studies suggest a fusion of MSCs with host cardiomyocytes as a prevalent mechanism [133].

5.3.2 Paracrine Pathway (Secretion of complex biological compounds):

Recent studies suggested that the ability of MSCs to regenerate or repair cardiac tissues is mediated by paracrine factors secreted by MSCs [134]. In paracrine signaling, MSCs positively influence the surroundings of cardiovascular tissue by the activation of several other signaling pathways. MSCs secrete biological active molecules like cytokines, remolding factors, and differentiation signals such as interleukine-6, a granulocyte, and macrophage colony-stimulating factors. These molecules secrete anti-apoptotic and angiogenic factors to inhibit cardiomytic apoptosis around the area of administration and induce cardioprotection. The release of various cytokines e.g. transforming growth factor β, vascular endothelial growth factor (VEGF), stromal cell-derived factor (SDF)-1, and epidermal growth factor (EGF) promotes various processes e.g. neovascularization, activation of tissue intrinsic progenitor cells, etc. Neovascularization which is referred to as the formation of new blood vessels is an important factor of the healing process as it re-supplies nutrients and oxygen to the damaged tissue. Studies showed 20% enhanced neovascularization in the MI mouse model due to the release of paracrine factors [135]. MSCs not only secret cytokines but they are also able to secrete exosomes. Exosomes are small extracellular vesiclescontaining important bioactive constituents with a diameter ranging from approximately about 40 to 160 nmcontaining microRNAs and they induce biological effects even at distant locations. Exosomes work by decreasing infarct size in a mouse model of myocardial ischemia. MSC-derived exosomes have growingly proved their cardiac repair effects through stimulating cardiomyocyte proliferation, vascular angiogenesis, immune-regulation, and inhibiting the progression of scar formation[136, 137].Exosomes plays important role in regulating CVD progression and act as a bioactive ingredient that stimulates repairing of cardiac injury via transpose and exchange of signal molecules. Exosomes delivered via intravenous route prove to effectively alleviate myocardial ischemia/reperfusion injury[138, 139].

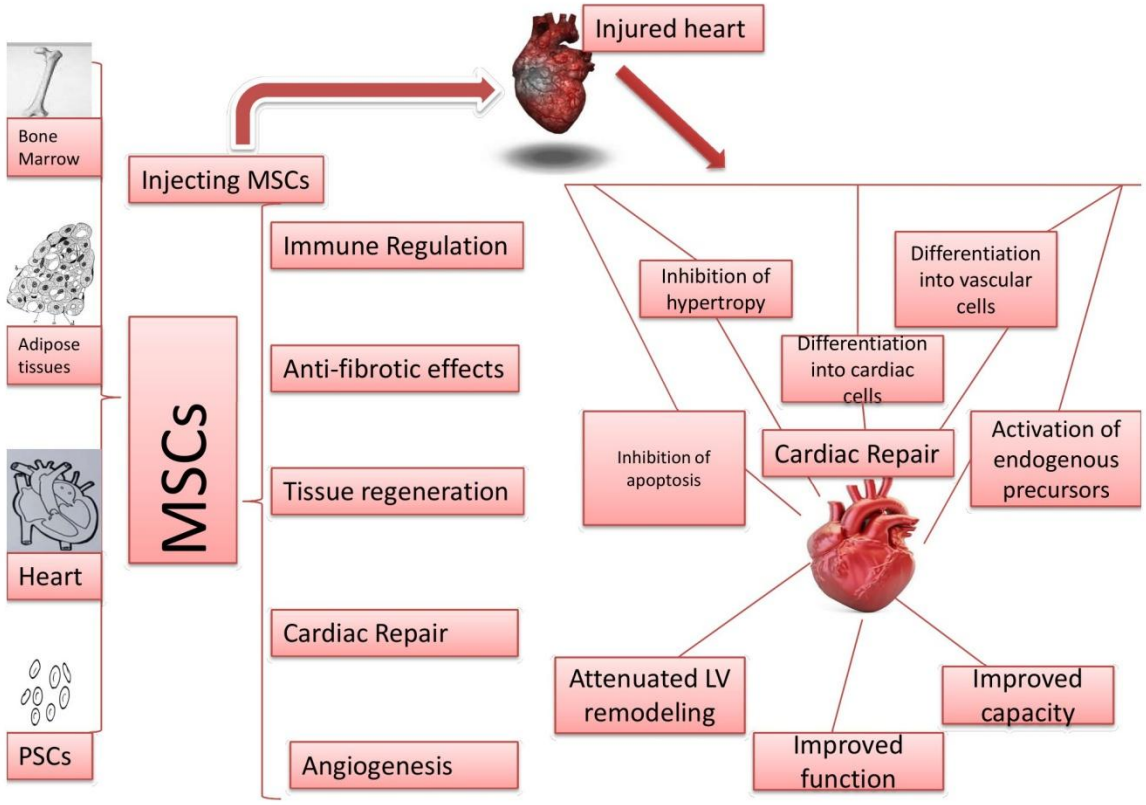

Figure 2MSCs applications in CVDs

Conclusions:

Cardiovascular diseases remain the leading cause of death worldwide, despite tremendous advancements in medical science. The rising incidence of cardiovascular diseases requires the investigation of new and promising treatment approaches to manage the rising risk of CVDs. Regenerative cardiovascular medicine now centresaround stem cell therapy, superseding all other forms of therapy and treatment. Because mesenchymal stem cells have such a large therapeutic potential, numerous clinical trials and studies have shown that stem cell therapy—and especially mesenchymal stem cells—is the most promising treatment option for cardiac diseases.Recent studies have demonstrated the beneficial effects of mesenchymal stem cells on a number of cardiac muscle disorders, including heart failure, vascular lining issues, damage from blood flow restriction, and elevated blood pressure in the lungs. The potential, preconditioning

strategies, administration approaches, and processes of mesenchymal stem cell (MSC) therapy for the treatment of cardiovascular diseases (CVDs) are specifically examined in this work.

References :

1. Meier, T., et al., *Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European Region from 1990 to 2016: a systematic analysis of the Global Burden of Disease Study.* European journal of epidemiology, 2019. **34**(1): p. 37-55.
2. Afrose, L. and J. Qamar, *Current Trends of Cardiovascular Risk Determinants in Pakistan.* Cureus, 2018. **10**(10).
3. Somaio Neto, F., et al., *Gene expression related to oxidative stress in the heart of mice after intestinal ischemia.* Arquivos brasileiros de cardiologia, 2014. **102**(2): p. 165-174.
4. Leitolis, A., et al., *Cardiomyogenesis modeling using pluripotent stem cells: The role of microenvironmental signaling.* Frontiers in cell and developmental biology, 2019. **7**: p. 164.
5. Nishtar, S., *Prevention of coronary heart disease in south Asia.* The Lancet, 2002. **360**(9338): p. 1015-1018.
6. Stewart, S. and J.J. McMurray, *Heart failure and the ageing population: An increasing burden in the 21st century?* Heart, Lung and Circulation, 2003. **12**(2): p. A86.
7. Guyette, J.P., et al., *Bioengineering human myocardium on native extracellular matrix.* Circulation research, 2016. **118**(1): p. 56-72.
8. Weinberger, F., I. Mannhardt, and T. Eschenhagen, *Engineering cardiac muscle tissue: a maturating field of research.* Circulation research, 2017. **120**(9): p. 1487-1500.
9. Tanaka, A., et al., *Cardiovascular disease modeling using patient-specific induced pluripotent stem cells.* International journal of molecular sciences, 2015. **16**(8): p. 18894-18922.
10. Sánchez, L.A., et al., *Use of stem cells in heart failure treatment: where we stand and where we are going.* Methodist DeBakey cardiovascular journal, 2013. **9**(4): p. 195.
11. Humbert, M., et al., *Advances in therapeutic interventions for patients with pulmonary arterial hypertension.* Circulation, 2014. **130**(24): p. 2189-2208.
12. Gao, X., J.J. Yourick, and R.L. Sprando, *Comparative transcriptomic analysis of endothelial progenitor cells derived from umbilical cord blood and adult peripheral blood: Implications for the generation of induced pluripotent stem cells.* Stem cell research, 2017. **25**: p. 202-212.
13. Liu, J., et al., *Progress in mesenchymal stem cells for treatment of atherosclerosis.* Sheng wu gong cheng xue bao= Chinese journal of biotechnology, 2013. **29**(11): p. 1538-1547.
14. Olin, J.W., et al., *Peripheral artery disease: evolving role of exercise, medical therapy, and endovascular options.* Journal of the American College of Cardiology, 2016. **67**(11): p. 1338-1357.
15. Schaun, M.I., et al., *Cell therapy in ischemic heart disease: interventions that modulate cardiac regeneration.* Stem cells international, 2016. **2016**.
16. Xin, H., Y. Li, and M. Chopp, *Exosomes/miRNAs as mediating cell-based therapy of stroke.* Frontiers in cellular neuroscience, 2014. **8**: p. 377.
17. Malliaras, K., et al., *Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction).* Journal of the American College of Cardiology, 2014. **63**(2): p. 110-122.

18. Urbanelli, L., et al., *Exosome-based strategies for diagnosis and therapy.* Recent patents on CNS drug discovery, 2015. **10**(1): p. 10-27.
19. Lou, G., et al., *Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases.* Experimental & molecular medicine, 2017. **49**(6): p. e346-e346.
20. Friedenstein, A., R. Chailakhjan, and K. Lalykina, *The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells.* Cell Proliferation, 1970. **3**(4): p. 393-403.
21. Kim, E.-J., N. Kim, and S.-G. Cho, *The potential use of mesenchymal stem cells in hematopoietic stem cell transplantation.* Experimental & molecular medicine, 2013. **45**(1): p. e2-e2.
22. Jackson, W., et al., *Mesenchymal progenitor cells derived from traumatized human muscle.* Journal of tissue engineering and regenerative medicine, 2009. **3**(2): p. 129-138.
23. Mohyeldin, A., T. Garzón-Muvdi, and A. Quiñones-Hinojosa, *Oxygen in stem cell biology: a critical component of the stem cell niche.* Cell stem cell, 2010. **7**(2): p. 150-161.
24. Karantalis, V. and J.M. Hare, *Use of mesenchymal stem cells for therapy of cardiac disease.* Circulation research, 2015. **116**(8): p. 1413-1430.
25. Chen, P.-M., et al., *Immunomodulatory properties of human adult and fetal multipotent mesenchymal stem cells.* Journal of biomedical science, 2011. **18**(1): p. 49.
26. Parolini, O., et al., *Concise review: isolation and characterization of cells from human term placenta: outcome of the first international Workshop on Placenta Derived Stem Cells.* Stem cells, 2008. **26**(2): p. 300-311.
27. Bieback, K. and H. Kluter, *Mesenchymal stromal cells from umbilical cord blood.* Current stem cell research & therapy, 2007. **2**(4): p. 310-323.
28. Ouyang, B., et al., *Human urine-derived stem cells alone or genetically-modified with FGF2 improve type 2 diabetic erectile dysfunction in a rat model.* PloS one, 2014. **9**(3).
29. Huang, G.-J., S. Gronthos, and S. Shi, *Mesenchymal stem cells derived from dental tissues vs. those from other sources: their biology and role in regenerative medicine.* Journal of dental research, 2009. **88**(9): p. 792-806.
30. Jo, C.H., et al., *Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A proof-of-concept clinical trial.* Stem cells, 2014. **32**(5): p. 1254-1266.
31. Murphy, M.B., K. Moncivais, and A.I. Caplan, *Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine.* Experimental & molecular medicine, 2013. **45**(11): p. e54-e54.
32. Amable, P.R., et al., *Mesenchymal stromal cell proliferation, gene expression and protein production in human platelet-rich plasma-supplemented media.* PloS one, 2014. **9**(8).
33. Islam, M.N., et al., *Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury.* Nature medicine, 2012. **18**(5): p. 759.
34. Prockop, D.J. and J.Y. Oh, *Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation.* Molecular therapy, 2012. **20**(1): p. 14-20.
35. Xu, S., C. Liu, and H.L. Ji, *Concise Review: Therapeutic Potential of the Mesenchymal Stem Cell Derived Secretome and Extracellular Vesicles for Radiation-Induced Lung Injury: Progress and Hypotheses.* Stem cells translational medicine, 2019. **8**(4): p. 344-354.
36. Zhang, L., Z.-f. Dong, and J.-y. Zhang, *Immunomodulatory role of mesenchymal stem cells in Alzheimer's disease.* Life Sciences, 2020: p. 117405.
37. Kim, Y.-H., et al., *Conditioned Medium from Tonsil-Derived Mesenchymal Stem Cells Relieves CCl 4-Induced Liver Fibrosis in Mice.* Tissue engineering and regenerative medicine, 2019. **16**(1): p. 51-58.
38. Li, F., X. Guo, and S.-Y. Chen, *Function and therapeutic potential of mesenchymal stem cells in atherosclerosis.* Frontiers in cardiovascular medicine, 2017. **4**: p. 32.

39. White, I.A., et al., *Mesenchymal stem cells in cardiology*, in *Mesenchymal Stem Cells*. 2016, Springer. p. 55-87.
40. Tomita, S., et al., *Autologous transplantation of bone marrow cells improves damaged heart function.* Circulation, 1999. **100**(suppl_2): p. II-247-Ii-256.
41. Wang, Z., et al., *Regenerative therapy for cardiomyopathies.* Journal of cardiovascular translational research, 2018. **11**(5): p. 357-365.
42. Lee, C.Y., et al., *Therapeutic potential of stem cells strategy for cardiovascular diseases.* Stem cells international, 2016. **2016**.
43. Pandey, K.N., *Genetic Ablation and Guanylyl Cyclase/Natriuretic Peptide Receptor-A: Impact on the Pathophysiology of Cardiovascular Dysfunction.* International journal of molecular sciences, 2019. **20**(16): p. 3946.
44. Carracedo, J., et al., *Endothelial extracellular vesicles produced by senescent cells: pathophysiological role in the cardiovascular disease associated with all types of diabetes mellitus.* Current vascular pharmacology, 2019. **17**(5): p. 447-454.
45. Touyz, R.M., et al., *Vascular biology of superoxide-generating NADPH oxidase 5—Implications in hypertension and cardiovascular disease.* Antioxidants & redox signaling, 2019. **30**(7): p. 1027-1040.
46. Johnson, J.L., *Elucidating the contributory role of microRNA to cardiovascular diseases (a review).* Vascular pharmacology, 2019. **114**: p. 31-48.
47. Orlando, A., et al., *Adiponectin and Cardiovascular Risk. From Pathophysiology to Clinic: Focus on Children and Adolescents.* International journal of molecular sciences, 2019. **20**(13): p. 3228.
48. Nishiyama, A., *Pathophysiological mechanisms of mineralocorticoid receptor-dependent cardiovascular and chronic kidney disease.* Hypertension Research, 2019. **42**(3): p. 293-300.
49. Rosengren, A., et al., *Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study.* The Lancet Global Health, 2019. **7**(6): p. e748-e760.
50. Gostner, J.M., K. Kurz, and D. Fuchs, *The significance of tryptophan metabolism and vitamin B-6 status in cardiovascular disease*. 2020, Oxford University Press.
51. Wang, J., et al., *Associations between family history and coronary artery calcium and coronary heart disease in British Europeans and South Asians.* International journal of cardiology, 2020. **300**: p. 39-42.
52. Li, J., et al., *Gender difference in the association of serum selenium with all-cause and cardiovascular mortality.* Postgraduate Medicine, 2020(just-accepted).
53. Fuchs, F.D. and P.K. Whelton, *High Blood Pressure and Cardiovascular Disease.* Hypertension, 2020: p. HYPERTENSIONAHA. 119.14240.
54. Chiva-Blanch, G. and L. Badimon, *Benefits and Risks of Moderate Alcohol Consumption on Cardiovascular Disease: Current Findings and Controversies.* Nutrients, 2020. **12**(1): p. 108.
55. Duiyimuhan, G., et al., *Cardiovascular Diseases and Hypertension*, in *Secondary Hypertension*. 2020, Springer. p. 403-460.
56. Mura, M., et al., *Vascular endothelial growth factor and related molecules in acute lung injury.* Journal of applied physiology, 2004. **97**(5): p. 1605-1617.
57. Rehan, M., et al., *Immunomodulatory role of vitamin D in infectious and non-infectious diseases.* Hosts and Viruses, 2019. **6**(5): p. 115-129.
58. Nowbar, A.N., et al., *Mortality From Ischemic Heart Disease: Analysis of Data From the World Health Organization and Coronary Artery Disease Risk Factors From NCD Risk Factor Collaboration.* Circulation: Cardiovascular Quality and Outcomes, 2019. **12**(6): p. e005375.
59. Moreira, A., S. Kahlenberg, and P. Hornsby, *Therapeutic potential of mesenchymal stem cells for diabetes.* Journal of molecular endocrinology, 2017. **59**(3): p. R109-R120.

60. Xie, F., et al., *Multi-lineage differentiation and clinical application of stem cells from exfoliated deciduous teeth.* Human Cell, 2020: p. 1-8.
61. Devine, S.M. and R. Hoffman, *Role of mesenchymal stem cells in hematopoietic stem cell transplantation.* Current opinion in hematology, 2000. **7**(6): p. 358-363.
62. Zachar, L., D. Bačenková, and J. Rosocha, *Activation, homing, and role of the mesenchymal stem cells in the inflammatory environment.* Journal of inflammation research, 2016. **9**: p. 231.
63. Sato, K., et al., *Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells.* Blood, 2007. **109**(1): p. 228-234.
64. Kyurkchiev, D., et al., *Secretion of immunoregulatory cytokines by mesenchymal stem cells.* World journal of stem cells, 2014. **6**(5): p. 552.
65. Oh, J.Y., et al., *Mesenchymal stem/stromal cells inhibit the NLRP3 inflammasome by decreasing mitochondrial reactive oxygen species.* Stem cells, 2014. **32**(6): p. 1553-1563.
66. Le Blanc, K. and D. Mougiakakos, *Multipotent mesenchymal stromal cells and the innate immune system.* Nature Reviews Immunology, 2012. **12**(5): p. 383-396.
67. Zhang, W., et al., *Effects of mesenchymal stem cells on differentiation, maturation, and function of human monocyte-derived dendritic cells.* Stem cells and development, 2004. **13**(3): p. 263-271.
68. Jiang, X.-X., et al., *Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells.* Blood, 2005. **105**(10): p. 4120-4126.
69. Gao, W.-X., et al., *Effects of mesenchymal stem cells from human induced pluripotent stem cells on differentiation, maturation, and function of dendritic cells.* Stem cell research & therapy, 2017. **8**(1): p. 48.
70. Xue, Q., et al., *The immunomodulatory function of human amniotic fluid stromal cells on B lymphocytes.* Journal of Neurorestoratology, 2018. **6**(1): p. 122-133.
71. Corcione, A., et al., *Human mesenchymal stem cells modulate B-cell functions.* Blood, 2006. **107**(1): p. 367-372.
72. James, A.W., *Review of signaling pathways governing MSC osteogenic and adipogenic differentiation.* Scientifica, 2013. **2013**.
73. Augello, A., et al., *Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway.* European journal of immunology, 2005. **35**(5): p. 1482-1490.
74. Chamberlain, G., et al., *Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing.* Stem cells, 2007. **25**(11): p. 2739-2749.
75. Gao, F., et al., *Mesenchymal stem cells and immunomodulation: current status and future prospects.* Cell death & disease, 2016. **7**(1): p. e2062-e2062.
76. Noverina, R., et al., *Growth factors profile in conditioned medium human adipose tissue-derived mesenchymal stem cells (CM-hATMSCs).* Clinical Nutrition Experimental, 2019. **24**: p. 34-44.
77. Ryan, J., et al., *Interferon-γ does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells.* Clinical & Experimental Immunology, 2007. **149**(2): p. 353-363.
78. Najar, M., et al., *Mesenchymal stromal cells and immunomodulation: a gathering of regulatory immune cells.* Cytotherapy, 2016. **18**(2): p. 160-171.
79. Castro-Manrreza, M.E., et al., *Human mesenchymal stromal cells from adult and neonatal sources: a comparative in vitro analysis of their immunosuppressive properties against T cells.* Stem cells and development, 2014. **23**(11): p. 1217-1232.
80. Groh, M.E., et al., *Human mesenchymal stem cells require monocyte-mediated activation to suppress alloreactive T cells.* Experimental hematology, 2005. **33**(8): p. 928-934.

81. Ramasamy, R., et al., *The immunosuppressive effects of human bone marrow-derived mesenchymal stem cells target T cell proliferation but not its effector function.* Cellular immunology, 2008. **251**(2): p. 131-136.
82. Aggarwal, S. and M.F. Pittenger, *Human mesenchymal stem cells modulate allogeneic immune cell responses.* Blood, 2005. **105**(4): p. 1815-1822.
83. Kronsteiner, B., et al., *Human mesenchymal stem cells from adipose tissue and amnion influence T-cells depending on stimulation method and presence of other immune cells.* Stem cells and development, 2011. **20**(12): p. 2115-2126.
84. Kapur, S.K. and A.J. Katz, *Review of the adipose derived stem cell secretome.* Biochimie, 2013. **95**(12): p. 2222-2228.
85. Ankrum, J.A., J.F. Ong, and J.M. Karp, *Mesenchymal stem cells: immune evasive, not immune privileged.* Nature biotechnology, 2014. **32**(3): p. 252.
86. Le Blanc, K. and O. Ringden, *Immunomodulation by mesenchymal stem cells and clinical experience.* Journal of internal medicine, 2007. **262**(5): p. 509-525.
87. Atoui, R., D. Shum-Tim, and R.C. Chiu, *Myocardial regenerative therapy: immunologic basis for the potential "universal donor cells".* The Annals of thoracic surgery, 2008. **86**(1): p. 327-334.
88. Galipeau, J. and L. Sensébé, *Mesenchymal stromal cells: clinical challenges and therapeutic opportunities.* Cell stem cell, 2018. **22**(6): p. 824-833.
89. Han, J., J. Choi, and S.H. Bhang, *Stem Cell Therapy in Cardiovascular Diseases:: The Reparative Mechanisms of Mesenchymal Stem Cells for Myocardial Infarction Treatment.* Journal of Cell Science & Therapy, 2014. **5**(3): p. 1.
90. Nagaya, N., *Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, Fujii T, Uematsu M, Ohgushi H, Yamagishi M, Tokudome T, Mori H, Miyatake K, Kitamura S.* Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation, 2005. **112**: p. 1128-1135.
91. Hatzistergos, K.E., et al., *Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation.* Circulation research, 2010. **107**(7): p. 913-922.
92. Shen, Y., et al., *The cardioprotective effects of hydrogen sulfide in heart diseases: from molecular mechanisms to therapeutic potential.* Oxidative medicine and cellular longevity, 2015. **2015**.
93. Mathiasen, A.B., et al., *Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial).* European heart journal, 2015. **36**(27): p. 1744-1753.
94. Der Sarkissian, S., T. Lévesque, and N. Noiseux, *Optimizing stem cells for cardiac repair: current status and new frontiers in regenerative cardiology.* World Journal of Stem Cells, 2017. **9**(1): p. 9.
95. Hilfiker, A., et al., *Mesenchymal stem cells and progenitor cells in connective tissue engineering and regenerative medicine: is there a future for transplantation?* Langenbeck's Archives of Surgery, 2011. **396**(4): p. 489-497.
96. Yu, S.P., Z. Wei, and L. Wei, *Preconditioning strategy in stem cell transplantation therapy.* Translational stroke research, 2013. **4**(1): p. 76-88.
97. Dhada, K.S., D.S. Hernandez, and L.J. Suggs, *In vivo photoacoustic tracking of mesenchymal stem cell viability.* ACS nano, 2019. **13**(7): p. 7791-7799.
98. Shende, P., S. Bhandarkar, and B. Prabhakar, *Heat shock proteins and their protective roles in stem cell biology.* Stem Cell Reviews and Reports, 2019. **15**(5): p. 637-651.
99. Das, R., et al., *The role of hypoxia in bone marrow–derived mesenchymal stem cells: considerations for regenerative medicine approaches.* Tissue Engineering Part B: Reviews, 2010. **16**(2): p. 159-168.
100. Singh, A., A. Singh, and D. Sen, *Mesenchymal stem cells in cardiac regeneration: a detailed progress report of the last 6 years (2010–2015).* Stem cell research & therapy, 2016. **7**(1): p. 82.

101. Wang, L., et al., *Increased leptin by hypoxic-preconditioning promotes autophagy of mesenchymal stem cells and protects them from apoptosis.* Science China Life Sciences, 2014. **57**(2): p. 171-180.
102. Hu, X., et al., *Transplantation of hypoxia-preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis.* The Journal of thoracic and cardiovascular surgery, 2008. **135**(4): p. 799-808.
103. Theus, M.H., et al., *In vitro hypoxic preconditioning of embryonic stem cells as a strategy of promoting cell survival and functional benefits after transplantation into the ischemic rat brain.* Experimental neurology, 2008. **210**(2): p. 656-670.
104. Haider, H.K. and M. Ashraf, *Preconditioning and stem cell survival.* Journal of cardiovascular translational research, 2010. **3**(2): p. 89-102.
105. Buemann, B. and K. Uvnäs-Moberg, *Oxytocin may have a therapeutical potential against cardiovascular disease. Possible pharmaceutical and behavioral approaches.* Medical Hypotheses, 2020. **138**: p. 109597.
106. Jung, C., et al., *Cardiac-specific overexpression of oxytocin receptor leads to cardiomyopathy in mice.* Journal of cardiac failure, 2018. **24**(7): p. 470-478.
107. Wang, P., et al., *Therapeutic potential of oxytocin in atherosclerotic cardiovascular disease: mechanisms and signaling pathways.* Frontiers in neuroscience, 2019. **13**: p. 454.
108. Hackfort, B.T. and P.K. Mishra, *Emerging role of hydrogen sulfide-microRNA crosstalk in cardiovascular diseases.* American Journal of Physiology-Heart and Circulatory Physiology, 2016. **310**(7): p. H802-H812.
109. DiNicolantonio, J.J., J.H. OKeefe, and M.F. McCarty, *Boosting endogenous production of vasoprotective hydrogen sulfide via supplementation with taurine and N-acetylcysteine: a novel way to promote cardiovascular health*. 2017, Archives of Disease in childhood.
110. Olas, B., *Medical functions of hydrogen sulfide*, in *Advances in Clinical Chemistry*. 2016, Elsevier. p. 195-210.
111. Xie, X., et al., *Transplantation of mesenchymal stem cells preconditioned with hydrogen sulfide enhances repair of myocardial infarction in rats.* Tohoku J Exp Med, 2012. **226**(1): p. 29-36.
112. Shao, L., et al., *MiRNA-sequence indicates that mesenchymal stem cells and exosomes have similar mechanism to enhance cardiac repair.* BioMed research international, 2017. **2017**.
113. Tam, C., et al., *Therapeutic potentials of short interfering RNAs.* Applied microbiology and biotechnology, 2017. **101**(19): p. 7091-7111.
114. Nayerossadat, N., T. Maedeh, and P.A. Ali, *Viral and nonviral delivery systems for gene delivery.* Advanced biomedical research, 2012. **1**: p. 27-27.
115. Golpanian, S., et al., *Rebuilding the damaged heart: mesenchymal stem cells, cell-based therapy, and engineered heart tissue.* Physiological reviews, 2016. **96**(3): p. 1127-1168.
116. Jinek, M., et al., *A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity.* Science (New York, N.Y.), 2012. **337**(6096): p. 816-821.
117. Motta, B.M., et al., *The Impact of CRISPR/Cas9 Technology on Cardiac Research: From Disease Modelling to Therapeutic Approaches.* Stem Cells Int, 2017. **2017**: p. 8960236.
118. Chadwick, A.C. and K. Musunuru, *Genome Editing for the Study of Cardiovascular Diseases.* Current cardiology reports, 2017. **19**(3): p. 22-22.
119. Vermersch, E., C. Jouve, and J.S. Hulot, *CRISPR/Cas9 gene-editing strategies in cardiovascular cells.* Cardiovasc Res, 2020. **116**(5): p. 894-907.
120. Lemcke, H., et al., *Recent progress in stem cell modification for cardiac regeneration.* Stem cells international, 2018. **2018**.
121. Li, L., et al., *How to improve the survival of transplanted mesenchymal stem cell in ischemic heart?* Stem Cells International, 2016. **2016**.

122. Sun, R., et al., *Advances in stem cell therapy for cardiovascular disease.* International journal of molecular medicine, 2016. **38**(1): p. 23-29.
123. Stamm, C., et al., *Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic ischemic heart disease: safety and efficacy studies.* The Journal of thoracic and cardiovascular surgery, 2007. **133**(3): p. 717-725. e5.
124. Patel, A.N., et al., *Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study.* The Journal of thoracic and cardiovascular surgery, 2005. **130**(6): p. 1631-1638. e2.
125. Dib, N., et al., *Cell therapy for cardiovascular disease: a comparison of methods of delivery.* Journal of cardiovascular translational research, 2011. **4**(2): p. 177-181.
126. Sheng, C.C., L. Zhou, and J. Hao, *Current stem cell delivery methods for myocardial repair.* Biomed Res Int, 2013. **2013**: p. 547902.
127. Wang, C.C., et al., *Direct intramyocardial injection of mesenchymal stem cell sheet fragments improves cardiac functions after infarction.* Cardiovasc Res, 2008. **77**(3): p. 515-24.
128. Bui, Q.T., Z.M. Gertz, and R.L. Wilensky, *Intracoronary delivery of bone-marrow-derived stem cells.* Stem Cell Res Ther, 2010. **1**(4): p. 29.
129. Liu, Z., et al., *Systemic and local delivery of mesenchymal stem cells for heart renovation: Challenges and innovations.* European Journal of Pharmacology, 2020: p. 173049.
130. Amoozgar, H., et al., *A Study of Intracoronary Injection of Hematopoietic Stem Cells in Pediatric Dilated Cardiomyopathy: Is It an Applicable Solution for Critically Ill Patients?* Iranian Journal of Pediatrics, 2019. **29**(3).
131. Gnecchi, M., et al., *Paracrine mechanisms in adult stem cell signaling and therapy.* Circulation research, 2008. **103**(11): p. 1204-1219.
132. Hare, J.M., et al., *Comparison of allogeneic vs autologous bone marrow–derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial.* Jama, 2012. **308**(22): p. 2369-2379.
133. Katarzyna, R., *Adult stem cell therapy for cardiac repair in patients after acute myocardial infarction leading to ischemic heart failure: an overview of evidence from the recent clinical trials.* Current cardiology reviews, 2017. **13**(3): p. 223-231.
134. Caplan, A.I. and J.E. Dennis, *Mesenchymal stem cells as trophic mediators.* Journal of cellular biochemistry, 2006. **98**(5): p. 1076-1084.
135. Mueller, P., H. Lemcke, and R. David, *Stem cell therapy in heart diseases–cell types, mechanisms and improvement strategies.* Cellular Physiology and Biochemistry, 2018. **48**(6): p. 2607-2655.
136. Rosenberger, L., et al., *XPS analysis of aluminum nitride films deposited by plasma source molecular beam epitaxy.* Surface and Interface Analysis: An International Journal devoted to the development and application of techniques for the analysis of surfaces, interfaces and thin films, 2008. **40**(9): p. 1254-1261.
137. Wang, X., et al., *The Application Potential and Advance of Mesenchymal Stem Cell-Derived Exosomes in Myocardial Infarction.* Stem Cells International, 2021. **2021**: p. 5579904.
138. Guo, D., et al., *Roles and Clinical Applications of Exosomes in Cardiovascular Disease.* BioMed Research International, 2020. **2020**: p. 5424281.
139. Tsao, C.-R., et al., *Mesenchymal Stem Cell Derived Exosomes: A New Hope for the Treatment of Cardiovascular Disease?* Acta Cardiologica Sinica, 2014. **30**(5): p. 395-400.