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REVIEW ARTICLE

# The potential and challenges of using stem cells for cardiovascular repair and regeneration

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**Abstract** Recent progress in using stem cells for tissue repair and functional restoration has aroused much attention due to its potential to provide a cue for many diseases such as myocardial infarction. Stem cell therapy for cardiovascular disease has been studied extensively at both experimental and clinical levels. Pluripotent stem cells and mesenchymal stem cells were proven to be effective for myocardial regeneration, angiogenesis, and cardiac functional restoration. In this review, we will concisely discuss advantages and disadvantages of currently-used stem cells for cardiovascular repair and regeneration. The limitations and uniqueness of some types of stem cells will also be discussed. Although substantial progress has been made over the last decade about stem cells in cardiovascular regeneration, many challenges lie ahead before the therapeutic potentials of stem cells can be fully recognized.


## Introduction

Although numerous pharmacological drugs are available, cardiovascular disease remains the leading cause of death worldwide.[1,2] There are over 5 million patients suffering from chronic heart failure post acute myocardial infarction due to no effective treatment.[1] With the advent of an aging society in developed countries, an increased risk for

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cardiovascular disease and huge burden on human resources and health budgets are promised in the near future.[3] Therefore, there is an urgent need to develop more effective therapeutic approaches for cardiovascular disease. The emerging of cardiovascular regenerative medicine may provide an encouraging direction for future therapeutics, which focuses on replacing or regenerating damaged myocardium and blood vessels to restore or establish normal cardiac function.[4] Great advantages exist in this new treatment compared to traditional therapy, which was considered only palliative strategy. Traditional cardiac therapy are effective in resolving the acute processes of the disease and extending the patient's lifespan, however, it does not provide the patients a cure, but rather leaving them with chronic diseases as sequelae.[5] In contrast, cardiovascular regenerative medicine makes it possible to replace damaged myocardial cells with the patient-specific pluripotent stem cell-derived cardiac myocytes, avoiding the aforementioned medical problems, and prevents or reverses the disease development.[4] Moreover, most of the pluripotent stem cells, except for embryonic stem cells, are derived from the patients and possess the same genotype and phenotype, and thus are significantly valuable tools for studying the molecular mechanisms of the disease and for developing patient-specific therapy.[6] Stem cell therapy has demonstrated beneficial effects on several cardiovascular diseases including ischemic heart disease,[7,8] heart failure,[9] endothelial dysfunction,[10,11] peripheral artery disease,[12,13] atherosclerosis,[14] and pulmonary hypertension[15,16] (Fig. 1).

Stem cells have potential to differentiate into several specific types of cells. Based on the source of origin, stem cells can be classified into embryonic stem cells (ESCs) and adult stem cells (ASCs), where the former comes from embryos and the latter originates from mature adults.[17] Furthermore, the ASCs can be divided into tissue-specific stem cells and bone marrow-derived stem cells (BMCs). Bone marrow contains at least two types of stem cells: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs) can also be found in the bone marrow.[18] In this review, we will summarize the properties of different types of stem cells and their regenerative capabilities to restore or repair cardiac structure and function. We will also discuss selection and acquisition of stem cells and evaluation of effectiveness of stem cell therapy for cardiovascular disease.

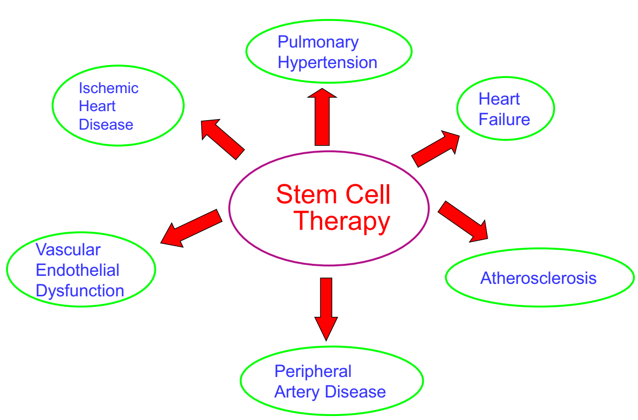


**Fig. 1** Potential stem cell therapy for major cardiovascular disorders.

## Pluripotent stem cells

The goal of cardiac stem cell therapy is to restore or regenerate myocardium. The challenge was to identify a suitable source for generating sufficient and phenotypically confirmed cardiomyocytes. Over the past decade, rapid progress has been made in identification, derivation, and characterization of stem cells or progenitor cells. Among these, the embryonic stem cells (ESCs) have attracted attention due to their unique properties.[6] ESCs are pluripotent stem cells which are derived from the inner cell mass of the blastocyst-stage embryo.[19] Specifically, these cells remain in an undifferentiated state in culture for a long period but retain the potential to differentiate into all cell types in the human body, including cardiomyocytes. Human ESCs (hESCs) were isolated by Thomson et al — more than a decade after the first isolation of mouse ESCs (mESCs) in 1981.[20,21] Since then, the potential for using these unending multipotent cells to treat congenital and degenerative diseases has aroused great interest. Theoretically, the hESCs are capable to differentiate into all three germ layers-endoderm, ectoderm, and mesoderm, so it is important to investigate the signaling pathways and transcription factors that direct its specific differentiation process.[19] From a large number of studies, researchers have identified several signaling molecules that are involved in early cardiac differentiation. Over-expression of transcriptional factors such as GATA4, Nkx2-5, or MEF2C can induce differentiation of hESCs into cardiomyocytes (Fig. 2), while inhibition of these factors halts the formation of cardiomyocytes.[22] Other factors like growth factors TGFβ1 and FGF2, cardiotrophin, reactive oxygen species (ROS), and dimethyl sulfoxide (DMSO) might also affect the differentiation process.[23,24]

Despite the exciting achievements of hESCs-differentiated cardiomyocytes in both murine and human models, several pressing issues limit its clinical application. First of all, hESCs research has raised some serious ethical problems due to the fact that the establishment hESCs required the destruction of early human embryos, which was considered crimes against humanity.[21] Additionally, the ESCs are generated from embryos and do not retain the same genome with the patients, thus has potential risk of immune rejection after transplantation.[6] Furthermore, grafted ESCs in mice only generated a minor population of cardiomyocytes, which was even less in the human model.[25]

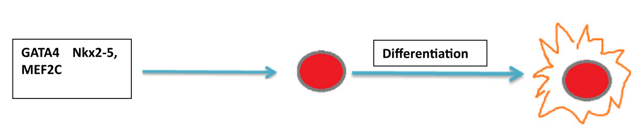


**Fig. 2** **Effects of transcription factors on hESC differentiation**. Over-expression of key transcriptional factors such as GATA4, Nkx2-5, or MEF2C leads to differentiation of human embryonic stem cells (hESCs) into cardiomyocytes. Inhibition of these transcription factors maintain hESC pluripotency.