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Review

# Potential benefits of cell therapy in coronary heart disease

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ABSTRACT

Cardiovascular disease is the leading cause of morbidity and mortality in the world. In recent years, there has been an increasing interest both in basic and clinical research regarding the field of cell therapy for coronary heart disease (CHD). Several preclinical models of CHD have suggested that regenerative properties of stem and progenitor cells might help restoring myocardial functions in the event of cardiac diseases. Here, we summarize different types of stem/progenitor cells that have been tested in experimental and clinical settings of cardiac regeneration, from embryonic stem cells to induced pluripotent stem cells. Then, we provide a comprehensive description of the most common cell delivery strategies with their major *pros* and *cons* and underline the potential of tissue engineering and injectable matrices to address the crucial issue of restoring the three-dimensional structure of the injured myocardial region. Due to the encouraging results from preclinical models, the number of clinical trials with cell therapy is continuously increasing and includes patients with CHD and congestive heart failure. Most of the already published trials have demonstrated safety and feasibility of cell therapies in these clinical conditions. Several studies have also suggested that cell therapy results in improved clinical outcomes. Numerous ongoing clinical trials utilizing this therapy for CHD will address fundamental issues concerning cell source and population utilized, as well as the use of imaging techniques to assess cell homing and survival, all factors that affect the efficacy of different cell therapy strategies.


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## Introduction

Despite the fact that the incidence of cardiovascular disease (CVD) has dramatically declined over the past four decades, due to the remarkable advances in the understanding of CVD pathophysiology and treatment, coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD) remain the leading causes of death and disability in Western countries [1]. In particular, myocardial infarction (MI) is associated with elevated mortality and morbidity because it causes heart failure (HF) by inducing cardiomyocyte (CM) death and apoptosis. Until now, reducing the established risk factors for CVD has worked successfully for both secondary and primary prevention. However, a novel and complementary approach, which could represent a major breakthrough in the field, would be the possibility to repair the damaged myocardium and/or blood vessels. This opportunity originates from the possibility of applying cell therapy to CVD and even more from the revolutionary concept that the human heart is not a post-mitotic organ, as traditionally believed, but an organ capable of regenerating its damaged and/or aged structures thanks to the activity of recently discovered endogenous or exogenous adult stem cells capable of improving tissue repair through regeneration of vessel and cardiac muscle cells [2]. Indeed, a burst of regenerative activity was observed in the heart of one-day-old mice after resection of the left ventricular apex [3].

Recent attempts based on transplantation of adult stem and progenitor cells to damaged areas of the cardiovascular system have produced interesting and promising results. However, to date there is still the need to address some fundamental unresolved issues, such as identifying the optimal cell type, delivery strategy, therapeutic dose and timing, as well as determining the extent of cell survival and retention in the different settings. In this context, current preclinical studies are aimed at ameliorating homing, cell survival, and retention and they are essentially based on genetic modifications and the use of biomaterials for cell delivering. It is crucial that ongoing and future clinical studies address these essential issues.

Here, we review the clinical aspects of different cell therapy strategies in patients with CHD; we will also focus on the current, both completed and ongoing, clinical trials utilizing bone marrow cells (BMCs) as source for cell therapy.

## Stem cell sources for cardiovascular regenerative therapy

Cell therapy for CHD can be different according to the disease progression, but it is invariably expected to provide a renewable source of proliferating, functional CMs. However, stem cells are rare in humans: approximately, only 1 out of 10,000–100,000 BMCs has been recognized as a hematopoietic stem cell, and only 1 out of 30,000 cells in the heart has been identified as a c-kit-positive cardiac stem cell (CSC) [4]. Cardiac niches have been identified that provide a harboring microenvironment to support and protect CSCs, as well as control their turnover and migration toward sites of myocardial injury [4]. Interestingly, canine pulmonary veins have been shown to host cardiac stem cell niches [5].

In both preclinical and clinical studies, different types of cells have been employed for cell therapy, mainly varying in regard to their origin, expression of surface markers, function, and ability to derive different cell types (Fig. 1a–d).

### *Embryonic stem cells*

Embryonic stem cells (ESCs), deriving from the embryo inner mass at the blastocyst stage, would be the ideal stem cells. These totipotent cells display the maximum potential for organ regeneration and can differentiate into a variety of cell types and tissues, including CMs and blood vessels, but they also increase the risk of teratoma formation [6,7]. In several animal models ESC transplants improved cardiac function [8] or blood perfusion [6,9]. Furthermore, genetically engineered human ESCs were able to electrically pace quiescent, recipient ventricular CMs *in vitro* and ventricular myocardium *in vivo* [10]. The advantage of using ESCs derives from their unlimited proliferative capacity and multilineage differentiation plasticity, whereas the main disadvantages are the social and ethical concerns due to the source and isolation methods. This ethical matter, together with their potential genetic instability and consequent risk of cancer development, renders these cells not suitable for clinical application.

### *Fetal stem cells*

As regard to cell source, fetal and human umbilical cord blood cells should have more plasticity than adult stem cells even though their pluripotency degree after *in vitro* expansion is still unclear. These cells, comprising hematopoietic stem cells (HSCs), mesenchymal stromal cells (MSCs), and somatic stem cells with proliferative capacity, have showed promising results in animal models, but no clinical studies were available until recently [11].

### *Adult stem cells*

#### *Bone marrow cells*

Although the ideal cell type for CHD cell therapy remains to be determined, most clinical trials refer to the use of adult stem cells from autologous bone marrow (BM) as the main source of adult stem cells for cardiac regeneration. Despite the more limited differentiation capacity, this choice can be explained by several reasons, which include their easy availability and safety, the possibility to expand and/or select them *in vitro*, the nonnecessity of an immunosuppressive treatment, and the lack of ethical controversies associated with the use of embryonic stem cells. Thus, most of the published studies have utilized these cells (see Tables 1 and 2).

BM contains different cell subpopulations that have the potential to migrate to distant sites and differentiate into cells with diverse phenotypes [12]. BMCs may be isolated by direct aspiration or by mobilization into the peripheral blood through the use of cytokines such as granulocyte-colony stimulating factor (G-CSF) [13,14]. The two main groups of BM-derived stem cells are the HSCs and the mesenchymal stem cells or MSCs, which can be further