Regenerative therapy for cardiovascular disease

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Recent insights into myocardial biology uncovered a hereto unknown regenerative capacity of the adult heart. The discovery of dividing cardiomyocytes and the identification and characterization of cardiac stem and progenitor cells with myogenic and angiogenic potential have generated new hopes that cardiac regeneration and repair might become a therapeutic option. During the past decade, multiple candidate cells have been proposed for cardiac regeneration, and their mechanisms of action in the myocardium have been explored. Initial clinical trials have focused on the use of bone marrow-derived cells to promote myocardial regeneration in ischemic heart disease and have yielded very mixed results, with no clear signs of clinically meaningful functional improvement. Although the efficiency of bona fide cardiomyocyte generation is generally low, stem cells delivered into the myocardium act mainly via paracrine mechanisms. More recent studies taking advantage of cardiac committed cells (eg, resident cardiac progenitor cells or primed cardiogenic mesenchymal stem cells) showed promising results in first clinical pilot trials. Also, transplantation of cardiomyogenic cells generated by induced pluripotent stem cells and genetic reprogramming of dividing nonmyocytes into cardiomyocytes may constitute attractive new regenerative approaches in cardiovascular medicine in the future. We discuss advantages and limitations of specific cell types proposed for cell-based therapy in cardiology and give an overview of the first clinical trials using this novel therapeutic approach in patients with cardiovascular disease. (Translational Research 2014;163:307–320)

Abbreviations: BMC = bone marrow-derived cell; BMSC = bone marrow stem cell; CADUCEUS = Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction; CD = Cluster of differentiation; SCF = stem cell factor; c-kit = receptor for SCF; CSC = cardiac stem cell; ESC = embryonic stem cells; HF = heart failure; iPS = induced pluripotent stem cell; MSC = mesenchymal stem cell; SCIPIO = Stem Cell Infusion in Patients With Ischemic Cardiomyopathy; SP = side population

Despite significant advances in the treatment of acute myocardial infarction, stroke, and hypertension, cardiovascular disease continues to remain the leading cause of death in developed countries.[1] As the common final sequel of virtually all cardiac diseases, heart failure (HF) is the major contributor to cardiovascular morbidity and mortality. In the Western world, an estimated 1%–2% of the population experience HF, with the prevalence exceeding 10% in people older than 70 years of age.[2] Today, HF has become the leading cause of hospitalization of patients older than 65 years, thus further challenging both public and private healthcare systems across the world. Although today's medical and device therapies aim to optimize cardiovascular hemodynamics and myocardial remodeling, they do not account for the loss of functional cardiomyocytes, which are at the core of the failing myocardium. In contrast to other muscle tissue, such as smooth muscle and skeletal

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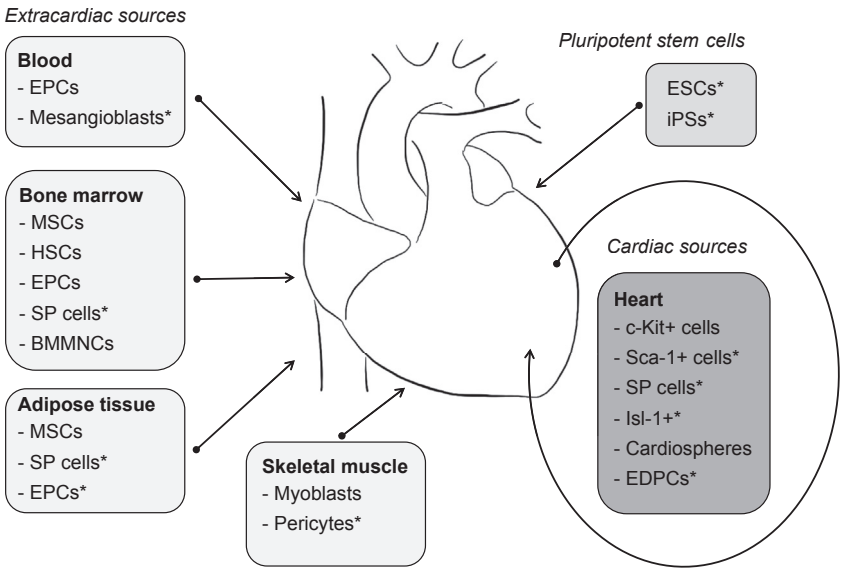

Fig 1. Sources of cells for cardiac repair. Overview of the various cellular sources considered for cell therapy. BMMNCs, bone marrow mononuclear cells; c-kit, receptor for SCF; EDPCs, epicardial-derived progenitor cells; EPCs, endothelial progenitor cells; ESCs, embryonic stem cells; HSCs, hematopoietic stem cells; iPSs, induced pluripotent stem cells; Isl-1, islet 1; MSCs, mesenchymal stem cells; Sca-1, stem cell antigen 1; SP, side population. *Not used in clinical trials.

muscle, the regenerative capacity of the adult myocardium is limited, and thus not sufficient to compensate for cell loss in acute and chronic cardiac injury. Therefore, for decades, the adult heart was considered a postmitotic organ, with virtually no inherent regenerative capacity. With the discovery of dividing cardiomyocytes after myocardial infarction and the documentation of cell chimerism in transplanted hearts, however, this static view of the myocardium was put into question.[3,4] Given the prospect of true myocardial regeneration, the quest for potential stem/progenitor cell sources with myogenic and angiogenic potential has generated great enthusiasm in the cardiovascular field. During the past decade, multiple candidate cells have been proposed for cardiac regeneration (Fig 1), and the first clinical trials using cell-based therapies have been performed. We discuss advantages and limitations of specific cell types proposed for cell-based therapy and give an overview of the first clinical trials using this novel therapeutic approach in patients with cardiovascular disease.

THE BONE MARROW AS A POTENTIAL SOURCE OF CARDIOGENIC CELLS

There is a vast body of evidence demonstrating that ischemic cardiac injury stimulates the recruitment and myocardial homing of endogenous bone marrow-derived cells bone marrow-derived cells (BMCs).[5-9] The inflammatory process associated with myocardial ischemia induces several conventionally "mobilizing cytokines," including granulocyte-colony stimulating factor, stem cell factor (SCF), vascular endothelial growth factor, stromal cell-derived factor 1, and erythropoietin.[10] Inability to mobilize and home BMCs properly to the heart after myocardial infarction resulted in early cardiac failure and death, as shown in a proof-of-concept study using transgenic mice overexpressing mutant c-kit.[7] Notably, restoring the capacity for mobilization and homing by bone marrow transplantation with wild-type BMCs could rescue cardiac function in this model. Also, stromal cell-derived factor 1 and its receptor chemokine (c-x-c motif) receptor 4 (CXCR4) are important for the mobilization of BMCs on myocardial infarction.[11] Taken together, these translational studies demonstrate clearly an important functional interaction between the bone marrow and the heart in the setting of cardiac injury.

The fact that allogeneic and autologous BMCs have the potential, functionally, to replace a radio- or chemotherapy-ablated hematopoietic system has revolutionized the treatment of malignant hemato-oncologic diseases and established bone marrow stem cells (BMSCs) as the epitome of adult stem cells. Early reports that BMSCs may transdifferentiate into nonhematologic cells such as skeletal muscle, hepatocytes, neurons, endothelial cells, and even cardiomyocytes prompted attempts to use BMSCs to promote cardiovascular regeneration after myocardial injury.[12-14] Preclinical animal studies isolated BMSCs expressing the stem cell receptor c-kit for direct injection into the border zone of infarcted myocardium in small- and