Editorial

Myocardial Regeneration: How far have We progressed?

Heart failure remains the leading cause of death in developed and developing countries. Myocardial infarction (MI) results in the loss of heart muscle cells, which causes heart failure. Medical therapy and mechanical left-ventricular assist devices are available for physicians to improve the prognosis of patients with MI and heart failure, but only half of the patients with end-stage heart failure survive for an year.[1] At the present time, allogeneic heart transplantation to extend life span, and to improve the quality of daily life is probably the preferred alternative treatment for patients with end-stage heart failure. Extreme organ shortage and chronic cardiac-rejection limit the therapy. In recent years, research on stem cells is leading scientists to investigate the possibility of cell-based therapies for cardiac repair, often referred to as regenerative or reparative medicine. Stem cell-based cellular cardiomyoplasty (CCM) for cardiomyocyte replacement or regeneration has been evaluated in animal models and clinical trials.[2-9] Transplantation of exogenous stem cells could regenerate damaged myocardium and improve cardiac function in failing hearts. Such treatment modalities may offer new options for treating patients with end-stage heart failure. The purpose of this article is to review a wide range of cellular and molecular approaches to strengthening the injured or weakened heart, focusing on strategies to replace dysfunctional, necrotic, or apoptotic cardiomyocytes with new cells.

The most widely used cell source in clinical trials has been the patient's own reconstituted bone marrow cell (BMC) aspirate (Table 1). Cell sources in human bone marrow include—hematopoietic stem cells, mesenchymal progenitor cells, and other cell types with many desirable characteristics (Table 1).[10] *In vitro*, they can be induced to become typical sarcomeres with centrally-positioned nuclei and abundant mitochondria and to express atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and contractile proteins including—myosin heavy chain, myosin light chain, and alpha actin.[11-16] Intracoronary BMC infusion significantly decreases infarct size, increases myocardial perfusion, and improves regional and global cardiac function. Meta-analyses of clinical trials of intracoronary autologous BMC infusion following acute MI reported that the mean absolute increase in ejection fraction (EF) is approximately 3 to 4%.[17] This modest improvement in function appears to persist for 1 year. Some trials have shown that clinical events are reduced at 12 months, but others have reported no long-term clinical benefit, and the only 5-year follow-up suggested persistent benefit with decreased mortality; but also little evidence of significant myocardial regeneration in humans. These results have led to effort to identify better cell sources and to create more conducive myocardial environment for cell proliferation. Among the cell types are—skeletal myoblasts, cardiac stem cells and induced pluripotent stem cells (Table 1). Environmental modifiers are designed

Table 1: Types of cells being tested for myocardial regeneration

Cell type	*Advantages*	*Disadvantages*
Embryonic stem cells opposition	Divide for indefinite periods Evolve with cardiomyocyte action Potential	Major ethical opposition Possibility of teratoma formation
Bone marrow stem cells	Become both myocytes and vascular Feasible and safe in humans Readily prepared in hospitals Possibility of 'off-the-shelf' use Readily obtained	Pluripotency uncertain Limited success in clinical trials
Skeletal myoblasts	Low-risk of tumor formation Survive and differentiate in human hearts Align parallel with host cardiac cells Resistant to ischemia	Do not form gap junctions Ventricular arrhythmias in clinical trial
Cardiac stem cells	Cardiac origin Differentiation into all cardiac lineages Readily obtained at cardiac biopsy Clinical trials underway	Cardiac stem cells isolated from an aging heart may not sufficiently improve function
Induced pluripotent cell	Readily obtained from skin and thus less invasive Closely resemble embryonic stem cells Differentiate into all cell lines Regenerate myocardium in animal studies	More invasive because biopsy should be obtained from the septum Long-term outcome not yet known potential for malignant transformation

to increase cell survival, persistence and proliferation.[10] None of the clinical trials have raised a concern about safety. An emerging consensus, however, is that in clinical application, there is little evidence to suggest significant myocardial regeneration, and that the modest reported functional and clinical benefit reflects paracrine effects. As a consequence, research has moved to seeking better cell sources, with increased attention to modifying the environment into which cells are delivered. The use of stem cells to regenerate myocardium has proven to be far more complex than originally envisioned, when the first animal laboratory report appeared in late 2001. Although the potential and promise of such therapy remains undiminished, subsequent years have shown the need to identify better cell sources, and the need to develop methods to deal with the problems of cell survival, persistence and proliferation. New phase I clinical trials represent a beginning of a new era.[10]

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