Editorial

Cardiac Stem Cell Transplantation

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Cardiac stem cell transplantation is being considered as a potential alternative for many patients with ischemic heart diseases. There is a variety of cells for this purpose including embryonic and adult stem cells each with unique advantages and limitations. Nevertheless, the most suitable stem cells for cardiac cellular therapy are usually characterized by their good potential for survival, growth, differentiation, and integration into the host myocardium as well as high availability and low immunogenicity and oncogenicity. Selection of proper timing and routes of delivery and the right dosings according to the lesion size and location is also critical for success of the stem cell therapy.

Today, ischemic heart diseases and the resultant heart failure are the leading cause of death and physical disability in many countries.[1] However, there are still considerable rates of morbidity and mortality despite contemporary medical treatments and interventional options thus leaving heart transplantation as the ultimate therapeutic choice in the most complicated cases.[2-3] Because of the many limitations of the mentioned approaches, cardiac stem cell transplantation is increasingly being considered as a potentially novel alternative to conventional therapies by restoring cardiac function and improving microcirculation in the damaged heart.[3]

The innovative concept and potential application of stem cells comes from the hematological field where bone marrow and hematopoietic stem cells have been used successfully for more than 30 years to treat diseases like leukemia.[4] Stem cells are a population of immature tissue precursors found in various organs among the body capable of proliferation as well as differentiation in to a spectrum of different cell types under proper circumstances. Stem cells in general share the following characteristics and have a high capacity for: 1) proliferation or self-renewal; 2) differentiation; 3) trans-differentiation or plasticity; and 4) ex-vivo cultivation for tissue engineering applications.[5,6] On the basis of their origins and biological potentials, stem cell can be classified into either embryonic or adult categories. Embryonic stem (ES) cells are derived from the inner mass of blastocysts and can virtually give rise to any cell type found in the body (i.e. more than 200 kinds of cells) including the cardiomyocytes.[3,7] This very high differentiation capacity of ES cells is referred to as totipotency (i.e. differentiating into all cell types of the embryonic three main layers) or pluripotency (i.e. differentiating into most body cell types excluding those belonging to the germinal lineage). Adult stem cells have a much lower differentiation capacity and usually produce only limited numbers of cell types; hence they are referred to as multipotent or oligopotent stem cells. Adult stem cells in certain tissues give rise only to one type of somatic cells (monopotent stem cells). Human ES cells, on the other hand, have the disadvantage of ethical and technical limitations associated with their use in clinical trials, higher risks of arrhythmogenicity and teratogenicity, and the need for immunosuppressive therapy after transplantation.[3]

The concept of cardiomyocyte transplantation has been advocated since the late 1990s.[8] Stem cell transplantation has since then opened a new frontier in the treatment of cardiovascular disorders. In addition to regeneration of new cardiomyocytes, stem cells can participate in angiogenesis and hence prevent remodeling in the diseased heart insulted by ischemic events.[8] There are several major issues in any cardiac stem cell therapy experiment including selection of a suitable source and type of stem cells, their right dosings, the optimum timing and proper routes of cell delivery, and to decide whether to expand and differentiate them in vitro prior to implantation. These issues are the keys to success of stem cell therapy. Stem cells should also be isolated and further reintroduced in a feasible, safe and minimally invasive approach. Hence, a well-designed study should provide the following conditions to achieve the most effective tissue repair and regeneration: 1) high rates of cellular survival and proliferation (i.e. they should be able to reach the injured area, stay alive, and proliferate in the injured tissues); 2) strong

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potency for cellular differentiation; 3) potential for highly effective engraftment and integration of implanted cells into the host myocardium (i.e. implanted cells should be able to contract after differentiation and form stable intercellular gap junctions and electromechanical couplings with surrounding cardiac cells thus enhancing the cardiac function).[3]

Currently, both embryonic and adult stem cells are used in experimental cardiac cell transplantation studies, while only adult stem cells (e.g. bone marrow-derived mononuclear or mesenchymal cells, skeletal myoblasts, endothelial progenitor cells) are widely used in clinical trials.[3,9-20] Each stem cell type has unique biological properties that offer both advantages and limitations to use as mentioned earlier.[21]

Combining cell transplantation with proangiogenic growth factors or gene-transfected cells may improve cellular survival, although supporting data are not sufficient.[3] A recent evidence suggests that direct injection of undifferentiated bone marrow cells into animal leads to apparent transdifferentiation, but in fact all differentiated cells are the result of cell fusion only, at least in liver, brain, and heart.[22] This would not then appear to be a reasonable strategy. The question thus arises whether adult stem cells from any source can be adequately expanded and induced to differentiate in culture to produce sufficient cell numbers for cell therapy in patients. It seems that expansion of the cells in culture and efficient introduction of differentiation to the required cell type (ventricular cardiomyocytes) is necessary for any cell-based cardiac therapy. As many as 10^9 differentiated cardiomyocytes would be required to replace those lost after myocardial infarction.[9]

Currently there are two main approaches for cellular delivery to target myocardium: 1) cellular cardiomyoplasty; defined as direct or indirect injection of isolated cells; and 2) tissue cardiomyoplasty; or development of scaffold-based cellular constructs in vitro that can be engrafted to the damaged myocardium during open-heart surgeries. Tissue engineered scaffolds can be provided in the forms of either biologic or synthetic materials.[10] The later approach has the benefit that relatively very large scale of cells could be delivered to the scar tissue via biodegradable scaffolds. These scaffolds play a prominent role both in promoting cell proliferation and in guiding cell growth and general tissue architecture. They can induce growth and proliferation of cardiac cells into biologically relevant contractile spindle structures.[23-25] Since the first human trial published in 2001 by Menasche et al.,[26] numerous clinical trials with promising results have been published so far employing various methods of cellular cardiomyoplasty including direct intramyocardial injection of cells through thoracotomy (transepicardial)[12,14,17,27-29] or transcoronary approaches,[30-32] transcatheter endomyocardial injection,[15,20,33] intracoronary cell injection,[11,13,16,35-37] and systemic intravenous injection.[38,39] Advantages and disadvantages of each mentioned approach are outlined in table 1.

Table 1. Advantages and disadvantages of various methods for cellular cardiomyoplasty.

Method	Advantages	Disadvantages
Transepicardial intramyocardial injection	• The most precise and accurate method • The most suitable approach in candidates of CABG	• The most invasive method • Requires general anesthesia • Prolonged recovery period
Transcatheter endomyocardial injection	• Less invasive than transepicardial approach • Its safety and accuracy have been demonstrated	• Limited technical feasibility • Requires advanced imaging technologies
Intracoronary cell injection	• Technical simplicity • Can be performed at the same time with PCI	• Non-selective distribution pattern of injected cells • Cells can not reach beyond occluded coronary arteries (infarcted scar zones are excluded) • Cell aggregates may occlude small coronary arteries and lead to microembolisms
Transcoronary intramyocardial injection	• Lacks limitations of the intracoronary approach	• Safety and feasibility have not yet been proved
Systemic intravenous injection	• The simplest and least invasive delivery route • Minimal complications • Easily repeatable if necessary	• Poor selectivity • Low efficiency

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