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REVIEW

Stem cells and cardiovascular tissue repair: Mechanism, methods, and clinical applications

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Summary Cardiac stem cell therapy is emerging as a potential novel treatment for patients with heart disease. Experimental studies and clinical trials have shown that stem cell transplantation can achieve certain degrees of success in enhancing myocardial perfusion, repair or regeneration, leading to improvement of cardiac function. Different types of stem cells including those from embryonic and adult tissues have been tested, and each stem cell type has advantages and disadvantages. The stem cell type(s) most suitable for cardiac cell therapy is hard to define, but such cells are usually characterized by their high potential for survival, growth, and differentiation as well as integration into the host tissue. Selection of proper delivery methods according to lesion size and location is also a critical factor for the success of stem cell therapy. Preliminary data from experimental stem cell research and clinical trials for cardiac stem cell therapy are controversial, yet encouraging.

Contents

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Introduction

In spite of great progress in intervention and medications, heart failure caused by atherosclerosis-associated ischemic injury remains a major cause of morbidity and mortality in developed countries. Clinical studies have shown that angiotensin-converting enzyme (ACE) inhibitors and β-receptor blockers can improve the survival rates of patients with chronic heart failure [1]. In the MERIT-HF study, however, the annual mortality of heart failure is still as high as 7.2% despite the most contemporary medical treatment [2]. In addition, ventricular resynchronization therapy (biventricular pacing) and ventricular assist devices can improve functional tolerance and myocardial remodeling, but their application does not help all patients [3].

Most patients with congestive heart failure have a history of atherosclerotic coronary artery disease (CAD). Severe atherosclerosis narrows the vascular lumens, stimulates thrombogenesis, restricts coronary flow, and ultimately causes ischemic cardiac injury. Post-injury adverse remodeling of the myocardium can cause ventricular dysfunction (left ventricular ejection fraction <40%) or heart failure [4]. As the primary etiology of heart failure, CAD occurs in more than 70% of patients [5].

In the failing heart, cardiac cells undergo degenerative changes, apoptosis, and hypertrophy [6]. The dying or dead cells in the heart include not only cardiac muscle cells but also vascular cells or other non-myogenic cells. With the loss of contractile myocytes, the heart increases production of fibrotic connective tissue, leading to formation of a hypocellular scar tissue and reduced contractility [7].

Heart transplantation remains a therapeutic option for patients at end stages of heart failure. The procedure of replacing the failing or failed heart with a normal one confronts several limitations including the poor availability of donor organs, immune rejection, and infectious complications as well as physical, rheologic, and thrombotic issues [8]. Because of these limitations, investigators have been searching for alternative treatments that can effectively repair the wounded heart and permanently restore its function. Among those approaches, stem cell transplantation is a potentially novel therapy that can repopulate functional cardiac myocytes and promote vascularization in the damaged heart [9]. In this review, we explore the potential mechanism by which stem cells repair the heart damaged by ischemic injury, the methods for delivery of cardiovascular stem cells into the myocardium, and the current states of clinical stem cell application.

Basics of stem cell biology

Stem cells are a population of immature tissue precursor cells capable of self-renewal or proliferation as well as differentiation into a spectrum of different cell types under appropriate conditions. In general, they share the following characteristics: (1) a high capacity for self-renewal; (2) the potential for multipotent differentiation potential; (3) the ability to be cultured ex vivo and used for tissue engineering (reprogramming); and (4) plasticity (transdifferentiating ability) [10,11].

The classification of stem cells is still evolving. On the basis of differentiating potential, stem cells can currently be classified into four categories: (1) totipotent, (2) pluripotent, (3) multipotent, and (4) monopotent or oligopotent (Table 1). Totipotent stem cells in general have the potential to differentiate into cells of all three main embryonal layers (ectodermal, endodermal, and mesodermal). One totipotent cell can differentiate into an intact organism with central and peripheral nervous systems if that cell is implanted into a functional uterus. In mammals, only zygotes and blastomeres at the early stage of cleavage are totipotent stem cells. With the progression of differentiation, zygotes (totipotent stem cells) form themselves into outer and inner layers of cells. The cells in the inner layer can give rise to every cell type in the body, but they cannot do so without the outer layer, which will become the placenta. The inner cells are called pluripotent stem cells. As pluripotent stem cells continue to divide, they begin to specialize further and become the progenitors of special tissues. At this stage, they