INDIAN STEMCELL STUDY GROUP ASSOCIATION (ISCSG)
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Role of Different types of Stem cells in patients with Congestive heart failure (CHF).

Introduction:

Congestive heart failure (CHF) is a chronic progressive condition that affects the pumping power of your heart muscles. While often referred to simply as "heart failure", CHF specifically refers to the stage in which fluid builds up around the heart causing it to pump inefficiently.

Heart attacks and congestive heart failure remain among the Nation's most prominent health challenges despite many breakthroughs in cardiovascular medicine. In fact, despite successful approaches to prevent or limit cardiovascular disease, the restoration of function to the damaged heart remains a formidable challenge. Recent research is providing early evidence that adult and embryonic stem cells may be able to replace damaged heart muscle cells and establish new blood vessels to supply them.

For those suffering from common, but deadly, heart diseases, stem cell biology represents a new medical frontier. Researchers are working toward using stem cells to replace damaged heart cells and literally restore cardiac function.

Types of Stem Cells Investigated to Regenerate Damaged Myocardial Tissue

Embryonic and adult stem cells have been investigated to regenerate damaged myocardial tissue in animal models and in a limited number of clinical studies.

Embryonic Stem (ES) Cells

Because ES cells are pluripotent, they can potentially give rise to the variety of cell types that are instrumental in regenerating damaged myocardium, including cardiomyocytes, endothelial cells, and smooth muscle cells. ES cells that were transplanted into ischemically-injured myocardium in rats differentiated into normal myocardial cells that remained viable for up to four months, suggesting that these cells may be candidates for regenerative therapy in humans.

However, several key hurdles must be overcome before human ES cells can be used for clinical applications. Foremost, ethical issues related to embryo access currently limit the avenues of investigation. In addition, human ES cells must go through rigorous testing and purification procedures before the cells can be used as sources to regenerate tissue.

Human Adult Bone-Marrow Derived Cells

Researchers have demonstrated that cardiomyocytes and endothelial cells could be regenerated in a mouse heart attack model through the introduction of adult mouse bone marrow-derived stem cells, and also its been shown that direct injection of mouse bone marrow-derived cells into the damaged ventricular wall following an induced heart attack led to the formation of new cardiomyocytes, vascular endothelium, and smooth muscle cells. Based on these findings, researchers have investigated the potential of human adult bone marrow as a source of stem cells for cardiac repair. In the past three years, the transplantation of bone marrow mononuclear cells (BMMNCs), a mixed population of blood and cells that includes stem and progenitor cells has been explored in more patients and clinical studies of cardiac repair than any other type of stem cell.

The results from clinical studies of BMMNC transplantation have been promising but mixed. However, it should be noted that these studies have been conducted under a variety of conditions, thereby hampering direct comparison. The cells have been delivered via open-heart surgery and endomyocardial and intracoronary catheterization. Several studies, including the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) and the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trials, have shown that intracoronary infusion of BMMNCs following a heart attack significantly improves the left ventricular (LV) ejection fraction, or the volume of blood pumped out of the left ventricle with each heartbeat. However, other studies have indicated either no improvement in LV ejection fraction upon treatment or an increased LV ejection fraction in the control group. An early study that used endomyocardial injection to enhance targeted delivery indicated a significant improvement in overall LV function. Discrepancies such as these may reflect differences in cell preparation protocols or baseline patient statistics. As larger trials are developed, these issues can be explored more systematically.

Resident Cardiac Stem Cells

Recent evidence suggests that the heart contains a small population of endogenous stem cells that most likely facilitate minor repair and turnover-mediated cell replacement. These cells have been isolated and characterized in mouse, rat, and human tissues. The cells can be harvested in limited quantity from human endomyocardial biopsy specimens and can be injected into the site of infarction to promote cardiomyocyte formation and improvements in systolic function. Separation and expansion ex vivo over a period of weeks are necessary to obtain sufficient quantities of these cells for experimental purposes. However, their potential as a convenient resource for autologous stem cell therapy has led the National Heart, Lung, and Blood Institute to fund forthcoming clinical trials that will explore the use of cardiac stem cells for myocardial regeneration.

Skeletal Myoblasts

While skeletal myoblasts (SMs) are committed progenitors of skeletal muscle cells, their autologous origin, high proliferative potential, commitment to a myogenic lineage, and resistance to ischemia promoted their use as the first stem cell type to be explored extensively for cardiac application. Studies in rats and humans have demonstrated that these cells can repopulate scar tissue and improve left ventricular function following transplantation. However, SM-derived cardiomyocytes do not function in complete concert with native myocardium. The expression of two key proteins involved in electromechanical cell integration, N-cadherin and connexin 43, are downregulated *in vivo*, and the engrafted cells develop a contractile activity phenotype that appears to be unaffected by neighboring cardiomyocytes.

To date, the safety and feasibility of transplanting SM cells have been explored in a series of small studies enrolling a collective total of nearly 100 patients. Most of these procedures were carried out during open-heart surgery, although a couple of studies have investigated direct myocardial injection and transcoronary administration. Sustained ventricular tachycardia, a life-threatening arrhythmia and unexpected side-effect, occurred in early implantation studies, possibly resulting from the lack of electrical coupling between SM-derived cardiomyocytes and native tissue. Changes in preimplantation protocols have minimized the occurrence of arrhythmias in conjunction with the use of SM cells, and Phase II studies of skeletal myoblast therapy are presently underway.

Mesenchymal (Bone Marrow Stromal) Cells

Mesenchymal stem cells (MSCs) are precursors of non-hematopoietic tissues (*e.g.*, muscle, bone, tendons, ligaments, adipose tissue, and fibroblasts) that are obtained relatively easily from autologous bone marrow. It is the observation that MSCs can differentiate into cardiomyocytes and endothelial cells *in vivo* when transplanted to the heart following myocardial infarct (MI) or non-injury in pig, mouse, or rat models. Additionally, the ability of MSCs to restore functionality may be enhanced by the simultaneous transplantation of other stem cell types.

Several animal model studies have shown that treatment with MSCs significantly increases myocardial function and capillary formation. One advantage of using these cells in human studies is their low immunogenicity; allogeneic MSCs injected into infarcted myocardium in a pig model regenerated myocardium and reduced infarct size without evidence of rejection. A randomized clinical trial implanting MSCs after MI has demonstrated significant improvement in global and regional LV function, and clinical trials are currently underway to investigate the application of allogeneic and autologous MSCs for acute MI and myocardial ischemia, respectively.

Endothelial Progenitor Cells

EPCs are precursor cells that express some cell-surface markers characteristic of mature endothelium and some of hematopoietic cells. EPCs home in on ischemic areas, where they differentiate into new blood vessels; following a heart attack, intravenously injected EPCs home to the damaged region within 48 hours. The new vascularization induced by these cells prevents cardiomyocyte apoptosis (programmed cell death) and LV remodeling, thereby preserving ventricular function. However, no change has been observed in non-infarcted regions upon EPC administration. Clinical trials are currently underway to assess EPC therapy for growing new blood vessels and regenerating myocardium.

Other Cells: Umbilical Cord Blood Stem Cells, Fibroblasts, and Peripheral Blood $CD34^+$ Cells

Several other cell populations, including umbilical cord blood (UCB) stem cells, fibroblasts (cells that synthesize the extracellular matrix of connective tissues), and peripheral blood $CD34^+$ cells, have potential therapeutic uses for regenerating cardiac tissue. Although these cell types have not been investigated in clinical trials of heart disease, preliminary studies in animal models indicate several potential applications in humans.

Conclusions

The evidence to date suggests that stem cells hold promise as a therapy to regenerate damaged myocardium. Given the worldwide prevalence of cardiac dysfunction and the limited availability of tissue for cardiac transplantation, stem cells could ultimately fulfill a large-scale unmet clinical need and improve the quality of life for millions of people with CVD. However, the use of these cells in this setting is currently in its infancy—much remains to be learned about the mechanisms by which stem cells repair and regenerate myocardium, the optimal cell types and modes of their delivery, and the safety issues that will accompany their use. As the results of large-scale clinical trials become available, researchers will begin to identify ways to standardize and optimize the use of these cells, thereby providing clinicians with powerful tools to mend a broken heart.

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