CARDIAC STEM CELL THERAPY AND IMAGING: A RAY OF HOPE FOR POOR HEARTS.

Coronary heart disease (CHD) is the leading cause of morbidity and death in the United States with a total economic burden due to CHD on health care system has reached an estimated $142 billion in 2006.[1] Despite substantial advances in treatment like drug therapy and revascularization strategies, ischemic cardiac injury and the ventricular dysfunction remain major source of concern throughout the world. The endogenous regenerative capacity of the heart appears inadequate to repair injured myocardium as most cardiomyocytes are terminally differentiated,[2] leading to the cumulative loss of cardiomyocytes over the lifetime of a patient.

In 2001 animal studies have successfully demonstrated the engraftment and differentiation of transplanted stem cells into cardiomyocytes in ischemic myocardium.[3,4] In addition, encouraging results illustrating the restoration of infarcted tissue, improvement of systolic function, and prolongation of survival by stem cell transplantation in animal experiments have paved the path for rapid transition of cardiac cell therapy into clinical trials possible.[5,6]

Basic Types of Stem Cell: Stem cells are undifferentiated cells having the ability of self-renewing and proliferating into multiple lineages.[7] There are 3 fundamental types of stem cells.

a) Totipotent stem cells: can be differentiated into all cell types and form a full organism.
b) Pluripotent stem cells: can give rise to three germ layers but lack the capacity to develop into a functional organism.
c) Multipotent stem cells: have limited lineages to which they are committed.

Types of Stem Cells Used For Cardiac Repair:

A. **Embryonic Stem (ES) Cells:** These are the most primitive of all stem cells and develop at the inner cell mass in human embryo at 5th after fertilization (blastocyst). These are pluripotent cells, can be readily and reproducibly obtained from inner layer of blastocyst and can undergo cell proliferation and form embryo like bodies in vitro (ebmbryoid bodies). Two major limitations of ES cells are immunological rejection and propensity to form teratoma when injected in-vivo.[8,9] Furthermore, legal and ethical concerns about ES cells have significantly hampered further research efforts.

B. **Adult Skeletal Myoblast (SM) Cells:** These are the first cell type to be explored in human cardiac cell therapy. They can proliferate abundantly in culture, and can be easily grown from patient themselves (self derived or autologous) thereby avoiding potential immune response. These myoblasts are relatively ischemia resistant and can withstand several hours of severe ischemia without becoming irreversibly damaged (as compared to cardiomyocytes which become injured within 20 minutes).[10] Clinical studies have shown improved ventricular wall motion and ejection fraction (EF) and even reversion of heart failure in some study subjects.[11,12,13] However, there are evidence of failure of myoblast to transdifferentiate to cardiomyocytes and importantly reports of high incidence of arrhythmia especially ventricular tachycardia within weeks of procedure.[11,13,14] Due to these observations, phase 2 clinical trial of Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) study has been ceased.[15] Based on these facts, it seems doubtful that skeletal myoblast will become a suitable choice in near future.

C. **Bone Marrow (BM) Derived Stem Cells:** Bone marrow contains several stem cell population with overlapping phenotypes, including hematopoietic stem cell (HSC), endothelial precursor cells (EPC) and mesenchymal stem cells (MSC). Bone marrow derived stem cells transplantation give rise to new cardiac myocytes and coronary vasculature by their neovascularization and

angiogenesis properties.[5] Autologous stem cell can be easily harvested, processed via bone marrow aspiration and lack of evidence of ventricular tachycardia or other adverse reactions has made BM cells a relatively safe compared with SMs.

D. **Adult Cardiac Stem (ACS) Cells:** The current information available on various stem cell populations in the adult heart has emerged from research in several laboratories. However, many questions remain concerning the origin, structure, precise location, function and regulation of these cells. The existence of Lin- c-kit+ cells in adult rat myocardium with the properties of stem cells has been reported.[16] These cells are self-renewing and can be propagated for several months, expandable in culture, and multipotent, and can give rise to cardiomyocytes, smooth muscle, and endothelial cells. When injected into an ischemic heart, the Lin- c-kit+ cells contribute to the formation of endothelium and vascular smooth muscle and to the regeneration of myocardium in the region of necrosis, improving its pump function and ventricular chamber geometry.[17] It is presumed that ACS cell transplantation might be more effective than BM since ACS may be better programmed. However, these cells have poor in-vitro growth and sensitive to ischemia or apoptotic cell death. Furthermore, as these cells are harvested from fetal, neonatal or adult sources (allogenic), immune rejection and ethical issues are important.

Possible Mechanisms of Cell Regeneration: Recent studies have shown that transplantation of SM,[18] BM[3] and ES[19] cells into infracted myocardium can help improve cardiac remodeling and function. The possible mechanisms for this regenerative process include the differentiation of stem cells into cardiomyocytes, secretion of paracrine factors, or recruitment of peripheral stem cells to the ischemic territory.[20]

Outcome of Clinical Trials: Currently the results of five major randomized clinical trials have been published and results are both encouraging as well as disappointing too.

1. REPAIR-AMI Trial[21] (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) by Schachinger et al is the largest, randomized double blind trial so far. At 4 months follow up, significant improvement in LVEF measured by angiography was seen in treated arm and benefit was greater in patient with worst baseline LVEF.
2. BOOST Trial[22] (Bone Marrow Transfer to Enhance ST Elevation Infarct Regeneration) by Wollert and Meyer et al is a randomized double blind trial which revealed significant improvement in LVEF at 6 months which remains no longer significant at 18 months follow up. This is a disappointing result indeed and raises the question of repeat therapy for sustain improvement.
3. Janssens et al[23] in 2006 published results of their randomized double blind trial which showed no significant difference in overall LVEF at 4 months follow up. However, they observed reduction in infarct size and better regional function in treated arm.
4. ASTAMI[24] (Autologous Stem Cell Transplantation in Acute Myocardial Infarction) trial published in 2006, revealed significant difference in LVEF in treated and placebo arm at 6 months follow up.
5. TOPCARE-CHD[25] (Transplantation of Progenitor Cell And Recovery of LV Function in Chronic Ischemic Heart Disease) is a randomized cross-over trial by Assmus et al. published 3 months follow up results in 2006. They found significant improvement in LVEF in BMC group than in group received circulating progenitor cell or placebo group.

Imaging of Transplanted Stem Cell: In-vivo imaging of transplanted stem cell to ascertain their localization and mobilization shortly after administration, survival, proliferation or differentiation into cardiomyocytes is important in assessing the success or failure of procedure.

The traditional imaging techniques like Single Photon Emission Computerized Tomography (SPECT), Positron Emission Tomography (PET), Computerized Tomography (CT), echocardiography or Magnetic Resonance Imaging (MRI) can indirectly assess functional changes like wall motion, perfusion, metabolism and contractility but cannot directly visualize the transplanted cells.

In-vivo molecular imaging has got ability to characterize and quantify the biological process at molecular and cellular level. Various radiolabeled probes like Technetium-99m exametazime[26] Indium-111–labeled cardiomyoblasts and Fluorine-18 FDG labeled BM cells[27] have been used by in clinical studies by some researchers with promising results. Kraitchman et al[28] first explored the utilization of MRI to image stem cell therapy for the heart by using ferumoxide (Feridex, Berlex Inc., Montville, NJ) labeled MSCs for transplantation into a swine infarction model. Reporter gene imaging[29] using radiolabeled or optical reporter probes is a new and highly sensitive technique in its initial phase.

Cardiac stem cell therapy although in its infancy but represents a viable therapeutic approach for repairing the injured myocardium. With robust advancement in cell engineering, we expect that this ray of hope for poor hearts would become a reality and could prevent the health care system from bankruptcy.

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