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Treatment of ischemic myocardium with autologous bone marrow cell transplantation

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The increasing interest in cardiovascular(CV) stem cells research could be the result of abundant evidence that suggests that stem cells may represent therapeutic entities. The CV stem cell research has raised the question the long-held paradigm that the heart cannot be repaired, and the possibility of cardiac regeneration. Several small-scale clinical trials have suggested that intracoronary transfer of autologous bone marrow (BM) cells may stimulate left ventricular (LV) functional recovery in patients with acute myocardial infarction (AMI) beyond the recovery seen with coronary stent implantation and optimal postinfarction pharmacotherapy. On the basis of these early clinical data and experimental results showing that certain BM cell populations can enhance tissue perfusion and contractile performance of the infarcted heart, it has been proposed that BM celltransfer may provide a means to achieve functional regeneration after AMI. However, these clinical studies addressing the effects of BM cell transfer after AMI have covered only limited time frames ranging from 3 to 6 months. Recently published the BOne marrOw transfer to enhance ST-elevation infarct regeneration (BOOST) trial conclude that a single dose of intracoronary BM cells does not provide long-term (18-month) benefit on LV systolic function after AMI as compared with a placebo, although they showed that the speed of LV ejection fraction (LVEF) recovery was significantly higher in the BM cell treatment group. An exception is the Transplantation Of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial. In this trial, 12-month follow-up suggests a preservation of benefit in LVEF observed 4 months after intracoronary transfer of culture-selected, BM–derived cells or circulating progenitor cells. These reports help to sharpen our focus on the important questions that face the nascent field of CV stem cell therapy like many good investigations. Which disease should we be treating? At what point in the disease process should we treat? Which cells should be used? How should these cells be delivered? What are the main mechanisms by which transplanted cells exert influence, if they do? Preclinical data are potentially informative in this regard. For example, Orlic group showed the improvement in outcome after MI with mobilization of stem cells, and they found it necessary to pretreat the mice with a mobilization agent before the onset of injury, an indication that the timing of therapy was critical. The potential impact of route of delivery was shown by Dimmeler group, who used In-labeling of EPCs, documenting the very low myocardial uptake of cells when administered by intraventricular injection. These studies also showed enhanced myocardial uptake in the presence of acute ischemia. It is noteworthy that this group used a novel technique of transient coronary occlusion for cell delivery in their clinical trial. The selection of cell type is perhaps one of the essential issues in the field. The use of an unselected BM mononuclear cell preparation is based on the fact that various stem and progenitors cells will be contained within this population and that the manufacturing process does not require expensive equipment or that the cell products meet specifications before administration, thus streamlining the procedure. The inherent liabilities in this strategy include the variability of the therapeutic being administered and the possibility that cells that may inhibit repair, or even potentially worsen outcome, might be present in varying quantities from patient to patient. Another question is whether the use of unselected BM mononuclear cells is optimal—the overwhelming evidence would argue that this is inconceivable. One of the advantages of cell-based therapies is that human cells can actually be tested for potency. Thus, the identification of subpopulations of cells with enhanced potency is possible. Many groups can phenotypically characterize cells that work versus those that don't and ultimately modify the cells to enhance their potency for specific indications. These latter points, of course, address the issue of mechanism. Human observational and animal data suggest that BM –derived cells play a role in the repair process after injury, but the precise means by which the repair process is effected remains incompletely defined. The contribution of circulating and resident cells to neovessel formation and to replacement of cardiomyocytes has been elegantly shown though not universally accepted, whereas paracrine mechanisms and fusion continue to be debated. A difficult issue in the field is the pharmacokinetics/pharmacodynamics of cell therapy. Dosing of cells is not straightforward. Should it refer to the number of cells delivered, the number of cells initially retained within tissue, or the number of cells eventually incorporated into myocardial structures? How should we measure the retention of cells in human trials? However, clinical trials have been completed or are underway for other conditions including chronic ischemic angina without conventional revascularization option, chronic ischemic heart failure, and nonischemic heart failure. Despite the myriad questions raised above, there have been multiple studies that have suggested clinical benefit from cell therapy for cardiac conditions, and these propel the field forward. We remain optimistic regarding the future of CV stem cell therapy . However, we suggest that the CV stem cell research requires a recommitment to preclinical investigation as a means of better understanding basic mechanisms and clinical trial design based on these preclinical data.

S6-4

Molecular therapy for heart failure

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During the past half century, the causes and treatment of heart failure(HF) have changed considerably. Once considered a simple problem of LV pump dysfunction, HF has now come to be understood as a highly complex clinical syndrome that is manifested by many extracardiac features, including neuroendocrine activation and cytokine release. A more contemporary working hypothesis is that HF is a progressive disorder of LV remodeling. The pathophysiology is exceedingly complex and involves structural changes such as loss of myofilaments, apoptosis and disorganization of the cytoskeleton as well as molecular changes. Our current therapy for HF is primarily palliative and is not biologically targeted. Genetically engineered mice and some larger animal models of HF have led to the elucidation of molecular targets in the failing myocardium. Candidate molecular and genetic targets for HF are intracellular calcium handling and homeostasis, β-adrenergic receptor signaling, cardiomyocyte survival signaling, antiapoptotic signaling, inhibition of pathologic hypertrophy, and myocardial angiogenesis. Although these molecular and genetic therapies relieved HF symptoms and improved heart function in animal model of HF and ex vivo studies, further studies have to be initiated in human subjects.

S6-5

Therapeutic angiogenesis and lymphangiogenesis using angiopoietins

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The angiopoietin (Ang) family of growth factors bind to the endothelial receptor tyrosine kinases Tie2 and Tie1. To investigate the role of angiopoietins on vascular and lymphatic remodeling, 1×109 pfu of adenoviral vector encoding Ang1, Ang2, Ang3, Ang4 or LacZ (control) were intravenoulsy treated on adult mice. In the normal ear skin, all angiopoietins induced vascular enlargement, while none of the angiopoietins induced lymphatic remodeling. However, in the margin of ear skin wounds, all angiopoietins strongly induced vascular and lymphatic enlargement, sprouting and filopodia. Thus, each angiopoietin acts differently on vascular and lymphatic remodeling in different situations. We have recently created a soluble, stable and potent Ang1 variant, COMP-Ang1. COMP-Ang1 induced a long-lasting vascular enlargement and increased tracheal blood flow. Re-establishment of structural and functional microvasculature with COMP-Ang1 could be beneficial to promote wound healing in diabetic patients. We recently determined the effectiveness of COMP-Ang1 on promotion of the healing process in cutaneous wounds of diabetic mice. COMP-Ang1 can promote wound healing in the diabetes through enhanced angiogenesis, lymphangiogenesis and blood flow.