Back to the bench: The rejuvenation of stem cell therapy—the therapeutic potential of CD133$^+$ progenitor cells

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Cell therapy promised to regenerate the heart after a myocardial infarction (MI). Indeed, preclinical studies demonstrated dramatic improvements in ventricular function after cells of various types were implanted into the damaged myocardium; however, cell therapy was less effective in the initial clinical trials. Investigators have thus returned to the bench to identify new approaches to stem cell therapy that can be used at the bedside. In this issue of the *Journal,* Zhang and colleagues[1] report a new approach to expand the number of enriched progenitor cells (CD133$^+$/CD34$^+$/VEGFR-2$^+$ cells) for implantation and produce more extensive angiogenesis in the ischemic myocardium. The second generation of cell therapies may finally achieve myocardial regeneration. This editorial reviews the results of the initial clinical trials, the potential benefits of expanded marrow stem cells, and the challenges facing cell therapy.

CLINICAL TRIALS OF CELL THERAPY

Schachinger and colleagues[2] reported that infusing bone marrow progenitor cells 3 to 7 days after reperfusion of an MI improved global and regional ventricular function. Cell therapy was associated with a decrease in end-systolic volumes and a 5% increase in ejection fraction (EF) in patients with baseline dysfunction. Meta-analyses[3] demonstrated that most clinical trials reported a similar statistically significant increase in EF that was smaller than that reported in the preclinical studies. However, stem cell therapy not only induced angiogenesis but also inhibited matrix degradation (which prevented ventricular dilatation) and recruited resident stem cells (which stimulated infarct healing).[4,5] Therefore, cell therapy produced more extensive beneficial effects on infarct size and ventricular volume than on EF.

The clinical impact of cell therapy deserves careful attention. One year after treatment in the REPAIR-AMI trial,[2] the patients randomized to progenitor cell therapy had fewer deaths or MIs and required fewer revascularization procedures (20%) compared with the placebo group (40%). In the BALANCE trial,[6] implanted bone marrow cells reduced infarct size and ventricular volumes and increased EF, but also improved survival at 4.6 years. A recent comparative analysis[7] demonstrated that the beneficial effects associated with cell implantation were similar to the established effects of reperfusion (stenting), beta-blockers, and angiotensin-converting enzyme inhibitors after an MI. The authors concluded their evaluation ''reveals that improvements in EF achieved by cell therapy are within an intriguingly similar range compared with established therapeutic strategies.'' Although many scientists were disappointed with the results of the initial clinical trials, cell therapy offers significant advantages over other approaches to prevent heart failure after an MI.

ENHANCED ANGIOGENESIS WITH CD133$^+$ CELLS

The CD133$^+$ fraction of the bone marrow contains hematopoietic stem cells and endothelial progenitor cells, and is therefore an excellent source of candidate cells for cell therapy. Implanted CD133$^+$ cells survived in the infarcted myocardium, inducing angiogenesis and supporting functional recovery. Injecting these cells into the infarct region during coronary artery bypass grafting significantly improved ventricular function at 6 months.[8] Unfortunately, the clinical utility of CD133$^+$ cells has been hampered by the limited number that can be isolated from patients with heart failure, who are most likely to benefit from cell therapy.[9]

Zhang and colleagues[1] describe innovative methods to increase the number of CD133$^+$/CD34$^+$/VEGFR-2$^+$ progenitor cells available from the pool of mononuclear cells. The expanded cells retained their angiogenic capacity, but the mechanisms responsible were not fully elucidated. Future studies will be required to determine which genes are expressed when CD133$^+$ cells evolve from the pool of CD133$^-$ cells. Genome-wide profiling may also help determine how these stem cells induce angiogenesis through paracrine signaling. Why do CD133$^+$ cells inhibit the generation of new CD133$^+$ cells? Do the CD133$^+$ cells secrete soluble factors that inhibit CD133 gene expression via an autocrine feedback loop?

The most interesting aspect of the study by Zhang and colleagues[1] is the finding that the induction of angiogenesis by CD133$^+$ cells exceeded that by mesenchymal stromal cells (MSCs), which are the other stem cells found in the bone marrow mixture that was used in the initial clinical trials.[2,3]

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The in vitro assessment reported by Zhang and colleagues supports the in vivo results of Mathieu and colleagues,[10] who also demonstrated that a bone marrow mixture enriched for hematopoietic precursors induced more angiogenesis than MSCs in a canine model of MI. However, although the $CD133^+$ fraction may induce more angiogenesis than MSCs, stromal cells also alter matrix remodeling, reduce ventricular volumes, and recruit autologous stem cells.[11] In addition, MSCs can be expanded in vitro, and their paracrine effects can be enhanced through gene transfection.[12] Gene-transfected MSCs have been demonstrated to boost angiogenesis, reverse matrix remodelling, and increase the recruitment of recipient stem cells. Extensive large animal and clinical trials will be necessary to determine which cell mixture best restores ventricular function after an MI.

CHALLENGES ASSOCIATED WITH CELL THERAPY

The main obstacle to the success of clinical cell therapy is the limited regenerative capacity of stem cells from aging patients with extensive comorbidities (eg, diabetes and extensive atherosclerosis). The present challenge is to rejuvenate these stem cells. Preconditioning is known to improve the survival and engraftment of bone marrow stem cells. However, reestablishing the paracrine capacity of either bone marrow cells or the $CD133^+$ fraction might not be possible in elderly patients. In that case, the restoration of ventricular function may be best achieved with allogeneic MSCs (from young, healthy adults) that may avoid rejection after implantation.[13]

CONCLUSIONS

Cell therapy continues to offer the promise to restore cardiac function after an MI. Informed by the results of the initial clinical trials, investigators have returned to the bench to develop new approaches. The unique method reported by Zhang and colleagues[1] to expand the stem cell-containing bone marrow fraction may expand the clinical utility of cell therapy. In the future, additional modifications may not only induce angiogenesis but also achieve infarct healing in the hearts of elderly patients who are at the greatest risk of heart failure.

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