Stem cell therapy for heart failure: Out with the new and in with the old?

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Stem cell (SC) therapies have long been touted as a novel therapy for advanced heart failure. A plethora of clinical trials have overwhelmingly demonstrated the safety of this therapy, but there are conflicting reports of efficacy or the lack thereof. To make sense of these disparate results it may help to review trends in our understanding of how this therapy may work.

Without question, our knowledge of the mechanisms by which implanted cells improve myocardial perfusion and function has expanded greatly in the past 2 decades. When cell therapy was in its infancy, the presumed mechanism of action was replacement of cardiomyocytes lost to myocardial infarction (MI) by functioning, contractile donor-derived myocytes, and the focus was on finding the right type of donor myocyte or on demonstrating transdifferentiation or fusion of multipotent donor cells. We now recognize that the dominant mechanisms of action of the cells evaluated during that era were via paracrine effects, amplifying the endogenous repair response of the myocardium and modulating extracellular matrix homeostasis. These insights led to changes in the cell types and strategies employed in clinical trials. However, in a return to the original strategy, the forced ex vivo differentiation of embryonic stem cells (ESCs) or induced pluripotent stem cells (PSCs) into phenotypically convincing cardiomyocytes for subsequent implantation is now 1 of the most hotly investigated areas of this field.

The advances in the understanding of donor cell biology and host response led to a change in the cell types being employed in clinical trials over time. The first trials utilized skeletal myoblasts, which improved cardiac function following injury in animal studies, but which failed to show efficacy in human patients.^{1,2} Skeletal myoblasts were also associated with significant arrhythmia risks³ and have fallen out of favor.

While most bone marrow cells (BMCs) are not stem cells, their reparative effect may be due to hematopoietic stem cells and endothelial progenitor cells promoting

angiogenesis and preventing left ventricle remodeling.⁴ Given the heterogeneity of BMCs,⁵ clinical experience has had conflicting results. In Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI), mononuclear BMCs delivered after acute MI increased left ventricular ejection fraction (LVEF), with the effect dependent on the interval between MI and cell delivery and baseline LVEF.⁶ This trial informed the design of subsequent large trials, including Transplantation in Myocardial Infarction Evaluation (TIME),⁷ LateTIME,⁸ and First Mononuclear Cells Injected in the United States Conducted by the Cardiovascular Cell Therapy Research Network (FOCUS-CCTR).⁹ These 3 well-designed trials demonstrated no significant change in LVEF or myocardial reversibility following BMC treatment at 3 days, 7 days, or several weeks after acute MI, or in patients with chronic ischemic cardiomyopathy unsuitable for conventional revascularization. There is currently much reduced enthusiasm for the use of otherwise unfractionated BMCs.

However, subfractions of the BMC population such as the CD133+ subpopulation have improved LVEF after coronary artery bypass grafting and cell delivery.¹⁰ The Implantation of Autologous CD133+ Stem Cells in Patients

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Central Message

Our understanding of how cell therapies work has come full circle, and the old paradigm may lead to the cell therapies of the future.

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Undergoing CABG (IMPACT-CABG) trial of CD133+ cell transplantation for ischemic cardiomyopathy has completed enrollment at 2 centers in Canada, while the Intramyocardial Transplantation of Bone Marrow Stem Cells for Improvement of Postinfarct Myocardial Regeneration in Addition to CABG Surgery (PERFECT) trial is currently enrolling patients at 6 German sites. These CD133+ cells may be particularly suited to vasculogenesis in ischemic cardiomyopathy, but more studies will be required to elucidate their reparative capabilities.

Mesenchymal stem cells (MSCs) are thought to mediate the stem cell niche¹¹ and may have immunomodulatory properties because they produce anti-inflammatory factors and do not express major histocompatibility complex class-II antigens.¹² Several clinical trials have demonstrated safety with varying delivery routes.¹³⁻¹⁶ In Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON), either autologous or allogeneic MSC injection improved quality of life, ventricular remodeling, and functional capacity.¹⁷ Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) demonstrated that autologous MSC injection in chronic ischemic cardiomyopathy increased LVEF and reduced scar size.¹⁸ The Transendocardial Autologous Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells in Ischemic Heart Failure Trial (TAC-HFT) trial compared MSCs and BMCs and showed reduction in infarct size and wall strain for MSCs, but not BMCs.¹⁹

Both BMCs and MSCs effect changes in infarcted hearts via paracrine mechanisms and modulation of the endogenous repair response and the extracellular matrix,²⁰ but they do not, unless induced,²¹ transdifferentiate into cells resembling normal cardiomyocytes. In contrast, human ESCs or induced PSCs may be guided to adopt many characteristics of cardiomyocytes at a significant rate.

PSCs can differentiate into all cell lineages. ESCs may be transplanted,^{22,23} although ethical issues²⁴ and uncertainty behind their functional engraftment and electromechanical compatibility with surrounding myocardium have limited their clinical use.²⁰ However, newer approaches generating large numbers of cardiomyocytes from ESCs or induced PSCs²⁵ in vitro for subsequent transplantation may offer promise, and differentiation protocols continue to be refined and will lead to higher cellular yields.²⁶ However, further work to quell concerns over teratoma formation will be required to facilitate the clinical application of both ESCs and induced PSCs.²⁷ In addition, induced PSC-derived cardiomyocytes may have inadequate action potentials and contractile properties,^{28,29} leading to poor biomechanical compatibility with native myocardium.

It is this work on induced differentiation of PSCs and to some extent cardiac progenitor cells that has occasioned a theoretical return to the original paradigm of direct

cardiomyocyte replacement as the goal of cell therapy, perhaps superseding the paracrine and endogenous repair effects that characterized BMCs and MSCs. Whether this conceptual shift back to its origins will be vindicated remains to be determined.

In general the efficacy of cell therapies in clinical trials has not matched that demonstrated in preclinical studies. This discrepancy may be due to the age of the patients used in the studies: Preclinical studies are routinely performed in young animals, but clinical trials are conducted in aged patients. It is well known that the quantity and regenerative capacity of SCs decrease with age³⁰; SCs isolated from young patients have a greater capacity for cardiac repair and restoration of heart function.³¹ When SCs were implanted into aged or young recipients to compare their ability to affect cardiac repair after MI³² and also reciprocal SC transplantation experiments with young and old mice to evaluate their response to tissue repair,³³ we demonstrated that the diminished response to tissue repair is influenced by the age of both the donor SCs and the recipient. Clearly, age-related effects play a critical role in determining the efficacy of cardiac cell therapy. Because BMC dysfunction resulted in decreased cardiac repair after an MI and BMCs in aged mice are dysfunctional and associated with progressive heart failure, suggesting the cardiac-bone marrow axis as a key factor in cardiac repair,³⁴ we reconstituted bone marrow in aged mice with young BMCs and found that cardiac function was restored after MI.³⁵ The rejuvenated cells mobilize from the bone marrow to the heart and other organs and play a vital role in restoring organ function after injury—the young BMCs are thus directly responsible for organ repair.³⁵ The accumulated evidence suggests that age is the most important factor for the limited clinical effectiveness of cardiac cell therapy, but translational research is needed to identify the best strategies to make this therapy clinically relevant.

Even if these next-generation stem cells are shown to engraft, integrate, and regenerate injured myocardium, it is unlikely that a single-faceted therapy alone will fully correct the complex interplay of factors leading to adverse ventricular remodeling. The cell therapy of tomorrow may encompass a range of therapies, including simultaneous delivery of growth factors, other cell types, and bioengineered matrices along with the rejuvenated cell population that will replace the lost recipient cardiomyocytes as was envisioned at the dawn of this field.

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