EDITORIAL COMMENT

From Mice to Men

Commonalities in Physiology for Stem Cell-Based Cardiac Repair*

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Current treatments for acute myocardial infarction (AMI) involving successful restoration of blood flow into the infarct-related artery either by percutaneous methods or by fibrinolytic therapy have shown to be of benefit in reduction of short-term mortality. While the advantages of these reperfusion strategies are well established, they do not address the loss of myocardium and adverse remodeling that occurs.

Beyond reperfusion therapy, the focus of treatment in AMI has shifted in the last few years toward the prevention and treatment of left ventricular dysfunction either through regeneration or optimization of functional myocardium with the goal of improving outcomes in patients with cardiovascular disease. While stem cells have been central to this effort, the cell types used have been as varied as the results obtained (1). Controversy in stem cell-based therapies exists regarding the questionable potential of adult stem cells to differentiate into cardiac myocytes (2).

In this issue of the Journal, Hare et al. (3) present data from a phase I dose-escalation study of intravenous allogeneic adult human mesenchymal stem cells (hMSCs) after AMI with the primary end point of safety at 6 months. While this is a phase I safety study with a limited number of patients making conclusions difficult, it is an important study as it focuses on the use of allogeneic cells and a new delivery strategy. While Chen et al. (4) previously reported the utility of autologous bone marrow hMSC coronary infusion post-AMI, this is the first demonstration of an “off-the-shelf” intravenously administered allogeneic hMSC preparation. The study reported on adverse events and effects of allogeneic hMSC from a single donor in 53 patients randomized in a double-blind placebo-controlled fashion. The authors were able to generate data suggesting the safety of these cells post-infarction including a reduction in arrhythmic events in those receiving hMSCs.

Although the trial was not designed to show efficacy, the authors demonstrated a significant improvement in ejection fraction by echocardiography at 3 months but not at 6 months, although some benefit was seen at 12 months by magnetic resonance imaging. A similar catch-up phenomenon was also observed in the placebo group that has been noted previously in the BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial (5). It is unclear whether or not this is related to a time-limited efficacy of stem cell therapy or simply to a more precise imaging modality in magnetic resonance imaging.

It is also interesting to note that the subset of patients with anterior wall AMI (n = 26) had a more robust response to hMSC therapy. This is consistent with observations from other studies demonstrating a relationship between response to treatment and extent of damage (6–8).

The findings of this study are potentially important as they extend the cells of interest for the early phase development of cell therapy for preserving myocardial function (9). Furthermore, this study demonstrates the use of allogeneic cells without immunosuppression and defines a new minimally-invasive route of delivery for myocardial cell therapy in AMI. Perhaps just as importantly, this study and its findings validate the approach and utility of pre-clinical studies undertaken to define mechanisms and test strategies for stem cell-based myocardial repair.

The putative steps involved in stem cell-based myocardial repair have been defined by multiple investigators over the past decade and are schematically represented in Figure 1. While the process is undoubtedly more detailed than depicted, the study by Hare et al. (3) validates the biology and physiology predicted by the pre-clinical studies that came before it.

Whether cells are directly injected into the myocardium, injected down the infarct-related vessel, or introduced via intravenous infusion, there are critical molecular signals released by the newly injured myocardium that induce the chemotaxis or homing of the stem cell to the area of myocardial injury (10,11). The observation that patients with significant lung dysfunction garnered benefit further supports the concept that hMSCs are capable of homing to and potentially repairing any tissue. Stromal cell-derived factor-1 was the first myocardial stem cell homing factor identified (12), and more recently, monocyte chemoattractant…

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From the Skirball Laboratory for Cardiovascular Cellular Therapeutics, Center for Cardiovascular Cell Therapy, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio. Supported by R01-HL074400, U01-HL087314, and the Skirball Foundation. Dr. Penn is named as an inventor on patent applications filed by the Cleveland Clinic for the use of SDF-1 for the prevention and treatment of cardiac dysfunction. He is the Founder and Chief Scientific Officer of Juventas Therapeutics, which has licensed these patent applications from the Cleveland Clinic. As such, he receives consulting fees and has the potential to receive equity and royalties. Dr. Nair is on the Medical Advisory Board of Boston Scientific and the Speaker’s Bureau of Sanofi-Aventis, Pfizer, Merck, and Schering-Plough.
tant protein-3 was identified as an hMSC homing factor capable of homing systemically-delivered hMSCs to areas of myocardial injury (13). Until this report by Hare et al. (3), it had been controversial as to whether homing of systemically-delivered hMSCs would translate from rodents to humans due to the greater blood volume and distances from injection site to the myocardium in humans. Interestingly, in this study the maximal dose of hMSCs was 5 million/kg, which is very close to the dose used in at least 1 rat study of 6 million/kg (14).

After homing of the stem cell to the myocardium, the cell releases paracrine factors into the myocardial tissue leading to preservation of cardiac myocytes, vascular growth, and improved left ventricular remodeling. Several studies have identified paracrine factors of interest including Sfrp2 (15), stromal cell-derived factor-1 (14,16), and interleukin-10 (17). Furthermore, studies have suggested strategies including Akt overexpression (18) or direct genetic overexpression (14) that could be used in future studies to enhance the effects of hMSC-based therapy.

The data generated by Hare et al. (3) did not reveal any evidence suggesting that hMSC dose affected myocardial function. Rather, their data suggest that infarct size mediated the degree of benefit. This observation is consistent with the concept that infarct size, perhaps due to degree of homing factor expression or perhaps number of cells at risk, is more important for regulating hMSC-based myocardial repair than the number of hMSCs in circulation.

Finally, there is the potential for prolonged engraftment and survival of hMSCs after intravenous infusion in AMI. Consistent with hMSC homing, engraftment, and survival in the myocardium is the observation of decreased arrhythmic events in patients that received hMSCs compared with control subjects. Furthermore, it is interesting to note that the inhibition of arrhythmias by hMSCs was dose-dependent. hMSCs have been shown to decrease the potential for re-entrant arrhythmias in rodent models of AMI. This decrease in re-entrant arrhythmias was associated with the increased recruitment of cardiac stem cells to the infarct border zone as well as the engraftment of connexin 43 and 45 expressing hMSCs in the infarct border zone (19). The fact that the dose of hMSCs inversely correlated with the number of premature ventricular contractions and arrhythmic events is consistent with the pre-clinical findings that the functional electrical size of the infarct is independent from the mechanical size of the infarct (16) and can be modulated by engraftment of cells capable of conducting action potentials (19).

In summary, the study by Hare et al. (3) clinically tested and validated the concepts of hMSC homing, and paracrine factor and cell-associated effects on the mechanical and electrical properties of myocardial repair. This study represents an important step along the path toward defining strategies for optimization of left ventricular function after AMI. With only modest observed benefits with initial studies of cell therapy, many questions remain, but there is excitement in what the future holds with regard to advances in this field. Hare et al. (3) are to be congratulated on the completion of this highly novel protocol that serves to highlight that the careful translation of well-founded pre-clinical strategies can be done safely and offers hope for improved patient outcomes in the future.

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References

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