The Changing Face and Abbreviated Lives of Bone Marrow Cells in the Heart

Scott T. Robinson, Natalia Landázuri, W. Robert Taylor

Cell therapy for treatment of myocardial injury is a therapeutic strategy that first garnered attention in the mid-1990s after several animal studies suggested that transplanted skeletal myoblasts could incorporate into native heart tissue. The generation of human embryonic stem cell lines raised the possibility of a new strategy for cardiac regeneration. The use of stem cells as a therapy offers a potential advantage over skeletal myoblasts in that, unlike their terminally differentiated counterparts, stem cells could form new myocardium that can seamlessly integrate with the existing tissue. The ability to form mature cardiac muscle was proposed to extend beyond stem cells, and progenitor cell populations were soon identified in adult tissues, most notably the bone marrow. These progenitor cells can be differentiated into cardiomyocytes. In contrast to embryonic-derived cells, adult stem cells can be isolated from an autologous source and therefore pose less risk of immunogenicity and do not warrant the same ethical considerations as embryonic stem cells. A natural reservoir of mesenchymal and hematopoietic stem cells, bone marrow cells can easily be isolated for reimplantation or purified and expanded in culture without significant manipulation. Therefore, bone marrow cells quickly evolved into a leading candidate for use in cell therapy for treatment of myocardial injury.

Unfortunately, bone marrow stem cells have shown only modest success in cardiac regeneration. Improvement in cellular imaging and lineage tracing techniques revealed that the spontaneous differentiation of bone marrow cells into cardiomyocytes following implantation into injured myocardium occurs with much less frequency than was initially reported. Furthermore, multiple investigators have suggested that improvement in cardiac function observed in animal studies may be due to the paracrine effects. Implanted cells may augment survival of damaged myocardium or enhance neovascularization through release of trophic and proangiogenic factors in ischemic tissue, rather than differentiating into cardiomyocytes. Despite promising results in animal studies that demonstrate a modest improvement in myocardial function following cell therapy, clinical trials using bone marrow-derived cells as treatment for myocardial injury have yielded mixed results. At the time of the writing of this editorial, results from the LateTime trial completed through the National Institutes of Health-sponsored Cardiovascular Cell Therapy Research Network were unavailable. Due to be released in November at the American Heart Association meetings, these results may provide further insight into the efficacy of bone marrow cell therapy in patients with moderate to large anterior myocardial infarctions. In the meantime, the lack of a clear clinical benefit from treatment with unselected bone marrow cells highlights the need to think carefully about cell therapy strategies and use a more mechanism-driven approach.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Sheikh et al examine the efficacy of bone marrow mononuclear cells (BMMCs) for treatment of myocardial injury in a murine model. The experimental approach by Sheikh et al replicates the clinical strategy used in several human trials by using an unpurified bone marrow cell population in the setting of acute myocardial injury. Sheikh et al used a rigorous and impressive multimodal approach to show that direct injection of BMMCs into the myocardium of mice following ischemia/reperfusion injury provided no functional improvement compared with control mice receiving injections of phosphate-buffered saline. Furthermore, positron emission tomography imaging of hearts following ischemia/reperfusion injury revealed that injections with BMMCs had no impact on myocardial viability. As an explanation for the lack of improvement after BMMC treatment, Sheikh et al used bioluminescent cell tracking to show that BMMCs injected at the infarct border zone had very limited short-term viability. The authors suggest that if myocardial repair occurs via paracrine signaling from the injected cells, then the poor viability prevents the cells from exerting their reparative effect at the site of injury, thus limiting therapeutic efficacy. As these data contrast results from a previous study from the same research group, which showed modest improvement in cardiac function following BMMC therapy in a setting of chronic myocardial ischemia, the alternative explanation is that BMMCs provide no or limited functional benefit only in the setting of acute myocardial ischemia.

Sheikh et al also very importantly highlight the need to understand cell-mediated mechanisms for tissue repair and regeneration. In an effort to address the ongoing debate as to whether cell therapy acts through paracrine mechanisms or through cell differentiation and incorporation into the newly formed tissue, they devised a novel approach to isolate...
BMMCs 4 days after injection for whole transcriptome analysis. They observed a downregulation of gene expression associated with differentiation pathways when cells were implanted in an ischemic myocardium, which is indicative of a paracrine mechanism. However, these results need to be interpreted with caution. The heterogeneity of the starting BMMC populations and the fact that cell therapy did not enhance tissue repair in their model complicate the interpretation of the transcriptome analysis. It is likely that the changes seen in the microarray data reflect not only changes in gene expression of the entire starting population but also the ability or inability of certain subpopulations of the bone marrow to survive or proliferate in ischemic and inflammatory microenvironments. The observed changes in gene expression may tell us more about the heterogeneity of the initial cell population than they do about changes in gene expression in the surviving cells.

The well-documented lack of efficacy of BMMC therapy reported by Sheikh et al10 does not suggest that a cell therapy approach for treatment of myocardial injury should be abandoned. Rather, it stresses the need to thoroughly understand the mechanisms and challenges of cell-based therapies. In fact, purified cell populations, enhanced delivery techniques, or ex vivo manipulation of cells could improve clinical outcomes. The work of Sheikh et al offers a thoughtful framework to advance the field of cell therapy for cardiovascular disease.

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References


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