Mesenchymal Stem Cells for Myocardial Infarction
Promises and Pitfalls
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Recent studies indicate that cardiac transfer of adult stem cells can have a favorable impact on tissue perfusion and contractile performance of the infarcted heart. Several cell sources are being explored in an effort to regenerate infarcted myocardium, including hematopoietic stem cells, endothelial progenitor cells, cardiac resident stem cells, bone marrow−derived multipotent stem cells, and mesenchymal stem cells (MSCs). Each of these cell types may have its own profile of advantages, limitations, and practicability issues in specific settings. Studies comparing the regenerative capacity of distinct cell populations are scarce. Most clinical investigators have therefore chosen a pragmatic approach by using unselected bone marrow cells that contain different stem cell populations. Basic scientists, by contrast, are focusing more on specific cell populations in a quest to understand the biological foundations of cell therapy and to identify the most promising stem cells for cardiac regeneration.1

MSCs are a rare population of self-renewing, multipotent cells present in adult bone marrow. Although MSCs represent <0.01% of all nucleated bone marrow cells, they can be readily expanded in vitro. In defined culture media, MSCs differentiate into several mesenchymal cell lineages, including cardiomyocytes.2,3 When injected into normal adult myocardium, MSCs differentiate into cardiomyocyte-like cells with sarcomeric organization.4 In an earlier study in pigs with myocardial infarction (MI), MSCs grafted into the infarcted area were shown to express muscle-specific markers and to improve regional wall motion.5 Ease of isolation, high expansion capability, and cardiomyogenic potential have led to the proposition that MSCs may be a good choice for cell-based therapies of MI.6

In a report published in this issue of Circulation, Dai et al7 have further explored the therapeutic potential of MSCs. Their study is unique because it provides a correlation between MSC engraftment/differentiation and functional outcomes at different time points during long-term follow-up after MI. As with any good research, this study has come up with some surprising results and new questions. The most salient findings can be summarized as follows: One week after permanent coronary artery ligation in rats (postacute phase of MI), culture-expanded MSCs were labeled with the fluorescent dye DiI and injected into the infarcted area. Four weeks after MSC transplantation, left ventricular systolic function was significantly improved. Although DiI-labeled MSCs were readily detectable in the infarct scar at this time point, they did not consistently express muscle-specific marker proteins or visibly replace the infarct scar with muscle tissue. Six months after cell transfer, left ventricular systolic function was no longer improved compared with the control group, yet ≈40% of the surviving DiI-positive MSCs now expressed muscle-specific markers. Of note, even at this later time point, differentiation of MSCs to cardiomyocytes was incomplete because only immature myofibrillar organization was detected. These intriguing observations indicate that MSCs lack the potential to acquire a mature cardiomyocytic phenotype in the infarcted myocardium and suggest that mechanisms apart from cell incorporation and differentiation contribute to the early functional effects of MSC transplantation.7 Although Dai et al have not further explored such alternative mechanisms, paracrine effects seem to be a plausible explanation because it has been shown that MSCs secrete a great number of growth factors and cytokines, including vascular endothelial growth factor, basic fibroblast growth factor, placental growth factor, transforming growth factor-β, tumor necrosis factor-α, hepatocyte growth factor, and insulin-like growth factor-1.8–11

Given the importance of paracrine signaling in MSC/hematopoietic stem cell interactions in the bone marrow niche,8,12 the capacity of MSCs to promote paracrine effects may not be surprising. The significance of paracrine factors in mediating MSC effects in ischemic tissues has been examined in the murine hindlimb ischemia model. On the basis of the observations that intramuscular injections of MSCs improve collateral formation and distal limb perfusion with no apparent incorporation into growing collaterals, and that the effects of MSC transplantation on hindlimb perfusion can be mimicked by intramuscular injection of MSC-conditioned media, it has been proposed that MSCs enhance collateral formation via paracrine effects.10,11 In line with this conclusion, many of the factors secreted from MSCs are well-known proangiogenic cytokines.

Do MSCs improve LV systolic function after MI by promoting proangiogenic effects and improving tissue perfusion, for example, in areas with hibernating myocardium? When transplanted during the postacute12 or chronic phase after MI,13 MSCs promote an increase in capillary density in the infarcted area, perhaps to a certain extent by incorporating...
into growing vessels. Although MSCs may promote capillaryization of the scar area, they do not enhance arteriolar density and regional blood flow. Therefore, the functional relevance of MSC-mediated proangiogenic effects after MI remains uncertain. It is conceivable, however, that cytokines secreted from MSCs mediate pleiotropic effects on a variety of nonvascular cell types in the heart, including cardiomyocytes, fibroblasts, and resident cardiac stem cells. In this regard, paracrine factors released from MSCs were recently shown to promote antiapoptotic effects in cardiomyocytes subjected to hypoxia. Future studies need to define the spectrum of paracrine factors secreted from MSCs and their progeny, the temporal pattern of their release, and the downstream targets of these factors in the infarcted heart.

The short-lived nature of the functional benefits in the present study would limit the attractiveness of MSC transfer as a therapeutic concept. It is possible that MSCs only transiently enhance cardiac contractility without promoting structural repair; alternatively, MSCs may expedite regenerative processes that also occur endogenously after MI, albeit at a slower pace. Although Dai et al have detected MSCs in the infarct area for up to 6 months, the percentage of transplanted cells that survived in the infarct scar is not known (but the number is probably small). Long-term survival and functional effects of MSCs may be substantially improved if cells were transplanted into a reperfused infarct area, which would also better reflect the clinical scenario in patients with MI. Also, Dai et al have transplanted MSCs during an intermediate postacute phase in their model, which actually does not mimic the situation in patients with acute MI or with chronic ischemic cardiomyopathy. If MSCs are to be applied late after MI with limited tissue perfusion, then survival of MSCs becomes crucial. Intriguingly, retroviral transduction of MSCs with the survival-promoting kinase Akt greatly increases the resistance of transplanted MSCs to apoptosis and enhances their beneficial effects on systolic function in a rat model of acute MI. Of note, paracrine antiapoptotic effects on resident cardiomyocytes account for the marked protection of ischemic myocardium by Akt-modified MSCs. Thus, it will be interesting to see whether overexpression of Akt or specific paracrine factors enhances the therapeutic benefits of MSCs in the setting of chronic MI.

Let us speculate for a moment about the potential clinical implications of these findings. Recent studies have highlighted the potential of other bone marrow cell populations to promote paracrine effects in the infarcted myocardium. Considering the prominent role of stem cell–mediated paracrine effects, should we not try to identify and use specific factors for cardiac regeneration, thereby avoiding the practical and regulatory issues related to stem cell therapy? Compared with single-cytokine approaches, stem cells deliver a cocktail of paracrine factors that may promote additive or synergistic effects in ischemic tissues. Moreover, stem cells appear to express a unique set of cell surface receptors that may enable these cells to efficiently home and engraft in the infarcted myocardium. Another feature that may make MSCs particularly appealing for clinical use is their ability to be transplanted in an allogeneic setting, which may be related to their secretion of immunosuppressive factors. Allergic MSCs could be isolated and expanded from selected donors, tested for their functional capabilities in advance, and be available as a standardized cell preparation. If additional studies confirm that MSCs mediate only transient functional benefits and that genetic strategies are required to provide substantial efficacy of MSCs, then rapid translation into the clinic will not be feasible. Currently, retroviral transduction of stem cells is hampered by the possibility of serious side effects, including insertional mutagenesis. Nevertheless, newer approaches such as insertion-site targeting may circumvent these risks and may eventually allow us to exploit the full potential of MSCs not only in rats but also in patients with MI.

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