Mesenchymal Stem Cell–Derived IL-10 and Recovery From Infarction
A Third Pitch for the Chord

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Mesenchymal stem cells (MSCs) are multipotent cells found in several adult tissues that are capable of differentiating into a number of different mesenchymal tissues, including muscle, bone, adipose tissue, cardiac myocytes, and neural precursors. When transplanted into allogeneic tissues, these cells may persist for long periods of time, suggesting that they can evade immune surveillance and contribute to the repair of damaged tissues. Unfractionated or minimally refined bone marrow cell preparations, which probably contain a mixture of hematopoietic, mesenchymal, and endothelial precursor cells in addition to dendritic cells, can reduce myocardial infarct size and improve performance after infarction, both in rodent models and in human clinical trials, although the exact extent to which these cells form new cardiac myocytes and promote long-term improvement in functional capacity is still hotly debated.

One of the undisputed features of MSCs is their ability to produce a variety of trophic and immunomodulatory factors that can directly promote cell survival and reduce inflammation. A number of groups have explored the possibility that such MSC-derived factors may account for much or all of their therapeutic properties in vivo. Whether or not MSC-dependent myocardial salvage involves cardiomyogenic differentiation or long-term persistence of the cells, factors secreted by MSCs appear to contribute importantly to the outcome. Genetic or preconditioning-mediated enhancement of such factors has been shown to improve the therapeutic properties of MSCs. Obviously identification of the factors responsible for these beneficial effects would have both scientific and practical impact. However, the factors produced by native MSCs have yet to be fully elucidated. In particular, the immunomodulatory properties of MSCs in the setting of myocardial infarction are poorly understood.

In this issue of Circulation Research, Burchfield et al report that production of the immune regulator IL-10 is critical to the therapeutic benefits of injected MSCs after myocardial infarction in mice. IL-10 is a negative immunomodulator involved in the differentiation of regulatory T cells, which play a critical role in the suppression of autoimmune reactivity and in termination of the inflammatory response. Dendritic cells producing IL-10, or DCs infected with an IL-10–expressing adenovirus, induce naïve CD4+ T cells to become regulatory T cells that themselves produce IL-10, and thereby preempt the alternative pathway in which CD4+ cells become proliferative T helper cells in response to inflammatory signals. MSCs are known to produce high levels of IL-10; the present article shows that endothelial progenitor cells also express and secrete high levels of IL-10, and continue to express IL-10 up to 3 days after injection into the infarct zone of mice. Thus it is realistic to consider a role for IL-10 in some of the previously demonstrated therapeutic benefits of human endothelial progenitor cells as well as of bone marrow–derived MSCs.

To address this question directly, the authors obtained MSCs from bone marrow of mice with homozygous inactivation of IL-10. These mice are viable, and after myocardial infarction are not different from wt in survival, fibrosis, or myocardial remodeling. The authors confirm this finding as well as showing that apoptosis rates at 4 days and capillary growth at 14 days after MI are similar. They also show that the spectrum and quantity of MSC-secreted cytokines are identical for the 2 genotypes. As anticipated, direct injection of wt MSCs into the infarct border zone resulted in improvement in cardiac function, documented not only by the normalization of ventricular pressure-volume relationships but also by the biologically relevant readout of reduced compensatory hypertrophy. In contrast, IL-10–deficient MSCs were no more effective than diluent media. Despite this striking result, infarct size was not altered, and there was no detectable effect on apoptosis rates. The authors propose that IL-10 is responsible for the therapeutic efficacy of MSCs, and that these exogenously delivered cells act by reducing T cell infiltration in the infarcted myocardium.

Two previously offered explanations for MSC efficacy, to wit, myocyte replacement and paracrine factor–mediated enhanced cell survival, do not appear to explain the observations presented here. On the other hand, a longstanding body of evidence supports a role for IL-10 in mediating inflammatory responses in the heart. Loss of IL-10 shortens cardiac allograft survival together with exacerbation of IFN-gamma and iNOS-mediated inflammation, and cell- or virus-delivered IL-10 moderates cardiac allograft rejection and lengthens graft survival. If repression of cell-mediated inflammation by IL-10 accounts for the benefits of MSC transplantation, (and this still remains to be directly demonstrated), then the authors have uncovered a third paradigm for
MSCs in this myocardial repair assay. Further studies of biological differences between IL-10 KO and WT MSCs may help to determine this.

A final question is whether this observation excludes or minimizes the potential role of other cytokprotective or regenerative factors secreted by MSCs. Certainly not. In the current study, there was no reduction in infarct size by MSC transplantation; in other models and in other studies there have been quite striking reductions in myocardial scarring together with functional and metabolic improvements that suggest either improved myocyte survival or replacement. Within the repertoire of known cardioprotective factors, some clearly act by promoting survival, and others by enhancing regeneration, for example HMGB-1. However, the present findings open up a new (in this context) and potentially important scope of action for MSCs as well as giving further impetus to studies of IL-10 as a therapeutic agent. The replacement of cells by their secreted factors in treatment of MI is conceptually a step closer.

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