stem cell therapy has generated significant interest for the treatment of cardiovascular disease at the bench and in the clinic. Many clinical studies have demonstrated significant potential for the prevention and treatment of cardiac dysfunction. A significant number of studies over the past many years in laboratories throughout the world have been focused on elucidating the mechanisms of action for stem cell-based repair of the heart.

As schematized in the Figure (A), the early conclusion regarding bone marrow-derived adult stem cells was that they homed to areas of newly injured myocardium and differentiated into cardiac myocytes regenerating lost cardiac myocytes and restoring contractile function. Although this was revolutionary and exciting, follow-up data have challenged whether adult stem cells were capable of differentiating into adult cardiac myocytes. Importantly, although myocardial regeneration appears unlikely to be a relevant mechanism of action with bone marrow-derived adult stem cells, both preclinical and clinical data suggested that their delivery at the time of acute myocardial infarction led to preservation of cardiac tissue and improvement in overall cardiac function.

The improvement seen with adult stem cells in the absence of myocardial regeneration led many to propose that the benefits associated with the engraftment of stem cells in the peri-infarct period were due to local paracrine factor release (Figure B) into the newly injured tissue. Early on, Dzau and colleagues demonstrated that conditioned media from Akt overexpressing mesenchymal stem cells (MSC) resulted in similar improvements in left ventricular function following acute myocardial infarction as the engraftment of the cells themselves. We have recently extended our understanding of paracrine factor mediated signaling to include modulation of disabled-2, a key regulator of β-catenin activity by miR-145.

We have previously demonstrated that MSC-mediated SDF-1 release results in the recruitment of cardiac stem cells to the infarct border zone as well as decreased infarct expansion and overall improved cardiac function. We have recently demonstrated that in the absence of myocardial CXCR4 expression there is no benefit to MSC engraftment in the peri-infarct period despite intact myocardial neovascularization in response to MSC. These data and others strongly demonstrate the role of local paracrine factor expression on adult stem cell function.

In this issue of the journal, Nakajimi and colleagues importantly extend our understanding of how bone marrow-derived stem cells can impact cardiovascular disease. They studied endothelial-dependent relaxation in the mesenteries artery of endothelial nitric oxide synthase null (eNOS−/−) mice. They made the novel observation that transplantation of eNOS−/− mice with wild-type bone marrow restored arterial vasodilation in response to acetylcholine. Most importantly, this improvement vascular function occurred in the absence of bone marrow engraftment into the endothelial cell layer or arterial wall. Rather, the effect of the wild-type bone marrow was mediated through the hormonal release of adiponectin leading to the local upregulation of neuronal NOS (nNOS) in the eNOS null (Figure C). Consistent with these conclusions, wild-type bone marrow transplantation did not restore vascular function in eNOS−/− nNOS−/− mice or eNOS−/− adiponectin−/− mice. It should also be noted that the approach taken by Nakajimi and colleagues highlights the utility of using specific receptor knockout mice to identify and test the importance and effects of specific paracrine factors or hormones released by stem cells.

The findings of the Nakajimi study have multiple novel potential implications. They suggest that homeostasis of the bone marrow space could have systemic effects on cardiovascular homeostasis in the absence of stem cell release, engraftment, and local paracrine factor release or stem cell differentiation. Furthermore, these data suggest that restoring the fidelity of the bone marrow space could lead to improvements in global microvascular function. Is syndrome X or small vessel vascular disease a disorder of the bone marrow? Or could we treat these patients’ microvascular disease at a distance through manipulation of the bone marrow? These are some of the questions that the findings of Nakajimi and colleagues raise. To be sure, these initial findings were reported based on a specific vascular defect that could be rescued by the upregulation of a single factor; however, these findings once again highlight that we do not yet understand endogenous stem cell repair to the extent we think we do.

Sources of Funding
Dr Penn is funded by the generous support of the Skirball Foundation.
Disclosures

None.

References

6. Gneccchi M, He H, Liang OD, Melo LG, Morello F, Mu H, Noiseux N, Zhang L, Pratt RE, Ingwall JS, Dzau VJ. Paracrine action accounts for marked protection of ischemic heart by akt-modified mesenchymal stem cells. Nat Med. 2005;11:367–368.
Stem Cell Effects at a Distance
Marc S. Penn

Circ Res. 2012;111:12-13
doi: 10.1161/CIRCRESAHA.112.271833

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/111/1/12

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/