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 paracrine factor mediated signaling to include modulation of cell-based repair of the heart.

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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.

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Disclosures

None.

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