S

tax cell therapy has generated significant interest for the

treatment of cardiovascular disease at the bench and in

the clinic. Many clinical studies have demonstrated signifi-
cant 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 differenti-
ated into cardiac myocytes regenerating lost cardiac myo-
cytes and restoring contractile function.1 Although this was

revolutionary and exciting, follow-up data have challenged

whether adult stem cells were capable of differentiating

into adult cardiac myocytes.2-3 Importantly, although myo-
cardial 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

similar improvements in left ventricular function following

overexpressing mesenchymal stem cells (MSC) resulted in

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, Dzuu

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.6 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-

145.7,8 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.9,10 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 neovascular-

ization in response to MSC.10 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.11 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.10-12

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 cardio-

vascular homeostasis in the absence of stem cell release,

engraftment, and local paracrine factor release or stem cell
derdifferentiation. Furthermore, these data suggest that restoring

the fidelity of the bone marrow space could lead to

improvements in global microvascular function. Is syn-

drome X or small vessel vascular disease a disorder of the

bone marrow? Or could we treat these patients’ microvascu-

lar 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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