Bone Marrow Stem Cells for Myocardial Infarction
Effector or Mediator?

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I’ll be back!
—Arnold Schwarzenegger, The Terminator

When news broke in 2001 that bone marrow-derived stem cells (BMCs) regenerate cardiac myocytes after myocardial infarction (MI), the prospects of regenerative therapy suddenly dawned on the horizon of cardiovascular medicine. Along with reports about differentiation of BMCs into neurons, hepatocytes, and muscle,1–4 BMCs delivered to the heart were shown to transdifferentiate into cardiac myocytes and to rescue cardiac function after infarction.5,6 In fact, the initial reports by Anversa’s group,5,6 supported by numerous similar findings, spurred the translation of stem cell therapy into the clinical arena, although the cell isolation and delivery strategies for patients with acute MI differed considerably from the experimental procedures of direct myocardial injection. Indeed, a number of clinical trials now suggest not only safety and feasibility of stem cell therapy but also significant improvement of left ventricular function in patients with acute myocardial infarction.7–10

However, the ability of BMCs to transdifferentiate into cardiac myocytes has recently been questioned by various groups that failed to demonstrate permanent engraftment of transplanted BMCs in the infarcted heart. Because improvements in cardiac function were still noted despite the lack of myocyte transdifferentiation, alternate mechanisms of BMC action have been suggested to support cardiac recovery.11–13 Accompanying editorials questioned the methodological approach by Anversa’s group and the early translation of “controversial findings” into clinical trials.14 After all this heat, Anversa’s group was tuned “to be back” (like the Terminator). In this issue of Circulation Research, Kajstura et al15 add new fuel to the stem cell controversy. Supporting their initial observations, they not only provide evidence for extensive BMC transdifferentiation, but also present some evidence against a significant contribution of other mechanisms to cardiac recovery.

To address the question of BMC fate, they injected genetically tagged c-kit+ BMCs of male donor mice into the myocardium of female recipients after experimental MI. Injection sites were marked with fluorescent microspheres and BMCs or their progeny identified on tissue sections with antibody costaining against the GFP-tag and markers for cardiac differentiation at 5 and 10 days after transplantation. Depicted in convincing fluorescent micrographs in overlay technique, in successfully injected infarcts there were abundant regenerated myocytes, which had a small size and stained positive for GFP and the Y chromosome, suggesting BMC origin. In addition, BMCs also contributed to newly formed endothelial and smooth muscle cells in the infarct area, although at much lower frequency. In addition, BMC injection improved cardiac performance 10 days after MI. To exclude the phenomenon of cell fusion as an explanation for the presence of the GFP-tag myocyte nuclei were analyzed by sex chromosome staining. Although spared myocytes stained positive for two X chromosomes, newly formed cells only had one set of X and Y chromosomes. Finally, finding no evidence of angiogenesis or myocyte proliferation in remote parts of the heart, the authors exclude paracrine effects of injected BMCs in myocardial recovery.

These findings support previous reports in which either directly injected lin− c-kit+ BMCs, or cytokine mobilized BMCs, transdifferentiated into cardiac myocytes and improved left ventricular function.5,6 Thus, Kajstura et al15 have clearly reproduced their initial findings, which is indicative of the great care with which all their studies have been conducted. In fact, the authors should be congratulated for the technically excellent visualizations by which they underscore impressively the principal claim of cardiac transdifferentiation by BMCs.

Yet, these results are challenged by three recent reports that found no evidence of BMC transdifferentiation using the same cell type and mode of delivery.11–13 Kajstura et al discuss at length the technical issues, which may explain negative observations by others.15 Let’s have a closer look. In these studies, sophisticated genetic reporters were used to detect cardiac differentiation, or fusion, in addition to tagged BMCs and conventional staining techniques. Injected lin− c-kit+ BMCs could be detected in the infarcted heart after 9 days but not after 28 days, which demonstrates a lack of long-term engraftment. The transplanted cells showed markers of hematopoietic differentiation, whereas typical cardiac markers were absent. Therefore, initial graft failure through unsuccessful injection or rejection cannot explain the discrep- ant results. Unfortunately, Kajstura et al do not provide an analysis of long-term engraftment in their system. Using highly sensitive and specific reporter systems for cardiac
differentiation, no BMC-derived myocytes could be detected, whereas transplanted fetal cardiac myocytes were readily detected by this method. Thus, a failure of the genetic reporter system is unlikely. In addition, no or only sporadic BMC-derived cardiac myocytes could be detected at the single cell level after Langendorff perfusion and dissociation of transplanted hearts. Other BMC populations, such as whole bone marrow, c-kit–enriched or lin− c-kit− sca-1+ BMCs, were tested with essentially identical results. Using differentially tagged bone marrow and heart, fusion could be detected in one study at very low frequency outside the area of infarcts.13 Even though no long-term engraftment could be documented, BMC transplantation still improved LV function significantly.11 These and other observations have entertained the idea that paracrine effects, ie, secretion of growth factors from subsets of bone marrow resident cells, may be involved in the beneficial effects. In other words, “bone marrow delivers
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cell populations is required to achieve maximum regeneration, as
differentiation, myocytes adopting a myogenic cell fate, although at very low frequency.

As the present controversy addresses a fundamental biologi-
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