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EDITORIAL COMMENT

Macrophage-Stem Cell Crosstalk After Myocardial Infarction*

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Myocardial infarcts are wounds inflicted by ischemic injury of the heart muscle. As in any other wound, a sufficient healing process after acute injury is prerequisite to the recovery and integrity of the organ's function. If infarct healing derails, fibrosis may be insufficient or too widespread, either endangering the left ventricle's geometry or increasing its stiffness, especially if fibrosis occurs in the remote myocardium. The imminent threat of insufficient healing is a weak scar that may rupture, often a deadly complication. More frequently, the weak infarct scar acutely maintains the ventricle's integrity but expands over time, thus causing chronic post-myocardial infarction (MI) remodeling and heart failure. Macrophages are centrally involved in wound healing, including healing of the heart (1). These cells are also part of the causal pathology leading to ischemia of the heart because macrophages destabilize atherosclerotic plaques, rendering them prone to rupture (1).

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These insights have formed our current view of atherosclerosis as a chronic inflammatory disease, and we are beginning to understand that plaques and infarcts are not isolated local events but rather local manifestations of systemic disease, caused by, among other risk factors, hypercholesterolemia and overproduction of leukocytes in the bone marrow (1). One consequence of the leukocytosis that occurs in progressive atherosclerosis is the increased availability of inflammatory monocytes, macrophage progenitors, in circulation. In the presence of atherosclerosis, the expanded supply of inflammatory blood monocytes leads to increased and prolonged recruitment into the infarct, impairing cardiac healing. This has been modeled by inducing MI in *Apoe*$^{-/-}$ mice with atherosclerosis (2). Leukocytosis predicts higher infarct mortality and occurrence of heart failure in patients (3,4). Defunct resolution of inflammation in the infarct due to oversupply of inflammatory cells is a likely cause for these findings. The transition from the initial inflammatory wound-healing phase, dominated by inflammatory neutrophils, monocytes, and M1 macrophages, to the inflammation resolution phase, dominated by M2 macrophages, may be delayed or impaired in many patients. Thus, the typical functions pursued by M2 macrophages during repair could be insufficient. These include putative macrophage instruction of resident cells, including myocytes, endothelial cells forming neovessels, and fibroblasts that supply the new extracellular matrix, that provides a durable scar and resists the mechanic forces in the heart (5). Increasingly, it is believed that the transition of macrophage polarization from the classical M1 toward a lesser inflammatory M2 phenotype is a key event in infarct repair (1,6).

The stem cell field started out with the goal of restoring the integrity of the infarcted left ventricle. The hope is that someday the myocytes that died because of ischemia can be replaced by progenitors that give rise to new myocytes (7). Current candidate cells are cardiac progenitors that naturally occur in the heart and can be harvested, multiplied, and reinjected (8), as well as inducible pluripotent stem cells (iPS), which are reprogrammed from differentiated lineages, for instance, skin fibroblasts (9). An exciting new avenue is in situ reprogramming of fibroblasts into myocytes (10), but this technology is still in its infancy. Nevertheless, many preclinical and clinical trials reported beneficial effects of stem cell therapy on infarct healing, despite lack of evidence for stem cell survival after transplantation into the heart and the cell's failure to give rise to new functional myocytes. Many in the field assigned the observed benefits to paracrine effects of transplanted cells. The study by Ben-Mordechai et al. (11) in this issue of the *Journal* provides an insightful explanation of how mesenchymal stromal cell (MSC) injection could positively affect infarct healing by crosstalk between injected stem cells and macrophages (Fig. 1).

The investigators confirm the previously reported (12,13) biphasic myeloid cell response after acute MI. Using flow cytometry, they describe an early dominance of inflammatory M1 macrophages followed by abundance of M2 macrophages on day 7 after ischemic injury. Interestingly, injection of MSC reshaped the macrophage response by favoring M2 polarization. The MSC injection increased the numbers of M2 macrophages as compared to saline or bone marrow mononuclear cell injection. The treatment further changed the cytokine profile of macrophages (e.g., more interleukin-10 production) and increased the elaboration of macrophage-derived factors involved in wound healing, including vascular endothelial growth factor and platelet factor-4. Proteolytic cathepsin activity was reduced by MSC

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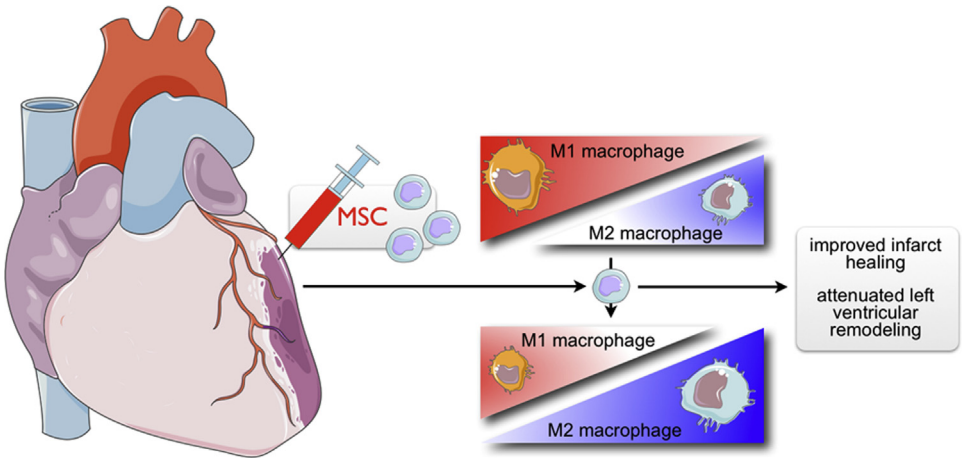

Figure 1 **Modulation of Macrophage Polarization by MSC Injection**

The key finding of Ben-Mordechai et al. (11) is the modulation of macrophage polarization by mesenchymal stroma cell (MSC) injection. If macrophages are depleted, the positive effects of MSC treatment are lost.

treatment, which may change the post-MI balance of matrix production and its digestion by proteases (14), favoring infarct stability. The MSC treatment further improved regional myocardial function as measured with speckle tracking strain echocardiography and attenuated post-MI heart failure.

When Ben-Mordechai et al. (11) depleted macrophages with clodronate liposomes, the beneficial effects of MSC treatment were lost. The 30-day mortality was worse and infarct size increased. Macrophage depletion accelerated LV remodeling, resulting in larger hearts and a lower ejection fraction. Of note, clodronate liposomes can likely deplete inflammatory and noninflammatory subsets of monocyte and macrophages. Nevertheless, these data imply that positive effects of stem cell therapy may arise from the influence of stem cells on macrophage polarization in the wound. Stem cell therapy may usher in resolution of inflammation and support the salutary effects of M2 macrophages during healing.

Interesting open questions remain: how do MSC change macrophage polarization? Is it facilitated through direct cell-cell contact? Do MSC provide specific cytokines that influence macrophage polarization? Answering these questions may require directly observing MSC-macrophage crosstalk using intravital microscopy of infarcted hearts (15). If there is a defined MSC-derived factor that acts on wound healing and on infarct macrophages, its discovery may augment pharmacologic, namely, cell-independent treatment of infarct healing. Another interesting question is whether MSC-macrophage crosstalk is unidirectional or whether macrophages "talk back," namely, whether there is reversed signaling. It is conceivable that macrophages also influence rare autologous cardiac progenitor cells, or injected stem cells, as they do with the more numerous progenitors of fibroblasts and endothelial cells that take up residence in acute infarcts. Recent macrophage depletion experiments in salamanders, which regrow limbs after amputation, showed that limb regeneration depended on an intact macrophage repertoire (16), suggesting macrophage-progenitor crosstalk.

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REFERENCES

1. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science 2013;339:161–6.
2. Panizzi P, Swirski FK, Figueiredo JL, et al. Impaired infarct healing in atherosclerotic mice with Ly-6C(hi) monocytosis. J Am Coll Cardiol 2010;55:1629–38.
3. Engstrom G, Melander O, Hedblad B. Leukocyte count and incidence of hospitalizations due to heart failure. Circ Heart Fail 2009;2:217–22.
4. Tsujioka H, Imanishi T, Ikejima H, et al. Impact of heterogeneity of human peripheral blood monocyte subsets on myocardial salvage in patients with primary acute myocardial infarction. J Am Coll Cardiol 2009;54:130–8.
5. Nahrendorf M, Swirski FK. Monocyte and macrophage heterogeneity in the heart. Circ Res 2013;112:1624–33.
6. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res 2012;110:159–73.
7. Anversa P, Kajstura J, Rota M, Leri A. Regenerating new heart with stem cells. J Clin Invest 2013;123:62–70.
8. Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011;378:1847–57.
9. Yoshida Y, Yamanaka S. iPS cells: a source of cardiac regeneration. J Mol Cell Cardiol 2011;50:327–32.

10. Song K, Nam YJ, Luo X, et al. Heart repair by reprogramming non-myocytes with cardiac transcription factors. Nature 2012;485: 599–604.
11. Ben-Mordechai T, Holbova R, Landa-Rouben N, et al. Macrophage subpopulations are essential for infarct repair with and without stem cell therapy. J Am Coll Cardiol 2013;62:1890–901.
12. Nahrendorf M, Swirski FK, Aikawa E, et al. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. J Exp Med 2007;204:3037–47.
13. Troidl C, Mollmann H, Nef H, et al. Classically and alternatively activated macrophages contribute to tissue remodelling after myocardial infarction. J Cell Mol Med 2009;13:3485–96.
14. Jourdan-Lesaux C, Zhang J, Lindsey ML. Extracellular matrix roles during cardiac repair. Life Sci 2010;87:391–400.
15. Lee S, Vinegoni C, Feruglio PF, et al. Real-time in vivo imaging of the beating mouse heart at microscopic resolution. Nat Commun 2012; 3:1054.
16. Godwin JW, Pinto AR, Rosenthal NA. Macrophages are required for adult salamander limb regeneration. Proc Natl Acad Sci U S A 2013; 110:9415–20.

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