EDITORIAL COMMENT
Mobilizing Cells to the Injured Myocardium

A Novel Rescue Strategy or an Unwelcome Intrusion?*

Wilbur Y. W. Lew, MD, FACC†
San Diego, California

In acute myocardial infarction (MI), salvaging viable myocardium and minimizing adverse ventricular remodeling are effective strategies for preserving cardiac function and reducing mortality. Advances in stem cell biology have generated excitement that this paradigm may be expanded to include transplanting or mobilizing stem cells to repair the injured myocardium (1). The study by Maekawa et al. (2), in this issue of the Journal, provides a precautionary tale about the hazards of mobilizing the wrong cells at the wrong time in acute MI.

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Adult stem cells in MI. Adult stem cells (e.g., hematopoietic) and progenitor cells can differentiate into mature tissue-specific cells to repair damaged organs, including the heart (1). In experimental studies, transplanting stem cells and progenitor cells into the heart induces angiogenesis and replaces damaged myocardium (3). Recent studies indicate that hematopoietic stem cells do not transdifferentiate into cardiac myocytes (4,5). This challenges the concept that any beneficial effects are related to myocardial regeneration.

Adult stem cell therapy has been applied clinically in feasibility and safety studies. Intracoronary injections of bone marrow-derived or circulating blood-derived progenitor cells have been given to patients early (four to nine days) after acute MI (6–8). Intramyocardial injections of autologous skeletal muscle myoblasts and bone marrow-derived stem cells have been performed in patients with ischemic heart failure (e.g., >3 to 4 months after MI) (9–11). These studies were not designed to evaluate efficacy, but suggest that ventricular function may improve, albeit with potential complications, such as arrhythmias. Placebo-controlled, randomized studies are needed to assess the benefits of therapy, as ventricular function after MI reflects several factors, including reperfusion, revascularization, myocardial stunning, and ventricular remodeling.

Mobilized stem cells to treat MI. Stem cells circulate in peripheral blood in low numbers, but possess an enormous capacity for cell expansion. Granulocyte colony-stimulating factor (GCSF) mobilizes endothelial progenitor cells into the peripheral circulation, which can be harvested and injected intravenously to stimulate angiogenesis and preserve cardiac function after MI (12). Intravenously delivered stem cells incorporate into peri-infarct regions. This provides an alternative to direct intramyocardial or intracoronary injections. Mobilizing stem cells from the bone marrow also increases delivery to the heart. Experimental studies support this approach. In a murine model, stem cell factor and GCSF treatment for three to five days after MI decreased infarct size, remodeling, and mortality (13,14). There was evidence of vascular growth and myocardial regeneration related to the mobilization of stem cells. In a non-human primate model, treatment increased myocardial blood flow to the infarct region by increasing angiogenesis without evidence of myocyte regeneration (15). Indeed, recent studies demonstrate that adult hematopoietic stem cells do not transdifferentiate into cardiac myocytes in acute MI (4,5).

Mobilizing endogenous stem cells is an attractive strategy because it obviates the use of exogenous cells and avoids ethical and immunity issues, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and GCSF are used clinically (e.g., in patients with immunosuppression, after bone marrow transplantation, or to mobilize progenitor cells into peripheral blood for harvesting). Homing of endothelial progenitor cells to the heart is enhanced in acute MI (16), suggesting a potential benefit for early therapy. The milieu of acute tissue damage contains signaling factors (not well characterized) that enhance homing, engraftment, and differentiation of adult stem cells (1,3). Stem cell factor and GCSF therapy are beneficial in experimental acute MI (13–15). In patients with coronary artery disease, GM-CSF improves coronary collateral blood flow (17), but this therapy has not been evaluated in the clinical setting of acute MI.

Mobilizing cells with GM-CSF in acute MI. In addition to stem cells, GM-CSF also mobilizes granulocytes and monocytes. This may have undesirable effects, because these cells play a prominent role in inflammatory responses in acute MI (18). In the study by Maekawa et al. (2) in this issue of the Journal, romurtide, an inducer of GM-CSF, was given for one week in an experimental model of MI (2). Treatment induced circulating monocytosis and increased GM-CSF expression and infiltration of macrophages into the infarct site. Treatment had adverse effects on ventricular remodeling, with greater infarct expansion, poorer left ventricular function, and increased mortality. These results are consistent with their previous clinical study that associated peripheral monocytosis with worse left ventricular function and remodeling in patients with acute MI (19).

Mobilizing neutrophils, macrophages, and monocytes...
may be undesirable early during MI. These cells release toxic substances (e.g., reactive oxygen species) that may exacerbate inflammation and tissue injury, damage collagen and other structural components, and adversely affect ventricular remodeling (18,20). Ventricular remodeling occurs over weeks to months with time-dependent changes in key mediators. Mobilizing cells with GM-CSF during the first several days of acute MI adversely affects this process (2), but may be effective if delayed after several days (13). This may be due to subsidence of acute inflammatory responses. The optimal timing for stem cell therapy requires understanding the homing signals from damaged tissue, the fate of transplanted cells (e.g., ability and/or requirement for stem cells to engraft and transdifferentiate into specific cell types), and the mechanisms of beneficial effects (e.g., angiogenesis, replacing damaged tissue to improve scaffolding, facilitation of normal repair processes).

Conclusions. Mobilizing stem cells to treat acute MI has shown promise in experimental studies, but several issues need to be resolved before this can be applied clinically. This includes understanding the mechanisms by which stem cells improve tissue repair and how mobilizing inflammatory cells at the wrong time may exacerbate tissue injury. As future studies address the efficacy of this novel therapy, the “do not harm” principle mandates vigilance to avoid potential adverse effects, such as arrhythmias and ventricular remodeling.

Reprint requests and correspondence: Dr. Wilbur Y. W. Lew, Cardiology Section 111A, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, California 92161. E-mail: wlew@ucsd.edu.

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