Blood-Derived Progenitor Cells After Recanalization of Chronic Coronary Artery Occlusions in Humans

James T. Willerson, Edward T.H. Yeh, Yong-Jian Geng, Emerson C. Perin

The first studies to treat patients with acute ST segment elevation myocardial infarction were by Strauer et al and Zeiher et al.1,2 In these studies, percutaneous transluminal coronary angioplasty (PTCA) was used to open the infarct related artery, and bone marrow–derived mononuclear cells or circulating endothelial progenitor cells were injected into the infarct-related arteries.1,2 The cell-based therapy in these 2 initial studies improved coronary blood flow and segmental left ventricular (LV) function in the treated regions. Wollert et al subsequently reproduced the earlier findings in a blinded randomized study, again in patients with acute ST segment elevation myocardial infarcts (MIs).3 These 3 studies were the first to treat patients with acute ST segment elevation MIs after PTCA with cell-based therapy, and each used intracoronary injections in patients who did not have severe heart failure.

At the same time that Strauer et al and Zeiher et al were performing their initial studies in Germany (2000–2002), Texas Heart Institute cardiologists, Drs Perin and Willerson and Brazilian cardiologists led by Dr Dohmann in Rio de Janeiro, Brazil, were treating patients with chronic coronary heart disease, prior myocardial infarction, and severe heart failure with transcatheter injections of bone marrow–derived mononuclear cells using electromechanical mapping to identify sites of reversible myocardial injury.4 This was the initial study in the world done with cell-based therapy for patients with severe heart failure with direct transcatheter injections of bone marrow–derived mononuclear cells into the human heart. We also reported improved coronary blood flow and segmental and global LV function within two months after the cell-based treatment.4 The imaging results in these patients suggesting improved coronary blood flow were confirmed by postmortem examination in 1 patient who died of a seizure 11 months after treatment.5 New blood vessel formation and new myocytes in the treated region were found at post-mortem examination in this patient.5

Erbs et al, in this issue of Circulation Research, present a randomized blinded study in humans with chronic coronary artery occlusions but without heart failure.6 The occluded arteries were opened by PTCA, and circulating progenitor mononuclear cells were injected into the opened coronary arteries after 4 days of subcutaneous administration of granulocyte colony stimulating factor to increase the numbers of circulating progenitor stem cells. The investigators found improved endothelium-dependent vasodilator responses, decreases in coronary vasoconstrictor responses, and improved segmental and global LV function in the treated patients. Inflammatory responses as judged by serum CRP levels were similar in the stem cell and control treated patients. In this study, the circulating progenitor cells were enriched CD34+ and CD133+ cell populations. Erbs et al’s study extends previous observations to show that stem cell therapy may help patients with chronic coronary artery occlusions. However, the relatively small numbers of patients evaluated and the short term follow-up are limitations of both this study and some of the earlier ones as well.

Thus it appears that at least some patients with acute and chronic myocardial infarction and with and without heart failure have improved coronary blood flow and LV segmental wall motion after intracoronary or transendocardial injections of bone marrow–derived mononuclear cells or circulating progenitor cells for at least several months after the procedure and without any evidence of their having been harmed by the treatment.1–6 In the earlier heart failure study in patients, symptomatic improvement, enhanced exercise capability, and increased myocardial oxygen consumption were documented out to 1 year after treatment.7 In cell-based treatment of patients with acute and chronic coronary heart disease, there has also been a prevention of further increases in LV diastolic volume, ie, an attenuation of the remodeling process.1–6

Mechanisms responsible for these beneficial effects in humans are not clearly defined. Some investigators have been unable to show transformation of stem cells injected into animal hearts after an experimentally-created myocardial infarct.8 Others have provided evidence that paracrine mechanisms are important, ie, the injected putative stem cells release cytokines that recruit circulating stem cells and activate resident stem cells that themselves become new blood vessel cells and myocytes.9 Jiang et al have shown the pluripotency of mesenchymal stem cells derived from adult bone marrow.10 Orlic et al have demonstrated that bone marrow cells regenerate infarcted myocardium in experimental animals.11 Resident cardiac stem cells may also be activated by intracoronary or transendocardial injections of bone marrow–derived stem cells, and they may contribute to new myocytes and blood vessel development.12 When injected into the left ventricular cavities of immunocompromised (SCID) mice with experimentally-created infaracts, we have shown that human peripheral blood CD34+ cells

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transform into new blood vessel cells, smooth muscle cells, and new myocytes with more of the injected human progenitor cells fusing to reversibly injured murine myocytes.\textsuperscript{13,14} In the same experiments, human peripheral CD34\textsuperscript{+} cells were shown to directly differentiate into endothelial cells.\textsuperscript{14} The importance of the fusion phenomenon of progenitor cells with other cells is under investigation, but we believe it represents a “resuscitation” attempt to assist reversibly injured myocytes by the fused stem cell. We have also shown that bone marrow–derived mesenchymal cells differentiate into smooth muscle cells and endothelial cells with improvement in coronary blood flow in a canine model of chronic myocardial ischemia.\textsuperscript{15}

The initial results of treating acutely and chronically infarcted human hearts with stem cells are encouraging, but much remains to be done. A better understanding of the mechanisms responsible for improved myocardial blood flow and function with cell-based treatment is needed. Studies that identify the best stem cell type(s) for treating injured hearts and blood vessels need to be done. In addition, many questions need to be answered, including some of the following: (1) Are adult stem cells equivalent to earlier lineage stem cells from the placenta, cord blood, or embryonic cells in regenerative medicine for injured hearts and blood vessels? (2) Can one create stem cells for a specific organ, such as the heart, without using human embryos by nuclear cloning, cell fusion, or some other technique? (3) Can one develop a universal stem cell(s) for different organs, such as the heart, that will ultimately allow it to be replaced without rejection? (4) Can one use stem cells as vehicles for genetic restitution of an injured organ? (5) Are fetal cells rejected when used in humans for regenerative medicine? (6) What stem cell type(s) bring increased risks for uncontrolled cell growth that might lead to tumors when placed into injured organs? There are many challenges in the future for regenerative medicine. However, it should be kept in mind that every human being is a product of stem cells, male sperm and female egg, and therefore, every human is, in fact, a product of stem cell biology. Ultimately, it will be possible to repair, regenerate, and, almost certainly, even replace injured organs in humans by stem cell procedures. We must answer the important questions before us and, as we do, we will also solve one of the major biologic questions of our time, ie, how do 2 cells become the organs of the human body? Simultaneously, we will develop the means to repair, regenerate, and even replace, when necessary, injured human organs.

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