Clinical Implications of Stem Cell Plasticity: Repair of the Infarcted Heart by Cytokine-Mobilized Bone Marrow Stem Cells

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Stem cell plasticity refers to the recently discovered ability of bone marrow stem cells (BMSCs) to generate non-hematopoietic cell types, such as epithelial, skeletal muscle, bone, liver, and neural cells. Dr. Orlic and his group have investigated the ability of adult mouse BMSCs to differentiate into myocardial cells within ischemia-damaged myocardium in two series of experiments. In the first, BMSCs taken from the bone marrow of adult male mice were directly injected into damaged myocardium. In the second, BMSCs were mobilized by several injections of stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF).

In the first series of experiments, hematopoietic stem cells of adult transgenic male mice that expressed enhanced green fluorescent protein (eGFP) were isolated by their expression of c-kit. The c-kit - bone marrow cells were used as negative controls. Left ventricular ischemic infarcts in adult female mice were induced by ligation of the left coronary artery (LCA). Five hours after the LCA occlusion, the harvested BMSCs were directly injected into the healthy myocardium at the periphery of the infarct. Nine days after transplant, a band of eGFP-positive, Y chromosome-positive cells was seen within the damaged myocardium. These Y chromosome bearing cells also stained positive for the myocyte-specific proteins cardiac myosin, GATA-4, MEF2, Csx/Nkx2.5 and the gap junction related protein connexin 43. Developing capillaries were seen within the damaged myocardium, with smooth muscle cells and endothelial cells that were also positive for eGFP and Y chromosome. There was no evidence of myocardial repair. This indicates that both the myocytes and the new blood vessels were derived from the donor BMSCs. The left ventricular end diastolic pressure (LVEDP) and left ventricular developed pressure (LVDP) were 30-40% higher in the hearts that had been transplanted with c-kit + cells were compared to the control hearts that had been injected with c-kit - cells, indicating improved myocardial function in the former group.

In the second set of experiments, autologous BMSCs were mobilized with peripheral injections of SCF and G-CSF. Infarct was induced by coronary artery occlusion. Twenty-seven days after cytokine treatment, the damaged left ventricle showed a new band of myocardium that stained positive for Csx/Nkx2.5, GATA-4, MEF2, and connexin 43. The arterioles seen within the damaged myocardium contained red blood cells, implying blood flow and therefore connection with vessels in the undamaged myocardium. Improved heart function and greater survival were also seen; LVEF at day 9, 16, and 26 after coronary artery occlusion was 48%, 62%, and 114% greater in the treated mice than the untreated mice. Eleven out of 15 (73%) of treated mice were alive 27 days after cytokine treatment, compared with 9/52 (17%) of untreated mice.

Dr. Orlic concluded that circulating hematopoietic stem cells 1) traffic to the ischemic infracted myocardium and 2) differentiate into cardiac myocytes and vascular endothelial and smooth muscle cells. The plasticity of BMSCs extended to cell types from all three embryonic layers, and BMSCs have the potential for repair in acute ischemic heart disease.

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