New Horizons for Clinical Therapies with Stem/Progenitor Cells that Can Repair Most Tissues

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The Reparative Power of Multipotent Stromal Cells from Marrow and Other Tissues. Darwin J. Prockop, Center for Gene Therapy, Tulane University Health Sciences Center, New Orleans, LA 70112

Recent publications have demonstrated that most tissues contain stem-like progenitor cells that play a key role in the repair of tissue injury. When the endogenous stem/progenitor cells in a tissue are exhausted, they are supplemented by similar stem/progenitor cells from the bone marrow. A major focus has been on the stem/progenitor cells from bone marrow referred to as mesenchymal stem cells or multipotent stromal cells (MSCs). MSCs and similar cells from other tissues have been shown to repair tissues by differentiating so as to replace injured cells, by producing chemokines, and in part by cell fusion. However, there has been no obvious explanation for repeated observations that MSCs enhance repair of tissues in experimental models in which their level of engraftment is extremely low. We have recently found that MSCs can repair injured cells and tissues by two additional mechanisms: Stimulation of the proliferation and differentiation of stem cells that are endogenous to a tissue and by transfer of mitochondria or mitochondrial DNA to cells with non-functional mitochondria. Human MSCs infused into the hippocampus of immunodeficient mice stimulated proliferation of and neurogenesis by endogenous neural stem cells (Munoz et al. PNAS, 2005). Co-culture of human MSCs with a line of pulmonary epithelial cells with non-functional mitochondria generated clones of the epithelial cells with functional mitochondria as a result of active transfer of either mitochondria or mitochondrial DNA from the MSCs (Spees, Olson, et al., PNAS, 2006). More recently we observed that intravenously infused human MSCs lowered the blood sugar, increased mouse insulin and decreased renal damage in streptozocin-treated diabetic mice (NOD/SCID). The human MSCs engrafted into the pancreas and increased both the number of islets and the immuno-reactive mouse insulin per islet. In kidneys of MSC-treated diabetic mice, human cells were found in the glomeruli and there was a decrease in mesangial thickening, and a decrease in macrophage infiltration. A few of the human cells appeared to differentiate into glomerular endothelial cells. Therefore there are now multiple strategies for developing new therapies for a broad range of diseases by enhancing one or more of the multiple mechanisms whereby MSCs normally repair tissues. Supported in part by grants from NIH grants AR48323, HL 073755, HL075161, and HL073252; HCA the Healthcare Company, and the Louisiana Gene Therapy Research Consortium.