SYNERGETIC EFFECT OF STROMAL CELL-DERIVED FACTOR-1 AND GRANULOCYTE COLONY STIMULATING FACTOR ON NEOVASCULARIZATION

Yaohong Tan, Hongwei Shao, Zhe Yang, Luis Alonso-Diaz, Darwin Eton, Hong Yu*

Department of Surgery, Vascular Biology Institute, University of Miami, School of Medicine, P.O. Box 019132 (R104), Miami, Florida 33101, USA
*Hyu@med.miami.edu

INTRODUCTION. Endothelial progenitor cells (EPC) play an important role in angiogenesis following ischemic injury. Granulocyte colony-stimulating factor (G-CSF) mobilizes progenitor cells from the bone marrow to the peripheral blood. Stromal cell-derived factor-1 (SDF-1) is a chemokine which can increase neovascularization in vivo by augmenting EPC recruitment into the ischemic tissues. We hypothesize that injection of cells retrovirally engineered to deliver SDF-1 into ischemic tissue will enhance the homing of G-CSF mobilized progenitor cells. SDF-1 in combination with G-CSF should thus synergistically boost angiogenesis.

METHODS. NIH 3T3 cells were transduced with a retroviral vector carrying mouse SDF-1α gene to overexpress SDF-1. The left femoral artery of male C57BL/6J was resected to produce unilateral hindlimb ischemia. The mice were divided into 5 groups: Group 1. Saline intramuscular injection (IM) into the ischemic limb as a negative control; Group 2. NIH 3T3/SDF-1 cells (10^6 cells/mouse) injection IM into the ischemic limb; Group 3. G-CSF (25 µg/kg) intraperitoneal (IP) injection for 3 days; Group 4. G-CSF IP and non-SDF-1 transduced NIH 3T3 cells IM; Group 5. Both G-CSF IP and NIH 3T3/SDF-1 cells IM into the ischemic limb. Each group has 6 mice (n=6). The blood flow of the limbs was measured with a laser Doppler perfusion image (LDPI) analyzer.

RESULTS. NIH 3T3/SDF-1 (10^6 cells) cultured for 24 hours yielded 0.7 µg of SDF-1 in the supernatant. Injection of G-CSF or 3T3/SDF-1 improved neovascularization. The ratio of ischemic/non-ischemic perfusion in the treated
mice increased from 0.29 ± 0.03 immediately after surgery to 0.57 ± 0.03 and 0.50±0.06, respectively, three weeks after the surgery. The blood flow rate in the control mice recovered moderately from 0.29 to 0.41± 0.01 (group 1 vs 2 & 3, p<0.05). The combined use of G-CSF and NIH 3T3/SDF-1 improved revascularization more rapidly (0.69 ± 0.08, p< 0.05) (Fig.)

**DISCUSSION.** The combination of SDF-1 and G-CSF resulted in improved recovery of blood flow in the ischemic limb. Local over-expression of SDF-1 facilitated the homing of the EPC mobilized by G-CSF into the ischemic site. Stimulation of progenitor cell production coupled with targeted recruitment to the ischemic bed is a novel treatment strategy of limb ischemia warranting further study.

**REFERENCES**