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ADMINISTRATION OF HEMATOPOIETIC PROGENITOR CELLS IMPROVED LIMB PERFUSION AND NEOVASCULOGENESIS VIA BY UPREGULATION OF THE ANG-2/TIE-2 PATHWAY

Moderated Poster Contributions
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Background: Bone marrow derived progenitor cells have been suggested to promote postnatal neovascularization. In this study we investigated whether direct intramuscular infusion of enriched hematopoietic cells, improved limb perfusion in a murine model of hind limb ischemia.

Methods: Wild type C57BL/6 male mice underwent unilateral hind-limb ischemia, were divided in three groups (n=12/group) and received a single intramuscular injection of 1x106 Lin-/sca+ cells, or granulocyte colony-stimulating factor (G-CSF) for 7 days or normal saline. Each group mice underwent Laser Doppler perfusion Imaging on days 1, 7 and 28 after surgery for the estimation of the bilateral hind-limb perfusion. At day 28 they were sacrificed and quantitative real time RT-PCR was performed to the muscle tissues from both limbs to analyze the differential gene expression of vascular endothelial growth factor (VEGF), Tie-2, Ang-1 and Ang-2. Muscle tissue sections were stained with rat anti-CD31antibody. Capillaries and arterioles in the ischemic areas were counted with confocal microscopy at day 28.

Results: Ischemic/non ischemic ratio was significantly increased in ischemic limbs of cell- and G-CSF-treated mice versus control mice at 7 days ($p<0.05$ vs control), which was maintained at 28 days ($p<0.05$ vs control) only in the cell-treated group. There was no significant increase of ischemic/nonischemic ratio in the cell-treated mice compared with G-CSF at day 7 or day 28 (p=NS). Capillary density was increased in the cell-treated group compared to G-CSF-treated group and control ($p<0.05$). No difference in the capillary density between the G-CSF-treated and the control group was observed. Compared to the G-CSF and control group, the expression of VEGF ($p<0.05$), Ang-2 ($p<0.05$) and sTie-2 ($p<0.05$) were significantly increased in the ischemic limbs of the Epo-treated group. In contrast, the Ang-1 expression didn't significantly differ between the three groups.

Conclusion: Direct intramuscular infusion of lin-/sca+ significantly improves blood flow and increases neoangiogenesis by upregulation of the Ang-2/Tie-2 pathway when compared with G-CSF and control treatment in ischemic limbs.