

# Stem Cells and Distraction Osteogenesis: Endothelial Progenitor Cells Home to the Ischemic Generate in Activation and Consolidation

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**Background:** Ischemia is a limiting factor during distraction osteogenesis. The authors sought to determine the extent of ischemia in the distraction zone and whether endothelial progenitor cells home to the distraction zone and participate in local vasculogenesis.

**Methods:** Laser Doppler imaging was used to assess the extent of blood flow in the distraction zone in gradually distracted, immediately distracted, and osteotomized rat mandibles during activation and consolidation. Animals ( $n = 50$ ; 25 rats with unilateral gradual distraction and contralateral osteotomy as an internal control, and 25 rats with unilateral immediate distraction) were examined on postoperative days 4, 6, and 8 of activation, and after 1 and 2 weeks of consolidation. Endothelial progenitor cells isolated from human peripheral blood were labeled with fluorescent DiI dye, and  $0.5 \times 10^6$  cells were injected intra-arterially under direct vision into each carotid artery at the start of activation in nude rats ( $n = 18$ ) that then underwent the distraction protocol outlined above.

**Results:** Doppler flow analysis demonstrated relative ischemia during the activation period in the distraction osteogenesis group and increased blood flow in the os-

teotomized control group as compared with flow in a normal hemimandible [normal, 1 (standardized); distraction osteogenesis,  $0.58 \pm 0.05$ ; control,  $2.58 \pm 0.21$ ;  $p < 0.05$  for both results]. We observed a significantly increased endothelial progenitor cell population at the generate site versus controls at midactivation and at 1 and 2 weeks of consolidation [ $25 \pm 1.9$  versus  $1 \pm 0.3$  DiI-positive cells per high-power field ( $p < 0.05$ ),  $124 \pm 21$  versus  $8 \pm 4$  DiI-positive cells per high-power field ( $p < 0.05$ ), and  $106 \pm 18$  versus  $9 \pm 3$  DiI-positive cells per high-power field ( $p < 0.05$ ), respectively].

**Conclusions:** These data suggest that the distraction zone becomes relatively ischemic during activation and that endothelial progenitor cells home to the ischemic generate site during the activation phase and remain during the consolidation phase. Selective expansion of these stem cells may be useful in overcoming ischemic limitations of distraction osteogenesis. Moreover, their homing capability may be used to effect site-specific transgene delivery to the generate. (*Plast. Reconstr. Surg.* 116: 1053, 2005.)

Distraction osteogenesis has revolutionized the treatment of craniofacial hypoplasias<sup>1</sup>; yet,