

Bone Marrow Origin of Endothelial Progenitor Cells Responsible for Postnatal Vasculogenesis in Physiological and Pathological Neovascularization

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Abstract—Circulating endothelial progenitor cells (EPCs) have been isolated in peripheral blood of adult species. To determine the origin and role of EPCs contributing to postnatal vasculogenesis, transgenic mice constitutively expressing β -galactosidase under the transcriptional regulation of an endothelial cell-specific promoter (Flk-1/LZ or Tie-2/LZ) were used as transplant donors. Localization of EPCs, indicated by *flk-1* or *tie-2/lacZ* fusion transcripts, were identified in corpus luteal and endometrial neovasculature after inductive ovulation. Mouse syngeneic colon cancer cells (MCA38) were implanted subcutaneously into Flk-1/LZ/BMT (bone marrow transplantation) and Tie-2/LZ/BMT mice; tumor samples harvested at 1 week disclosed abundant *flk-1/lacZ* and *tie-2/lacZ* fusion transcripts, and sections stained with X-gal demonstrated that the neovasculature of the developing tumor frequently comprised Flk-1- or Tie-2-expressing EPCs. Cutaneous wounds examined at 4 days and 7 days after skin removal by punch biopsy disclosed EPCs incorporated into foci of neovascularization at high frequency. One week after the onset of hindlimb ischemia, lacZ-positive EPCs were identified incorporated into capillaries among skeletal myocytes. After permanent ligation of the left anterior descending coronary artery, histological samples from sites of myocardial infarction demonstrated incorporation of EPCs into foci of neovascularization at the border of the infarct. These findings indicate that postnatal neovascularization does not rely exclusively on sprouting from preexisting blood vessels (angiogenesis); instead, EPCs circulate from bone marrow to incorporate into and thus contribute to postnatal physiological and pathological neovascularization, which is consistent with postnatal vasculogenesis. (*Circ Res.* 1999;85:221-228.)

Key Words: vasculogenesis ■ endothelial progenitor cell ■ bone marrow transplantation
■ Flk-1 ■ Tie-2