Adult vasculogenesis occurs through in situ recruitment, proliferation, and tubulization of circulating bone marrow–derived cells

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Ischemia is a known stimulus for vascular growth. Bone marrow (BM)–derived endothelial progenitor cells (EPCs) are believed to contribute to new blood vessel growth, but the mechanism for this contribution is unknown. To elucidate how BM cells are able to form new blood vessels, a novel murine model of soft tissue ischemia was developed in lethally irradiated mice with BM reconstituted from either tie2/lacZ or ROSA/green fluorescent protein (GFP) mice (n = 24). BM-derived EPCs were recruited to ischemic tissue within 72 hours, and the extent of recruitment was directly proportional to the degree of tissue ischemia. At 7 days, there were persistently elevated levels of vascular endothelial growth factor (VEGF) (2.5-fold) and circulating VEGF receptor-2/CD11$^-$ (flk-1$^+$/CD11$^-$) cells (18-fold) which correlated with increased numbers of BM-derived EPCs within ischemic tissue. The cells were initially located extravascularly as proliferative clusters. By day 14, these clusters coalesced into vascular cords, which became functional vessels by day 21. In vitro examination of human EPCs from healthy volunteers (n = 10) confirmed that EPC proliferation, adhesion, and chemotaxis were all significantly stimulated in hypoxic conditions. We conclude that BM-derived cells produce new blood vessels via localized recruitment, proliferation, and differentiation of circulating cells in a sequence of events markedly different from existing paradigms of angiogenesis. (Blood. 2005; 105:1068-1077)