

Homing to Hypoxia: HIF-1 as a Mediator of Progenitor Cell Recruitment to Injured Tissue

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The identification of bone marrow-derived endothelial progenitor cells has altered our understanding of new blood vessel growth and tissue regeneration. Previously, new blood vessel growth in the adult was thought to only occur through angiogenesis, the sprouting of new vessels from existing structures. However, it has become clear that circulating bone marrow-derived cells can form new blood vessels through a process of postnatal vasculogenesis, with endothelial progenitor cells selectively recruited to injured or ischemic tissue. How this process occurs has remained unclear. One common element in the different environments where vasculogenesis is believed to occur is the presence of a hypoxic stimulus. We have identified the chemokine stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 as critical mediators for the ischemia-specific recruitment of circulating progenitor cells. We have found that the endothelial expression of SDF-1 acts as a signal indicating the presence of tissue ischemia, and that its expression is directly regulated by hypoxia-inducible factor-1. Stromal cell-derived factor 1 is the only chemokine family member known to be regulated in this manner. Later events, including proliferation, patterning, and assembly of recruited progenitors into functional blood vessels, are also influenced by tissue oxygen tension and hypoxia. Interestingly, both SDF-1 and hypoxia are present in the bone marrow niche, suggesting that hypoxia may be a fundamental requirement for progenitor cell trafficking and function. As such, ischemic tissue may represent a conditional stem cell niche, with recruitment and retention of circulating progenitors regulated by hypoxia through differential expression of SDF-1. (Trends Cardiovasc Med 2005;15:57–63) © 2005, Elsevier Inc.