

Adventitial progenitor cells and vasculogenesis.

Tigges Ulrich, PhD, Burnham Institute for Medical Research, 10901 North Torrey Pines Rd., La Jolla, CA, 92037, USA, Tel: (858) 646 3100 x3220, Fax: (858) 646 3197, utigges@burnham.org

Tigges Ulrich, PhD, Masanobu Komatsu, PhD, Stallcup William, PhD
San Diego, CA, 92037, USA

Neovascularization can occur either through de novo assembly of progenitor cells to yield a primitive vascular plexus (vasculogenesis) or through sprouting of new vessels from existing vessels (angiogenesis). Vasculogenesis predominates during embryonic development, while angiogenesis becomes prevalent during later stages of development. However, an increasing body of evidence suggests that vasculogenic mechanisms are common during pathological neovascularization in adult animals. In this context, much attention has been paid to the contribution of bone marrow-derived progenitor cells to the formation of neovascular structures. Less well-studied is the contribution to vasculogenesis made by resident vessel wall progenitor cells.

In our laboratory we have used a murine Matrigel plug model to show that FGF2 induces a series of vasculogenic events in which 50% of all pericytes and 10% of endothelial cells are derived from bone marrow progenitors. This leaves open the question of the origin of the remaining vascular cells. Interesting candidates in this regard are the above-mentioned resident vessel wall progenitors found in the adventitia of many vessels. These cells exhibit many hallmarks of progenitors and have, for example, been shown by different groups to function as myogenic precursor cells. The potential of these progenitors in the context of vasculogenesis is illustrated by an experiment in which we excised a small piece of thoracic aorta from an EGFP reporter mouse, embedded it in Matrigel containing FGF2, and implanted the Matrigel plug under the skin of a wild type mouse. EGFP-labeled progenitor cells from the thoracic explant contribute both endothelial cells and pericytes to the vascular network that forms in the Matrigel.

It has been suggested that different layers of the vessel wall might serve as niches for different populations of stem or progenitor cells. We have used a vascular injury model to look for evidence in support of this hypothesis. Following a wire injury in which the femoral artery endothelium is stripped away and the smooth muscle cells of the media are forced into apoptosis, progenitor cells contribute in diverse ways to the repair process. Significantly, bone marrow transplantation from EGFP donors confirms that many of these progenitor cells are not derived from the bone marrow. Many vascular progenitors in this experiment are EGFP-negative, identifying them as being derived from non-bone marrow sources such as the adventitia. Immunohistochemical analysis of various progenitor markers in femoral arteries at different time points before and after injury reveals a high degree of adventitial progenitor heterogeneity, congruent with the idea that the adventitia provides a niche for more than one type of progenitor cell. All of these observations support the concept that resident adventitial progenitor cells play key roles during pathological vasculogenesis.