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The VEGF Family, the Inside Story

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The role of paracrine signaling by vascular endothelial growth factor (VEGF) in the formation and maintenance of blood vessels has been studied extensively. In this issue, Lee et al. (2007) report unexpected results showing that endogenous VEGF produced by endothelial cells is also crucial for vascular homeostasis.

The function of vascular endothelial growth factors (VEGFs) in the formation and growth of blood vessels has been well characterized. In addition to VEGFs, vascular growth also depends on a bilateral paracrine signaling of factors including platelet-derived growth factor (PDGF) and angiopoietins (Ang), which are involved in stabilizing the vasculature and protecting the endothelium by providing survival signals (Figure 1). The prevailing view is that an endothelial cell protects itself by secreting PDGF-B that acts on pericytes (which cover blood vessels) that in turn secrete Ang1, resulting in the stabilization of blood vessels (von Tell et al., 2006). Endothelial cells were not thought to produce VEGF until recently (Maharaj et al., 2006), but in this issue, Lee et al. (2007) now reveal the surprising result that endogenous VEGF produced by endothelial cells is crucial for vascular homeostasis. These authors demonstrate that in the absence of their own autocrine VEGF, endothelial cells commit suicide causing collateral damage by

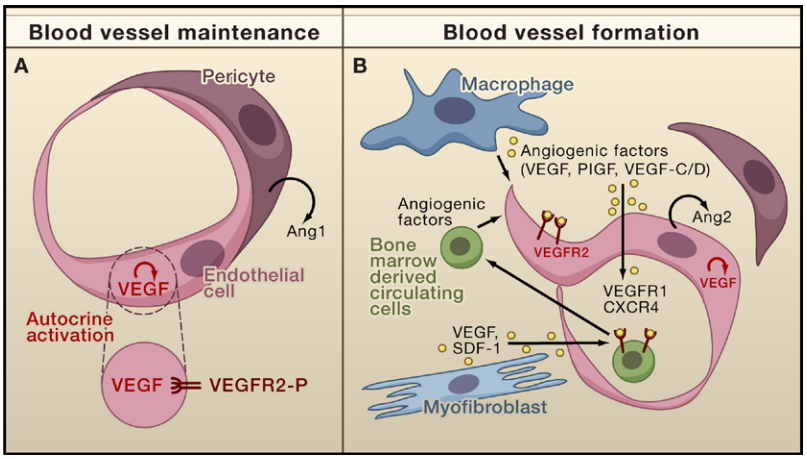

Figure 1. Paracrine and Autocrine Effects of Growth Factors in Capillaries
(A) During steady-state conditions paracrine angiopoietin-1 (Ang1) and low levels of paracrine vascular endothelial growth factor (VEGF) are produced by pericytes and other cell types associated with the endothelium. Lee et al. (2007) show that VEGF produced by endothelial cells promotes intracellular autocrine stimulation of VEGFR2 that supports endothelial cell survival. (VEGFR-2-P, phosphorylated VEGFR2.)
(B) Several pathways are activated during the formation of new blood vessels (angiogenesis). VEGF production increases in response to ischemia/tissue hypoxia that is in part responsible also for autocrine production of Ang2 involved in pericyte detachment (Yancopoulos et al., 2000). VEGF and placental growth factor (PlGF) as well as stroma-derived factor-1 (SDF-1)—produced by perivascular myofibroblasts—recruit mononuclear cells into the perivascular space by binding to the receptors VEGFR1 and CXCR4, respectively (Grunewald et al., 2006; Luttun et al., 2002). These cells and related macrophages produce additional angiogenic factors including VEGF, VEGF-C, and VEGF-D, and they may in some cases be responsible for why tumors are refractory to continued anti-VEGF treatment (Shojaei et al., 2007).

blocking vascular traffic and inducing thrombosis. Accumulation of such damage in various regions of the entire vascular system leads to catastrophic circulatory collapse and the death of mice deficient in endothelial VEGF (Lee et al., 2007).

Lee et al. specifically deleted VEGF in the endothelial cells and in mature hematopoietic cells of mice by using a vascular endothelial cadherin-driven Cre recombinase. They found that mice that lacked VEGF in their endothelial cells had signs of severe failure of the cardiovascular system such as hemorrhages, microinfarcts, endothelial cell rupture, and vascular constriction. Interestingly, Lee et al. found no phenotype when they deleted only one allele of the endothelial VEGF gene in mice even though a single VEGF allele is not sufficient to support development of mouse embryos (Carmeliet, 2005; Red-Horse et al., 2007). Furthermore, although prior studies have shown that intracellular VEGF also regulates hematopoietic stem cell survival (Gerber et al., 2002), such an effect was not seen in the present study, where more mature cells were targeted.

Lee et al. report that exogenous VEGF is unable to compensate for the loss of endogenous VEGF in endothelial cells, despite the fact that signaling through VEGFR2 activates several downstream pathways, including the PI3K/AKT pathway responsible for cell survival (Olsson et al., 2006). VEGFR2 has been reported to signal for cell survival also in the nervous system, where bouts of relative hypoxia can provoke VEGF expression. This function may be subtly impaired in amyotrophic lateral sclerosis (ALS), which is characterized by the degeneration of motor neurons (Lambrechts and Carmeliet, 2006). Indeed, patients with ALS express genetically distinguishable VEGF alleles that show reduced VEGF gene transcription and translation, decreased VEGF levels, and increased disease susceptibility.

The Lee et al. findings reveal new insights into VEGF signaling in endothelial cells. McDonald and colleagues have shown that removing exogenous paracrine VEGF—for example by using soluble VEGFR—led to pruning of the vascular network in tissues characterized by a fenestrated endothelium (Kamba et al., 2006). In adult mice, treatment with a low-molecular weight tyrosine kinase inhibitor that targets VEGFR2 as well as some other tyrosine kinases resulted in an even greater reduction in blood vessel density. The extracellular inhibitors of VEGF did not affect the survival of endothelial cells in culture; however, Lee et al. (2007) now show that a small molecular weight tyrosine kinase inhibitor acting at the intracellular level inhibited survival of endothelial cells if no other growth factors were present. This may in part relate to the internal autocrine VEGF loop in endothelial cells. Results from inhibition of VEGF signaling indicate that both autocrine and paracrine VEGF—which is produced in small amounts by many nonendothelial cells in various tissues—are crucial for maintenance of blood vessels. That tyrosine kinase inhibitors and antibodies against VEGF could cause pruning of normal blood vessels is an important issue because these compounds are used in the clinics to prevent blood vessel formation in tumors.

The importance of intracellular autocrine VEGF produced by endothelial cells for supporting the vasculature is surprising. If single genes prove as complex as VEGFs, it is unlikely that even systems biology can produce a reasonable model of the biological complexity of the numerous vascular signal transduction networks for a long time to come. In addition, other members of the VEGF family can also function in neovascular growth. VEGF-C and VEGF-D, originally thought to be involved only in lymphangiogenesis, can also participate in pathological angiogenesis (Laakkonen et al., 2007). Furthermore VEGF-B—currently the least studied member of the family—could promote vascular functions predominantly in tissues such as heart and brown adipose tissue, where it is highly expressed. This would make the VEGF dynasty one of the most influential gene families known.

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