VEGF-B Taken to Our Hearts
Specific Effect of VEGF-B in Myocardial Ischemia

Lena Claesson-Welsh

Vascular endothelial growth factor-B (VEGF-B, see Olofsson et al1) is one of 5 mammalian VEGF family members, the others being VEGF-A, VEGF-C, VEGF-D, and placental growth factor (PIGF). VEGF-B binds to 1 of the VEGF receptor tyrosine kinases, namely VEGF receptor-1 (VEGFR1, Flt1), but not to VEGFR2 and VEGFR3. In addition, VEGF-A and placental growth factor (PIGF) bind to VEGFR1 with high affinity.2 The biology of most of the VEGF family of ligands and receptors has to a considerable extent been sorted out, greatly aided by in vivo analyses of transgenic mice. The remaining enigma has been the role of VEGF-B. In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Li and coworkers show that VEGF-B is uniquely required for myocardial angiogenesis.3 These elegant data make it highly interesting to use VEGF-B therapeutically for treatment of ischemic heart disease.

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Analysis of transgenic mouse models has shown that the VEGF family of ligands and receptors in many cases have a critical role in de novo formation of the vasculature. Thus, loss of only 1 allele of vegfa leads to embryonic lethality and arrest in vascular development. Gene inactivation of vegfr2 phenocopies the effects of vegfa, indicating that VEGF-A/VEGFR2 are main regulators of endothelial cell development. Modulation of VEGF-A/VEGFR2 expression during development and disease and the recent successful introduction of inhibitors of VEGF-A/VEGFR2 function in treatment of excessive angiogenesis in cancer and retinopathy,4–6 have reinforced the notion that this ligand/receptor complex is of pivotal role for many aspects of endothelial biology.

VEGF-C and-D, which bind to VEGFR3, may also serve important roles in blood vascular function but are first and foremost critical regulators of lymphatic endothelial development and function.7 The details, in particular of the biology of VEGF-D, remain to be defined, however.8

The role of VEGFR1 and its specific ligands VEGF-B and PIGF have been more challenging to sort out. Gene targeting of VEGF-B or PIGF still allows embryonic development. In contrast, mice deficient in VEGFR1 die at embryonic day 9 because of increased proliferation of endothelial cells that fill and obstruct the vessel lumen.9 The underlying mechanism is believed to involve excess stimulation of VEGFR2 by the higher availability of VEGF-A. It is surprising that VEGFR1 would have as a main function to serve as a VEGF-trap, to fine-tune the amount of VEGF-A acting on VEGFR2. However, other genetic models verify that activation of the VEGFR1 tyrosine kinase is not required for endothelial cell function.10

There is a need for neoangiogenesis during different stages of development and in adulthood, during physiological (wound healing, ovulation, build-up of the endometrium, etc) and pathological (tumor growth, chronic inflammation, etc) events. Although there are clear overlaps in the molecular mechanisms involved in different types of vascular processes, an increasing amount of data indicate that there are also distinct molecular mechanisms in physiological and pathological angiogenesis.11,12

Thus, although PIGF is not required for embryonic development, it has a critical role in pathological angiogenesis. Elegant data from among others, the Carmeliet and Persico laboratories, have shown that growth and vascularization of tumors or ischemia-induced vascularization is deteriorated in plgf−/− mice.13,14 This is mechanistically coupled to a decreased infiltration of proangiogenic monocyte/macrophages into the tumor tissue. In agreement, transgenic mice expressing a truncated VEGFR1 lacking the kinase domain display no aberrations during development. However, when challenged with tumors, the vegfr1TK/− mice show decreased monocyte/macrophage infiltration in the tumor tissue and therefore a reduced tumor growth rate.15 This concept may be exploited therapeutically in cancer therapy by use of antibodies that neutralize PIGF and prevent it from binding to VEGFR1, leading to reduced migration of inflammatory cells.13

These data clarify the role of the extracellular domain of VEGFR1 in binding VEGF-A and the requirement of the intracellular tyrosine kinase domain of VEGFR1 in migration of inflammatory cells (see Figure). But what about VEGF-B? Gene inactivation in different genetic backgrounds shows that it is dispensable for developmental angiogenesis.16,17 There are conflicting reports on the potential role of VEGF-B in pathological angiogenesis. Li et al now convincingly demonstrate using both loss- and gain-of-function models, that VEGF-B is required for efficient revascularization after myocardial infarction, but not for revascularization of the ischemic mouse hindlimb.1 VEGF-B is also not required for angiogenesis in other tissues than the myocardium, such as the skin, lung, or retina. Thus, each of the different VEGFR1 ligands transduce distinct biological responses!

How can such a specific function be attained? Is VEGF-B the only VEGF family member expressed in the myocardium...

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Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org

DOI: 10.1161/ATVBAHA.108.170878
and therefore uniquely responsible for myocardial angiogenesis? No, several other VEGFs are expressed in the heart, and based purely on the ability to activate VEGFR1 it is unexpected that VEGF-B would have a limiting function in this tissue. One highly interesting possibility is that VEGF-B–induced myocardial angiogenesis requires the participation of a hitherto unknown coreceptor (outlined in green). EC indicates extracellular domain; TK, tyrosine kinase domain.

**Figure.** Schematic outline of VEGFR1 and its specific function in different cell types: In endothelial cells by sequestering of VEGF-A to achieve a balanced signaling via VEGFR2, in inflammatory cells for PlGF–induced tyrosine kinase activity and downstream signaling to induce cell migration, and in myocardial angiogenesis which may require complex-formation with an hitherto unknown coreceptor (outlined in green). EC indicates extracellular domain; TK, tyrosine kinase domain.

and therefore uniquely responsible for myocardial angiogenesis? No, several other VEGFs are expressed in the heart, and based purely on the ability to activate VEGFR1 it is unexpected that VEGF-B would have a limiting function in this tissue. One highly interesting possibility is that VEGF-B–induced myocardial angiogenesis requires the participation of a hitherto unidentified VEGF coreceptor or accessory molecule. Several VEGF coreceptors have been described, such as heparan sulfate and neuropilins (for a review, see Olsson et al.), however, there is no specificity for VEGF-B compared to other VEGFs in binding to these molecules. Thus, available data suggest that there are yet distinct and specific molecular players or processes to be identified within the VEGF family of angiogenic regulators.

**Disclosures**

None.

**References**


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doi: 10.1161/ATVBAHA.108.170878
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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