Almost 20 years ago, in 1989, 2 independent research groups reported their discoveries of a new peptide that increased vascular permeability and stimulated endothelial cells to divide.1,2 The proposed name of the peptides, vascular permeability factor, was later changed to vascular endothelial growth factor (VEGF). A year later Clauss et al1 showed that VEGF was a chemoattractant for monocytes, a finding that greatly interested me because my colleagues and I had shown, much earlier, that monocytes played an important role in coronary arteriogenesis,4,5 the process by which ischemic myocardium produced an arterial bypass circulation that circumvents occlusions and salvages ischemic myocardium. VEGF was a significant contributor to the emerging field of angiogenesis that was promoted by the late Judah Folkman6 and had been dominated, up to that time, by research on the fibroblast growth factor (FGF) family.7 That VEGF was regulated by the oxygen availability of the tissue8,9 strengthened the belief that ischemia, a consequence of arterial occlusions, was the key factor for all vascular adaptations that tried to improve tissue perfusion. On the other hand, inhibition of VEGF production could in principle starve cancers to death. Thus, VEGF research nourished the hope that the scourge of mankind, atherosclerosis and cancer, could be cured from 1 and the same principle: stimulation or inhibition of VEGF.

An enormous wave of research began, especially when the groups of Carmeliet and Risau10 and Ferrara11 showed that even heterozygote knockouts were not viable, underscoring the central role that VEGF played in the development of the vascular system. Close to a quarter of a million publications are listed in PubMed with VEGF in the title, large amounts of money flowed for patents and licenses, and the first results are now reported in the battle against cancer and in the angiogenic form of macular degeneration.

Unfortunately, the other half of the dream, the battle against atherosclerosis via angiogenesis, was not rewarding: in spite of numerous anecdotal clinical evidence12 and in spite of sensational animal studies in which a single VEGF injection restored blood flow after total resection of the femoral artery,13 controlled clinical studies did not live up to the expectations.

Meanwhile, the VEGF family had grown, and in 1996, VEGF-B was discovered, as well as VEGF-C and -D; the latter 2 were key to open the field of lymphangiogenesis.14 VEGF-B167, the predominant form in humans, is sequestered in the extracellular matrix and is abundantly present in brown adipose tissue and skeletal and cardiac muscle.15 It binds to the VEGF receptor 1 and neuropilin-1 and can also form heterodimers with placenta growth factor.16 However, until now, no specific function had been found for VEGF-B. It was not an angiogenic growth factor like VEGF-A or arteriogenic like placenta growth factor,17 it was not regulated by tissue oxygenation, it was not induced by inflammatory cytokines, and it did not substitute for VEGF-A when that was neutralized in adult organisms with antibodies.18–20 When the VEGF-B gene was genetically disrupted, the animals were viable and behaved normally, and only a somewhat smaller heart was noted but only in a specific genetic background.21 VEGF-B167 overexpression failed to enhance vascular growth in the skin or in the ischemic limb.22

This was disappointing and unexpected, but the renaissance of VEGF-B as an important cardiovascular agent has been heralded by a recent multicenter study with the participation of the laboratories of Carmeliet, Eriksson, and Alitalo showing that adenoviral VEGF-B overexpression results in improved vascular regeneration in the infarcted mouse myocardium.22 This is indeed a major, but also an unexpected, finding because mouse myocardium dies fast and necrosis sets in approximately 20 minutes after the occlusion.23,24 Within that time, the factor must reach the poorly perfused ischemic myocardium and start the cell cycle of the endothelial cells, which takes, when sprouting, approximately 18 hours, during which time, the myocardium is usually dead.25 Apparently, all of these hindrances were overcome. Another forthcoming report from a Finnish–Belgian collaboration, led by Seppo Ylä-Herttuala, demonstrates that expression of VEGF-B186 by direct injection into pig myocardium via an adenoviral vector increased blood vessel area, ejection fraction, and collateral artery formation (J. E. Markkanen et al, submitted for publication).

In this issue of Circulation Research, Karpanen et al26 obtained a completely novel finding from transgenic overexpression of VEGF-B167 in mouse hearts, which resulted in a lower heart rate and blood pressure, as well as hypertrophy of cardiac myocytes, leading to cardiomyopathy characterized by accumulation of ceramide, increased mitochondrial lysis, and accumulation of intracellular lipid membrane vacuoles and increased incidence of death in these transgenic mice. The hypertrophy may be like that of athletes, but when cells...
are overfed with long-chain fatty acids, mitochondria are known to finally fail after prolonged exposure, as had occurred in the transgenic mice. It is interesting to recall that VEGF-B is expressed in tissues with a very high energy metabolism, and it is also of note that the tight link between energy metabolism and blood flow, a link known to physiologists for more than half a century, is not known on the molecular level. It is not adenosine, nor NO, nor K⁺ channels, nor endothelium-derived relaxing factor, etc. 27–29 On the basis of the new findings by Alitalo and colleagues, a new lead has opened for research to resolve this very important problem. It appears that the new findings have opened the “box,” the tunnel vision that had confined the VEGFs to the vascular system, which, by itself, is unthinkable without the metabolism that it must supply.

A full understanding of the VEGF-B–induced hypertrophy and the VEGF-B–signaling pathways is important not only in normal physiology but also for understanding metabolic diseases including atherosclerosis and type 2 diabetes, which is associated with tissue dyslipidemia, ceramide production, and insulin resistance. Successful entry into these health problems would certainly mean a big step for the understanding of major human diseases.

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References
2. Keck PJ, Hauser SD, Krivi G, Sanzo K, Warren T, Feder J, Connolly DT. \( \text{VEGF-B} \) is expressed in tissues with a very high energy metabolism, and it is also of note that the tight link between energy metabolism and blood flow, a link known to physiologists for more than half a century, is not known on the molecular level. It is not adenosine, nor NO, nor K⁺ channels, nor endothelium-derived relaxing factor, etc. 27–29 On the basis of the new findings by Alitalo and colleagues, a new lead has opened for research to resolve this very important problem. It appears that the new findings have opened the “box,” the tunnel vision that had confined the VEGFs to the vascular system, which, by itself, is unthinkable without the metabolism that it must supply.

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