Vascular Endothelial Growth Factor
A Jack-of-All-Trades or a Nonspecific Stress Gene?
Matthias Clauss, Wolfgang Schaper

In this issue of Circulation Research, D’Arcangelo et al. report highly interesting and unexpected results in that acidosis inhibits proliferation and migration of cultured endothelial cells, inhibits the formation of capillary tubes, but simultaneously increases expression of the endothelial growth factors vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)-2. In addition, VEGF expression was caused neither by hif-1 activation nor increased mRNA stability. In line with the latter observation may be that VEGF transgenic mice in which a reporter gene is controlled by the VEGF promoter missing the VEGF mRNA stabilizing downstream 3’ sequences still show expression in the periphery of tumors but restricted to non–tumor fibroblast-like cells.

However, a word of caution should be permitted with regard to the interpretation of results. A 2-fold overexpression detected by a semiquantitative polymerase chain reaction method may not be extremely convincing, and the unorthodox mechanism of expression may be the result of simply no significant induction. Perhaps these findings may not have attracted so much attention were it not for the special relevance to tumor angiogenesis. In tumors, acidosis is the expected metabolic event, because most tumors prefer anaerobic glycolysis above the aerobic pathway even in the presence of oxygen, as we know from the pioneering work of Warburg et al. Another reason for acidosis in tumors is the hypoxia due to deficient capillarization.

The failing capillarization of growing tumors, which ultimately leads to a necrotic core, may have to do with the acidosis that apparently counteracts the hypoxic angiogenic growth stimulus. Also, the fact that tumor vessels are immature, leaky, and inferior blood conductors may be related to the inhibitory actions of acidosis—so much for a beautiful hypothesis. However, the ugly truth, at least in most experimental brain tumors, is that not acidosis reigns in the core but rather alkalosis, and this in the presence of increased concentrations of lactate.

These comments are speculations from which the authors wisely refrained, but the matter may be more complex, considering the fact that not only glucose deprivation, which would reduce glycolysis and acidosis, is reported to increase VEGF expression but also so were various inhibitors of the mitochondrial electron transport chain, including barbiturates, rotenone, and FCCP. Most of these metabolic interventions have little if anything to do with angiogenesis, and it is tempting to hypothesize that VEGF may not exclusively be the endothelial specific mitogenic and angiogenic factor as it was originally believed, but rather, in the adult organism, also a stress-induced gene. As such, it is produced by both oxygen and glucose deregulation, by acidosis (reported by D’Arcangelo et al.), as well as within the first 2 hours after pulmonary artery banding in the right ventricular hypertrophy.

But what is the function of VEGF in the adult if it is not to induce angiogenesis? There is now increasing evidence that VEGF also, if not predominately, effects endothelial cell growth by increasing cellular survival. During remodeling of the retina vasculature, platelet-derived growth factor-B treatment leads to pericyte dropout, rendering the endothelium extremely sensitive to oxidative stress. It may be possible that in tumors low pH is essentially protective for the tumor endothelium that is only poorly covered with pericytes. These immature vessels essentially depend on VEGF as a survival factor because they are selectively obliterated by VEGF withdrawal. These findings are likely to explain an observation known as a therapeutic window in many experimental tumors that is accompanied by the formation of immature blood vessels in the periphery of the tumor. During this window, certain experimental tumors are extremely sensitive to treatment with tumor necrosis factor (TNF), which induces hemorrhagic necroses restricted to tumors. TNF was demonstrated tomediate this induction by evoking vascular effects, including the endothelial-dependent coagulation. This unexpected finding of a procoagulant endothelium was explained by the ability of TNF to synergistically interact with VEGF in the production of very high amounts of endothelial tissue factor. This finding also led to the recognition of VEGF as an endothelial-activating factor, which not only induces vascular permeability but also the production of proteases and the transmigration of monocytes through endothelial cell monolayers.

VEGF-mediated survival for endothelial cells may be of relevance not only for angiogenic vessels but also for preexisting ones. In certain human tumors, growth of tumor cells along small blood vessels is observed. Whether or not VEGF is needed in this condition as a survival factor has not been addressed. In experimental tumors, a balance of autocrine angiopoietin-2 production, causing the regression of preexisting vessels and subsequent paracrine production of VEGF, leading to angiogenesis, was hypothesized. However, the situation becomes even more complicated when the ability of VEGF to attract and stimulate monocytes and pericytes is taken into account. Again, in tumors, the ability of VEGF to block monocyte differentiation

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to dendritic cells was suggested to contribute to tumor-mediated immune suppression and may provide an additional mechanism by which anti-VEGF therapy leads to tumor regression.15

The notion that VEGF and FGF-2 are angiogenic factors, depending on which other factors are expressed, may also explain another finding. In hibernating myocardium, a condition where reversible ischemia is believed to recur often and even basic VEGF levels are high in comparison to other tissues, capillary density is lower than normal.16 In this context, VEGF treatment of arteries after endothelial injury did not increase endothelial regrowth despite the fact that both VEGF receptors were present. Furthermore, microsphere-bound FGF-2 when injected into the normal coronary circulation was taken up by the nuclei of fibroblasts that subsequently entered the cell cycle, but endothelial cells remained quiescent and angiogenesis did not take place.17 Consistent with the hypothesis that VEGF is not the sole-acting angiogenesis factor are also results from “therapeutic angiogenesis” with VEGF in the heart, which failed to be beneficial for patients with coronary heart diseases in clinical phase II studies (the VIVA trial).

This may also be the right place to redefine the use of the term “angiogenesis,” which is strictly reserved for the sprouting of capillaries but is more often used for all vascular types of adaptation in response to arterial occlusion. Angiogenesis in its strict definition cannot replace an occluded artery, regardless of the number of new vessels created. Because the source of a new capillary is an already existing one that experiences only low capillary pressures, the pressure in the recipient bed will also be low. Only in the border zone between an ischemic and a normally perfused region can a connection between a new and existing capillary occur. The new capillaries that may form in the center of ischemia, which may be remote from the borders, may not be connected at all.

An occluded artery can only be replaced by arteries that form a low-resistance connection between a normal-zone artery and the poststenotic arterial distribution system of the recipient and potentially ischemic region (=arteriogenesis). These low-resistance connections are preexistent in the vascular periphery of practically all mammals but not in all hearts. Only a few species (guinea pigs, dogs, and humans, ranked in the order of magnitude18) exhibit sufficient arteriolar connections that a low-resistance connection between a normal-zone artery and the recipient bed will also be low. Only in the border zone between an ischemic and a normally perfused region can a connection between a new and existing capillary occur. The new capillaries that may form in the center of ischemia, which may be remote from the borders, may not be connected at all.

In conclusion, the finding that acidosis inhibits endothelial cell migration and proliferation in spite of the fact that acidosis increases expression of VEGF and FGF-2 is a strong case for the heretofore hypothetical maintenance and survival function of these two multifunctional angiogenic factors. The localization of endothelium constitutively producing VEGF at sites of high shear stress10 appears therefore highly plausible.

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