Double Face of VEGF

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The Roman god Janus (Figure) was the guardian of gates and doors and was believed to represent beginnings and endings; he is hence represented by a double-faced head. He particularly presided over all that is double-edged in life and represented the transition between the primitive and civilization, between the countryside and the city, peace and war, and the growing-up of young people. The controversy over vascular endothelial growth factor’s (VEGF) role in pathologic angiogenesis and the transition from a healthy to a diseased state is thus symbolized to a certain extent by the “gatekeeper” function that Janus played in Roman mythology.

The concept of angiogenesis as a disease pathophysiology was born out of observations made by Folkman and colleagues regarding the enhanced vascularity of tumors. Folkman “simply” noted that tumors were bloodier than surrounding healthy tissues, positing that the tumors must have an auxiliary means of augmenting vessel growth to accommodate the expansion of unhealthy tissue. The Folkman laboratory then demonstrated that tumors produced substances capable of stimulating vessel growth, igniting an entirely new field of research. One of these angiogenic factors, of course, is VEGF, and the supporting role of VEGF in tumor growth has been established by the success of VEGF neutralizing antibody for the treatment of certain solid tumors. The Folkman hypothesis was strengthened by studies by Williams and colleagues, demonstrating that administration of antiangiogenic agents, reduced the rate tumor growth has been established by the success of VEGF neutralizing antibody for the treatment of certain solid tumors in humans. VEGF expression has also been noted in human atherosclerotic plaque. Accordingly, the notion that VEGF may also be a key component of plaque growth is grounded in solid experimental and clinical science.

For more than half a century the role of the periadventitial microvasculature, or vasa vasorum, in atherosclerosis has been the subject of study, scrutiny, and debate. The association between advancing plaque burden and extension of the vasa vasorum into the media was first made by Geiringer and was strengthened by studies by Williams and colleagues, revealing regression of the vasa in animal models of atherosclerosis regression. The controversy over vascular endothelial growth factor’s (VEGF) role in pathologic angiogenesis and the transition from a healthy to a diseased state is thus symbolized to a certain extent by the “gatekeeper” function that Janus played in Roman mythology.

The development of endothelial specific inhibitors then led to a provocative series of experiments by Moulton and coworkers that revealed that attenuation of the vasa vasorum, by administration of antiangiogenic agents, reduced the rate of fatty streak formation in ApoE-deficient mice. The reduction in plaque size was accompanied by reduced plaque vascularity, underscoring the intimate relationship between the vasa vasorum and neointimal lesion formation. Celletti et al extended this concept by administering recombinant human VEGF to cholesterol-fed New Zealand White rabbits or ApoE/ApoB100-deficient (ApoE−/−/ApoB100−/−) mice, showing an increase in the rate and degree of fatty streak formation associated with an increase in the infiltration of macrophages in the thoracic aorta.

The extrapolation of these observations has fueled concern that attempts at therapeutic neovascularization of ischemic tissue may promote plaque growth by driving angiogenesis in the vasa vasorum, thereby increasing rather than decreasing the overall ischemic burden. In contrast, however, human clinical trial experience has provided no evidence to support the concept that administration of angiogenic agents to patients with already advanced atherosclerosis will lead to disease progression. Although each of the clinical trials done to date has been relatively small, the cumulative experience now exceeds 1000 patients, with no evidence suggesting disease progression induced by administration of angiogenic agents.

The disparate findings in the animal models versus human clinical trial experience raises multiple questions, among them the fidelity of animal models for human atherosclerosis. The study by Leppänen et al precisely addresses this point. Using adenoviral gene transfer or recombinant VEGF protein administration, the authors showed that VEGF exposure, even for prolonged periods, has no impact on atherosclerosis progression in the LDLR/ApoB48-deficient mouse model. The authors examined the progression of atherosclerosis in the aorta after intravenous administration of VEGF-A, -B, -C, and -D, and lacZ expressing adenovirus or recombinant human VEGF-A protein. Human VEGF-A, -B, -C, and -D were detectable, peaking at 4 days and persisting for 4 to 6 weeks in the peripheral blood after adenoviral gene transfer. In contrast, the clearance of human VEGF-A protein was only 15 minutes after human VEGF-A protein injection. Human VEGF-A gene was expressed in the aorta at 4 to 10 times’ higher level than endogenous VEGF-A 5 days after VEGF-A adenovirus injection. These data are critically important when comparing the present study with previous studies in which VEGF protein was reported to augment plaque vascularity. In the present study, despite the prolonged exposure to increased VEGF levels, there were no significant differences in atherosclerotic lesion area, macrophage content, and interestingly, no increased neovascular-
apoE and the ultimate need for verifying hypotheses in the clinical setting. The potential for therapeutic benefit via modulation of angiogenesis is an established fact. Our caution in attempting therapeutic neovascularization in patients with intractable ischemia must be balanced against the ongoing harm and suffering inflicted by the disease itself, and must be informed by our continuously evolving understanding of the biology we are attempting to modulate. In this regard, Leppänen and colleagues have added important data, consistent with clinical observation, supporting the safety of continued development of these novel strategies for patients who have exhausted all available therapies.

References


