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.

See p 1347

The concept of angiogenesis as a disease pathophysiology was borne 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,1 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 tumors2 and the development of vascular endothelial growth factor specific inhibitors. These drugs, called anti-VEGF antibodies and small molecules, have been shown to reduce tumor growth and enhance tumor response to chemotherapy. The concept that administration of angiogenic agents to tumors may promote plaque growth by driving angiogenesis in the vasa vasorum, thereby increasing rather than decreasing the overall ischemic burden,2,3 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.14–20 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 al21 in this issue of Circulation precisely addresses this point. Using adenoviral gene transfer or recombinant VEGF protein administration, the authors document that VEGF exposure, even for prolonged periods, has no impact on atherosclerosis progression in the LDLR/ApoE0/0 mouse model. The authors examined the progression of atherosclerosis in the aorta after intravenous administration of VEGF-A, -B, -C, -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.10 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

Together, these features suggest that the LDLR
ApoE expression in bone marrow– derived macrophages as large-sized lipoprotein (VLDL) is 2-fold higher in ApoE LDLR transplantation of apoE animal model selection, study design, and data interpretation tant, this study has illuminated the critical importance of findings of the Leppänen et al study and its predecessors will debate? Clearly not. Mechanisms to explain the contrasting animal model, and the clinical experience to date, suggests is whether short-term exposure to angiogenic agents alone can accelerate atherosclerosis. The present data, in a suitable animal model, and the clinical experience to date, suggests that the answer is no. So, can we close the curtain on this debate? Clearly not. Mechanisms to explain the contrasting findings of the Leppänen et al study and its predecessors will continue to be the subject of intense scrutiny. More important, this study has illuminated the critical importance of animal model selection, study design, and data interpretation 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


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Double Face of VEGF
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