The vasa vasorum consist of blood vessels that vary in size from vessels with single or multiple smooth muscle cell layers to simple endothelial channels. In all but large and/or atherosclerotic vessels, the vasa vasorum are confined essentially to the adventitia of the blood vessel wall. This microcirculatory system presumably exists for the purpose of nourishing large and medium blood vessels, including the aorta and epicardial coronary arteries. The vasa vasorum also constitute a reservoir for postnatal angiogenesis that has been studied for its potential contribution to the growth and development of neointimal thickening. It is thus intriguing to consider developing primary or restenotic lesions as relatively underperfused and, as is the model for tumor development, dependent for continued growth on augmented vascularization.

In the current issue of Circulation, Moulton and coworkers observed intimal vessels in 15 (13%) of 114 advanced lesions in the aortic root and descending aorta of apolipoprotein E -/- mice fed a cholesterol-supplemented diet from 8 to 20 weeks of age. Median plaque area measured in the aortic root was 0.250 mm². Intimal vessels were rarely seen when neointimal thickness was <250 μm; of 15 plaques with histologically documented vascularity, 13 (87%) were >250 μm thick. This finding is itself intriguing in that it is only 250 μm removed from the observation made by Geiringer nearly a half-century before that vasa are required to extend beyond the adventitia into the media when arterial wall thickness exceeds 0.5 mm. The current findings are thus consistent with the notion that the growth of vasa vasorum represents a compensatory mechanism capable of augmenting perfusion of the artery wall when increased wall thickness diminishes the extent to which mural perfusion can be satisfactorily achieved by diffusion of O₂ from luminal blood.

The novel finding of Moulton et al is that plaque area can be reduced by an angiogenesis inhibitor. When the same animal model was returned to a normal diet and treated for the subsequent 16 weeks with endostatin and TNP-470, median plaque area was reduced by 85% and 70%, respectively. It is critical to the authors’ interpretation of these results to note that evidence from their laboratory indicates that endostatin and TNP-470 inhibit endothelial cell (EC) proliferation and migration, and thereby angiogenesis, in an apparently cell-specific manner. The percentage of aortic sinus plaques that contained any intimal vessels was smaller in mice treated with either endostatin (5%; n=22; P=0.032) or TNP-470 (0%; n=27; P=0.003) than in untreated controls (29%; n=24).

These Findings Suggest for the First Time That Vasa Vasorum Are Necessary but, As Is the Case for Cancer, not Necessarily Sufficient for Plaque Growth

Previous investigations have established evidence that plaque growth is associated with proliferation of vasa vasorum. Williams et al further showed that plaque regression, accomplished by withdrawal of a hypercholesterolemic diet, was associated with loss of vasa vasorum and a profound reduction in blood flow through vasa to the coronary intima and media. The development of potent, apparently EC-cell–specific inhibitors of angiogenesis in the senior authors’ laboratory allowed them to design the complementary experiment, ie, to replace atheroma with vascularity as the independent variable to measure the impact of restricted neovascularization on plaque development. The authors’ data strongly suggest that if one limits the pace at which vascular development can keep pace with plaque growth, then plaque growth may be correspondingly limited.

Moulton et al thus advance the association implicit in the work of Williams et al and others an important step forward, indicating that neovascularization appears to constitute a necessary condition for plaque growth. Equally important, however, is the caveat regarding what these experiments do not show, namely, that promotion of angiogenesis is in and of itself sufficient for the development of atherosclerosis. In this regard, the relationship between neovascularity and atherosclerosis is again analogous to neovascularity and cancer. As previously outlined by Folkman:

The hypothesis that tumor growth is angiogenesis-dependent is consistent with the observation that angiogenesis is necessary but not sufficient for continued tumor growth. While the absence of angiogenesis will severely limit tumor growth, the onset of angiogenic activity in a tumor permits, but does not guarantee, continued expansion of the tumor population.

Thus, although the findings by Moulton et al are perhaps the most persuasive evidence to date that neovascularization...
is a prerequisite for plaque growth, the data should not be overinterpreted to suggest that if the constellation of etiologic factors and pathogenetic mechanisms that contribute to atherogenesis is not present, local synthesis or systemic administration of ≥1 angiogenic growth factor will be sufficient to progress atherosclerosis.

What Implications Do These Experiments Have for Current Clinical Trials in Which Angiogenic Growth Factors Are Used to Promote Collateral Vessel Development?

On the basis of favorable results in animal models,9 as well as preliminary reports in patients,9–13 angiogenic growth factors are currently being investigated in clinical trials of therapeutic angiogenesis. An issue that previously has been only a nagging concern but is likely to be fueled by the article by Moulton et al3 is the magnitude of risk posed by angiogenic cytokine therapy for accelerating atherosclerosis. Indeed, it should be made explicit that the experiments performed by Moulton et al were designed to test the hypothesis that “inhibition of plaque angiogenesis would reduce the growth of atherosclerotic lesions.” Their experiments were not designed to test the hypothesis that administration of agents that promote angiogenesis would enhance atherosclerosis. It turns out, however, that experiments that test the latter hypothesis have been previously performed and reported and in fact refute this hypothesis. A total of 4 separate studies performed in our laboratory investigated the direct application of vascular endothelial growth factor (VEGF) as naked DNA or recombinant protein to arteries that were aggressively injured by balloon endothelial denudation, (VEGF) as naked DNA or recombinant protein to arteries that were aggressively injured by balloon endothelial denudation, or with14,15 or without16,17 an endovascular stent. In all 4 cases, no evidence of accelerated atherosclerosis was observed. The outcome was in fact quite the opposite: in all 4 cases, intimal thickening and mural thrombus formation were reduced to an extent that was highly statistically significant.

In each of these animal experiments, the inhibition of neointimal thickening by angiogenic cytokines was shown to result from expedited reendothelialization of a freshly injured arterial segment. These findings are consistent with the notion that VEGF functions as an endogenous regulator of endothelial integrity, physiological as well as anatomic, in the artery wall.18

The testing of this concept has not been limited to animal models. More than 30 patients have now undergone direct intra-arterial gene transfer of naked DNA encoding for VEGF (phVEGF165) to a freshly injured arterial surface. In 12 patients, phVEGF165 was administered to normal or moderately diseased arterial segments by use of a hydrogel-coated angioplasty balloon to promote therapeutic angiogenesis.9 Follow-up angiography and intravascular ultrasound showed no evidence of disease progression after gene transfer (J.M. Isner, MD, et al, unpublished data). In 20 other patients, the same delivery strategy was used to accelerate reendothelialization after percutaneous revascularization of femoral arteries occluded or severely narrowed by advanced atherosclerosis. Follow-up examination up to 18 months after gene transfer19 disclosed evidence of restenosis in only 5 patients (25%), approximately 50% of the anticipated incidence of restenosis predicted by historical controls.

These animal and clinical studies, although certainly preliminary, nevertheless fail to provide any support whatsoever for the notion that accelerated atherosclerosis is a likely consequence of the administration of angiogenic cytokines.

Other Therapeutic Implications

The extent to which the often intangible implications of basic science may be quickly translated into more tangible indicators of the world around us was aptly demonstrated by the reception that the current report received from Wall Street. On the day after presentation of the current findings at the 71st Scientific Sessions of the American Heart Association in Dallas, Tex, in November 1998, heavy trading of one company whose lead product is an angiogenesis inhibitor advanced its stock price by ≥3 points, or 12.5%. Thus, the possible implications that these findings may have in the design of novel treatment strategies for atherosclerosis and restenosis cannot be ignored. With regard to primary atherosclerosis, one may envision at least 3 potential applications of therapies targeted at the vasa vasorum. The first, as primary prevention, is restriction of plaque growth and development. The second, the holy grail of secondary prevention, involves the ability to medically reduce established plaque mass. A third potential application concerns acute stabilization of the so-called vulnerable lesion. Rupture of the vasa vasorum has been proposed previously as the basis for plaque rupture and hemorrhage, the pathological substrate considered to underlie most cases of acute myocardial infarction. Given the limited options available for passivation of destabilized lesions in patients with preinfarction angina, the logic of choking the putative microvascular source of intraplaque instability is appealing.

Although the observations of Moulton et al3 thus support a number of logical strategies for targeting the vasa vasorum to develop novel therapeutic paradigms, the complexity of these proposals should not be underestimated. In particular, timing (when to initiate and how long to treat) is a difficult issue generic to any preventive therapy. Compounding the difficulty in this case is the relatively narrow window of opportunity suggested by the authors’ data. Little effect was observed when the angiogenesis inhibitors were administered during the early stages of plaque development. Of greater concern was the reduced impact observed when treatment was delayed until age 32 weeks. It is important to understand that what makes angiogenesis inhibitors attractive from a clinical standpoint is a feature shared in common by cancer chemotherapeutics in general: activity that is principally directed, if not limited, to nonquiescent, actively proliferating (in this case, endothelial) cells. The limitations that this may impose on treating the established microvasculature of established, complex atherosclerotic lesions ≥40 years of age remain to be defined.

Unanswered Questions

The hallmark of a seminal publication is that it raises more questions than it answers. The article by Moulton et al3 satisfies this criterion in spades. It is now widely accepted
that for a neoplasm to grow and/or metastasize, a subgroup of cancerous cells must undergo a “switch” to an angiogenic phenotype. A critical corollary of this concept is that such a switch involves a change in the local equilibrium between positive and negative endogenous regulators of postnatal angiogenesis. Just as the presence of tumor cells or macrophages that have switched to the angiogenic phenotype may be necessary but not sufficient for tumor progression, the nature of host “brakes” and the extent to which they must be disrupted for plaque neovascularization to commence remain to be elucidated.

In this regard, there is no shortage of suspects. Such endogenous negative regulation may well involve inhibitors to transcendingothelial migration of the Trojan cells bearing angiogenic cytokines; matrix proteins, such as metalloproteinase inhibitors, which inhibit matrix degradation required for angiogenesis to occur; other matrix proteins, such as heparan sulfate, that typically immobilize the release or activity of otherwise bound angiogenic proteins; or still other matrix proteins, such as thrombospondin, which in and of themselves downregulate angiogenesis. The growing complexity of angiogenesis regulation has now been extended beyond these extracellular factors to intracellular mechanisms that govern life or death of the cellular elements required for blood vessel growth, including intracellular enzymes or cell surface integrins that modulate cell survival. Novel regulatory paradigms suggest that certain growth factors, such as angiopoietin 2, may be required to destabilize intact vasculature for neovascular sprouting or may modulate neovascularization poietin 2, may be required to destabilize intact vasculature for neovascular sprouting or may modulate neovascularization.

Thus, the laboratory that has for the last third of the 20th century established itself as the cradle of angiogenesis has given us once again important, challenging, and intriguing homework to carry us into the next millennium.

References

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