Angiogenic Therapy of the Human Heart

Judah Folkman, MD

The field of angiogenesis research was initiated 27 years ago by a hypothesis that tumors are angiogenesis-dependent. Shortly thereafter, in the early 1970s, it became possible to passage vascular endothelial cells in vitro for the first time. Bioassays for angiogenesis were developed subsequently throughout that decade. The early 1980s saw the purification of the first angiogenic factors. By the mid-1980s, angiogenesis inhibitors began to be discovered. Translation of these laboratory findings to clinical application started in 1989, when interferon alfa was first used for the treatment of life-threatening hemangiomas in infants.

Clinical applications of angiogenesis research are being pursued along three general lines: (1) prognostic markers in cancer patients, (2) antiangiogenic therapy (for review, see Reference 15), and (3) angiogenic therapy. The first angiogenic therapy of ischemic vascular disease was the administration of vascular endothelial growth factor (VEGF)/vascular permeability factor to patients with severe peripheral vascular disease in the lower limbs.

In a landmark paper, Schumacher and colleagues now report the first angiogenic therapy of human coronary heart disease. It is an important study, not only because the authors describe how they produced their own recombinant human fibroblast growth factor-1 (FGF-1, also called acidic fibroblast growth factor) and tested it in vitro and in vivo but also because they conducted a randomized controlled clinical trial. In 20 patients with three-vessel coronary artery disease who underwent two or three venous bypass grafts and one from the internal mammary artery, the angiogenic protein FGF-1 was injected into the myocardium close to the left anterior descending coronary artery and distal to its anastomosis with the internal mammary artery. FGF-1 was injected during extracorporeal surgery and again after completion of the anastomosis. Transfemoral, intra-arterial digital subtraction angiography 12 weeks later showed coronary artery neovascularization extending out from the area of FGF-1 injection. Stenoses distal to the anastomosis were bridged by neovascularization. This was similar to the neovascularization observed by the authors in rat hearts injected with FGF-1. Histological sections of rat myocardium showed a threefold increase in microvessel density. In 20 patients undergoing similar coronary artery bypass surgery in whom inactivated FGF-1 was injected, there was no evidence of myocardial neovascularization on the 12-week angiogram.

An advantage of this approach is that it induces local angiogenesis and appears to avoid high levels of circulating angiogenic activity that could possibly stimulate plaque angiogenesis and secondary plaque growth. Why does neovascularization persist for at least 12 weeks after only a single set of intramyocardial injections of the angiogenic protein? Perhaps persistent neovascularization was facilitated by upregulation of VEGF and its receptors in hypoxic tissue. Furthermore, basic FGF and VEGF are synergistic mitogens for endothelial cells in vitro. Also, FGF can increase expression of (or mobilize) VEGF.

This report uses primarily anatomic studies to demonstrate increased myocardial neovascularization after angiogenic therapy. We look forward to the follow-up of these patients to learn whether they have significant functional improvement compared with the control group of patients who received inactive FGF. It may be difficult to discriminate the extent to which functional improvement is due to the angiogenic therapy per se, despite use of a control group, because of the concomitant internal mammary artery anastomosis and the relatively small number of patients in this study. Nevertheless, the angiographic documentation of myocardial revascularization suggests that functional improvement should follow.

Although major therapeutic advances in cardiology have been based on the general principles of control of blood pressure, regulation of cardiac rhythm, enhancement of myocardial contractile strength, increased diameter of narrowed coronary arteries, and lysis of intravascular thromboses, the report by Schumacher et al introduces a new modality, the regulation of blood vessel growth. If angiogenic therapy of the myocardium continues to live up to its potential as indicated by this report, we may witness novel refinements in future years as the molecular biology of endothelial cell and smooth cell growth is gradually uncovered. For example, the therapeutic induction of coronary arterial collaterals may someday be optimized by administration of appropriate mixtures of molecules that target different components of the vasculature, ie, the FGFs are mitogenic for vascular endothelial cells and smooth muscle, VEGF is mitogenic primarily for endothelial cells, angiopoietin-1 mediates the recruitment of smooth muscle cells to the wall of new vessels, and angiopoietin-2 appears to prevent or downregulate smooth muscle apposition to the walls of microvessels. It is interesting that the methodology to discover these different vascular cell growth proteins emerged largely from investigations of mechanisms of tumor angiogenesis in studies funded primarily by the National Cancer Institute over many years. The report by Schumacher et al illustrates how unpredictable are the clinical applications that may arise from basic research in a different field.
References

Key Words: Editorials ■ angiogenesis ■ growth substances
Angiogenic Therapy of the Human Heart
Judah Folkman

Circulation. 1998;97:628-629
doi: 10.1161/01.CIR.97.7.628

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/97/7/628

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/