Gene Therapy
A New Approach to the Treatment of Cardiovascular Disease

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Somatic gene therapy, the alteration of the genetic information contained in specific cells of an organism, has recently received much attention in scientific journals and the lay press.1 This exciting technology promises to provide a new approach to the prevention and treatment of a wide variety of human diseases. The article by Dichek et al in this issue2 heralds the premier of this technology in Circulation. These authors have used a novel strategy in an attempt to prevent the acute thrombosis of intravascular stents. This report, together with two other recent reports,3,4 illustrates the potential of recombinant gene therapy in the treatment of cardiovascular disease.

Significant efforts are underway in many laboratories to perfect the use of intravascular stents for the treatment of coronary and peripheral vascular disease. Both absorbable and nonabsorbable stents show promise in maintaining patent arteries, but early thrombosis of these prosthetic devices is an important clinical problem. Seeding of stents with endothelial cells before placement in patients may reduce the risk of thrombosis. An additional advantage would be gained if the endothelial cells used to seed the stents were engineered to express enhanced anticoagulant activity. Dichek et al2 used a two-step approach to accomplish just this.

These investigators first demonstrated that an indicator gene could be stably introduced into endothelial cells and that these cells would express the introduced gene when attached to metal stents in vitro. The endothelial cells remained in place on the stent even after the stent was expanded by balloon dilatation. The investigators then demonstrated that the gene encoding tissue-type plasminogen activator (t-PA) could be introduced into endothelial cells by retroviral expression vectors, that these cells could then be used to seed metal stents in vitro, and that the genetically modified endothelial cells continued to express t-PA while attached to the stent. Finally, they showed that the amount of t-PA produced by the genetically modified endothelial cells was significantly more than that normally produced by human endothelial cells in vitro. The number of endothelial cells seeded on a stent would not be expected to produce a systemic anticoagulant effect when implanted in vivo, but the local concentration of t-PA might well be sufficient to produce a thrombolytic environment at the stent surface. Thus, compared with unseeded stents and stents seeded with unmodified endothelial cells, stents seeded with endothelial cells engineered to express t-PA are expected to be less subject to thrombosis when implanted in vivo.

Although these in vitro results appear promising, the authors correctly point out that in vivo studies are needed to assess the potential clinical efficacy of this strategy. Because endogenous endothelial cells express both procoagulant and anticoagulant molecules, the net in vivo effect of enhancing the capacity of endothelial cells to secrete t-PA remains to be determined. In addition, the ability of engrafted endothelial cells to continue to stably express the exogenously added gene product must be examined. In this respect, the two recent reports provide important information. Nabel et al5 were able to show that endothelial cells genetically modified in vitro to express an indicator gene could be used to seed denuded iliofemoral arteries in vivo and that these endothelial cells continue to express the indicator gene for at least 4 weeks after implantation. Wilson et al6 seeded Dacron grafts with endothelial cells that also were modified to express an indicator gene, and they implanted these grafts into the carotid arteries of dogs. These investigators were also able to show that genetically engineered endothelial cells were still able to express the introduced gene at the time of examination 5 weeks later. Thus, these two studies indicate that it is reasonable to expect that therapeutically important gene products can be stably expressed by genetically modified endothelial cells in vivo for substantial periods of time.

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The aforementioned studies provide only a glimpse at what will be possible in the future. Many therapeutically important proteins could be introduced into endothelial cells (or other cell types) to provide for their local release in vivo. Proteins that induce angiogenesis, inhibit vascular smooth muscle proliferation, or produce vasodilatation are but a few of the possible gene products that are candidates for introduction by gene therapy. Future strategies may also involve synthesizing mutant proteins that could act by inhibiting their normal protein counterpart through a dominant negative effect.

The implantation of genetically altered endothelial cells could not only provide increased local concentrations of proteins but, if expressed in sufficient quantities, also allow for systemic drug delivery. Although the initial studies have been performed by genetically engineering endothelial cells in vitro, endothelial cells and other cell types (such as cardiac and skeletal myocytes) may well be amenable to the direct introduction of gene transfer vectors into these cells in the intact animal. Thus, in vivo gene delivery could allow the creation of customized, discreetly localized “cellular factories” in individual patients for the endogenous production of therapeutically efficacious drugs targeted at specific disease processes. Although formidable obstacles such as the regulation of production of gene products obscure the path to the routine use of gene therapy in human disease, the first steps down that path have recently been successfully taken.

References

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