Thinking Globally, Acting Locally
The Promise of Cardiovascular Gene Therapy

Toren Finkel

Most diseases are local problems, whereas most treatments are systemic in nature. This simple, maddening imbalance remains one of the major causes of the ineffectiveness of our current pharmacological armamentarium. The notion of treating local disease with localized therapy has however emerged as one of the great promises of gene therapy. Two articles1,2 in this issue of Circulation Research eloquently demonstrate this point. Although the major rationale for early gene therapy efforts was to deliver functional copies of defective genes for a variety of inherited conditions, the emphasis has most recently shifted. As demonstrated in the two articles published in this issue, there is increasing interest in using gene therapy techniques to deliver therapeutic products to diseased tissues or organs for any of a number of acquired conditions. Underlying these efforts is the hope to express therapeutic molecules that have great local benefit but which have limiting systemic toxicities.

The study of Nishida and colleagues1 applies this concept to a model of arterial thrombosis. To achieve their local objectives, they have constructed a recombinant adenovirus encoding tissue factor pathway inhibitor (TFPI). TFPI is a curious molecule whose biological activity was noted more than 40 years ago but was only cloned relatively recently. The molecule is composed of three tandem Kunitz-type proteinase domains that appear to be responsible for the interaction of TFPI with factor Xa.4 Indeed, TFPI is thought to form a quaternary complex composed of Xa, as well as factor VIIa and tissue factor.5 This complex results in reduced thrombin generation and hence a reduction in local platelet aggregation. TFPI can be produced by a variety of cells in culture, although the endothelium is thought to be the major site of production in vivo where its production may be regulated by shear stress.6 Its role in human thrombogenesis has not been clearly established, in large part, because no inherited or acquired deficiency of TFPI has been described, which subsequently results in an increased thrombotic tendency.

The results, therefore, of Nishida and colleagues1 are particularly interesting in their demonstration that TFPI by regulating local thrombogenesis can in turn influence cyclic flow variations (CFV). They are consistent with previous results, however, that suggest that a monoclonal antibody that inhibits tissue factor activity also blocks CFV.7 Interestingly, in the setting of TFPI local overexpression, not only were basal CFV inhibited, but also epinephrine-stimulated CFV were absent. Such results were achieved without systemic ill effects, at least as evidenced by the observation that there was no change in the prothrombin time, partial thromboplastin time, or ex vivo platelet aggregation.

The study of Champion and colleagues2 has used a similar adenoviral delivery system, but in this case, to express endothelial nitric oxide synthase (eNOS) in the lung. These authors demonstrate a rightward shift of the pressure-flow relationship in animals overexpressing eNOS. In addition, pulmonary vasopressor responses to endothelin-1 or angiotensin II were reduced, but the response to agents such as norepinephrine was unchanged. Again, as was the case with the study of Nishida et al,1 no systemic vascular effects were evident.

The experience with nitric oxide synthase (NOS) gene transfer is significantly more mature than with TFPI. At least 10 previous studies using vascular gene transfer of eNOS have been performed, demonstrating that such maneuvers alter vasomotor function.8 Interestingly, in studies of vascular gene transfer, eNOS delivered adventitially appears to be efficacious.9,10 This degree of laxity in the target cell for NOS expression is also evident in the pulmonary circulation. Previously, infection of rat lungs with an aerosol of an adenovirus encoding eNOS demonstrated a therapeutic attenuation of the hypoxic pulmonary vasoconstrictive response.11 Infection under these conditions led to transduction of cells in the alveoli as well as endothelial and adventitial cells of small- and medium-sized pulmonary vessels. Similarly, in the study of Champion and colleagues,2 when an adenovirus encoding a marker gene was used, the adventitial cells of medium- and resistance-sized arteries appeared transduced. Thus, it appears that eNOS expressed outside the endothelium may still have significant therapeutic benefits.

Although the articles presented in this issue represent significant achievements, considerable roadblocks still exist before they are practical in the clinical setting. Both studies are limited by the time of transgene expression. For the case of Nishida and colleagues,1 expression may be too late to be practical, whereas for Champion and colleagues,2 expression may be too short. In particular, evidence suggests that tissue factor levels increase within hours of vessel injury.12 In contrast, the kinetics of in vivo gene transfer require at least 12 to 24 hours before there is most likely enough transgene expression to be therapeutically significant. This disparity suggests that such therapies may have limited utility during the most vulnerable period of thrombi generation after angio-

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plasty or stent implantation. In contrast, for chronic conditions such as pulmonary hypertensive diseases, the window of therapeutic expression after adenoviral gene therapy is probably too short to be practical. Fortunately, this problem is more amenable to a solution than the practical problem encountered with TFPI expression. A variety of evidence suggests that transgene expression in vivo is largely determined by the host immunological response. Part of that immune response can be directed against the transgene itself. Evidence in mice suggests that adenoviral delivery of murine erythropoietin has a longer in vivo half-life than adenoviral delivery of human erythropoietin. The destruction of adenoviral transduced cells can also result from production of low amounts of adenoviral gene products. To counter this, a considerable amount of effort has been expended to create “gutless” adenoviral vectors that maintain the useful properties of conventional adenoviruses (easy production of high-titer stocks) but lack the elements in the adenoviral genome that elicit a host response. Interestingly, in the study by Champion and colleagues the persistence of in vivo expression of a β-galactosidase marker gene construct differed significantly if the promoter was cytomegalovirus (CMV) based or Rous sarcoma virus (RSV) based. The reason for this difference is not clear; however, it may relate to the relative strength of these promoters to cryptically transactivate low levels of adenoviral gene products. Although newer-generation adenoviruses appear to show longer in vivo expression, because the virus remains episomal, even in the absence of immunological selection, transgene expression should eventually fall in dividing cells. To combat this problem, significant efforts are underway to explore the potential of other viral vectors that stably integrate into chromosomal DNA. In particular, it would appear that adeno-associated virus (AAV) as well as lentivirus may offer the potential of other viral vectors that stably integrate into chromosomal DNA. In particular, it would appear that adeno-associated virus (AAV) as well as lentivirus may offer the potential of other viral vectors that stably integrate into chromosomal DNA. In particular, it would appear that adeno-associated virus (AAV) as well as lentivirus may offer the potential of other viral vectors that stably integrate into chromosomal DNA.

In summary, the two studies presented in this issue provide significant contributions to our understanding of cardiovascular physiology. In addition, they provide the blueprint for novel treatment strategies to what, up until now, have been therapeutically resistant clinical syndromes. The secret to their success lies in large part to localized in vivo overexpression of known therapeutic molecules. They offer a glimpse into a future where systemic therapy gives way to localized treatment, and drugs are replaced by genes.

References


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