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In vivo gene transfer, Koch's postulates, and renal disease.

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Editorial

In this issue of *The Journal,* Isaka et al. (1) report on the successful transfection of the human PDGF B chain gene and the TGF-β gene into the rat kidney (1). A liposomal delivery system was prepared using hemagglutinating virus of Japan to facilitate fusion of the liposome to cell membranes, and high mobility group 1 protein to facilitate entry of the plasmid DNA into the nuclei. The infusion of these liposomes into the renal artery resulted in a transfection rate of 35% of the glomeruli. PDGF-transfected glomeruli demonstrated marked mesangial cell proliferation with mild matrix expansion; in contrast, TGF-β-transfected glomeruli primarily demonstrated mesangial matrix expansion characteristic of a sclerotic process (1).

In vivo gene transfer represents a major research breakthrough from the perspective of understanding disease pathogenesis, as well as for potential gene therapy of inherited or acquired disorders. The ability to introduce a gene into a target organ of interest, in this case the glomerulus, is highly preferable to the systemic overexpression of genes, which can occur with transgenic animals. In the study by Isaka et al. (1), the transfection appeared to selectively involve the glomeruli. While the paper is innovative, it would have been strengthened by showing photographs of human PDGF expression in transfected glomeruli, and by confirming the mRNA expression by Northern analyses of glomerular RNA. Additional studies will also be helpful in verifying the methodology and confirming its application to our understanding of glomerular disease processes.

One consequence of the transfection of a gene into a target organ is allowing one to examine the potential biological consequence of overexpression of that particular gene. Indeed, the study by Isaka et al. (1) essentially completes Koch's postulates in establishing a role for PDGF as a mediator of mesangial cell proliferation (with a milder stimulation of extracellular matrix) and for TGF-β as a mediator of extracellular matrix expansion. Previous studies had demonstrated that: (*a*) PDGF and TGF-β mediate cell proliferation and matrix synthesis in mesangial cells in vitro; (*b*) PDGF and TGF-β are expressed in experimental and human mesangial proliferative disease in which matrix expansion is present; and (*c*) inhibition of these growth factors with neutralizing antibodies prevents or reduces the proliferation and/or matrix expansion in experimental disease (reviewed in references 2 and 3). The final step was to show that introduction of the growth factors into animals can induce the biologic process, much like Koch proved that mycobacteria were the cause of tuberculosis by inoculating susceptible animals with purified mycobacterial cultures (4). This has now been achieved by the study of Isaka et al. (1), and is confirmed by studies in this issue by our group (5) in which it was shown that intravenous administration of PDGF protein to rats also results in mesangial cell proliferation and matrix expansion, especially if rats are pretreated with subnephritogenic doses of anti-mesangial cell antibodies.

The ability to specifically introduce a gene of interest into intrinsic glomerular cells in vivo will permit a more physiological evaluation of the role of peptide growth factors in both normal and diseased glomeruli. Ultimately, it may also be possible to turn off gene expression through the use of antisense constructs and thereby ameliorate proliferative and sclerotic disease processes. The potential applications of this approach are enormous, and may be limited only by our creativity and resourcefulness.

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