Toward an effective gene therapy in renal disease

Since the first reports of the generation of transgenic mice in 1980 [1], technology aimed at manipulating the mammalian genome has yielded fruitful information regarding the potential physiological roles of gene products in vivo. From these technologies spawned the field of gene therapy, the goal of which is to treat human diseases through the introduction of foreign genetic material. The development of such technology may offer the best hope in the future treatment of monogenic diseases such as cystic fibrosis where current treatments do not address the underlying cause. Gene therapy need not solely exist for the treatment of such genetic disorders, but may find widespread utility in treating acquired diseases in which a protein is under- or over-expressed.

Despite the ever-increasing knowledge of the genetic nature of diseases (that is, the identification of “culprit” genes which lack proper function or proper expression), several practical considerations have kept gene therapy a “future prospect.” These considerations include: (1) the method of introduction of foreign genetic material; (2) the ability to target the expression of genetic material to relevant cell types; (3) the demonstration of practicality in animal models of diseases; (4) the ability to utilize this technology in patients without severe side-effects. The reader is referred to the excellent article by Lipkowitz et al [2] that outlines several advances in these first two considerations. Several options such as the adenovirus, adeno-associated virus, retroviruses or the direct injection of DNA using lipofection reagents, continue to be refined as a means to introduce foreign DNA into mammalian cells. Furthermore, tissue and cell specificity, at least in kidney, appear likely to be achieved via a combination of cell-specific promoters in combination with the proper vector and physical route of administration [2]. Experiments geared toward demonstrating the practicality of a genetic approach toward therapy in animal models of renal disease would appear to be the next major step.

The problem of target specificity appears less important when humoral factors are involved. Evidence has accumulated suggesting a key role for transforming growth factor-beta (TGF-β) as a possible mediator of several renal fibrotic diseases of both glomerular and tubular origin. In vitro, TGF-β is a potent stimulator of extracellular matrix synthesis. Evidence that TGF-β might contribute to fibrotic renal disease include: (1) the demonstration of enhanced expression of TGF-β peptide and/or mRNA in human renal fibrotic diseases and animal models of renal diseases [3]; (2) the demonstration that increased TGF-β activity in vivo, by gene transfer or transgenic methods, results in glomerular extracellular matrix accumulation, proteinuria, tubulointerstitial fibrosis and the onset of chronic renal failure [4-6]; (3) the demonstration that proteinuria and extracellular matrix (ECM) accumulation associated with anti Thy-1.1 nephritis was attenuated by a neutralizing antibody to TGF-β or the TGF-β antagonist, decorin [7, 8]. Thus, strategies that intervene with TGF-β extracellularly may be of therapeutic utility.

In this issue of Kidney International, Isaka et al report a novel and exciting twist on gene therapy strategies designed to reduce TGF-β hyperactivity in a rat model of glomerulonephritis [9]. TGF-β’s biological effects are manifested through signal-transducing receptors on the cell surface which are referred to as TGF-β receptors type I and II, (TβRI and TβRII). While both receptor subtypes possess serine kinase domains, active TGF-β has strong affinity for the extracellular domain of TβRII and only interacts with TβRII after association with TβRII on the cell surface. It has been shown that a soluble recombinant peptide containing the ligand binding domain of TβRII competitively inhibits TGF-β activity in vitro [10]. The report by Isaka et al [9] takes advantage of this observation. The authors have designed a chimeric gene product containing the ligand binding domain of the TβRII molecule with the Fc region of the IgG heavy chain that contains intermolecular cysteine disulfide bonds. The resulting stabilized chimeric dimer is a potent competitive inhibitor of TGF-β in vitro. Following transfection into muscle in vivo, the expressed protein is released extracellularly and is detected in kidney glomeruli. Its efficacy was determined by administration of the chimeric construct one day after treatment with anti-Thy 1.1 serum to rats. These animals manifested significantly less glomerular matrix expansion than mock-vector treated controls. This same group of investigators has published similar findings following the in vivo transfecation of the natural occurring TGF-β inhibitor, decorin [11]. Therefore, this report strengthens the argument that TGF-β be considered a molecular target in the setting of renal fibrotic disease.

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There is much room for optimism at the future prospects of such an approach. Other questions remain to be addressed. A challenge will certainly be devising a regimen to yield an effective dose of TβRII-chimera in vivo. Aside from obvious toxicity issues, one must be cautious with regard to the loss of TGF-β activity systemically. While no adverse effects were reported by the authors in these short-term experiments, potential effects on immune suppression or wound healing may be observed after longer periods. Nephrologists will obviously be interested in determining whether or not this approach can be effective at treating other diseases thought to result from TGF-β over-expression. Since tubulointerstitial fibrosis is closely associated with progression to ESRD, it is important to note that the authors localized the chimeric gene product in the glomerulus but not in the tubulointerstitium. Could a modified approach be used to treat diseases of the tubulointerstitium? In addition, since Isaka et al performed gene transfection 1 day following administration of anti-Thy 1.1 administration, it is unclear whether this approach will be effective in the treatment of established renal disease.

Despite the uncertainties, Isaka et al have outlined a strategy to treat fibrotic renal disease by targeting the activity of TGF-β. The in vivo data suggest that this strategy is feasible, overcoming several of the aforementioned difficulties associated with “conventional” gene therapy strategies. With the ever increasing evidence implicating TGF-β as a mediator of renal fibrotic diseases and a pharmaceutical industry poised to undertake gene therapy trials, it would appear that the future is closer than we thought.

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