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EDITORIAL

Evidence that TGF-β should be a therapeutic target in diabetic nephropathy

Diabetic nephropathy is now the most common cause of end-stage renal disease in North America and Europe. New evidence suggests that the majority of diabetic patients, whether insulin-dependent or not, are developing fibrotic changes in glomeruli that, if they live long enough, will manifest as overt nephropathy. It is also clear that the current therapy, optimal glycemic control combined with an angiotensin II antagonist and possibly a low protein diet, can slow, but not prevent the development or progression of diabetic nephropathy in most patients.

At the molecular level, the pathological features of fibrosis in the diabetic kidney resemble fibrosis in other progressive forms of renal disease, as well as in fibrotic disorders of a variety of other organs and tissues. Indeed, the most constant molecular feature of pathological tissue fibrosis leading to organ failure is overexpression of the cytokine transforming growth factor-β (TGF-β) [1]. These common molecular features between the kidney and other tissues suggest the presence of a generic process underlying fibrotic diseases, rather than unique organ- or tissue-specific processes. The concept of a common process of fibrogenesis is good news for the clinician because it implies that therapies effective in one fibrotic disorder may be beneficial in a number of other disorders.

TGF-β's fibrogenic potential is uniquely powerful because of three simultaneous actions: (1) stimulation of matrix synthesis, (2) inhibition of matrix degradation, and (3) modulation of matrix receptor expression to facilitate cell-matrix interactions. TGF-β initiates its fibrogenic effects by acting as a transcription factor for several genes involved in regulating matrix deposition and cell growth, including a recently discovered gene, whose product may function as a cell adhesion protein. This gene is βig-h3 (TGF-β-induced gene human clone 3). TGF-β has been shown to induce βig-h3 in a number of cultured cell lines, and βig-h3 is overexpressed in human atherosclerotic and restenotic vascular lesions. In this issue of *Kidney International*, Gilbert and coworkers provide evidence that βig-h3 is expressed in normal kidney and its overexpression in the diabetic kidney is closely correlated with that of TGF-β and type IV collagen [2].

Key words: fibrosis, matrix degredation, cell-matrix interaction, βig-h3, glycemic control.

The evidence implicating TGF-β overexpression in the pathogenesis of experimental and human diabetic nephropathy is now overwhelming [reviewed in 3, 4]. In the pre-cytokine era a number of factors were thought to play a role in diabetic nephropathy. These factors, including high levels of glucose, increased glomerular pressure and flow, mesangial cell stretch, activation of renin-angiotensin II, hypertension and non-enzymatic glycation of proteins, have all been shown to induce TGF-β production in the kidney or in cultured mesangial or tubular cells [4]. Indeed, as soon as a rat is made diabetic, glomerular expression of TGF-β is increased along with the glomerular production and deposition of matrix components and protease inhibitors induced by TGF-β [5]. Treating diabetic rats with insulin suppresses the renal production and secretion of TGF-β, but not to normal levels. Thus, as in humans, the disease process is retarded, but not prevented.

Renal hypertrophy is one of the earliest findings in experimental and human diabetes. Although called a growth factor (all growth factors are cytokines but not all cytokines are growth factors), TGF-β inhibits the cell cycle in most types of cells, leading to an increase in volume and DNA and protein content, that is, hypertrophy. Proximal tubular cells cultured in high glucose show increased production of TGF-β and undergo hypertrophy that is blocked by a neutralizing TGF-β antibody. In two models of spontaneous-insulin dependent diabetes, the biobreeding (BB) rat and the nonobese diabetic (NOD) mouse, the development of renal hypertrophy was closely correlated with the increased renal expression of TGF-β [4]. Streptozotocin-induced diabetic mice rapidly develop increased renal expression of TGF-β, collagen and fibronectin, elevated urinary TGF-β and renal hypertrophy. Administration of a neutralizing TGF-β antibody suppressed renal TGF-β, collagen and fibronectin production, and reduced the expected increase in kidney weight by over 50% [6].

TGF-β overexpression is also tightly linked to the development of human diabetic nephropathy [5]. The glomeruli and tubulointerstitium in humans with biopsy-proven diabetic nephropathy show very high levels of the three TGF-β isoforms along with matrix proteins induced by TGF-β such as fibronectin EDA+ and plasminogen activator inhibitor-1 (PAI-1). In an earlier study in *Kidney International*, the levels of TGF-β mRNA were quantitated in diabetic glomeruli dissected from human biopsies [7]. TGF-β mRNA levels were found to be elevated early in diabetic

nephropathy and to correlate with the patients' HbA1c levels. These data, along with the evidence showing that high glucose induced TGF-β production in cultured renal cells, strongly suggest that poor glycemic control is a key factor in inducing TGF-β in the diabetic kidney. In a recent elegant clinical study, Sharma and coworkers showed that the human diabetic kidney is a factory for producing TGF-β and releasing it into the circulation [8]. In contrast to normal kidneys that extract TGF-β from the blood, diabetic kidneys produce and release TGF-β into the renal veins, leading to elevated plasma and urinary levels in diabetic patients.

Another clinically fascinating aspect of TGF-β is the growing evidence of a complex and rich interaction between TGF-β and the renin-angiotensin system (RAS) in which both act at various points to regulate the actions of the other [reviewed in 9]. Conceptually, TGF-β and RAS act together in tissue injury as biological "911" molecules to maintain homeostasis and initiate repair. Indeed, not only do they engage in cross-talk, but they have broadly overlapping properties. For example, angiotensin II is being evaluated as a topical agent to enhance wound healing, and infusion of TGF-β into volume depleted rats produced vasoconstriction and acute renal failure. Indeed, the TGF-β induced overexpression of βig-3h in the diabetic kidney was not in the glomerulus, but in the vascular component of the juxtaglomerular apparatus and the *pars recta* of proximal tubules.

The interaction of the RAS and TGF-β has important clinical implications [9, 10]. Angiotensin II blockade reduces tissue levels of TGF-β in kidney and heart, and there is now a consensus that TGF-β is a key mediator of renal and cardiac fibrosis associated with activation of the RAS. In experimental and human kidney diseases, the protective effect of inhibition of the RAS correlates closely with a partial suppression of TGF-β production [9, 10]. This suggests that more complete suppression of TGF-β should be a therapeutic target in order to achieve a greater anti-fibrotic effect. There is evidence that this might be accomplished by using higher doses of drugs that block the RAS or entirely new drug strategies may be needed. In diverse disease models, suppressing TGF-β with neutralizing TGF-β antibodies, the proteoglycan decorin or other novel approaches has been shown to be therapeutic [1]. With the discovery of βig-h3 in the kidney, it joins a list of tissue markers of TGF-β bioactivity including: TGF-β, PAI-1, fibronectin EDA+, type I collagen and plasma or possibly urinary levels of TGF-β. One of more of these TGF-β markers could be used as a therapeutic measure of TGF-β suppression. The clinical application of a TGF-β marker along with a direct TGF-β antagonist combined with blockade of angiotensin II may prove to be synergistic and offer new hope to patients who suffer from fibrotic diseases such as diabetic nephropathy.

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