S 1. ROLE OF CYTOKINES IN PROGRESSIVE RENAL FIBROSIS

Wayne A. Border, M.D.

University of Utah Health Sciences Center, Salt Lake City, U.S.A.

We investigated whether transforming growth factor-B1 (TGF-β1) expression might underly development of progressive fibrosis in the kidney. We found that TGF-β1 expression and increased matrix production is transient and self-limited in nephritic glomeruli from rats with acute, reversible glomerulonephritis induced by a single injection of an antibody reactive with glomerular mesangial cells. In contrast, in rats given a second antibody injection, 1 week later, the glomerular expression of TGF-β1 mRNA and TGF-β1 protein remained elevated through 18 weeks and was associated with a large infiltration of mononuclear cells, with staining features of fibroblastic/myofibroblastic cells, strongly expressing TGF-β1 in the tubulointerstitium of the kidney. By 18 weeks kidneys from animals receiving 2 antibody injections showed glomerulosclerosis and tubulointerstitial fibrosis with striking deposition of collagens type I and III; wherease, kidney tissue from animals given 1 antibody injection was indistinguishable from normal control. The histological changes were accompanied by persistent proteinuria and elevated levels of blood urea nitrogen. Extracellular matrix markers of TGF-β1 activity, a special isoform of fibronectin, tenascin, biglycan and plasminogen activator inhibitor-1, were significantly elevated in kidneys undergoing fibrosis. There data suggest that sustained TGF-β 1 expression contributes to the development of progressive kidney fibrosis.