L 1. MOLECULAR PATHOGENESIS OF KIDNEY DISEASE

Wayne A. Border, M.D.

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

TGF-β, a multifunctional cytokine, plays an important role in embryogenesis and in regulating repair and remodeling following tissue injury. Many of the biological actions of TGF-β are mediated by widespread effects on deposition of extracellular matrix. TGF-β stimulates the synthesis of individual matrix components including proteoglycans, collagens and glycoproteins. TGF-β also blocks matrix degradation by decreasing the synthesis of proteases and increasing the synthesis of protease inhibitors. Finally, TGF-β increases the synthesis of matrix receptors and alters their relative proportions on the surface of cells in a manner that could facilitate adhesion to martix. All of these events have largely been demonstrated in vitro in cultured cells. In an experimental model of glomerulonephritis we have shown that TGF-β is responsible for the accumulation of pathological matrix in the gomeruli following immunologic injury. Furthermore, all three of TGF-β's actions on extracellular matrix: increased synthesis, decreased degradation and modulation of receptors have now been documented to be involved in matrix deposition in vivo in this model. Administration of the proteoglycan decorin suppressed TGF-β-induced matrix depostion in the nephritic glomeruli, thus confirming a physiological role for decorin as a regulator of TGF-β. Inhibitors of TGF-β may by important future drugs in treating fibrotic diseases caused by overproduction of TGF-β.