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The Role of Endothelial Cells in Renal Fibrosis

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Most forms of chronic renal disease tend to progress to tubulointerstitial fibrosis. The severity of tubulointerstitial changes is the best indicator of the progression of renal dysfunction. Injury to the renal microvasculature can be a important factor contributing to the progression of renal disease. In particular, injury to the peritubular capillary network of the kidney is a key factor in renal fibrosis. Renal ischemia caused by vascular obliteration may be a major contributor to renal scarring.

Renal tubulointerstitial fibrosis is a common feature in unilateral ureteral obstruction (UUO). In humans, chronic and acute ureteral obstruction can occur in various clinical situations. Therefore, UUO model is used as a renal interstitial fibrous disease. Recently, Ohashi et al. (J Am Soc Nephrol 13:1795, 2002) have suggested that peritubular capillary regression may contribute to tubulointerstitial scarring in the UUO model. Thus, endothelial cells play an important role in renal disease progression in the UUO kidney. Because renal microvasculature injury has beenshown to be an important mechanism in renal fibrosis, a growth factor or cytokine with an endothelial protective or angiogenic effect may have a beneficial role in renal fibrosis in the UUO model.

Angiopoietin-1 (Ang1) is a widely expressed ligand for the Tie2 tyrosine kinase receptor expressed on endothelial cells, and it regulates vascular growth, development, maturation, and permeability. Ang1 has potential therapeutic applications in inducing angiogenesis, enhancing endothelial cell survival, and preventing vascular leakage. It has been reported that Ang1 increases endothelial survival and has an anti-inflammatory effect (Circ Res 89:477, 2001; Circulation 101:2317, 2000). In kidney development Ang1 and Tie2 play roles in the maturation of glomeruli and the vasa rectae. In addition, Ang1 expression is increased in folic acid-induced nephrotoxicity. A soluble and potent Ang1 variant, COMP-Ang1, which is more potent than native Ang1 in phosphorylating Tie2 and signaling via Akt in primary cultured endothelial cells has been developed. Therapeutic application of Ang1 in kidney disease has not been studied.

We have investigated the protective effects of COMP-Ang1 on the renal fibrogenic process in unilateral ureteral obstruction model (Am Soc Nephrol 17:2474, 2006). Morphologic examination demonstrated less tubular injury and tubulointerstitial fibrosis in mice receiving COMP-Ang1 than vehicle-treated mice. COMP-Ang1 preserved renal renal endothelial cells and also decreased interstitial type I collagen and myofibroblast deposition. We also found that COMP-Ang1 treatment decreased monocytes/macrophages infiltration, tissue levels of TGF-1, and Smad 2/3 phosphorylationin obstructed kidney. These results suggested that COMP-Ang1 treatment can decrease the progression of renal fibrosis in unilateral ureteral obstruction. COMP-Ang1 can be a novel, endothelium-specific therapeutic modality in fibrotic renal disease.

Injury to the renal microvasculature may be a major factor in the progression of renal fibrosis, thus protection of endothelial cells in renal vasculature may have a therapeutic role in renal fibrosis.