The Cell Biology of Obstructive Nephropathy

Robert L. Chevalier, M.D.

University of Virginia, Charlottesville, Virginia, USA

Congenital obstructive nephropathy is one of the major causes of renal insufficiency in children.

1. Apoptosis and tubular atrophy

Using neonatal rodents, we have demonstrated that chronic unilateral ureteral obstruction (UUO) impairs renal growth and development by inhibiting cellular proliferation and stimulating apoptosis. Apoptosis in the obstructed kidney is stimulated by increased production of reactive oxygen species, sphingolipids (ceramide), and cytokines such as transforming growth factor-β1. UUO also reduces the renal production of inhibitors of apoptosis, such as bcl-2 and epidermal growth factor (EGF). We have reported recently that the administration of exogenous EGF or insulin-like growth factor (IGF-1) to neonatal rats with UUO markedly reduces tubular apoptosis and consequent tubular atrophy.

2. Renin

UUO significantly stimulates the recruitment of renin-producing cells, and the renal production of renin is greatly enhanced in the neonate compared to the adult. The increased angiotensin II produced in the neonatal kidney as a result of UUO suppresses renal cellular proliferation and stimulates apoptosis through the predominant AT2 receptors. In the neonatal obstructed kidney, through the activation of AT2 receptors, angiotensin II stimulates the renal production of clusterin, a glycoprotein that is likely protective against apoptosis. In contrast, in the adult, angiotensin inhibits the production of clusterin through the activation of the predominant AT1 receptors. This is an example of the markedly differing effects of UUO on the developing compared to the adult kidney.

3. Interstitial fibrosis

In addition to tubular atrophy, UUO induces progressive interstitial fibrosis of the ipsilateral kidney. The severity of interstitial fibrosis is aggravated by chronic dietary sodium depletion, a maneuver that reduces the intrarenal production of antioxidant enzymes. We have demonstrated that endogenous angiotensin stimulates TGF-β1, a fibrogenic cytokine, which in turn contributes to the progressive interstitial fibrosis of the obstructed kidney. Most recently, we have reported that the severity of interstitial fibrosis is directly related to the number of copies of functional angiotensinogen genes in the neonatal mouse with UUO. Thus, the evolution of interstitial fibrosis is quantitatively linked to the intrarenal production of angiotensin.

It is anticipated that further elucidation of the renal celluar responses to UUO in the developing kidney will lead to improved therapies for obstructive nephropathy, including gene therapy.