Cytokine and Growth Factor Expression in Remnant Kidney Model

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Many cytokines and growth factors have been implicated as important mediators of renal injury. The magnitude of gene expression of these factors in the remnant kidney, a model of renal injury, may depend on the remaining renal mass as well as the time period after renal ablation. To investigate the time dependent changes of gene expression after variable degrees of renal ablation, blocking of renin-angiotensin system (RAS) with angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist (AT1 RA), and endothelin receptor A antagonist, we measured the mRNA expression of MCP-1, IL-6 TNF-alpha, endothelin and TGF-beta in 1/6, 3/6 (uninephrectomy), 4/6 and 5/6 nephrectomized (NPX) Munich-Wistar rats by competitive RT-PCR. We sacrificed the animals at 3 days, 2, 4, 12 weeks after renal ablation. Systolic blood pressure (SBP) and 24 hour urine protein excretion rate (UprotV) were also measured at each time point. The magnitude of gene expression was determined by the ratio to beta-actin. SBP and UprotV of 4/6 and 5/6 NPX rats significantly increased at 2 weeks after surgery compared to Sham operated rats. These parameters of 1/6 NPX rats increased slightly only at 12 weeks after surgery. 3/6 NPX rats did not show any physiologic change. The expression of all the studied genes except iNOS was elevated throughout all the time point (3 days to 12 weeks) in 5/6 NPX kidney. In 4/6 NPX kidney, delayed increased expression of these genes was observed, and the extent of these increases was less than 5/6 NPX kidney at 12 weeks. 1/6 and 3/6 NPX kidnies showed a slight elevation of only TGF-beta mRNA compared to Sham-operated rats. ACEI and AT1 RA could suppress development of hypertension and proteinuria in 5/6 NPX rats for 12 weeks. Those treatments also prevented the expression of TGF-beta, MCP-1, endothelin, IL-6 and TNF-alpha in remnant kidny. However, endothelin receptor A antagonist could not suppress such gene expression significantly, although it decreased slightly the magnitude of proteinuria and hypertension in 5/6 NPX rats.

In conclusion, cytokines and growth factors such as MCP-1, TGF-beta, IL-6, TNF-alpha and endothelin contribute to the progression of renal injury from an early stage after excessive renal ablation. The suppression of RAS may slow progression of renal injury by favorable intrarenal hemodynamic effects and/or modulation of cytokine and growth factor gene expression. However, further studies about the non-hemodynamic effect of angiotensin II on the regulation of these gene expressions will be needed to address the role of RAS in the pathogenesis of progressive renal injury.