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Role of soluble guanylate cyclase in progressive renal fibrosis

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Pathological expansion of extracellular matrix proteins is a hallmark of acute and chronic kidney diseases. In both, matrix accumulation results from an orchestrated overexpression of the key profibrotic cytokine transforming growth factor(TGF)-β and subsequent increases in matrix protein production and decreases in matrix protein degradation. A critical role of soluble guanylate cyclase (sGC) and nitric oxide(NO)-dependent cGMP production for glomerular matrix expansion has recently been documented in acute anti-thy1 glomerulonephritis, a rat model of short-term acute, reversible glomerular TGF-β overexpression and matrix protein accumulation [1]. Subsequently, we have analyzed the renal activity of the NO-cGMP signaling cascade in and the effect of the specific sGC stimulator Bay 41-2272 on anti-thy1-induced chronic glomerulosclerosis (cGS), a long-term rat model with progressive fibrosis of the whole organ and progressive renal insufficiency [2].

Anti-thy1-induced chronic glomerulosclerosis was induced injection of anti-thy1 antibody into uni-nephrectomized Wistar rats. One week after disease induction, animals were randomly assigned to: cGS, cGS plus Bay 41-2272 (10 mg/kg body weight/d) or cGS plus hydralazine (15 mg/kg body weight/d).

After 16 weeks of treatment, systolic blood pressure was comparably decreased by both treatments. In the untreated cGS animals, expression of sGC mRNA and NO-stimulated cGMP production was up-regulated in the tubulointerstitium, while it was decreased in the glomeruli. Bay 41-2272 significantly increased glomerular and tubulointerstitial NO-cGMP signaling. This went along with marked reductions in glomerular and tubulointerstitial matrix accumulation and TGF-beta1 protein expression. Bay 41-2272 treatment reduced renal cell proliferation and infiltration with macrophages. In contrast, hydralazine did not affect significantly glomerular and tubulointerstitial NO-cGMP signaling, cell proliferation and infiltration as well as matrix protein expansion.

In conclusion, expression and activity of soluble guanylate cyclase is markedly up-regulated in tubulointerstitial fibrosis of anti-thy1-induced chronic renal fibrosis, while it is reduced in its persisting glomerulosclerosis. Specific stimulation of sGC signaling by Bay 41-2272 significantly limits the progressive course of this model towards tubulointerstitial fibrosis and impaired renal function at least partially in a manner independent of systolic blood pressure. Since progressive renal fibrosis is key to the common final pathway shared by most, if not all, chronic renal diseases, these novel findings may be well relevant for other progressive kidney disorders, such as diabetic and hypertensive nephropathy.

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