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Activation of the nitric oxide-cGMP signaling pathway precedes resolution in acute anti-thy1 glomerulonephritis

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Aim

Resolution of acute anti-thy1 glomerulonephritis by itself indicates an endogenous program of disease regression is operating. Given the renoprotective effects of the endothelial nitric oxide (NO)-cGMP pathway, the present study analyzed expression and activity of NO-cGMP signaling during a time course of acute anti-thy1 glomerulonephritis.

Methods

Rats with anti-thy1 glomerulonephritis were sacrificed at 0.5 and 1 day (injury), 5 and 10 days (matrix expansion) and 15 and 20 days (resolution) after OX-7 antibody injection. Measures of disease activity included glomerular matrix accumulation, transforming growth factor-beta1 (TGF-beta1) expression as well as glomerular platelet deposition, macrophage infiltration and cell proliferation. NO-cGMP signaling was characterized by measuring glomerular NO and cGMP production as well as glomerular mRNA expression of endothelial NO synthase (eNOS), inducible NOS (iNOS), alpha1 and beta1 soluble guanylate cyclase (sGC) and phosphodiesterase-5 (PDE-5). Results are expressed in relation to normal day 0 controls (=100%) (*$p < 0.05$ versus normal day 0 controls).

Results

In the injury phase, mesangial cell lysis was paralleled by markedly induced glomerular NO production (+673%*, iNOS expression +742%*), but loss of NO-stimulated glomerular cGMP production (-63%*) due to reduced alpha1 (-63%*) and beta1 sGC expression(-63%*). Disruption of NO-cGMP signaling was followed by marked increases in glomerular TGF-beta1 expression (+545%*), matrix accumulation (+187%*), platelet deposition (+5677%*), leukocyte infiltration (+513%*) and cell proliferation (+432%*) at day 5 (matrix expansion phase). Glomerular disease indicators returned towards normal at day 20. Resolution of glomerular matrix expansion was preceded by a significant up-regulation of NO-stimulated glomerular cGMP (+8860%*), alpha1 (+1459%*) and beta1 sGC (+972%*) and PDE-5 expression (+170%*) at day 5.

Conclusion

An activation of the NO-cGMP pathway precedes resolution of acute anti-thy1 glomerulonephritis. Enhancing NO-cGMP signaling, for instance by using activators of soluble guanylate cyclase or inhibitors of PDE-5, may serve as pharmacological approach for regressing tissue fibrosis in established kidney disease.