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Receptor guanylyl cyclase-G-deficient mice are protected against renal ischemia-reperfusion injury by preventing apoptosis and inflammation

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Background

Guanylyl cyclase-G (GC-G) is the last member of the receptor GC family which has so far been identified. However, the specific endogenous ligands, tissue distribution and function of GC-G remain largely unknown. Our studies in mice demonstrated by RT-PCR and immunohistochemistry that GC-G mRNA and protein are expressed in the kidney, specifically within renal tubular epithelial cells. To elucidate the renal functions of GC-G *in vivo*, we produced a new genetic mouse model with targeted disruption of the GC-G gene (GC-G$^{-/-}$). Because increased expression of GC-G mRNA was observed in response to ischemia-reperfusion (I/R), we studied renal function of GC-G$^{-/-}$ mice and their wild-type (WT) counterparts not only at baseline but also after I/R.

Materials and methods

WT and GC-G$^{-/-}$ mice were subjected to bilateral renal artery occlusion (45 min) followed by reperfusion (24 h). Markers for renal dysfunction, histopathology, apoptosis, and inflammation were evaluated.

Results

Under normal conditions, no apparent renal histological alterations were observed in GC-G$^{-/-}$ mice. However, I/R-induced renal dsyfunction, as evident by the elevation of serum creatinine and urea levels, was significantly attenuated in GC-G$^{-/-}$ mice compared with WT mice. Furthermore, genetic ablation of GC-G prevented tubular disruption, tubular cell apoptosis, and caspase-3 activation, which was accompanied by a marked reduction in neutrophil infiltration number, myeloperoxidase activity, or induction of proinflammatory cytokine interleukin (IL)-6 and adhesion molecule P-selectin in renal tissues under I/R in GC-G$^{-/-}$ compared to levels seen in WT mice. In addition, gel mobility shift assay demonstrated that nuclear factor (NF)-κB-promoter binding activity is markedly suppressed under renal I/R in GC-G-deficient mice compared to WT controls.

Conclusion

Together, our study demonstrates for the first time that GC-G may play critical apoptotic and inflammatory roles during I/R-induced acute renal failure. This knockout mouse provides an excellent model to further elucidate the signalling pathway and the (patho)physiological functions mediated by GC-G.