Disruption of guanylyl cyclase-G protects against acute renal injury

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摘要

Abstract

The membrane forms of guanylyl cyclase (GC) serve as cell-surface receptors that synthesize the second messenger cGMP, which mediates diverse cellular processes. Rat kidney contains mRNA for the GC-G isoform, but the role of this receptor in health and disease has not been characterized. It was found that mouse kidney also contains GC-G mRNA, and immunohistochemistry identified GC-G protein in the epithelial cells of the proximal tubule and collecting ducts. Six hours after ischemia-reperfusion (I/R) injury, GC-G mRNA and protein expression increased three-fold and remained upregulated at 24 h. For determination of whether GC-G mediates I/R injury, a mutant mouse with a targeted disruption of the GC-G gene (Gucy2g) was created. At baseline, no histologic abnormalities were observed in GC-G(-/-) mice. After I/R injury, elevations in serum creatinine and urea were attenuated in GC-G(-/-) mice compared with wild-type controls, and this correlated with less tubular disruption, less tubular cell apoptosis, and less caspase-3 activation. Measures of inflammation (number of infiltrating neutrophils, myeloperoxidase activity, and induction of IL-6 and P-selectin) and activation of NF-kappaB were lower in GC-G(-/-) mice compared with wild-type mice. Direct transfer of a GC-G expression plasmid to the kidneys of GC-G(-/-) mice resulted in a dramatically higher mortality after renal I/R injury, further supporting a role for GC-G in mediating injury. In summary, GC-G may act as an early signaling molecule that promotes apoptotic and inflammatory responses in I/R-induced acute renal injury.