Kidney injury accelerates cystogenesis via pathways modulated by heme oxygenase and complement.

AKI accelerates cystogenesis. Because cystogenic mutations induce strong transcriptional responses similar to those seen after AKI, these responses may accelerate the progression of cystic renal disease. Here, we modulated the severity of the AKI-like response in Cys1(cpk/cpk) mice, a model that mimics autosomal recessive polycystic kidney disease. Specifically, we induced or inhibited activity of the renoprotective enzyme heme oxygenase (HO) and determined the effects on renal cystogenesis. We found that induction of HO attenuated both renal injury and the rate of cystogenesis, whereas inhibition of HO promoted cystogenesis. HO activity mediated the response of NFκB, which is a hallmark transcriptional feature common to both cystogenesis and AKI. Among the HO-modulated effects we measured, expression of complement component 3 (C3) strongly correlated with cystogenesis, a functionally relevant association as suggested by Cys1(cpk/cpk) mice with genetically induced C3 deficiency. Because both C3 deficiency and HO induction reduce cyst number and cyst areas, these two factors define an injury-stimulated cystogenic pathway that may provide therapeutic targets to slow the formation of new renal cysts and the growth of existing cysts.

DOI 10.1681/ASN.2011050442