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Acute kidney injury induces disruption of cholangiocyte primary cilia via oxidative stress

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Objectives: Acute kidney injury (AKI) commonly causes remote hepatic injury. However, its molecular mechanisms and pathological changes remain to be defined. The primary cilium, an organelle that protrudes into the cell surface, is associated with the pathogenesis of various diseases. In the liver, cholangiocyte, an epithelial cell lining intrahepatic bile ducts, only has primary cilia. In chongiocytes, primary cilia sense stimulation and regulate bile secretion, and their defects are involved in various liver diseases. Recent studies have demonstrated that primary cilia shorten are shedding is associated with the progression of diseases, suggesting that primary cilia could be a new target for disease treatment. Therefore, in this study, we investigated whether AKI-induced hepatic injury is associated with the damage of cholangiocyte primary cilia.

Methods: *AKI is induced by bilateral kidney* ischemia and reperfusion (I/R) *in mice*. *Some mice were treated with* N-acetyl cysteine (NAC; a producer of antioxidant).

Results: Kidney I/R caused leukocyte accumulation in sinusoid and vacuolization in the hepatocytes, and increased BUN, ALT and AST concentration in plasma. In addition, kidney I/R resulted in the disruption of cholangiocyte cilia, and ciliary fragments were detected in bile. Kidney I/R decreased cystathione γ-lyase (CSE, a producing enzyme of H_2S which plays an antioxidant and cysteine which is a component of GSH) expression, H_2S, and total glutathione (tGSH) in the liver, and increased hydrogen peroxide level in liver and lipid peroxidation in the bile. NAC treatment attenuates those kidney I/R-induced hepatic injuries including the disruption of cholangiocyte cilia.

Conclusions: Data show for the first time that kidney I/R induces the disruption of cholangiocyte cilia in the liver and that these damages are associated with reduced CSE/H_2S/tGSH/oxidative stress/liver damage. These findings suggest that the cholangiocyte primary cilia could be a new therapeutic target in kidney I/R-induced hepatic injury.