2017

The Scaffolding Protein IQGAP1 Promotes Hepatic Proliferation and Protects the Liver from Injury

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Background: Bile acids (BA) are elevated in liver disease and are known liver tumor promoters. BAs induce expression of the scaffolding protein IQGAP1, which is overexpressed in numerous cancers. However, the contribution of IQGAP1 in BA-induced tumorigenesis is unknown.
Objective: To examine role for IQGAP1 in liver proliferation and tumor development.
Methods: Adult male WT and *Iqgap1*$^{-/-}$ mice were fed either a 1% cholic acid (CA) diet (mild) or a 0.1% 3,5-diethyoxycarbonyl-1,4-dihydrocollidine (DDC) diet (severe) for two weeks to study liver injury. Another cohort of mice were treated with 10 mg/kg diethylnitrosamine (DEN), a liver carcinogen, at 2 weeks and aged to 52 weeks. Serum and livers were collected for biochemical, histological, and gene expression analysis.
Results: CA and DDC treatments robustly induced hepatic IQGAP1 expression in WT mice and suggest a dose-effect. Importantly, loss of IQGAP1 did not alter BA metabolism, validating our previous data that IQGAP1 functions downstream of BAs. *Iqgap1*$^{-/-}$ mice fed CA diet showed reduced hepatic proliferation, whereas ectopic expression of IQGAP1 in *Iqgap1*$^{-/-}$ livers restored BA-induced proliferation. The DDC diet resulted in elevated serum BAs and total bilirubin, which was higher in *Iqgap1*$^{-/-}$ mice. Consistently, histological analysis revealed liver damage including increased inflammation and fibrosis along with increased BA accumulation in the livers of *Iqgap1*$^{-/-}$ mice.
Conclusion: The short-term role for IQGAP1 downstream of BA signaling includes controlling hepatic proliferation, maintaining biliary homeostasis and protecting against injury. Therefore, analysis of DEN-treated *Iqgap1*$^{-/-}$ mice with and without CA should reveal an important role for IQGAP1 in tumor promotion and initiation downstream of BA signaling.