A082 Loss of β-Catenin Increases α-Naphthylisothiocyanate-Induced Mortality and Cholestatic Liver Injury

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Introduction: Cholestasis is an intractable liver disorder that results from impaired bile flow. Bile acids consequently build up in the liver, causing hepatic injury, biliary fibrosis, and eventual liver failure. We have recently shown that mice with surgically induced cholestasis by bile duct ligation (BDL) exhibited less severe liver damage in the absence of β-catenin, the effector of the Wnt signaling pathway. Therefore, we hypothesized that loss of β-catenin would also protect mice from exposure to α-naphthylisothiocyanate (ANIT), a xenobiotic that causes biliary damage and intrahepatic cholestasis. **Methods:** ANIT was administered for one or two weeks to compare the response of mice with liver-specific knockout (KO) of β-catenin to wild type (WT) mice during cholestasis. Serum biochemistry was measured and liver tissue examined for histology (H&E), fibrosis (Sirius red), ductular response (A6), and inflammation (CD45). **Results:** We found that unlike after BDL, the presence of β-catenin was protective against ANIT, as KO mice had a significantly lower survival rate than WT mice. Interestingly, however, serum markers of liver damage were not significantly different between KO and WT mice after 1 week or 2 weeks of ANIT. Total liver bile acid levels were also equivalent between WT and KO at all time points. Histologically, WT livers had more biliary infarcts than KO starting at 1 week of ANIT; however, KO livers showed sinusoidal dilatation without evidence of occlusion. Sirius red staining showed mild to moderate portal fibrosis in WT while in KO livers concentric fibrosis around bile ducts were observed as early as 1 week after ANIT. Immunohistochemistry for A6, a biliary marker, showed that KO bile ducts were dilated and contained enlarged atypical ductular cells after 1 week, whereas WT ducts appeared relatively normal. Finally, in WT, inflammation was localized to the portal triads and infarcts, whereas in KO inflammatory cells also invaded the parenchyma. **Conclusions:** KOs displayed increased fibrosis, ductular response, and diffuse inflammation after ANIT compared to WT, which likely contributed to mortality. Future studies will uncover the mechanisms underlying increased susceptibility to ANIT in the absence of β-catenin.