

Asbt Vivo-Morpholino Reduces Hepatic Inflammation And Fibrosis And Alters Bile Acid Composition In Cholestatic Mice

Background: Primary Sclerosing Cholangitis (PSC) is characterized by increased ductular reaction (DR), biliary senescence, liver fibrosis, and mast cell (MC) infiltration. $Mdr2^{-/-}$ mice, model of PSC, mimic some features of PSC. In PSC there is (i) increased total bile acid (TBA) levels, (ii) dysregulation of BA synthesis and (iii) higher cholangiocyte expression of the apical sodium bile acid transporter (ASBT). Hydrophobic BAs enhance cholestasis and ASBT expression. Ileal inhibition of ASBT has been shown to reduced cholestatic damage in $Mdr2^{-/-}$ mice, murine model of PSC. No information exists to demonstrate if blocking hepatic and ileal ASBT inhibits subsequent liver damage in $Mdr2^{-/-}$ mice. **Methods:** 12 wk male FVBN/J (WT) and $Mdr2^{-/-}$ mice were treated with control or ASBT Vivo-Morpholino (2 injections, 12.5 mg oligo/kg BW via tail vein for 1 wk). Liver damage was determined by H&E and serum enzyme levels. Ductular reaction (DR) and inflammation were evaluated by immunohistochemistry (IHC) for CK-19 and F4/80 in liver. ASBT expression was measured by immunofluorescence (IF) and IHC in liver and ileum. Hepatic fibrosis was determined by Fast Green/Sirius Red staining and qPCR. BA composition was measured in liver and feces in all groups by LCMS. Fecal samples were collected for microbiome composition analysis. Spheroids containing isolated cholangiocytes from healthy and PSC patients, immortalized mast cells, and immortalized hepatic stellate cells were generated. ASBT expression and histamine secretion were measured in spheroids. **Results:** $Mdr2^{-/-}$ mice with Control Vivo-Morpholino have increased large DR, hepatic fibrosis, inflammation, and hepatic TBA levels, which decrease in $Mdr2^{-/-}$ ASBT Vivo-Morpholino mice. Inhibition of ASBT in WT and $Mdr2^{-/-}$ mice reduced biliary and intestinal ASBT expression and fecal TBA levels. PSC spheroids displayed increased ASBT expression and histamine secretion compared to healthy control. **Conclusion:** Elevated TBA levels seen in PSC lead to altered intestinal BA transport and increased biliary ASBT, which alters the BA pool. Vivo-Morpholino inhibition of hepatic and ileal ASBT blocks hepatic damage and alters BA composition. Further, PSC spheroids show increased ASBT expression and histamine secretion indicating crosstalk between mast cells and damaged cholangiocytes during cholestasis. Total ASBT inhibition may provide a novel therapeutic strategy for the management of PSC.