

Histamine Increases Hepatic and Intestinal Mast Cell Activation and Regulates Bile Acid Signaling During PSC

Vik Meadows¹, Debjyoti Kundu¹, Vincent Zhou², Lindsey Kennedy², and Heather Francis²

¹Department of Biochemistry and Molecular Biology, ²Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

Background: Primary sclerosing cholangitis (PSC) is characterized by ductular reaction (DR), impaired bile flow, altered bile acid (BA) composition and increased histamine (HA) levels/mast cell (MC) activation. Master BA regulator, Farnesoid X receptor (FXR), is dysregulated in PSC patients altering intestinal BA transport via apical sodium BA transporter (ASBT) leading to irritable bowel disease (IBD). MCs secrete HA; catalyzed by L-histidine decarboxylase (HDC). *Hdc*^{-/-}/*Mdr2*^{-/-} (DKO) mice exhibit reduced DR, hepatic fibrosis, and total BA (TBA) compared to *Mdr2*^{-/-} mice. Biliary BA toxicity is reduced via expression of fatty acid binding protein (FABP6). MCs and cholangiocytes both express FXR and ASBT and secrete fibroblast growth factor (FGFs), which are elevated in cholestatic liver disease and involved in BA enterohepatic circulation.

Aim: To investigate HA regulation and MC activation of BA circulation and signaling during PSC.

Methods: 16 wk old wild-type (WT), *Mdr2*^{-/-} (PSC model) and DKO mice, treated with exogenous NaCl or HA via osmotic minipump for 1 month, were used in this study. Serum, liver and small intestine was collected from all groups. Serum and hepatic TBA, chenodeoxycholic acid (CDCA) and cholic acid (CA) were measured in all groups. FXR and biliary BA transporter (ASBT) expression were measured by qPCR in total liver and by immunofluorescence (IF), co-stained with CK-19 to mark bile ducts. Intracellular biliary BA binding protein was assessed by IF for FABP6, co-stained with CK-19. Serum and hepatic FGF15 was measured by EIA and IF, co-stained with CK-19. Intestinal MC activation (chymase, tryptase and FcεR1α) was measured in small intestine via qPCR and IHC.

Results: *Mdr2*^{-/-} mice had elevated (i) serum and hepatic TBA, CDCA and CA, (ii) serum FGF15, (iii) hepatic FXR and (iv) biliary FABP6 compared to WT, which were reduced in DKO mice. Exogenous HA increased all these parameters in DKO mice compared to WT and DKO. Biliary ASBT increased in *Mdr2*^{-/-} compared to WT, whereas these were reduced in DKO mice. DKO + HA had increased BA transporter expression compared to DKO. There was increased MC presence and BA transporter expression in small intestine of *Mdr2*^{-/-} compared to WT and DKO. Exogenous HA increased intestinal BA transport and MC activation markers in DKO mice.

Conclusion: MCs infiltrate the intestine and liver during cholestatic liver disease and lead to increased hydrophobic BA and TBA pool, FGF15 secretion, increased enterohepatic BA circulation and biliary BA cholehepatic shunting. Inhibition of MC activation may provide therapeutic intervention for patients with PSC and IBD co-morbidities.