A032 Bile Acids Modulate Colonic MAdCAM-1 Expression in a Murine Model of Combined Cholestasis and Colitis

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Introduction: Primary Sclerosing Cholangitis (PSC) is a progressive cholestatic liver disease of unknown etiology that carries a strong association with inflammatory bowel disease (IBD). PSC-associated IBD (PSC-IBD) displays a unique colitis phenotype characterized by right side predominant inflammation and an increased risk of colorectal cancer compared to non-PSC-IBD. Although the initiation/progression PSC-IBD remains unclear, evidence supports an integral role for the gut-specific mucosal vascular addressin cell adhesion molecule (MAdCAM-1) in modulating both hepatic and intestinal inflammation. Multidrug resistance protein 2 (Mdr2) knockout mice develop spontaneous cholestatic liver injury mirroring human PSC. To elucidate mechanisms of PSC-IBD, we combined Mdr2-/- mice with the chemically inducible model of DSS colitis (Mdr2-/-/DSS). We hypothesize that alterations in bile acids promote mucosal inflammation in this murine model of combined cholestasis/colitis*. There are currently no good models for PSC-IBD, thus our objective is to develop a murine model mimicking PSC-IBD for studying the gut-liver axis and proinflammatory crosstalk.* **Methods:** Mice were fed 1.5% DSS for 5 days and recovered for 4 days. Transformed sinusoidal endothelial cells (TSECs) were treated with 5 ng/ml of TNF-α and/or 100μM of ursodeoxycholic acid (UDCA). UDCA treated mice were fed 0.5% UDCA fortified chow for 2 weeks prior and throughout DSS course. **Results:** Mdr2-/- mice displayed marked alterations in intestinal bile acid composition and significantly increased susceptibility to DSS colitis (based on weight loss, disease activity index, histology, intestinal permeability, and inflammatory cytokines). Mdr2-/- mice also displayed an upregulation of colonic MAdCAM-1 expression compared to colitis controls. *In vitro* work utilizing TSECs revealed that MAdCAM-1 was potently induced by TNF-α and that this induction was significantly attenuated by co-treatment with UDCA. *In vivo*, DSS-treated Mdr2-/- mice fed with UCDA fortified chow demonstrated significant attenuation of colitis susceptibility and decreased colonic MAdCAM-1 expression as compared to standard chow controls. **Conclusions:** These findings suggest a unique interplay between alterations in bile acid homeostasis and intestinal MAdCAM-1 expression in modulating pro-inflammatory crosstalk along the gut-liver axis and identify intestinal bile acid signaling as a potential therapeutic target for the treatment of PSC-IBD.