Investigating the Liver Disease Phenotype in IL-10 Knockout Mice Treated with DDC as a Novel Model for IBD-Associated Primary Sclerosing Cholangitis

Anna Schwarz[1,2], Ramesh Kudira PhD[1], Alexander Miethke MD[1]

[1]Division of Pediatric Gastroenterology, Hepatology and Nutrition; General Clinical Research Center; Cincinnati Children's Hospital Medical Center; [2]University of Cincinnati College of Medicine

Introduction

Primary sclerosing cholangitis (PSC) is a chronic disease that involves autoimmune inflammatory bile duct injury progressing to liver failure. To date, the sole curative treatment is liver transplant. Approximately 70% of PSC patients have Inflammatory Bowel Disease (IBD). PSC-IBD is characterized by progressive biliary strictures, liver fibrosis, pancolitis, and rectal sparing. Current mouse models of PSC do not accurately demonstrate this phenotype. PSC-IBD models are needed for therapeutic development.

Hypothesis

We hypothesize IL10KO mice fed a diet admixed with 0.05% of xenobiotic DDC better recapitulate the PSC-IBD phenotype. Specifically, we will compare large bile duct injury and hepatic fibrosis to a standard PSC model of wild-type (WT) mice treated with DDC.

Methods

13 IL10KO and 14 WT male mice were divided into four groups. Mice were fed either a control diet, 7-day 0.05% DDC diet, 14-day 0.05% DDC diet, or 14-day 0.05% DDC diet followed by 28-day control diet. After harvesting, gross images of bile ducts were captured. Bile ducts and livers were sectioned and stained with H&E or Sirius Red for histopathological analysis and morphometry. Colorimetric assays measured Serum liver biochemistries, and hepatic cytokine responses were quantitated via Taqman-based qPCR.

Results

IL10KO mice demonstrated shorter colon lengths compared to WT mice, consistent with colitis. Serum total bilirubin, ALT, and ALP levels increased upon challenge with DDC, but did not differ between both genotypes. Qualitative review of Day 7 and 14 IL10KO/DDC bile ducts showed cystic dilatations and strictures not seen in WT/DDC bile ducts. DDC-treated livers showed periductal inflammatory infiltrate. Sirius Red quantification of 14+28 livers showed significantly increased liver fibrosis in IL10KO compared with WT mice (percent fibrosis: 1.4% vs 0.9% in IL10KO vs WT, $p<0.05$). These findings were corroborated by upregulation of comparative 14+28 IL10KO mRNA expression for *TIMP1* and *aSMA* by 1.6- and 3.1-fold, respectively ($p<0.05$).

Conclusions

The IL10 KO with 0.05% DDC mouse model shows promise for recapitulating the PSC-IBD phenotype as it shows large bile duct damage, which is currently lacking in existing animal models of PSC. Mechanisms by which IL10KO mice promote progressive liver fibrosis following toxic bile induced epithelial injury require further investigation.

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