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Cholestasis induced intestinal dysbiosis augments liver disease in a murine model of primary sclerosing cholangitis

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Background & Aims: A growing body of evidence highlights the pivotal role of intestinal dysbiosis and gut-liver crosstalk during progression of alcoholic and non-alcoholic fatty liver disease. Despite the striking association between human cholestatic liver disease and inflammatory bowel disease, the functional implications of the intestinal microbiota and the inflammasome mediated innate immune response for cholestatic liver disease remain elusive. In this context, we investigated the functional role of gut-liver crosstalk and NLRP3 inflammasome activation for cholestatic liver disease using the murine Mdr2 knockout ($Mdr2^{-/-}$) model resembling human primary sclerosing cholangitis (PSC).

Methods: Male $Mdr2^{-/-}$, $Mdr2^{-/-}$ crossed with hepatocyte-specific deletion of capsase-8 ($Mdr2^{-/-}$/$Casp8^{Dhepa}$) and wildtype (WT) control mice were housed for 8w or 52w respectively to characterize the impact of Mdr2 deletion on liver and gut including bile acid and microbiota profiling. A comprehensive analysis of NLRP3 inflammasome and caspase activation in the gut-liver axis was performed. To functionally block caspase activation, a pan-caspase inhibitor (IDN-7314) was administered.

Results: $Mdr2^{-/-}$ mice displayed significantly increased serum liver function tests (LFTs) compared to WT controls and developed progressive periportal fibrosis. The bile acid composition in $Mdr2^{-/-}$ mice was associated with an altered intestinal microbiota composition. This was linked to an impaired intestinal barrier, including colonic mucus layers, reduction of tight junction expression and increased permeability evidenced by an in-vivo FITC-dextran assay. Intestinal dysbiosis in $Mdr2^{-/-}$ mice prompted increased translocation of endotoxin and augmented the hepatic innate immune response. Mechanistically, pronounced hepatic NLRP3 inflammasome activation via caspase 1 triggered neutrophil infiltration and caspase-3, - 8 and -9 mediated apoptotic cell death. However, by introducing $Mdr2^{-/-}$/ $Casp8^{Dhepa}$ animals the $Mdr2^{-/-}$ phenotype could not be rescued indicating that hepatocytic caspase-8 activation is a downstream consequence and dispensable for the inflammatory response. Strikingly, IDN-7314 dampened inflammasome activation and ameliorated liver injury as evidenced by significantly improved LFTs, periportal inflammation as well as bile duct proliferation and serum bile acid profile.

Conclusions: Our data demonstrate that Mdr2 associated cholestasis triggers intestinal dysbiosis. In turn, translocation of endotoxin in the portal vein and subsequent NLRP3 inflammasome activation contribute to higher liver injury. This process can be blocked by pancaspase, but not hepatocytic caspase-8 inhibition.

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