PS-004

The gut-liver axis is essential for disease progression in the Mdr2−/− mouse model of primary sclerosing cholangitis

L. Liao[1,2], K.M. Schneider[1], M. Frissen[1], T. Strowig[3], H.-U. Marschall[4], A. Wahlström[5], G. Eric[3], A. Mohs[1], P. Jin[1], J. Jung[1], J. Reissing[1], H. Sun[1], C. Elfers[1], V. Bieghs[1], F.J. Cubero[6], C. Trautwein[1]. *[1]University Hospital, Department of Internal Medicine III, Aachen, Germany; [2]Renji Hospital, Shanghai Jiao Tong University, Department of Pain Management, Shanghai, China; [3]Helmholtz Centre for Infection Research, Braunschweig, Germany; [4]University of Gothenburg, Wallenberg Laboratory, Gothenburg; [5]University of Gothenburg, Wallenberg Laboratory, Gothenburg, Sweden; [6]Complutense University School of Medicine, Department of Immunology, Madrid, Spain*
Email: liaolijunxiao@gmail.com

Background and Aims: Primary sclerosing cholangitis (PSC) is strongly associated with inflammatory bowel disease. The gut-liver axis plays a critical role in PSC onset and progression. However, the functional implications of intestinal microbiota and inflammasome mediated innate immune response for PSC is unclear. Here, we investigated gut-liver crosstalk and NLRP3 inflammasome activation in the murine Mdr2 knockout ($Mdr2^{-/-}$) model resembling PSC.

Method: $Mdr2^{-/-}$, WT control mice, $Mdr2^{-/-}/Casp8^{\Delta hepa}$ and $Mdr2^{-/-}/Casp8^{f/f}$ were housed for 8w or 52w. Only male mice were used in this study. The relevance of Mdr2 deletion on liver injury as well as gut microbiota and bile acid profile were studied. NLRP3 inflammasome and caspase activation in the gut-liver axis were comprehensively analyzed. Pan-caspase inhibitor (IDN-7314) was treat to block caspase activation, and the effect of IND-7314 on gut-liver axis was detected.

Results: $Mdr2^{-/-}$ mice displayed significantly increased serum transaminases and liver peridutular inflammation compared to WT mice. $Mdr2^{-/-}$ liver was characteristic presenting a strong induction of apoptotic cell death, progressive bile duct proliferation and periportal fibrosis development over time (52 weeks). The abnormal 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 urged increased translocation of endotoxin and bacterial, further augmented the hepatic innate immune response. Mechanistically, enhanced hepatic NLRP3 inflammasome activation via caspase-1 triggered macrophage and neutrophil infiltration and caspase-3, -8 and -9 mediated apoptotic cell death. However, by introducing $Mdr2^{-/-}/Casp8^{\triangle hepa}$ 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, a pan-caspase (IDN-7314) dampened inflammasome activation and ameliorated liver injury, periportal inflammation, serum bile acid profile as well as intestinal dysbiosis.

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