including primary biliary cirrhosis. IL-17 related cytokines have multiple effects on parenchymal cells in different tissues and may be involved in both effector responses and repair and regeneration. We recently reported increased numbers of liver infiltrating IL-17 secreting CD4 and CD8 T cells in chronic inflammatory liver disease. These cells also secrete IL-21 and IL-22 cytokines reported to promote epithelial repair. In the present study we report the pattern of IL-17, IL-21 and IL-22 receptor expression on hepatic parenchymal cells and demonstrate cell-specific effects of T_{h17} cytokines on these target cells.

Aim To assess the functional impact of Th17/Tc17 associated cytokines on hepatic parenchymal cells.

Method Primary human cholangiocytes, hepatocytes and sinusoidal endothelial cells were assessed for IL-17, IL-21 and IL-22 receptor expression. The effects of stimulation with recombinant IL-17, IL-21, IL-22, TNF-a or IFN-g alone or in combination were compared on apoptosis, proliferation and cytokine secretion using flow cytometry with annexin or 7-AAD staining and in situ Ki67 staining and measurement of IL-1b, IL-6, IL-23 and TGF-b1 secretion by ELISA.

Results All the parenchymal cell types expressed IL-21R and IL-22R. Th17 and Tc17 cytokines did not cause apoptosis but alone and in combination led to parenchymal cell proliferation. Cholangiocytes and hepatocytes responded best to IL-17, whereas sinusoidal endothelial cells were responsive to IL-22. Cholangiocytes responded to Th17/Tc17 cytokines by secreting high levels of IL-1b, IL-6, IL-23 and TGF-b1 all cytokines that support the survival of Th17 and Tc17 cells.

Conclusion Liver parenchymal cells express IL-17, IL-21 and IL-22 receptors and proliferate in response to Th17/Tc17 cytokines. Cholangiocytes also respond to such cytokines by secreting Th17 polarising cytokines. Thus IL-17 related cytokines secreted by infiltrating lymphocytes may activate the epitheliome to generate a local environment characterised by cholangiocyte proliferation and Th17 cell survival. This response may contribute to the bile duct proliferation and persistent chronic inflammation that characterised many liver diseases.

P99 FXR STIMULATION WITH INT-747 IN A RAT BILIARY DRAINAGE MODEL PROTECTS FROM HEPATOCELLULAR INJURY AFTER LOSS OF ENTEROHEPATIC CIRCULATION

doi:10.1136/gutjnl-2011-300857a.99

[1 2]R G J Visschers, [1 2]K V K Koelfat, [1 2]C M Hodin, [2 3]R Shiri-Sverdlov, [1 2]W A Buurman, [4]R Mookerjee, [1 2]K Lenaerts, [1 2 5]S W M O Damink. *[1]Department of Surgery, Maastricht University Medical Centre+, Maastricht University, Maastricht, the Netherlands; [2]Nutrition and Toxicology Research Institute Maastricht, Maastricht University, the Netherlands; [3]Department of Molecular Genetics, Maastricht University Medical Centre+, the Netherlands; [4]UCL Hepatology, Royal Free Hospital, University College London, London, UK; [5]Department of HPB Surgery and Liver Transplantation, Royal Free Hospital, University College London, London, UK*

Introduction Enterocutaneous fistula are often associated with development of intestinal failure associated liver disease (IFALD), ultimately leading to liver damage. We hypothesise that this is caused by reduced farnosoid X receptor (FXR) stimulation, due to interruption of the enterohepatic circulation and consequent impact on bile acid synthesis.

Aim We aimed at investigating the effect of specific stimulation of the farnosoid X receptor (FXR) with INT-747, a synthetic agonist, in a rat biliary diversion model.

Methods Four groups of rats (n=6–8) were studied; two groups underwent bile duct cannulation and externalisation to achieve continuous biliary drainage, daily receiving either vehicle or INT-747 (Intercept Pharm LtD); two groups underwent laparotomy without cannulation also receiving either vehicle or INT-747. Loss of bile was recorded daily. After 7 days, plasma, serum and liver and intestinal tissue were collected. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), γ glutamyl transpeptidase (GGT) and total bilirubin were assessed, together with histological scoring of necrosis, inflammation, bile duct proliferation, fibrosis and steatosis. Expression of genes involved in the FXR pathway, and lipid and cholesterol metabolism were quantified by qPCR.

Results Loss of bile was significantly reduced in the INT-747 group compared to the vehicle group. Serum levels of ASAT, ALAT, AP, GGT, bilirubin (total and direct) were all significantly increased in the bile drainage group when compared to controls ($p<0.05$), suggesting hepatocellular damage. Interestingly, all parameters were significantly decreased in the bile drainage group receiving INT-747 ($p<0.05$). Histological analyses showed normal liver histology in both sham groups. In contrast, large necrotic areas were observed in the biliary diversion group receiving vehicle with a high number of infiltrating inflammatory cells, which decreased significantly in the biliary diversion group receiving INT-747 ($p<0.05$). Biliary diversion induced hepatic fibrosis and bile duct proliferation, which were both attenuated by INT-747 supplementation ($p<0.05$). Although genes involved in the FXR pathway (FXR, SHP, CYP7A1 and CYP8B1) were influenced by bile drainage, no significant change was observed when rats received INT-747.

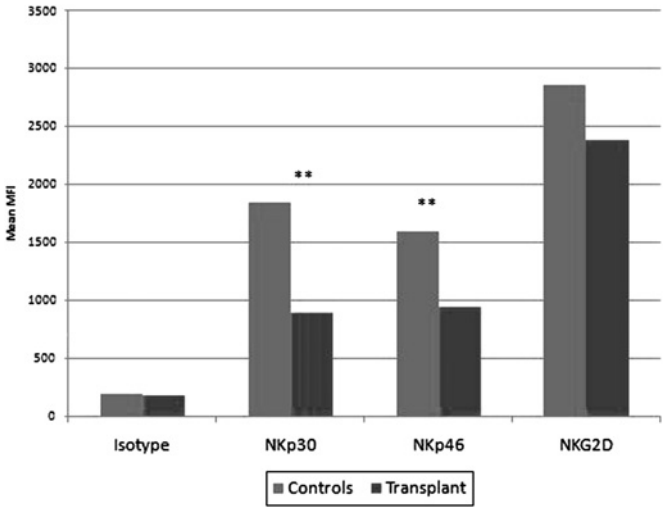
Conclusion The present data demonstrate that stimulation of FXR with INT-747 can attenuate hepatocellular damage in an experimental model of IFALD. The results suggest a role of FXR in the development of hepatocellular damage, hepatic fibrosis and necrosis during biliary diversion. FXR stimulation has the potential to be a novel therapy for patients with IFALD.

P100 LIVER TRANSPLANTATION (LT) RESULTS IN REDUCED RECIPIENT NATURAL KILLER (NK) CELL ACTIVATION WITH ASSOCIATED DOWN REGULATION OF ACTIVATING RECEPTORS NKP30 AND NKP46 BUT NOT NKG2D

doi:10.1136/gutjnl-2011-300857a.100

[1]K M Jamil, [1]K S Cheent, [2]K Agarwal, [3]G J Alexander, [2]M A Heneghan, [1]S I Khakoo. *[1]Imperial College London; [2]King's College Hospital, London; [3]Addenbrookes Hospital, Cambridge*

Introduction In solid organ transplantation, the effect of the allograft on recipient NK cell function is poorly understood. NK cells recognise self through inhibitory receptors for HLA class I, so that they



Abstract P100 Figure 1 Expression of activating receptors on NK cells.

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