



Abstract PTU-029 Figure 1

Conclusion Using a non-invasive MRI protocol, we have measured haemodynamics in four compartments contemporaneously in cirrhosis. The detection of significant changes in early cirrhosis, suggests this technique has potential to (a) study the evolution of portal hypertension with accompanying changes in splanchnic, renal and systemic circulation as well as (b) assess the haemodynamic response to novel therapeutic agents in cirrhosis.

Competing interests None declared.

REFERENCE

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PTU-030 SELECTIVE GUT DECONTAMINATION REDUCES HEPATIC EXPRESSION OF TOLL-LIKE RECEPTOR (TLR) 4 AND DEVELOPMENT OF CIRRHOSIS BUT DOES NOT PREVENT DEVELOPMENT OF HEPATOCELLULAR CARCINOMA (HCC)

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Introduction Recent studies suggest that TLR4 inhibition may prevent fibrosis in murine models. Chronic antigenic stimulation due to increased bacterial gut translocation leads to upregulation of hepatic TLR4 and this may lead to fibrosis, cirrhosis and HCC. The aims of this study were to determine whether gut decontamination with Norfloxacin prevents cirrhosis and HCC in rodent model of cirrhosis and HCC.

Methods 18 Fisher rats divided into three groups; 1st treated with DEN and NMOR (carcinogens). 2nd was treated with the same carcinogens + Norfloxacin from the beginning to 14 weeks (end of experiment). 3rd group was control. H&E, reticulin and Immunohistochemistry were done also liver function and TNF- α were measured.

Results All the rats in 1st and 2nd groups developed HCC, the severity of which was not different between groups. With reticulin stain there was significantly reduced fibrosis in the group treated with Norfloxacin (score: 1 (0–2)) compared with the untreated group (score: 4 (3–5)) ($p < 0.03$). The expression of TLR4 in both carcinogen groups in the background liver was significantly greater than control rats but lower in the Norfloxacin group compared with the untreated group ($p < 0.0016^{**}$). No difference in TLR4 expression was observed in the HCC nodules in both groups. There was a reduction of ALT ($p < 0.05$) and AST ($p < 0.01$) in the Norfloxacin treated comparing to DEN and NMOR group. There was a also reduction of TNF- α level in the Norfloxacin treated group.

Conclusion The results of this study suggest that selective decontamination of the gut may be a novel strategy to prevent cirrhosis probably by inhibiting hepatic TLR4 expression. In this model of cirrhosis and HCC, reduction of hepatic TLR4 does not prevent development of HCC suggesting that the mechanisms of its development are unrelated to severity of fibrosis and TLR4 related mechanisms.

Competing interests None declared.

PTU-031 DOWNREGULATION OF THE VITAMIN B₁₂ RECEPTOR IN FIBROLAMELLAR CARCINOMA OF THE LIVER: THE FIRST CONSISTENT MOLECULAR ABNORMALITY

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Introduction Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare tumour of young adults that is characterised by the presence of large tumour cells with strongly eosinophilic cytoplasm, surrounded by fibrous lamellae, in the absence of chronic liver disease. No consistent molecular abnormalities have been detected to date but an elevation of serum vitamin B₁₂ binding capacity has been described.

Methods Up to 80% of vitamin B₁₂ (cobalamin), is stored in the liver after endocytosis via the transcobalamin receptor (CD320). We hypothesised that disruption to the transcobalamin receptor (hereafter referred to as CD320) might render the liver locally B₁₂ deficient and elicit a compensatory production of the serum B₁₂ binding protein (TCN1). We sought a functional mutation of CD320 in 15 cases of FLHCC and 30 cases of conventional hepatocellular carcinoma (HCC), 10 cases with cirrhosis (C-HCC) and 20 cases with no cirrhosis (NC-HCC) acting as control tissues. cDNA was synthesised using RNA purified from formalin fixed paraffin embedded (FFPE) tissues and primers were designed to amplify the region spanning exon2/3 across the mutation site.

Results Sequencing analysis showed ~5% (1/18) mutation in NC HCC. However, 60% (9/15) of the FLHCC cohort did not show any amplification while 80% of NC-HCC (16/20) and C-HCC (8/10) tumours tested positive. The quality of purified mRNA was verified by amplifying for two different housekeeping genes, tubulin and β -glucuronidase. To determine the reason for non-amplification of CD320exon2/3, we sequenced the promoter and promoter regulator region of CD320 using DNA purified from FFPE tissue. Comparison of the sequences of CD320 (+) and (-) representative samples showed no difference in their DNA sequence. Methylation analysis of the methylation sensitive promoter regulator region of NC-HCC, and FLHCC showed a correlation between the level of methylation and CD320 suppression in NC-HCC but not for FLHCC. To address this discrepancy, a second region of CD320, spanning exon3/4 was amplified. Interestingly, all the FLHCC samples were positive giving an amplification product for this region. Immunostaining for CD320 was in agreement with the exon 3/4 amplification data.

Conclusion Taken together, these results indicate that the expression of a non-functional splice variant (variant 2), which lacks the crucial triple glutamic acid repeat within the exon 2 necessary for the receptor's function, may contribute to the increased serum Vitamin B₁₂ binding capacity in FLHCC.

Competing interests None declared.