OWE-014 WHOLE TRANSCRIPTOME SHOTGUN SEQUENCING REVEALS SIGNIFICANT UPREGULATION OF COLONIC MUCOSAL IMMUNE-MEDIATED ANTI-MICROBIAL MECHANISMS IN PSC-UC

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Introduction Primary sclerosing cholangitis is a hepatobiliary disorder of unknown aetiology that is commonly associated with ulcerative colitis (PSC-UC). We have previously demonstrated that patients with PSC-UC have significant alterations in their gut microbiota compared to patients with UC alone and healthy controls. The mechanisms by which these alterations influence pathogenesis is unclear.

Methods Shotgun sequencing was performed on whole transcriptomic libraries of colon biopsies obtained from 10 patients with PSC-UC and 10 healthy controls. Differential gene expression analysis with false discovery rate correction was performed with limma and edgeR. In addition lamina propria mononuclear cells were analysed by multicolour flow cytometry.

Results The colonic transcriptome of patients with PSC-UC demonstrated 6774 significantly differentially expressed genes compared to healthy controls. Gene expression in PSC-UC clustered separate to healthy controls on multidimensional scaling ($p=0.006$). Gene enrichment analysis revealed 280 significantly altered biological processes. PSC-UC was characterised by an overexpression of processes associated with regulation of anti-microbial immune responses compared to healthy controls ($p<0.0001$). These immunological responses were enriched with pathways associated with innate, cell-mediated and humoral immunity, autophagy, complement activation and chemokine signalling ($p<0.0001$). Expression of genes associated with microbial handling including defensins, mannose receptors and anti-microbial peptides were significantly upregulated in PSC-UC. Paired CD4 T cell immunophenotyping of colon biopsies revealed a significant increase in the population of Th17 cells and IL-17 producing cells in PSC-UC in comparison to healthy controls (18.6% vs 8.5%; $p=0.0007$ 8.5% vs 5.6%; $p=0.005$ respectively).

Conclusion We have for the first time demonstrated the colonic mucosal transcriptional response in PSC-UC. In comparison to healthy controls, patients with PSC-UC have highly significant expression of genes associated with overrepresentation of multiple immunological processes, many of which are directed against bacteria. Consistently patients with PSC-UC have a significant increase in colonic mucosal Th17 and IL-17 cell population compared to healthy controls.

OWE-015 PROSTAGLANDIN E2 MEDIATES INNATE IMMUNE SUPPRESSION IN ACUTE-ON-CHRONIC LIVER FAILURE VIA THE EP4 RECEPTOR

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Introduction Bacterial infection is a major cause of hospital admission in liver cirrhosis and patients are highly prone to nosocomial infection. Innate immune dysfunction is strongly implicated in these patients.

We showed prostaglandin E2 (PGE₂) was markedly increased in those patients that demonstrated an immune-suppressive phenotype(1). However, using NSAIDs to reduce PGE₂ production is contraindicated due to renal side effects. We aimed to investigate PGE₂ downstream signalling pathways to identify a potential druggable target to reverse immune dysfunction in acute-on-chronic liver failure (ACLF).

Methods Peripheral whole blood of healthy volunteers (HV) and ACLF patients was studied. Plasma was analysed for cytokine and PGE₂ levels.

Blood was stimulated *ex vivo* with combinations of lipopolysaccharide (LPS, 1 ng/ml), PGE₂ (1 ng/ml) and EP2/EP4 receptor blockers for 4 hours. Supernatants were analysed for cytokines. qPCR using Taqman primers was used to assay PGE₂ production, enzymes and cell receptors (EP1-4).

Results ACLF patients (mean MELD score 19) were assessed. PGE₂ levels in plasma were significantly increased between HV (163.9 pg/ml) and ACLF (563.8 pg/ml). ACLF patients showed a marked increase in inflammatory cytokines, including IL-1b, IL-6, IL-8, IL-10 and TNF. *Ex vivo* stimulation of whole blood with LPS produced significantly lower levels of TNF in ACLF blood (2.178 ng/ml) vs HV (6.649 ng/ml). This was matched by IL-6 production (12.256 ng/ml vs 4.492 ng/ml). This was further reduced by addition of exogenous PGE₂. Blockade of the EP4 receptor *completely* reversed reduction in both TNF and IL-6, while EP2 blockade had no effect. qPCR of the EP receptors and PGE₂ synthetic enzymes from monocytes and neutrophils from ACLF patients, showed changes in receptor profile and enzymatic machinery used to produce PGE₂. These changes were confirmed by Western Blot.

Conclusions ACLF patients are at great risk of morbidity and mortality due to infection caused by multi-factorial immune dysfunction. We have demonstrated that they have a pro-inflammatory cytokine profile, but an immune-fatigued response to inflammatory stimulus, which mirrors the phenotype seen in the clinic. PGE₂ is significantly raised in these patients, however NSAID use is not possible due to risk of renal dysfunction. We demonstrated that PGE₂ causes immune dysfunction exclusively via activation of the EP4 receptor and blockade of this receptor restored immune function. EP4 blockade has been shown to have a safe renal profile and we suggest this is a valid target for future immune therapy in ACLF.