samples. In fact, UC patients displayed higher levels of eukaryotic Hepadnaviridae transcripts by comparison with both Ctrl ($p = 0.004$) and CD patients ($p = 0.0001$), indicating this viral family to specifically characterise UC virome in the early stage of the disease. In contrast, CD patients showed higher levels of Hepeviridae by comparison with Ctrl ($p = 0.002$), suggesting this eukaryotic family as a candidate triggering stimulus in CD patients. Interestingly, Hepadnaviridae in UC negatively correlated with Polyadnaviridae and Tymoviridae ($R^2 = -0.25$, $p < 0.00001$; $R^2 = -0.11$, $p < 0.00001$), whereas in CD Hepeviridae negatively correlated with Virgaviridae ($R^2 = -0.25; p < 0.00001$), indicating that, in IBD-specific viromes, some viral entities prevail over others. Finally, these results were validated in a separate cohort of patients.

Conclusions: Our results indicated that specific eukaryotic viral infections occurring in both early UC and CD patients may underlie IBD aetiogenesis. Further analysis demonstrating the role of these viruses in triggering intestinal inflammation may open new frontiers in early IBD therapy exploiting specific antiviral drugs to control intestinal inflammation.

DOP017
Increased intestinal aryl hydrocarbon receptor expression and pathway sensitivity in Crohn’s disease

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Background: The aryl hydrocarbon receptor (AHR) is a transcription factor activated by dietary and bacteria-derived ligands. In mice, AHR signalling regulates specialised intestinal immune cell survival and function and activating AHR improves outcomes in diverse models of colitis. AHR gene variants are associated with susceptibility to IBD but little is known about the role of AHR in the human intestine. AHR directly regulates expression of cytochrome p450 enzymes (CYP1A1 and CYP1B1). In this study, we identify colonic cell populations responsive to AHR ligands and use quantitative assessment of CYP enzyme expression to compare resting AHR pathway activity and AHR ligand responsiveness in health (HC) and Crohn’s disease (CD).

Methods: Cells expressing AHR protein were visualised using both multicolour confocal microscopy of tissue sections and cytospin preparations of isolated cells. Expression of AHR and regulated genes was determined by qRT-PCR of cells isolated from endoscopic biopsies and purified by MACS or FACS sorting. Functional AHR signalling was determined by expression CYP1A1 in sorted cell populations cultured with AHR ligand (FICZ 10–100 nM) and/or antagonist (CH223191 100 μM).

Results: Expression of CYP1A1 was detected in snap-frozen whole biopsy tissue suggesting activation of the AHR pathway in vivo. AHR expression and a functional AHR pathway was detected in leukocytes (CD45+), epithelial cells (EpCAM+), stroma cells (EpCAM−, CD31−) and primary cultured fibroblasts but not endothelial cells in both HC and CD. AHR expression was significantly higher in CD45+ and CD45− cells from patients with CD compared with HC. AHR-dependent CYP1A1 expression was detectable in freshly isolated CD45+ and CD45− cells in the absence of stimulation but could be further upregulated upon exposure to ligand in vitro. There was a direct correlation between AHR expression and resting CYP1A1 expression. CD45− cell CYP1A1 expression in response to FICZ was significantly higher in CD compared with HC (Figure 1).

Conclusions: This is the first demonstration of a functional AHR pathway in both immune and non-immune cell populations in the human intestine in health and IBD. Our results suggest basal AHR pathway activity in vivo. Crohn’s disease associated changes in AHR expression and function may represent changes in cell populations, intestinal ligand exposure or sensitivity in the pathway. A better understanding of the role of AHR in diverse intestinal cells, will inform the use of ligands as potential therapeutic agents in IBD.

DOP018
Baseline ILC1 distribution in blood predicts response to ustekinumab in patients with refractory Crohn’s disease

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Background: Innate lymphoid cells (ILCs) are recently identified immune cells with a high cytokine producing capacity at mucosal barriers. In patients with active Crohn’s disease (CD), a shift in is observed from homeostatic ILC3s towards pro-inflammatory ILC1s in the intestines. Ustekinumab (UST), targeting the IL-12/23 shared p40 subunit, was recently approved by FDA and EMA for treatment of moderate-to-severe CD. As IL-12 and IL-23 play distinct roles in the plasticity of ILC1 and ILC3s, we studied the effect of ustekinumab on ILC populations in blood.

Methods: We included 46 CD patients (68% female, median age 42) refractory to anti-TNF therapy and vedolizumab with a median Simplified Endoscopic Score (SES-CD) of 16.5, initiating UST (6 mg/kg IV at induction, followed by subcutaneous UST 90 mg q8w thereafter). Blood samples were prospectively collected before start and at 4, 8 and 24 weeks. Endoscopic response was assessed at week 24, and defined as a >50% SES-CD decrease. ILCs were studied in isolated flow cytometry.

Results: Patients with ($n = 6$) and without ($n = 40$) endoscopic response at week 24 had a similar inflammatory burden, reflected by similar median faecal calprotectin (1800 vs. 1225 μg/g, $p = 0.44$) and C-reactive protein (23.9 vs. 10.3 mg/l, $p = 0.10$) levels at baseline. Though, baseline endoscopic activity was much higher in patients
responding to UST, compared with non-responders (median SES-CD 22 vs. 14, \( p = 0.02 \)). Baseline contribution of ILC1s in the total ILC pool was significantly lower in responders compared with non-responders before start of therapy (7.39% vs. 16.90%, \( p = 0.017 \)) (Figure 1A). In contrast, ILC2s were elevated in responders as compared with non-responders at baseline (70.1% vs. 40.8%, \( p = 0.02 \)) (Figure 1B). There was no significant difference in NCR-ILC3s \( (p = 0.12) \). After week 4 treatment a significant increase in NCR-ILC3 frequency was observed as compared with baseline independent of response \( (p < 0.001) \). This trend persisted at 8 weeks \( (p = 0.02) \) but could no longer be observed after 24 weeks \( (p = 0.19) \).

Conclusions: This study is the first to show how biological therapy impacts ILC populations in peripheral blood. Increased levels of ILC1s in peripheral blood at baseline may be a predictive biomarker for non-response to UST. Non-response may be explained by an increased reservoir of pro-inflammatory ILC1s in the circulation which can migrate towards the gut to annihilate treatment effects. Validation is needed in a larger and independent cohort with inclusion of biopsies. Overall these findings may guide individualised selection of biological agents in Crohn’s disease, and provide mechanisms of primary (non-)response to UST.

DOP Session 3: Old and new immunomodulators

DOP019

Immunomodulators reduce the risk of surgery and hospitalisation in Crohn’s disease in a prospective European population-based inception cohort: the Epi-IBD cohort

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Abstract DOP019 – Figure 1. Prevalence of treatments for Crohn’s disease patients on any given day during follow-up.