and 52d) during food re-introduction (FR). Microbiome was assessed by 16s rRNA gene sequencing of the V4 region performed on the MiSeq (Illumina). Community structure was resolved at 97% similarity operational taxonomic unit (OTU). Short chain fatty acids (SCFA) were quantified with gas chromatography and are expressed in µmol/g. Faecal calprotectin (FC) was measured using the CALPROLAB0170 (ALP) (Lysaker, Norway) ELISA kit. Continuous data are present as mean and standard deviation unless otherwise stated.

Results 66 CD patients were recruited (Female 25; age 13.4 yr). Clinical remission (wPCDAI<12.5) was achieved in 41 (62%). During EEN there was an increase in Shannon diversity (start: 0.3 [0.22] vs 30d EEN: 0.48 [0.2], p<0.001; vs 56d EEN: 0.43 [0.27], p=0.05). During FR these indices did not change.

Based on β-diversity dispersion analysis, estimated using Bray-Curtis distance, EEN induced clear alterations to the microbiome. Permutation ANOVA was used to identify significant changes to the microbiome during EEN. Most of the change that occurred was apparent within the first 4 weeks of treatment with R2: 4.7%, (p=0.001) and by the end of EEN R2: 3.2%, (p=0.001).

In patients to enter remission using EEN, we observed a quick reversion in the microbiome composition to that of pre-treatment (p=0.23).

Assessing the metabolic activity of the microbiome we observed a significant decrease in the concentration of acetate (start: 423.6 [183.6], end: 224.9 [101.5]; p< 0.001), propionate (start: 93.8 [50.6], end: 55.7 [27.3]; p< 0.001) and butyrate (start: 95.0 [64.2], end: 41.0 [50.7]; p< 0.001). During FR, there was a rapid reversion in levels of acetate and propionate (acetate EEN end: 224.9 [101.5] vs 17d FR: 362.4 [179.7]; p=0.003; propionate EEN end: 55.7 [27.3] vs 17d FR: 93.0 [46.9]; p=0.002).

Faecal calprotectin significantly decreased during EEN (start: 1402.4 [586.3]; 4wk EEN: 877.5 [593.1], p<0.001; 8wk EEN: 720 [664], p<0.001) and was quickly reversed during food re-introduction (17d FR: 1025 [603], p=0.025; 52d FR: 1105 [651], p=0.003)

Conclusions EEN induces specific effects on faecal microbiome and markers of functional activity. This is characterised by a reduction in metabolic activity during EEN, with reversion to pre-EEN state during food re-introduction paralleling an elevation of faecal calprotectin

013 REGULATION AND ROLE OF ALPHAE INTEGRIN IN MIGRATION AND RETENTION OF LYMPHOCYTES IN INTESTINAL MUCOSA

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Introduction Targeting integrins that mediate adhesion and migration of lymphocytes to the gastrointestinal (GI) tract is an effective therapy in inflammatory bowel disease (IBD). α4β7 and α4β1 are expressed on circulating lymphocytes that may mediate inflammation, while αEβ7 integrin is expressed primarily on a subset of T cells within the mucosa. Etrolizumab is a humanized monoclonal antibody that selectively binds the β7 subunit of the α4β7 and αEβ7 integrin heterodimers. The relative role of individual integrin heterodimers in lymphocyte migration and retention in the GI tract remains to be characterized.

Methods pSMAD3, MAdCAM, VCAM and ICAM levels were measured in colonic and ileal biopsies. α4β7+ and α4β7- human T cells were induced to express αE integrin by TGF-β 1 stimulation followed by qPCR array gene expression analysis. A murine photo-convertible reporter system was used to determine the effect of blockade of α4β7 and/or αEβ7 integrins on lymphocyte migration and retention. T cell-epithelial cell interactions were evaluated using intravital two-photon microscopy.

Results pSMAD3 was observed in the epithelium and lamina propria in IBD biopsies, suggesting active TGF-β signalling. Adhesion molecule expression was increased in inflamed biopsies. TGF-β1 stimulation induced αE integrin expression on both α4β7+ and α4β7- circulating T cells. αEβ7+ cells derived from α4β7+ and α4β7- progenitors had similar cytokine, chemokine, transcription factors and effector molecule gene expression. In a mouse model of T cell migration, combined blockade of both α4β7 and αEβ7 with anti-β7 (etrolizumab surrogate) led to a greater reduction of T cell accumulation in the intestinal mucosa and epithelium compared to single blockade of either α4β7 or αEβ7. Further intravital two-photon microscopy and photo-specific labelling experiments revealed that blockade of αEβ7 reduces T cell:epithelial cell interactions, increases the migratory speed of activated T cells in the intestinal mucosa, and facilitates effector T cell egress from the intestinal mucosa through lymphatic vessels.

Conclusions αEβ7 is induced by TGF-β1 on both α4β7+ or α4β7- T cells. Co-blockade of α4β7 and αEβ7 together leads to greater inhibition of T cell accumulation in gastrointestinal tissues through a stepwise inhibition of T cell migration and subsequent tissue retention.

014 WHOLE BLOOD PROFILING OF T-CELL DERIVED MIRNA ALLOWS THE DEVELOPMENT OF PROGNOSTIC MODELS IN IBD

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Introduction There is an unmet need for blood-based biomarkers that help predict disease and its course at inception to allow tailoring of treatments, achieve early mucosal healing and improve clinical outcomes. In our study, we explore the clinical utility of miRNAs in Inflammatory bowel disease (IBD).

Methods A 2-stage prospective multi-centre case control study was performed. Small RNA sequencing was performed on a discovery cohort of immunomagnetically separated leucocytes (90 CD4+ & CD8+ T-lymphocytes and CD14+ monocytes)

from 32 patients (9 CD, 14 UC, 8 healthy controls) to identify differentially expressed cell-specific miRNAs.

Top miRNAs were then validated in whole blood in 294 treatment naïve newly diagnosed IBD and non-IBD patients (97 UC, 98 CD, 98 non-IBD) using RT-qPCR, recruited across 5 centres in UK and Europe. Phenotype and outcome data were collected and cox proportional hazards were derived to assess the contribution of each miRNA to disease outcomes; defined as the need for 2 or more immunosuppressants and/or surgery after initial disease remission. RT-qPCR target miRNA relative quantification were calculated using $2-\Delta\Delta Cq$ method.

Results Each leucocyte subset (30 CD4+ T-cells, 28 CD8+ T-cells and 32 CD14+ monocytes) was analysed between disease and controls, adjusting for age, gender and batch effects. A total of 3 miRNAs differentiated IBD from controls in CD4+ T-cells including miR-1307-3p (False discovery rate (FDR) p=0.01), miR-3615 (p=0.02) and miR-4792 (p=0.01); these signals being UC specific. In CD8 T-cells, miR-200b-3p was the only differentially expressed miRNA and no CD14+ signals were seen.

Three miRNAs were validated in whole blood in an independent multi-centre cohort of 294 patients using RT-qPCR. miR-1307-3p predicted IBD(1.55 fold change (fc),IQR: 1.00–1.87; $p=2.77\times10^{-5}$),in particular UC (1.69 fc, IQR:1.01–2.00; $p=1.56\times10^{-6}$). Similarly, miR-3615 and miR-4792 were up-regulated in UC compared to controls (1.21fc, IQR:0.91–1.48; $p=8.26\times10^{-4}$and 1.91 fc, IQR: 0.81–2.56; $p=9.21\times10^{-3}$ respectively).There was no correlation with conventional inflammatory markers.

Follow up data were available on 195 IBD patients of which 80 patients required treatment escalation over a median time of 371 days (IQR: 140–711).miR-1307-3p was able to predict disease course in IBD (HR 1.98, IQR:1.20–3.27;log-rank $p=1.80\times10^{-3}$), in particular CD (HR 2.81; IQR: 1.11–3.53, $p=6.50\times10^{-4}$). In UC, both miR-3615 (HR 3.34, CI:1.43–7.78, p=0.01) and miR-4792 (HR 3.96, CI:1.65–9.52; $p=2.11\times10^{-3}$) predicted treatment escalation.

Conclusion We have identified unique CD4+ T-cell miRNAs that are differentially regulated in IBD. These blood-based miRNAs are able to predict treatment escalation at disease inception and have the potential for clinical translation.

015 EVOLUTIONARY CHARACTERISTICS OF NEOANTIGENS IN INFLAMMATORY BOWEL DISEASE AND COLORECTAL CANCER

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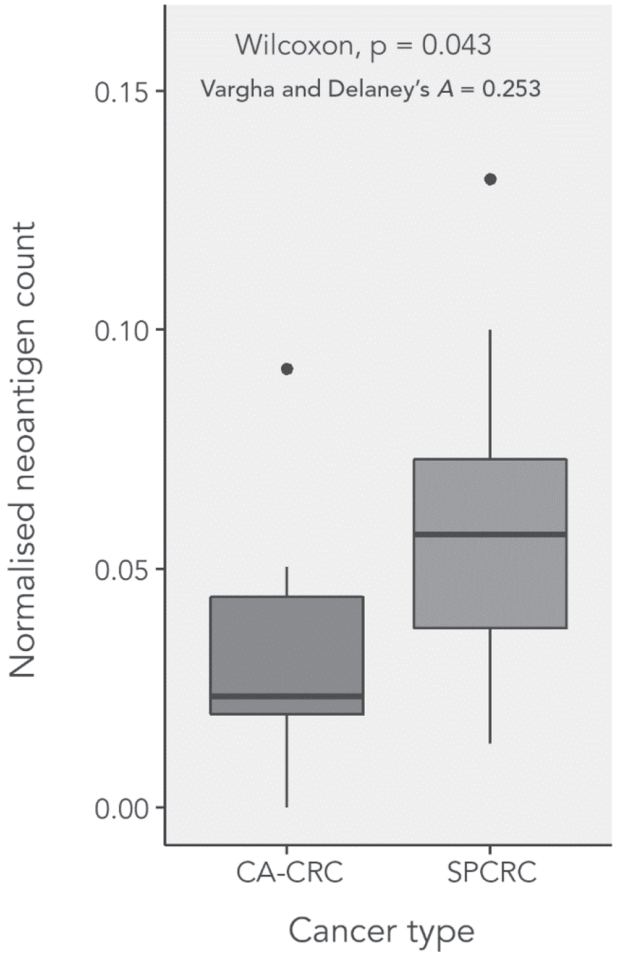
Introduction The immune system plays an active role in fighting growing tumours via recognising tumour-specific neoantigens and initiating an immune response. Consequently, the abundance and diversity of tumour neoantigens is shaped by the interaction with immune cells. Colonic mucosa in patients with inflammatory bowel disease (IBD) has a high immune cell presence, and we hypothesised this would cause increased immune predation on neoantigen-bearing epithelial cells. To test this, we compared neoantigen burdens in ulcerative colitis-associated colorectal cancers (CA-CRCs) and sporadically arising colorectal cancers (SPCRCs).

Methods Existing multi-region whole-exome and whole-genome sequencing data[1] [2] from CA-CRCs (n=15) and SPCRCs (n=10) was used to computationally predict the abundance and diversity of immunogenic neoantigens using NeoPredPipe.[3] Variant call data was filtered to retain high confidence variants. Neoantigen burden was compared between groups using a normalised measure, representing the proportion of non-synonymous mutations predicted to produce ≥1 immunogenic neoantigen. Multi-region data from normal, histologically normal adjacent-to-tumour (NAT) and tumour samples was used to calculate the clonality and subclonality of neoantigens.

Results The neoantigen burden of CA-CRCs was lower than SPCRCs (figure 1). Excluding cancers with microsatellite instability, CA-CRCs had relatively higher numbers of subclonal neoantigens per clonal neoantigens (p=0.029, Wilcoxon test), suggesting a greater degree of intra-tumour heterogeneity in CA-CRCs. In a subset of patients with CA-CRCs, 50–100% of clonal neoantigens found in tumour samples were shared with NAT samples in the same patient, revealing evidence of field cancerisation at the neoantigen level.

Conclusions These novel results support the hypothesis of increased immune surveillance in CA-CRCs compared to SPCRCs. Subclonal neoantigens accrue following immune escape, and so the higher burden of subclonal neoantigens in CA-CRCs points to the early evolution of effective immune



Abstract O15 Figure 1 Comparison of neoantigen burden between CA-CRCs and SPCRCs