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 from CA-CRCs (n=15) and SPRCRCs (n=10) was used to computationally predict the abundance and diversity of immunogenic neoantigens using NeoPredPipe. 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 SPRCRCs (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 SPRCRCs. 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 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 (SPSRCRs).

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-DDCq 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=2.77×10^-9), in particular UC (1.69 fc, IQR:1.01–2.00; p=1.56×10^-10). Similarly, miR-3615 and miR-4792 were up-regulated in UC compared to controls (1.21 fc, IQR:0.91–1.48; p=8.26×10^-4 and 1.91 fc, IQR: 0.81–2.56; p=9.21×10^-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=1.80×10^-3), in particular UC (1.69 fc, IQR:1.01–2.00; p=1.56×10^-10). 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=2.11×10^-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.

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Abstract 015 Figure 1 Comparison of neoantigen burden between CA-CRCs and SPRCRCs

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References


Abstract O16 COMBINED IMPACT AND RESISTANCE TRAINING IN ADULTS WITH STABLE CROHN’S DISEASE: PROTECT RANDOMISED CONTROLLED TRIAL

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Introduction Reduced bone mineral density (BMD) and muscle dysfunction are complications of Crohn’s Disease (CD). This study evaluates the effect of exercise on BMD and muscular function in adults with CD.

Methods This was a randomised, parallel-group and assessor-blind trial (Trial registration: BRCNTRN11470370). Adults (>16 years) in clinical remission or with a mildly active CD (Crohn’s Disease Activity Index <220; Faecal Calprotectin <250 mcg/g) were recruited from The Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK. Eligible patients were randomly allocated (1:1) to receive either a 60-minute, thrice-weekly, 6-month progressive impact and resistance training programme with usual care or usual care only, stratified by gender and disease activity using a computer based programme. Primary outcomes were BMD, (lumbar spine (L2-L4), femoral neck, total hip, greater trochanter) and muscle function parameters at 6 months in the intention-to-treat population, with analyses adjusted for baseline values, gender and disease status.

Results Between February 2018 and March 2019, 76 patients were assessed for eligibility, of whom 47 patients were recruited and randomised (68% female; mean age 49.3 [SD 13.0] years) to the exercise intervention (n= 23) or control (n=24). 6-month follow up data were recorded for 43 (91%) of 47 participants. At 6 months, BMD values were superior in the exercise group at the lumbar spine (adjusted mean difference 0.036 g/cm², 95% CI 0.024 to 0.048; p<0.001) and femoral neck (0.018 g/cm², 0.001 to 0.035; p=0.039), but not at the greater trochanter (0.013 g/cm², -0.019 to 0.045; p=0.415). Muscular function parameters were also superior in the exercise group: grip strength (8.3 kg, 6.2 to 10.5; p<0.001), 30-seconds bicep curl test (7 reps, 5 to 8; p<0.001), 30-seconds chair stand test (4 reps, 3 to 6; p<0.001), isokinetic knee extension strength at angular velocities of 60°/s and 180°/s and isokinetic elbow flexion strength at angular velocities of 60°/s and 120°/s (all p<0.001). Three exercise-related adverse events were recorded: light-headedness (n=2) and nausea (n=1).

Conclusions Progressive impact and resistance training is a safe and effective method to enhance BMD and muscular function in adults with CD and should be considered as a therapeutic option for the preservation of bone and muscle parameters. Due to the small sample size, further larger-scale studies are warranted.

Abstract O17 Multi-centre Validation of UC-Care: A Cancer Risk Prediction Tool for Colitis-associated Low Grade Dysplasia

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Introduction Ulcerative colitis (UC) patients diagnosed with low grade dysplasia (LGD) are at increased risk of developing high grade dysplasia (HGD) and colorectal cancer (CRC); together termed advanced neoplasia (AN). We aimed to develop and validate a predictor of AN risk in UC-LGD patients and create a visual risk communication web-tool.

Methods We performed a retrospective multi-centre cohort study. Adult UC patients with an index diagnosis of LGD were identified in four UK tertiary centres between 2001 and 2018. Patients were followed until progression to AN or censoring. Data from a single centre (n=248) was used as a discovery cohort, and Cox proportional hazards regression was performed to create a multivariate risk prediction model based on endoscopic features. The model was then validated on the pooled cohort of patients from the 3 external centres (n=201).

Results In the discovery cohort, the 4 clinical variables that were significantly associated with future AN progression and were included in our final multivariate model were: Presence of endoscopically-visible LGD lesion > 1 cm (HR = 2.8; 95% CI 1.3–6.0; p=0.008), incomplete endoscopic resection of index LGD (HR = 2.9; 95% CI 1.3–6.9; p=0.009), moderate/severe histological inflammation in the 5 years before...