Background Tumor immune evasion is an important hallmark of cancer. The roles of long non-coding RNAs (lncRNAs) in the process of cancer immunosurveillance remain largely unknown. In this study, we aimed to identify oncogenic lncRNAs that are involved in the immunosuppression of esophageal squamous cell carcinoma (ESCC) and investigate underlying mechanisms.

Methods High-throughput sequencing and bioinformatics analysis were used to identify lncRNAs that are highly expressed in ESCC tissues and blood. Using the data from a cohort of patients in the clinical trial JSOO1, the relationship between lncRNA expression level and PD-1 mAb response (ORR and DCR) was analyzed. RNA interference and CRISPR-Cas9 were used to explore the functional roles of the lncRNA. In vivo, the human PBMC engrafted humanized xenograft model was established to assess the therapeutic responses of that specific lncRNA inhibitor and its combination with PD-1 mAb.

Results Increased expression of LRTIS was observed in ESCC and was correlated with poor prognosis. Conversely, LRTIS high expression group responded better to immunotherapy (ORR 19.56% vs 9.09%, DCR 54.35% vs 18.18%). In vivo, LRTIS knockout significantly inhibited tumor growth in Hu-PBMC mice, and increased sensitivity to PD-1 mAb treatment, as shown by an increased proportion of IFN-γ+CD8+ T cells in xenografts. LRTIS could inhibit the expression of immuno-checkpoints such as PD-L1, PD-L2 and IDO1. Mechanistically, LRTIS was directly associated with MLL1 and significantly affected MLL1 stability by inhibiting its ubiquitination and subsequent proteasomal degradation. LRTIS competitively bonded to MLL1 preventing ASB2 from binding to MLL1, which explained MLL1 ubiquitination inhibition. Knocking out LRTIS, resulted in MLL1 mediated H3K4me decrease in the promoter region of immuno-checkpoints, causing their down-regulation. Clinically, dysregulation of LRTIS-MLL1-PD-L1 axis could also be observed in patients.

Conclusions The LRTIS plays an essential role in ESCC immunosuppression by binding to and stabilizing MLL1. This study identified a novel immuno-checkpoint regulating lncRNA and revealed a novel mechanism underlying lncRNA-mediated cancer immuno-microenvironment remodeling. Translational studies further implicated that LRTIS is a promising prognostic biomarker for cancer immunotherapy, and a potential target for immunotherapy.

Basic hepatology

IDDF2020-ABS-0166

NOVEL MIRNA-BASED DRUG CD5–2 REDUCES LIVER TUMOUR GROWTH IN DIETHYLNITROSAMINE (DEN)-TREATED MICE BY NORMALISING TUMOUR VASCULATURE AND ALTERING IMMUNE INFILTRATE

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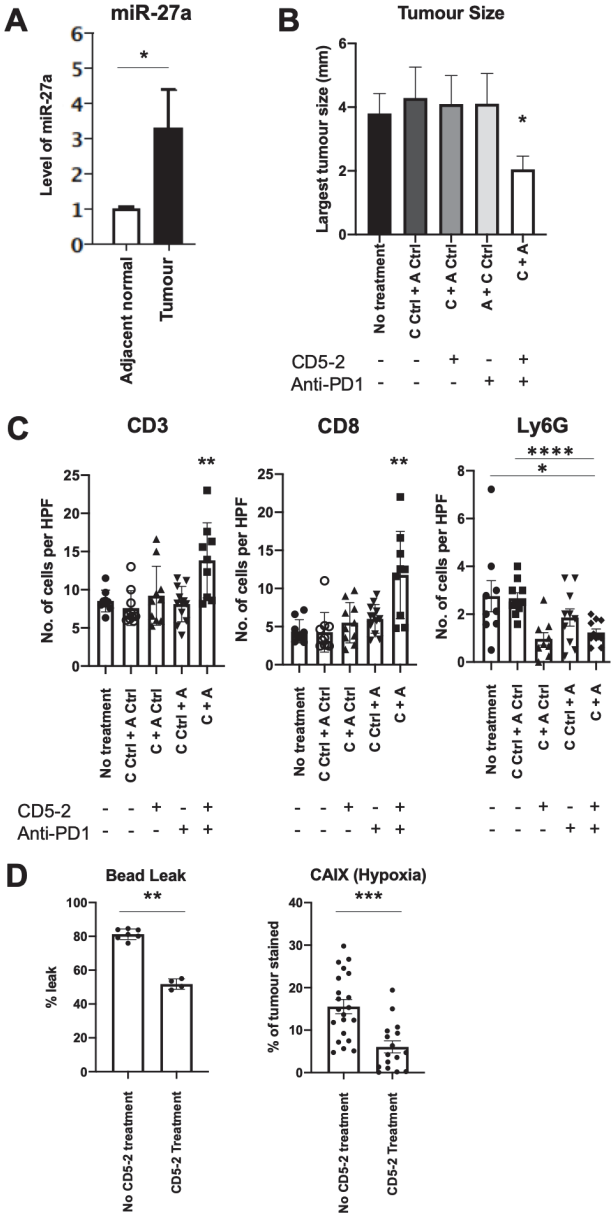
Background Hepatocellular carcinomas (HCC) exhibit abnormal (leaky) vasculature, hypoxia and an immunosuppressive microenvironment. The normalisation of tumour vasculature is an emerging approach to treat many cancers. Blockmir CD5-2 is an oligonucleotide-based inhibitor of the miR-27a interaction with VE-Cadherin, the endothelial specific cadherin. We previously showed CD5-2 normalises tumour vasculature by increasing VE-Cadherin expression (Zhao *et al*. Cancer Res. 2017). We studied the effect of CD5-2 combined with checkpoint inhibition on liver tumour growth, vasculature and immune infiltrate in the DEN-induced mouse model.

Methods DEN was given (25 mg/kg intraperitoneally) to male C57BL/6 mice at postnatal day 14. CD5-2 (30 mg/kg intravenously fortnightly) and/or anti-PD1 antibody (250µg intraperitoneally every 4 days) with their respective controls (4 groups) were given to the mice from age 7-months until harvest at age 9-months. Livers from treated and untreated mice were analysed.

Results We analysed human HCC data from The Cancer Genome Atlas and found high miR-27a and low VE-Cadherin were both associated with poorer survival (Log-Rank $P=0.02$ and $P=0.01$, respectively). In untreated mice, miR-27a



Abstract IDDF2020-ABS-0166 Figure 1

expression was significantly increased in tumours compared to adjacent normal tissue (figure 1A). Mice treated with CD5-2 + anti-PD1 antibody had significantly smaller tumours (50% reduction) compared to mice treated with either agent alone, controls, or untreated mice (figure 1B). Histologically, tumours in the CD5-2 + anti-PD1 group exhibited a more favourable immune infiltrate (significantly higher CD3+ and CD8+ T-cells and lower Ly6G+ neutrophils) compared to tumours in other groups (figure 1C). Tumours in CD5-2-treated mice had less leaky vasculature (as measured by Dextran beads extravasation) and less tumour hypoxia (carbonic anhydrase IX staining) compared to non-CD5-2-treated mice (figure 1D).

Conclusions In the DEN model, CD5-2 normalised tumour vasculature and reduced tumour hypoxia. CD5-2 plus anti-PD1 antibody reduced tumour size possibly by altering immune infiltrate to being immunosupportive. The combination of vascular normalisation by targetting VE-Cadherin and immunotherapy is a promising novel approach to treat HCC.

IDDF2020-ABS-0213 CXCR2 BLOCKADE DISRUPTS TUMOR TRAFFICKING OF MDSC TO POTENTIATE IMMUNOTHERAPY EFFICACY

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10.1136/gutjnl-2020-IDDF.5

Background The heterogeneity and diverse pathogenic conditions of HCC construct an immunosuppressive tumor microenvironment (TME) which may lead to low immune checkpoint blockade (ICB) therapeutic responsiveness. Therefore, alleviating immunosuppression to potentiate ICB anti-cancer immunity is in urgent need. Myeloid-derived suppressor cells (MDSCs) with potent T cell suppressive property are correlated with poor prognosis and unsatisfactory ICB response in HCC. In this study, we aimed to study the potential efficacy and functional mechanisms of targeting C-X-C motif chemokine receptor 2 (CXCR2) chemotaxis pathway to block MDSC tumor infiltration, enhancing ICB efficacy using preclinical orthotopic HCC mouse models.

Methods CXCR2-chemotaxis pathway activation in MDSCs was determined by multi-color flow cytometry in tumor and paired non-tumor liver specimens from HCC patients, as well as healthy blood samples. Therapeutic efficacy of CXCR2 blockade was conducted in an orthotopic mouse model using AZD5069 (100 or 150 mg/kg) which is a CXCR2 antagonist currently undergoing clinical trials and in combination with anti-PD-L1 antibody (10F.9G2). Tumorigenic monitor, immune profiling and survival analysis were performed. Mechanistic study was determined using lentivirus-based gene knockdown in human-blood cell models.

Results The result showed that both monocytic (M-MDSC) and polymorphonuclear (PMN-MDSC) populations are elevated in HCC liver tissue compared to healthy donor (HD) control. CXCR2 was widely expressed in immune cells, in particular for MDSC, while its ligand interleukin-8 (IL-8) was expressed in the majority of tumor cells, as well as $CD45^+$ leukocytes in HCC. Notably, the blockade of CXCR2 chemotaxis pathway significantly inhibits MDSC trafficking into tumor microenvironment in HCC orthotopic mouse model. Furthermore, co-blockade of CXCR2 and PD-L1 remarkably reduced tumor weight when compared to a single treatment, in which intratumoral $CXCR2^+PD\text{-}L1^+$ MDSC was positively associated with tumor burden.

Conclusions Our data demonstrated the intricate link between IL-8/CXCR2 axis and MDSC trafficking to TME, providing insight into the immunosuppression mechanism in HCC. Targeting IL-8/CXCR2 chemotaxis pathway may potentiate ICB responsiveness, serving as a novel potential therapeutic option for effectively combined immunotherapy in liver cancer.

Clinical gastroenterology

IDDF2020-ABS-0033 THE EFFECT OF IMMUNOMODULATORS AND OTHER FACTORS ON THE PERSISTENCE OF BIOLOGICAL AGENTS FOR CROHN'S DISEASE AND ULCERATIVE COLITIS: DATA FROM THE AUSTRALIAN POPULATION-BASED REGISTRY

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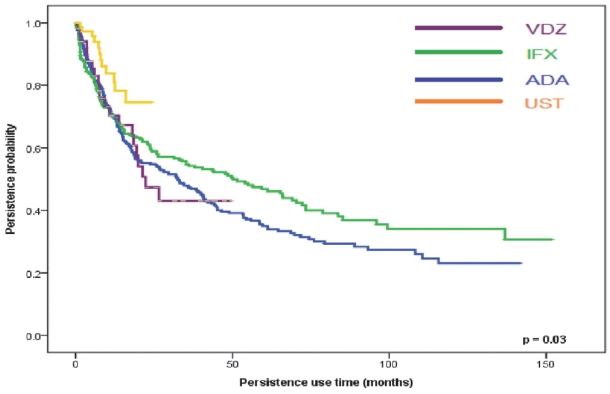
10.1136/gutjnl-2020-IDDF.6

Background Treatment persistence (duration of medication use) provides real-world evidence on therapeutic effectiveness, tolerability and prescriber and patient preferences. Biological agent persistence in Crohn's disease (CD) and ulcerative colitis (UC) was compared from the national population-based registry with no hierarchical prescribing order. We hypothesized immunotherapy co-therapy would increase persistence through decreased immunogenicity.

Methods A randomly selected ten percent subgroup of the prospectively collected population-based registry from the Australian Pharmaceutical Benefits Scheme between June 2005-June 2019 was analysed. Treatment persistence of adalimumab (ADA), infliximab (IFX), vedolizumab (VDZ) and ustekinumab (UST) was compared.

Results 2499 patients were included consisting of 3713 lines of therapy (2864 CD, 849 UC) which equated to 7470 person-years of follow-up. In CD, UST had the highest overall persistence rate (median persistence rate >74.6% where 24.6 months is the maximum follow up time recorded), followed by VDZ, IFX and ADA (p=0.03) (figure 1). In UC, VDZ had



Abstract IDDF2020-ABS-0033 Figure 1 Persistence Kaplan meier graphs- Luminal crohn's disease persistence