GI highlights from the literature

Philip J Smith

BASIC SCIENCE

Mapping the microbiome-derived metabolism of drugs

Javdan B, Lopez J, Chankhamion P, *et al*. Personalized mapping of drug metabolism by the human gut microbiome. *Cell* 2020;1817:1661–79.

The gut microbiome is encoded by an estimated 100 times more genes than the human genome. Microbiome-derived metabolism (MDM) is the processing of a drug into metabolites by microbiome-derived enzymes. Previously monocultures have been used to study drug metabolism. This paper characterises the diversity of the microbiome and provides a framework for mapping MDM. An ex vivo culture system from a pilot donor stool sample was optimised and incubated with various orally administered drugs. A drug was MDM+ if in culture the drug was no longer detected, it produced a new metabolite and it was metabolised in the same way in at least two experiments. Of 575 drugs tested, 76% were successfully analysed, and of these 13% were MDM+ (ie, the microbiota could alter the medication). Several MDM reactions had been previously described but 80% were novel reactions. Next, an additional 20 healthy donor stool samples were cultured and quantitative metabolomics was used to determine MDM for 23 drugs. Some drugs were MDM+ across donors; some MDM− across donors and others exhibited variability. Functional metagenomics was employed to identify metabolising enzymes. Finally, to test whether these interactions occur in vivo, two groups of mice were treated with antibiotics to abolish their native microbiome and one group colonised with pilot donor stool. One reaction, the deglycosylation of fluoropyrimidine capecitabine, which occurred in donor stool, was tested, and this occurred only in the colonised mice. In summary, new microbiome–drug interactions were identified and there was interindividual variability, of relevance in personalised drug development.

Single cell approaches unravel molecular circuits driving checkpoint inhibitor-associated colitis

Luoma A, Suo S, Williams H, *et al*. Molecular pathways of colon inflammation induced by cancer immunotherapy. *Cell* 2020;182(3):655–71.e22. doi: 10.1016/j.cell.2020.06.001.

The monoclonal antibodies ipilimumab and pembrolizumab, two of the most widely used check point inhibitors (CPI), promote antitumour immune responses by blocking signalling via either the cytotoxic T-lymphocyte antigen 4 (CTLA-4) pathway or the programmed cell death protein 1 pathway, respectively. Both these molecules play a central role in regulating immune cell responses and can be hijacked by tumours to allow them to evade immunosurveillance. Immune checkpoint inhibition takes the brakes off immune system responses and restores effective immunosurveillance and tumour killing. It is not selective though and lowering the threshold for immune activation leads to unwanted, immune-mediated side effects like CPI-induced enterocolitis. In this paper, Luoma *et al* provide an extremely granular view of the molecular pathways involved in CPI colitis. Including two control groups (CPI recipients, healthy controls) and combining transcriptomic (single cell RNA sequencing) and proteomic (multiparametric flow cytometry) assays at single cell level, the authors were able to delineate changes at tissue level due to CPI and inflammation. An interesting observation was the expansion of the cytotoxic effector CD8 T-cell cluster that is reminiscent of previous immunophenotyping works in classical UC. Intriguing was also the persistence and expansion of CTLA-4 regulatory T cells (Tregs). Depletion of CTLA-4+ Tregs has been proposed as a mechanism for CPI-related immune-mediated adverse events but the findings of this study do not appear to support this hypothesis. This work will also prove an excellent resource for future analyses that may provide an additional layer to our understanding of immune-mediated responses in the gut.

Targeting senescent cells in hepatocellular carcinoma

Li F, Huangyang P, Burrows M, *et al*. FBP1 loss disrupts liver metabolism and promotes tumorigenesis through a hepatic stellate cell senescence secretome. *Nat Cell Biol* 2020;22(6):728–39. doi: 10.1038/s41556-020-0511-2.

Effective targeted therapy for hepatocellular carcinoma (HCC) is greatly needed. Senescence, a state of permanent cell cycle arrest, is induced by various cell stressors including oncogene activation and injury. It is associated with progressive chronic liver disease, the premalignant state of HCC. New, so-called 'senolytic' drugs kill senescent cells and are in numerous early-phase clinical studies. In this study, the researchers first used published data from the human HCC transcriptomes to show that three rate-limiting enzymes in gluconeogenesis are reduced in HCC. They then investigated the role of one of these key enzymes, fructose 1,6-bisphosphatase 1 (FBP1), in HCC formation by creating a mouse in which this gene could be deleted specifically in hepatocytes. Deleting this gene resulted in hepatic steatosis and also promoted the formation of HCCs, consistent with FBP1's reported role as a tumour suppressor. In these models, they observed excessive scar formation together with an increase in senescent scar-forming myofibroblasts around the tumour. These senescent changes were potentially induced by high-mobility group box-1 released directly from the tumour. In cell culture they showed senescent myofibroblasts promote growth of an HCC cell line. Next, in an elegant study, they transplanted both myofibroblasts and cancer cells into mice showing that senescent myofibroblasts also promote cancer growth in vivo compared with non-senescent counterpart. Finally, in their FBP1-deficient mouse models of HCC they used therapeutic senolytic strategies to target the senescent cells, which resulted in a reduction in HCCs, highlighting this as a potential targeted therapeutic strategy for HCC.

CLINICAL PRACTICE

Upadacitinib for Crohn's disease

Sandborn W, Feagan B, Loftus E, *et al*. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease. *Gastroenterology* 2020;158:2123–38.

Janus kinase (JAK) inhibitor therapy is an emerging class of small molecule therapy for IBD and can be administered orally with no immunogenicity. There are four isoforms of the JAK family of proteins: JAK 1, 2, 3 and tyrosine kinase 2. The pan-JAK inhibitor, tofacitinib, is licensed for UC but a phase 2 study in Crohn's disease (CD) did not show evidence of efficacy. This phase 2 randomised, double-blind study evaluated the efficacy and safety of upadacitinib, a selective JAK 1 inhibitor, in CD. Patients with moderate to severe CD and an inadequate response or intolerance to immunosuppressants or tumour necrosis factor antagonists were randomly assigned (1:1:1:1:1:1) to placebo; or 3, 6, 12 or 24 mg upadacitinib twice daily; or 24 mg upadacitinib once daily. Patients were evaluated by

ileocolonoscopy at week 12 or 16 of the induction period. Patients who completed week 16 were rerandomised to a 36-week period of maintenance therapy. The primary endpoints were clinical remission at week 16 and endoscopic remission at week 12 or 16. Clinical remission was only higher compared with placebo in the 6 mg group ($p<0.1$ vs placebo). Between 8% and 22% of patients receiving the different doses of upadacitinib achieved endoscopic remission compared with none in the placebo group with higher endoscopic remission rates seen with higher doses of upadacitinib. Efficacy was maintained for both clinical and endoscopic endpoints during the maintenance phase. Patients in the 12 and 24 mg group had elevations of high-density and low-density lipoprotein levels.

A surgical approach to fatty liver

Lassailly G, Caiazzo R, Ntandja-Wandji L, *et al*. Bariatric surgery provides long-term resolution of non-alcoholic steatohepatitis and regression of fibrosis. *Gastroenterology* 2020;S0016-5085(20):34758–2. doi: 10.1053/j.gastro.2020.06.006

The 'obesity pandemic' drives the rise of non-alcoholic fatty liver disease (NAFLD). There are no approved drugs for non-alcoholic steatohepatitis (NASH) and guidelines advocate weight loss as first-line treatment. Bariatric surgery achieves long-term weight loss in obese patients and improves comorbidities at 1 year. This study evaluated the long-term effect of bariatric surgery on NASH and fibrosis.

Between 1994 and 2017, one hundred and eighty morbidly obese adults (body mass index >35), undergoing bariatric surgery in Lille, France, were enrolled in this trial. Surgery varied through the years with sleeve gastrectomy and gastric bypass replacing gastric band procedures. All subjects underwent liver biopsy at time of surgery and follow-up biopsy at 1 year (74% of participants) and 5 years (68% of participants). Pathologists analysed biopsies for NASH (Brunt and NAFLD Activity Score (NAS) scores) and fibrosis (Kleiner score=F1–F4). NASH resolution without worsening fibrosis at 5 years (primary endpoint) occurred in 84.4% of patients with the NAS score dropping by at least two points, independent of baseline severity but related to weight reduction. Fibrosis improved at 5 years in 70.2% of patients: complete resolution in 62.9% and 45.5% of patients with ≤F3 and F3–F4 at baseline, respectively. The authors also observed comparable improvements in biochemical parameters (liver test and insulin resistance). Patients with poor response to bariatric surgery were likely to show persistent NASH and fibrosis at 5 years. While this study confirms that weight loss and insulin resistance amelioration are effective in improving liver histology, further data are required to assess the risks associated with surgery for the management of NAFLD.

Cognitive deficit and white matter changes in coeliac disease

Croall I, Sander D, Hadjivassiliou M, *et al*. Cognitive deficit and white matter changes in persons with coeliac disease: a population-based study. *Gastroenterology* 2020;158:2112–22. doi: 10.1053/j.gastro.2020.02.028

Croall *et al* used the data stored in the National UK Biobank to look at the prevalence of neuropsychological dysfunction in people with coeliac disease. Previous literature has suggested an association between cognitive deficit and coeliac disease, but there has been debate about the available evidence being affected by positive ascertainment and referral bias. The authors used the biobank to identify an independent data set, comparing scores from five cognitive tests, questions about mental health and MRI of the brain in 104 individuals with coeliac disease and 198 matched controls. Neither group had any significant comorbidity, nor were they on any psychoactive medications. The authors found that in patients with coeliac disease, there were significant differences in reaction time ($p=0.004$), indications of anxiety ($p=0.025$), depression ($p=0.015$) and thoughts of self-harm ($p=0.025$) compared with controls. This was the first study of its kind to look at MRI diffusion tensor imaging (DTI) in this group of patients. MRI DTI is particularly sensitive at detecting white matter changes, and tract-based spatial statistic analysis was used to create images allowing comparison of white matter between groups. Significant differences were seen in axial diffusivity between the coeliac and control groups, demonstrating white matter changes in the patients with coeliac disease. These findings highlight the importance of awareness among gastroenterologists about neurological involvement in patients with coeliac disease, and should be used to provide properly targeted care and follow-up.

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JOURNALS REVIEWED

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