GI highlights from the literature

Philip J Smith

BASIC SCIENCE

New insights into the contribution of the gut microbiome to irritable bowel syndrome

Mars R, Yang Y, Ward T, *et al*. Longitudinal multi-omics reveals subset-specific mechanisms underlying irritable bowel syndrome. *Cell* 2020;182:1460–73.e17. doi: 10.1016/j.cell.2020.08.007.

While perturbation of the composition of the gut microbiome has been previously observed in patients with irritable bowel syndrome (IBS), the specific mechanisms by which this may contribute to the onset or progression of the condition are not well defined. To explore this further, researchers performed longitudinal analysis (over 6 months) of samples collected from 77 well-phenotyped IBS patients and healthy controls; this was primarily via stool and serum analysis, but also via colonic biopsy in approximately half of participants. Samples were analysed by systems biology techniques which evaluated both host mucosa and gut microbiome function (including shotgun metagenomics, metabonomics, transcriptomics and epigenetics), and an integrative multiomics approach was used to interrogate data. Distinctive patterns of alterations in metabolites derived from gut microbial activity were found to characterise different IBS subtypes, with reduced short-chain fatty acids observed in those with IBS and constipation, while an increase in both tryptamine and primary bile acids was identified in those with diarrhoea-variant IBS. However, of greatest interest was the novel finding of a reduction in faecal hypoxanthine in patients with both main variants of IBS compared with controls, and the subsequent demonstration of increased degradation of purine nucleotides by both the gut microbiome and the host mucosa in IBS. The researchers concluded that such 'purine starvation' in IBS may result in a reduced source of energy to the mucosal epithelium (as well as reduced capacity for repair), and that this mechanism may be key in linking altered host−microbiome interactions to the pathogenesis of IBS.

The relationship between fatty liver and insulin resistance: a mystery to solve

Lyu K, Zhang Y, Zhang D, *et al*. A Membrane-Bound Diacylglycerol Species Induces PKCε-Mediated Hepatic Insulin Resistance. *Cell Metab* 2020; S1550-4131(20)30414–9. doi: 10.1016/j.cmet.2020.08.001.

Hepatic steatosis is associated with hepatic insulin resistance (HIR) but which lipids directly contribute to dysregulation of hepatic insulin signalling remains unresolved. In this paper, Lyu *et al* investigate the relationship among diacylglycerols, activation and translocation to plasma membrane (PM) of Protein kinase C epsilon (PKCε), which phosphorylates the hepatic insulin receptor kinase causing lipid-induced HIR.

Lyu *et al* created acute diacylglycerol-acyltransferase-2 (DAGT2) knocked down (KD) rats, which lack the endoplasmic-reticulum (ER) enzyme which catalyses diacylglycerols into triglycerides and leading to diacylglycerols accumulation in the liver. Following hyperinsulinaemic-euglycaemic clamp tests, DAGT2-KD rats show reduction of >50% of phosphorylation of insulin receptor kinase with a twofold increase activation of PKCε compared with controls. The authors separate liver tissue by differential centrifugation among ER, mitochondria, lipid droplets, cytosol and PM and analysed diacylglycerols content using liquid-chromatography tandem mass spectrometry in each tissue. In DAGT2-KD rats, diacylglycerol-stereoisomer1,2 content was respectively 50% and 80% higher in ER and PM compared with other tissues and controls. Comparable results were observed in human tissues. In liver-specific PKCε-KD rats (using a modified model 2'-methoxyethyl-antisense oligonucleotide with N-Acetyl Galactosamine to improve hepatocytes delivery) at day 4 of high fat diet, hyperinsulinaemic-hyperglycaemic clamp tests induced a raise in glycogen hepatic content, reduction of insulin receptor kinase-T1160 levels and reduction in plasma glucose and insulin following oral glucose tolerance test. In parallel, overexpression of PKCε activated isoform doubles PKCε levels resulting in reduction of hepatic glycogen content after hyperinsulinaemic-hyperglycaemic clamp. These results suggest DAGs and PKCε may be suitable targets to ameliorate lipid-induced HIR.

Predictive capacity of interleukin-6 and tumour necrosis factor alpha in COVID-19 severity and survival

Del Valle D, Kim-Schulze D, Huang S, *et al*. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;26:1636–43. doi: 10.1038/s41591-020-1051-9.

The hyperinflammatory response, or cytokine storm, is well described in SARS-CoV-2 infection, and has led to multiple immune modifying drugs entering COVID-19 clinical studies. However, important unmet clinical needs are biomarkers to predict disease severity, which may facilitate targeting of therapies in those at risk, to guide treatment selection, and reduce risk of adverse effects. Del Valle *et al* studied the predictive capacity of four serum cytokines; interleukin-6 (IL-6), tumour necrosis factor alpha (TNF), IL-1β and IL-8 (IL-8), in COVID-19 disease course and outcome. Therapies targeting these proteins or associated immune pathways exist for many inflammatory diseases. A total of 1484 hospitalised patients in New York with suspected or confirmed COVID-19 were followed from the day of admission to the day of discharge or death. IL-6 was significantly higher in men vs women with confirmed COVID-19, and levels of IL-6, TNFα and IL-8 increased with age. TNFα and IL-8 were significantly elevated in chronic kidney disease, diabetes and hypertension. Stratifying patients by a median threshold of each cytokine in COVID-19 separated 'high' versus 'low' serum cytokine concentrations. Analysis, including validation in a second cohort, showed that following adjustment for oxygen saturation, blood pressure, demographics, comorbidities and laboratory inflammatory markers; high IL-6 and TNFα remained significant and independent predictors of disease severity and death. While further prospective studies are needed, this study highlights the potential role of these cytokines in patient selection for interventions to avoid or manage severe COVID-19, supports ongoing mechanistic studies around IL-6 and TNFα, and supports clinical intervention to modulate these immune pathways in COVID-19.

CLINICAL PRACTICE

Eflornithine and sulindac for familial adenomatous polyposis

Burke CA, Dekker E, Lynch P, *et al*. Eflornithine plus Sulindac for Prevention of Progression in Familial Adenomatous Polyposis. *N Engl J Med* 2020;383(11):1028–39. doi: 10.1056/NEJMoa1916063.

Familial adenomatous polyposis (FAP) is a rare systemic colorectal cancer syndrome, characterised by progressive development of adenomatous polyps. Conventional management is with panproctocolectomy and ileorectal anastomosis. Complication rates are high with 30% proctectomy rates from polyposis or cancer, upper gastrointestinal polyps in 80% and 5%–15% risk of duodenal or periampullary cancers. Trials of pharmacological interventions to delay major surgery have yielded poor results to date in FAP. Yet in sporadic adenomas patients, a randomised trial of eflornithine (an irreversible inhibitor of ornithine decarboxylase)

plus low-dose sulindac demonstrated a 90% reduction in subsequent advanced adenomas compared with placebo. Burke *et al* evaluated the safety of this combination as compared with either drug alone in FAP patients over 48 months. The study was powered to detect an incidence of disease progression 40% lower with combination *vs* monotherapy (defined as a composite of major surgery, endoscopic excision of advanced adenomas, diagnosis of high-grade dysplasia in the rectum or pouch, or progression of duodenal disease). Of 171 patients randomised no significant difference was detected between the groups with a HR of 0.71 (95% CI 0.39 to 1.32) for eflornithine–sulindac as compared with Sulindac (p=0.29) and 0.66 (95% CI 0.36 to 1.24) for eflornithine–sulindac as compared with eflornithine. However, in the precolectomy subgroup, patients who received combination therapy did not have any gastrointestinal polyposis or did not require lower gastrointestinal tract surgery. Further studies are required to understand a possible benefit of combination therapy in FAP prior to colectomy.

The effect of the COVID-19 pandemic on cancer survival in the UK

Sud A, Torr B, Jones M, *et al*. Effect of delay in the 2-week wait cancer referral pathway during COVID-19 pandemic on cancer survival in the UK: a modelling study. *Lancet Oncol* 2020;21(8):1035–44. doi: 10.1016/S1470-2045(20)30392-2.

The restrictive public health measures enforced by the UK government during the first wave of the coronavirus disease 2019 (COVID-19) pandemic led to a dramatic reduction in 2-week wait referrals for suspected gastrointestinal malignancies.

Using age-stratified and tumour stage-stratified 10-year UK survival estimates, linked to waiting times data from National Health Service digital, the authors modelled the effect of increasing diagnostic delay on cancer outcomes for the 20 most common malignancies.

Overall, their model predicts that COVID-19-related delays in presentation, diagnosis and treatments will result in loss of life and life-years that vary widely according to age and tumour type. For a 3-month delay in the diagnosis of oesophageal, gastric, liver and colorectal cancers the authors predict a 10%–20%reduction in overall 10-year survival. Moreover, because they are typically less aggressive and more readily treated, a disproportionate increase in lives and life-years lost will be seen with progressive delays in the diagnosis of colorectal tumours than upper gastrointestinal or liver cancers. While data on just how disrupted our services have been are slowly emerging, there is an urgent need to deal efficiently with the backlog. Faecal immunochemical testing should be used to streamline lower gastrointestinal referrals to colonoscopy. It is clear, however, that changes need to be made to maintain patient confidence in physical distancing in acute hospitals/diagnostic settings. Furthermore, every effort needs to be made to ensure that endoscopy and diagnostic services are not closed during further waves of COVID-19.

Navigating acute decompensation of cirrhosis: can we predict the clinical course?

Trebicka J, Fernandez J, Papp M, *et al*. The PREDICT study uncovers three clinical courses of acutely decompensated cirrhosis that have distinct pathophysiology. *J Hepatol* 2020;73:842–54.

Acute decompensation is a defining moment for all patients with cirrhosis. An episode of decompensation presents a great degree of uncertainty for both patient and clinician regarding the future clinical course. In this prospective observational study (PREDICT: Patterns of Acute Decompensation in Cirrhosis) the authors followed 1071 patients with decompensated cirrhosis requiring hospitalisation and identified three phenotypes that had differing natural histories. The real strength of this study is the large number of patients involved. The three differing clinical courses of preacute on chronic liver failure, unstable decompensated cirrhosis and stable decompensated cirrhosis had distinctly different outcomes with 67.4%, 35.6% and 9.5% 12-month mortalities, respectively. Interestingly, these clinical courses were independent of aetiology of cirrhosis or active alcoholism indicating outcomes were dependent on other methods. Systemic inflammation, bacterial infection and portal hypertension are all key predictors of clinical course. The identification of different clinical courses at the time of presentation of acute decompensation may allow more personalised delivery of care for patients including the management setting for example, regular ward, high-dependency unit or intensive care setting. The only available treatment for decompensated liver disease is transplantation. Identification differing phenotypes may aid decision making in terms of expediting transplantation or in goals of care planning and indeed palliation. The authors acknowledge future research would be needed to develop more sensitive clinical tools/nomograms to stratify patients at the time of presentation with decompensation. In summary, the PREDICT study is the first study to describe the heterogeneous phenotypes that occur after hospitalisation for acute decompensation of cirrhosis.

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JOURNALS REVIEWED

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