GI highlights from the literature

Philip J Smith

BASIC SCIENCE

MYC activation in liver non-parenchymal cells drives hepatic damage in acute liver failure

Kolodziejczyk A, Federici S, Zmora N *et al*. Acute liver failure is regulated by MYC- and microbiome-dependent programs. *Nat Med* 2020; doi: 10.1038/s41591-020-1102-2

Acute liver failure (ALF) remains a devastating condition with a high mortality and limited treatment options short of liver transplantation. It is therefore imperative that we develop a deeper understanding of the cellular and molecular mechanisms regulating ALF, with the hope of identifying novel therapeutic targets. In this study, Kolodziejczyk *et al* have employed a cutting-edge single-cell RNA-sequencing approach to study transcriptional changes in mouse non-parenchymal liver cells following ALF induced by either acetaminophen (APAP) or thioacetamide (TAA). As anticipated, they showed significant alterations in the phenotype of hepatic stellate cells, endothelial cells and macrophages following ALF. Strikingly, however, comparative analyses demonstrated a conserved injury response signature of 77 genes across these different cell lineages, which was enriched for binding sites of the transcriptional regulator MYC. Inhibition of MYC attenuated liver injury in mouse ALF and prevented the development of these activated non-parenchymal cell populations. Furthermore, this MYC activation signature was reduced in germ-free mice, following antimicrobial treatment and in response to inhibition of toll-like receptor signalling in the liver. Overall, these data suggest that a combination of liver cell death and translocation of gut microbial products results in hepatic MYC upregulation, which propagates liver non-parenchymal cell activation, tissue damage and inflammation in ALF. Hepatic MYC protein levels were also increased in patients with ALF, suggesting that targeting MYC may represent a potential treatment for patients. However, more detailed characterisation of non-parenchymal cell phenotypes in human ALF is required, before the true translational relevance of these findings can be fully understood.

Human-Gut-DNA virome variations across geography, ethnicity and urbanisation

Zuo T, Sun Y, Wan Y *et al*. Human-Gut-DNA virome variations across geography, ethnicity, and urbanization. *Cell Host Microbe* 2020; 28 (5): 741–751.e4. doi: 10.1016/j.chom.2020.08.005

The gut virome is highly diverse and individual specific. In this study, Zuo *et al* reported the faecal DNA virome of 930 healthy adult individuals from two different regions in China, Hong Kong and Yunnan, spanning six ethnicities (Han, Zang, Miao, Bai, Dai and Hani), in both urban and rural areas within the two regions. The gut virome of Hong Kong population was significantly different from that of the Yunnan population, with marked geography (urban vs rural) and ethnicity difference. Subjects from Hong Kong, a highly urbanised area, had enrichment of the Microviridae family and lack of phages from the order Caudovirales, compared with subjects in Yunnan. Compared with gut bacteriome, the human gut DNA virome was more heterogeneous. Both geographical locations and dietary factors, including frequency of meat and vegetable consumption and alcohol intake, had a significant impact on gut-DNA virome. Other factors included medications used, urbanisation, ethnicity and anthropometrics. Urbanisation differentially impacted the diversity, evenness and richness of gut-DNA virome, with levels significantly lower in subjects in Hong Kong than those in Yunnan. Subjects in the Hong Kong population had depleted phages infecting bacterial pathogens, including *Escherichia coli* O157 phage, *Shigella* phage, *Salmonella* phage, *Vibrio* phage and *Klebsiella* phage compared with the Yunnan population. Duration of residence in urban areas showed a positive association with multiple bacteriophages, including *Lactobacillus* and *Lactococcus* phages. This large-scale population-based study highlights the variation and the importance of host and environmental factors in shaping human-gut-DNA virome. Further studies are needed to investigate the role of gut virome in disease development.

The role of *Proteus mirabilis* in Crohn's disease inflammation

Zhang J, Hoedt E, Liu Q *et al*. Elucidation of *Proteus mirabilis* as a key bacterium in Crohn's disease inflammation. *Gastroenterology* 2020; doi: 10.1053/j.gastro.2020.09.036

Several microbes, including *Enterococci* and *Clostridia*, have been identified as potential triggers for Crohn's disease (CD) progression through their ability to generate extracellular toxins capable of initiating an inflammatory mucosal response. However, the relatively low abundance of *Proteus* species has made their study difficult, meaning they may be excluded from microbiome analysis. *Proteus* is Gram-negative facultative anaerobic bacilli, recognised for their urease activity, and is known to drive infection and inflammation in urinary tract infections and cholangitis. Elevated levels of urease activity have recently been identified as one of the key functional changes associated with microbial dysbiosis in CD.

Zhang *et al* found that the abundance of *Proteus* species in terminal ileal and right colonic biopsies from 54 patients with CD was higher compared with corresponding healthy controls, with a prevalence of around 65%. Within patient samples, a greater relative *Proteus* abundance was seen in samples from inflamed tissue, and cohorts with a higher abundance had higher activity index (CDAI) scores than patients with low abundance. More severe histologic inflammation was seen in the colons of germ-depleted mice gavaged with *Proteus mirabilis (P. mirabilis)* strains when compared with controls receiving *Escherichia coli*. *P. mirabilis* was also able to induce cell death when co-cultured with human colonic epithelial cells in vitro, with evidence of cell invasion and activation of proinflammatory NF-κB and tumour necrosis factor alpha (TNFα) pathways. Together, the findings suggest that *Proteus* species can drive inflammatory pathways in gut epithelial cells and may play an important role as a trigger for CD inflammation.

CLINICAL PRACTICE

Machine Learning algorithms enable assessment of endoscopic disease activity in ulcerative colitis

Gottlieb K, Requa J, Karnes W *et al*. Central reading of ulcerative colitis clinical trial videos using neural networks. *Gastroenterology* 2020; S0016-5085(20)35283-5. doi: 10.1053/j.gastro.2020.10.024

Assessment of endoscopic disease activity in patients with ulcerative colitis is indispensable in respective clinical trials and recommended in daily clinical practice. In this study, a recurrent neural network (RNN) was trained post hoc to predict central reader scores of colonoscopy video recordings from a phase 2, randomised trial with the IL-23 inhibitor mirikizumab in moderate-to-severely active ulcerative colitis patients. The Machine Learning model (MLM) was

created to predict the centrally read endoscopic Mayo (eMs) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scores. The used dataset consisted of 795-recorded endoscopy procedure videos, collected from 249 patients, with a total of 19.5 million image frames across all videos.

The primary evaluation metric was a quadratic weighted kappa (QWK) interobserver statistic for summarising inter-rater agreement of the machine-read endoscopy with the central reader score. The model's agreement metric was in almost perfect agreement with QWK of 0.844 (95% CI 0.787 to 0.901) for eMS and 0.855 (95% CI 0.80 to 0.91) for UCEIS. The obtained results of the study indicate that machine-based reading of endoscopy videos has the capacity to make an impact on future clinical trials, not only from an operational point of view, but also enabling a more objective assessment of existing endoscopic disease activity. The presented MLM needs further validation in clinical trials, but may represent the first step towards implementation of automated endoscopic disease activity scoring in ulcerative colitis.

Anti–Siglec-8 antibody for eosinophilic gastritis and duodenitis

Dellon E, Peterson K, Murray J *et al*. Anti-Siglec-8 antibody for eosinophilic gastritis and duodenitis. *N Engl J Med* 2020; 383 (17): 1624–34.

Eosinophilic GI diseases are chronic inflammatory conditions characterised by GI symptoms and infiltration of the gastric mucosa by eosinophils. Sialic acid–binding immunoglobulin-like lectin 8 (Siglec-8) is an inhibitory receptor expressed on mast cells and mature eosinophils. The monoclonal antibody Lirentelimab (AK002) is a humanised non-fucosylated IgG1 anti–Siglec-8 antibody that depletes eosinophils and inhibits mast-cell activation therefore leading to reduced degranulation and secretion of inflammatory mediators.

The aim of this multicentre randomised double-blind placebo-controlled phase 2 trial in the USA was to assess the safety and efficacy of AK002 in eosinophilic gastritis, duodenitis or both. Eligible patients were assigned in a 1:1:1 ratio to receive 4 monthly intravenous infusions of low-dose AK002, high-dose AK002 or placebo (volumetric equivalent). Patients were included if they had moderate-to-severe symptoms.

Out of 65 randomised patients, 43 received AK002 and 22 received placebo. In the combined AK002 group, the mean percentage change in GI eosinophil count was −86%; placebo group 9% ($p<0.001$). Treatment response occurred in 63% of patients who received AK002; placebo group 5% ($p<0.001$). A histological response (defined by <30 eosinophils per high-power field at the end of treatment) was observed in 37 patients who received AK002 and 3 patients who received placebo. A higher percentage of patients receiving AK002 had a mild-to-moderate infusion-related reaction (60% in the combined AK002 group, 23% in the placebo group). Therefore, AK002 was more effective than placebo in reducing symptoms and eosinophils in patients with eosinophilic gastritis or duodenitis. Results of phase 3 trials are expected in the near future.

Fibrates for itch (FITCH): a new therapy in the treatment paradigm for cholestatic liver disease?

de Vries E, Bolier R, Goet J *et al*. Fibrates for itch (FITCH) in fibrosing cholangiopathies: a double blind, randomised, placebo-controlled trial. *Gastroenterology* 2020; doi: 10.1053/j.gastro.2020.10.001

Itch in patients with cholestatic liver disease is associated with reduced quality of life (QoL). New safe, effective and tolerable therapies are needed to improve the QoL of affected patients. Bezafibrate is a peroxisome proliferator-activated receptor (PPAR) agonist which the authors proposed could reduce itch by decreasing formation and secretion of an unidentified 'biliary factor X' via reduction in hepatobiliary cholestasis and injury.

In this double blind, randomised, placebo-controlled trial, the effect of bezafibrate versus placebo on patient-reported itch intensity (measured by visual analogue scale; VAS) in patients with cholestatic disease and moderate to severe itch was assessed. Once daily bezafibrate or placebo was administered for 21 days. A ≥50% reduction in the VAS after 21 days was seen in 45% of the bezafibrate group and 11% of the placebo group. The treatment effect was lost by day 35. In the treatment group, reduction in alkaline phosphatase (ALP) correlated with reduction in VAS score. Reduced itch intensity in the bezafibrate group was associated with an improvement in some aspects of QoL.

This study was unable to show longer-term safety or efficacy for bezafibrate in the management of pruritus. It was difficult to recruit to, due in part to concerns regarding patients receiving placebo having intolerable itch throughout the study period.

Although these initial data are promising and demonstrate a short-term effect, studies assessing the longer-term benefit are required. Such a study may be challenging to recruit to and data may become available from longer-term studies of bezafibrate as second-line therapy in primary biliary cholangitis.

REVIEWERS

Dr Prakash Ramachandran, MRC Clinician Scientist and Honorary Consultant Hepatologist, University of Edinburgh Centre for Inflammation Research, The Queen's Medical Research Institute, Edinburgh BioQuarter, Edinburgh, UK

Dr Joyce Mak, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China

Dr Jennie Clough, IBD Research Fellow, Guy's and St Thomas' NHS Trust and King's College London, London, UK

Professor Raja Atreya, University of Erlangen-Nuremberg, Erlangen, Germany

Dr Aaron S Bancil, Department of Nutritional Sciences, King's College London, London, UK

Dr Mhairi C Donnelly, Consultant Hepatologist, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

JOURNALS REVIEWED

Nature Medicine, *Cell Host Microbe*, *Gastroenterology* and *New England Journal of Medicine*

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Smith PJ. *Gut* 2021;**70**:215–216. doi:10.1136/gutjnl-2020-323644

ORCID iD
Philip J Smith http://orcid.org/0000-0003-1568-3978