GI highlights from the literature

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BASIC SCIENCE

Targeted microbial therapy for NAFLD

Yuan J, Chen C, Cui J *et al*. Fatty liver disease caused by high-alcohol-producing *Klebsiella pneumoniae*. *Cell Metabolism* 2019;30:675–688.

The gut microbiota is of research interest in non-alcohol-related fatty liver disease (NAFLD). This paper describes bedside-to-bench research, starting from an intriguing case of a patient who developed high alcohol levels after consuming carbohydrate, with steatohepatitis on liver biopsy. A strain of *Klebsiella pneumoniae* that metabolised carbohydrate to produce ethanol was isolated from stool. A diagnosis of autobrewery syndrome was made, as well as (questionably) NAFLD. A further cohort of individuals with or without NAFLD was analysed for the presence of alcohol-producing *K. pneumoniae*. The overall abundance did not differ between cases and controls, but the presence of high alcohol-producing strains and the degree of alcohol production was considerably higher in NAFLD. Given that alcohol production depended on the microbial culture environment, this hints at a connection between diet and endogenous alcohol production. This is further emphasised by the observation that weight loss reduced prevalence and ethanol production of *K. pneumoniae*. Liver steatosis and inflammation were induced in germ-free mice by the administration of ethanol-producing *K. pneumoniae* or microbiota transplantation from patients with NAFLD. Finally, a bacteriophage that selectively destroyed ethanol-producing *K. pneumonia* rendered this faecal microbial transplant harmless. The presence of alcohol-producing bacteria has long been discussed in NAFLD. These are the first data to document the pathological effects of a particular strain. The findings need to be reproduced in a larger cohort. If validated, treating for ethanol-producing *K. pneumoniae* may be an unexpected exemplar of personalised medicine for NAFLD.

Immune cell heterogenicity in Crohn's disease (CD) is aligned to treatment response

Martin JC, Chang C, Boschetti G, *et al*. Single-cell analysis of Crohn's disease lesions identifies a pathogenic cellular module associated with resistance to anti-TNF therapy. *Cell* 2019;178:1493–1508.

Not all patients with IBD respond to currently available treatments. As an example, around 65% of patients will achieve clinical benefit from anti-tumour necrosis factor (TNF) biologic therapy. This study aimed to identify whether cellular heterogeneity contributed to anti-TNF therapy treatment resistance. Using single-cell sequencing, the authors showed that a subset of patients with ileal CD expressed a unique inflamed tissue cellular module comprising IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells and stromal cells. Presence of this module was identified in four independent ileal CD cohorts, and its presence at disease diagnosis correlated with failure to achieve corticosteroid-free remission following anti-TNF therapy. The activated dendritic cells (DCs) within the cellular module expressed high levels of CCL19, CCL17 and CCL22 (all T cell ligands), indicating a potential role for DCs in the activation, expansion and spatial organisation of the adaptive immune response. The cellular module also contained activated macrophages, which were thought to derive from circulating classical monocytes and to contribute to stromal-cell activation. Tissue-resident macrophages were present in all lesions, independent of the cellular module. The study demonstrated that TNF production differed, depending on the presence of the cellular module, with TNF mainly produced by T cells in the absence of the module, while both T cells and inflammatory macrophages produced TNF in patients with the cellular module. The study suggests that using precision medicine to identify future combination therapies that supplement anti-TNF approaches may limit disease progression in a subset of patients.

Stem cell biology of the gastric corpus gland

Han S, Fink J, Jorg DJ *et al*. Defining the identity and dynamics of adult gastric isthmus stem cells. *Cell Stem Cell* 2019;25(3):342–356.

The normal gastric corpus gland is thought to be maintained by a population of stem cells responsible for maintaining a functional gland. Dogma states that these glands are clonal. However, recent data have revealed potentially two populations of stem cells at the isthmus and at the base of the gland. This raises important questions on the dynamics of gastric corpus glands in homeostasis and how this impacts on disease. The authors use the confetti reporter mouse that stochastically induces expression of multiple fluorescent colours in cells to understand how clones develop within each gland. This revealed two stem cell populations, with one at the isthmus and one at the base. The isthmus population maintains the 'pit' cells. These cells are actively cycling and are maintained through a process of neutral loss/replacement within the isthmus and maintain clone size in the long term, punctuated by the presence of parietal cells acting as a 'road block'. Single-cell RNA sequencing showed that the isthmus population was highly enriched for cell cycling genes (Stmn1 and Ki67) and only expressed pit and base lineage markers at low level which increased as the expression of cell cycling genes reduced (reflecting differentiation). The base stem cell population is far less dynamic and is characterised by slow-cycling stem cells. Interestingly, the clones derived from both populations rarely span across the isthmus/neck, and clonal glands were infrequently observed. This work helps define stem cell biology in the gastric corpus gland. The next step requires translation to human modelling.

CLINICAL PRACTICE

Artificial intelligence-assisted upper GI endoscopy for cancer

Huiyan L, Xu G, Li C *et al*. Real-time artificial intelligence for detection of upper gastrointestinal cancer by endoscopy: a multicentre, case-control, diagnostic study. *Lancet Oncol* 2019;Oct 4. pii: S1470-2045(19)30637-0. doi: 10.1016/S1470-2045(19)30637-0.

Oesophageal and gastric cancers present late and have an overall poor prognosis. Early diagnosis is therefore important. There is a risk of missing suspicious lesions at endoscopy, especially in centres where there are a small number of patients with upper GI cancers. Narrow-band imaging, confocal laser endomicroscopy and blue laser imaging can improve detection rates. However, clinical application of these technologies is limited due to the training and expertise needed for image interpretation. In this study, Huiyan and colleagues performed a large, multicentre, case–control, diagnostic study to determine whether artificial intelligence could improve the diagnostic accuracy of upper GI malignancy at endoscopy. Using

over one million endoscopy images, the group used a deep learning semantic segmental model to construct and validate the Gastrointestinal Artificial Intelligence Diagnostic System (GRAIDS). GRAIDS was accurate in identifying malignant lesions in the internal (0.955, 95% CI 0.952 to 0.957) and prospective (0.927, 95% CI 0.925 to 0.929) validation cohorts. This success was matched in five external validation cohorts from municipal and provincial hospitals across China, with sensitivity, specificity and negative predictive values of >0.9. The diagnostic ability of GRAIDS was also compared with an 'expert', 'competent' and 'trainee' endoscopist's performance. The diagnostic sensitivity of GRAIDS was similar to that of the expert ($p=0.692$) and superior to that of the competent ($p<0.001$) and trainee ($p<0.001$) endoscopists. In summary, GRAIDS can provide real-time and retrospective assistance to improve the diagnostic accuracy of upper GI cancer at endoscopy, particularly in the non-specialist setting.

Ustekinumab as maintenance and induction therapy for UC

Sands BE, Sandborn WJ, Panaccione R, *et al*. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2019;381(13):1201–1214.

Ustekinumab, a biologic to the p40 subunit of interleukin (IL)-12 and IL-23, is an established and effective treatment for CD. Previously, there has been no direct evidence for the efficacy of targeting this molecule in UC. Sands and colleagues report the results of a phase III trial (the UNIFI study), which aimed to establish whether ustekinumab is also useful for inducing and maintaining clinical remission in UC. A total of 961 patients were recruited to an induction cohort and were randomised to receive either 130 mg or 6 mg/kg ustekinumab or placebo as induction therapy. Eight weeks after induction, clinical remission rates based on total Mayo scores were similar in each treatment group (15.5% and 15.6%, respectively) and were significantly higher than those observed in the placebo group (5.3%, $p<0.001$). Subsequently, 523 individuals who responded to either induction therapy or a further dose of 90 mg subcutaneous ustekinumab were entered into a maintenance study. These participants were randomised to receive 90 mg subcutaneous ustekinumab 8 or 12 weekly, or placebo. At week 44, 38.4% of patients receiving 12 weekly ustekinumab, and 43.8% receiving eight weekly ustekinumab had achieved clinical remission, compared with 24% in the placebo arm ($p=0.002$ and $p<0.001$, respectively). Adverse events were similar in the placebo and drug arms. This study provides the first evidence that targeting p40 is an effective strategy for inducing and maintaining remission in UC and has led to the European Medicines Agency licencing ustekinumab for use in patients with moderately to severely active UC.

Preventing procedure-related bleeding in chronic liver disease: time for platelets to be replaced?

Peck-Radosavljevic M, Simon K, Iacobellis A *et al*. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). *Hepatology* 2019;70:1336–1348.

Thrombocytopaenia in chronic liver disease results from sequestration of thrombocytes in the spleen, bone marrow suppression and immunological removal of circulating platelets. Severe thrombocytopaenia (platelet count $<50\times10^9$/L) is commonly a barrier to performing invasive procedures, due to a perceived increased risk of bleeding. Platelet transfusion can be problematic, with a short duration of therapeutic effect and transfusion reactions. Lusutrombopag is an oral thrombopoietin receptor agonist that stimulates platelet production. This randomised double-blind placebo-controlled study assessed the ability of lusutrombopag to decrease the need for preprocedural platelet transfusions and to decrease requirement for rescue therapy for bleeding in adults with Childs-Pugh A or B cirrhosis and severe thrombocytopaenia undergoing an elective invasive procedure. In both the intention-to-treat (ITT) and per-protocol analyses, significantly more patients receiving lusutrombopag met the combined endpoint (ITT 64.8% vs 29.0%, $p<0.0001$). No patients in the lusutrombopag group required rescue therapy for bleeding. However, the stage of liver disease is associated with bleeding risk, and more patients in the treatment group had Childs-Pugh A disease. Lusutrombopag was associated with a greater and sustained maximum change in platelet count from baseline compared with placebo. Portal vein thrombosis has been a concern in other studies of thrombopoeitin agonists in this setting. There was no difference in the number of thrombotic events between the two groups in this study. Lusutrombopag is a promising new therapeutic strategy in patients with thrombocytopaenia undergoing elective invasive procedures. However, platelet transfusions will continue to be the mainstay of treatment in patients with chronic liver disease undergoing emergency procedures due to their availability and rapid onset of action.

REVIEWERS

Dr Richard Parker, Dr Georgina Hold, Dr Stuart McDonald, Dr Ross Porter, Dr Michael Burkitt, Dr Mhairi Donnelly

JOURNALS REVIEWED

Cell Metabolism, Cell, Cell Stem Cell, The Lancet Oncology, New England Journal of Medicine, Hepatology

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 McLean MH. *Gut* 2020;**69**:187–188. doi:10.1136/gutjnl-2019-320268

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