GI highlights from the literature

Philip J Smith

BASIC SCIENCE

Gut microbiome-metabonome interactions protect against liver injury

► Saeedi B, Liu K, Owens J, *et al*. Gut-resident Lactobacilli activate hepatic Nrf2 and protect against oxidative liver injury. *Cell Metabolism* 2020; 315,: 956-968.e5.

Several strands of evidence support a role for the gut microbiome in influencing liver physiology and the host's propensity to liver injury, although which specific bacteria may be implicated—and mechanistically how they crosstalk with the liver—remains poorly understood. In this study, researchers first performed a comparative transcriptomic and metabonomic analysis of liver tissue obtained from conventional mice and those that were germ-free (ie, sterile and lacking a gut microbiome). It was observed that only the conventional mice had hepatic transcripts of *Nrf2* (nuclear factor erythroid 2–related factor 2), a transcription factor that is recognised as a master regulator of host antioxidant and xenobiotic responses. To explore further, researchers used a transgenic *Nrf2* reporter *Drosophila melanogaster* screening assay, and identified that members of the bacterial genus *Lactobacillus* were capable of potently stimulating *Nrf2* signalling. Furthermore, oral administration of the human commensal bacterium, *Lactobacillus rhamnosus* GG (LGG), to conventional mice resulted in potent hepatic *Nrf2* activation and this was sufficient to protect against acute oxidative liver injury in two separate mouse models (paracetamol overdose and acute ethanol toxicity). Using tandem mass spectrometry to analyse portal blood from LGG-treated mice, researchers identified the presence of 5-methoxyindole acetic acid (5-MIAA). This is a small molecule produced by LGG and an activator of *Nrf2*. Collectively, these data delineate a novel specific mechanism by which the gut microbiome influences hepatic physiology, and where perturbation of the gut microbiome may increase vulnerability to liver injury.

Ileal organoids as a model system to study infection and replication of SARS-CoV-2 within human enterocytes

► Lamers M, Beumer J, van der Vaart J *et al*. SARS-CoV-2 productively infects human gut enterocytes. *Science* 2020; eabc1669 (Online first) doi: 10.1126/science.abc1669.

Angiotensin-converting enzyme 2 (ACE2) is the receptor for both severe acute respiratory syndrome coronavirus (SARS-CoV), a virus emerging in 2003 that was responsible for SARS, and SARS-CoV-2, a novel transmissible coronavirus responsible for the COVID-19 pandemic. The highest expression of ACE2 in humans is the enterocyte brush border. Gastrointestinal symptoms are recognised in subgroups of patients with COVID-19, and SARS-CoV-2 RNA has been identified in rectal swabs from some patients. However, mechanistic understanding of viral pathogenesis and transmission, including the potential for faecal-oral spread is limited. *Lamers et al* used human small intestinal organoids to derive new knowledge regarding SARS-CoV-2 infection of epithelial cell subtypes in vivo, using SARS-CoV as a comparator virus. SARS-CoV-2 was confirmed to infect and replicate within progenitor and differentiated enterocyte lineage cells, but not goblet or enteroendocrine cells. Despite approximately 1000-fold higher gene expression of ACE2 on differentiated relative to progenitor enterocytes, similar infection rates of both cell types were observed suggesting viral entry may be facilitated by even low levels of the receptor. Enterocyte infection with SARS-CoV-2 induced expression of cytokine and interferon stimulated genes consistent with type I and type III interferon responses. A stronger interferon response was seen during SARS-CoV-2 infection in comparison to SARS-CoV infection. This study confirms the usage of human small intestinal organoids as a relevant experimental model to study cellular infection, replication and immune consequences of SARS-CoV-2 in vivo.

Hormonal suppression of stem cells inhibits gastric tumourigenesis

► Chang W, Wang H, Kim W *et al.* Hormonal suppression of stem cells inhibits symmetric division and gastric tumourigenesis. *Cell Stem Cell* 2020; 26 (5): 739–754.E8 doi: 10.1016/j.stem.2020.01.020.

The regulation of gastric epithelial stem cells is poorly understood. It is known that a stem cell population exists around the isthmus region of the body type glands and at the base of antral and body type glands. Indeed, *Lgr5 (Leucine-rich repeat-containing G protein-coupled receptor 5)* a well-defined intestinal stem cell marker has been shown to be an antral stem cell marker. Previous work by this group has shown that the gastrin receptor *Cck2r* (cholecystokinin 2 receptor) also marks a stem cell population within the gastric antrum. Here, they demonstrate that gastrin can regulate stem cell function and also inhibit the formation of Wnt and p53-dependendent tumours. Lineage tracing studies were employed that demonstrated single *Cck2r*+ stem cells could clonally convert antral glands even when *Lgr5* was deleted, suggesting that *Cck2r* not *Lgr5* is critical for homoeostasis. The authors showed that only single *Cck2r*+ stem cells are present despite their progeny (*Cck2r*-) tracing throughout the gland. In the intestinal crypt, symmetric division (where one stem cell divides to form two daughter stem cells) is thought to predominate but here *Cck2r* expression was only inherited by a single daughter (asymmetry). The authors then showed that gastrin can inhibit symmetric division and the loss of this results in increased antral stem cell and gland division. A combination of the loss of APC/TP53 resulted in tumour formation and gastrin pumps prevented this. Loss of gastrin in these tumour models also resulted in greater number of mutations. This paper demonstrates potent anti-tumourigenic effect of gastrin in normal gastric antral stem cells.

CLINICAL PRACTICE

Disease modification in early Crohn's disease

► Ungaro R, Yzet C, Bossuyt P *et al.* Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease. *Gastroenterology* 2020; doi: 10.1053/j.gastro.2020.03.039.

Rheumatoid arthritis has long been used as a parallel for Crohn's disease (CD), in which the course of an immune-mediated disease can be modified by early aggressive treatment. The randomised, multicentre CALM study demonstrated that a 'tight control' (TC) strategy of early treatment escalation to azathioprine and/or adalimumab was more effective at inducing endoscopic and deep remission in patients with early CD than standard clinical symptom-based management. Deep remission is defined as a CD endoscopic index of severity <4, with no deep ulcerations or steroid treatment for more than 8 weeks, and has been recommended by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) programme as the preferred treatment target in CD. Follow-up data was available for approximately half of the CALM patient cohort (n=122), with a median follow-up of 3.02 years (range 0.05 to 6.26 years). Patients who achieved deep remission by the end of CALM had an 81% decrease in risk of disease progression over the follow-up period, irrespective

of whether they had been in the TC arm. Disease progression was recorded as a composite of major adverse outcomes, including the development of new fistulae, abscesses or strictures, or the need for surgery. The study further justifies the use of deep remission as a target to avoid complications of CD progression. However, the small proportion of patients who were able to achieve this remission target at the end of the CALM trial (n=36) indicates that this remains a challenging aim despite early and aggressive biologic use.

Synbiotics alter gut microbiota but do not improve non-invasive markers of liver fibrosis in patients with NAFLD

► Scorletti E, Afolabi P, Miles E *et al.* Synbiotics alter faecal microbiomes, but not liver fat or fibrosis, in a randomized trial of patients with non-alcoholic fatty liver disease. *Gastroenterology* 2020; 158: 1597–1610.

Dysbiosis (altered gut microbiota) is associated with endotoxin production and increased intestinal permeability. Previous studies have identified an association between non-alcoholic fatty liver disease (NAFLD) and dysbiosis. Synbiotics are a mixture of probiotics and prebiotics that reduce dysbiosis. Whether alteration of the gut microbiota using synbiotics directly benefits the liver in patients with NAFLD has not been definitively studied. Synbiotics are an attractive, low-cost treatment option with minimal side effects.

This proof-of-concept, phase-2, randomised controlled trial (RCT) studied the effect of synbiotic treatment on changes in gut microbiota, liver fat content measured by MR-spectroscopy (MRS), liver fibrosis scores and liver stiffness measurement in patients with NAFLD. Patients were randomly assigned to intervention or placebo for 10 to 14 months.

In the intention-to-treat analysis total faecal bacterial levels were not altered, however a change in diversity of the gut microbiota was observed. There was no significant difference in MRS liver fat content between the treatment and placebo groups. On multivariable regression analysis, weight loss was the only independent factor associated with reduction in liver fat. There was no significant change in non-invasive fibrosis scores, or improvement in liver stiffness measurements with synbiotic treatment.

This RCT assessing the effect of synbiotics on clinical markers of NAFLD has not shown a reduction in liver fat or improvement in fibrosis biomarkers. Only one synbiotic combination was studied and other combinations may be beneficial. Although new therapeutics for NAFLD are required, provision of adequate lifestyle advice including weight loss should continue to be the mainstay of treatment.

Efficacy of real-time computer-aided detection of colorectal neoplasia

► Repici A, Badalamenti M, Maselli R *et al.* Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial. *Gastroenterology* 2020; doi: 10.1053/j.gastro.2020.04.062.

There is a known variability in adenoma detection rate (ADR) among endoscopists. Failure in polyp recognition is a major factor in missed colorectal neoplasia. Each colonoscopy is made of approximately 50 000 frames and a single polyp may be recognisable in only a few frames, explaining why polyps are missed, as well as variations in endoscopist skill, level of cleansing, withdrawal time and other factors. Computer-aided polyp detection (CADe) systems are highly accurate in polyp detection when applied to retrospective colonoscopy videos. This parallel multicentre randomised trial was performed to assess the safety and the efficacy of an artificial intelligence-based medical device system designed to process colonoscopy images, superimposing a green box over suspected lesions in real-time, removing the need for the endoscopist to identify lesions. Subjects were aged between 40 to 80 years old and were undergoing colorectal cancer screening, post-polypectomy surveillance, had positive faecal immunochemical tests or signs and symptoms of colorectal cancer. Endoscopies were performed in three centres by six experienced endoscopists. Three hundred and forty-one patients were allocated in the CADe arm and 344 in the control arm (standard high-definition colonoscopy without CADe). The ADR was significantly higher in the CADe arm (relative risk 1.30; 95% CI 1.14 to 1.45). Adenomas detected per colonoscopy were also higher in the CADe group (incidence rate ratio 1.46; 95% CI 1.15 to 1.86) with a significantly higher detection rate for adenomas <10 mm without increasing withdrawal time. The unnecessary resection of non-neoplastic polyps did not increase between groups. Therefore, CADe could be of significant importance in improving future detection of colorectal neoplasia.

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JOURNALS REVIEWED

Cell Metabolism, Science, Cell Stem Cell, Gastroenterology

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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* 2020;**69**:1533–1534. doi:10.1136/gutjnl-2020-322008

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