IN BRIEF

GUT MICROBIOTA

Gut mucosal virome altered in ulcerative colitis

The gut microbiota has been implicated in the development of IBD, but little is known about the role of the viral intestinal communities. A new study demonstrates that ulcerative colitis is characterized by substantial changes in the mucosal virome, namely a high abundance of *Caudovirales* bacteriophages but decreased diversity, richness and evenness of mucosal *Caudovirales* in comparison with healthy individuals. Deep metagenomic sequencing of viral-like particle preparations and bacterial 16S ribosomal RNA sequencing were performed on rectal mucosal samples from 91 individuals with ulcerative colitis and 76 healthy individuals as controls. Sequencing data were then correlated with patient metadata. Additional analysis revealed that this altered mucosal virome was associated with intestinal inflammation and altered virulence functions and interkingdom correlations between mucosal viruses and bacteria in the context of ulcerative colitis.

ORIGINAL ARTICLE Zuo, T. et al. Gut mucosal virome alterations in ulcerative colitis. *Gut* https://doi.org/10.1136/gutjnl-2018-318131 (2019)

SURGERY

Gastric bypass — weight loss and metabolic outcomes similar with OAGB versus RYGB

Bariatric surgery is an effective approach in the management of obesity. Although one anastomosis gastric bypass (OAGB) is increasingly used, the efficacy and safety outcomes in comparison to standard Roux-en-Y gastric bypass (RYGB) are debated. Results from the YOMEGA randomized trial now show that OAGB is not inferior to RYGB with respect to weight loss and metabolic improvements at 2 years. The trial included 253 individuals aged 18–65 years ($n = 129$ OAGB; $n = 124$ RYGB). After 2 years, mean percentage excess BMI loss was similar between the two groups (−87.9% for OAGB versus −85.8% for RYGB). However, there were higher numbers of serious adverse events reported in the OAGB group than in the RYGB group, with increased incidence of diarrhoea, steatorrhoea and nutritional adverse events with 200 cm biliopancreatic limb OAGB that were suggestive of malabsorptive effects.

ORIGINAL ARTICLE Robert, M. et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. *Lancet* https://doi.org/10.1016/S0140-6736(19)30475-1 (2019)

PANCREATIC CANCER

Metabolite crosstalk could modulate chemotherapy response in pancreatic cancer

Macrophages are highly abundant in the microenvironment of pancreatic ductal adenocarcinoma (PDAC), with reported roles of tumour-associated macrophages (TAMs) in chemotherapy resistance. New research now provides clues to the influence of TAMs in pancreatic cancer therapy, demonstrating that pyrimidine nucleoside release (notably deoxycytidine) from macrophages inhibits the effectiveness of gemcitabine treatment of pancreatic cancer. Macrophages programmed by PDAC cells released a spectrum of pyrimidine species, including deoxycytidine, in vitro. Crucially, deoxycytidine inhibited gemcitabine, directly competing with drug uptake and metabolism. In mouse models of PDAC, genetic or pharmacological depletion of TAMs sensitized these tumours to gemcitabine treatment.

ORIGINAL ARTICLE Halbrook, C. J. et al. Macrophage-released pyrimidines inhibit gemcitabine therapy in pancreatic cancer. *Cell Metab.* https://doi.org/10.1016/j.cmet.2019.02.001 (2019)

PANCREATIC CANCER

Autophagy inhibitor combination strategies for pancreatic cancer

A new study has unexpectedly shown that the suppression of KRAS increases autophagy in *KRAS*-mutant pancreatic ductal adenocarcinoma (PDAC). Similar results were reported with suppression of the KRAS effector, ERK mitogen activated protein kinase (MAPK), which might lead to novel pharmacological combination strategies to effectively treat PDAC.

The prevalence of *KRAS* driver mutations in PDAC has spurred research into anti-KRAS therapies. One strategy is to target KRAS-dependent metabolic functions such as autophagy, which is upregulated in *KRAS*-mutant PDAC and is crucial for tumorigenic growth. "We hypothesized that mutant KRAS signalling must be driving the high levels of autophagy observed in PDAC," explains first author Kirsten Bryant. "We were surprised to observe the opposite result."

Using multiple assays to monitor autophagy, the authors first showed that *KRAS* ablation led to further upregulation of autophagy. ERK MAPK is thought to be a key effector pathway in *KRAS*-mutant PDAC. Pharmacological ERK inhibition was found to phenocopy *KRAS* suppression and also increase autophagic flux in PDAC.

Using a variety of experimental approaches, the researchers then showed that ERK inhibition impaired metabolic processes in PDAC, such as glycolysis and mitochondrial function, which consequently led to a greater dependence on autophagy. "We then demonstrate that inhibition of ERK MAPK in combination with autophagy synergistically suppressed PDAC proliferation and enhanced apoptosis," reports Bryant.

"Our study suggests that by making PDAC more reliant on autophagy

LIVER FIBROSIS

LSEC stretch promotes fibrosis during hepatic vascular congestion

Liver sinusoidal endothelial cells (LSECs) respond to mechanical forces in portal hypertension by recruiting neutrophils that promote fibrosis, according to a new study.

Mechanical forces, induced by altered liver haemodynamics, are important mediators of portal hypertension and fibrogenesis. For instance, congestive hepatopathy, which can occur in the setting of congestive heart failure, leads to increased central and portal venous pressure and fibrosis. In previous work, Vijay Shah and coworkers showed that LSECs, sinusoidal thrombosis and mechanical forces have important roles in mediating these pathogenic events, yet the mechanisms underlying these effects remained poorly understood.

In their new work, Shah and colleagues first stretched primary mouse LSECs and assessed changes in gene expression. Levels of chemotactic cytokines were increased, including the neutrophil chemoattractant CXCL1. Neutrophils have previously been implicated in sinusoidal thrombogenesis, leading the researchers to focus on these cells.

Next, they explored the role of neutrophils in a mouse model of congestive hepatopathy, mediated by partial inferior vena cava ligation (pIVCL). Neutrophils accumulated in the liver 24 h after ligation and formed aggregates with platelets. Platelet–neutrophil interaction is a key mechanism promoting the formation of prothrombotic neutrophil extracellular traps (NETs), and extensive NET formation was seen after pIVCL. Importantly, genetic disruption or pharmacological inhibition of NET formation decreased portal hypertension and liver fibrosis induced by pIVCL.