IN BRIEF

PANCREATIC CANCER

Modified FOLFIRINOX superior to gemcitabine in resected pancreatic ductal adenocarcinoma

Results of a new clinical trial show that patients with resected pancreatic ductal adenocarcinoma treated with a modified FOLFIRINOX (mF) regimen had longer survival than those treated with gemcitabine. A total of 493 patients were randomly allocated to either treatment for 24 weeks. At 33.6 months median follow-up, median disease-free survival was 21.6 months and 12.8 months ($P < 0.001$) and 3-year disease-free survival was 39.7% and 21.4% in the mF group and the gemcitabine group, respectively. Median overall survival was 54.4 months and 35.0 months ($P = 0.003$) and 3-year overall survival was 63.4% and 48.6% in the mF group and the gemcitabine group, respectively. 75.9% in the mF group and 52.9% in the gemcitabine group experienced grade 3 or 4 adverse events.

ORIGINAL ARTICLE Conroy, T. et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N. Engl. J. Med.* **379**, 2395–2406 (2018)

NAFLD

Panel of 10 serum metabolites shows promise in the non-invasive detection of advanced fibrosis

Accurate non-invasive assessment of disease severity in patients with NAFLD is an urgent clinical need. A new proof-of-concept study demonstrates that a panel of 10 serum metabolites has high diagnostic accuracy and is superior to FIB-4 and the NAFLD Fibrosis Score (NFS) in detecting advanced fibrosis. The cross-sectional analysis included a prospective derivation cohort of 156 patients with biopsy-proven NAFLD and two validation cohorts, one including 142 participants who were assessed by MRI elastography (MRIE) and one including 59 patients with biopsy-proven NAFLD. In the derivation cohort, 32 of 652 assessed metabolites were associated with advanced fibrosis. The combined area under the receiver operating characteristic curve (AUROC) for the detection of advanced fibrosis with a panel of the top 10 metabolites was higher than that of FIB-4 and NFS ($P = 0.002$ and $P = 0.017$, respectively). The AUROC c-statistics of the panel were 0.94 and 0.84 for the MRIE and liver biopsy validation cohorts, respectively.

ORIGINAL ARTICLE Caussy, C. et al. Serum metabolites detect the presence of advanced fibrosis in derivation and validation cohorts of patients with non-alcoholic fatty liver disease. *Gut* https://doi.org/10.1136/gutjnl-2018-317584 (2018)

OBESITY

Reduction of visceral adipose tissue mass requires IL-6 signalling

Visceral adipose tissue (VAT) is detrimental to health, but physical activity can reduce VAT mass. During exercise, skeletal muscle releases IL-6, and IL-6 has been shown to stimulate lipolysis. A new randomized controlled trial investigated changes in VAT mass in 83 adults with abdominal obesity, allocated to receive the IL-6 receptor antibody tocilizumab or placebo during a 12-week intervention of bicycle exercise or no exercise. In participants receiving placebo, exercise reduced VAT mass (−225.1 g, 95% CI −446.7 g to −3.4 g; $P = 0.047$). By contrast, in participants performing exercise, VAT mass was increased in the tocilizumab group compared with the placebo group (278.2 g, 95% CI 61.69–494.73 g; $P = 0.013$), indicating that IL-6 is required for VAT mass reduction through exercise.

ORIGINAL ARTICLE Wedell-Neergaard, A. S. et al. Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: a randomized controlled trial. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.12.007 (2018)

GUT MICROBIOTA

Gut microbiota-mediated liver inflammation in PSC

The inflammatory liver disease primary sclerosing cholangitis (PSC) is often associated with ulcerative colitis (PSC–UC). A new study has shed light on this association, showing that specific gut bacteria can disrupt gut barrier integrity and then initiate inflammatory responses in the liver following translocation.

Observations of portal bacteraemia and elevated endotoxin levels in cholangiocytes have implicated the gut microbiota in PSC. One possible explanation for PSC–UC is that colonic inflammation leads to increased intestinal epithelium permeability and bacterial translocation to the liver, eliciting a T helper 17 (T_H17) immune response. "We aimed to clarify the specific gut microbiota that contribute to PSC pathogenesis, and the underlying mechanism, by using humanized mice," reports author Nobuhiro Nakamoto.

"First, we used a gnotobiotic system with faecal samples from patients with PSC–UC to reveal the direct contribution of specific bacteria to bacterial translocation and the subsequent immune priming in the liver," explains Nakamoto. The investigators found increased serum levels of endotoxin and T_H17 priming in the livers of mice inoculated with faecal samples from patients with PSC–UC, but not in mice with microbiota from healthy individuals. Bacterial culturing of the mesenteric lymph nodes from the PSC–UC humanized mice isolated *Klebsiella pneumoniae*, *Proteus mirabilis* and *Enterococcus gallinarum*, which were also found to be prevalent in faecal samples from patients ($n = 18$) with PSC–UC.

"We then established a monolayered culture system using human intestinal organoids to clarify the mechanism of how

LIVER

ACLF monocyte dysfunction

A new study explores the pathways underlying monocyte dysfunction in patients with acute-on-chronic liver failure (ACLF). Immune response and cell activation genes were downregulated in monocytes from patients with ACLF in contrast to those from patients with decompensated cirrhosis (DC). Plasma from patients with ACLF induced impaired phagocytosis and metabolic reprogramming in healthy monocytes, but glutamine synthetase (GLUL) inhibition partially restored inflammatory capacity.

The team investigated the function of monocytes from patients with ACLF or DC and from healthy controls. Human leukocyte antigen DR isotype (HLA-DR) expression was lower in ACLF and DC classical monocytes than in healthy classical monocytes. Following lipopolysaccharide exposure, intracellular IL-10 levels were higher in classical and intermediate ACLF monocytes than in DC and healthy monocytes, suggesting increased immunosuppressive characteristics. Transcriptome analysis of the classical monocyte subsets showed that genes involved in immune response and cell activation were upregulated in DC monocytes but downregulated in ACLF monocytes, compared with healthy monocytes.

Characterization of antibacterial response capacity revealed decreased expression of TLR2 and TLR4 on DC and ACLF monocytes. Following *Escherichia coli* exposure, DC and ACLF monocytes showed decreased phagocytosis, which was more pronounced in ACLF monocytes; oxidative burst response was also decreased in ACLF monocytes.

Previous findings indicate that metabolic features can control monocyte function. Exposing healthy monocytes to ACLF plasma ex vivo induced transcriptional and functional profiles similar to ACLF monocytes. These induced ACLF