In the news

DIGITAL ILC 2020

In August 2020, *Nature Reviews Gastroenterology & Hepatology* attended The Digital International Liver Congress (ILC) 2020, hosted by the European Association for the Study of the Liver (EASL). This year, owing to the ongoing coronavirus disease 2019 (COVID-19) pandemic, the conference moved online. The virtual meeting was attended by ~7,400 people from 114 countries.

The event boasted a stylish user interface and featured exciting preclinical and clinical research on fields such as cirrhosis, liver tumours, metabolism and viral hepatitis. Each day kicked off with sessions from the EASL Studio, in which topics such as hepatitis C virus elimination and the therapeutic pipeline for hepatitis B virus were discussed. Abstract sessions, on fields as varied as liver immunology and the drug pipeline for nonalcoholic fatty liver disease (NAFLD), and digital poster sessions provided a platform for the latest findings and trial results.

Notable research highlights included the presentation of positive phase II results for use of the FGF19 analogue aldafermin in patients with nonalcoholic steatohepatitis (NASH), encouraging phase IIb results of the ATLAS trial for cilofexor and firsocostat combination therapy in patients with bridging fibrosis and cirrhosis due to NASH, and a genome-wide association study for alcohol-related cirrhosis that identified two new risk loci in *MARC1* and *HNRNPUL1*.

A common theme across the conference was the role of the gut microbiota in liver disease. For example, novel data from mouse studies suggested that intestinal dysbiosis drives hepatocarcinogenesis by shaping the hepatic inflammatory microenvironment. The genetic and metabolic aspects of NAFLD were also well represented. Indeed, the contested proposed name change of NAFLD to metabolic associated fatty liver disease (MAFLD) cropped up frequently.

Also included were presentations on the use of FXR and PPAR agonists for cholangiopathies, as well as a session on the latest developments in pathogenesis and treatment of hepatitis E virus infection — the session highlighted how much work there is left to do regarding this virus. A timely session on COVID-19 and the liver explored the implications of, for example, the pandemic on liver transplantation programmes.

In contrast to this year's virtual setting, ILC 2021 is due to take place in Amsterdam, The Netherlands, next June.

Jordan Hindson

NEUROGASTROENTEROLOGY

Regional ENS effects from gut microbiota

A new study in *Science* has shown that enteric nervous system (ENS) neurons in mice are both affected by the gut microbiota and functionally tuned according to the gut segment they occupy. Furthermore, a subset of microbiota-responsive neurons was found to be capable of metabolic control independent of the central nervous system.

Intrinsic ENS-associated neurons (iEANs) innervate the gastrointestinal tract and respond to various environmental stimuli. Using transgenic mouse models and microbial manipulations, the new study performed by the lab of Daniel Mucida at Rockefeller University, USA, examined how the gut microbiota affects iEANs and the subsequent effects on host physiology.

By comparing the translational profiles of mouse iEANs from duodenum, ileum and colon, iEAN subsets were found to segregate according to their anatomical location. "Additionally, we found that the microbiota has a substantial effect on ENS regional programming," reports co-first author Paul Muller. The team found little effect of microbial colonization on iEANs from microbiota-poor regions, but in microbiota-rich regions, microbial manipulations led to substantial differences in iEAN gene expression profiles and neuropeptide levels.

"We discovered that one of the microbiota-modulated neuropeptide iEAN populations, positive for cocaine amphetamine related transcript (CART), was capable of controlling blood glucose levels through sympathetic modulation of the pancreas and liver," says Muller. "This finding assigned a new and unexpected role for the ENS in metabolic control."

The researchers are now looking into why particular iEAN subsets are affected the by the gut microbiota, which could lead to novel treatments or prevention of neuropathies. "Given the surprising finding that a subset of iEANs can control hepatic and pancreatic function, it will be fascinating to see whether they have a role in the course of metabolic disease or if they can be manipulated as a form of treatment," concludes Mucida.

Iain Dickson

ORIGINAL ARTICLE Muller, P. A. et al. Microbiota-modulated CART$^+$ enteric neurons autonomously regulate blood glucose. *Science* https://doi.org/10.1126/science.abd6176 (2020)

INFLAMMATION

Haemolysis and liver macrophages

In the liver, macrophages phagocytose damaged erythrocytes. A new study suggests that this process, known as erythrophagocytosis, drives liver macrophages towards an anti-inflammatory phenotype that can attenuate inflammatory diseases in mouse models.

Using mouse models of haemolysis and single-cell RNA sequencing of mouse macrophages, the researchers identified an anti-inflammatory transcriptional phenotype of liver macrophages that was characterized by, for example, high expression of the scavenger receptor MARCO. The transcription factor NFE2L2 was identified as a potential driver of the altered gene expression patterns. The macrophage transformation was replicated in vitro as a result of haem exposure to bone marrow-derived mouse and human macrophages. In addition, NFE2L2 deficiency restored haem-suppressed inflammation. These data suggest that a haem–NFE2L2 signalling pathway might drive this anti-inflammatory polarization of macrophages towards the phenotype that the researchers term 'erythrophagocytes'.

Interestingly, erythrophagocytosis attenuated disease development in mouse models of macrophage-driven inflammatory disease. In mice with diet-induced nonalcoholic fatty liver disease, liver histology revealed extensive steatosis in wild-type mice but not in mice with hereditary haemolytic anaemia. Similarly, in mice with an anti-CD40-induced systemic inflammatory syndrome, inflammatory disease was attenuated in mice with hereditary haemolytic aneaemia compared with wild-type mice.

Together, the findings indicate a pathway linking haemolysis and erythrophagocytosis via the differentiation of liver macrophages towards a newly identified anti-inflammatory phenotype. The results might help us to further our understanding of the immunopathology of haemolytic disorders such as sickle cell anaemia and spherocytosis.

Jordan Hindson

ORIGINAL ARTICLE Pfefferlé, M. et al. Hemolysis transforms liver macrophages into antiinflammatory erythrophagocytes. *J. Clin. Invest.* https://doi.org/10.1172/JCI137282 (2020)