IN BRIEF

PAEDIATRICS

Maternal IgA is necessary for preventing necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is a potentially lethal disease that affects preterm neonates and involves exaggerated intestinal inflammation in response to colonizing bacteria. The incidence of NEC is known to be reduced in infants fed with maternal milk but a new study has now shown that immunoglobulin A (IgA) in maternal milk is a crucial protective factor. By analysing immunoglobulin binding of gut bacteria in faecal samples from preterm infants at the time of NEC diagnosis ($n = 30$) and age-matched controls ($n = 39$), a decrease in IgA-bound bacteria was found to be associated with the development of NEC, and maternal milk was found to be the predominant source of IgA in the first month of life. Using a mouse model of NEC, the investigators then confirmed the importance of maternal IgA in preventing the disease by finding that pups reared by IgA-deficient mothers were still susceptible to NEC despite exposure to maternal milk.

ORIGINAL ARTICLE Gopalakrishna, K. P. et al. Maternal IgA protects against the development of necrotizing enterocolitis in preterm infants. *Nat. Med.* https://doi.org/10.1038/s41591-019-0480-9 (2019)

IBD

Pregnancy safe and beneficial for women with IBD

A new study examining the immunological and microbial profiles of pregnant patients with IBD suggests that pregnancy is safe and potentially beneficial for women with IBD. In this study, faecal and serum samples were obtained from 46 patients with IBD (31 with Crohn's disease and 15 with ulcerative colitis) and 170 healthy control individuals at various time points before, during and after pregnancy. Circulating pro-inflammatory cytokine levels (IL-6, IL-8, IL-12 and TNF) markedly decreased after conception in pregnant patients with IBD. Microbiome analyses showed that although microbial diversity was reduced in patients with IBD compared with healthy women before and during early pregnancy, this IBD-associated dysbiosis was absent during middle and late pregnancy.

ORIGINAL ARTICLE van der Giessen, J. et al. Modulation of cytokine patterns and microbiome during pregnancy in IBD. *Gut* https://doi.org/10.1136/gutjnl-2019-318263 (2019)

THERAPY

Exclusion diet plus partial enteral nutrition sustains remission in children with Crohn's disease

In children with mild-to-moderate Crohn's disease, exclusive enteral nutrition (EEN) is recommended but challenging to implement. In a 12-week prospective randomized controlled trial, 78 children with Crohn's disease were assigned to either receive the Crohn's disease exclusion diet (CDED) plus 50% of calories from formula for 6 weeks followed by CDED plus 25% partial enteral nutrition (PEN) for a further 6 weeks, or to receive EEN for 6 weeks and then a free diet plus PEN for a further 6 weeks. The combination of CDED plus PEN was found to be better tolerated than EEN. Although both diets were found to induce corticosteroid-free remission by week 6, the combination of CDED plus PEN led to sustained remission in significantly ($P = 0.01$) more patients than EEN at week 12. The CDED plus PEN combination also led to changes in the faecal microbiome that were associated with remission, further supporting this approach in children with Crohn's disease.

ORIGINAL ARTICLE Levine, A. et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. *Gastroenterology* https://doi.org/10.1053/j.gastro.2019.04.021 (2019)

NAFLD

Organoid modelling of NAFLD

A novel method to co-differentiate parenchymal and nonparenchymal liver cells from pluripotent stem cells (PSCs) can generate multicellular human liver organoids (HLOs) to model NAFLD, reports a new study.

Despite huge interest from industry in developing therapies for NAFLD, efforts to translate promising agents from animal and cell models have failed to yield any regulatory approvals. One contributing factor might be a lack of human modelling systems suitable for high-throughput compound screening. Cell-based culture systems have increased in sophistication over the past few years, yet often fail to model the complex multicellular environment in NAFLD. Prior co-culture approaches with PSCs used a parallel differentiation approach, whereby individual hepatic cell types are derived independently and then combined in culture. However, this method only models inflammation and fibrosis, limiting its use in NAFLD research.

To create an improved in vitro model of NAFLD, Takanori Takebe and colleagues generated an organoid model by co-differentiating human PSCs into epithelial and stromal lineages to form multicellular HLOs. Using an established approach, they first differentiated PSCs into foregut spheroids. These spheroids were then embedded in Matrigel and cultured with retinoic acid, before hepatocyte differentiation was induced using hepatocyte maturation media.

Single-cell RNA sequencing of the resulting HLOs revealed five distinct cell clusters, comprising cells expressing markers of hepatocytes, stellate cells, cholangiocytes, biliary stem cells and Kupffer cells. Functional characterization of hepatocyte-like, stellate-like and Kupffer-like cells supported the presence of distinct hepatic cell types similar to those seen in human liver. When HLOs were exposed to fatty acids (FAs), hepatocyte-like cells developed steatosis and ballooning,

VIRAL HEPATITIS

TCR-grafted T cells restore antiviral immunity

A new study reports that adoptive transfer of T cells engineered to express HBV-specific T cell receptors (TCRs) — an emerging therapeutic approach to restore antiviral immunity — elicits robust antiviral responses in preclinical models.

Using retroviral transduction, $CD4^+$ and $CD8^+$ T cells — derived from healthy donors and patients with chronic hepatitis B (CHB) — were engineered to stably express high-affinity TCRs specific for HBV envelope or core proteins. In HBV-infected hepatoma cells, co-culture with these TCR-grafted T cells led to undetectable levels of viral antigens and covalently closed circular DNA (cccDNA), suggesting their capacity for virological control.

In HBV-infected humanized mice, a single transfer of TCR-grafted T cells was sufficient to achieve strong HBV control, leading to the robust clearance of HBV-infected hepatocytes. Indeed, compared to mock-treated and untreated mice, adoptive transfer induced major decreases in HBV viraemia as well as serological and intrahepatic markers of infection, such as cccDNA.

In partially HBV-infected humanized mice (which mimic the clinical scenario, in which only a small percentage of hepatocytes are infected), injection of TCR-grafted T cells led to specific elimination of infected hepatocytes without damaging non-infected cells, as evidenced by only a transient elevation of alanine aminotransferase levels (indicative of hepatocyte death), which subsequently returned to baseline. Interestingly, co-administration of TCR-grafted