LIVER

Replenishing hepatocytes

New research provides insights into hepatocyte renewal during maintenance and repair, with the identification of a subset of hepatocytes expressing telomerase ($TERT^{High}$ hepatocytes) that can repopulate the liver during homeostasis and after injury.

Understanding the mechanisms of liver regeneration has been an intense area of research, particularly with respect to the cellular sources that maintain and repair the liver. Existing evidence linked telomerase to long-term renewal in stem cells, and germline inactivating mutations in telomerase genes have been shown to predispose mice and humans to liver cirrhosis. Given these observations, Lin et al. reasoned that telomerase expressed in liver cells could have unique properties and wanted to characterize this particular subset of cells.

Using a series of experiments in mice (including lineage tracing analysis), the researchers identified $TERT^{High}$ hepatocytes throughout the liver, representing 3–5% of hepatocytes. Crucially, during homeostasis, they found that this subset of liver cells could repopulate the liver, comprising ~30% of the liver at 1 year. Moreover, these $TERT^{High}$ hepatocytes were distributed throughout all lobular zones (the majority located in the periportal and midlobular areas), and yielded expanding hepatocyte clones by a self-renewal and differentiation mechanism.

After chemical injury (a single dose of carbon tetrachloride damaging the liver periportal zone), repopulation by $TERT^{High}$ hepatocytes was accelerated and their progeny could cross zonal boundaries during repair. Furthermore, these cells contributed to hepatocyte regeneration after diet-induced liver injury, and genetic ablation of $TERT^{High}$ cells combined with diet-induced injury resulted in a marked increase in hepatic stellate cell activation and liver fibrosis in the mice.

The authors propose a 'distributed model' to explain hepatocyte renewal. "According to this model, rare $TERT^{High}$ hepatocytes located throughout the lobule form enlarging clones during homeostasis in response to hepatocyte loss, and this response is accelerated during liver injury," they write.

Katrina Ray

ORIGINAL ARTICLE Lin, S. et al. Distributed hepatocytes expressing telomerase repopulate the liver in homeostasis and injury. *Nature* **556**, 244–248 (2018)

GENETICS

An *HSD17B13* variant reduces cirrhosis risk

A newly identified gene variant reduces risk of chronic liver disease (CLD) and cirrhosis, according to a new study.

CLD and cirrhosis are important global causes of morbidity and mortality. Whereas the environmental factors contributing to the development and progression of CLD, such as alcohol and viral hepatitis, are well-understood, a large proportion of the genetic risk component is either unexplained or poorly characterized. For instance, the mechanisms underlying the association between *PNPLA3* sequence variance and increased risk of NAFLD and cirrhosis remain unclear a decade after this relationship was first reported.

To identify additional genetic associations with CLD, Abul-Husn and colleagues tested exome sequence data from 46,544 individuals (median BMI 30 kg/m^2) for associations between single-nucleotide polymorphisms and serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This analysis uncovered a novel association between a variant in *HSD17B13*, which encodes hydroxysteroid 17-β dehydrogenase 13, and decreased ALT and AST levels. The variant allele (allele frequency 26%) was also negatively associated with CLD: in heterozygotes, risk of alcoholic cirrhosis and nonalcoholic cirrhosis was decreased 42% and 26% respectively; for homozygotes, the respective risk reductions were 73% and 49%. Notably, the variant was not associated with simple steatosis, suggesting that it mitigates CLD progression.

Functional analyses revealed that HSD17B13 was enriched on membranes surrounding lipid droplets in human hepatocyte cell lines. The *HSD17B13* variant was found to alter mRNA splicing, yielding a truncated protein with reduced enzymatic activity against the experimentally determined enzymatic substrates of HSD17B13, steroids (such as estradiol) and bio-active lipids (such as leukotriene B_4). These findings suggest that modulating HSD17B13 activity could be a therapeutic target for treating CLD.

Hugh Thomas

ORIGINAL ARTICLE Abul-Husn, N. S. et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. *N. Engl. J Med.* **378**, 1096–1106 (2018)

PANCREATIC CANCER

Microbiome promotes pancreatic cancer

According to a new study, the cancerous pancreas in mice and humans harbours an abundant microbiota that promotes immune suppression and oncogenesis.

Few studies have established a link between the gut microbiota and carcinomas in organs separate from the gastrointestinal tract. "In pancreatic ductal adenocarcinoma (PDAC), we previously reported that activation of pattern recognition receptors accelerates tumorigenesis via induction of innate and adaptive immune suppression," explains author Mautin Hundeyin. "Therefore, we hypothesized that microbial dysbiosis can drive PDAC progression by promoting immune tolerance and targeting the microbiome can reverse this process."

Using 16 S ribosomal RNA fluorescent probes and quantitative PCR, a 1,000-fold increase in intrapancreatic bacteria was found in human PDAC compared with normal pancreatic tissue. Select bacteria were increased in PDAC compared with the gut and were found to translocate via the pancreatic duct. "This was an interesting finding as the pancreas has traditionally been considered a sterile organ," says Hundeyin.

In preinvasive and invasive mouse models of PDAC, bacterial ablation using germ-free mice or antibiotics was shown to protect against PDAC growth and was associated with immunogenic reprogramming of the tumour microenvironment. The decrease in select Toll-like receptor activation on monocytic cells led to increased tumour-protective M1 macrophage polarization, which promoted infiltration and activation of T helper cells and cytotoxic T cells.

Bacterial ablation also upregulated T-cell PD1 expression, suggesting an approach that could synergize with checkpoint-based immunotherapy. "Based on this finding, we are starting a clinical trial where patients with locally advanced PDAC will receive antibiotics and pembrolizumab prior to resection," concludes Hundeyin. The data also suggest that elements of the microbiota might be useful in PDAC diagnosis.

Iain Dickson

ORIGINAL ARTICLE Pushalkar, S. et al. The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. *Cancer Discov.* **8**, 403–416 (2018)