GI highlights from the literature

Mairi H McLean, *Education editor*

BASIC SCIENCE

A novel method of liver preservation may alleviate the shortage of donor organs

▸ Berendsen TA, Bruinsma BG, Puts CF, *et al.* Supercooling enables long-term transplantation survival following 4 days of liver preservation. *Nat Med* 2014;20:790–3.

There is a shortage of donor organs for transplantation worldwide. One strategy to increase availability is to enhance organ preservation and allow more potentially available organs to be used successfully. Currently, viable preservation is available up to 12 h. Although various methods of supercooling to enhance preservation have been assessed, there are many challenges in applying this to whole organs and thus far this approach has been relatively unsuccessful in animal models. This current paper reports a novel 4-step method to extend preservation of fresh rat liver to beyond 72 h and still achieve successful transplantation outcome. The method employs supercooling, the use of 2 cryoprotectants (polyethylene glycol for extracellular cell membrane protection and a non-metabolised glucose derivative for intracellular protection) and subnormothermic machine preservation (SNMP) to overcome ischaemic–reperfusion injuries. Fresh rat liver preserved in this way for 72 and 96 h resulted in 100% and 58% post-transplant survival at 3 months, respectively. The authors were able to assess recovery parameters extensively throughout the SNMP phase and identified that the parameter of hepatic resistance at 30 min predicted organ viability and subsequent survival. This method is under further optimisation; validation in a larger experimental cohort is required and there may be challenges with interspecies translation. However, the undeniable proof-of-concept success of this method offers an exciting future advancement in transplant medicine.

The role of autophagy in liver regeneration

▸ Toshima T, Shirabe K, Fukuhara T, *et al.* Suppression of autophagy during liver regeneration impairs energy charge and hepatocyte senescence in mice. *Hepatology* 2014;60:290–300.

The liver has the unique ability to regenerate itself through a complex multistep process. Specifically, hepatocytes must awaken from senescence, enter cell cycle, replicate and finally return to a senescent state. Though this process is well known, the underlying mechanisms as to how the liver reacts metabolically during this regenerative process remain unclear. Autophagy is a cellular mechanism that breaks down proteins and damaged organelles such as mitochondria. This produces amino acids essential for ATP homeostasis. Therefore, it is likely that autophagy is critical during processes such as liver regeneration. To test this notion, Toshima and colleagues used a liver-specific knockout of autophagy-related gene 5 (L-Atg5KO) in a murine partial hepatectomy (Phx) model. Interestingly, L-Atg5KO mouse survival and liver regeneration were impaired after Phx with enhanced liver damage, including elevations in serum transaminase. Autophagy was evident 18 h post Phx in wild-type mice, and this was significantly blunted in L-Atg5KO mice. L-Atg5KO mice displayed increased levels of ubiquitinated proteins, enhanced mitochondrial damage, reduced fatty acid oxidation and weakened ATP generation; all markers of autophagic disruption. Lastly, L-Atg5KO mice were locked into senescence evidenced by cell cycle arrest, elevations to p21 and senescence-associated β-galactosidase, as well as secretion of senescence-associated molecules such as interleukin (IL)-6 and IL-8. These results suggest that autophagy is a critical component in liver regeneration, likely by allowing hepatocytes to properly process proteins and damaged mitochondria, thus preventing cellular damage and hepatocyte senescence.

TP53 mutations in the non-cancerous stomach

▸ Shimizu T, Marusawa H, Matsumoto Y, *et al.* Accumulation of somatic mutations in TP53 in gastric epithelium with *Helicobacter pylori* Infection. *Gastroenterology* 2014;147:407–17.

Gastric cancer remains a common cancer worldwide with poor prognosis. *Helicobacter pylori* infection is a well-known risk factor. The application of deep-sequencing technologies to gastric cancer has identified a number of mutations within coding regions, although very few are considered driver mutations (conferring selective advantage), as opposed to passenger mutations (occurring coincidently to driver). The precise evolution of such mutations and the earliest point at which they occur remain unknown. Shimizu and colleagues performed whole-exome sequencing and additional deep sequencing of matched pairs of gastric cancer and non-cancerous gastritis tissues in patients with chronic *H. pylori* infection to determine if mutations in known cancer-associated genes are present in *H. pylori*-associated inflammation. To define the normal variants from the somatic mutations, they determined whole-exome sequences of matched peripheral lymphocytes in each patient. The authors readily detected low-abundance *TP53* and *ARID1A* mutations in non-cancerous gastritic areas in *H. pylori*-associated gastric cancer patients. They were also able to show mutations in areas of *H. pylori* gastritis in patients without cancer, but not in the normal gastric mucosa of uninfected individuals with cancer. To determine why mutations arise in the inflamed gastric mucosa, the authors expressed human *TP53* in mice that constitutively express activation-induced cytidine deaminase, previously shown to be expressed in patients with gastric cancer, and showed that the human *TP53* gene became mutated. In addition, the number of non-silent mutations correlated with microsatellite instability status. The mutational signature they identified suggests that cytidine to uracil deamination is implicated in the mutational process underlying *H. pylori*-induced carcinogenesis. They conclude that *TP53* mutations occur in the very earliest stage of gastric tumourigenesis, and while these mutations themselves are not cancer-causing, they clearly result in the priming of the cancer cascade.

CLINICAL PRACTICE

Fully covered self-expanding metal stents as treatment for benign biliary strictures

▸ Devière J, Nageshwar Reddy D, Püspök A, *et al.* Successful management of benign biliary strictures with fully covered self-expanding metal stents. *Gastroenterology* 2014;147:385–95.

Benign biliary strictures (BBS) occur following surgical bile duct injury, at the anastomotic site following liver transplantation or as a consequence of chronic pancreatitis (CP), and can lead to chronic cholestasis, cholangitis and secondary biliary cirrhosis. Treatment with endoscopically placed plastic stents results in effective stricture resolution in most patients, but is time-consuming, expensive and requires on average 5 ERCPs over a period of 1 year or more. Fully covered self-expanding metal

stents (FCSEMS) provide an alternative approach with potential benefits of enhanced biliary drainage, decreased rates of stent blockage and effective stricture dilatation, and their design may eliminate the need for multiple ERCPs. This multicentre prospective non-randomised study assessed the ability to achieve successful FCSEMS placement and removal, and frequency and durability of stricture resolution after prolonged placement of FCSEMs. One hundred and eighty-seven patients with BBS received FCSEMS at ERCP. Stent removal was scheduled at 10–12 months for individuals with CP or surgical bile duct injury, and 4–6 months for those with BBS following liver transplantation. FCSEMS placement was successful in all patients; stent positioning was satisfactory in 185/187. Of these, 131/177 (74.6%) underwent per protocol FCSEMS removal within the defined timescale. Of these, 25/177 underwent early stent removal for complications, mainly cholangitis; 16/177 had complete distal migration of the FCSEMS and 5/177 were lost to follow-up. Endoscopic stent removal was successful at the first time of asking in 149/155 (96.1%). Of these, 135/177 (76.3%) had successful resolution of stricture without need for re-stenting through follow-up (median 20 months). FCSEMS migration was encountered in 55 individuals. Sixty-two stent-related or stent removal-related adverse events occurred in 51 individuals (27%), mainly cholangitis. These data support the use of FCSEMS for BBS, but head-to-head studies versus plastic stents are needed. Future studies should determine the optimal time between stent deployment and removal for the varying causes of BBS.

Screening and surveillance colonoscopy—two new data sets!

- Lieberman DA, Holub JL, Morris CD, *et al.* Low rate of large polyps (>9 mm) within 10 years after an adequate baseline colonoscopy with no polyps. *Gastroenterology* 2014;147:343–50.
- Lieberman DA, Williams JL, Holub JL, *et al.* Race, ethnicity, and sex affect risk for polyps >9 mm in average-risk individuals. *Gastroenterology* 2014;147:351–8.

National guidelines for colorectal neoplasia screening and surveillance in the USA have long advised colonoscopy as the gold standard, despite the lack of any randomised controlled trials demonstrating survival benefit. Two interesting data sets have recently been published; the first analysed future polyp risk in those with a negative screening colonoscopy and the second studied patient demographics and polyp risk in the screening population. In the first paper, Lieberman and colleagues investigated diagnostic yield of repeat colonoscopy within 10 years of a negative examination in 17 525 patients. Of those who underwent a repeat procedure within 1 year (usually due to poor preparation or incomplete initial examination), the large polyp prevalence (>9 mm) was similar to that in the average-risk screening population at 6.5% (95% CI 5.3% to 7.6%). However, if the baseline negative colonoscopy was deemed adequate, the yield of advanced neoplasia was low at 3.7% within 5–10 years even if the indication for repeat was bleeding or anaemia. Thus, it would appear repeat surveillance colonoscopy within 10 years of a negative adequate/complete examination in an average-risk population may not be indicated. Attention to improving bowel preparation and completion rates seems merited. In the second paper, they prospectively analysed any associations between large polyps (>9 mm) and patient demographics in 323 375 patients undergoing screening colonoscopy in several US centres. Accepting that large polyps are only a surrogate marker, the inaccuracies in assessment of polyp size, the lack of histology in this data set and the variable numbers of ethnic minorities represented, the authors did find significant differences. In particular, the risk of colonic neoplasia appears higher in men (although the risk rises in women with increasing age) and in black patients, while it was lower in Hispanics. It may well be that combining such demographic parameters with others will allow calculation of individual risk of colonic neoplasia in future. While the outcomes of several randomised controlled trials on the benefits of screening colonoscopy are eagerly awaited, these two papers add useful insights suggesting individualised tailoring of both screening and surveillance colonoscopies may be of clinical benefit. The exact method by which one would tailor such a programme on a national level is a matter of debate.

The gut microbiome is altered in patients with cirrhosis

- Qin N, Yang F, Li A, *et al.* Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014;513:59–64.

The critical role of the gut microbiome in the pathogenesis of liver disease is well documented. Earlier culture-based methods were unable to characterise the nature of this, but with the advent of newer molecular methods the understanding of 'intestinal dysbiosis' in cirrhosis is increasingly understood. This paper outlines a comprehensive comparative analysis of the faecal microbiota of 123 patients with liver cirrhosis and 114 control subjects. A total of 2.69 million gene sets were generated and compared with three other gut microbial catalogues. At the phylum level, cirrhotic subjects had fewer Bacteroidetes but higher levels of Proteobacteria and Fusobacteria. At the generic level, *Veillonella*, *Streptococcus*, *Clostridium* and *Prevotella* were enriched in the liver cirrhosis group. Of the 20 species which were significantly enhanced in cirrhotic subjects, four were *Streptococcus* spp and six were *Veillonella* spp, which normally reside in the oral cavity. There was a documented increase of 28 clusters representing cognate bacterial species in cirrhotic subjects, with 54% of these species possibly of buccal origin. This finding is interesting as it marks a shift of these bacteria from their secure ecological niche. In the functional analysis, there was a preponderance of ammonia-producing bacteria in patients with cirrhosis, suggesting a potential role of this dysbiosis in hepatic encephalopathy. The authors also constructed a cluster of 15 gene markers to create a patient discriminatory index and studied its use in a smaller validation cohort. This showed an excellent discrimination between cases and controls ($p<8.18\times10^{-5}$, Wilcoxon rank sum test). However, this finding must be interpreted with caution as the gene set generated from these Chinese subjects had 36.1% of novel genes when compared with the existing data sets. The pooling of genetic information from different populations may identify a faecal bacterial genetic biomarker that could herald the onset of liver cirrhosis.

Reviewers

Dr Mairi H McLean, Dr Walter Baseler, Dr Georgina Hold, Dr Stuart McDonald, Dr Jonathan MacDonald, Dr Dan Gaya and Dr Ashis Mukhopadhya

Journals reviewed

Nature Medicine, Gastroenterology, Hepatology, Nature.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite McLean MH. *Gut* 2014;**63**:1819–1820.

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Gut 2014 63: 1819-1820
doi: 10.1136/gutjnl-2014-308320

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