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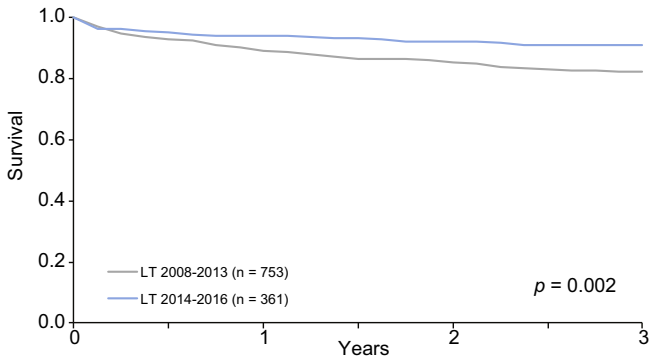
From the Editor's desk....

Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucman-Rossi, Rajiv Jalan

SELECTION OF THE MONTH

Changing face of hepatitis C virus (HCV)-related liver transplantation

The changing frequency in the listing of patients with end-stage HCV-induced liver disease for transplant, and the improvement of the typically impaired post-transplant survival seen in these patients, can be taken as early and strong indicators of direct acting antiviral (DAA) therapy's positive impact on HCV-associated disease burden. The study by Crespo *et al.* compared the composition of the liver transplant waiting list and the early post-transplant survival in the years before and after the availability of DAAs. **The percentage of HCV-associated liver diseases on the waitlist significantly decreased from 47% to 35% two years after the advent of DAAs, and the three-year post-transplant survival improved from 82% to 91%.** The survival benefit was solely driven by the HCV-infected cohort in whom survival significantly increased from 76% to 91%. This important paper adds to the increasing body of evidence showing that DAAs are changing the face of HCV-related liver transplantation.



Crespo *et al.*, 2018
The changing face of HCV-related liver transplantation

LIVER INJURY AND REPAIR

Role of glycogen synthase kinase β (GSKβ) and prostaglandin E_2 (PGE_2) in hepatic ischaemia/reperfusion (I/R) injury

Liver inflammation triggered by I/R involves innate immune cells such as macrophages and pattern-recognition receptors (*e.g.*, Toll-like receptors, TLRs). GSKβ (encoded by *Gsk3b*) is a ubiquitously expressed constitutive serine-threonine kinase which is known to contribute to liver inflammation triggered by I/R. However, nothing is known about the role and the mechanism of action of macrophage GSKβ in hepatic I/R injury. Zhou *et al.* created a myeloid-specific *Gsk3b* KO strain to study macrophage Gsk3β function in a murine liver partial warm ischaemia model. Here, they reveal that **during liver injury caused by I/R, Gsk3β promotes innate pro-inflammatory immune response by decreasing stimulation of AMP-activated protein kinase (known as AMPK)**. Pharmacological manipulation of the GSK3β-AMPK pathway could be a novel approach in the treatment of hepatic I/R injury.

PGE2, an important mediator of inflammation, is a metabolite of arachidonic acid produced via cyclooxygenase. The final step of PGE_2 generation is catalysed by specific PGE synthases (PGESs), of which there are at least three isoforms: cytosolic PGES (cPGES, encoded by *Ptges3*), and two types of microsomal PGES, mPGES-1 (encoded by *Ptges*) and mPGES-2 (encoded by *Ptges2*). mPGES-1 is the dominant source of PGE_2 biosynthesis under basal conditions or during inflammatory states. To date, the implication of PGE2 in hepatic I/R injury remains controversial. On one hand, PGE_2 is known to promote hepatocyte growth. On the other, the administration of an agonist for the prostanoid EP4 receptor, one of the PGE receptor subtypes, protects against ischaemic injury in the liver. Nishizawa *et al.* addressed this controversy by investigating hepatic I/R in *Ptges*-deficient mice and their wild-type counterparts. Their results reveal that **PGE_2 derived from inducible mPGES-1 exerts an endogenous, pro-inflammatory, and suppressive tissue-regenerative action in hepatic I/R injury through EP4 signalling**. Inhibition of mPGES-1 could have therapeutic potential to promote liver repair after acute liver injury.

ALCOHOL-INDUCED LIVER DISEASE (ALD)

Mechanisms of gut leakiness and role of SNX10 in ALD

Heavy alcohol consumption causes gut leakiness, endotoxaemia and inflammatory liver injury, yet the underlying mechanisms are largely unknown. In this issue, Cho *et al.* investigated the cellular and molecular mechanisms of leaky gut in experimentally-induced ALD. **Binge alcohol exposure caused apoptosis of gut enterocytes and subsequent endotoxaemia along with nitrated proteins and apoptosis-related marker proteins**. Analyses of the tight junctions enriched fractions of intestinal epithelial layers revealed that several key-proteins involved in the integrity of tight junctions and desmosomes (*e.g.*, claudin-1, occluding, β-catenin, *etc.*) were altered. These proteins were nitrated and degraded via ubiquitin-dependent proteolysis. Genetic and pharmacological ablation of Cyp2e1 prevented these effects. These results demonstrated a critical role for CYP2E1, apoptosis of enterocytes and degradation of proteins involved in intestinal integrity in alcohol-induced gut leakiness. Targeting these cellular and molecular drivers could be beneficial for the treatment of ALD.

In another interesting article in this issue, You *et al.* studied the mechanisms involved in cell death caused by autophagy in ALD. In particular, they studied the involvement of chaperone-mediated autophagy in regulating hepatic lipid metabolism in ALD. *Snx10* KO mice exhibited a significant amelioration in ethanol-induced liver injury and hepatic steatosis. **SNX10 deficiency resulted in increased chaperone-mediated autophagy via LAMP-2A, Nrf2 and AMPK**. Pull-down assays revealed an interaction between SNX10 and cathepsin A, the key enzyme for LAMP-2A degradation. Deficiency of SNX10 inhibited cathepsin A maturation and increased the stability of LAMP-2A,

resulting in the increased autophagy. These results reveal that SNX10 controls chaperone-mediated autophagy through mediating cathepsin A maturation, playing essential roles in alcohol-induced liver injury and steatosis. These novel molecular targets should be tested in further preclinical studies and represent a novel therapeutic approach for ALD.

HEPATITIS C VIRUS (HCV) INFECTION

Carotid atherosclerosis improvement after DAA therapy

Whether chronic HCV infection increases cardiovascular morbidity and mortality by increasing arteriosclerosis is still a matter of debate. In this issue of the *Journal*, Petta *et al.* evaluated for the first time the effects of DAA treatment on carotid atherosclerosis in a well-controlled prospective study. Carotid atherosclerosis (intima-media thickness [IMT], carotid thickening and carotid plaques) was evaluated at baseline and 9–12 months after the end of DAA therapy in a blinded fashion in patients with advanced fibrosis or compensated cirrhosis. **A significant improvement in IMT and carotid thickening was observed after therapy, which was independent of the severity of the disease**. These findings raise hope that in the long-term the eradication of chronic HCV infection may also contribute to a reduction in the HCV-associated cardiovascular risk.

HEPATITIS E VIRUS (HEV) INFECTION

Do we underestimate the risk of blood-born HEV infection?

In Western countries HEV is mainly transmitted via undercooked pork meat. Transfusion-transmitted infections may, however, also contribute to the epidemiology, and are of special concern for immunosuppressed patients. Although several European countries recently introduced molecular screening of blood donations for HEV RNA, the compelling need for a universal blood donor screening remains highly debated. In order to gain more insight in this issue, Westhölter *et al.* prospectively screened all blood donations at the University Medical Center Hamburg-Eppendorf for the presence of HEV RNA. **Out of 18,714 donors, 23 HEV RNA positive donors were identified corresponding to a prevalence rate of 0.12%, and an HEV positive blood donation prevalence of one out of 815 donations**. Alanine aminotransferase (ALT) levels were normal in most of these donors, indicating that ALT screening is not sufficient to identify HEV infection blood donors, and even more intriguing, hepatitis E viraemia persisted in most of these asymptomatic and immunocompetent donors for more than three months, challenging our current definition for chronicity. Evidence for HEV infection was found in 2 out of 14 recipients receiving HEV RNA positive blood products. Hence, the jury is still out on whether universal blood donor screening is cost-effective or whether Western countries should concentrate on eradicating HEV in the livestock.

HEPATITIS DELTA VIRUS (HDV) INFECTION

Unravelling the key pattern-recognition receptor for HDV

HDV superinfection almost always takes a chronic course which is known for its poor interferon responsiveness indicating that this viral infection has evolved mechanisms to effectively evade the innate immune response. Zhang *et al.* from Stephan Urban's laboratory now tried to identify the pattern-recognition receptor that sense HDV and the types of interferons that are induced by its replication. By using NTCP-expressing cell lines and primary human hepatocytes **they elegantly demonstrate that among intracellular RNA sensors, MDA-5, but not RIG-I or TLR3, is the key sensor recognizing HDV replication hereby mediating the activation of an interferon beta and lambda response**. Quite interestingly, however, the MDA-5-mediated interferon response did not impact HDV replication efficiency. The authors conclude that these findings contribute to a better understanding of the interaction between HDV and the innate immune system, and help to understand the limited efficacy of current interferon-based therapies.

ACUTE LIVER FAILURE

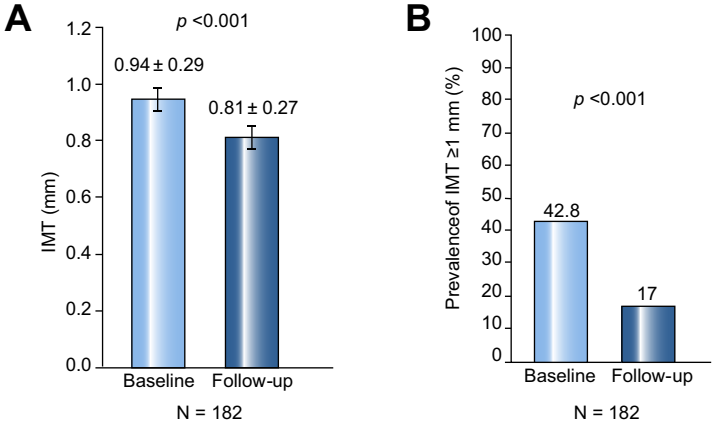
Gut microbiome and diurnal variation of paracetamol-induced acute liver injury

It is well known that paracetamol-induced liver injury is worse when administered at night compared with administration during the day. Although the mechanism of this was hypothesised to be due to alterations in hepatic gene expression, it has become clear that the activity of the gut microbiome undergoes significant diurnal variation. In this important study, **Gong *et al.* explored this hypothesis by administering paracetamol to mice at different times during the day. They show for the first time that the greater liver injury observed in the animals after night time administration was possibly mediated by the microbiome as treatment with antibiotics reduced the severity of injury**. They went on to identify that 1-phenyl-1,2-propanedione (PPD), a metabolite produced by the microbiome at night was possibly responsible and co-administration of PPD exacerbated the severity of paracetamol-induced liver injury. These provocative data provide the rationale to target the microbiome to prevent the progression of acute liver injury.

LIVER TRANSPLANTATION

A new score identifies patients at high risk of post-transplant morbidity and mortality

At present, most countries have adopted a system of organ allocation based on the model for end-stage liver disease system, where the sickest patients have the highest priority for organs. This policy allows transplantation of very sick patients but the impact of this approach on long-term post-transplant morbidity and mortality is



Petta *et al.*, 2018
Carotid atherosclerosis improvement after DAA therapy