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SELECTION OF THE MONTH

Big Title: New DAAs for HCV reduces mortality and transplant need

Transfusion-transmitted HEV infection

The key pattern-recognition receptor for HDV

Cirrhosis title: Gut microbiome and paracetamol-induced liver injury

LIVER INJURY AND REPAIR

Role of glycogen synthase kinase β (GSK β) and prostaglandin E₂ (PGE₂) in hepatic ischemia/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). GSK β (encoded by *Gsk3b*) is an 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 GSK β in hepatic I/R injury. Zhou *et al.* created a myeloid-specific *Gsk3 β* KO strain to study macrophage Gsk3 β

function in a murine liver partial warm ischemia model. Here, they reveal that **during liver injury caused by I/R, Gsk3 β promotes innate pro-inflammatory immune response by decreasing stimulation of AMP-activated protein kinase (known as AMPK)**. Pharmacological manipulation of the GSK3 β -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 PGE₂ generation is catalyzed 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 PGE₂ biosynthesis under basal conditions or during inflammatory states. To date, the implication of PGE₂ in hepatic I/R injury remains controversial. On one hand, PGE₂ is known to promote hepatocyte growth. On the other, the administration of agonist for the prostanoid EP4 receptor, one of the PGE receptor subtypes, protects against ischemic injury in the liver. Nishizawa *et al.* addressed this controversy by investigating hepatic I/R in *Ptges*-deficient mice and their wild counterpart. Their results reveal that **PGE₂ derived from inducible mPGES-1 exerts an endogenous, pro-inflammatory, and suppressive tissue-regenerative action in hepatic I/R injury through EP4 signaling**. Inhibition of mPGES-1 could provide a 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, endotoxemia and inflammatory liver injury, yet the 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 endotoxemia 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 to treat ALD.

In another interesting article in this issue, You *et al.* studied the mechanisms involved in cell death due to 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 assay 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 pre-clinical studies and represent a novel therapeutic approach for ALD.

HEPATITIS C VIRUS (HCV) INFECTION

The changing face of HCV-related liver transplantation, carotid atherosclerosis improvement after DAA therapy

A changing frequency in the listing of patients with end-stage HCV-induced liver disease to transplant, but also demonstrating an improvement of the typically impaired post-transplant survival seen in these patients, can be taken as early and strong indicators how direct acting antiviral (DAA) therapy impacts 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% already two years after the advent of DAAs, and the 3-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 how rapidly DAAs help to change the face of HCV-related liver transplantation.

Whether chronic HCV infection increase 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 eradicating 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.** ALT levels were normal in most of these donors, indication that ALT screening is not sufficient to identify HEV infection blood donors, and even more intriguing, hepatitis E viremia persisted in most of these asymptomatic and immunocompetent donors for more than 3 months, challenging our current definition for chronicity. An evidence for HEV infection was found in 2 out of 14 recipients receiving HEV RNA positive blood products. Hence, the jury is still open 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. 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 hypothesized to be due to alteration 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 time 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 posttransplant morbidity and mortality

At present, most countries have adopted a system of organ allocation based on the use of the MELD 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 not entirely clear. **Asrani *et al.*** aimed to address this issue by examining the national and center-specific transplant databases. **They identified factors such as ventilator support, recipient age >60 years, hemodialysis, diabetes or serum creatinine ≥ 1.5 mg/dL without hemodialysis as factors associated with poor 5-year survival.** They attributed different points to these based upon their importance in defining the outcome and generated a new scoring system. Their data suggest that a score of >8 is associated with a lower chance of 5-year graft survival. These data were confirmed in the center-specific study. This important observation has serious implications for future organ allocation policies if this is validated by other studies.

CHOLESTASIS

Ketamine abuse induces a reversible cholangiopathy

Ketamine abuse has been linked with bile duct abnormalities but the biliary characteristics of the cholangiopathy have not been fully described. In this incredible study from China, **Seto, Mak and Chiu *et al.*** recruited 257 out of 343 Ketamine abusers from the community and studied them with the performance of blood tests and MR Cholangiography. **Their data showed that 159 of these individuals had significant abnormalities of their biliary system affecting both the extra and intrahepatic biliary system. Increased alkaline phosphatase of >113U/l was able to identify these individuals with high degree of accuracy. Importantly, they confirmed that these abnormalities were reversible with abstinence.** The data has important implications for managing the health issues stemming from Ketamine abuse and may provide clues to the pathogenesis of idiopathic cholangiopathies.

HEPATOCELLULAR CARCINOMA (HCC) BASIC

Dichotomy of Shp2

Tyrosine-protein phosphatase non-receptor type 11 (short name, Shp2), which is encoded by *Ptpn11*, is a member of the protein tyrosine phosphatase (PTP) family. Shp2 is an SH2-tyrosine phosphatase acting downstream of receptor tyrosine kinases. Shp2 may have a liver tumor-suppressing role because deleting *Ptpn11* in hepatocytes aggravates HCC induced by chemical carcinogen or loss of phosphatase and tensin homolog (encoded by *Pten*). Liu *et al.* aimed to investigate the effect of *Ptpn11* deficiency on liver tumorigenesis driven by classical oncoproteins c-Met (receptor for

hepatic growth factor), β -catenin and the serine/threonine protein kinase PIK3CA. For this, they performed hydrodynamic injection of two pairs of plasmids expressing c-Met and β -catenin, or c-Met and PIK3CA into *Ptpn11*-deleted mice and wild type counterparts. **Intriguingly, results show that Shp2 loss both, suppresses liver tumorigenesis driven by c-Met/ β -catenin or c-Met/PIK3CA, and triggers a tumor-promoting hepatic microenvironment.** These findings suggest that an effective therapy must block both cell-intrinsic and stromal oncogenic signals.

HEPATOCELLULAR CARCINOMA (HCC) CLINICAL

Surgical resection for perivascular HCC, intraarterial chemotherapy for advanced HCC

The therapeutic outcomes for perivascular HCC between surgical resection (SR) and radiofrequency ablation (RFA) are poorly known. Lee *et al.* aimed to compare SR with RFA as first-line treatment in patients with perivascular HCC and to evaluate the long-term outcomes of both therapies. For this they retrospectively analyzed 283 consecutive patients with small perivascular HCCs (≤ 3 cm, Barcelona Clinic Liver Cancer stage 0 or A) who underwent SR ($n = 182$) or RFA ($n = 101$) as a first-line treatment. **They show that among patients with small perivascular HCCs, those who received SR have better long-term tumor control and overall survival than those who received RFA.** These beneficial results of SR were particularly observed in patients with periportal tumors.

Hepatic arterial infusion (HAI) of oxaliplatin plus fluorouracil, and leucovorin (FOLFOX) has been proposed for the treatment of advanced HCC. Lyu *et al.* conducted a retrospective study which enrolled 412 patients with advanced HCC, among which 232 patients were treated with 'standard' sorafenib and the remaining 180 patients were given HAI with FOLFOX therapy because they refused sorafenib. **The results are consistent with potential beneficial effects HAI of FOLFOX therapy over sorafenib therapy in terms of progression-free and overall survival (7.1 vs. 3.3 months [according to Response Evaluation Criteria in Solid Tumors - RECIST - version 1.1 criteria] and 14.5 vs. 7.0 months; respectively).** These promising results should be confirmed by randomized clinical trials.