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SELECTION OF THE MONTH

Big Title: *PNPLA3* increases risk of death in alcoholic hepatitis

Small title: Carvedilol increases survival of decompensated cirrhosis patients

LIVER INJURIES

Thymic MAP3K14 and liver homeostasis, deciphering chemotherapy-related liver injuries (CALI)

Breakdown of liver immune privilege can develop in chronic liver disease; however, the role of adaptive immunity in liver injury is poorly defined. Here Shen *et al.* investigated the role of *mitogen-activated protein kinase kinase kinase 14* (*MAP3K14*, also known as *NIK*) because it is involved in NF-κB activation in immune cells and

because of its role in maintaining liver homeostasis is unknown. For this, they deleted *MAP3K14* systemically or conditionally in mice. They reveal that thymic *MAP3K14* suppresses development of autoreactive T cells against liver antigens, and *MAP3K14* deficiency in the thymus results in $CD4^+$ T cell-orchestrated autoimmune hepatitis and liver fibrosis. Thus, **thymic *MAP3K14* is indispensable for the maintenance of liver immune privilege and liver homeostasis.**

CALI increase the risk of liver resection and may prejudice further surgery and chemotherapy. No data regarding reversibility of CALI are available. Vigano *et al.* retrospectively analyzed the reversibility of CALI in patients undergoing liver resection for colorectal metastases. They found that **CALI persists for a long time after chemotherapy. The sinusoidal obstruction syndrome and nodular regenerative hyperplasia regress only after nine months without chemotherapy, whereas steatosis and steatohepatitis persist.**

CHOLANGIOCARCINOMA (CCA)

SOX17 in CCA

CCA is a biliary malignancy associated with epigenetic abnormalities, such as hypermethylation of the promoter of *SOX17* (for *Sex Determining Region Y [SRY]-box 17*). SOX19 is one of the 19 genes of the gene family of SRY-boxes (HUGO Gene Name nomenclature; http://www.genenames.org) that encode transcription factors involved in the regulation of embryonic development and in the determination of the cell fate. The transcription factor encoded by SOX17 binds to DNA sequences 5'-AACAAT-'3 or 5'-AACAAAG-3'. It modulates transcriptional regulation via WNT3A, inhibits Wnt signaling and promotes degradation of activated CTNNB1. Here, Merino-Azpitarte *et al.* investigated the role of *SOX17* in cholangiocyte differentiation and cholangiocarcinogenesis. For this, they studied SOX17 expression/function along the differentiation of **human induced pluripotent stem cells** into cholangiocytes, in the dedifferentiation process of normal human cholangiocytes in culture and in cholangiocarcinogenesis. They show that ***SOX17* regulates the differentiation and maintenance of the biliary phenotype and functions as a tumor suppressor for CCA, suggesting a potential prognostic marker and a promising therapeutic target.**

HEPATOCELLULAR CARCINOMA (HCC)

Early events determine the outcome of successfully treated HCC in patients with HCV-related cirrhosis

Here, Cabibbo *et al.* aimed to estimate the impact on 5-year overall survival of early (occurring within 12 months after complete radiological response) time-dependent events (HCC recurrence or hepatic decompensation) in a large cohort of successfully treated HCC patients with HCV-related cirrhosis. They reveal that **survival in HCV-infected cirrhotic patients with successfully treated HCC is mainly influenced by early hepatic decompensation.** These findings suggest that the use of direct antiviral agents may improve survival of patients with HCV-related cirrhosis and successfully treated HCC; this hypothesis deserves to be addressed in future studies.

GENETICS IN LIVER DISEASE

Genetic determinants to drug-induced liver injury (DILI) by minocycline, NASH, and alcoholic hepatitis-associated mortality

Factors predisposing to **minocycline-induced hepatotoxicity** are unknown. Fontana *et al.* performed genome-wide genotyping in a well characterized cohort. Most patients were women and 90% had positive ANA. **A significant association was noted between a HLA class I histocompatibility antigen, B-35 alpha chain (HLA-B*35:02) and risk for minocycline-DILI** (16% carrier frequency in DILI cases compared to 0.6% in population controls). HLA-B*35:02 carriers had similar presenting features and outcomes compared to noncarriers. In silico modeling studies supported the hypothesis that direct binding of minocycline to this novel HLA risk allele might be an important initiating event in minocycline-DILI. If confirmed in other cohorts, this HLA allele may prove to be a useful diagnostic marker of minocycline DILI.

Carriers of a variant in the *transmembrane 6 superfamily member 2* (*TM6SF2*) gene that results in a E167K substitution in the encoded protein, have increased risk of NASH. Interestingly, these subjects lack hypertriglyceridemia and have lower risk of cardiovascular disease. In animals, phosphatidylcholine (PC) deficiency results in a similar phenotype. Luukkonen *et al.* studied the **effect of the TM6SF2 E167K on these lipids in human livers and cultured hepatocytes**. Patients with TM6SF2 EK/KK had higher liver triglycerides but lower PCs. Also, incorporation of PUFA into triglycerides and PCs in *TM6SF2* knockdown hepatocytes was decreased. As expected, hepatic expression of *TM6SF2* was decreased in variant carriers, and was coexpressed with genes regulated by PUFAs. This interesting study demonstrates that **hepatic lipid**

synthesis from PUFAs is impaired and could contribute to deficiency in PCs and increased intrahepatic triglycerides in TM6SF2 E167K variant carriers.

Carriage of an allele in *PNPLA3* (rs738409[G], encoding I148M) is associated with an increased risk of developing alcohol-related cirrhosis. In an important study in this issue of the Journal, Atkinson *et al.* assessed whether carriage of rs738409[G] has an additional detrimental effect on survival in patients with alcoholic hepatitis, the most deadly form of ALD. Almost **900 patients from the STOPAH trial and 2,000 alcohol dependent controls were included**. The frequency of rs738409[G] was significantly higher in cases than controls (29% vs. 19%; p=2.15x10-15). There was no association between rs738409[G] and 28-day mortality. However, **mortality in the period day 90-450 was higher in survivors who subsequently resumed drinking and individuals homozygous for rs738409[G]** (HR 1.69, 95% CI 1.02-2.81, p=0.04). This study suggests that homozygosity for rs738409[G] in *PNPLA3* confers significant additional risk of medium-term mortality in patients with severe alcoholic hepatitis.

HEPATITIS C VIRUS (HCV) INFECTION

DAA treatment in prior HCC patients - the Veterans Affairs experience, curing HCV in HIV co-infection, lower than expected increase in DAA prescriptions

The effectiveness of direct acting antivirals (DAAs) in patients with a history of HCV-induced HCC is largely unknown as these patients were systematically excluded from prospective controlled trials. The objective of the study by Beste *et al.* was to describe the characteristics of HCC patients who receive DAA-based antiviral treatment and to report the rates and predictors of SVR by using the Veterans Affairs Corporate Data Warehouse which includes the largest cohorts of HCV and HCC patients in the US. Of 17,487 HCV treatment recipients, 624 (3.6%) had prior HCC, and these patients were divided into those who were treated with liver transplantation after HCC diagnosis, and those treated with other modalities prior to antiviral therapy. After adjustment for confounders, the presence of HCC was associated with lower likelihood of SVR (74.5%) when DAA treatment was applied prior to liver transplantation as compared to those patients with HCC receiving DAA therapy after liver transplantation (93.4%) but also as compared the overall non-HCC group (91.9%). **The findings suggest that patients with HCV-induced HCC listed for transplantation may benefit from deferring HCV treatment until after transplantation**. Further studies should explore the impact of HCV treatment on subsequent HCC behavior.

With the advent of potent DAA combination regimens for the first time similar SVR rates were achieved in the formerly named difficult-to-cure HIV-HCV-co-infected, and HCV-mono-infected patients in clinical trials. However, participants in clinical trials are not always fully representative of patients followed in “real-life”. Piroth, Wittkop *et al.* report the efficacy and safety of all-oral DAA-based regimens according to the concomitant antiretroviral regimen in HIV-HCV co-infected patients enrolled the French nationwide ANRS CO13 HEPAVIH observational cohort. **A high overall SVR12 of 93.5% was observed in the real-life setting, and neither the HCV type nor fibrosis status influenced SVR rates.** This study confirms the impressive safety and efficacy of DAA regimens in a large nationwide cohort of HIV-HCV co-infected patients.

In Germany, in contrast to most other European countries, all patients with chronic HCV infection are eligible for treatment, regardless of the clinical stage of liver impairment. The aims of the study by Zimmermann *et al.* were to determine the monthly number of HCV antiviral treatments prescribed for HCV patients with statutory health insurance in Germany between January 2010 and December 2015, but also how DAA treatment options influenced the treatment rates. **Given an estimated number of 160,000 patients with diagnosed HCV infection in Germany, a much lower than expected increase of monthly prescriptions of HCV treatment have been observed since 2010.** Limited access to specialized health care, ambiguities in the reimbursement system, but also a smaller than estimated pool of HCV infected patients may explain these results. This study provides important information how to improve linkage to care in order achieve the goal of eliminating HCV infection just by antiviral treatment.

(Thomas: Would suggest to show the graphical abstract figure for this contribution; RM: Agree)

CIRRHOSIS

Carvedilol administration increases the survival of cirrhotic patients with ascites

Non-selective beta-blockers (NSBB) have been the mainstay of treatment of patients with portal hypertension for over 3 decades but their use in patients with refractory ascites has been under scrutiny. Carvedilol is also an NSBB but in addition has alpha-1 receptor agonist properties and has been shown in many studies to effectively reduce portal pressure. Sinha *et al.* performed an extremely important study in cirrhotic patients with ascites treated with carvedilol and compared this with a propensity score

matched patient population. **The study shows that the carvedilol treated patients had a staggeringly low mortality of 2% compared with the control group of 24% (p<0.0001).** These data would change practice if they were confirmed in randomized studies.

CHOLESTASIS AND RENAL DYSFUNCTION

Nor Urosdeoxycholic (NorURSO) acid is a novel strategy to treat cholestasis associated nephropathy

The occurrence of renal dysfunction on the background of cholestasis, referred to as cholemic nephropathy is associated with poor clinical outcomes. *Nor*UDCA is a bile acid derivative that allows excretion of toxic bile acids through alternative excretory routes. **Krones *et al.* administered *Nor*UDCA to bile duct ligated rats and show that the animals administered the drug had significantly better renal function, reduced urinary NGAL and preserved renal histology compared with untreated controls.** The data provide a novel approach to the treatment of cholemic nephropathy, which can be translated readily into the clinic as NorUDCA is already a Phase 2 compound.

CELL TRANSPLANTATION

Mesenchymal stromal cell (MSC) infusion for tolerance induction post liver transplantation

MSCs are multipotent progenitors within the bone marrow that can differentiate into multiple cell types. They modulate inflammatory responses and have the ability to potentially induce tolerance. **Detry *et al.* performed a Phase I/II clinical trial infusing MSCs into patients soon after undergoing liver transplantation. They show for the first time that this approach is safe and can be performed without increasing the risk of infection or development of cancer.** Although the data did not show that this induces tolerance, it provides important safety data to further develop this or a similar cellular approach for patients undergoing liver transplantation.