From the Editor's Desk

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SELECTION OF THE MONTH

Big Title: HCV eradication and the risk of HCC

Small titles: Validation of Liver stiffness in Autoimmune Hepatitis

The nature of serum HBV RNA

KUPFFER CELLS (KCS)

Differences in liver macrophages

KCs, the resident tissue macrophages of the liver, can sense a broad variety of stresses and trigger a response aimed to maintain or restore tissue homeostasis. Some stresses are extreme deviations of tissue homeostasis (e.g., oxidative stress, osmotic stress) while others are challenges that can cause a disruption of homeostasis (e.g., presence of bacterial pathogens). Recent studies have identified KCs as a yolk sac (YS)-derived resident macrophage population that is replenished independently of

monocytes in the steady state. However, following local tissue injury, bone marrow-derived monocytes may infiltrate the tissue and differentiate into macrophages. Beattie *et al.* now show that **YS-derived KC and bone-marrow-derived macrophages, can exhibit distinct phenotypes depending on the context.** For example, the latter are much more effective than the latter, for clearing bacterial pathogens. In addition, they show that an ion homeostasis gene signature, including genes associated with scavenger receptor function and extracellular matrix deposition, allows discrimination between the two macrophage populations. Future studies should investigate whether there is a division of labor among liver macrophages according to the two main categories of stresses: extreme deviation of regulated variables from normal values vs. challenges that can cause a disruption of tissue homeostasis.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Factors in early life that predict development of NAFLD, effect of long-term exercise on NAFLD

Early detection of NAFLD could prevent the development of advanced liver disease. In this issue, Suomela *et al.* aimed to identify **childhood risk factors** of fatty liver in adulthood in a population-based group of Finnish adults. The study included more than 2,000 individuals aged 3-18 years at baseline in 1980. During the latest follow-up in 2011, the presence of fatty liver was assessed. The study found that history of **small size for gestational age, genetic factors** (variants in *PNPLA3* and *TM6SF2*), **BMI and serum insulin** predicted the development of fatty liver. This study strongly suggests that prenatal, genetic as well as diet-associated factors in early life influence the development of fatty liver.

In this issue, an interesting study by Sung *et al.* investigated the amount of exercise that is associated with either development or resolution of fatty liver. This large study (233,676 individuals) was performed between 2002 and 2014. Half of the participants did not have fatty liver at baseline and more than 10% developed fatty liver during follow-up. Conversely, out of 42,536 individuals with liver fat at baseline, it resolved in one third of them during follow up. After full adjustment, compared to no exercise, **exercise ≥5 times per week was associated with benefit for both outcomes**. This impressive study concludes that moderate to vigorous exercise is beneficial in **decreasing risk** of development of new fatty liver or **improving resolution** of existing fatty liver during 5 years of follow up.

GENETIC LIVER DISEASES

Gene therapy for acute intermittent porphyria

Acute intermittent porphyria (AIP) results from porphobilinogen deaminase (PBGD) insufficiency, which leads to hepatic over-production of the neurotoxic heme precursors porphobilinogen (PBG) and delta-aminolevulinic acid (ALA) and the occurrence of neuro-visceral attacks. Severe AIP is a devastating disease that can only be corrected by liver transplantation. Gene therapy represents a promising curative option. The study by D'Avola *et al.* investigate the safety of a recombinant adeno-associated vector expressing PBGD (rAAV2/5-PBGD) administered for the first time in humans for the treatment of AIP. Treatment was safe and there was a trend towards a reduction of hospitalizations and heme treatments, although ALA and PBG levels remained unchanged. **This promising study should foster future research to develop effective gene therapy approaches for this severe disease.**

HEPATITIS C VIRUS (HCV) INFECTION

Treating HCV improves portal hypertension, HCV recurrence after OLT - not a concern anymore!

To what extent portal pressure may improve after curing chronic hepatitis C virus (HCV) infection is not well studied so far. Mandorfer, Kozbial, *et al.* aimed to investigate the impact of sustained virologic response (SVR) to IFN-free therapies on HCV-induced portal hypertension assessed by hepatic venous pressure gradient (HVPG) measurement, and to elucidate predictors of HVPG decrease. 60 patients with portal hypertension who achieved SVR underwent HVPG and transient elastography (TE) measurement before and after IFN-free therapy. **Regardless of the stage of HVPG at baseline** (i.e. 6-9 mm Hg; 10-15 mm Hg or ≥ 16 mm Hg) **SVR to IFN-free therapies was associated with a significant decrease in HVPG**. However, HVPG amelioration was less likely in patients with more advanced liver dysfunction. Authors could also demonstrate that TE might be useful in the prediction of portal hypertension after SVR. Further long-term studies are needed to fully estimate the effects of DAA therapy on portal hypertension and its complications.

Graft hepatitis due to HCV recurrence has been a major concern for patients receiving liver transplantation for end stage HCV-induced liver disease because of its association with a significant impaired graft and patient survival. All our attempts in the

recent decades to prevent or treat graft reinfection hereby improving patients' outcome were more or less frustrating. The message from the large French prospective multicenter compassionate use program (ANRS CULPIT) is that **graft hepatitis can now be cured by direct acting antivirals in nearly every patient without a significant risk of major side effects or drug-drug interactions**. Out of 137 patients with HCV recurrence who were treated with sofosbuvir plus daclatasvir ± ribavirin, whatever the genotype or fibrosis stage, only two patients suffered from virologic failure as demonstrated by Coilly *et al.* No doubt, HCV recurrence after liver transplantation is not frightening anymore.

Hepatitis B Virus (HBV) infection

Response-guided hepatitis B treatment? Persistence of intrahepatic viral DNA synthesis under long-term tenofovir, the nature and origin of serum HBV RNA

The concept of response-guided therapy (RGT), which has been successfully applied in the management of chronic hepatitis C in the peginterferon alpha (pegIFNa) era, has not been studied so far in patients with chronic hepatitis B treated with pegIFNa therapy. Sun *et al.* performed for the first time a prospective, randomized, open-label trial aiming to improve the outcomes of HBeAg positive patients with incomplete or partial response to pegIFNa-2a by extending treatment to 96 weeks, and/or by adding the nucleotide analog adefovir. Unfortunately, **neither treatment extension to 96 weeks nor adding adefovir helped to improve treatment outcome in patients with non-early response** defined as HBsAg ≥ 1500 IU/mL or HBV DNA ≥10^5 copies/mL at treatment week 24. The results of this study may stimulate further investigations in order to establish new treatment strategies but also stopping rules for patients not responding early to pegIFNa.

The formation of HBV covalently-closed circular DNA (ccc-DNA) within the hepatocyte being essential for the production of viral RNAs remains intact during treatment with potent nucleoside/nucleotide analogues such as tenofovir (TDF) or entecavir. The study by Boyd *et al.* is one of the first that comprehensively examined the levels of intrahepatic viral load specifically in patients co-infected with HBV and the human immunodeficiency virus (HIV) under long-term antiviral treatment. **Although TDF appears to provide substantial reductions in intrahepatic viral load among HIV-HBV co-infected patients, viral replication and ccc-DNA persist even after roughly three years of treatment**, strongly suggesting that TDF is unable to

completely block intracellular viral DNA synthesis which could in turn account for continuous replenishment of the ccc-DNA pool. A difference in the average half-life of total intrahepatic HBV DNA and ccc-DNA between HBeAg-positive and HBeAg-negative infection as well as a strong relationship between lower levels of both ccc-DNA and total intrahepatic DNA with higher nadir CD4+ cell counts, and longer cumulative duration of TDF were further intriguing observations of this unique study using the largest collection of liver biopsies in HIV-HBV co-infected patients to date. The study also provides evidence that past severe immunosuppression could affect intrahepatic viral levels.

HBV replicates its DNA genome through reverse transcription from pre-genomic RNA (pgRNA). HBV RNA which can be detected in the serum of patients with chronic hepatitis B might serve as an interesting novel biomarker for disease progression and treatment outcome prediction as recently discussed. In this study by Wang *et al.*, the nature and origin of serum HBV RNA was investigated in both *in vitro* and *in vivo* experiments to mechanistically determine the potential clinical significance of HBV RNA in serum. **A series of experiments found the serum HBV RNA to be pgRNA and not preC mRNA and present in virus-like particles**. The discovery of HBV pgRNA virions implies that HBV may have another natural virion form in which the nucleic acid is composed of pgRNA, and which has the potential to infect hepatocytes. Besides the importance of these findings for our understanding of the HBV biology, the study also provides evidence that the level of HBV pgRNA virions in serum may be associated with risk of HBV viral rebound after treatment withdrawal, hence representing a potential powerful predictive biomarker to monitor the safe discontinuation of oral antiviral therapy.

HEPATOCELLULAR CARCINOMA (HCC)

Issues with direct acting antiviral (DAA) therapy?

Oral DAA therapy is a major breakthrough in the treatment of HCV infection. In this issue of the Journal, two articles raise concerns about this therapy while two other provide relatively good news. In the first of the two “alarming” study, Reig *et al.* show **an unexpected early tumor recurrence in patients with HCV-related HCC undergoing DAA therapy**. HCC recurrence coincides with HCV clearance. In the second study providing bad news, Conti et al. show that **in patients with HCV-related cirrhosis, DAA-induced resolution of HCV infection does not seem to reduce**

occurrence of HCC, and patients previously treated for HCC have still a high risk of tumor recurrence, in the short term. In contrast, in a third study, Cheuk Men Cheung et al. find that **DAA therapy in patients with decompensated cirrhosis leads to sustained improvement in liver function, with no evidence of increase in HCC development**. Finally, Pol by analyzing **three distinct prospective cohorts, and a large number of patients, finds no increased risk of HCC recurrence after DAA therapy, in particular in those who underwent curative HCC treatment including liver transplantation.** All these studies were performed in European countries. Together these studies indicate that there is an urgent need for large prospective studies, performed in different continents, evaluating the impact of DAA therapy on the risk of HCC, in particular, in patients with HCV-related cirrhosis.

AUTOIMMUNE HEPATITIS

Validation of Liver stiffness in Autoimmune Hepatitis

Although measurement of liver stiffness using TE has gained widespread popularity for staging patients with a wide variety of liver diseases, its role in autoimmune hepatitis is not yet clear. **Johannes *et al.* aimed to validate TE in patients with autoimmune hepatitis and present exciting new data showing a good correlation between TE measurements and the severity of fibrosis diagnosed on liver biopsy.** Their own observations were confirmed in validation cohorts. They suggest that if the measurements are performed 6 months after initiation of immunosuppressive therapy and a cut off of 16kPa is used the AUROC for the diagnosis of cirrhosis is 1.0.