From the Editor's Desk May 2016

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

SELECTION OF THE MONTH

Urgent need to increase awareness and screening programs for HCV infection

Reliable data about the population-based prevalence of hepatitis C virus (HCV)-induced cirrhosis are unavailable for most countries. Udompap *et al.* addressed this question by determining the cirrhosis prevalence using the National Health and Nutrition Examination Survey (NHANES), which contains a population generalizable to the entire United States households. The authors also raised the important question of whether awareness of the infection impacts cirrhosis prevalence. While the overall prevalence of HCV infection has decreased over time from 1.5% in 1988-94 (Era 1), to 1.2% in 1999-2006 (Era 2), and then to 1.0 in 2007-12 (Era 3), the proportion of HCV patients with cirrhosis has more than doubled during the study period reaching 17% in the latest era. **Most importantly, cirrhosis prevalence in patients unaware of their infection was as high as in those with established HCV diagnosis.** The study emphasizes the need for implementing HCV awareness and screening programs for primary prevention of cirrhosis and its complication.

LIVER INFLAMMATION

IL-23/IL-17 axis makes liver immunopathology, biliary epithelium surveillance by Mucosal-Associated Invariant T (MAIT) cells

Excessive type 1 immune responses, for example those involving the interleukin (IL)-23/IL-17 axis, contribute to immunopathology in the context of auto-immune diseases. Noll *et al.* now show that **the IL-23/IL-17 axis plays a crucial role in the immunopathology of hepatic amebiasis.** They also find that $CD^{11b+}Ly6C^{low}$ monocytes may contribute to liver repair via the secretion of IL-13 (a cytokine of the type 2 immunity). These findings suggest that stimulation of IL-13 signaling may improve liver damage caused by the engagement of the IL-23/IL-17 axis.

Mucosal-Associated Invariant T (MAIT) cells are innate-like T cells characterized by the invariant TCR-chain, Vα7.2-Jα33, and are restricted by the major histocompatibility

complex class I-related gene protein (encoded by *MR1*), which is an antigen-presenting molecule specialized in presenting microbial vitamin B metabolites. MAIT cells play a crucial role in antibacterial immunity of different mucosa but their role in the biliary epithelium defense is unknown. Here Jeffery *et al.* show evidence of an **immune surveillance effector response for intra-hepatic MAIT cells toward biliary epithelial cells in the human liver**. MAIT cell usage may be a novel approach in the treatment of biliary diseases.

LIVER REGENERATION

A matter of TNF and TNF receptors super-families

Tumor necrosis factor (TNF) receptor (TNFR) superfamily member 3 (also known as lymphotoxin B receptor) which is encoded by *Ltbr* (alias *Tnfrsf3*) is known to be involved in liver regeneration in response to injury. The receptor binds different members of the TNF ligand superfamily, including lymphotoxin-alpha and –beta, and tumor necrosis factor ligand superfamily member 14 (also known as Light). Sorg *et al.,* using a model of liver regeneration in genetically modified mice reveal that **lymphotoxin B receptor is essential for effective liver regeneration and cooperates with TNFR superfamily member 1A (also known as p55, and encoded by *Tnfrsf1a*) in this process. p55 receptor recognizes lymphotoxin-alpha and the soluble form of TNFα.** Together these findings suggest that inhibition of TNF signaling may be harmful in the context of liver regeneration

HEPATOCELLULAR CARCINOMA (HCC)

Effect of *salt-inducible kinase 1* (*SIK1)* silencing, diagnostic criteria for HCC ≤3 cm, a trial of sorafenib plus DEB-TACE

SIK1 encodes the serine/threonine-protein kinase SIK1 which is known to be involved in various processes such as cell cycle regulation, gluconeogenesis and lipogenesis regulation, muscle growth and differentiation and tumor suppression. However, little is known about the role of *SIK1* function in HCC. Qu *et al.* show in this issue of the *Journal* that ***SIK1* silencing promotes HCC progression and WNT/β-catenin pathway activation, suggesting new diagnostic and therapeutic approaches in liver cancer.**

Current diagnostic imaging criteria for (HCC) are dedicated to imaging with nonspecific extracellular contrast agents. Choi *et al.* investigated diagnostic criteria for HCC ≤3 cm

on magnetic resonance imaging (MRI) with a hepatocyte-specific contrast agent through an inception cohort study. They report two interesting findings. **First, EASL criteria exhibit the best diagnostic performance for HCC ≤3 cm on hepatocyte-specific contrast-enhanced MRI. A newly identified criterion (arterial-phase hyper-intensity and hepatobiliary phase hypo-intensity) may increase the diagnostic sensitivity of small (≤2 cm) HCC.**

Transarterial chemoembolization with doxorubicin-eluting beads (DEB-TACE) is effective in patients with BCLC stage B hepatocellular carcinoma (HCC). Sorafenib enhances overall survival and time to tumor progression in patients with advanced HCC. Lencioni *et al.* report the results of an exploratory phase II trial tested the efficacy and safety of sorafenib plus DEB-TACE in patients with intermediate-stage HCC. **They show the technical feasibility of sorafenib plus DEB-TACE, but find no advantage in terms of outcome in using this combination therapy compared to DEB-TACE alone.**

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Hepatic lipidomic analysis in patients with NASH

Recent data have identified ***de novo* ceramide** synthesis as important mediators of hepatic insulin resistance (IR), which participates in NASH progression. In this issue, Luukkonen *et al.* determined which bioactive lipids co-segregate with IR in the human liver, and its relationship with ***PNPLA3* genotypes**. By performing liver lipidome analysis in patients with and without IR and different *PNPLA3* genotypes, they demonstrated that steatosis and NASH prevalence were similarly increased in patients with IR and *PNPLA3*$^{148MM/MI}$ at rs738409. The liver in patients with IR had increased triacylglycerols as well as markers of *de novo* ceramide synthesis. In contrast, livers from patients with *PNPLA3*$^{148MM/MI}$ have increased polyunsaturated triacylglycerols while other lipids were unchanged. This study suggests the composition liver fat in NASH depends on the PNPLA3 genotype.

HEPATITIS C VIRUS (HCV) INFECTION

Increasing prevalence of HCV-induced cirrhosis in the United States, risk of HCV reinfection in injecting drug users – how sustained is sustained response?

Current guidelines support that HCV-infected people who inject drugs (PWID) are a high priority population for anti-viral treatment due to the potential HCV transmission

prevention benefit. Nevertheless, access to anti-viral treatment is limited in this patient population because of, amongst others, the potential risk of HCV reinfection. However, solid follow-up data on the true incidence of chronic reinfection are sparse in this setting. Midgard *et al.* have now showed in a 7 year follow-up study, that the rate of persistent HCV reinfection among 94 Norwegian patients with a history of intravenous drug use prior to treatment was 11% (incidence 1.7/100 person-years). **Reinfection only occurred among those who had relapsed to intravenous drug use (incidence 4.9/100 person-years)**, and the relapse to intravenous drug use was the only baseline factor associated with reinfection. The study proves the need for systematically addressing HCV reinfection risk in PWID and that preventing intravenous drug relapse remains the main preventive strategy in a field moving rapidly forward.

HEPATITIS B VIRUS (HBV) INFECTION

"Liver directed" peg-interferon lambda in chronic HBV infection

Peg-interferon lambda-1a is a polyethylene glycol chain conjugated recombinant human Type-III interferon with documented activity against HBV and hepatitis C virus (HCV) *in vitro*. Whereas interferon-alpha receptors are expressed by many cell types, lambda receptor expression is more restricted to epithelial cells, hepatocytes and plasmacytoid dendritic cells, raising hope that a more liver-targeted interferon response induced by lambda interferon may lead to a higher anti-viral efficacy and better tolerability as compared to alpha interferons. In a proof-of-concept phase 2b study (LIRA-B), Chan *et al.* evaluated the efficacy and safety of peg-interferon lambda *vs*. peg-interferon alfa-2a monotherapy over 48 weeks in HBeAg-positive chronic HBV infection. The major finding from this study was, however, that **peg-interferon lambda did not meet the criteria for noninferiority to peg-interferon alfa-2a for the primary efficacy endpoint of HBeAg seroconversion at week 24 post-treatment follow-up (14% vs. 30%),** although on-treatment HBV-DNA and HBsAg suppression was more pronounced in the peg-interferon lambda treated patients. Due to these findings the further development of peg-interferon lambda in chronic hepatitis B was stopped.

HEPATITIS E VIRUS (HEV) INFECTION

A mouse model for hepatitis E virus infection

With approximately 20 million new infections per year, HEV is a leading cause of acute hepatitis worldwide and may cause numerous extrahepatic manifestations but also chronic liver disease in immunocompromised patients. Models to study the molecular biology of HEV infection *in vivo*, and thus the possibility to find new treatment options, are still limited to non-human primates and other mammals, and none of these models can mimic chronic HEV infections. In this issue of the *Journal*, Allweiss *et al*. **described the first mouse model of HEV infection by employing a human liver chimeric mouse (uPA/SCID/beige mice)** in which HEV infection and spreading could be monitored in blood, liver and other types of tissue down to the single cell level. The new in vivo model will be of significant importance in order to study the pathogenicity of different HEV strains, innate immunity as well as potential antiviral agents including vaccine-induced neutralizing antibodies.

CIRRHOSIS

Modulation of TLR7/8 restores bactericidal activity of neutrophils, obeticholic acid (OCA) restores intestinal permeability, and the disturbances in the metabolome predicts mortality in acutely decompensated cirrhosis patients.

Alterations in liver function, liver injury, bacterial translocation and immune dysfunction are inter-related phenomenon in cirrhotic patients. Three excellent papers in the current issues of the *Journal* address these pointing also to potential therapeutic strategies.

In very novel and exciting studies, Boussif *et al.* define the possible mechanisms of why neutrophils from patients with cirrhosis have reduced bactericidal activity. They show that the release of neutrophilic myeloperoxidase, which is a key enzyme involved in bacterial killing is impaired in cirrhosis. **They show that the Akt/MAP kinase pathway may be involved in this and the killing function of the cells can be restored using a TLR7/8 agonist, providing a potential novel strategy to reduce infection rates in cirrhosis patients.**

Ubeda *et al.* show that the FXR agonist, **OCA, when administered to cirrhotic rats with ascites significantly reduced the severity of bacterial translocation through many associated mechanisms including restoration of the gut tight junctions**. As a result, the animals had improved liver function and severity of fibrosis, suggesting that OCA approach may be useful in preventing the complications of cirrhosis.

McPhail and Shawcross *et al.* performed an extremely novel and extensive study focusing on describing the metabolome of patients with acute decompensation of cirrhosis. **Their data suggest that the alteration in the metabolome defines the prognosis of these patients and provides a potentially important biomarker.** Of course, better understanding of the specific alterations may well provide novel therapeutic targets.

LIVER FAILURE AND GROWTH

Hepatocyte Transplantation in Acute Liver Failure

The treatment of acute liver failure remains an unmet need. Hepatocyte transplantation is an attractive strategy that may allow time for hepatic regeneration while liver function is maintained with transplantation of hepatocytes. However, the results of hepatocyte transplantation remain poor mainly because of issues related to engraftment of the transplanted hepatocytes. **Nagamoto *et al.* address this issue of hepatocyte engraftment using a novel cell sheet engineering technology for experimental hepatocyte transplantation.** The human iPS-HLC sheets were attached onto the liver surfaces of mice with liver injury. This strategy was significantly more successful than conventional method in reducing the severity of liver injury indicating a potential future solution.

Richard Moreau* at Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Clichy and Paris, France; UMRS1149, Université Paris Diderot, Paris, France; DHU UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; Laboratoire d'Excellence (Labex) Inflamex, ComUE Sorbonne Paris Cité, Paris, France;*Corresponding author *E-mail address*: richard.moreau@inserm.fr

Ramon Bataller at Division of Gastroenterology and Hepatology, Departments of Medicine and Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Thomas Berg at Section Hepatology, Clinic for Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany.

Jessica Zucman-Rossi at Inserm UMR-674; Génomique Fonctionnelle des Tumeurs Solides; IUH; Paris, France; Université Paris Descartes; Labex Immuno-oncology; Faculté de Médecine; Sorbonne Paris Cité; Paris, France.

Rajiv Jalan at Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Hospital, UK