

From the Editor's Desk January 2016

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

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) Inflammex, 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 Immunoncology; 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

SELECTION OF THE MONTH

Big title: Plasma exchange improves survival of Acute Liver Failure patients

Small Titles: Maternal exercise during pregnancy protects from hepatic steatosis in mice, Secretion of infectious hepatitis E virus in urine

LIVER INJURY

TRAF3 and NK cells in hepatic ischemia/reperfusion injury

Hepatic ischemia/reperfusion (I/R) injury that includes cell death and inflammation complicates diverse surgical procedures, such as liver transplantation. In this issue of the *Journal* two articles provide new insights into mechanisms that promote hepatic I/R injury or conversely protect the liver against this injury. Hu *et al.* show that the protein **TRAF3 (TNF receptor associated factor 3) promotes liver damage and inflammation** via TAK 1 (TGF- β -activated kinase 1)-dependent activation of the

mitogen-activated protein kinase and I κ B kinase pathways. These findings identify targets for novel therapeutic approaches. Eggenhofer *et al.* investigated the role retinoic acid receptor-related orphan nuclear receptor (ROR γ T)-expressing, IL-22-producing NKp46+ cells (NK22) which are unconventional subsets of NK cells. They show that **ROR γ T-expressing NK22 play a crucial protective role against hepatic I/R injury in mice.**

LIVER FIBROSIS

Role of Hic-5 and age

TGF- β (transforming-growth factor β) is a key stimulus for hepatic stellate cell activation and production of extracellular matrix (ECM) component. Hic-5 (hydrogen peroxide-inducible clone-5), also known as Tgfb1i1 (TGF- β 1-induced transcript 1 protein), is a TGF- β -target gene whose function is elusive. Using models of fibrosis in wild-type and *Hic-5* KO mice, Lei *et al.* now show that **Hic-5 deficiency attenuates the activation of HSCs and liver fibrosis** though reducing the TGF- β /Smad2 signaling by upregulation of Smad7. Therefore, inhibition of HIC-5 might be beneficial for treating liver fibrosis.

Little is known on the impact of age on ECM turn-over. Karsdal *et al.* addressed this question by investigating ECM fragments in serum of rats aging from 1 to 12 months. They show here that ECM turnover rates were consistently different in young vs old animals, up to 30 fold. This appears to be due to body growth, a different ECM composition and a higher regenerative capability of connective tissues in young versus old animals. **These findings should be considered when developing diagnostic and therapeutic biomarkers of fibrosis based on serum levels of ECM fragments.**

INFLAMMATORY HEPATOCELLULAR ADENOMAS

Protective role of Nrf2 and p65

Hepatocyte homeostasis is frequently challenged by overproduced oxygen reactive species. The resulting oxidative stress induces a cell-autonomous (intrinsic) response aimed to restore cell homeostasis. Nrf2 (encoded by *Nfe2l2*) is a transcription factor of the bZIP family which is induced by oxidative stress. It binds to antioxidant response (ARE) elements in the promoter regions of target genes and plays a crucial role in the restoration of homeostasis in response to oxidative stress. Khöler *et al.*

were interested in the cross-talk of Nrf2 and NF- κ B/p65 (encoded by *RelA*) and investigated mice KO for both *Nfe2l2* and *RelA*. They show that the double mutant female mice develop benign liver tumors that are inflammatory recapitulating human inflammatory hepatocellular adenomas. They also find a **functional cross-talk of Nrf2 and NF- κ B/RelA in hepatocytes, which plays an important homeostatic role by protecting the liver from necrosis, inflammation and fibrosis.**

HEPATOCELLULAR CARCINOMA (HCC)

Preoperative HVPG

Predicting post-hepatectomy liver failure in patients undergoing liver resection for HCC is not easy. It has been suggested that a pre-operative HVPG (hepatic venous pressure gradient) of 10 mm Hg or more may be associated with a significant risk of post-hepatectomy liver failure. However, Cucchetti *et al.* show that **if the value of pre-operative HVPG can be used before surgery to stratify the risk of post-hepatectomy liver failure, the proposed cut-off of 10 mm Hg excludes approximately 25% of the patients who otherwise would benefit from surgery without short to mid-term postoperative sequelae.**

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Gestational and risk of steatosis in mice, chemokines regulate inflammation in steatohepatitis

Maternal exercise confers protection to adult offspring against various diseases, but its influence on the development of liver diseases is largely unknown. In this issue, Sheldon *et al.* investigates if **maternal exercise during gestation** would reduce high fat diet induced hepatic steatosis in adult rat offspring. The authors convincingly demonstrate that offspring mice from mothers that exercise during pregnancy that were fed with a high fat diet had reduced body fat, better glucose tolerance and **less hepatic steatosis**. These beneficial effects were associated with increased markers of hepatic mitochondrial biogenesis and hepatic triacylglycerol secretion. This important experimental study, which should be confirmed in epidemiological studies, reinforces recent research published in the *Journal* indicating that **exercise** has protective effects against fatty liver diseases.

CXC chemokines are chimio-attractants for neutrophils, which typically infiltrate the livers from patients with non-alcoholic steatohepatitis (NASH). In this issue, Zhang *et*

a/. performed a translational study using human samples as well as mice with genetic and/or pharmacological blockade of the **CXC3 receptor**. The authors found that CXCR3 was significantly up-regulated in liver tissues of patients with NASH and that **Cxcr3^{-/-} mice were more resistant to diet-induced steatohepatitis**. Importantly, Cxcr3 activation mediated autophagosome-lysosome impairment and endoplasmic reticulum stress in experimental NASH. These intriguing results suggest that targeting CXC chemokines could be an appealing strategy to treat steatohepatitis in humans. The main concern of this approach is that CXC chemokines are essential for defense against bacterial infections. Further studies should explore whether this approach is safe when administered for prolonged periods of time.

HEPATITIS C

Better is the enemy of good – MALACHITE Phase IIIb trial: The last gem of the puzzle, new concepts in HCV-induced alterations of lipid metabolism

The advantages of the current interferon-free direct acting antiviral (DAA) regimens with respect to their safety and efficacy in comparison to the previous DAA-based triple regimens including peg-interferon (IFNa) plus ribavirin (RBV) have never been demonstrated by direct comparison in a randomized fashion. In two open-label, phase 3b trials Dore *et al.* compared safety and efficacy of all-oral ombitasvir/paritaprevir/ritonavir and dasabuvir+/- RBV and telaprevir-based triple peg-IFNa plus RBV regimen in treatment-naïve (MALACHITE-I) or -experienced (MALACHITE-II) non-cirrhotic patients with hepatitis C virus (HCV) type 1 infection. Among treatment-naïve patients SVR rates with IFNa-free versus triple regimen were 97% and 80%, and among experienced patients 99% and 66%. **A striking difference was also observed concerning patient-reported outcomes, premature treatment discontinuation and severe adverse events also favoring the interferon-free regimen.** Is there any reason to further consider interferon-based regimens? The answer from the gem study is no.

HCV highjacks lipid metabolism pathway for proper viral replication leading to dyslipidemia, reduced serum cholesterol levels and hepatic steatosis – a hallmark of HCV type 3 infection – but also modifications of antiviral treatment response. The aims of the elegant study by Younossi *et al.* were to assess HCV type-specific changes in serum lipids and sterol metabolites in HCV type 2 and 3 infections based on disease severity and response to treatment with sofosbuvir and ribavirin.

Reduced *de novo* lipogenesis resulting in relative hypocholesterolemia was observed in HCV type 3 infection due to either disturbance in the distal cholesterol biosynthesis pathway, or a selective derangement of hepatocyte lipid secretion which, however, can be restored by sofosbuvir-induced suppression of viral replication. This study provides new insights into the selective dysregulation of post-squalene sterol and lipid metabolism in chronic HCV infection.

HEPATITIS E

Secretion of infectious hepatitis E virus in urine

Hepatitis E virus (HEV) mainly replicates in the liver but a broader organ tropism of HEV have been demonstrated in recent animal studies including small intestines, lymph nodes, colon, brain, and kidneys, and this might be an explanation for the significant number of extrahepatic manifestations which have been linked to this infection. The study by Geng *et al.* **described for the first time the detection of HEV RNA and HEV antigen in the urine of patients with acute and persistent HEV infection and the infectivity of urine-derived HEV was proven by inoculation studies in monkeys.** The study provides not only new insights into the mechanisms of HEV replication, and the dynamics of HEV dissemination but also implicates that HEV-Ag testing in urine may become a useful new marker for the diagnosis of hepatitis E viremia.

ACUTE LIVER FAILURE & LIVER REGENERATION

Plasma exchange improves survival of ALF patients and liver derived exosomes can improve hepatic regeneration

Despite improvements in our understanding of acute liver failure, mortality of patients without liver transplantation remains unacceptably high. The study of Larsen *et al.* describes the results of a landmark randomized clinical trial that took over 10-years to perform **and shows that treatment with plasma exchange can improve the survival of ALF patients**, providing proof of concept for 'detoxification' systems.

Also, in the present issue, an exciting paper by Nojima *et al.* suggests **that exosomes derived from hepatocytes but not other cell types can enhance liver regeneration *in vitro* and *in vivo* in animal models.** Their data suggests that the operative mechanism is through hepatic transfer of sphingosine kinase 2, which

increases the synthesis of sphingosine-1-phosphate within the target hepatocyte providing a translatable strategy.

CIRRHOSIS

NF- κ B-induced STS may cause feminization to limit inflammation; hepatic tissue factor mediates hypercoagulable state in cirrhosis

The exact mechanism of feminization in cirrhosis is unclear and the role of elevated estrogens in regulating inflammation is unknown. Xie *et al.* show that STS (encoding steroid sulfatase) is a novel NF- κ B target gene that is induced in the liver of patients with cirrhosis. Their **data strongly suggest that the inflammatory induction of STS may be the cause of estrogen excess in chronic liver disease.** They hypothesize that this estrogen may also regulate hepatic inflammation through a negative feedback mechanism.

Mechanisms of coagulation disturbances in cirrhosis are unclear as many studies suggest that despite increased prothrombin time, the patients are hypercoagulable. A very important paper in animal models by Rautou *et al.* **showed incontrovertibly the importance of hepatic 'tissue factor' (TF) as being important in mediating the hypercoagulable state observed in these animals.** Knocking out hepatic but not myeloid TF prevented this hypercoagulable state.