

## From the Editor's Desk November 2016

### Draft #3

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

**Richard Moreau\*** at Centre de Recherche sur l'Inflammation (CRI), INSERM, 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 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

## SELECTION OF THE MONTH

**Big Title:** Population burden of alcoholic cirrhosis is related to daily alcohol consumption

**Small titles:** Late viral hepatitis diagnosis – a missed opportunity, Testosterone: a novel approach to treat sarcopenia in male cirrhotics

## LIVER FIBROSIS

### Involvement of cartilage oligomeric matrix protein (COMP)

COMP which is known to interact with other extracellular matrix (ECM) proteins such as the collagens and fibronectin, is expressed in different fibrotic tissues such as cirrhotic livers, among others. Magdaleno *et al.* now show that **COMP contributes to liver fibrosis by regulating the deposition of fibrillary collagen-I, a major ECM component, via aCD36 (known as platelet glycoprotein 4)-dual specificity**

mitogen-activated protein kinase kinase 1/2 (known as MEK1/2)-phospho-ERK1/2 module.

### HEPATOCELLULAR CARCINOMA (HCC)

**Novel tumor-promoting signals, “non-canonical” induction of interferon (IFN)-stimulated genes (ISGs), portal vein tumor thrombosis (PVTT) and liver resection**

The 14-3-3 proteins are a family of 28-33 kDa peptides including seven mammalian isoforms ( $\alpha/\beta$ ,  $\gamma$ ,  $\sigma$ ,  $\epsilon$ ,  $\zeta$ ,  $\eta$ , and  $\theta/\tau$ ), which regulate multiple cellular functions via interactions with intracellular proteins by phosphoserine and phospho-threonine binding. Each protein is encoded by a gene belonging to the family of tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (*YWHA*). 14-3-3 proteins can regulate cancer cell proliferation, survival, migration/invasion, and function. Five members of 14-3-3 family proteins ( $\alpha/\beta$ ,  $\gamma$ ,  $\sigma$ ,  $\epsilon$ , and  $\zeta$ ) may be involved in the HCC progression, including tumor growth, metastasis, and resistance to sorafenib, however, the functions and clinical significances of 14-3-3 $\theta/\tau$  and 14-3-3 $\eta$  (i.e., 14-3-3 protein eta, encoded by *YWHAH*) in HCC are poorly known. Here, Shen *et al.* show that **the 14-3-3 $\eta$ -ERK1/2 pathway promotes HCC, not only by acting in tumor cells but also in tumor vessels. Moreover, 14-3-3 $\eta$  may be a potential therapeutic target for HCC and a biomarker for predicting sorafenib treatment response.**

Liver graft injury and tumor recurrence are major challenges in patients who receive a liver transplant for HCC. In the context of liver graft injury, recruitment of regulatory T cells (Tregs) leads to late phase tumor recurrence after liver transplantation. However, the mechanisms for recruitment of Tregs is unknown. Li *et al.* now report that, **at liver graft injury, the C-X-C motif chemokine 10 (known as IP-10; encoded by *CXCL10*) and its receptor CXCR3 are overexpressed; enhanced IP-10 signaling leading to recruitment of Tregs.** Future studies should elucidate the mechanisms for IP-10 overexpression at the site of liver injury.

Type 1 IFNs signal through a common heterodimeric receptor (IFNAR1/IFNAR2) or through IFNAR1 alone to induce hundreds of ISGs. Receptor engagement results in the activation of “canonical” signaling pathways involving JAK1 and TYK2 kinases that phosphorylate STAT1 and STAT2 transducers, which then associate with IRF9 to form the ISGF3 complex, which induces transcription of antiviral effectors (*OAS*, *IFIT*, *MX*, or *GBP* families). However, type 1 IFNs also activate several “non-canonical” signaling

pathways, e.g., other STAT family members such as STAT3, PI-3K, the mTOR-Akt-S6K axis. The role of “non-canonical” signaling pathways is incompletely understood; they are thought to play a crucial role in the induction of the inflammatory and anti-tumoral action of type 1 IFNs. Brisac *et al.* now identify a novel “non-canonical” signaling pathway used by type 1 IFNs in hepatoma cells. **They find that following IFNAR engagement, the IQ-motif containing GTPase activating protein 2 physically interacts with the transcription factor p65 of the NF-κB family to induce a subset of anti-viral ISGs (e.g., MX1, RSAD2, EIF2AK2), independently of the “canonical” JAK/STAT pathway.** These intriguing findings suggest that type 1 IFNs can use “non-canonical” signaling to induce antiviral effectors and for this reason deserve to be confirmed in cells other than hepatoma cells.

The presence of PVTT in patients with HCC indicates an advanced stage, and liver resection is not recommended. Kokudo *et al.* evaluated survival associated with liver resection in a series of 6,474 patients with HCC and PVTT by analyzing data from a Japanese nationwide survey. **They show that as long as the PVTT is limited to the first-order branch, liver resection is associated with a longer survival outcome than non-surgical treatment.**

### NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD).

#### NGAL as an inflammatory mediator, preserved hemostatic status in NAFLD

The molecular mechanisms that mediate inflammation in patients with non-alcoholic steatohepatitis (NASH) are not well known. In this issue, Dewei *et al.* investigated the role of neutrophil gelatinase-associated lipocalin (NGAL, encoded by *LCN2*), a known biomarker of acute kidney injury in humans that also acts as a pro-inflammatory cytokine. The authors showed that **NGAL hepatic expression and serum levels were increased** in patients and in rodents with NASH. Importantly, infiltration of neutrophils and macrophages were attenuated in mice lacking *Lcn2*. In contrast, administration of NGAL **exacerbated diet-induced liver injury, inflammation and macrophage accumulation.** The effects of NGAL were mediated by CXCR2. This translational study suggests that NGAL could be a potential therapeutic target to attenuate inflammation in patients with NASH.

NAFLD is associated with an increased risk of thrombosis, yet the mechanisms are largely unknown. In this issue, Potze *et al.* investigated whether hypercoagulability contributes to this risk. The authors performed an in depth hemostatic profile in a cohort

of patients with NAFLD and both lean/overweight and diseased controls. **Platelet activation markers, thrombomodulin-modified thrombin generation and thromboelastography test were comparable** between patients with non-cirrhotic NAFLD and controls. Plasma fibrinolytic potential and clot permeability were decreased in overweight controls and noncirrhotic NAFLD. This study reveals that the overall hemostatic profile is comparable between patients with non-cirrhotic NAFLD and controls. Interestingly, **prothrombotic features in patients with NAFLD are likely driven by obesity.**

### ALCOHOLIC LIVER DISEASE.

#### Daily alcohol intake at the population level predicts the weight of alcohol cirrhosis

Most studies assessing alcohol as a cause of cirrhosis at the population level focus on per capita consumption. In this issue, Stein *et al.* performed a comprehensive analysis of the WHO 2014 Global Status Report on Alcohol and Health and countries were categorized based on daily consumption. The WHO 2014 Report found **that half of cirrhosis mortality worldwide is attributable to alcohol.** The designation of countries by **moderate or heavy daily drinking had the strongest influence** on the weight of alcohol in the cirrhosis burden. Importantly, drinking patterns and the type of alcohol did not independently predict the weight of alcohol as a cause of cirrhosis. This study strongly suggest that **reducing heavy drinking** should be considered as an important target for public health policies to reduce the burden of alcoholic cirrhosis.

### VIRAL HEPATITIS

#### Late viral hepatitis diagnosis – a “missed opportunity”, Molecular mechanisms of HBV-induced hepatocarcinogenesis

Timely and effective care to people chronically infected with hepatitis B (HBV) and C virus (HCV) infection is essential to prevent clinical endpoints and to reduce the rising burden of liver disease, whereas late hepatitis notification may increase the risk of advanced liver disease complications, including decompensated cirrhosis and hepatocellular carcinoma (HCC). The large population-based study by Alavi *et al.* linked HBV/HCV notifications in 1995-2012 to cancer registry and hospital admissions in New South Wales, Australia between 1995-2012 in 50,958 HBV- and 79,727 HCV-infected individuals. **Although the percentage of both, late HBV and HCV**

**notifications declined in more recent years** - which can be taken as an indicator of enhanced viral hepatitis screening - **still 17-29% of the population were diagnosed late**, defined as either after, at the time, or within two years before disease decompensation or HCC development. The results of this elegant population-based study shows the importance to improve our screening strategies and linkage to care early in the chronic course of the infection

Hepatic cancer stem cells (hCSCs) detected in liver cancers of various etiologies are characterized by expression of certain cell surface markers like among others the epithelial cell adhesion molecule (Ep-CAM), prominin-1 (also known as CD133), and CD44 antigen. Their presence may define a certain subset of HCCs with poor prognosis and resistance to sorafenib and therefore provide a new prognostic tool for precise HCC classification. The study by Mani *et al.* nicely describes a **novel molecular mechanism by which HBV generates the expression of an hCSC-like gene signature**. Since the expression of the hCSC-like gene signature in HBV replicating cells and X/c-myc liver tumors was mediated by Ep-CAM regulated intramembrane proteolysis and Wnt pathway activation, inhibition of these pathways could serve as potential therapeutic strategies for this subtype of HBV-associated HCCs.

## CIRRHOSIS

### **Novel therapeutic approach to sarcopenia and new insight into pathogenesis, biomarkers and novel therapeutic targets for cirrhosis**

Sarcopenia is a dreadful complication of cirrhosis and is an independent predictor of mortality. The mechanisms underlying its pathogenesis are poorly understood and there are no specific therapies. Two papers in the present issue of the Journal address this issue. Sinclair *et al.* describe the results of the first and important randomized controlled clinical trial comparing testosterone with placebo in male cirrhotic patients with low testosterone. **The data provide clear evidence that administration of testosterone is safe and is associated with an improvement in muscle and bone mass and, a reduction in fat mass and HbA1c.** Another paper in this issue addresses possible pathophysiologic mechanisms underlying sarcopenia. Davuluri *et al.* **provide solid evidence for a novel hypothesis linking sarcopenia, hyperammonemia and reduction in protein synthesis. They suggest that L-**

**leucine may rescue protein synthesis that is inhibited by ammonia.** New therapeutic targets for sarcopenia are identified in this paper.

Prognostic criteria defining outcome of cirrhotic patients is currently based on a collection of clinical and biochemical variables, which are not direct targets of therapy. There are 3 highly relevant papers in the present issue of the Journal that highlight pathophysiological markers that may be usable as potential therapeutic targets, while maintaining their prognostic ability. **Kalambokis *et al.* provide exciting new data in cirrhotic patients with thrombocytopenia indicating that they are hypercoagulable and that vWF-Ag and FVIII-to-PC ratio independently predicts decompensation providing a new therapeutic target.**

Circulatory dysfunction is closely correlated with poor clinical outcome of cirrhotic patients. Vasopressin is increased in cirrhotic patients but its role is difficult to study because of its short half-life and methodological issue with its measurement. Copeptin is stable and released stoichiometrically with vasopressin. **Sola *et al.* show that plasma copeptin levels accurately identifies cirrhotic patients at risk of dying and then validate their results in an independent cohort.** Their data may allow development of copeptin as a companion biomarker to identify patients likely to benefit from aquaretics.

At present, cirrhotic patients require screening endoscopy at regular intervals to identify those at risk of bleeding. The Baveno VI guidelines propose that cirrhotic patients with a liver stiffness measurement (LSM)  $<20\text{kPa}$  and a platelet count  $>150000/\mu\text{L}$  can avoid screening endoscopy but this guideline has not been validated independently. **In an important study, Maurice *et al.* studied over 300 patients and showed an accuracy of about 98% confirming the validity of the Baveno proposal.** This observation has the potential to avoid unnecessary endoscopies.