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From the Editor's desk...

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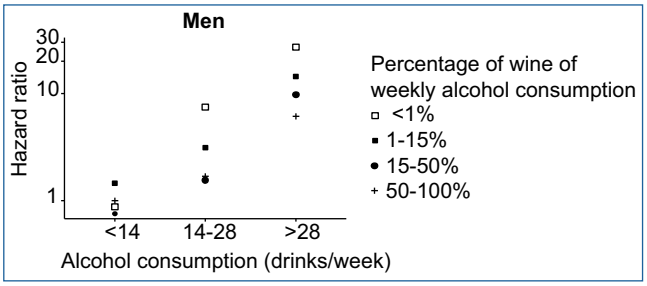
Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucman-Rossi, Rajiv Jalan

SELECTION OF THE MONTH

Daily drinking and consuming more than 14 units of alcohol per week increases risk of alcoholic cirrhosis

Deaths from liver disease have increased dramatically over the past 30 years and one of the culprits for this increase is excessive alcohol consumption. Using the Danish Cancer, Diet, and Health study, which included 55,917 participants over an 8-year period, Askgaard and colleagues showed that **daily drinking was worse than drinking 3–4 days per week and the risk of liver cirrhosis started at 14 units consumption per week**. This is important given that the current recommendation regarding safe limits of alcohol is 21 units per week. Clearly, current recommendations will need to be revisited. Also the study provided novel data showing that compared to beer and liquor, wine might be associated with a lower risk of alcoholic cirrhosis.



Askgaard et al., 2015

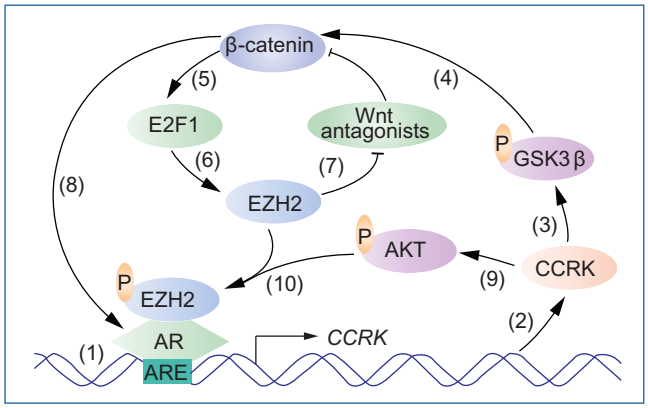
LIVER CANCER

Gender and histone modifications, HCC in patients who achieved serum HBsAg clearance, radiological assessment after TACE, sorafenib therapy, liver resection

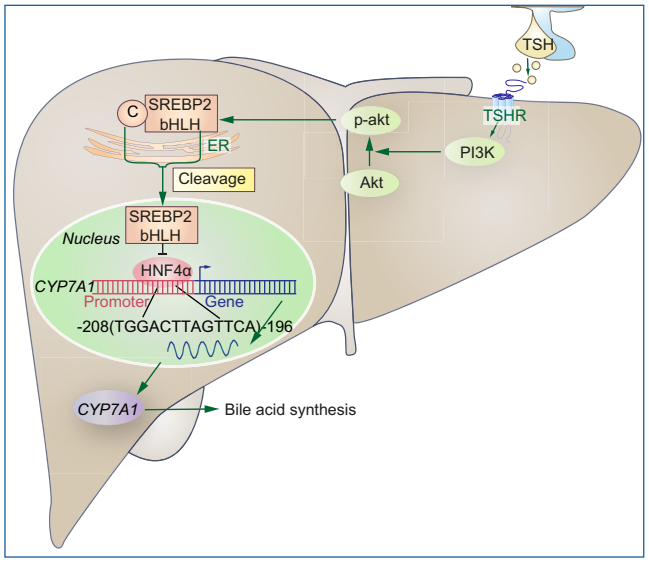
HCC is most common in males than females and the reasons for this difference are poorly known. Lysine methyl transferases (KMTs) catalyze the transfer of one, two, or three methyl groups from *S*-adenosyl-L-methionine to the ε-amino group of a lysine residue on a histone to generate mono-, di-, and trimethylated histones. The KMT6 family methylates histone H3K27 and exists within a complex. The methylase activity of KMT6 is due to enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2); the other components of the complex are SUZ12, EED, and RBBP4/7. Deregulation of certain members of the KMT6 complex has been shown in cancer. Cell cycle-related kinase (CCRK, encoded by *CDK20*) is involved in liver carcinogenesis. Feng *et al.*, using sophisticated approaches, investigated the potential cross-talk between the EZH2 and CCRK in the context of liver cancer. They showed that CCRK expression in immortalized human liver cells resulted in increased EZH2 and H3K27 trimethylation and stimulated proliferation and tumor formation. CCRK by inhibiting glycogen synthase kinase 3β stimulated a β-catenin/TCF/E2F1/EZH2 module that epigenetically enhanced androgen receptor (AR) signaling. Simultaneously, CCRK facilitated the co-occupancy of CCRK promoter by EZH2-AR and its subsequent transcriptional activation. **These findings reveal an epigenetic vicious cycle in liver carcinogenesis that involves reciprocal regulation of CCRK and EZH2 suggesting targets for new therapies**.

Whether patients with chronic hepatitis B who have achieved serum HBsAg clearance should be screened for hepatocellular carcinoma (HCC) development is unknown. Kim *et al.* addressed this question in a retrospective analysis of a cohort of 829 Korean patients. **They showed that the presence of HCC should be screened in patients with cirrhosis, and in patients who do not have cirrhosis if these are males, older than 50 years and infected with HBV genotype C**. Clearance HBsAg from serum in individuals of 50 years or more is an independent predictor for HCC.

Kim *et al.* retrospectively investigated which is the best radiological method for measuring HCC treated by



Feng et al., 2015



Song et al., 2015

trans-arterial chemoembolization (TACE) in order to assess suitability for liver transplantation. A total of 271 patients with HCC treated with TACE prior to liver transplantation were classified according to both the Milan and up-to-seven criteria after TACE using the enhancement or size method on computed tomography images. **The authors found that enhancement method is appropriate for assessing the control or down-staging of HCC within Milan after TACE**. However, the size method seems to be better when applying the up-to-seven criterion.

Sorafenib therapy is used for HCC with extrahepatic spread. However, sorafenib therapy is frequently discontinued due to adverse events such as deterioration of liver function and/or performance. Sohn *et al.* investigated retrospectively the outcome and prognostic factors of sorafenib treatment in 254 patients with HCC and extrahepatic spread in whom sorafenib was administered for at least 8 weeks. **Sorafenib prolonged survival in patients with extrahepatic spread who achieved disease control (defined when the tumor response was satisfactory, i.e., complete or partial remission, or evidence of stable disease according to the RECIST criteria)**. Intrahepatic tumor is a poor prognostic factor for both disease progression and overall survival in HCC patients with extrahepatic spread treated with sorafenib.

Repeated hepatectomy is used to treat recurrent HCC or liver metastasis from colorectal cancer. However, repeated hepatectomy may result in postoperative adhesion and decrease in liver regenerative capacity. Inagaki *et al.* asked whether a fetal liver mesothelial cells (FL-MCs) sheet could solve these two clinical issues simultaneously. They showed that the FL-MCs sheet was able to both prevent postoperative adhesion and promote liver regeneration in both syngeneic and allogeneic transplantation, and **hence FL-MCs may serve as a potentially useful cell source for regenerative medicine after hepatectomy**.

Treatment decisions for HCC are guided by tumor size. Kluger *et al.* aimed to analyze resection outcomes according to tumor size and characterize prognostic factors. By studying a large group of 303 patients across a distribution of tumor sizes and background liver diseases, they found that size alone provided limited prognostic information. **Tumor biology and underlying liver function were better predictors of prognosis and should be taken into account.**

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Anthocyanins, TRAIL receptor, disease progression, TSH and bile acids, early menarche and disease risk

Anthocyanins are water-soluble flavonoids that have beneficial effects due to its antioxidant properties. In this issue, Morrison *et al.* demonstrate that mirtoselect, an anthocyanin-rich bilberry extract, attenuates the degree of steatosis and inflammation in experimental NASH. Further studies should investigate the safety and efficacy of this promising type of compounds in humans.

Targeting inflammatory mediators could be beneficial in patients with metabolic syndrome. Idrissova *et al.* provide convincing evidence that **TRAIL receptor** (encoded by *TNFSF10*, a gene of the TNF receptor superfamily) signaling plays an important role in the pathogenesis of obesity-associated inflammation. Genetic deletion of trail receptor completely repressed weight gain, adiposity and insulin resistance and attenuated the development of NASH in high fat-fed mice. These data advance the concept that macrophage-associated hepatic and adipose tissue inflammation of nutrient excess requires trail receptor signaling.

The factors that predict **progression of NAFLD** are not well known. In this issue, McPherson *et al.* performed a relevant study using paired biopsies in patients with NAFLD. Almost half of the patients have fibrosis progression, some of them to advanced forms. Interestingly, some patients with simple steatosis at baseline developed fibrosis, suggesting that the **current dogma that simple steatosis is a benign condition should be revisited**.

Elevated **TSH levels** are frequently found in patients with NAFLD. Bile acids play a crucial role in dietary fat digestion and in the regulation of lipid, glucose, and energy metabolism. Song *et al.* investigated the impact of TSH on **bile acid homeostasis**. They demonstrated that TSH represses hepatic bile acid synthesis via SREBP-2/HNF-4α/CYP7A1 axis, which strongly supports that TSH is an important regulator of bile acid homeostasis in liver independently of thyroid hormones.

The percentage of girls with early menarche has increased in the last two decades worldwide. Girls who experienced early menarche are significantly more often overweight/obese. However, whether early menarche predisposes to NAFLD was unknown. In this issue of the *Journal*, Ryu *et al.* identified an inverse association between **age at menarche and NAFLD** in a large sample of middle-aged Korean women. This association was partially mediated by adiposity. The findings of this study suggest that obesity prevention strategies are needed in women who undergo early menarche to reduce the risk of NAFLD.

HEPATITIS C

SART-1 regulates antiviral effector genes, new treatment approaches for HCV type 4, simeprevir-associated resistance

How interferons (IFN) exert their antiviral state in HCV infection still remains unclear. However, there is growing evidence that many host factors, independent

of the classical JAK-STAK pathway, are involved. Now Lin *et al.* showed that **SART-1** (squamous cell carcinoma antigen recognized by T cells), a component of the spliceosome involved in mRNA processing and splicing **regulates HCV replication through differential expression and alternative splicing** of mRNAs expressed by antiviral effector genes including *MX1* and *OAS3*. The observation that HCV infection reduces SART1 expression may be taken as a strong argument that HCV promotes its persistence through suppression of multiple levels of host innate immunity, hereby including not only the classical IFN-JAK-STAT pathway but also host components of the spliceosome.

HCV type 4 accounts for approximately 13% of the world's HCV-infected population and is the most prevalent HCV type in North Africa/Middle East and Central Sub-Saharan Africa. However, limited data are available at present to guide clinical decision-making in patients with chronic HCV type 4 infection. In this issue of the *Journal* three studies focus exclusively on the treatment of HCV type 4 and were further highlighted by an Editorial.

In a response guided concept study Moreno *et al.* evaluated in an open-label, single-arm study (RESTORE) the **efficacy and safety of a 12 week simeprevir with PegIFN/ribavirin triple regimen** followed by 12–36 weeks of PegIFN/RBV maintenance in naïve or experienced patients chronically infected with HCV genotype 4. Sustained response rates were especially high in treatment-naïve and prior relapser patients fulfilling response-guided criteria for 24 weeks (93.5% and 95.0%, respectively), but limited efficacy was shown for prior partial and null responders (60% and 40%, respectively).

The study by Ruane *et al.* in which 60 patients of Egyptian ancestry were randomly allocated in a 1:1 ratio to receive an **IFN-free regimen of sofosbuvir and ribavirin** for 12 or 24 weeks clearly demonstrates the **advantage of extending treatment duration to 24 weeks** hereby increasing SVR rates from 68% (12 weeks) to 93%.

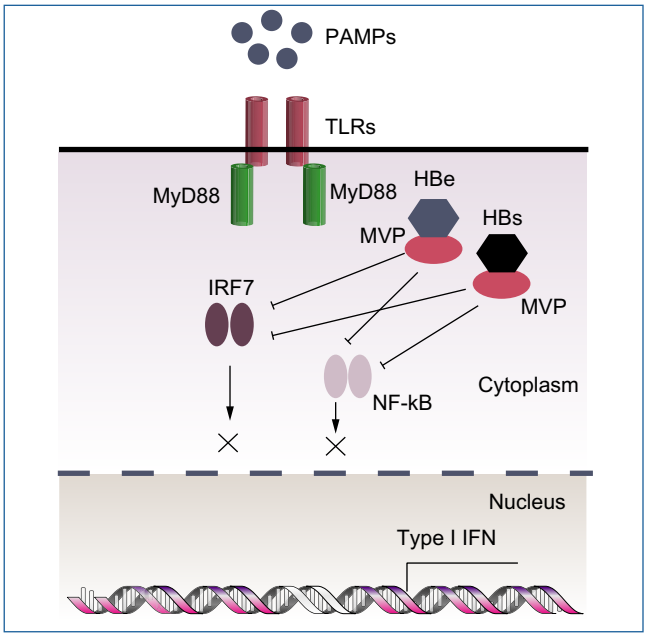
A 12 week regimen of three direct acting antivirals – the NS5A inhibitor daclatasvir, the NS3 protease inhibitor asunaprevir plus the non-nucleoside NS5B polymerase inhibitor beclabuvir (either 75 mg or 150 mg) – **resulted in a 100% SVR rate** as shown by Hassanein *et al.* in their exploratory study in 21 non-cirrhotic HCV type 4-infected patients from the United States.

Simeprevir plus PegIFNα/ribavirin treatment of HCV genotype 1a patients with a NS3 protease Q80K polymorphism at baseline is not recommended according to clinical guidelines. Lenz *et al.* analyzed this problem in more depth by describing mechanisms that may lead to lower SVR rates in this patient population. Undertaken were also **comprehensive characterizations of emerging resistant mutations** in patients not achieving SVR in clinical phase II and III studies. Given the wide use of simeprevir in combination with other drugs these findings are highly relevant.

HEPATITIS B

Predicting HBsAg loss by hepatitis B viral diversity, immune evasion by disrupting MVP-MyD88 interaction

To date, little is known about the predictive nature of any viral factors for loss of HBsAg under nucleos(t)ide analog therapy. In an elegant study, Charuworn *et al.* showed for the first time that **certain patterns in inter-patient viral diversity** across the entire HBV type A and D coding region observed at the time of treatment initiation **were associated with HBsAg loss** on TDF therapy. These results suggest that it should be possible to construct a model that can predict prior to the start of antiviral therapy which patients might achieve HBsAg loss, which would be a significant step forward in the care of chronically HBV-infected patients.



Liu et al., 2015

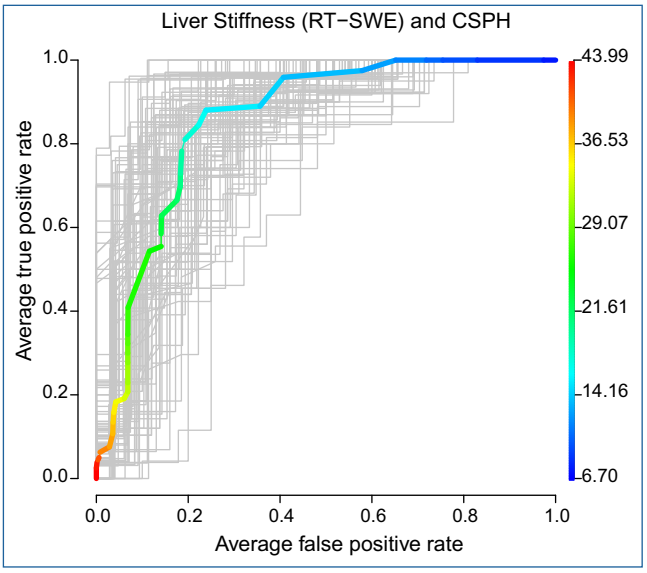
The mechanisms that are involved in establishing and maintaining chronic HBV infections are still not well understood. Major vault protein (MVP) is a novel virus-induced host factor which upregulates type-I IFN production, leading to cellular antiviral response. Liu *et al.* are providing a new model of innate immune escape in chronic HBV infection by demonstrating that **HBsAg as well as HBeAg specifically bind virus-induced MVP**, which in turn led to blocking of the molecular interaction between MVP and MyD88 (an adaptor that transduces toll-like receptor signaling), and suppression of the MVP-induced NF-κB and IFN signaling.

CIRRHOSIS AND PORTAL HYPERTENSION

Proton pump inhibitors and SBP, non-invasive diagnosis of clinically significant portal hypertension

The debate about whether consumption of proton pump inhibitors increase the risk of spontaneous bacterial peritonitis in cirrhotic patients has been ongoing for a considerable length of time fuelled by data from small retrospective studies. The study by Terg *et al.* from Argentina, prospectively included 700 patients in 23 centers and **showed conclusively that intake of proton pump inhibitors is NOT associated with SBP**. These data provide a convincing and clear answer to a longstanding ongoing debate.

One of the major limitations to adequate management of portal hypertension and drug development in this area is the need for invasive measurements of portal pressure. The paper by Procopet *et al.* provides new and exciting data showing convincingly that an ultrasound machine based technology, **real**



Procopet et al., 2015

time shear wave elastography, provides reliable data to diagnose clinically significant portal hypertension in the vast majority of patients with a high degree of certainty.

LIVER INJURY

Paracetamol can produce liver toxicity in pregnant mothers and fetuses

Recent studies have shown that administration of paracetamol (acetaminophen) during pregnancy can increase the risk of asthma in children. It has also been argued for some time that paracetamol may not be completely safe from liver toxicity even when administered in recommended doses. The study by Karimi *et al.* explores the question whether paracetamol can produce liver injury in the pregnant mother and the newborn fetus in an animal model. **They show that paracetamol administration can result in liver toxicity in the pregnant mother and reduces stem cells in the fetus as well as inducing inflammation of the airways**. Their results could change clinical practice if confirmed.

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; 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 Clinic for Gastroenterology, Section Hepatology, 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.