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From the Editor's desk....

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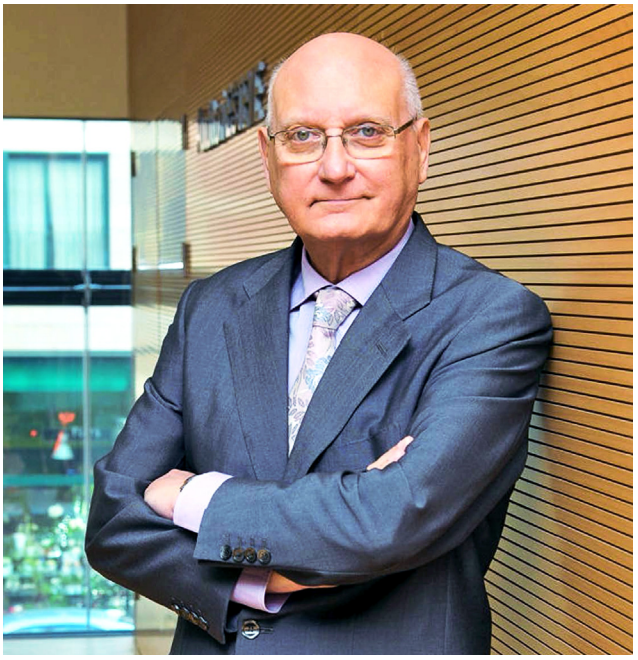
SELECTION OF THE MONTH

The legacy of Juan Rodés (1938–2017)

This issue of the ***Journal of Hepatology*** is dedicated to the memory of Prof. Juan Rodes (1938–2017), one of the most influential European hepatologists. His vision integrated clinical and research activities and his leadership resulted in seminal advances in the management of patients with cirrhosis. The Journal of Hepatology and EASL family would like to highlight his human and scientific dimensions and express our most sincere condolences to his family and friends.



ACUTE LIVER INJURY

Protective action of coagulation in acetaminophen (APAP)-induced liver injury

APAP-induced liver injury is associated with the activation of the blood coagulation cascade but the consequences of this are not understood. Here Kopec *et al.* reveal a novel pathway of liver repair after APAP overdose in mice; **fibrin(ogen) engages aMb2 integrin expressed at leukocyte surface to stimulate production of macrophage metalloelastase (encoded by *Mmp12*), that protects against liver injury after APAP overdose**. Studies on the role of coagulation activation in APAP overdose in humans are needed.

LIVER FIBROSIS

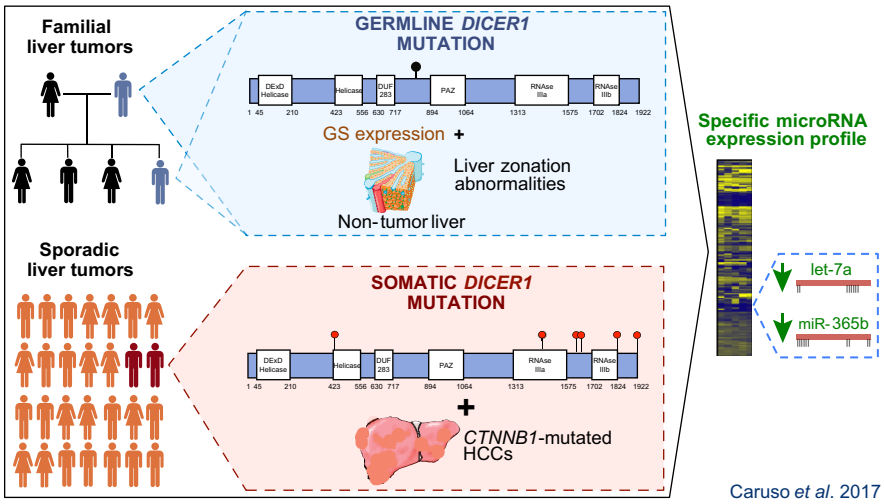
Transcriptional control of hepatic stellate cell (HSC) activation

Transcription factors that control HSC transdifferentiation into activated myofibroblasts is a crucial event in hepatic fibrogenesis. Here Ceni *et al.* investigate the role of the transcription factor called COUP (chicken ovalbumin upstream promoter) transcription factor 2 (short name COUP-TF2; encoded by *NR2F2*) in HSC activation and in the multifunctional role of HSCs during the response to liver injury. They show that **in HSC, COUP TF2 is involved in the acquisition of a hypoxia-independent proangiogenic phenotype and regulates the paracrine signals between HSC and sinusoidal endothelial cells during hepatic wound healing**. It is interesting to note that COUP-TF2 is a ligand-activated transcription factor; ligands being metabolites of retinol (i.e., vitamin A) such as 9-cis-retinoic acid and all-trans-retinoic acid (ATRA). The liver plays a central role in the production of ATRA which is the biologically active form of retinol with multiple functions including stem cell differentiation, macrophage polarization, among others. **Future studies should explore the link between vitamin A metabolism and HSC activation**.

HEPATOCELLULAR CARCINOMA (HCC)

Mutated *DICER1*, C-C motif chemokine 5 drives HCC

There is evidence that a genetic predisposition increases the risk of developing HCC, independently of other risk factors. Caruso *et al.* were interested in mutations in Dicer 1, ribonuclease III (*DICER1*, encoding the endoribonuclease Dicer) in the context of HCC. This is because it is a double-stranded RNA (dsRNA) endoribonuclease, which plays a central role in short dsRNA-mediated post-transcriptional gene silencing. It cleaves naturally occurring long dsRNAs and short hairpin pre-microRNAs (miRNAs) into fragments of twenty-one to twenty-three nucleotides, with a 3′ overhang of two nucleotides, producing short interfering RNAs (siRNA) and mature microRNAs respectively. siRNAs and miRNAs serve as a guide to direct the RNA-induced silencing complex (RISC) to complementary RNAs to degrade them or prevent their translation. Gene silencing



mediated by siRNAs, also called RNA interference, controls the elimination of transcripts from mobile and repetitive DNA elements of the genome but also the degradation of exogenous RNA of viral origin for instance. The miRNA pathway on the other side provides a mechanism for specifically regulating the expression of target genes. Caruso *et al.* reveal **the role of *DICER1* mutations in liver carcinogenesis in a specific subtype of familial and sporadic HCCs associated with b-catenin activation**. In sporadic cases, some mature miRNAs were specifically downregulated, raising the possibility of an important role of small non-coding RNAs in liver carcinogenesis.

Liver inflammation plays a crucial role in the progression of fibrosis and promotes liver cancer. The inflammatory signals involved in these effects are poorly known. *Mohs et al.* now show that C-C motif chemokine 5 (also known as T cell-specific protein RANTES and encoded by *CCL5*) is an important mediator for liver carcinogenesis. This chemokine and its receptor (C-C chemokine receptor type 5) are overexpressed in liver tissues from patients with chronic liver disease. In a mouse model of HCC, *Ccl5* deletion resulted in a reduced number of infiltrating immune cells (granulocytes, inflammatory monocytes and $CD4^+$ and $CD8^+$ T cells) and development of tumors (that were smaller and less proliferative as compared to tumors in wild-type mouse). The authors identify hematopoietic cells as major source of C-C motif chemokine 5. Together these findings illuminate the role of inflammatory cues and effector cells related to innate and adaptive immunity in HCC promotion. They suggest that **C-C motif chemokine 5 and signaling pathways could be a target for novel therapeutic approaches in patients with HCC**.

FATTY LIVER DISEASES

MicroRNA and microbiota in the pathogenesis of non-alcoholic and alcoholic fatty liver disease

Insulin resistance and lipogenesis play an important role in NAFLD. Identifying the underlying molecular drivers could result in novel targeted therapies. In this issue of the *Journal*, Wu *et al.* studied the implication of **microRNA-206 (miR-206)**, a key regulator of many pathophysiological processes in humans. **Delivery of miR-206 into the livers of obese mice resulted in the strong therapeutic effects on hepatosteatosis and hyperglycemia**. By interacting with polyribonucleotide nucleotidyltransferase (*PTPN1*) and **modulating lipogenesis and insulin signaling**, miR-206 reduced lipid and glucose production in human hepatocytes and livers of obese mice. This intriguing study reinforces the important regulatory properties of microRNA in fatty liver diseases and suggest that miR-206 could be a novel therapeutic target for fatty liver and type 2 diabetes.

This issue contains another interesting study on the pathogenesis of fatty liver disease. The paper by Ferrere *et al.* investigated the implication of fecal microbiota in alcoholic liver disease. This study is very timely since fecal transplantation is currently being tested in patients with alcoholic hepatitis. The authors used alcohol-sensitive and resistant mice to test the efficiency of two complementary strategies (**fecal microbiota transplantation and prebiotic treatment**) to reverse dysbiosis and prevent alcoholic liver disease. Ethanol induced steatosis and liver inflammation, which were associated with disruption of gut homeostasis, in alcohol-sensitive, but not alcohol-resistant mice. Interestingly, the fecal content of *Bacteroides* was in alcohol-sensitive mice. **By treating mice with pectin**, which induced major modifications of the microbiota, or **fecal microbiota transplantation**, which resulted in a microbiota similar to that in resistant donor mice, the authors were able to **prevent liver inflammation and restore gut homeostasis**. This study confirms the recent studies in patients with alcoholic hepatitis showing that manipulation of fecal microbiota can prevent alcohol-induced liver injury.

HEPATITIS C VIRUS (HCV) INFECTION

HCV type 2 – not so weak, direct-acting antivirals (DAAs) in kidney transplant recipients, the unhappy few – resistance analysis of DAA failure patients

HCV type 2 genotype has been typically considered to be a weak genotype, easy to cure even with a short-term interferon-based regimen. Studies evaluating interferon-free sofosbuvir-based regimens seemed to confirm this typical feature, as sofosbuvir given for only 12 weeks and boosted only by ribavirin was sufficient to cure nearly all HCV type 2-infected patients. However, real life cohorts showed lower cure rates, especially in patients with cirrhosis and in those with intergenotypic viral chimeras (recombinant HCV genotype 2 k/1b strains), not recognized by the commonly used genotyping assay. Mangia *et al.* now investigated the effect of extending sofosbuvir plus ribavirin treatment duration to 16–20 weeks in a large Italian real life HCV type 2-infected cohort with bridging fibrosis or cirrhosis. **Cure rates in those with cirrhosis were 95% after 16 or 20 weeks of treatment, and 99% in those with bridging fibrosis, respectively**. No 2 k/1b strains were identified in this Italian cohort. The study highlights the need for extending sofosbuvir/ribavirin treatment duration beyond 12 weeks in HCV type 2-infected patients with advanced fibrosis especially in those countries in which more robust pangenotypic regimens containing sofosbuvir plus ledipasvir are not available.