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SELECTION OF THE MONTH

Title of the Month: Big Title: Juan Rodes (1938-2017) [*Joel, please confirm that the obituary will be published in the April issue*

Small titles

New therapy for Portal hypertension

miRNA-206 and fecal microbiota in fatty liver diseases

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**

αMβ2 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 (TFs) that control HSC transdifferentiation into activated myofibroblasts is a crucial event in hepatic fibrogenesis. Here, Cena *et al.* investigate the role of the transcription factor called COUP (for 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 transcription factor 2 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 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 3' overhang of two nucleotides, producing respectively short interfering RNAs (siRNA) and mature microRNAs. SiRNAs and miRNAs serve as 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 is a mean to specifically regulate 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 ß-catenin activation.** In sporadic cases, some mature miRNAs were specifically downregulated raising the possibility of an important role of small non-coding RNAs in the 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) as well is overexpressed in liver tissues from patients with chronic liver disease. In a mouse model of HCC, *Ccl5* deletion resulted in 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 novel therapeutic target for fatty liver and type 2 diabetes. This issue contains another interesting study on the pathogenesis of fatty liver disease. In particular, the paper by Ferrere *at 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 two 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, DAAs in kidney transplant recipients, the unhappy few – resistance analysis of DAA failure patients

HCV type 2 has been typically considered to be a weak genotype, easy to cure even with a short-term interferon-based regimen. First 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 2k/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, respectively, and 99% in those with bridging fibrosis**. No 2k/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.

The study by Fernández *et al.* is one of largest evaluating interferon-free direct-acting antivirals in HCV-infected kidney transplant patients prospectively collected in a Spanish registry (Hepa-C). Among the 103 patients treated mainly with sofosbuvir plus either ledipasvir or daclatasvir ± ribavirin, cure rates were 98%. Dose adjustment of the immunosuppressive regimen was required in 55%, and 16% of the patients' experienced renal dysfunction, a side effect that was associated with the presence of cirrhosis. **The study shows that being kidney transplanted has no negative impact on the efficacy of the direct-acting antiviral (DAA) regimens, but a non-negligible number of patients, most of them cirrhotic, developed mild allograft dysfunction and a significant proportion of patients required immunosuppression dose adjustment, warranting a close follow-up during therapy**.

The small proportion of patients who fail treatment with potent DAA regimens are at high risk to harbor viral variants with drug-resistance associated substitutions (RAS). With the aim to characterize drug resistance, Wyles *et al.* performed HCV NS5A and NS5B deep sequencing in HCV type 1-infected who participated in the large ledipasvir/sofosbuvir phase 2 and 3 clinical trials (N=2,144). **The majority of patients with virologic failure (74.5%) had detectable ledipasvir-specific NS5A RAS (75%), and many of them had ledipasvir RASs at baseline**. In contrast, resistance to sofosbuvir was uncommon with only 3 patients showing detectable NS5B RAS. As the duration of treatment increased from 6 to 12, the proportion of patients with relapse decreased dramatically, while the proportion with RASs detected at the failure time point increased, suggesting that the reason for relapse following less than 12 weeks of treatment is mainly due to incomplete clearance of HCV, rather than selection of drug resistance. The persistence of NS5A RAS at high frequencies within the viral quasispecies for up to 96 weeks posttreatment is of relevant concern when considering re-treatment strategies in these unhappy few patients.

HEPATITIS B VIRUS (HBV) INFECTION

Specific HBV entry inhibition by cyclosporine A derivatives, HBV interference with innate immunity

Inhibiting the HBV entry receptor sodium taurocholate cotransporting polypeptide (NTCP) represents a highly interesting approach to further improve the HBV treatment efficacy. NTCP inhibition, however, can impair its transporter activity for bile acid uptake, and thus may potentially cause significant adverse effects. The aim of the elegant study by Shimura S et al. was to identify small molecules that inhibit HBV entry but not affecting the NTCP transporter function. **Several cyclosporine A derivatives were identified which effectively inhibit HBV attachment to host cells by directly interacting with the NTCP protein. Compounds were described that did not impair the NTCP dependent uptake of bile acids, suggesting that the anti-HBV activity can be functionally separated from bile acids transport**. These intriguing findings may further stimulate HBV entry inhibition drug development.

HBV has developed numerous mechanisms for interfering with the immune system and maintaining viral persistence. In the present study, Yu *et al.* demonstrated for the first time that HBeAg reduces lipopolysaccharide-induced NOD-like receptor (NLR; also known as nucleotide binding domain and leucine-rich repeat containing receptor)-family pyrin domain-containing 3 (NLRP3) inflammasome activation and subsequent IL-1β secretion in Kupffer cells via suppressing NF-κB pathway and ROS production. **This finding provides a novel mechanism for how HBeAg interferes with intracellular innate immune pathway to escape immune recognition, and contributes to the HBV persistence.** The study also provides new therapeutic targets for chronic HBV infection and related diseases.

PORTAL HYPERTENSION

Farsenoid X receptor is a target for treatment of portal hypertension

In cirrhotic patients, the severity of portal hypertension is closely associated with progression to decompensation and increased mortality. Therapeutic options for the treatment of portal hypertension is limited to non-selective beta blockers, which has limited effectiveness and many patients find it difficult to tolerate. **The paper by Schawbl *et al.* shows that, the non-steroidal FXR agonist PX20606, a drug in clinical development effectively reduces the severity of portal hypertension in two animal models confirming FXR as a therapeutic target.** They also show, that the drug achieves this through effects on modulating the severity of fibrosis and mediators of intrahepatic resistance. Data from clinical trials are eagerly awaited.

LIVER TRANSPLANTATION

Alloantigen gene transfer to hepatocytes promotes tolerance to allogenic graft

Donor major histocompatibility complex (MHC) molecules represent the main targets of the allogeneic immune response of patients who receive a transplant. Induction of immune tolerance to donor is a good alternative to chronic life-long immunosuppression for these patients. Le Guen *et al.* are the first to show that adeno-associated viral-mediated long-term expression of a single MHC class I molecule in the liver induces the generation of a subset of allospecific $CD8^+$ regulatory T cells, which promote tolerance toward fully allogeneic graft. They conclude that **liver gene transfer represents a promising strategy for in vivo induction of donor-specific tolerance.**