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#4Draft

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SELECTION OF THE MONTH

Big Title: Transplantation reduces deaths of advanced ACLF patients

Small titles:

Estimating the impact of HCV chimera

A new HDV mouse model

LIVER INFLAMMATION AND FIBROSIS

P2XY receptor signaling and the protective role of CD39 in sepsis, type II NKT cells drive inflammation, anti-fibrotic macrophage polarization

The mechanism of liver injury and progressive cholestasis during sepsis is unknown. Extracellular ATP (eATP) is increased in sepsis and is known to trigger a pro-inflammatory process through the purinergic receptor P2X 7 (hereafter P2X7) pathway. CD39 (also known as ectonucleoside triphosphate diphosphohydrolase 1, encoded by

ENTPD1) is known to scavenge eATP and generate adenosine, which limits P2X7 activation and therefore, inflammation. **In a series of elegant experiments in animal models, Savio *et al.* show for the first time that CD39 is important in limiting the severity of liver injury observed in sepsis by scavenging eATP.** Their data support the development of novel strategies to augment CD39 expression to limit the deleterious effect of sepsis on the liver.

T cells are usually viewed as being specific for peptide antigens that are presented on classical MHC molecules. However, many T cells actually respond to lipid-based antigens that are presented by the CD1 family of MHC-like molecules, which are typically expressed by professional antigen-presenting cells. The CD1 family is subdivided into at least three groups: group 1 comprises CD1a, CD1b and CD1c; group 2 comprises CD1d; and group 3 comprises CD1e. The most extensively studied type of lipid-reactive T cell is the CD1d-restricted natural killer T (NKT) cell. The interaction between the NKT cell antigen receptor — i.e., the T cell receptor (TCR) expressed by NKT cells — and the antigen–CD1d complex is a central event leading to NKT cell activation. **There are two main NKT cell subsets: type I NKT cells are typically characterized by the expression of a semi-invariant TCR, whereas the TCRs expressed by type II NKT cells are more diverse.** Here Weng *et al.* report the results obtained in sophisticated transgenic mouse models designed to address the role of poorly-known role of type II NKT in the development of chronic liver inflammation. Their results unravel that **an enhanced crosstalk between type II NKT cells and conventional T cells can give rise to a T helper 1-skewed inflammatory milieu, leading to the development of chronic autoimmune liver disease.**

Tissue macrophages are multifunctional and heterogeneous cell types which monitor local environment and maintain homeostasis. They express a broad array of sensing molecules, (e.g., pattern recognition receptors), which allows macrophages to monitor tissue microenvironments and act as sentinel cells for infection and tissue damage. In addition, macrophages perform many tissue-specific functions, which is reflected in their phenotypic diversity. Moreover, mature macrophages can undergo functional polarization in response to environmental signals. **Two macrophage polarization programs are classically activated (M1) and alternative activated (M2) macrophages** that are induced by different stimuli such as LPS plus interferon-γ and IL-4, respectively. Ma *et al.* polarized bone-marrow–derived macrophages into M1 or M2 phenotype and then administered these cells in different animal models of fibrosis.

They show that **the administration of M1 macrophages, but not M2, is an effective cell therapy for experimental liver fibrosis.**

FATTY LIVER DISEASE

Steatosis and fibrosis progression in HIV and germline mutations in the Hedgehog signaling and NAFLD. Liver disease are prevalent among HIV infected patients, in part due to high rate of Canadian cohort of unselected HIV- infected adults, the presence of steatosis and fibrosis was assessed by transient elastography and CAP. Prevalence of steatosis did not differ between HIV mono-infected and HIV/HCV co-infected patients. Interestingly, rate of steatosis progression was greater in HIV mono-infection and steatosis is associated with liver fibrosis progression in this cohort of patients. This study indicates that steatosis accelerates the rate of fibrosis progression in patients with HIV mono-infection. Manoeuvers aimed at decreasing steatosis (i.e. weight loss, alcohol abstinence, etc) are advised among HIV infected patients. In another study in this issue of Journal of Hepatology, interesting genetic determinants of NAFLD were uncovered. Activation of hedgehog (Hh) signaling has been implicated in the progression of NAFLD. In a translational study combining human and mice data, Guillen-Sacoto M et al studied the effect of germline mutations disrupting the Hh signaling pathway on NAFLD. In humans, the authors found that patients with holoprosencephaly (HPE), a disorder associated with germline mutations disrupting the Sonic Hh pathway, have increased incidence of NAFLD. The results were confirmed in mice with Hh signaling attenuation (Gli2 heterozygous null: Gli2+/-). Exposure of Gli2+/- mice to fatty liver-inducing diets resulted in increased liver steatosis compared to wild-type mice. Similar to humans, this effect was independent of obesity in the mutant mice and was associated with decreased expression of pro-fibrotic and pro-inflammatory genes, and increased expression of PPAR, a potent anti-fibrogenic regulator. This intriguing study suggest that germline mutations disrupting Hh signaling promote liver steatosis, independent of obesity. Further studies are required to evaluate the long-term effects of mutations affecting this pathway.

HEPATITIS C VIRUS (HCV) INFECTION

To be 2 or not true 2 – Estimating the impact of HCV chimera, pooled safety of the 3D regimen in cirrhosis

Inter-genotypic recombinant HCV strains containing genomic fragments of both genotype 2 and 1 will be misclassified as genotype 2 by standard genotyping methods, hence leading to inappropriate treatment decisions. In this issue of the *Journal*, Susser *et al.* provided the first large scale study evaluating the origin, prevalence and response to treatment of these HCV 2k/1b chimera. **Whereas chimera frequency was 14% and 25% in Germany and Israel, respectively, no chimeras were observed in Italy. Standard type 2 treatment with sofosbuvir plus ribavirin failed in HCV genotype 2k/1b-infected patients, but genotype 1-based regimens were effective in eradicating the recombinant strains**. Phylogenetic analyses revealed that migration flows from the former Soviet Union contributed to a relatively high number of the HCV genotype 2k/1b variant in Germany and Israel, and provide a basis for country and migration-based screening strategies to identify recombinant viruses.

Although direct acting antivirals (DAAs) are considered safe in patients with chronic hepatitis C, benefit-risk profile may look differently in patients with already established cirrhosis. An international group of investigators headed by Poordad *et al.* should be congratulated for performing a comprehensive safety analysis of all 1,066 HCV-infected patients with Child-Pugh A cirrhosis who have been treated in phase II and III trials with the combination regimen of ombitasvir, paritaprevir, and ritonavir, with or without dasabuvir (OBV/PTV/r ± DSV, i.e. 3D regimen). **Serious treatment-emergent adverse events leading to study drug discontinuation were observed in 2.2%, and were consistent with hepatic decompensation in about half of them (1.2%)**. Risk factors for decompensation were evidence of more advanced compensated cirrhosis with low baseline albumin and HCV RNA levels as well as a prior history of non-selective beta-blocker use for varices. These data support the use of OBV/PTV/r ± DSV ± RBV in patients with cirrhosis, but these regimens should be avoided in patients with a history of hepatic decompensation.

HEPATITIS B VIRUS (HBV) INFECTION

Alternative splicing modifies immune-mediated inflammation

Immune escape represents a central mechanism for establishing viral persistence. Duriez *et al.* identified a novel mechanism how the crosstalk between virus and host

may contribute to this immune escape by altering the spliceosome machinery in HBV-infected hepatocytes. Alternate splicing regulation of HBV transcripts leading to defective HBV circulating particles was already described more than 20 years ago, and considered playing a role in regulating viral replication but also liver disease progression. **Now the authors report that alterations of the spliceosome machinery in HBV expressing cells are switched on by liver injury and enable a striking reduction in liver monocyte/macrophage recruitment**. These findings reveal a novel paradigm whereby alternate splicing can generate a viral product able to inhibit immune-mediated inflammation and thereby down-modulate organ damage. The mechanism described in this elegant work may form a background for new immunotherapies facilitating HBV cure by targeting the immune tolerance established during chronic viral infection.

HEPATITIS DELTA VIRUS (HDV) INFECTION

A new mouse model to study HDV infection

Drug development for chronic HDV infection – the most severe form of chronic viral hepatitis – is hampered by the limited availability of adequate immune competent small animal models. Suarez *et al.* described a new mouse model which mimics several important features of human HDV infection and disease. **By the delivery of HDV- and HBV-replication competent genomes to the liver of immunocompetent adult mice (C57BL/6) via an adeno-associated virus vector**, **authors were able to establish sustained HDV replication leading to typical liver pathology with portal and lobular inflammation**. Hence, this model represents an interesting tool that will allow testing of new antiviral strategies, studying the mechanism of pathogenesis, as well as the adaptive and innate immune responses to HDV infection.

LIVER CANCER

Tumor suppressor inhibition via histone-modifying enzyme activity, osteopontin as a biomarker of cholangiocarcinoma, dendritic cell-derived exosomes for HCC immunotherapy,

Investigating histone-modifying enzymes in the context of hepatocellular carcinoma (HCC) is of major interest. Several distinct classes of enzymes can modify histone proteins at multiple sites; these include acetyltransferases, lysine (K) methyltransferases (KMTs), and lysine demethylases. Here we are interested in KMTs

that catalyze the transfer of one, two, or three methyl groups from *S*-adenosyl-L-methionine SAM to the ε-amino group of a lysine residue on a histone to generate mono-, di-, and trimethylated histones. Their output can be either activation or repression of transcription. In this issue of the *Journal*, Wei *et al.* report results of their study of the histone-lysine N-methyltransferase EHMT2 (encoded by *EHMT2,* also known as *G9a*), which is known to catalyze methylation at K9 in histone 3, resulting in formation of heterochromatin (i.e., silent chromatin, which is "inaccessible" for transcription). They show ***EHMT2* upregulation in HCC which is due to downregulation of its inhibitor miR-1 and associated with disease progression and aggressive clinic pathological features. *EHMT2* upregulation results in inhibition of the expression of retinoic acid receptor responder 3 (*RARRES 3*), a tumor suppressor.** Therefore, *EHMT2* expression could be a target for future therapeutic approaches in HCC.

Integration of clinical, pathological, and molecular "orthogonal" data sets from patients with HCC is a challenge. Here Calderaro *et al.* show results of data integration which represent a new step toward the development of personalized medicine for HCC. They show that **mutations in *CTNNB1* (symbol for the catenin beta 1 gene) and *TP53* (symbol for the tumor protein p53 gene) are mutually exclusive, defining two major groups of HCC characterized by distinct phenotypes.** For example, *CTNNB1*-mutated tumors are large, well-differentiated, cholestastic, with microtrabecular and pseudoglandular patterns and without inflammatory infiltrates. *TP53*-mutated tumors are poorly-differentiated with compact pattern, multinucleated and pleomorphic cells, and frequent vascular invasion. Interestingly, the transcriptome profile is also distinct between the two major mutated groups (subgroups 5-6 versus subgroups 1-3, respectively). These findings may help in translating our knowledge of HCC biology into clinical practice.

Osteopontin (encoded by *SPP1* [also known as *OPN*] belonging to the SIBLING gene family) is a secreted phosphoprotein which can be produced by biliary cells. Loosen *et al.* show here that serum osteopontin levels correlate with osteopontin upregulation in cholangiocarcinoma tumor cells and the tumor stroma. Moreover, pre- and postoperative elevations of osteopontin showed a striking association with poor postoperative survival. Therefore, **measurements of serum osteopontin concentrations could be helpful to guide preoperative treatment decisions and to identify patients that particularly benefit from extended liver surgery.**

Dendritic cell (DC)-derived exosomes (DEXs) form a new class of vaccines for cancer immunotherapy. Lu *et al.* provide interesting results on DEXs in three different HCC mouse models. **They show that AFP-enriched DEXs can trigger potent antigen-specific antitumor immune responses and reshape the tumor microenvironment in HCC mice and thus provide a cell-free vaccine option for HCC immunotherapy.**

LIVER TRANSPLANTATION

Liver transplantation is feasible and effective in reducing mortality of ACLF patients

Acute on chronic liver failure (ACLF) is a newly defined entity that complicates the course of relatively well patients with chronic liver disease and depending upon its severity can have 28-day mortality rates ranging from about 15% to over 80%. Treatment options for this condition are limited to supportive medical care and the role of transplantation is unknown. Louvet *et al.* report the results of a multicenter study assessing the outcomes of patients transplanted for severe ACLF (Grade 3) performed in France. **Their remarkable study shows for the first time that the 1-year survival of patients with ACLF Grade 3 is similar to those with no ACLF (84% vs 90%). The 1-year survival of ACLF Grade 3 patients who were not transplanted was only 8%.** These data are extremely provocative and likely to change clinical practice allowing these very sick patients to be considered as suitable candidates for transplantation.