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SELECTION OF THE MONTH

Big title: DAAs reduce post-transplant mortality

Cirrhosis (small title): Autoimmune Hepatitis: A familial disease?

LIVER INJURY

α1-antitrypsin deficiency (A1ATD) induces hepatocyte ER^{UPR} and inflammatory signals, protective role of CARD6 against hepatic ischemia/reperfusion injury

A1ATD is an autosomal recessive disorder caused by mutations in the *SERPINA1* gene. Individuals with the Z variant (Gly342Lys) retain polymerized, misfolded proteins in the endoplasmic reticulum (ER) of their hepatocytes, predisposing them to liver disease. To gain insight into the hepatocyte response to protein misfolding, Segertiz *et al.* leveraged the availability of patient-specific human induced pluripotent stem cells

called ZZ-hepatocyte-like cells (ZZ-HLCs) derived from a patient with the ZZ form of A1ATD. They show that abnormal A1AT polymer ER processing occurs and is associated with features of ER stress, disrupted mitochondrial structure, presence of the oncogenic protein AKR1B10 and upregulated genes including members of inflammatory pathways (*IL18* and *CASP4*) and genes such as *Calnexin* and *Calreticulin*, which are involved in ER^{UPR}, i.e., ER unfolded protein response. **These new findings link liver ER stress to inflammation in the context of A1ATD and suggest that hepatocyte ER stress may result in the induction of pro-inflammatory signals and cause damage of the surrounding liver tissue.**

The caspase recruitment domain (CARD)-containing protein 6 (encoded by *CARD6*) contains a CARD, which is an antiparallel six-helical bundle that mediates homotypic protein-protein interactions. The protein is a microtubule-associated protein that has been shown to interact with receptor-interacting protein kinases and positively modulate signal transduction pathways converging on activation of the inducible transcription factor NF-kappaB. Qin *et al.* using elegant mouse models now show that **CARD6 is a novel protective factor of hepatic ischemia/reperfusion injury that suppresses inflammation and liver cell death by inhibiting mitogen-activated protein kinase kinase kinase 5 (also known as ASK-1, for apoptosis signal-regulating kinase 1) signaling.**

LIVER REGENERATION

A role for long non-coding RNAs (lncRNA) via chromatin remodeling

LncRNAs are defined as transcripts longer than 200 nucleotides that are not translated into protein. Their role in regulation of gene expression and biological processes are still poorly understood. In this issue of the Journal, Wang *et al.* reveal that deletion of a lncRNA called lncHand2 abrogates liver regeneration and repopulation capacity. Furthermore, they show that lncHand2 recruits the INO80 remodeling complex which, with SWR1 complex, belong to the INO80 subfamily of ATP-dependent chromatin-remodeling complexes. These complexes interact with nucleosomes and remodel chromatin by either sliding nucleosome along the DNA or exchanging histones within nucleosomes. Finally, they found that **INO recruitment initiates Nkx1-2-induced, c-Met-mediated liver repopulation, showing for the first time a role for lncRNA in liver regeneration.**

HEPATOCELLULAR CARCINOMA (HCC) BASIC-TRANSLATIONAL

Mutational landscape of a chemically-induced mouse model of HCC, annexin A3 makes HCC-resistance to sorafenib

It is of major interest to know whether genomic alterations driving carcinogen-induced mouse tumor genomes are comparable to those found in human tumors. Connor *et al.* analyzed whole-exome sequences of liver tumors arising in mice exposed to the carcinogen diethylnitrosamine. In this issue of the *Journal*, they show four recurrently mutated genes are identified that are putative oncogenic drivers of HCC in this model. Every neoplasm carried activating hotspot mutations either in *Hras*, *Braf* or in *Egfr*. Truncating mutations of *Apc* occur in 21% of neoplasms, which are exclusively carcinomas supporting a role for deregulation of Wnt/β-catenin signaling in cancer progression. **This study provides detailed insight into the mutational landscape of tumors arising in a commonly-used carcinogen model of HCC, facilitating the future use of this model to understand the human disease.**

Little is known about the mechanisms explaining resistance to sorafenib in patients with advanced HCC. Tong *et al.* investigated the role of annexin A3 (also known as Inositol 1,2-cyclic phosphate 2-phosphohydrolase, or lipocortin III) in resistance to sorafenib in HCC cells. They show that overexpression of annexin A3 in sorafenib-resistant HCC cells inhibited PKCδ/p38-induced apoptosis and activated autophagy for cell survival. Clinically, annexin A3 expression was associated with poor overall survival in patients who went on to receive sorafenib treatment. Therapy with anti-annexin A3 monoclonal antibody combined with sorafenib/regorafenib impaired tumor growth in vivo and significantly increased survival. Together these findings suggest that **anti-annexin A3 therapy in combination with sorafenib/regorafenib may be a novel therapeutic strategy for HCC treatment. The level of annexin A3 expression could be a predictive biomarker used to stratify HCC patients for sorafenib treatment.**

NON-ALCOHOLIC FATTY LIVER DISEASES

Modeling global NAFLD burden, non-invasive prediction of varices in NAFLD cirrhosis and role of intestinal HIF-1α in alcoholic steatohepatitis.

NAFLD is increasingly a cause of cirrhosis and HCC globally. This burden is expected to increase as epidemics of obesity, diabetes and metabolic syndrome continue to grow. In this issue, Estes *et al.* used a Markov model to forecast NAFLD disease

burden. If obesity and diabetes level off in the future, the authors **project a modest growth in total NAFLD cases (0-30%), between 2016-2030, with the highest growth in China** as result of urbanization and the lowest growth in Japan as result of a shrinking population. However, at the same time, **NASH prevalence will increase 15-56%, while liver mortality and advanced liver disease will increase more than double** as result of an aging/increasing population. This study strongly indicates that NAFLD represents a large and growing global public health problem and policies to mitigate the disease burden are urgently needed. In another paper in this issue, NAFLD specific criteria for non-invasive diagnosis of esophageal varices was developed. Recent BAVENO VI criteria can avoid the need for endoscopy (EGD) to screen for varices in a proportion of compensated viral and alcoholic cirrhotics. Sebastiani *et al.* performed a multicenter study in 790 patients to validate these criteria in patients with NAFLD and analyzed the performance of elastography using M and XL probes. In the training set use of Baveno VI and expanded Baveno VI criteria reduced by 33 % and by 58% the number of EGD, missing 1% and 4% of large varices needing therapy (VNT), respectively. **The best thresholds to rule-out VNT were identified at platelets >110,000 and LSM<30 KPa for M probe, and platelets >110,000 and LSM<25 KPa for XL probe (NAFLD cirrhosis criteria)**. Usage of NAFLD cirrhosis criteria would have thus led to an absolute reduction in the number of EGD screened patients of 34.7% and 10.5% with respect to BAVENO VI and expanded BAVENO VI criteria respectively. These new NAFLD cirrhosis criteria can reduce by more than half the use of EGD to screen for VNT. Besides this epidemiological and clinical studies, an elegant translational study by Shao *et al.* demonstrated a role for intestinal HIF-1α in alcoholic liver disease (ALD), a disease linked to intestinal dysbacteriosis and leaky gut. HIF-1α has been implicated in transcriptional regulation of intestinal barrier integrity and inflammation. In this study, intestinal epithelial-specific HIF-1α knockout mice (IE-*Hif-1α*$^{-/-}$) were exposed to alcohol-containing diet. As expected, alcohol feeding increased serum levels of ALT and LPS, hepatic triglyceride concentration, and liver injury in the WT mice. These **deleterious effects were exaggerated in IE-*Hif-1α*$^{-/-}$ mice**. In these mice, alcohol exposure resulted in greater reduction of the expression of key intestinal epithelial tight junction proteins in IE-*Hif-1α*$^{-/-}$ mice. Metagenomic analysis showed an **increased gut dysbiosis with a significantly decreased firmicutes/bacteroidetes ratio in IEhif-1α-/- mice**. Interestingly, nonabsorbable antibiotics reversed the liver steatosis in both WT and IE-*Hif-1α*$^{-/-}$ mice.

This study shows that intestinal HIF-1α regulates intestinal microbiota and barrier function in experimental alcohol-induced liver injury and could represent a target for therapy to treat patients with ALD.

HEPATITIS C VIRUS (HCV) INFECTION

Find the missing millions

Nine out of 10 individuals living with viral hepatitis world-wide are estimated to be unaware of their infection, raising the issue of a more universal hepatitis screening approach. Also the European strategy to screen mainly people at high risk of HCV infection would leave a large proportion of all HCV infections undetected. The optimal screening approach for western European countries, however, remain largely unclear. The aim of the study by Deuffic-Burban *et al.* was to evaluate the cost-effectiveness of different screening strategies in France. **The provocative conclusion of this study is that universal screening of all individuals at the age of 18-80 years is the most effective and cost-effective strategy** when considering treatment for all patients irrespective of fibrosis stage.

HEPATITIS B VIRUS (HBV) INFECTION

TREAT-B in resource limited settings, aiming for ALT normalisation - new implications for an old biomarker

The decision whether to treat or not to treat chronic HBV infection is mainly based on the levels of alanine transaminases (ALT) and HBV DNA but also disease severity according to liver histology and/or elastography. For the majority of people living in resource limited low- and middle-income countries, however, neither real-time PCR, the current standard assay to measure viral load, nor sophisticated liver fibrosis evaluations are accessible and affordable. **By using a large dataset of African patients, Shimakawa *et al.* developed a new diagnostic score (TREAT-B) to assess treatment eligibility for HBsAg positive individuals in resource-limited countries.** This simple score based on HBeAg and ALT, laboratory tests that are available in most countries, showed a high diagnostic accuracy for selecting patients for HBV treatment when compared to the AASLD, EASL, APASL and WHO guidelines. This important study may have major implications concerning global viral hepatitis elimination plans as diagnostic tools like this are required to facilitate scale-up of treatment programs in resource-poor countries.

A significant proportion of patients under long-term oral antiviral therapy do not normalize their ALT levels despite achieving complete suppression of viral replication. Underlying NAFLD co-morbidity is believed to be one explanation for this intriguing phenomenon but also viral factors as well as drug class-specific features might be involved. Whether the persistence of elevated ALT levels under oral polymerase inhibitor therapy may negatively affect the patients' long-term prognosis has not been answered yet. The large-scale study by Wong *et al.* is the first evaluating the clinical implication of ALT response under entecavir and tenofovir therapy. More than 20,000 patients with chronic hepatitis B were included and approximately half of them had elevated ALT levels 12 month after starting antiviral therapy. **Hepatic events, mostly hepatocellular carcinoma, developed significantly more often in patients without ALT normalization, and the higher the on-treatment ALT levels, the higher the risk of hepatic events**. Although the overall hepatic event rate was small, the study clearly implies that persistence of elevated ALT levels during long-term antiviral therapy should not be neglected but considered as a risk factor especially for the on-treatment HCC development. The therapeutic implications of these findings need further investigations.

CIRRHOSIS

Mortality of acute on chronic liver failure (ACLF) on ICU is similar to sepsis patients

ACLF is a newly defined entity, which occurs in patients with cirrhosis and is characterized by multiorgan failure and high rates of short-term mortality. The clinical manifestation of ACLF is therefore similar to those of Sepsis patients. Yet, ACLF patients have lower priority of access to multiorgan support in the Intensive care units. In this important study, **Meersseman *et al.* interrogated a large database of patients admitted to the ICU and matched patients with ACLF with those with sepsis and compared their outcomes. Their data showed that the ICU, hospital and 90-day mortality were similar in the two patient cohorts. Intriguingly, the cytokine profile of these two groups of patients on Day-1 was also very similar.** These data argue strongly against denying patients with ACLF access to multiorgan support in an Intensive Care setting.

AUTOIMMUNE HEPATITIS (AIH)

Increased risk of AIH amongst 1st degree relatives of patients with AIH

The mechanisms involved in the pathogenesis of AIH are unknown and although a familial link is hypothesized, the degree of familial clustering is unknown. **Gronbaek *et al.* interrogated the Danish nationwide registries accessing data collected between 1977 and 2011 to address this question. Intriguingly, their data show that there is a definite but a small risk of AIH in the first-degree relatives but not in the second-degree relatives of patients with AIH.** Interestingly, the probandwise concordance rate, which is a measure of heritability, was higher in monozygotic than in dizygotic twins. These data provide important insight into the possible mechanisms underlying the pathogenesis of AIH and, has diagnostic and therapeutic implications.

LIVER TRANSPLANTATION

DAAs improve post-transplant survival in HCV cirrhosis and Karnofsky Performance Score (KPs) defines outcome

Directly acting antiviral drugs (DAAs) to treat HCV infection has changed the natural history of this disease but the impact of introduction of DAAs on the posttransplant outcomes of patients is not clear. Belli *et al.* explored the European Liver Transplant Registry comprising over 60,000 patients of who 36,382 patients had HCV cirrhosis to address this question. **Their data showed a significant reduction in the percentage of patients transplanted for HCV from about 21% to about 11%. Additionally, the three-year survival of HCV cirrhosis patients undergoing OLT improved from 65.1% in the IFN/RBV era to 76.9% in the DAA era.** The data provide clear and exciting evidence of the huge impact of DAAs on the outcome of liver transplantation for HCV cirrhosis.

Organs are a scarce resource and therefore appropriate selection of patients for transplantation is crucial to allow good post-transplant outcomes. KPS has been used for nearly 70 years as a quick end-of-bed test to determine the functional status of patients. Thuluvath *et al.* interrogated the UNOS registry and studied about 50,000 patients to determine whether KPS provides posttransplant prognostic information. **Their important data incontrovertibly showed that low or intermediate KPS were independent predictors of graft and patient survival adjusting for other confounders. An inability to improve KPS after transplantation was associated with a 1-year survival of about 30%.** The data provide compelling evidence to use

KPS in selection of patients for liver transplantation.