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SELECTION OF THE MONTH

Big title: Big title: Long-term albumin in cirrhosis: The jury is still out

miRNAs as biomarkers for NASH

Addressing HBV cycle

LIVER METABOLISM AND IMMUNITY AT BIRTH

The "first breath" of the liver

Liver is the main hematopoietic site in embryos, and plays a key role in metabolic homeostasis and immunity in adults. How the liver adapts enzymes involved in key metabolic pathways and immune system during initial periods after birth is poorly known. Methods: Nakagaki *et al.* addressed these questions through elegant studies performed in liver samples from mice on day 0 after birth up to adults, and human biopsies from newborns and adults. They show here that **liver immunity and**

metabolic profile in newborns are dramatically different from adults, because of differences in the liver cell repertoire and phenotype. In addition, they provide fascinating results suggesting that dietary and antigen stimuli are crucial to guide liver development during postnatal phase.

CHOLESTASIS

Beneficial cell-specific caspase-8 inhibition

There are several forms “programmed cell death”, including apoptosis, necroptosis, and pyroptosis. Apoptosis is a nonlytic form of death, mediated by proteases of the caspase family, that minimizes its impact on neighboring living cells. In contrast, necroptosis and pyroptosis are lytic forms of death resulting in release of the dying cell’s intracellular components, whose effects on neighboring cells can yield inflammation. The engagement of tumor necrosis factor receptor superfamily member 6 (encoded by *FAS*) by extracellular cues, can induce apoptosis through the activation of intracellular signaling cascades in which the cystein-aspartate protease caspase-8 (encoded by *CASP8*) has a proximal localization. Although the receptor-interacting protein kinase–3 (RIPK3) is a key molecule in the signaling pathway leading to necroptosis, it can also contribute to other processes such as the caspase-8 mediated apoptosis. Cubero *et al.* investigated the role of caspase-8-dependent and -independent pathways during cholestasis. They investigated liver biopsies from patients with stage IV primary biliary cholangitis. Wild-type mice and mice that were specifically deleted for *Casp8* either in liver parenchymal cells or hepatocytes were investigated after bile-duct ligation. They also investigated *Ripk3*-deleted mice. Finally, they studied the effects of a pan-caspase inhibitor. **Livers from patients had features of overactivation of caspase-8 and caspase-3 (which is an “executioner” caspase, distal to caspase-8), and RIPK3. After BDL, mice deleted for *Casp8* in liver parenchymal cells had decreased necrotic foci, serum transaminase levels and apoptosis, and diminished compensatory proliferation and ductular reaction. These results correlated with a decreased inflammatory profile and ameliorated liver fibrogenesis. A similar phenotype was observed in Ripk3-deleted mice.** In contrast, broad pan-caspase inhibition may trigger undesirable side-effects. The authors suggest that specific inhibition of caspase-8 in liver parenchymal cells, in particular cholangiocytes, may be beneficial for treating cholestasis. **Future**

studies should investigate the respective role of caspase-8 and RIPK3 in cell death associated with cholestasis.

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Cryptogenic *vs.* NASH cirrhosis, lifestyle intervention in non-obese NASH and role of microRNA as biomarkers

Distinguishing between cryptogenic and “burn-out” NASH cirrhosis is clinically challenging. Moreover, it is unclear whether these two conditions have different prognosis. In this issue, Younossi *et al.* studied a large cohort of patients with cryptogenic (<5% steatosis) *vs.* NASH-related cirrhosis during a median follow-up of 29 months. Age, gender, BMI, *PNPLA3* rs738409 genotype, and prevalence of diabetes were similar in the two groups. **As compared to patients with NASH, patients with cryptogenic cirrhosis had more intense fibrogenic markers in the liver biopsy and experienced significantly shorter mean time to liver-related clinical events**.

In another article in this journal, the effect of lifestyle interventions in patients with NASH but without obesity was assessed. In fact, 10% to 20% of patients with NAFLD are non-obese. The benefit of weight reduction in such patients is unclear. To address this question, Wong *et al.* studied the **efficacy of lifestyle intervention in non-obese patients with NAFLD and identify predicting factors for treatment response**. Patients with NAFLD were randomly assigned to either 12-month lifestyle intervention program and regular exercise or receive usual care. The primary outcome was remission of NAFLD by proton-magnetic resonance spectroscopy. **The primary outcome occurred more frequently among patients of the intervention group than among those of the control group, regardless of baseline BMI**. Lifestyle intervention, lower baseline intrahepatic triglyceride, and reduction in body weight and waist circumference were independent factors associated with remission of NAFLD in non-obese patients. This study strongly suggests that even in non-obese NAFLD patients, lifestyle intervention can lead to disease reversibility.

MicroRNAs (miRNAs) are important biomarkers and disease drivers in inflammatory conditions including NASH. In this issue, Liu *et al.* performed a meta-analysis on the potential role of miRNA in NASH. Thirty-seven studies of miRNA expression profiles and 6 studies of diagnostic accuracy were included. **miRNA-122 and miRNA-192 were up-regulated and was particularly useful to distinguish NAFLD severities**.

Importantly, the miRNA expression correlation between the serum and liver tissue was inconsistent across studies, suggesting that the liver is not the only source of circulating miRNA in chronic liver diseases. Moreover, **miRNA-34a distinguished NASH from non-alcoholic fatty liver.** This meta-analysis confirms that miRNA 34a, miRNA-122 and miRNA-192 are potential diagnostic markers to segregate simple steatosis from NASH. Circulating miRNA represent novel non-invasive biomarkers for potential clinical use in patients with fatty liver disease.

GENETIC LIVER DISEASES

Prevalence and risk factors of fibrosis in adults with alpha-1 deficiency

The prevalence and risk factors for fibrosis development in adults with alpha-1 antitrypsin deficiency (AATD) are not well known. In this issue, Clark *et al.* assessed the prevalence and severity of liver fibrosis in an adult with AATD. **The prevalence of significant fibrosis (F≥2) was of 35%. As it could be anticipated, metabolic syndrome was strongly associated with the presence of clinically significant fibrosis** (odds ratio of 14.2). Additionally, the presence of accumulated abnormal alpha-1 antitrypsin in hepatocytes, portal inflammation, and hepatocellular degeneration were associated with fibrosis. Finally, transient elastography detected F≥2 fibrosis with lower accuracy than in other etiologies (area under the ROC of 0.70). This clinical study reveals that one-third of adults with 'PI*ZZ' AATD have significant liver fibrosis and that the existence of metabolic syndrome is a major co-factor of fibrosis development. Patients with AATD should be advised and assisted to prevent obesity and related metabolic syndrome.

HEPATITIS C VIRUS (HCV) INFECTION

Three against HCV resistance

The antiviral triple regimen - sofosbuvir, velpatasvir plus voxilaprevir (SOF/VEL/VOX) - targeting three major replication-important HCV proteins, the NS5B polymerase, NS5A, and NS3/4A protease has become the gold standard for patients failing all oral antiviral regimens. The current study by Sarrazin *et al.* presents, for the first time, a comprehensive clinical and virologic assessment of the small, but complex and heterogeneous population of patients who have failed highly effective DAA therapy and have been re-treated with SOF/VEL/VOX as part of the phase III POLARIS-1 and -4 studies. **Although the presence of baseline resistance associated substitutions**

(RASs) was very common in this patient population (in around 80%), the triple regimen was highly effective regardless of the presence of RASs and neither NS3/4A- nor NS5A-specific RASs significantly impact treatment outcome to the triple regimen. Hence, for the resistant virus, three's a crowd.

HEPATITIS B VIRUS (HBV) INFECTION

A glimpse into HBV infection kinetics

A more detailed understanding of HBV infection kinetics and the genesis and maintenance of episomal nuclear DNA pools, so called covalently closed circular (ccc) DNA, is needed to guide the development of HBV cure strategies. Ko *et al.* studied for the first time cccDNA dynamics and defined pathways maintaining the pool of episomal viral DNA by generating a highly permissive cell culture system that supports the full HBV life-cycle over up to 6 weeks. The infections kinetics observed were remarkably low requiring 3 days to establish the cccDNA pool and initiate transcription. The average cccDNA copies per infected cell were 5.0-12.5, and cccDNA half-life approximately 40 days. ***De novo* infection and intracellular recycling of HBV genomes were the two major roots of cccDNA replenishment utilized by HBV**. These infection model-based data extend our understanding of so far poorly characterized steps in the HBV cycle being fundamental for future drug development.

CIRRHOSIS

Long-term albumin infusion in decompensated cirrhosis, palliative care provision for cirrhosis patients

Many studies have indicated a beneficial role of albumin in cirrhotic patients, which extends much beyond its fluid expansion effect. Recently, a randomized multicenter study from Italy, the ANSWER study suggested widespread beneficial effects of repeated albumin administration to decompensated cirrhotic patients including a reduction in mortality. **Sola *et al.* performed a randomized placebo-controlled study to evaluate the role of long-term administration of midodrine and albumin to patients with decompensated cirrhosis. Unlike the ANSWER study, their data did not show any difference in cirrhosis-related complication or survival between the two groups.** The different outcome of a similar intervention is intriguing and an accompanying editorial discusses the possibilities.

Treatment options for some patients with end-stage cirrhosis are limited and it is clear that palliative care approaches in this group of patients may be useful. **Low *et al.*** performed a systematic review to explore issues surrounding communication, delivery of palliative care and how these may be improved. **The results provide alarming insight into how little information patients and their relatives had about their disease, its potential outcomes and treatments. They highlight that the general practitioners also lacked confidence to discuss prognosis and issues relating to future care.** Most importantly, they indicate the potential role of palliative care for this group of patients and how this may impact on their quality of life. The paper supports the urgent need to incorporate palliative care into the management algorithms of end-stage cirrhosis patients in whom curative options are not available.

DRUG INDUCED LIVER INJURY

Genetic susceptibility to terbinafine-induced hepatoxicity confirmed

Terbinafine is an orally administered antifungal drug that is used to treat superficial infections. Hepatotoxicity from terbinafine was recently shown in a European study to be associated with human leukocyte antigen (HLA)-A*33.01 positive allele. **Fontana *et al.* reviewed the clinical features and outcomes of patients with terbinafine hepatotoxicity in the DILIN registry in the US. They confirm the strong association of terbinafine hepatoxicity with the presence of HLA-A*33.01 allele and extend the observations by indicating that this can result in chronicity in about 50% cases and acute liver failure in 1 patient.** The data argue strongly for genetic testing prior to the prescription of terbinafine to Caucasians.

IDIOPATHIC NON-CIRRHOTIC PORTAL HYPERTENSION (INCPH)

Good Maternal and Fetal outcomes in INCPH

The outcome of pregnancy in patients with INCPH, a syndrome characterized by portal hypertension is unknown. Therefore, at present it is not possible to describe the risks of pregnancy. **Andrade *et al.*** analyzed data from the Vascular Liver Disease Interest Group database and provide important insight into the outcome of pregnancy in 16 women with 24 pregnancies. **The data suggest that the outcome of pregnancy in women with INCPH is associated with about 25% fetal loss before 20 weeks. About 30% of women develop reversible complications of portal hypertension.**

These data will be hugely useful to inform the women with INCPH of risks and allow the clinicians to monitor these patients better during pregnancy.

HEPATOCELLULAR CARCINOMA (HCC)

Assessing HCC risk in patients with compensated alcoholic cirrhosis, evaluating risk of recurrence before and after resection for early HCC

In the context of the observational, prospective CIRRAL study, Ganne-Carrié *et al.* assessed the incidence of HCC (primary outcome) among 652 patients with biopsy-proven compensated alcoholic cirrhosis, enrolled at 22 French and Belgian centers. The authors here provide very interesting findings. First, as expected in patients with alcoholic cirrhosis, the retention in the study was of only 76%. Second, **the annual incidence of HCC was of 2.9 per 100 patients-year, a finding that should be into account when planning surveillance of patients with compensated alcoholic cirrhosis.** Third, a high proportion of HCC were within the Milan criteria, but only one-half of detected cases were referred for curative treatments. Finally, the 2-year mortality rate was of 7%.

Resection is the most widely used potentially-curative treatment for patients with early HCC. However, recurrence within 2 years occurs in 30-50% of patients, being the major cause of mortality. Chan *et al.*, in the context of an international collaborative study, aimed to develop models, based on widely available clinical data, allowing risk of early recurrence to be assessed before and after resection. A total of 3903 patients undergoing surgical resection with curative intent were recruited. Two models for early recurrence, one using preoperative and one using pre and post-operative data were built and internally validated in the Hong Kong cohort. The models were then externally validated in European, Chinese and US cohorts. Multivariable analyses identified **male gender, large tumor size, multinodular tumor, high albumin-bilirubin grade and high serum alpha-fetoprotein as predictors of early recurrence. Using these variables, a pre-operative model gave three risk strata for recurrence-free survival: low risk, intermediate risk, and high risk. The discrimination between the three strata was enhanced in the postoperative model which included "microvascular invasion".** These models will be valuable in guiding surveillance follow-up and in the design of post-resection adjuvant therapy trials.