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FINAL

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SELECTION OF THE MONTH

Big Title: "Fibrosis stage predicts mortality in patients with NAFLD"

Small Title:

The negative liaison between monocytes and NK cells (in HCV infection)

(Cirrhosis): Factors leading to ACLF in outpatients identified

LIVER INJURY

Sterile inflammation in hepatic ischemia-reperfusion injury (IRI)

Hepatic IRI, which is characterized by local inflammation and hepatocellular death, represents a risk factor for acute and chronic rejection in liver transplantation. To gain new insights into mechanisms underlying hepatic IRI, Nakamura *et al.* performed elegant translational research in human liver transplants and primary murine macrophage cultures. They reveal that, **in macrophages, a signaling axis involving**

heme oxygenase 1, NAD-dependent protein deacetylase sirtuin-1, and p53 plays a crucial role in the development of hepatic sterile inflammation. This may lead to novel therapeutic approaches in patients who receive a liver transplant.

LIVER REGENERATION

Serotonin: friend of foe?

Besides its critical role during liver regeneration, serotonin (also as 5-hydroxytryptamine, 5-HT) is known to be a mitogenic factor in several cancers. Padickakudy *et al.* evaluated whether intra-platelet 5-HT was associated with oncological outcome after liver resection and also evaluated its ability to serve as a therapeutic target to promote liver regeneration. **Their results show for the first time that intra-platelet 5-HT is associated with early disease recurrence after liver resection in humans.** Thus, pharmacological intervention aimed to promote 5-HT-mediated liver regeneration should be considered with caution. A careful definition of indications and timing is needed to promote liver regeneration without inducing deleterious effects.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD increases the risk of chronic kidney disease and fibrosis stage predicts mortality in NAFLD patients

NAFLD is a growing cause of chronic liver disease worldwide. Identifying NAFLD patients at an increased risk for mortality and liver-specific morbidity is mandatory. In this issue, Hagström *et al.* conducted a retrospective cohort study of 646 biopsy-proven NAFLD patients and matched controls. During a follow-up of 20 years, 12% of NAFLD patients developed severe liver disease (only 2.2% of controls). **The risk of severe liver disease increased per stage of fibrosis** (HR ranging from1.9 in F0 to 104.9 in F4). **Similar results were seen for overall mortality**. Importantly, **the presence of NASH did not change these estimates significantly**. This important study strongly suggests that all patients with NAFLD should undergo non-invasive assessment of the stage of liver fibrosis. Preventive and therapeutic maneuvers aimed at attenuating the progression of liver fibrosis in NAFLD patients should be implemented. In another article in this issue of the *Journal*, Sinn *et al.* studied the association between NAFLD and chronic kidney disease (CKD) a frequent co-morbidity in patients with metabolic syndrome. The authors performed a retrospective cohort study of 41,430 adult men

and women without CKD at baseline who underwent repeated health check-up examinations. During a median follow-up of 4.15 years, they identified 691 incident CKD cases. **The risk of CKD increased progressively with increased NAFLD severity**. The multivariable-adjusted hazard ratios for CKD of participants with a NAFLD Fibrosis Score (NFS) ≥ -1.4 was 1.58, suggesting that existence of advanced stages of NAFLD predisposes to the development of CKD. This clinically relevant study suggests that **NAFLD may adversely affect renal function** and may need careful attention for an increased risk of CKD.

HEPATITIS C VIRUS (HCV) INFECTION

Impact of coffee consumption on all-cause mortality in HIV-HCV coinfection, the long-term sequelae of the Irish single source HCV outbreak, clinical outcomes after delisting from the liver transplant waiting list, the negative liaison between monocytes and NK cells

Polyphenols and caffeine in coffee have several well described hepato-protective properties but coffee consumption has been also associated with a 14% risk reduction in all-cause mortality in the general population. The study by Carrieri *et al.* is the first to investigate the relationship between coffee consumption and all-cause mortality risk in HIV and HCV co-infected patients by using data from a large five-year longitudinal follow-up study in the ANRS CO13-HEPAVIH French national cohort of HIV-HCV co-infected patients. **Drinking three or more cups of coffee per day halved all-cause mortality risk in HIV-HCV infected patients, and this association remained significant even after adjustment for relevant co-factors** like severe liver fibrosis, and smoking status. Further research will help to better elucidate the causal mechanisms of this relationship; but in the meantime, certain at-risk populations like HIV-HCV coinfected patients should be aware of these results to adapt their coffee drinking behavior individually.

Between 1977-1979, over 800 women were infected in Ireland with HCV genotype 1b via contaminated anti-D immunoglobulin from a single donor. Initially, after 17 years, a quite benign course with a low rate of cirrhosis development (2%) was reported in this group, but almost 20 years have elapsed since then. Now, **approximately 36 years after infection, Garvey *et al.* demonstrated a substantial increase in cirrhosis, HCC and liver-related death which doubled in the latest five years of follow-up**. Although the overall progression rate remains relatively slow in this cohort, nearly every

5th patient has now reached a disease state that is probably not any more reversible by treatment, and harbors a significant life-time risk for HCC development. This happened despite regular medical supervision, highlighting once more the limited effect of our previous interferon-based treatment strategies in altering the population-based HCV-associated morbidity and mortality - a finding that will hopefully change when follow-up data will be collected after direct acting antivirals entered the scene.

Treating patients with HCV-induced decompensated cirrhosis while on the liver transplant waiting list offers the chance for delisting due to improvement of liver function. The long-term efficiency of this strategy in terms of clinical outcomes, however, remains largely unclear. Pascasio *et al.* further expanded on this important issue by following the course of patients treated on the liver transplant waiting list. **They confirmed that approximately a quarter of the treated patients with decompensated disease presented a significant improvement in liver function that allowed delisting, and 80% of them remained stable after a median follow-up of 88 weeks**. These results are of high importance as they imply that delisting due to improvement in liver function is overall a safe strategy helping to save organs for those with the highest transplantation need. However, close monitoring of the delisted patients is mandatory given the significant risk of HCC development in this particular group.

Coordination and collaboration between immune cells are essential to fight pathogens and the interplay between natural killer (NK) cells and monocytes represents one first-line of protection from pathogens and takes place during the early stages of innate immune responses against them. The authors of the current study have previously shown that peripheral blood NK cells from HCV-infected patients fail to upregulate TRAIL expression after exposure to HCV, a process accompanied by impaired cytolytic potential and Extracellular Signal-Related Kinase 1 (ERK) activity. Now, **Mele *et al.* were able to demonstrate that during HCV infection monocytes secrete interleukin (IL)-18 and IL-36 inhibitory proteins, reducing NK cell activation, and consequently inhibiting their ability to express TRAIL and kill target cells**. This important study confirms the essential role of monocytes as negative regulators of NK cell activation in HCV infection, and of cellular cross-talk in NK cell activation in general.

CIRRHOSIS

Identification of factors associated with development of acute on chronic liver failure (ACLF) in outpatients, declining mortality of cirrhotic patients admitted to the intensive care units

Hospitalized cirrhotic patients who develop ACLF have high mortality rates. At present it is unclear which patients attending the outpatient department will develop ACLF. The paper by Piano *et al.* addresses this important question. **The authors followed 466 cirrhotic outpatients in a tertiary center for a mean of about 4 years. 118 patients developed ACLF during follow up and these patients had a 3-month mortality of 44%. They identified that the MELD score, mean arterial pressure and hemoglobin were independent predictors of ACLF development.** These data will help stratify patients in the outpatient department at high-risk of developing ACLF so that measures to prevent its development can be instituted.

Previous studies have suggested that the mortality of cirrhotic patients admitted to the ICU was higher than non-cirrhotic patients and the incidence was increasing. Majumdar *et al.* describe the results of an important study from Australia, where they interrogated the ANZ Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database over a 15-year period. **They show for the first time that although cirrhosis was an independent predictor of mortality, the decline in mortality rate observed in non-cirrhotic patients was similar to the cirrhotics. They confirm the importance of organ failures in defining the risk of death and also show for the first time that risk-adjusted mortality rates were similar in the ICU's of the transplant centers compared with the non-transplant centers.** These data illustrate the improvement in outcomes possibly due to the greater awareness and understanding of organ failures in cirrhosis.

CHOLESTASIS

Mutations in key genes observed in about 30% patients with cholestasis

Bile salt exporters, BSEP, ABCB11; multidrug resistance protein 3, MDR3, ABCB4; and the ATPase familial intrahepatic cholestasis 1, FIC1, ATP8B1 mediate bile formation. Mutations in these genes underlie many cholestatic liver diseases such as intrahepatic cholestasis of pregnancy, benign recurrent intrahepatic cholestasis or low phospholipid-associated cholelithiasis to progressive familial intrahepatic cholestasis but which disorder is associated with which mutation is not known. **Droge *et al.***

describe the results of an exciting new study where they included 427 patients with various cholestatic diseases and studied the role of these genetic defects. They identified that 149-patients carried at least one disease-associated mutations. In all, 154 different mutations were identified comprising 25 novel ones. These data support the idea that genetic variants can be found in a significant proportion of cholestatic patients and develops the idea of possible future companion biomarkers.

CHOLANGIOCARCINOMA

Pan-mTOR inhibitor for intrahepatic cholangiocarcinoma

The mechanistic target of rapamycin (mTOR) coordinates eukaryotic cell growth and metabolism with environmental inputs, including nutrients and growth factors. Deregulated mTOR signaling is implicated in the progression of cancer. MLN0128, a second generation pan-mTOR inhibitor, shows efficacy for several tumor types. Intrahepatic cholangiocarcinoma is a cancer without effective treatment options. Zhang *et al.* developed a mouse model of intrahepatic cholangiocarcinoma to assess the efficacy of MLN0128 in this cancer. Their findings strongly suggest that **mTOR inhibitors may be beneficial for the treatment of intrahepatic cholangiocarcinoma, even in tumors that are resistant to standard of care chemotherapeutics such as gemcitabine-oxaliplatin—based regimen, especially in the subset exhibiting activated AKT/mTOR cascade.**

HEPATOCELLULAR CARCINOMA (HCC)

Trunk alterations in early HCC, DDA and HCC risk

Trunk alterations arise at early stages of cancer and are shared among all malignant cells of the tumor. In order to identify trunk alterations in HCC, Torrecilla *et al.* characterized early stages of hepatocarcinogenesis represented by dysplastic nodules and small lesions. They show that **mutations in *TERT* (telomerase reverse transcriptase), *TP53* (tumor protein p53) and *CTNNB1* (catenin beta 1) genes were the only ones found at this early stage.** Analyses in more advanced lesions showed that mutations in these same genes were shared between different regions of the same tumor and between primary and metastatic tumors, suggesting their trunk role in this disease.

Risk of HCC occurrence or recurrence following direct-acting antiviral (DAA) HCV therapy remains unclear. Waziry *et al.* aimed to compare the rate of HCC occurrence following DAA versus interferon (IFN)-based cure performed a study in patients with HCV-related cirrhosis. In addition, they also aimed to compare the rate of HCC recurrence following DAA versus IFN-based cure in patients who received curative HCC treatment. A search was conducted for reports published between January 2000 and February 2017. Random effects meta-analyses were undertaken to determine a combined estimate of HCC incidence rate per 100/person years. **The results show no evidence for differential HCC occurrence or recurrence risk following cure from DAA and IFN-based therapy.**