From the Editor's Desk May 2019

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SELECTION OF THE MONTH

Physical activity prevents liver cancer

The association between physical activity and risk of liver cancer is debated. Using data of the European Prospective Investigation into Cancer and Nutrition cohort (known as EPIC) which is composed of 467,336 men and women, **Baumeister *et al.* now show that physical activity is associated with a reduced risk of developing liver cancers over the next decade.** This risk was independent of other liver cancer risk factors, and did not vary by age, gender, smoking status, body weight, and alcohol consumption.

METABOLIC LIVER DISEASES

Improved β-cell function after OLT and role of IRF3 in alcoholic steatohepatitis

Diabetes is a common complication in cirrhotic patients that can persist after orthotopic liver transplantation (OLT). However, the natural history and mechanisms are not well known. In this issue, Grancini V et al. performed a longitudinal study assessing the relationship between the time-courses of changes in all 3 direct determinants of glucose regulation, i.e., β-cell function, insulin clearance and insulin sensitivity, and diabetes regression after OLT. Over the 2-year follow-up, **two-thirds of diabetic patients regressed to non-diabetic glucose regulation, while 10% of non-diabetic subjects progressed to diabetes**. Parameters indicative of beta-cell, function increased in regressors and decreased in progressors, whereas they remained stable in non-regressors. Insulin sensitivity improved at month 3 in all groups, but thereafter it continued to improve only in regressors, whereas it returned

to baseline values in the other groups. This clinical study provides evidence that **increased insulin bioavailability driven by improved β-cell function plays a central role in diabetes regression after OLT**. Maneuvers promoting insulin synthesis in patients with persistent diabetes could be clinically useful. In another interesting article in this issue, new mechanisms of alcohol-induced steatohepatitis have been uncovered. Interferon regulatory factor 3 (IRF3), a transcription factor that mediating anti-viral responses, also modulates the inflammatory response to injury. Sanz-Garcia C et al studied of IRF3 modules alcohol-induced steatohepatitis. Mice exposed to ethanol activated IRF3 signaling and showed hepatocellular injury. Moreover, **Irf3 deficient mice were protected from alcohol-induced steatohepatitis**. Protection from ethanol-induced injury in Irf3-/- mice was associated with an increased ratio of Ly6Clow (restorative) to Ly6Chigh (inflammatory) cells. In vitro, activation of macrophages induced **translocation of IRF3 to mitochondria, and subsequent activation of apoptotic pathways**. This study shows that IRF3 modulates the immune and hepatocellular response to ethanol exposure and represents a promising target for therapy.

HEPATITIS C VIRUS (HCV) INFECTION

Control of HCV replication normalizes patient and graft survival after kidney transplantation, HCV treatment behind bars

The influence of chronic HBV and HCV infection on patient and graft survival after kidney transplantation was revisited by analyzing the large prospective French national database which included 31,433 kidney transplant recipients. As before the use of antiviral therapy, HBV and HCV infection were associated with a poor outcome in kidney transplant recipients, a special emphasis of this study by **Fontaine *et al.*** was to update, how control of viral replication by antiviral therapy affected these endpoints. Whereas - thanks to control of HBV replication by nucleoside analogues - ten-year

patient and graft survival was similar between HBV-infected and non-infected control kidney recipients, it was significantly lower in those infected with HCV. **However, in the HCV group with undetectable viremia, graft and patient survival normalized to those observed in uninfected recipients**. This study underlines the deleterious effects of HCV replication on patients' and kidney transplant survival and provides clear-cut evidence for systematically treating HCV-infected kidney recipients or candidates to renal transplantation with DAAs.

Targeting the high burden of HCV infection among prisoners worldwide represents one important strategy to achieve the World Health Organization's (WHO) HCV elimination goals. However, although the HCV seroprevalence among incarcerated PWID may reach up to 50%, and ongoing incident HCV infections still occur among prisoners, the implementation of prison treatment programs in Europe is limited. **Papaluca *et al.*** now evaluated for the first time a prospective decentralized nurse-led model of care for viral hepatitis assessment and treatment in all prisoners across all 14 prisons in the state of Victoria, Australia. Out of the 416 prisoners included, 96% achieved a sustained viral response in the per protocol analysis. Hence, the prison systems provide a unique opportunity to scale up hepatitis C treatment, and **the demonstrated feasibility and efficacy of the novel decentralized, nurse-led model of hepatitis C care reported here makes it an interesting approach and potential world-wide role model for HCV elimination in prisons**.

CHOLESTASIS

IL-17: A novel therapeutic target to prevent bone loss in Primary Sclerosing Cholangitis (PSC)

Bone loss in patients with PSC is a serious issue that is independent of the severity of underlying liver disease, which can seriously impact the quality of life of the patients. The mechanisms underlying this is unclear and therefore, there are no known therapies. **Schmidt *et al.*** provide novel data exploring the role of CD4+ T helper type 17 cells (Th17) in the pathogenesis of low bone mass in patients with PSC. **Their data show for the first time that the increased bone resorption that was observed in PSC patients correlated closely with the frequency of the Th17 cells in the blood. They went on to show in animal models that depleting Th17 corrected the bone loss phenotype confirming that Th17 may well be a novel therapeutic target to**

prevent bone loss in PSC patients. The data justifies further clinical development of this therapeutic strategy.

CIRRHOSIS

Ammonia induces peripheral inflammation, reduced muscle mass and female sex underestimates the severity of renal dysfunction

In patients with liver disease, hyperammonemia is commonly observed. Traditionally, elevated ammonia levels are thought to predispose to the development of hepatic encephalopathy (HE) through its metabolic effects. More recently, elevated ammonia levels have been linked with portal hypertension, neutrophil dysfunction and sarcopenia. The mechanisms of the non-neurological deleterious effects of ammonia is unknown. **Balzano *et al.* performed a series of investigations and induced hyperammonemia with an ammonia-enriched diet in normal rodents and showed for the first time that increasing ammonia levels to that commonly seen in patients with cirrhosis was associated with marked peripheral inflammation characterized by an increase in prostaglandins and inflammatory cytokines.** Intriguingly, the inflammatory effect of ammonia was prevented by administration of infliximab providing clues to the mechanism underlying the pleiotropic deleterious effect of hyperammonemia.

The severity of renal dysfunction is an independent predictor of mortality of patients with cirrhosis. Creatinine concentration is a component of the MELD score, which is used for organ allocation for liver transplantation in most countries. **Kim *et al.*** performed a large study into how sex and muscle mass contributed to the actual measured glomerular filtration rate (GFR) using isotopic techniques and compared that to creatinine-based GFR (e-GFR) and cystatin-based GFR (c-GFR) estimation. **The e-GFR was overestimated in 47% patients and the muscle mass and female sex were independent predictors of this. The correlation between the measured GFR correlated much more closely with c-GFR, which also related closely to clinical outcome.** The data argue strongly for a change in clinical practice and to move towards c-GFR based estimation of GFR.

LIVER TRANSPLANTATION

Greater survival of patients on waiting list who accept organs from deceased donors (DCD)

About 23% patients wait listed for liver transplantation in the UK die or are removed from the waiting list due to delays in obtaining organs. The use of DCD donors has helped to reduce this risk but it is well known that the complications and mortality of using DCD organs is higher. In order to guide the patients, **Taylor *et al.*** address the important question whether using these organs reduces the mortality rate for patients on the waiting list despite the known poorer outcome of using DCD organs. **They confirm that the survival of patients receiving a DCD organ was about 69% compared with about 78% in those receiving an organ from a brain dead (DBD) donor. Despite this, they show that patients who received DCD livers had a significantly lower risk-adjusted hazard of death than those who remained on the waiting list for a potential DBD organ.** The data from this study are hugely important as it helps guide decision making for the patient.

DRUG-INDUCED LIVER INJURY

Efavirenz toxicity through PXR

The most prescribed non-nucleoside transcriptase inhibitor efavirenz, has been associated with elevated risk for dyslipidemia and hepatic steatosis in patients with human immunodeficiency virus infection, but the underlying mechanisms remain elusive. **Gwag *et al.*** were interested in the role of liver pregnane X receptor (PXR) in mediating the adverse effects of efavirenz on lipid homeostasis. **They show that efavirenz can activate liver PXR which mediates the adverse effects of efavirenz on lipid levels in mouse models.**

HEPATOCELLULAR CARCINOMA (HCC) – TRANSLATIONAL

HBx genotype associated with better outcomes, a long noncoding RNA promotes HCC

Genetic variability in the Hepatitis B virus X gene (HBx) is frequently observed and is associated with hepatocellular carcinoma (HCC) progression. However, a genotype classification based on the full-length HBx sequence and the impacts of genotypes on hepatitis B virus (HBV)-related HCC prognosis are poorly known. **Xu *et al.*** enrolled a large cohort of patients with HBV-related HCC to classify the genotypes of the full-length HBx gene through sequencing and perform cluster analysis of HBx DNA. Now they show that the HBx DNA can be classified into three genotypes. Of these, a genotype called HBx-E2 is associated with better outcomes than other genotypes.

Mechanistically, HBx-E2 lost its proliferation-promoting function in HCC cells and normal hepatocytes and failed to activate the Janus kinase 1 (JAK1)/signal transducer and activator of transcription 3 (STAT3)/STAT5 pathway. **Together, these findings identify a novel HBx genotype that results in a loss of proliferation promotion function in patients with HBV-related HCC.**

Liver cancer stem cells harbor high tumor-initiating potential and confer resistance to typical therapies, but the mechanism underlying their self-renewal remains elusive. Long noncoding RNAs (lncRNAs), which lack protein-coding capacity are distinct from structural RNAs (rRNAs, tRNAs, snRNAs, and snoRNAs) or small regulatory RNAs. LncRNAs arise from intergenic, antisense, or promoter-proximal regions and range in size from ~200 nt to >20 kb. LncRNAs have been shown to be involved in the modulation of several biological processes. **Wu *et al.*** aimed to define the role of lncHDAC2 (for lnc in association for histone deacetylase 2 [HDAC2]) in the tumorigenesis of HCC. They show that LncHDAC2 augments the self-renewal of liver cancer stem cells, promoting tumor propagation. In liver cancer stem cells, lncHDAC2 activates Hedgehog signaling to initiate liver tumorigenesis. **These findings suggest that lncHDAC2 and the Hedgehog signaling pathway can serve as biomarkers and potential drug targets for hepatocellular carcinoma.**

LIVER CANCER – CLINICAL

DAAs and the risk of de novo HCC, the six-and-twelve score for assessing TACE prognosis, warning about rapid post-RFA HCC recurrence beyond transplantation criteria

Despite the very high efficacy of direct-acting antiviral agents (DAAs) to eradicate HCV infection, the impact on HCC development is debated. **Mariño *et al.*** retrospectively analyzed the clinical and radiological outcome of 1123 patients with cirrhosis treated with interferon-free regimens, to estimate the risk of developing HCC. They show that although a high rate of sustained virological response was achieved (>95%), a 3.73% risk of developing de novo HCC per 100 persons/year with a clear-cut time association with antiviral therapy was registered. The presence of non-characterized nodules in radiologic assessments before starting DAA was associated to a 9.6% risk of developing hepatocellular carcinoma per 100 persons/year among patients with cirrhosis treated with DAA. **Time association between starting DAA and developing HCC, together with the association with the presence of non-characterized**

nodules at baseline ultrasound, may suggest that antiviral therapy elicits mechanism(s) priming the growth of HCC. Obviously, well-conducted prospective studies are needed.

There is currently no prognostic model specifically developed for recommended ideal transarterial chemoembolization (TACE) candidates with HCC, despite these patients being frequently identified as the best target population in pivotal randomized controlled trials. **Wang *et al.*** aimed to develop an easy-to-use tool specifically for these patients. Here they show that a score they named “the six-and-twelve score” provides patient survival prediction, especially in ideal candidates of TACE, outperforming other currently available models in both training and validation sets, as well as different subgroups. With cut-off values of 6 and 12, the score can stratify ideal TACE candidates into 3 strata with significantly different outcomes and may shed light on risk stratification of these patients in clinical practice as well as in clinical trials. **Together the results indicate that the six-and-twelve score may prove an easy-to-use tool to stratify recommended TACE candidates (Barcelona Clinic Liver Cancer stage-A/B) and predict individual survival with favorable performance and discrimination.**

Radiofrequency ablation (RFA) and liver transplantation are treatment options for early-stages of HCC. After RFA some patients can experience recurrence or metastatic spread of the initial tumor, or may develop new tumors within the liver. Despite close follow-up, these recurrences can progress rapidly and exceed transplant criteria, thereby preventing the patient from receiving a transplant and losing the potential for cure. **Doyle *et al.*** investigated the incidence and risk factors for recurrence beyond transplant criteria in patients treated with RFA that could have otherwise received a transplant. Here, they show that, among 301 patients, recurrence beyond transplant criteria occurs in 28%, despite undergoing close radiological follow-up. They also reveal that patients with HCC >2 cm and higher serum alpha fetoprotein levels are at greater risk of recurrence beyond the transplant criteria. **These data suggest that liver transplantation should be considered right after the first HCC recurrence for these patients.**

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