From the Editor's Desk November 2018

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SELECTION OF THE MONTH

Big title: Ex-vivo liver resection and autotransplantation

The ongoing and continuous risk of HCV reinfection

A web-based program for weight loss in NAFLD

Environmental trigger of PBC

LIVER PHYSIOLOGY

The bile acid receptor regulates fasting hepatic production

Fasting hepatic gluconeogenesis plays a crucial role in blood glucose homeostasis. hepatic gluconeogenesis is controlled through allosteric regulation of gluconeogenic enzymes and by glucagon/cyclic AMP (cAMP)-dependent transcriptional regulatory pathways. The bile acid receptor (also known as farnesoid X-activated receptor, FXR,

encoded by *NR1H4*) is expressed in the liver but the effects of its on gluconeogenesis are debated. Lefebvre et al addressed this question through elegant studies. They now show that **hepatic glucose production is regulated during physiological fasting by the bile acid receptor which integrates the glucagon/cAMP signal upon its post-translational modifications and by engaging protein-protein interactions with hepatocyte nuclear factor 3-beta (encoded by *FOXA2*), which is a transcription factor of the forkhead class of DNA-binding proteins.**

ALCOHOLIC AND NON-ALCOHOLIC FATTY LIVER DISEASES

An internet-based program for weight loss and novel mechanisms of neutrophil dysfunction after binge drinking

The main effective therapy for most patients with NAFLD is weight loss. There important barriers for lifestyle interventions and web-based tools could be useful. In this issue, Mazzotti *et al.* treated 716 consecutive NAFLD cases either with a program including dietitians and psychologists or with a web-based intervention with interactive material and mail contacts with the center. During a 2-year follow-up, healthy lifestyle changes were similarly observed in both groups and BMI decreased by almost 2 points. Similarly, liver enzymes and markers of liver fibrosis decreased in both groups and normalized more frequently in the group treated with the web-based program. **This interesting study reveals that internet-based tools could useful for patients that cannot physically attend dieticians. Web-based programs should be implemented in hospitals seen patients with obesity-related NAFLD.**

Another paper in this issue reports novel mechanisms of alcohol-related steatohepatitis. Neutrophils are the main inflammatory cell type involved in progression of alcoholic steatohepatitis. Increasing attention is being paid to neutrophil extracellular traps (NETs), which are typically used by neutrophils to kill microorganisms. Bukong *et al.* studied the role of NETs and studied phagocytosis of NETosing neutrophils by macrophages (efferocytosis) in acute sepsis following binge-drinking. They first showed increased levels of known NETs inducers (i.e., LPS) in humans after binge drinking. Ex vivo, alcohol attenuated NET formation upon stimulation by cytokines. Moreover, binge alcohol administration to mice reduced LPS-induced NET formation and resulted in a diffuse distribution of neutrophils in the liver. In the efferocytosis phase, alcohol decreased clearance of NETs. In vitro, alcohol reduced efferocytosis and phagocytosis of NETosing neutrophils. Finally, depletion of neutrophils prior to

binge alcohol ameliorated LPS-induced systemic inflammation and liver injury in mice. This translational study indicates **that dysfunctional neutrophil NETosis and efferocytosis after binge drinking may exacerbate liver injury associated with sepsis. These results could partially explain the increased incidence of infections and associated liver injury in patients after excessive alcohol intake.**

HEPATITIS C VIRUS (HCV) INFECTION

The ongoing and continuous risk of HCV reinfection

HCV reinfection after successful direct-acting antiviral (DAA) therapy is linked to ongoing exposure risk but larger population-level reports of reinfection rates after DAA therapy are lacking. The study by Rossi *et al.* is the first that estimated population-based HCV reinfection rate among a large Canadian real-world cohort which included ~1.7 million individuals screened for HCV. In the overall population, HCV reinfection rate following successful treatment with DAA therapies was 1.44 per 100 person-years, and was highest among patients who injected drugs recently, and being HIV coinfected and born after 1975. In contrast, the daily use of opioid-agonist therapy significantly lowered the risk of reinfection. **This important study provides first population-based evidence of HCV reinfection risk in the real-world setting and provides useful early knowledge on what would be needed to prevent reinfection as we expand access to treatment.**

CHOLESTASIS

Environmental xenobiotic may trigger PBC, inflammasome-mediated epithelial injury in biliary atresia

The mechanism of development of primary biliary cirrhosis (PBC) is unknown although autoimmunity is clearly involved. This is thought to be related to environmental factors such as exposure to xenobiotics. **Probert *et al.* studied landfill and soil samples obtained from a region where high prevalence of PBC was known to be present. They used several analytical and bio-assays to analyze these samples and identified a novel xenobiotic that could induce apoptosis of the hepatic progenitor cells and could replace lipoic acid in the PBC autoantigen.** The data provide convincing evidence for the potential existence of an environmental xenobiotic that could be important in the pathogenesis of PBC and allow development of preventative strategies.

The role of disturbances in the innate immune system and activation of the inflammasome in mediating the progression of many liver diseases is being established but its role in the progression of biliary atresia (BA) is unknown. **Yang *et al.* studied livers of patients and animal models of BA to test the hypothesis that disruption of the inflammasome would prevent experimental BA. They convincingly show that inflammasome-associated genes are overexpressed in the livers of patients and animal models. Importantly, they go on to show that targeted loss of *IL1R1* (encoding interleukin-1 receptor type 1) and *NLRP3* (encoding NACHT, LRR and PYD domains-containing protein 3) but not *CASP1* (encoding caspase-1) protected the mice from development of BA.** The data provide potentially novel approaches to the treatment of BA.

CIRRHOSIS

Novel MRI techniques to assess multiorgan perfusion in cirrhosis

Advancing severity of cirrhosis is characterized by progressive reduction in perfusion and function of multiple organs. The available technology does not allow quantitative determination of these perfusion defects and therefore it not possible to define which cirrhotic patients will develop organ dysfunction. **Bradley *et al.* have developed a novel MRI based technique that allows simultaneous assessment of perfusion abnormalities in the liver, spleen, kidneys; blood flow in the splanchnic arteries and cardiac index. Their data shows that these measurements were able to define the risk of subsequent liver-related outcomes.** With further validation, this technique could become an important warning tool to allow adequate management of cirrhosis and prevent complications.

LIVER TRANSPLANTATION

Chimeric organ and graft modeling, liver transplantation in patients with multiorgan failure, feasibility of ex-vivo liver resection and transplantation

Organ shortages have led to development of chimeric animals that carry human tissue but the performance of these organs that are contaminated by native xenogenic cells is unknown. **Oldani *et al.* transplanted chimeric organs developed in mice into rats with or without immunosuppression. They observed that without immunosuppression the mortality was universal, but all animals treated with immunosuppression survived.** The transplanted chimeric grafts underwent

extensive remodeling and the mouse hepatocytes were fully replaced by rat hepatocytes. This was associated with normal production of albumin, development of rat bile ducts and patchy areas of the host endothelium. These exciting new data allow real possibilities for the future use of chimeric organs for transplantation.

Multiorgan failure is a common complication of cirrhosis and is associated with high risk of death in the short-term. This condition has recently been defined clinically, prognostically and pathophysiologically and collectively termed acute-on chronic liver failure (ACLF). At present, the outcome of patients with ACLF on the waiting list for liver transplantation and their survival with transplantation is unknown. **Thuluvath *et al.* interrogated the UNOS database to address these questions. They provide important evidence that about 4.1% patients died within 30-days and the risk of being alive for more than 30-days decreased progressively with increasing number of organ failures.** Three-month and 1-year survival rates were 90% and 81% respectively in patients with 5 or 6 organ failures arguing strongly in favor of revising the current allocation criteria to allow for patients with advanced ACLF to be successfully transplanted.

Large, benign space occupying lesions in the liver such as echinococcosis often require liver transplantation because of the sheer size of the lesions. Access to liver transplantation is limited by availability of organs and risk of recurrence. **In a very innovative surgical program, Aji *et al.* undertook a heroic surgical approach that combined ex-vivo extended hepatectomy and auto transplantation of the remnant liver. Their data show a 3-month mortality of about 7% with acceptable complications confirming the feasibility of this approach.** With further refinement, it is possible that this approach may even be useful for patients with extensive hepatic metastatic disease, in whom liver transplantation is currently contraindicated.

HEPATOCELLULAR CARCINOMA (HCC) BASIC-TRANSLATIONAL

Warburg effect promotes liver tumors, targeting activated MAP kinases to potentiate sorafenib

Alterations in the homeostasis hepatic glucose metabolism can contribute to HCC development through as-yet poorly understood mechanisms. Glucose-6-phosphatase (encoded by *G6PC*) plays a major role in hepatic glucose production through glycogenolysis and gluconeogenesis. Mutations in *G6PC* cause glycogen storage glycogen storage disease type Ia (GSDIa) which is a rare genetic disease associated

with glycogen accumulation in hepatocytes and steatosis. Adult patients with GSDIa develop hepatocellular adenomas (HCA), which can progress to HCC. Gjorgjieva et *al.* leveraged the availability of hepatocyte-specific *G6pc* (L.*G6pc*$^{-/-}$) deficient mice (which recapitulate phenotypic characteristics of GSDIa, including the development of liver tumors) to characterize metabolism reprogramming and cellular defense alterations during tumorigenesis in the liver. The effects of high fat/high sucrose diet were investigated in livers from L.*G6pc*$^{-/-}$ and wild-type mice. **The results show metabolic remodeling (here, the existence of Warburg effect, with the overexpression of pyruvate kinase M2) in livers from L.*G6pc*$^{-/-}$ mice that generates a preneoplastic status and leads to a loss of cellular defenses and tumor suppressors that facilitates tumor development in GSDI.**

Sorafenib is a multikinase inhibitor used as the standard therapy for advanced hepatocellular carcinoma patients, but it provides limited survival benefit. To investigate the cause of the limited therapeutic effect of sorafenib, Wang *et al.* performed a CRISPR-Cas9 based synthetic lethality screen to search for kinases whose knockout synergize with sorafenib. They show that inhibition of mitogen-activated protein kinase 1 (a serine/threonine kinase also known as ERK-2) sensitizes several liver cancer cell lines to sorafenib. **Since 30% of liver cancers exhibit accumulation of phosphorylated (i.e., activated) ERK, the present findings suggest that these tumors with ERK overactivity are most likely to benefit from such combinatorial treatment.**

HCC CLINICAL

Assessing HCC risk on antiviral therapy in USA and Asia

It is of most importance to assess the risk of developing HCC in patients who received DAA drugs. Ioannou *et al.* identified 45,810 patients who initiated antiviral treatment in the Veterans Affairs national healthcare system; of these 64% received DAA-only regimens and the remaining received interferon with or without DAA drugs. They developed models predicting HCC risk using baseline characteristics at the time of antiviral treatment. Here the Authors show that **four predictors (age, platelet count, serum AST/ALT ratio and albumin) accounted for most of the prediction** with smaller contributions from sex, race-ethnicity, HCV genotype, body mass index, hemoglobin and serum alpha fetoprotein. These models could be used to inform risk-based HCC surveillance strategies in individual patients.

Recently, PAGE-B score and Toronto HCC risk index (THRI), which both are based on age, gender and platelets, have been developed to predict the risk of HCC in Caucasian patients with chronic hepatitis B (CHB). Kim *et al.* aimed to validate PAGE-B scores and THRI in 3,001 Asian patients with CHB receiving entecavir/tenofovir therapy. **They now show that PAGE-B and THRI scores are accurate in Asian patients with CHB receiving entecavir/tenofovir therapy. However, a modified PAGE-B (called mPAGE-B) scores including additional albumin levels has better predictive performance than the PAGE-B score.**