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SELECTION OF THE MONTH

Big Title: Obese adolescents at high risk of severe liver disease in later life

Small title Cirrhosis and Liver Failure: Moderate hypothermia in ALF

ACUTE LIVER FAILURE (ALF)

Autophagy cleans acetaminophen protein adducts, moderate hypothermia and intracranial hypertension in ALF

Acetaminophen (APAP)-induced liver injury is the most common cause of acute liver failure worldwide. APAP metabolism gives rise to metabolites NAPQI, which bind to cellular and mitochondrial proteins to form APAP protein adducts (APAP-AD). Mitochondrial APAP-AD trigger mitochondrial damage which may result in necrotic cell

death and subsequent liver injury. Little is known on how hepatocytes can remove APAP-AD. Using elegant approaches (*in vivo* mouse model and *in vitro* experiments), Ni *et al.* show that APAP-AD are removed through selective autophagy. The autophagy receptor protein p62 is recruited to APAP-AD, which could facilitate APAP-AD transition to the detergent insoluble form and allow their recognition and enwrapment by autophagosomes. Pharmacological induction of autophagy (Torin 1) or inhibition of autophagy (Leu or CQ) improves or impairs autophagic removal of APAP-AD and results in protection or exacerbation of APAP-induced necrosis and liver injury, respectively. They suggest that **pharmacological induction of autophagy may be a novel approach for treating APAP-induced liver injury.**

In patients with ALF, the occurrence of encephalopathy defines the condition and is associated with increased risk of death. Cerebral edema is a characteristic feature of encephalopathy in ALF patients and about 15% patients die from the effects of increased intracranial pressure (ICP). When the increase in ICP is uncontrolled with medical management, application of moderate hypothermia is effective at controlling ICP. **Bernal *et al.* performed the first randomized and controlled clinical trial of moderate hypothermia in ALF patients to determine whether it could *prevent* the development of increased ICP. The study revealed that moderate hypothermia *did not confer benefit in prevention* of intracranial hypertension or in overall survival compared with standard of care.** The data do not support the use of moderate hypothermia in a prophylactic mode.

FIBROSIS

A novel antifibrotic approach

Interleukin (IL)-15 binds with high affinity to IL-15 receptor subunit alpha (IL-15RA) to activate Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathways. IL-15 (and IL-2 as well) stimulates the proliferation of T cells; induces the generation of cytotoxic T lymphocytes (CTLs); facilitates the proliferation of, and the synthesis of immunoglobulin, by B cells; and induces the generation and persistence of natural killer (NK) cells. IL-15 is important for the maintenance of long-lasting, high-avidity T-cell responses to invading pathogens, and it achieves this by supporting the survival of CD8+ memory T cells. IL-15RA is expressed in immune cells and hepatic resident cells. Jiao *et al.* hypothesized that IL-15RA engagement by its agonist may result in antifibrotic actions. They show that in mice IL-15RA activation

results in anti-fibrotic effects through direct effects on hepatic stellate cells (HSC), independently of any action on natural killer homeostasis. **They suggest that future studies should explore the anti-fibrotic potential of enhancing IL-15 signaling in hepatic stellate cells.**

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Overweight in late adolescence and severe liver disease in adults, Sitagliptin therapy in pre-diabetic or diabetic patients with NAFLD.

The increased prevalence of overweight has been suggested to contribute to the worldwide increase in liver diseases. Hagström *et al.* analyzed a cohort study using data from 45,000 young men in Sweden 1970 and collected from the participants any diagnosis of severe liver disease until 2009. The authors found **that overweight was strongly associated with an increased risk of development of severe liver disease.** This important epidemiological data suggests that early interventions in young overweight individuals could prevent the development of severe liver disease. Uncontrolled studies show sitagliptin, an oral DPP-4 inhibitor, may decrease ALT and improve histology in patients with NAFLD. In this issue, Cui *et al.* performed a placebo-controlled trial assessing the efficacy of sitagliptin in pre-diabetic and diabetic patients with NAFLD. Fifty NAFLD were randomized to sitagliptin orally 100 mg/day or placebo for 24 weeks. **Sitagliptin was not significantly better than placebo in reducing liver fat (measured by MRI-PDFF) nor decreased ALT, HOMA and liver stiffness.** The study clearly demonstrated that Sitagliptin was safe but not better than placebo in patients with NAFLD.

GENETIC LIVER DISEASES

Respiratory mitochondrial complex III regulates liver adaptation to fasting

The respiratory complex III, which has 11 structural subunits and requires several assembly factors, plays an important role in liver homeostasis. Kremer *et al.* report the case of a child with complex III defect and acute liver dysfunction with lactic acidosis, hypoglycemia, and hyperammonemia. Homozygous, truncating, mutations were found in *LYRM7* and *MTO1*. The protein encoded by *LYRM7* is a nuclear-encoded mitochondrial matrix protein that stabilizes Rieske Fe-S protein (known as UQCRC1) and chaperones it to the inner mitochondrial membrane complex III (CIII, which is the main enzyme complex in the mitochondrial respiratory chain). *MTO1* encodes a

mitochondrial protein thought to be involved in mitochondrial tRNA modification. Comparison of the patient's clinical history to previously reported patients with complex III defect due to nuclear DNA mutations showed striking similarities. This intriguing study demonstrates that **profound complex III defect in liver impedes liver adaptation to prolonged fasting leading to severe lactic acidosis, hypoglycemia.**

HEPATITIS C VIRUS (HCV) INFECTION

HCV screening strategies in the US, spontaneous HCV clearance in chronic infection, viral escape by HCV core sequence-specific modulation of NK cell function

As curing chronic hepatitis C virus (HCV) infection can be now effectively achieved in nearly all patients, strategies to bring patients being unaware of their infection into medical care is of utmost importance in order to reduce the future population-based HCV-related disease burden. To achieve this goal, the Centers for Disease Control and the United States Preventive Services Task Force recommended universal one-time anti-HCV testing for Americans born 1945-1965, as more than 70% of all HCV infections in the U.S. belong to this birth cohort. Sarkar *et al.* studied patterns and predictors of HCV testing across the U.S. within this birth cohort utilizing data from the national corporate data warehouse of the U.S. Veterans Administration health system. From the more than 4.2 Million birth cohort veterans being in medical care only 51% had HCV testing with significant variations in testing among the different centers (Range: 7-83%). **Hence, further improvement in HCV screening is needed and the current work may provide an important basis in order to optimize future national HCV screening strategies.**

Spontaneous clearance of chronic HCV infection is believed to occur only exceptionally but valid estimates about its true incidence are missing. To elucidate the true spontaneous clearance rate in chronically infected patients, Bulteel *et al.* used retrospective data obtained on HCV testing between 1994 and 2013 in the West of Scotland and defined spontaneous HCV clearance as ≥ 2 sequential samples positive for HCV RNA ≥ 6 months apart followed by ≥ 1 negative test. The incidence rate of spontaneous HCV clearance was surprisingly high with 0.36/100 person-years follow-up among 10,318 untreated patients with chronic HCV infection, and female gender, younger age at infection, lower HCV RNA load and co-infection with hepatitis B virus were positively associated with this event. **This important study highlights that**

spontaneous clearance may occur in certain subgroups even after a prolonged duration of chronic infection more frequently as expected. Further work is required to identify the mechanisms underlying spontaneous clearance.

Viral host interactions involving regulators of the innate and adaptive immune system play an important role in viral escape mechanisms, and in this process the level of interaction is also driven by both, host but also viral genetic variants. The study by Lunemann *et al.* provides new insights how HCV type specific viral peptides influence natural killer (NK) cell function by targeting the killer cell immunoglobulin like receptors (KIRs), which interact mainly with HLA class I molecules on the surfaces of other cells. The authors show that the HCV core-derived viral epitope YIPLVGAPL increases binding of the inhibitory *KIR2DL3*-encoded protein to the respective HLA C*03:04/peptide complex, leading to a significant inhibition of *KIR2DL3*+ NK cell function. **They provide first evidence of a novel pathway by which HCV might be able to evade NK cell-mediated recognition.**

HEPATOCELLULAR CARCINOMA (HCC)

Biomarkers for HCC, histone deacetylase inhibitors for HCC

Two translational studies published in this issue of the Journal provide new perspectives in the development of biomarkers in patients with HCC. Ogle *et al.* investigated blood in patients with HCC and controls, using an imaging flow cytometry method (with immunofluorescence of cytokeratin, EpCAM, AFP, glypican-3 and DNA-PK) together with analysis of size, morphology and DNA content. **They show that in patients with HCC, the use of multiple parameters enhances detection sensitivity of circulating tumor cells, revealing biological associations and predictive biomarker potential that may guide future research.** Zhu *et al.* investigated whether baseline plasma and archival tissue specimens collected from patients enrolled in the EVOLVE-1 trial (a randomized phase 3 study of everolimus in HCC) were associated with prognosis, etiology or ethnicity. They find that the higher plasma levels of two proteins, vascular endothelial growth factor and soluble vascular endothelial growth factor receptor 1 (both known to be involved in the angiogenesis process), the poorer the prognosis. Moreover, **their results reveal potential differences in cMet (hepatocyte growth factor receptor) and mTOR (mammalian target of rapamycin) pathway activation between Asian and non-Asian patients, suggesting that these differences should be considered in future clinical trials.**

Bitzer *et al.* enrolled patients with HCC and radiologically confirmed progression on sorafenib in a phase I/II trial. This trial aimed to investigate safety, pharmacokinetics (PK) and potential biomarkers of the histone deacetylase (HDAC) inhibitor resminostat and a combination therapy with resminostat and sorafenib. They show that **the combination of sorafenib and resminostat is safe and may have early efficacy.** Sorafenib does not alter the PK profile of resminostat or its HDAC inhibitory activity in vivo. Moreover, they find that baseline levels of zinc finger protein 64 levels in blood cells may be a predictor of overall survival in HCC.