From the Editor's Desk September 2018

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SELECTION OF THE MONTH

Big title: Community testing for fibrosis severity

Small title (Transplantation): Hepatic Inflammation in long-term transplant survivors

Liver stiffness measurement in primary care

LIVER FIBROSIS

Is extracellular adenosine triphosphate (ATP) a DAMP causing liver damage?

Extracellular adenosine triphosphate, a damage-associated molecular pattern (DAMP) released by dying or stressed cells, signals through purinergic receptors. In general, the primary objective of DAMPs is to stimulate 'beneficial' inflammatory mechanisms that restore tissue homeostasis. However, some DAMPs may elicit deleterious

responses. ATP is released during liver injury. Although the P2X4 purinergic receptor (P2X4) is highly expressed in the liver, its functions in hepatic myofibroblasts during liver fibrogenesis was unknown. Using in vivo and in vitro models, **Le Guilcher *et al.* show here that P2X4 expression and activation by the DAMP ATP is critical for hepatic myofibroblast to maintain their activated and fibrogenic phenotype. These interesting findings suggest that P2X4 inactivation could be of therapeutic interest during liver fibrotic diseases.**

LIVER IMMUNE CELLS

Addressing tissue γδ T cells

Several properties distinguish γδ T cells from αβ T cells, including: γδ T cell receptors (TCRs) recognize a broad set of antigens; γδ T cells are rapid responders; γδ T cells are developmentally pre-programmed; **γδ T cells predominantly reside in specific tissues;** and γδ T cells have a broad contribution to immune responses. Current knowledge of human γδ T-cells is primarily based on peripheral blood subsets, while little is known on tissue-associated subsets. To address this gap of knowledge, **Hunter *et al.*** characterized the TCR diversity, immunophenotype and function of human liver infiltrating γδ T cells, focusing on the predominant tissue-associated Vδ2neg γδ subset, which is implicated in liver immunopathology. Their results suggest **These findings suggest that the ability of Vδ2neg γδ T-cells to undergo clonotypic expansion and differentiation is crucial in permitting access to solid tissues such as the liver.** Peripheral and liver-resident memory γδ T-cell subsets might be distinct.

LIVER REGENERATION

‘Junk’-induced Indian hedgehog (IHH) signaling,

In a mouse model called “Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS)”, IHH signaling from stellate cells is an early contributor to augmented regeneration. **Langiewicz *et al.*** investigated upstream regulators of IHH in this model. **They now show that mitogen-activated protein kinase 8 (called by them JNK1) induces IHH paracrine signaling from HSCs, which is essential for accelerated regeneration of parenchymal mass.** The MAPK 8/IHH axis is a mechanism unique to ALPPS surgery and may point to therapeutic alternatives for patients with insufficient regenerative capacity.

HEPATOCELLULAR CARCINOMA (HCC) BASIC

Deregulated Kelch-like ECH-associated protein 1 (Keap1)-Nuclear factor erythroid 2-related factor 2 pathway

Nuclear factor erythroid 2-related factor 2 (encoded by *Nfe2l2*, also known as *Nrf2*) is a transcription activator that binds to antioxidant response (ARE) elements in the promoter regions of target genes. KEAP1 acts as a substrate adapter protein for the E3 ubiquitin ligase complex formed by CUL3 and RBX1 and targets NRF2 for ubiquitination and degradation by the proteasome, thus resulting in the suppression of its transcriptional activity and the repression of ARE-mediated detoxifying enzyme gene expression. Deregulation of the KEAP1-NRF2 pathway may play a role in cancer development. Here, **Orrù *et al.*** examined whether NRF2 activation occurs at early steps of rat hepatocarcinogenesis. Using a rat model that mimics hepatocarcinogenesis in human NAFLD, **they show that NRF2 is activated at early steps of the tumorigenic process. Moreover, NRF2 is mandatory for the clonal expansion of initiated cells, indicating that this molecule is critical in the onset of HCC.**

FATTY LIVER DISEASES

Increased prevalence of hip fracture in alcoholic cirrhosis and role of β-hydroxybutyrate and CD36 palmitoylation in steatohepatitis

Cirrhosis and abusive alcohol intake are known risk factors for osteoporosis; making alcoholic cirrhosis susceptible to hip fractures. Whether this patient population has increased prevalence of hip fractures is not well known. In this issue, **Otete *et al.*** followed two large cohorts from the UK and Denmark with alcoholic cirrhosis, as well as matched controls. The **5-year hip fracture risk was raised both in the UK (2.9% vs 0.8% for controls) and Denmark (4.6% vs 0.9% for controls).** With confounder adjustment, cirrhotics had 5-10-fold increased rates. Importantly, in patients with alcoholic cirrhosis, **30-day mortality following a hip fracture was around 10%.** This important epidemiological study shows that alcoholic cirrhosis has a markedly increased risk of hip fracture and post-hip fracture mortality compared with the general population. Measures improving osteoporosis and avoiding falls are important in this patient population. Two other studies in this issue discovered novel mechanisms of alcoholic and non-alcoholic steatohepatitis (NASH). In the first study, **Chen *et al.*** described a new endogenous mechanism (i.e., β-hydroxybutyrate) that protects from

alcohol-induced liver injury in the setting of alcoholic hepatitis. The authors studied Hcar2, a G-protein which is activated by β-hydroxybutyrate, a source of ketone bodies synthesized from acetoacetate. **Humans with AH have reduced hepatic β-hydroxybutyrate, and its inhibition in mice aggravated ethanol induced alcoholic steatohepatitis**. Conversely, supplementation of β-hydroxybutyrate reduced ALT levels, steatosis and neutrophil influx and promoted macrophage M2 polarization through Hcar2. This translational study suggests that **β-hydroxybutyrate has an anti-inflammatory and hepatoprotective roles through a Hcar2 dependent pathway** and introduces the concept of metabolite-based therapy for alcoholic hepatitis. In another translational mechanistic study in this issue, **Zhao *et al.*** demonstrated a role for CD36 palmitoylation, an important immunoregulator, in NASH. **CD36 expression and palmitoylation were markedly increased in hepatocytes from human and experimental NASH**. Inhibition of CD36 palmitoylation protected mice from developing NASH. Moreover, CD36 **palmitoylation modulated fatty acid uptake, intracellular lipid accumulation and the inflammatory response**. This intriguing study demonstrates a key role of palmitoylation in regulating CD36 distributions and its functions in NASH. The authors propose that inhibition of CD36 palmitoylation may represent a novel therapeutic strategy in NASH patients.

HEPATITIS B VIRUS (HBV) INFECTION

T cell phenotyping following nucleos(t)ide analogue treatment discontinuation

Although discontinuation of long-term nucleoside/nucleotide analogue (NA) treatment in HBeAg negative chronic hepatitis B is typically followed by a viral rebound, it may also trigger HBsAg loss, i.e., a functional cure. The hypothesis behind these intriguing observations is that of a flare-induced stimulation of HBV-specific immune responses facilitating HBsAg loss. The study by **Rinker *et al.*** is the first to investigate HBV-specific T cell responses in this setting by following 15 patients who stopped NAs in a prospective proof-of-concept study. **Stopping long-term NA therapy led to changes in T cell phenotype and enhanced responsiveness to *in vitro* peptide stimulation of HBV-specific T cells.** The authors hypothesize that the relapse of HBV replication could create a cytokine milieu associated with an increased responsiveness of HBV-specific T cells, a concept which might be also of interest for designing new therapeutic approaches to induce HBsAg decline or loss.

HEPATITIS C VIRUS (HCV) INFECTION

Have you had your liver stiffness measurement? The intercellular HCV communication network

In order to reach the WHO goal of HCV elimination, Australia has already expanded the role of primary care with an attempt to prioritize therapy to those with advanced HCV-induced liver disease being at highest risk for liver-related morbidity and mortality. However, as advanced liver disease remains often undetected, and its prevalence in primary care management is unknown, **Bloom *et al.*** were interested to evaluate liver stiffness measurement (LSM) as a screening tool to detect individuals with advanced liver disease and predict liver related events in a prospective cohort of patients with chronic hepatitis C recruited from 21 primary care practices. Quite surprisingly, **the rate of advanced fibrosis in the community, although often underdiagnosed, was comparable to rates seen in specialist referral centers, and nearly 10% of those with advanced fibrosis (LSM ≥ 12.5 kPa) suffered from a liver-related event**. This study supports the use of LSM as a community screening tool for the HCV-infected population and indicates a possible role in predicting liver-related events.

HCV replication can substantially influence the intercellular communication signals decisive for immune cell recruitment by influencing the production of several chemokines. However, the mechanisms involved in the regulation of chemokine production by HCV are not understood in detail. In their elegant work, **Groepper *et al.* provide evidence that HCV replication upregulates epidermal growth factor (EGF) expression hereby enhancing the release of members of the chemokine family that specifically recognize the chemokine receptor CXCR2**. The cytokine-chemokine pattern induced by the EGF and its receptor (EGFR)-mediated signaling pathway in HCV-infected cells also mediates recruitment of neutrophil granulocytes, thus describing a novel mechanism how HCV modulates inflammation and the antiviral immune response.

CIRRHOSIS

Low subcutaneous fat in cirrhotic women predicts mortality and morbidly obese patients have high risk of developing ACLF

Recent studies have confirmed that alterations of body composition in patients with cirrhosis define the risk of death. New prognostic scores have been developed that incorporate measures of muscle mass into the equations. **Ebadi *et al.* evaluated the**

prognostic significance of alterations in subcutaneous fat, visceral fat and muscle mass in cirrhotic patients. Their data provide the first clear indication that although the muscle mass provides prognostic information in cirrhotic men it is the subcutaneous fat index that is of prognostic importance in cirrhotic women. These important data not only provide potential modifications to prognostic scoring systems in cirrhosis but also new insight into the biological functions of adipose tissue.

In another paper in this same issue, **Sundaram *et al.*** explored the role of obesity in defining the risk of developing acute on chronic liver failure (ACLF) in cirrhotic patients on the waiting list for liver transplantation. **They studied large patient cohort in the UNOS database and also those taken from the Nationwide Inpatient Sample and show for the first time that cirrhotic patients with morbid obesity have a higher risk of developing ACLF and renal failure is more prevalent in this population.** These data have important consequences for risk stratification and institution of appropriate management strategies.

LIVER TRANSPLANTATION

Hepatic transcriptomic signature in long term transplant survivors

Liver biopsies obtained from long term survivors of liver transplantation often show evidence of ongoing inflammation and in some patients, there is evidence of hepatic fibrosis. The mechanisms behind these changes are unknown. The important paper by **Londono *et al.*** aimed to address the mechanism behind these changes by studying biopsies obtained from liver transplant patients who were otherwise well and had been transplanted >10 years previously. **They performed transcriptomic analysis of the obtained biopsies and show for the first time that a large proportion of these patients had subclinical histological changes and their expression profile closely resembled T cell mediated rejection.** These data have implications for managing immunosuppression in long-term survivors of liver transplantation.

CHOLESTASIS

Macrophages are novel therapeutic targets for Primary Sclerosing Cholangitis (PSC)

There are no therapies known to prevent the progression of PSC and its treatment is an unmet medical need. Although macrophages are implicated in the pathogenesis of

many liver diseases, their role in PSC is not clear. **Guicciardi *et al.*** performed a series of innovative experiments in animal models of PSC and human samples and explored the role of macrophages. **Their studies showed evidence of peribiliary infiltration of monocyte-derived macrophages in the liver. Both pharmacological and genetic manipulation of this macrophage infiltration reduced the severity of liver injury and the associated fibrosis.** These data provide a novel approach for the treatment of PSC that should be possible to translate into generating benefit for patients.