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SELECTION OF THE MONTH

Title of the Month: Big Title: Fructose increases risk of NAFLD in children

Small title:

Intrahepatic innate immunity in chronic HBV infection

A comprehensive view on NS5A resistance

Abnormal IFN signaling in cirrhosis PBMCs

HEPATOCYTE POLARITY

Role of VPS33B

Hepatocyte polarization is crucial for normal cell function. Several cholestatic liver diseases with defects of hepatocyte polarity have been identified, but little is known about the molecular mechanisms explaining these defects. The attention of Hanley *et*

al. was drawn on a protein called “vacuolar protein sorting-associated protein 33B” (encoded by *VSP33B*) because a syndrome called “arthrogryposis, renal dysfunction and cholestasis” is most often caused by *VPS33B* mutations. Therefore, they investigated mice that were selectively deleted for *Vsp33b* in the liver. Their results indicate that ***Vsp33b* in mice has a key role in establishing structural and functional aspects of hepatocyte polarity suggesting that *VSP33B* could be a target for gene replacement therapy in humans.**

LIVER SINUSOIDAL ENDOTHELIAL CELLS (LSECS)

LSECS function as immunological platforms

LSECs play a crucial role in liver physiology and pathophysiology. A function which is not well known by hepatologists is **antigen presentation**. In this issue of the Journal, Wittlich *et al.* present a scenario involving two categories of signals that modulate the production of the cytotoxic granzyme B by CD8 T cells. **The primary signal is the activation CD8 T cells via engagement of T cell receptor by antigen presented by LESCs.** In primed CD8 T cells additional **interleukin (IL)-6 trans-signaling** increases the expression of granzyme B, which depends on the stimulation of the **IL-2-receptor by IL-2 secreted from T_h1 cells**. Accordingly, in this scenario IL-6 trans-signaling plays an important role in CD8 T cell activation and deserves some comment. The fully competent IL-6 receptor is composed of a type 1 cytokine α-receptor subunit (IL-6R, also known as CD126; encoded by *IL6R*), which binds IL-6, and a signal-transducing β-receptor subunit (gp130; also known as CD130; encoded by *IL6ST*). The expression of gp130 is ubiquitous on cells of the immune system and those not of the immune system. In contrast, IL-6R expression is restricted largely to hepatocytes, leukocytes and megakaryocytes. ‘Classical’ IL-6 receptor signaling denotes activities mediated via the membrane-bound IL-6R subunit and is relevant only to cells that express both receptor subunits. **IL-6 “trans-signaling” refers to a process in which a soluble form of IL-6R binds secreted IL-6 to form a complex that binds any cell that expresses only gp130 which hence acquires IL-6 responsiveness.**

HEPATOCELLULAR CARCINOMA (HCC)

Mutated *ARID2*, tumor suppressive microRNAs, modified RECIST

SWI/SNF family complexes. are large chromatin-remodeling machines that move or eject nucleosomes, providing proper nucleosome positioning and density at genes and

other loci. SWI/SNF-family complexes are involved in a broad variety of functions including transcription, DNA repair, cell cycle and differentiation, and tumor suppression, among others. The AT-rich interaction domain 2 gene (*ARID2*) encodes a DNA-binding protein known as BAF200 which is one of the subunit composing SWI/SNF complexes. Although inactivating *ARID2* mutations are known to be associated with HCC, the impact of *ARID2* deletion was poorly understood until recently. To address this question, Oba *et al.* deleted *ARID2* using **CRISPR/Cas9 system** in HCC cell lines. They show that *ARID2* knockout contributes to disruption of nucleotide excision repair process through inhibiting the recruitment of a protein called "DNA repair protein complementing XP-G cells" (encoded by *ERCC5* also known as *XPG*, *XPGC*). *ARID2* deletion resulted in increased susceptibility to carcinogens and potential hyper mutation. **These findings have far-reaching implications for therapeutic targets in HCC with *ARID2* mutations.**

MicroRNAs (miRNAs) are short (20-24 nt) non-coding RNAs that are involved in post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. MiRNAs regulate the expression of a broad variety of genes and therefore impact multiple functions. MiR-499a has been shown to have anti-cancer effects in HCC lines. Here, Sandboth *et al.* report their investigations on three members of the miR-499 family (miR-499a, miR-499b, and miR-499c). They show **distinct tumor suppressive effects and target specificities of miR-449a, miR-449b, and miR-449c.** Moreover, their results suggest that miR-449a and miR-449b could be considered for miRNA replacement therapy to prevent HCC progression and metastasis.

The Response Evaluation Criteria in Solid Tumors (RECIST) have been challenged in HCC due to the nature of effective treatments. This is why these criteria have been changed giving rise to modified RECIST (mRECIST). Lencioni *et al.* investigated whether objective response by mRECIST accurately predict overall survival in patients with advanced HCC treated by systemic therapies. For this they performed an individual patient data analysis of BRISK-PS, a phase III trial comparing brivanib and placebo in the second line setting. They show that **objective response by mRECIST in advanced HCC predicts overall survival and thus can be considered as a candidate surrogate for prognostic end point.**

FATTY LIVER DISEASE

Fructose consumption and hyperuricemia in young population, CAP technology and inflammasome blockade in NAFLD

Excessive fructose intake is known to increase serum uric acid concentrations. In an important study by Mosca *et al.* a large cohort of children and adolescents with proven NAFLD (37% with NASH) were studied. Hyperuricemia was present in 47% of patients with NASH compared with 29% of Not-NASH patients. Importantly, both **uric acid concentration and fructose consumption were independently associated with NASH**, after adjustment for multiple confounders. Importantly, **fructose consumption was the only factor independently associated with serum uric acid concentration**. This study suggests that excessive fructose consumption could lead to hyperuricemia and contribute to NASH development in young populations. Public health policies aimed at preventing excessive fructose-containing beverages among children are warranted. In another study in this issue, Karlas *et al.* study the **usefulness of ultrasound-based controlled attenuation parameter (CAP) in detecting steatosis**, an increasing liver condition worldwide. In an individual patient data meta-analysis, the authors gathered data from 19 studies comprising more than 3.000 patients. Seventy percent of patients have viral hepatitis and 20% NAFLD. CAP values in dB/m were influenced by several covariates with an estimated shift for NAFLD, diabetics and per BMI unit. Optimal cutoffs were 248 and 268 for those above S0 and S1. The authors conclude that **CAP provides a standardized non-invasive measure of hepatic steatosis and that the etiology, diabetes, and BMI deserve consideration when interpreting CAP**. This study should be confirmed in populations with alcoholic liver disease.

Finally, in this issue of the *Journal* a new potential targeted therapy for NAFLD was proposed. NOD-like receptor protein 3 (NLRP3) inflammasome activation occurs in both alcoholic and non-alcoholic fatty liver. Mridha *et al.* used the first small molecule NLRP3 inhibitor, MCC950, in two murine models of steatohepatitis. **MCC950 treatment lowered serum transaminases, reduced the severity of liver inflammation and fibrosis and reduced caspase activation**. In vitro, MCC950 attenuated the effect of cholesterol crystals on Kupffer cells and macrophages to release inflammatory mediators. These preclinical research strongly indicates that targeting NLRP3 is a promising therapeutic option in patients with NAFLD and deserves clinical attention.

HEPATITIS B VIRUS (HBV) INFECTION

Intrahepatic innate immunity in chronic HBV infection,

Most of our knowledge on HBV specific host immune responses was obtained from studies with peripheral blood rather than by studying the liver. The study by Lebossé *et al.* is the first that examines in detail the intrahepatic innate immune gene expression in chronic HBV compared to healthy livers. Their results indicate that **chronic HBV infection has a profound suppressive effect on host innate immune responses, which was more pronounced in the presence of high levels of hepatitis B virus surface antigen (HBsAg).** These data provide novel insight into the complex virus-host interactions and the mechanisms of HBV persistence in the liver, and suggest that novel HBsAg targeting approaches may also restore immune responsiveness (see also the Editorial by Vanwolleghem and Boonstra).

HEPATITIS C VIRUS (HCV) INFECTION

A comprehensive view on NS5A resistance, persistence of immunosuppressive Tregs after SVR, autocrine regulation of HCV replication

The extent by which the presence of NS5A resistance-associated substitutions (RASs) can affect the efficacy of NS5A inhibitor-containing antiviral regimens in previously untreated as well as treatment-experienced HCV-infected patients is still a matter of debate. Zeuzem *et al.* reviewed results from 35 clinical trials where patients with HCV type 1 infection received treatments that included ledipasvir plus sofosbuvir. They found that by using a 15% cut-off, ledipasvir-specific NS5A RASs were present in 8-16% prior to treatment, and had a negative impact on treatment outcome in certain subsets of patients, in particular treatment-experienced patients with HCV subtype 1a. **This comprehensive large scale analysis teaches us the importance of a balanced approach when considering RAS testing before NS5A-containing regimens but also that large numbers are needed to uncover small differences.**

During chronic hepatitis C, effector T cells become progressively exhausted and exhibit reduced antiviral activity, while $CD4^+$ regulatory T cells (Tregs) gradually expand and accumulate in the liver and being linked to fibrogenesis and liver cancer development. Langhans *et al.* studied the long-term evolution of Tregs in HCV-infected patients treated with either interferon (IFN)-containing or IFN-free direct acting antiviral (DAA) treatment. Although IFN-based DAA therapy induced transient expansion of activated

$Foxp3^+CD25^+CD4^+$ T cells, neither IFN-based nor IFN-free DAA regimens normalized frequencies and activation status of Tregs one year after viral elimination. **The persistence of immunosuppressive Tregs may thus contribute to complications of liver disease even long-term after HCV elimination, following the concept that cure of the infection does not necessarily means cure of the disease.**

The protein called **"ectonucleotide pyrophosphatase/phosphodiesterase family member 2"** (known as autotaxin; encoded by *ENPP2*, alias *ATX*), hydrolyzes lysophosphatidylcholine (LPC) to the growth factor lysophosphatidic acid (LPA). The autotaxin-LPA signaling axis plays an important role in both normal physiology and disease pathogenesis, and recently has been linked to pruritus in chronic cholestatic liver diseases. The current elegant study by Farquhar *et al.* uncover a role for the autotaxin-LPA signaling axis to positively regulate HCV replication by activating PI3K and stabilizing HIF-1α, hereby providing evidence for an autocrine LPA feedback loop to promote viral replication. The data support a model where **HCV infection increases hepatocellular autotaxin expression that promotes viral replication and establishes a paracrine LPA-signaling environment leading to fibrosis and HCC pathogenesis.**

CIRRHOSIS

IFN signaling in PBMCs of alcoholic cirrhosis patients

Patients with decompensated alcoholic cirrhosis show evidence of widespread disturbances in immune function ranging from inflammatory phenotype to that of a reparative anti-inflammatory phenotype. Type I interferons are a family of cytokines that play a crucial role in the immune response to viral pathogens that result in transcription of interferon stimulated genes (ISG). **Weiss *et al.* studied the peripheral blood mononuclear cells from a large number of patients with alcoholic cirrhosis and show for the first time that both constitutive and stimulated ISG expression was abnormal and, the higher the baseline ISG expression, the greater was the risk of death.** The data provide the basis of a novel biomarker to identify those patients at risk and also a potential therapeutic target.