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SELECTION OF THE MONTH

Big Title: Something about Liver Transplantation as a tribute to Thomas Starzl

Small titles:

Early initiation of supplementary milk during breastfeeding increases the risk of NAFLD in adolescents.

Intrahepatic myeloid cells drive liver inflammation

Visualization of HEV RNA and proteins in human livers

Cirrhosis: Should MELD be uncapped?

ACUTE LIVER INFLAMMATION

Paradoxical effects of interleukin-10 promoting acute liver immunopathology

Besides secreting pro-inflammatory cytokines, chemokines and effector molecules, effector $CD8^+$ T cells that arise upon acute infection with certain viruses have been shown to produce the anti-inflammatory cytokine interleukin (IL)-10 (a **class 2 α-helical cytokine**, whose initial name was cytokine synthesis inhibitory factor [CSIF]), containing immunopathology. Whether the same occurs during acute hepatitis B virus (HBV) infection and the role that IL-10 might play in liver disease is currently unknown. Fioravanti *et al.* addressed this question using mouse models of HBV pathogenesis. **They reveal that the IL-10 produced by effector $CD8^+$ T cells promoted their own intrahepatic survival and, thus, supported, rather than suppressed, liver immunopathology.** Studies should now investigate whether these findings (which challenge our traditional view of IL-10) are also observed with other infections in the liver and in other organs.

IRON OVERLOAD

Non-invasive assessment of liver iron

Accumulation of liver iron is an independent factor of survival and carcinogenesis in various chronic liver diseases. Mueller *et al.* evaluated the ability of a novel room-temperature susceptometer (RTS) to noninvasively assess liver iron concentration (LIC) in a prospective cohort of 264 patients with or without signs of iron overload or liver disease. **They show that RTS allows the rapid and non-invasive measurement of liver iron.** In comparison to magnetic resonance imaging, RTS could be a cost-effective bedside method for liver iron screening.

ALCOHOLIC AND NON-ALCOHOLIC STEATOHEPATITIS

Early detection of “high risk” alcohol consumption, influence of maternal obesity and early initiation of supplementary milk on adolescent NAFLD, use of CAP to detect fatty liver.

Many patients with advance alcoholic liver disease have previous history of recurrent admissions to hospital, representing missed opportunities for intervention. Westwood *et al.* screened admissions to a major hospital to identify patients at increasing risk of alcohol harm. Patients with alcohol misuse were referred for either brief intervention or assessment by an alcohol specialist nurse. Out of 48,211 admissions that completed alcohol screening, 2.3% were classified at "increasing", and 4.0% at "high" risk of alcohol harm. **High risk patients had more admissions** in the

previous three years and more emergency department attendances. Importantly, **high risk patients had distinct diagnostic profiles in the admissions, including liver disease-related hospitalizations**. This important study suggests that early identification and counseling in patients with hazardous alcohol intake could prevent hospitalization due to alcohol-induced organ damage.

The prevalence of NAFLD in adolescent is increasing worldwide. Identifying early events leading to increased risk to develop NAFLF is critical to implementing health policy measures. There is inadequate knowledge regarding associations between infant nutrition and subsequent NAFLD. In this issue of the *Journal*, Ayonrinde *et al.* examined the association of maternal factors and infant nutrition, with the subsequent diagnosis of NAFLD in adolescents in Australia. **NAFLD was diagnosed in 15% of the 1,170 adolescents examined. Breastfeeding without supplementary milk ≥6 months, maternal pre-pregnancy obesity and adolescent obesity were associated with NAFLD** independent of a Western dietary pattern at age 17 years. Supplementary milk intake starting before 6 months was associated with a higher prevalence and ultrasound severity of NAFLD. This relevant study suggests that **maternal obesity and early initiation of supplementary mils increases the risk of NAFLD at young ages**.

Besides epidemiological studies, another paper in this issue investigated the diagnosis of NAFLD. Non-invasive methods to diagnose fatty liver disease are increasingly used in clinical practice. Controlled attenuation parameter (CAP) can be performed together with liver stiffness measurement (LSM) by transient elastography to diagnose fatty liver. However, the validity criteria are not well defined. Wong *et al.* performed a large multicentric study in Europe and Hong Kong using CAP to estimate the presence of steatosis in patients undergoing a liver biopsy. **The AUROC for CAP to diagnose fatty liver was more than 0.80** across the different cohorts. The accuracy of CAP in detecting grade 2 and 3 steatosis was lower among patients with body mass index ≥30 kg/m2 and F3-4 fibrosis. Importantly, **the validity of CAP for the diagnosis of fatty liver was lower if the IQR of CAP is ≥40 dB/m**. This study will be useful to establish the parameters for an accurate assessment of fatty live using the CAP technology

HEPATITIS C VIRUS (HCV) INFECTION

Estimating the consequences of alcohol use disorders in chronic hepatitis C, Apo-E-mediated HCV immune escape, KIR and HLA genetics contributes to HCV susceptibility, intrahepatic myeloid cells drive liver inflammation via activation of translocated intestinal bacterial products

The inter-individually variable rate of disease progression is a well-recognized but poorly understood feature of chronic hepatitis C virus (HCV) infection. Alcohol use disorders – often associated with HCV infection – may accelerate the disease course but the extent to which alcohol contributes to the HCV-associated disease burden has not been carefully explored yet. In a French nationwide study, Schwarzinger *et al.* tracked liver-related complications and mortality over a 5-year period in 97,347 young and middle-aged patients with chronic HCV infection according to the presence or absence of alcohol use disorders. **The most prominent findings of this provocative study were that alcohol use disorders might contribute to more than two-thirds of all liver transplantations, and liver deaths recorded in patients with chronic HCV infection but also that alcohol rehabilitation and abstinence will be associated with a 50% risk reductions of liver-related complications.** This important study supports the promotion of alcohol abstinence and rehabilitation programs to reduce HCV-related complications.

HCV replication is linked to host factors and cellular pathways involved in lipid metabolism like apolipoproteins (Apo) -E and C-I facilitating infection by increasing virus attachment or membrane fusion, respectively. Little is known, however, about particle maturation processes outside of the virus producing cells including their impact for cell entry and immune evasion. Bankwitz *et al.* now report on a role of secreted Apo-E in ensuring the propagation of HCV in an environment with potentially neutralizing antibodies, and that the **Apo-E-HCV interaction might be a crucial step to shield the virus particles from neutralizing antibodies**. This elegant study further improves our understanding of HCV-Apo-E interaction and viral immune escape mechanisms which may guide the pathway towards a prophylactic HCV vaccine.

Natural killer (NK) cell function may be critically involved in protection from infection prior to seroconversion but also resolution of acute hepatitis C. Killer-cell immunoglobulin-like receptors (KIRs) on NK cells interact with human leukocyte antigen (HLA) class I molecules on infected cells resulting in NK cell activation or inhibition. In order to further elucidate potential mechanisms of protective immunity

against HCV, genetically determined combinations of KIR and KIR-ligands on the outcome of HCV infection were studied by Thoens C *et al.* in individuals with high-risk behavior for HCV infection, i.e., persons who inject drugs (PWID). **Whereas the presence of a *KIR3DL1/HLA-Bw4-80T* genotype was associated with spontaneous clearance of HCV infection, a protective state against primary infection was mediated by *HLA-Bw4* alleles**. These data suggest that superior functionality of NK cells against HCV plays an important mechanistic role for the advantageous effect of high HLA-Bw4 copy numbers and the *KIR3DL1/HLA-Bw4-80T* genotype on the natural outcome of HCV infection.

Monocytes and macrophages form a heterogeneous population of myeloid cells which have been recently recognized as important players in promoting angiogenesis, liver fibrosis and HCC development. Tan-Garcia *et al.* defined the contribution of intrahepatic $CD14^+$ myeloid cells to chronic liver inflammation in patients with viral-related end-stage liver disease. **Activated myeloid cells (particularly $CD14^+HLA\text{-}DR^{hi}CD206^+$ cells) which spontaneously produced pro-inflammatory mediators were enriched in advanced viral-induced liver disease, and showed enhanced responses to bacterial product stimulation**. The intriguing findings that treatment with oral antibiotics normalized intrahepatic $CD14^+HLA\text{-}DR^{hi}CD206^+$ myeloid cell numbers may indicate that liver inflammation can be sustained by a pathogenic gut-liver interaction but also implies to give microbiome-modifying or myeloid-depleting therapies greater considerations in advanced liver disease.

HEPATITIS E VIRUS (HEV) INFECTION

Visualization HEV RNA and proteins in human livers

Hepatitis E virus infection gathered increasing interest as the most common cause of acute viral hepatitis worldwide and a pathogen associated with a large number of extrahepatic manifestations but also chronic liver disease in immunosuppressed patients. Yet, accurate serologic and histopathologic diagnosis of HEV infection is challenging. Lenggenhager *et al.* systematically evaluated immunohistochemistry (IHC) and *in situ* hybridization (ISH) for visualizing HEV proteins and RNA in cell lines and human liver tissues, and determined the value of these tools in a diagnostic setting. They showed that **HEV ORF2 protein can be taken as a robust marker for tissue-based diagnostics but also described for the first time a subcellular**

distribution pattern of the ORF2 protein including a nuclear localization which suggest a redistribution of the virus during infection. Precise knowledge of the temporal and spatial viral distribution in the liver during infection would not only be of advantage for developing tissue-based diagnostics, but is also a prerequisite for a better understanding of HEV pathogenesis.

PRIMARY SCLEROSING CHOLANGITIS

norURSO: A novel strategy to treat PSC

The treatment of PSC is an unmet medical need. 24-*nor*ursodeoxycholic acid is an analogue of UDCA that has been shown to have anti-fibrotic and anti-inflammatory effect in animal models. In a vital study, Fickert *et al.* performed a large dose ranging, placebo-controlled clinical trial of *nor*URSO in patients with PSC. **They showed that all the doses were safe, well-tolerated and significantly reduced serum alkaline phosphatase and others markers of liver injury justifying a Phase 3 trial of *nor*URSO in PSC patients.**

SPLANCHNIC VEIN THROMBOSIS

Prediction of presence of calreticulin gene (*CALR*) mutation

Splanchnic vein thrombosis (SVT) is associated with myeloproliferative neoplasm and JAK mutations in about 80-90% patients. *CALR* mutations are found in only 2% cases. At present it is not clear which patients should be tested for this mutation. **In a large prospective study, Rautou *et al.* showed that *CALR* mutation was likely to be present in the patients with SVT that were negative for the *JAK* mutation, had a spleen size of more than 16 cm and a platelet count of more than 200 x 10^9/L.** They validated these criteria in an independent cohort and the application of this strategy would reduce the need for *CALR* testing by 96%.

TIPS AND HEPATIC ENCEPHALOPATHY

8mm covered shunts reduces the risk of hepatic encephalopathy (HE)

The occurrence of HE is a devastating complication of TIPS and current strategies fail to identify patients at risk. Wang *et al.* performed a very important, large randomized clinical trial comparing 8mm stents versus 10mm stents. **The data show that shunt insufficiency was similar between the groups but the risk of HE was significantly lower in the patients receiving the 8 mm stents compared with the**

patients receiving the 10 mm stents. The 47% risk reduction in the occurrence of HE argues strongly for the routine use of the 8mm shunts for TIPS.

HEPATOCELLULAR CARCINOMA (HCC)

Predicting microvascular invasion

Microvascular invasion (MVI) of HCC is a major risk factor for early recurrence within the first 2 years after curative treatment. Although macrovascular invasion can be frequently detected prior to surgery by complementary imaging modalities including computed tomography and magnetic resonance imaging, MVI can rarely be determined preoperatively because it is a histopathological diagnosis. It is therefore of great importance to identify preoperative imaging biomarkers for predicting MVI. Here, Lee *et al.* report the results of a study aimed to identify preoperative magnetic resonance imaging biomarkers for predicting MVI, determine their diagnostic performance, and evaluate whether they are associated with early recurrence after surgery for single HCC. **They reveal that a combination of two or more among arterial peritumoral enhancement, non-smooth tumor margin, and peritumoral hypointensity on hepatobiliary phase can be used as a preoperative imaging biomarker for predicting MVI with a specificity of more than 90%**. Combination of these criteria is associated with early recurrence after surgery of single HCC.

LIVER TRANSPLANTATION

Rationale for uncapping the MELD score

Assigning priority for liver transplantation using the MELD score has made the distribution of organs more equitable. However, the MELD score is capped at 40, which means that although the patients with a MELD score of more than 40 have a higher mortality, these patients do not have priority for liver transplantation. **Mitra *et al.* performed an important study using the data from the UNOS database and showed that the patients with a MELD score of more than 40 had a significantly higher risk of death within 30 days but the 1- and 3-year survival rates with transplantation were similar.** The data argue strongly for uncapping the MELD score.