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From the Editor's desk...

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SELECTION OF THE MONTH

In Memoriam: The Contributions of Thomas Earl Starzl (1926–2017)

Dr Thomas Starzl revolutionized the perception and management of end-stage organ failure through his pioneering work in organ transplantation. Numerous seminal advances, including techniques for immunosuppression and organ storage, can be attributed to him. Alongside these discoveries, he contributed to the understanding of many basic physiological pathways relevant to clinical development. He has had an immense impact in shaping healthcare and providing hope to patients with end-stage organ failure. His pioneering work has earned him the lifelong admiration and respect of surgeons and scientists alike.

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 triggered by acute infection with certain viruses have been shown to produce the anti-inflammatory cytokine interleukin (IL)-10 (a **class 2 a-helical cytokine**, whose initial name was cytokine synthesis inhibitory factor [CSIF]). 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

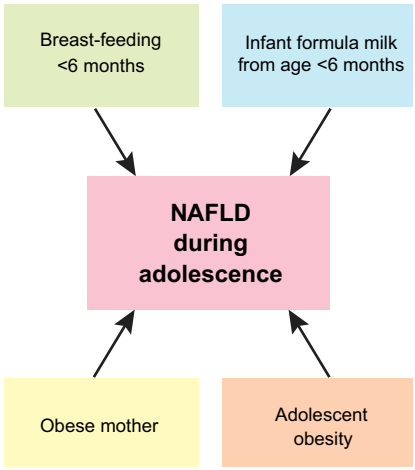
Accumulation of liver iron is an independent factor of survival and carcinogenesis in various chronic liver diseases. Mueller *et al.* evaluated the ability of a novel room-temperature susceptometer (RTS) to non-invasively assess liver iron concentration (LIC) in a prospective cohort of 264 patients 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 advanced alcoholic liver disease have a previous history of recurrent hospital admissions, representing missed opportunities for intervention. Westwood *et al.* screened hospital admissions to identify patients at increased 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 adolescence is increasing worldwide. Identifying early events leading to NAFLD increased



Ayonrinde *et al.* 2017
Infant nutrition and maternal obesity influence the risk of NAFLD in adolescents

risk is critical to implement 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. Breast-feeding 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 six months was associated with a higher prevalence and ultrasound severity of NAFLD. This relevant study suggests that **maternal obesity and early initiation of supplementary milk increases the risk of NAFLD in adolescence**.

Besides epidemiological studies, another paper in this issue investigated the methods of NAFLD diagnosis. 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/m^2 and F3-4 fibrosis. Importantly, **the validity of CAP for the diagnosis of fatty liver is 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 liver using the CAP technology.

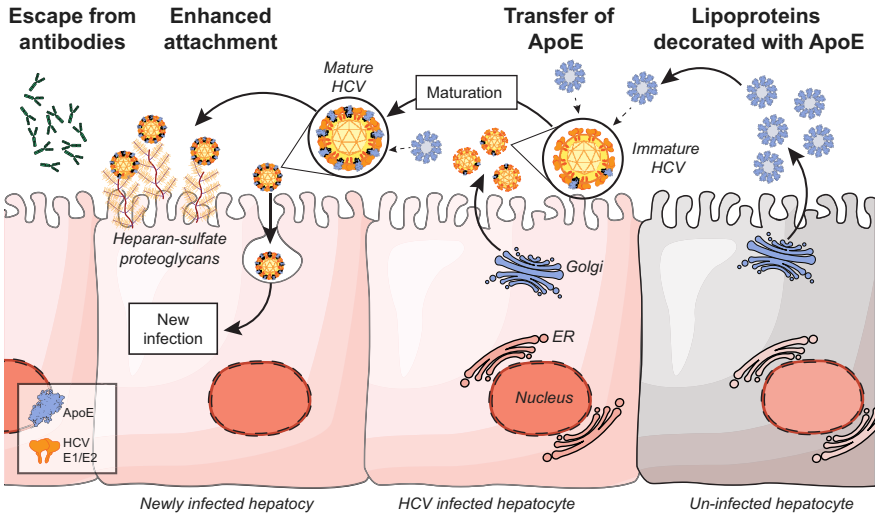
HEPATITIS C VIRUS (HCV) INFECTION

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 thoroughly 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 reduction 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. However, little is known about particle maturation processes outside of the virus producing cells, including their impact on 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 the protection from infection prior to seroconversion but also in the resolution of acute hepatitis C.



Bankwitz *et al.* 2017
Maturation of secreted HCV particles by incorporation secreted apoE protects from antibodies