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FINAL

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SELECTION OF THE MONTH

Big Title: A fatty liver leads to a broken heart

Small titles:

NGAL: A novel biomarker for ACLF

Deferring treatment increase HCV-associated mortality

FIBROSIS

In vivo monitoring of hepatic myofibroblasts

In vivo assessment of hepatic myofibroblasts would be useful for the diagnosis of fibrosis and evaluating the effects of anti-fibrotic therapies. Oakley *et al.* fluorescently labelled a single chain antibody (C1-3) that is known to bind hepatic myofibroblasts to

monitor fibrogenesis in vivo. They found that IVIS detection of fluorescently labelled-C1-3 but not a control antibody discriminates between fibrotic and non-fibrotic liver in acute and chronic liver fibrosis models. **These findings reveal a novel approach in the in vivo monitoring of pro-fibrotic cells.**

LIVER PROTECTION DEVICE

Gene- and cell-based therapy

Liver injuries result in decreased clearance bile acids and their subsequent spill over into the peripheral circulation where they can activate the G-protein coupled bile acid receptor 1 (also known as GPCR19 or BG37 and is encoded by *TGR5*). Engagement of GPCR19 initiates a variety of processes that are protective for the liver. Bai *et al.* developed a GPCR19-expressing liver-protection device that detected pathologic serum bile acid levels and produced therapeutic hepatocyte-growth factor levels that protected the animals from acute drug-induced liver failure. These important results demonstrate that **genetically engineered cells containing theranostic gene circuits which dynamically interface with host metabolism could provide novel opportunities for preventing liver diseases.**

NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic liver disease: relationship with atherosclerosis and identification of novel mechanisms

Whether steatosis is incidentally or causally associated with carotid atherosclerosis is a matter of intense debate. In this issue, Pais *et al.* conduced a large epidemiological study, including transversal and longitudinal cohorts, to address this question. In the transversal cohort, the authors found that **steatosis predicted carotid intima-media thickness** better than diabetes or dyslipidemia. In the longitudinal cohort (mean follow-up 8±4 years), **steatosis at baseline predicted carotid plaque occurrence**, independent of classical cardiovascular risk factors. This important study demonstrates that in patients with metabolic syndrome at risk for cardiovascular events, steatosis contributes to early atherosclerosis.

The development of novel targeted therapies for NAFLD is hampered by a poor knowledge of the cellular and molecular drivers. In this issue of the *Journal*, three studies have revealed important mechanisms of NAFLD that could represent new druggable targets for therapy. In the first study, Ntambi *et al.* demonstrated that

hepatic oleate, a monounsaturated fatty acid -MUFA-, regulates liver stress response partially through PGC-1α. MUFA are synthesized by the stearoyl-CoA desaturase (SCD) family of enzymes, during lipogenic dietary conditions. By using sophisticated dietary and genetic models in mice, the authors demonstrate an indispensable role of hepatic oleate in protection against lipogenic diet-induced hepatic injury, especially regarding the development on ER stress, and a crucial role for PGC-1α in this biological effect. In the second study, Li *et al.* studied the role of tumor necrosis factor receptor-associated factor 5 (TRAF5) regulating hepatic steatosis. In this translational study, TRAF5 expression was decreased in the fatty livers of both NAFLD patients and obese mice, and in palmitate-treated hepatocytes. Loss and gain-of-function studies in experimental models of NASH in mice demonstrated that **TRAF5 negatively regulates NASH and related metabolic dysfunctions by blocking JNK1 activity**, which represents a potential therapeutic target for obesity-related metabolic disorders. In the third study, coming from the same Institution as the second one, Li *et al* studied the role of Dickkopf-3 (DKK3), a protein belonging to the DKK family, in NAFLD. DKK3 expression was significantly decreased in the livers of NAFLD patients and of obese mice as well as in cultured hepatocytes stimulated with palmitate. Further experimental approaches showed that **DKK3 regulates insulin sensitivity and glucose tolerance as well as the inflammatory response in hepatocytes and in vivo**. The mechanisms underlying this effect involve with ASK1 and p38/JNK pathway. All these mechanistic studies have identified pathways that regulate the development of NAFLD and other metabolic condition as a response of a lipogenic diet.

GENETIC METABOLIC LIVER DISEASE

Iron overload in Tyrosisemia Type 1

In this issue, Bao *et al.* investigated disordered iron metabolism in a murine model of hereditary tyrosinemia type I (HT1), a disease of the tyrosine degradation pathway. The authors analyzed the status of iron accumulation in a murine model for HT1. Severe iron overload was observed in the murine model of HT1 with dramatically elevated hepatic and serum iron levels. Mechanistic studies revealed that downregulation and dysfunction of Tfr2 decreased hepcidin, leading to iron overload. Interestingly, low-iron food intake effectively reduced the iron deposits, protected the liver and prolonged the survival in these mice. This interesting study convincingly

demonstrates that **iron was severely overloaded in the HT1 mice via the Sp1/Tfr2/Hepcidin axis**. Maneuvers aimed at reducing iron accumulation could be potentially beneficial in patients with HT1.

HEPATITIS C VIRUS (HCV) INFECTION

Deferring treatment increase HCV-associated liver-related mortality, assessing patient-reported outcomes (PROs), treating HCV in patients under hemodialysis

Due to its high costs, treatment of chronic hepatitis C virus (HCV) infection is reimbursed in many countries only for those patients reaching advanced stages of disease. We do not know, however, if treatment can be safely deferred until advanced fibrosis stages without increasing the risk of liver-related complications. Zahnd *et al.* set out to estimate the impact of deferring HCV treatment on of liver-related complications in HIV/HCV co-infected individuals by using a model of liver disease progression and care with data from the Swiss HIV Cohort Study (SHCS) and the published literature. **The percentage of individuals who died of liver-related complications increased from 2% if treatment was initiated in stage F0 or F1 to 7%-22% if treatment was deferred until reaching fibrosis stages F3-F4.** The strategy to defer treatment also significantly increased the time spent with replicating HCV.

In line with these findings are the results of the study by Martin *et al.* who evaluated the optimal HCV treatment prioritization strategy for interferon-free HCV direct-acting antivirals by disease stage and risk status incorporating treatment of people who inject drugs (PWID). Their dynamic HCV transmission and progression model showed that **treating PWID with moderate or mild disease with direct acting antivirals is cost-effective compared to delay until cirrhosis**. From a public health prevention strategy perspective both studies highlighting the need for scaling-up HCV treatment in order to reduce population-based liver-related mortality as well as HCV prevalence and transmission – which is likely to happen only once the costs of therapy are reduced.

Treatment of chronic HCV infection may not only prevent hepatic disease progression but also improve patient-reported outcomes (PROs) such as health-related quality of life, fatigue, and work productivity, which have been shown to be significantly reduced in the HCV infected population. Younossi *et al.* assessed PROs with the new pan-genotypic regimen - sofosbuvir plus velpatasvir - in 624 patients as compared to the placebo-treated group (n=116). **Improvements in general health, emotional**

wellbeing, and all domains of Chronic Liver Disease Questionnaire were observed already 4 weeks after starting treatment, and continued to improve at the end of therapy and thereafter. The greatest PRO benefits related to SVR were seen in those patients with substantially more pre-treatment PRO impairments. In contrast, the only PRO that improved in patients receiving placebo was the worry domain. This comprehensive and placebo-controlled analysis shows the impact on patients' experience using validated instruments for assessment of patient-reported outcomes which is of significant importance when considering the effect of HCV treatment regimens.

Sofosbuvir represents a backbone for many direct antiviral regimens but little is known about the use of sofosbuvir-containing regimens in end-stage renal disease. Desnoyer *et al.* described the pharmacokinetics, safety and efficacy of 400 mg sofosbuvir given either daily or three times a week in 12 HCV-infected patients requiring hemodialysis. **Plasma concentrations of sofosbuvir or its inactive metabolite sofosbuvir-007 did not accumulate with either regimen between hemodialysis sessions** or throughout the treatment course. All patients receiving the daily regimen were cured, but two relapses occurred in the sofosbuvir three times daily group. Although the data speak for the safety and efficacy of the daily 400 mg sofosbuvir regimen in patients requiring hemodialysis, close clinical and drug monitoring especially for those having also advanced cirrhosis must be ensured until these findings are confirmed in larger trials.

HEPATITIS B VIRUS (HBV) INFECTION

Hepatitis B core-related antigen (HBcrAg) as HCC predictor in low-risk patients

Hepatitis B core-related antigen (HBcrAg) comprises HBV products of the precore/core gene and shares the first 149 amino acids of the hepatitis B core antigen. As serum HBcrAg may probably reflect transcriptional activity of the covalently closed circular HBV DNA (ccccDNA) it could be a useful novel biomarker for the prediction of disease activity, treatment response, and HCC development. In a large cohort of 1,031 patients with mild disease activity, and who were not treated with nucleos(t)ide analogues, Tada *et al.* analyzed HBV markers associated with the development of HCC. Independent predictors of HCC development were HBcrAg levels > 2.9 log U/mL and the presence of basal core promotor (BCP) mutations. **HBcrAg was superior to HBV DNA also in predicting HCC risk throughout the follow-up period by time-dependent ROC**

analysis. If confirmed by others, measuring HBcrAg may become an interesting tool to study HCC risk in low risk HBV-infected populations.

CIRRHOSIS

NGAL improves the prediction accuracy of the ACLF prognosis prediction models

Acute on chronic liver failure (ACLF) is a newly defined syndrome that occurs in cirrhotic patients with acute deterioration requiring hospital admission. The diagnosis of the syndrome is made using the CLIF organ failure scoring system and the prognosis of patients is made using the CLIF ACLF score, which is an aggregation of readily available clinical and biochemical data. **Ariza *et al.* use the data and samples from the CANONIC study and show that the addition of a measurement of urinary NGAL (neutrophil gelatinase-associated lipocalin), a marker of inflammation can significantly improve the performance of the currently available prognostic scores significantly.** These exciting data could be translated into clinical practice with further independent validation.

REGENERATION

CAR is a central regulator of hepatic regeneration

Recovery from liver resection is centrally dependent upon the ability of the liver to regenerate. The study from Tschuor *et al.* provides exciting new data describing the potential role of the nuclear receptor called nuclear receptor subfamily 1 group I member 3 (also known as constitutive androstane receptor, CAR; encoded by *NR1I3*) in mediating hepatic regeneration. **Through many excellent investigations in appropriate models, they showed for the first time that the lack of appropriate CAR activity reduces the ability of the liver to regenerate following hepatectomy.** They also show that using pharmacological strategies, enhancement of CAR could enhance hepatic regeneration providing a potential therapeutic target. The implications of this research to clinical practice could be enormous.