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SELECTION OF THE MONTH

Big Title: Gene therapy for Wilson's disease: A distinct possibility

Small titles,

Cirrhosis: Multi-parametric MRI: A novel prognostic tool

Phase 3b TURQUOISE-III trial

Sequestrating miRNA-122 by chimeric HBV integration transcripts

LIVER REGENERATION

Gsα drives liver regeneration, biliary cell-driven hepatocyte regeneration, role of the gut-liver axis, PP2A terminates liver regeneration

The stimulatory G protein α subunit (Gsα) participates in diverse cell processes and activates the cyclic AMP (cAMP)-dependent pathway by stimulating the production of cAMP. The role of Gsα in liver regeneration is poorly understood. Liu *et al.* addressed this question by using hepatocyte-specific Gsα gene knockout mouse. They now

show that **the growth factor signaling pathway which promotes hepatocyte proliferation depends on Gsα signaling.**

During liver regeneration, liver cells are derived from pre-existing hepatocytes. If hepatocyte proliferation is compromised, biliary epithelial cells (BECs) can become the source of new hepatocytes but the mechanisms of how this is regulated is unknown. The paper by Ko *et al.* points to **the important role of bromodomain and extraterminal (BET) proteins in driving biliary cell-driven hepatocyte regeneration** providing novel investigational and therapeutic targets.

Whether gut microbiota contributes to liver regeneration is unknown. Results by Liu *et al.* reveal that **intestinal microbiota is involved in gene expression in regenerating livers.** They also found that gene expression in these livers may be modulated by certain gut microbiome-derived bile acids.

Little is known on inhibitors and stop signals that regulate liver regeneration. Lai *et al.* investigated the role of *Ppp2cb* (*protein phosphatase 2 (formerly 2A), catalytic subunit, beta isoform,* encoding PP2Ac) by performing 70% partial hepatectomy in hepatocyte-specific *Ppp2cb*-deleted and wild-type mice. They found that **PP2Ac through the Akt/Gsk3β/cyclin D1 pathway, plays a crucial role in the termination of liver regeneration.**

HEPATOCELLULAR CARCINOMA (HCC)

Role of fatty synthase synthase in Akt-mediated hepatocarcinogenesis

Aberrant lipogenesis may play a role in HCC. This is why Li *et al.* investigated the oncogenic potential of fatty acid synthase (encoded by *Fasn*) in the mouse liver. **They show that fatty acid synthase overexpression is not oncogenic *per se* but is necessary for Akt-mediated cell survival oncogenesis.** They found that fatty acid synthase activates Akt via the stimulation of the mammalian target of rapamycin complex 2 (known as mTORC2). The target for fatty acid synthase seems to be the rapamycin-insensitive companion of mTOR (known as RICTOR). Finally they show results suggesting that **pharmacological blockade of fatty acid synthase is a promising approach for human HCC characterized by the activation of pro-survival AKT.**

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Methionine and SAMe and steatosis, GLP-1 analogues in NASH, central obesity

and non-cirrhotic portal-vein thrombosis

Autophagy plays a critical role in lipid catabolism (lipophagy), and defects in autophagy have been related to liver steatosis development. Since methionine and its metabolite S-adenosylmethionine (SAMe) are well known inactivators of autophagy, Zubiete-Franco *et al.* aimed to examine whether high levels of both metabolites could block autophagy-mediated lipid catabolism. By performing elegant human and experimental studies, the authors demonstrate that **elevated levels of methionine and SAMe can inhibit autophagic catabolism of lipids contributing to liver steatosis in mice and humans**.

GLP-1 (Glucagon-like peptide-1) analogues are useful for patients with type 2 diabetes, but no prospective experimental data exists in NASH. Armstrong *et al.* determined the effect of a long-acting GLP-1 analogue, liraglutide, on organ-specific insulin sensitivity, hepatic lipid handling and adipose dysfunction in biopsy-proven NASH. They randomized 14 patients with NASH to receive either liraglutide or placebo for 12-weeks. **Liraglutide reduced metabolic dysfunction, insulin resistance and lipotoxicity** in the key metabolic organs in the pathogenesis of NASH. This study strongly suggests that liraglutide may offer the potential for a disease modifying intervention in NASH.

Almost half of patients with non-cirrhotic portal vein thrombosis (PVT) do not have a clear predisposing factor, so they are considered idiopathic. Bureau *et al.* studied a series of patients with PVT and found that **patients with idiopathic thrombosis have more frequently metabolic syndrome and central obesity** than patients with a known predisposing factor. These results confirm previous studies showing that patient with fatty liver diseases and obesity are predisposed to develop PVT. Overall, these studies suggest that obesity and the resulting metabolic syndrome have prothrombotic effects and predispose to PVT.

GENETIC METABOLIC DISEASES.

Gene therapy for Wilson disease

Current treatments for Wilson Disease (WD) are based on lifelong copper chelating drugs, which may cause side effects and do not restore normal copper metabolism. In this work, Murillo *et al.* assessed the efficacy of gene therapy by transducing the liver of the *Atp7b*$^{-/-}$ WD mouse model with an adenovirus encoding the human *ATP7B* cDNA. They observed a **dose-dependent therapeutic effect of the gene therapy**

approach manifested by the reduction of serum transaminases and urinary copper excretion, normalization of serum holoceruloplasmin, and restoration of physiological biliary copper excretion in response to copper overload. The liver of treated animals showed normalization of copper content and absence of histological alterations. These promising preclinical studies highlight that potential of gene therapy to treat patients with WD.

HEPATITIS C

Phase 3b TURQUOISE-III trial, effectiveness of polymerase inhibitor-free dual DAA combination

Getting rid of ribavirin as part of all oral direct-acting antiviral (DAA) regimens represents a next important step in the global antiviral strategy implementing safe and easy-to-use treatment regimens aiming to eradicate hepatitis C virus (HCV) infection. While in patients with easy-to-treat characteristics adding ribavirin is not beneficial concerning antiviral response rates, its use is still recommended in more difficult-to-treat patients with cirrhosis. In the single arm phase IIIb study (Turquoise-III), Feld *et al.* demonstrated, however, that **a 12 week ribavirin-free 3D regimen consisting of ombitasvir, ritonavir-boostered paritaprevir and dasabuvir cured all 60 patients with HCV subtype 1b-induced compensated cirrhosis.** Thus, the “ribavegan” 3D regimen can be given safely without sacrificing efficacy in compensated cirrhosis induced by HCV subtype 1b infection but should not be used in patients with subtype 1a infection or a decompensated stage of the disease.

Nucleosidic polymerase inhibitors (NUC) are an important backbone of interferon-free dual DAA regimens due to their high antiviral efficacy and high barrier to resistance, and are mainly used either in combination with an NS5A or protease inhibitor. However, whether a NUC-free dual regimen containing a first generation protease inhibitor plus NS5A inhibitor may represent an equally effective approach has not been widely studied in Caucasian patients. The phase II study by Zeuzem *et al.* is the first, evaluating the efficacy and safety of the combination of simeprevir (SMV) plus daclatasvir (DCV) when given for either 12 or 24 weeks with or without ribavirin in HCV subtype 1a or 1b responder as well as non-responder patients to previous interferon-containing regimens. **The overall response to the SMV plus DCV regimen was variable in the different subgroups (67-95%), and less robust as compared to NUC-containing dual, or non-NUC containing triple combinations**. Altogether, the

results of this study together with more recent findings describing single virologic breakthroughs under SMV plus DAC therapy do not support further evaluation of this regimen.

HEPATITIS B

Cleaved c-FLIP mediates TNF-α-induced HBV suppression, sequestrating miRNA-122 by chimeric HBV integration transcripts – a new model for HBV-induced hepatocarcinogenesis

Reactivation of hepatitis B virus (HBV) infection have been observed in patients taking tumor necrosis factor alfa (TNF-α) blocking agents indicating a significant role of this cytokine in HBV replication control. TNF-α inhibits HBV replication in cell culture models, but the molecular mechanism and the downstream effector molecules involved its inhibitory action remain poorly understood. Park *et al.* were now able to demonstrate in an elegant study that **p22-FLIP, a newly discovered anti-apoptotic cellular FLICE-inhibitory protein (c-FLIP) cleavage product, is generated by TNF-α/NF-κB signaling pathway and strongly represses HBV replication** at the transcriptional level through dysregulation of hepatocyte nuclear factors. The description of a novel function of p22-FLIP as a natural inhibitor of HBV infection, provides a novel mechanism by which TNF-α suppresses HBV non-cytolytically, and may open up new options for controlling HBV infection.

HBV exerts its well established oncogenic potential by both direct as well as indirect mechanisms. However, HBV integration into the host genome represents most likely a key in the malignant transformation of the hepatocyte into liver cancer cells which occurs not randomly but rather within or near-repetitive, noncoding sequences, such as long interspersed nuclear elements (LINEs) and short interspersed nuclear elements (SINEs). Liang *et al.* describes for the first time that **a HBV-human chimeric transcript, HBx-LINE1, possesses six binding sites for miR-122, and thus serves as a molecular sponge to sequester cellular miR-122**, the most abundant liver-specific miRNA which serves as a tumor suppressor and have been shown to be markedly decreased in HBV-infected liver cells and HBV-positive HCC tissues. The elegant study describes a novel mechanism by which HBV modulates hepatic cell function potentially involved in hepatocarcinogenic transformation.

IMAGING

The Liver inflammation and Fibrosis score

Rapid advances in technology have contributed to huge improvements in imaging. Pavlides *et al.* **use simultaneous assessment of fibrosis, steatosis and iron using MRI scanning to define a novel prognostic score, the Liver inflammation and Fibrosis score (LIFs)** and show its utility in predicting clinical outcomes in patients with chronic liver disease accurately. Further validation in large cohort will lead to an exciting new tool for prognostication.