Should We Sweat the Small Stuff in HBV?

Yecheskel Schneider* and Robert S. Brown, Jr.

Treatment of chronic hepatitis B virus (HBV) has the potential to decrease the incidence of hepatocellular carcinoma (HCC). Some patients on therapy may develop persistent or intermittent low-level (<2,000 IU/mL) HBV viremia (LLV), but its significance is not well understood. Kim et al. conducted a retrospective cohort study to evaluate the clinical significance of LLV after achieving a negative viral load. A retrospective cohort of 875 treatment-naïve patients on entecavir monotherapy were followed for the development of HCC. HCC developed more frequently in those with LLV, compared to those with persistently undetectable HBV DNA. This difference was over 2-fold higher and was significant in patients with cirrhosis, but not in patients without cirrhosis. This suggests that LLV may have clinical implications, and more data are needed to guide clinical practice. (HEPATOLOGY 2017;66:335-343)

Ledipasvir-Sofosbuvir—A New “Treat” for Children With Hepatitis C?

Yecheskel Schneider* and Robert S. Brown, Jr.

Despite recent advancements in all-oral hepatitis C virus (HCV) therapies, no such regimen is approved for use in children. In this phase 2 open-label study, Balistreri et al. evaluated the safety, efficacy, and pharmacokinetics of ledipasvir-sofosbuvir for adolescents (12-17 years old) with genotype 1 chronic HCV. One hundred participants received the medication for 12 weeks, and 10 patients underwent pharmacokinetics evaluation. Ninety-eight percent of participants reached sustained virological response (SVR) at 12 weeks with no virological failures and there were no serious adverse events. Pharmacokinetics showed higher serum levels of sofosbuvir and ledipasvir, but less than 200%, and was considered comparable to the pharmacokinetics in adults. Although the higher drug levels need further study in smaller children and those with cirrhosis, this important study opens the door for children to benefit from the therapeutic advances for HCV. (HEPATOLOGY 2017;66:371-378)

What Lies Beneath the Surface in HBV Reactivation

Monica Saumoy* and Robert S. Brown, Jr.

HBV reactivation is well documented with immunosuppressive chemotherapy for hematological malignancies, particularly with rituximab, even in those that are HBV surface antigen negative. However, it is unclear whether hepatitis B surface (anti–HBs) is protective compared to those with isolated core (anti–HBc) antibody. Paul et al. conducted a meta-analysis of 20 studies involving 1,672 patients with hematological malignancies, who did not receive HBV prophylaxis. Reactivation risk was 14% in patients with only anti-HBc and decreased to 5% in patients who also had anti–HBs. Anti–HBs, compared with anti–HBc, reduced reactivation risk with a pooled odds ratio of 0.21 (95% confidence interval, 0.14-0.32), and this was also observed in the lymphoma and rituximab-only subgroups. The investigators suggest that patients without anti–HBs are at higher risk for HBV reactivation, but that all should likely receive prophylaxis, at least with rituximab-based therapy. (HEPATOLOGY 2017;66:379-388)
Treating the Untreatable in Hepatitis C

Monica Saumoy* and Robert S. Brown, Jr.

There are highly effective regimens of direct-acting antivirals (DAAs) for HCV therapy, but there are limited options for those with virological failure to a DAA regimen. Poordad et al. performed a phase 2, open-label trial (Magellan-1) with 12 weeks of glecaprevir (GLE), and pibrentasvir (PIB), new pan-genotypic protease inhibitor and nonstructural (NS) 5A inhibitor, respectively, with or without ribavirin for 50 HCV genotype 1 patients without cirrhosis with previous virological failure to a variety of DAA regimens, including protease inhibitors, nucleotides, and NS5A inhibitors. SVR at 12 weeks was observed in almost all patients (from 86% to 100%) with only two virological failures and minimal drug-related adverse events. Adding ribavirin did not improve SVR. The investigators conclude that 12 weeks of GLE plus PIB is a potential option for these hard-to-treat patients. (HEPATOLOGY 2017;66:389-397)

Regulating the HBV Engine, PRMT5 on the Brake

Robert E. Schwartz

Chronic HBV infection is a major global health problem. The HBV-DNA minichromosome (cccDNA) serves as the template for viral RNA transcription and plays a key role in HBV persistence. Several studies have shown that cccDNA transcription is epigenetically regulated by posttranslational modifications of histones. In this report, Zhang et al. screened a series of methyltransferases and demethylases and identified that protein arginine methyltransferase 5 (PRMT5) restricts HBV transcription and replication. Overall, they show that PRMT5 represses HBV replication by two mechanisms. They find that PRMT5 regulates methylation on cccDNA-bound histone-4, which results in repression of cccDNA transcription. Moreover, they find that PRMT5 inhibits HBV core DNA production by preventing pregenomic RNA encapsidation. These results suggest new therapeutic targets for impacting the HBV virus and life cycle. (HEPATOLOGY 2017;66:398-415)

New Insights Into Energy Homeostasis

Yecheskel Schneider* and Robert E. Schwartz

Farnesoid X receptor (FXR) and small heterodimer partner (SHP) are nuclear receptors involved in bile acid homeostasis. Previous work has shown that loss of both FXR and SHP signaling (DKO) results in severe cholestasis and hepatic injury. These nuclear receptors have also been suggested to regulate glucose and fatty acid homeostasis. Kim et al. found that DKO in aged mice suppressed weight gain and adiposity. Liver-specific FXR and SHP double knockout mice were phenotypically like DKO mice and, notably, had improved insulin tolerance and accelerated fatty acid utilization. Further evaluation revealed that the loss of hepatic FXR and SHP altered white and brown adipose tissue to increase fatty acid utilization and suggest that FXR/SHP may play a more expanded role in whole-body energy homeostasis than previously thought. (HEPATOLOGY 2017;66:498-509)

Fibrosis, in the Nerves?

Vikas Gupta* and Robert E. Schwartz

Neuropeptides are short-chain polypeptides that serve as mediators of neuronal signaling, but are also secreted by various cell types. Substance P (SP) is a neuropeptide appreciated for its role in neurogenic inflammation; however, it has also been described in the pathogenesis of many disease states. In this issue, Wan et al. find that SP, and its receptor neurokinin-1 receptor (NK-1R), are important players in cholestatic-mediated liver fibrosis. They show that NK-1R is expressed on hepatic stellate cells (HSCs) and levels of SP are increased in cholestatic injury. The group blocked SP signaling using NK-1R knockout mice or small molecules and found reduced liver fibrosis and enhanced senescence of HSCs. Importantly, hepatic and serum samples from patients with primary sclerosing cholangitis (PSC) displayed elevated levels of SP and NK-1R. This work suggests the SP/NK-1R axis as a potential therapeutic target in PSC. (HEPATOLOGY 2017;66:528-541)
Fut2: A PSC Risk Factor
Gene Causes Liver Disease in Mice

Monica Saumoy* and Robert E. Schwartz

Previous genome-wide association studies have identified genetic variants of fucosyltransferase 2 (FUT2) as a risk factor for PSC. Maroni et al. investigated the biliary and vascular phenotypes of Fut2–/– mice. Fut2–/– mice were viable, but 50% of Fut2–/– mice were found to have significantly elevated serum bile salt levels (Fut2–/–high), whereas the remainder had normal bile salt levels (Fut–/–low). Fut2–/– mice appeared normal with normal serum liver tests, bile flow, biliary bile salt secretion, and fecal bile salt loss, indicating that the elevated bile salts in Fut2–/–high mice were not explained by cholestasis. Histomorphological evaluation showed that Fut2–/–high mice had congenital portosystemic shunts associated with periductal fibrosis and were highly sensitive to hepatobiliary damage when exposed to human hydrophilic bile salt. This is the first experimental evidence that inactivation of FUT2 affects hepatic anatomy/physiology. (HEPATOLOGY 2017;66:542-554)

Only the Strong Survive

Russell Rosenblatt* and Robert S. Brown, Jr.

Although the Model for End-Stage Liver Disease (MELD) and now MELD-Na score have been the gold standard for predicting liver transplant waitlist mortality, the physical assessment of patients with cirrhosis has always been lacking from the score. Given that frailty significantly affects the outcomes of patients with cirrhosis, Lai et al. created a Frailty Index as an adjunct to the MELD-Na score to improve the ability to predict waitlist mortality. The Frailty Index, comprising grip strength, chair stands, and balance, was developed in 536 waitlisted patients at a single center, and was able to reclassify 19% of patients, who were at high risk of mortality when added to MELD-Na. If validated, the Frailty Index could objectively measure frailty and, when added to the MELD-Na, enhance prediction of waitlist mortality in patients with cirrhosis. (HEPATOLOGY 2017;66:564-574)

MicroRNAs Impact the Show in ETOH Injury

Russell Rosenblatt* and Robert E. Schwartz

Kupffer cells increase inflammatory signals in patients with alcoholic liver disease. In a study by Saikia et al., Toll-like receptor 4 (TLR-4)-mediated signaling in Kupffer cells was evaluated between rats exposed to ethanol after treatment with a hyaluronic acid of ~35 kD (HA35), which normalized TLR-4 signaling ex vivo. Next-generation sequencing of microRNAs identified miR181b-3p, which was impacted by both ethanol and HA35. Importin α5, involved in translocation of p65 to the nucleus, was a target of miR181b-3p. In a mouse model of alcoholic liver disease, ethanol decreased miR181b-3p in the liver, resulting in increased importin α5 expression, which was reversed by HA35 and protected mice from further injury. Therefore the miR181b-3p/importin-α5 axis may represent a new and novel therapeutic target for alcohol-induced liver injury and alcoholic liver disease in general. (HEPATOLOGY 2017;66:602-615)