Welcome to the fifteenth issue of Hepatitis Research Review.

Experiments using hepatitis B virus (HBV)-infected human liver chimeric mice have revealed that HBV infection alters the bile acid metabolism gene profile. The study authors note that this link underlines the importance to exploit further metabolic pathways, and it may lead to the discovery of new therapeutic possibilities.

Another study reports finding a virulent mutation in the hepatitis E virus (HEV) genome that contributes to increased HEV replication and may explain why ribavirin treatment failures occur. The study authors suggest ribavirin dosage may need to be increased or administered for a longer duration, to effectively eradicate this virulent mutation.

I hope you enjoy the selection in this issue and I welcome your comments and feedback.

Professor Stephen Riordan
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Binding of hepatitis B virus to its cellular receptor alters the expression profile of genes of bile acid metabolism

Authors: Oehler N et al.

Summary: This investigation into the effects of HBV upon the liver metabolic profile used HBV-infected and uninfected human liver chimeric mice. Compared with uninfected controls, HBV-infected animals exhibited modest changes in lipid metabolism and significantly elevated human cholesterol 7α-hydroxylase (human \([h]CYP7A1\); median 12-fold induction; \(p<0.0001\)), the rate-limiting enzyme promoting the conversion of cholesterol to bile acids, and of genes involved in transcriptional regulation, biosynthesis, and uptake of cholesterol (human sterol-regulatory element-binding protein 2, human 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and human LDL receptor). These changes were validated by liver biopsy samples obtained from patients with chronic HBV, which demonstrated significant \([h]CYP7A1\) induction and reduction of human small heterodimer partner, the corepressor of \([h]CYP7A1\) transcription. A comparable murine \([h]CYP7A1\) induction was observed after uninfected mice were administered Myrcludex-B, an entry inhibitor derived from the pre-S1 domain of the HBV envelope, thus providing evidence for the pre-S1 domain as the viral component triggering such metabolic alterations.

Comment: The identification of the sodium/taurocholate co-transporter polypeptide (NTCP), located on the basolateral plasma membrane of hepatocytes, as an entry receptor for HBV, consequent to binding by the pre-S domain of the HBV envelope protein, represents an important advance in our understanding of the pathogenesis of HBV. In this study, Oehler et al. use human liver-chimeric immunodeficient mice to demonstrate that HBV infection alters bile acid and cholesterol metabolism due to impaired bile acid uptake. The full clinical implications of this phenomenon and to what extent it may be exploited in future by host-targeted antiviral therapies remain to be determined.

Reference: Hepatology. 2014;60(5):1483-93

Abstract

Abbreviations used in this review:
- CCRK = cell cycle-related kinase
- HBV = hepatitis B virus
- HCC = hepatocellular carcinoma
- HCV = hepatitis C virus
- HEV = hepatitis E virus
- IFN = interferon
- PegIFN = pegylated interferon
- SVR = sustained virological response
- TE = transient elastography
- TGF = transforming growth factor
- Tregs = regulatory T cells

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**Human OX40 tunes the function of regulatory T cells in tumor and nontumor areas of hepatitis C virus-infected liver tissue**

Authors: Piconese S et al.

Summary: This paper describes how regulatory T cells (Tregs) differ by phenotype and function according to distinct microenvironmental signals within the same organ (liver) derived from patients with chronic hepatitis C virus (HCV). Whereas cirrhotic and tumour fragments were moderately and highly infiltrated by Tregs, respectively, expressing OX40 and a T-bet**

**Comment**: Tregs are important for the maintenance of immunological homeostasis. This study identifies key differences in the phenotype and function of intrahepatic Tregs in the settings of hepatitis C virus (HCV)-related chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). In particular, a suppressive (Th1-suppressing) subset of Tregs was identified in cirrhosis and HCC, while a more inflammatory, γ-interferon-producing subset was found to predominate in non-cirrhotic chronic hepatitis. The study is important in that it represents the first analysis of the functional complexity of intrahepatic Tregs within diverse tissue microenvironments. The data suggest that a cirrhotic microenvironment favours the recruitment of Tregs that promote immune tolerance and, eventually, oncogenesis, while Tregs recruited to an inflammatory environment serve to amplify the inflammatory response.


**Abstract**

**Independent commentary by Professor Stephen Riordan**, Senior Staff Specialist, Gastrointestinal and Liver Unit, Prince of Wales Hospital and Conjoint Professor of Medicine, University of New South Wales, Sydney.

**Impaired interferon signaling in chronic hepatitis C patients with advanced fibrosis via the transforming growth factor beta signaling pathway**

Authors: Shirasaki T et al.

Summary: Outcomes are discussed from in vitro and in vivo investigations into the effects of transforming growth factor (TGF)-β signalling on IFN signalling and HCV replication. Expression levels of forkhead box O3A (Foxo3a), suppressor of cytokine signalling 3 (Socs3), c-Jun, activating transcription factor 2, ras homologue enriched in brain, and mammalian target of rapamycin complex 1 (mTORC1) were examined in Huh-7.5 cells and findings were confirmed in liver tissue samples obtained from 91 patients with chronic HCV treated with pegylated-IFN and ribavirin combination therapy.

Comment: The mechanisms by which the virological response to IFN-based anti-HCV treatments is reduced in patients with advanced liver fibrosis are yet to be fully elucidated. In this study, Shirasaki et al. investigated the potential interaction between profibrotic TGF-β and IFN signalling within the liver in patients with chronic HCV infection. TGF-β was found to inhibit intrahepatic IFN signalling, particularly in the setting of the treatment-resistant IL28B genotype. Inhibition of TGF-β signalling by use of a TGF-β receptor inhibitor both improved intrahepatic IFN signalling and augmented boceprevir-related inhibition of HCV replication. Supplementation with branched chain amino acids (BCAAs) was also found to inhibit TGF-β signalling, improve IFN signalling and potentiate the anti-HCV effect of boceprevir. Future studies will be required to stratify the clinical impact of TGF-β inhibition and BCAA supplementation on current and evolving anti-HCV therapies.


**Abstract**
**Cell cycle-related kinase mediates viral-host signalling to promote hepatitis B virus-associated hepatocarcinogenesis**

Authors: Yu Z et al.

Summary: These researchers sought to determine the molecular function of cell cycle-related kinase (CCKR) in HBV-associated HCC. In HBV X protein (HBx) transgenic mice, overexpression of CCKR, but not its kinase-defective mutant, activated β-catenin/TCF transcription factor signalling through phosphorylation of glycogen synthase kinase-3β (GSK-3β) at Ser9, led to up-regulation of androgen receptor (AR) transcriptional activity and, subsequently, expression of HBx. The viral transactivator in turn induced CCKR expression through enhanced AR signalling, forming a positive regulatory loop. RNA interference silencing of CCKR suppressed the CCKR/GSK-3β-β-catenin/AR regulatory loop, significantly suppressed HBx-induced hepatocellular proliferation (p<0.001) and transformation (p<0.01), and reduced dihydrotestosterone-mediated hepatocarcinogenesis (p=0.80) in HBx transgenic mice. Patients with HBV-associated HCC with concordant overexpression of CCKR, GSK-3β phosphorylation at Ser9, active dephosphorylated β-catenin and AR phosphorylation at Ser81, had poorer overall (HR 31.26; p<0.0001) and disease-free (HR 3.60; p<0.01) survival rates.

**Reference:** Gut. 2014;63(11):1793-804

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**Sustained virological response with telaprevir in 1078 patients with advanced hepatitis C: The international telaprevir access program**

Authors: Colombo M et al.

Summary: The telaprevir early access program (Hep3002) recruited 1078 patients who had bridging fibrosis (n=552) or cirrhosis (n=526) due to HCV genotype 1 (GT1), compensated bone marrow (neutrophils>1500/mm³, Hb>12/13 g/dL) and liver function (albumin>3.5 g/dL, platelets>90,000/mL), and were treated with telaprevir, pegIFN and ribavirin for 12 weeks, followed by pegIFN/ribavirin alone for an additional 12 or 36 weeks (based on treatment response).

In an intention-to-treat analysis, 614 patients (57%) achieved an SVR at week 24 (SVR24). SVR24 rates were 68% in 221 treatment-naïve patients (62.8% F4), 72% in 356 prior relapsers (64.4% F4), 55% in 139 partial responders (63.2% F4), and 34% in 294 null responders (28.6% F4). The SVR24 rate to response-guided therapy (24 weeks treatment duration if undetectable virusia at weeks 4 and 12) was 84% in 222 naive/relapse F3 patients.

**Reference: J Hepatol. 2014;61(3):976-83**

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**A mutation in the hepatitis E virus RNA polymerase promotes its replication and associates with ribavirin treatment failure in organ transplant recipients**

Authors: Debing Y et al.

Summary: These researchers examined the blood samples of 15 solid organ recipients with chronic hepatitis E virus (HEV) infection who were treated with ribavirin. Two patients did not respond to treatment and 1 of them died. A G1634R mutation in viral polymerase was detected in the HEV RNA of both nonresponders; this mutation did not result in viral resistance to ribavirin in vitro. However, the mutant form of a subgenomic replicon of HEV GT3 replicated more efficiently in vitro than HEV without this mutation, and the same was true for infectious virus, including in competition assays. Similar results were obtained for HEV GT1.


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**Relationship of vitamin D status with advanced liver fibrosis and response to hepatitis C virus therapy: A meta-analysis**

Authors: Garcia-Alvare M et al.

Summary: This meta-analysis included data from 14 studies published up to April 2014 that assessed the relationship of plasma/serum vitamin D levels with advanced liver fibrosis (ALF) and/or sustained virological response (SVR) in treatment-naïve patients with chronic HCV (CHC) and in CHC patients receiving pegylated IFNα/ribavirin therapy. Seven studies assessed ALF (n=2,672). For liver fibrosis, low vitamin D status was related to a significant associations between vitamin D deficiency/insufficiency and a reduced likelihood of achieving an SVR to pegIFN/ribavirin therapy. Seven studies assessed ALF (n=1,083) and 11 assessed SVR (n=3,656). Both vitamin D deficiency and insufficiency were associated with increased odds of ALF and/or SVR failure. A meta-analysis, performed in patients with chronic HCV infection, adds to an earlier analysis of literature to March 2012. The analysis found the efficacy of vitamin D supplementation to improve SVR rates and a reduced likelihood of achieving an SVR to pegIFN therapy. These findings suggest that future strategies to specifically inhibit CCKR may have therapeutic value against HCC in patients with HEV infection.

**Reference: Hepatology. 2014;60(5):1531-40**

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**Growing evidence points to an association between vitamin D status and chronic HCV infection, including that related to chronic HCV infection, exposure of the vitamin D receptor in the liver is reduced in patients with more histologically advanced chronic hepatitis C, while vitamin D has antifibrotic effects on the liver. This meta-analysis, performed in patients with chronic HCV infection, adds to an earlier analysis of literature to March 2012. The analysis found significant associations between vitamin D deficiency/insufficiency and a reduced likelihood of achieving an SVR to pegIFN/ribavirin therapy. The findings provide rationale for further trials investigating the efficacy of vitamin D supplementation to improve SVR rates in vitamin D-deficient/insufficient HCV patients, especially as the results of a relatively small number of such analyses performed to date are conflicting.


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**Callender B et al.**

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Daclatasvir-like inhibitors of NS5A block early biogenesis of hepatitis C virus-induced membranous replication factories, independent of RNA replication

Authors: Berger C et al.
Summary: This paper demonstrates that a potent daclatasvir-like non-structural protein 5A (NS5A) inhibitor abrogates formation of the membranous web, the presumed replication site of HCV.

Comment: This important study, elegantly and comprehensively reviewed in an accompanying Editorial, sheds new light on the hitherto uncertain mechanism of action of NS5A inhibitors, a particularly potent class of anti-HCV agents. The authors convincingly demonstrate that these agents prevent the formation of the “membranous web” in which HCV viral replication occurs. Disruption of the development of this virus-induced replication factory, a central element facilitating replication of all plus-strand RNA viruses, is a novel effect that likely constitutes a major mode of action of this class of antiviral drugs.


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Staging chronic hepatitis B into seven categories, defining inactive carriers and assessing treatment impact using a fibrosis biomarker (FibroTest®) and elastography (FibroScan®)

Authors: Poynard T et al.
Summary: This study pooled 10-year updated individual data of 1434 patients with chronic HBV from two prospective cohorts. The purpose of this investigation was firstly to extend the validation of FibroTest® (FT) and transient elastography (TE) as markers of occurrence of cirrhosis without complications (F4.1), oesophageal varices (F4.2), and severe complications (F4.3) in patients with chronic HBV. Secondly, it aimed to validate a previous definition of an inactive carrier based on normal FT and ActiTest® (normal-FT-AT). Thirdly, it evaluated the long-term dynamics of fibrosis in patients with SVR. Among 1312 patients without a history of complications, varices had occurred after 10 years in 14 patients (F4.2, incidence of 1.7%), and severe complications in 25 (F4.3, incidence of 3.7%), including HCC in 21 (3.7%). In Cox multivariate analyses adjusted for treatment, viral load, HBeAg status and ALT, FT and TE were both predictive of liver complications (AUROCs of 0.83 and 0.82, respectively; p<0.0001 for both). For both cohorts of patients, normal FT-AT performed better than the ALT-based standard definition in the identification of patients with lower fibrosis progression.

Comment: This study, based on a larger patient cohort and longer follow-up than previous reports, assesses the performance of a fibrosis biomarker test (FibroTest®, FT) and elastography for predicting various clinical end-points in patients with chronic HBV infection. Perhaps the most interesting analysis involves the ability of the FibroTest® to identify HBV “inactive carriers”. FT was found to be more accurate than consideration of the ALT level in identifying patients not at risk of fibrosis progression, with, in particular, a FT score ≤0.27 imparting a better negative predictive value than a serum ALT level persistently ≤40 IU/mL. The validation of FT as a robust means of accurately identifying “inactive carriers”, as suggested by this study, would both simplify and improve current clinical decision making.


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