Editorial Desk

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From the Editor's desk...

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SELECTION OF THE MONTH

Urgent need to increase awareness and screening programs for HCV infection

Reliable data about the population-based prevalence of hepatitis C virus (HCV)-induced cirrhosis are unavailable for most countries. Udompap *et al.* addressed this question by determining the cirrhosis prevalence using the National Health and Nutrition Examination Survey (NHANES), which contains a population generalizable to the entire United States households. The authors also raised the important question of whether awareness of the infection impacts cirrhosis prevalence. While the overall prevalence of HCV infection has decreased over time from 1.5% in 1988-94 (Era 1), to 1.2% in 1999–2006 (Era 2), and then to 1.0 in 2007–12 (Era 3), the proportion of HCV patients with cirrhosis has more than doubled during the study period reaching 17% in the latest era. **Most importantly, cirrhosis prevalence in patients unaware of their infection was as high as in those with established HCV diagnosis.** The study emphasizes the need for implementing HCV awareness and screening programs for primary prevention of cirrhosis and its complication.

LIVER INFLAMMATION

IL-23/IL-17 axis makes liver immunopathology, biliary epithelium surveillance by Mucosal-Associated Invariant T (MAIT) cells

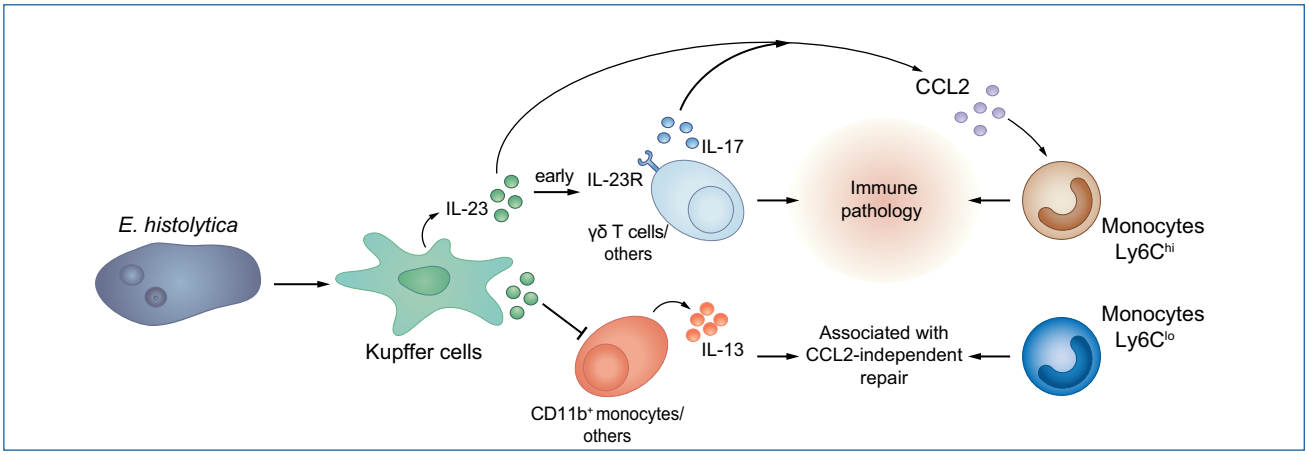
Excessive type 1 immune responses, for example those involving the interleukin (IL)-23/IL-17 axis, contribute to immunopathology in the context of auto-immune diseases. Noll *et al.* now show that **the IL-23/IL-17 axis plays a crucial role in the immunopathology of hepatic amebiasis.** They also find that $CD^{11b+}Ly6C^{low}$ monocytes may contribute to liver repair via the secretion of IL-13 (a cytokine of the type 2 immunity). These findings suggest that stimulation of IL-13 signaling may improve liver damage caused by the engagement of the IL-23/IL-17 axis.

Mucosal-Associated Invariant T (MAIT) cells are innate-like T cells characterized by the invariant TCR-chain, Vα7.2-Jα33, and are restricted by the major histocompatibility complex class I-related gene protein (encoded by *MR1*), which is an antigen-presenting molecule specialized in presenting microbial vitamin B metabolites. MAIT cells play a crucial role in antibacterial immunity of different mucosa but their role in the biliary epithelium defense is unknown. Here Jeffery *et al.* show evidence of an **immune surveillance effector response for intra-hepatic MAIT cells toward biliary epithelial cells in the human liver.** MAIT cell usage may be a novel approach in the treatment of biliary diseases.

LIVER REGENERATION

A matter of TNF and TNF receptor superfamilies

Tumor necrosis factor (TNF) receptor (TNFR) superfamily member 3 (also known as



Noll *et al.* 2016

lymphotoxin B receptor) which is encoded by *Ltbr* (alias *Tnfrsf3*) is known to be involved in liver regeneration in response to injury. The receptor binds different members of the TNF ligand superfamily, including lymphotoxin-alpha and –beta, and tumor necrosis factor ligand superfamily member 14 (also known as Light). Sorg *et al.*, using a model of liver regeneration in genetically modified mice reveal that **lymphotoxin β receptor is essential for effective liver regeneration and cooperates with TNFR superfamily member 1A (also known as p55, and encoded by *Tnfrsf1a*) in this process. p55 receptor recognizes lymphotoxin-alpha and the soluble form of TNFα.** Together these findings suggest that inhibition of TNF signaling may be harmful in the context of liver regeneration.

HEPATOCELLULAR CARCINOMA (HCC)

Effect of salt-inducible kinase 1 (*SIK1*) silencing, diagnostic criteria for HCC ⩽3 cm, a trial of sorafenib plus DEB-TACE

SIK1 encodes the serine/threonine-protein kinase SIK1 which is known to be involved in various processes such as cell cycle regulation, gluconeogenesis and lipogenesis regulation, muscle growth and differentiation, and tumor suppression. However, little is known about the role of *SIK1* function in HCC. Qu *et al.* show in this issue of the *Journal* that ***SIK1* silencing promotes HCC progression and WNT/β-catenin pathway activation, suggesting new diagnostic and therapeutic approaches in liver cancer.**

Current diagnostic imaging criteria for (HCC) are dedicated to imaging with nonspecific extracellular contrast agents. Choi *et al.* investigated diagnostic criteria for HCC ⩽3 cm on magnetic resonance imaging (MRI) with a hepatocyte-specific contrast agent through an inception cohort study. They report two interesting findings. **First, EASL criteria exhibit the best diagnostic performance for HCC ⩽3 cm on hepatocyte-specific contrast-enhanced MRI. A newly identified criterion (arterial-phase hyper-intensity and hepatobiliary phase hypo-intensity) may increase the diagnostic sensitivity of small (⩽2 cm) HCC.**

Transarterial chemoembolization with doxorubicin-eluting beads (DEB-TACE) is effective in patients with BCLC stage B hepatocellular carcinoma (HCC). Sorafenib enhances overall survival and time to tumor progression in patients with advanced HCC. Lencioni *et al.* report the results of an exploratory phase II trial tested the efficacy and safety of sorafenib plus DEB-TACE in patients with intermediate-stage HCC. **They show the technical feasibility of sorafenib plus DEB-TACE, but find no advantage in terms of outcome in using this combination therapy compared to DEB-TACE alone.**

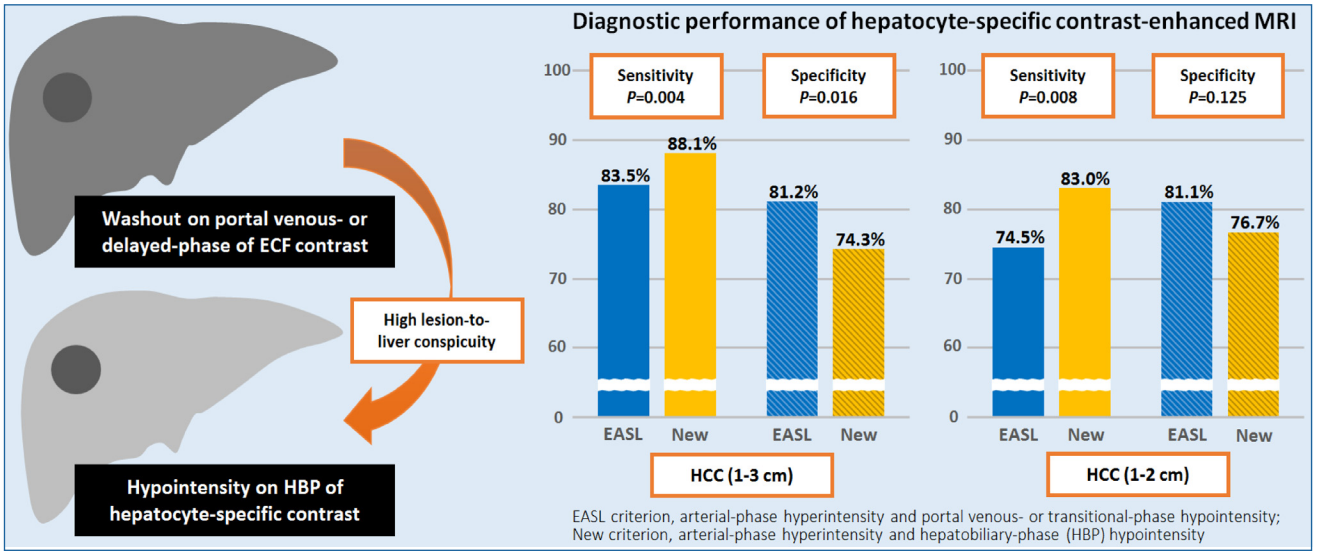
NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Hepatic lipidomic analysis in patients with NASH

Recent data have identified ***de novo* ceramide** synthesis as important mediators of hepatic insulin resistance (IR), which participates in NASH progression. In this issue, Luukkonen *et al.* determined which bioactive lipids co-segregate with IR in the human liver, and its relationship with ***PNPLA3* genotypes**. By performing liver lipidome analysis in patients with and without IR and different *PNPLA3* genotypes, they demonstrated that steatosis and NASH prevalence were similarly increased in patients with IR and $PNPLA3^{148MM/MI}$ at rs738409. The liver in patients with IR had increased triacylglycerols as well as markers of *de novo* ceramide synthesis. In contrast, livers from patients with $PNPLA3^{148MM/MI}$ have increased polyunsaturated triacylglycerols while other lipids were unchanged. This study suggests the composition liver fat in NASH depends on the *PNPLA3* genotype.

HEPATITIS C VIRUS (HCV) INFECTION

Increasing prevalence of HCV-induced cirrhosis in the United States, risk of HCV reinfection in injecting drug users – how sustained is sustained response?



Choi *et al.* 2016