JOURNAL
OF HEPATOLOGY

From the Editor's Desk. . .

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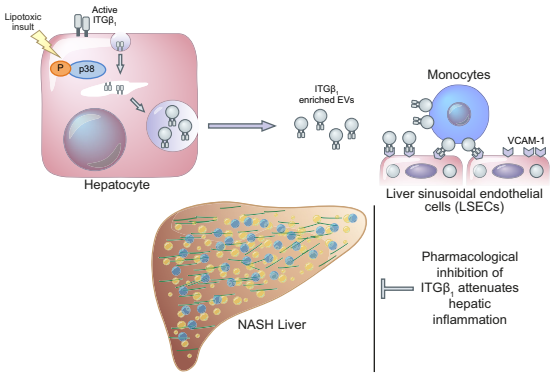
LIVER INFLAMMATION

Lipotoxicity promotes hepatic recruitment of inflammatory monocytes through integrin beta-1 enriched extracellular vesicles

Hepatic recruitment of monocyte-derived macrophages contributes to the inflammatory response in non-alcoholic steatohepatitis (NASH). However, how hepatocyte lipotoxicity promotes the recruitment of inflammatory monocyte-derived macrophages is unclear. **Using elegant murine models, Guo *et al.* show that hepatocytes under lipotoxic stress release active integrin beta-1-enriched extracellular vesicles (EVs).** They also reveal that lipotoxic hepatocyte-derived EVs enhance monocyte adhesion to liver sinusoidal endothelial cells mainly via their integrin beta-1 cargo. Integrin beta-1 neutralising antibody reduces proinflammatory monocyte hepatic infiltration in murine NASH. Blocking integrin beta-1 also attenuates liver inflammation, injury and fibrosis in murine NASH. **Together these findings suggest that blocking integrin beta-1 is a potential anti-inflammatory therapeutic strategy in human NASH.**



Guo *et al.*, 2019.
Lipotoxicity promotes hepatic recruitment of inflammatory monocytes.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Novel mechanism of gut-vascular barrier and increased incidence of gastrointestinal cancers in patients with NAFLD

There is mounting evidence that increased intestinal barrier permeability and translocation of bacterial products play an important role in NAFLD. However, the molecular mediators of this effect are only partially known. In this issue, **Mouries *et al.*** revealed novel molecular mechanisms mediating the altered gut barrier. The authors showed that **disruption of intestinal epithelial barrier and gut-vascular barrier (GVB) are early events in experimental NAFLD in mice.** Faecal microbiota transplantation from mice with diet-induced NAFLD into pathogen-free mice induced GVB damage, which was dependent on the Wnt-β-catenin signalling pathway. The bile acid analogue obeticholic restored this pathway in epithelial cells and protected against GVB disruption *in vivo*, which could partly mediate its beneficial effects in this condition. Importantly, the authors also demonstrated upregulation of the GVB leakage marker in the colon of patients with NASH. This important translational study provides evidence that the Wnt-β-catenin signalling pathway is a new player in NASH development by regulating the GVB. **Manoeuvres aimed at restoring the Wnt-β catenin signalling pathway in endothelial cells, such as obeticholic acid, could be beneficial for patients with fatty liver disease**.

In another interesting paper in this issue, **Allen *et al.*** studied the incidence of hepatic and extrahepatic cancers in patients with NAFLD. Previous studies indicate that obesity is a risk factor for cancers, yet the specific role of NAFLD in this association is unclear. The authors identified 4,722 incident cases of NAFLD in a US population (1997–2016) and compared them with 14,441 sex and age-matched controls. The median follow-up was 8 years. The presence of **NAFLD was associated with a 90% higher risk of malignancy (incidence rate ratio [IRR] of 1.9)**. The highest risk increase was found in liver cancer (IRR of 2.8), followed by uterine (IRR of 2.3), stomach (IRR of 2.3), pancreas (IRR of 2.0) and colon (IRR of 1.8). Importantly, compared to non-obese controls, the existence of NAFLD was associated with a higher risk of incident cancers (IRR of 2.0), while obesity alone was not (IRR of 1.0). This important epidemiological study demonstrated that **NAFLD is associated with increased cancer risk, particularity of gastrointestinal origin. In the absence of NAFLD, the impact of obesity on cancer risk is modest to non-existent.** These convincing results raise the possibility that NAFLD mediates the increased incidence of cancer previously described in obese individuals.

HEPATITIS B VIRUS (HBV) INFECTION

The Ying and Yang of liver macrophages

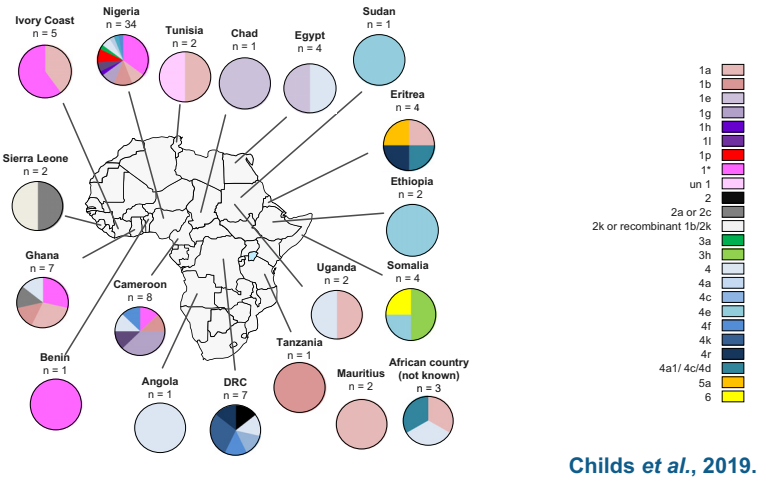
Immune-mediated mechanisms against HBV infection are a double-edged sword as they are critically involved in clearance of the virus but can trigger liver disease pathogenesis at the same time. Important drivers of inflammation and virus elimination are proinflammatory macrophages (M1), whereas anti-inflammatory macrophages (M2) are involved in the resolution of inflammation and tolerance mechanisms. **Faure-Dupuy *et al.*** investigated elegantly the mechanisms by which HBV regulates the phenotype, differentiation and cytokine expression of human liver resident or infiltrating macrophages. **The study provides strong evidence of a so far largely neglected crosstalk between HBV and liver macrophages, whereby HBV directly impairs the phenotype of proinflammatory macrophages but also increases the secretion of anti-inflammatory macrophages, establishing a micro milieu that favours tolerance**. Hence, promoting the differentiation of

proinflammatory liver macrophages over anti-inflammatory ones – a shift from Ying to Yang – represents a reasonable therapeutic strategy to break HBV-associated immune tolerance.

HEPATITIS C VIRUS (HCV) INFECTION

Unusual HCV genotype 1 subtypes from sub-Saharan Africa confer high-level DAA resistance, real-world efficacy of SOF/VEL/VOX in DAA failures, a decentralised care model to eliminate hepatitis C, extrahepatic disease burden largely reduced when curing the infection

Although an estimated 11 million HCV-infected people, *i.e.* 15% of the global burden of hepatitis C, are living in the World Health Organisation (WHO) Africa region, these populations have been heavily understudied and were underrepresented in all clinical approval trials. Moreover, no data on treatment outcomes have been reported in a sizeable real-world African patient cohort so far, although it is well known that HCV genotype distribution depends on geographic regions and responses to direct-acting antivirals (DAAs) differ depending on HCV types and subtypes. The study by **Childs *et al.*** is the first to report the HCV subtype distribution among patients from 18 different sub-Saharan African countries and their respective DAA treatment outcomes. **The authors observed a huge degree of viral diversity among patients from sub-Saharan Africa, with more than 50% of patients infected with unusual HCV genotype 1 subtypes like 1e, 1g, 1h, 1l, but also found a novel subtype 1p. Importantly these unusual HCV genotype 1 subtypes showed remarkably lower sustained virological response (SVR) rates when treated with first-generation NS5A inhibitor-based regimens compared to the typical Western world HCV subtypes 1a and 1b.** That commonly used first-generation NS5A-containing DAA regimens result in poorer response rates in patients infected with unusual African subtypes is alarming, and warrants further studies evaluating HCV subtype-dependent treatment optimisation, in order to achieve the global WHO HCV elimination goals.



Childs *et al.*, 2019.
Unusual HCV genotype 1 subtypes from sub-Saharan Africa confer high-level DAA resistance.

Sofosbuvir, velpatasvir, and voxilaprevir (SOF/VEL/VOX) is the approved primary salvage regimen for patients with chronic HCV infection who have not responded to at least 1 DAA regimen in the past. In well-controlled phase III clinical trials, patients failing a previous NS5A- or non-NS5A-based DAA regimen achieved cure rates of 96% and 98% with this triple regimen, respectively, but its real-world effectiveness is understudied. In this issue of the *Journal*, **Degasperi *et al.*** report on their experience in treating a large real-word cohort including all consecutive patients from 27 centres in Northern Italy who failed a previous DAA-based regimen with SOF/VEL/VOX (The NAVIGATORE Lombardia and Veneto Networks). **In the largest European real-world study of SOF/VEL/VOX to date, re-treatment led to an overall cure rate of 91% in the intention-to-treat and 96% in the per-protocol analysis. Although resistance-associated substitutions (RAS) were present in 82% of patients at baseline, the presence and type of RAS did not affect treatment outcome. In line with previous reports, the presence of cirrhosis and hepatocellular carcinoma (HCC) were the only factors associated with reduced cure rates**.

Eliminating HCV infection in high prevalence but low- and middle-income countries worldwide remains a challenge and requires the establishment of innovative community-based care strategies. In Punjab, India, an innovative interactive model of decentralised services using telementoring and algorithm-based treatment was introduced by the Mukh-Mantri Punjab Hepatitis C Relief Fund who provided free of charge generic DAAs to treat the estimated 728,000 HCV-infected people living in this area with the goal of eliminating hepatitis C from Punjab. During a 2-year period, 48,088 patients with chronic hepatitis C were treated by trained primary healthcare providers with generic DAAs and followed for at least 12 weeks after treatment. **With cure rates of nearly 92% without any significant difference across genotypes, degree of liver fibrosis or high-risk subgroups, Dhiman *et al.* impressively demonstrated the safety and efficacy of this decentralised care model. Even in the relatively large proportion of patients with early treatment interruption, nearly 90% were cured.** As highlighted by the authors, this important study clearly proves the effectiveness of a public health strategy using decentralised care to empower primary healthcare providers to combat and eliminate HCV globally.

Extrahepatic manifestations including metabolic, cardiovascular, renal, autoimmune, lymphoproliferative, as well as psychiatric and neurologic conditions are present in more than 30% of all chronically HCV-infected patients and contribute significantly to HCV-related morbidity and mortality worldwide. However, generalisable population-level estimates of the effect of antiviral treatment-induced cure of the infection (SVR) on the risk of developing extrahepatic manifestations

are lacking. **Rossi *et al.*** now estimated the burden of chronic HCV-related comorbidities other than liver disease between those who were cured and those who failed HCV treatment within the population-based cohort study in British Columbia, Canada, during the interferon era. **Among 10,264 HCV-infected patients, achieving viral cure was associated with a significant risk reduction in the incidence of type 2 diabetes, chronic kidney disease, end-stage renal disease, ischaemic or haemorrhagic stroke, as well as mood and anxiety disorders which ranged from 18% to 47%.** These findings support the extrahepatic benefit of achieving viral cure and suggest that expanded access to HCV treatments by a broader use of DAAs may reduce the growing burden and healthcare resource utilisation associated with chronic HCV-related extrahepatic diseases.

COMMUNITY SCREENING

Transient elastography (TE) is a cost-effective tool for fibrosis screening

Although the prevalence of alcohol-related liver disease and NAFLD in the community is high and TE is an accurate tool to assess severity of fibrosis, its cost-effectiveness in primary care as a screening tool is unknown. **Serra-Burriel *et al.*** performed an important study combining the results of 6 studies of TE in over 6,000 patients in primary care from Europe and Asia. **They showed that using TE in the community as a screening tool was more accurate compared with the fibrosis scores. They also clearly showed that using TE was cost-effective both for populations at risk, such as those with alcohol abuse, and also for the general population.** If TE-based algorithms can be refined, it could be readily incorporated into clinical practice.

CIRRHOSIS

Endothelial and muco-epithelial barrier are disturbed in cirrhosis

Pathological bacterial translocation (PBT) is central in mediating the complications of cirrhosis but the underlying mechanisms are unknown. A series of innovative experiments by **Sorribas *et al.*** shows that PBT is a feature of cirrhosis but not of portal hypertension alone. **They provide novel data showing reduced thickness of the mucus layer, which allows PBT. They also show that the GVB is disturbed allowing bacteria to translocate, which is possibly due to increased endothelial expression of plasmalemma-vesicle associated protein (short name, PV-1; encoded by *PLVAP*), an endothelial cell-specific protein that regulates vascular permeability.** They provide novel therapeutic approach to reduce PBT showing that these defects can be restored with FXR agonists. Further understanding of this approach will allow novel therapeutic approaches to be developed.

HCC BASIC - TRANSLATIONAL

Hepatoma stem cells interact with lymphatic endothelial cells, mutations in *WNK2* drive HCC recurrence

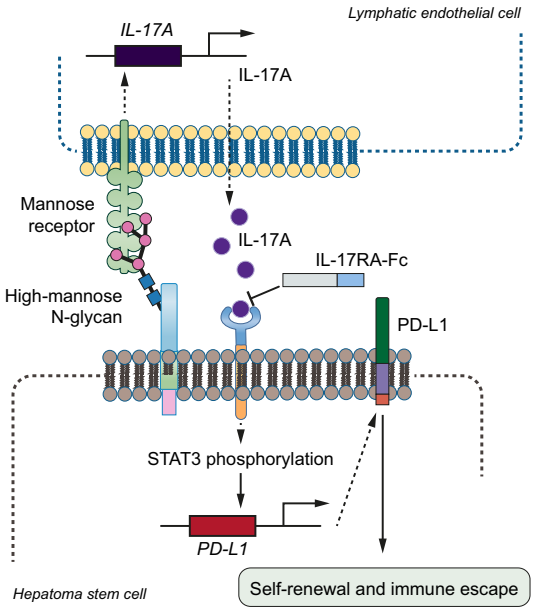
Microenvironment regulates hepatoma stem cells behaviours. The contributions of lymphatic endothelial cells in hepatoma stem cells niche remain largely unknown. In this issue of the Journal, **Wei *et al.*** show that CD133+ hepatoma stem cells preferentially interact with lymphatic endothelial cells through an interaction between mannose receptor and high-mannose type N-glycan. This interaction activates the expression of the cytokine interleukin (IL)-17A expression in lymphatic endothelial cells. IL-17A promotes hepatoma stem cells self-renewal and immune escape partly through upregulation of programmed cell death 1 ligand 1 (PD-L1) a ligand of the inhibitory receptor programmed cell death 1 (known as protein PD-1 or CD279). **These findings indicate that interaction between lymphatic endothelial cells and hepatoma stem cells promotes tumorigenesis and immune escape of hepatoma stem cells.**

Early recurrence of HCC after curative resection is common. However, the association between genetic mechanisms and early HCC recurrence, in particular in Chinese patients, remains largely unknown. Focusing on *WNK2* (encoding a protein named serine/threonine-protein kinase WNK2), **Zhou *et al.*** show that mutations in this gene occur in about 5% of their 736 HCC samples and are associated with lower gene-product protein levels, higher rates of early tumour recurrence, and shorter overall survival. Interestingly, they show a tumour-suppressor role for *WNK2*: its inactivation results in ERK1/2 signalling activation in HCC cells, infiltration by tumour-associated-macrophage, and tumour growth and metastasis. **Among Chinese patients with HCCs, *WNK2* is a driver of early HCC recurrence after curative resection.**

HCC – CLINICAL

SIRT plus sorafenib prolong survival in advanced HCC, Use of sorafenib improves with time

SORAfenib in combination with local MICro-therapy guided by gadolinium-EOBDTPA-enhanced MRI (SORAMIC) trial is a randomized controlled trial comprising diagnostic, local ablation and palliative cohorts (EudraCT 2009-012576-27, NCT0112 6645). Based on diagnostic study results, patients were assigned to local ablation or palliative cohorts. In the palliative cohort, 216 patients not eligible for TACE were randomized 11:10 to selective internal radiation therapy (SIRT, also



Wei *et al.*, 2019.
Hepatoma stem cells interact with lymphatic endothelial cells.

known as radioembolisation) plus sorafenib or sorafenib alone. The primary endpoint was overall survival in the intention-to-treat population. **Ricke *et al.*** report here the results of this trial. They show that **the overall survival was not significantly higher among patients assigned to SIRT to sorafenib than among those who were assigned to sorafenib alone (12.1 months *vs.* 11.4 months).**

Sorafenib is associated with multiple adverse events (AEs), which can lead to treatment discontinuation. The impact of the physicians' experience on the management of these AEs and the relative implications on clinical outcomes are unknown. **Tovoli *et al.*** aimed to verify if the AEs management changed over time and if these modifications impacted on treatment duration and overall survival. For this, they analysed prospectively collected data of 338 consecutive patients who started sorafenib between January 2008 and December 2017. Patients were divided into 2 groups according to the starting date: those who started between 2008–2012 (n = 154), and those who started between 2013–2017 (n = 184). They show here that overall survival was longer and the 2-year survival rate higher among patients who started therapy between 2013–2017 than among those who started between 2008–2012 (12.0 *vs.* 11.0 months, $p = 0.003$; and 28.1 *vs.* 18.4%, $p = 0.003$; respectively). The multivariate time-dependent Cox regression confirmed later period of treatment as an independent predictor of survival (HR 0.728; 95% CI 0.581–0.937; $p = 0.013$). Accordingly, **experience in the management of sorafenib-related AEs seems to prolong treatment duration and survival.**

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