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From the Editor's desk...

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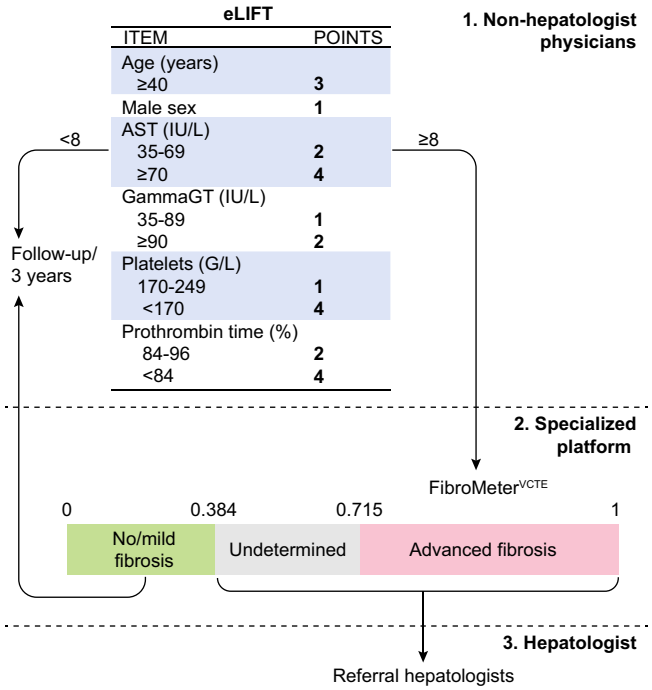
SELECTION OF THE MONTH

Simple, accurate and validated algorithm for hepatic fibrosis

With the introduction of non-invasive tests, the reliance on liver biopsy to stage liver disease has declined substantially. Boursier *et al.* performed a hugely important study in over 3,000 patients, to develop and validate an algorithm for the assessment of the severity of fibrosis. The newly developed eLIFT test, which combines routine biochemical data and many tests of liver fibrosis, performed better that any other first line test. The FibroMeter^{VCTE} (FM^{VCTE}) was the most accurate among the eight, fibrosis tests evaluated. **The sensitivity of the eLIFT-FM^{VCTE} algorithm (first line eLIFT, second-line FibroMeter^{VCTE}) was 76.1% for advanced fibrosis and 92.1% for cirrhosis. The test was also able to provide accurate prognostic information**. The data would allow further reduction in the need for liver biopsy.



Boursier *et al.* 2017

LIVER INJURY

RIPK1 activity in the liver does not mean R.I.P.

Upon ligand binding, receptor-interacting protein kinase-1 (RIPK1) is recruited to tumor necrosis factor receptor superfamily (TNFRSF) and Toll-like receptor (TLR) complexes promoting pro-survival and inflammatory signalling. RIPK1 also directly regulates caspase-8-mediated apoptosis or, if caspase-8 activity is blocked, RIPK3- mixed lineage kinase domain-like protein (MLKL)-dependent necroptosis (a form of programmed cell death). Necroptosis is characterized by early loss of plasma membrane integrity, leakage of intracellular contents, and organelle swelling. The cells dying through necroptosis lack the typical apoptotic characteristics, such as membrane blebbing, chromatin condensation, and intranucleosomal DNA cleavage into 180 bp DNA laddering, but may show TUNEL positivity. Here Filliol *et al.* show that, in the liver, lipopolysaccharide (LPS, a Gram-negative bacteria by-product and a pathogen-associated molecular pattern [PAMP]), is recognized by its TLR, and stimulates Kupffer cells to produce and secrete tumour necrosis factor alpha (TNF-α). This engages its cognate TNFRSF. In the absence of RIPK1, TNFRSF engagement by TNF-α causes hepatocyte apoptosis. **These data reveal the pivotal function of RIPK1 in maintaining liver homeostasis in conditions of macrophage-induced TNF-α burst in response to LPS (and perhaps other PAMPs) sensing.** Since RIPK1 inhibition or invalidation can lead to necroptosis and subsequent release of danger-associated molecular patterns resulting in systemic inflammation, future studies should investigate whether RIPK1 activity is decreased in liver diseases and could contribute to the development of systemic inflammation in these diseases.

HEPATOCELLULAR CARCINOMA (HCC)

Erbin promotes HCC, differences between human FGF-19 and its murine ortholog FGF-15, DAA failure in active HCC

Aberrant oestrogen receptor-α (ERα) expression and signalling are implicated in the development of HCC, but its regulation in HCC remains unknown. Wu *et al.* were interested in the Erbin protein, which contains 17 leucine-rich repeats and one PDZ domain. They show that Erbin expression is significantly elevated in human HCC tissue. This elevated expression of Erbin contributes to tumorigenesis of HCC by negatively regulating ERα signalling. **Restoring ERα signalling by inhibiting Erbin expression enhances the sensitivity of HCC cells to tamoxifen treatment, providing a new approach for tamoxifen treatment in HCC.**

From the Editor's desk

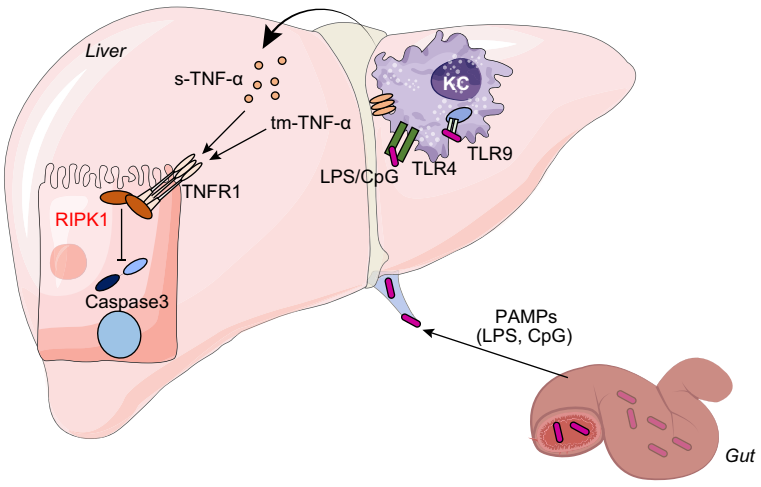
The bile acid receptor (also known as farnesoid X-activated receptor) is encoded by *NR1H4* (also known as *FXR*). This receptor is involved in many metabolic processes, including the regulation of bile acid, lipid and glucose homeostasis. A significant component of bile acid receptor-mediated events is related to induction of the enteric endocrine hormone fibroblast growth factor 19 (FGF-19) or its rodent ortholog, FGF-15. Zhou *et al.* compared the properties of human FGF-19 and murine FGF-15 in the regulation of hepatocarcinogenesis and metabolism in various mouse models of disease. They reveal that, although both hormones repress bile acid synthesis, murine FGF-15 lacks the profound, weight-independent HbA1c-cell-protective effects characteristic of human FGF-19 in *db/db* mice with overt diabetes. More strikingly, unlike FGF-19, FGF-15 does not induce HCC in three mouse models of metabolic diseases (*db/db*, diet-induced obese, and *Mdr2*-deficient mice). **They reveal striking species-associated differences between FGF-19 and FGF-15 that may restrict the relevance of mouse models for the study of the bile acid receptor/FGF19 pathway, and underscore the importance of clinical assessment of this pathway, with respect to both safety and efficacy, in humans**.

Patients with hepatitis C virus (HCV)-related cirrhosis and HCC can be treated with oral direct-acting antiviral (DAA) regimens. However, data on the use of DAAs in HCV-positive patients with HCC are scarce. Prenner *et al.* here show that **the presence of active HCC tumor at the initiation of HCV therapy is significantly associated with all-oral DAA treatment failure. HCV treatment after curative therapies for HCC resulted in excellent sustained virologic response**.

NON-ALCOHOLIC FATTY LIVER DISEASE

Role of integrin beta-7, MAdCAM-1 and dendritic cells in the pathogenesis of NASH

There is an urgent need to develop targeted therapies for non-alcoholic steatohepatitis (NASH). In particular, it is important to identify drivers of immune cell infiltration in order to attenuate the inflammatory response to fatty liver. Two interesting studies in this issue of the *Journal* have identified new molecular and cellular drivers of NASH. In a first study, Drescher *et al.* investigated the role of two molecules potentially implicated in neutrophil infiltration in response to fatty liver (*i.e.*, Integrin beta-7 and mucosal addressin cell adhesion molecule 1 [MAdCAM-1]). By using several transgenic mice subjected to animal models of NASH, the authors eloquently demonstrated that **while MAdCAM-1 (encoded by *Madcam1*) promotes steatohepatitis, integrin beta-7 (encoded by *Itgb7*, also known as *Ly69*) unexpectedly exerts protective effects**. *Itgb7*$^{-/-}$ mice showed earlier steatohepatitis initiation and significantly stronger fibrosis progression while *Madcam1*$^{-/-}$ mice showed less severe steatohepatitis. The interaction of integrin beta-7 and their receptor MAdCAM-1 provides novel targets for therapeutic interventions in NASH. In a second study, Heier *et al.* studied the role of CD103^{+} dendritic cells (DCs). These cells represent a heterogeneous cell population among which CD103^{+} DCs play a significant role in immunity and tolerance. The authors used several transgenic animals that lack CD103^{+} DCs. **Metabolic challenge to mice lacking CD103^{+} DCs resulted in the progression of steatosis towards steatohepatitis, manifesting in increased influx of inflammatory cells into the liver and elevated inflammatory cytokine production of myeloid cells upon innate stimuli**. Conversely, the adoptive transfer of CD103^{+} cells to DCs deficient animals reversed these observed changes and more importantly could attenuate cellular damage and inflammation in established murine steatohepatitis. This important study has identified the murine CD103^{+} cells as a protective DCs subtype that influences the pro-anti-inflammatory balance and protects the liver from metabolic damage.



Filliol *et al.* 2017

HEPATITIS C VIRUS (HCV) INFECTION

DAA in the real-world revisited, DAA going generic, HCV-induced natural killer (NK) cell activation results in altered NK-mediated antibody-dependent killing

Evaluation of DAA in the real-world setting where patient populations are more diverse and complex may provide significant additional information with respect to safety and efficacy of the regimens. Calleja and Crespo *et al.* investigated the two oral DAA combination regimens, ombitasvir/paritaprevir/ritonavir plus dasabuvir and ledipasvir/sofosbuvir, in a large Spanish national database, which includes almost 4,000 HCV type 1-infected patients (approximately half of them with cirrhosis). Cure rates were high with 96.8% and 95.8%, respectively after 12 weeks of therapy, and a similar efficacy rate was seen in the subgroup being eligible for a shorter 8-week treatment duration. **This real-world study – being one of the largest to-date – provides relevant and detailed new information regarding treatment efficacy and safety in certain subgroups which includes SAEs and SAE-associated treatment discontinuation rates as well as renal safety comparisons of both regimens but also addresses the controversial issue of HCC risk in DAA treated patients with cirrhosis**.