

## From the Editor's Desk January 2018

### Draft #5

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## SELECTION OF THE MONTH

**Big Title:** HOPE for patients' liver transplantation

### Small Title:

HCV impairs female fertility

Regulation of HBV core promoter transcriptional activity

(Cirrhosis): Early TIPS in France

## LIVER INFLAMMATION

**Role of the alarmin interleukin (IL)-33, protective dual specificity protein phosphatase 14 in hepatic ischemia-reperfusion injury (IRI)**

IL-33 is a cytokine member of the IL-1 family which functions as an alarmin (also known as danger-associated molecular pattern, DAMP), being released by damaged or necrotic barrier cells (endothelial and epithelial cells). **IL-33 can cause sterile**

**inflammation.** Full length IL-33 protein is active; but processing by inflammatory proteases can generate mature forms that have enhanced (up to 30 fold) cytokine activity. The mature forms of IL-33 (IL-33<sub>95–270</sub> and IL-33<sub>109–270</sub>) can be generated by both neutrophil and mast cell proteases and might be the major bioactive forms of IL-33 in diseased tissues. IL-33 was initially believed to induce type 2 immune responses, activating T helper 2 (T<sub>H</sub>2) cells and mast cells). We know now that IL-33 also stimulates T<sub>H</sub>1 cells, regulatory T (Treg) cells, group 2 innate lymphoid cells (ILC2s), CD8<sup>+</sup> T cells and natural killer (NK) cells. IL-33 exerts its cytokine activity by binding to a heterodimer formed by its specific primary receptor ST2 (suppression of tumorigenicity 2; also known as IL-1RL1, T1 and IL-33R) and co-receptor, IL-1 receptor accessory protein (IL-1RAcP; also known as IL1RAP). The IL-33–ST2 complex adopts a rigid conformation that provides a platform for the recruitment of IL-1RAcP. Juxtaposition of the ST2 and IL-1RAcP cytoplasmic Toll/IL-1R-MyD88 coupled domains in the ternary complex then results in activation of intracellular signaling pathways. IL-33 is a potent pro-inflammatory cytokine whose activity requires to be tightly regulated. Regulatory mechanisms include the retention of IL-33 in the nucleus of producing cells during homeostasis is crucial to avoid its constitutive release and lethal multi-organ inflammation by signaling through ST2. Cleavage by caspases in the IL-1-like cytokine domain could be an important mechanism of IL-33 inactivation during apoptosis. Extracellular mechanisms are also involved in the inhibition of IL-33 cytokine activity. Sequestration by the decoy receptor soluble ST2 (sST2) is likely to be crucial. Rapid oxidation and formation of disulfide bridges (S-S) in IL-33 following its extracellular release could be another crucial mechanism that limits the range and duration of ST2-dependent responses in vivo. The role of IL-33 signaling in the development of liver inflammation associated with alcoholic liver disease is unknown. This question has been addressed by Wang *et al.* who report their results in this issue of the *Journal*. **They reveal a dichotomous role of IL-33/ST2 signaling during ALD development. At early and mild stages, ST2 restrains the inflammatory activation of hepatic macrophages, through inhibiting nuclear factor (NF)-κB, and plays a protective function in an IL-33-independent fashion. During severe liver injury, significant cell death and marked IL-33 release occur, which triggers IL-33/ST2 signaling and exacerbates tissue damage, making IL-33 signaling a potential target for new therapies.**

Neutrophils and liver sinusoidal endothelial cells (LSECs) both contribute to sterile

inflammation which is involved in IRI. Infiltrating neutrophils form neutrophil extracellular traps (NETs), exacerbate IRI. Yazdani *et al.* investigated the role of IL-33 in NET formation during liver sterile inflammation. They now show that **IL-33, mainly released from LSECs, causes excessive sterile inflammation after hepatic I/R by inducing NET formation.** They suggest that therapeutic targeting IL-33 signaling could extend novel strategies to minimize organ damage in various clinical settings that are associated with sterile inflammation.

IRI is characterized not only by inflammation but also extensive cell death. Multiple signaling pathways, including NF- $\kappa$ B and the mitogen-activated protein (MAP) kinase c-Jun kinase (JNK), play important roles in IRI. Dual specificity protein phosphatase 14 (also known as MAP kinase phosphatase 6, MKP-6) is encoded by *DUSP14* and acts as a negative regulator of NF- $\kappa$ B signaling. Wang *et al.* now report that **MKP-6 via its interaction with TAK-1, and subsequent inhibition of JNK, is a protective factor in hepatic IRI.**

### NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

**NAFLD is associated with increased cancer incidence as well as microalbuminuria in Asian patients**

There is mounting evidence that obesity and metabolic syndrome increase the incidence of cancer. Whether this is also true for patients with NAFLD is now well documented. In a large study, Kim *et al.* investigated the cancer incidence rates in a cohort of Korean patients followed up for >1 year after having a health checkup. Of 25,947 subjects, 33.6% had NAFLD. **The cancer incidence rate of the NAFLD group was higher than that of the non-NAFLD group (HR 1.32).** When demographic and metabolic factors were adjusted, **NAFLD showed a strong association with three cancers: hepatocellular carcinoma (HCC; HR, 16.73), colorectal cancer in males (HR 2.0), and breast cancer in females (HR 1.92).** A high NAFLD fibrosis score (NFS) and a high FIB-4 score were associated with the development of all cancers and HCC. This relevant study strongly suggests that NAFLD is associated increased cancer risk in Korean patients. Besides increasing cancer risk, increasing evidence suggests that (NAFLD) may be an independent risk factor for chronic kidney disease (CKD). In this issue, Yeung *et al.* investigated the association between NAFLD and albuminuria, a marker of diabetic nephropathy. This study included a cohort of 1,763 Chinese patients with type 2 diabetes that underwent transient elastography and CAP

measurement. **The prevalence of albuminuria was higher in diabetic patients with liver steatosis and those with advanced fibrosis.** The odds of albuminuria increased with greater severity of liver fibrosis in a dose dependent manner. This important study suggests that advanced liver fibrosis is independently associated with albuminuria in Chinese patients with type 2 diabetes. Monitoring albuminuria might be clinically useful in patients with advanced NAFLD.

## HEPATITIS C VIRUS (HCV) INFECTION

**HCV impairs female fertility, direct-acting antiviral (DAA) treatment-induced SVR reduces the HCC risk in the VA cohort risk, a new cheap and effective DAA regimen to treat HCV type 4 in Egypt**

Previous data indicated that HCV-positive women of reproductive age already had similar low levels of anti-Müllerian hormone as menopausal women, indicating premature ovarian senescence as a potential additional extrahepatic manifestation of the HCV syndrome. The consequences of these findings in terms of reproductive function has now been further explored by Karampatou *et al.* in a large cohort study of HCV-positive and -negative women of childbearing age. **The study confirms that HCV-positive women of reproductive age display markers of ovarian senescence which is associated with an increased burden of infertility and adverse pregnancy outcomes, including still births, miscarriages, fewer live births and gestational diabetes.** Achieving SVR after antiviral treatment, however, reduced the risk of miscarriage, and it remains to be assessed whether antiviral therapy at a very early age can positively influence the occurrence of miscarriages and to prevent ovarian senescence, as the latter has a much broader health implication than simply preservation of fertility.

The risk of hepatocellular carcinoma (HCC) is reduced in HCV-infected patients achieving SVR induced by IFN $\alpha$ -based therapies. However, whether DAA-induced SVR reduces the HCC risk remains controversial, as recent studies demonstrated little or no impact of DAA-based antiviral treatment on HCC risk, and even suggested that DAAs might increase the risk of HCC recurrence. In this issue, Ioannou *et al.* retrospectively studied the association between SVR, either induced by IFN $\alpha$ -based or IFN $\alpha$ -free DAA therapies, and HCC risk in 62,354 patients who initiated antiviral treatment in the Veterans Affairs national healthcare system. **DAA-induced SVR was associated with a 71% reduction in HCC risk compared to treatment failure, and**

**the reduction in HCC risk was similar irrespective of whether SVR was achieved by DAA-only, DAA plus IFN $\alpha$  or IFN-only regimens.** No evidence was found that treatment with DAAs was associated with increased risk of HCC compared to treatment with IFN. This important study suggests that eradication of HCV reduces HCC risk independently of how it is achieved and helps to solve some confusion about the impact of DAAs on HCC risk.

The broad access to effective DAA-based treatment of chronic HCV infection in resource-limited countries is mainly limited by its high costs. This study from Egypt, the country with the highest HCV prevalence in the world, is the first to evaluate a new and cheap pan-genotypic HCV NS5A inhibitor, ravidasvir, in combination with generic sofosbuvir in a large group of HCV type 4-infected patients. The once daily regimen given for 12 or 16 weeks was well tolerated, and achieved high SVR rates (91% and 98% in patients with and 91% without cirrhosis) irrespective of the use of ribavirin. While there are several very effective treatments for HCV type 4, **this combination of ravidasvir plus generic sofosbuvir with an expected price of less than US\$300 as stated by Elbaz *et al.* has the potential to be a cheap and effective treatment option not only for Egypt but also other low- and middle-income countries.**

## HEPATITIS B VIRUS (HBV) INFECTION

**Low risk of HBsAg seroreversion after treatment-induced HBsAg loss, serum HBV RNA - a new biomarker for disease activity in NA-treated patients? -, regulation of HBV core promoter transcriptional activity**

Hepatitis B surface antigen (HBsAg) loss, named the functional cure, represents the main goal of all antiviral strategies in patients with chronic hepatitis B. Whether treatment-induced HBsAg loss, however, has a comparable high durability as the HBsAg loss which occurs spontaneously during the chronic course of the infection remains unclear. It is also an unanswered question whether the presence of anti-HBs, or applying any nucleos(t)ide (it is a typical abbreviation for nucleoside / nucleotide analogs) analogue (NA) consolidation therapy once HBsAg loss is reached may affect the outcome. To answer these questions, Yip *et al.* conducted a territory-wide cohort study using data from 4,080 patients with HBsAg seroclearance from the Hospital Authority, Hong Kong. **The most intriguing finding of this large-scale study was that HBsAg seroclearance induced by NA was as stable as that which occurs**

**spontaneously, and that the presence of anti-HBs may not be essential for maintaining HBsAg seroclearance after NA treatment.** This important study also suggests that longer consolidation treatment, may reduce the risk of HBsAg seroreversion, but the optimal duration of consolidation remains to be determined.

Serum HBV RNA may reflect HBV transcriptional activity in the liver, and is increasingly gaining importance as a potential new predictive biomarker for treatment outcome. In this study, Qiu *et al.* aimed to determine whether HBV RNA levels in serum are correlated with the levels of intrahepatic viral replicative forms and the severity of histological necroinflammation and fibrosis in NA-treated patients. **Authors show that HBV RNA levels in serum are indicative of the intrahepatic transcriptional activity of covalently closed circular DNA and are also associated with liver histological disease activity in NA-treated patients.** This elegant study highlights the importance of serum HBV RNA as a relevant (HBV DNA and HBsAg-independent) non-invasive diagnostic biomarker in chronic HBV infection which could be potentially used in predicting liver disease progression in patients with and without NA therapy.

After cell entry via NTCP and establishment of the nuclear covalently closed circular DNA, HBV replication is critically dependent on host transcription factors regulating the HBV core promoter transcriptional activity. The post-entry factors and mechanisms that are required for efficient HBV transcription but probably also explaining the hepatocyte tropism of this virus remain, however, largely unknown. **Besides the well-known effect of specific HNF4 $\alpha$  isoforms in enhancing the HBV core promoter transcriptional activity, Ren *et al.* discovered a previously unknown complementary role of a host factor-mediated inhibition of the promoter induced by zinc finger protein SNAI2 (encoded by SNAI2, also known as SLUG) and transcription factor SOX-7 (encoded by SOX7).** These host factors inhibit HBV core promoter transcription specifically by binding at the pgRNA initiator site and competitively displacing HNF4 $\alpha$ , respectively. The constitutive low expression levels of **zinc finger protein SNAI2 and transcription factor SOX-7** in hepatocytes may also contribute to the hepatocyte-specific cell tropisms of this virus. These findings, if confirmed, provide a new conceptual understanding of viral-host interactions and may also impact future drug development in HBV infection.

## CIRRHOSIS

### **Uptake of early TIPSS for patients with variceal bleeding in France is limited without affecting clinical outcomes**

The recommendations of BAVENO VI consensus meeting suggested that early insertion of a transjugular intrahepatic stent-shunt (TIPSS) was indicated in patients at high risk of rebleeding and mortality. The uptake of these recommendations is not known. Thabut *et al.* performed an important and large observational, multicenter study in France to evaluate the uptake of this recommendation and the attendant outcomes. **They clearly show that the uptake of the recommendation was only 7% in the cases that were thought to be suitable for early TIPSS. Also, the patients that underwent early TIPSS had less severe liver disease. Early TIPSS was not associated with increased survival. The only factor independently associated with survival was the severity of liver disease.** These data should alter recommendations about selection of patients for early TIPSS.

### **HEPATOCELLULAR CARCINOMA (HCC)**

#### **THRI for decisions regarding surveillance, time-to-surgery for early HCC**

Current guidelines recommend biannual surveillance for HCC in patients with cirrhosis. However, HCC incidence is not established for many causes of cirrhosis. Sharma *et al.* aimed to assess the disease-specific incidence of HCC among 2,079 patients with cirrhosis and develop a scoring system to predict HCC risk. **First, they showed that HCC incidence was different according to etiology.** Indeed, the 10-year cumulative incidence of HCC varied from 22% among patients with viral hepatitis, to 16% among those with steatohepatitis and 5% among those with autoimmune liver disease. Second, using multivariable Cox regression, they showed that age, sex, etiology and platelets were associated with HCC development. Points were assigned in proportion to each hazard ratio to create the Toronto HCC Risk Index (THRI). **THRI, had good predictive ability for HCC in patients with cirrhosis, and was validated in an external cohort.** They conclude that “this risk score may help to guide recommendations regarding HCC surveillance”.

The Barcelona Clinic Liver Cancer (BCLC) guidelines recommend liver resection in patients with very early and early HCC (i.e., BCLC stage 0-A single HCC). However, it is unknown whether a delay in resection from the time of diagnosis (the time-to-surgery (TTS), i.e., the elapsed time from diagnosis to surgery) affects outcomes. Lim *et al.* now show that **patients with BCLC stage 0-A single HCC can undergo surgery**

**with TTS  $\geq$  3 months without impaired oncologic outcomes.** They conclude that “an increase in the TTS within a safe range could allow time for proper evaluation before surgery, and ethical testing of new neoadjuvant treatments aiming to reduce the high rate of tumor recurrence despite curative resection”.

## LIVER TRANSPLANTATION

### **Hypothermic perfusion of liver grafts for patients with liver transplantation**

Deaths on the waiting list for liver transplantation are common and the ability to use marginal organs provides a strategy to expand the donor pool. Hypothermic, extracorporeal perfusion of the liver grafts has been shown to be a useful strategy both for grafts from deceased and brain-dead donors. Kron *et al.* describe data from an important piece of translational research evaluating the performance of hypothermic perfusion using the HOPE device in steatotic grafts both in rodents and also in humans. **The data provide mechanistic insight and the proof of concept that the application of the HOPE device can reduce reperfusion injury and perhaps allow these organs to be transplanted.** With further studies, these data can be translated rapidly into clinical practice.