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SELECTION OF THE MONTH

Big Title: alfapump: a new treatment for refractory ascites

Finite nucleos(t)ide analogue treatment for chronic hepatitis B

The ongoing HCC risk after HBsAg loss

Neurotropism of HEV revisited

ENDOPLASMIC RETICULUM (ER) HOMEOSTASIS IN LIVER DISEASES

Hepatic ER stress in obesity and hepatocellular carcinoma (HCC)

Professional secretory cells such as hepatocytes communicate with their environment using secreted proteins and proteins displayed on the cell surface. In order to reach their destinations, these proteins must enter the secretory pathway via insertion into the ER, where they are folded and matured. It is important to know that the concentration of proteins within the ER lumen is approximately 100 mg/mL. Moreover,

the protein synthesis rate in hepatocytes is estimated to 13 million secretory proteins per minute. To accomplish such a thermodynamically unfavorable process in an overwhelmingly crowded environment, the cell expends a large amount of energy to ensure that this quantitative achievement does not come at the price of quality. Homeostasis within the ER lumen (in particular that of Ca^{2+} concentration which is much higher in the ER lumen than the cytosol), is meticulously monitored and maintained. **A broad variety of insults can induce ER stress and lead to the activation of a coordinated adaptive program called the unfolded protein response (UPR), referred to as ER^{UPR} .** In response to the accumulation of unfolded proteins in the ER, the rate of general translation initiation is attenuated, the expression of ER resident protein chaperones and protein foldases is induced, the ER compartment proliferates, and ER-associated degradation is activated to eliminate the irreparably misfolded proteins. When the prosurvival efforts are exhausted, ER-stress related apoptosis commences. The outcome of the ER^{UPR} may be beneficial or detrimental depending on the context. This issue of the *Journal* provides two examples of different outcomes induced by the deregulation of ER homeostasis. The first study by Wires *et al.* reports results of elegant experiments investigating the effect of high fat diet on ER Ca^{2+} homeostasis in rat livers. They found that dietary fat intake correlates with a decrease in ER calcium levels in the liver. These findings should be interpreted knowing that: first, a decrease in ER Ca^{2+} concentration can induce ER^{UPR} , and second it has long been known that obesity can be associated with ER stress and subsequent induction of chronic ER^{UPR} in the liver, resulting in hepatic insulin resistance. Therefore, **the findings by Wilkes *et al.* strongly suggest that decreased Ca^{2+} concentration in hepatocyte ER lumen may be a primary inducer of inappropriate ER^{UPR} in the liver of obese individuals.** The second study is an example of beneficial ER^{UPR} . In this study, Ma *et al.* first showed that acyl-CoA desaturase (also known as stearoyl-CoA desaturase; encoded by *SCD*) was overexpressed in HCC and correlated with poor survival. Next, using different approaches (including pharmacological inhibitors) they found that acyl-CoA desaturase inhibition induced ER^{UPR} which suppressed liver tumor-initiating cells and sorafenib resistance. They concluded that **“targeting SCD1 alone or in combination with sorafenib might be a novel personalized medicine against HCC.”**

GENETIC LIVER DISEASES

A genetic variation associated with macro-AST

Macro-aspartate aminotransferase (macro-AST) is a rare genetic condition characterized by persistent elevation of AST levels, due to association of the protein with immunoglobulins. AST is encoded by *GOT1* (for glutamic-oxaloacetic transaminase 1). In this issue of the *Journal*, Kulecka *et al.* genotyped 32 patients with suspected familial macro-AST. **An allele in *GOT1* (rs374966349 [C] encoding p.Gln208Glu) was detected in 54% of probands from suspect families**, while its prevalence in healthy controls was only 0.18%. In silico analysis demonstrated that a negatively charged glutamate on the surface of the protein encoded by *GOT1* could strongly anchor serum immunoglobulins. This interesting study strongly suggest that testing for this genetic variant may be useful in diagnosis of macro-AST.

ALCOHOLIC LIVER DISEASE

MIF as a potential molecular driver of alcoholic liver injury

The only effective therapy for patient with alcoholic liver disease is alcohol abstinence. Identifying molecular drivers could help the development of new targeted therapies. In this issue of the *Journal*, Marin *et al.* performed a translational study to assess the role of macrophage migration inhibitory factor (MIF), a powerful inflammatory cytokine. They first found that cultured hepatocytes release MIF in response to ethanol. Then, using different transgenic models in mice, they provide evidence that ethanol intake upregulates MIF in hepatocytes that mediates the inflammatory changes in the liver. In patients with alcoholic hepatitis, MIF was found overexpressed in hepatocytes. Interestingly, serum levels of MIF in the suprahepatic vein were increase and correlated with disease severity. **These data provide evidence that hepatocyte-derived MIF is a molecular driver of ALD and represents a potential novel target for therapy.**

HEPATITIS C VIRUS (HCV) INFECTION

DAA and HCC risk - not so hot!

Whether interferon-free direct-acting antiviral (DAA) therapy has similar effects on early HCC occurrence or recurrence as interferon-based therapy is still a matter of debate. In a retrospective review of a large prospective database (n=1897), Nagata *et al.* were not able to demonstrate any significant difference in both HCC occurrence as well as recurrence rates between the groups treated with IFN-based or IFN-free

therapies. **Indeed, viral eradication had an early inhibitory effect on hepatocarcinogenesis irrespective of the type of antiviral therapy.** Biomarkers for HCC development were identified, and among others, authors described for the first time Wisteria floribunda agglutinin positive Mac-2 binding protein (WFA+M2BP) as a new predictor associated with HCC development after SVR, independently from the stage of liver fibrosis. This study adds to the increasing body evidence highlighting the importance of long-term HCC surveillance of certain risk groups after viral eradication but speaks against a specific role of the type of antiviral treatment concerning the tumor risk in general.

HEPATITIS B AND C DIAGNOSIS

Don't be late

Late diagnosis of HBV and HCV represents a missed opportunity to reduce the risk of serious liver disease. The timing of HBV and HCV diagnoses relative to the detection of decompensated cirrhosis and hepatocellular carcinoma was measured between 1990 and 2012 by Samji *et al.* in the British Columbia Hepatitis Testers Cohort (n=90,510). **Although marked improvement in late diagnosis has been observed for both HBV and HCV over time, still between 46%-49% of HBV and between 31%-40% of HCV cases were diagnosed late.** The authors make an important point that timely diagnosis can reduce morbidity and mortality, particularly in the era of highly effective therapy, and that screening for viral hepatitis remains important as not all affected persons report risk factors.

HEPATITIS B VIRUS (HBV) INFECTION

Less can be more – Finite NA treatment in HBeAg-negative chronic hepatitis B, the ongoing risk of HCC after HBsAg loss – is it all about gender and age?

Stopping nucleos(t)ide analogue (NA) treatment in chronically HBV-infected patients often leads to viral relapse and therefore life-long therapy is usually considered the optimal strategy. However, uncontrolled studies suggest that a relapse-associated HBV-specific immune response may lead to long-term remission even with HBsAg loss. The controlled study by Berg *et al.* is the first that investigated the potential to discontinue tenofovir disoproxil fumarate (TDF) therapy in HBeAg-negative patients in a randomized fashion. **Main findings of this proof-of-concept study were that 2 years after treatment cessation, 50% of the patients remained free of therapy and**

a total of 19% lost HBsAg, whereas no significant decline in HBsAg levels were observed in those who continued on TDF. Although the sample size of this proof-of-concept study was small, the findings open the way for a more individualized strategy in the long-term management of NA-treated patients. Further studies should concentrate on the issue which group of patients are most likely to benefit from this finite approach.

Genetic instability due to integration of parts of the HBV DNA into the human genome as well as the life-long persistence of covalently closed circular DNA serve as explanations for the ongoing risk of HCC development in HBV-infected patients even after loss of HBsAg. Previous studies suggested that the risk is especially high for male patients with advanced fibrosis, and being above 50 years old at the time of HBsAg seroclearance. The study by Yip *et al.* aimed to evaluate the risk of HCC after HBsAg seroclearance, and the impact of gender on HCC development in a large group of 4,568 patients from Hong Kong. The cumulative HCC incidence after HBsAg seroclearance was 0.9%, 1.3% and 1.5% at one, three and five years of follow-up, respectively. **Age above 50 years and male gender were two independent HCC risk factors, whereas female patients aged ≤ 50 years had no risk of HCC development within 5 years.** This study has important clinical implications as HCC surveillance may not be necessary for female patients with HBsAg seroclearance at 50 years or younger, but may still be cost-effective for other patients.

HEPATITIS E VIRUS (HEV) INFECTION

Neurotropism of HEV revisited

Neurologic illnesses are by far the most commonly reported extrahepatic manifestation of HEV infection but the causality has not yet been established. Dalton *et al.* addressed this question by performing a prospective study in which consecutive patients with acute non-traumatic neurological illnesses attending four hospitals in three European countries were systematically screened for HEV infection. They observed an at least ten times higher point prevalence of HEV viremia in neurological patients as compared to recent studies in blood donors. **The most striking observation of the current study is that three of five cases of neuralgic amyotrophy diagnosed during the study were HEV-associated.** This study underlines the neurotropism of HEV, and provides evidence of a specific, likely causal, association between neuralgic amyotrophy and HEV infection. The intriguing finding that ALT levels were normal or

only modestly elevated in the HEV-infected neurological patients could imply that some strains of HEV are primarily neurotropic rather than hepatotropic.

HCC

Predictors of sorafenib benefit, use of AGREE II instrument for quality control of guidelines

Two phase III, randomized, double-blind, placebo-controlled trials of sorafenib, have shown that this treatment significantly prolonged overall survival in patients with unresectable HCC. Bruix *et al.* here report their assessment of prognostic factors for HCC and predictive factors of sorafenib benefit, using a pooled exploratory analysis from these placebo-controlled phase III studies. They show that presence of macroscopic vascular invasion, high alpha-fetoprotein, and high neutrophil-to-lymphocyte ratio (NLR) were predictors of poor overall survival. Sorafenib benefit was consistently observed irrespective of prognostic factors. **Lack of extrahepatic spread, presence of HCV, and lower NLR were predictive of longer overall survival with sorafenib.**

The Appraisal of Guidelines for Research & Evaluation (AGREE II) is the only validated instrument to assess the methodological quality of guidelines. Azoulay *et al.* evaluated the methodological quality of existing guidelines for the resection of HCC using the AGREE II instrument. They reveal that the methodological quality of guidelines for the surgical management of HCC is generally poor. **Future guideline development should be informed by the use of the AGREE II instrument. Guidelines based upon high quality evidence could improve stratification of patients and individualized treatment strategies.**

CIRRHOSIS

alfapump insertion effectively reduces the need for large volume paracentesis in patients with refractory ascites, gut-derived endotoxin contributes to endothelial dysfunction and Factor VIII release

Treatment options for patients with refractory ascites are limited to liver transplantation and a selected group of patients benefit from insertion of transjugular intrahepatic portosystemic stent-shunt. The rest of the patients require repeated large volume paracentesis (LVP). alfapump is a novel, fully implantable, automated, low flow system that automatically moves ascitic fluid into the urinary bladder. **Bureau *et al.* describe**

the results of the first, multicenter, European study comparing alfapump with LVP. The trial data confirm that insertion of the alfapump is associated with significant reduction in the need for LVP, improvements in the quality of life and nutritional state. The incidence of acute kidney injury was higher in the alfapump treated patients but this did not impact negatively on survival. Further improvements in the technology and regular albumin infusions may allow the alfapump to emerge as an important new therapeutic for this group of patients.

The mechanisms underlying the increased risk of portal vein thrombosis (PVT) in patients with cirrhosis is unclear. Studies have suggested that an elevated concentration of factor VIII was associated with risk of PVT. **Carnevale *et al.* describe the results of an important study demonstrating an association between endotoxemia, Factor VIII and von Willebrand's factor levels cirrhosis patients.** They go on to show in isolated endothelial cells that blocking toll-like receptor 4, which inhibits endotoxin signaling prevents LPS-induced release of Factor VIII from the endothelial cells. The result of this study implicates the microbiome in the pathogenesis of PVT and may have implications for future preventative approaches for PVT.

ACUTE LIVER FAILURE

MiR 1224 negatively affects the outcome of acute liver failure (ALF) by inhibiting cell proliferation

The outcome of patients with ALF is determined by a balance between cell death and regeneration. Strategies to enhance regeneration of patients with ALF are lacking. **Roy *et al.* investigated the role of micro RNA 1224, which is a small non-coding RNA that is expressed in hepatocytes. Their important data suggests that during acute injury in a mouse model, miR1224 was expressed in the hepatocytes and this was associated with reduced proliferation and increased apoptosis.** These data were confirmed in the liver of patients with ALF. Furthermore, miR 1224 could be detected in the serum and elevated levels predicted poorer survival. These novel data provide a potential novel biomarker and also a therapeutic target.

LIVER TRANSPLANTATION

Transplantation of organs from deceased donors (DCD) to patients with primary sclerosing cholangitis (PSC) does not impact outcomes

Liver transplantation is the only treatment known to prolong the survival of patients with

PSC. In order to increase the donor pool, greater numbers of organs from donors after death are being used for transplantation. One of the complications of using these organs is the risk of post-transplant biliary strictures. Liver transplantation for PSC across many centers is restricted to the usage of grafts from brain dead donors (DBD) due to apprehensions of post-transplant biliary complications. **Trivedi *et al.* analyzed outcomes of liver transplantation of PSC patients who received either organs from brain dead donors (n=108) and deceased donors (n=35). Intriguingly, their data show that there was no significant difference in the outcome of patients receiving DBD or DCD graft in terms of graft and patient survival. The risk of post-transplant biliary strictures was also similar between the groups.** Increasing the donor pool by allowing patients with PSC to be transplanted with DCD organs has the potential reducing deaths on the waiting list.