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From the Editor's desk...

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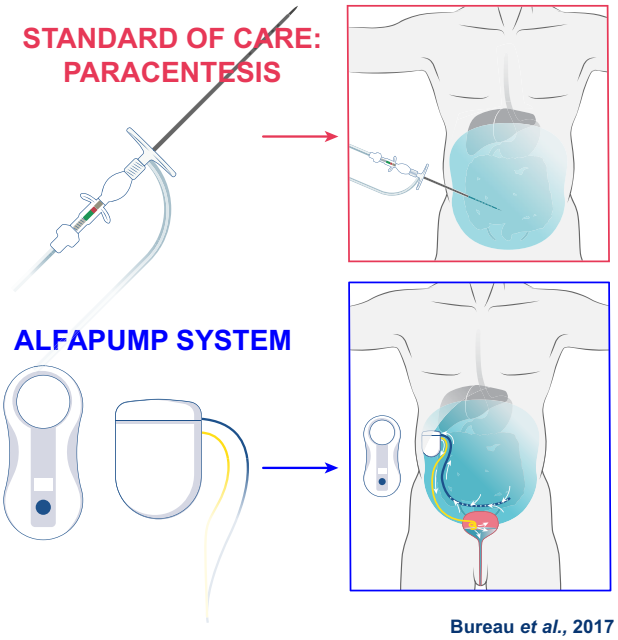
SELECTION OF THE MONTH

alfapump: a new treatment for refractory ascites

Treatment options for patients with refractory ascites are limited to liver transplantation and insertion of transjugular intrahepatic portosystemic stent-shunt, in a selected group of patients. All other 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 patients treated with alfapump, 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.



Bureau *et al.*, 2017
Alfapump System *vs.* large volume paracentesis for refractory ascites

ENDOPLASMIC RETICULUM (ER) HOMEOSTASIS IN LIVER DISEASES

Hepatic ER stress in obesity and hepatocellular carcinoma (HCC)

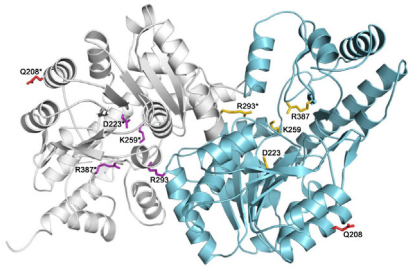
Professional secretory cells, such as hepatocytes, communicate with their environment using secreted proteins and proteins displayed on the cell surface. In order to reach their destinations, these proteins must enter the secretory pathway via insertion into the ER, where they are folded and matured. 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 be 13 million secretory proteins per minute. To accomplish such a thermodynamically unfavourable 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 programme 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 a 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 with the knowledge that a decrease in ER Ca^{2+}concentration can induce ER^{UPR}, and that 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 Wires *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 tumour-initiating cells and sorafenib resistance. They concluded that "**targeting SCD1 alone or in combination with sorafenib might be a novel personalised medicine against HCC.**"

GENETIC LIVER DISEASES

A genetic variation associated with macro-aspartate aminotransferase (macro-AST)

Macro-AST is a rare genetic condition characterised by persistent elevation of AST levels, due to association of the protein with immunoglobulins. AST is encoded by *GOT1* (*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 families suspected of having macro-AST**, 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 suggests that testing for this genetic variant may be useful in the diagnosis of macro-AST.



Kulecka *et al.*, 2017
A heterozygous mutation in *GOT1* is associated with familial macro-aspartate aminotransferase.

ALCOHOLIC LIVER DISEASE

Migration inhibitory factor (MIF) as a potential molecular driver of alcoholic liver injury

The only effective therapy for patients 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 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 mediate 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 increased 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

Direct-acting antiviral (DAA) and HCC risk - not so hot!

Whether interferon-free 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 = 1,897), Nagata *et al.* were not able to demonstrate any significant difference in either HCC occurrence or 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 sustained virologic response, independently from the stage of liver fibrosis. This study adds to the increasing body of evidence highlighting the importance of long-term HCC surveillance in certain at-risk groups after viral eradication, but speaks against the type of antiviral treatment having a specific role in tumour risk, in general.

HEPATITIS B AND C DIAGNOSIS

Don't be late

Late diagnosis of hepatitis B virus (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 HCC 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, between 46%–49% of HBV and between 31%–40% of HCV cases were still 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.

HBV INFECTION

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

Stopping NA treatment in patients with chronic HBV infections 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 randomised fashion. **The main findings of this proof-of-concept study were that two years after treatment cessation, 62% of the patients remained off-therapy and a total of 19% lost HBsAg, whereas no significant decline in HBsAg levels was observed in those who continued on TDF**. Although the sample size of this proof-of-concept study was small, the findings open the door for a more individualised strategy in the long-term management of NA-treated patients. Further studies should concentrate on the issue of 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, above the age of 50 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