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SELECTION OF THE MONTH

Title of the Month: Ageing increases risk of alcohol related liver fibrosis

Cirrhosis (small title): 50% children with chronic liver disease have hepatic encephalopathy

Treating the extreme - When is old too old for HCV treatment?

LIVER REGENERATION

Indian hedgehog protein accelerates liver regeneration

Portal vein ligation (PVL)-induced liver growth is being exploited for the surgical removal of certain liver tumors. A novel approach called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) combines PVL with parenchymal transection. This accelerates compensatory growth, enabling much faster and more

extensive tumor removal. Langiewicz *et al.* addressed the role of secreted factors in the acceleration of the regenerative process following ALPPS. They found that **Indian hedgehog protein (short name: IHH) and subsequent and hedgehog pathway activation is the first signal for the acceleration of liver regeneration following ALPPS surgery in mice. Moreover, they showed elevated plasma IHH early after ALPPS surgery in humans.** Using recombinant IHH may have a potential interest in stimulating liver regeneration.

HEPATOCELLULAR CARCINOMA (HCC)

Regional inequities in HCC management in France, AFP model for predicting HCC recurrence, toward immunotherapy for HCC?

Little is known on the incidence, management, and prognosis of HCC at the national level. Here, Goutte *et al.* investigated data from French administrative databases for more than 30,000 patients with HCC diagnosed between 2009 and 2012, followed up to 2013. They reveal that **despite full insurance coverage for all citizens, national measures to reduce inequities in the management of cancer patients, standardized recommendations for HCC surveillance and management, the percentage of patients undergoing curative treatment and their survival may vary fourfold depending on their postcode.** The hospital in which patients are first managed influences both accessibility to good care and survival.

The French study group for Liver Transplantation developed a new predictive model for HCC recurrence. This model, called AFP model, was based on tumor staging and AFP values at listing and follow-up time points. Notarpaolo *et al.* aimed to evaluate the AFP model in a non-French and for this investigated 574 patients transplanted for HCC in 4 Italian centers. Of note all patients had chronic viral hepatitis-related cirrhosis. **They show that the AFP model identifies HCC candidates at low risk of recurrence otherwise excluded by Milan criteria.** They also suggest that the AFP score could be proposed for selection of HCC candidates in programs with a high proportion of patients with chronic viral hepatitis-related cirrhosis.

In the context of cancer, inhibition of T cell cytotoxicity may favor tumor survival. Interestingly, two therapeutic approaches used for HCC, transcatheter arterial chemoembolization (TACE) and ablation by themselves have been shown to induce a peripheral immune response which might have anti-tumor effects. Of note, T cells require two signals for optimal activation. The first signal is delivered to the T cell

receptor (TCR) by processed antigen displayed by major histocompatibility complex (MHC) molecules. The second signal, known as the costimulatory signal, is delivered to receptors on T cells by costimulatory molecules. Costimulatory signals can have either stimulatory or inhibitory effects on T cells. The best described costimulatory interactions are those in the B7/CD28 family. B7 family members typically act as ligands for CD28 receptor family members. For example, B7-1 or B7-2 expressed at the surface of antigen-presenting cells engage cytotoxic T lymphocyte-associated protein-4 (CTLA-4, also known as CD152) to inhibit TCR-mediated activation. Tremelimumab is a fully human monoclonal antibody that binds to CTLA-4 and results in inhibition of B7-CTLA-4-mediated downregulation of T-cell activation. Duffy *et al.* addressed the hypothesis that, in HCC, peripheral immune stimulation induced by the ablative procedure could be amplified by blockade of the B7-CTLA-4-mediated T-cell inhibition. For this, they conducted a pilot study in 32 patients with HCC. They show that **tremelimumab in combination with tumor ablation in patients with advanced HCC is safe and that an increase in intra-tumoral $CD8^+$ T cells occurs among patients who benefit the combination therapy.**

ALCOHOLIC AND NON-ALCOHOLIC FATTY LIVER DISEASE (ALD AND NAFLD).

Determinants of prognosis in ALD and role of sirtuin 1 on the effect of age and PARP

Compared to NAFLD, few studies have investigated the determinants of disease progression in patients with ALD. Lackner *et al.* assessed the prognostic impact of clinical, biochemical and histological parameters on long-term prognosis in patients with early/compensated and decompensated ALD. **In early/compensated ALD patients, long-term prognosis was determined by fibrosis stage**, but not by clinical or biochemical variables. Importantly, severe fibrosis was present in have of the patients with compensated disease. **In decompensated patients, markers of liver failure (bilirubin, INR), and pericellular fibrosis predicted long-term survival**. Remarkably, **abstinence was an important predictor of survival** in both early/compensated and decompensated ALD. Besides this clinical study, an intriguing paper in this issue investigates the mechanisms by which aging exacerbates the progression of ALD. Ramirez *el al.* demonstrate that, compared to young mice, **middle-aged and old mice are more susceptible to alcohol-induced liver injury**. Importantly, **restoring hepatic expression of sirtuin 1** (Gene Symbol: *Sirt1*), which

is markedly lower in older mice, **ameliorates subacute liver injury** induced by alcohol and also the **fibrogenic response** to chronic liver injury. A role for *Sirt1* in mediating the effects of aging in experimental ALD was confirmed in *Sirt1*-deficient mice. These intriguing results were confirmed at the cellular level, since **hepatic stellate cells from older mice express lower levels of the *Sirt1* gene product**, which regulates their profibrogenic actions. This important study shows that aging exacerbates ALD in mice through the downregulation of *Sirt1* in the liver. Finally, a third study by Mukhopadhyay *et al.* investigates the role of Poly(ADPribose) polymerases (PARPs), key regulators of intermediary metabolism through SIRT1, on alcoholic and nonalcoholic steatohepatitis (ASH/NASH). The authors found PARP activity increased in ASH livers together with decreased NAD+ content and SIRT1 activity. **Pharmacological and/or genetic ablation of PARP attenuated the decrease in SIRT1 activation and reduced hepatic triglyceride accumulation, metabolic dysregulation, or inflammation and/or fibrosis in models of Ash and NASH.** These results suggest that PARP inhibition is a promising therapeutic strategy in steatohepatitis.

HEPATITIS B VIRUS (HBV) INFECTION

Liver disease progression in HBV infection, stem cell-derived hepatocyte-like cells to study the biology of HBV infection

Liver and non-liver related risk factors may contribute to the prognosis of patients chronically infected with HBV. However, neither these factors per se nor their relative contribution to the population-based risk of HBV disease progression have been well defined in the Western world. In the largest Western cohort studied so far including 48,189 HBV-infected patients, Mallet *et al.* showed that **about three-quarters of patients with chronic hepatitis B who progressed to a liver-related complication, including liver transplantation and liver-related death, had an additional liver-related risk factor**. For hepatitis D virus co-infection, hepatitis C virus co-infection, alcohol use disorders, diabetes mellitus, and other rare causes of chronic liver the adjusted hazard ratios for liver disease progression of disease were 1.44, 1.77, 3.37, 1.40, and 2.19, respectively. The fact that HBV HIV co-infected patients without AIDS had better outcomes, despite a higher prevalence of liver-related risk factors, may be taken as a hint how improved linkage to care provided to this special patient population can be also a concept to improve long-term prognosis also in HBV mono-infected patients.

Although HBV was identified more than 50 years ago many fundamental aspects of the virus' biology remain poorly understood mainly due to the lack of physiological cell culture systems permitting efficient HBV infection, replication and dissemination. Xia *et al.* **described a novel *in vitro* HBV infection model, based on stem cell-derived hepatocyte-like cells (HLCs), that fully supports HBV infection for at least one month**. HLCs closely resemble primary human hepatocytes, which makes them suitable for many applications including virus-host interaction studies and drug development in genetically defined hepatocytes but also HBV spreading. By using this model, authors also identified two host-targeting agents, Genistin and PA452, as novel antivirals against HBV infection. This robust model offers a unique opportunity to advance our understanding of the molecular mechanisms of HBV life cycle, to further characterize virus-host interactions, and to define new targets for HBV curative treatment.

HEPATITIS C VIRUS (HCV) INFECTION

What happens after HCV eradication? Treating the extreme - When is old too old for HCV treatment?

With the increasing number of patients achieving direct antiviral agents (DAA)-induced sustained viral eradication (SVR) there is increasing interest in studying the SVR-associated long-term consequences, and to figure out to what extent viral eradication also translates into a reduction of liver disease-associated complications – mainly HCC development. Van der Meer *et al.* followed 1000 patients from previously reported Western cohort studies with chronic HCV infection and bridging fibrosis or cirrhosis who attained SVR. **The study confirmed an annual HCC risk after SVR of approximately 1% in HCV-induced cirrhosis but also showed for the first time a significant risk of clinical disease progression**. After 8 years 4.2% of patients with bridging fibrosis and 15.8% of patients with cirrhosis experienced clinical disease progression. In a second study in this issue the effect of SVR on the estimated HCC incidence post SVR was evaluated by Janjuain *et al.* in a large population-based Canadian cohort (N=8,147). **SVR after interferon-based treatment substantially reduced HCC risk with an incidence rate of 1.1/1000 person-years (PY) as compared to 7.2/1000 PY among the non-SVR group**. Factors associated with HCC development post-SVR were cirrhosis, age ≥ 50 years and being male. These studies

highlight the need of early HCV diagnosis and to start HCV eradication before advanced fibrosis is established.

Extremely aged patients, i.e., those aged 80 years or older, have been rarely considered eligible for antiviral treatment in the interferon era, and it remains to be seen whether this population derives similar clinical benefits from DAA-induced HCV eradication as younger patients. In the present study, Toyoda *et al.* analysed the efficacy and tolerability of an interferon-free daclatasvir plus asunaprevir regimen in patients ≥ 80 years, and compared the results with those of patients aged ≥ 70 and < 80 years and those aged <70 years. They found a similar tolerability and efficacy of the DAA regimen irrespective of patients' age but more importantly, **the HCV eradication resulted in a significant survival benefit even in patients aged ≥ 80 years**. In ≥ 80 years-old patients with persistent HCV infection, the 1-year mortality due to liver-related diseases was 8.1%, but none of the patients with SVR died from liver disease. According to the results of this important study there seems to be no age limit at which one should withheld DAA treatment in the increasingly ageing HCV infected population.

CIRRHOSIS

50% children with chronic liver disease have minimal hepatic encephalopathy

Minimal hepatic encephalopathy (MHE) is a common feature of cirrhosis in adults but its presence, frequency and pathophysiology is not clear in children with chronic liver disease. **The paper by Srivastava *et al.* provides the first comprehensive insight into the problem suggesting that about 50% of children with chronic liver disease have features of MHE, that may result in poor quality of life, risk of overt HE and mortality.** Parameters identified on MRI scanning had a high sensitivity and specificity for identification of those with MHE. The paper also describes that the pathophysiological mechanisms underlying this syndrome is similar to that in adults, suggesting that clinical trials of available agents to treat MHE may be justifiable in children as well. Although further validation of these data is needed, this seminal observation will allow further studies.

CHOLESTASIS

ACOX2 deficiency as a novel cause of abnormal liver function of unknown cause

ACOX2 (official full name: acyl-coenzyme A oxidase 2) encodes a peroxisomal

enzyme involved in shortening of C27 cholesterol derivatives to C24 bile acids. Deficiencies in the metabolic pathways of cholesterol-bile acid metabolism have been shown to be associated with hepatic and neurologic dysfunction. **In looking for possible mechanisms underlying abnormal liver function tests in an adolescent patient, Marin *et al.* discovered for the first time evidence of *ACOX2* deficiency as the underlying cause.** They showed that this patient had evidence of elevated C27 intermediates but almost completely absent C24 metabolites. Exons amplification/sequencing of enzymes potentially involved revealed a homozygous missense mutation (c.673C>T; R225W) in *ACOX2*. Other data generated by the group provide and insight into the operative mechanisms. This case study may have relevance to investigating patients with abnormal function tests of unknown cause.