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FINAL

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SELECTION OF THE MONTH

Big title: Treated HCV cirrhosis patients can have normal life expectancy

Small Titles:

HBV integration generates oncogenic chimera

Is there a place for response-guided DAA treatment?

Potential novel biomarker to predict beta-blocker response in cirrhosis

Type 2 diabetes and the burden of chronic liver diseases

ACUTE HEPATITIS

Role of cytotoxic CD8 T lymphocytes (CTLs)

Acute hepatitis can be a result of CTL action but factors that limit CTL-mediated liver injury are poorly understood. Vo *et al.* addressed this question using elegant strategies aiming to investigate the role of regulation of T cell death, regulation of CTL function and T cell inhibitory molecules, independently of TCR affinity, T cell help and antigen dose. In the setting of high-level persistent antigen expression in the liver, the degree and duration. Their results show that liver damage is predominantly regulated by genes controlling the function of effector cells rather than those affecting T cell lifespan. Persistence of liver damage is actually limited by functional T cell exhaustion. **These data suggest that immunotherapies aimed at increasing the number of CTLs in patients with liver disease should be combined with strategies that enhance T cell effector function and interfere with T cell exhaustion**.

LIVER REGENERATION

Human embryonic stem cell (hESC) utilization

Hepatocytes differentiated from human embryonic stem cells (hESCs) might be a response brought to the shortage of primary hepatocytes for clinical use and drug development. Touboul *et al.* hypothesized that the functionality of hESC-derived hepatocytes could be improved by making the differentiation method more similar to normal in vivo liver development. They show for the first time that **stage-specific regulation of the WNT/β-catenin pathway results in improved differentiation of hESCs to functional hepatocytes.**

CANCER

Role of clock genes in cholangiocarcinoma, long non-coding RNA (lncRNA) in hepatocellular carcinoma (HCC)

Although disruption of circadian rhythm is associated with cancer development and progression, little is known on gene regulation of circadian rhythm in cholangiocarcinoma. Han *et al.* investigated the role of period circadian clock 1 (which is encoded by *Per1* and is a transcriptional repressor that forms a core component of the circadian clock) and related microRNAs. They show that **disruption of circadian rhythms of clock genes, via miR-34a overexpression, contributes to the malignant phenotypes of human cholangiocarcinoma.**

Activation of the autocrine interleukin (IL)-6/signal transducer and activator of transcription 3 (STAT3) signaling is known to promote liver inflammation and

tumorigenesis. Wang et al. show here that low expression of lnc-DILC (for lncRNA down-regulated in liver cancer stem cells (LCSCs) markedly enhance LCSC expansion via an autocrine activation of IL-6/STAT3 signaling. Mechanistically they found that low lnc-DILC levels allowed an increased binding of the transcription factor nuclear factor (NF)-κB to *IL6* promoter and therefore in increased *IL6* induction. This autocrine loop may be favored pro-inflammatory cytokines such tumor necrosis α and IL-1β that activate NF-κB. Interestingly they found low lnc-DILC levels in livers from patients with HCC; moreover, the lower lnc-DILC the poorer the outcome. They suggest that "**lnc-DILC could be not only a potential prognostic biomarker, but also a therapeutic target against LCSCs.**"

ALCOHOLIC AND NON-ALCOHOLIC STEATOHEPATITIS

Type 2 diabetes increases the risk of hospitalizations due to chronic liver diseases, TRAF1-ASK1 signaling and miR-155 play a crucial role in non-alcoholic (NASH) and alcoholic steatohepatitis (ASH), respectively

The impact of type 2 diabetes (T2DM) on hospital admissions and deaths due to common chronic liver diseases is uncertain. In a large retrospective study in Scotland, Wild *et al.* found that **T2DM is associated with increased risk of hospital admission or death for all common chronic liver diseases**. In people with T2DM, the most common disease was NAFLD, as expected. This study has important public health implications since it suggests that increasing prevalence of T2DM is likely to result in increasing burden of all chronic liver diseases.

The molecular mechanisms of NASH and ASH are largely unknown, and translational studies are needed to identify novel targets for therapy. Tumor necrosis factor receptor-associated factor 1 (TRAF1) is an important regulator of inflammation. The role of this factor in non-alcoholic steatohepatitis (NASH) is unknown. In this issue, Li *et al.* performed a translational study including human samples and functional studies in animal models of NASH. They convincingly demonstrate that **TRAF1 functions as a positive regulator of insulin resistance, inflammation, and hepatic steatosis** in NASH, dependent on the activation of ASK1-p38/JNK axis. In another translational study, Bala *et al.* demonstrate a role for the microRNA 155 (miR-155) in ASH. Genetic or pharmacological **inhibition of miR-155 resulted in increased PPARα (miR-155 target) binding and decreased cytokine production**. Importantly, Kupffer cells isolated from miR-155 KO mice exhibited a M2 phenotype, which is less inflammatory.

Finally, **miR-155 regulated the induction of fibrogenic genes and collagen deposition** in several animal models. These results suggest a role for this microRNA in ASH and in experimental liver fibrogenesis.

HEPATITIS C VIRUS (HCV) INFECTION

HCV – a silent killer among young and middle-aged men in Egypt? Viral eradication in early HCV cirrhosis normalize life expectancy, DAA treatment improves outcome of decompensated hepatitis C

The majority of people chronically infected with hepatitis C virus (HCV) reside in low- and middle-income countries, and with an estimated 10% Egypt has the highest HCV prevalence in adults. Excess mortality rate associated with chronic HCV infection was evaluated by Mostafa *et al.* in a community-based cohort study in rural Egypt among 18,111 survey participants enrolled in 1997-2003 of whom 9.1% were chronically infected. Depending on age groups the mortality rate ratios (MRR) in men ranged between 2.87 to 2.22, and the **all-cause mortality rate attributable to chronic HCV infection was 5.7%, while the liver-related mortality was 45.5%.** The excess mortality described here among young and middle-aged men should be used for prioritization of patients in the Egypt National DAA Treatment Programme.

That the induction of a sustained virologic response (SVR) is associated with an improved outcome of chronic hepatitis C virus (HCV) infection, has been demonstrated in several studies by comparing patients with and without SVR. The study by Bruno *et al.,* however, is the first to demonstrate that **patients with compensated cirrhosis who achieve SVR will have a life expectancy similar to that of the sex- and age-matched general population**. Included patients were enrolled in historical prospective cohort studies from tertiary referral centers from Northern and Southern Italy, representative of the Italian general population allowing for adequate comparison of patients long-term 10- and 20-year survival with national data. The intriguing observations of a trend to worse survival observed in patients with compensated cirrhosis Child Class A6 as compared to A5 but also that the incidence of hepatocellular carcinoma (HCC) during follow-up after SVR was not negligible, underscore the need for early treatment initiation hereby preventing cirrhosis development as the main HCC determinant.

Treatment of decompensated HCV-induced cirrhosis remains challenging even in the DAA era and it has to be determined to which extend treatment-induced viral

eradication impacts liver function and long-term outcome. In an NHS England Expanded Access Programme study by Foster *et al.* 467 HCV-infected patients with decompensated cirrhosis or at risk of irreversible disease were treated for 12 weeks with sofosbuvir combined with the NS5A inhibitors ledipasvir or daclatasvir, with or without ribavirin. Functional outcome was retrospectively compared to untreated patients with decompensated cirrhosis who were registered on the HCV Research UK database 6 months before treatment was available. **Viral eradication** was achieved in 90.5% and 67% of type 1 and 3 infected patients, respectively, and **was associated with a significant improvement of the MELD score** but also significantly fewer treated patients developed a profound worsening in MELD as compared to the untreated controls. Although a substantially lower chance of benefit was seen in older patients with low albumin or sodium concentrations, the predictive power of these parameters were low and they should not be used for making treatment decisions so far.

CIRRHOSIS

Novel biomarker to determine portal pressure response to non-selective beta-blockers (NSBB)

Assessment of whether a patient is likely to have a portal pressure response to NSBBs requires catheterization of the portal vein. In a very provocative study, **Trebicka *et al.* show exciting new data showing for the first time that measuring beta-arrestin-2, a vasoactive mediator, the expression of which is upregulated in the cirrhotic stomach and its levels predict response to NSBBs.** If these data can be made more quantitative and further validated, it may lead to the development of an important decision-making tool to decide on selection of patients for NSBB therapy.

TRANSPLANTATION

Insights into regulation of rejection and tolerance following liver transplantation

Although the potential role of Programmed death 1 (PD-1) receptor and its ligand PD-L1, which are known to fine tune immune responses have been shown to be important in maintaining allograft tolerance in animal models, their role is unknown in humans. **Shi *et al.* provide the first indication that the interplay between donor PD-L1 and recipient PD-1, are also involved in the counter regulation of allograft rejection and may therefore be a potential target for inducing tolerization.**

CHOLESTASIS

CFTR correctors can rescue defective plasma membrane ATP8B1 and is a potential novel therapeutic approach

Treatment options for familial intrahepatic cholestasis are limited with many patients needing liver transplantation as the only therapeutic option. **A very important paper by van der Woerd *et al.* shows that the plasma membrane defect of *ATP8B1* mutation that results in protein misfolding can be corrected using the known correctors of cystic fibrosis conductance regulator (CFTR) gene mutation *in vitro***. If this in vitro observation can be confirmed in vivo, a new therapeutic for this type of diseases may emerge as the correctors of CFTR are already clinically available.

HEPATOCYTE TRANSPLANTATION

Biliary fibrosis induces proliferation of transplanted hepatocytes and phenotype switch

The clinical application of hepatocyte transplantation has been limited by the ability of the transplant cells to populate the recipient liver. Many lines of investigation provide evidence that liver injury provides a stimulus for liver repopulation with the transplanted cells. **The paper by Yovchev *et al.* provides important new data that inducing biliary fibrosis is associated with increased ability of the transplanted hepatocytes to proliferate, and start to express biliary markers.** They suggest that these effects may be mediated by osteopontin, providing a potentially translatable strategy.