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From the Editor's desk...

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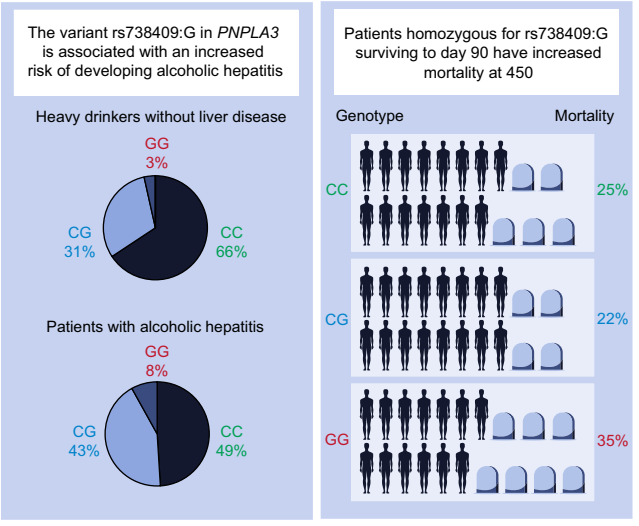
SELECTION OF THE MONTH

PNPLA3 increases risk of death in alcoholic hepatitis

Carriage of an allele in *PNPLA3* (rs738409[G], encoding I148M) is associated with an increased risk of developing alcohol-related cirrhosis. In an important study in this issue of the *Journal*, Atkinson *et al.* assessed whether carriage of rs738409[G] has an additional detrimental effect on survival in patients with alcoholic hepatitis, the most deadly form of ALD. Almost **900 patients from the STOPAH trial and 2,000 alcohol dependent controls were included**. The frequency of rs738409[G] was significantly higher in cases than controls (29% *vs.* 19%; $p = 2.15 \times 10^{-15}$). There was no association between rs738409[G] and 28-day mortality. However, **mortality in the period day 90–450 was higher in survivors who subsequently resumed drinking and individuals homozygous for rs738409[G]** (hazard ratio 1.69, 95% confidence interval 1.02–2.81, $p = 0.04$). This study suggests that homozygosity for rs738409[G] in *PNPLA3* confers significant additional risk of medium-term mortality in patients with severe alcoholic hepatitis.



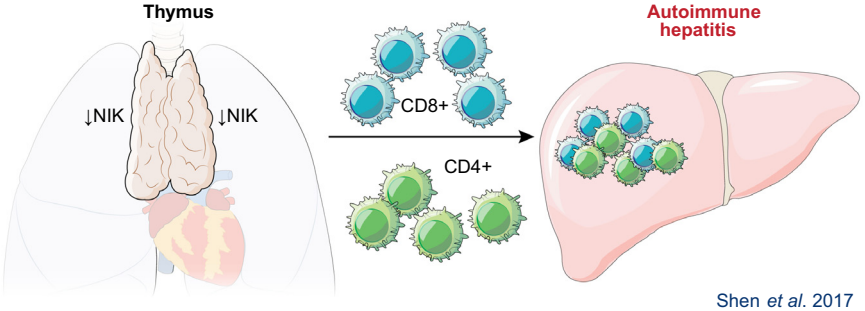
Atkinson *et al.* 2017

LIVER INJURIES

Thymic *MAP3K14* and liver homeostasis, deciphering chemotherapy-related liver injury (CALI)

Breakdown of liver immune privilege can develop in chronic liver disease; however, the role of adaptive immunity in liver injury is poorly defined. Here Shen *et al.* investigated the role of mitogen-activated protein kinase kinase kinase 14 (*MAP3K14*, also known as *NIK*) because it is involved in NF-jB activation in immune cells and because of its role in maintaining liver homeostasis is unknown. To achieve this, they deleted *MAP3K14* systemically or conditionally in mice. They reveal that thymic *MAP3K14* suppresses development of autoreactive T cells against liver antigens, and *MAP3K14* deficiency in the thymus results in $CD4^+$ T cell-orchestrated autoimmune hepatitis and liver fibrosis. Thus, **thymic *MAP3K14* is indispensable for the maintenance of liver immune privilege and liver homeostasis**.

CALI increases the risk of liver resection, and may prejudice further surgery as well as chemotherapy. No data regarding reversibility of CALI are available. Vigano *et al.* retrospectively analyzed the reversibility of CALI in patients undergoing liver resection for colorectal metastases. They found that **CALI persists for a long time after chemotherapy. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia regress only after nine months without chemotherapy, whereas steatosis and steatohepatitis persist**.



Shen *et al.* 2017

CHOLANGIOCARCINOMA (CCA)

SOX17 in CCA

CCA is a biliary malignancy associated with epigenetic abnormalities, such as hypermethylation of the promoter of *SOX17* (Sex Determining Region Y [SRY]-box 17). SOX19 is one of the 19 genes of the gene family of SRY-boxes (HUGO Gene Name nomenclature; http://www.genenames.org) that encode transcription factors involved in the regulation of embryonic development and in the determination of the cell fate. The transcription factor encoded by *SOX17* binds to DNA sequences 5′-AACAAT-′3 or 5′-AACAAAG-3′. It modulates transcriptional regulation via WNT3A, inhibits Wnt signaling and promotes degradation of activated CTNNB1. Here, Merino-Azpitarte *et al.* investigated the

role of *SOX17* in cholangiocyte differentiation and cholangiocarcinogenesis. For this, they studied SOX17 expression/function along the differentiation of **human induced pluripotent stem cells** into cholangiocytes, in the dedifferentiation process of normal human cholangiocytes in culture and in cholangiocarcinogenesis. They show that ***SOX17* regulates the differentiation and maintenance of the biliary phenotype and functions as a tumor suppressor for CCA, suggesting a potential prognostic marker and a promising therapeutic target**.

HEPATOCELLULAR CARCINOMA (HCC)

Early events determine the outcome of successfully treated HCC in patients with HCV-related cirrhosis

Here, Cabibbo *et al.* aimed to estimate the impact of early (occurring within 12 months after complete radiological response) time-dependent events (HCC recurrence or hepatic decompensation), on 5-year overall survival in a large cohort of successfully treated HCC patients with HCV-related cirrhosis. They reveal that **survival in HCV-infected cirrhotic patients with successfully treated HCC is mainly influenced by early hepatic decompensation**. These findings suggest that the use of direct antiviral agents may improve survival of patients with HCV-related cirrhosis and successfully treated HCC; this hypothesis deserves to be addressed in future studies.

GENETICS IN LIVER DISEASE

Genetic determinants of drug-induced liver injury (DILI) by minocycline, and NASH

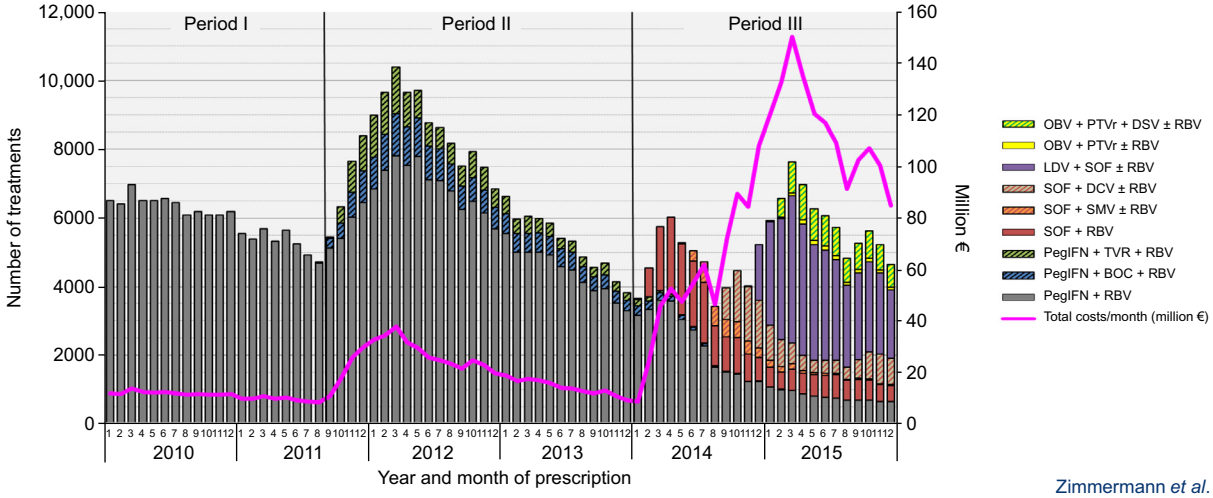
Factors predisposing to **minocycline-induced hepatotoxicity** are unknown. Urban *et al.* performed genome-wide genotyping in a well characterized cohort. Most patients were women and 90% had positive antinuclear antibodies. **A significant association was noted between a HLA class I histocompatibility antigen, B-35 alpha chain (HLA-B*35:02) and risk for minocycline DILI** (16% carrier frequency in DILI cases compared to 0.6% in population controls). HLA-B*35:02 carriers had similar presenting features and outcomes compared to non-carriers. In silico modeling studies supported the hypothesis that direct binding of minocycline to this novel HLA risk allele might be an important initiating event in minocycline DILI. If confirmed in other cohorts, this HLA allele may prove to be a useful diagnostic marker of minocycline DILI.

Carriers of a variant in the transmembrane 6 superfamily member 2 (*TM6SF2*) gene that results in a E167K substitution in the encoded protein, have increased risk of NASH. Interestingly, these subjects lack hypertriglyceridemia and have lower risk of cardiovascular disease. In animals, phosphatidylcholine (PC) deficiency results in a similar phenotype. Luukkonen *et al.* studied the **effect of the *TM6SF2* E167K on these lipids in human livers and cultured hepatocytes**. Patients with *TM6SF2* EK/KK had higher liver triglycerides but lower PCs. Also, incorporation of polyunsaturated fatty acids (PUFA) into triglycerides and PCs in *TM6SF2* knockdown hepatocytes was decreased. As expected, hepatic expression of *TM6SF2* was decreased in variant carriers, and was coexpressed with genes regulated by PUFAs. This interesting study demonstrates that **hepatic lipid synthesis from PUFAs is impaired and could contribute to deficiency in PCs and increased intrahepatic triglycerides in *TM6SF2* E167K variant carriers**.

HEPATITIS C VIRUS (HCV) INFECTION

DAA treatment in prior HCC patients – the Veterans Affairs experience, curing HCV in HIV co-infection, lower than expected increase in DAA prescriptions

The effectiveness of direct acting antivirals (DAAs) in patients with a history of HCV-induced HCC is largely unknown, as these patients have been systematically excluded from prospective controlled trials. The objective of the study by Beste *et al.* was to describe the characteristics of HCC patients who received DAA-based antiviral treatment and to report the rates



Zimmermann *et al.* 2017