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From the Editor's desk...

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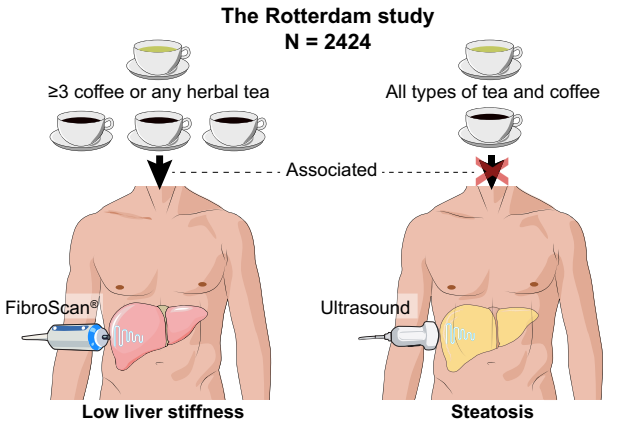
SELECTION OF THE MONTH

Coffee and herbal tea consumption is protective of liver stiffness in the general population

It has been proposed that coffee and tea have beneficial effects on liver diseases, including hepatocellular carcinoma (HCC) development. Alferink *et al.* analyzed the participants who underwent transient elastography, ultrasound and completed a food frequency questionnaire from the Rotterdam study, a large prospective population-based cohort study. The authors included 2,424 participants, of whom 5% had liver stiffness measure (LSM) ⩾8.0 kPa and 34% had steatosis. **The proportion of participants with LSM ⩾8.0 kPa decreased with higher coffee consumption.** Among tea consumers, **only herbal tea consumers (36%) had lower log-transformed transient elastography levels**. Subtypes of tea were associated with steatosis in univariate, but not multivariable analysis. This important epidemiological study suggests that in the general population frequent coffee and herbal tea consumption are inversely related to liver stiffness, but not steatosis. These results should be confirmed in prospective longitudinal studies.



Alferink *et al*. 2017
Coffee and herbal tea consumption is protective of liver stiffness

METABOLIC LIVER DISEASES

Cyclic AMP-dependent activating transcription factor 3 (ATF-3), beta-catenin and CD44: new molecular drivers of non-alcoholic steatohepatitis (NASH) and iron-overload induced liver injury

ATF-3 (encoded by *ATF3*) plays a role in type 2 diabetes and insulin resistance. In this issue of the Journal, Kim *et al.* studied its role in non-alcoholic fatty liver disease (NAFLD). ATF-3 was highly expressed in the livers of patients with NAFLD and in Zucker diabetic fatty (ZDF) rats. Insulin resistance and hepatic steatosis were associated with increased ATF-3 expression and decreased fatty acid oxidation. Importantly, ***Atf3* suppression ameliorated glucose intolerance and inflammatory responses in ZDF rats**. In patients with NAFLD, ATF-3 expression correlated with surrogate markers of type 2 diabetes and hepatic inflammation. Collectively, the results of this translational study suggest a role for ATF-3 in insulin resistance and hepatic inflammation, in patients with NAFLD. Consequently, ATF-3 is proposed as a novel therapeutic target. In another interesting study Preziosi *et al.* investigated the link between beta-catenin (encoded by *Ctnnb1* in mice), iron-overload and liver injury. *Ctnnb1*-knockout mice were exposed to an iron-overload diet in the presence or absence of N-Acetyl-L-(+)-cysteine (NAC), an antioxidant. ***Ctnnb1*-deficient mice exposed to iron exhibited remarkable inflammation, fibrosis and occasional occurrences of HCC**. Interestingly, antioxidant therapy ameliorated these changes. Addition of **NAC to drinking water protected mice from liver injury** and prevented the activation of pro-inflammatory signaling pathways. This study reveals a new role for beta-catenin and suggests that antioxidants may have a protective role against iron-induced liver injury. Finally, another study from this issue analyzes the role of CD44, a receptor that regulates adipose tissue inflammation in obesity. Patouraux *et al.* provide elegant evidence that mice deficient in *CD44 antigen* (*Cd44*) are resistant to the development of liver inflammation and fibrosis, after a fibrogenic insult. Interestingly, *Cd44* deficiency enhanced the M2 polarization and strongly decreased the activation of macrophages by lipopolysaccharide, hepatocyte damage-associated molecular patterns, and saturated fatty-acids. Neutralization of CD44 antigen protein decreased macrophage infiltration. Importantly, in NASH patients hepatic CD44 and soluble CD44 antigen in serum was increased and correlated with the severity of liver injury. **This study suggests that CD44 is a biomarker and a molecular player in NASH through its regulation of macrophage infiltration and polarization**.

HEPATITIS C VIRUS (HCV) INFECTION

Global epidemiology of HCV subtypes and resistance-associated substitutions, next generation pangenotypic direct-acting antiviral (DAA) combination, trends in HCV incidence among HIV-positive men who have sex with men (MSM), scavenger receptor class B member 1 genetic variants modulate HCV infection

HCV genotypes and subtypes, as well as the presence of baseline resistance-associated substitutions (RASs), represent key viral determinants for the selection of DAA treatment regimens. The study by Welzel *et al.* is the first comprehensive global molecular epidemiological analysis of HCV subtypes and subtype-specific RASs. The analyses were performed by both INNO-LiPA and sequencing on 12,615 patient samples, from 28 different countries, across five geographic regions. Whereas genotyping concordance was high between methods, INNO-LiPA had significant limitations for subtyping, especially types 2, 3, 4 and 6. **Not only the observed variations in regional subtype epidemiology, but also subtype-specific RAS prevalence, may have crucial implications when designing future global HCV treatment strategies**.

Aiming for antiviral regimens that are highly effective, irrespective of the HCV type/subtype and presence of baseline resistance-associated variants, was the rationale behind second generation DAA drug development. The NS3/4A protease inhibitor glecaprevir and NS5A inhibitors pibrentasvir (G/P) have potent antiviral activity *in vitro* against all six major HCV genotypes, with a high barrier to the selection of common viral variants with RASs. Kwo *et al.* present results from two phase II studies (SURVEYOR-I and SURVEYOR-II, parts 1 and 2) designed to evaluate the efficacy and safety of various doses of G/P, with or without ribavirin, for the treatment of non-cirrhotic patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection. Eight-week treatment with the dosage-optimized regimen yielded SVR rates of 97–98% in HCV type 1–3 infection (with no virologic relapses), while 100% of type 4–6 infected patients achieved SVR after a 12-week course. **These studies demonstrate the ability of the G/P combination to treat all six major HCV genotypes with a single ribavirin-free regimen regardless of baseline resistance-associated polymorphisms, and with treatment durations as short as eight weeks in populations without cirrhosis**.

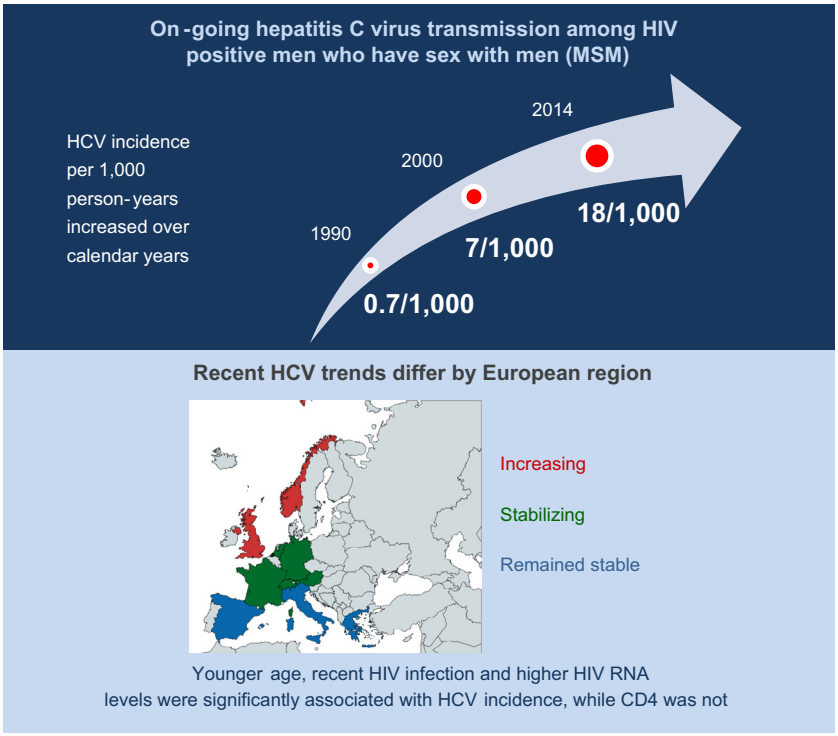
HCV infection continues to spread among HIV-positive MSM, especially among younger individuals. This cohort study from Europe, Australia and Canada aimed to estimate trends in HCV incidence among HIV-positive MSM with well-estimated dates of HIV seroconversion from the CASCADE Collaboration, while also assessing the association between HCV incidence and geographical region, age, HIV RNA and CD4 count. Van Santen *et al.* showed that **HCV incidence significantly increased after 1990, with no evidence of a decline in recent years. However, trends seem to differ by geographical region.** While HCV incidence appears to have stabilized in Western Europe, and remained stable in Southern Europe, an increase in HCV incidence was observed in Northern Europe. Interestingly, a higher HIV RNA and younger age were associated with a higher HCV incidence. This large-scale study adds important data to the current body of evidence regarding HCV trends among HIV-positive MSM and the association of HIV-related factors with HCV infection.

Scavenger receptor class B member 1 (SRB1) is one of four hepatocyte surface expressed molecules regarded as essential for HCV host cell entry. Physiologically, SRB1 functions as a multiligand receptor that binds lipoproteins. Numerous studies indicate that genetic variations in the *SCARB1* gene that encodes SRB1 are associated with clinical phenotypes, yet their impact on HCV infection is incompletely understood. Westhaus *et al.* performed the most comprehensive study to date evaluating the impact of *SCARB1* genetic variants on the molecular biology of HCV and the clinical course of hepatitis C. **They found evidence that both coding and non-coding genetic variants affect the HCV replication cycle, as well as clinically relevant HCV-related parameters, in HCV infected individuals.** Moreover, genetic deletion of *SCARB1* from an HCV permissive cell line resulted in a markedly reduced susceptibility to HCV infection. Overall, this important study adds to our understanding of the role of genetic host factors in modulating disease characteristics, hereby explaining – at least in part – the remarkably high degree of inter-individual variation seen during HCV infection.

HEPATITIS B VIRUS (HBV) INFECTION

A potential high-risk mutation for HBV-infected individuals selected during tenofovir (TDF) and entecavir (ETV) combination therapy

Long-term treatment with antiviral drugs carries the risk of selecting mutations in the HBV polymerase. Shirvani-Dastgerdi



van Santen *et al*. 2017
Trends in HCV incidence among HIV-positive MSM