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NAFLD in 2018: a spotlight on pathogenesis, interactions and novel therapeutic options

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The new frontier in liver disease is represented by Non-alcoholic Fatty Liver Disease (NAFLD), the leading aetiology of chronic hepatitis in the Western world and the only one whose prevalence is steadily rising over time, particularly in the developing countries (e.g. the Middle East or South America) (1). Up to 15% of subjects with NAFLD will develop the active form of the disease, namely Non-Alcoholic Steato-Hepatitis (NASH), characterized by the three histological hallmarks of steatosis, lobular inflammation and hepatocyte ballooning, not associated with significant alcohol intake (by definition < two drinks/day). Patients with NASH can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) and have an increased likelihood of liver-related mortality, which is the third cause of death in these subjects compared to the thirteenth in the general population.

As HCC in NAFLD can develop also in the absence of cirrhosis, defining the mechanisms of carcinogenesis is one of the most important unmet need in the field. In the last year, Liu et al. have put the light on the role of squalene epoxidase (SQLE) for the development of HCC (2). RNA sequencing analysis of NAFLD-HCC samples revealed SQLE as the top outlier metabolic gene overexpressed in NAFLD-HCC patients, also associated with poor patients' outcome. In an animal model on high-fat and high cholesterol diet, hepatocyte-specific *Sqle* transgenic expression was able to favour the onset of HCC via the biosynthesis of cholesteryl ester and an increase of the NADP⁺/NADPH ratio, in turn leading to increased cell growth and activation of the oxidative stress cascade. Of note, the authors also demonstrated that the antifungal and anti-SQLE drug terbinafine was capable of blocking the SQLE-oncogenic activity, suggesting a new potential target for the treatment of HCC in these patients (2).

A progress in understanding the genetic basis of liver damage in NAFLD has been achieved by Abul-Husn et al. (3). By using exome sequence data and electronic health records from 46,544 individuals of the DiscovEHR human genetics study, they found that a splice variant (rs72613567:TA) in HSD17B13, encoding the hepatic lipid droplet protein hydroxysteroid 17-beta dehydrogenase 13, is associated with lower levels of transaminases. In addition, this variant, when homozygous, is associated to a reduced risk of NAFLD and NAFLD-cirrhosis by 30% and 49% respectively. In human liver samples rs72613567:TA was associated with lower odds of NASH and fibrosis by 52% and 61% respectively in homozygous carriers. Analysing the interaction between the rs72613567:TA splice variant and the PNPLA3 p.I148M allele, the authors observed that each rs72613567:TA allele mitigated the increases in aminotransferase levels associated with each

PNPLA3 148M allele. Moreover, RNA sequencing analyses showed that HSD17B13 rs72613567:TA was associated with decreased PNPLA3 messenger RNA (mRNA) expression in an allele dose-dependent manner, resulting in an unstable and truncated protein with reduced enzymatic activity. Associations with liver function tests were replicated in two different cohorts (1357 persons of European origin from the Dallas Heart Study and 8526 persons of European ancestry from the Penn Medicine BioBank respectively); while the association with chronic liver disease was replicated in 517 cases and 4279 controls from the Dallas Heart Study.

In the perspective of new targets for treatment, it is crucial to unravel the role of gut microbiota in NAFLD. Lesley Hoyle et al combined shotgun sequencing of fecal metagenomes with molecular phenomics (hepatic transcriptome and plasma and urine metabolomes) in two well-characterized cohorts of morbidly obese women recruited to the FLORINASH study (4). They found that patients with steatosis have low microbial gene richness and increased genetic potential for the processing of dietary lipids and endotoxin biosynthesis (notably from Proteobacteria), hepatic inflammation and dysregulation of aromatic and branched-chain amino acid metabolism. Fecal microbiota transplants (FMT) and chronic treatment with phenylacetic acid, a microbial product of aromatic amino acid metabolism, successfully triggered steatosis and branched-chain amino acid metabolism (4). Although FMT is not ready for clinical use in this context yet, the reciprocal interactions between gut-liver axis, gut microbiota and diet are worthy to be deeply explored.

International guidelines for the management of NAFLD (5) indicate that, while simple steatosis is relatively benign, a pharmacological treatment would be indicated in patients with NASH that halt progression of fibrosis and have the potential to reduce liver-related morbidity and mortality. As of 2018, there are no approved drug treatments for NASH, which basically relies on lifestyle change only. Nevertheless, promising results are emerging from the various ongoing pharmaceutical trials (6). Excess lipotoxic metabolites in the liver are believed to provide the primary insult in the pathogenesis of NASH, but recent evidence supports a role for bile acids in the pathogenesis of liver inflammation and fibrosis (7). Fibroblast growth factor 19 (FGF19), an endocrine gastrointestinal hormone, controls bile acid metabolism via actions on CYP7A1 and regulates glucose homeostasis, but also has a tumorigenic activity by activating STAT3 signalling (8). A randomised, double-blind, placebo-controlled, phase 2 study, recently tested the safety and efficacy of NGM282, a non-tumorigenic analogue of FGF19, in adult patients with biopsy-confirmed NASH (9). After only 12 weeks, 20 (74%) patients in the 3 mg dose group and 22 (79%) in the 6 mg dose group achieved at least a 5% reduction

in absolute liver fat content from baseline, and a concomitant reduction of markers of inflammation and fibrosis, versus two (7%) in the placebo group. Overall the safety profile was good, with adverse events including injection site reactions and GI discomfort (diarrhoea, abdominal pain and nausea), thus encouraging larger trials of longer duration to fully assess the safety and efficacy of this compound.

In summary, we are experiencing an exciting time for science and discovery in order to tackle the threat of liver-related morbidity and mortality, often overlooked, associated to the pandemic of obesity. In the near future, the big effort in detangling the complexity of mechanism leading to liver damage will effectively translate into a personalized medical care in NAFLD patients.

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