commentary

Beyond fat accumulation, NAFLD genetics converges on lipid droplet biology[1]

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Nonalcoholic fatty liver disease (NAFLD) is epidemiologically associated with obesity, insulin resistance, and dyslipidemia, and is rapidly becoming the leading cause of liver disease. The presence of NAFLD is associated with an increased risk of cardiovascular events and neoplastic diseases, cirrhosis, and hepatocellular carcinoma. However, there is a huge interindividual variability in the susceptibility to develop liver-related complications, which is partly accounted for by genetic predisposition (1). Common genetic variants in *PNPLA3* (I148M) and *TM6SF2* (E167K), but also in *MBOAT7*, *GCKR*, and *PPP1R3B*, predispose an individual to the full spectrum of NAFLD by facilitating fat accumulation within intracellular lipid droplets in hepatocytes in the presence of environmental triggers (1, 2). Importantly, a close correlation has been demonstrated between the impact of these genetic variants on hepatic fat and fibrosis development, which suggests that the accumulation of lipids within intracellular droplets is not an innocent bystander in liver disease progression, but is causally involved in triggering liver damage (3–5).

Recently, a splice variant (rs72613567:TA) in *HSD17B13*, encoding the hepatic lipid droplet protein hydroxysteroid 17-β dehydrogenase 13, has been associated through exome-wide studies with protection against progressive liver damage in both alcoholic and nonalcoholic fatty liver disease in large independent cohorts of individuals from the general population (6). The variant results in a truncated unstable protein with reduced activity (6). Interestingly, the impact on liver damage was independent of hepatic fat accumulation. However, carriage of the rs72613567 variant exerted a more marked protection against liver damage in carriers of the *PNPLA3* I148M risk variant (6). In this issue of the *Journal of Lipid Research*, Pirola et al. (7) now confirm, in a case-control study conducted in 429 patients with histological NAFLD and 180 controls from South America, that the minor rs72613567 risk allele protects against NASH and fibrosis (7). Indeed, carriers of the truncated variant had reduced disease activity (ballooning and inflammation) but not reduced steatosis (7). They went on to shown that, in a subset of patients, the risk allele was associated with reduced *HSD17B13* expression in hepatocytes. In a subgroup analysis, patients positive for the risk allele also displayed dysregulation of genes involved in immune response, among other pathways, findings consistent with less severe histological inflammation (7). Therefore, despite limitations of the relatively small sample size, this study provides a nice validation of previous findings observed in Caucasians in a cohort of individuals of different ethnicity, which was characterized by a lower prevalence of the variant under study (6, 7). Furthermore, although gene expression profiles associated with the *HSD17B13* variant should be confirmed in larger independent cohorts, this analysis provides further insight into the link between the rs72613567 variant and its phenotypic manifestations. In keeping with these results, a contemporary study identified an association of the rs72613567 and rs62305723 (encoding the P260S mutation) *HSD17B13* variants with reduced liver enzymes in the general population, and with protection against disease activity, in a large cohort of patients with histological NAFLD (8). An important novel finding was that, when targeted to the lipid droplets and able to recruit cofactors, the HSD17B13 protein exhibited retinol dehydrogenase activity, and both the rs72613567 and rs62305723 variants resulted in a loss-of-function (8). Together with evidence that the PNPLA3 protein is also involved in retinol metabolism (9), which may partly account for the impact of the I148M *PNPLA3* variant on fibrogenesis, these data suggest that impairment of retinol metabolism at the level of lipid droplets in hepatocytes and/or hepatic stellate cells is involved in the pathogenesis of NAFLD.

Therefore, the mechanisms behind progressive NAFLD do not seem to be limited to "simple" fat accumulation, but rather involve the remodeling and metabolism of specific lipid species and retinol within lipid droplets (**Fig. 1**). Besides further improving risk stratification of progressive NAFLD, identification of *HSD17B13* loss-of-function mutations as protective against NAFLD has possible further

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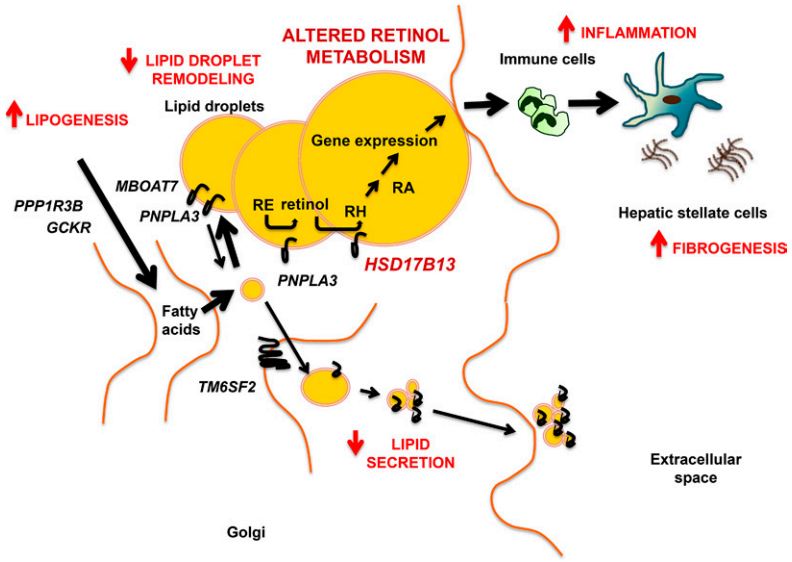

Fig. 1. Role of proteins, whose variation has been identified by unsupervised screening in the population and robustly validated, in the pathogenesis of NAFLD, with a special focus on HSD17B13. *GCKR*, glucokinase regulator; *MBOAT7*, membrane-bound O-acyl transferase 7; *PNPLA3*, patatin-like phospholipase domain-containing 3, *PPP1R3B*, protein phosphatase 1 regulatory subunit 3B; RE, retinyl-esters; RH, retinaldehyde; RA, retinoic acid; *TM6SF2*, transmembrane 6 superfamily member 2.

translational relevance. Further studies are now necessary to understand how reduced retinol conversion to retinaldehyde in lipid droplets can protect against liver damage, inflammation, and fibrogenic progression.

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