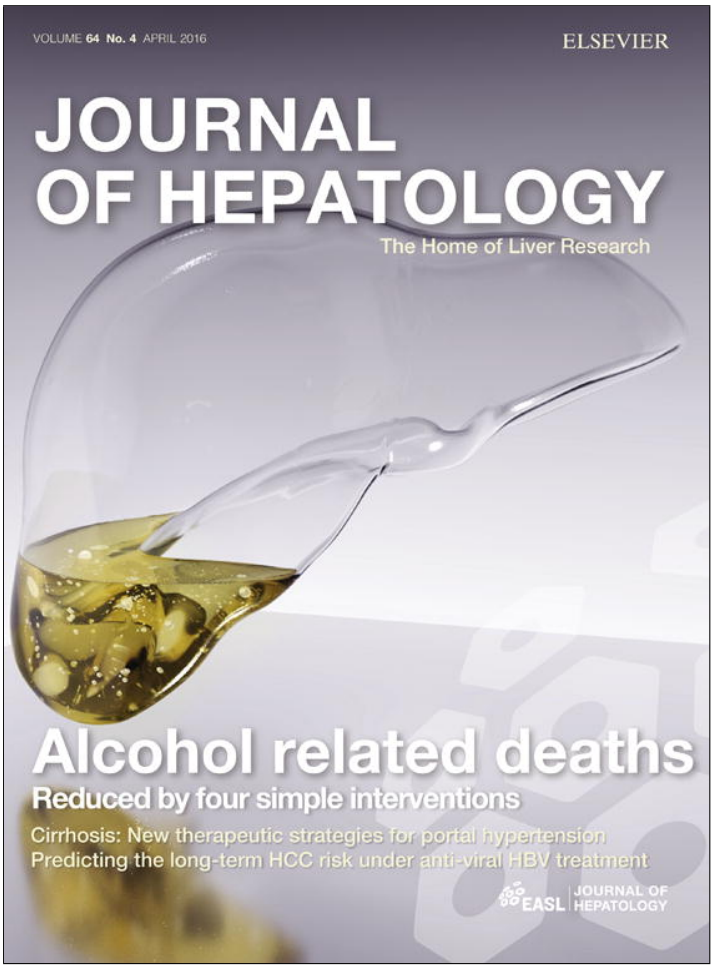

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The modulation of liver methylome in liver diseases

To the Editor:

We read with great interest the elegant study by Page and co-workers [1], which describes the role of DNA hydroxymethylation and Ten-Eleven-Translocation (TET) proteins in liver fibrogenesis. The authors robustly proved their hypothesis by using different approaches, including samples from freshly explanted primary sclerosing cholangitis livers and rat-hepatic stellate cells (rHSC) from experimental models of liver fibrosis, including chemically or bile duct ligation-induced fibrosis, and methionine-choline–deficient (MCD) diet. Based on the whole evidence, the authors concluded that DNA methylation/hydroxymethylation is a crucial step in HSC activation and therefore fibrogenesis.

The importance of 5-Hydroxymethylcytosine (5-hmC) in the biology of non-cancerous human liver diseases, particularly non-alcoholic fatty liver disease (NAFLD), was recently described for the first time by our group [2]. We observed that nonnuclear-5-hmC, which is probably located in mitochondria, is lower in NAFLD as compared with controls. Therefore, 5-hmC may be involved in the modulation of the mitochondrial DNA methylome and gene expression, in particular components of the oxidative phosphorylation-chain, a finding that could explain much of the changes that occur during NAFLD disease progression, including fibrogenesis [3].

Of note, Page *et al.* observed that liver fibrosis in a rodent model of NAFLD (MCD) is accompanied by loss of 5-hmC and modulation of DNA (cytosine-5-)-methyltransferases (DNMTs) and TETs; specifically, the authors reported an induction of DNMT3a and DNMT3b during HSC transdifferentiation [1]. In line with these findings, earlier data from our patient-oriented research in NAFLD demonstrated that hepatic expression of *DNMT1* is significantly higher in the liver of NASH patients as compared with patients with simple steatosis [3]; in fact, we examined the liver expression levels of the *DNMT1* isoform in biopsy-proven NAFLD patients, and we observed that the disease severity is associated with a higher than 1000-fold increase in the *DNMT1* transcriptional activity [3].

Finally, Page *et al.* [1] observed a decrease in the expression of TET-proteins in both human and rat models tested, suggesting a major role for epigenetic mechanisms in HSC biology. Accordingly, we described the role of genetic variation in *TET1* locus in the modulation of programmed liver-cell death during liver fat transformation, a finding that reinforces the concept of a potentially "TET-mediated fine-tuning" of some of the molecular changes associated with liver injury that precede liver fibrosis [2]. We found that subjects carrying the missense p.Ile1123Met variant (*TET1*-rs3998860) had significantly lower liver expression levels of TET1 protein in association with increased levels of circulating CK18 (caspase-mediated cleavage of the CK18) levels [2]. In addition, the *TET2* locus may be involved in the modulation of the liver *PPARGC1A* methylation/demethylation balance, which is altered in NAFLD [4]; PPARGC1A is a main transcription factor modulating mitochondrial biogenesis and a sensor of changes in the cellular metabolism.

Finally, by targeted deep sequencing of the entire *TET2* locus, we found a low frequency missense variant, the rs62621450 (H1778R) (which is rare in Caucasian population, MAF 0.02) in three out of 380 subjects, who developed progressive NAFLD at early age (unpublished data) and also have family history of advanced liver disease.

In conclusion, by examining the impact of epigenetic changes, including DNA hydroxymethylation and TET proteins, in the biology of NAFLD, a highly prevalent human liver disease that progresses towards liver cirrhosis in a significant proportion of affected patients [5], we agree with Page and co-workers that DNMTs and TETs may be potential new targets for treatment of NAFLD disease progression and fibrosis.

Conflict of interest

The authors who have taken part in this study declared that they do not have any conflict of interest.

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Authors' contributions

CJP and SS wrote the letter, and approved the final version.

Letters to the Editor

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