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## BILE ACIDS AND NON-ALCOHOLIC FATTY LIVER DISEASE: AN INTRIGUING RELATIONSHIP

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To the Editor:

Non-alcoholic fatty liver disease (NAFLD) stands nowadays as a leading cause of progressive impairment of liver function.

We read with great interest the paper by Nagahashi et al. recently published in the Journal<sup>1</sup> which highlights the role of conjugated bile acids, sphingosine-1 phosphate receptor 2 and sphingosine kinase 2 in regulating hepatic lipid metabolism and liver lipid content. Such results are exciting and stimulating.

The role of bile acids in the modulation of hepatic lipid metabolism is interesting and controversial; previous evidence by Watanabe et al<sup>2</sup> showed an inhibitory effect of bile acids on lipogenesis, which was attributed to the activation of the FXR-SHP axis and consequent depression of the LXR $\alpha$ -SREBP-1c lipogenic pathway. Evidence from our research group has shown that both exogenous administration of bile acids and endogenous exposure to bile acid overload (as in cholestasis) may reduce hepatic fat accumulation in rat models, although by different mechanisms<sup>3</sup> : the first, by activating of the FXR-SHP axis, the second by inducing CYP7A1 that leads to reduced oxysterols hepatic bioavailability and in turn downregulation of the LXR $\alpha$ -controlled lipogenic pathway.

The findings in the paper by Nagahashi et al<sup>1</sup> are quite surprising, showing the development of fatty liver disease in SphK2 -/- mice, in association with a decreased expression of SREBP1c and lipogenic enzymes like FAS. As the Authors comment, hepatic fat accumulation might be induced by mechanisms different from increased lipogenesis, such as the reduction of lipid and lipoprotein output from the liver, according to previous evidence in humans<sup>4</sup>. Data from our group are consistent with this hypothesis. Indeed, we detected a beneficial effect of cholic acid feeding in the choline-deficient dietary model (in which hepatic lipid export is reduced) but not in the high-fat model<sup>2</sup>. In other words, the metabolic effects of bile acids on hepatic lipid metabolism seem to be strictly dependent on the experimental model utilized to induce fat liver accumulation, as well as on the modality of bile acid exposure (exogenous vs endogenous) and the relative activation of the LXR/FXR pathways.

Experimental evidence like that brought by Nagahashi et al<sup>1</sup> may bring an enormous contribution in this field, in the perspective of novel pharmacological targets for the treatment of NAFLD.

## References

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