Non-alcoholic fatty liver disease (NAFLD), and its subtype non-alcoholic steatohepatitis (NASH), prevalence is increasing worldwide leading to major complications such as cirrhosis and hepatocellular carcinoma (HCC) [1]. An exact assessment of NAFLD prevalence is still difficult given the lack of sensitive and specific biomarkers to avoid histological assessment which needs liver biopsy. Similarly, the lack of appropriate therapeutic agents to modify the biology of the disease is a main limit to prevent its complications.

In this issue of EBioMedicine Yanan Cao and coworkers describe an intriguing cross-talk between microRNA 221/222 and TIMP3 [2], an inhibitor of metalloproteinase previously involved in hepatic inflammation and steatosis [3,4].

Using genetically modified mouse models the authors were able to knockdown miR-221/222 specifically in the hepatocyte which led to a dramatic reduction of inflammation, steatosis and fibrosis when the mice were exposed to agents inducing NASH such as methionine and choline deficient diet or CCl4 treatment.

The highly conserved cluster miR-221 and 222 has been reported in HCC, liver of NASH patients [5,6] and they are believed to affect tumorigenesis process [6]. To provide evidence that miR-221/222 are functionally related to NASH progression Yanan Cao and coworkers performed both targeted inhibition of miR-221/222 by locked nucleic acid (LNA)-anti-miRNA and re-expression of miR-221/222 in vivo [2]. These elegant experiments provided a clear role for the miR-221/222 cluster in NASH pathogenesis. Furthermore, the miR-221/222 inhibitors could be candidate in miRNA-based gene therapies for the intervention of NASH.

Given that miR-221/222 are increased in HCC the targeted inhibition of miR-221/222 by locked nucleic acid (LNA)-anti-miRNA paves the way to clinical applications [10]. Since RNA is a gene regulator that can be edited, it has the potential to be translated to the clinical practice. Today RNA therapeutics is already in clinical trials in liver related disorders such as familial hypercholesterolemia, diabetes mellitus and hypertriglyceridemia.

Future work will establish whether measuring circulating miR-221/222 will improve diagnosis and treatment of NASH and related complications.

Conflict of Interest

None.

Acknowledgements

M.F. research was in part funded by Ministry of Education, University and Research (MIUR) Progetti di Ricerca di Interesse Nazionale (PRIN) protocol number 2015MPESJS_004.

References

[1] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018 Jul;24(7):908-22. https://doi.org/10.1038/s41591-018-0104-9.
[2] Jiang Xiuli, Jiang Lei, Shan Aijing, Su Yutong, Cheng Yulong, Song Dalong, et al. Targeting hepatic miR-221/222 for therapeutic intervention of nonalcoholic steatohepatitis in mice. EBioMedicine 2018;37:307–21.

[3] Casagrande V, Mauriello A, Bischetti S, Mavilio M, Federici M, Menghini R. Hepato-cyte specific TIMP3 expression prevents diet dependent fatty liver disease and hepatocellular carcinoma. Sci Rep 2017 Jul 27;7(1):6747. https://doi.org/10.1038/s41598-017-06439-x.

[4] Mavilio M, Marchetti V, Fabrizi M, Stöhr R, Marino A, Casagrande V, et al. A Role for Timp3 in Microbiota-Driven Hepatic Steatosis and Metabolic Dysfunction. Cell Rep 2016 Jul 19;16(3):731–43. https://doi.org/10.1016/j.celrep.2016.06.027.

[5] Pineau P, Volinia S, McJunkin K, et al. miR-221 overexpression contributes to liver tumorigenesis. Proc Natl Acad Sci U S A 2011;107:264–9.

[6] Park JK, Kogure T, Nuovo GJ, et al. miR-221 silencing blocks hepatocellular carcinoma and promotes survival. Cancer Res 2011;71:7608–16.

[7] Hoyles L, Fernández-Real JM, Federici M, Serino M, Abbott J, Charpentier J, et al. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nat Med 2018 Jul;24(7):1070–80. https://doi.org/10.1038/s41591-018-0061-3.

[8] Pirola CJ, Fernandez Gianotti T, Castano GO, Mallardi P, San Martino J, Gonzalez Mora, et al. Circulating microRNA signature in non-alcoholic fatty liver disease: from serum non-coding RNAs to liver histology and disease pathogenesis. Gut 2015;64:800–12. https://doi.org/10.1136/gutjnl-2014-306996.

[9] Singh AK, Rooge SB, Varshney A, Vasudevan M, Bhardwaj A, Venugopal SK, et al. Global microRNA expression profiling in the liver biopsies of hepatitis B virus-infected patients suggests specific microRNA signatures for viral persistence and hepatocellular injury. Hepatology 2018 May;67(5):1695–709. https://doi.org/10.1002/hep.29690.

[10] Li F, Wang F, Zhu C, Wei Q, Zhang T, Zhou YL. miR-221 suppression through nanoparticle-based miRNA delivery system for hepatocellular carcinoma therapy and its diagnosis as a potential biomarker. Int J Nanomedicine 2018 Apr 13;13:2295–307. https://doi.org/10.2147/IJN.S157805.