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Commentary

MicroRNA 221/222 cluster kicks out Timp-3 to inflame the liver

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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-221/22 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 the broad effects of miR-221/222 they also looked for target genes and among many candidates that were involved in metabolic and inflammatory pathways such as PGC-1b (Ppargc1b), glucose-6-phosphatase-α (G6pc), Ddit4 and Bmf, they focused on Timp3 (tissue inhibitor of metalloproteinase 3). Timp3 is a secreted protein that once bound to extracellular matrix retains the ability to block activation of several cell-membrane metalloproteases such as ADAM-17, the TNF-alpha converting enzyme, and other members of the ADAM family which control EGFR and NOTCH signaling pathways. Experimental models revealed that lack of TIMP3 accelerate the onset and progression of NASH while forcing its expression restrains hepatic inflammation, lipid deposition and fibrosis.

To provide a direct clue between miR-221/222 and Timp3 in vivo Yanan and coworkers inhibited Timp3 expression in mice lacking miR-221/222 which lost the protection from steatohepatitis. This pleasingly simple experiment clearly evidenced a loop between miR-221/222 and Timp3 which has important clinical and therapeutic implications,

NASH diagnosis has several drawbacks, the most important is the need of a liver biopsy to obtain a slice of tissue large enough to show the typical features of steatohepatitis such as necrosis and cell ballooning. Works from several laboratories are trying to improve this limitation using biomarker i.e. circulating factors that are highly sensitive and specific. Gut microbiome derived metabolites and RNA derived molecules are promising candidates [7–9]. Circulating microRNAs are therefore emerging as potential biomarkers to be added to other clinical measurements such as liver elastography to improve risk prediction in NAFLD subjects.

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.

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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.

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https://doi.org/10.1016/j.ebiom.2018.10.040

[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. Hepatocyte 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.