Editorial Commentary

Mitochondrial targeted nanoparticle encapsulated circRNA attenuates NASH: one step closer to the therapeutic application of circRNA in liver diseases

Taihua Yang[1,2], Bing Li[3], Zhen Dai[2]

[1]Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; [2]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [3]Weifang Medical University, Weifang, China

Correspondence to: Taihua Yang, PhD. Department of Gastroenterology, Hepatology and Endocrinology, REBIRTH-Research Center for Translational Regenerative Medicine, Hannover Medical School, Hannover, Germany. Email: Yang.taihua@mh-hannover.de.

Comment on: Zhao Q, Liu J, Deng H, *et al.* Targeting Mitochondria-Located circRNA SCAR Alleviates NASH via Reducing mROS Output. Cell 2020;183:76-93.e22.

Received: 15 December 2020; Accepted: 10 January 2021; Published: 10 April 2021.

doi: 10.21037/ncri-2020-007

View this article at: http://dx.doi.org/10.21037/ncri-2020-007

Non-alcoholic steatohepatitis (NASH) is the progressive state of non-alcoholic fatty liver disease (NAFLD). Instead of hepatitis, NAFLD has become the major concern among liver diseases with the change of lifestyle and chronic alcoholism as well as over nutrition (1). There will be 15–20% of NAFLD patients becomes NASH and nearly 20% of NASH patients then further develop into cirrhosis, which permanently irreversible and liver transplantation is needed. Despite the increasing prevalence, currently, there are limited approved therapeutic drugs available for NASH (2).

Recently, Zhao *et al.* from Sun Yat-sen University provided a novel circular RNA (circRNA) based therapy for NASH (3). Specifically, they showed that mitochondrial steatohepatitis-associated circRNA ATP5B Regulator (SCAR) could inhibit mitochondrial ROS (mROS) output and fibroblast activation via blocking mitochondrial permeability transition pore opening. Notably, PGC1-α, a key transcriptional co-activator modulating mitochondrial biogenesis (4), were predicted as the regulator to the consensus site which is responsible for SCAR transcription in fibroblast. Interestingly, the authors clearly revealed the mechanism between PGC1-α and SCAR and further clarified a CHOP-PGC1-α- SCAR axis under the ER Stress induced by lipid overload. Moreover, the authors successfully deliver SCAR to mitochondrial and overexpression of circRNA could attenuate the high fat diet-induced cirrhosis and insulin resistance in vivo. To be mentioned, the function and mechanism of circRNA are still under the center of the storm of controversy. It is no doubt that this study showed the new evidence that circRNAs could serve as the putative therapeutic target in liver disease. Compared with the viral based gene therapy, there is more and more fundamental evidence highlight that RNA molecular could be the future for next generation gene therapy (5). Viral approaches including lentivirus and AAV may lead to genome integration, insertional mutagenesis and carcinogenesis. Thus, non-genome integration platforms such as in vitro transcribed mRNA or circRNA, modified RNA and even nanoparticle mediated overexpression plasmid delivery could enhance the safety concern. In addition, compare to linear RNA, special structure of circRNA results the high RNase resistance and longer expression lifespan (6), suggesting the high application value.

Multiple mechanisms have been investigated for circRNA's effect in NASH (7,8). One of the approved mechanism is the circRNA-miRNA-mRNA axes (9,10). Guo *et al.* reported that both circRNA_046366 and circRNA_046367 could enhance the expression of miR-34a and indirectly remove the inhibitor of transcribed peroxisome proliferator-activated receptor α mRNA abundance (11,12). A similar mechanism didn't apply for circRNA SCAR when Zhao *et al.* tries to find out its sponged microRNAs. The SCAR also did not have any effect on its host gene's transcripts. Instead, they find the circRNA-protein directly binding pathway. The double-stranded stem-loop structure of

circRNA SCAR severed as a binding site for ATP5B protein. Inconsistent with their previous hypothesis, they launched an attractive mechanism to investigate circRNA (13).

The mechanism under NASH is still suitable for the two hits theory (14). The fat accumulation and metabolic syndrome caused the first hit for the liver. The following reactive oxygen species stimuli and inflammation infiltration induced a second hit to the function imbalanced liver and result in steatohepatitis and cirrhosis. To interfere with the early-stage mitochondrial ROS generation in activated hepatic myofibroblasts could reduce the second hit and inhibit its dominoes pro-inflammatory effect efficiently. The majority of the anti-fibrotic investigations are focus on reversing the activated hepatic myofibroblasts, the combination strategy of targeting mitochondrial and reduce mROS maybe accelerate the generation of new powerful drugs in anti-fibrotic weaponry (15).

Another highlight of the study is the pioneering application of mitochondrial-targeted nanoparticles. The PH-sensitive polymers and integrated triphenylphosphonium (TPP)-decorated amphiphilic cationic peptides (TACP) allow the circRNA released from the endosome and entered the double-shell mitochondrial. The innovative mitochondrial targeting peptide provides a novel cell organelle targeting possibility. However, the delivery system could be improved by adding organ and cell targeting peptides. Regarding the hepatic myofibroblast delivery, the peptides including PDGFRβ and P75NTR could be applied to improve the fibroblasts targeting effect (16,17). Besides, the off-target of the nanoparticle delivery is another concern.

Overall, the unprecedented work done by Zhao *et al.* provided a better understanding of the process of NASH-developed cirrhosis. A promising future clinical application is expected with further improvement of the delivery system and circRNA optimization.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dongchao Lu (Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hannover, Germany).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri-2020-007). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sheka AC, Adeyi O, Thompson J, et al. Nonalcoholic Steatohepatitis: A Review. JAMA 2020;323:1175-83.
2. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol 2018;53:362-76.
3. Zhao Q, Liu J, Deng H, et al. Targeting Mitochondria-Located circRNA SCAR Alleviates NASH via Reducing mROS Output. Cell 2020;183:76-93.e22.
4. Lin S, Wu X, Tao L, et al. The Metabolic Effects of Traditional Chinese Medication Qiliqiangxin on H9C2 Cardiomyocytes. Cell Physiol Biochem 2015;37:2246-56.
5. Lu D, Thum T. RNA-based diagnostic and therapeutic strategies for cardiovascular disease. Nat Rev Cardiol 2019;16:661-74.
6. Kristensen LS, Andersen MS, Stagsted LVW, et al. The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet 2019;20:675-91.
7. Chien Y, Tsai PH, Lai YH, et al. CircularRNA as novel biomarkers in liver diseases. J Chin Med Assoc 2020;83:15-7.
8. Pirola CJ, Sookoian S. Epigenetics factors in nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol 2020;1-16.
9. Jin X, Feng CY, Xiang Z, et al. CircRNA expression pattern and circRNA-miRNA-mRNA network in the pathogenesis of nonalcoholic steatohepatitis. Oncotarget 2016;7:66455-67.

10. Jin X, Gao J, Zheng R, et al. Antagonizing circRNA_002581-miR-122-CPEB1 axis alleviates NASH through restoring PTEN-AMPK-mTOR pathway regulated autophagy. Cell Death Dis 2020;11:123.
11. Guo XY, Chen JN, Sun F, et al. circRNA_0046367 Prevents Hepatoxicity of Lipid Peroxidation: An Inhibitory Role against Hepatic Steatosis. Oxid Med Cell Longev 2017;2017:3960197.
12. Guo XY, Sun F, Chen JN, et al. circRNA_0046366 inhibits hepatocellular steatosis by normalization of PPAR signaling. World J Gastroenterol 2018;24:323-37.
13. Xia P, Wang S, Ye B, et al. A Circular RNA Protects Dormant Hematopoietic Stem Cells from DNA Sensor cGAS-Mediated Exhaustion. Immunity 2018;48:688-701.e7.
14. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology 1998;114:842-5.
15. Begriche K, Igoudjil A, Pessayre D, et al. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion 2006;6:1-28.
16. Kaps L, Schuppan D. Targeting Cancer Associated Fibroblasts in Liver Fibrosis and Liver Cancer Using Nanocarriers. Cells 2020;9:2027.
17. Song G, Pacher M, Balakrishnan A, et al. Direct Reprogramming of Hepatic Myofibroblasts into Hepatocytes In Vivo Attenuates Liver Fibrosis. Cell Stem Cell 2016;18:797-808.

doi: 10.21037/ncri-2020-007
Cite this article as: Yang T, Li B, Dai Z. Mitochondrial targeted nanoparticle encapsulated circRNA attenuates NASH: one step closer to the therapeutic application of circRNA in liver diseases. Non-coding RNA Investig 2021;5:2.

