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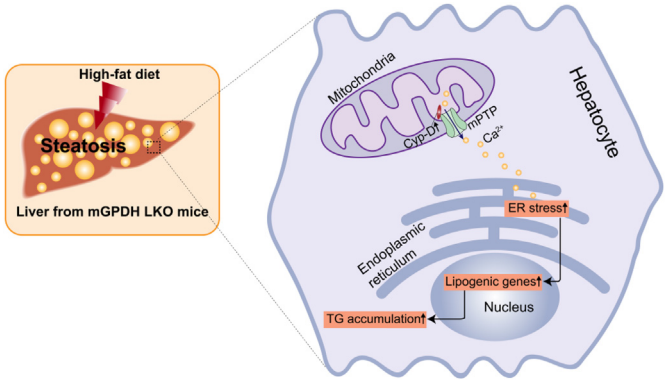
Mitochondrial glycerol 3-phosphate dehydrogenase deficiency aggravates hepatic triglyceride accumulation and steatosis

Nonalcoholic fatty liver disease (NAFLD) is characterized by excess hepatic triglyceride (TG) overload, and has more than double increase in the incidence during the past 20 years [1]. Due to the high prevalence and its potential for serious metabolic derangements, understanding the mechanisms causing NAFLD is taking precedence. In a recent research article entitled "Deficiency of the mitochondrial glycerol 3-phosphate dehydrogenase contributes to hepatic steatosis", Zheng Y. et al. illustrated a potential mechanism underlying excessive hepatic TG accumulation and steatosis during NAFLD [2].

Mitochondrial glycerol 3-phosphate dehydrogenase (mGPDH) is defined as a component in the respiratory chain, functioning to be a rate-limiting for the glycerophosphate-shuttle [3]. It was reported mGPDH played an important role of gluconeogenesis in the liver [4], however, its function in hepatic lipid metabolism was still unrevealed. Zheng Y. and colleagues identified a novel role of mGPDH for modulating lipid metabolism in NAFLD. Its deficiency stimulated endoplasmic reticulum (ER) stress via suppressing cyclophilin-D (Cyp-D) degradation, subsequently causing excessive hepatic TG accumulation and steatosis.

In the presented study, Zheng Y. et al. found the expressions of mGPDH were inhibited in fatty livers from NAFLD patients and mice (*ob/ob*, HFD and *db/db*), which brought in a basic and clinical pathological insight of an association between downregulated mGPDH with hepatic steatosis. *In vivo* and *in vitro* evidence have validated this correlation, that mGPDH liver specific knockout mice or mGPDH knockdown in hepatocytes exacerbated diet-induced TG accumulation and steatosis through enhancing lipid biosynthesis. This increased steatosis phenotype by mGPDH deletion on a HFD condition was via activated ER stress, proven by the results from RNA-sequencing analyses and ER stress inducer (TM)/inhibitor (TUDCA) interferences. ER is vital for the regulation of lipid metabolism, and its perturbations - ER stress was reported to reinforce hepatic steatosis [5]. Moreover, the induced ER stress by mGPDH insufficiency was through inhibiting Cyp-D degradation by ubiquitination pathway, which might be an undisclosed mechanism for initiating lipid-related chronic ER stress during NAFLD. Cyp-D, a mitochondrial peptidyl-prolylcis-trans isomerase, was considered a key regulator for mitochondrial Ca^{2+} conductance channel mPTP [6], and the regulation of mPTP/Cyp-D on ER stress was disclosed recently [7]. The study of Zheng Y. et al. provided further evidence for this concept, indicating mGPDH might act as upstream component of Cyp-D during this process.

Furthermore, restoring the low expressions of mGPDH seen in the livers of NAFLD mice remarkably eased TG accumulation and hepatic steatosis in diet- and genetic-induced models. Therefore, mGPDH may be a potential new therapeutic target for treating NAFLD (see Scheme 1).



Scheme 1. Model depicting a pivotal regulator of mGPDH in hepatic lipid metabolism. Hepatic mGPDH deficiency induced ER stress via activating mPTP/Cyp-D signaling, thereby causing excessive hepatic TG accumulation and steatosis.

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References

[1] Cassidy S, Syed BA. Nonalcoholic steatohepatitis (NASH) drugs market. Nat Rev Drug Discov 2016;15:745–6.
[2] Zheng Y, Qu H, Xiong X, Wang Y, Liu X, Zhang L, Liao X, Liao Q, Sun Z, Ouyang Q, Yang G, Zhu Z, Xu J, Zheng H. Deficiency of the mitochondrial glycerol 3-phosphate dehydrogenase contributes to hepatic steatosis. Hepatology 2019 Jan 17. https://doi.org/10.1002/hep.30507.
[3] Eto K, Tsubamoto Y, Terauchi Y, Sugiyama T, Kishimoto T, Takahashi N, et al. Role of NADH shuttle system in glucose-induced activation of mitochondrial metabolism and insulin secretion. Science 1999;283:981–5.

https://doi.org/10.1016/j.metop.2019.02.002

[4] Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 2014;510:542–6.
[5] Wang M, Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Nature 2016;529:326–35.
[6] Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, Hambleton MA, et al. Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death. Nature 2005;434:658–62.
[7] Wang X, Du H, Shao S, Bo T, Yu C, Chen W, et al. Cyclophilin D deficiency attenuates mitochondrial perturbation and ameliorates hepatic steatosis. Hepatology 2018;68:62–77.

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