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Hepatology. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Hepatology. 2023 October 01; 78(4): E82–E83. doi:10.1097/HEP.0000000000000541.

Reply: Loss of hepatic DRP1 exacerbates alcoholic hepatitis by inducing megamitochondria and mitochondrial maladaptation

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Keywords

alcohol-associated liver disease; innate immunity; mitochondrial dynamics; cGAS-STING; mtDNA

To the editor:

We thank Dr. Liu and colleagues for their interest in our recent work, which we demonstrated that loss of DRP1 impairs alcohol-induced mitochondria adaptation resulting in increased mtDNA release, cGAS-STING-IRF3/7-mediated innate immune response and cell death to exacerbate alcohol-associated liver disease (ALD). However, Dr. Liu and colleagues concerned the relevance of cGAS-STING pathway activated by mtDNA in the mouse ALD model to human alcoholic hepatitis (AH).

Human AH is featured with fibrosis, ductular reaction, increased immune cell infiltration, and hepatocyte degeneration (1). No current mouse model can phenocopy human AH. The widely used “Gao-binge alcohol” model (used in this study) only represents early stage of ALD that has increased steatosis, hepatocytes death, mild neutrophil infiltration with little fibrosis and hepatic megamitochondria. Therefore, it is not surprising that Gao-binge alcohol feeding alone had little effect on the cGAS-STING pathway. The activation of cGAS-STING pathway is likely mediated primarily by the chronic hepatic megamitochondria accumulation resulting from long term alcohol consumption in humans but not by Gao-binge alcohol feeding in mice. Loss of hepatic DRP1 in mice is sufficient to activate cGAS-STING pathway with little effect from further Gao-binge alcohol feeding. However, we cannot rule out whether prolonged alcohol feeding in DRP1 KO mice may further enhance the activation of cGAS-STING pathway.

Regarding extracellular mtDNA, we showed increased intracellular (hepatocyte cytoplasm) and extracellular (mouse serum) mtDNA release in DRP1 KO mice regardless of alcohol

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Author contributions: X.M. and W.X.D. conceived the idea and wrote the manuscript.

Potential conflict of interest:

The authors have no conflicts to report.

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feeding, which is more relevant to ALD development as opposed to detecting mtDNA from a cell culture medium (2). To our knowledge, the widely used mtDNA measurements from serum and cytoplasm are the most realistic quantitative methods to assess the levels of mtDNA release in vivo. However, how mtDNA was released from hepatocytes to serum as well as its downstream signaling events contributing to the pathogenesis of ALD remain unclear.

It is still controversial regarding the expression levels of cGAS and STING in different cell types in the liver. Human transcriptomic data from more than 100,000 single liver cells showed a moderate expression level of TMEM173 (gene name of STING) in both hepatocytes and non-parenchymal cells, indicating various types of liver cells are likely using this pathway for DNA sensing (3). This hypothesis is further supported by our finding that cGAS is not only expressed in macrophage/Kuffer cells but also enriched in the nuclear of hepatocytes. Future studies are needed to better understand the crosstalk between hepatocytes and non-parenchymal cells in sensing intracellular and extracellular mtDNA in ALD development.

In conclusion, while the exact role of cGAS-STING signaling pathway and mechanisms of mtDNA release in the pathogenesis of ALD remain to be further investigated, our study showed a convincing positive correlation of megamitochondria with the activation of cGAS-STING pathway, which may help to better understand the role of mitochondrial dynamics and megamitochondria in the development of ALD.

FINANCIAL SUPPORT

This study was supported in part by the National Institute of Health (NIH) funds R37 AA020518.

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