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Letter To Editor

ACMSD inhibition corrects fibrosis, inflammation, and DNA damage in MASLD/MASH

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Abstract

We read with foremost interest the article titled "ACMSD inhibition corrects fibrosis, inflammation, and DNA damage in MASLD/MASH" by Yasmin J. Liu and colleagues1. The study's findings are compelling, proposing ACMSD inhibition as a promising therapeutic strategy for metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).

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Introduction

We read with foremost interest the article titled *"ACMSD inhibition corrects fibrosis, inflammation, and DNA damage in MASLD/MASH"* by Yasmin J. Liu and colleagues[1]. The study's findings are compelling, proposing ACMSD inhibition as a promising therapeutic strategy for metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).

The authors have produced a commendable study. We would like to contribute additional perspectives, underscoring the importance of enhancing hepatic NAD^+ levels to mitigate fibrosis, inflammation, and DNA damage—key hallmarks of MASLD/MASH progression[2,4,5].

As the global burden of MASLD/MASH continues to rise, with limited pharmacological interventions currently available, this study initiates a novel therapeutic approach by targeting α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), a critical enzyme regulating NAD^+ synthesis in the liver. The results reveal that pharmacological inhibition of ACMSD leads to increased NAD^+ availability, enhanced mitochondrial respiration, and decreased genomic instability in hepatocytes. These outcomes were consistent across murine models and human liver organoids, strengthening the translational relevance of ACMSD inhibition.

Given the significant role of mitochondrial dysfunction and DNA damage in MASLD/MASH, the data presented by Liu et al. pave the way for molecular-level treatments that directly target the pathophysiology of the disease. However, further clinical validation is warranted.

Another critical aspect to consider is the potential impact of ACMSD inhibition on other metabolic pathways beyond NAD^+ synthesis. Given its role in tryptophan metabolism, further research is warranted to determine whether ACMSD inhibition has broader systemic effects, including on immune function, neurological health, and overall metabolic homeostasis[3]. A deeper understanding of these broader implications could help refine its therapeutic application while minimizing unintended side effects.

In summary, while Yasmin J. Liu presents encouraging data on ACMSD inhibition, we believe this study offers a strong foundation for further exploring ACMSD inhibitors as potential therapeutic agents in the fight against MASLD/MASH. Nonetheless, it is premature to draw definitive conclusions without comprehensive clinical trials. This study marks a step forward, but it would be premature to rely solely on these findings to fully endorse ACMSD inhibition. We hope our concerns and insights will be taken into consideration.

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Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Zeeshan Ali, Muhammad Anwar, Wasiq Subhani and Syeda Alizay Kirmani jointly conceived the comment, reviewed the literature, and contributed equally to writing and revising the manuscript.

Data availability statement

Not applicable**.**

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