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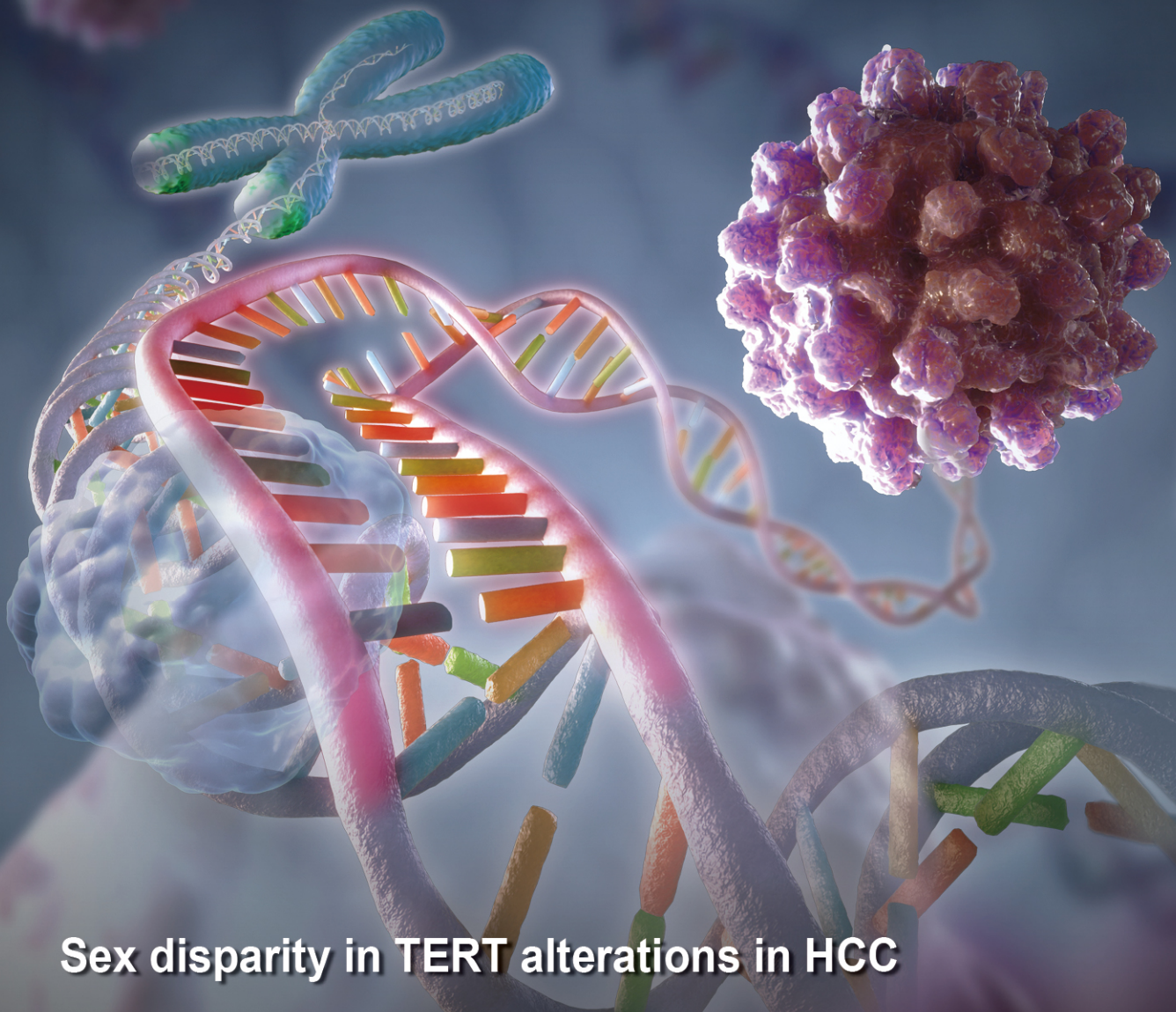

## Sex disparity in TERT alterations in HCC

Economic evaluation of hepatitis C elimination
GOLM1 promotes MASH-related gallstone formation
Molecular characterization of sarcomatoid HCC

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## Reply to Correspondence

# Reply to correspondence 2 on "GOLM1 promotes cholesterol gallstone formation via ABCG5-mediated cholesterol efflux in MASH livers"

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**Keywords:** GOLM1; FXR; Bile acids

Dear Editor,

We read the Correspondence by Li et al.[1] with great interest and appreciate their effort in further expanding the discussion on the research directions we presented in our editorial. Li et al. reported that GOLM1 regulates the expression of ABCG5, thereby promoting cholesterol efflux and influencing the formation of cholesterol gallstones (CGS).[2] In our editorial, we previously suggested that GOLM1 may not only regulate cholesterol metabolism but also play a role in bile acid metabolism and gut microbiota modulation.[3] Additionally, we discussed the potential of combining GOLM1 inhibition with FXR agonism as a therapeutic strategy for regulating cholesterol and bile acid homeostasis.

In their Correspondence, Li et al. proposed that GOLM1 may be linked to the FXR signaling pathway, potentially regulating an alternative bile acid synthesis pathway mediated by CYP27A1 and CYP7B1. These enzymes function in a pathway distinct from the classic CYP7A1-dependent bile acid synthesis pathway and are known to metabolize cholesterol to convert into bile acids.[4] However, GOLM1-mediated molecular mechanisms to control alternative bile acid synthesis pathways still remain unclear.

Furthermore, Li et al. proposed that alterations in GOLM1 expression may regulate bile acid metabolism and immune responses, highlighting the potential roles of GOLM1-mediated bile acids to control immune activities. In particular, they emphasized that lithocholic acid (LCA) suppresses T-cell function, whereas ursodeoxycholic acid (UDCA) counteracts this effect.

In this Reply, we aim to further discuss the potential roles of GOLM1 in alternative bile acid synthesis through CYP27A1 and CYP7B1, its interaction with FXR, its impact on gut microbiota and immune regulation, and the potential therapeutic implications of targeting GOLM1 alongside FXR modulation.

Despite reduced cholesterol excretion into bile in GOLM1-deficient mice, Li et al. demonstrated that hepatic and serum total cholesterol (TC) levels, as well as VLDL (TG, TC) levels, still remained unchanged. This observation suggests that, in addition to the GOLM1-OPN-ABCG5 axis, compensatory cholesterol efflux pathways may be activated.

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Accordingly, Li et al. proposed that GOLM1 may regulate CYP27A1 and CYP7B1 expression via FXR signaling. However, whether this regulation is direct or occurs through a feedback mechanism still remains to be determined.

FXR, a nuclear receptor known to regulate bile acid homeostasis, controls the transcription of multiple target genes, including CYP7A1, which it represses.[5] However, Li et al. reported no significant change in CYP7A1 expression in GOLM1-deficient mice, suggesting that GOLM1 may not directly regulate CYP7A1 via FXR, or that compensatory mechanisms may be involved. Additionally, Li et al. suggested that FXR may regulate CYP27A1 and CYP7B1 expression, but whether this occurs through direct transcriptional control or through indirect bile acid-mediated signaling remains unverified.

Another compensatory mechanism that warrants consideration is the activation of Transintestinal Cholesterol Efflux (TICE). TICE is an alternative cholesterol excretion pathway that operates independently of bile acid-mediated excretion, directly exporting cholesterol from the intestines via ABCG5/ABCG8. It has been reported that when hepatic cholesterol efflux through VLDL secretion is reduced, TICE can be activated as a compensatory pathway.[6] Given that Li et al. observed no significant alterations in hepatic and serum total cholesterol levels in GOLM1-deficient mice, the potential activation of TICE cannot be excluded.

To verify this hypothesis, further studies are required to assess changes in the expression of TICE-related genes (NPC1L1, ABCG5/ABCG8) in the intestinal tissues of GOLM1-deficient mice and to evaluate the role of bile acid metabolism in this process.

Additionally, GOLM1 deficiency may lead to the redistribution of cholesterol to other metabolic tissues. One possible consequence is its impact on steroid hormone biosynthesis in the adrenal glands and gonads (ovaries/testes). Cholesterol serves as a precursor for key steroid hormones, including cortisol, aldosterone, testosterone, and estrogen,[7] and GOLM1 deficiency may influence these biosynthetic pathways.

Thus, experimental validation is needed to determine whether GOLM1 deficiency results in increased steroid hormone synthesis or alters cholesterol homeostasis in the adrenal glands and gonads. To address this, future studies should focus on analyzing circulating steroid hormone levels and assessing cholesterol accumulation in these tissues in GOLM1-deficient mice.

Moreover, GOLM1 is likely to function as a key metabolic regulator beyond cholesterol homeostasis, influencing various metabolic pathways. In particular, the interplay between bile acid metabolism and gut microbiota suggests that GOLM1-mediated metabolic regulation may have broader implications for immune responses.

Both our editorial and Li et al.'s Correspondence discussed the potential role of GOLM1 in immune modulation via alterations in bile acid synthesis and composition. Furthermore, Li et al. emphasized that FXR agonists could control immune responses not only by alleviating metabolic syndrome but also through the modulation of gut microbiota. Bile acids play crucial roles in regulating the growth of gut microbiota, particularly through the conversion of primary bile acids into secondary bile acids by gut microbiota, a process essential for maintaining the intestinal environment.[8] Recent studies have suggested that gut microbiota-mediated bile acid metabolism can modulate immune cell function. For example, Ma et al. demonstrated that secondary bile acids produced by gut microbiota regulate hepatic NKT cell accumulation, thereby suppressing hepatocarcinogenesis.[9]

These findings indicate that alterations in bile acid metabolism modulate not only digestive processes but also immune cell activation. Furthermore, it has been reported that changes in bile acid flow can change gut microbiota composition and immune responses. A previous study showed that disruptions in bile acid flow lead to alterations in gut microbiota, triggering immune responses and promoting inflammation associated with liver injury.[10]

Collectively, these findings suggest that changes in bile acid composition play a crucial role beyond digestion, particularly in immune regulation within the gut-liver axis. Given that Li et al. proposed a potential link between GOLM1

**Abbreviations:**

ABCG5/8, ATP-binding cassette subfamily G members 5 and 8; CGS, cholesterol gallstone disease; CYP27A1, sterol 27-hydroxylase; CYP7A1, cholesterol 7 alpha-hydroxylase; CYP7B1, oxysterol 7-alpha-hydroxylase; FXR, farnesoid X receptor; GOLM1, Golgi membrane protein 1; MASH, metabolic dysfunction-associated steatohepatitis; TC, total cholesterol; TG, triglyceride; THR-β, thyroid hormone receptor beta; TICE, transintestinal cholesterol efflux; LCA, lithocholic acid; UDCA, ursodeoxycholic acid; VLDL, very low-density lipoprotein

and inflammation as well as bile acid metabolism, it is necessary to consider the impact of GOLM1 on gut microbiota and immune responses through its regulation of bile acid synthesis and composition. To address this, further studies are required to analyze gut microbiota composition and immune cell activation in GOLM1-deficient mice.

Lastly, both our editorial and Li et al.'s Correspondence discussed the potential synergistic effects of GOLM1 inhibition and FXR agonists in regulating cholesterol and bile acid metabolism as a therapeutic strategy. We believe that this approach may serve as a promising strategy for treating gallstone formation and metabolic liver diseases. FXR agonists reduce bile acid synthesis by inhibiting CYP7A1, while GOLM1 modulates cholesterol excretion via ABCG5/ABCG8. Thus, a combination therapy involving GOLM1 inhibition and FXR activation could exert synergistic effects on cholesterol excretion and bile acid homeostasis.

Additionally, considering recent reports that Resmetirom may promote gallstone formation, further investigation into the role of GOLM1 in cholesterol and bile acid metabolism is warranted. Resmetirom, a THR-β agonist, has been approved for noncirrhotic NASH (fibrosis stages F2–F3); however, it has been reported to increase the risk of gallstone formation.[11]

Given the impact of cholesterol excretion and bile acid synthesis regulation on gallstone formation, a more precise characterization of GOLM1's function is essential. Building upon the findings of this study, future research should explore the potential of targeting GOLM1 as a novel therapeutic strategy to prevent gallstone formation in patients with MASH (Metabolic dysfunction-Associated SteatoHepatitis).

The study by Li et al. provides critical insights into the role of GOLM1 in cholesterol metabolism and bile acid regulation in cholesterol gallstone (CGS) formation. Expanding on these findings, we have examined the potential role of GOLM1 in regulating alternative bile acid synthesis pathways via CYP27A1 and CYP7B1, as well as its involvement in gut microbiota–immune interactions.

Current research suggests that GOLM1 deficiency may alter bile acid composition, impacting gut microbiota and immune responses, which could play a significant role in metabolic interactions and immune regulation within the gut-liver axis. Moving forward, further studies are needed to elucidate the effects of GOLM1 on gut microbiota and immune cell activity, ultimately paving the way for novel therapeutic approaches to prevent MASH and gallstone formation.

## Authors' contribution

N.H.: Writing – Review & Editing. S.F.: Writing – Original Draft Preparation, Review & Editing. Corresponding author.

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## Conflicts of Interest

The authors have no conflicts to disclose.

## REFERENCES

1. Li YT, Shao WQ, Chen ZM, Lin J, Chen JH. GOLM1 and bile acid synthesis: Correspondence to editorial on "GOLM1 promotes cholesterol gallstone formation via ABCG5-mediated cholesterol efflux in MASH livers". Clin Mol Hepatol 2025;31:e189-e191.
2. Li YT, Shao WQ, Chen ZM, Ma XC, Yi CH, Tao BR, et al. GOLM1 promotes cholesterol gallstone formation via ABCG5-mediated cholesterol efflux in metabolic dysfunction-associated steatohepatitis livers. Clin Mol Hepatol 2025;31:409-425.
3. Hwang N, Fang S. Bridging the gap: The GOLM1-OPN-ABCG5 axis in MASH and gallstone disease: Editorial on "GOLM1 promotes cholesterol gallstone formation via ABCG5-mediated cholesterol efflux in MASH livers". Clin Mol Hepatol 2025;31:631-634.
4. Chiang JY. Regulation of bile acid synthesis: pathways, nuclear receptors, and mechanisms. J Hepatol 2004;40:539-551.
5. Fleishman JS, Kumar S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets. Signal Transduct Target Ther 2024;9:97.
6. Duan Y, Gong K, Xu S, Zhang F, Meng X, Han J. Regulation of cholesterol homeostasis in health and diseases: from mechanisms to targeted therapeutics. Signal Transduct Target Ther 2022;7:265.
7. Hu J, Zhang Z, Shen WJ, Azhar S. Cellular cholesterol delivery, intracellular processing and utilization for biosynthesis of

steroid hormones. Nutr Metab (Lond) 2010;7:47.
8. Guzior DV, Quinn RA. Review: microbial transformations of human bile acids. Microbiome 2021;9:140.
9. Ma C, Han M, Heinrich B, Fu Q, Zhang Q, Sandhu M, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science 2018;360:eaan5931.
10. Leung H, Xiong L, Ni Y, Busch A, Bauer M, Press AT, et al. Impaired flux of bile acids from the liver to the gut reveals microbiome-immune interactions associated with liver damage. NPJ Biofilms Microbiomes 2023;9:35.
11. Levien TL, Baker DE. Resmetirom. Hosp Pharm 2024 Sep 5. doi: 10.1177/00185787241278571.