

Commentary

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Metabolism, sex, and what lies beyond the scalpel in MASLD

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Abstract

The discovery of the one-carbon metabolism-homocysteine-metabolic dysfunction-associated steatotic liver disease (OCM-Hcy-MASLD) axis has renewed our understanding of MASLD-related primary liver cancer (PLC). Based on Suzuki *et al.*'s mathematical modeling findings of diminished cystathionine β -synthase (CBS) and phosphatidylethanolamine N-methyltransferase (PEMT) expression in MASLD, this commentary analyzes recent findings regarding sex-specific variations in this axis and their implications for surgical management. We highlight how the integration of OCM-Hcy pathway modulation with precise surgical interventions could enhance perioperative outcomes and long-term prognosis. The emerging evidence suggests that targeted metabolic interventions, particularly those accounting for sex differences, may complement traditional surgical approaches by addressing the systemic nature of MASLD-related PLC. This paradigm shift from purely surgical resection toward comprehensive metabolic regulation marks a significant advance in precision medicine for hepatobiliary surgery, potentially improving both perioperative safety and oncological outcomes.

Keywords: MASLD, OCM, primary liver cancer, sex differences, precision medicine



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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) currently exceeds a 30% global prevalence, making it a primary contributor to the contemporary burden of liver disease^[1]. In the ongoing quest to elucidate MASLD pathogenesis, the emerging centrality of the one-carbon metabolism (OCM) pathway and its regulatory product, homocysteine (Hcy), has become increasingly apparent. Through mathematical modeling, Suzuki *et al.* substantiated that diminished expression of two key OCM enzymes - cystathionine β -synthase (CBS) and phosphatidylethanolamine N-methyltransferase (PEMT) - correlates significantly with the progression of hepatic fibrosis in individuals with MASLD^[2]. Their work further indicates that strategic OCM cofactor supplementation may effectively modulate hepatic Hcy levels, while highlighting the pivotal role of sex-related factors in both disease progression and therapeutic response. Collectively, these findings point toward a new frontier in the stratified treatment of MASLD.

Moreover, given that MASLD has been identified as an independent risk factor for primary liver cancer (PLC), including hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA)^[3,4], the elucidation of this metabolic pathway holds profound implications for the field of hepatobiliary surgery. The bidirectional interplay between metabolic derangement and tumorigenesis is reshaping traditional surgical strategies. The liver's role as a central metabolic hub, coupled with the systemic nature of PLC, compels a critical reappraisal of the limitations inherent in surgical resection alone. In the era of precision medicine, integrating metabolic characteristics into preoperative assessment and implementing targeted metabolic interventions during the perioperative period may fundamentally enhance both surgical outcomes and patient prognosis.

Accordingly, this paper endeavors to systematically analyze the findings of Suzuki *et al.*, sketch the molecular landscape of the OCM-Hcy-MASLD axis, underscore the significance of sex-based modulation within this continuum, and examine its transformative potential for PLC surgery^[2]. By highlighting these insights, we strive to extend the reach of precision medicine into both the mechanistic understanding of hepatic metabolic disorders and the evolving surgical strategies that address them.

ADVANCES IN CLINICS AND MECHANISM

The intersection of OCM and hepatic pathology was first documented in 1974 when Gaull *et al.* observed hepatocellular enlargement and microvesicular steatosis in liver biopsies from patients with severe hyperhomocysteinemia due to CBS deficiency^[5]. This association was mechanically confirmed by Torres *et al.*, who found that homocysteine induced TIMP-1 and K1(I) procollagen expression by activating the AP-1 transcription factor, which may promote liver fibrosis^[6]. These seminal findings established the foundational link between OCM dysregulation and hepatic lipid accumulation, suggesting potential therapeutic implications for metabolic liver diseases.

Subsequent mechanistic investigations have elucidated four primary pathogenic pathways through which OCM perturbation and Hcy elevation promote liver injury: oxidative stress induction^[7], endoplasmic reticulum stress activation^[8], reduced nitric oxide bioavailability^[9], and protein homocysteinylation-mediated cellular dysfunction^[10]. These molecular mechanisms collectively contribute to hepatic inflammation and fibrosis progression, highlighting the multifaceted role of the OCM-Hcy axis in MASLD pathogenesis.

The clinical relevance of this pathway was further validated by Gulsen *et al.*, who demonstrated a robust correlation between serum Hcy levels and MASLD severity^[11]. Their findings established Hcy as an independent risk factor for hepatic inflammation and fibrosis progression, providing a strong rationale for

therapeutic targeting of the OCM-Hcy axis in MASLD treatment. This clinical correlation has profound implications for surgical decision making, as elevated Hcy levels may serve as a biomarker for disease severity and surgical risk stratification.

Recent advances^[12,18] have substantiated the causal relationship within the OCM-Hcy-MASLD axis [Table 1], elucidating the regulatory effects of OCM cofactors on Hcy homeostasis and MASLD progression. This emerging molecular landscape not only provides multiple therapeutic targets but also highlights the promising therapeutic potential of OCM cofactor intervention strategies. The intricate molecular mechanisms underlying the OCM-Hcy-MASLD axis have been progressively unveiled.

SEX-SPECIFIC REGULATION MATTERS

Although a growing body of literature now identifies the OCM-Hcy-MASLD axis as a key mediator of hepatic injury, the sex-specific intricacies of these interlinked mechanisms have often been overlooked. Most studies to date have not stratified participants by sex or age, limiting the ability to capture how hormonal subpopulations might respond differently to OCM-targeted interventions.

Indeed, estrogens and androgens distinctly regulate key steps within the OCM-Hcy axis, exerting divergent effects on critical enzymes^[19]. These divergent influences, in turn, translate into differing metabolic landscapes for men and women, shaping both the natural history of MASLD. A prominent meta-analysis by Balakrishnan *et al.* underscores this sexual dimorphism, revealing that while women have a 19% lower risk of MASLD (formerly termed NAFLD), they exhibit a 37% higher risk of developing advanced fibrosis compared with men^[20]. Notably, menopause at approximately age 50 modifies the effect of sex on disease aggressiveness, with postmenopausal women facing elevated odds of MASH (metabolic dysfunction-associated steatohepatitis, previously known as NASH) and advanced fibrosis. Emerging genetic evidence suggests that this disparity is amplified by PNPLA3 variant interaction - the rs738409-CG polymorphism shows a 40% higher penetrance of fibrosis in men^[21]. This was further supported by mechanistic findings from Vilar-Gomez *et al.*, who found that PNPLA3 risk variants disrupt hepatic methionine metabolism^[22].

These findings collectively suggest that hormonal fluctuations exert profound effects on hepatic metabolism and disease progression. Women may benefit from protective hormonal profiles during their premenopausal years; yet, once this protective window closes, the subsequent rise in fibrotic burden may be heightened by metabolic perturbations that were previously attenuated. Considering sex, age, and reproductive status (e.g., menarche and menopause) is therefore emerging as a pivotal element in designing precision medicine approaches for MASLD^[23].

Against this backdrop, Suzuki *et al.* [Figure 1] take a bold step forward by pairing traditional clinical insights with a sophisticated mathematical approach, offering more than a descriptive account of Hcy dysregulation^[2]. Their simulations of distinct OCM cofactor regimens in men and women deliver practical guidance on how vitamins B6, B12, folate, and betaine might be harnessed synergistically for maximum Hcy-lowering impact. While prior studies have confirmed the importance of OCM cofactors in reducing liver injury, the novelty of Suzuki *et al.*'s model lies in its capacity to capture subtle sex differences that could otherwise remain obscured^[2]. Specifically, the data suggest that although folate alone confers a potent Hcy-lowering effect in both sexes, combining all available cofactors consistently yields the greatest reduction, hinting at untapped therapeutic synergies. This approach powerfully illustrates how theory-driven modeling can accelerate translational research, refining our understanding of MASLD phenotypes and illuminating personalized interventions.

Table 1. Mechanistic studies of OCM-Hcy-MASLD axis

Authors	Year of publication	Country	Sample source	Related conclusion
Ai <i>et al.</i> ^[12]	China	2017	C57BL/6J mice	ER stress and PERK-eIF2 α pathway mediate Hcy-induced MASLD progression via SREBP-1c activation and <i>de novo</i> lipogenesis
Liang <i>et al.</i> ^[13]	China	2019	C57BL/6J mice and human HepG2 cells	Orphan nuclear receptor NR4A1 suppresses Hcy-induced MASLD through H3K27 acetylation, with its agonist CsnB as a potential therapeutic target
Yan <i>et al.</i> ^[14]	China	2020	C57BL/6J mice and Human plasma	Hcy induces MASLD via HIF1 α -ERO1 α -dependent oxidative stress pathway, while adipocyte-specific HIF1 α deletion ameliorates this pathological process
Tripathi <i>et al.</i> ^[15]	Singapore	2022	C57BL/6J mice, primate models and human serum and liver tissue	Hcy promotes MASH progression through STX17 homocysteinylation and ubiquitination-mediated autophagy dysfunction, which can be improved by vitamin B12 and folate supplementation
Bagherieh <i>et al.</i> ^[16]	Iran	2023	Human HepG2 cells	Folate ameliorates palmitate-induced inflammation in HepG2 cells by reducing Hcy levels, ROS production, and NF- κ B pathway activation
Wang <i>et al.</i> ^[17]	China	2023	Macrophage-specific PDHA1 gene knockout mice	Macrophage-specific PDHA1 deletion exacerbates Hcy-induced MASLD through enhanced hepatocyte apoptosis
Xiang <i>et al.</i> ^[18]	China	2023	C57BL/6J mice	Hcy activates NLRP3 inflammasome via MDM2-mediated HSF1 K372 ubiquitination, leading to MASLD and insulin resistance

OCM-Hcy-MASLD: One-carbon metabolism-homocysteine-metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis.

BRIDGING THE MECHANISMS AND BEDSIDE PROTOCOLS: LIMITATIONS AND OPPORTUNITIES

Despite the promising insights derived from foundational research, several pivotal challenges must be addressed before OCM-targeted interventions can be fully integrated into clinical practice.

First, much of the current understanding of the OCM-Hcy-MASLD axis remains anchored in cellular and animal models, with only limited human validation. Given the complex interplay among genetic susceptibilities, environmental influences, and metabolic shifts in human MASLD, bridging this translational gap is paramount. Large-scale, longitudinal clinical trials that incorporate diverse patient populations will be critical for confirming the therapeutic potential and safety profile of OCM cofactor supplementation.

Second, although emerging data underscore the heterogeneity in Hcy metabolism - particularly between males, females, and distinct age groups - research to date has only begun to explore how these differences might inform individualized treatment. Suzuki *et al.*'s findings highlight sex-specific responses to OCM cofactor supplementation, but additional factors, such as menopausal status and genetic polymorphisms, could further refine intervention outcomes^[2]. A comprehensive understanding of these demographic nuances is indispensable for moving from a one-size-fits-all paradigm toward precision-based approaches.

Third, existing studies often focus on isolated enzymes or substrates in the OCM pathway, an approach that risks oversimplifying the broader metabolic interactions within the liver's intricate network. Of particular translational relevance, emerging evidence reveals interconnected metabolic networks extending beyond classical OCM components. Recent clinicopathological studies have identified significant polyamine pathway dysregulation in MASLD progression, manifested through elevated ornithine decarboxylase (ODC1) expression and putrescine accumulation in both preclinical models and human biopsies^[24]. Notably, this pathway's perturbation not only exacerbates lipotoxic stress responses but also demonstrates a

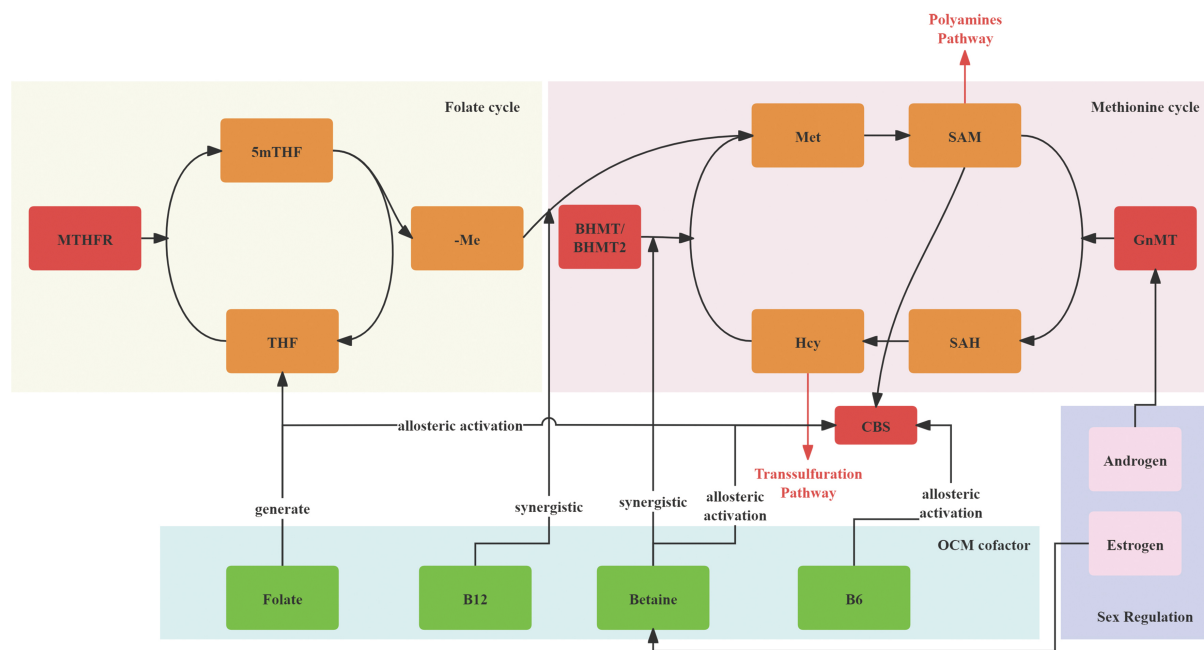


Figure 1. OCM Cofactor Mediated Hcy Regulation^[2]: This figure delineates Hcy metabolic regulation, comprising two core cycles (folate cycle and methionine cycle), two exit pathways (transsulfuration and polyamine pathways), with OCM cofactors and sex hormones demonstrating tissue-specific regulatory effects on Hcy levels. Yellow box: Folate cycle. MTHFR catalyzes THF reduction to 5mTHF, which serves as a methyl donor for Hcy methylation. BHMT/BHMT2 mediates 5mTHF regeneration to THF, completing the cyclical process. Red box: Methionine cycle. Met undergoes ATP-dependent conversion to SAM. Subsequent demethylation by GnMT generates SAH, which is hydrolyzed to Hcy. BHMT/BHMT2-mediated methylation regenerates SAM using folate-derived methyl groups. Red arrows: Exit pathways. (1) Transsulfuration: CBS-mediated conversion of Hcy to cysteine permanently removes it from core cycles; (2) Polyamine pathway: SAM decarboxylation yields spermidine/spermine, with final hydroxymethylmethionine exiting the system. Blue box: OCM cofactor regulation. (1) Folate: THF precursor and CBS allosteric activator; (2) B12: Mediates Hcy remethylation; (3) Betaine: Enhances BHMT/BHMT2 efficiency and CBS activation; (4) B6: Essential cofactor for CBS catalytic activity. Purple box: Sex hormone modulation. Estrogen upregulates betaine biosynthesis and CBS activation (Hcy-lowering). Androgen inhibits transsulfuration enzyme expression/activity (Hcy-accumulating). OCM: One-carbon metabolism; THF: tetrahydrofolate; MTHFR: methylenetetrahydrofolate reductase; 5mTHF: 5-methyltetrahydrofolate; -Me: methyl; Met: methionine; SAM: S-adenosylmethionine; GnMT: glycine N-methyltransferase; SAH: S-adenosylhomocysteine; CBS: cystathionine beta-synthase; Hcy: homocysteine; BHMT: betaine-homocysteine methyltransferase.

strong correlation with histopathological severity indices, implying potential mechanistic convergence with the OCM-Hcy axis that warrants systematic exploration. Given that MASLD is, by nature, a multifaceted disease involving dysregulated lipid, glucose, and amino acid metabolism, these findings collectively reinforce the essentiality of a systems biology perspective. To fully unravel the complex crosstalk among these pathways, multifactorial models - particularly those integrating transcriptomic, proteomic, and metabolomic datasets - must be prioritized. Such integrated approaches may yield a more holistic roadmap of OCM-Hcy perturbations and their synergistic contributions to disease progression.

Finally, the pathway from bench to bedside faces logistical difficulties related to the clinical implementation of OCM-targeted therapies. Standardized protocols for quantifying tissue-specific Hcy levels and assessing OCM enzyme activities are lacking, complicating both diagnostic precision and treatment monitoring. The optimal dosing strategy, combination of cofactors, and timing of intervention (including perioperative administration) are similarly undefined. Addressing these gaps will likely require well-designed, controlled trials that incorporate biomarker-driven end points and evaluate real-world efficacy in combination with surgery or other standard-of-care therapies.

Moving forward, robust, multicenter collaborations will be pivotal for generating consensus on clinical endpoints, bridging methodological discrepancies, and establishing universally accepted treatment algorithms. Integration of big data analytics, coupled with machine learning techniques, may further refine patient stratification and illuminate novel, sex-specific targets amenable to OCM-based interventions. Ultimately, these interdisciplinary efforts stand to elevate MASLD management, opening new avenues not only for preventing advanced disease but also for mitigating the oncogenic potential associated with MASLD over the long term.

BEYOND THE SCALPEL: METABOLIC AND PRECISION MEDICINE INSIGHTS

In recent years, PLC has come to be recognized as a systemic metabolic disease rather than a strictly localized malignancy. From an anatomical perspective, the liver functions as the central hub of whole-body metabolism, and recurrence or metastasis - rather than merely the primary tumor load - remains a leading cause of mortality in PLC^[25]. Concurrently, tumorigenesis in PLC is fundamentally driven by metabolic reprogramming^[26], signifying that no extent of local surgical excision can wholly resolve this global metabolic disorder. Given that MASLD is an established risk factor for PLC, and in light of the promising implications of the OCM-Hcy-MASLD axis, there is a need for a comprehensive treatment paradigm that addresses the metabolic underpinnings of disease. However, it is important to note that the current evidence on the role of OCM in hepatocarcinogenesis is still limited, and further research is needed to fully understand its impact on PLC development and progression.

Revisiting oncological priorities in MASLD-related PLC

MASLD-associated hepatic dysfunction presents unique surgical challenges, particularly regarding compromised hepatic reserve and altered regenerative capacity. Current evidence suggests R0 resection should be balanced with functional preservation^[27], especially given the increased perioperative risks in metabolically compromised patients. Emerging data indicate that preoperative metabolic optimization may improve surgical tolerance, though specific protocols require further validation.

Incorporating the OCM-Hcy pathway into full-cycle intervention

The OCM-Hcy axis represents one of several metabolic pathways implicated in MASLD progression. While Suzuki *et al.*'s modeling provides theoretical support for cofactor supplementation, clinical translation requires rigorous validation^[2]. Current evidence supports considering metabolic status during surgical planning rather than implementing specific OCM-targeted protocols.

Refining perioperative management in metabolically at-risk patients

Recent studies have emphasized the need for comprehensive metabolic assessment in patients with MASLD undergoing hepatectomy, and the study by Lopez-Pascual *et al.* has created a new way to develop perioperative management strategies for patients with MASLD from the perspective of nanomaterials^[28]. Sex-specific metabolic changes merit consideration but should not override established perioperative protocols.

Anticipating future directions for MASLD-related PLC management

Therapeutic interventions targeting metabolic pathways, such as the OCM-Hcy-MASLD axis, may reduce perioperative risks. For patients with MASLD-related PLC, leveraging this axis through targeted pharmacotherapy - e.g., Hcy-lowering agents and metabolic regulators - could disrupt tumor-promoting processes while simultaneously improving hepatic reserve. Moreover, integrating these regimens with minimally invasive surgical approaches has the potential to minimize postoperative morbidity, especially in individuals burdened by obesity or other metabolic derangements.

CONCLUSION

In conclusion, the discovery of the OCM-Hcy-MASLD axis and its sex-specific characteristics has opened new avenues for improving perioperative management and long-term prognosis. Looking ahead, the integration of multi-omics data - including metabolomics, epigenomics, and microbiomics - coupled with the establishment of an OCM-Hcy axis-centered biomarker monitoring system and the combination of precision surgery with individualized metabolic interventions, holds promise for fundamentally enhancing outcomes in patients with MASLD-related PLC. This paradigm shift not only represents an evolution from mere surgical resection to comprehensive metabolic regulation but also marks a significant step forward in hepatobiliary surgery toward the era of precision medicine.

DECLARATIONS

Authors' contributions

Conceptualized the commentary, conducted the literature review, and contributed to the writing and editing of the manuscript: Li ZL, Tang ZH

Assisted in the literature: Chen JL, Tang Y, Qin DL

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Conflicts of interest

Tang ZH is a Junior Editorial Board member of the journal *Metabolism and Target Organ Damage*. Tang ZH was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling and decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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