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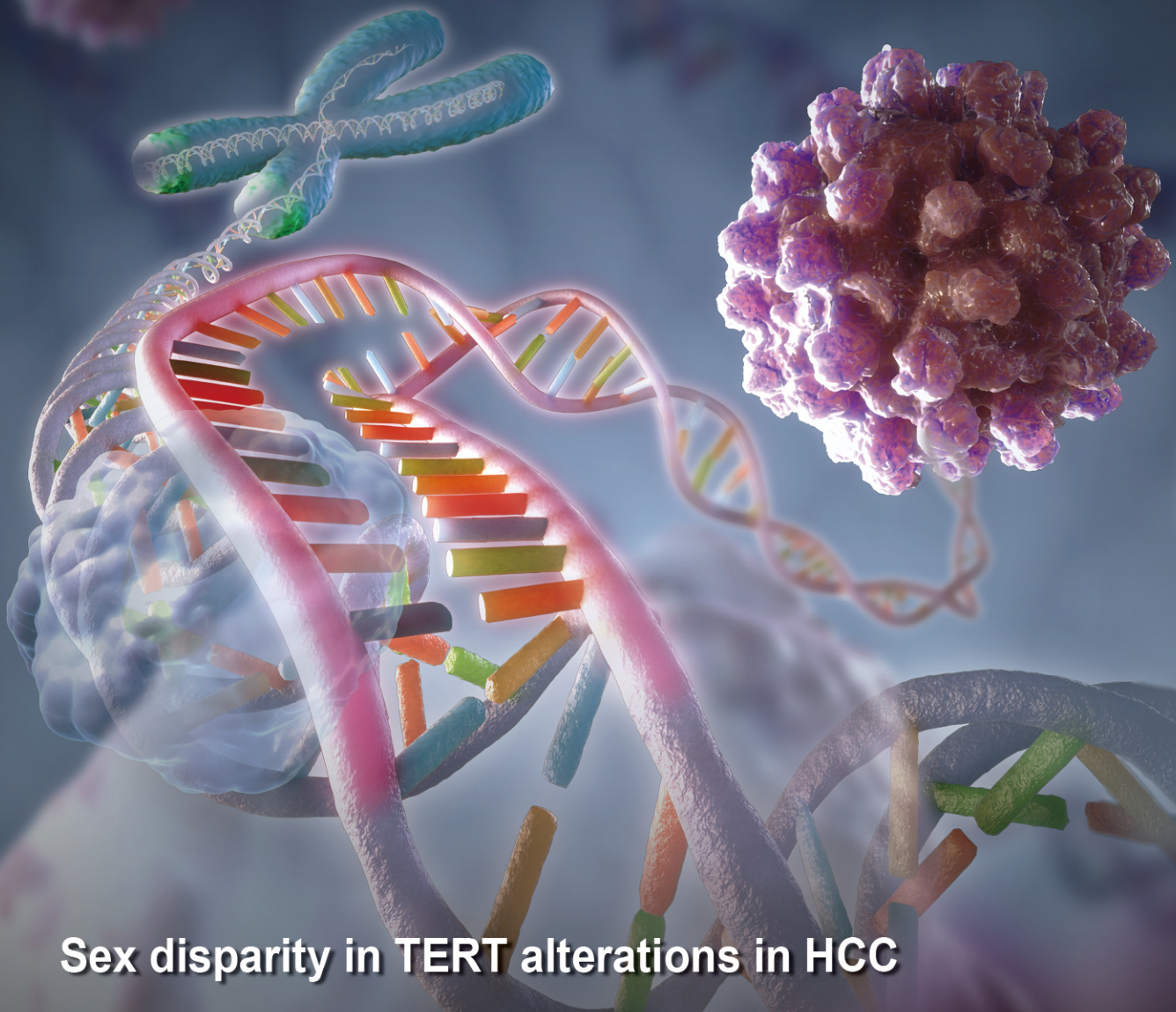

Sex disparity in TERT alterations in HCC

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

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Editorial

Unraveling the role of GOLM1-OPN-ABCG5 axis in MASH: Editorial on "GOLM1 promotes cholesterol gallstone formation via ABCG5-mediated cholesterol efflux in MASH livers"

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Metabolic dysfunction-associated steatohepatitis (MASH), characterized by fatty liver disease and inflammation, is a common manifestation of metabolic syndrome. It is a major risk factor for complications such as cirrhosis and hepatocellular carcinoma, when advanced to an irreversible stage, liver transplantation often becomes the only viable treatment option.[1,2] Although the U.S. Food and Drug Administration (FDA) has recently approved the thyroid hormone receptor-β (THR-β) agonist Resmetirom for the treatment of MASH, additional therapeutic approaches are still needed. Several challenges remain, including the need for better correlation between clinical outcomes and histologic data, uncertainty regarding the safety of long-term clinical outcomes, and the potential for combination therapies to enhance efficacy.[3,4]

The formation of cholesterol gallstones (CGSs) is a prevalent clinical issue that affects a significant portion of the global population.[5] CGSs are the primary type of gallstone, caused by an imbalance in bile components and the supersaturation of cholesterol in bile.[6] The pathophysiology of CGS formation is complex and multifactorial, including dysregulation of hepatic and biliary systems.[5,7] The liver plays a pivotal role in cholesterol metabolism, such as cholesterol synthesis, secretion, and efflux into bile.[8] Thus, defects in

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cholesterol metabolism and transport in the liver can lead to cholesterol supersaturation, which may significantly contribute to gallstone formation. Recent studies have emphasized a significant link between liver diseases, particularly metabolic-associated fatty liver disease (MAFLD) and its more aggressive form, MASH, and the increased risk of CGSs, indicating an association between liver dysfunction and the pathogenesis of CGS formation.[9,10] However, the underlying mechanism between liver disease and CGS formation remains unclear.

In the current issue of *Clinical and Molecular Hepatology*, Li et al.[11] investigated the association between hepatic inflammation and CGS formation. To first determine the relationship between MASH and cholelithiasis, they analyzed data from the UK Biobank (UKB). Their results revealed that the incidence of cholelithiasis is higher in patients with MASH compared to those with simple steatosis or healthy participants. Based on their findings, Li et al.[11] concluded that MASH is strongly associated with the development of cholelithiasis. Notably, this study showed that Golgi membrane protein 1 (GOLM1), a protein involved in hepatic cholesterol metabolism, plays a crucial role as a mediator of cholesterol efflux in MASH-related CGS. Mechanistically, the study demonstrated that GOLM1 enhances cholesterol efflux from the liver via the upregulation of ATP-binding cassette subfamily G member 5 (ABCG5). Li et al.[11] elucidated that GOLM1 translocates to the nucleus, where it activates the transcription of osteopontin (OPN), which subsequently enhances the expression of ABCG5. This GOLM1-OPN-ABCG5 axis enhances cholesterol secretion in the bile, contributing to CGS formation. Furthermore, the authors confirmed that interleukin-1β (IL-1β), a key inflammatory factor associated with MASH, upregulates GOLM1 expression in a dose-dependent manner. This finding highlights that GOLM1 may play a crucial role in the connection between liver inflammation and CGS formation.

This study represents significant progress in understanding the molecular mechanisms that serve as the basis for the increased risk of CGSs in patients with MASH. However, it is important to acknowledge the limitations of this study. First, classical biochemical findings suggest that some steroid hormones, such as testosterone and estradiol, are derived from cholesterol, and therefore gender effects may contribute to an increased risk of CGS formation,[12,13] possibly linked to the regulation of GOLM1 expression. However, since the study included only male animals, it did not investigate the potential role of females. Further studies are needed to explore the relationship between gender effects and GOLM1 expression associated with MASH. Second, this study used only a global knockout (KO) mouse model, which may not fully represent the tissue-specific role of GOLM1 in liver inflammation and cholesterol metabolism. For example, adipose tissue is an endocrine gland, that plays an important role in systemic metabolism, releasing free fatty acids (FFAs), adipokines, and cytokines, and MASH development.[14,15] The pathophysiological role of adipose tissue-derived GOLM1 in CGS formation and liver inflammation remains unclear. Indeed, potential compensatory mechanisms in other tissues or cell types can affect the interpretation of the results in the context of MASH-related CGS formation. The final limitation of this study is that Li et al.[11] used a high-fat diet (HFD) model to induce MASH in vivo, which did not fully recapitulate the typical histologic features of MASH, such as lobular inflammation and hepatocyte ballooning. Instead of an HFD-induced MASH model, recent studies have used fatty acid diets, choline-deficient L-amino-defined diets (CDAA), methionine choline deficient diets (MCD), or high-fat, high-cholesterol diets (HFHC) to induce MASH in vivo.[16] Therefore, the findings from these studies may not fully represent the complete spectrum of MASH pathogenesis in humans, and further validation of MASH dietary models to mimic MASH in vivo is necessary.

Despite these limitations, Li et al.[11] offer progressive insights into the molecular mechanisms driving CGS formation in MASH. By identifying GOLM1 as a key regulator of cholesterol efflux through the OPN-ABCG5 axis, the authors highlight a potential therapeutic option for preventing gallstone formation in patients with MASH. Further studies should validate these findings in clinical cohorts and in vivo models that better mimic MASH, and explore targeted ther-

Abbreviations:

ABCG5, ATP-binding cassette subfamily G member 5; CDAA, choline-deficient L-amino-defined diet; CGSs, cholesterol gallstones; FDA, Food and Drug Administration; FFA, free fatty acid; GOLM1, Golgi membrane protein 1; HFHC, high-fat, high-cholesterol diet; HFD, high-fat diet; IL-1β, Interleukin-1β; MAFLD, metabolic-associated fatty liver disease; MCD, a methionine choline deficient; metabolic dysfunction-associated steatohepatitis; OPN, osteopontin; THR-β, thyroid hormone receptor-β

apies to modulate cholesterol metabolism in patients with MASH of all genders.

Authors' contributions

YSH designed and wrote the manuscript; WK and SJK supervised the project and wrote the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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