

Commentary

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Intestinal TM6SF2 and the gut-liver axis in MASLD: new insights

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) involve a complex interplay of genetics, metabolism, and the gut-liver axis. In a new study, Zhang *et al.* assess a previously unrecognized role of the intestinal epithelium in protecting against MASH by focusing on Transmembrane 6 Superfamily Member 2 (TM6SF2), a gene highly expressed in both the liver and intestine, whose common loss-of-function variant (E167K) is a well-established genetic risk factor for MASLD/MASH in humans. Herein, we provide an overview of Zhang *et al.*'s study and highlight the clinical significance of these new findings by focusing on two specific areas: the gut-liver axis in MASLD and the modification of the intestinal microbiota.

Keywords: TM6SF2, E167K, microbiome, gut-liver axis, LPA pathway

Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) is now the leading cause of chronic liver disease in many regions, whereas its progressive form, metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH), affects ~20%-25% of MASLD patients^[1]. These conditions involve a complex interplay of genetics, metabolism, and the gut-liver axis. One prominent



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genetic factor is the Transmembrane 6 Superfamily Member 2 (TM6SF2) gene, identified in 2014 via exome-wide association as a susceptibility gene for fatty liver disease^[2]. TM6SF2 encodes a transmembrane protein highly expressed in the liver and small intestine and was previously known to regulate hepatic lipid metabolism by influencing VLDL triglyceride secretion and fat storage in hepatocytes^[3]. A new study by Zhang *et al.* assesses a previously unrecognized role of the intestinal epithelium in protecting against MASH^[4]. The authors focus on TM6SF2, whose common loss-of-function variant (E167K) is a well-established genetic risk factor for MASLD/MASH in humans.

In their study, Zhang *et al.* employed an intestinal epithelial cell (IEC)-specific knockout mouse model (*Tm6sf2*^{ΔIEC}) to assess the function of TM6SF2 outside the liver. Interestingly, mice lacking TM6SF2 were fed either normal chow (NC) or a choline-deficient high-fat diet (CD-HFD). Even under NC, knockout mice exhibited markedly worsened liver pathology compared to wild-type controls. The disease was further exacerbated under CD-HFD, and mice with TM6SF2 loss in their gut epithelium developed severe steatohepatitis, whereas the presence of TM6SF2 appeared to slow disease progression. These findings suggest that systemic TM6SF2 loss promotes severe steatohepatitis, independent of dietary fat content^[4]. Histologically, the knockout mice showed increased hepatic fat accumulation and inflammation consistent with MASH, alongside evidence of an impaired intestinal barrier and alterations in gut microbiota composition. In particular, loss of intestinal TM6SF2 led to an overgrowth of certain “pathobiont” bacteria (potentially harmful microbes), indicating microbial dysbiosis. To confirm that the microbiome changes were functionally relevant, the authors transplanted stool from TM6SF2-deficient mice into germ-free mice, and this was sufficient to induce steatohepatitis in the recipient mice, suggesting that a transmissible microbiota factor contributed to liver disease. Conversely, co-housing TM6SF2-deficient mice with wild-type mice (allowing them to exchange microbiota) significantly alleviated the development of MASH in the knockouts^[4]. These experiments suggest that gut microbiota dysbiosis, secondary to intestinal TM6SF2 loss, can drive liver inflammation, implying a causal gut-liver axis in this genetic context.

Zhang *et al.* also discovered that intestinal cells lacking TM6SF2 secreted an excess of free fatty acids (FFAs) into the gut lumen^[4]. They specifically identified an interaction between TM6SF2 and fatty acid-binding protein 5 (FABP5) in enterocytes. Normally, TM6SF2 appears to partner with FABP5 to facilitate intracellular fatty acid trafficking or lipoprotein assembly. Without TM6SF2, this partnership is lost, leading to the accumulation and aberrant release of FFAs from enterocytes. The surplus FFAs in the gut can directly injure the intestinal barrier and facilitate the growth of pathobionts. Indeed, TM6SF2-deficient mice demonstrated compromised gut barrier integrity (as measured by permeability assays) when exposed to the excess FFAs, linking intestinal lipid mishandling to barrier dysfunction. A notable downstream consequence was a marked increase in lysophosphatidic acid (LPA) levels in the intestine and portal circulation of TM6SF2-deficient mice. LPA is a pro-inflammatory lipid mediator generated from lysophospholipids (often via the enzyme autotaxin) and known to act on LPA receptors in multiple organs^[5]. Zhang *et al.* found that these elevated LPA levels likely originated in the dysbiotic gut environment and then translocated to the liver via the portal vein, where LPA promoted hepatic fat accumulation and inflammation^[4]. In other words, excess FFAs → gut barrier damage and dysbiosis → LPA production → liver injury emerged as a pathway linking intestinal TM6SF2 loss to steatohepatitis. Of note, the authors validated this mechanism by pharmacologically targeting it with an LPA receptor antagonist, which significantly suppressed the development of steatohepatitis in TM6SF2-intestinal knockout mice. Treated mice had reduced liver fat and inflammatory markers, confirming that LPA signaling was a key driver of disease in this model. Intriguingly, the same LPA receptor blocker also mitigated diet-induced steatohepatitis in wild-type mice, suggesting that the LPA axis is not only relevant to TM6SF2 deficiency but may be a more general mediator of MASH pathogenesis^[5]. Taken together, these findings position intestinal TM6SF2 as a

potential “gatekeeper”, which normally reduces FFA release and prevents gut-derived pro-inflammatory signals, thereby protecting the liver from metabolic injury.

The discovery that intestinal TM6SF2 guards against steatohepatitis carries significant implications for MASLD. As noted, carriers of the TM6SF2 *E167K* variant accumulate hepatic triglycerides and are at ~1.8-fold higher odds of developing MASH and advanced fibrosis^[6]. Paradoxically, they tend to have lower serum LDL cholesterol and a reduced risk of cardiovascular events due to impaired lipid enrichment of VLDL^[6]. The study by Zhang *et al.* provides a link that may explain part of the variant’s effect on liver outcomes beyond the liver itself^[4]. The findings suggest that individuals with TM6SF2 dysfunction could have subtle intestinal abnormalities - a “leaky gut” with altered microbiota - that predispose them to liver inflammation. Indeed, leaky gut features are common in metabolic liver disease and specifically in patients with MASLD^[7], while circulating gut-derived toxins correlate with MASH severity^[8]. Here, the toxic mediator is not a microbial product like LPS but an endogenous lipid (LPA) produced in the dysbiotic gut. Of note, LPA is emerging as an important driver of metabolic inflammation^[9]. Taken together, the study by Zhang *et al.* highlights two specific strategies to target the gut-liver axis in MASLD: microbiome modulation and LPA pathway inhibition^[4]. Modifying the intestinal microbiota, e.g., with fecal microbiota transplantation (FMT), could hypothetically restore barrier integrity and reduce pro-steatotic metabolites^[10].

On the other hand, the LPA signaling pathway may also offer a drug target. The current study’s use of an LPA receptor antagonist achieving therapeutic benefit in mice reinforces the translational potential of this approach. If the gut-derived LPA mechanism is confirmed in MASLD patients, LPA-LPAR inhibitors might be explored as novel treatments to prevent progression from simple steatosis to steatohepatitis. In essence, this work shifts some focus beyond the liver and toward the intestine in MASH. It suggests that comprehensive management of MASLD could require not only addressing hepatic metabolism and systemic risk factors, but also maintaining a healthy gut barrier and microbiome. The concept that a patient’s genetics (TM6SF2 status) might inform gut-targeted interventions could be a compelling step toward personalized therapy.

While the findings are exciting, there are several limitations. First, murine physiology differs from that of humans. Mice lacking intestinal TM6SF2 developed spontaneous steatohepatitis over months, but human carriers of TM6SF2 variants do not uniformly develop MASH - indicating the gene’s effect in humans is modulated by diet, environment, and other genes. The study’s mice were housed in specific pathogen-free facilities; their microbiome changes, though striking, may not exactly reflect the diverse gut flora of humans across different lifestyles. It will be important to verify in intestinal organoids or patient cohorts whether TM6SF2 variant carriers show signs of gut barrier impairment or altered fecal metabolites (like LPA)^[11]. In addition, Zhang *et al.* provide mechanistic evidence linking intestinal TM6SF2 deficiency to MASH; their findings are primarily based on mouse models that lack advanced fibrosis and may better represent early disease stages^[4]. Therefore, therapeutic targets like TM6SF2 or LPA signaling are most likely applicable to early stages of MASH, pending validation in human studies and fibrosis-focused models. Second, the causal metabolite LPA identified here is one of many potential gut-derived factors. LPA likely works together with other microbial products to exacerbate liver injury. Isolating the contribution of LPA from these factors in humans will require careful biochemical and microbiome analyses. Another limitation is that the study primarily examined one genetic mutation in isolation. In reality, patients often carry multiple risk alleles [e.g., in Patatin-like phospholipase domain-containing protein 3 (PNPLA3), 17-beta-hydroxysteroid dehydrogenase 13 (HSD17B13), Apolipoprotein E (APOE), *etc.*], and the combined effects on the gut-liver axis are unknown. TM6SF2’s impact might be less pronounced in the presence of stronger drivers like

PNPLA3. Additionally, the therapeutic experiment used an LPA receptor antagonist in mice, but such compounds may have off-target effects or different pharmacokinetics in humans. For example, in a phase 2 trial, the LPA₁ antagonist BMS-986020 caused hepatobiliary toxicity (elevated ALT, AST, and cholestatic injury) that was later attributed to off-target inhibition of bile acid transporters^[12]. Finally, while histologic liver injury and inflammatory markers improved with LPA blockade in mice, it is unclear if this approach can reverse advanced fibrosis once established. MASH is a chronic, multifactorial disease, and targeting a single pathway might yield only partial benefit. Therefore, clinical translation will require rigorous testing - first in *ex vivo* human systems and eventually in trials, perhaps stratifying patients by TM6SF2 genotype.

Despite these caveats, the study by Zhang *et al.* opens several avenues for future investigation and potential therapy and the need to demonstrate relevance in humans^[4]. Future studies could examine whether individuals carrying the TM6SF2 E167K variant have a distinct gut microbiome signature or higher portal blood LPA levels. If such correlations exist, it would strengthen the case that the mouse findings reflect an analogous human pathway. Future work should address these gaps to validate the intestine-microbiome-LPA axis as a therapeutic target in MASLD.

In addition, the TM6SF2-FABP5-LPA mechanism likely represents one piece of the MASH puzzle. Other genetic factors (e.g., variants in PNPLA3, HSD17B13, or APOE) and environmental factors (dietary choline content, alcohol use, *etc.*) also modulate the gut-liver axis. Future research should explore how these factors interact. For instance, does the presence of a *PNPLA3* risk allele exacerbate or mitigate the gut permeability seen with TM6SF2 loss? Are there additive effects on liver injury when multiple “at-risk” microbiome profiles overlap? Understanding these interactions could inform risk stratification - perhaps defining a subset of patients as “gut-dominant” vs. “metabolism-dominant” in terms of disease-driving pathways, which might guide personalized therapy. In addition, as MASLD is a polygenic and multifactorial disease, multi-gene research models may offer more accurate predictions of disease susceptibility, severity, and progression^[13].

In summary, the work by Zhang *et al.* underscores the importance of the gut-liver axis in MASLD/MASH and provides a blueprint for new research directions^[4]. The present study not only advances our understanding of MASH pathogenesis but also points to tangible targets (microbes and molecules) that could be manipulated for therapeutic benefit. By highlighting a protective role of intestinal TM6SF2, this research adds a new dimension to our conceptual model of steatotic liver disease. If future studies confirm these findings in humans, we may move closer to interventions that break the gut-liver cycle, offering patients innovative ways to halt or even reverse the progression of MASLD.

DECLARATIONS

Authors' contributions

Contributed equally to writing and editing the manuscript: Kalligeros M, Henry LL, Younossi ZM

Approved the final submitted manuscript: Kalligeros M, Henry LL, Younossi ZM

Availability of data and materials

Not applicable.

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Conflicts of interest

Henry LL is an Editorial Board member of the journal *Metabolism and Target Organ Damage*. Henry LL was not involved in any steps of the editorial process, including reviewer selection, manuscript handling, or decision making. Younossi ZM is a consultant or has received research funding from Intercept, Cymabay, Boehringer Ingelheim, Ipsen, Gilead Sciences, Inventiva, BMS, GSK, NovoNordisk, Siemens, Madridgal, Merck, Akero, and Abbott. Kalligeros M 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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