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AASLD The Liver Meeting®

ABSTRACT SUPPLEMENT

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AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

The Liver Meeting

Washington, DC

Nov 7-11, 2025

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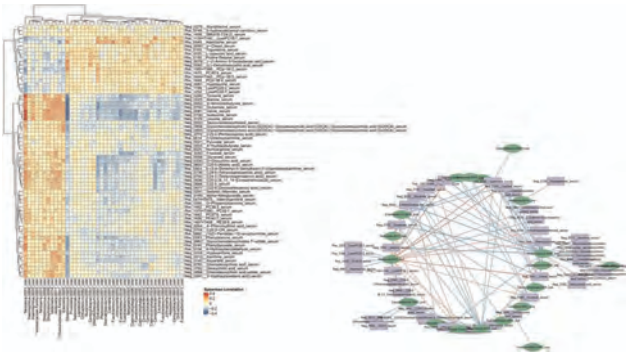
Background: Previous studies have primarily focused on the role of the intestinal microbiome in metabolic dysfunction-associated steatotic liver disease (MASLD). While the impact of the gut microbiome is well-documented, the role of the oral microbiome in influencing the gut microbial environment and metabolic pathways has been unveiled. We aimed to investigate the association between the oral microbiome and its potential impacts on gut microbiomes, metabolites, and metabolic risk factors. **Methods:** This study was conducted as a multicenter cross-sectional study involving 206 healthy individuals and 206 diagnosed with MASLD. The oral and stool microbiomes were analyzed using the V3–V4 hypervariable region of the 16S rRNA gene, following the Illumina 16S Metagenomic Sequencing Library Preparation protocol. Serum and stool metabolites were also analyzed using LC-MS. **Results:** There was a lower diversity of oral microbiota and distinct microbial distributions in MASLD compared to controls. Notably, prevalence of oral Neisseria sp. 0031, Veillonella sp. 0011, and Streptococcus sp. 0009 were higher in MASLD compared to non-SLD. These oral microbiomes showed positive associations with body mass index, waist circumference, and adverse lipid profiles, alongside a correlation with elevated liver enzymes. Additionally, specific gut microbes like Weissella sp.001 and Tyzzerella sp. 001 were more abundant in MASLD. Interestingly oral Neisseria sp. 0031, Veillonella sp. 0011, and Streptococcus sp. 0009 showed positive correlation with intestinal Weissella sp.001 and Tyzzerella sp. 001. Presence of Streptococcus sp. 0009 in MASLD was associated with higher levels of lysophosphatidylcholines (15:0), (17:0) and negative correlation with correlation with N-(1-Deoxy-1-fructosyl) aline, succinylcarnitine in serum. **Conclusion:** The oral microbiome, specifically Streptococcus sp. 0009, showed a positive correlation with intestinal microbiome, obethogenic metabolites as well as cardiometabolic parameters in patients with MASLD.



Disclosures: Dae Won Jun: Nothing to Disclose, Hyo Young Lee: Nothing to Disclose, Sang Bong Ahn: Nothing to Disclose, Hyunwoo Oh: Nothing to Disclose, Eileen Yoon: Nothing to Disclose, Ju Hyun Oh: Nothing to Disclose, HA IL KIM: Nothing to Disclose

◆ 4343 | CARBOXYMETHYLCELLULOSE AND POLYSORBATE 80: BRIDGING ULTRAPROCESSED FOOD AND MASLD-ASSOCIATED HEPATOCARCINOGENESIS

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Background: Hepatocellular carcinoma (HCC) is the main primary liver neoplasia and the 3rd deadliest type of cancer worldwide, whereas metabolic-dysfunction associated liver disease (MASLD) has become the fastest-growing cause of liver disease. Carboxymethylcellulose (CMC) and polyssorbate 80 (P80) emulsifiers are extensively consumed as food additives by the global population and regarded as potential drivers of metabolic diseases by disrupting the gut-liver axis balance. Nevertheless, it is still uncertain whether these compounds modulate MASLD-associated liver carcinogenesis. **Methods:** Male 14-day-old C57BL/6 mice received an intraperitoneal protocol of diethylnitrosamine (DEN, 25 mg/kg of b.w., 1x/week) or saline vehicle, for 4 weeks, and were allocated into 8 experimental groups (G1-G8). From the 6th week on, mice (G2-G8) were kept for 24 weeks on a western diet (WD) protocol or regular diet (G1). Mice also received daily intragastric doses (5x/week), for 20 weeks, of CMC (370 and 740 mg/kg of b.w., G3 and G4, respectively), P80 (100 and 200 mg/Kg of b.w., G5 and G6, respectively), or their combination (370 +100 and 740 +200 mg/Kk of b.w., G7 and G8, respectively) or ultrapure water vehicle. A glucose tolerance test (GTT) was performed and obesity-related outcomes assessed. Hepatic tumoral/non-tumoral samples were collected for further histopathological and molecular analysis. Fecal samples were collected for gut microbiome profiling. Data were analyzed by one/two-way ANOVA or Kruskal-Wallis and Tukey's/Dunn's *post hoc* tests ($p \leq 0.05$). The Shannon's test was used for checking fecal samples' diversity. For the transcriptomic data, a Log2 Fold Change > 1 and padj < 0.05 were defined for the identification of differentially expressed genes. **Results:** G5/G7 had increased final body weight and adiposity index ($p < 0.0001$), while G6/G8 groups showed a higher proportion of larger tumors (> 50 mm^3, $p < 0.0001$). All WD-fed groups showed a glucose

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intolerance state, as depicted by the GTT area under the curve ($p < 0.0001$), and no effects were observed on serum parameters (alanine aminotransferase, total cholesterol, and triglycerides). Surprisingly, G5-G7 had a pronounced MASLD activity score, featuring a mixed macro/microvesicular steatosis background ($p < 0.0001$) with clear signs of hepatocellular hypertrophy ($p < 0.0001$). G3/G7 featured profound gut microbiome changes, following Shannon's diversity test ($p = 0.0282$ and $p = 0.0472$) at phylum, classes, order, and genera levels. Our bulk RNA-seq analysis revealed a dissimilar impact of food additives on both tumor and adjacent liver, with prominent effects of P80 over inflammation-, lipid-, and microbiome-related genes. **Conclusion:** Our findings revealed that the exposure to populational-relevant doses of CMC and P80 or their combination promote MASLD-associated liver carcinogenesis through the modulation of the gut-liver axis.
Disclosures: Gabriel Bacil: Nothing to Disclose, Leticia Valente: Nothing to Disclose, Heloiza Ferreira: Nothing to Disclose, Julia Noveti: Nothing to Disclose, Keila Cavalcante: Nothing to Disclose, Diego Alonso: Nothing to Disclose, Paulo Ribolla: Nothing to Disclose, Daniel Cardoso: Nothing to Disclose, Guilherme Romualdo: Nothing to Disclose, Luis Fernando Barbisan: Nothing to Disclose

◆ 4344 | LOSS OF HEPATIC VACUOLE MEMBRANE PROTEIN 1 PROTECTS AGAINST ACETAMINOPHEN-INDUCED LIVER INJURY

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Background: Acetaminophen (APAP) is an analgesic and antipyretic drug that is commonly used worldwide. Although APAP is considered safe at therapeutic doses, APAP overdose may cause severe liver injury and acute liver failure (ALF). Metabolism of APAP results in formation of APAP protein adducts (APAP-AD) in hepatocytes and triggers mitochondrial dysfunction and necrosis. One proposed mechanism to counteract APAP-induced hepatotoxicity is autophagy, a highly conserved intracellular degradation pathway protecting the cell via the removal of APAP adducts and damaged mitochondria. Vacuole membrane protein 1 (VMP1) is an ER transmembrane protein essential for the elongation and closure of autophagosomes. Deletion of VMP1 in the liver leads to impaired autophagy. However, the role of VMP1 in APAP-induced liver injury is unknown. **Methods:** RNAseq database from human APAP ALF and mouse APAP overdose livers were analyzed. Liver-specific VMP1 knockout ($Vmp1^{LKO}$) and matched wild-type ($Vmp1^{LWT}$), and the liver tissues were collected at different time points. Liver injury and necrosis were assessed by serum ALT, hematoxylin and eosin (H&E), and TUNEL staining. APAP metabolism, autophagy, APAP adduct formation, and liver regeneration were also examined. **Results:** Increased mRNA levels of *VMP1* and autophagy genes, *LC3B* and *SQSTM1/p62* in human APAP ALF livers. Serum ALT and necrosis were increased in WT mice following APAP treatment and peaked at 6 hours with increased phosphorylated JNK in mouse livers. LC3B-II and p62 were increased and peaked at 24 hours, but VMP1 protein was decreased in WT mouse livers following APAP treatment. Liver injury was markedly decreased in $Vmp1^{LKO}$ mice compared with their WT littermates with reduced serum ALT and necrotic areas. No difference in basal levels of Cyp2E1 and GSH was found between WT and KO mouse livers. The protein level of phosphorylated JNK was reduced in $Vmp1^{LKO}$ mouse livers. Interestingly, APAP adduct formation and mitochondrial damage were similar in WT and $Vmp1^{LKO}$ mouse livers after APAP, but peroxynitrite formation was decreased in $Vmp1^{LKO}$ mouse livers. Furthermore, GSH replenishment was faster in $Vmp1^{LKO}$ mice than in WT. The number of PCNA-positive cells and hepatic protein levels of PCNA were higher in $Vmp1^{LKO}$ mouse livers. **Conclusion:** Loss of hepatic VMP1 does not affect APAP metabolism and APAP adduct formation but protects APAP-induced liver injury by reducing peroxynitrite formation and enhancing liver regeneration.
Disclosures: Hong-Min Ni: Nothing to Disclose, Khue Nguyen: Nothing to Disclose, Mengwei Niu: Nothing to Disclose, Wen-Xing Ding: Nothing to Disclose

◆ 4345 | KINASE INHIBITOR INDUCED LIVER INJURY

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Background: Protein Kinase Inhibitors (KIs) are important therapies for both neoplastic and serious non-neoplastic diseases. Since 2003, more than 100 KIs have been approved for use in the US. Many KIs are associated with aminotransferase elevations during therapy, but little has been reported on serious and clinically apparent KI-induced liver injury (KILI). We aimed to assess the frequency, clinical features, and genetic associations of KILI enrolled in the Drug-Induced Liver Injury Network (DILIN) retrospective and prospective studies. **Methods:** Cases of KILI enrolled in

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