P- 9 BIOMARKERS OF THE BACTERIAL, VIRAL AND HUMAN GUT TRANSCRIPTOME IN METABOLIC ASSOCIATED FATTY LIVER DISEASE (MAFLD) IN ARGENTINA

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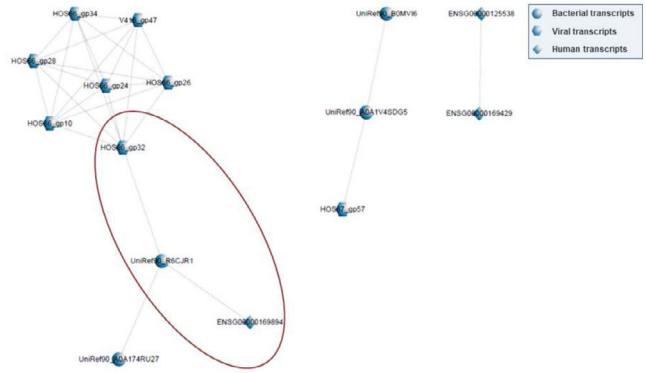
Introduction and Objectives: The functional dynamics of the gut microbiome and its interactions with the human transcriptome represent a niche for non-invasive biomarkers to risk-stratify MAFLD. This study aimed to identify gut transcriptomic signatures associated with MAFLD in Argentina.

Materials and Methods: Stool samples, diet, demographic and clinical data were obtained from 33 biopsy-proven MAFLD patients (12 simple steatosis -SS- and 21 steatohepatitis -SH-) and 19 healthy volunteers (HV). RNA-seq was performed in NovaSeq6000®. Data were analyzed with Maaslin2-v1.2.0, bioBakery-v1.8 and DESeq2-v4.1. Co-expression analysis was performed with Hmisc-v4.7-0.

Results: BMI was higher in MAFLD, particularly in SH patients ($q=4.49 \times 10^{-6}$). After adjusting for BMI, differentially expressed genes (DEGs) were found when comparing MAFLD *vs.* HV and SH *vs.* SS in bacterial (5 and 13, respectively), viral (112 and 26, respectively) and human (4 and 46, respectively), transcriptomes ($q<0.01$). Functional profiling of DEGs in MAFLD and SH patients revealed augmented bacterial sulfur and uric acid metabolisms, viral life cycle and viral regulation of the host immune system. Inflammatory regulation, lipid, iron and carbohydrate metabolisms, and response to oxidative stress were enhanced among human DEGs. After comparing transcript abundance, the most active bacterial families were *Bactereoidaceae*, *Rikenellaceae*, *Oscillospiraceae* and *Prevotellaceae* in all groups. *Bifidobacteriaceae* expression occurred mostly in HV, while *Prevotellaceae* prevailed in MAFLD patients. The *Firmicutes*/*Bacteroidetes* ratio was higher in MAFLD and SH. *Myoviridae*, *Podoviridae*, *Siphoviridae* and *Microviridae* were the most transcriptionally active viral families in all groups. *Myoviridae* and *Microviridae* showed up-regulated activity in MAFLD (FDR=0.006 for *Microviridae*) and SH groups (FDR=0.01 and 4.2×10^{-6}, respectively), whereas *Podoviridae* and *Siphoviridae* were less active in these groups. Significant correlations were observed between the expression of Faecalibacterium phage Mushu, *Prevotella copri* and the human mucin gene (Figure).

Conclusions: We identified specific signatures of the interaction between microbial and human gut transcriptomes that could be useful as non-invasive biomarkers of MAFLD diagnosis and progression.



Correlation network of the significant human, bacterial and viral transcriptome parameters of the MAFLD patients (p<0.01).
Edges represent positive correlations.
Significant correlations between expression of *Faecalibacterium phage Mushu* (HOS66_gp32), *Prevotella copri* (UniRef90_R6CJR1) and human mucin gene (ENSG00000169894) are highlighted.

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P-10 PATTERNS OF PROGRESSION AND TREATMENT DISCONTINUATION IN A REAL LIFE LATIN AMERICAN PROSPECTIVE COHORT STUDY OF INTERMEDIATE-ADVANCED HEPATOCELLULAR CARCINOMA: SECOND INTERIM ANALYSIS

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Introduction and Objectives: Previously published regional real-world results of overall survival (OS) in Barcelona Clinic Liver Cancer (BCLC) B and C patients demanded a prospective cohort study nested in a systematic and continuous medical educational networking group. This study aimed to describe and evaluate the treatment decisions in patients with hepatocellular carcinoma (HCC) within BCLC B and C stages.

Materials and Methods: A multicenter prospective cohort study, conducted in different Latin American centers from Argentina, Brazil and Colombia, started on 15th May 2018 (delayed recruitment during COVID locked-down period). Patients within BCLC B or C stages were included. Survival, tumor progression and patterns of treatment suspension were evaluated.

Results: At this second interim analysis (projected final analysis March 2023), 390 HCC BCLC-B or C patients were included (n=15 excluded); mean age 65 years, 75.6% males and 89.5% cirrhotic. Median OS since HCC diagnosis was 27.2 months. Among BCLC-B patients, the most frequent therapy was transarterial chemoembolization (TACE, 42.3%); 51.8% using drug-eluting beads and 47.4% conventional TACE; with a median OS since 1st TACE of 41.9 months. Similar radiological responses after 1st TACE were observed between both modalities. Overall, 48.2% of the cohort received systemic therapy for HCC (n=188), 23.7% still on BCLC-B stage. The most frequent systemic treatments were Sorafenib (74.5%), atezolizumab bevacizumab (17.5%), and lenvatinib (12.2%), with a median OS since systemic therapy of 15.7 months. Lenvatinib or atezolizumab bevacizumab was used as the second line following sorafenib in 5 and 3 patients, respectively. The most common causes of systemic treatment discontinuation were tumor progression and liver function deterioration (15% to 36.4%). Patterns of tumor progression were not specifically associated with prognosis or treatment discontinuation.

Conclusions: Liver function deterioration occurs in a third of patients following systemic therapies. The complexity of treatment decisions underly the need for a multidisciplinary team and the role of hepatologists.

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P- 11 PROTUMORIGENIC GALECTINS 1 AND 3 ARE UPREGULATED IN THE LIVER OF MICE EXPOSED TO CONTINUOUS GROWTH HORMONE LEVELS

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Introduction and Objectives: Human and animal evidence revealed a link between growth hormone (GH) and cancer risk. GH excess is implicated in rodent hepatocarcinogenesis. Transgenic mice overexpressing GH (GH-Tg) develop hepatocellular tumors at old ages, with preneoplastic liver pathology similar to that observed in humans at a high risk of developing hepatic cancer. Galectin 1 (GAL1) is involved in liver tumorigenesis in humans. We reported that GAL1 is upregulated in GH-Tg mice liver, even before histopathological alterations are detected, and particularly enhanced in liver tumors. This study aimed to evaluate if GH modulates the hepatic expression of GAL3, another protumorigenic galectin. As many proteins exhibit sexually dimorphic liver expression, mainly determined by distinct GH secretion patterns between males (intermittent) and females (more continuous), we assessed if GAL1 and GAL3 liver expression was affected by GH secretion patterns.

Materials and Methods: Hepatic GAL1 or GAL3 were analyzed by immunoblotting in GH-Tg mice exposed to continuously elevated GH levels and in Swiss-Webster mice treated with GH during five weeks by implantation of osmotic pumps (continuous treatment) or by two daily injections (intermittent treatment). Statistics: Student's t-test or two-way ANOVA; $P<0.05$, significant; at least nine animals/experimental group.

Results: In GH-Tg mice (both sexes), GAL3 was not increased in the liver at early ages, when minimal histopathological alterations are found, but it was upregulated in young adults with preneoplastic livers and in older mice that develop liver tumors. However, GAL3 was not increased in tumors compared with the adjacent non-tumoral region. In Swiss-Webster mice, GAL1 and GAL3 expression were higher in females than in males. GH continuous treatment produced a significant increase in GAL1 and GAL3 expression in both sexes and loss of sexual dimorphism, while GH injections showed no effect.

Conclusions: GH continuous exposure upregulates protumorigenic GAL1 and GAL3 in mice liver. More studies are required to evaluate its impact on humans.

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P- 12 PATHOGENIC VARIANT OF PNPLA3 DOES NOT ASSOCIATE WITH HEPATOCELLULAR CARCINOMA IN SOUTH AMERICANS. A REPORT FROM THE ESCALON NETWORK

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