[3] *Hospital del Mar Medical Research Institute (IMIM), 08003 Barcelona, Spain*
[4] *Department of Cell Biology, Faculty of Biological Sciences, Universidad de Concepción, Concepción, Chile*
[5] *Department of Cell Biology, Physiology and Immunology, University of Cordoba; Maimonides Biomedical Research Institute of Cordoba (IMIBIC); UGC Nephrology, Hospital Universitario Reina Sofía, 14004 Cordoba, Spain*

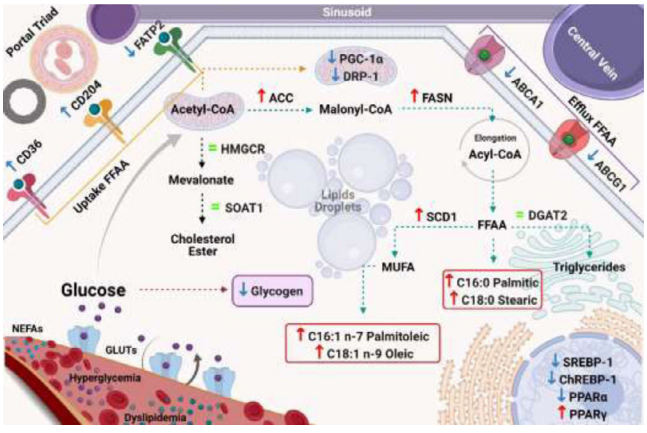
Introduction and Objectives: The new recommendations suggesting changing the current nomenclature from Non-Alcoholic Fatty Liver Disease (NAFLD) to Metabolic associated fatty liver disease (MAFLD) are primarily aimed at improving the understanding of the disease. MAFLD is a hepatic manifestation of metabolic syndrome and is usually associated with obesity and type 2 diabetes, excluding other causes not associated with positive energy balance. This study aimed to characterize the pathophysiological mechanism involved in MAFLD development in susceptible-strain Black Tan and brachyuric (BTBR) insulin-resistant mice in combination with leptin deficiency (ob/ob).

Materials and Methods: We studied liver morphology and biochemistry on our diabetic and obese mice model (BTBR ob/ob) as well as a diabetic non-obese control (BTBR + streptozotocin) and non-diabetic control mice (BTBR wild type) from 4-22 weeks. The lipid composition was assessed and lipid-related pathways were studied at transcriptional and protein levels.

Results: Microvesicular steatosis was evident in BTBR ob/ob from week 6, progressing to macrovesicular in the following weeks. At the 12th week, inflammatory clusters, activation of STAT3 and Nrf2 signaling pathways, and hepatocellular ballooning. At 22 weeks, the histopathological features previously observed were maintained and no signs of fibrosis were detected. Liver gene-expression analysis demonstrated modifications in fatty acid transporters associated with uptake (Cd36, Cd204, Fatp4)/efflux (Abca1, Abcg1), *de novo* fatty acid synthesis enzymes (ACC, FASN, SCD-1) and transcription factors related to lipogenic pathways (Pparα/γ, Srebp-1, Chrebp-1). Additionally, the lipidomic analysis showed profiles associated with de novo lipogenesis (DNL), showing a significant increase in palmitic acid (C16:0), palmitoleic acid (C16:1n7) and oleic acid (C18:1n9).

Conclusions: BTBR ob/ob mice develop MAFLD profiles that resemble pathological features observed in humans, with overactivation of inflammatory response, oxidative stress and DNL signaling pathways. Therefore, BTBR ob/ob mouse is an excellent model for the study of the steatosis to steatohepatitis transition.

Figure 1:



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P-3 PLASMA EXCHANGE WITH ALBUMIN INCREASES EFFECTIVE ALBUMIN LEVELS IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Raquel Horrillo[1], Anna Mestre[1], Alba Pérez[1], Jordi Vidal[1], Estefania Alcaraz[1], Mireia Torres[1], Vicente Arroyo[2], Javier Fernández[2,3], Joan Clària[2,3,4], Montserrat Costa[1]

[1] *Scientific Innovation Office, Grifols, Barcelona, Spain*
[2] *Ef Clif, Easl-Clif Consortium and Grifols Chair, Barcelona, Spain*
[3] *Hospital Clinic, Idibaps and Ciberehd, Barcelona, Spain*
[4] *Department of Biomedical Sciences, University of Barcelona Medical School, Barcelona, Spain*

Introduction and Objectives: Non-oncotic albumin functions such as transport, antioxidant and immunomodulatory capacities may be associated with the beneficial effects of albumin therapy in liver disease patients. For acute-on-chronic liver failure (ACLF) patients, characterized mainly by severe systemic inflammation and organ failure, plasma exchange with human serum albumin (PE-A5%) may be an effective treatment. In fact, the effects of PE-A5% on short-term survival in patients with ACLF are currently under investigation (APACHE phase 3 trial, NCT03702920). To characterize albumin levels with intact structure (effective albumin) in patients with ACLF compared with healthy controls (HC) and to assess the effect of PE-A5% treatment on eAlb levels in patients with ACLF.

Materials and Methods: Plasma samples from 10 patients included in the Pilot-APACHE trial (NCT01201720) were assessed. This was a prospective, open-label, non-controlled study in which ACLF patients were treated with six PE-A5% for 10 days. At baseline, results were compared with HC (n=10). Albumin post-translational modifications (PTMs) were determined by mass spectrometry (LC_ESI_qTOF-MS). Native albumin (%) (the primary structure preserved form without PTMs) and effective albumin levels (mg/mL) (calculated as (total albumin x native albumin)/100)) were evaluated. Results were expressed as median (IQR).

Results: At baseline, ACLF patients showed a significantly lower proportion of native albumin, 19.4% (10.0-28.5), compared with HC, 51.3% (49.0-52.6), P<0.0001. Similarly, effective albumin levels, 6.8 mg/mL (3.5-8.9), were lower than HC, 19.8 mg/mL (18.9-20.7), P<0.0001. This reduction in native albumin was associated with higher cysteinylated and glycated isoforms. After six PE-A5%, native albumin (27.6% (17.1-35.3), p=0.036) and effective albumin (10.4 mg/mL (6.4-13.8); p=0.0067) were significantly increased. Remarkably, this effect was observed right after each PE-A5% session.

Conclusions: ACLF patients presented albumin structural abnormalities that led to decreased effective albumin levels. PE-A5% not only improved non-oncotic albumin functions[1] but increased structurally preserved albumin in these patients.

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P-4 RISK OF HCC IN SOUTH AMERICANS ASSOCIATED WITH TLL1 VARIANT SINGLE NUCLEOTIDE POLYMORPHISM

Andre Boonstra[1], Domingo Balderramo[2], Dhamina Karim[3], Jhon Prieto Ortiz[4], Javier Diaz Ferrer[5], Angelo Mattos[6], Marcos Arrese Jimenez[7], Enrique Carrera Estupinan[8], Zwier Groothuismink[1], Jeffrey Oliveira[1], Jose Debes[9]

[1] *Department of Gastroenterology, Erasmus MC, Rotterdam, Netherlands*
[2] *Department of Gastroenterology, Hospital Privado Universitario de Córdoba. Instituto Universitario de Ciencias Biomédicas de Córdoba, Córdoba, Argentina*
[3] *Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN, USA*
[4] *Department of Gastroenterology, Centro de Enfermedades Hepáticas y Digestivas (CEHYD), Bogotá, Colombia*
[5] *Department of Gastroenterology, Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru*
[6] *Department of Gastroenterology, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil*
[7] *Department of Gastroenterology, Pontificia Universidad Católica de Chile, Santiago, Chile*
[8] *Department of Gastroenterology, Hospital Eugenio Espejo, Quito, Ecuador*
[9] *Department of Medicine, University of Minnesota, Minneapolis, MN, USA*

Introduction and Objectives: Hepatocellular carcinoma (HCC) is the third cause of cancer-related death worldwide. Assessment of genetic components has been used to better stratify those at risk. However, most studies have been performed in Asian or Caucasian populations. Tolloid-like protein 1 (*TLL1*) is one such SNP that has been shown to increase risk in hepatitis C virus (HCV)-associated HCC. We evaluated the risk association of TLL1 in a South American cohort.

Materials and Methods: This is a cross-sectional analysis performed in South Americans with HCC as well as cirrhotic controls through the ESCALON network. We analyzed 120 HCC blood samples and 293 cirrhotic controls from Argentina, Chile, Brazil, Colombia, Ecuador and Peru. The pathogenic variant of *TLL1* (rs1704200) was evaluated using TaqMan-genotyping assay. Multiple logistic regression was used to establish the association between *TLL1* and HCC.

Results: The median age of HCC patients was 68 years (IQR 62-72) and of cirrhotics 64 years IQR 68-70). The most common underlying liver disease in both groups was Non-alcoholic fatty liver disease (NAFLD) at 58% and 59%, respectively. The proportion of individuals who developed HCC with a *TLL1* pathogenic variant (AT/TT) was 18.2% in the South American cohort. The calculated Odds-Ratio (OR) for HCC among South Americans with the TLL1 variant was 0.69 (CI 0.37-1.29), suggesting a non-significant decrease odds for HCC. Interestingly, different results were found when examining HCV-associated HCC (11% of the cases and 6% of controls). The OR for HCV-associated HCC in Latin Americans was 2.07 (CI 0.93-4.58), suggesting a non-significant increased odd of being diagnosed with HCC in South Americans with the variant.

Conclusions: *TLL1* mutations do not seem to associate with HCC development in South American patients with liver disease. However, preliminary results show that the presence of *TLL1* SNP could confer an increased risk for HCC in South Americans with HCV infection.

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P-5 THREE-DIMENSIONAL SINGLE-CELL ATLAS OF LIVER TISSUE ARCHITECTURE

Dilan Martinez[1], Maldonado Valentina[1], Cristian Perez[1], Valeria Candia[1], Hernán Morales-Navarrete[2], Fabián Segovia-Miranda[1]

[1] *Department of Cell Biology, Faculty of Biological Sciences, Universidad de Concepción, Concepción, Chile*
[2] *Department of Systems Biology of Development, University of Konstanz, Konstanz, Germany*

Introduction and Objectives: The liver is an organ that performs a wide variety of functions that are highly dependent on its complex 3D structure. Geometrical models (digital representations of tissues) represent a versatile technique to characterize 3D tissues as well as to get quantitative insights into the link between their structure and function. Until now, these models have only focused on some tissue (sinusoids and bile canaliculi) and cellular components (hepatocytes), leaving out important cellular populations such as stellate cells and Kupffer cells. One of the major bottlenecks for a complete tissue reconstruction is the limitation on the number of markers that can be imaged by fluorescence microscopy (up to 4-5). This study aimed to generate a "3D single-cell atlas of liver tissue architecture", i.e., a full 3D geometrical model which includes all tissue and cellular components simultaneously.

Materials and Methods: We overcome the technical constraints by using deep tissue immunostaining, multiphoton microscopy, deep learning techniques, and 3D image processing. As a proof of concept, we used the 3D atlas to describe the morphological changes that occur in the mouse liver during post-natal early development and adulthood.

Results: We described how liver tissue architecture progressed from post-natal day one to adulthood by a novel set of morphometric cellular and tissue parameters. Our analysis revealed unknown details about the spatial organization of different liver cell types. Unexpected spatiotemporal patterns of non-parenchymal cells and hepatocytes with differing in size, number of nuclei, and DNA content were uncovered. We also provided information regarding the remodeling of the bile canaliculi and sinusoidal networks.

Conclusions: These findings revealed novel characteristics of liver heterogeneity and have important implications for both the structural organization of liver tissue and its functional features. 3D single-cell atlas will provide a powerful tool to understand liver tissue architecture under both physiological and pathological conditions.

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P-6 PATTERNS OF ANTIBIOTIC RESISTANCE IN PATIENTS WITH CIRRHOSIS AND SPONTANEOUS BACTERIAL INFECTIONS: ANALYSES OF THE MULTICENTER STUDY FROM ARGENTINA AND URUGUAY

Sebastián Marciano[1,2], Maria Nelly Gutierrez Acevedo[3], Sabrina Barbero[4], Lorena del Carmen Notari[4], Marina Agozino[5], Jose Luis Fernandez[5], Maria Margarita Anders[6], Nadia Grigera[6], Florencia Antinucci[6], Orlando Federico Orozco Ganem[6], Maria Dolores Murga[7], Daniela Perez[7], Ana Palazzo[7], Liria Martinez Rejtman[8], Ivonne Giselle Duarte[3], Julio Vorobioff[9], Victoria Trevizan[9], Sofía Bulaty[9], Fernando Bessone[9], Marcelo Valverde[10], Martín Elizondo[10], José Daniel Bosia[11], Silvia Mabel Borzi[11], Teodoro E. Stieben[12], Adriano Masola[12], Sebastian Eduardo Ferretti[13], Diego Arufe[14], Ezequiel Demirdjian[14], Maria Pia Raffa[14], Mirta Peralta[15], Hugo Alberto Fainboim[15], Cintia Elizabet Vazquez[16], Pablo Ruiz[16], José Emanuel Martínez[17], Leandro Alfredo Heffner[18], Andrea Odzak[18], Melisa Dirchwolf[19], Astrid Smud[20], Manuel Mendizabal[21], Carla Bellizzi[22], Ana Martinez[22], Jesica Tomatis[19], Andres Bruno[18], Agñel Ramos[13], Josefina Pages[21], Silvina Tevez[5], Diego Giunta[2,23], Adrian Gadano[1,2]