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SPECIAL ARTICLE

Novel therapeutic avenues for the study of chronic liver disease and regeneration: The foundation of the Iberoamerican Consortium for the study of liver Cirrhosis

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Abstract Unfortunately, there is a gap of understanding in the pathophysiology of chronic liver disease due to the lack of experimental models that exactly mimic the human disease. Additionally, the diagnosis of patients is very poor due to the lack of biomarkers than can detect the disease in early stages. Thus, it is of utmost interest the generation of a multidisciplinary consortium from different countries with a direct translation. The present reports the meeting of the 2021 Iberoamerican Consortium for the study of liver Cirrhosis, held online, in October 2021. The meeting, was focused on the recent advancements in the field of chronic liver disease and cirrhosis with a specific focus on cell pathobiology and liver regeneration, molecular and cellular targets involved in non-alcoholic hepatic steatohepatitis, alcoholic liver disease (ALD), both ALD and western diet, and end-stage liver cirrhosis and hepatocellular carcinoma. In addition, the meeting highlighted recent advances in targeted novel technology (-omics) and opening therapeutic avenues in this field of research.
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◊ Please see a list of the members of the Iberoamerican Consortium for the Study of Liver Cirrhosis group in Appendix A.

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PALABRAS CLAVE
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Regeneración hepática;
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Cirrosis;
Enfermedad hepática crónica

Nuevas dianas terapéuticas para el estudio de la enfermedad hepática crónica: la creación del Consorcio Iberoamericano para el estudio de la cirrosis hepática

Resumen Desafortunadamente, existe una brecha sobre la comprensión en la fisiopatología de la enfermedad hepática crónica debido a la falta de modelos experimentales que recapitulan con exactitud la enfermedad humana. Además, el diagnóstico de los pacientes es muy pobre debido a la falta de biomarcadores que puedan detectar la enfermedad en etapas tempranas. Por ello, es de sumo interés la generación de un consorcio multidisciplinar de diferentes países con una traducción directa. El presente artículo informa sobre la reunión del Consorcio Iberoamericano para el estudio de la cirrosis hepática 2021, celebrado de manera virtual en octubre del 2021. La reunión se centró en los avances recientes en el campo de la enfermedad hepática crónica y la cirrosis, con un enfoque específico en la patobiología celular y regeneración hepática, dianas moleculares y celulares involucradas en la esteatohepatitis hepática no alcohólica, la enfermedad hepática alcohólica (ALD), tanto la ALD como la dieta occidental, y la cirrosis hepática en etapa terminal y el carcinoma hepatocelular. Además, la reunión destacó los avances recientes en tecnología (ómica) y la apertura de vías terapéuticas en este campo de investigación.
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Introduction

The Iberoamerican Consortium for the study of Cirrhosis is a collaboration platform under the umbrella of the Iberoamerican Union of Universities (UIU) and constituted by researchers and physician-scientists from Universidad Complutense Madrid (UCM) and Universidad de Barcelona (UB), UNAM (Universidad Nacional Autónoma de México), Universidad de Sâo Paolo (USP) and Universidad de Buenos Aires (UBA), thus encompassing institutions from five different countries including Spain, Mexico, Argentina, Brazil and Argentina. The goal of the meeting held online on October 21, 2021 was to share new data on recent discoveries in the progression of cirrhosis due to several etiologies and to promote future collaborations between the universities involved in this Consortium. During the meeting, advances in the understanding of the basic biology and pathobiology of liver cells were discussed. In particular, liver cell pathobiology – hepatocytes, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), and Kupffer cells (KCs), and the relevance of the gut-liver axis in the development of cirrhosis. Recent advances in cell biology and their contribution to the development of liver diseases, including NASH, ALD, both alcoholic and non-alcoholic hepatic steatohepatitis (dUAL) and hepatocellular carcinoma (HCC) were further discussed. Moreover, recent data on liver regeneration along with the development of nanoparticles delivery and the use of -omics to unveil specific mechanisms were also covered.

Chronic liver disease (CLD) refers to a long-term pathological process of continuous injury of the liver parenchyma and its gradual substitution with fibrous tissue and occasionally a fatal outcome. CLD is a major cause of morbidity and mortality in many countries and is caused by diverse etiologies including viral infections, drug toxicity, alcohol, metabolic and autoimmune diseases.[1] The progression of CLD ranges from steatosis, steatohepatitis, fibrosis, cirrhosis and end-stage hepatocellular carcinoma (HCC). Beside the cell stress and injury caused by different pathogenic factors, there is an intricate link between gut and liver, which allows nutrients and bacterial debris to travel to the liver and activate KCs, which increase the expression of pro-inflammatory mediators and recruit other cell types of the immune system.[2] Uncontrolled inflammation activates the HSC that start depositing extracellular matrix (ECM) and promote liver fibrogenesis.[3] Although this progression is reversible, further accumulation of ECM could lead to irreversible stages including cirrhosis and HCC.[3] The liver has the property to regenerate: a perfect balance between injury and regeneration allows the liver to correctly function. However, an imbalance in the system may disrupt liver regeneration and finally trigger disease.[4]

In the last decades, considerable effort has been made to understand the development of CLD. Along with the discovery of the new -omics (transcriptomics, metabolomics, proteomics), several pathways became pivotal for the study of liver disease as well as for the elucidation of novel therapeutical targets and possible biomarkers for early detection of CLD.[5] Pathways related with inflammation (Toll like receptor (TLR)4 – nuclear factor (NF)-κB axis), lipid metabolism (fatty acid β-oxidation) or endoplasmic reticulum (ER) stress and unfolded protein response (UPR) are a few examples.[6–8] However, a reliable treatment to ameliorate the progression of liver disease is still missing, albeit some drugs (i.e.: statins) may have a positive effect on the disease outcome.[9]

Endoplasmic reticulum stress: insights from the gut and the liver

In the last decade, many studies addressed the importance of the gut-liver axis in the progression of CLD. Dietary requirements absorbed in the gut by the intestinal epithelial cells (IECs) travel to the liver through the bloodstream; however, alterations in IECs, including the disruption of tight

junctions, could lead to increased permeability of the gut and the release of bacterial products to the portal vein.[10] The intracellular pathways activated in response to the bacterial debris cause cellular stress to the hepatic cells, loss of function and inflammation. Different pathological conditions such as inflammation can alter the endoplasmic reticulum (ER) homeostasis causing accumulation of unfolded proteins within the ER lumen, a condition known as ER stress that triggers the unfolded protein response (UPR). UPR plays a critical role in maintaining the homeostasis of the intestinal epithelium by keeping the balance between flora, the epithelium and the immune response in the intestine.[11] The UPR has 3 different branches of activation: protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), activation transcription factor 6 (ATF6) and inositol requiring-kinase 1-alpha (IRE1α). Downstream of these proteins appears X-box binding protein-1 (XBP1) that after its splicing, becomes activated, translocate into the nucleus and performs its transcriptional response.[12] In the past few years, several reports showed the connection between XBP1 and liver injury in different mouse models, although its function in the intestine remains elusive. In that context, the group of Eduardo Martinez-Naves (UCM) showed the connection between ER stress and inflammation in the gut. A mouse with a specific deletion of the XBP1 gene in IECs showed spontaneous enteritis associated with an increase of ER stress in IECs. The ER stress enhances autophagic flux in the IECs, which acts as a compensatory mechanism to restore the homeostasis in the intestinal epithelium, since blocking autophagy in IECs resulted in exacerbation of the intestinal inflammation.[13] The UPR response induces the expression of NKG2D ligands on the IECs which activate the response of type 1 Innate Lymphocytes (ILC1s) which are activated through their NKG2D receptor. Blocking the activity of ILC1s reduced the inflammation in these mice.

The liver is one of the most important organs with vital functions like detoxification of the blood coming from the digestive tract. A highly orchestrated network of cells governs the correct function of the liver: LSECs form a net of fenestrated capillaries for the exchange of biomolecules between the bloodstream and liver parenchymal cells (approximately 70–75% are hepatocytes); KCs acting as the first line of defense of the immune system; HSCs that reside in the space of Dissé store vitamin A in lipid droplets and are the major contributor to fibrosis in the injured liver whilst hepatocytes represent the main component of the liver with a major metabolic function.[10] The activation of parenchymal cells triggers the initiation of a cascade of events where several intracellular pathways are activated and the inefficiency to restore the balance, may promote the progression of liver disease. Thus, the UPR has a very important role by inducing the expression of chaperones and controlling the misfolded proteins.[12] Cubero and colleagues (UCM) showed that mice with specific deletion of ER stress in IECs challenged to experimental models of alcoholic liver disease (ALD) and both ALD and Western diet (WD) presented increased liver injury with high transaminases, steatosis, fibrosis and inflammation. These experimental models showed higher gut permeability compared with control mice.[11] Additionally, the role of ER stress in HSCs seems to be essential since experimental models of liver fibrosis in HSC-specific knockout mice for effectors of ER stress showed higher levels of fibrosis and HSC activation. These data were also validated in the human HSC cell line (LX2) with increased expression of pro-fibrotic genes after TGFβ challenge. Thus, it was concluded with the importance of ER stress in the study of liver fibrosis and in the context of the gut-liver axis.

Liver regeneration

The liver has the unique capacity of regeneration from acute injuries. Since the liver function is vital for body homeostasis, several compensatory mechanisms occur during its regeneration. These mechanisms have evolved to guarantee the activity of the liver under different circumstances. Although the signaling pathways associated with liver regeneration are not fully understood, a lot of effort has been made in the two last decades to improve the knowledge in this context.[5] Partial hepatectomy (PHx) is a method extensively used to challenge the regeneration capacity of liver. It is well-known that after 2/3 PHx, mouse liver restores most of its mass within 7–8 days by cellular hyperplasia, with complete restoration after 3 weeks.[5,16] Several studies revealed an increase in the size and width of hepatocytes plates, with a phenotypic fidelity. In healthy liver, regeneration is based on the proliferation of mature cells thus, hepatocytes produce hepatocytes and the same for the other liver cell type.[14] Very early after the insult, the remodeling the hepatic ECM occurs within the first minutes, with activation of MMP and TIMS, and the expression of factors like hepatocyte growth factor (HGF) to the peripheral blood. After 2–5 h, the expression of regenerative growth factors including IL-6 or TNFα increase to prime 1/3 of the hepatic parenchyma cells to proliferate. Several hours after injury, growth factors induce both hepatocytes to progress through the cell cycle (proliferative phase) and the expression of metabolic genes to maintain liver functions. For instance, gluconeogenic genes are induced to restore glucose homeostasis after the consumption of the glycogen stores. Other hepatic cells such as KCs and cholangiocytes trigger its proliferation program 24 h after hepatocytes. Several days after injury, when the hepatic mass is recovered, TGFβ and IL-1β signaling pathways suppress the proliferation program. In this context, Dr. Carles Rentero and Dr. Carlos Enrich (UB) explored the hepatic function of AnxA6, a Ca^{2+}-dependent membrane binding protein involved in the regulation of intracellular trafficking, cellular signaling and glucose homeostasis,[15–17] using AnxA6 knock-out mice and 2/3 PHx. This approach showed that 75% of the AnxA6-ko mice died due to a sustained hypoglycemia 48–72 h after surgery.[18] The PHx-induced hypoglycemia in wild-type mice was reversed 24 h after surgery through the activation of the gluconeogenic pathway. Notably, AnxA6-ko mice survived 2/3 PHx when supplied with 10% glucose supplemented drinking water. AnxA6-ko mice showed compromised L-alanine uptake pathway in the liver, the main hepatic gluconeogenic substrate, due to a deficient recycling mechanism of the liver-specific L-alanine transporter SNAT4 to the plasma membrane during the liver regeneration.

Liver regeneration is a well-orchestrated response in the context of healthy liver, however, under chronic liver injury liver regeneration is deregulated and plasticity events take

place. In this context, a frequently observed histopathological feature in liver regeneration during chronic injury is the ductular reaction, by which cells of biliary origin or transdifferentiated hepatocytes expand to the biliary cell population. Several differentiation and embryonic pathways (i.e. YAP, Notch or FGF7) have been defined to be involved in this atypical regenerative response of the liver.[19] The group of Pau Sancho-Bru (UB) investigated the impact of the ductular reaction in chronic liver injury, and showed its correlation with the severity of liver injury and markers of liver function and injury (CHILD score, transaminases, liver albumin). RNA seq experiments of laser micro dissected ductular reaction revealed several pathways involved in inflammation and angiogenesis. By using organoids derived from cirrhotic tissue, they explore the role of ductular reaction in angiogenesis and inflammation. With biliary organoids, they demonstrated a crosstalk between neutrophils and biliary cells of the ductular reaction which promote intrahepatic inflammation. Moreover, coculture of organoids with endothelial cells showed the impact of the biliary compartment in the induction of intrahepatic angiogenesis by the SLIT2- ROBO1 pathway.[20] Thus, these studies demonstrated that biliary organoids from human liver tissue are an excellent tool to investigate the role of the biliary epithelium in chronic liver diseases.

Translational medicine

Currently, there is not effective treatment for liver disease. The only curative treatment available is liver transplant and only for end-stage liver disease; however, the development of new strategies to prevent complications and slow the progression of liver disease is ongoing. After diagnosis, changes in diet and exercise are made to improve clinical outcomes and quality of life in patients with liver disease, especially in those with cirrhosis. Malnutrition (including sarcopenia[21]) is a highly prevalent complication in cirrhosis, therefore interventions including exercise plus nutritional therapy, are highly recommended in this population both for prevention and treatment of this complication. Physical exercise exerts metabolic, cardiac and bone mineral density benefits, and it is associated with decreased morbidity and mortality. Although the first reports found an increase in hepatic venous pressure gradient (HVPG) while the patients with cirrhosis were exercising, this change was only seen in the acute setting. However, according to the results presented by Ricardo Ulises Macias-Rodríguez (UNAM), who has been working in implementing physical exercise in cirrhotic patients, the effect of a well-structured exercise program plus nutritional therapy, actually decreases portal hypertension. Data from the first trial showed that, after 14 weeks of exercise, the group with exercise and diet decreased the portal pressure and ammonia levels (NH4) in blood. In the second clinical trial, they focused on cerebral and hepatic hemodynamics, with a home-based exercise program, monitored with an accelerometer-based bracelet, being the main findings an improvement in portal pressure, cerebral hemodynamics, nutritional status and cognitive function in the exercise group compared with the control group. Finally, the last trial evaluated endothelial function, nutritional status and neuro-psychometric tests after monitored exercise during 8 weeks in patients with cirrhosis. The main findings in this clinical trial were an improvement in quality of life, nutritional status and endothelial function, after increasing, at least, 2500 steps/day.

Statins, blockers of the hepatic HMG-CoA reductase, are molecules with high impact in cardiovascular diseases and it has been shown that reduce cholesterol deposition, inflammation and the activation of the isoprenoids intermediates. However, their contribution to liver disease is still unclear and may cause a severe drug-induced liver failure due to its administration.[22] In the last years, many studies associated statins with the improvement of some effects related with CLD: portal pressure, fibrosis or liver sinusoidal epithelial cells (LSECs) morphology and function, for example; but they are also related with other diseases like cholangitis or HCC.[23] The transition from murine models to human is accomplished by randomized trials that probe the effectivity of every compound. Actually, one is already performed and others are still ongoing. The combination of all this data allows us to understand to toxicity of the statins in the human metabolism as well as improvement of several parameters related with CLD.[23] In this context, Alberto E. Muñoz (UBA) presented interesting data about three different trials in decompensated cirrhosis patients treated with simvastatin. The first trial demonstrated that the simvastatin group increased the survival rate (107 months) compared with the control group (20 months) with no secondary effects after the treatment.[24] The second trial focused on the safety of the patients treated with simvastatin 40 mg/day for one year. Thus, the only significant adverse event was the muscle injury that appears to be related to the simvastatin dosage and the degree of cirrhosis severity (Child $\leq$ 6, MELD > 12). Noticeably, no liver injury was recorded.[25] The third was an additional analysis of the previous study. It showed a higher white blood cell count at baseline (systemic inflammation), and a higher serum albumin concentration, and a lower proportion of ascites (liver function) at ending, in patients with lower severity of cirrhosis -Child–Pugh class A versus Child–Pugh class B/C at the end of the trial. This study concluded that in patients with the ABCD-WC acronym at baseline (Albumin > 3.0, Bilirubin < 1.5, Child $\leq$ 6, MELD $\leq$ 12, WBC > 5000), chronic simvastatin treatment would improve liver function and decrease cirrhosis severity with a fewer probability of adverse events.

The new approach: -omics

The development of high-throughput technologies has created new classifications with the suffix ''omics'', meaning ''totality''. Describing each biological phenomena from the basis of the genome to the final molecules, just as proteins, lipids, or glycans we find: genomics, proteomics, metabolomics, transcriptomics, lipidomics, glycomics and finally epigenomics.[26,27] Several reports showed the importance of using these techniques for the study of CLD in the last years. One example is the discovery of the phenotypic pattern of cells and lipid droplets in a model of non-alcoholic fatty liver disease (NAFLD). With the new era of omics, there is now a ''sea of data'' available for most diseases and human conditions. The network medicine provides a method

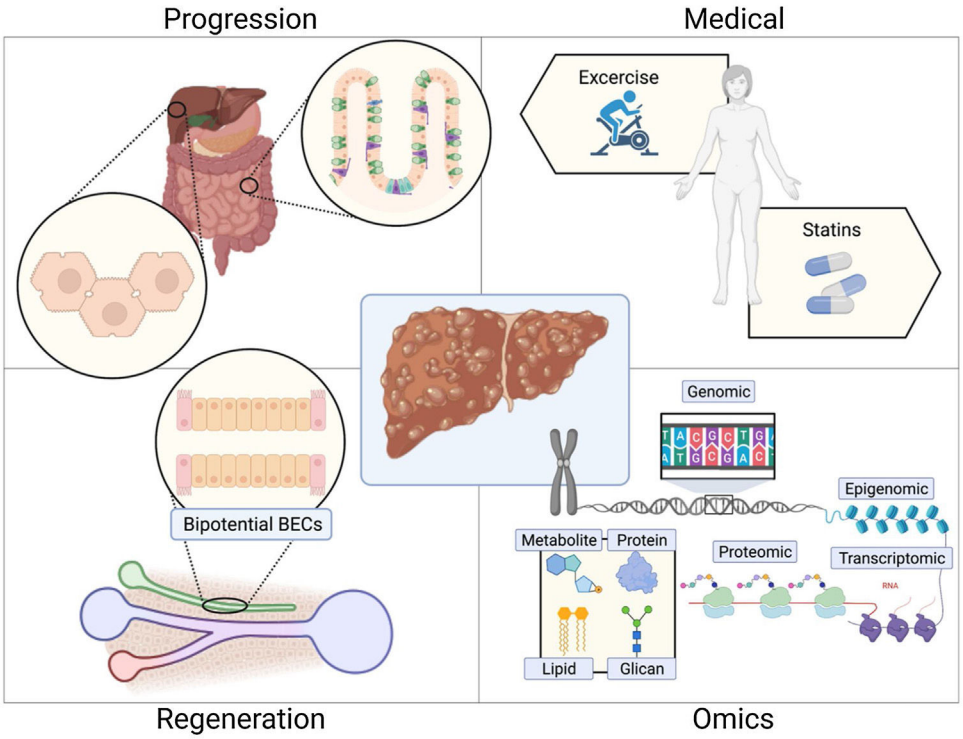

Figure 1 Summary overview of the topics addressed in the 2021 Iberoamerican Consortium for the study of Cirrhosis. From the basics with the relationship between ER stress in the liver and in the gut and the progression of CLD or different mechanism of liver regeneration (associated with glucose metabolism and novel tools for the study of liver regeneration: organoids), to clinical human trials where exercise and statins were evaluated. In addition, the use of novel technologies like -omics was also covered at this meeting.

to ''fish'' important insights and hypothesis from this sea of data. It utilizes graph theory, mathematical modeling and omics data to investigate alterations in the network of biological components associated with health and disease. Helder Nakaya (USP) presented several examples of network medicine applied to a broad range of diseases, including gut-related chronic inflammatory diseases,[28] infectious diseases,[29] and neurological disorders.[30] In most cases, transcriptomic and protein-protein interaction data were used to construct the biological networks. However, he also showed that using machine learning algorithms to text mining millions of articles from PubMed, knowledge networks can also be constructed. Those networks capture the human knowledge about connections between genes, diseases and drugs. Network medicine can then be applied to study inflammatory diseases or psychiatric diseases, or even the molecular mechanisms shared between very different diseases. Dr. Nakaya also showed single cell RNA sequencing studies that revealed a clear location of a specific cell type in the organ of study. This spatial single cell transcriptomic technique could help to improve the knowledge of the cirrhotic or cancer areas and the cells around these areas. Finally, he introduced the new computational tool his lab is developing: BioFeatS. By using feature selection methods and machine learning algorithms, the tool can prioritize the importance of any kind of biological component derived from high-throughput technologies, i.e., cytokines, proteins, microRNAs, metabolites, RNAs. This tool may soon be applied to (re-) analyze CLD -omics data.

Conclusions

This meeting discussed the advances in our understanding of the basic biology and pathobiology of the cells in the progression to cirrhosis. Advances in the understanding of IEC and hepatic cells in UPR, pathways that mediate liver regeneration and human trials with several drugs where discussed (Fig. 1). The symposium again demonstrated that basic and translational research it is very necessary for the complete understanding of cirrhosis.

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Conflict of interest

The authors state that they have no conflict of interest.

Appendix A. Rest of members of the Iberoamerican Consortium for the Study of Liver Cirrhosis

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