

First description of the involvement of chemical modification of proteins in liver fibrosis progression and regression

CIC bioGUNE and CIBEREHD researchers describe a new mechanism of fibrosis progression and use specific inhibitors of that mechanism as a potential treatment for the disease

The work has been published in the prestigious journal *Hepatology* and features on the front cover of the February 2017 edition

The research project has been part-funded by the AECC (Spanish Association Against Cancer), the AECC Provincial Executive in Bizkaia and EiTB Maratoia

(Bilbao, 25 January 2017). CIC bioGUNE and CIBEREHD researchers have described for the first time the involvement of certain chemical modifications of liver proteins in the progression and regression of liver fibrosis, an integral part of chronic liver disease prior to progression to cirrhosis and liver cancer. The research findings have been published in the prestigious journal *Hepatology*. Furthermore, a summary image of the research work, featuring a photomicrograph of a liver biopsy from a patient with fibrosis alongside a graphic representation of the proposed mechanism of fibrosis regression, has been selected as the front cover of the February 2017 issue of the journal.

Preclinical studies described in the research paper by using a specific pharmacological inhibitor of this new mechanism highlight a novel attractive therapeutic approach to treat liver fibrosis. Mention is to be made of the fact that this drug is already undergoing Phase II clinical trials for cancer treatment.

The main author of the study has been the Ph.D. student Imanol Zubiete-Franco, a study led by Drs. María-Luz Martínez-Chantar and Teresa Cardoso Delgado, from the Liver Disease Laboratory at CIC bioGUNE and the Biomedical Research Networking Centre in Hepatic and Digestive Diseases (CIBEREHD).

The research project has been part funded by not-for-profit organisations such as the AECC (Spanish Association Against Cancer, #interfresacontraelcancer), the AECC Provincial Executive in Bizkaia and EiTB Maratoia, an initiative of the media group Euskal Irrati Telebista, all of which are supported by contributions from individual donors. As Dr. Martínez-Chantar explains: “The paper is the result of 4 years of research involving considerable national and international collaboration, and has

provided invaluable training for young researchers with a great future ahead of them. None of this would have been possible without the participation of many anonymous donors who have played their part in us being able to progress towards our end goal: the treatment of liver fibrosis and the mitigation of its grave consequences”.

Chronic liver diseases represent an important cause of morbidity and mortality and weigh heavily on society in social, medical and financial terms. Liver fibrosis is associated with the progression of chronic liver disease, which ultimately leads to cirrhosis and liver cancer, a pathology which causes over 600,000 deaths worldwide every year. Though viral hepatitis has historically been the major risk factor for liver fibrosis, the combination of type 2 diabetes and obesity (diabesity) is now emerging as the most common cause of liver fibrosis and, on account of our modern lifestyle, fast becoming an epidemic of the 21st century. In fact, rather than a fall in the incidence of liver cancer as a result of the success of new pharmacological treatments for viral hepatitis, liver cancer in developed countries has actually increased in recent years as a result of the rising prevalence of “diabesity”.

Despite significant investment made by various health systems worldwide, alternative therapeutic approaches capable of reversing or halting fibrosis progression to cirrhosis are scarce. As Dr. Martínez-Chantar points out: “A greater knowledge of the mechanisms underlying liver fibrosis can provide us with new strategies to develop new treatments and drugs”.

Dr. Martínez-Chantar explains further: “When hepatocytes, the main type of hepatic cell, suffer some kind of damage, the immune system kicks in with the main purpose of healing. In these conditions, the hepatic stellate cells are activated and produce substances, which are secreted in the liver. In turn, these substances provoke an accumulation of scar tissue, thereby causing liver fibrosis. The fact that liver fibrosis may affect many types of cell present in the liver increases the complexity of the disease and, inevitably, its possible resolution. We believe that the capacity to model the different types of cells that play a key role in liver fibrosis is critical in our efforts to find new therapies for this disease. As such, what we have observed in this study is an increase in certain chemical modifications of the liver proteins present in the different types of cells in the liver during the progression of the fibrosis. Furthermore, the use of chemical inhibitors which prevent these modifications in the proteins brings about a general improvement in the hepatocytes and a decrease in the production of harmful substances by the hepatic stellate cells”.

About CIC bioGUNE

The Centre for Cooperative Research in Biosciences (CIC bioGUNE), located in the Bizkaia Technology Park, is a biomedical research organisation conducting cutting-edge research at the interface between structural, molecular and cell biology, with a particular focus on the study of the molecular bases of disease, for use in the development of new diagnostic methods and advanced therapies.

About CIBEREHD

The mission of the Biomedical Research Networking Centre in Hepatic and Digestive Diseases (CIBEREHD), part of the Carlos III Institute of Health of the Ministry of Economics, Industry and Competitiveness and co-funded by FEDER, is the promotion and protection of health by fostering research in both the basic field and in the approach to clinical and translational aspects in the field of Liver and Digestive Diseases. The end purpose of the activity of the Centre is to innovate in the prevention of these diseases and to promote significant progress in the field of science and health by collaboration with cutting-edge Spanish groups.