PRESS RELEASE

A new therapy for paracetamol-induced fulminant liver damage

A team of researchers from CIC bioGUNE, CIBEREHD and the University of Vermont College of Medicine has identified the MCJ protein as a potential therapeutic target in patients with fulminant liver failure caused by the overuse of paracetamol

The work has been published in the journal Nature Communications

The current treatment with antioxidant N-acetylcysteine (NAC) is only effective the first eight hours after ingestion

(Bilbao, 18 December 2017). A team of researchers from CIC bioGUNE, the National Institute for the study of Liver and Gastrointestinal Diseases (CIBEREHD) and the University of Vermont College of Medicine has conducted preclinical studies on paracetamol toxicity models, identifying the MCJ protein as a potential therapeutic target in patients with fulminant hepatic failure eight hours after ingestion of the drug.

Acetaminophen (APAP), commonly known as paracetamol, is the active component of many commonly prescribed over-the-counter medications used to treat pain and fever worldwide. Though classified as a safe analgesic, paracetamol has been recognised as the main cause of acute liver failure both in the United States and in Europe when consumed in high doses.

It has been estimated that over 60 million people take paracetamol on a weekly basis in the United States. Around 30,000 people are admitted to hospital every year for intensive care treatment with liver damage caused by a high intake of paracetamol.

Treatment with the antioxidant N-acetylcysteine (NAC) is the standard therapy upon hospitalisation and is recommended to be given as an antidote even before the diagnosis is confirmed. However, NAC as a treatment for APAP-induced liver failure is only effective the first eight hours after ingestion, after which, if the patient's condition is not seen to be improving, the only option is a liver transplant. Around 29% of patients with APAP-induced acute liver failure undergo a liver transplant, so there is a clear need for new and accessible treatments to be defined and which are effective beyond the first eight hours after ingestion.

The published research has been focused on the MCJ protein. As Dr. Mª Luz Martínez Chantar, a CIC bioGUNE researcher explains: "the MCJ protein is present in mitochondria, which are instrumental in cellular respiration and generate cell energy, essentially in highly metabolic tissues such as the liver. This protein limits the function of the respiratory chain and is a key regulator of the function of these organelles. Modulation of its levels through gene therapy therefore gives rise to mitochondria

which are resistant to damage by paracetamol, avoiding hepatocyte necrosis and fomenting liver regeneration".

The findings of the study conducted by researchers from the CIC bioGUNE Liver Disease Laboratory (led by Dr. Mª Luz Martínez Chantar and Dr Juan Anguita), from the National Institute for the study of Liver and Gastrointestinal Diseases (CIBEREHD) and from the University of Vermont College of Medicine (led by Dr. Mercedes Rincón), have been published in the journal Nature Communications under the title "The mitochondrial negative regulator MCJ is a therapeutic target for acetaminophen-induced liver injury".

A consortium of national and international researchers from hospitals and both basic and translational research centres - *Hospital Marqués de Valdecilla* (Santander, Spain), *Hospital Virgen de la Victoria* (Málaga, Spain), Hospital NHS Foundation (Newcastle-upon-Tyne, U.K.), *Hospital di Módena* (Módena, Italy), the Cedars-Sinai Healthcare Organisation (Los Ángeles, USA), *Instituto de Investigación en Biomedicina* (Barcelona) and the CIBER on Diabetes and Associated Metabolic Diseases (CIBERDEM) - has also collaborated in the study.

The lead authors of the work have been Drs. Lucía Barbier Torres (CIC bioGUNE) and Paula Iruzubieta (*Hospital Marqués de Valdecilla*).

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 generating knowledge on the molecular bases of disease, for use in the development of new diagnostic methods and advanced therapies.