Involvement of the CREB-E2F2-PPAR axis in non-alcoholic fatty liver disease development and progression to hepatocarcinoma

D.M. Congregado1,2, I. Aurrekoetxea1,2, B.G. Santos2, D.S. de Urturi2, M. Núñez2, J.L.G. Rodríguez2, F. González-Romero2, L.F. Ares1,2, A. Iglesias1, I. Bernales4, P. Iruzubieta2, V.G. de Juan6, M. Varela-Rey6, and D.M. Congregado1,2, I. Aurrekoetxea1,2, B.G. Santos2, D.S. de Urturi2, D.M. Congregado1,2, I. Aurrekoetxea1,2, B.G. Santos2, D.S. de Urturi2, D.M. Congregado1,2, I. Aurrekoetxea1,2, B.G. Santos2, D.S. de Urturi2, D.M. Congregado1,2, I. Aurrekoetxea1,2, B.G. Santos2, D.S. de Urturi2, D.M. Congregado1,2, I. Aurrekoetxea1,2, B.G. Santos2, D.S. de Urturi2

Method:

Involvement of the CREB-E2F2-PPAR axis in non-alcoholic fatty liver disease (NAFLD) development. Modulation of intestinal microbiota (IM) emerge as a promising therapeutic strategy for obesity-associated NAFLD. This study aims to determine the effect of IM transplantation and quercetin supplementation in a high fat diet (HFD)-based NAFLD model in germ free mice (GMf).

Background and Aims: Dysbiosis and gut-liver axis alteration have been pointed as important contributors to obesity and non-alcoholic fatty liver disease (NAFLD) development. Modulation of intestinal microbiota (IM) emerge as a promising therapeutic strategy for obesity-associated NAFLD. This study aims to determine the effect of IM transplantation and quercetin supplementation in a high fat diet (HFD)-based NAFLD model in germ free mice (GFm).

Method: Donor mice were selected from conventional raised mice as follows: control (dc), control supplemented with quercetin (dCQ), responder and non-responder to the HFD (dhFD+ and dhFD−) and highest response to quercetin with HFD (dhFDQ). GMf were colonized with IM from donors and fed with HFD or control diet supplemented or not with quercetin for 16 weeks. Gut bacterial communities were identified by 16S-rRNA pyrosequencing.

Results: A remarkable higher detection of Verrucomicrobi phylum and Akkermansia genus was observed in HFD-fed dc, dCQ, dhFD− and dhFDQ-receiver groups and a predisposal to IM transplantation resulted in a definite microbiota imbalance evidenced by reduced SCFAs (acetate, propionate and butyrate) production. dhFD− and dhFDQ microbiota transplantation reduced endotoxemia and ethanol production in HFD-fed mice attenuating gut liver axis activation and contributed to partially restore SCFAs profile. These alterations also correlated with Akkermansia abundance, positively for butyrate production and negatively for NLRP3 expression.

Conclusion: IM transplantation resulted in a definite microbiota composition establishment which determines susceptibility to NAFLD and metabolic syndrome development, highlighting the significant role of Akkermansia genus in the maintenance of a healthy metabolic profile, in a mechanism involving IM functionality and gut barrier integrity. Supported by BFU2013-48141-R, LE063U16 (JCyL and FEDER) and GRS 1428/A/16. CIBERehd is funded by ISCIII.