acid. On the other hand, treatment with oleic acid for 6 hours enhanced the expression of phospho-mTOR and suppressed LC3-II expression in isolated hepatocytes. Subsequent incubation in media without oleic acid for 12 hours decreased the activation of mTOR; however, nicotine treatment maintained mTOR activation. Moreover, suppression of lipolysis due to nicotine was ameliorated by the co-incubation with mTOR inhibitor rapamycin. Treatment with only oleic acid did not affect cell viability; however, addition of nicotine to oleic acid decreased cell viability to 62.5 ± 2.42%. Interestingly, mTOR inhibitor rapamycin suppressed cell death by combination of nicotine and oleic acid to 73.8 ± 2.05%.
Conclusion: These results indicated that exposure to nicotine blunts lipolysis via suppression of autophagy. Moreover, it was suggested that suppression of autophagy by nicotine enhances cell death. In conclusion, suppression of autophagy due to nicotine may contribute the progression of liver diseases observed in smokers.

THU-458

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

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Background and Aims: Obese patients with non-alcoholic fatty liver disease (NAFLD) are at increased risk of developing hepatocellular carcinoma (HCC). However, the mechanisms that promote HCC development in NAFLD patients are not fully understood. Here we investigated the role of E2F2 transcription factor in NAFLD development and progression to HCC.
Method: E2F2$^{-/-}$ and control mice (WT) were used. Liver disease in mice was induced by administration of diethylnitrosamine (DEN) (25 mg/kg) at 14 days-old plus high-fat (HFD) or chow diet until sacrificed at 3 (3m) or 9 months-old (9m). A cohort of 67 obese patients, 15 of which exhibited normal liver (NL) and 52 NAFLD, and 18 samples from non-obese liver donors were used. Protein and lipid content, and metabolic fluxes were analyzed.
Results: In liver, according to oncomine database E2F2 expression is increased in tumoral vs non-tumoral human tissue. We observed that E2F2 expression is also higher in DEN-HFD induced HCC vs NL mice. The number and size of tumors and the content in neutral lipids were higher in 9m DEN-HFD WT mice than in the other WT groups. At 9m, E2F2$^{-/-}$ mice were resistant to HCC development and to lipid accumulation, which was linked to decreased lipogenesis and increased B-oxidation as the metabolic fluxes and the transcriptome showed. This metabolic profile was also evident when E2F2 was kd in HepG2 cells and in 3m mice, in which E2F2$^{-/-}$ mice were totally resistant to hepatoesteatosis. E2F2 protein levels were increased in obese NAFLD patients when compared to non-obese or obese NL subjects, in which E2F2 levels were already higher than in non-obese NL individuals. The anti-steatotic effect in E2F2$^{-/-}$ mice was linked to decreased PPARγ and increased PPGC1 levels, both controlled by CREB. CREB kd demonstrated its involvement in the regulation of lipogenesis and B-oxidation when E2F2 was also kd.
Conclusion: E2F2 is a master regulator of metabolism in obesity related liver disease progression. It regulates the CREB-PPAR axis, involved in the homeostasis of liver lipid metabolism. Deficiency of E2F2 avoids the lipid storage required for NAFLD development and progression to HCC, which points out the value of E2F2 as a therapeutic target.

THU-459

Akkermansia spp. mediates protection from obesity-associated NAFLD development in germ free mice following intestinal microbiota transplantation from high fat diet and quercetin treated donors

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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). GFm 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 *Verrucomicrobia* phylum and *Akkermansia* genus was observed in HFD-fed dC, dCQ, dHFD− and dHFDQ-receiver groups, which were undetectable in dHFD+ recipients independently of the diet. Relative abundance of *Akkermansia* genus inversely correlated with body weight gain, NAFLD activity score and insulin resistance development (HOMA-IR). Evaluation of these parameters unveiled two protective metabolic phenotypes exhibited by dHFD− and dHFDQ-receiver groups and a predisposal to NAFLD development phenotype showed by dHFD+ transplanted mice. Gut-liver axis alteration was involved in predisposition to NAFLD as showed by enhanced expression of TLR4 and NLRP3 in dHFD+ recipients independently of the diet, associated to IM 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.