OC.05.6

TARGETING RUVBL1 REDUCES MTOR-DRIVEN NASH-HCC DEVELOPMENT IN MICE

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Background and aim: RuvBL1 belongs to the highly conserved AAA+ ATPases. It is deregulated in various human cancers and its expression correlates with a worse prognosis in HCC patients. We previously found that RuvBL1 haploinsufficiency impairs the PI3 K/Akt/mTOR pathway in liver. Given the relevance of mTOR pathway hyperactivation in HCC, we hypothesized that RuvBL1 genetic targeting could reduce mTOR-driven hepatocarcinogenesis.
Material and methods: Ptenhep−/− and Ruvbl1hep+/− mice were crossed to generate Ptenhep-/-Ruvbl1hep+/− mice. The impact of RuvBL1 haploinsufficiency on NASH development was assessed by histology at 12 weeks of age. Metabolic and inflammatory markers were evaluated by qPCR and IHC. mTOR pathway was analysed by WB of liver lysates. PPARalpha transcriptional activity was evaluated by luciferase reporter assay. The identification of RuvBL1-protein interactions was achieved by MS proteomics analysis of RuvBL1 immunoprecipitation. AML-12 PTEN KO cells were generated by CRISPR-Cas9 genome editing. The impact of RuvBL1 haploinsufficiency on HCC development was assessed by multiplicity evaluation of macroscopic tumours and by histological classification by Edmondson-Steiner grading system at 15 months of age.
Results: Ptenhep−/−Ruvbl1hep+/− developed significantly less steatosis, fibrosis, and inflammation compared to Ptenhep−/− mice. The mTOR-driven lipogenic targets were similarly expressed in the two mice models. However, Ppara and its target CPT1 was increased in Ptenhep−/−Ruvbl1hep+/−. The spontaneous and insulin-induced accumulation of lipid droplets in PTEN KO AML-12 cells was completely abrogated by RuvBL1 inhibition with CB-6644. Inhibition of RuvBL1 activity by CB-6644 increased PPARalpha transcriptional activity in AML-12 WT and PTEN KO. Analysis of RuvBL1-IP in AML-12 revealed that RuvBL1 interacts with members of the lysosomal AMPK complex. Furthermore, p-AMPK and p-RAPTOR were increased in Ptenhep−/−Ruvbl1hep+/− compared to Ptenhep−/−mice. Finally, Ptenhep−/−Ruvbl1hep+/-mice aged to 15 months showed better survival than Ptenhep−/− which developed significantly more HCC and of higher grade. qPCR analysis showed a significant upregulation of key lipolytic genes, such as Cpt1a, Acadl, Acadvl and Ppara, in Ptenhep−/−Ruvbl1hep+/− at 15 months of age.
Conclusions: RuvBL1 targeting reduces mTOR hyperactivation hampering NASH-HCC progression in Ptenhep−/− mice, likely promoting the switch from mTOR-driven lipogenesis to AMPK-induced fatty acid catabolism.

OC.05.7

CHOLESTASIS IMPACTS ON PERFORMANCE OF NON INVASIVE TESTS FOR RULING OUT HIGH-RISK ESOPHAGEAL VARICES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND COMPENSATED ADVANCED CHRONIC LIVER DISEASE

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Background and aim: Non-invasive tests (NITs) to identify patients with Primary Biliary Cholangitis (PBC) and compensated Advanced Chronic Liver Disease (cACLD) who can avoid esophago-gastroduodenoscopy (EGDS) are lacking. Aims of this study were to evaluate the diagnostic performance of NITs to rule out high-risk esophageal varices (HRV) in patients with PBC-related cACLD and to assess the influence of cholestasis on the NITs performance.
Material and methods: Data of patients with cACLD from 24 centres participating to "Italian PBC registry," were captured. All PBC patients who performed an EGD for evaluation of signs of portal hypertension were analyzed. Outcome was the presence of HRV at index EGD. RESIST criteria (platelets - PLT >120 × 109/L and serum albumin >3.6 g/dL) were compared with elastography-based criteria (Baveno VI, Expanded Baveno VI, and Baveno VII) in patients with Alkaline Phosphatase (ALP) < or ≥1.67 ULN. Decision curve analysis (DCA) of NITs were calculated.
Results: The cohort consisted of 250 patients. At EGDS, 137 patients (54.8%) had no varices, 79 (31.6%) had low-risk varices and 34 (13.6%) had HRV. Liver stiffness by Fibroscan was available in 186 patients (74.4%). Overall, the proportion of correctly spared endoscopies for HRV was 61.1%, 54.1%, 31.4% and 18.2% for RESIST, Expanded Baveno VI, Baveno VI and Baveno VII criteria, respectively. and RESIST criteria were associated with the lowest rate of missing HRV (2.9%). In patients with ALP ≥1.67 ULN (101, 40.4%) the rate of missing HRV for Baveno VI and Expandend Baveno VI criteria were 23.8 and 18.9% respectively. In the same category of patients RESIST criteria false negative rate was 6%. DCA demonstrates the highest net benefit of RESIST criteria compared to elastography-based criteria for ruling out HRV both in patients with ALP < or ≥1.67 ULN (Figure 1).