**Background and Aims:** Chronic hepatitis C virus (HCV) infection is a major cause of hepatic steatosis and metabolic disease. We previously demonstrated that HCV infection impairs protein tyrosine phosphatase receptor type delta (PTPDRD), a candidate tumour suppressor associated with poor prognosis and enhanced signal transducer and activator of transcription (STAT3) transcription (Van Renne, Roca Suarez et al. Gut 2018). Since HCV-induced STAT3 activity perturbs peroxisomal beta-oxidation (Lupberger et al. Gastroenterology 2019) and somatic mutations of PTPRD associate with diabetes type II (Chen et al., Oncotarget 2015), we aim to study the role of PTPRD as regulator of hepatocyte metabolism and liver disease.

**Method:** Based on liver transcriptomic data, non-infected normal and obese patients were classified according to hepatic PTPRD expression levels and diabetic blood markers. Gene set enrichment analysis (GSEA) was performed in order to identify signalling pathways associated with low PTPRD expression. Results were validated in primary human hepatocytes (PHH) by RNAi and western blotting, and in livers of PTPRD-deficient mice following 8 weeks of choline-deficient high-fat diet (CD-HFD) feeding.

**Results:** Livers of normal patients with low PTPRD expression exhibit an enrichment of genes associated with peroxisomal function, inflammation and glucose metabolism suggesting PTPRD as regulator of hepatic fat metabolism and insulin signalling. Indeed, silencing PTPRD in PHH impairs Akt phosphorylation following insulin stimulation. Livers of PTPRD-deficient mice (Ptprd+/−) mice exhibit higher STAT3 phosphorylation levels and present hepatic transcriptional changes similar to healthy patients with low PTPRD levels. Moreover, induction of liver disease in PTPRD-deficient mice using CD-HFD cause a diabetic phenotype including increased fasting blood glucose levels in absence of weight gain in Ptprd+/− animals. In obese patients with low hepatic PTPRD expression, we found increased blood levels of fasting glucose, glycated haemoglobin (HbA1c) and elevated insulin resistance scores (HOMA2). Statistical analysis (GSEA) was performed in order to identify signalling pathways associated with low PTPRD expression. Results were validated in primary human hepatocytes (PHH) by RNAi and western blotting, and in livers of PTPRD-deficient mice following 8 weeks of choline-deficient high-fat diet (CD-HFD) feeding.

**Conclusion:** Our data suggests an important regulatory role of the hepatic PTPRD-STAT3 axis in fatty acid and glucose homeostasis, which is associated with clinical manifestations of metabolic disease. We suggest that targeting PTPRD downstream signalling represents a potential strategy to restore metabolic pathways and hepatic steatosis in risk patients.

**SAT004 LncRNA-H19 as a marker of liver progression from steatosis to hepatocellular carcinoma**

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**Background and Aims:** The main aims of this study were: a) Isolation, characterization and analysis of the epigenetic profile of liver cancer stem cells (LCSC) b) Assessment of H19 in a NAFLD-HCC animal model c) Validation of H19 as a diagnostic biomarker in HCC patients.

**Method:** a) In vitro LCSC were isolated from a Huh7.5 cell line by FACS (EpCAM+CD133+) and H19 expression was evaluated by qPCR b) A total of 31 6w-old male C57BL/6J were fed with a HPHCC diet (40% Kcal-fat, 1%cholesterol and 42 g/L glucose/fructose in drinking water) (n = 26) or standard diet(n = 5) for 52w. Histological, biochemical and metabolic profiles were measured and H19 liver expression was assessed by qPCR c) H19 levels were determined in 14 liver tissues from cirrhotic patients, with HCC (n = 7) or without (n = 7).

**Results:** a) An increase in size and number of spheroids was observed in EpCAM+CD133+ cells (LCSC vs. Huh7.5: fold-square number: 2.15 ± 0.96; p = 0.004 and fold-size μm2: 3.04 ± 1.93; p < 0.001). LCSC showed higher expression of H19 levels than Huh7.5 (fold-2.18 ± 0.32; p = 0.003) b) HPHCC-diet induced steatosis within the first 39w and NASH at 52w. Nodules were detected in 33% of mice, being classified into adenosas or well-differentiated HCC. Qpcr expression was significantly raised in presence of HCC (p < 0.0001). H19 was upregulated in NASH and HCC liver tissue when compared to steatosis (p = 0.05 and p = 0.001) and control group (p = 0.011 and p = 0.016). Also, H19 was increased in ballooning (p = 0.003), oval cells proliferation (p < 0.001) and advanced fibrosis (p = 0.010). There was not found association with steatosis and lobular inflammation c) H19 was found significantly increased in liver tissue from HCC patients compared to cirrhotic patients (fold-4.0 ± 2.55; p = 0.020). In addition, H19 was found upregulated in plasma from HCC vs. cirrhotic patients without development of HCC (2.60 ± 2.29 vs 1.02 ± 0.58 copies/μL; p < 0.001). Cirrhotic patients who developed HCC during the follow-up period showed higher levels of H19 compared to non-HCC cirrhotic patients (4.42 ± 3.96 vs 1.02 ± 0.58, copies/μL p = 0.089).

**Conclusion:** H19 was found to be increased in LCSC, promoters of the carcinogenesis. Also, it was found upregulated in both NASH and tumors in a NAFLD pathological model, as well as in liver tissue and plasma from HCC patients. Therefore, H19 could constitute a biomarker of disease progression from liver steatosis to HCC.

**SAT005 The lipid composition of the liver: assessing differences in obese patients with and without non-alcoholic steatohepatitis**

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**Background and Aims:** Obesity and associated co-morbidities are reaching pandemic proportions in developed countries. Non-alcoholic steatohepatitis (NASH) is the hepatic co-morbidity of this disease and is gaining interest due to the metabolic importance of the liver. The aim of our study was to assess the lipid composition of the liver from patients with obesity and with or without NASH.

**Method:** Obese patients were divided into NASH group (n = 50) or non-NASH group (n = 50) depending on their non-alcoholic steatohepatitis activity score (NAS). To assess the lipid liver composition, 10 mg of liver were homogenized and lipids were extracted by using a solution of chloroform – methanol (2: 1 proportion). After different centrifugation, the apolar phase was dried, reconstituted in methanol – MTBE (9: 1 proportion) and placed into vials for the UHPLC-ESI-QTOF-MS.

**Results:** Cholesterol esters were the main lipid species in the liver composition. The lipid categories present in the livers were similar in patients with and without NASH. However, their concentrations and therefore percentages were different: especially note cholesterol esters, which were statistically increased in obese patients with NASH (70.9% in non-NASH vs 89.8% in NASH) (Figure 1A). We observed that all lipids were generally increased in livers with NASH, except phosphatidylcholines, which were all decreased (Figure 1B). In a