GPNMB induces hepatic steatogenesis and modulates liver cancer cells

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Abstract

Lipid accumulation in liver cells predisposes to non-alcoholic fatty liver disease (NAFLD) including its severe disease forms non-alcoholic steatohepatitis (NASH), fibrosis/cirrhosis, and HCC. Hepatocyte (HC)-derived glycoprotein non-metastatic melanoma B (Gpnmb) was previously reported as a regulator of fat metabolism in adipose tissue, however, its role in the pathogenesis of NAFLD-related HCC is not yet elucidated.

We started with an analysis of published microarray data from human patients and found Gpnmb upregulated in NAFLD/NASH and HCC, as compared to healthy livers. We next confirmed a progressively increasing expression of GPNMB in NAFLD/NASH (6, 8, and 12 weeks) and HCC stages (20 weeks) of STAM or Western diet (WD) fed mice (8-40 weeks). We then ectopically overexpressed GPNMB with recombinant AAV8 infection in WD-fed mice (for 8 and 16 weeks). With IHC, we locate GPNMB expression in HC and HC-derived cancer cells. We next modulated GPNMB expression in primary HC and AML12 with(out) oleic acid (OA)-treatment and investigated the fatty HC phenotype. Gpnmb depletion increases triglycerides accumulation and mRNA expression of lipogenic genes namely, sterol regulatory element-binding protein- 1c (Srebp-1c), peroxisome proliferator-activated receptor alpha (Pparα), peroxisome proliferator-activated receptor gamma (Pparγ), fatty acid synthase (Fasn) and stearoyl-CoA desaturase 1 (Scd1). Unexpectedly, carnitine palmitoyltransferase I (Cpt1) and acyl-CoA oxidase 1 (Acox1), members of antioxidant genes, are also upregulated. Complementary results were obtained upon GPNMB overexpression. Moreover, in Huh7, HLE and HLF liver cancer cells, GPNMB facilitates death signals as measured by time-lapse cell imaging and caspase assay. Mechanistically, GPNMB facilitates cell death in HCC cells by interfering with AKT phosphorylation-dependent survival signals. Surprisingly, liver weight is higher in GPNMB overexpressing WD-fed mice, which present with more deposited lipid droplets. This might be explained that AAV8-infection induces overexpression of the extracellular domain (ECD) of GPNMB which has a steatogenic impact. GPNMB is a consistently upregulated gene in NASH and HCC. GPNMB is expressed in HC and HC-derived cancer cells. In fatty liver, GPNMB is upregulated to tone down lipogenesis, however, overexpression of its extracellular domain in WD-fed mice acts lipogenic. In liver cancer cells, GPNMB acts as a tumor suppressor by providing cytostatic effects.