Hepatic Notch1 deletion predisposes to diabetes and steatosis via glucose-6-phosphatase and perilipin-5 upregulation

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Notch signaling pathways have recently been implicated in the pathogenesis of metabolic diseases. However, the role of hepatic Notch signaling in glucose and lipid metabolism remains unclear and needs further investigation as it might be a candidate therapeutic target in metabolic diseases such as nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD). We used hepatocyte-specific Notch1 knockout (KO) mice and liver biopsies from NASH and NAFLD patients to analyze the role of Notch1 in glucose and lipid metabolism. Hepatocyte-specific Notch1 KO mice were fed with a high fat diet (HFD) or a regular diet (RD). We assessed the metabolic phenotype, glucose and insulin tolerance tests, and liver histology. Hepatic mRNA expression was profiled by Affymetrix Mouse Gene arrays and validated by quantitative reverse transcription PCR (qPCR). Akt phosphorylation was visualized by immunoblotting. Gene expression was analyzed in liver biopsies from NASH, NAFLD, and control patients by qPCR. We found that Notch1 KO mice had elevated fasting glucose. Gene expression analysis showed an upregulation of glucose-6-phosphatase, involved in the final step of gluconeogenesis and glucose release from glycogenolysis, and perilipin-5, a regulator of hepatic lipid accumulation. When fed with an HFD KO mice developed overt diabetes and hepatic steatosis. Akt was highly phosphorylated in KO animals and the Foxo1 target gene expression was altered. Accordingly, a reduction in Notch1 and increase in glucose-6-phosphatase and perilipin-5 expression was observed in liver biopsies from NAFLD/NASH compared with controls. Notch1 is a regulator of hepatic glucose and lipid homeostasis. Hepatic impairment of Notch1 expression may be involved in the pathogenesis of human NAFLD/NASH.