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Opposing Roles of Notch1 and Notch2 in Metabolic Dysfunction-Associated Steatohepatitis

Background: With the rising prevalence of obesity, understanding the molecular pathogenesis of obesity-associated metabolic disease is critical in order to better stratify risk as well as to devise treatment approaches. Metabolic dysfunction-associated steatotic liver disease (MASLD) is an obesity-associated disease that is now the most common chronic liver disease and its more progressive form, Metabolic dysfunction-associated steatohepatitis (MASH), is frequently encountered in patients with obesity seen by endocrinologists. Reactivation of the quiescent Notch pathway has been identified as a driver of disease progression and to the critical outcome of fibrosis in MASH, however it is not clear which nodes within the Notch signaling cascade cause this deleterious effect.
Methods: Mice exposed to MASH-inducing diets were treated with antisense oligonucleotides (ASO) directed at Notch1 or Notch2 and analyzed after sacrifice for Notch protein and activity, as well as key readouts of MASH: hepatocyte steatosis and injury, and liver inflammation and fibrosis.
Results: Notch2 ASO treatment decreased Notch pathway activity and fibrosis while Notch1 ASO treatment caused unexpected increased hepatocyte Notch2 protein, leading to higher Notch pathway activity, liver injury, inflammation, and fibrosis.
Conclusions: Our data highlight the critical role of Notch2 activity in MASH pathogenesis and suggest post-translational level cross-regulation by Notch1 of Notch2. These findings suggest unexpected regulatory circuits in the Notch pathway that may dampen the maladaptive response to obesity and caloric excess intrinsic to MASH.