Title: Effects of hepatocyte-specific EGFR and ERBB3 deletion in murine fast-food diet model of MASLD

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most prevalent chronic liver disorder, with no approved treatment. Our previous work demonstrated the efficacy of a pan-ErbB inhibitor, Canertinib, in reducing steatosis and fibrosis in a murine fast-food diet (FFD) model of MASLD. The current study explores the effects of hepatocyte-specific ERBB1 (EGFR) and ERBB3 receptors deletion in the FFD model.

Methods: EGFR & ERBB3 specifically in hepatocytes, were fed a FFD diet for 2 or 5 months.

Results: Hepatocyte-specific EGFR deletion reduced serum triglyceride levels but did not prevent steatosis. Transcriptomic analysis revealed significant alteration of lipid metabolism pathways in EGFR -KO mice with changes in several relevant genes, including downregulation of fatty-acid synthase and induction of lipolysis gene, Pnpla2, without impacting overall steatosis. Interestingly, EGFR downstream signaling mediators, including AKT, remain activated in EGFR -KO mice, which correlated with increased activity pattern of other receptor tyrosine kinases, including ERBB3, in transcriptomic analysis. Further, Canertinib treatment in EGFR-KO mice, which inhibits all ERBB3 receptors, successfully reduced steatosis, suggesting the compensatory roles of ERBB3 receptors in supporting MASLD without EGFR. In contrast to EGFR-KO, ERBB3-KO showed strikingly reduction in steatosis and liver to body weight ratio along with improved glucose tolerance and insulin tolerance. Further, the expression of PPARγ and ATP citrate lyase, the key transcription factor and enzyme, respectively, that regulate fatty acid biosynthesis, were remarkably reduced in ERBB3-KO

Conclusions: Hepatocyte-specific EGFR-KO did not impact steatosis, but ERBB3-KO reduced steatosis in the FFD model of MASLD, indicating an important role of ERBB3 in regulating liver lipid metabolism.