

Targeted Deletion of Hepatocyte ERBB3 (HER3) Attenuates MASLD Progression and Reprograms the PPAR γ –HNF4 α Metabolic Axis

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Abstract:

Background and Aims:

MASLD progression involve hepatocyte reprogramming characterized by increased PPAR γ -driven lipid storage and reduced HNF4 α -controlled hepatocyte gene expression. However, the hepatocyte membrane receptor that regulates this transcriptional switch remains elusive. Our previous studies show that while pharmacologic pan-ERBB inhibition modulates this switch resolving hepatic steatosis in murine MASLD models, hepatocyte-specific EGFR deletion fails to reproduce this benefit with compensatory ERBB3 activation. Here, we investigated whether hepatocyte ERBB3 drives MASLD progression and regulates the PPAR γ –HNF4 α metabolic switch.

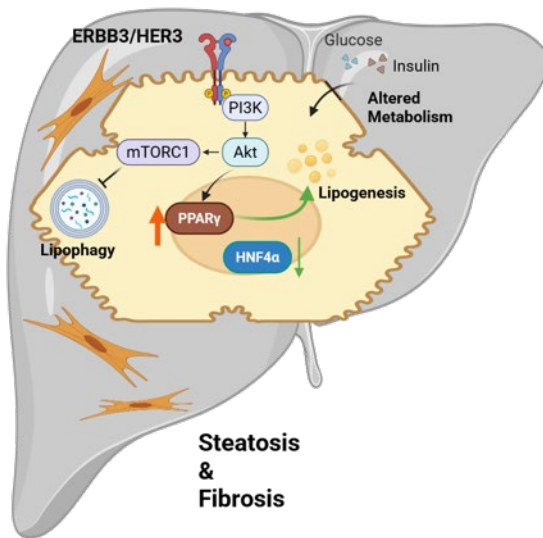
Methods: Hepatocyte-specific ErbB3 mice (ERBB3-KO^{Hep}) were challenged with a fast-food diet for 5 months. MASLD phenotypes were assessed by histology, biochemical assays, and immunoblotting, ERBB3–PI3K (p85) co-immunoprecipitation and multi-omics analysis. Therapeutic relevance was tested using lipid nanoparticle-delivered siERBB3 *in vivo* and siRNA-mediated ERBB3 knockdown in primary human MASH hepatocytes.

Results: ERBB3 signaling was activated in both human and murine MASLD livers. ERBB3-KO^{Hep} mice were protected against FFD-induced steatosis, with reduced liver triglyceride and improved glucose homeostasis. ERBB3 deletion attenuated PI3K–AKT–mTOR signaling, suppressed PPAR γ expression and its lipogenic program and restored HNF4 α expression. This was accompanied with reduced lipogenesis, lipid uptake, and lipid droplet stabilization, and increased autophagy/lipophagy associated markers. ERBB3 loss also suppressed fibrogenic programs, stellate cell activation and collagen deposition. Therapeutic ERBB3 silencing via LNP in mice with established MASLD, and ERBB3 knockdown in primary human MASH hepatocytes reduced lipid accumulation that was associated with decreased PPAR γ expression and downstream lipogenic reprogramming.

Conclusions: Our study uncovered that ERBB3, a largely understudied ERBB receptor in liver, has a central role in hepatocyte lipogenic reprogramming during MASLD progression by regulating the PPAR γ –HNF4 α switch. ERBB3 inhibition restores hepatocyte metabolic identity, and attenuates fibrosis, revealing ERBB3 as a promising therapeutic target for MASLD.

Graphical Abstract

ERBB3/HER3 Activation



ERBB3/HER3 Inhibition

