IECC 2026 Conference
The 5th International Electronic Conference on Cancers
10–12 June 2026 | Online
MDPI

Exploring the mechanism of ID1-dependent liver inflammation induced by dietary fat and a therapeutic approach to target IDs in cancer

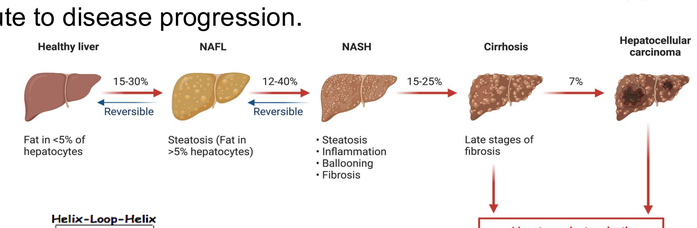
Riddhi Shah[1], Davide Pradella[2], Ashley Sullivan[3], Ana Marie Perea[3], Daniel Heller[3], Robert E. Schwartz[4], Robert Benezra[2]

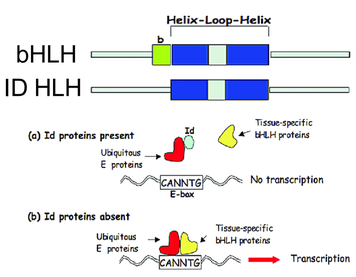
[1] Independent, [2] Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center, [3] Pharmacology Program, Memorial Sloan Kettering Cancer Center
[4] Division of Regenerative Medicine, Weill Cornell Medicine

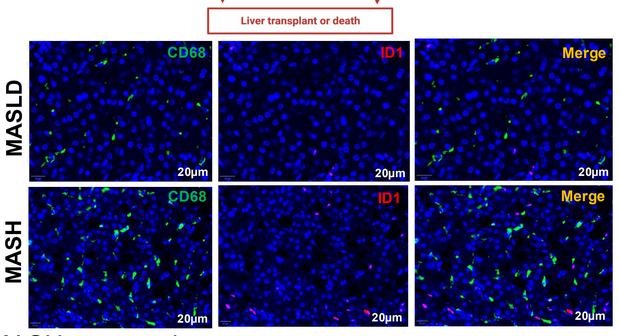
INTRODUCTION & AIM

INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive inflammatory liver disease and a major risk factor for hepatocellular carcinoma (HCC). The mechanisms linking steatosis to chronic liver inflammation remain incompletely understood. We previously identified elevated expression of the transcriptional regulator **ID1** in liver-resident macrophages (Kupffer cells; KCs) in both murine MASH models and human MASH biopsies, suggesting that ID1 may contribute to disease progression.





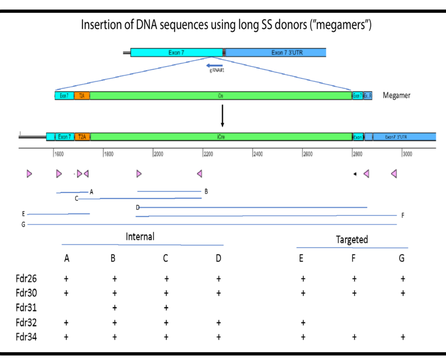


AIM

This study aimed to:

- Investigate the role of ID1 in MASH progression.
- Define ID1-regulated inflammatory pathways.
- Assess nanoparticle-mediated ID targeting.

METHOD



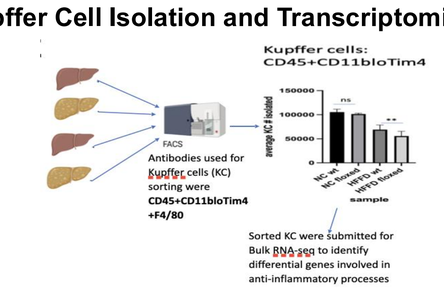
KC-Specific Id1 Knockout Generation

- Generated Kupffer cell (KC)-specific Id1 knockout mice by targeted insertion of iCre into the Clec4f locus, a KC-restricted marker.
- Crossed Clec4f-iCre mice with Id1floxed mice to achieve selective deletion of Id1 in liver-resident macrophages.
- Confirmed successful targeting and recombination using PCR-based genotyping and lineage-tracing approaches.
- Utilized KC-specific Id1 knockout mice to investigate the role of ID1 in MASH progression and liver inflammation.

MASH Induction Protocol

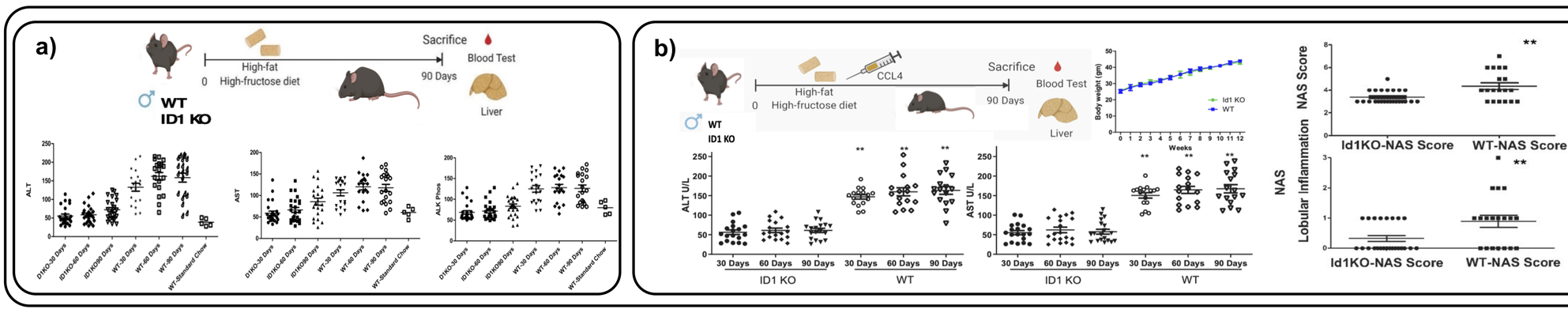
- WT and KC-specific Id1 knockout mice were fed a high-fat, high-fructose Western diet supplemented with fructose-containing drinking water for 24 weeks to induce MASH.
- Disease severity was evaluated by serum liver enzyme measurements, histological assessment, and NAS scoring.
- Liver tissues were collected for Kupffer cell isolation, transcriptomic profiling, and downstream analyses.

Kupffer Cell Isolation and Transcriptomic Analysis



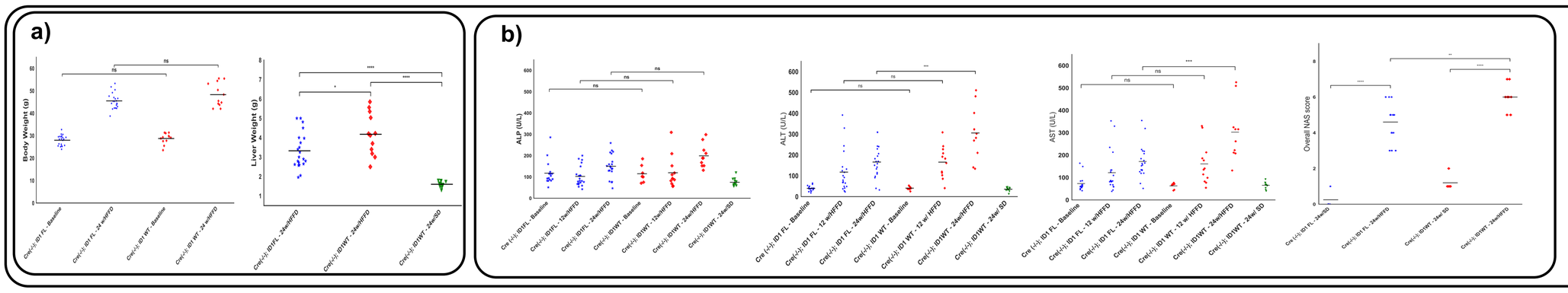
- Liver-resident Kupffer cells were isolated by flow cytometry using a CD45⁺CD11b^loTim4⁺F4/80⁺ gating strategy and were subjected to bulk RNA sequencing.
- Differential gene expression analysis was performed to identify ID1-regulated inflammatory and lipid metabolic pathways associated with MASH progression.

RESULTS & DISCUSSION



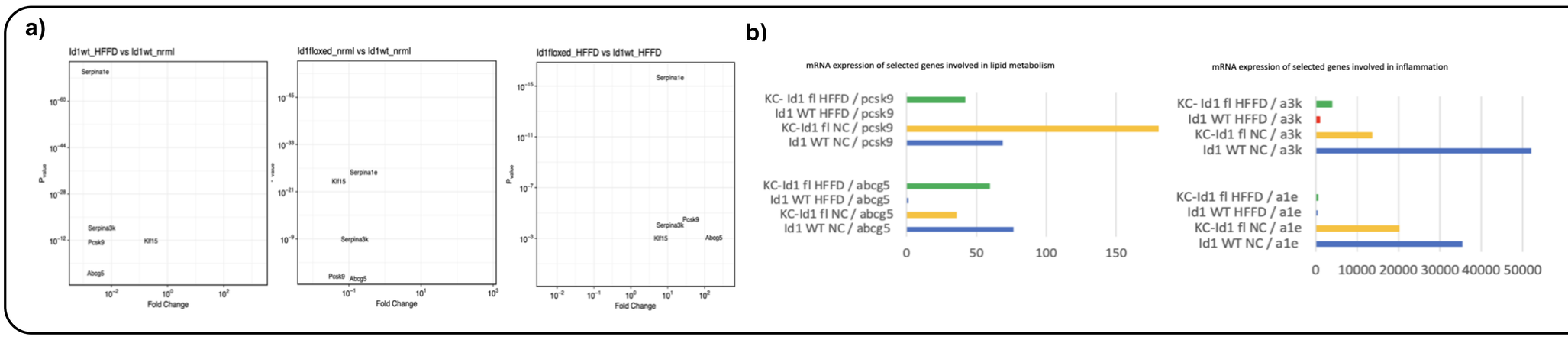
Key Finding

Loss of ID1 protects against liver injury and inflammation across multiple preclinical models - (a) diet-induced MASH and (b) CCL4-induced liver injury models, identifying ID1 as a key driver of MASH progression.



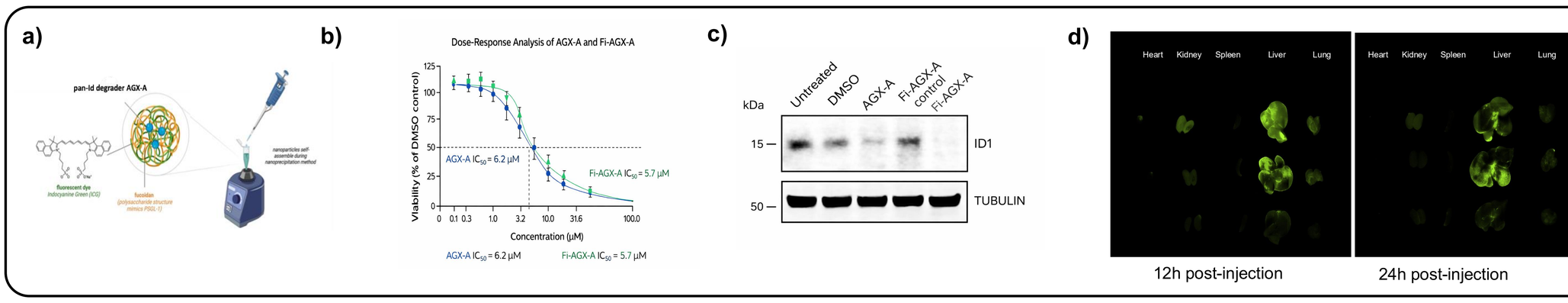
Key Finding

Kupffer cell-specific deletion of ID1 reduced liver injury and disease severity, identifying ID1 as a key driver of MASH progression.



Key Finding

Loss of ID1 altered the expression of inflammatory and lipid-regulatory genes, including Serpina1e, Serpina3k, Abcg5, and Pcsk9, highlighting molecular pathways associated with MASH progression.



Key Finding

Nanoparticle-mediated delivery enabled efficient ID1 targeting and degradation, supporting the therapeutic potential of ID-directed strategies in MASH.

CONCLUSIONS

- ID1 drives Kupffer cell–mediated inflammation during MASH progression.
- Loss of ID1 protects against liver injury and disease severity.
- ID1 represents a promising therapeutic target for MASH.

FUTURE WORK AND ACKNOWLEDGMENT

Future evaluation of ID-targeted nanoparticle therapy in MASH. Supported by Geoffrey Beene Cancer Research Center and Breast Cancer Research Foundation.