

HLF and PPAR α axis regulates metabolic-associated fatty liver disease through extracellular vesicles derived from the intestinal microbiota

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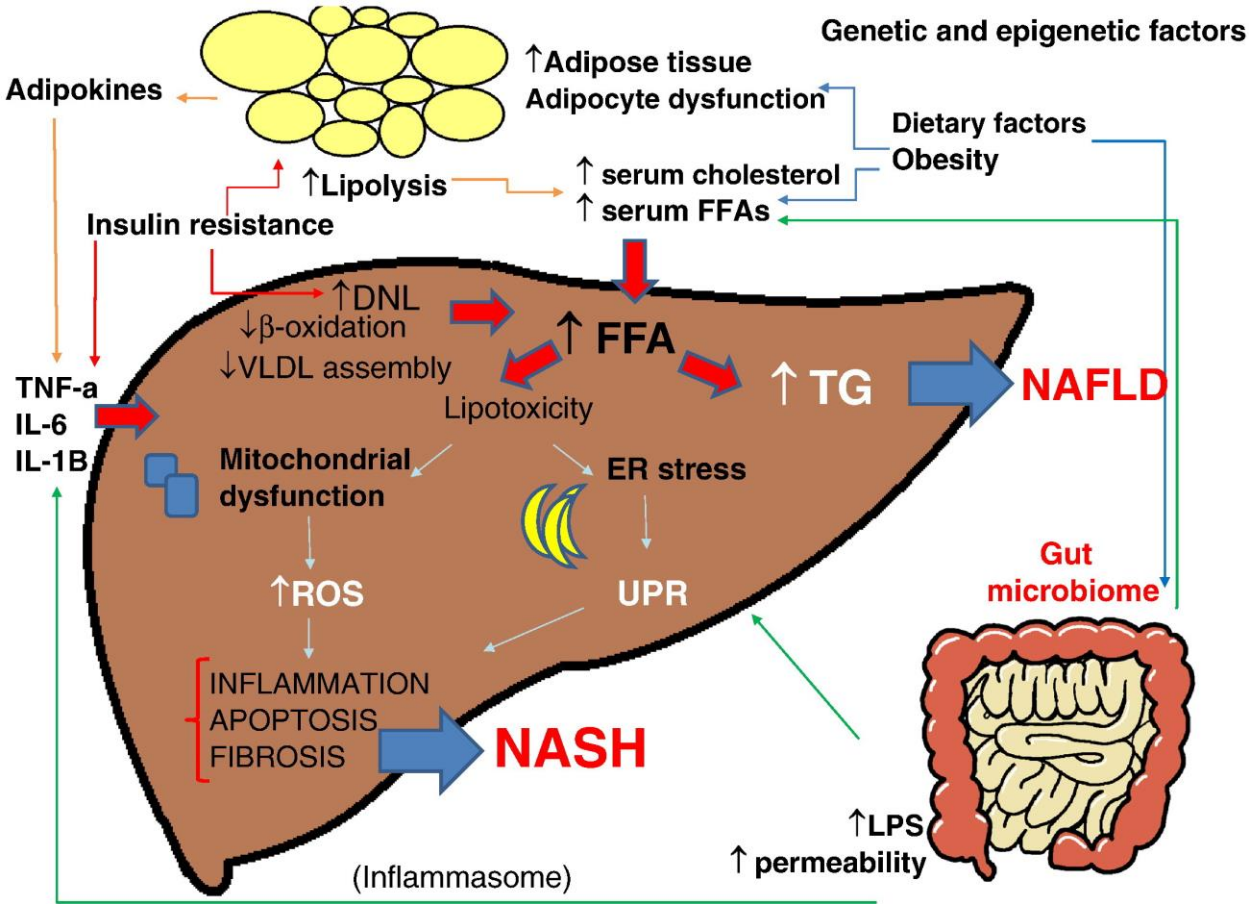
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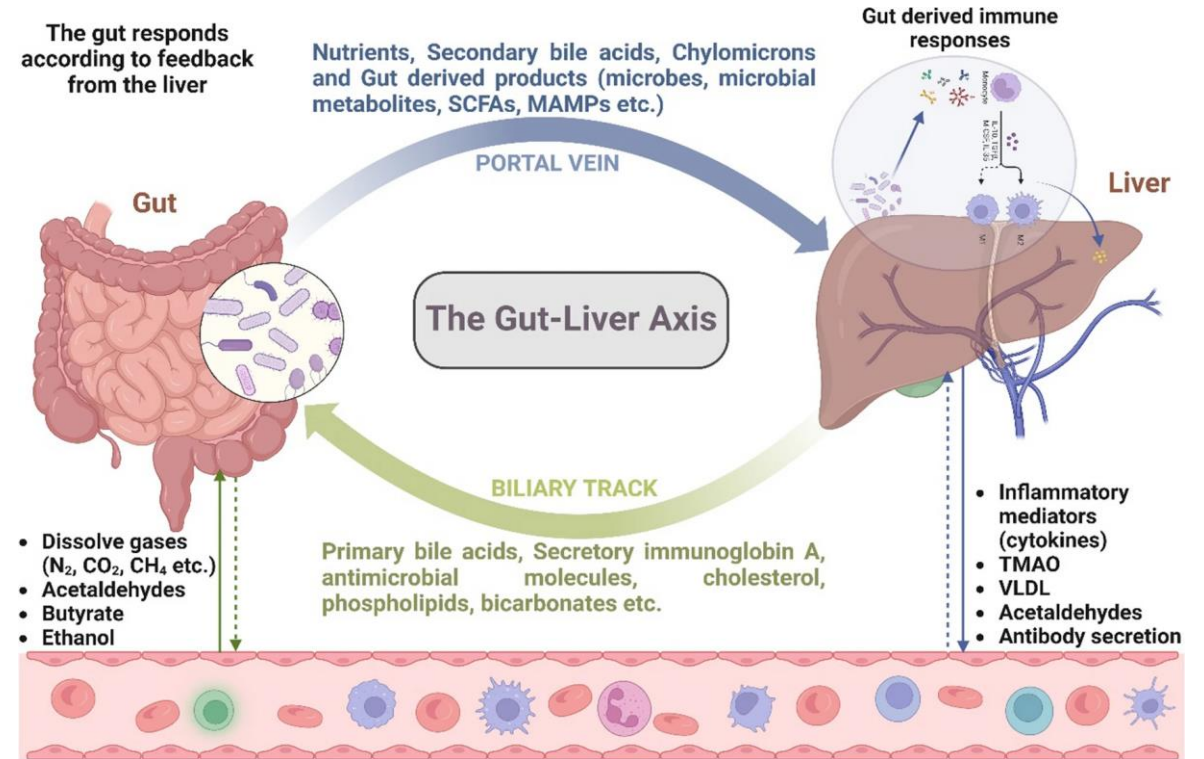
Introduction

The multiple-hit hypothesis for the development of MAFLD (NAFLD)



Metabolism, 2016

Schematic illustration of the gut-liver axis



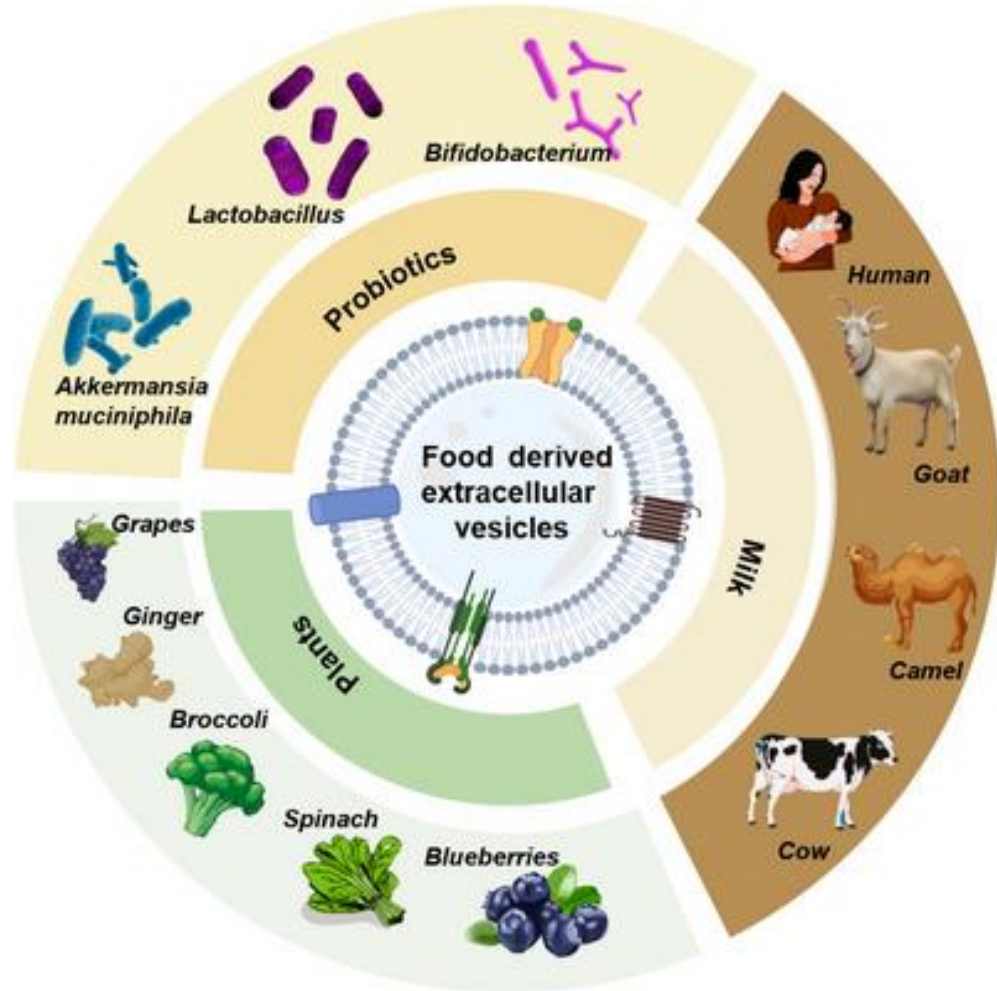
MAMPs: Microbe-Associated Molecular Patterns, SCFAs: Short-Chain Fatty Acids, TMAO: Trimethylamine N-Oxide, VLDL: Very Low-Density Lipoprotein

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Introduction

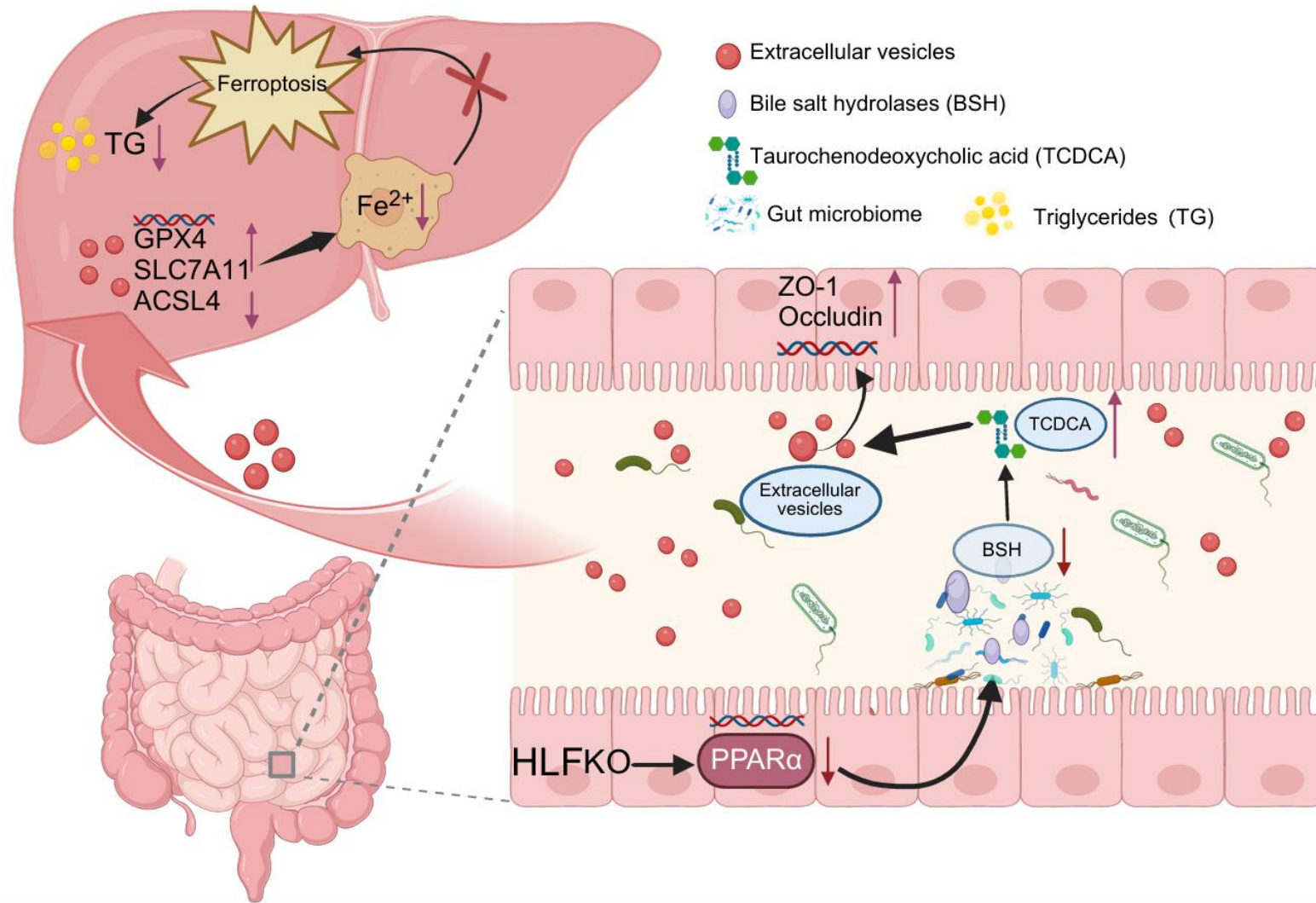
The primary sources of extracellular vesicles (EVs)



Extracellular vesicles (EVs) are natural nanoparticles ranging from 30 to 500 nm that carry bioactive molecules (e.g., proteins and miRNAs) for intercellular communication. Recent studies have demonstrated that orally administered EVs can protect the liver from injury and improve metabolic conditions. These findings offer promising prospects for fEVs-based therapeutic strategies for liver diseases and metabolic disorders.



Highlights



① Intestinal-specific lack of hepatic leukemia factor (HLF) can improve metabolic-associated fatty liver disease (MAFLD).

② HLF plays a role in fat metabolism regulation through peroxisome proliferator-activated receptor alpha (PPAR α).

③ The HLF/PPAR α axis regulates the gut microbiome and influences the composition of gut microbiota-derived extracellular vesicles (fEVs).

④ The bound bile acid taurochenodeoxycholic acid (TCDCA) is a key regulatory factor for fEVs to improve MAFLD.

HLF is a novel target for regulating intestinal lipid absorption

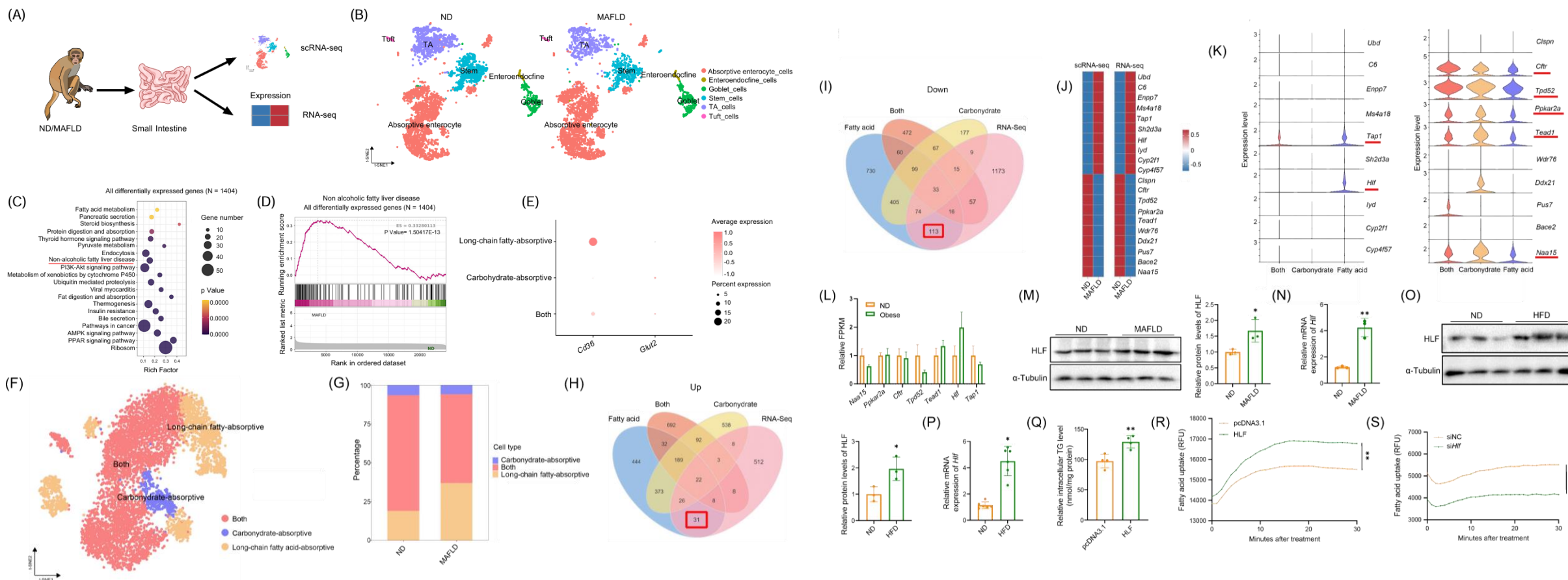


Figure 1. Hepatic Leukemia Factor (HLF) is a Novel Target for Regulating Intestinal Lipid Absorption

HLF deficiency improves MAFLD

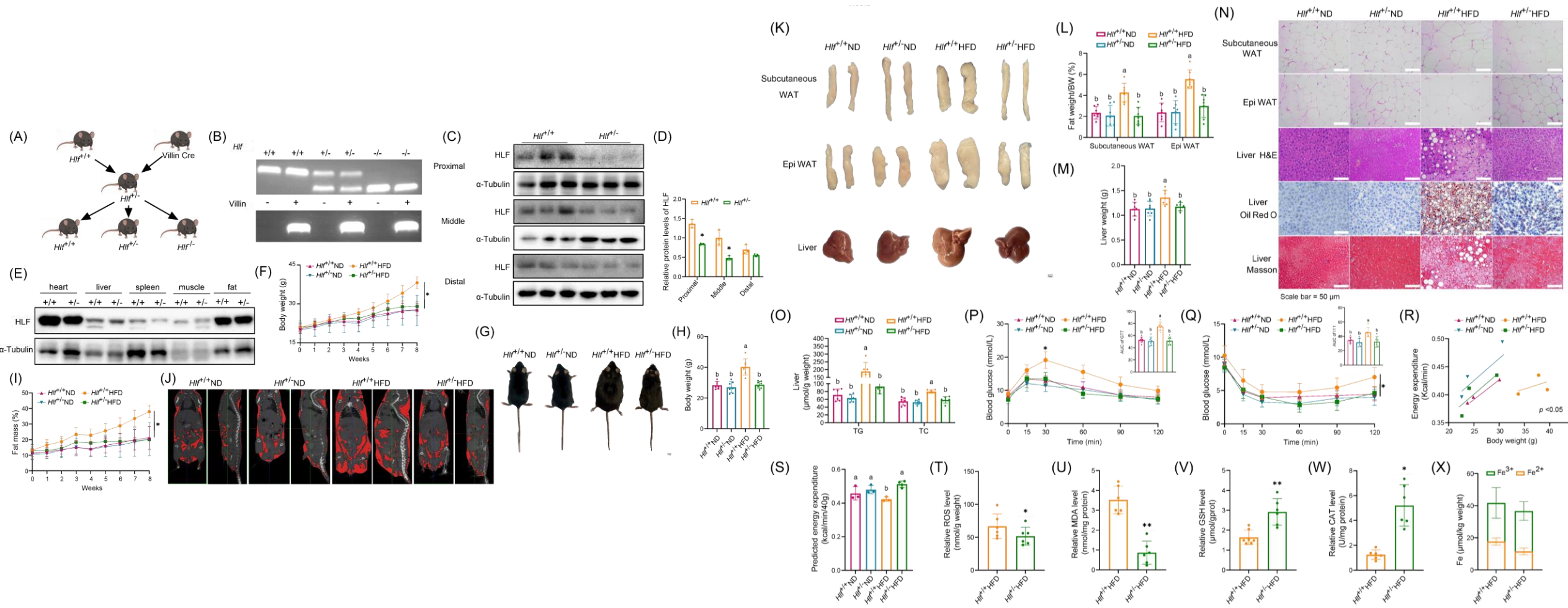


Figure 2. Partial Hepatic Leukemia Factor (HLF) Deficiency Improves Metabolic-Associated Fatty Liver Disease (MAFLD)

HLF regulates the expression of Ppara

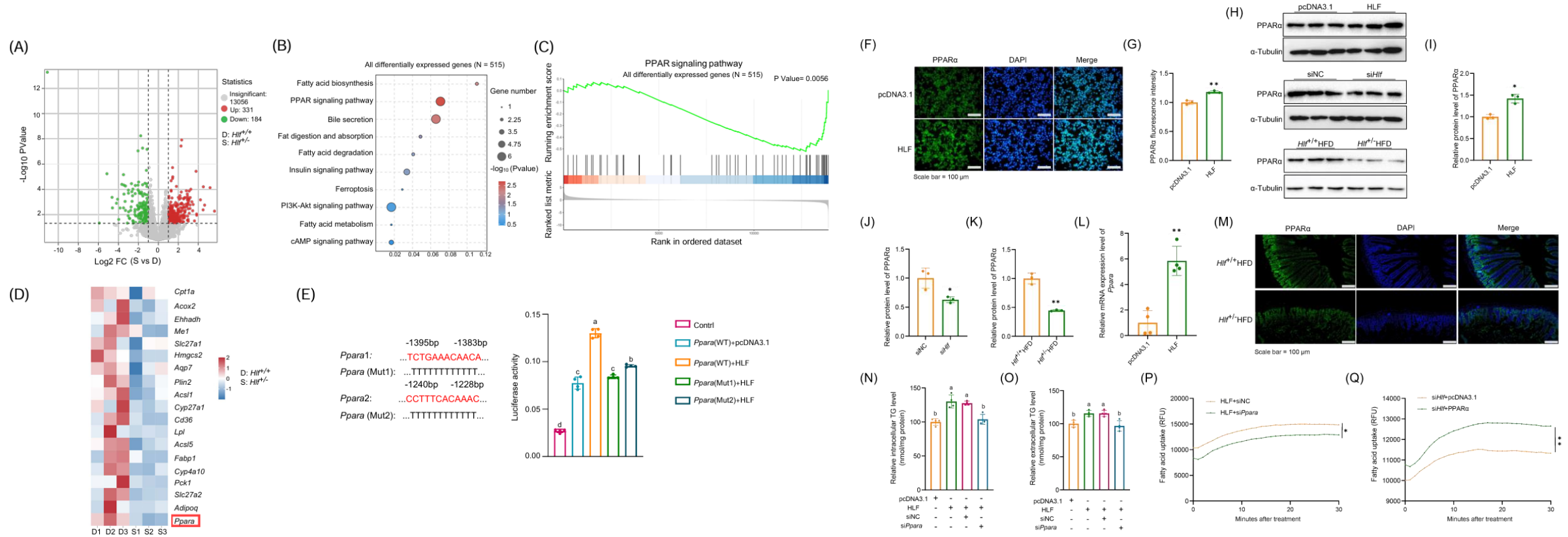


Figure 3. Hepatic Leukemia Factor (HLF) Regulates Peroxisome Proliferator-Activated Receptor Alpha (PPAR α) Expression



Inhibition of PPAR α alleviates MAFLD

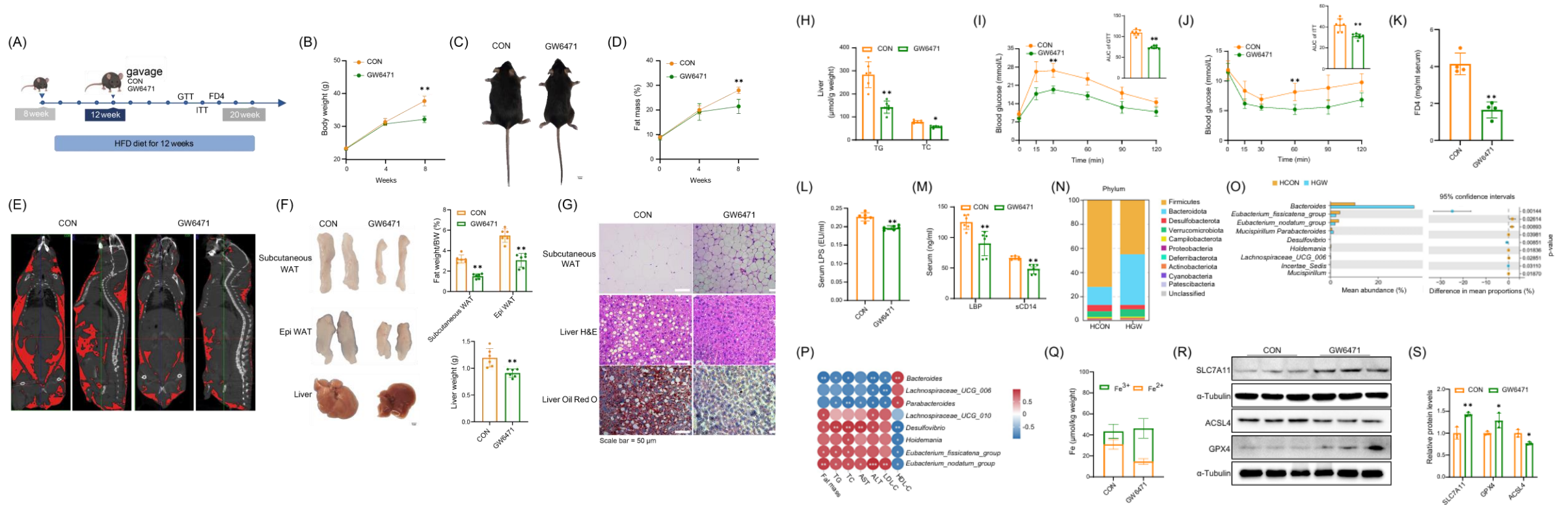


Figure 4. Inhibition of Peroxisome Proliferator-Activated Receptor Alpha (PPAR α) Alleviates Metabolic-Associated Fatty Liver Disease (MAFLD)

fEVs from GW6471-treated mice improve intestinal permeability and inhibit ferroptosis

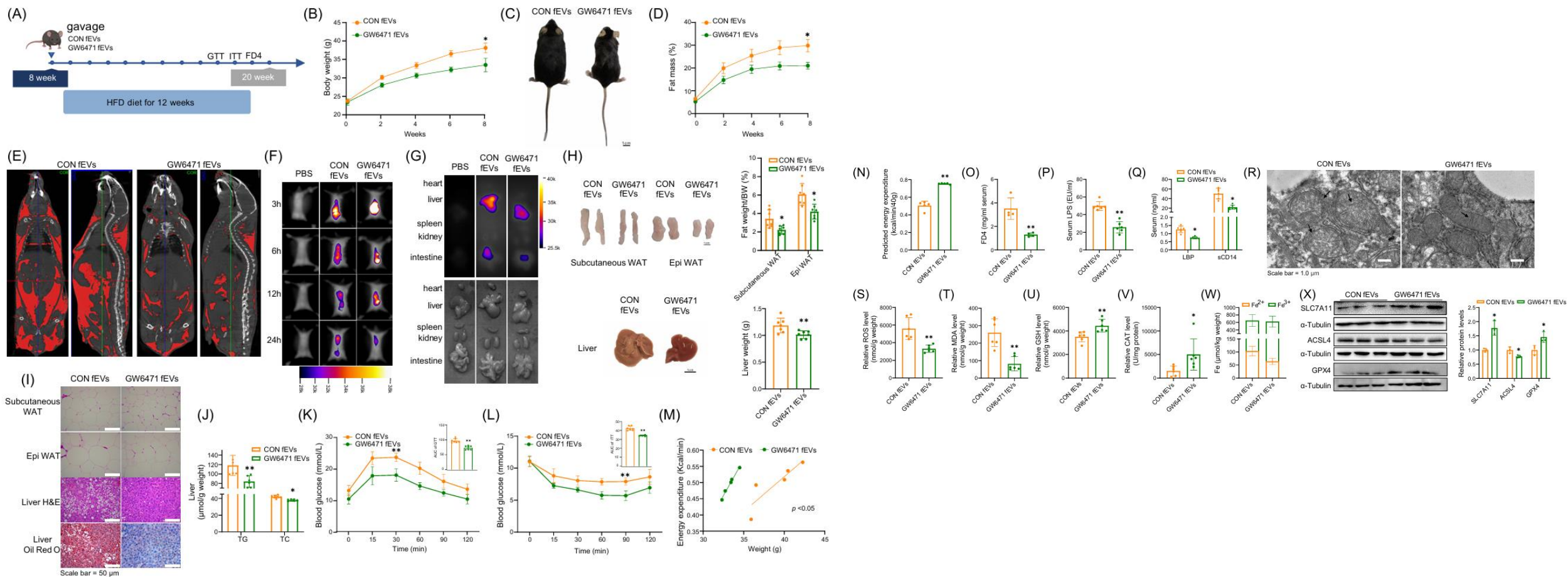


Figure 5. Gut Microbiota-Derived Extracellular Vesicles (fEVs) from GW6471-treated mice Improve Intestinal Permeability and Inhibit Ferroptosis

Lipids in fEVs affect hepatic steatosis

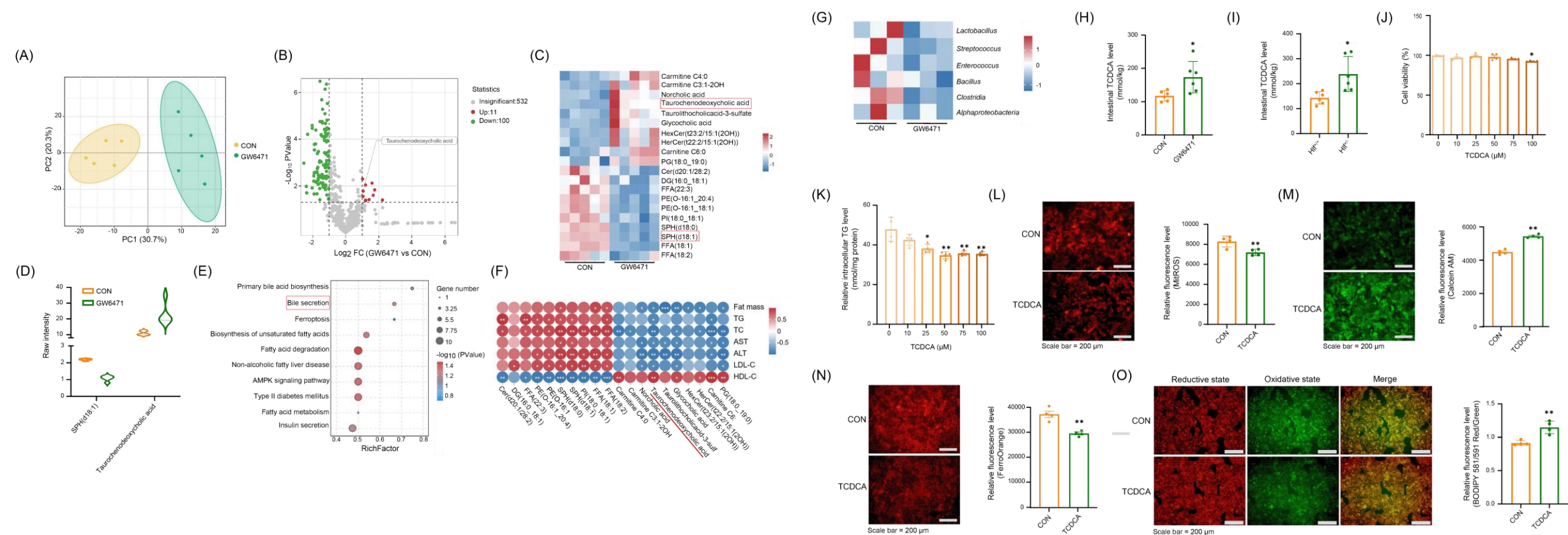


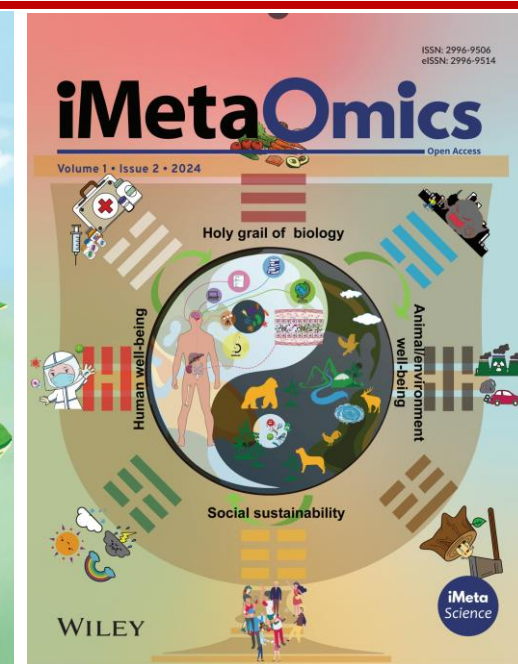
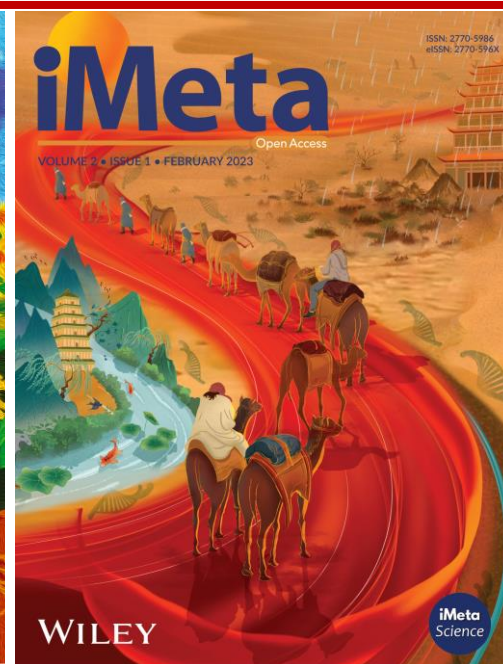
Figure 6. Lipid Alterations in Gut Microbiota-Derived Extracellular Vesicles (fEVs) Influence Hepatic Steatosis



Summary



- ❑ In this study, the HLF/PPAR α axis regulated the gut-liver cycle and hepatic ferroptosis via gut microbiota-derived EVs.
- ❑ The conjugated bile acid TCDCA was identified as the key mediator of the lipid-lowering activity of fEVs.
- ❑ These findings clarify the function of intestinal HLF in regulating MAFLD and offer new therapeutic perspectives for treating the disease.

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