

MIMERET, a Novel Mitochondrial-Targeted Drug, Improves Hepatic Steatosis by Stimulating Mitochondrial Fatty Acid Beta-Oxidation to Prevent Lipid Accumulation

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INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is a prevalent liver disease associated with metabolic syndrome, marked by hepatic steatosis, inflammation, and fibrosis. The disease poses significant health risks, including progression to cirrhosis and hepatocellular carcinoma. Resmetirom, recently approved by the FDA, has shown efficacy in MASH treatment but presents limitations, particularly in addressing weight management and fully ameliorating the metabolic profile. Given these limitations, novel therapeutic strategies that can comprehensively target MASH pathology are urgently needed. This study investigates the efficacy of MIMERET, a mitochondrial-targeted therapeutic, in an amylin diet-induced mouse model of MASH, assessing its impact on liver histology, function, inflammation, and body weight.

AIM

The study aimed to evaluate MIMERET's effectiveness in treating MASH by improving liver histology, function, and inflammation, while also examining its effects on weight management, adiposity, and distinct mechanisms through gene expression profiling.

METHOD

- Model and Groups:** Male C57BL/6J mice were fed a Gubra-Amylin NASH (GAN) diet for 41 weeks, with drug treatment administered during the final 8 weeks. Mice were divided into five groups: vehicle, Resmetirom, MIMERET 4 mg/kg, MIMERET 8 mg/kg, and a normal chow diet control group.
- Treatment:** Drugs were administered orally once daily during the 8-week treatment period.
- Assessments:** Liver histology, function, serum lipids, inflammatory cytokines, body weight, and fat mass were analyzed. RNA sequencing identified MIMERET-related gene expression profiles.

RESULTS

Figure 1. MIMERET ameliorates hepatic function in GAN diet-induced obese mice.

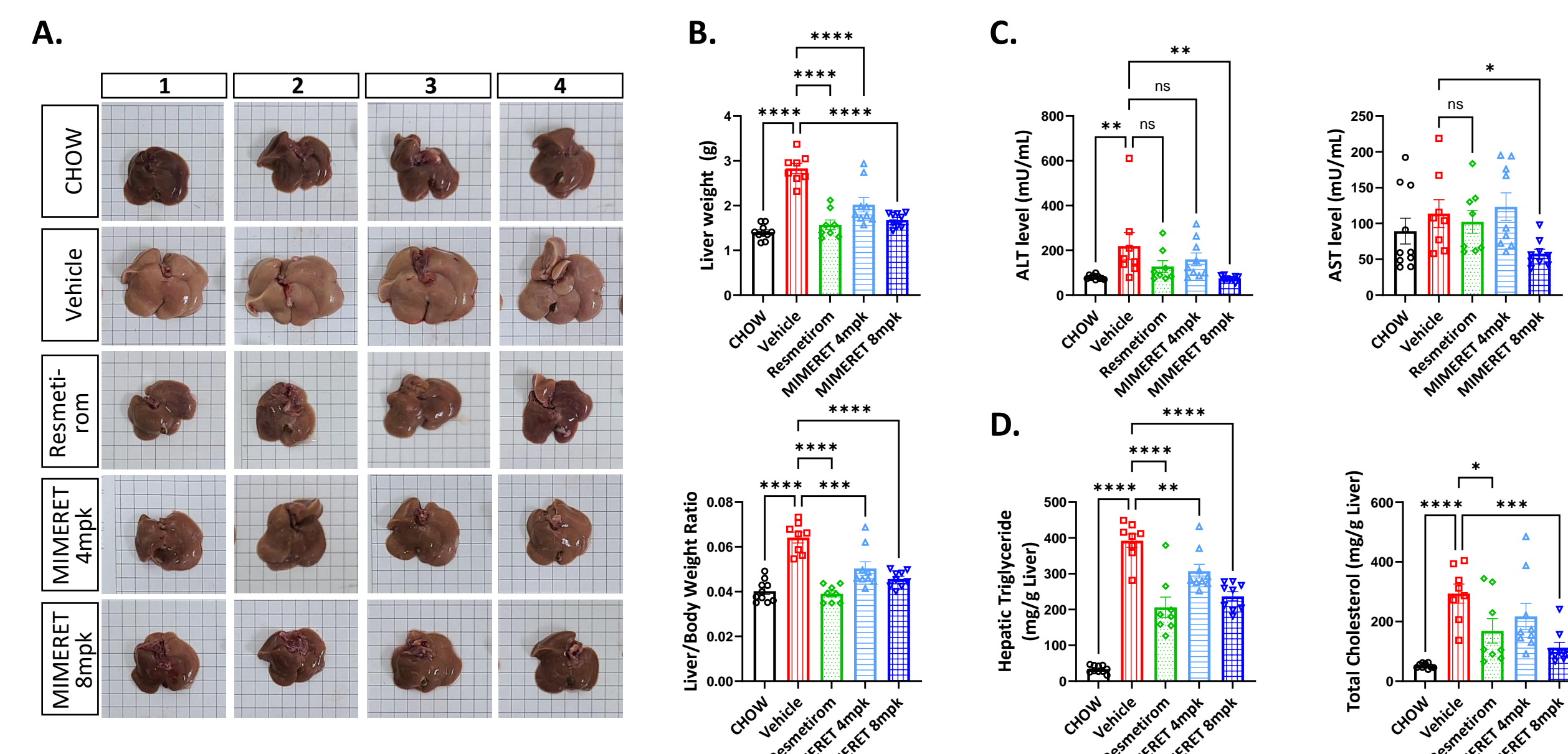


Figure 2. MIMERET Improves Liver Histopathological Hallmarks in GAN Diet-Induced Obese Mice.

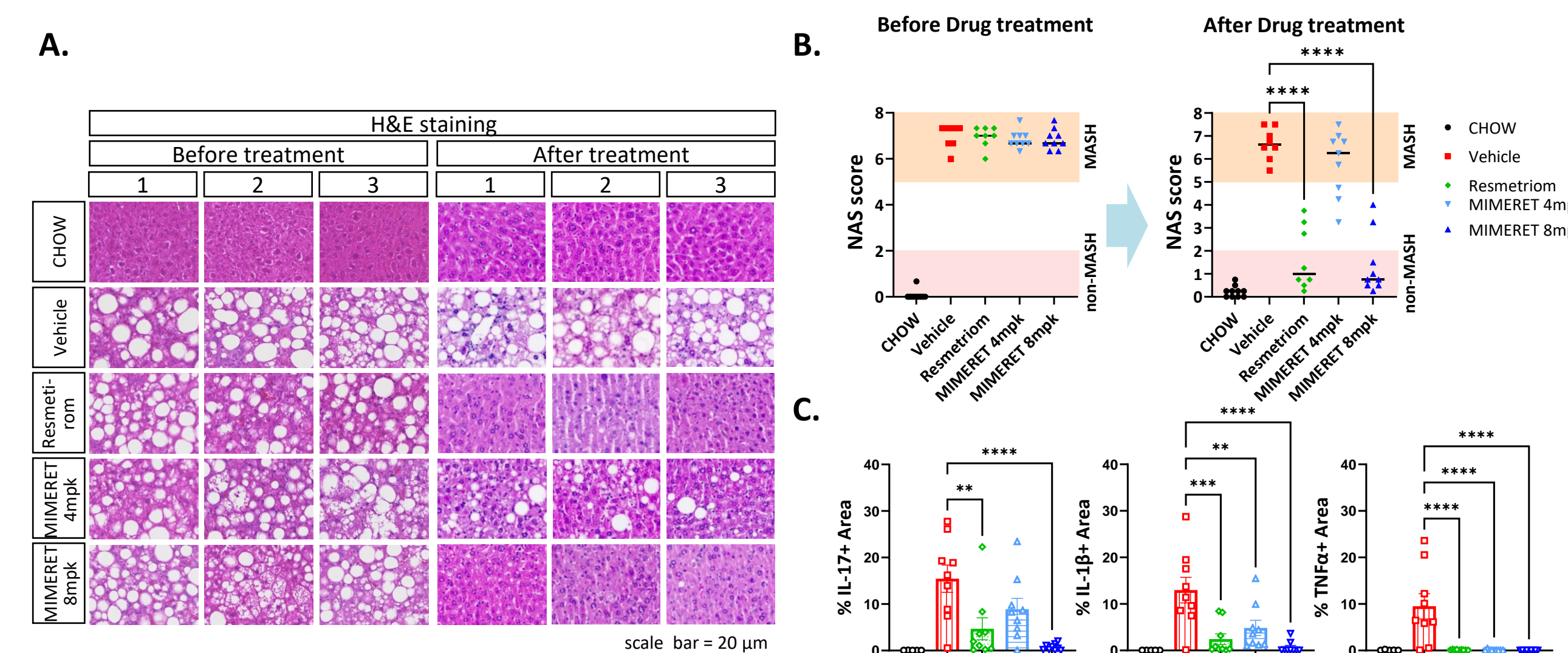


Figure 3. MIMERET effectively inhibited hepatic fibrosis in GAN diet-induced obese mice.

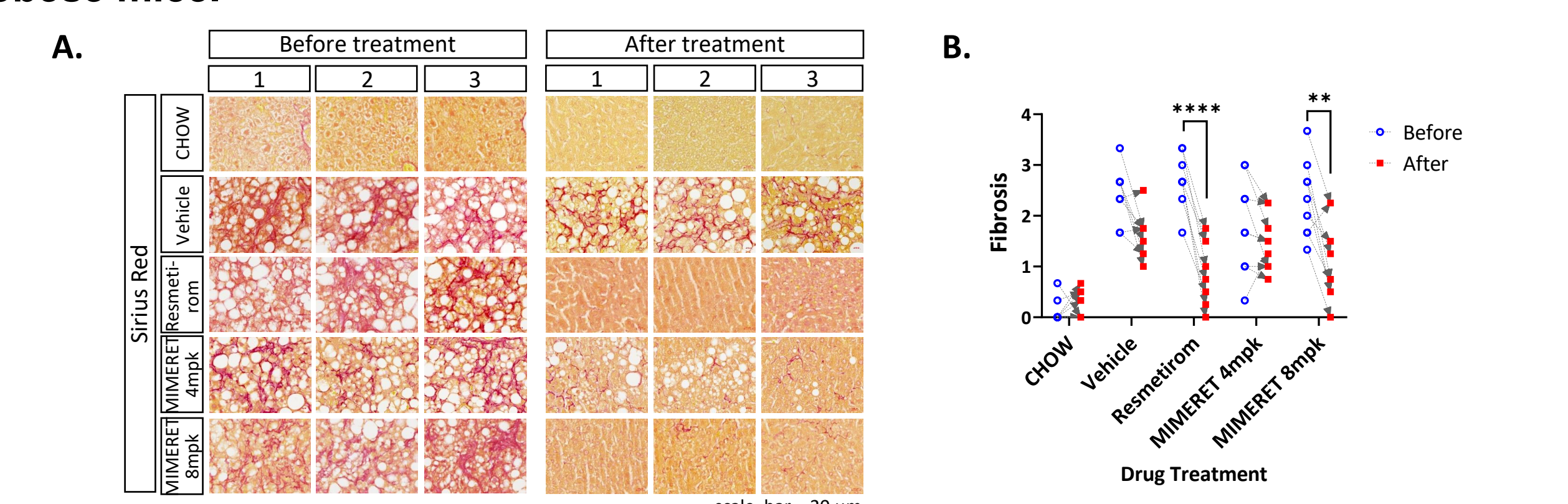


Figure 3

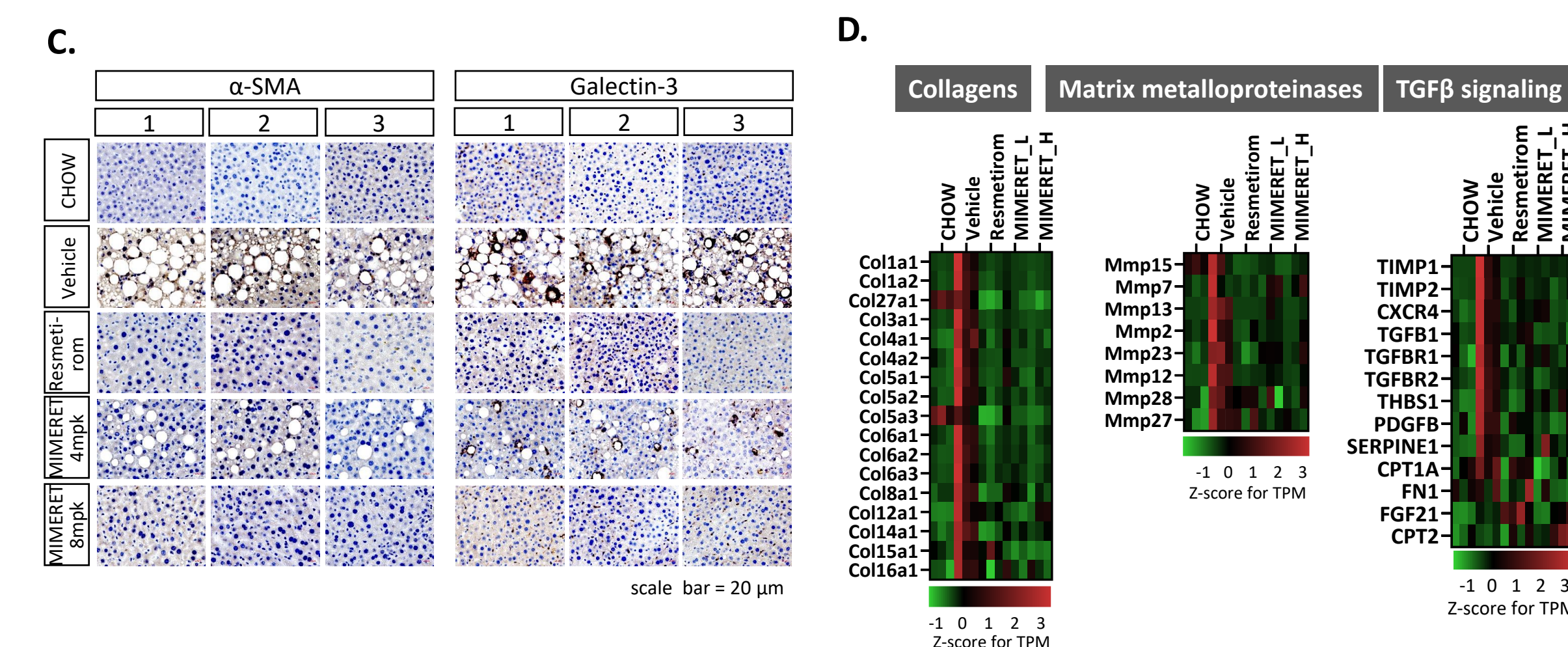


Figure 4. MIMERET Induced Reductions in Both Body Weight and Adipocyte Size in GAN Diet-Induced Obese Mice.

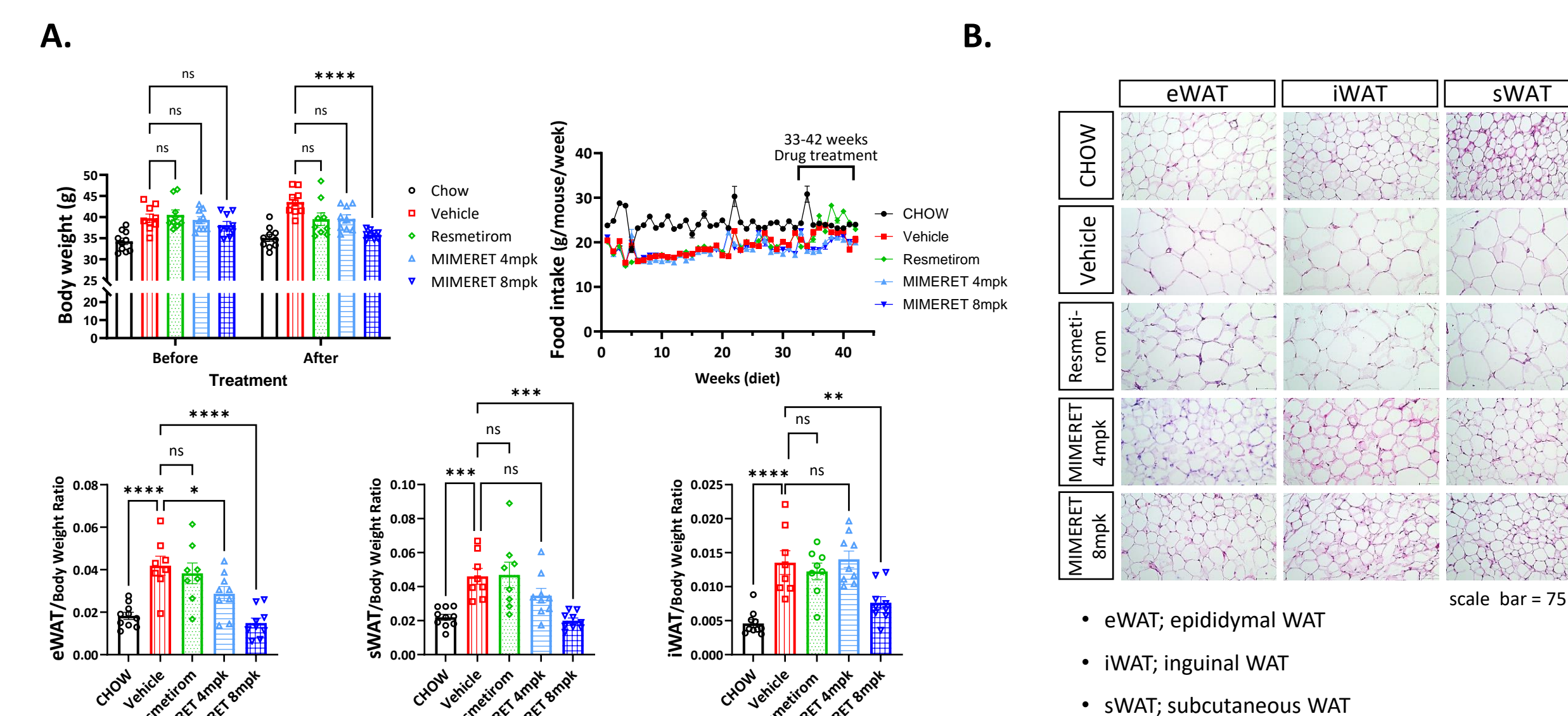
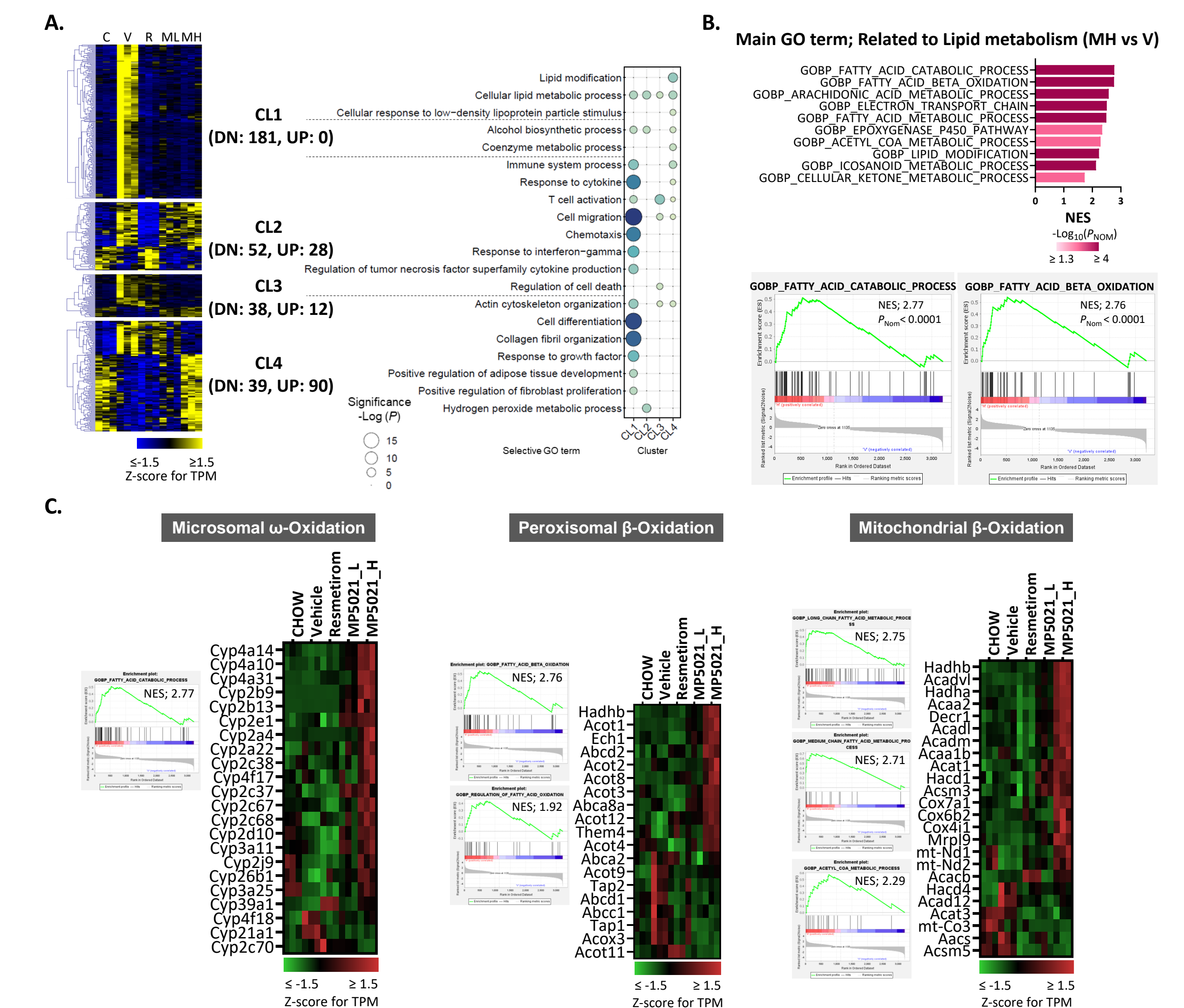
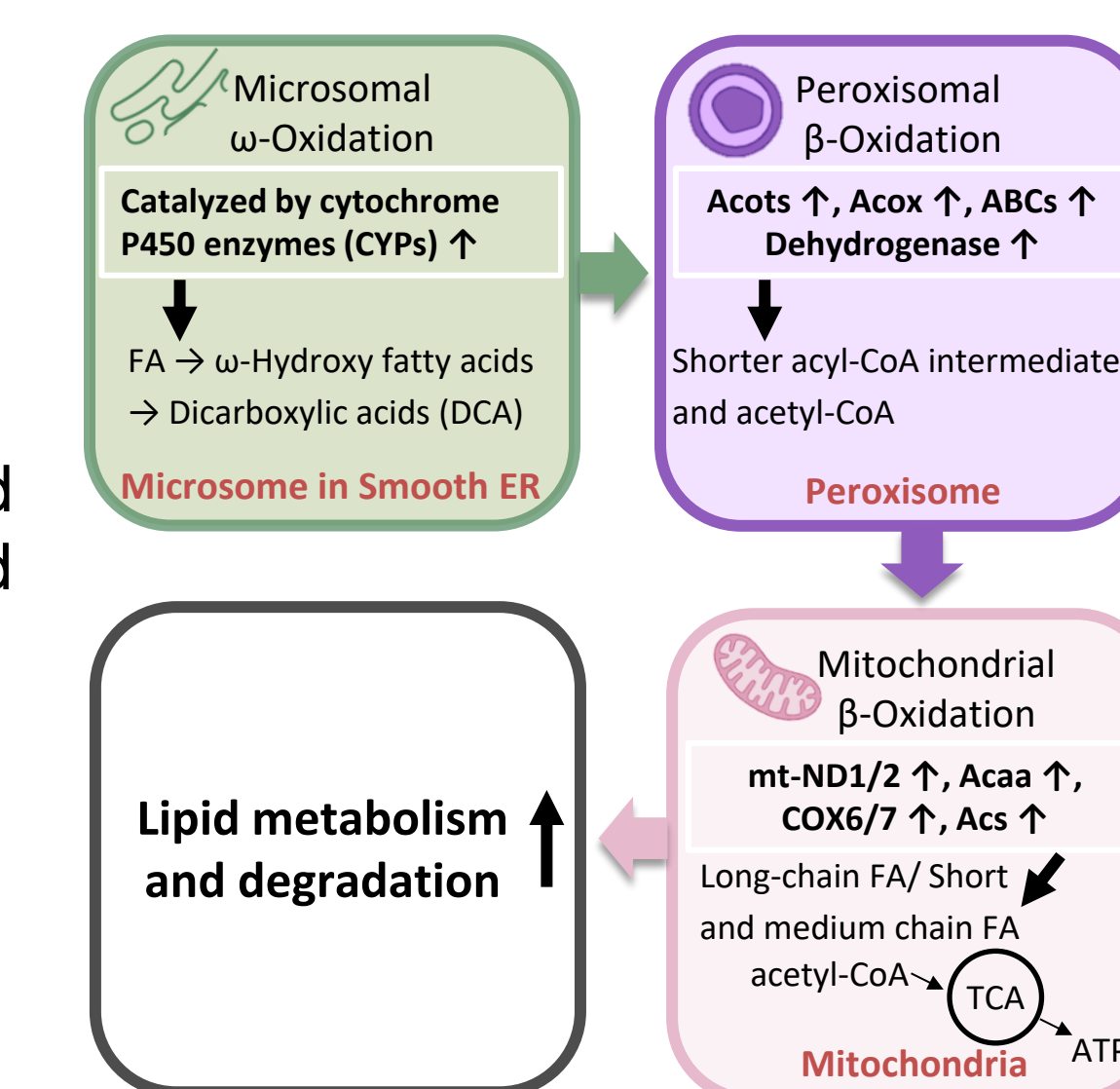


Figure 5. mRNA sequencing was performed to analyze the MASH-related MIMERET transcriptomic signature.



SUMMARY

- Significantly improved liver histopathology, NAS score and fibrosis grade in MASH.
- Enhanced liver function and reduced pro-inflammatory cytokines.
- Decreased hepatic steatosis and promoted weight loss by upregulating genes involved in microsomal, peroxisomal, and mitochondrial fatty acid oxidation.
- Demonstrated a distinct gene expression profile with strong enrichment in lipid metabolism pathways.



CONCLUSIONS

- MIMERET effectively regulates metabolic balance, offering dual benefits for MASH and obesity treatment without notable adverse events.
- MIMERET's unique gene expression profile and promotion of mitochondrial fatty acid beta-oxidation position it as a promising alternative to current MASH treatments, with added metabolic health advantages.

REFERENCES

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