DA-1241, a GPR119 agonist, ameliorates fatty liver through the upregulation of TFEB-mediated autophagy

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INTRODUCTION

- G protein-coupled receptor 119 (GPR119) has emerged as a novel therapeutic target for the treatment of dyslipidemia and type 2 diabetes mellitus (T2DM) and is mainly expressed in the liver.
- DA-1241, a novel GPR119 agonist, induces autophagy flux, resulting in the offset of hyperglycemia, and decreases the serum cholesterol and hepatic triglyceride (TG) levels in HFD-fed mice.
- Transcription factors EB (TFEB) is a master regulator of basic cellular processes such as lysosomal biogenesis and autophagy.

METERIALS and METHODS

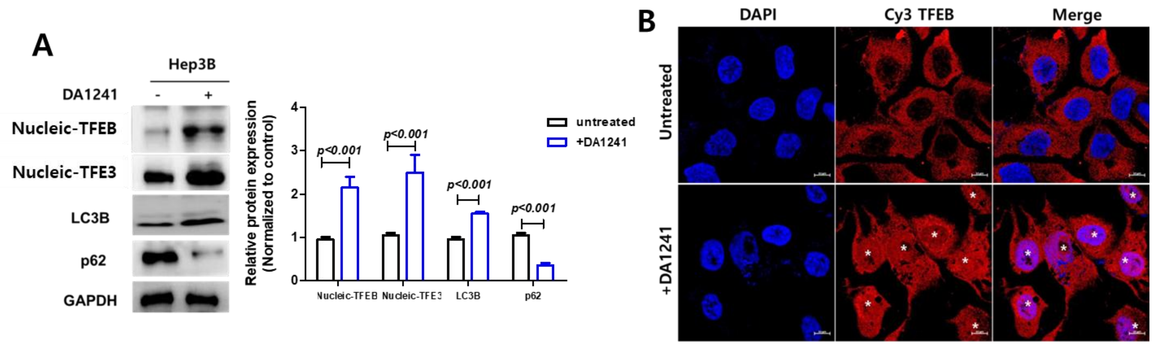
- Human Hep3B, *tfeb* WT, and *tfeb* KO HeLa cells treated with 100uM DA-1241were used to evaluate the role of TFEB/autophagy on fatty liver.
- To in duces fatty liver, C57BL/6J- and liver-specific *Tfeb* KO-mice fed with normal chow diet (ND) or high fat diet (HFD, 60% fat) for 9weeks. After 9weeks, ND or HFD fed mice treated with or without DA-1241 for 4 weeks.
- The effects of DA-1241 on the hepatic fat content, metabolism, and autophagy functional dependence of TFEB were investigated.

AIMS

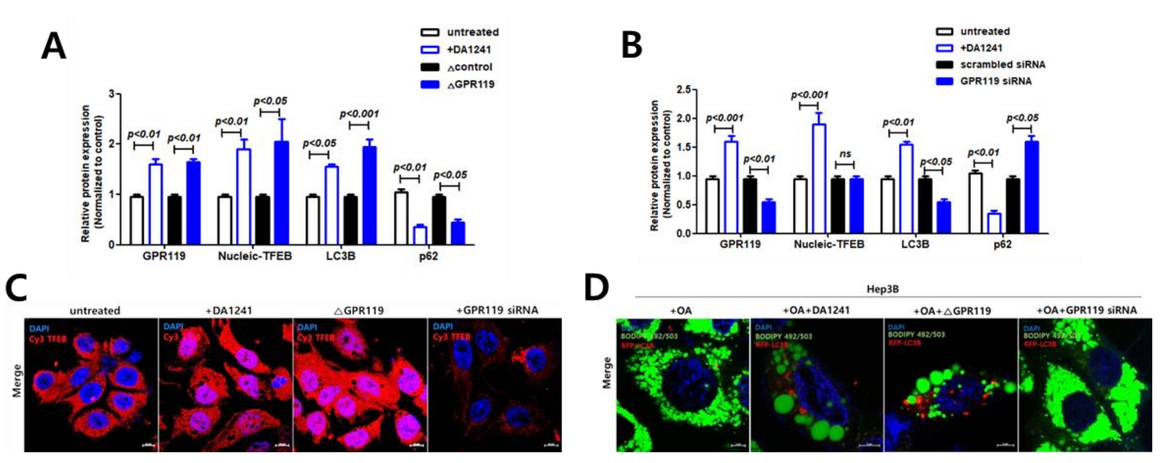
We investigate whether DA-1241 ameliorates NAFLD by regulating TFEB and autophagy.

RESULTS

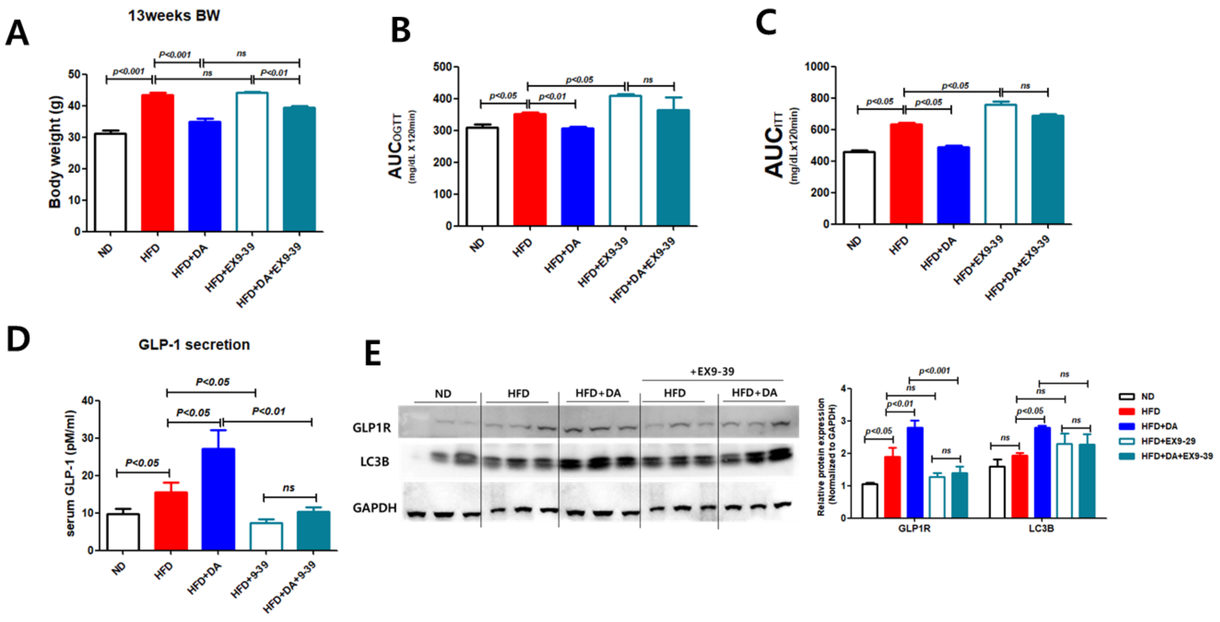
1. DA-1241 induces autophagy and TFEB and TFE3 nuclear translocation



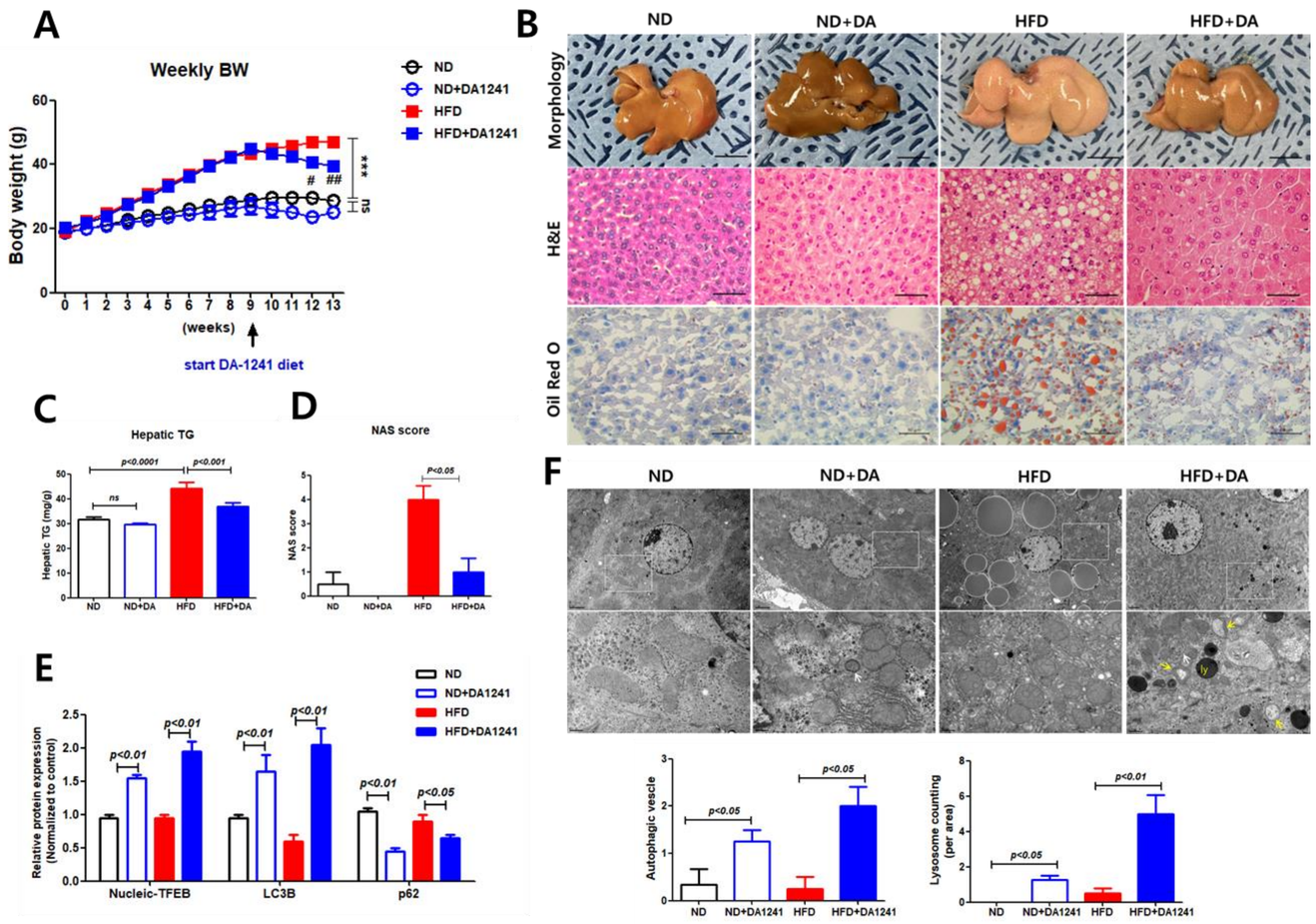
2. DA-1241 induces the expression of genes associated with autophagy and ameliorates fat accumulation in hepatocytes in a GPR119-dependent manner.



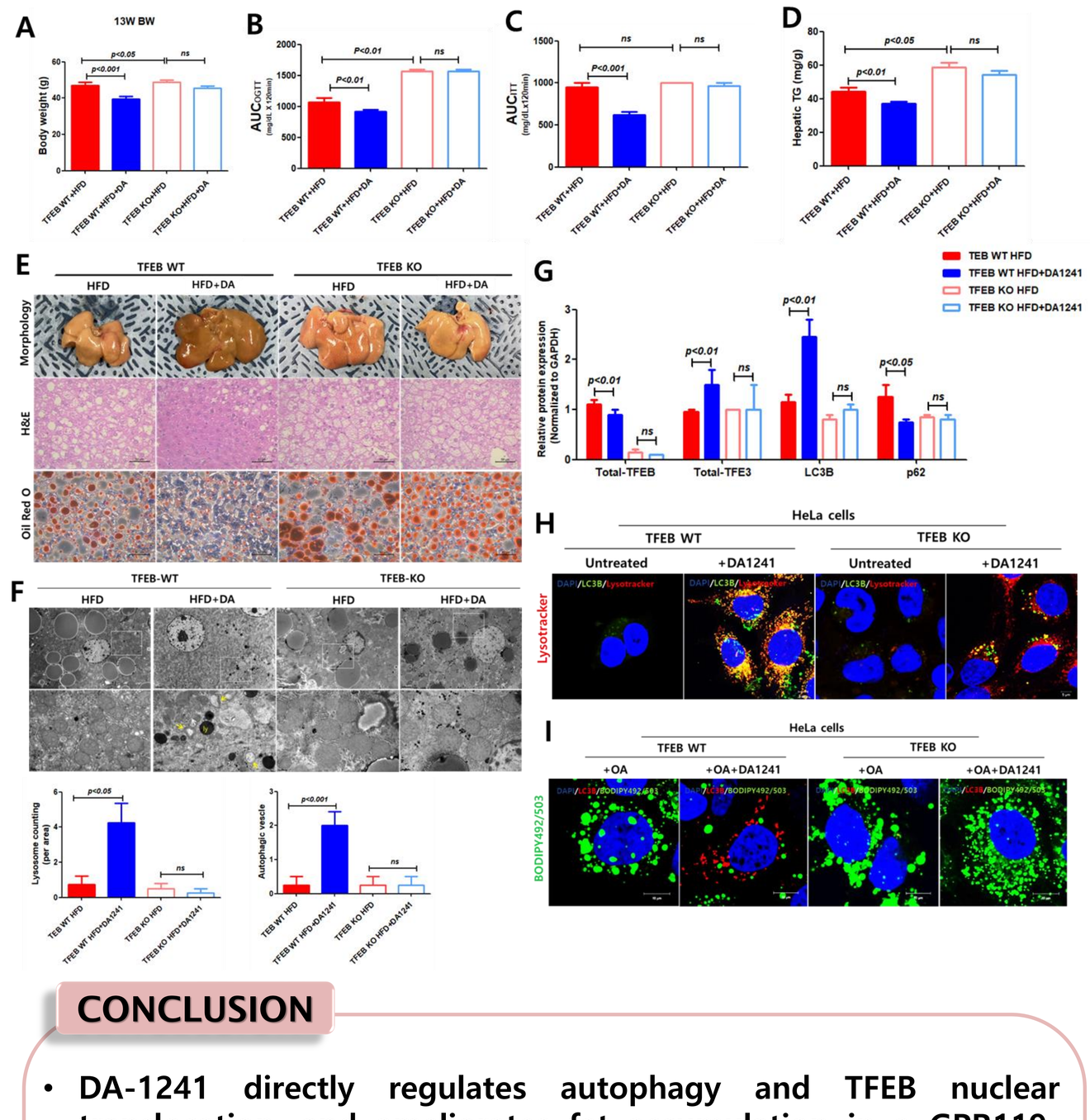
3. DA-1241 induces autophagy independent of GLP-1 secretion in HFD-fed mice.



3. DA-1241 attenuates hepatic steatosis and liver injury by induces TFEB-autophagy in HFD-fed mice



4. Knockout of TFEB offsets the effects of DA-1241 on fatty liver attenuation and autophagy induction



CONCLUSION

- DA-1241 directly regulates autophagy and TFEB nuclear translocation, and ameliorates fat accumulation in a GPR119-dependent manner.
- DA-1241 alleviates fatty liver disease by regulating autophagy and lysosomal biogenesis independently of GLP-1 secretion.
- DA-1241 may be a major regulator of the reduction in hepatic steatosis via the upregulation of TFEB-mediated autophagy in NAFLD.

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