The E3 ubiquitin ligase MDM2 acts as a key determinant of hepatic VLDL-triglycerides and ketone body production in obesity.

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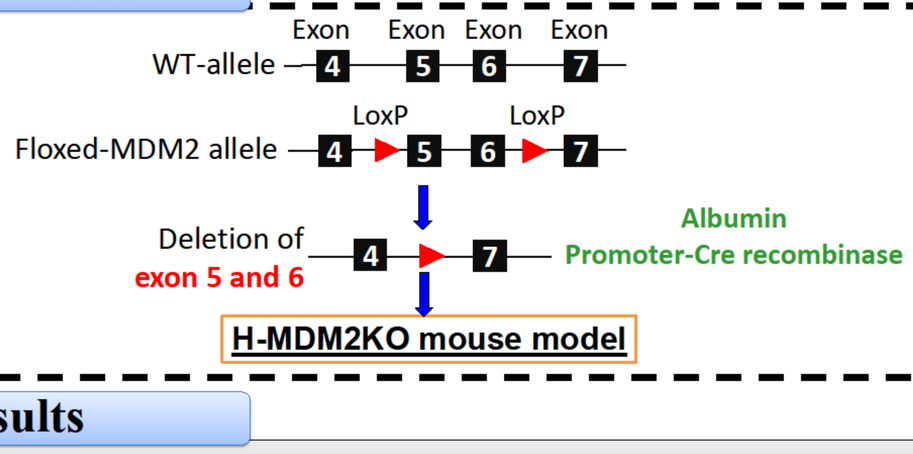
Introduction

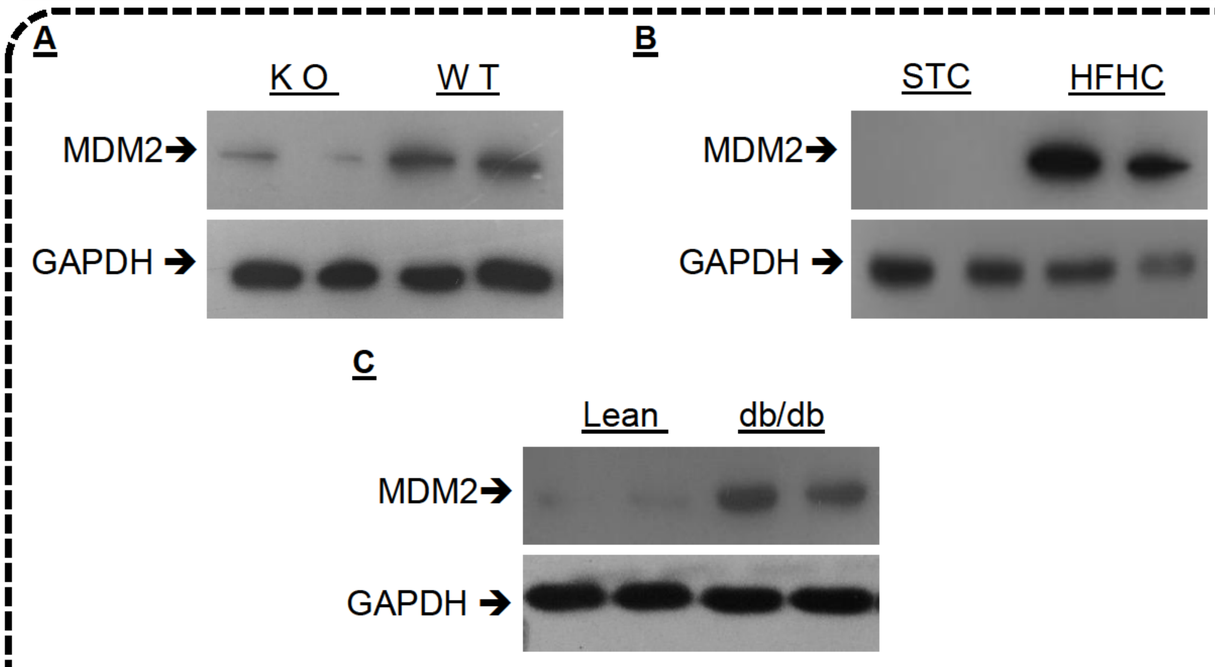
Obesity is a major risk factor for the development of hyperlipidemia and its related cardiovascular complications. Apart from its well-established role in cancer biology, the MDM2-p53 axis has been recently shown to regulate glucose and lipid metabolism. Our preliminary data indicated that MDM2 is dramatically induced in the liver of obese mice. In this study, we aimed to investigate the potential role of hepatic MDM2 in controlling systemic lipid homeostasis using a hepatocyte-specific MDM2 knockout (H-MDM2KO) mouse model.

Mouse Model



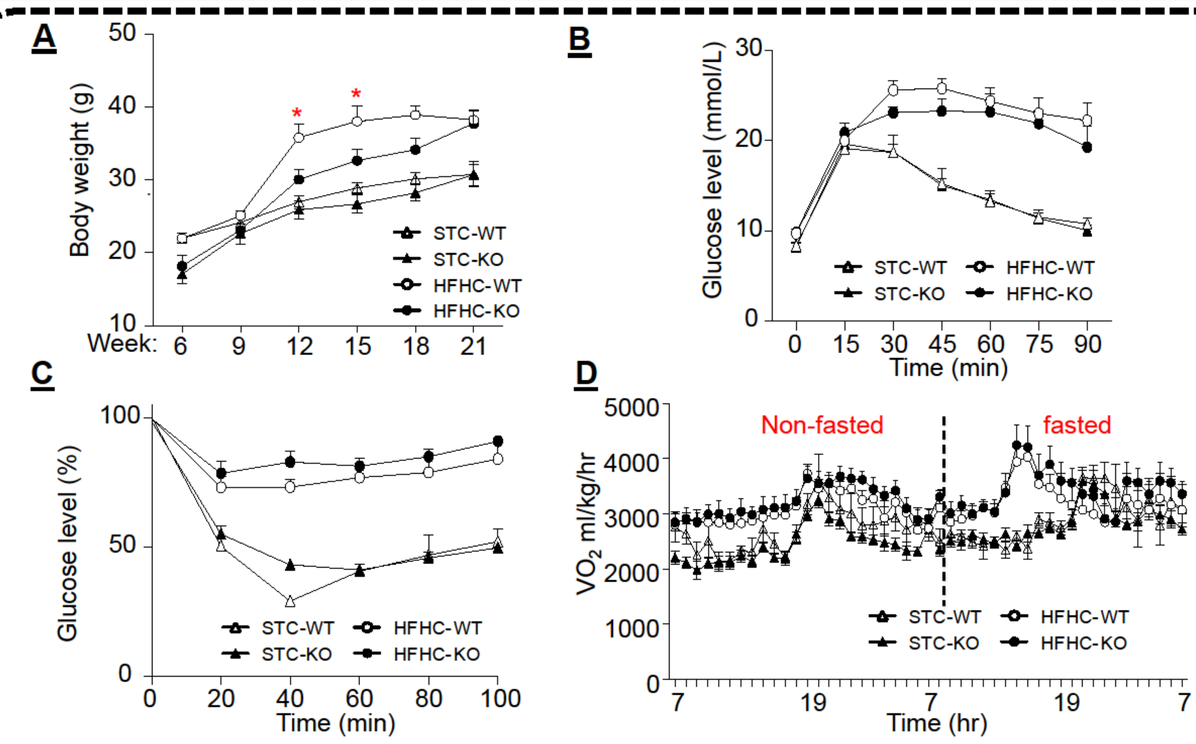
Results

Figure 1. MDM2 is induced in liver of obese mice.



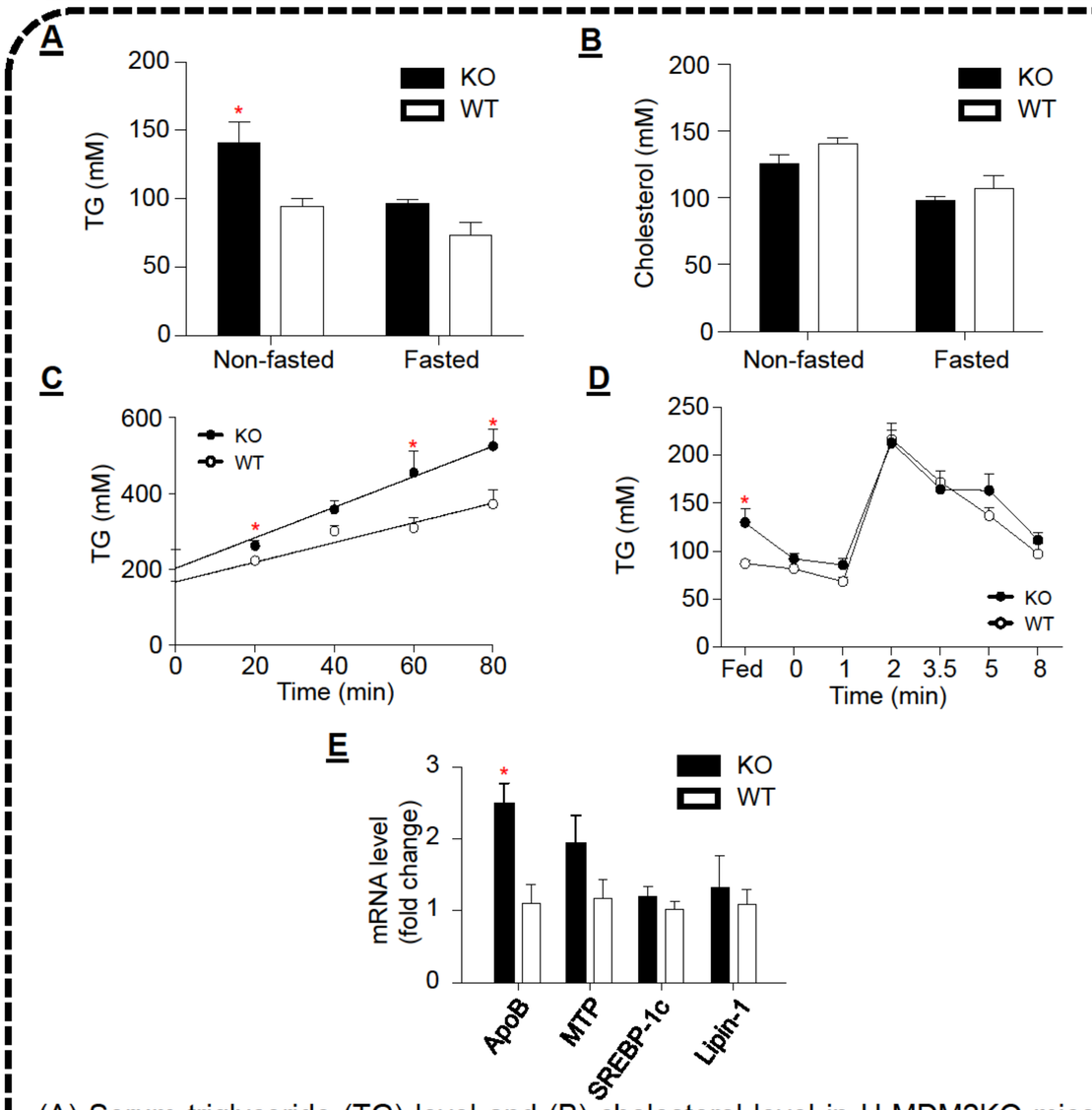
(A) Expression of MDM2 in liver of H-MDM2KO mice and its wild-type (WT) littermates, as determined by western blot analysis. (B) Expression of MDM2 in liver of WT mice fed with standard chow (STC) or high fat high cholesterol diet (HFHC), as determined by western blot analysis. (C) Expression of MDM2 in liver of lean mice and db/db obese mice, as determined by western blot analysis.

Figure 2. Genetic deletion of hepatic MDM2 has no impact on glucose and energy metabolism.



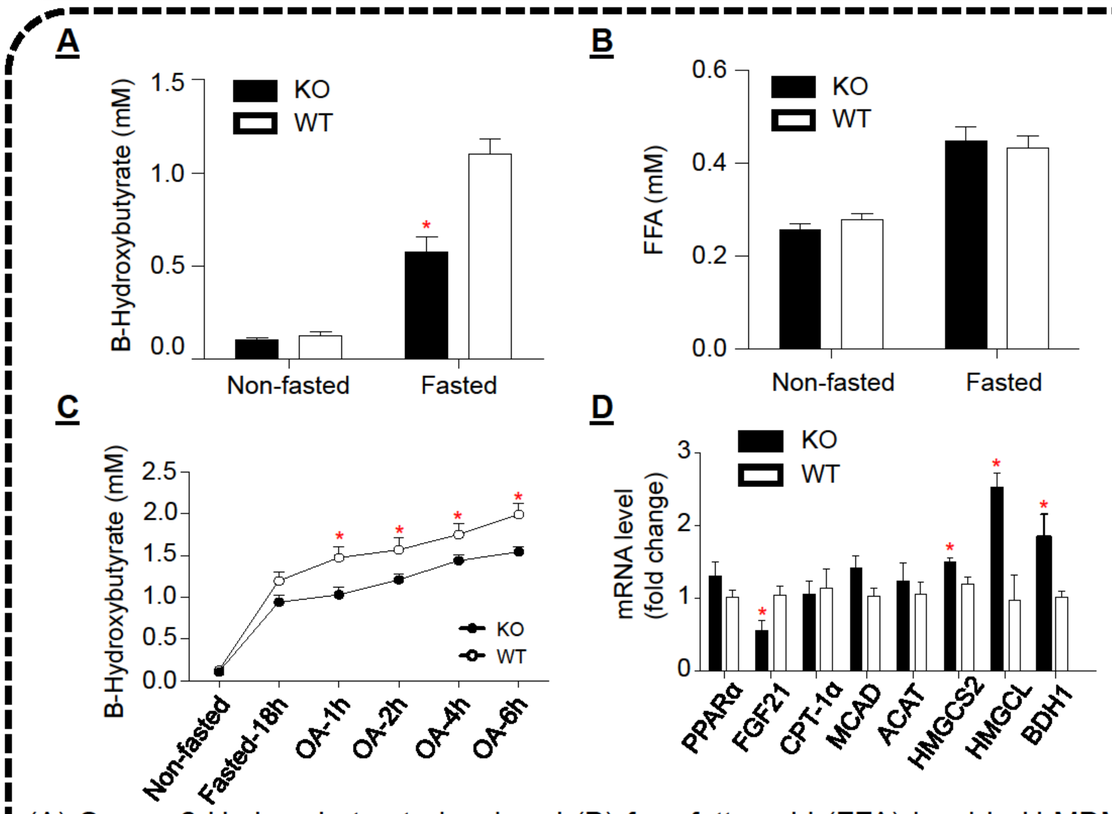
(A) Body weight of H-MDM2KO mice and its WT controls fed with STC or HFHC from week 6 to week 21. (B) Glucose tolerance test in mice fasted for 16 hours (2g/kg of glucose was intraperitoneally injected). (C) Insulin tolerance test in mice fasted for 6h and were intraperitoneally injected with insulin (0.75U/kg). (D) Oxygen consumption of H-MDM2KO mice and its WT controls subjected to metabolic cage assessment. (n=5) . *p<0.05

Figure 3. Hypertriglyceridemia of H-MDM2KO mice is caused by increased VLDL-TG secretion.



(A) Serum triglyceride (TG) level and (B) cholesterol level in H-MDM2KO mice and its WT controls fed with HFHC under non-fasted and 24h fasted condition. (n=5) (C) VLDL secretion assay of 22-week-old male H-MDM2KO mice and its WT littermates fed with HFHC. Mice were fasted for 18h, followed by i.v. injection of tyloxapol (inhibit Plasma VLDL clearance) at 500mg/kg, followed by measurement of serum TG by colorimetric assay. (D) Oral fat tolerance test of 24-week-old male H-MDM2KO mice and its WT littermates fed with HFHC. Mice were oral gavage with 500ul olive oil after 16h fasting and serum TG levels were measured by colorimetric assay at indicated time points. (n=9~12) (E) QPCR analysis for mRNA level related to VLDL assembly in liver of H-MDM2KO mice and its WT littermates fed with HFHC. Data are expressed as fold change over expression level of WT controls. (n=5), *p<0.05.

Figure 4. H-MDM2KO mice exhibit impaired fasting-induced ketogenesis.



(A) Serum β-Hydroxybutyrate level and (B) free fatty acid (FFA) level in H-MDM2KO mice and its WT controls fed with HFHC under non-fasted and 24h fasted condition. (n=5) (C) H-MDM2KO mice and its WT controls fed with HFHC were i.p injected with octanoic acid (0.5g/kg) after 18h fasting, followed by the measurement of serum β-hydroxybutyrate at indicated time points. (n=9~12) (D) QPCR analysis for mRNA level related to fatty acid oxidation (FAO) and ketogenesis in liver of H-MDM2KO mice and its WT littermates. Data are expressed as fold change over expression level of WT controls. (n=5) . *p<0.05

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