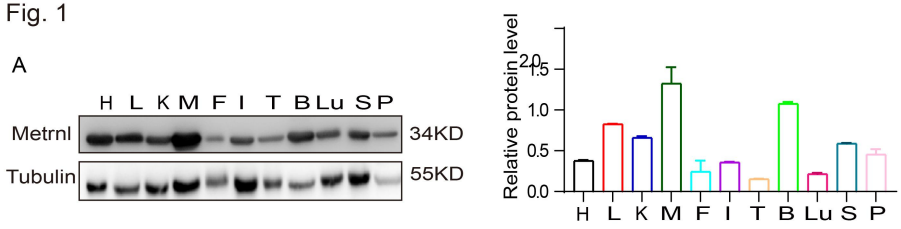
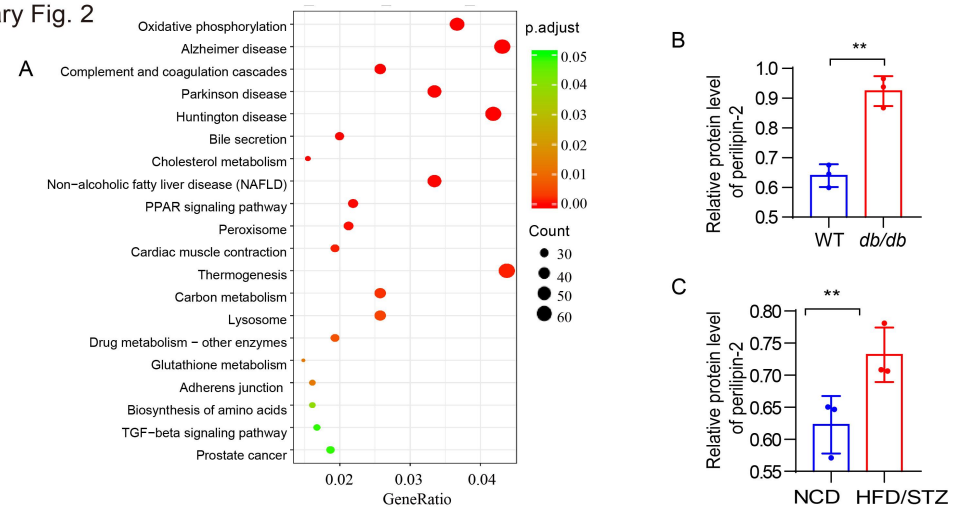
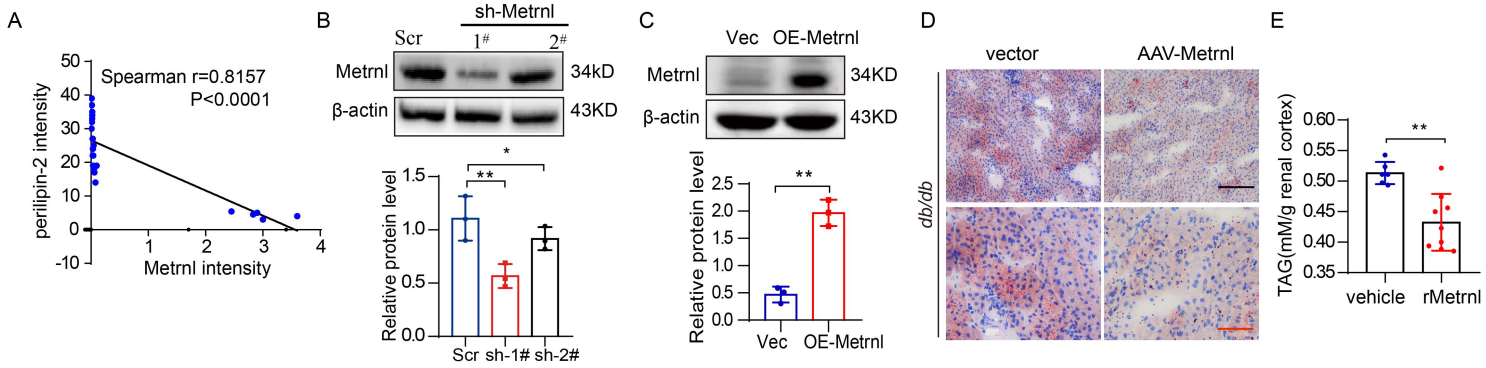
Supplementary Fig. 1



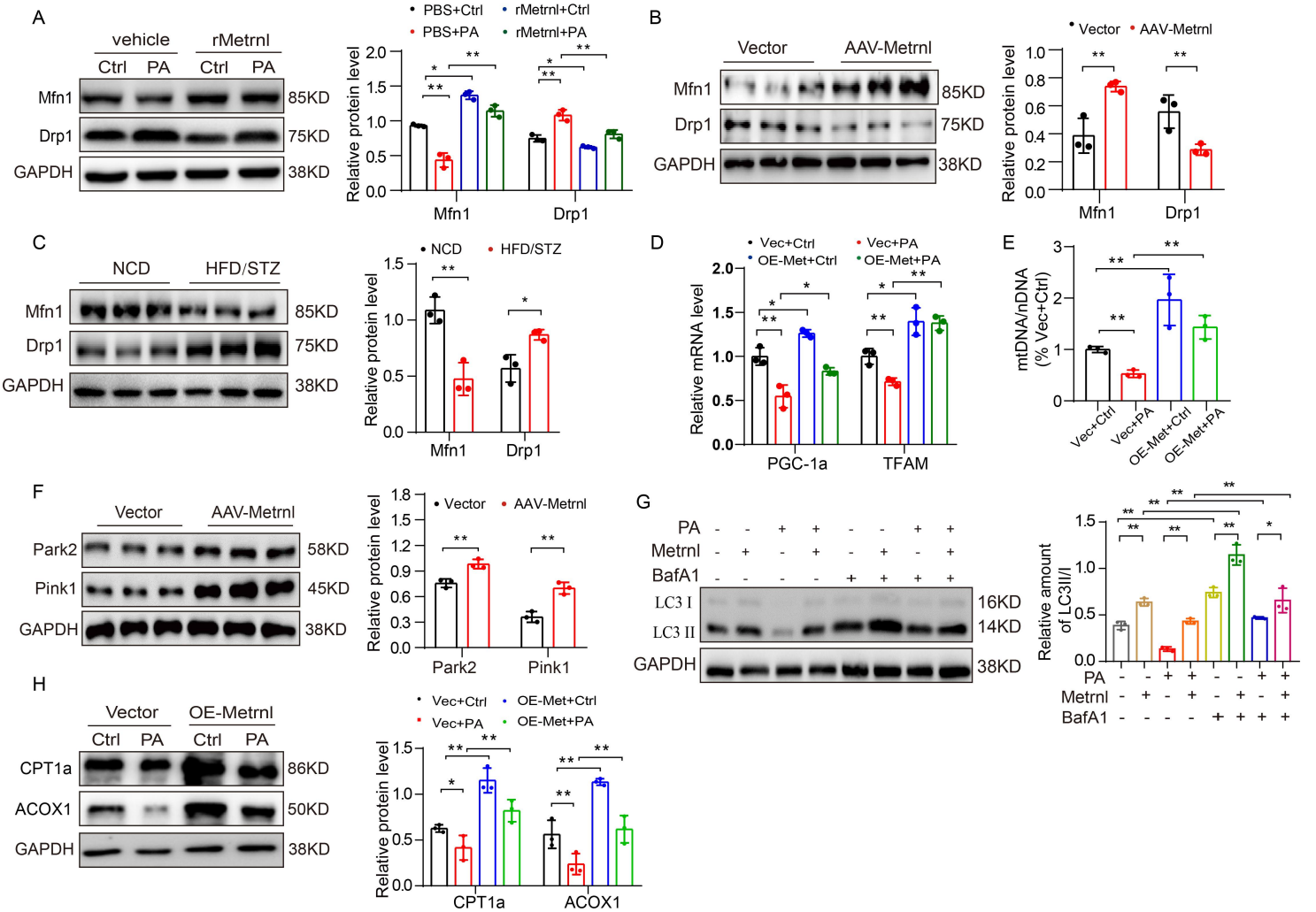
Supplementary Fig. 2



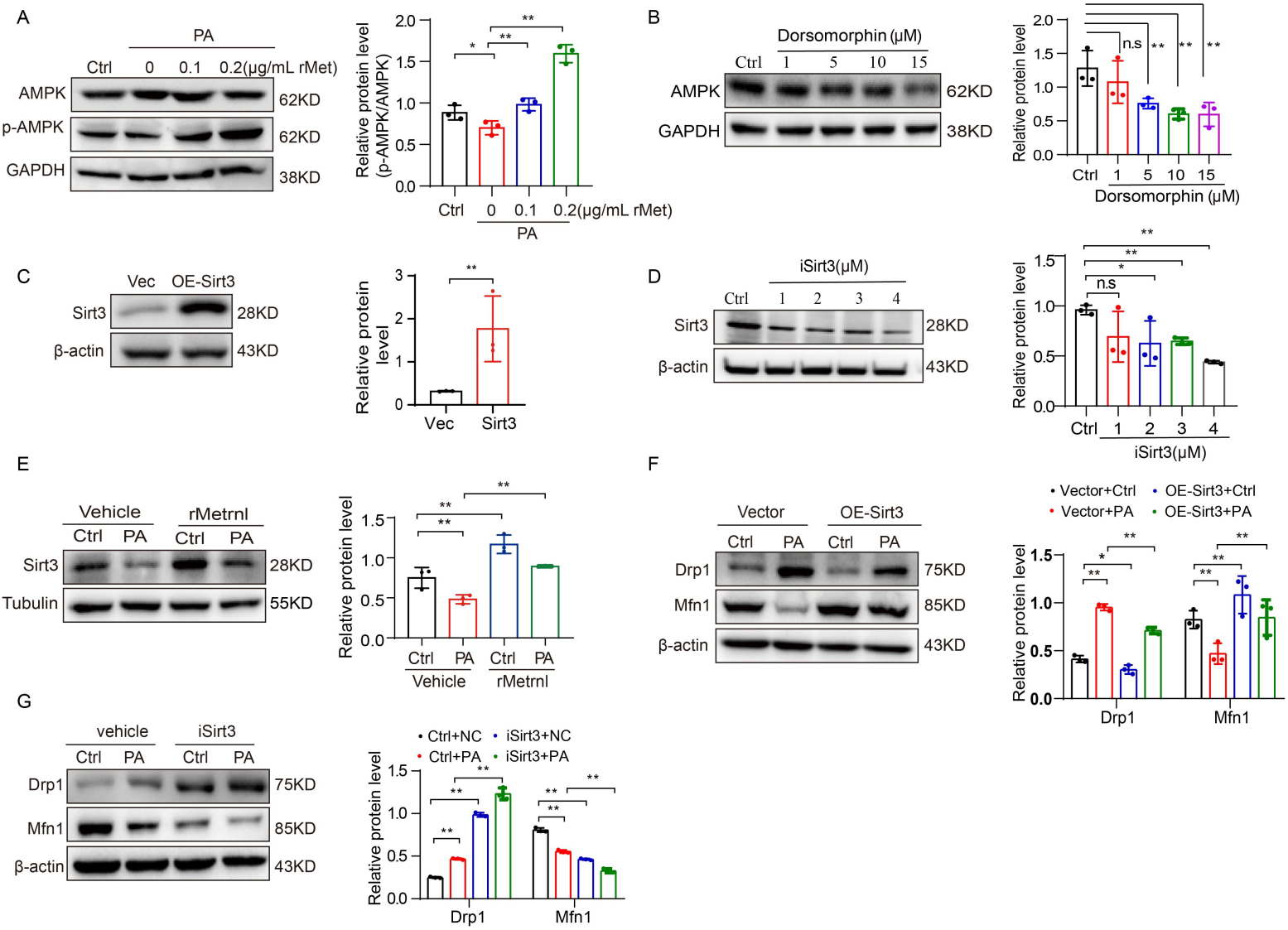
Supplementary Fig. 3



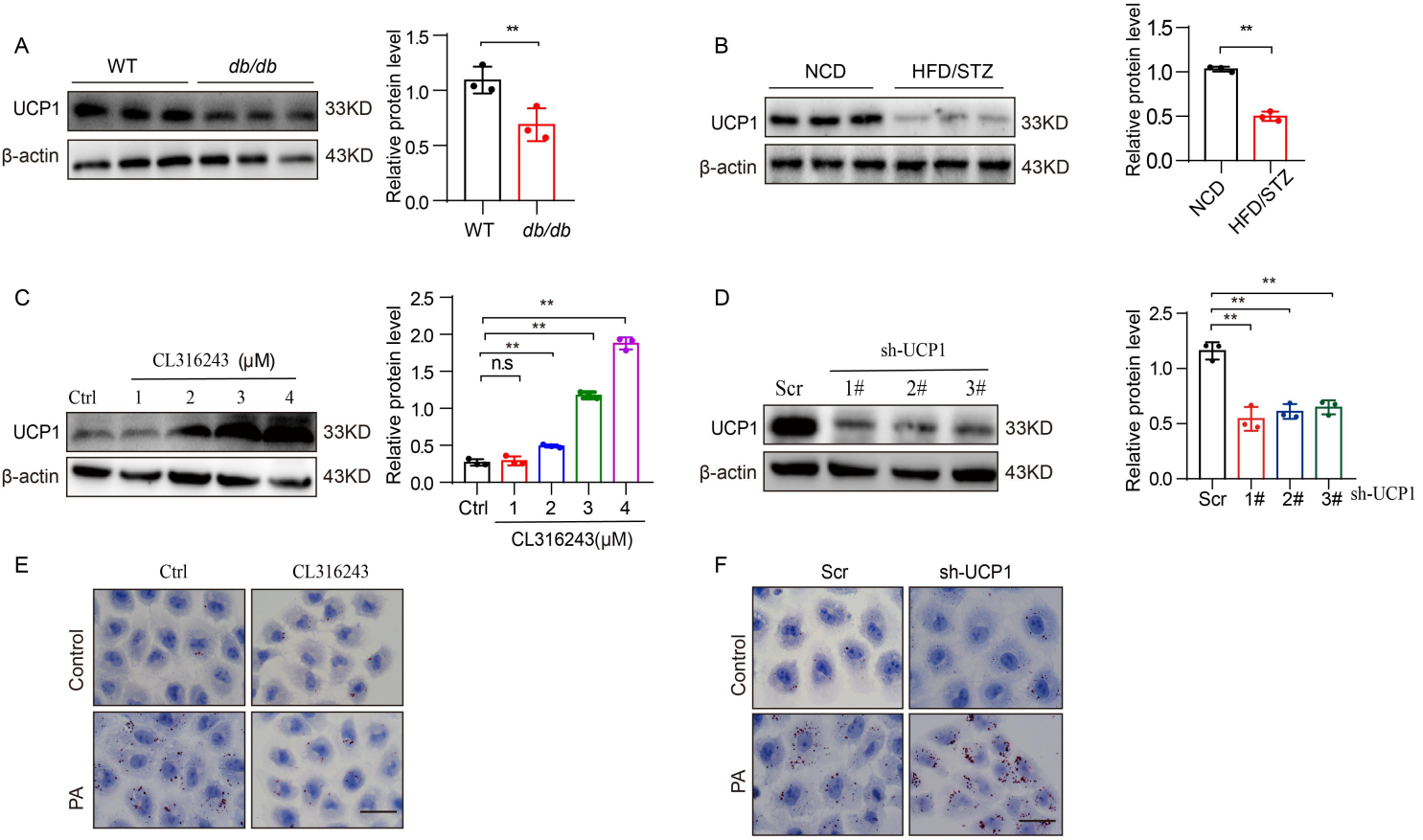
Supplementary Fig. 4



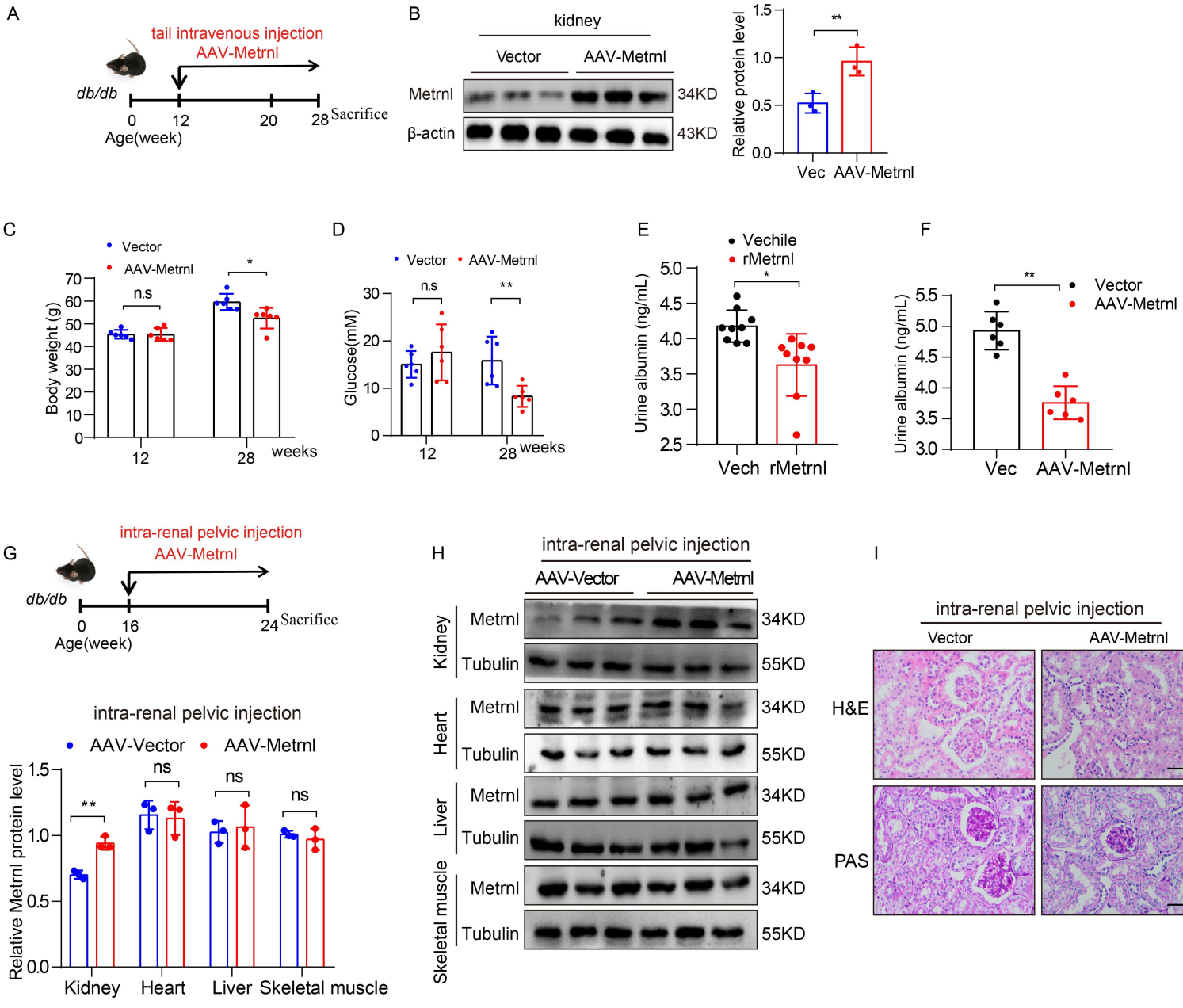
Supplementary Fig. 5



Supplementary Fig. 6



Supplementary Fig. 7



Supplementary Figure Legends

Supplementary Figure. 1

A. Representative Western blot and quantification of Metrnl expression in murine tissues including heart, liver, kidney, muscle, fat, intestine, testis, brain, lung, spleen and pancreas (n=3 blots).

Supplementary Figure. 2

A. Functional enrichment analyses using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways based on RNA-seq data.

B-C. Quantification of perilipin-2 expression for Fig 2H in the renal cortex from *db/db* mice (B) and STZ/HFD-induced diabetic mice (C), compared with control mice (n=3 blots).

Data are mean ± SD. *p < 0.05, **p < 0.01.

Supplementary Figure. 3

A. Correlation between Metrnl expression (Fig.1B) and perilipin-2 expression (Fig.2K) in human renal cortical tissues from DKD patients and compared with normal kidney poles in all subjects (n=23).

B. Gene silencing efficiency of Metrnl by western blot analysis in Metrnl knockdown (shRNA-1$^{\#}$ and shRNA-2$^{\#}$) stable NRK-52E cells with lentivirus-mediated, compared with transfected scramble (Scr). shRNA-1$^{\#}$ was selected to establish stable cells for subsequent experiments (n=3 blots).

C. Representative Western blot and quantification of Metrnl for gene overexpression efficiency by western blot analysis in Metrnl overexpression stable NRK-52E cells with lentivirus-mediated (n=3 blots).

D. Representative images of Oil Red O staining of kidney in AAV-Metrnl overexpressing *db/db* mice. Scale bar: black 50μm, red 20μm

E. Triglyceride (TAG) levels in renal cortex of *db/db* mice after rMetrnl treatment (vehicle, n=6 and rMetrnl n=9) by assay kits.

Data are mean ± SD. *p < 0.05, **p < 0.01.

Supplementary Figure. 4

A. Representative Western blot and quantification images of the mitochondrial fission machinery dynamin 1 like protein (Drp1) and mitofusins (Mfn1) expression in rMetrnl treatment NRK-52E cells (n=3 blots).

B. Representative Western blot and quantification of Drp1 and Mfn1 expression in renal tissue of AAV-Metrnl overexpressing *db/db* mice (n=3 per group).

C. Representative Western blot and quantification of Mfn1 and Drp1 expression in renal tissue of HFD/STZ mice (n=3 per group).

D. The mRNA level of PGC-1α and TFAM in Metrnl-overexpressing RTEC cells exposed to PA or not (n=3 per group).

E. Relative mitochondrial DNA content (mtDNA/nDNA; COX2/β-actin) in Metrnl-overexpressing RTEC cells exposed to PA or not. The results were normalized to the ratio of mtDNA:nDNA of control-treated RTEC cells with vector transfection (n=3 per group).
F. Representative Western blot and quantification of Park2 and Pink1 expression in renal tissue of AAV-Metrnl overexpressing *db/db* mice (n=3 per group).
G. Representative Western blot and quantification of LC3 II/I expression in NRK-52E cells after rMetrnl treatment under autophagolysosome inhibitor Bafilomycin (BafA1, 50nM) stimulation for 48 hours (n=3 blots).
H. Representative Western blot and quantification of CPT1a and ACOX1 expression in Metrnl-overexpression NRK-52E cells with PA cultured for 48 hours (n=3 blots).
Data are mean ± SD. *p < 0.05, **p < 0.01.

Supplementary Figure. 5
A. Representative Western blot and quantification (p-AMPK/AMPK) of the protein levels of AMPK and AMPK phosphorylation (p-AMPK) in NRK-52E cells stimulated with PA while treated by rMetrnl (0, 0.1, 0.2 μg/mL) for 48 hours (n=3 blots).
B. Representative Western blot and quantification of the protein levels of AMPK in NRK-52E cells with AMPK inhibitor (Dorsomorphin, 1,5,10,15μM) treatment for 48 hours (n=3 blots).
C. Representative Western blot and quantification of Sirt3 for gene overexpression efficiency by western blot analysis in Sirt3 overexpression stable NRK-52E cells with lentivirus (OE-Sirt3) (n=3 blots).
D. Representative Western blot and quantification of Sirt3 expression in NRK-52E cells with Sirt3 inhibitor (3-TYP, 1, 2, 3, 4 μM) for 48 hours (n=3 blots).
E. Representative Western blot and quantification of Sirt3 expression in NRK-52E cells with rMetrnl treatment under PA for 48 hours (n=3 blots).
F-G. Representative Western blot and quantification of the protein levels of the Drp1 and Mfn1 in OE-Sirt3 (F) and Sirt3 inhibitor (3-TYP, 2μM) (G) treated NRK-52E cells under PA stimulation for 48 hours (n = 3 blots).
Data are mean ± SD. *p < 0.05, **p < 0.01.

Supplementary Figure. 6
A-B. Representative Western blot and quantification of UCP1 expression in the kidney of *db/db* mice (A) or HFD/STZ mice (B) (n=3 blots).
C. Representative Western blot and quantification of the protein levels of UCP1 in NRK-52E cells with UCP1 agonist (CL316243, 1,2,3,4μM) treatment for 48 hours (n =3 blots).
D. Gene silencing efficiency of UCP1 by western blot analysis in sh-Metrnl ($1^{\#}$, $2^{\#}$, $3^{\#}$) stable NRK-52E cells with lentivirus, and Scramble (Scr) as control (n = 3). shRNA-$1^{\#}$ was selected to establish stable cells for subsequent experiments (sh-UCP1) (n=3 blots).
E-F. Representative images of Oil Red O staining in UCP1 agonist treatment (CL316243, 2μM) (E) or UCP1 knockdown (sh-UCP1) (F) NRK-52E cells for 48

hours in different groups. Scale bar, 20μm.

Data are mean ± SD. *p < 0.05, **p < 0.01.

Supplementary Figure. 7

A. Beginning at 12 weeks of age, male *db/db* mice were followed by tail intravenous injection of Metrnl over-expressing adeno-associated virus (AAV-Metrnl) or AAV-vector for one time, and continue feeding to 28 weeks to sacrifice.

B. Representative Western blot and quantification of Metrnl expression in kidney of *db/db* mice conducted with AAV-Metrnl or AAV-vector adeno-associated virus (n=3 blots).

C-D. The body weight gains (C) and plasma glucose (D) at 12 and 28weeks of mice conducted with AAV-Metrnl virus (AAV-vector n=6; AAV-Metrnl n=6).

E-F. Urine albumin levels of mice after rMetrnl treatment (vehicle, n=9 and rMetrnl, n=9) (E) or overexpressing AAV-Metrnl virus (AAV-vector n=6, AAV-Metrnl n=6) (F).

G. 16-week-old male *db/db* mice were conducted with renal pelvic injection AAV-Metrnl or AAV-Vector virus, and feed to 24 weeks to sacrifice.

H. Representative Western blot and quantification of Metrnl expression in kidney, heart, liver and skeletal muscle tissue of *db/db* mice conducted with renal pelvic injection AAV-Metrnl virus (n=3 blots).

I. Representative H&E and PAS staining images in *db/db* mice after renal pelvic injection of AAV-Metrnl virus. Scale bar, 50μm.

Data are mean ± SD. *p < 0.05, **p < 0.01.