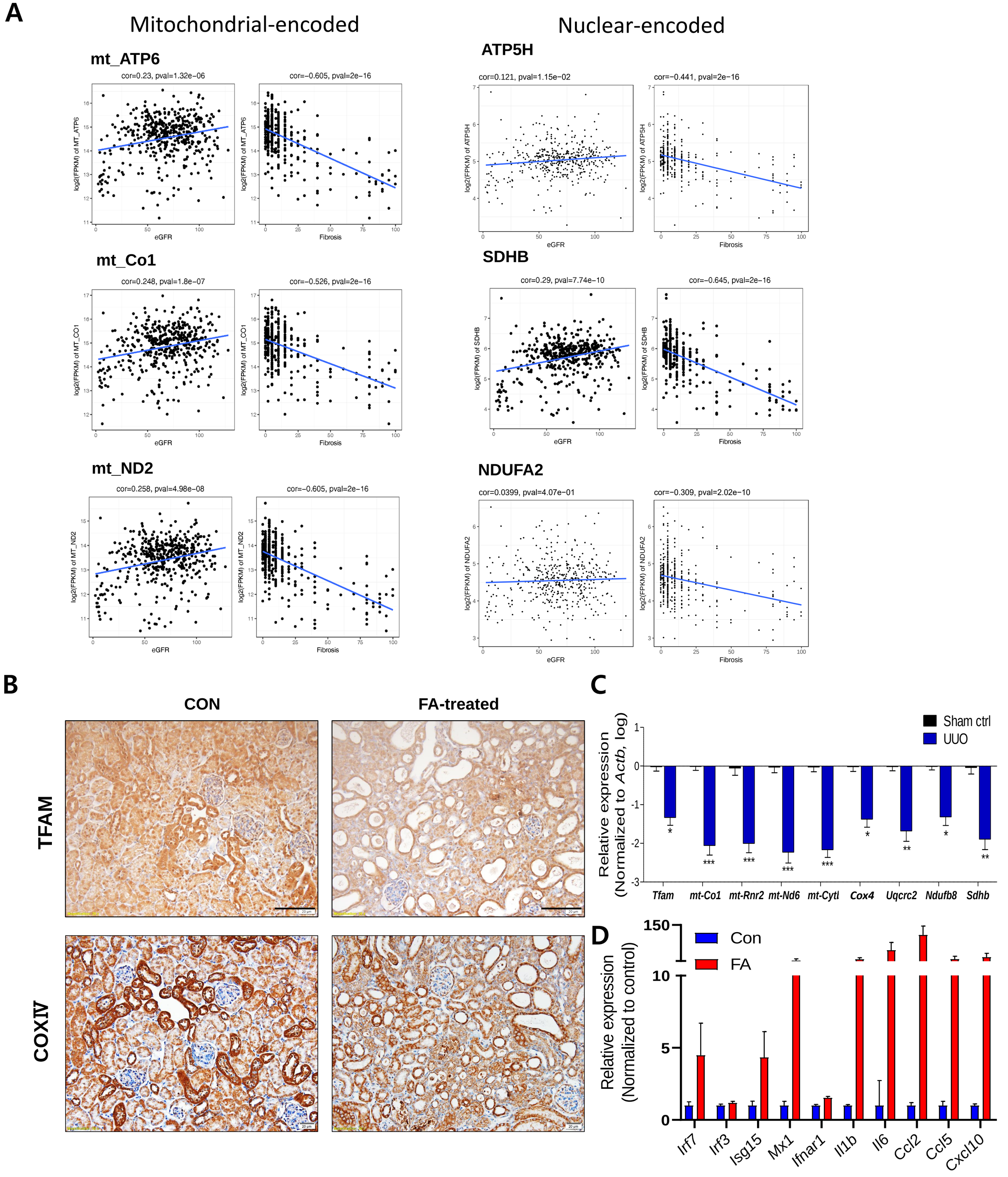
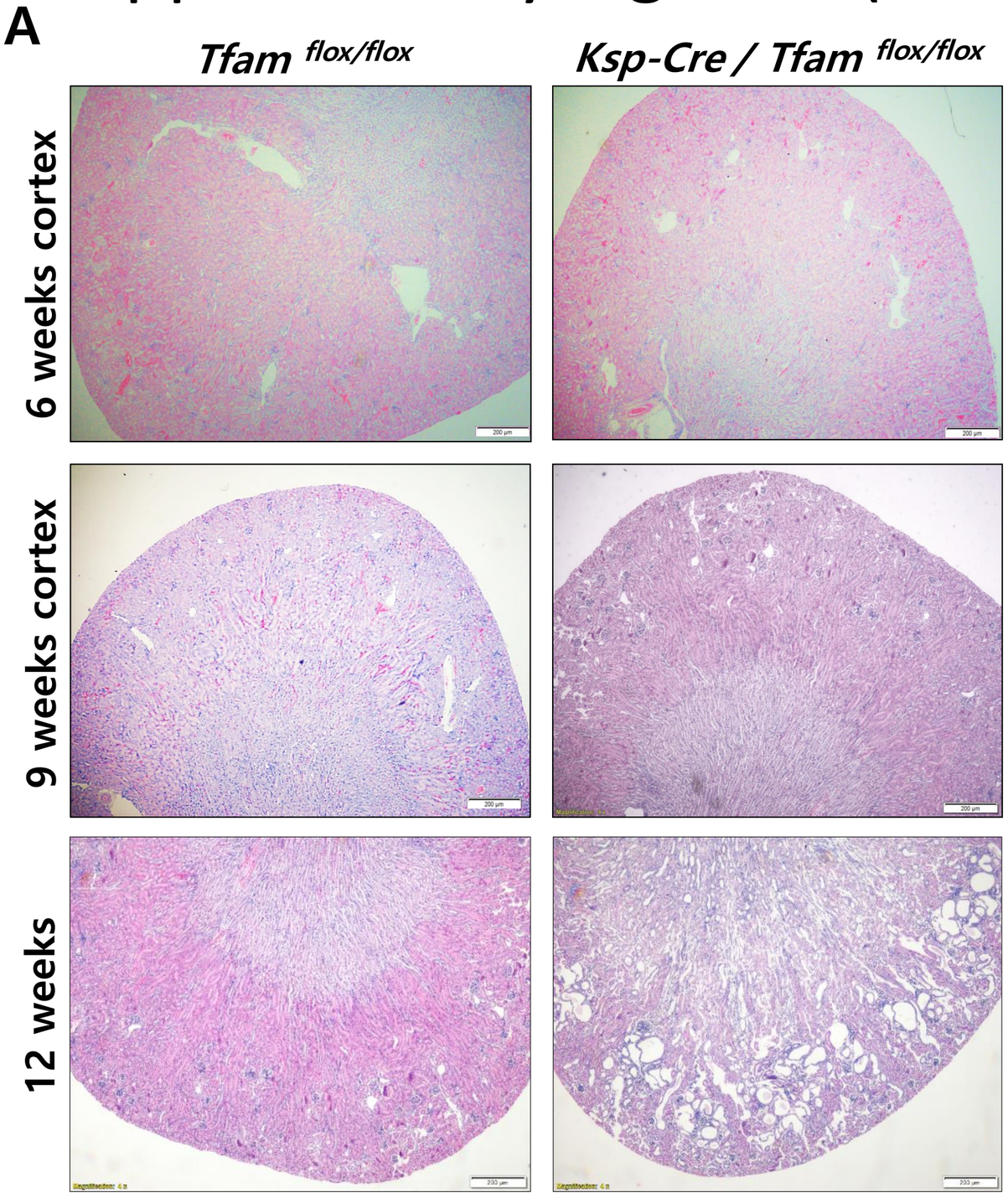
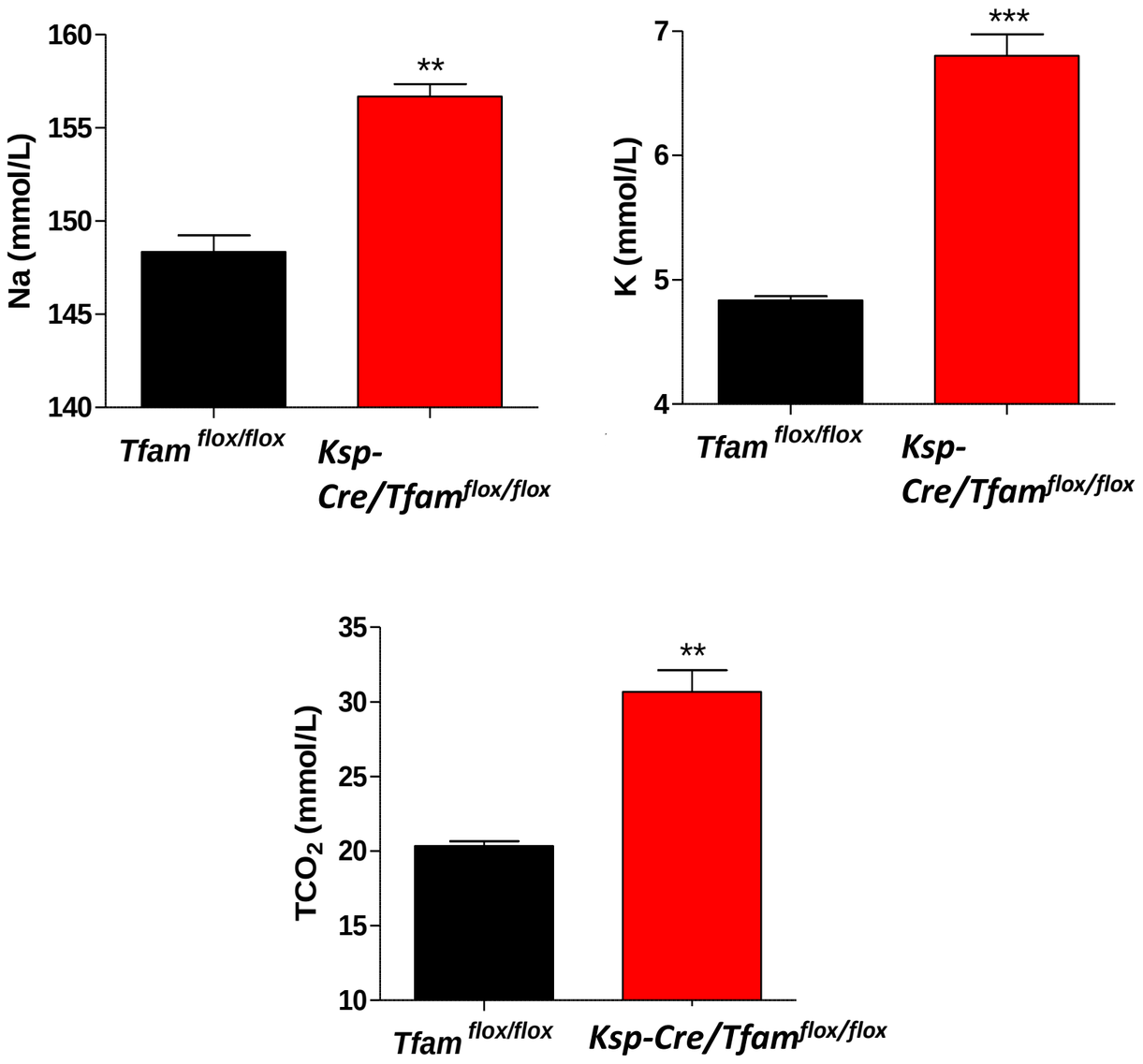
Supplementary Figure 1 (Related to Figure 1)

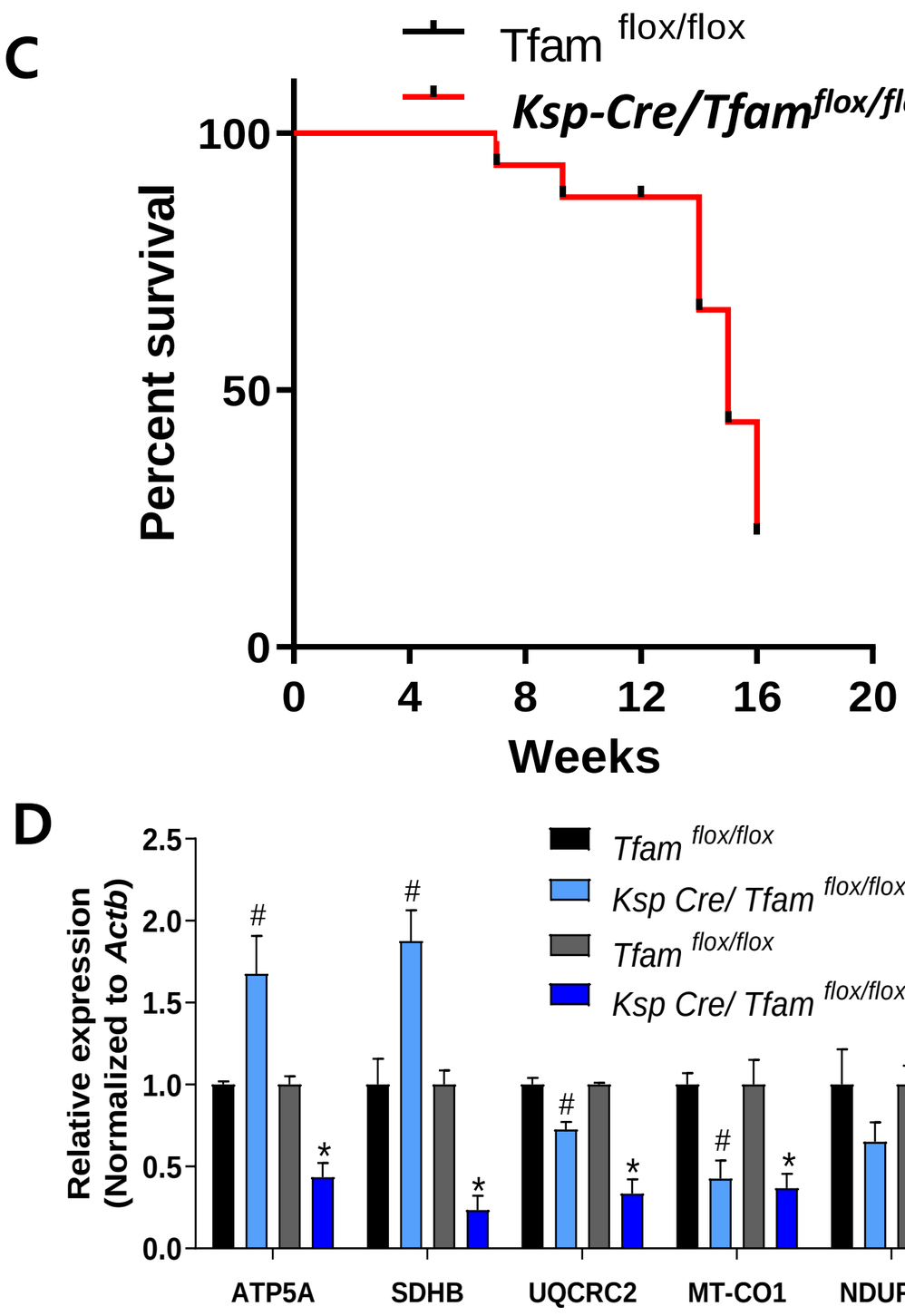


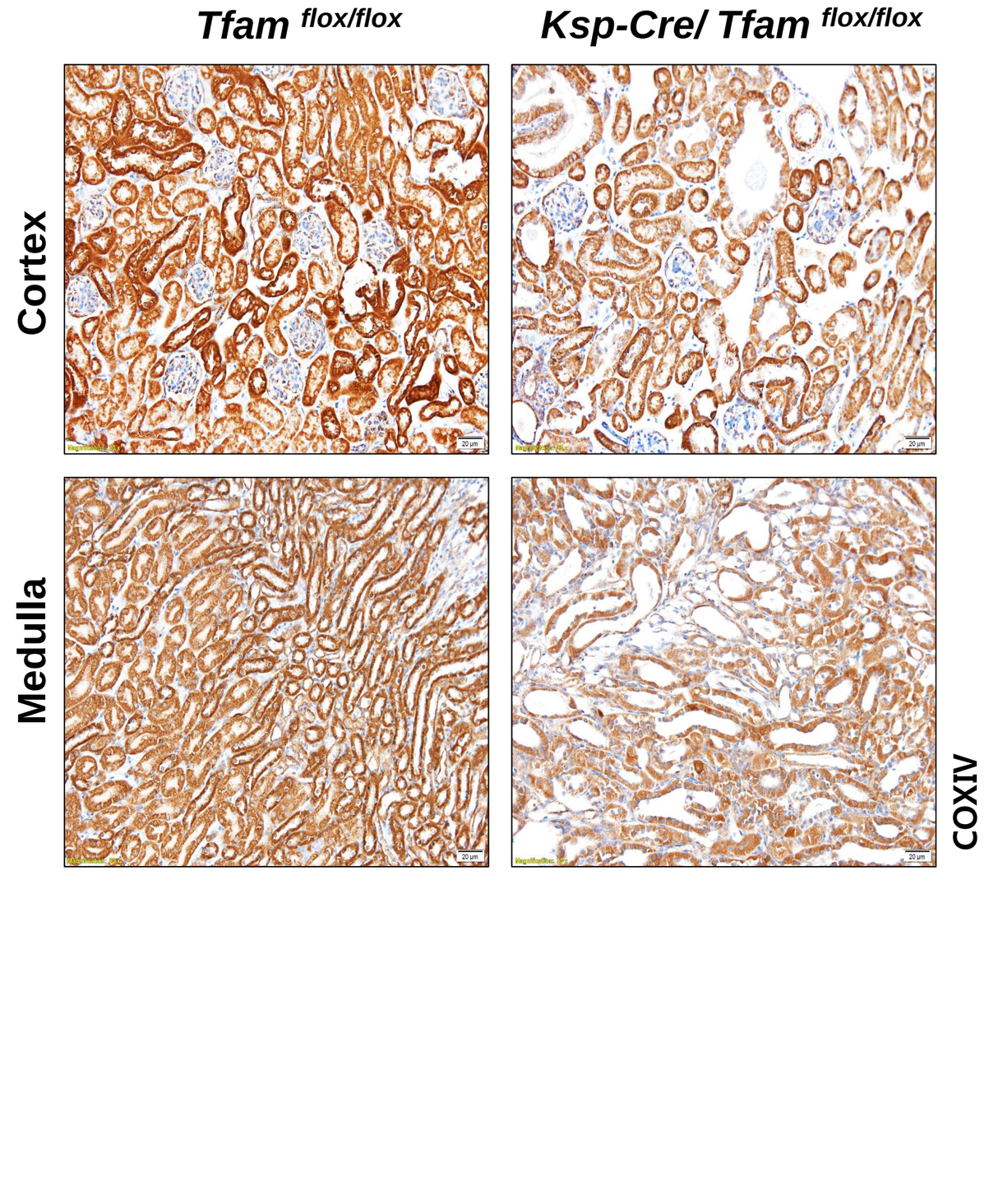
Supplementary Figure 1 (Related to Figure 1). Mouse and human kidney disease is characterized a decrease in and metabolic genes and increase in inflammatory genes. (**A**) Transcript level (RNAseq) of mitochondrial genes (*mtATP6, ATP5H, mtCO1, SDHB, mtND2, NDUFA2*) correlates with the degree of kidney fibrosis and kidney function (eGFR) of 433 microdissected human kidney samples. (**B**) TFAM and COXIV expressions in FA treated kidney fibrosis model were visualized by immunohistochemical (IHC) staining. Scale bar = 20 µm. **(C)** Relative mRNA levels of *Tfam* and mitochondrial OXPHOS genes (*mt-Co1, mt-Rnr2, mt-Nd6, mt-Cytb, Cox4, Uqcrc2, Ndufb8*, and *Sdhb*) in folic acid (FA)-induced mice kidney fibrosis model. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ *vs.* Control. (**D**) Expression levels of IFN and proinflammatoy genes (RNAseq) in FA-induced kidney fibrosis mice model.

Supplementary Figure 2 (Related to Figure 2)



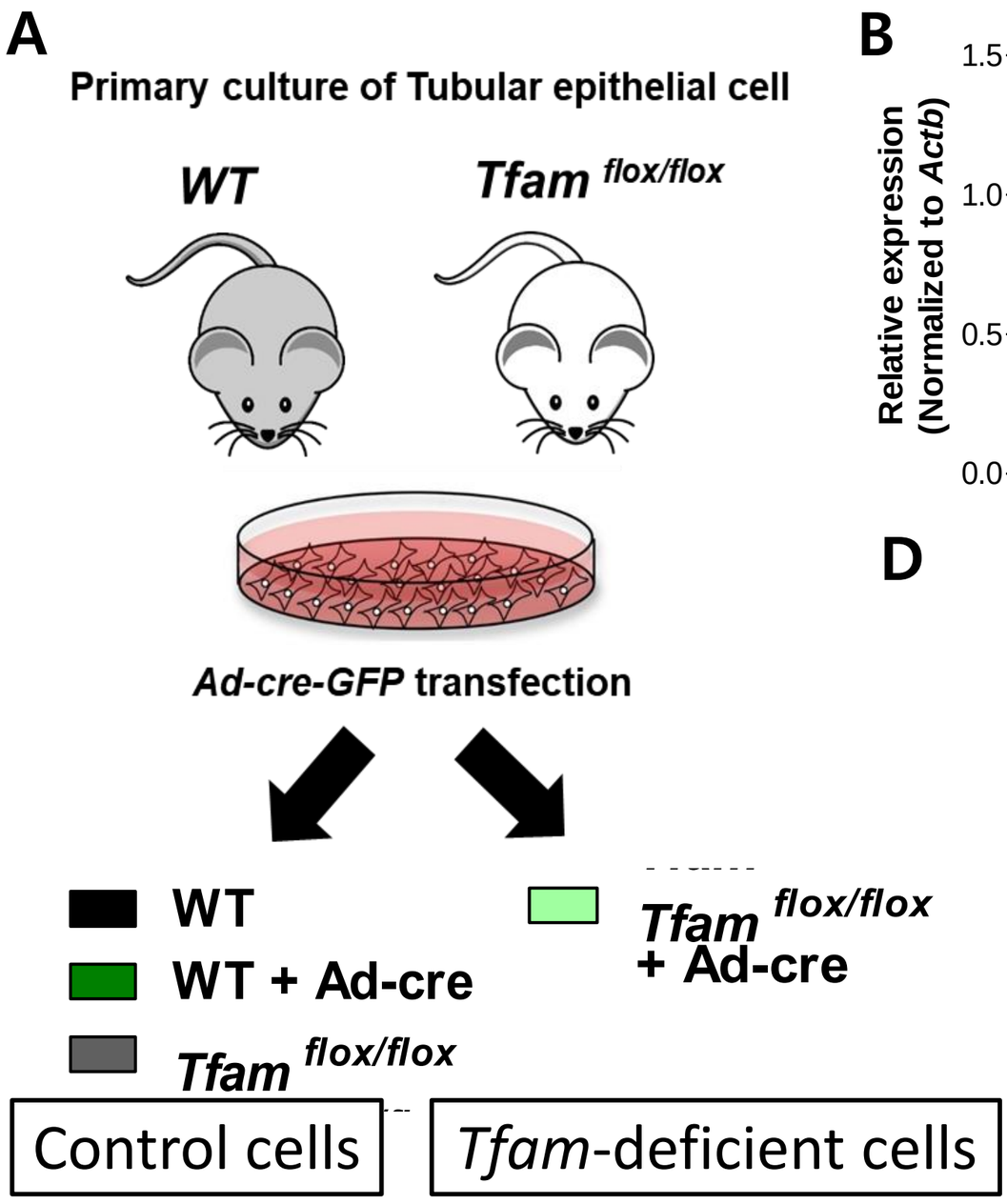


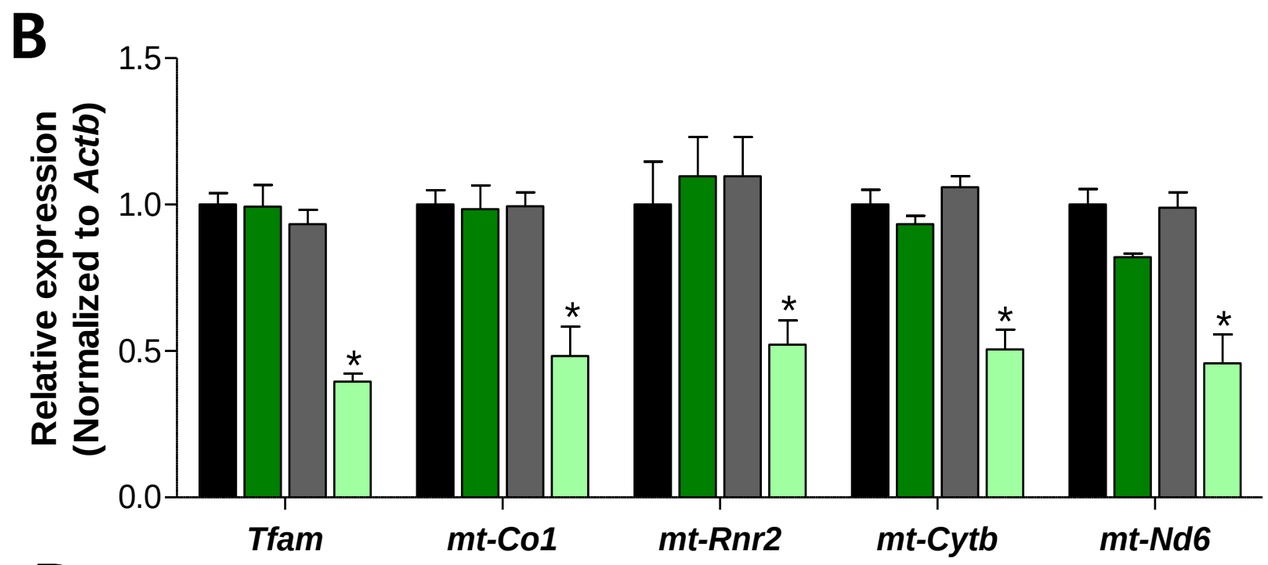


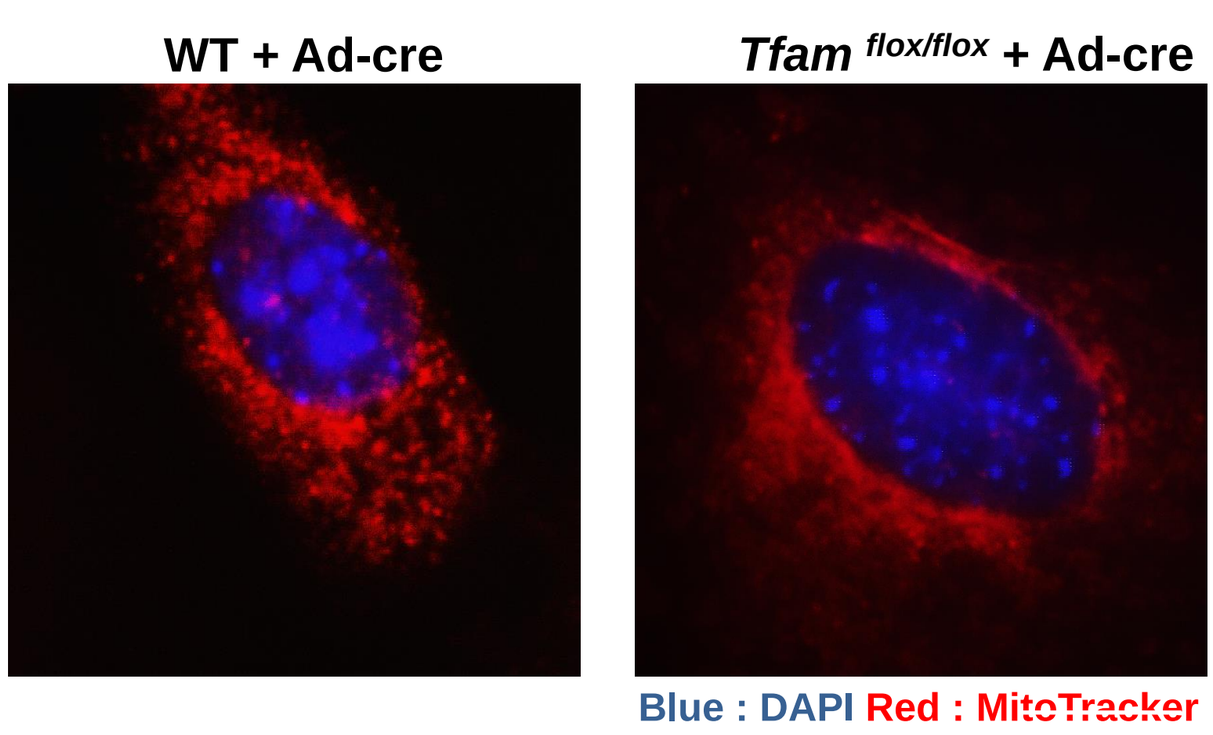


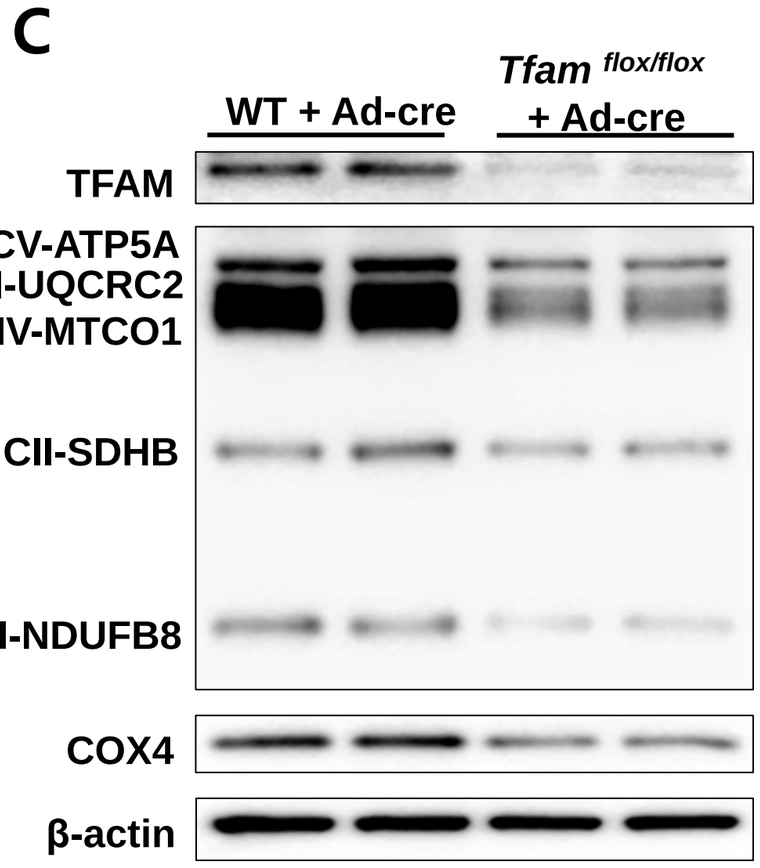
Supplementary Figure 2 (Related to Figure 2). Tubule specific TFAM deletion in mice causes renal failure.
(A) Representative images of haematoxylin and eosin (H&E) staining of 6 weeks, 9 weeks and 12 weeks old *Ksp-Cre/Tfam*$^{flox/flox}$ mice and WT/*Tfam*$^{flox/flox}$ kidney. Scale bar = 200 µm. (**B**) Blood sodium, potassium and total CO_2 levels in 12 weeks old *Ksp-Cre/Tfam*$^{flox/flox}$ and WT/*Tfam*$^{flox/flox}$ mice ***$P < 0.001$. (**C**) Survival curve of *Ksp-Cre/Tfam*$^{flox/flox}$ and WT/*Tfam*$^{flox/flox}$ mice. (**D**) Relative protein levels (densitometry) of mitochondrial proteins (ATP5A, SDHB, UQCRC2, MT-CO1, NDUF8B, and COX4) in 6 weeks and 12 weeks of Ksp-Cre/*Tfam*$^{flox/flox}$ mice and WT/*Tfam*$^{flox/flox}$ mice kidney. * $P < 0.05$ vs. 6 weeks WT/Tfam$^{flox/flox}$. # $P < 0.05$ vs. 12 weeks WT/*Tfam*$^{flox/flox}$. (**E**) Representative immunostaining of COXIV of 12 weeks of *Ksp-Cre/Tfam*$^{flox/flox}$ mice and WT/*Tfam*$^{flox/flox}$ mice kidney.

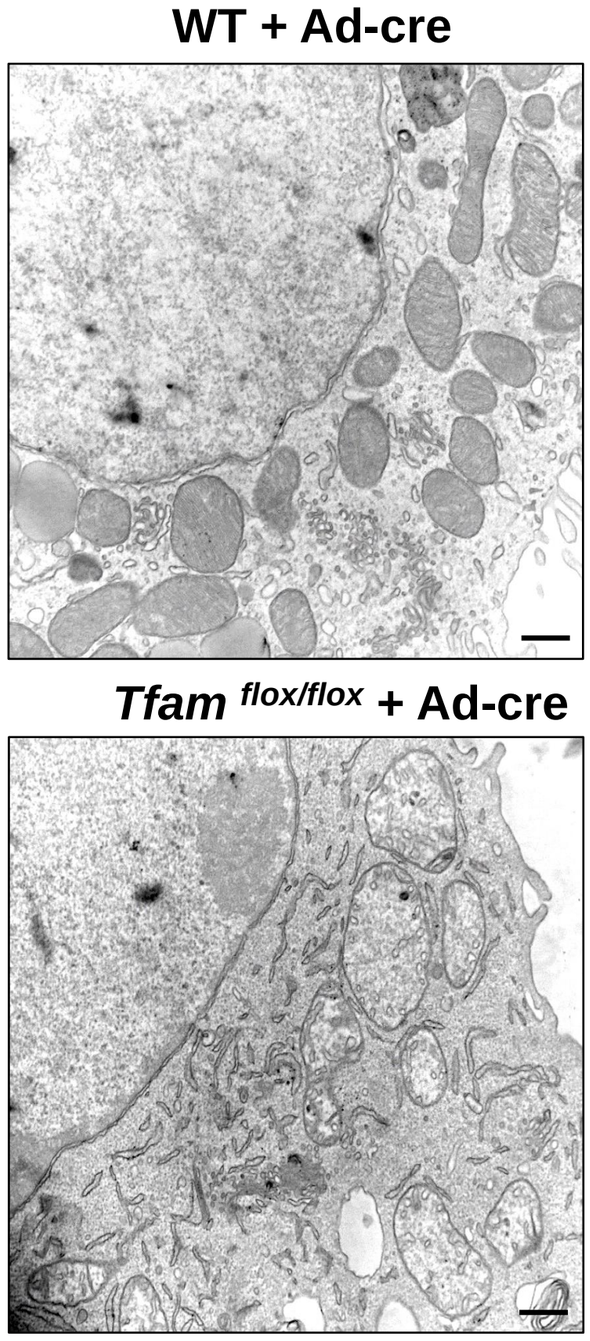
Supplementary Figure 3 (Related to Figure 3)

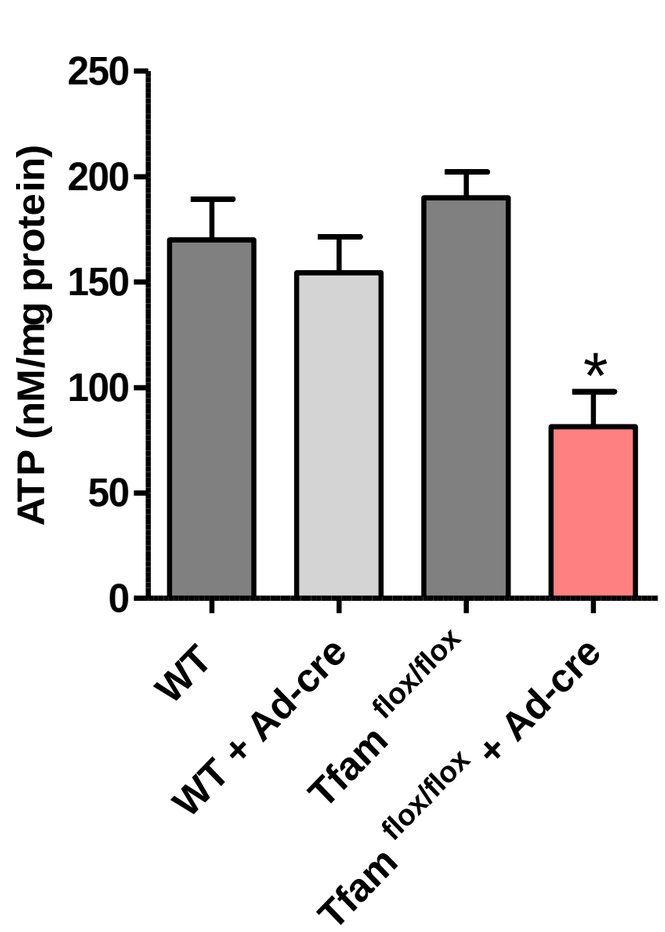






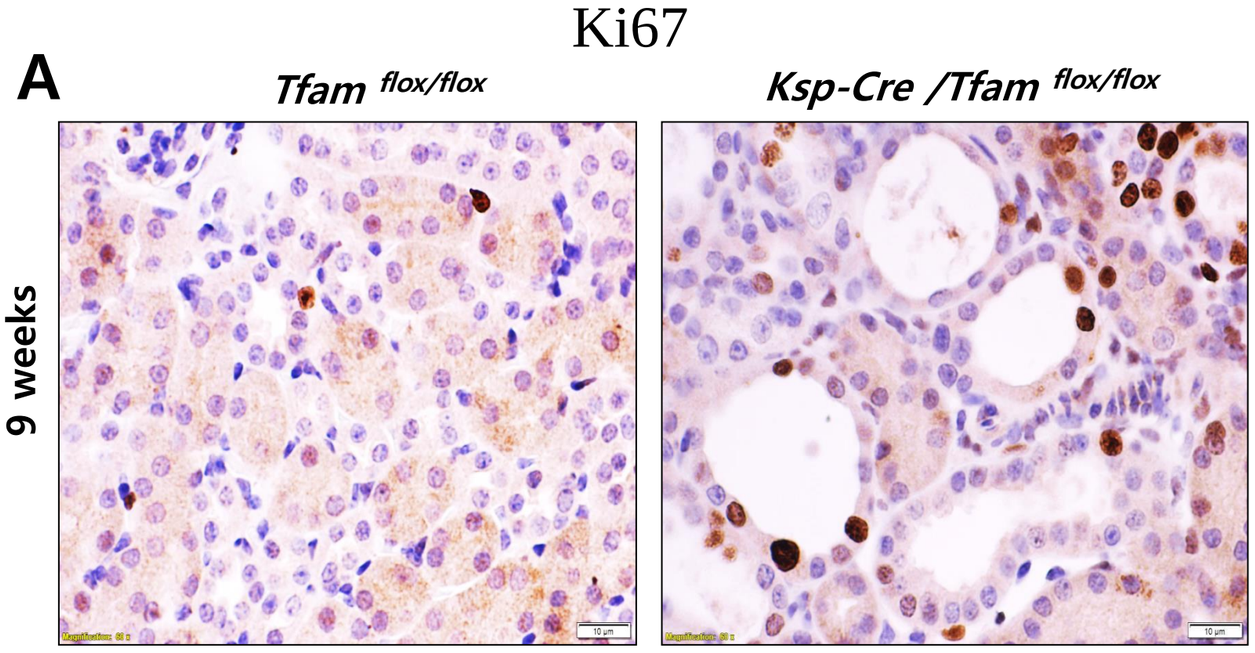


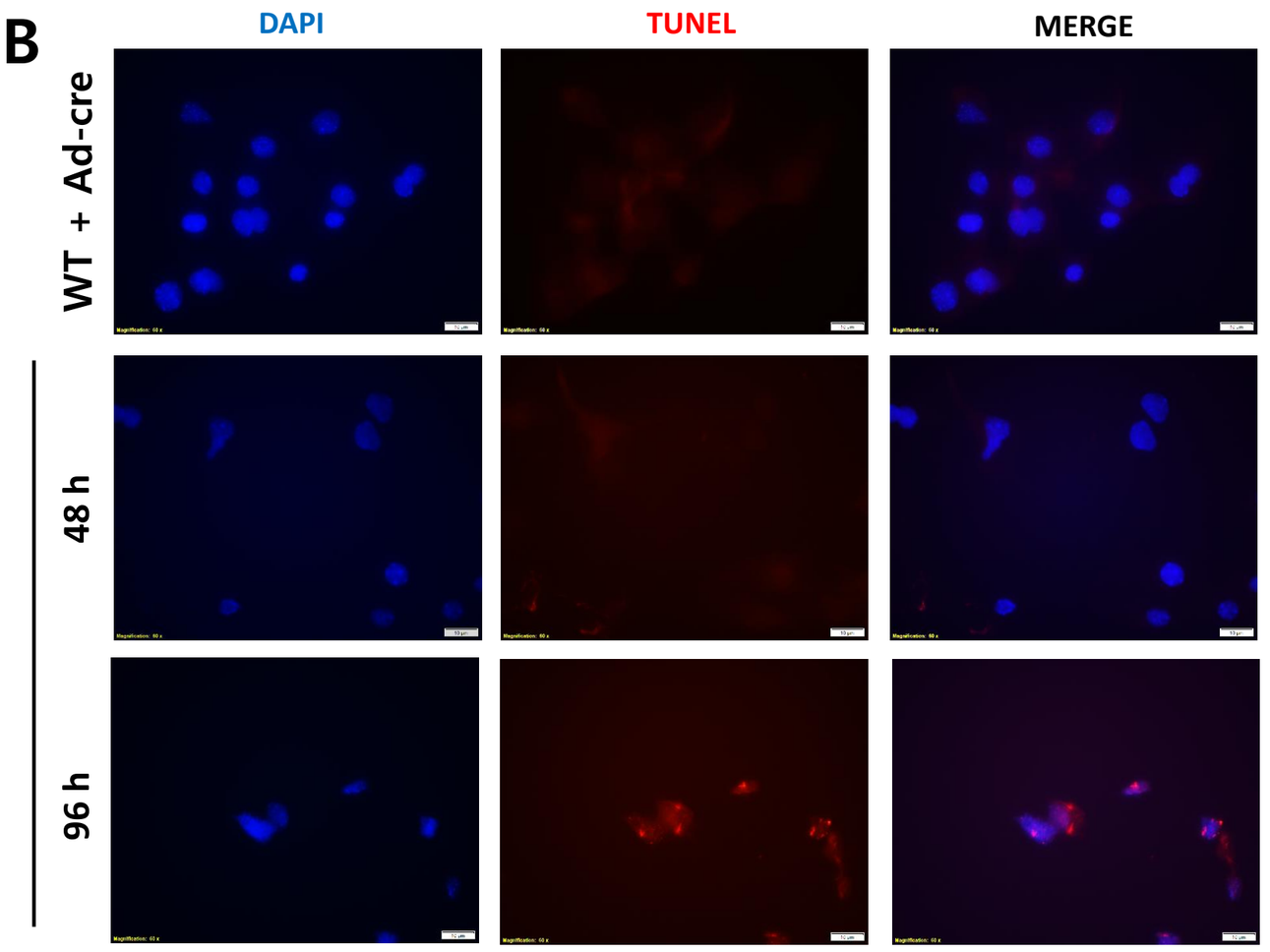


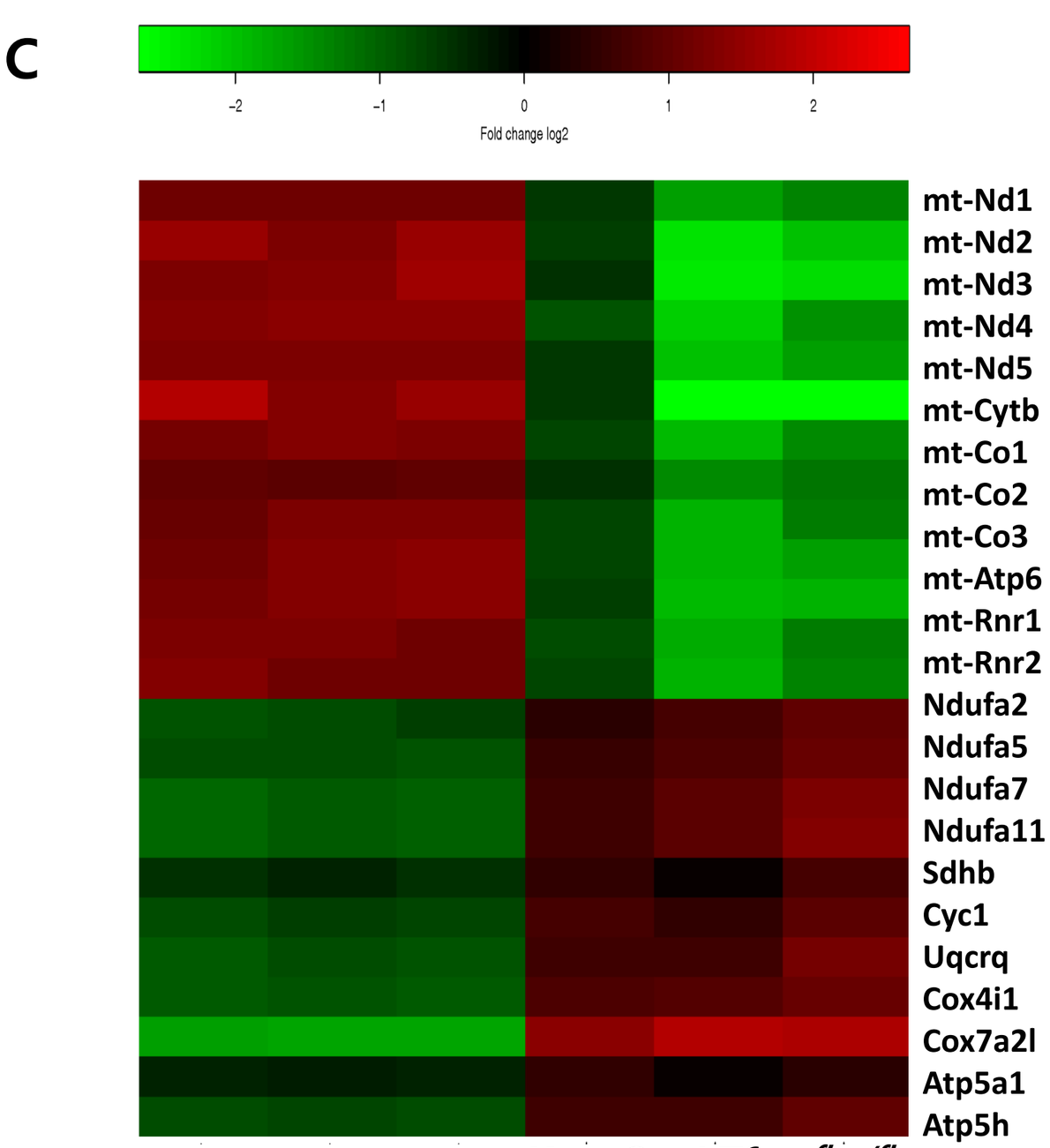


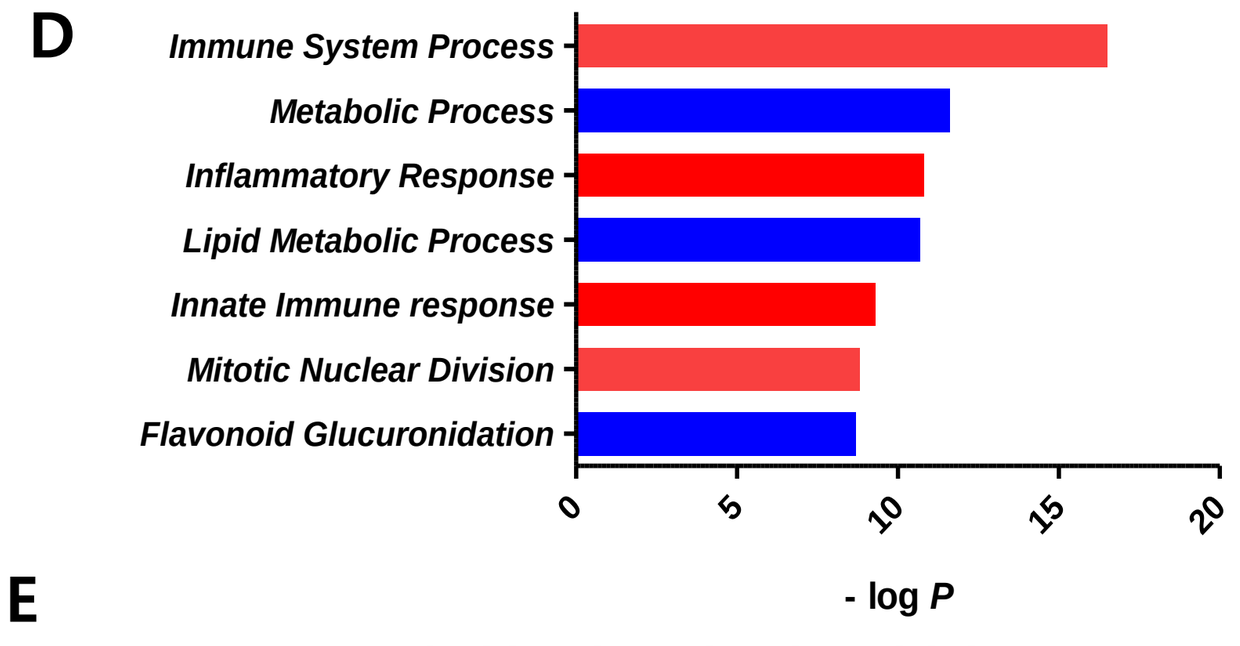
Supplementary Figure 3 (Related to Figure 3). *Tfam* deletion in primary tubule cells leads to severe metabolic defect
(A) Experimental design to generate control and *Tfam* knock-out TECs. Cells were cultured from wild type of Tfam$^{flox/flox}$ mice and infected with Ad-Cre-GFP to generate control (wild type) and *Tfam*-deficient cells. (**B**) Relative transcript levels of mitochondrial genes expression of wild type cells and *Tfam*$^{flox/flox}$ cells transfected with Ad-Cre-GFP. (**C**) Mitochondrial OXPHOS proteins expression in control and *Tfam* knock-out cells. (**D**) Representative images of control and *Tfam* knock-down TECs stained with DAPI and mitotracker. (**E**) Representative electron micrographs of control and *Tfam* knock-down TECs. (**F**) Cellular ATP content normalized to total protein of control and *Tfam* knock-down TECs.

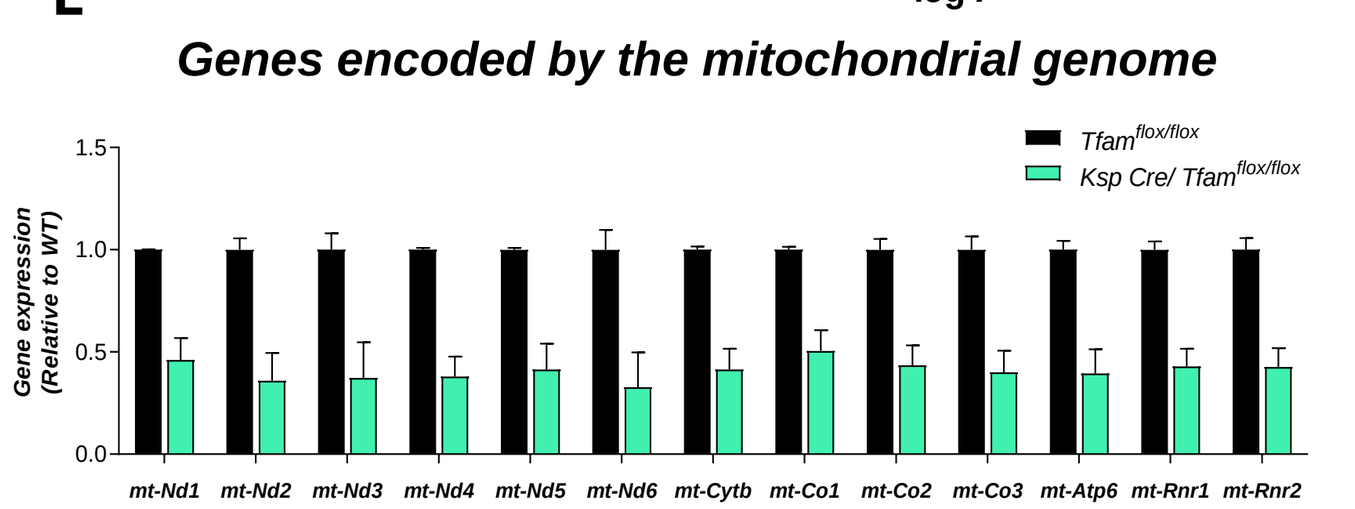
Supplementary Figure 4 (Related to Figure 4)

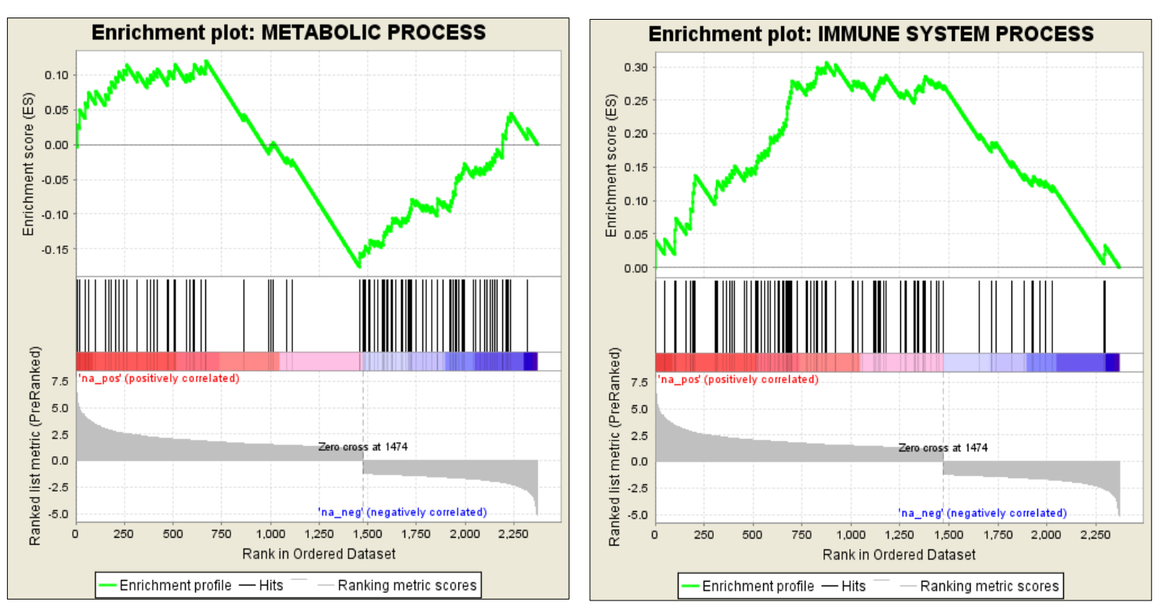


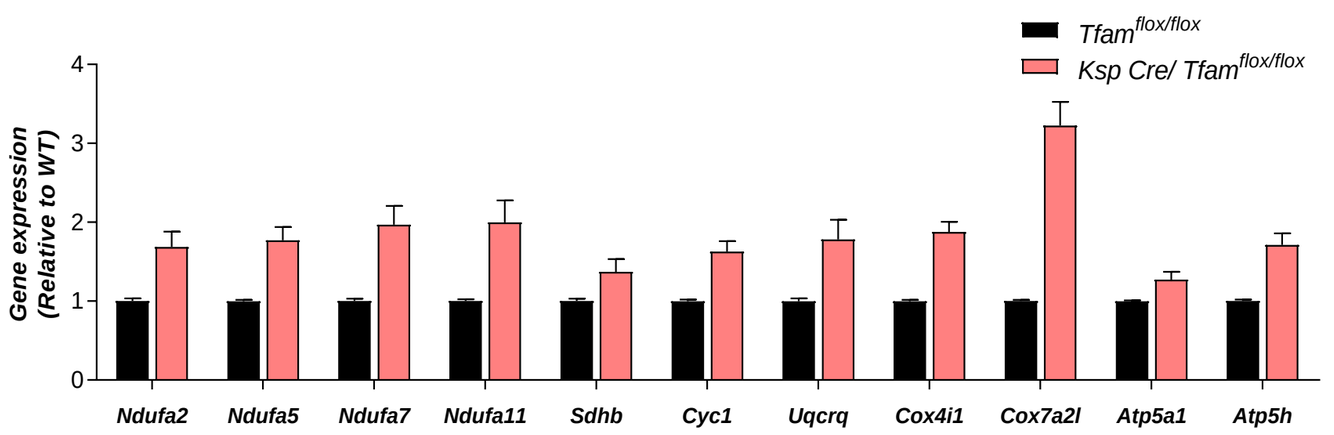






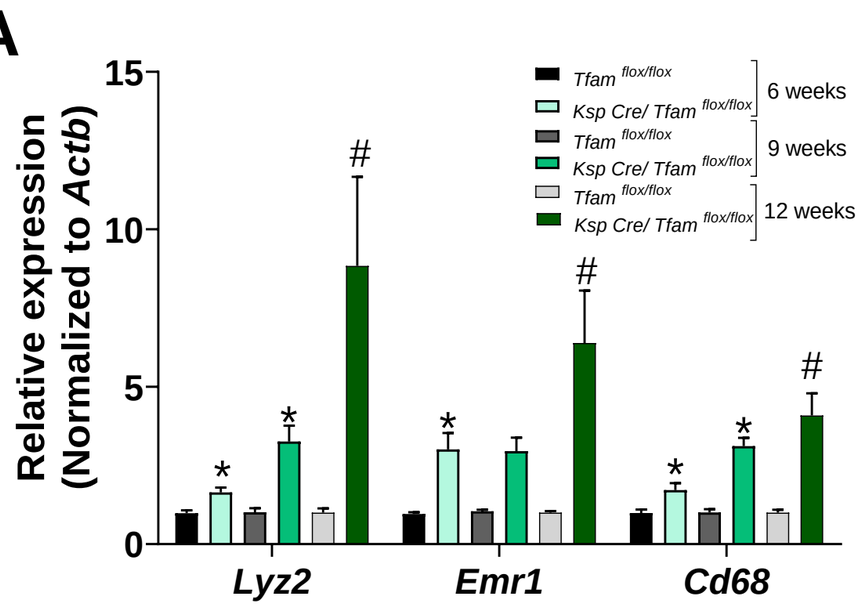


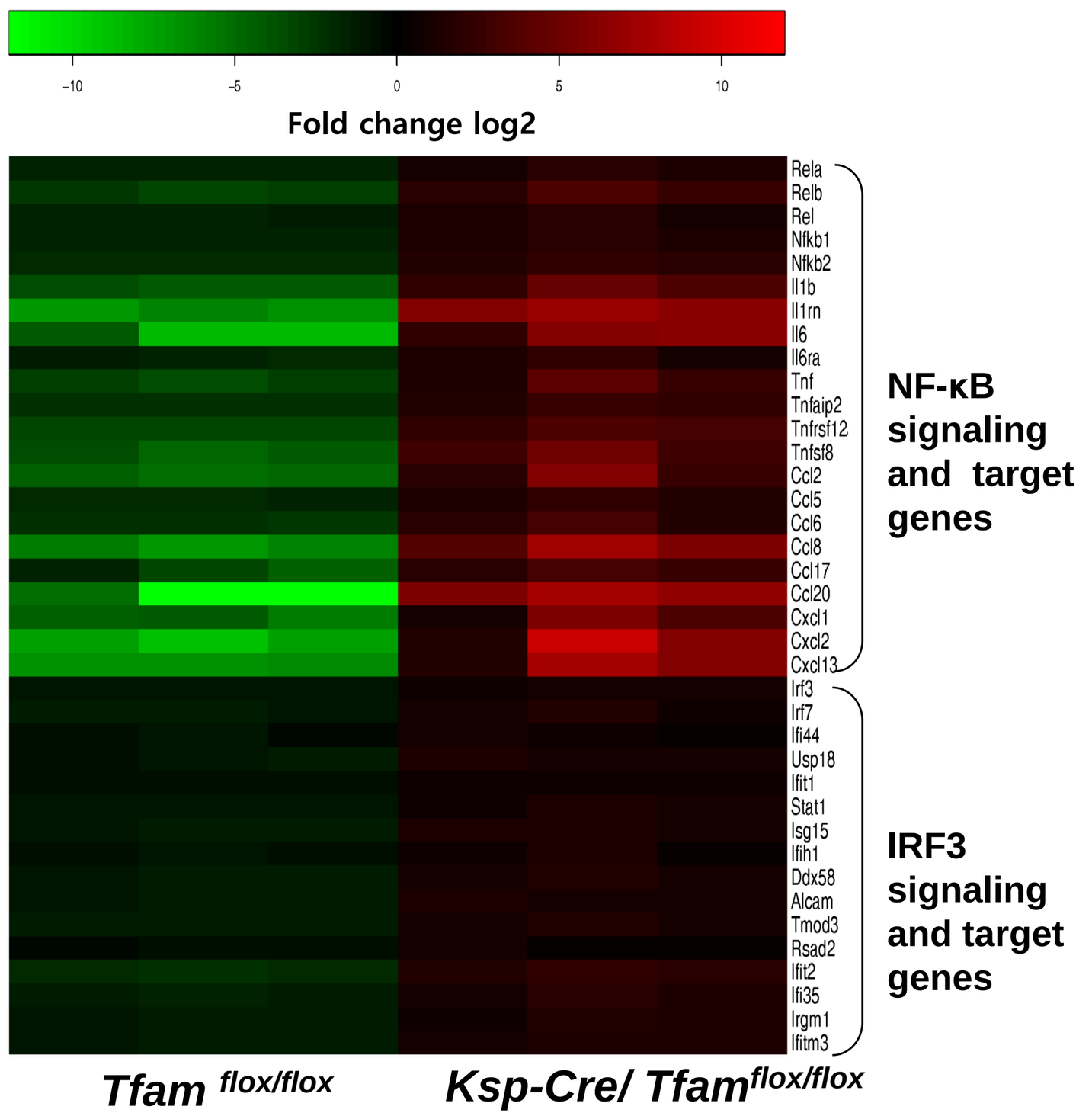


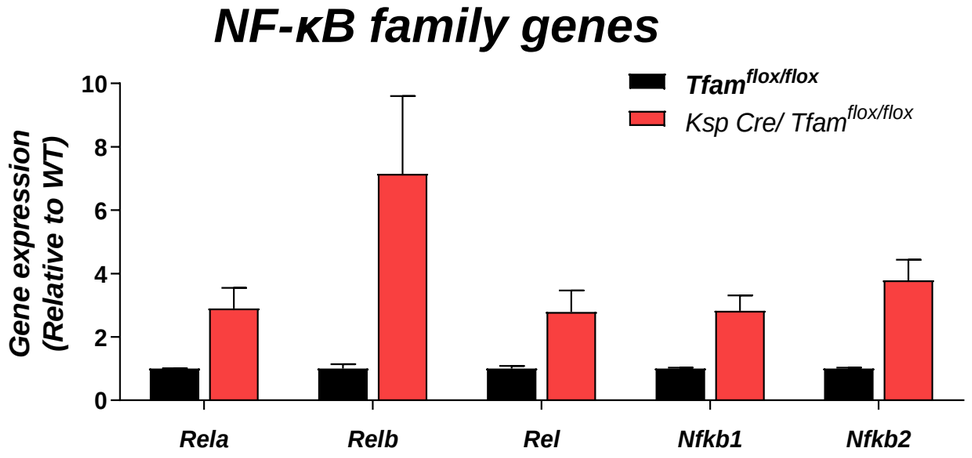


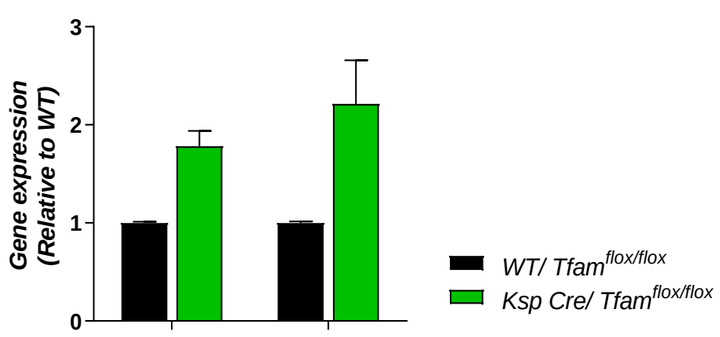
Supplementary Figure 4 (Related to Figure 4). Expression of mitochondrial genes in *Ksp-Cre/ Tfam*$^{flox/flox}$ mice. (**A**) Ki76 staining of 9 weeks old control WT and Ksp-Cre/*Tfam*$^{flox/flox}$ mice. (**B**) Represent -ative images of TUNEL staining in primary cultured cells treated with or without Cre adenovirus at 48 an d 96 hrs. Scale bar = 10 µm. (**C**) Heatmap of gene expression from RNAseq dataset. (**D**) RNA-sequencing was performed on kidneys of 12-week-old control (*n* = 3 WT/*Tfam*$^{flox/flox}$) and *Ksp-Cre/Tfam*$^{flox/flox}$ (*n* = 3) mice. Gene ontology analysis (DAVID) of the differentially expressed genes in TFAM deficient mice. The graph shows –log P values calculated using modified Fisher Exact Test of a specific pathway. Relative gene expression of mitochondrial-encoded (**E**) or (**F**) nuclear-encoded mitochondrial genes in 12 week old control and *Ksp-Cre/Tfam*$^{flox/flox}$ mice (**G**) Gene set enrichment analysis of the differentially expressed genes highlighting strong enrichment for the immune system process and metabolic process in samples.

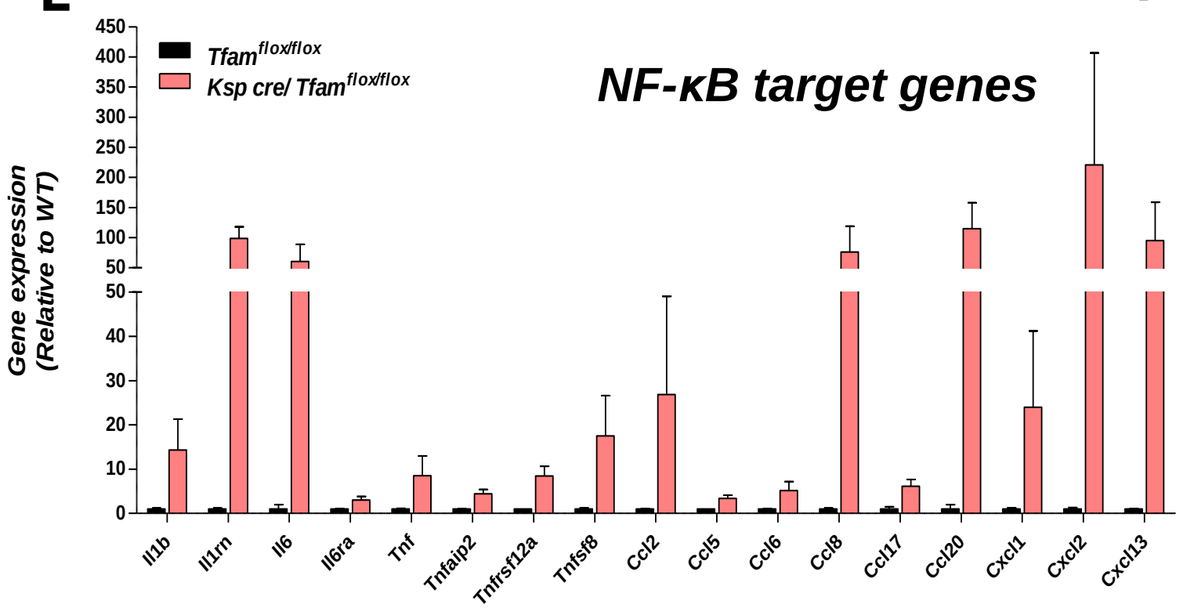
Supplementary Figure 5 (Related to Figure 4)

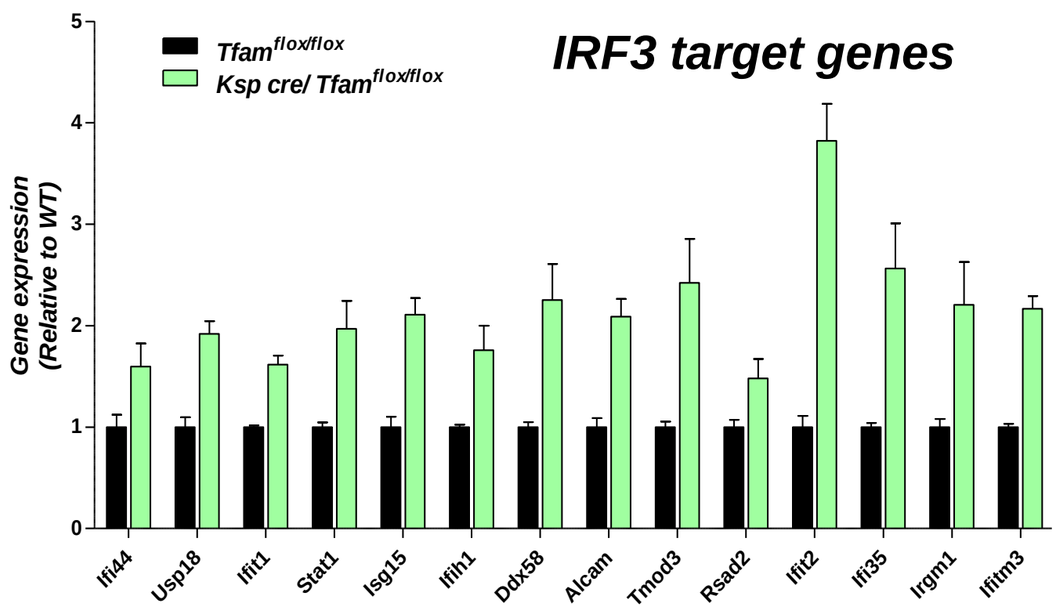


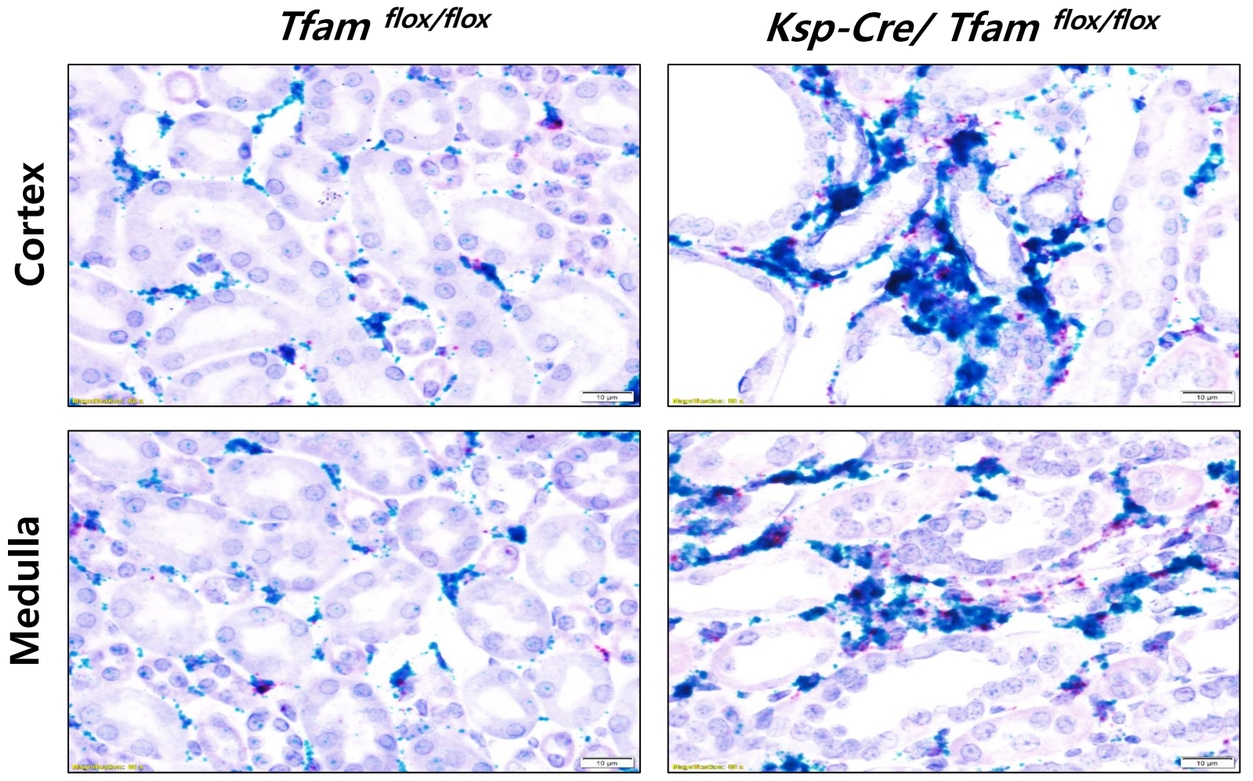








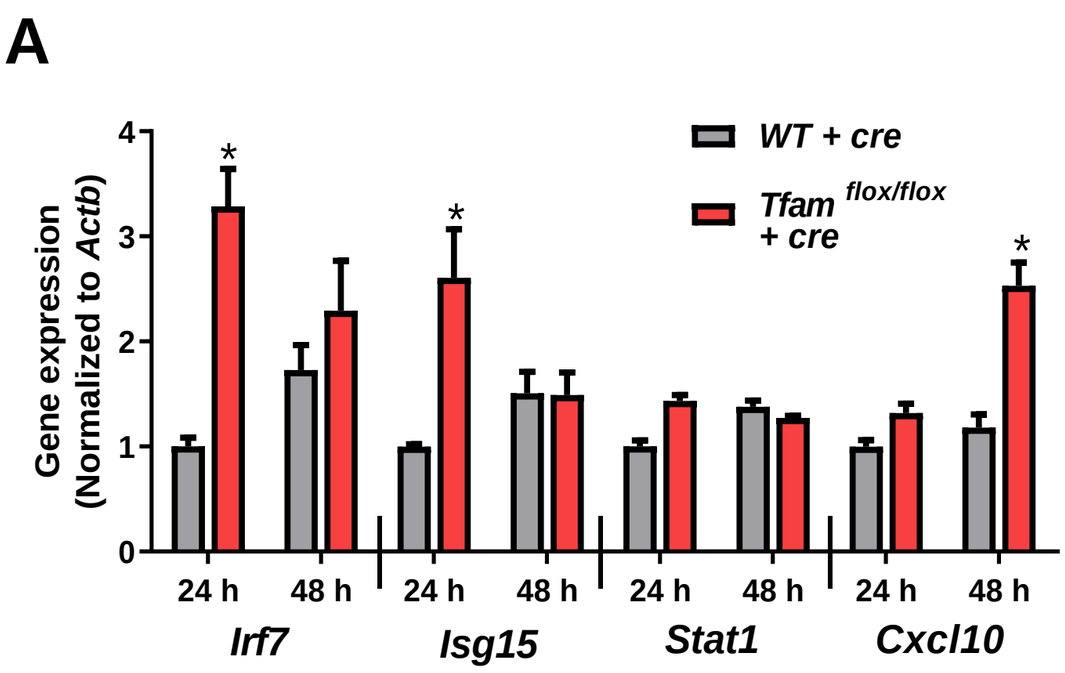


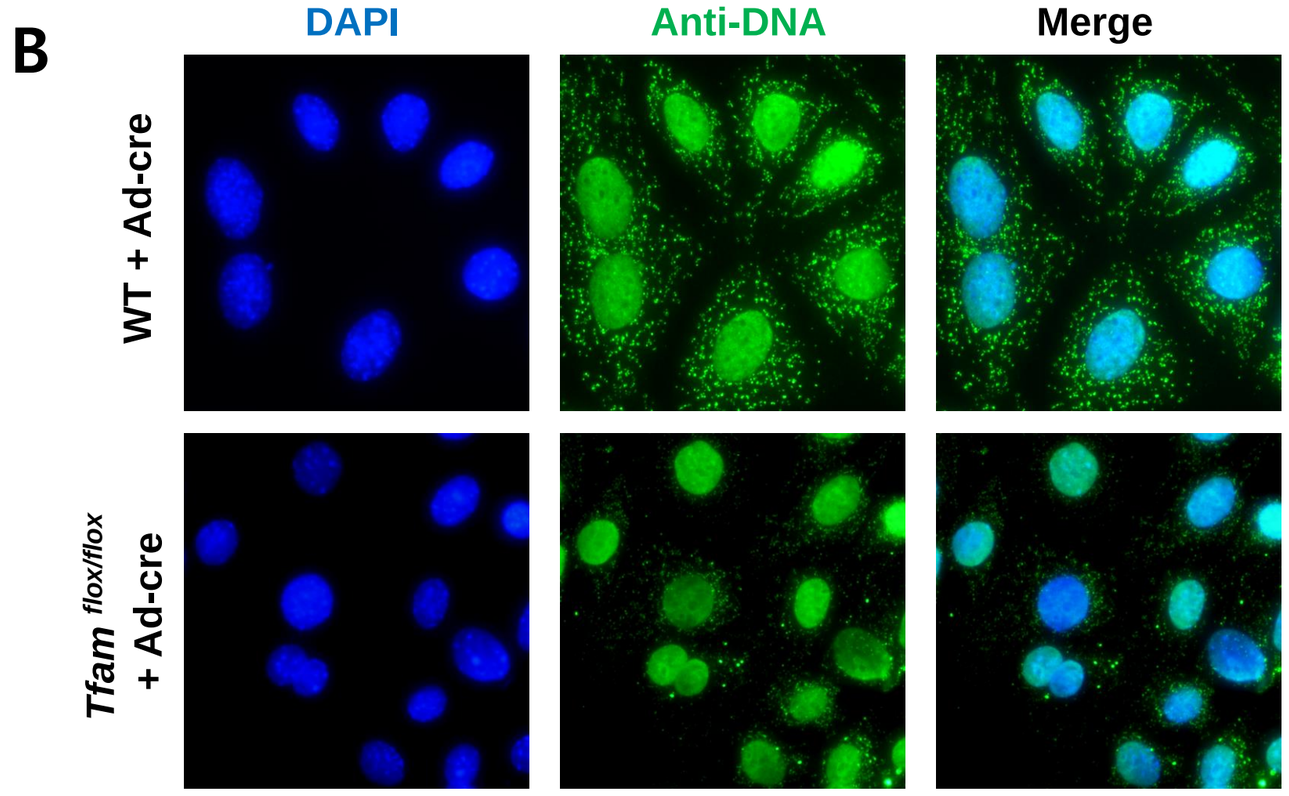


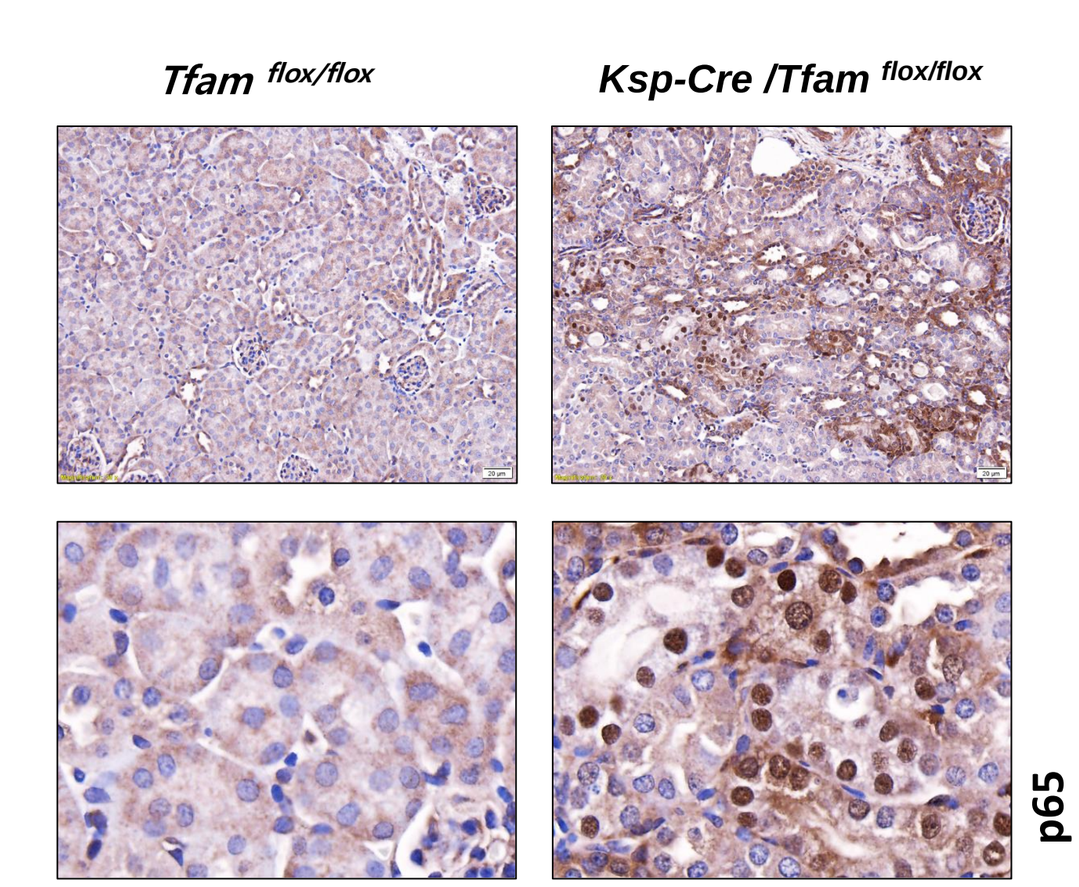
Supplementary Figure 5 (Related to Figure 4). Expression of inflammatory genes in control and *Ksp-Cre/Tfam*$^{flox/flox}$

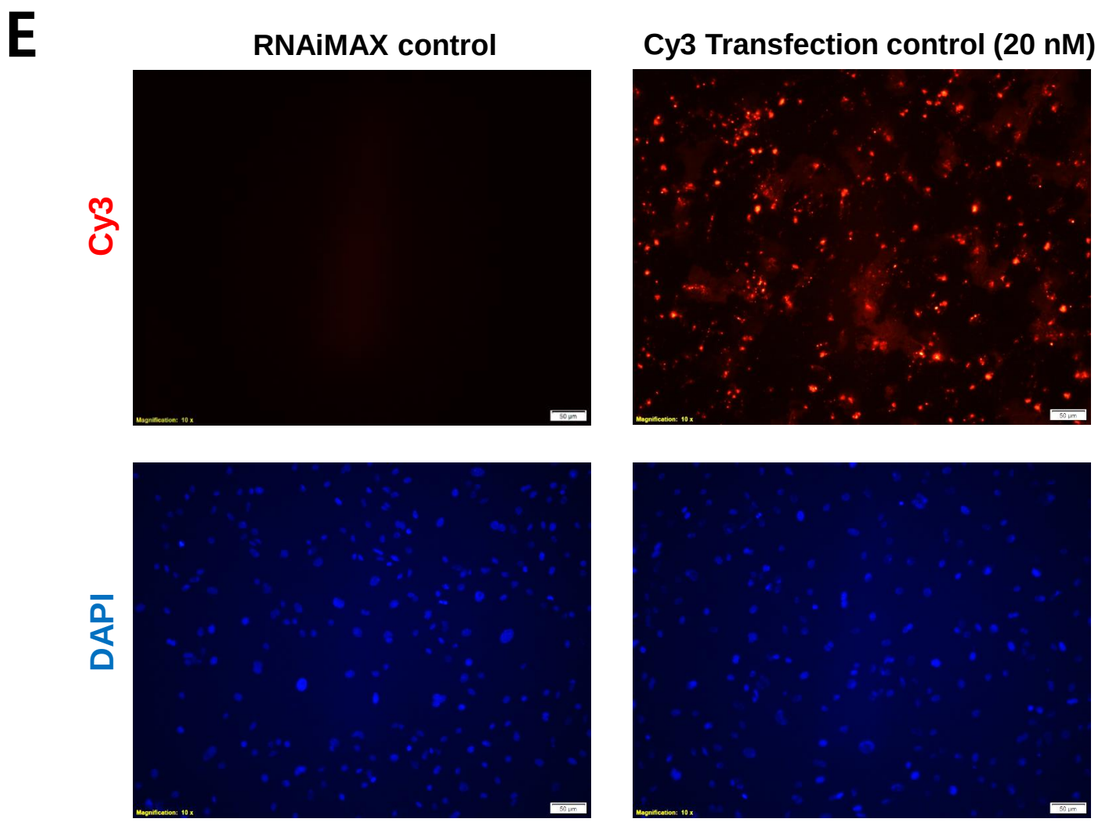
(**A**) Relative mRNA levels of inflammatory cell marker genes (*Lyz2, Emr1,* and *Cd68*) of 6 weeks, 9 weeks and 12 weeks old *Ksp-Cre/Tfam*$^{flox/flox}$ mice *vs WT/Tfam*$^{flox/flox}$ mice. ** P < 0.05* vs. 6 weeks WT/Tfam$^{flox/flox}$. **P* <0.05 *vs*. 9 weeks WT/ *Tfam*$^{flox/flox}$. *# P < 0.05* vs. 12 weeks WT/*Tfam*$^{flox/flox}$. (**B**) Heatmap of gene expression (from RNAseq) of NF-kB and IRF3 target genes (**C**) Expression of NF-kB and (D) IRF family genes (**E**) and NF-kB and IRF target genes in control and *Ksp-Cre/ Tfam*$^{flox/flox}$ mice. (**F**) Representative images of double staining by in situ hybridization with *Emr1* (red) and Col1a2 (Green) probe in *Tfam*-deficient kidney cortex and medulla. Scale bar = 10 μm.

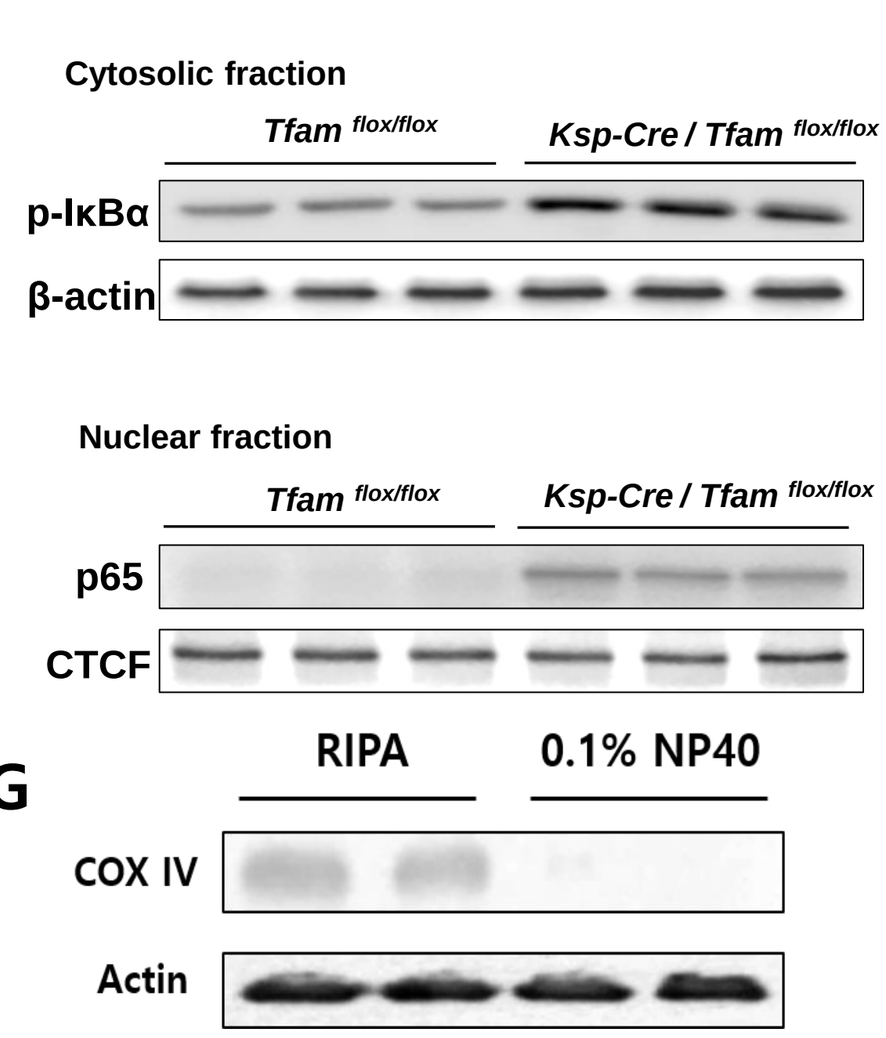
Supplementary Figure 6 (Related to Figure 5)

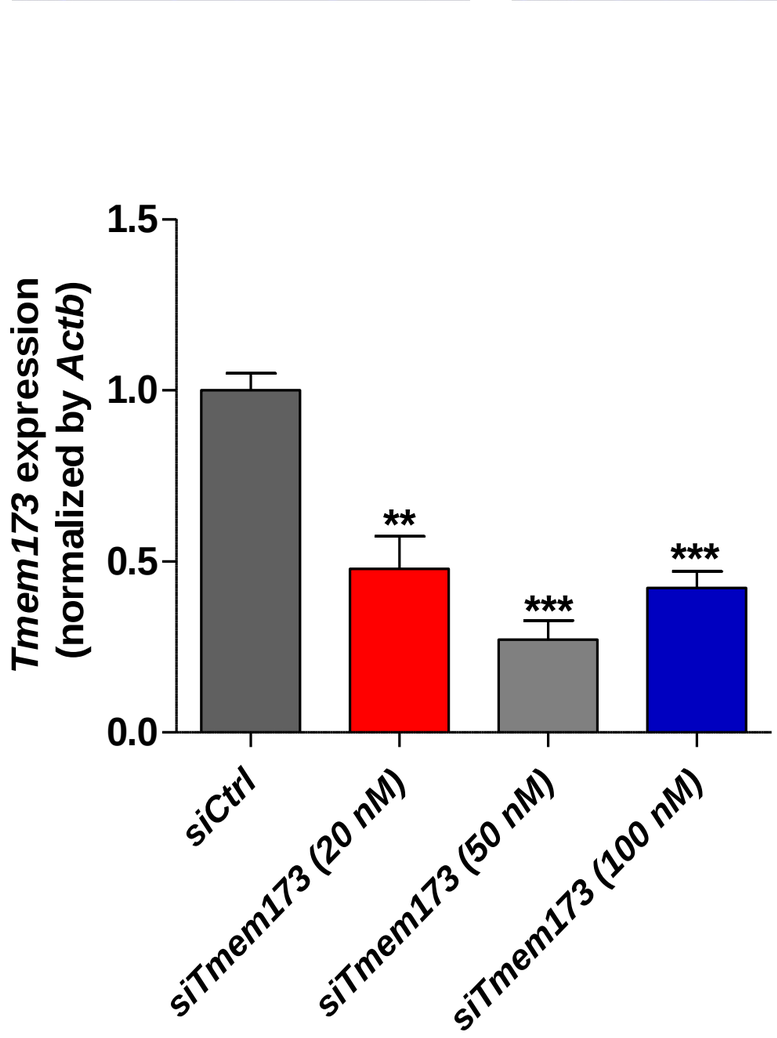






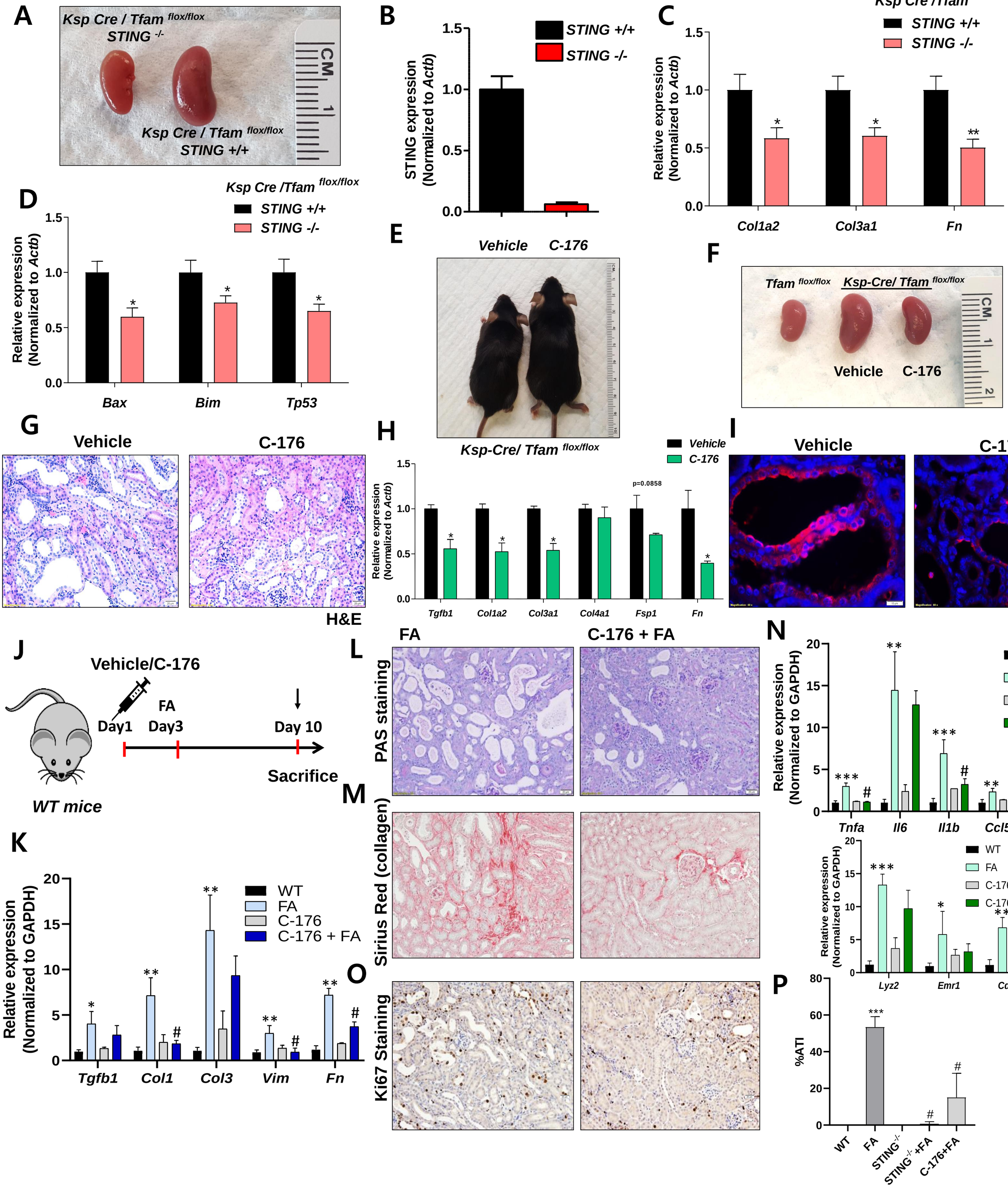






Supplementary Figure 6 (Related to Figure 5). TFAM loss in TECs induces cytokine expression via the activation of cGAS-STING pathway (A) Relative mRNA levels of IFN response genes (*Irf7, Isg15, Stat1,* and *Cxcl10*) in *Tfam*-deficient TECs. **P* < 0.05. (**B**) Representative immunofluorescence images of control and *Tfam* knock-out TECs, stained with DAPI and anti-DNA antibody. Scale bar = 10 μm. (**C**) Representative images of p65 immunostaining of control and *Ksp-Cre/ Tfam*$^{flox/flox}$ mouse kidneys. **(D)** Cytosolic protein levels of phosphorylated IκBα and nuclear p65 levels in primary culture of control and *Tfam*-null TECs. (**E)** Transfection efficiency showed by Cy3 transfection control. (**F**) Relative *Tmem173* transcript level in primary TEC cells transfected with control siRNA and 20, 50 or 100 nM of siTmem173. (**G**) Immunoblotting of cytosolic fractions prepared 1% or 0.1% of NP40 with COX IV to confirm the lack of cross contamination with membrane fractions.

Supplementary Figure 7 (Related to Figure 6 and 7)



Supplementary Figure 7 (Related to Figure 6 and 7). Genetic deletion or pharmacological inhibition of STING attenuates renal disease of TFAM-deficient kidneys. (**A**) Gross kidney morphology of *Ksp-Cre/Tfam*$^{flox/flox}$ and *Ksp-Cre/Tfam*$^{flox/flox}$*STING*$^{-/-}$ mice (**B**) Relative mRNA levels of STING, (**C**) profibrotic genes (*Col1a2, Col3a1, Fn*) and (**D**) apoptosis-associated genes (*Bax, Bim, Tp53*) in *Ksp-Cre/Tfam*$^{flox/flox}$ and *Ksp-Cre/Tfam*$^{flox/flox}$*STING*$^{-/-}$ mice (**E**) Representative pictures of the mice and (**F**) kidneys of *Ksp-Cre/Tfam*$^{flox/flox}$ mice treated with C-176/vehicle. * $P < 0.05$ *vs.* vehicle treated mice, # $P < 0.05$ *vs.* vehicle treated mice. (**G**) Representative images showing H&E staining of 12 weeks old *Ksp-Cre/Tfam*$^{flox/flox}$ mice treated with C-176 or vehicle. (**H**) Relative mRNA levels of profibrotic genes levels (*Tgfb1, Col1a2, Col3a1,Col4a1, Fsp1, Fn*) in *Ksp-Cre/Tfam*$^{flox/flox}$ mice treated with C-176 or vehicle. * $P < 0.05$ *vs.*vehicle treated mice. (**I**) Representative images showing TUNEL staining of 12 weeks old *Ksp-Cre/Tfam*$^{flox/flox}$ mice treated with C-176 or vehicle. (**J**) Experimental scheme: *WT* mice were injected with STING inhibitor (C-176)/vehicle intraperitoneally every day and treated with single dose of folic acid (250mg/kg body weight) or vehicle on day 3. Mice were euthanized on day 10 (7 days post FA injection) ($n = 3$). (**K**) Relative mRNA of pro-fibrotic genes (*Tgfb1, Col1, Col3, Vim,* and *Fn1*).* $P < 0.05$, ** $P < 0.01$ vs. *Wt*. # $P < 0.01$ *vs.* FA mice **(L**) Representative images of PAS stained (**M**) Sirius red (**O**) Ki67staining of FA-injected and C-176 + FA-injected mice kidney. Scale bar = 20µm. (**N**) Relative mRNA of proinflammatory cytokines (*Tnfa, Il1b, Il6, Ccl5* and *Cxcl10*) and immune cell markers (*Lyz2, Emr1, Cd68*) in mice injected with FA and C-176 + FA. ** $P < 0.01$ vs. WT. # $P < 0.01$ *vs.* FA mice. (**P**) STING activity ablation reduced the acute tubular injury score. *** $P < 0.001$ vs. WT. # $P < 0.01$ *vs.* FA mice.