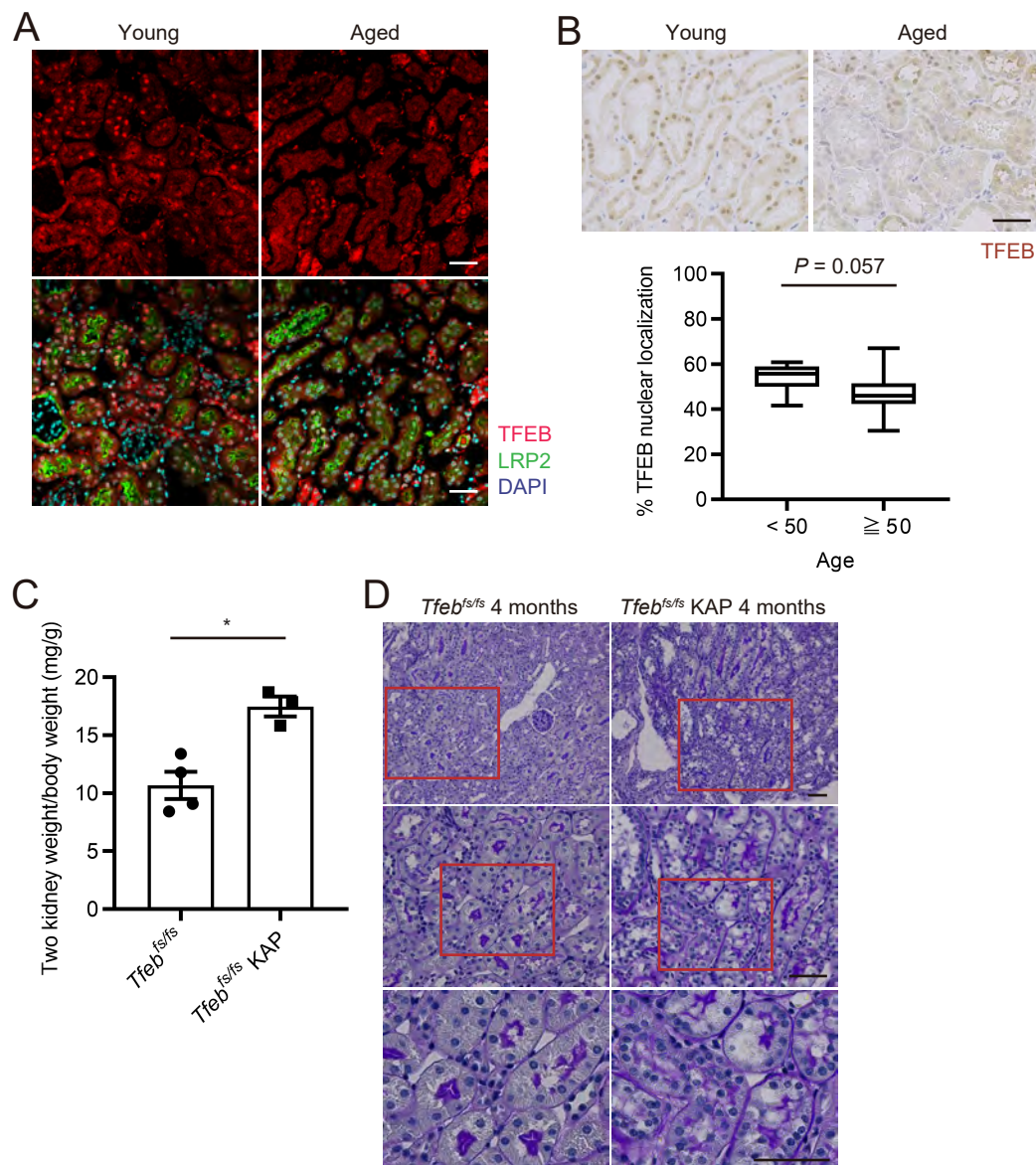
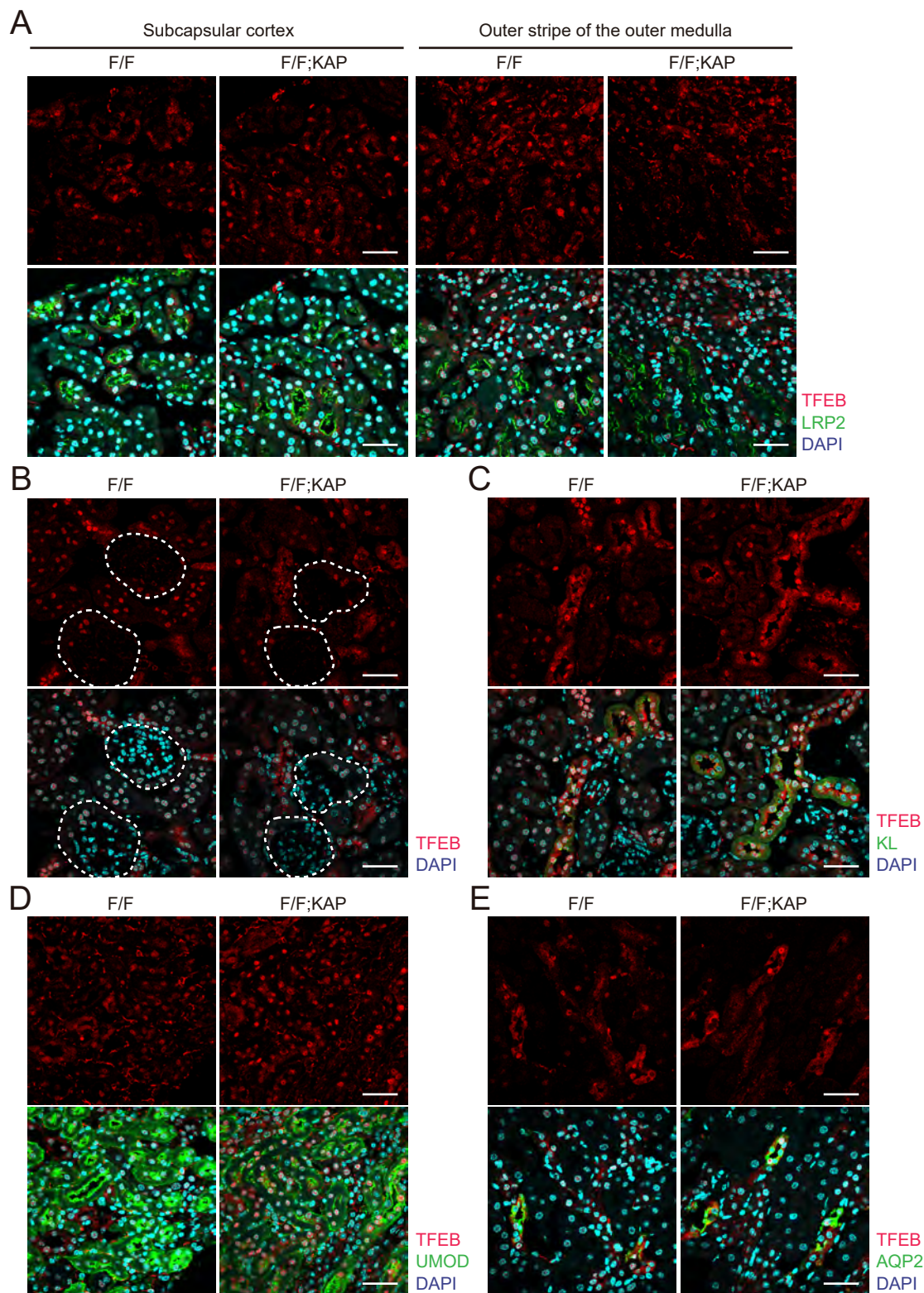
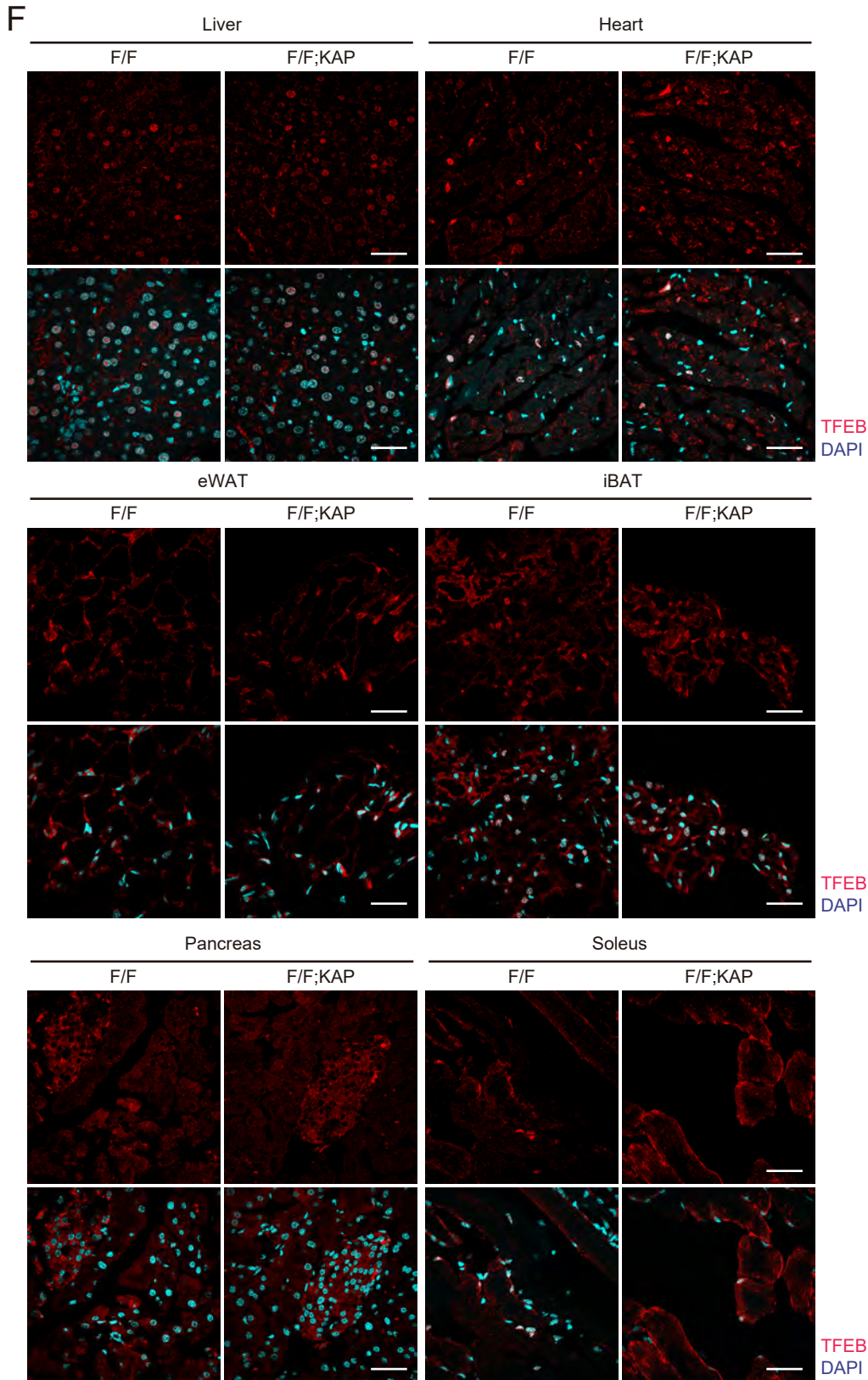


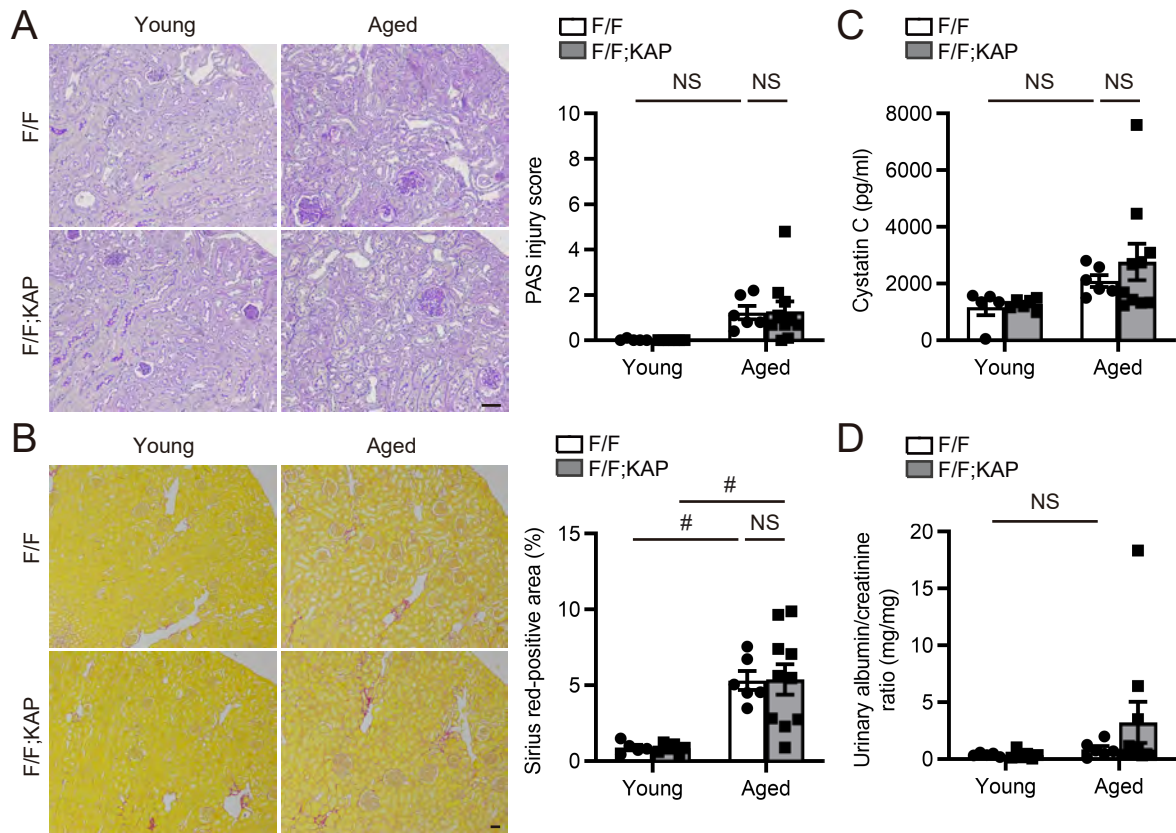


Supplemental Figure 1. PTEC-specific *Tfeb*-overexpressing mice shows aberrant cell proliferation. (A) Representative low-magnification images showing TFEB in the kidney cortical regions of young (6-week-old) or aged (2-year-old) mice ($n = 11$). Sections were immunostained for LRP2, a marker of proximal tubules (green) and counterstained with DAPI (blue). (B) Representative images of immunohistochemical staining for TFEB on kidney specimens obtained from young (under 50 years old) or aged (over 50 years old) patients. Specimens were counterstained with hematoxylin. Kidney biopsy samples from CKD patients were analyzed, using the dataset previously reported in our papers (ref. 20 ($n = 21$)). (C) The ratio of the combined kidney weight to the total body weight of 4-month-old $Tfeb^{fs/fs}$ or $Tfeb^{fs/fs}$ KAP mice ($n = 3-4$). (D) Representative images of PAS staining in the kidneys of 4-month-old $Tfeb^{fs/fs}$ or $Tfeb^{fs/fs}$ KAP mice ($n = 3-4$). Magnified images in $Tfeb^{fs/fs}$ KAP mice show aberrant cell proliferation and vacuolar degeneration in proximal tubules. Bars: 40 μm (A) and 50 μm (B and D). Data are provided as bar graphs showing means $\pm$ standard error (SE) or box plots showing median values and interquartile range. Boxes represent the 25th and 75th percentile, lines inside the boxes represent medians, whiskers are plotted by Tukey method. Statistically significant differences: * $P < 0.05$ versus $Tfeb^{fs/fs}$ control littermates (B, Wilcoxon rank sum test; C, two-tailed Student's t test). $Tfeb^{fs/fs}$, mice carrying *Tfeb-3xFlag*^{fs/fs} under the control of a strong CAG promoter; $Tfeb^{fs/fs}$ KAP, mice carrying *Tfeb-3xFlag*^{fs/fs} under the control of a strong CAG promoter crossed with the KAP-Cre.

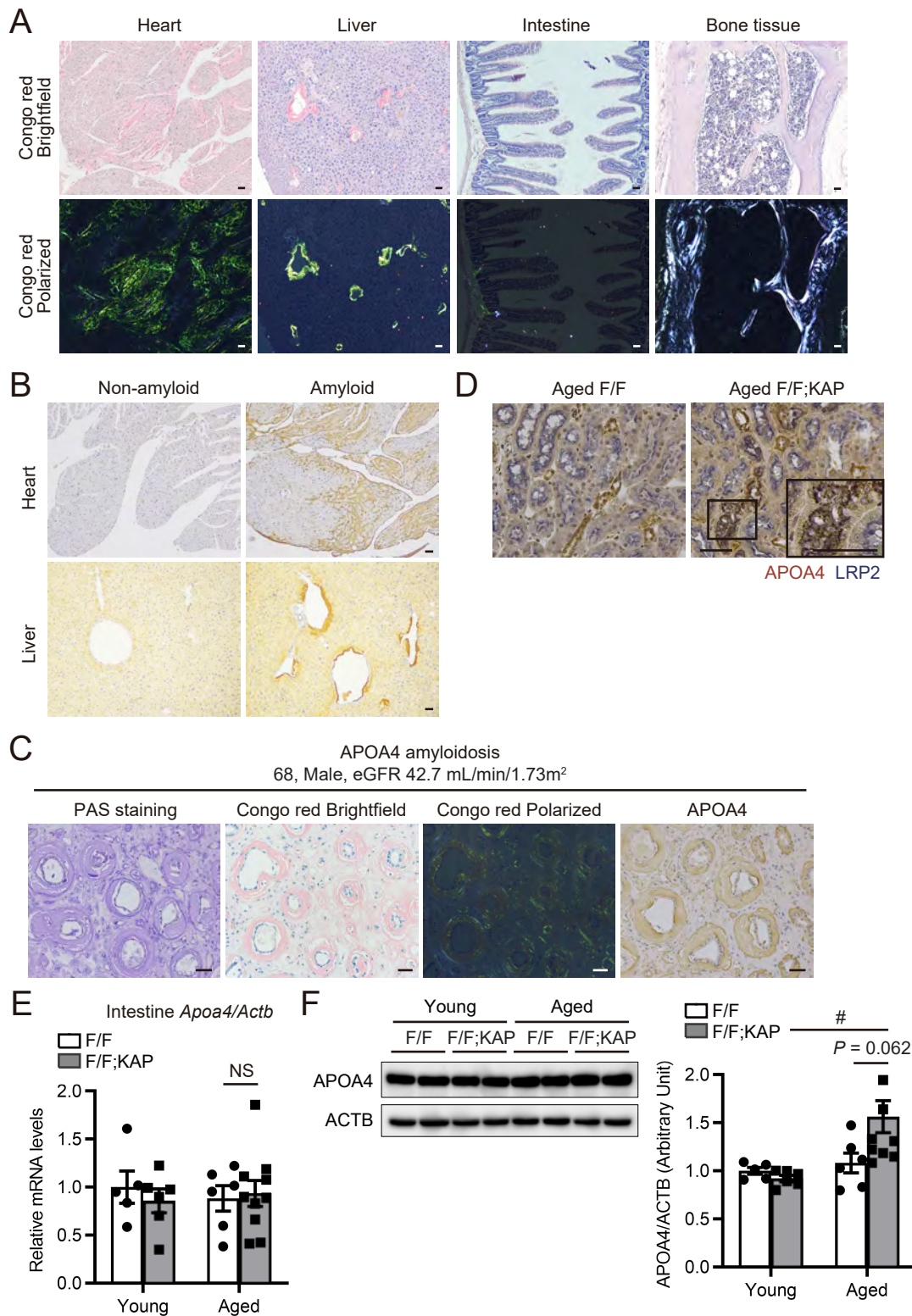




Supplemental Figure 2. TFEB is specifically deleted in the S3 segment of the proximal tubules. (A–E) Representative immunofluorescence images showing TFEB in different segments of the kidneys of young mice. Sections were coimmunostained with LRP2 (a marker of the proximal tubules) (A), KL (mainly expressed in the distal tubules) (C), UMOD (mainly expressed in the thick ascending limbs of the loop of Henle) (D), or AQP2 (a marker of the collecting ducts) (E). S1/S2 segments are mainly distributed in the subcapsular cortex, while S3 segments are mainly distributed in the outer stripe of the outer medulla (A). White dotted lines enclose renal corpuscles, which consist of glomeruli and Bowman's capsules (B). (F) Representative immunofluorescence images showing TFEB in different organs. Sections were counterstained with DAPI. Bars: 40 μ m. F/F, *Tfeb^{fl/fl}* mice; F/F;KAP, *Tfeb^{fl/fl}* KAP mice.

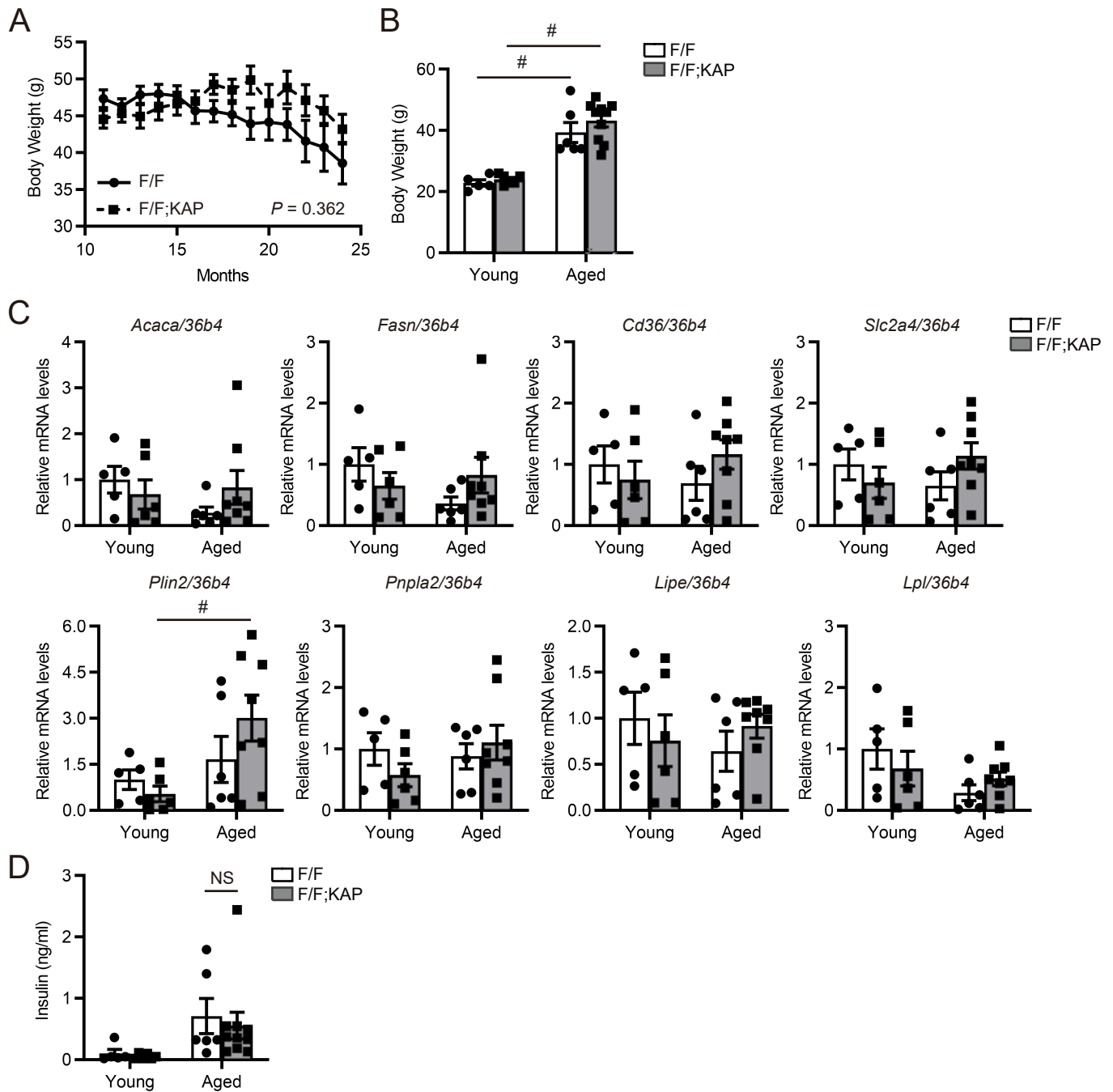


Supplemental Figure 3. Long-term TFEB deficiency in PTECs does not largely induce renal dysfunction. (A and B) Representative images of PAS staining (A) and picrosirius red staining (B) in the kidneys of young (6-week-old) and aged (2-year-old) *Tfeb^{fl/fl}* or *Tfeb^{fl/fl}* KAP mice (n = 5–10). The tubular injury score and the sirius red-positive area was shown. (C and D) Plasma cystatin C concentrations and urinary albumin/creatinine ratio in the young and aged *Tfeb^{fl/fl}* or *Tfeb^{fl/fl}* KAP mice (n = 5–10). Bars: 50 μ m. Data are provided as bar graphs showing means $\pm$ standard error (SE). Statistically significant differences: #*P* < 0.05 versus young mice (one-way ANOVA followed by the Tukey-Kramer test). F/F, *Tfeb^{fl/fl}* mice; F/F;KAP, *Tfeb^{fl/fl}* KAP mice.

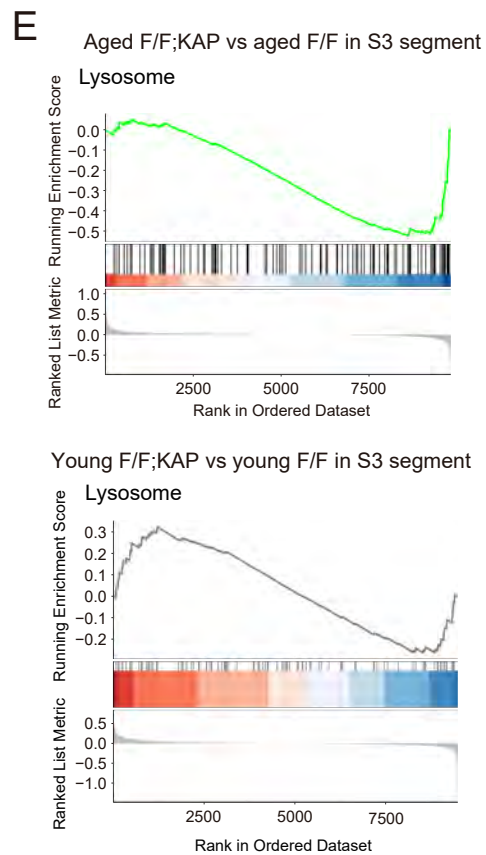
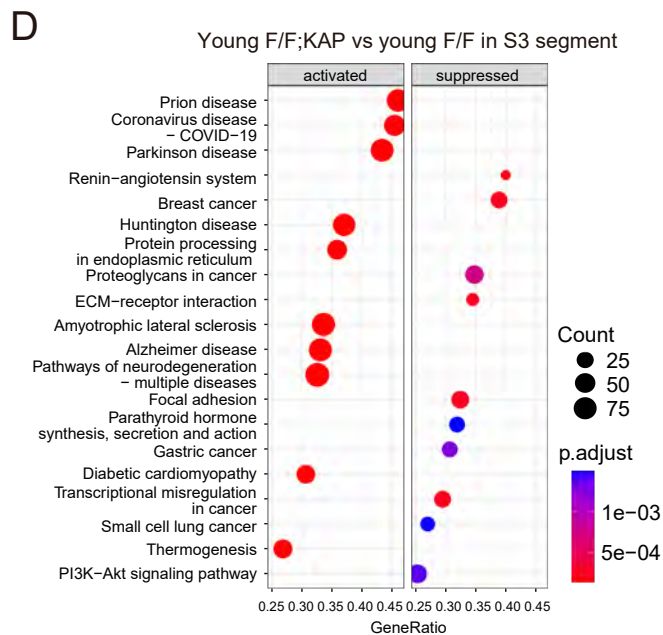
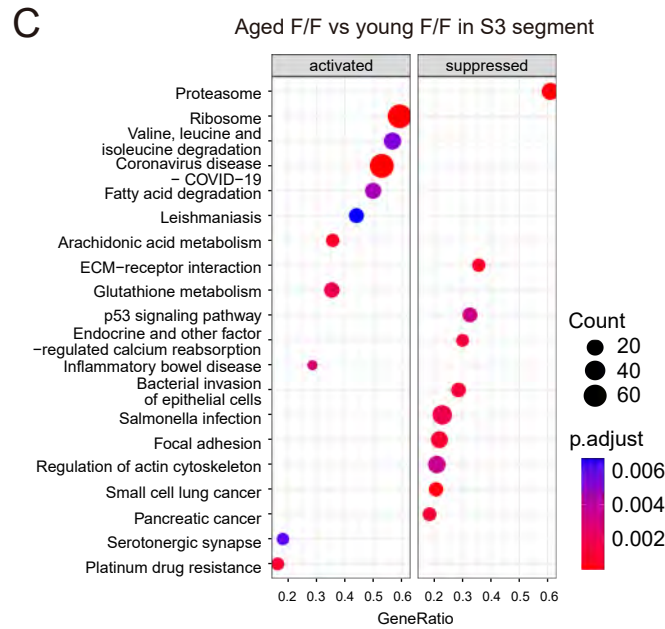
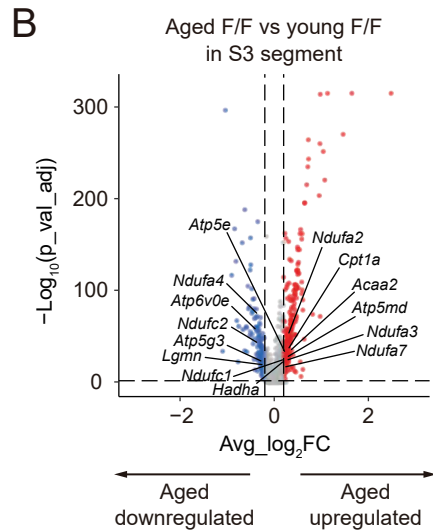
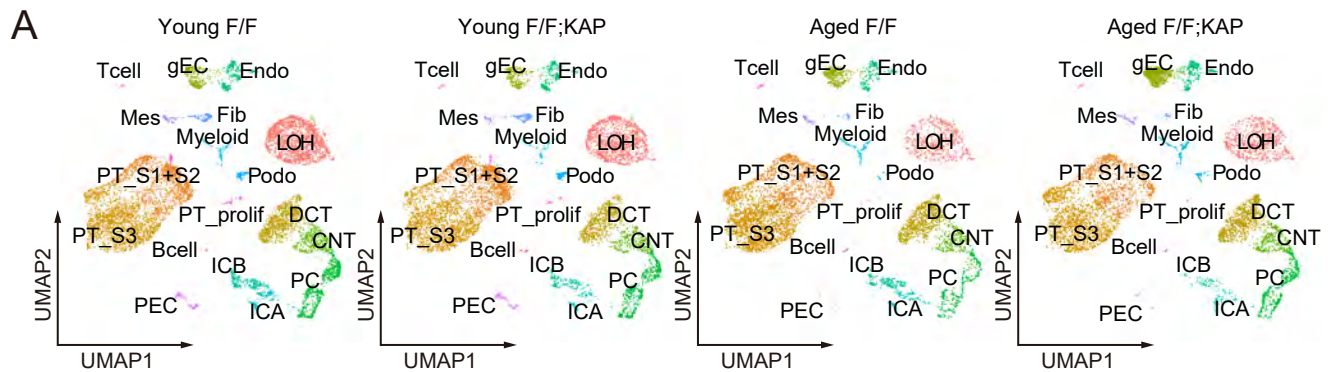


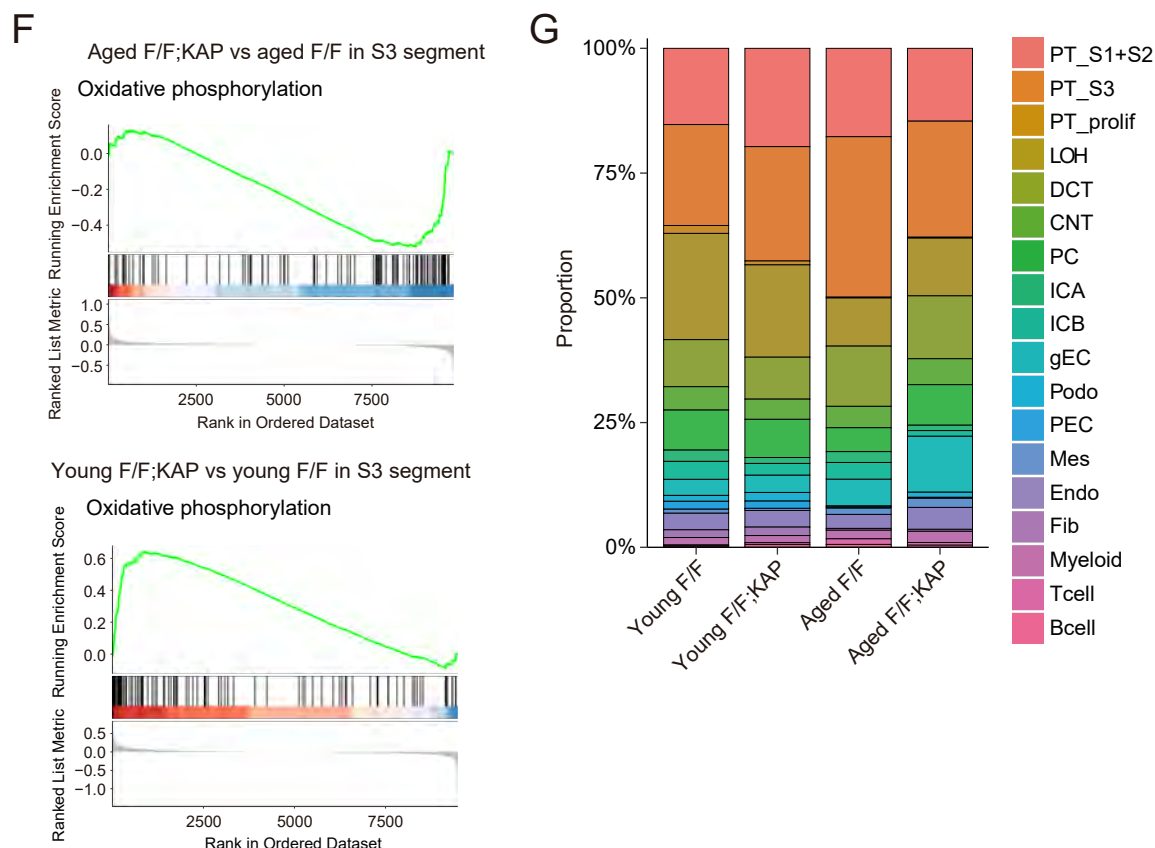
Supplemental Figure 4. TFEB deficiency in PTECs causes systemic APOA4 amyloidosis with age. (A and B)

Representative images of Congo red staining (A) and APOA4 immunostaining (B) in various organs of aged (2-year-old) *Tfeb^{fl/fl}* KAP mice with (A and B) or without (B) amyloid deposits. Sections were counterstained with hematoxylin. (C) Representative images of PAS staining, Congo red staining, and immunohistochemical staining for APOA4 in the medulla regions of human autopsy kidney samples. Specimens were counterstained with hematoxylin. (D) Representative images of APOA4 immunostaining in the kidneys of aged *Tfeb^{fl/fl}* or *Tfeb^{fl/fl}* KAP mice. Sections were immunostained for LRP2, a marker of proximal tubules (blue) and counterstained with hematoxylin. (E) *Apoa4* mRNA levels relative to *Actb* in the intestine of young and aged *Tfeb^{fl/fl}* or *Tfeb^{fl/fl}* KAP mice (n = 5–10). (F) Representative western blot images of APOA4 in liver lysates of young and aged *Tfeb^{fl/fl}* or *Tfeb^{fl/fl}* KAP mice (n = 5–10). Blots were set up in parallel and run contemporaneously. Values are normalized by the mean value of young *Tfeb^{fl/fl}* mice. Statistically significant differences: # $P < 0.05$ versus young mice (E and F, 1-way ANOVA followed by the Tukey-Kramer test). Bars: 50 μ m (A–D). Data are provided as bar graphs showing means $\pm$ standard error (SE). Bright field images of Congo red staining were captured along with corresponding apple green birefringence under polarized light. F/F, *Tfeb^{fl/fl}* mice; F/F;KAP, *Tfeb^{fl/fl}* KAP mice; eGFR, estimated glomerular filtration rate.

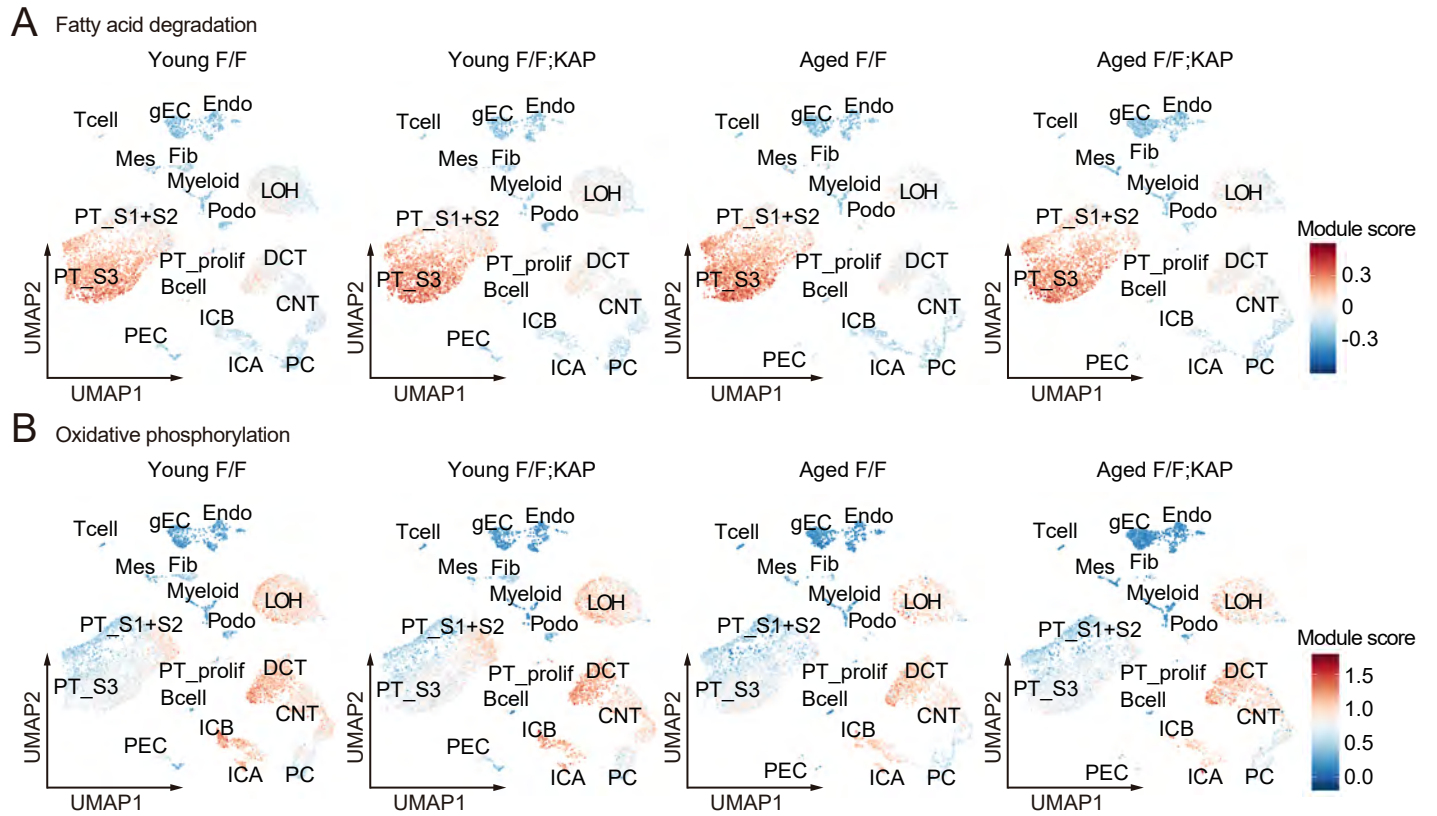


Supplemental Figure 5. TFEB deficiency in PTECs increases adipogenesis in aged mice. (A) Body weight chart for *Tfeb^{fl/m}* (n = 13) or *Tfeb^{fl/m}* KAP mice (n = 15). (B) Body weight at terminal sacrifice of young (6-week-old) and aged (2-year-old) *Tfeb^{fl/m}* or *Tfeb^{fl/m}* KAP mice (n = 5–10). (C) mRNA levels relative to *36b4* in epididymal white adipose tissue of young and aged *Tfeb^{fl/m}* or *Tfeb^{fl/m}* KAP mice (n = 5–8). Values are normalized by the mean value of young *Tfeb^{fl/m}* mice. (D) Plasma insulin levels of young and aged *Tfeb^{fl/m}* or *Tfeb^{fl/m}* KAP mice (n = 5–10). Data are provided as bar graphs showing means $\pm$ standard error (SE). Statistically significant differences: # $P < 0.05$ versus young littermates (one-way ANOVA followed by the Tukey-Kramer test). Mixed-effects analysis was used to assess body weight progress. F/F, *Tfeb^{fl/m}* mice; F/F;KAP, *Tfeb^{fl/m}* KAP mice.



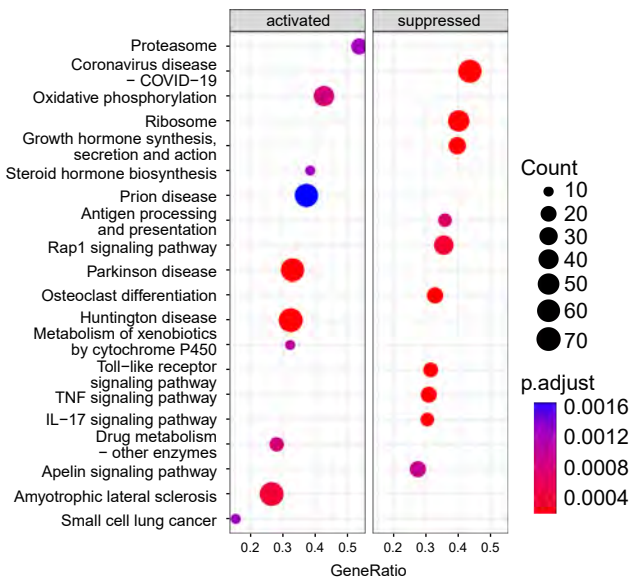


Supplemental Figure 6. TFEB deficiency does not cause downregulation of lysosome or oxidative phosphorylation pathway in the S3 segment of young mice. (A) Cells in each group were mapped by UMAP separately. (B) Volcano plots depicting differentially expressed genes. Plots were discriminated based on adjusted P value < 0.05 and $\log_2$ fold change threshold = 0.20. Colored dots correspond to individual genes whose expression levels were downregulated (blue) and upregulated (red). (C and D) Results of KEGG pathway gene set enrichment analyses using the gseKEGG in the R package clusterProfiler. The dot size represents the numbers of genes. The dot color scale corresponds to the adjusted P value. (E and F) GSEA-based KEGG-enrichment plots show that the “Lysosome” and “Oxidative phosphorylation” pathway in S3 segment were downregulated not in young *Tfeb*^{fl/fl} KAP mice, but in aged *Tfeb*^{fl/fl} KAP mice. The running enrichment score is plotted as a function of the position in the ranked list of genes. (G) Bar plots showing the relative proportion of each cluster. p_val_ad, adjusted P value; Avg_log₂FC, average log₂ fold change; F/F, *Tfeb*^{fl/fl} mice; F/F;KAP, *Tfeb*^{fl/fl} KAP mice.

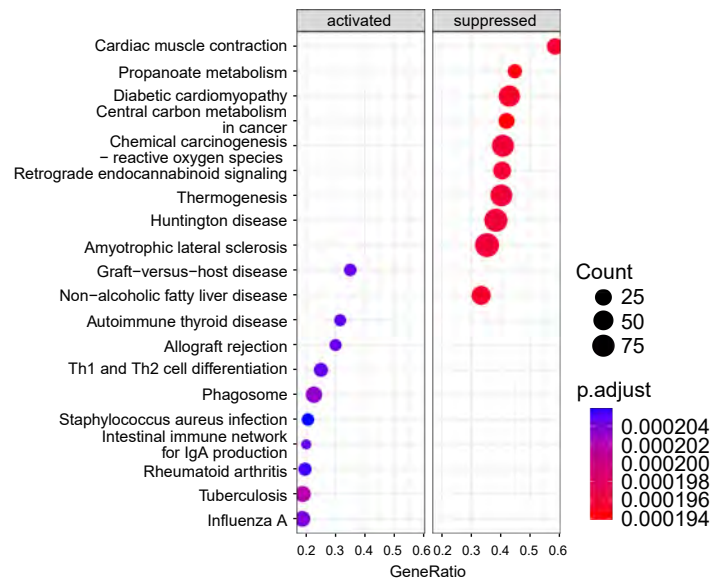


Supplemental Figure 7. Module score distribution. (A and B) The module score distribution in UMAP using “Fatty acid degradation” and “Oxidative phosphorylation” gene sets. F/F, *Tfeb^{fl/fl}* mice; F/F;KAP, *Tfeb^{fl/fl}* KAP mice.

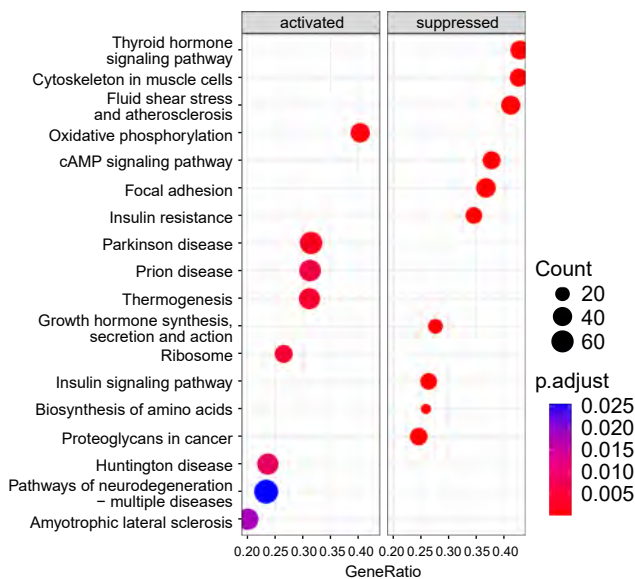
Aged F/F;KAP vs aged F/F in S1 + S2 segment



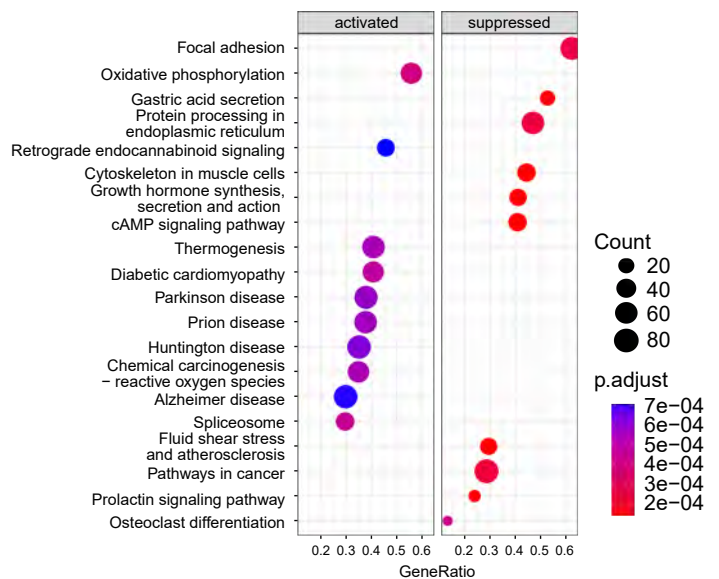
Aged F/F;KAP vs aged F/F in Proliferative-PT



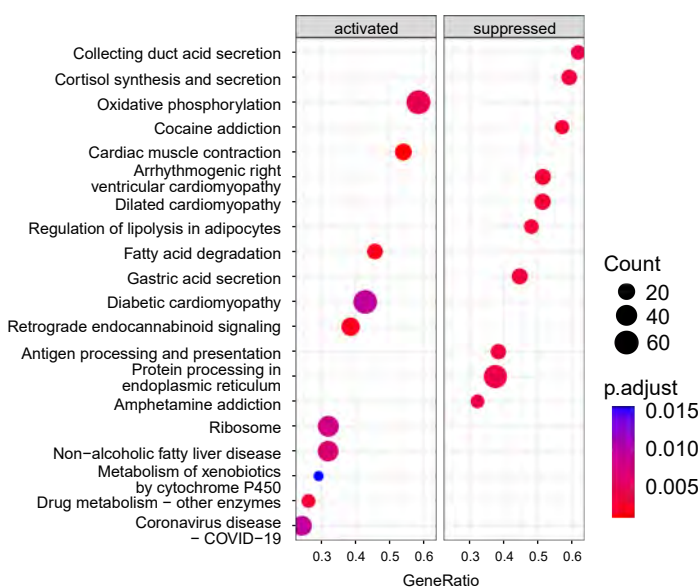
Aged F/F;KAP vs aged F/F in LOH



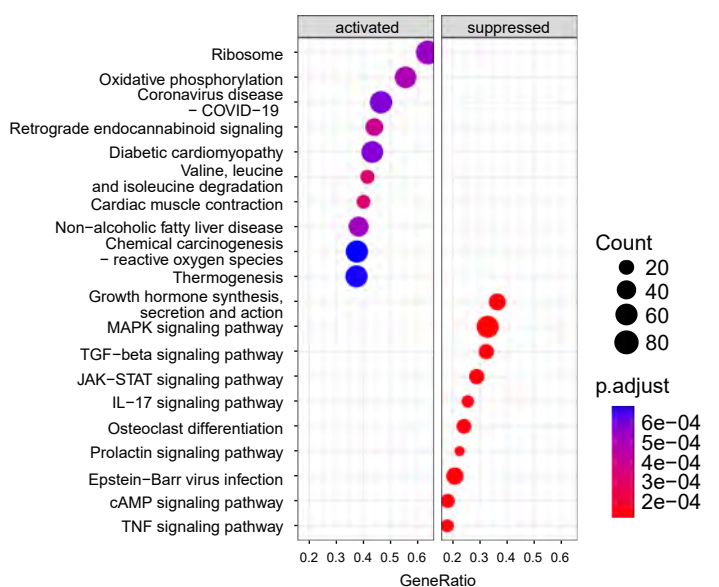
Aged F/F;KAP vs aged F/F in DCT

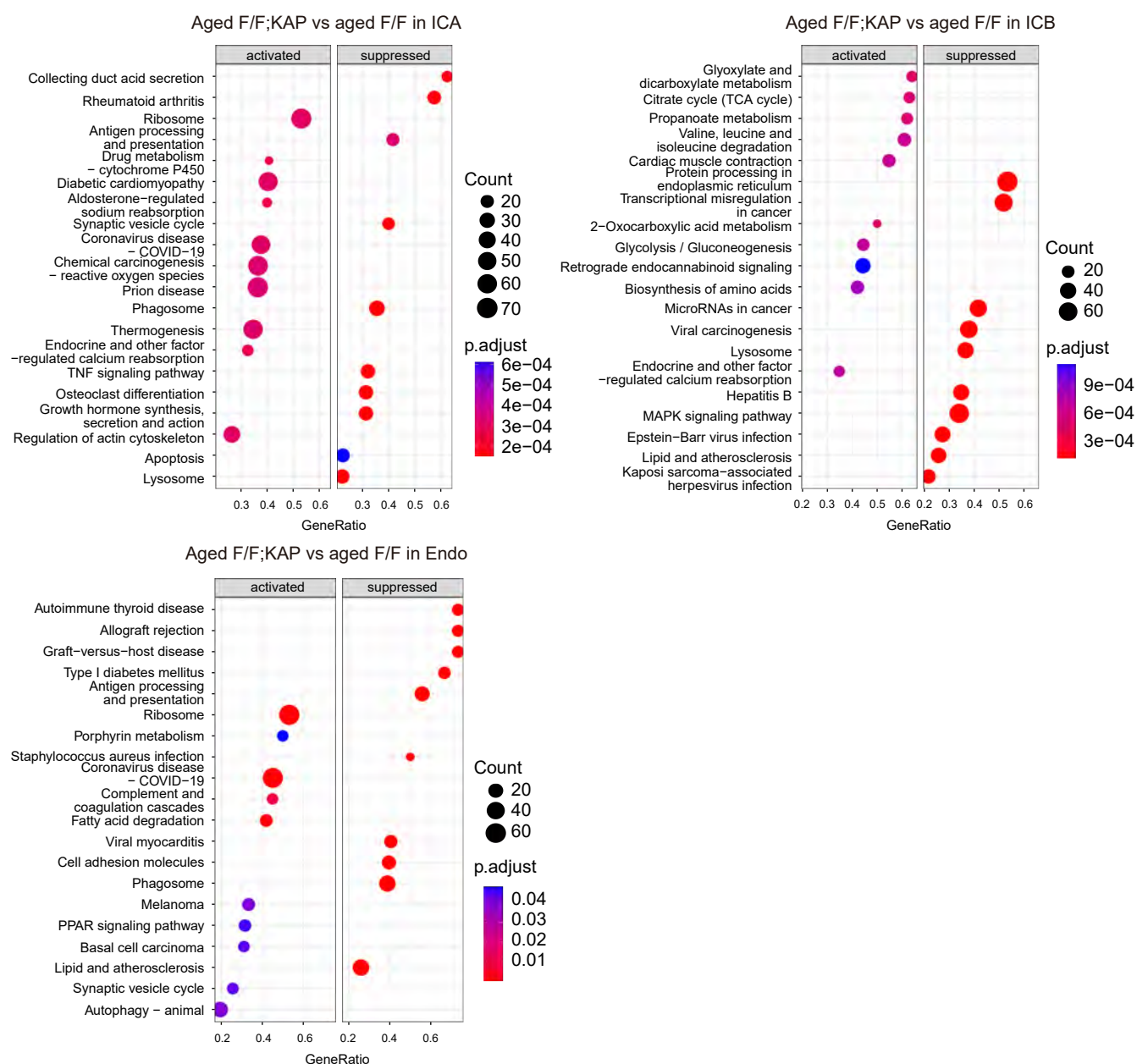


Aged F/F;KAP vs aged F/F in CNT



Aged F/F;KAP vs aged F/F in PC





Supplemental Figure 8. KEGG pathway gene set enrichment analyses. Results of KEGG pathway gene set enrichment analyses in each cluster other than S3 segment, using the gseKEGG in the R package clusterProfiler. The dot size represents the numbers of genes. The dot color scale corresponds to the adjusted *P* value. F/F, *Tfeb*^{fl/m} mice; F/F;KAP, *Tfeb*^{fl/m} KAP mice.

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AEX20370.1-----

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Supplemental Figure 9. APOA4-derived peptides identified by proteomics. APOA4-derived peptides detected from this mice study were highlighted in yellow (UniProt accession: P06728). Peptides identified in other human and monkey studies (ref.48 and 79) were also highlighted in green and blue, respectively (UniProt accession: P06727 and NCBI accession: AEX20370.1, respectively). Red underline shows APOA4 signal sequence reported in ref.74.