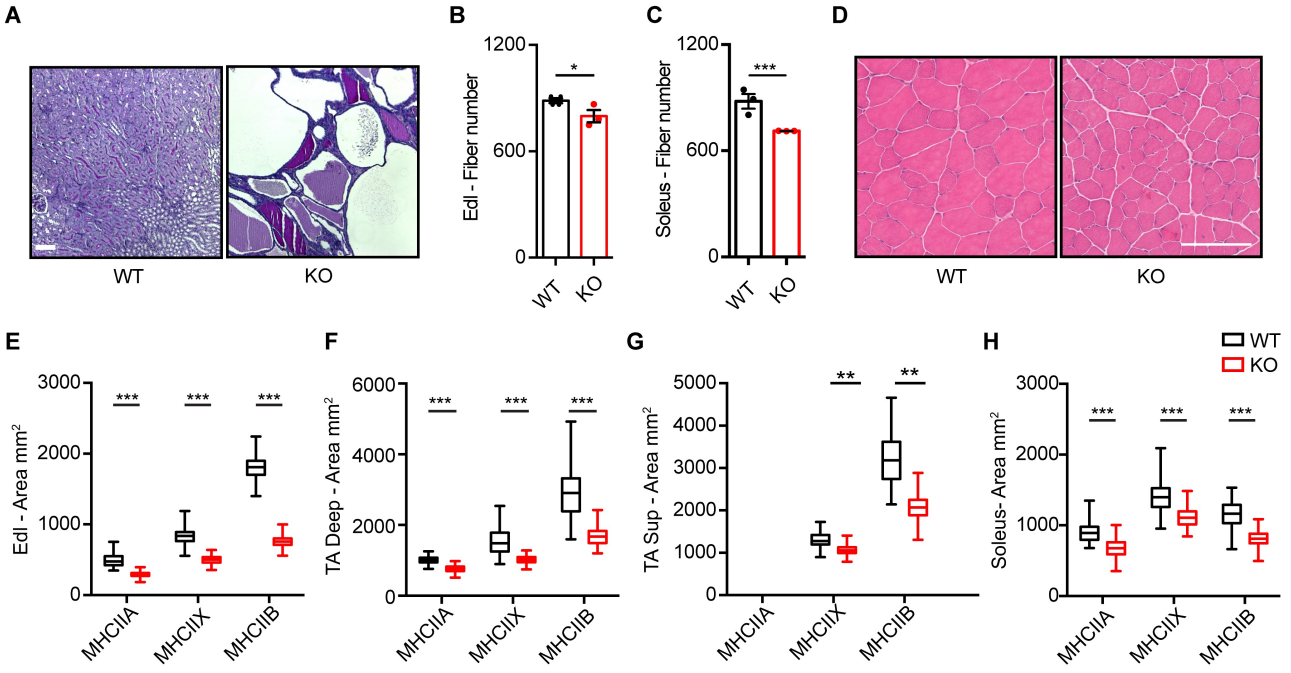
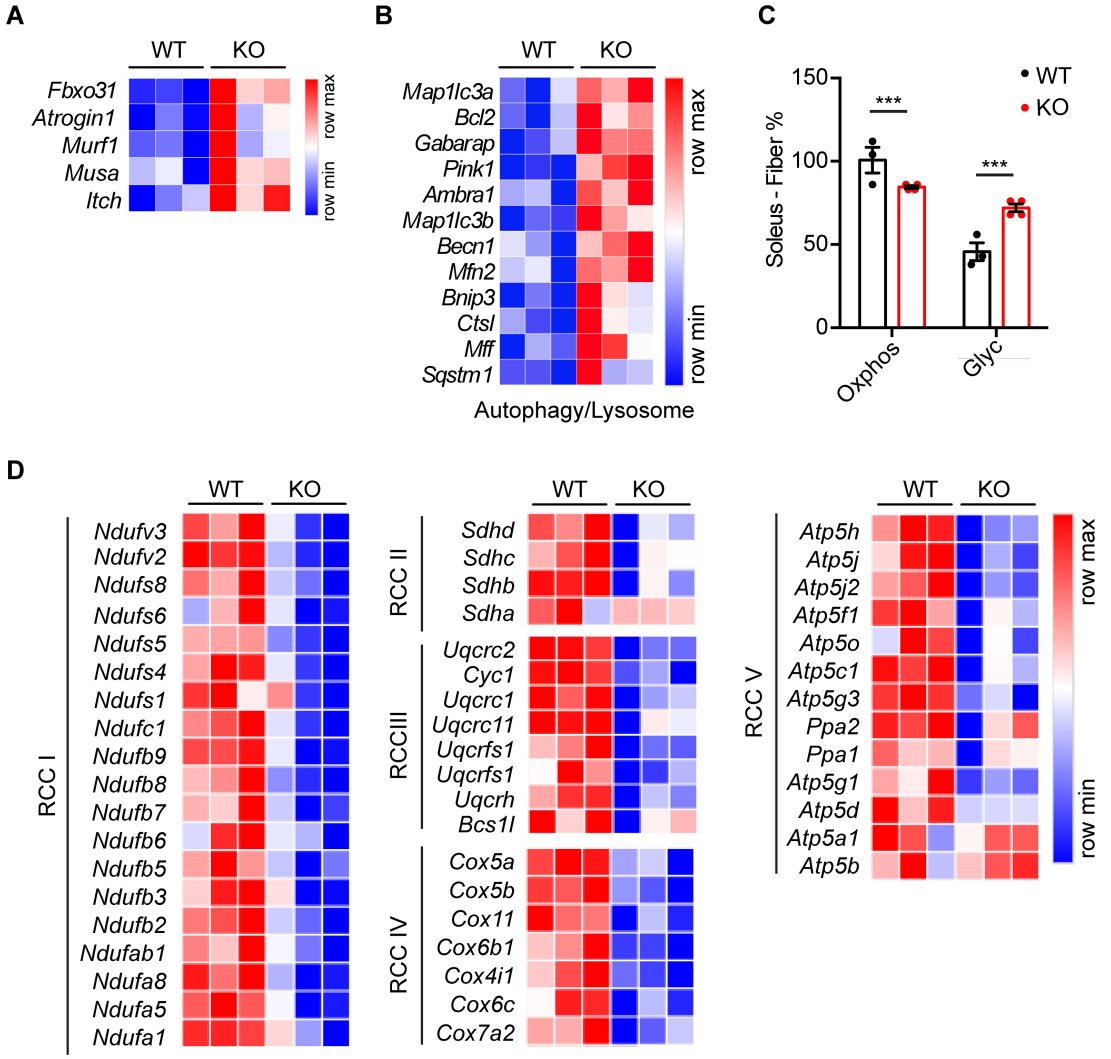
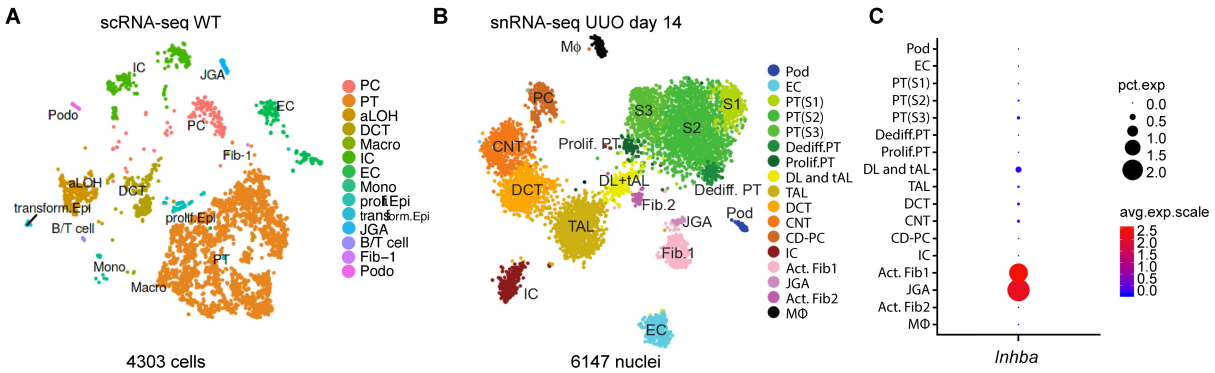


Supplementary Figure 1.
(**A**) Representative images of the renal histology of the kidney of 6 weeks old WT and Kif3aΔTub mice. (**B** and **C**) Analysis of the number of fibers per muscle from WT and Kif3aΔTub mice (n = 3 mice). (**D**) Representative H&E staining of TA muscle in WT, Kif3aΔTub mice. (**E,F,G,H**) Cross-sectional fiber areas assigned to specific MHC isoforms of indicated muscle from WT and Kif3aΔTub mice (n = 3 mice). The minimum, the 25th percentile, the median, the 75th percentile, and the maximum values are indicated in the whiskers plot. Values are mean ± SEM. Student's t-Test used for statistical significance, unless otherwise stated. *p<0.05, **<0.01, ***<0.001.



Supplementary Figure 2.
(**A**) Quantitative gene expression of atrophy-related ubiquitin ligases genes in GC muscle from 6 weeks old WT and Kif3aΔTub mice (n = 4 mice). (**B**) Quantitative gene expression of autophagy/lysosome genes in GC muscle from 6 weeks old WT and Kif3aΔTub mice (n = 4 mice). (**C**) SDH quantification of soleus muscles of WT and Kif3aΔTub mice (n = 3 mice). (**D**) Quantitative gene expression of genes encoding for respiratory chain complex (RCC) proteins in gastrocnemius muscle from 6 weeks old WT and Kif3aΔTub mice (n = 4 mice). Values are mean ± SEM. Student's t-Test used for statistical significance, unless otherwise stated. *p<0.05, **<0.01, ***<0.001.



Supplementary Figure 3.
(**A**) t-SNE projection of 4303 cells from the 5 weeks control kidney demonstrating 14 cell types (n = 1 mouse). (**B**) Data from Wu et al. snRNA-seq of day 14 unilateral ureteral obstruction (UUO) kidney, the t-distributed stochastic neighbour embedding (tSNE) shows 17 separate cell clusters. (**C**) Inhba expression.

A

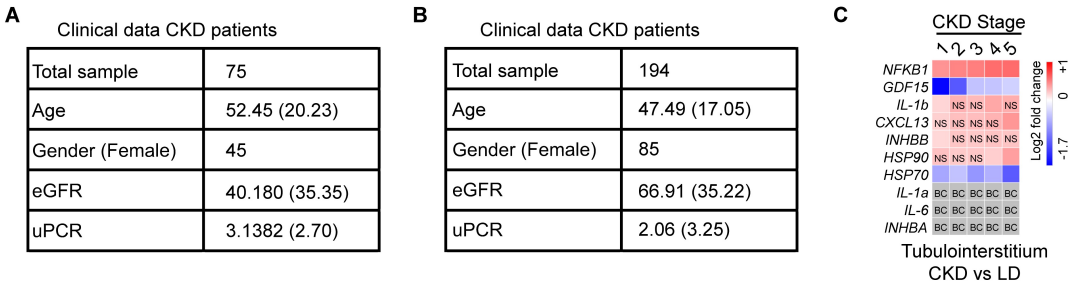
Clinical data CKD patients

Total sample	75
Age	52.45 (20.23)
Gender (Female)	45
eGFR	40.180 (35.35)
uPCR	3.1382 (2.70)

B

Clinical data CKD patients

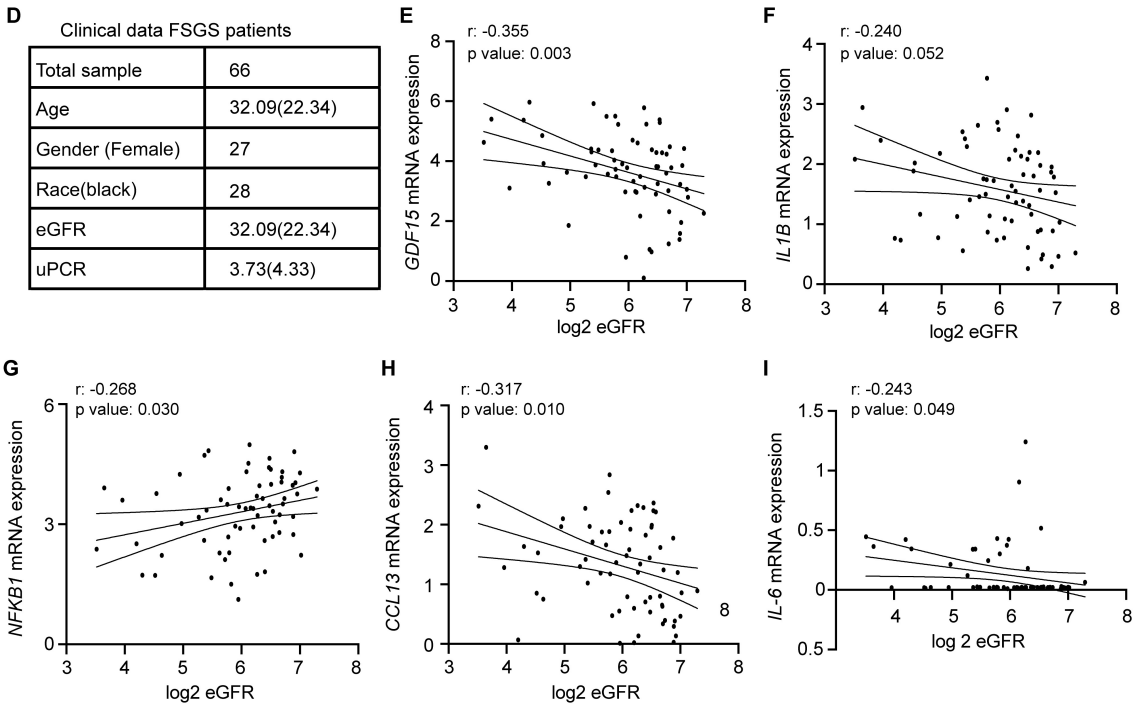
Total sample	194
Age	47.49 (17.05)
Gender (Female)	85
eGFR	66.91 (35.22)
uPCR	2.06 (3.25)



D

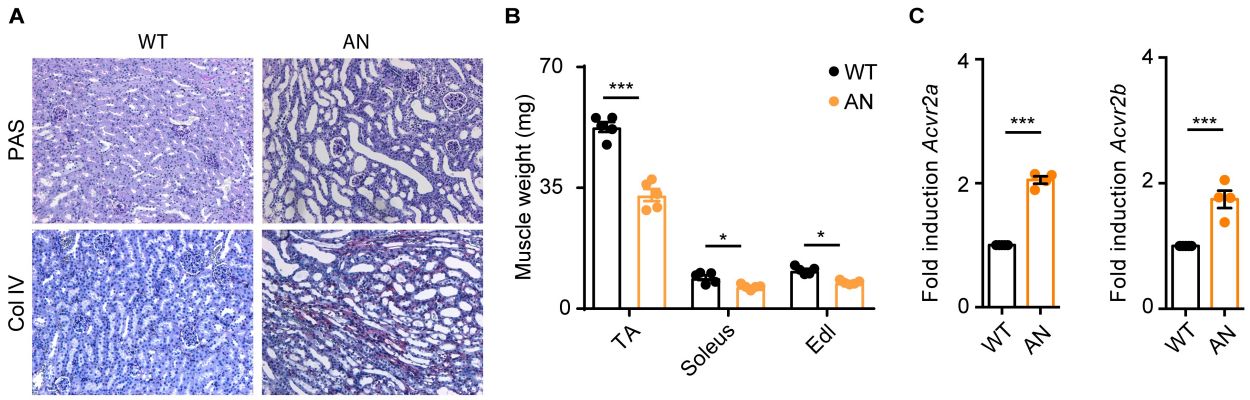
Clinical data FSGS patients

Total sample	66
Age	32.09(22.34)
Gender (Female)	27
Race(black)	28
eGFR	32.09(22.34)
uPCR	3.73(4.33)

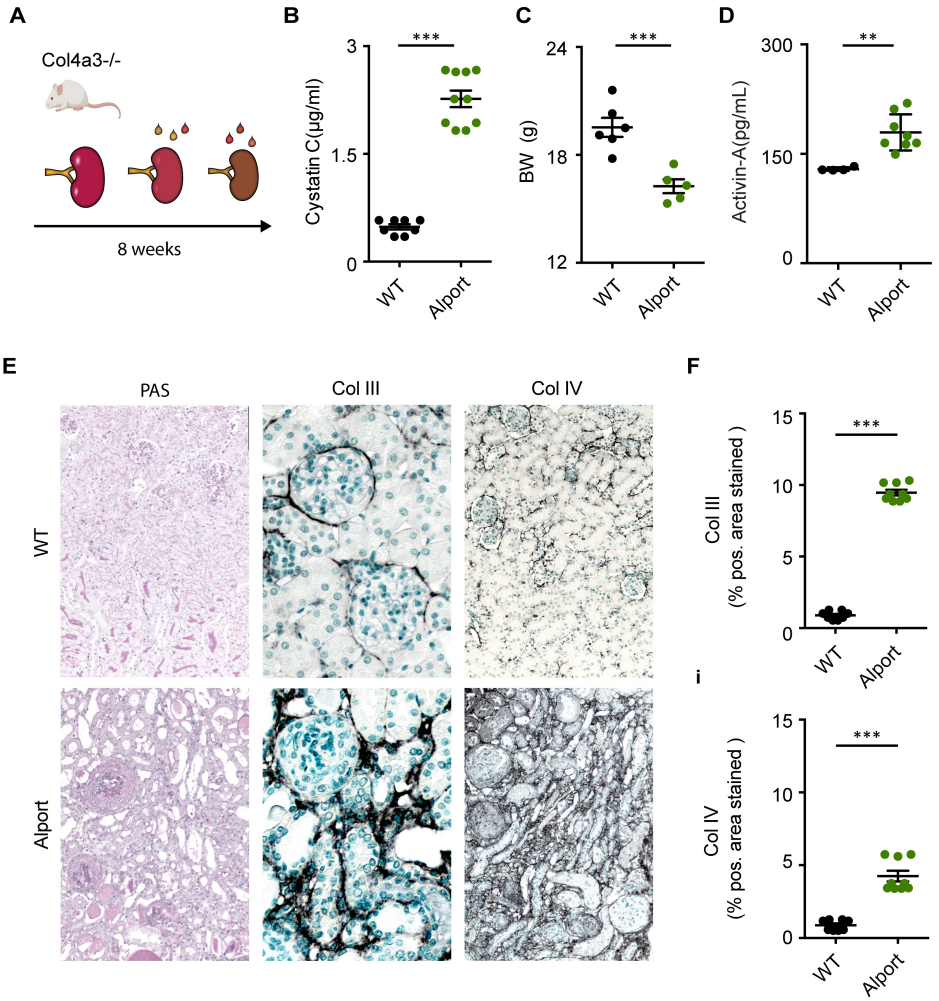


Supplementary Figure 4.

(**A** and **B**) Clinical data of cohorts of human samples. (**C**) Log fold change of quantitative gene expression of genes encoding for pro-cachectic factors in tubulointerstitium of manually microdissected biopsies from patients with different CKD stages (Glom: CKD1: n=55; CKD2: n=52; CKD3: n=44; CKD4: n=26; CKD5: n=10; Tub: CKD1: n = 56; CKD2: n = 46; CKD3: n = 37; CKD4: n = 26; CKD5: n = 10; LD: n = 42). A q-value below 5% was considered to be statistically significant. Non-significantly changed genes are denoted as ns, genes below background cut-off as BC. (**D**) Clinical data of cohorts of human samples. (**E,F,G,H,I**) Spearman correlation analysis of indicated gene mRNA expression with log2eGFR.

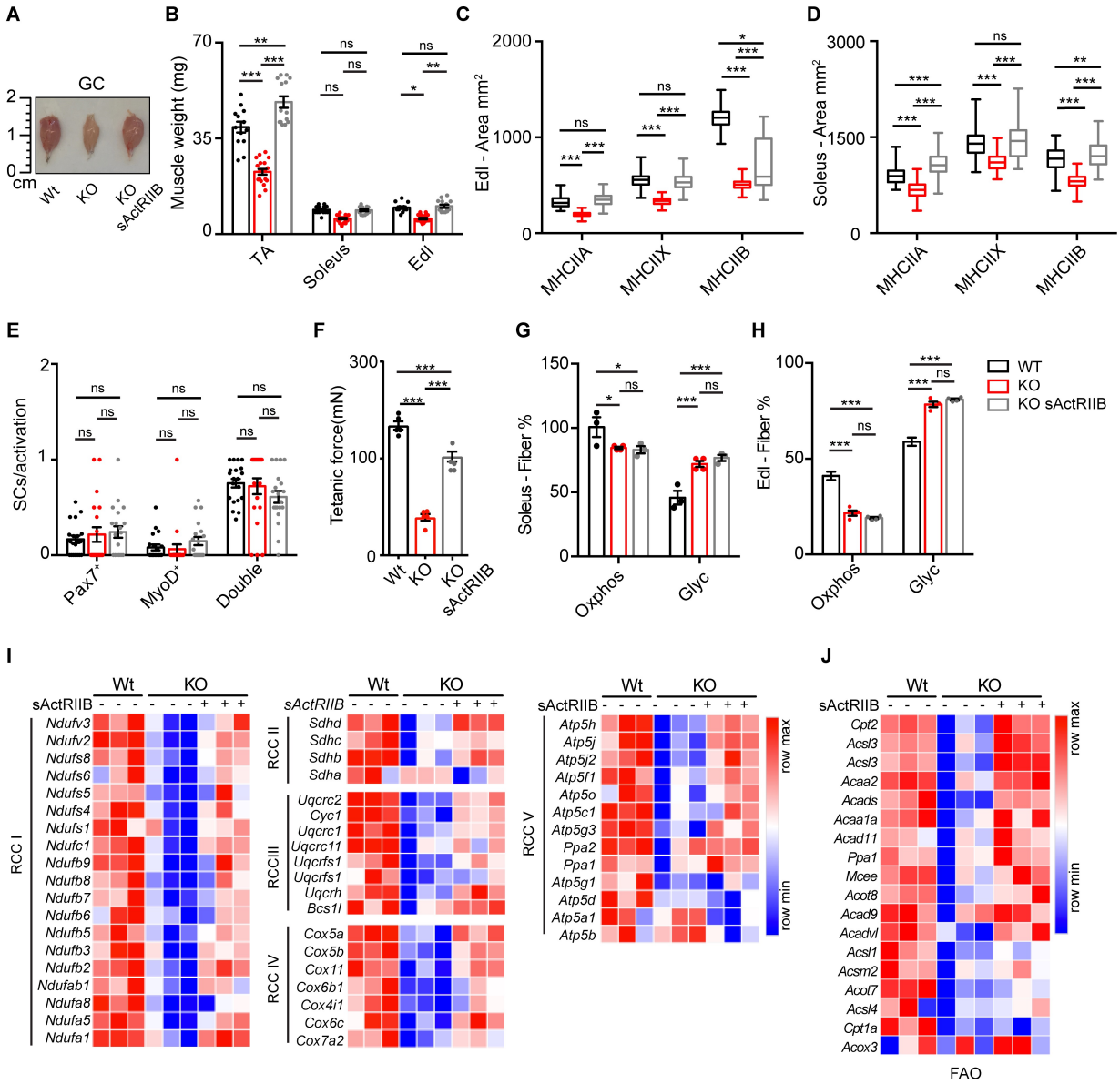


Supplementary Figure 5.
(**A**) Representative images of PAS and collagen type IV staining of kidney of WT and AN mice. (**B**) Muscle tissues were measured in WT and AN mice (n = 5 mice). (**C**) Quantitative gene expression of Acvr2a and Acvr2b in muscles of WT and AN mice (n = 4 mice). Values are mean ± SEM. Student's t-Test used for statistical significance. *p<0.05, **<0.01, ***<0.001.



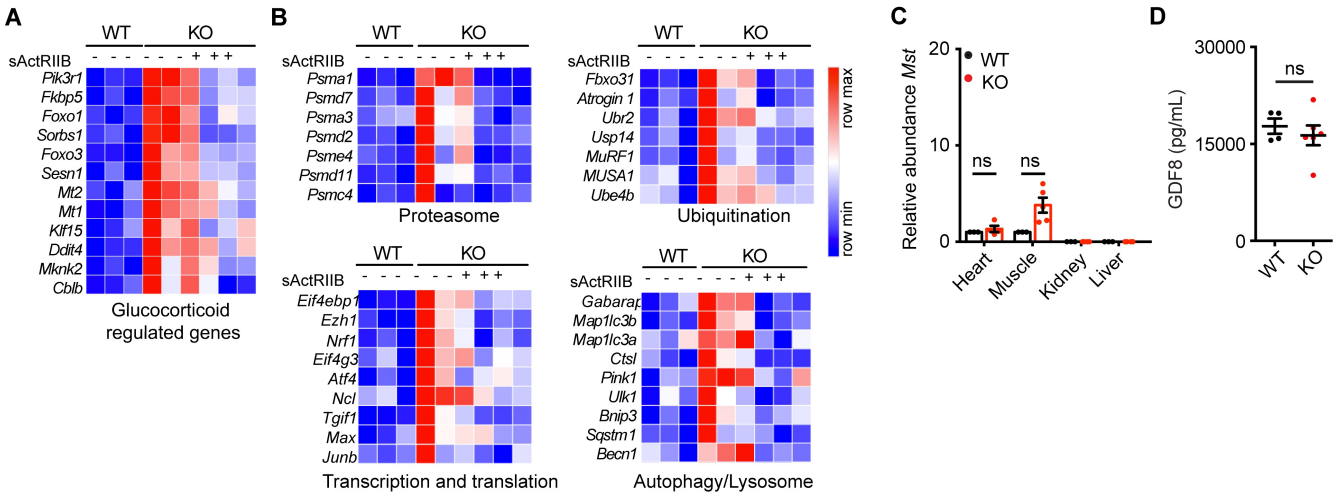
Supplementary Figure 6.

(**A**) Schematic representation of Alport model. (**B**) Cystatin C(ug/ml) measurement (n = 10 mice). (**C**) Body weight was measured in WT and Alport mice (n = 5 mice). (**D**) Blood levels of Activin A in WT and Alport mice determined by ELISA (n = 8 mice). (**E**) Representative images of PAS, collagen type III and collagen type IV staining of kidney of WT and Alport mice. (**F**) Quantification of collagen type III and collagen type IV (% pos. area stained) in kidney of WT and Alport mice (n = 9 mice).. Values are mean ± SEM. Student's t-Test used for statistical significance. *p<0.05, **<0.01, ***<0.001.



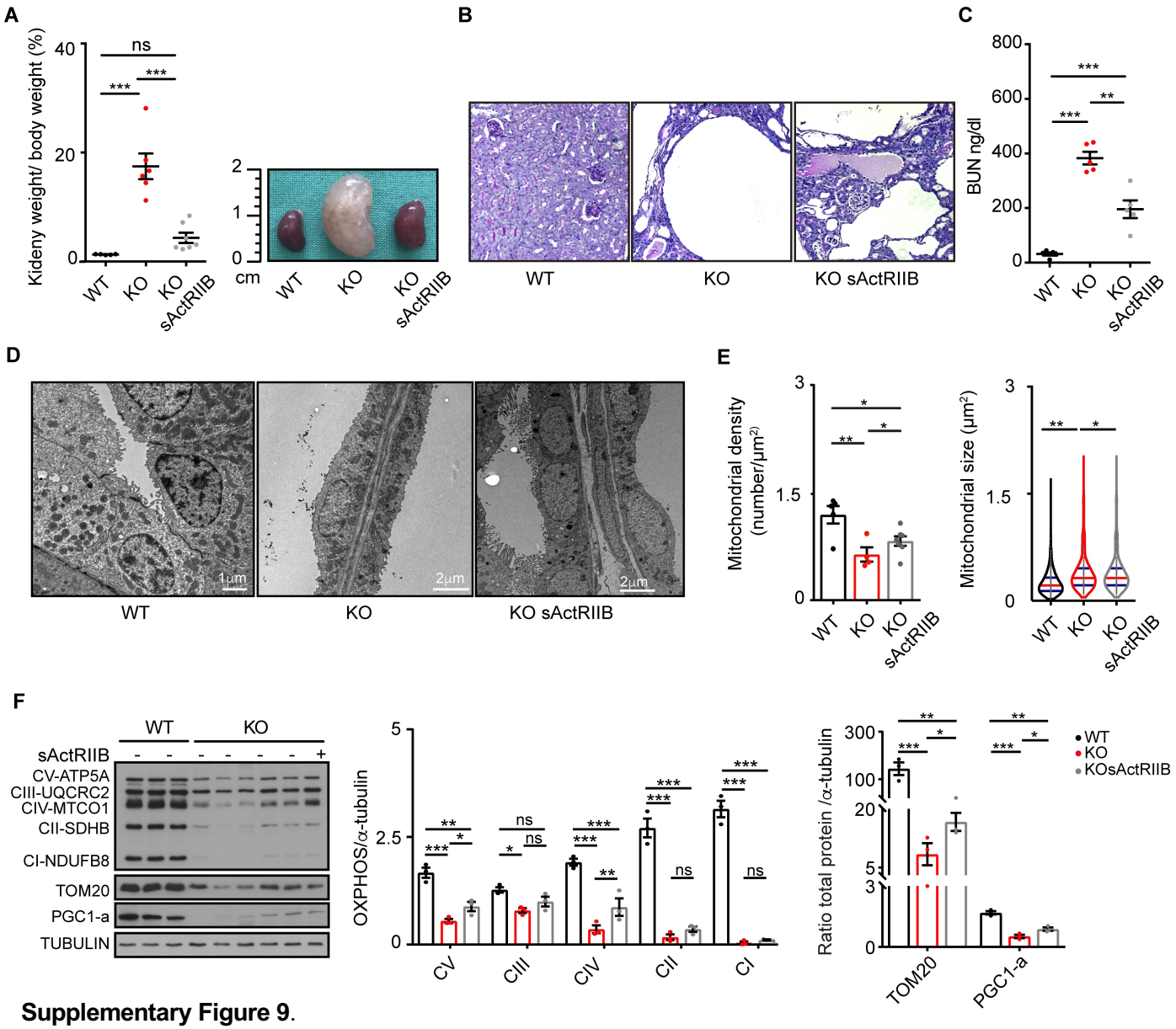
Supplementary Figure 7.

(**A**) Representative image of GC muscle from 6 weeks old WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice. (**B**) Weight of the indicated muscles from WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 14 mice). Data of WT and Kif3aΔTub muscle have already been presented in Supplemental Figure 1E. (**C** and **D**) Cross-sectional fiber areas assigned to specific MHC in EDL and Soleus muscle from WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 3 mice). The minimum, the 25th percentile, the median, the 75th percentile, and the maximum values are indicated in the whiskers plot. Data of WT and Kif3aΔTub muscle have already been presented in figure 1E and H. (**E**) Profiling of SCs differentiation. Data of WT and Kif3aΔTub muscle have already been presented in figure 2B. (**F**) Tetanic force of the EDL muscle from WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice. (**G** and **H**) SDH quantification of EDL and Soleus muscles in Wt, Kif3aΔTub and Kif3aΔTub sActRIIB mice. Representative image of WT and Kif3aΔTub muscle have already been presented in figure 1F. (n = 3 mice). (**I**) Quantitative gene expression of genes encoding for respiratory chain complex (RCC) proteins, in GC muscle from 6 weeks old WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 4 mice). (**J**) Quantitative gene expression of genes encoding for fatty acid oxidation (FAO) proteins, in GC muscle from 6 weeks old WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 4 mice). Values are mean ± SEM. Comparisons of more than two groups were calculated using one-way ANOVA with Tukey multiple comparison tests. *p<0.05, **<0.01, ***<0.001, ns: not statistically significant.



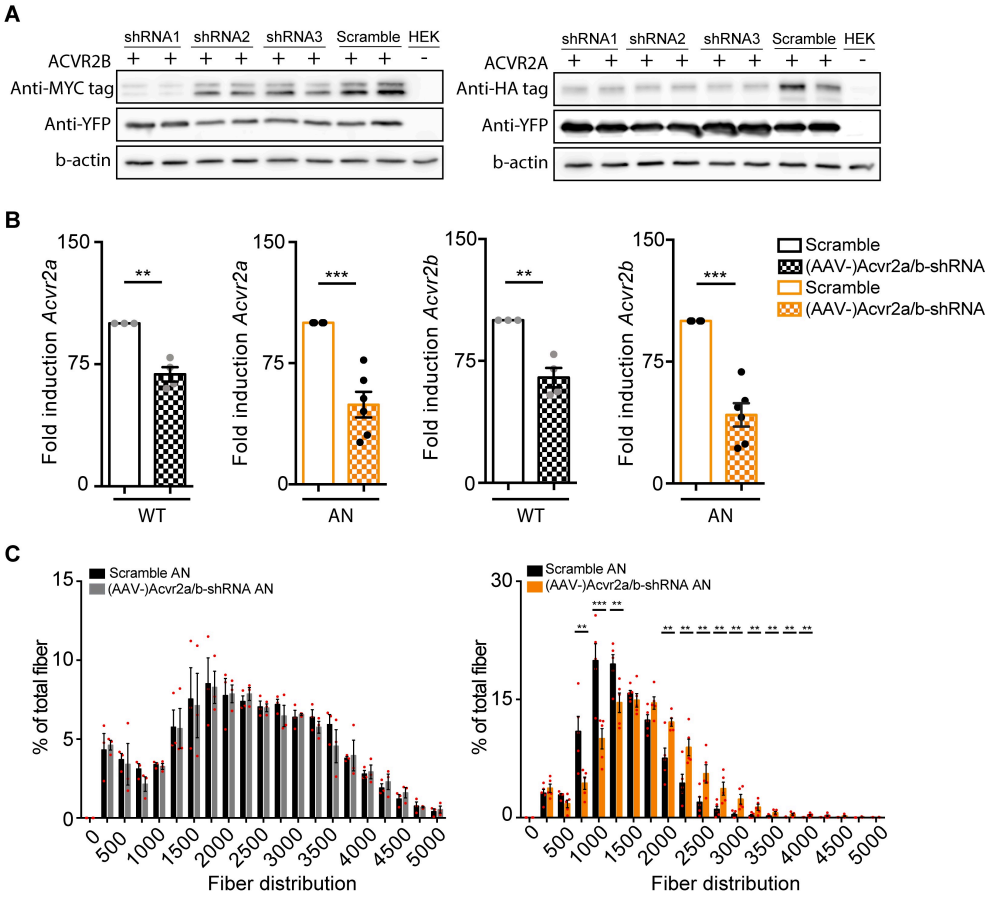
Supplementary Figure 8.

(**A**) Quantitative gene expression of glucocorticoids regulated genes in GC muscle from 6 weeks old WT and Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 4 mice). (**B**) Quantitative gene expression of FoxOs dependent genes in GC muscle from 6 weeks old WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 4 mice). (**C**) Quantitative RT-PCR analysis of Myostatin (Mst) in different organs (n = 4 mice). (**D**) Blood levels of GDF 8 determined by ELISA (n = 6 mice). Values are mean ± SEM. Student's t-Test used for statistical significance, unless otherwise stated. *p<0.05, **<0.01, ***<0.001



Supplementary Figure 9.

(**A**) Left panel: The 2KW/BW expressed as a percentage was measured in WT and Kif3aΔTub and Kif3aΔTub sActRIIB mice; Right panel: representative images of the kidney of 6 weeks old WT, Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 5 mice). 2KW/BW and representative image of WT and Kif3aΔTub kidney have already been presented in figure 1B. (**B**) Representative images of the renal histology of the kidney of 6 weeks old Kif3aΔTub and Kif3aΔTub sActRIIB mice. (**C**) BUN level in Kif3aΔTub and Kif3aΔTub sActRIIB mice (n = 5 mice). BUN level in WT and Kif3aΔTub mice have already been presented in figure 1C. (**D**) Electron microscopy images of kidney from WT, Kif3aΔTub and Kif3aΔTub sActRIIB. (**E**) Quantification of mitochondrial density and size in proximal tubules. One-way ANOVA followed by Bonferroni's multiple comparison tests (n = 3 mice). (**F**) Representative western blots depicting protein levels of mitochondrial OXPHOS proteins and indicated proteins in WT, Kif3aΔTub mice and Kif3aΔTub sActRIIB kidney. Alpha-TUBULIN was used as loading control (n = 3 mice). Values are mean ± SEM. Comparisons of more than two groups were calculated using one-way ANOVA with Tukey multiple comparison tests. *p<0.05, **<0.01, ***<0.001, ns: not statistically significant.



Supplementary Figure 10.
(**A**) Efficiency of the shRNA for Acvr2a and Acvr2b in HEK cells transfected with a mouse ACVR2A-HA and ACVR2B-MYC. (**B**) Quantitative gene expression of Acvr2a and Acvr2b in (AAV-)Acvr2a/b-shRNA and scramble infected muscles of WT and AN mice (n = 6 mice). (**C**) Frequency histogram showing the distribution of cross-sectional areas (µm2) of (AAV-)Acvr2a/b-shRNA and (AAV-)Scramble-shRNA infected muscles of WT and AN mice (n = 4 mice). Values are mean ± SEM. Student's t-Test used for statistical significance, unless otherwise stated. *p<0.05, **<0.01, ***<0.001

Supplemental material

Table. S1 Antibody list for all experiments

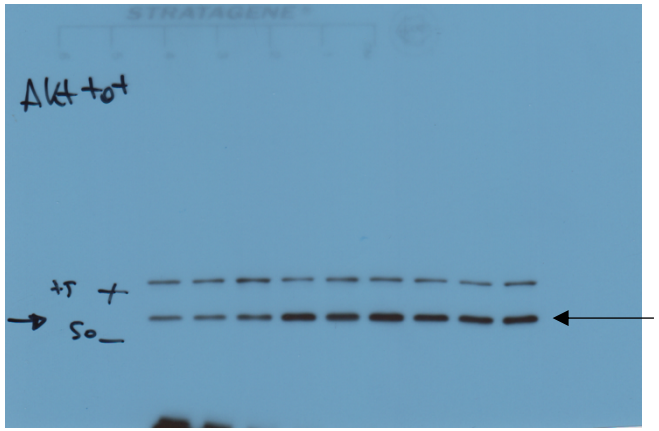
Primary antibodies:

Antigen	Species	Dilution	Supplier
P-Akt (Ser473)	Rabbit	1:1000	Cell signalling Technology #4060
Akt	Rabbit	1:1000	Cell signalling Technology #9272
P-S6 Ribosomal Protein(Ser235/236)	Rabbit	1:1000	Cell signalling Technology #4857
S6 Ribosomal Protein	Rabbit	1:1000	Cell signalling Technology #2215
4E-BP1	Rabbit	1:1000	Cell signalling Technology #9452
P-FoxO1 (Ser256)	Rabbit	1:1000	Cell signalling Technology #9461
FoxO1	Rabbit	1:1000	Cell signalling Technology #9946
P-FoxO1(Thr24)/ FoxO3a (Thr32)	Rabbit	1:1000	Cell signalling Technology #9464
FoxO3	Rabbit	1:1000	Cell signalling Technology #9946
LC3B	Rabbit	1:1000	Cell signalling Technology #2775
Anti-p62/SQSTM1	Rabbit	1:1000	Sigma P0067
P-p38MAPK (Thr180/Tyr182)	Rabbit	1:1000	Cell signalling Technology #9211
p38MAPK	Rabbit	1:1000	Cell signalling Technology #9212
P-Stat3(Tyr705)	Rabbit	1:1000	Cell signalling Technology #9145
Stat3	Rabbit	1:1000	Cell signalling Technology #30835
PGC-1α	Rabbit	1:1000	Cell signalling Technology #2178
TOM20	Mouse	1:1000	Santa Cruz (Sc-11415)
GAPDH	Mouse	1:10000	Abcam (ab8245)
Puromycin	Mouse	1:5000	Millipore
OXPHOS Cocktail	Mouse	1:10000	Abcam (ab110413)
α –Tubulin	Mouse	1:5000	Sigma Aldrich T9026
Anti-HA Tag	Rabbit	1:5000	Cell signalling Technology #2276
Anti-Myc Tag	Mouse	1:1000	Cell signalling Technology #3724
Anti-GFP	Rabbit	1:1000	Abcam (ab290)
Anti-beta-Actin	Mouse	1:10000	Sigma Aldrich A5441-100UL
Anti-Laminin	Rabbit	1:500	Abcam (ab11575)

Secondary antibodies:

Antigen	Species	Dilution	Supplier
Anti-rabbit IgG, HRP-linked	Goat	1:1000	Cell signalling Technology #7074
Anti-Mouse IgG , HRP-linked	Goat	1:5000	BioRad#1706516
Alexa fluor 555 anti-rabbit	Donkey	1:1000	Invitrogen # A-31572

Full unedited gels for Figure 7c



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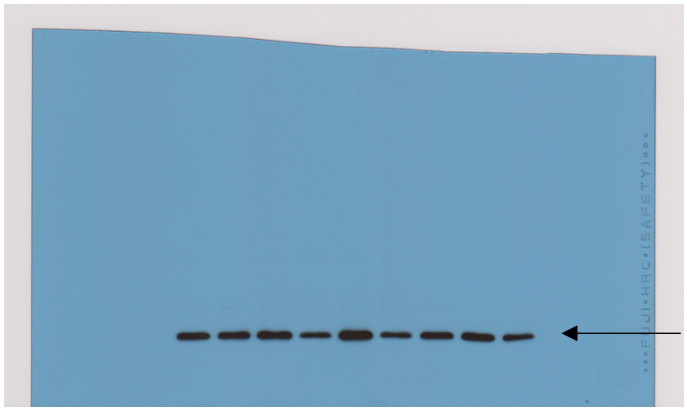
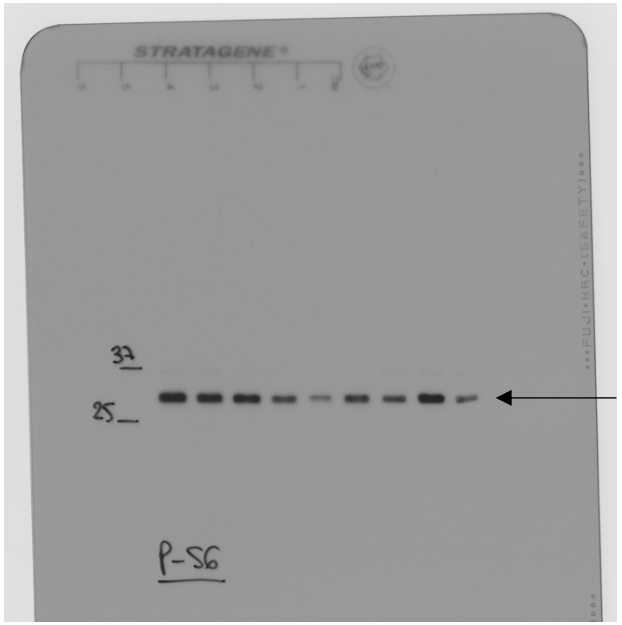


P-Akt



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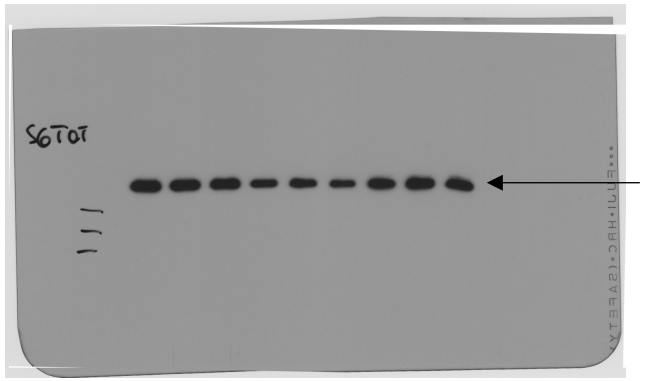
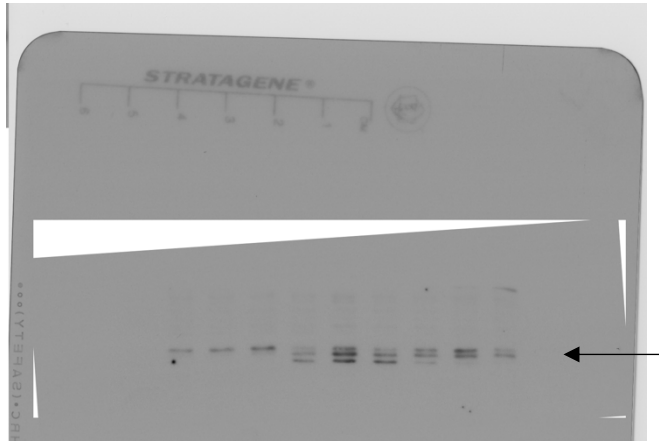


S6



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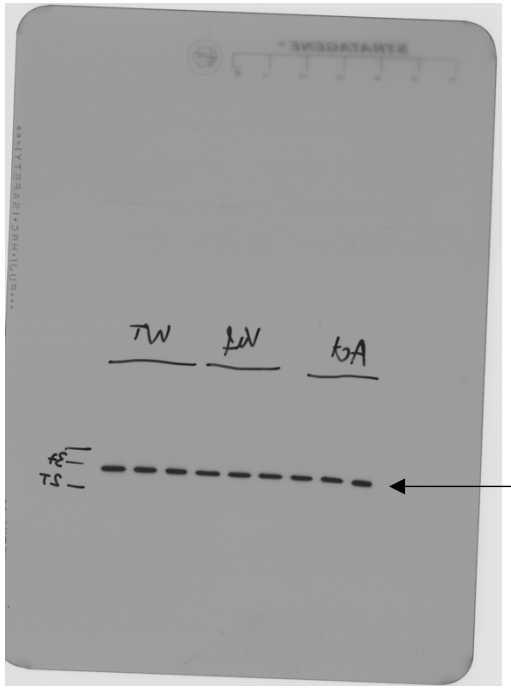
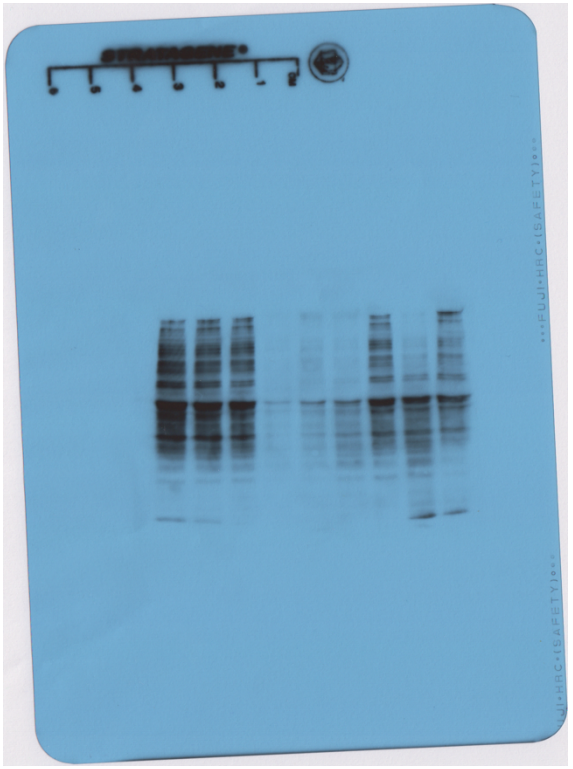


GAPDH

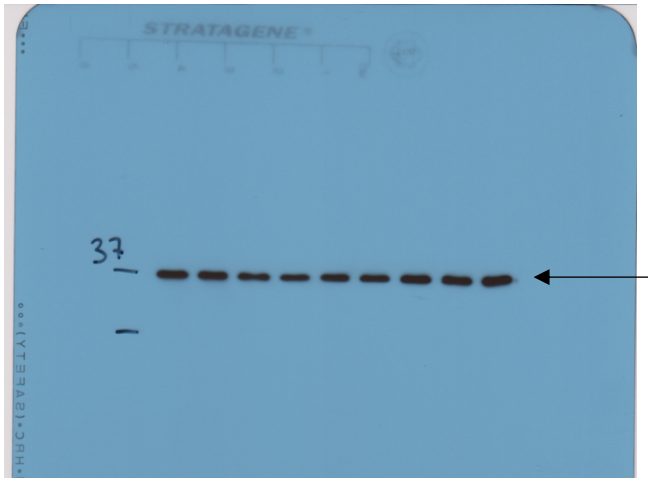
Full unedited gel for Figure 7d



Anti-puromycin

Full unedited gels for Figure 7e

P-p38



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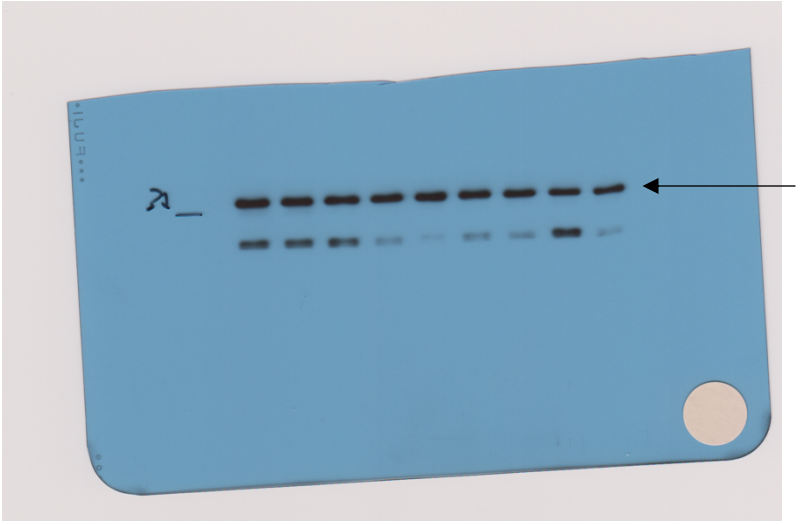

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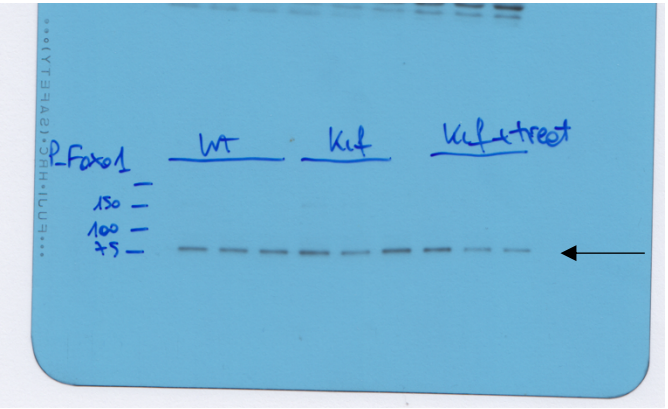

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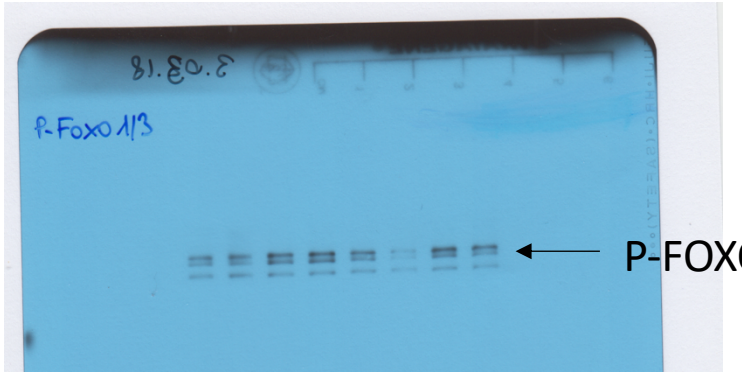

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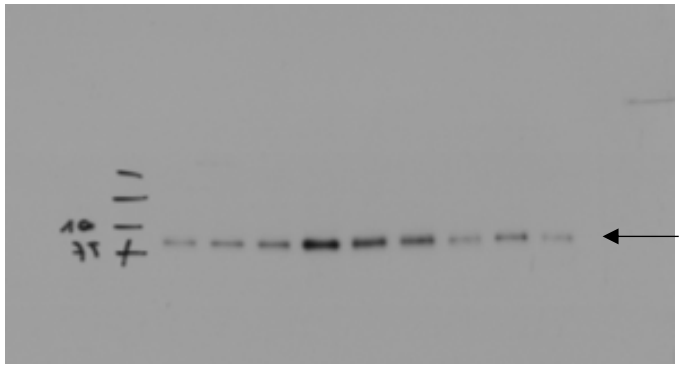

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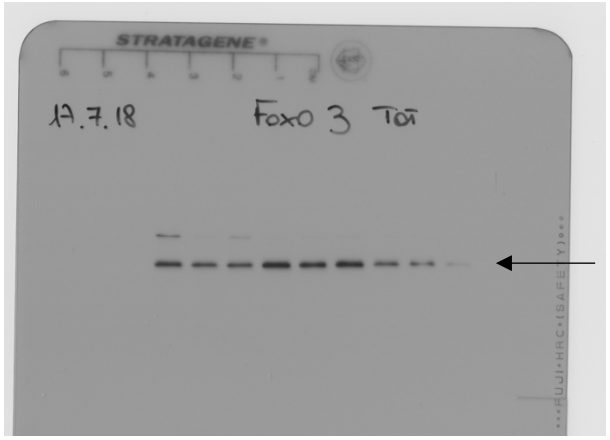

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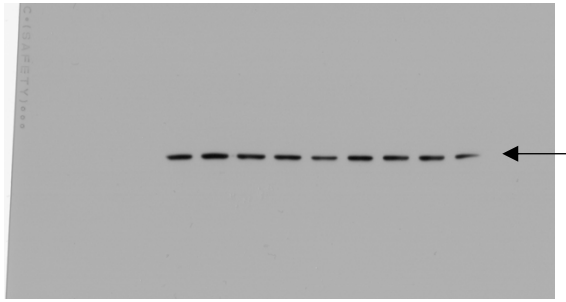
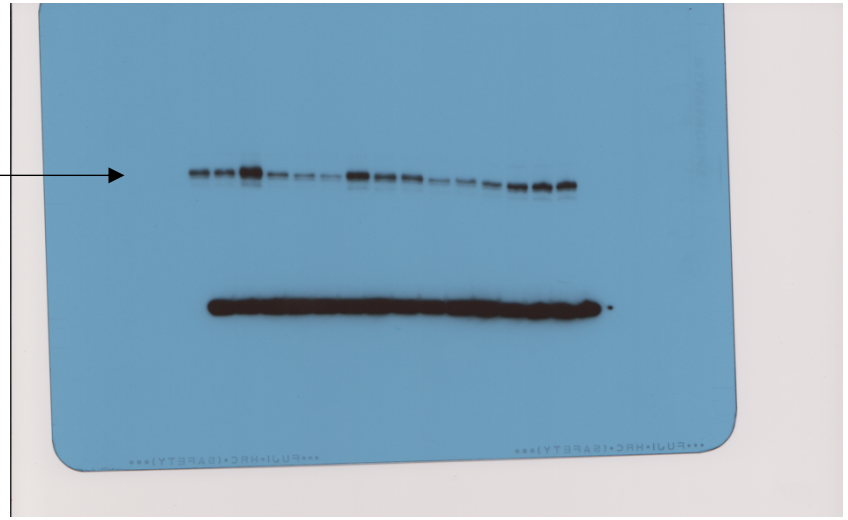
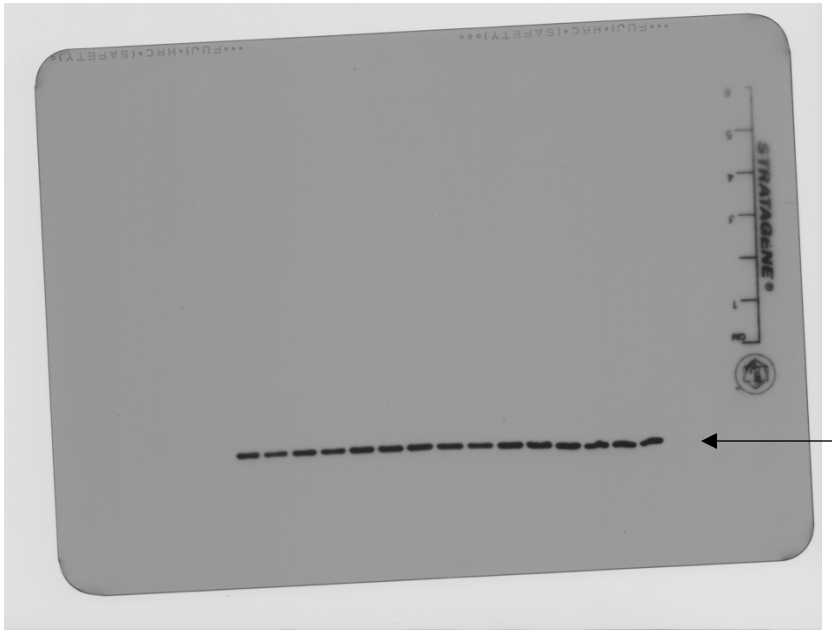


GAPDH

Full unedited gels for Figure 7g

p62





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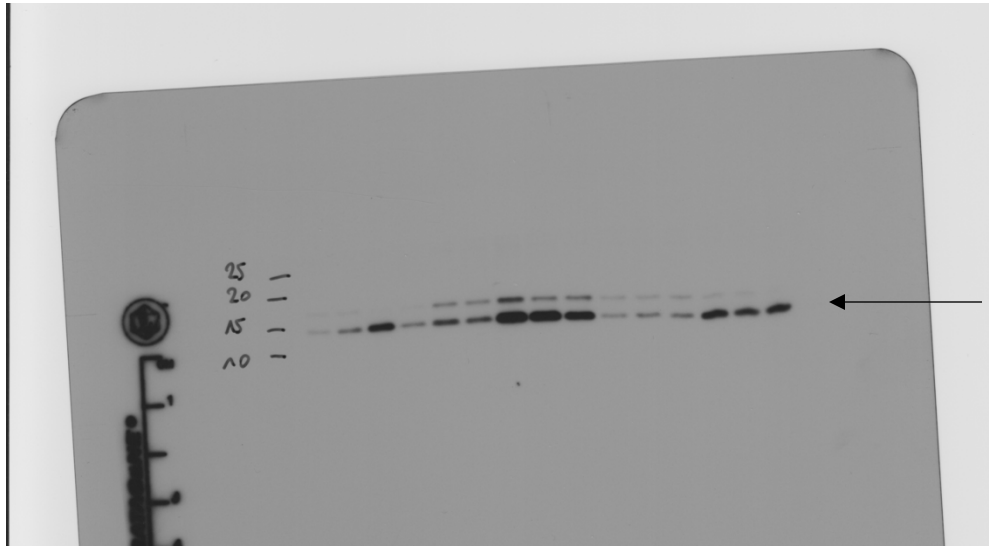

LC3

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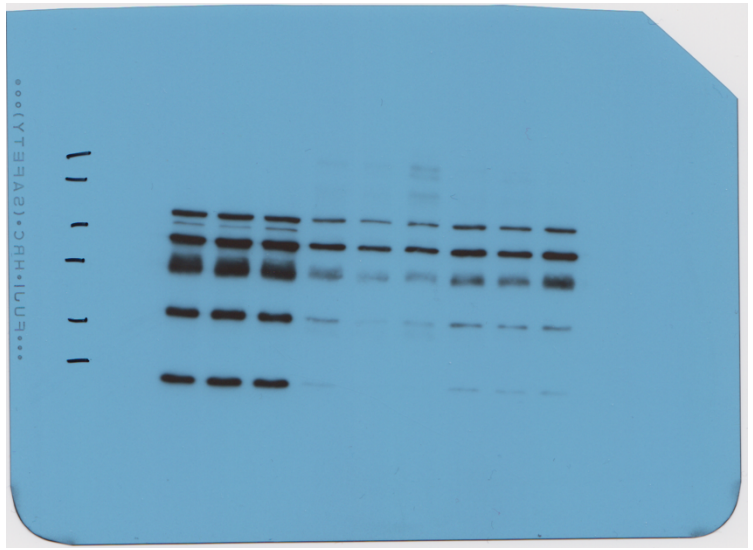

OXPHOS

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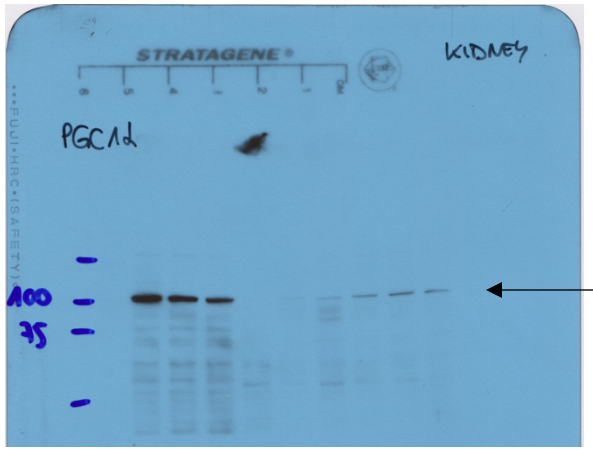

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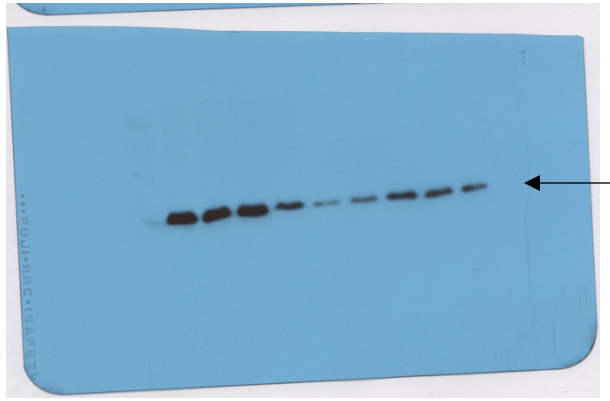

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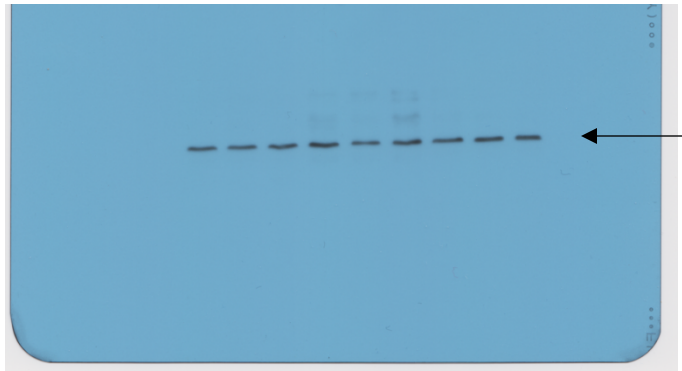

TUBULIN

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