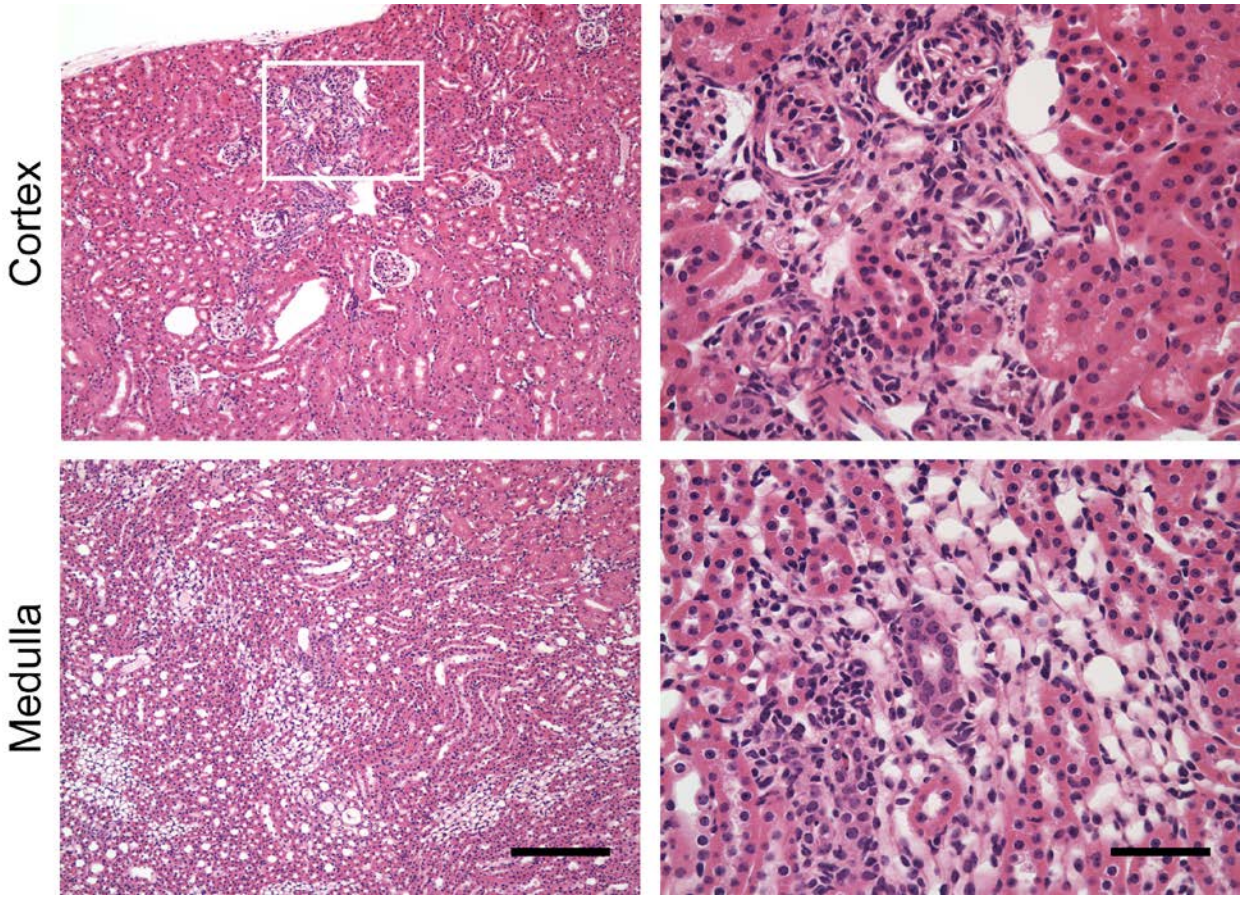
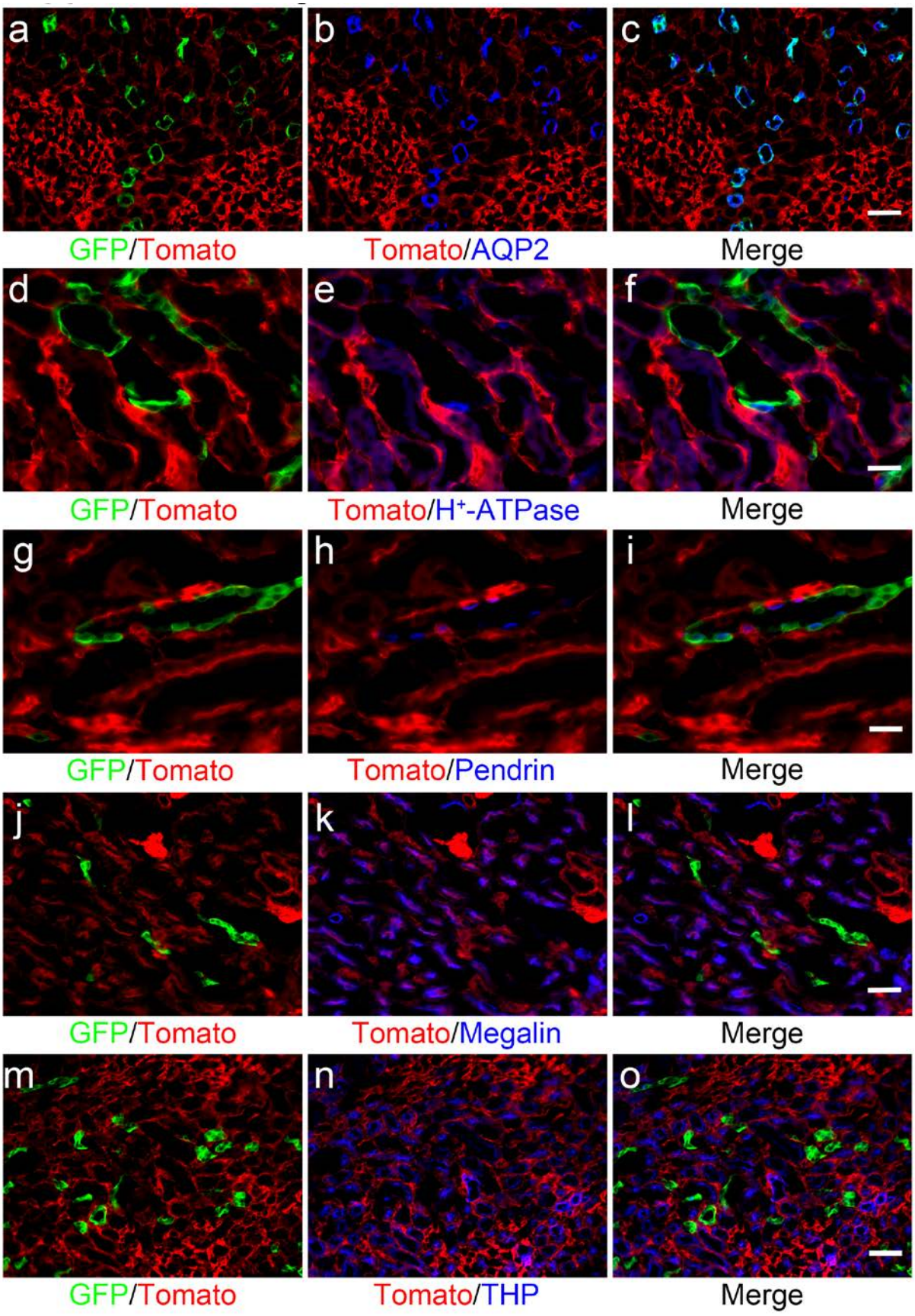
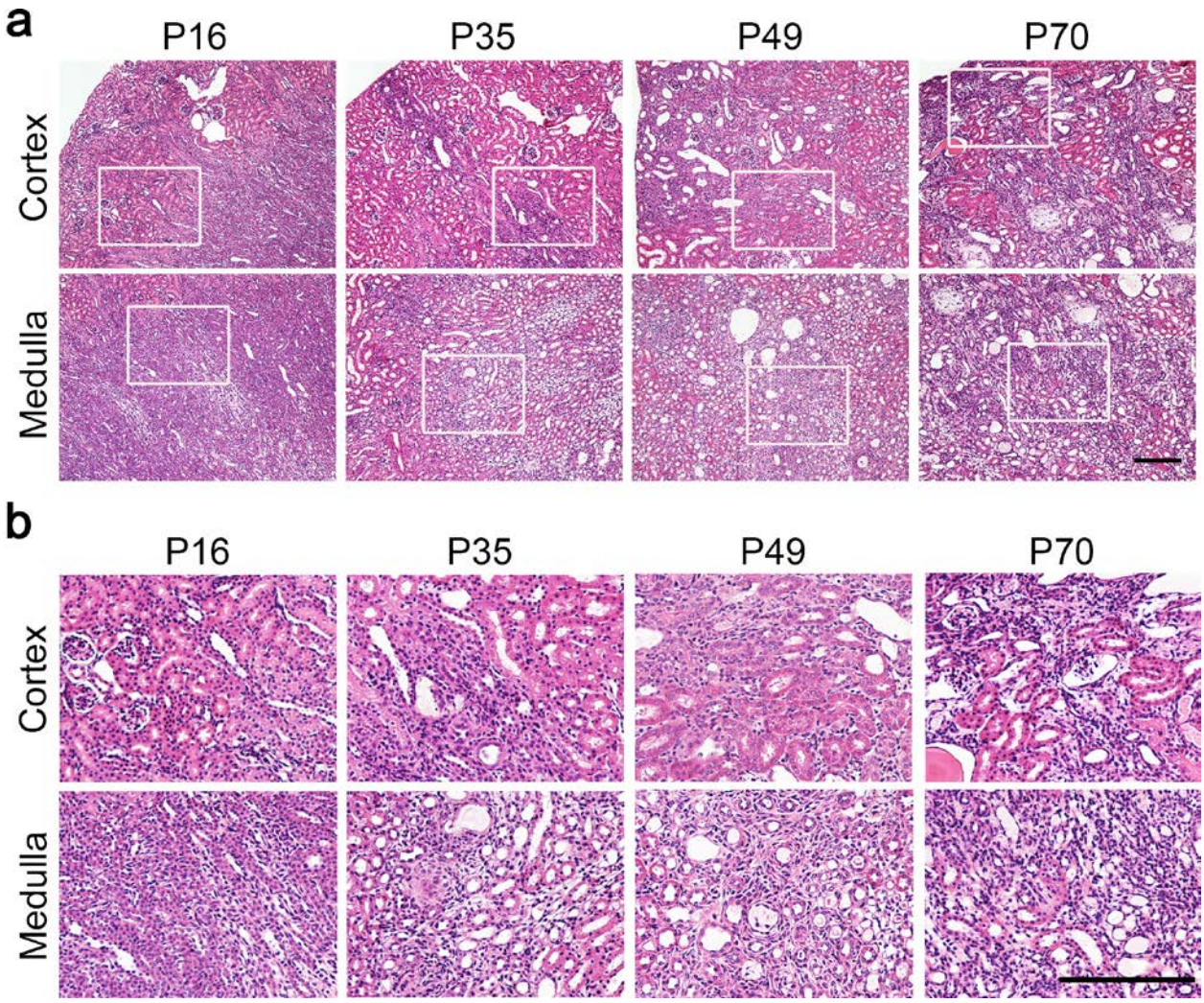
Supplemental Material Table of Contents



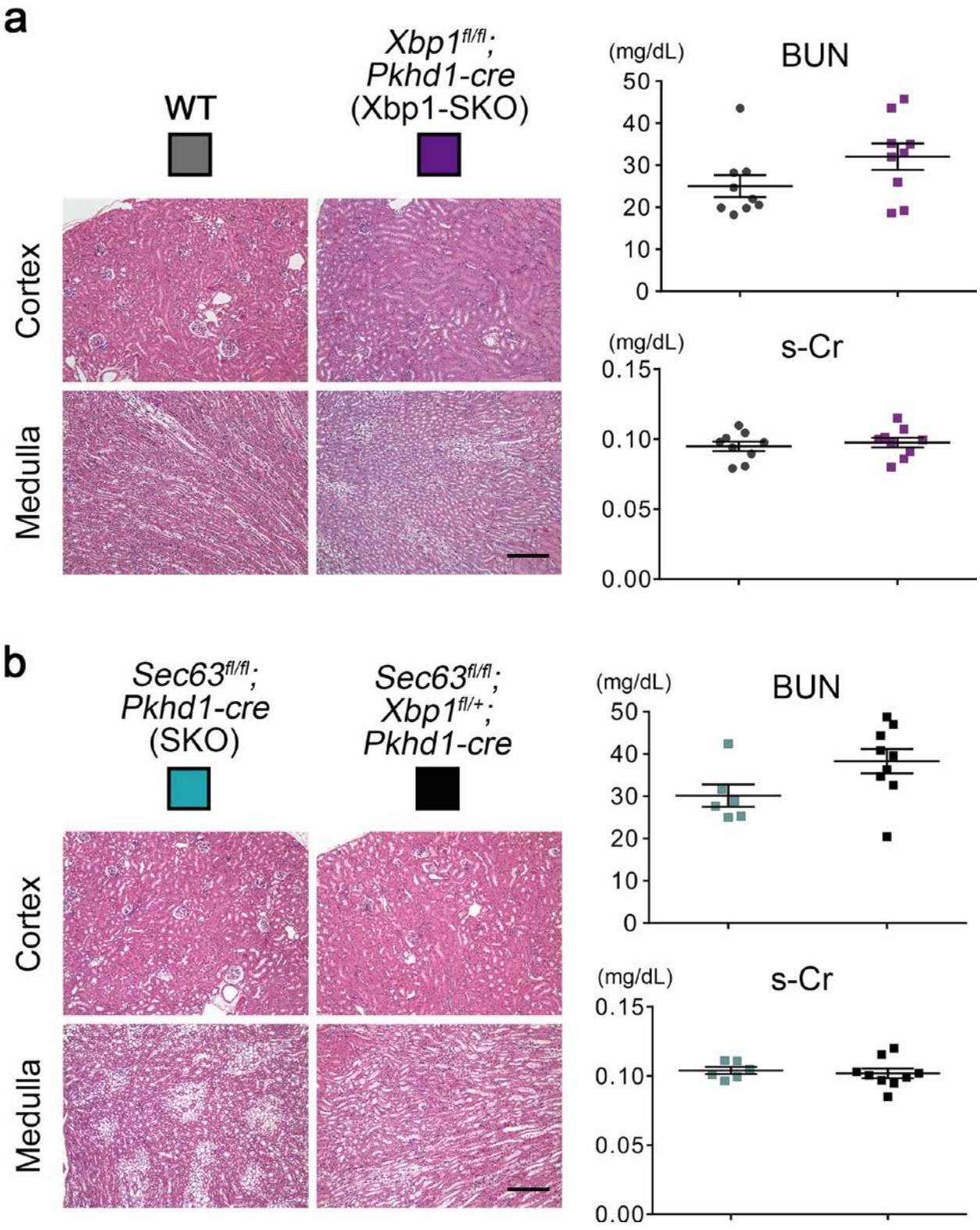
Supplemental Figure 1: Mild inflammation in *Sec63* single mutant kidneys at P120. Hematoxylin and eosin (H&E) staining of *Sec63$^{fl/fl}$; Pkhd1-cre* (SKO) kidneys at P120 showing areas with inflammation in both renal cortex and medulla. Boxed region in cortex image on right is shown in the left panel. Scale bar, 500 µm (*left* panels) and 100 µm (*right* panels).


a
b
c
GFP/Tomato
Tomato/AQP2
Merge
d
e
f
GFP/Tomato
Tomato/H+-ATPase
Merge
g
h
i
GFP/Tomato
Tomato/Pendrin
Merge
j
k
l
GFP/Tomato
Tomato/Megalin
Merge
m
n
o
GFP/Tomato
Tomato/THP
Merge

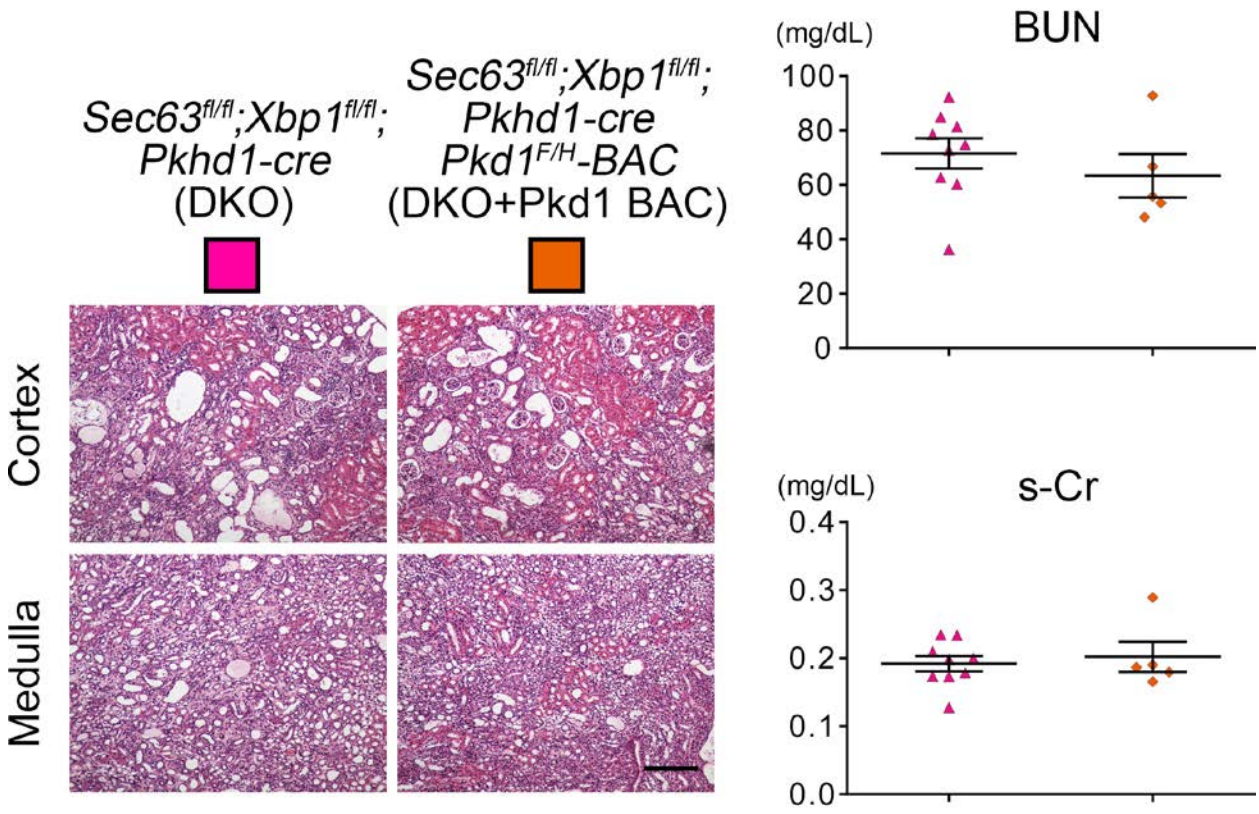
Supplemental Figure 2. *Pkhd1-cre* expression examined with the *Rosa*$^{mT/mG}$, double-fluorescent Cre reporter that express membrane-targeted tandem dimer Tomato-red prior to Cre-mediated excision, and membrane-targeted green fluorescent protein (GFP) after excision. *Pkhd1-cre*; *Rosa*$^{mT/mG}$ mice examined at P35. Cre expression (GFP, green) co-localized with (**a-c**) AQP2 positive (blue) collecting duct principal cells, (**d-f**) H^+-ATPase positive (blue) collecting duct Type A intercalated cells and (**g-i**) pendrin positive (blue) collecting duct Type B intercalated cells. Cre expression was not detected in (**j-l**) proximal tubule cells marked by megalin (blue) and (**m-o**) thick ascending loop of Henle cells marked by Tamm-Horsfall protein (THP, blue). Scale bar: 50 µm (a-c, j-o); 25 µm (d-i).



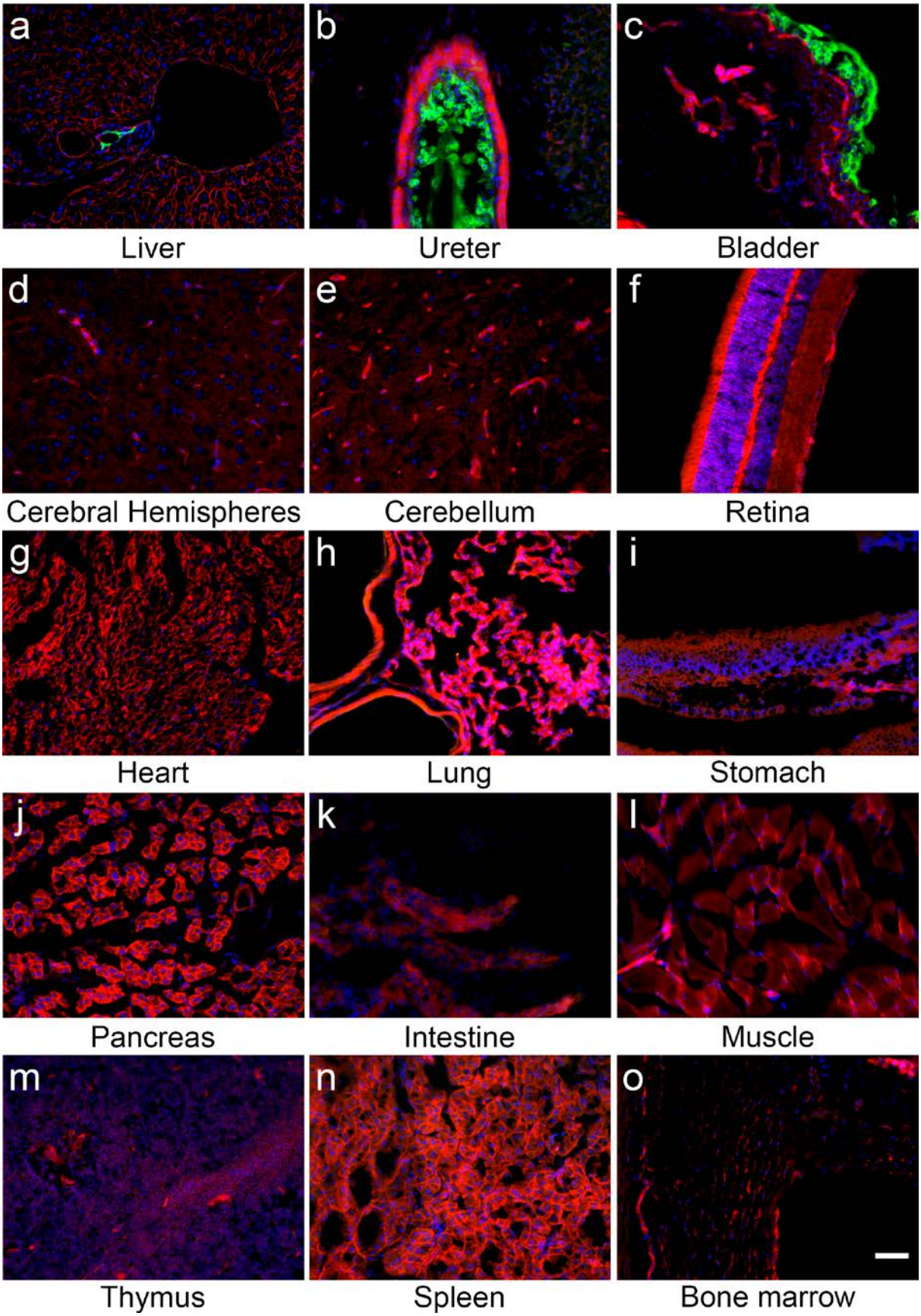
Supplemental Figure 3: Progression of inflammatory infiltrates in *Sec63$^{fl/fl}$; Xbp1$^{fl/fl}$; Pkhd1-cre* kidneys. (**a**) H&E staining of renal cortex and outer medulla of *Sec63$^{fl/fl}$; Xbp1$^{fl/fl}$; Pkhd1-cre* DKO kidneys at the indicated time points. (**b**) Higher magnification of the respective boxed regions in **a**. Histology shows progressive inflammation beginning at P35. Scale bar, 500 µm.


a
WT
Xbp1fl/fl; Pkhd1-cre (Xbp1-SKO)
Cortex
Medulla
(mg/dL)
BUN
50
40
30
20
10
0
(mg/dL)
s-Cr
0.15
0.10
0.05
0.00
b
Sec63fl/fl; Pkhd1-cre (SKO)
Sec63fl/fl; Xbp1fl/+; Pkhd1-cre
Cortex
Medulla
(mg/dL)
BUN
50
40
30
20
10
0
(mg/dL)
s-Cr
0.15
0.10
0.05
0.00

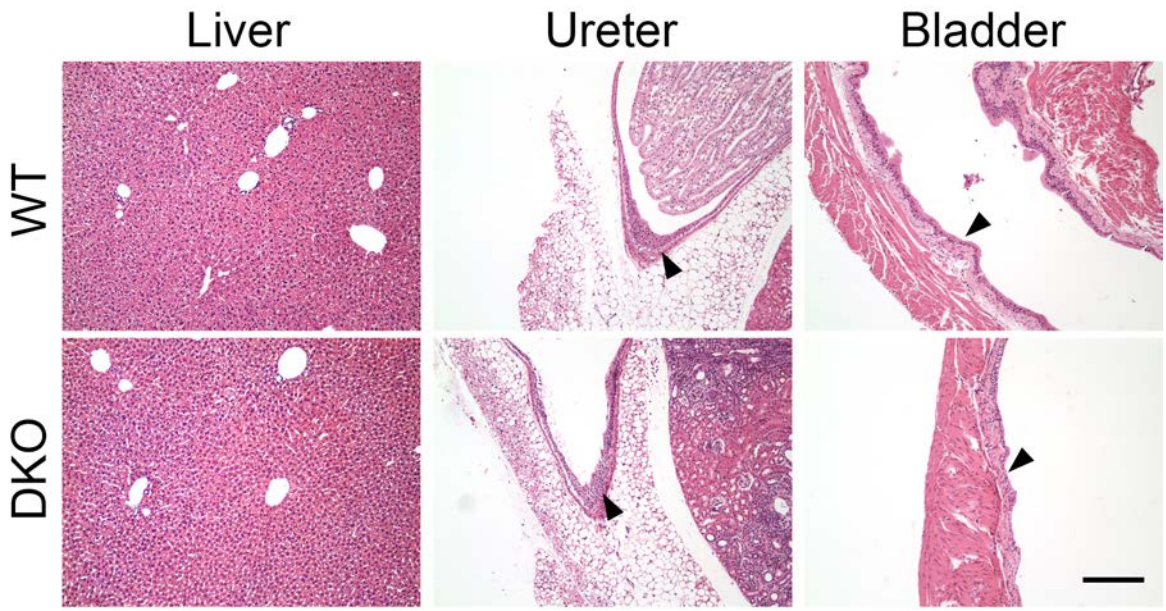
Supplemental Figure 4: Collecting duct inactivation *Xbp1* does not result in inflammation or kidney dysfunction. (**a**) Deletion of *Xbp1* alone using *Pkhd1-Cre* does not cause any morphological or functional defects in the kidney. H&E staining of renal cortex and medulla of wild type (WT) and *Xbp1$^{fl/fl}$; Pkhd1-cre* (Xbp1-SKO) at P70 (*P*=0.13, BUN, ns; *P*=0.65, s=Cr, ns). (**b**) H&E staining of renal cortex and medulla of the indicated genotypes at P70; *Sec63$^{fl/fl}$; Xbp1$^{fl/+}$; Pkhd1-cre* kidneys have no interstitial inflammation (*P*=0.07, BUN, ns; *P*=0.60, s-Cr, ns). Scale bars, 500 µm. Statistical measurements were performed using the Mann-Whitney test with a *P* value <0.05 considered significant.



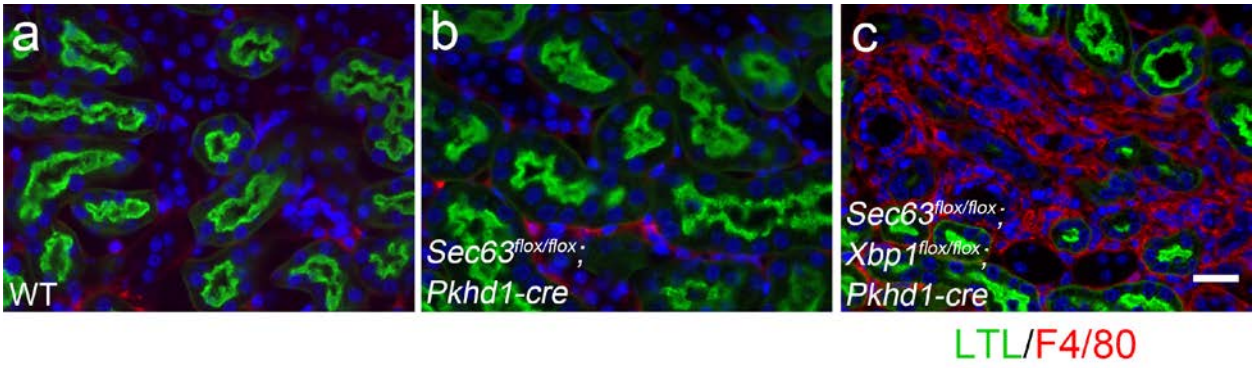
Supplemental Figure 5: *Pkd1$^{F/H}$-BAC* does not rescue the inflammatory phenotype in DKO mouse kidneys indicating the observed phenotypes are not *Pkd1*-dependent. H&E staining of renal cortex and medulla of *Sec63$^{fl/fl}$; Xbp1$^{fl/fl}$; Pkhd1-cre* (DKO) and *Sec63$^{fl/fl}$; Xbp1$^{fl/fl}$; Pkhd1-cre; Pkd1$^{F/H}$-BAC* (DKO+Pkd1 BAC) at P70. Scale bar, 500 µm. Kidney function was assessed by blood urea nitrogen (BUN; P=0.34, n.s.) and serum creatinine (s-Cr; P=0.94, n.s.). Statistical measurements were performed using the Mann-Whitney test with a P value <0.05 considered significant.


a
b
c
Liver
Ureter
Bladder
d
e
f
Cerebral Hemispheres
Cerebellum
Retina
g
h
i
Heart
Lung
Stomach
j
k
l
Pancreas
Intestine
Muscle
m
n
o
Thymus
Spleen
Bone marrow

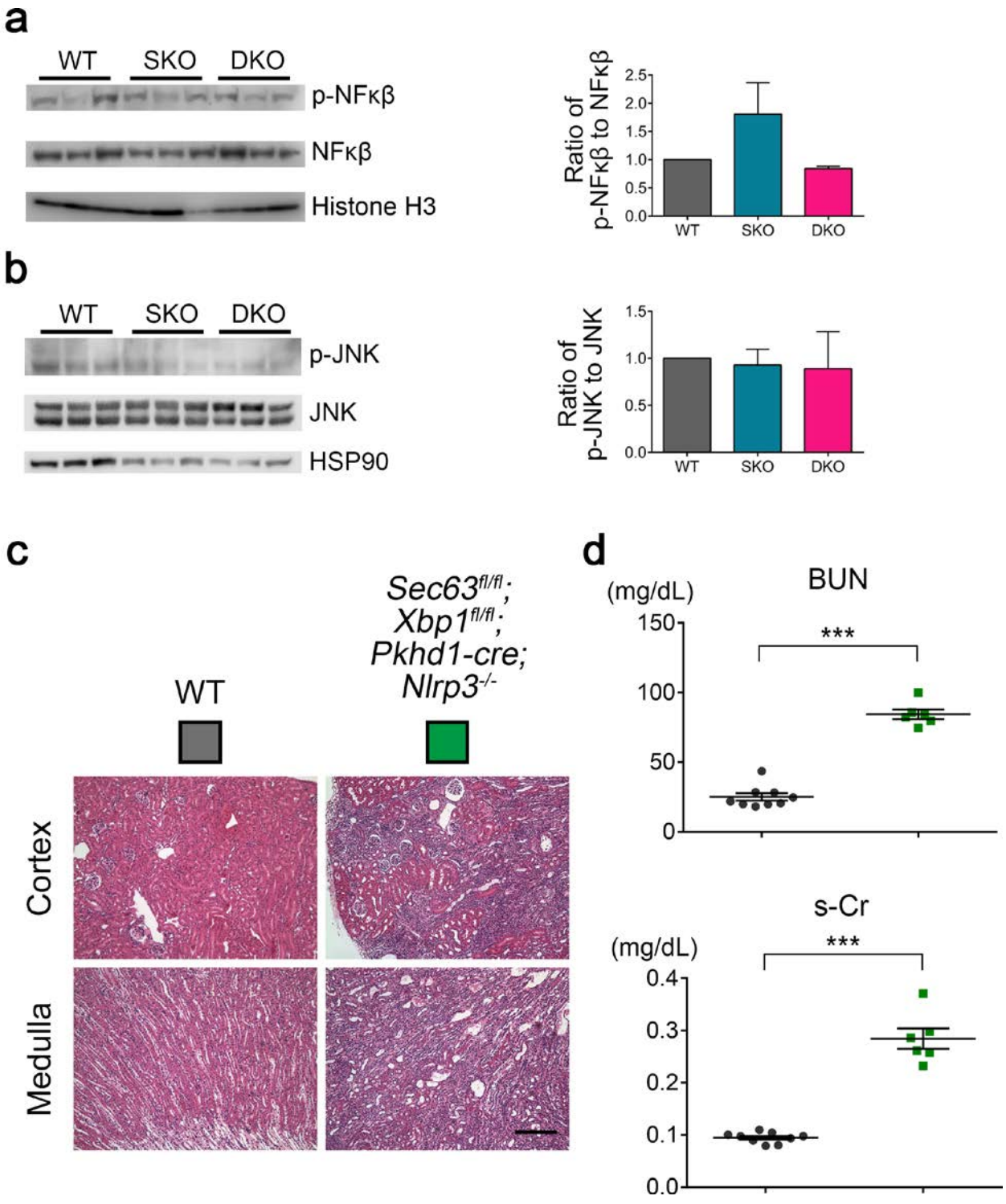
Supplemental Figure 6: Extra-renal activity of *Pkhd1-cre*. Images from the indicated tissues of *Pkhd1-cre*; *Rosa*$^{mT/mG}$ mice at P35. Cre activity is indicated by GFP expression (green) whereas absence of activity is indicated to Tomato epifluorescence (red). Extra-renal Cre activity was found in (**a**) some periportal areas in the liver and in the transitional epithelium of (**b**) ureter and (**c**) bladder. Cre activity was not observed in (**d**) cerebral hemispheres (contains cortex) , (**e**) cerebellum (contains cortex), (**f**) retina, (**g**) heart, (**h**) lung, (**i**) stomach, (**j**) pancreas, (**k**) intestine, (**l**) muscle (striated), (**m**) thymus, (**n**) spleen and (**o**) bone marrow. Nuclei stained by Hoechst (blue). Scale bar, 50 µm.



Supplemental Figure 7. H&E staining of liver, ureter and bladder of WT and *Sec63-Xbp1* mutants (DKO) at P70. Histology shows absence of inflammation in both WT and DKO. Arrow heads in the middle panels denote the transitional epithelium (urothelium). Scale bar, 500 µm.

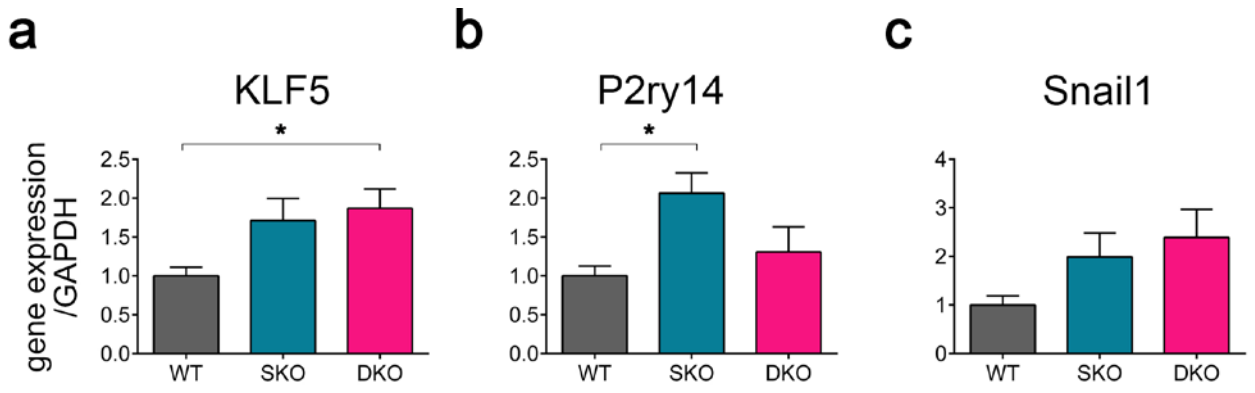


Supplemental Figure 8. High magnification view of extensive macrophage infiltration indicated by F4/80 staining in *Sec63$^{fl/fl}$; Xbp1$^{fl/fl}$; Pkhd1-cre* (DKO) kidneys compared to WT and *Sec63$^{fl/fl}$; Pkhd1-cre* (SKO) at P35. Scale bar, 25 μm.

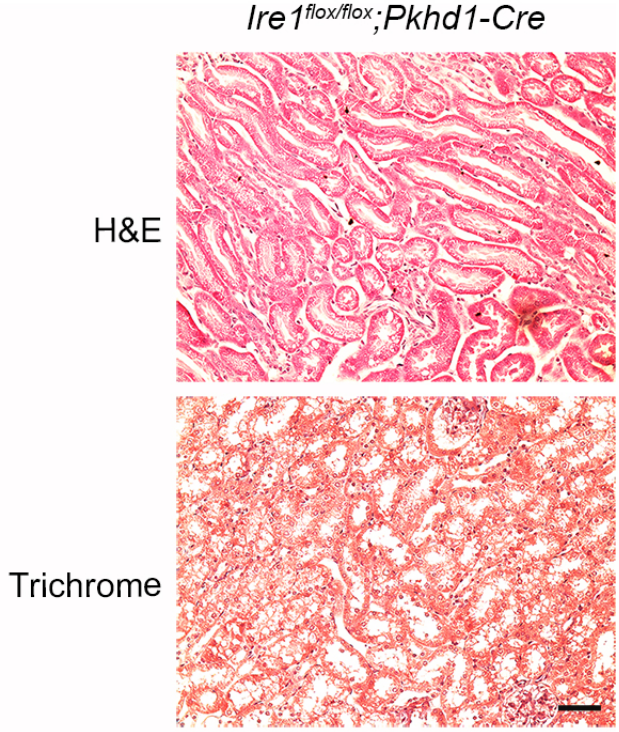


Supplemental Figure 9. NFκβ, JNK and Nlrp3 are not the inflammatory signals in DKO kidneys. (**a**) Representative immunoblots and aggregate densitometric quantification of nuclear extracts from kidney lysates shows that levels of phosphorylated NFκβ are no different between *Sec63*

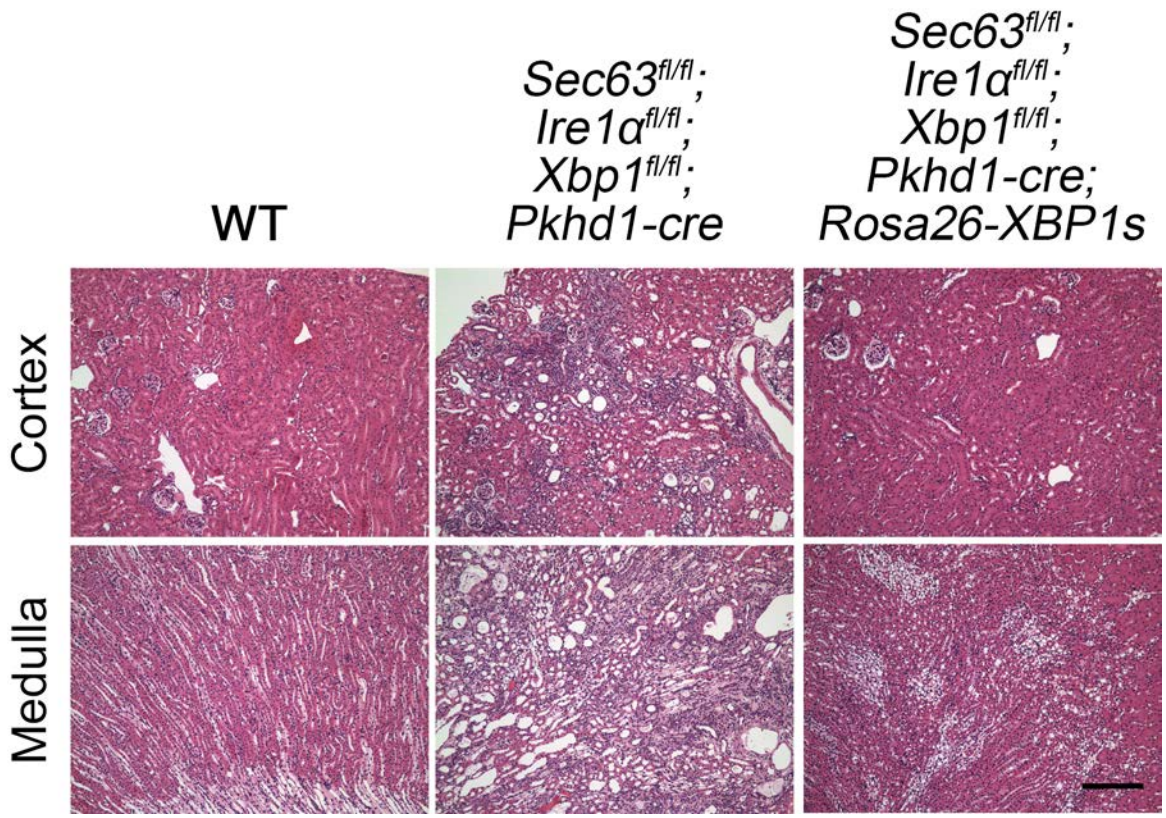
single (SKO) and *Sec63-Xbp1* double mutant (DKO) kidneys at P35 (*n*=3 mice in each group). Results are shown as mean +/- SEM (ANOVA). (**b**) Representative immunoblots and aggregate densitometric quantification of whole kidney lysates shows that levels of phosphorylated JNK is no different among WT, SKO and DKO kidneys at P35 (*n*=3 mice in each group). Results are shown as mean +/- SEM (ANOVA). (**c**) H&E staining of renal cortex and medulla of the indicated genotypes at P70 showing chronic kidney injury in DKO is not reversed by simultaneous inactivation of *Nlrp3*. Scale bar, 500 µm. (**d**) BUN and s-Cr show impaired kidney function at P70 in DKO mice with simultaneous inactivation of *Nlrp3*. ***, *P*<0.001. Results are shown as mean +/- SEM (ANOVA).



Supplemental Figure 10. KLF5, P2ry14 and Snail1 are unchanged between SKO and DKO kidneys at P35. Gene expression of (**a**) KLF5, (**b**) P2ry14 and (**c**) Snail1 indicates no difference in mRNA levels between SKO and DKO kidneys. *n*=3 mice per group; *, *P*<0.05. Results are shown as mean +/- SEM (ANOVA).



Supplemental Figure 11. Five month-old *Ire1α*$^{fl/fl}$*;Pkhd1-cre* mice do not display signs of inflammation or fibrosis. Scale bar, 50µm



Supplemental Figure 12. XBP1s transgene rescues kidney injury in *Sec63*, *Ire1α*, *Xbp1* triple knockout kidneys. H&E staining of renal cortex and medulla of the indicated genotypes at P70. The expression of XBP1s rescued renal inflammation of *Sec63*, *Ire1α*, *Xbp1* triple mutant mouse Scale bar, 500 μm.