Dissecting the Role of ATF6α and ATF6β in Podocyte Homeostasis and Injury Response

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COI Disclosure

I have the following relationships to disclose any COI for this research presentation within the period of 36 months.

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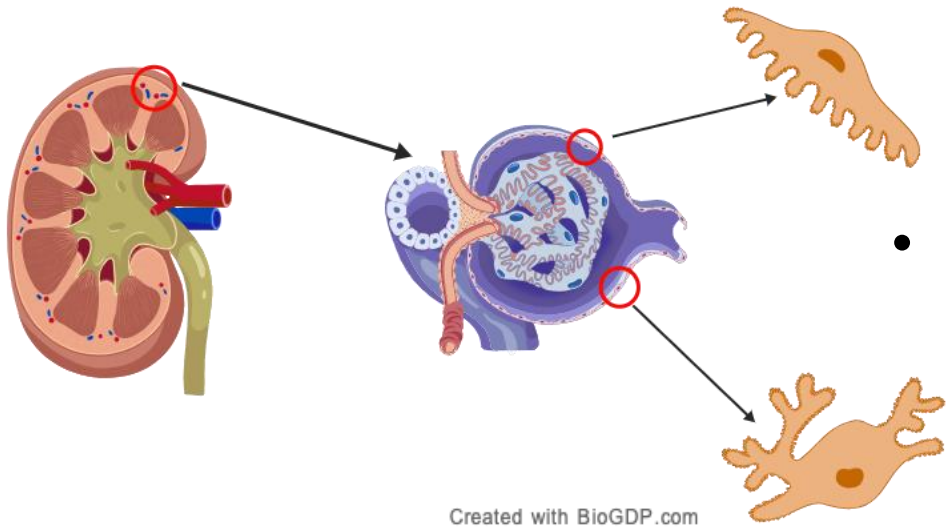
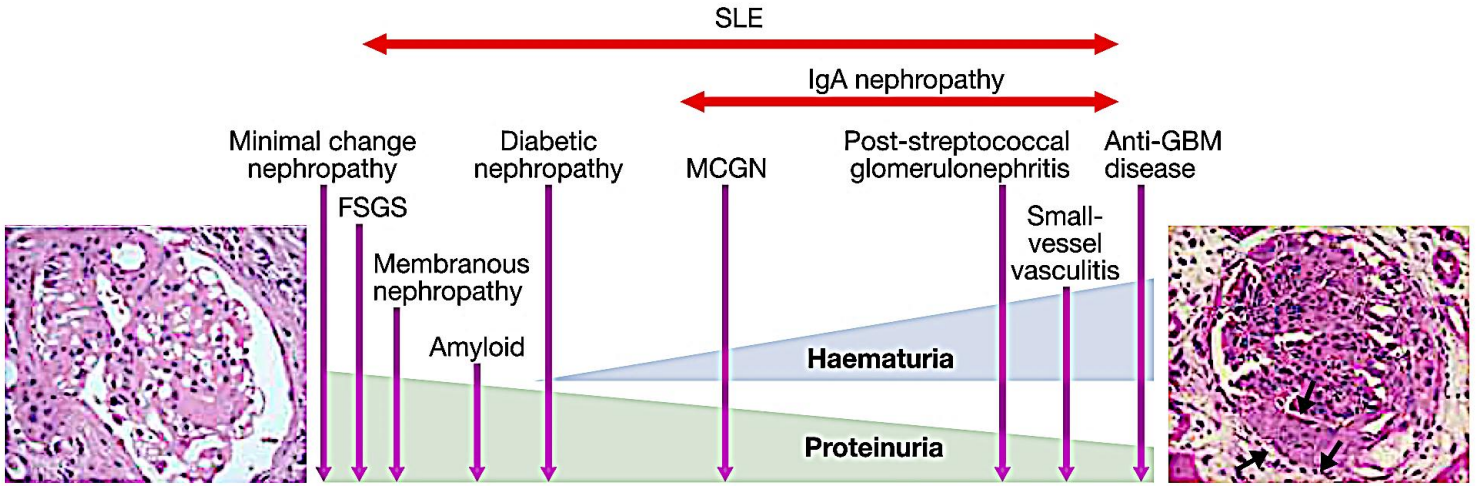
Introduction: *Glomerular diseases & podocyte injury*

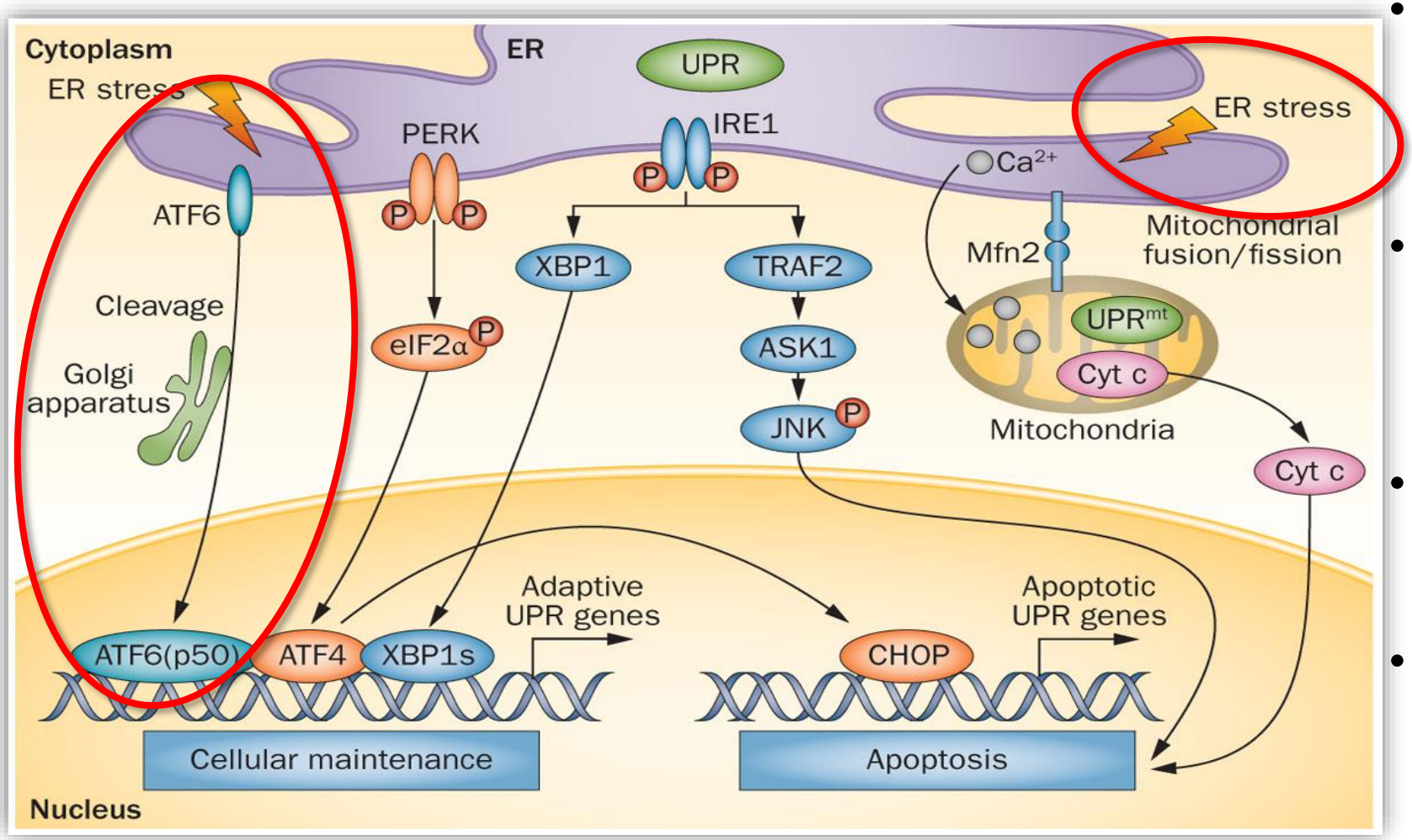


- Glomerular diseases share a common feature of podocyte injury.
- Podocyte loss or dysfunction leads to disruption of the glomerular filtration barrier → proteinuria → glomerulosclerosis.
- Podocyte injury involves multiple cellular stress responses, including endoplasmic reticulum (ER) stress.



Davidson's Prinnciples annd Practice of Medicine 23rd edition

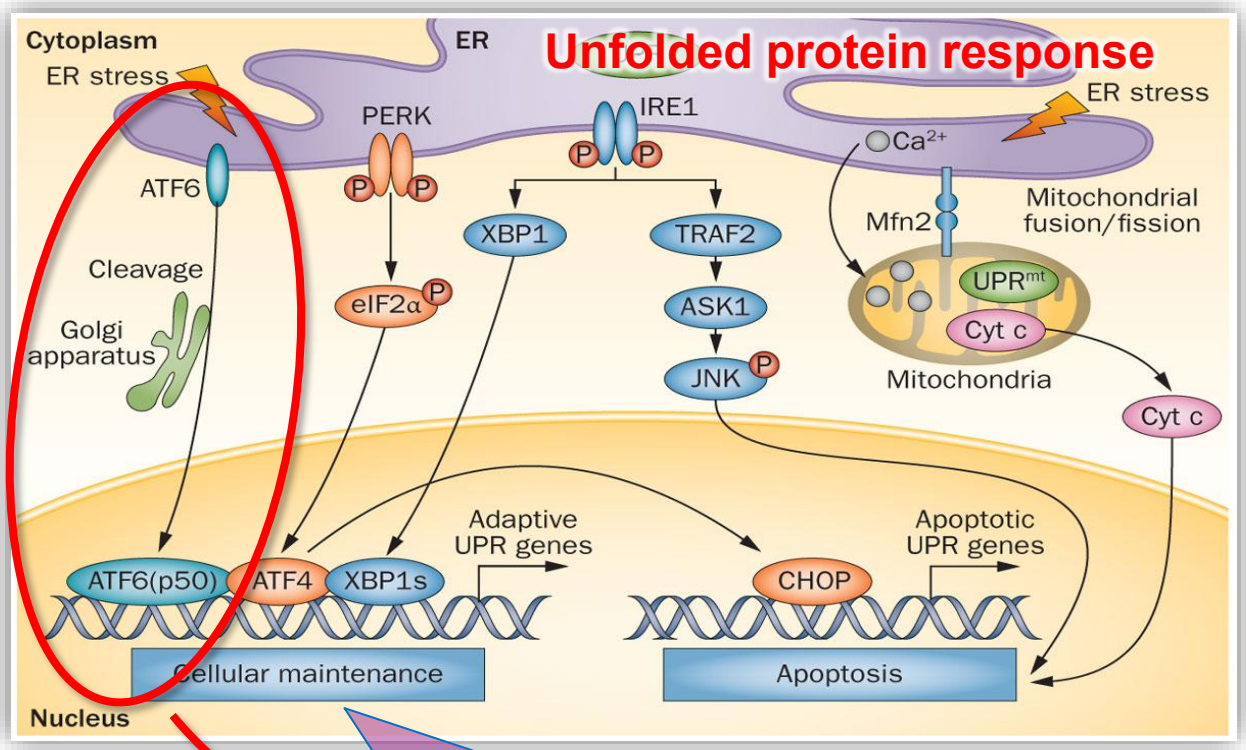
Introduction: *Endoplasmic Reticulum Stress & UPR*



Inagi, R.
Nat Rev Nephrol. 2014

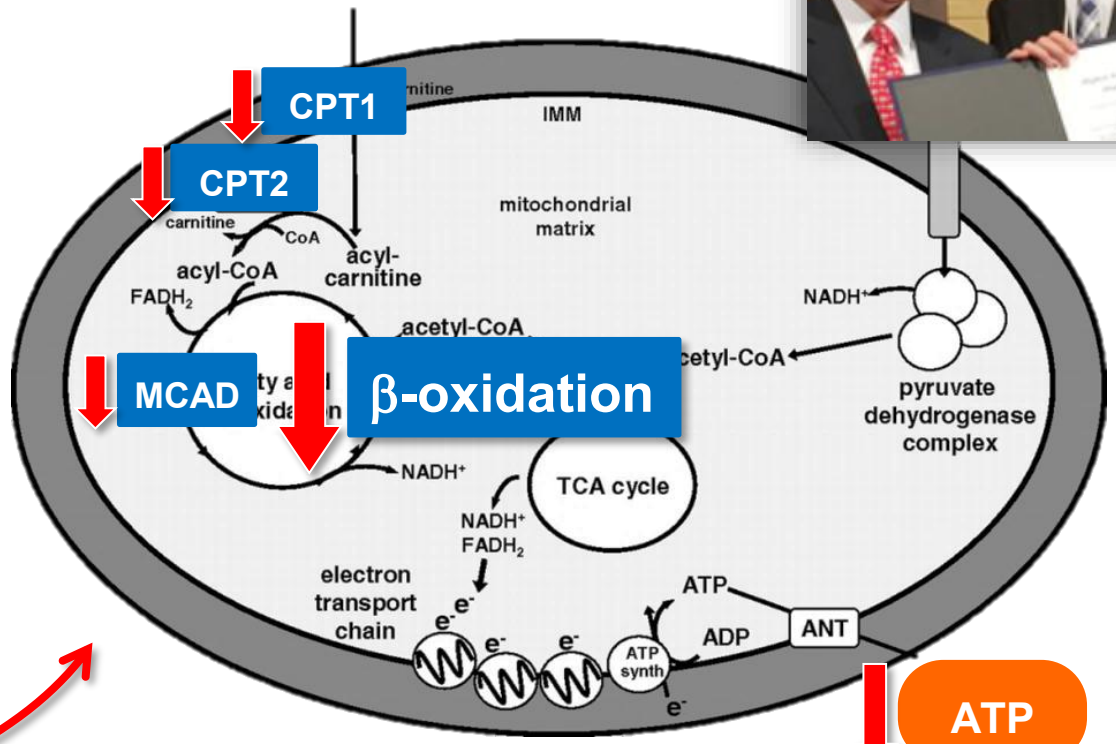
- ER stress arises from accumulation of misfolded/ unfolded proteins in the ER.
- The unfolded protein response (UPR) is activated to restore ER homeostasis.
- UPR Pathway: PERK, IRE1, ATF6
- Chronic or unresolved ER stress contributes to podocyte injury and glomerular disease progression.

Introduction: *Damaged ER-mitochondrial metabolic axis causes lipotoxicity-mediated tubular fibrosis*



Metabolic homeostasis

Inagi, R.
Nat Rev Nephrol. 2014



ATP

Respiration

PPARα promoter activity

Lipid droplets

Jao TM, Kidney Int. 2019

Introduction: *Aim & Hypothesis*

Aim:

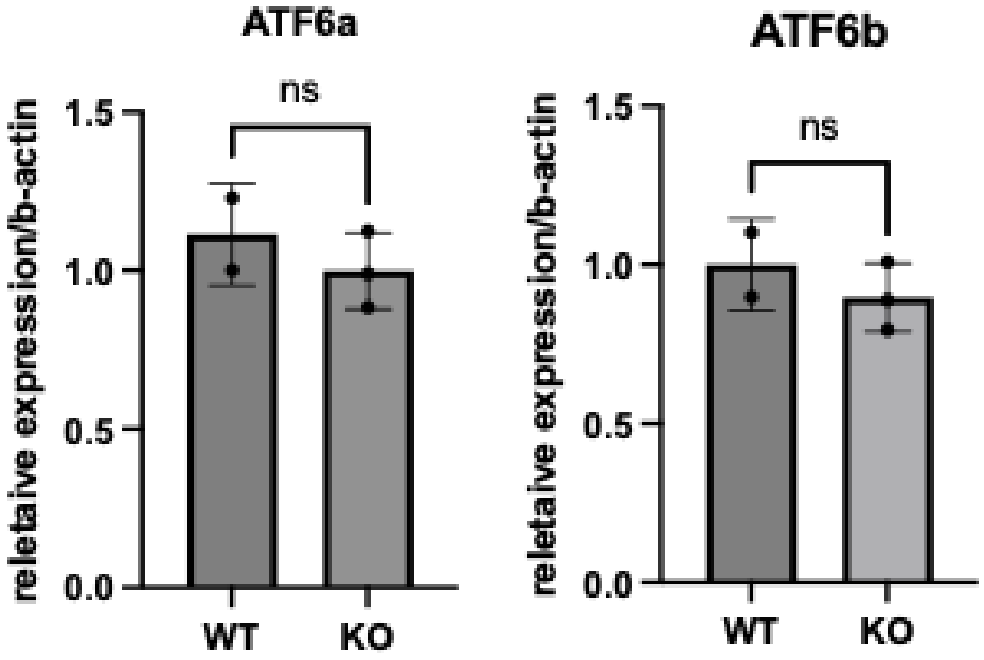
To clarify how ATF6α/β signaling in podocytes maintains glomerular homeostasis under both physiological and stress conditions.

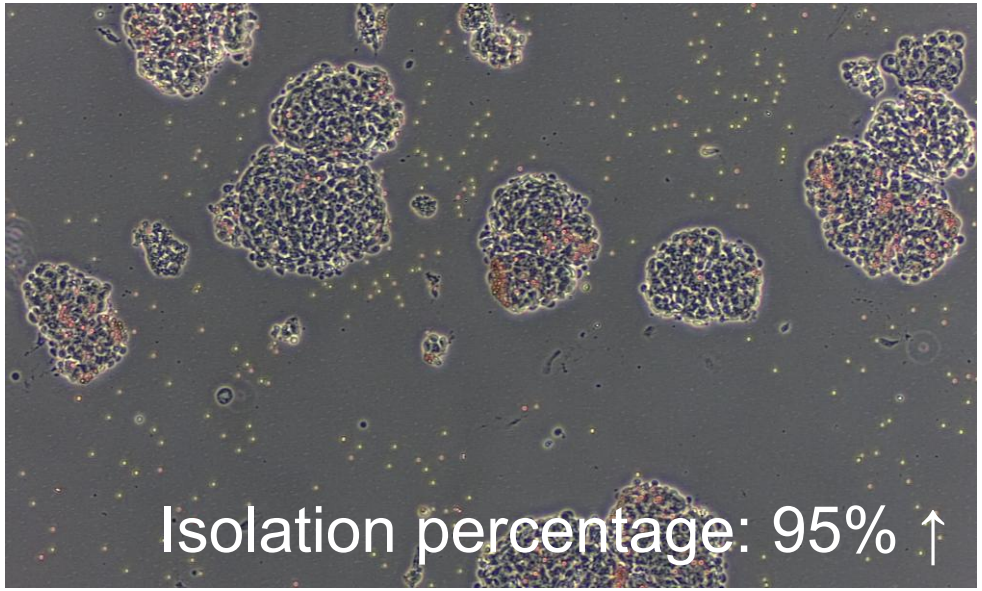
Hypothesis:

- In podocytes, ATF6α/β signaling protects glomeruli by promoting adaptive responses to stress signals.
- Loss of ATF6α/β impairs these defenses, leading to podocyte dysfunction and aggravated glomerular damage under stress.

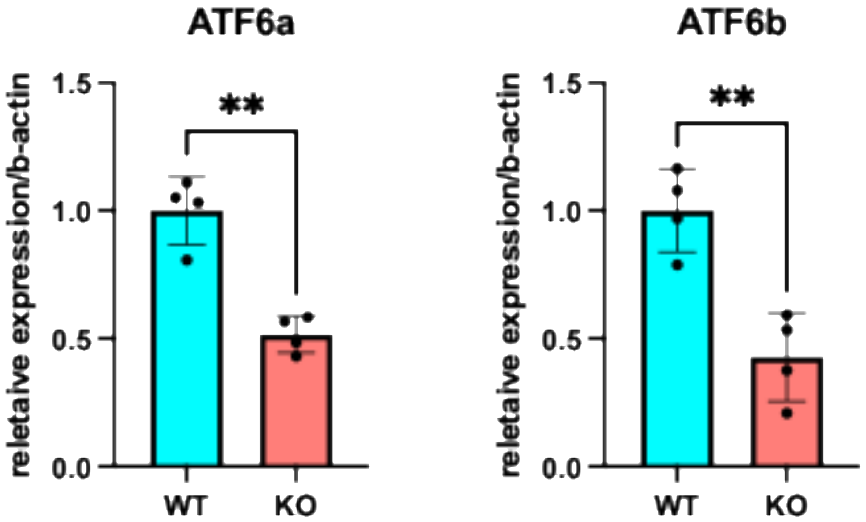
Results: *Glomerular Isolation & Knockout Efficacy in podocyte-specific ATF6α/β KO mice*

Whole Kidney

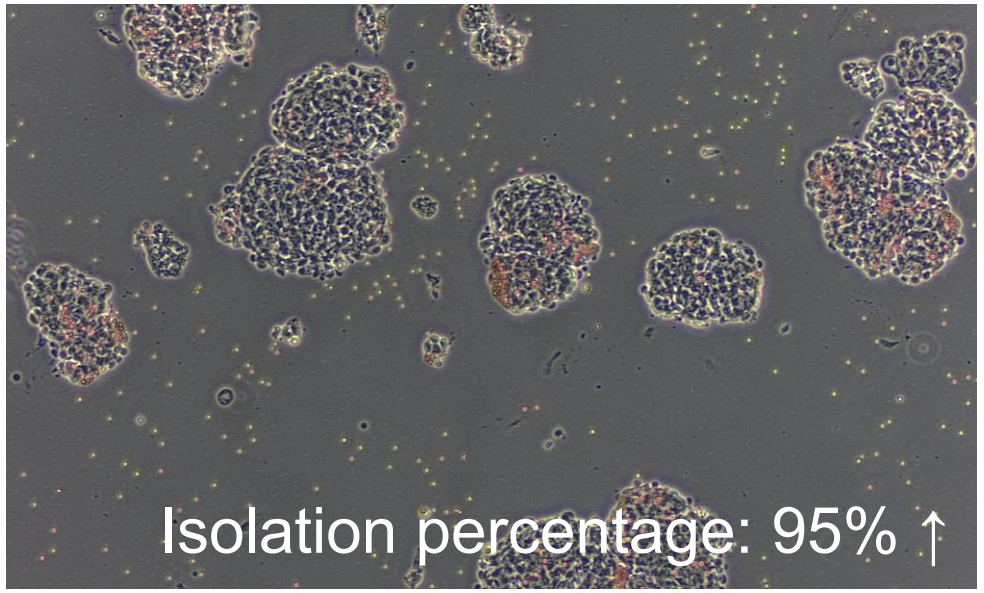




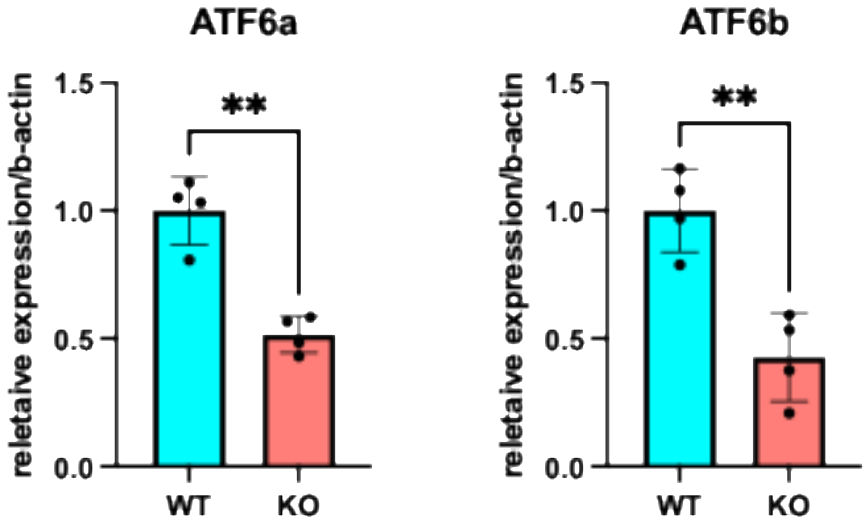
Glomerulus



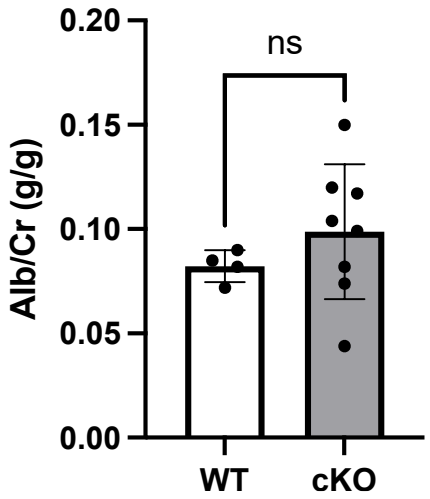
Results: *Glomerular Isolation & Knockout Efficacy in podocyte-specific ATF6α/β KO mice*



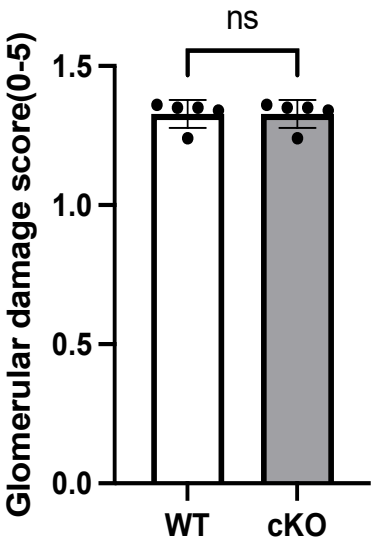
Glomerulus

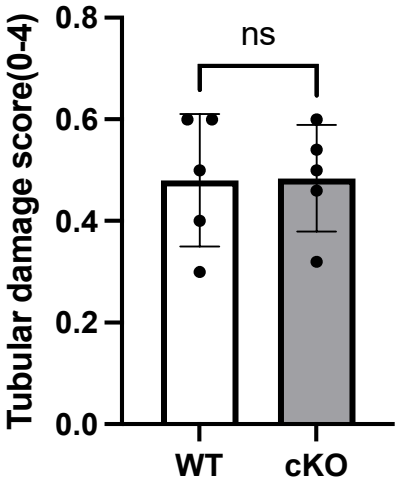


➢ Kidney Function



➢ Kidney Morphology

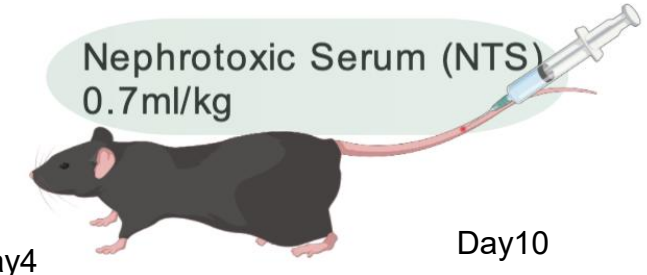




- Efficient podocyte-specific knockout of ATF6α and ATF6β was confirmed in isolated glomeruli
- No significant differences in baseline kidney function or morphology were observed between WT and ATF6α/β cKO mice

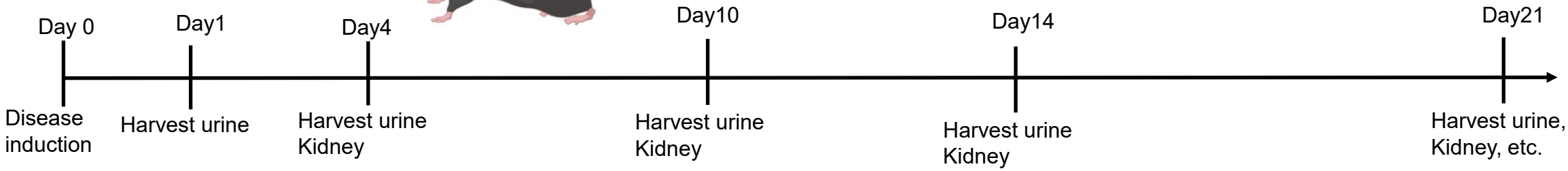
Results: *Podocyte-specific ATF6α/β deficiency exacerbates albuminuria in anti-GBM glomerulonephritis in the late phase*

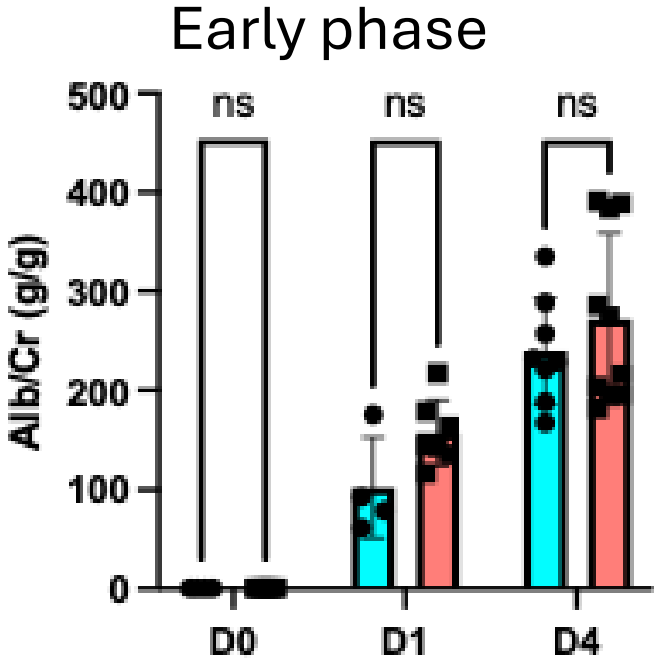
Anti-GBM nephritis

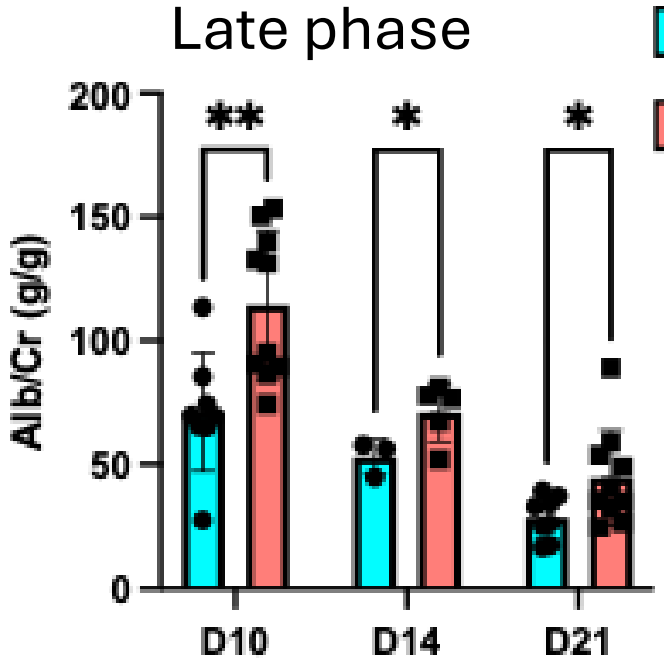


WT: ATF6α/β$^{fl/fl}$

cKO: Podocin-Cre; ATF6α/β$^{fl/fl}$

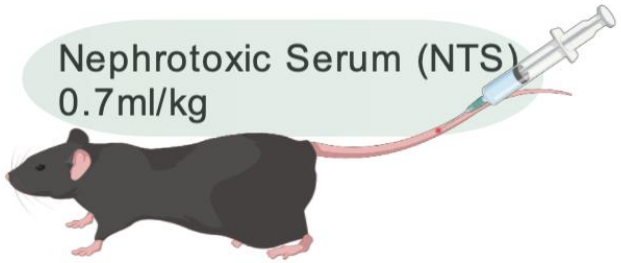






- Disease induction was comparable between WT and cKO mice
- Podocyte ATF6α/β deficiency aggravated albuminuria as glomerular damage progressed

Result: *Podocyte-specific ATF6α/β deficiency exacerbates glomerular damage in anti-GBM glomerulonephritis in the late phase*



Anti-GBM glomerulonephritis

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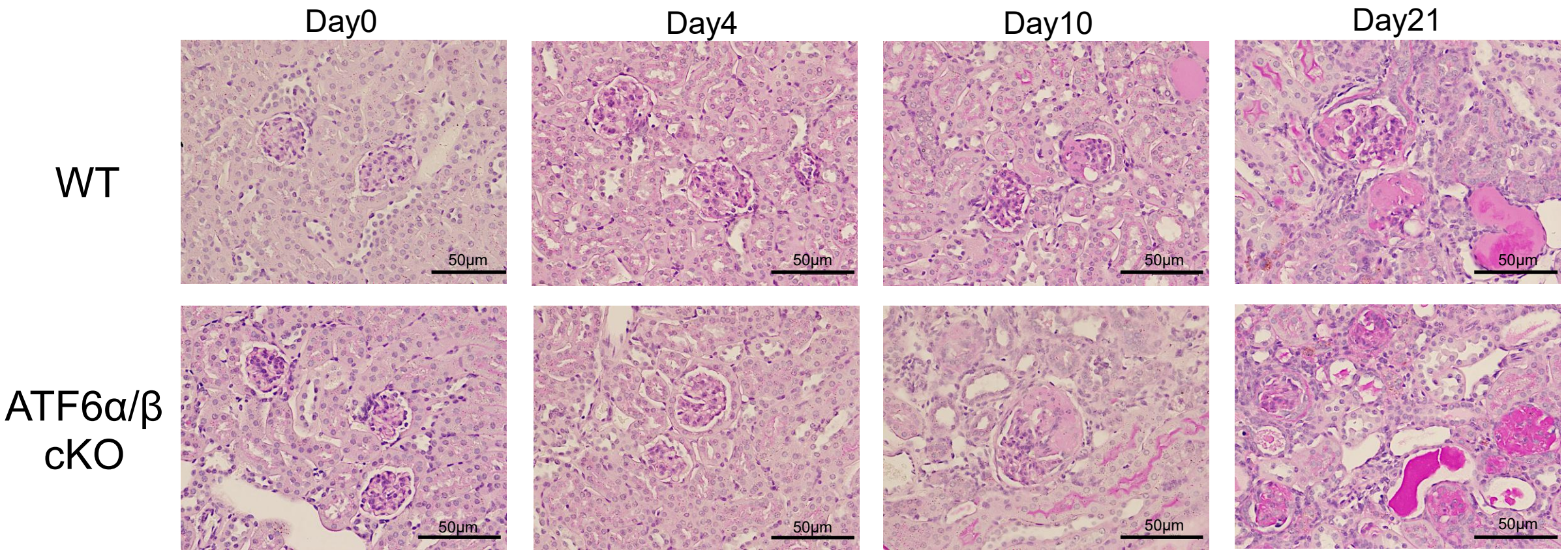
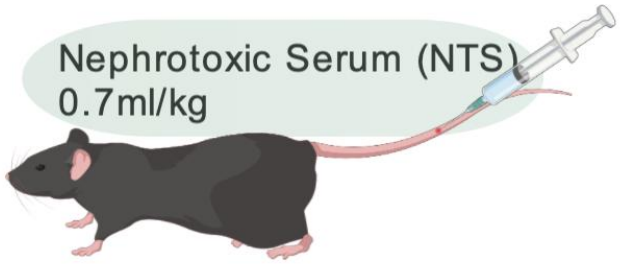


Scale bar = 50 μm

Result: *Podocyte-specific ATF6α/β deficiency exacerbates glomerular damage in anti-GBM glomerulonephritis in the late phase*



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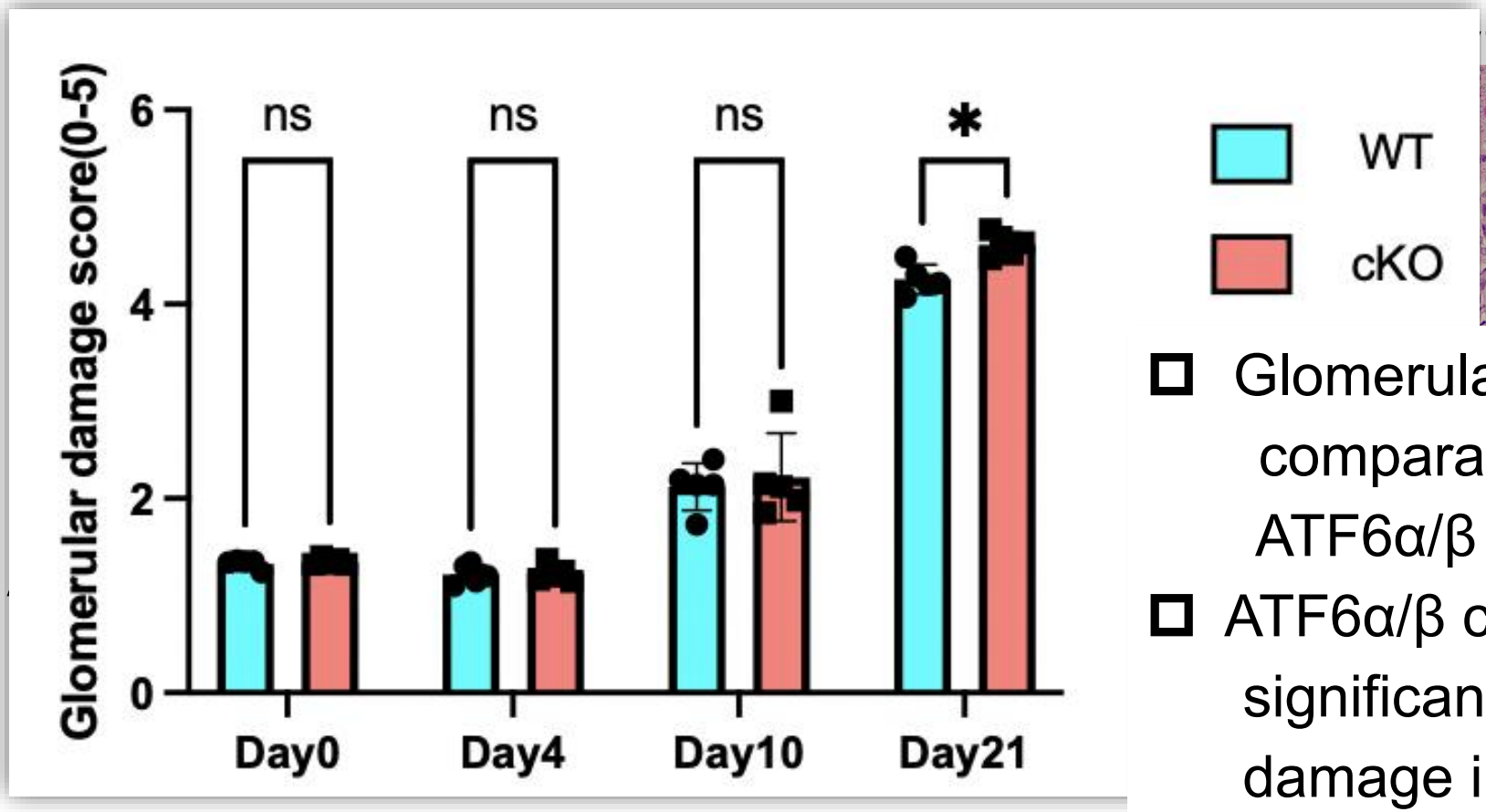

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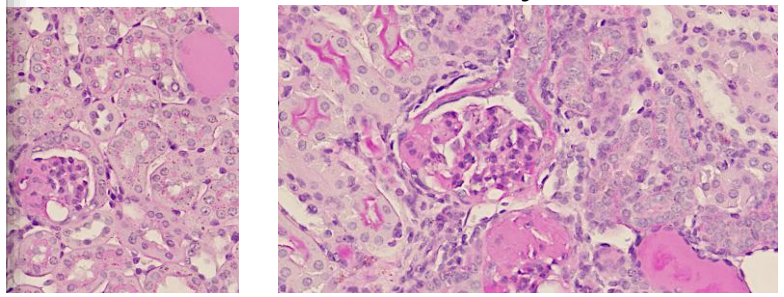
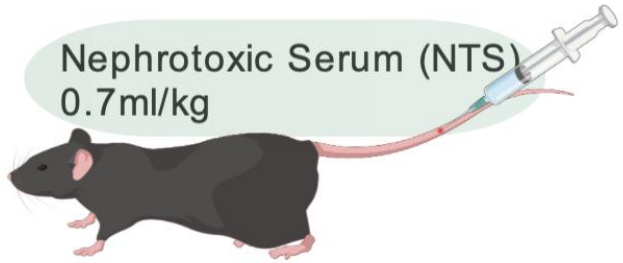
Day21



- Glomerular damage scores were comparable between WT and ATF6α/β cKO mice in the early phase
- ATF6α/β cKO mice showed significantly more severe glomerular damage in the late phase

Result: *Podocyte-specific ATF6α/β deficiency exacerbates tubular damage in anti-GBM glomerulonephritis in the late phase*



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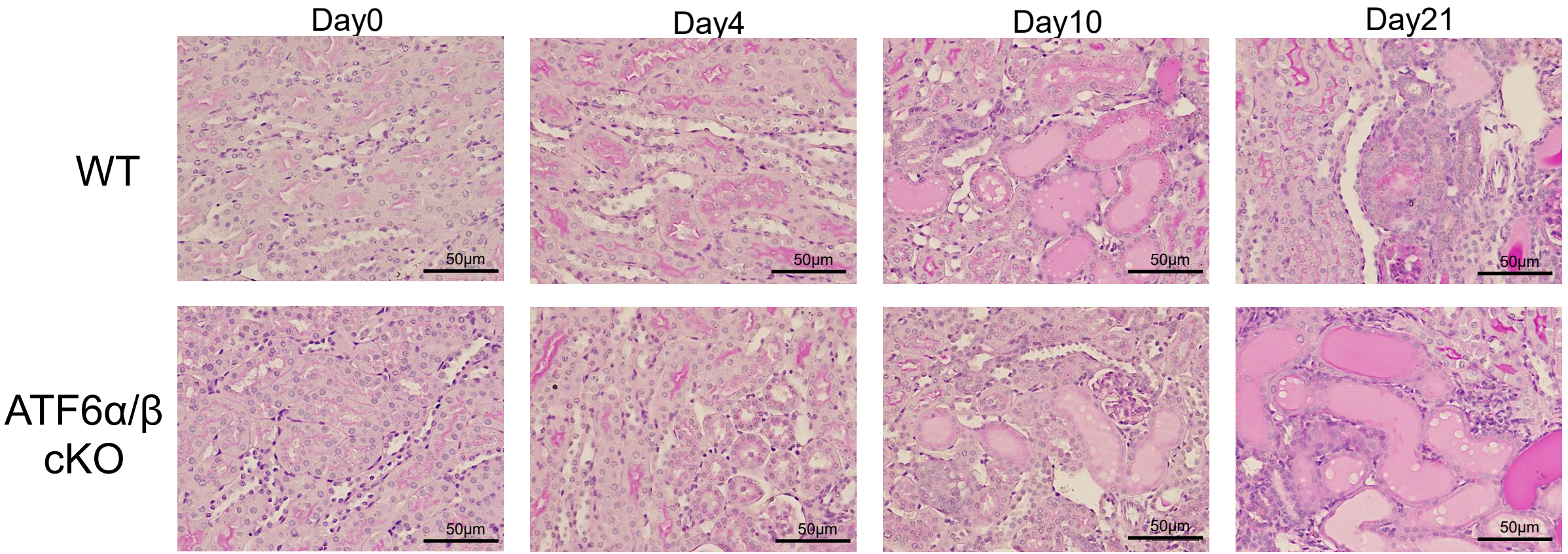

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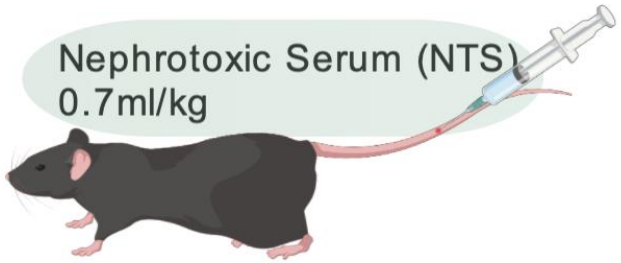

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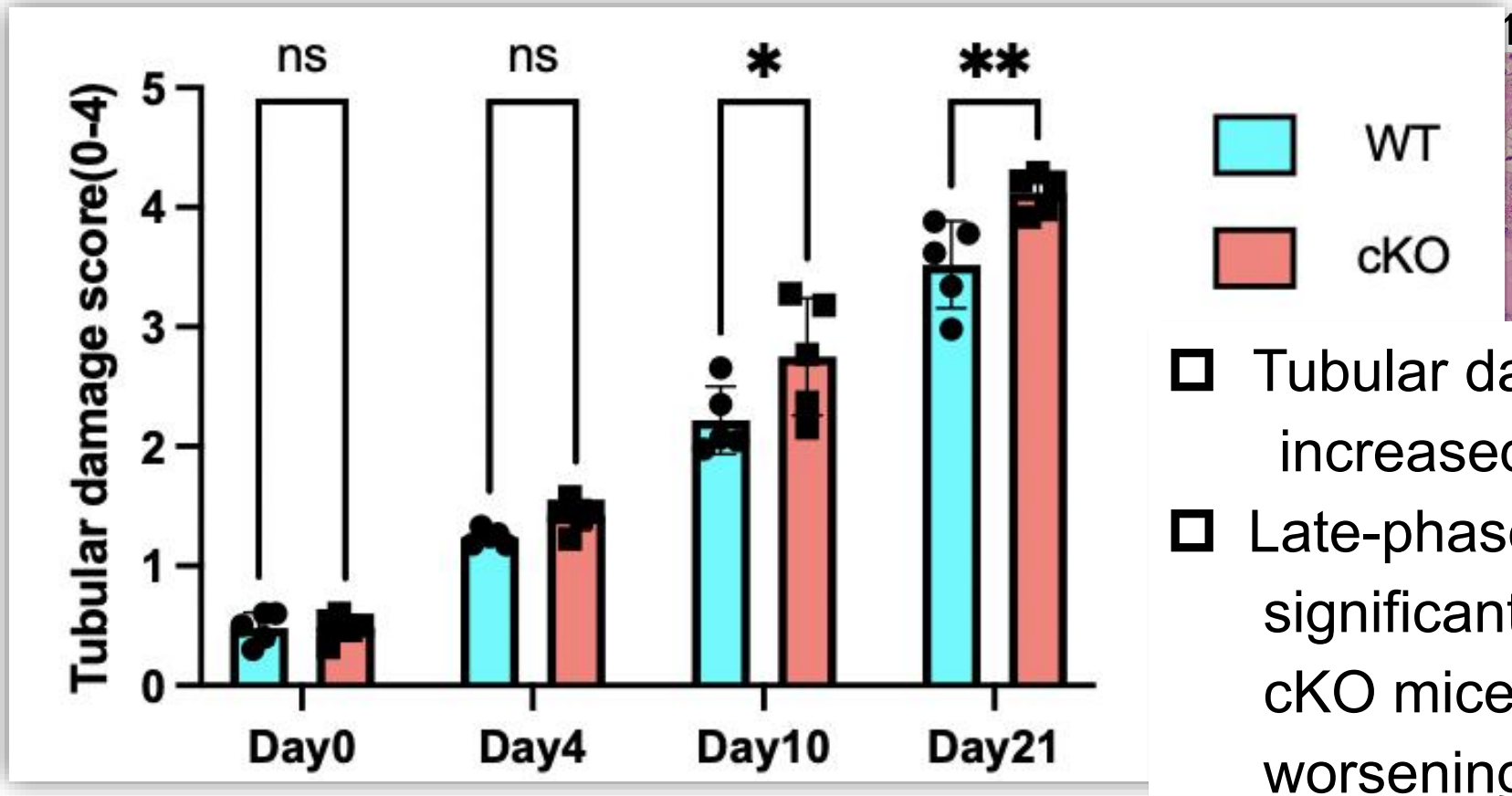
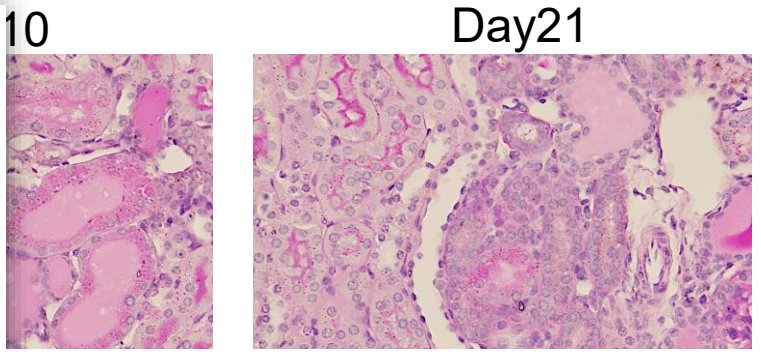
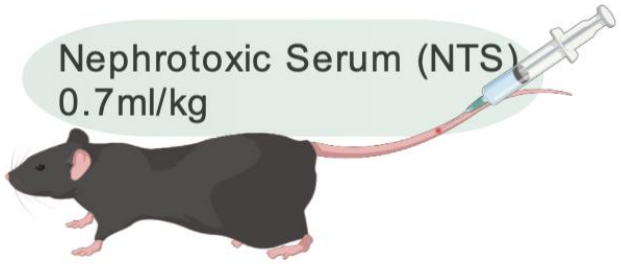




- Tubular damage progressively increased in both genotypes
- Late-phase tubular injury was significantly aggravated in ATF6α/β cKO mice, in parallel with the worsening glomerular damage

Result: *ATF6α/β deficiency causes a dysregulated ERAD response with late Derl3 induction*



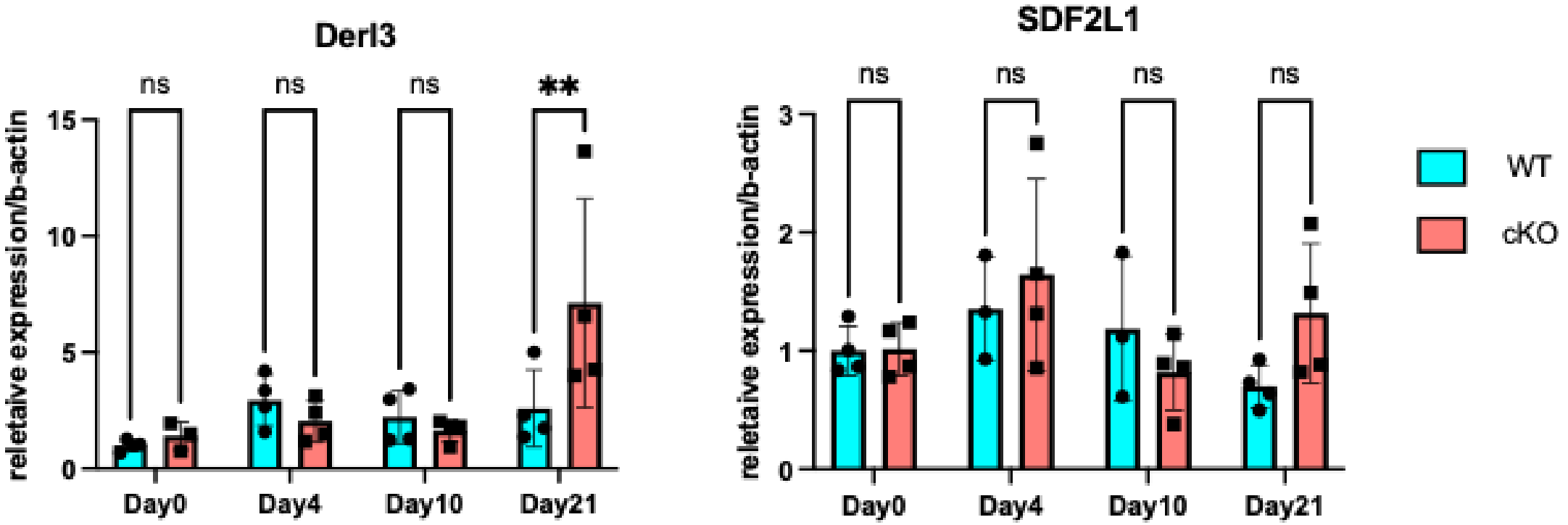
Anti-GBM glomerulonephritis

WT: ATF6α/$\beta^{fl/fl}$

cKO: Podocin-Cre; ATF6α/$\beta^{fl/fl}$

→ Isolation of glomeruli

ERAD: ER–associated degradation, representative ATF6 downstream genes



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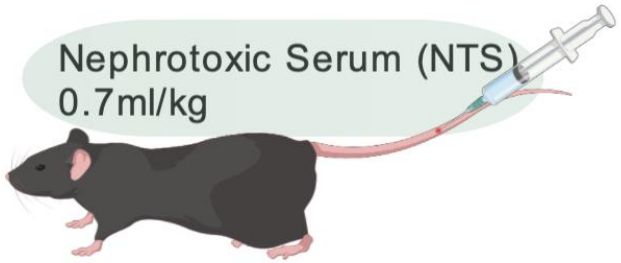

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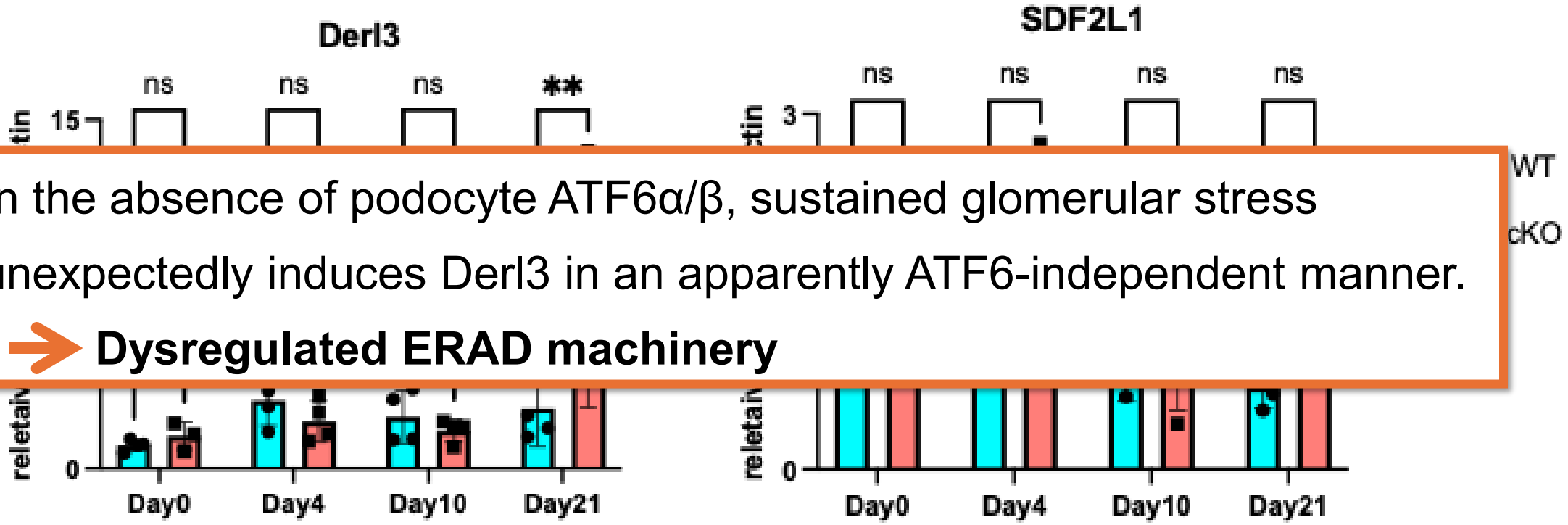

☐ In the absence of podocyte ATF6α/β, sustained glomerular stress unexpectedly induces Derl3 in an apparently ATF6-independent manner.

→ **Dysregulated ERAD machinery**

Summary: *Generation and validation of podocyte-specific ATF6α/β cKO mice*

- Podocyte-specific ATF6α/β KO mice show no significant changes in kidney function or morphology under physiological conditions.
- In nephrotoxic serum–induced anti-GBM glomerulonephritis, disease induction and early albuminuria were comparable between WT and ATF6α/β cKO mice.
- In the late phase, however, ATF6α/β cKO mice developed exacerbated albuminuria with more severe tubular and, at later time points, more pronounced glomerular damage.

Podocyte ATF6α/β signaling limits glomerular damage progression under stress conditions