



Role of Podocyte Ceramide Synthase 6 in Renal Aging: Mechanistic Insights from Non-Human Primate and Genetic Mouse Models

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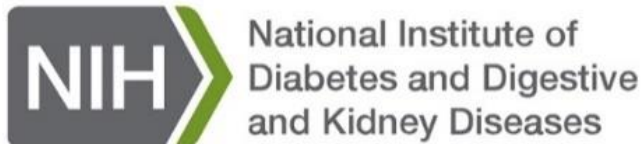


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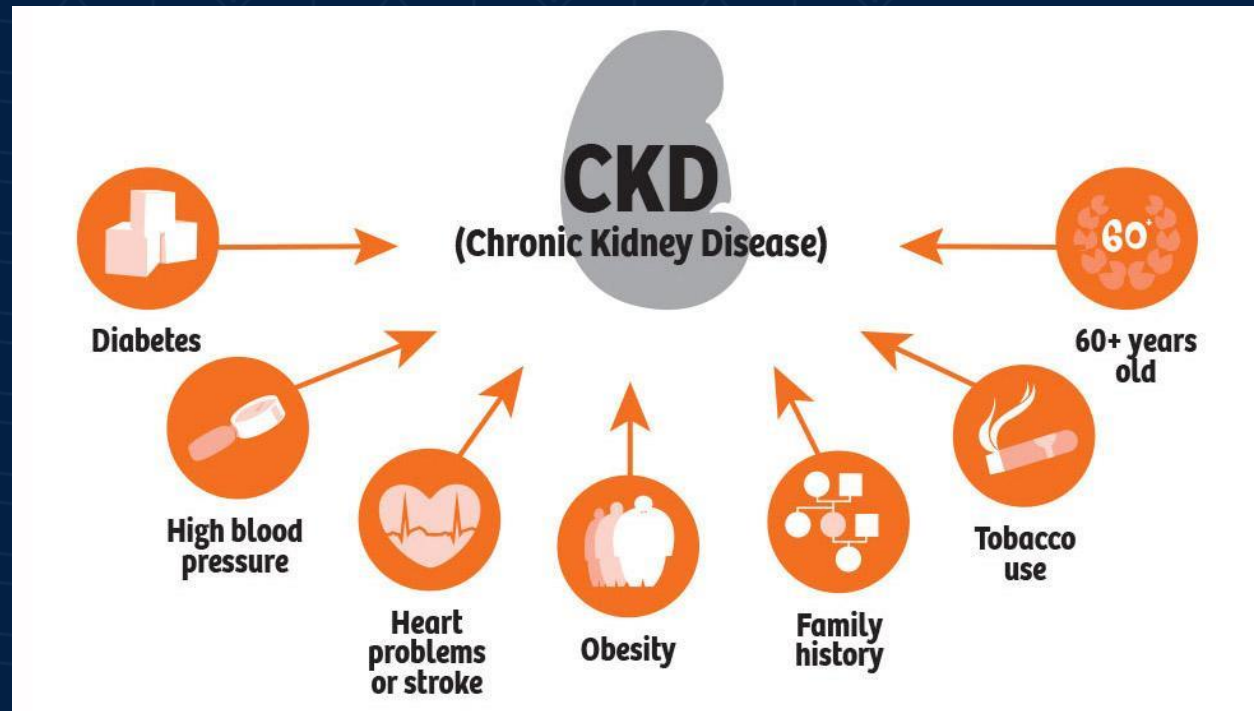


Non-Disclosure

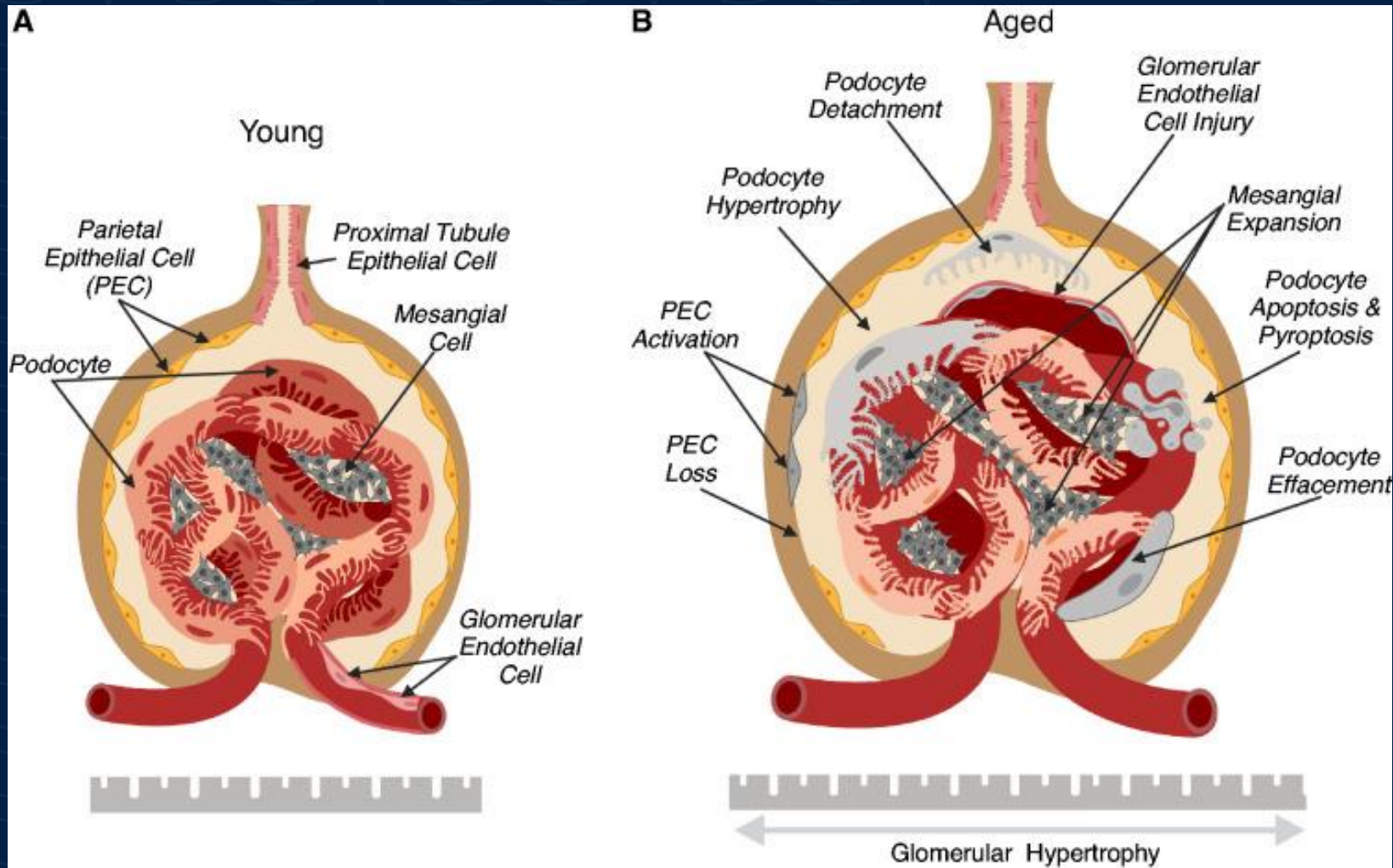
- Guanshi Zhang, PhD has no conflicts to report.

Chronic Kidney Disease: Common, Serious, and Costly

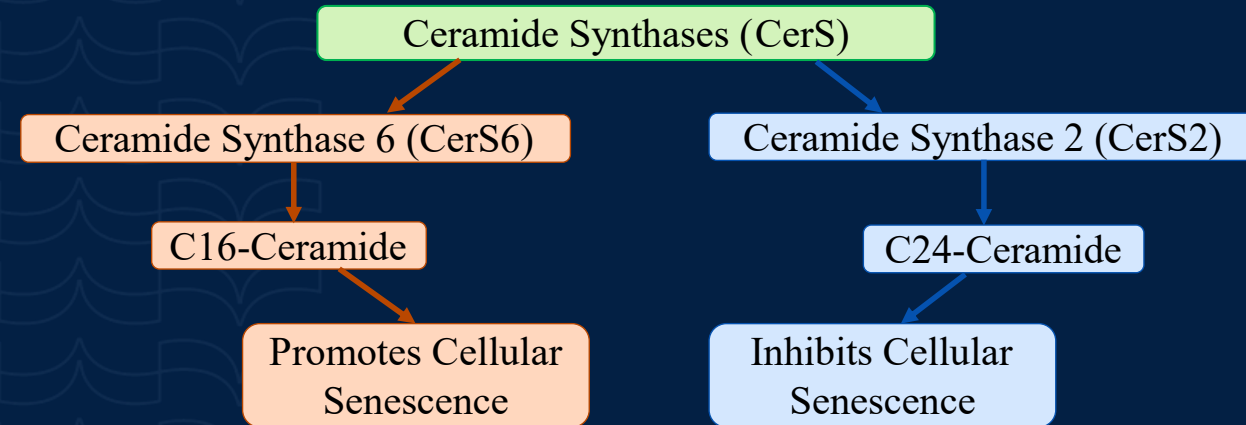
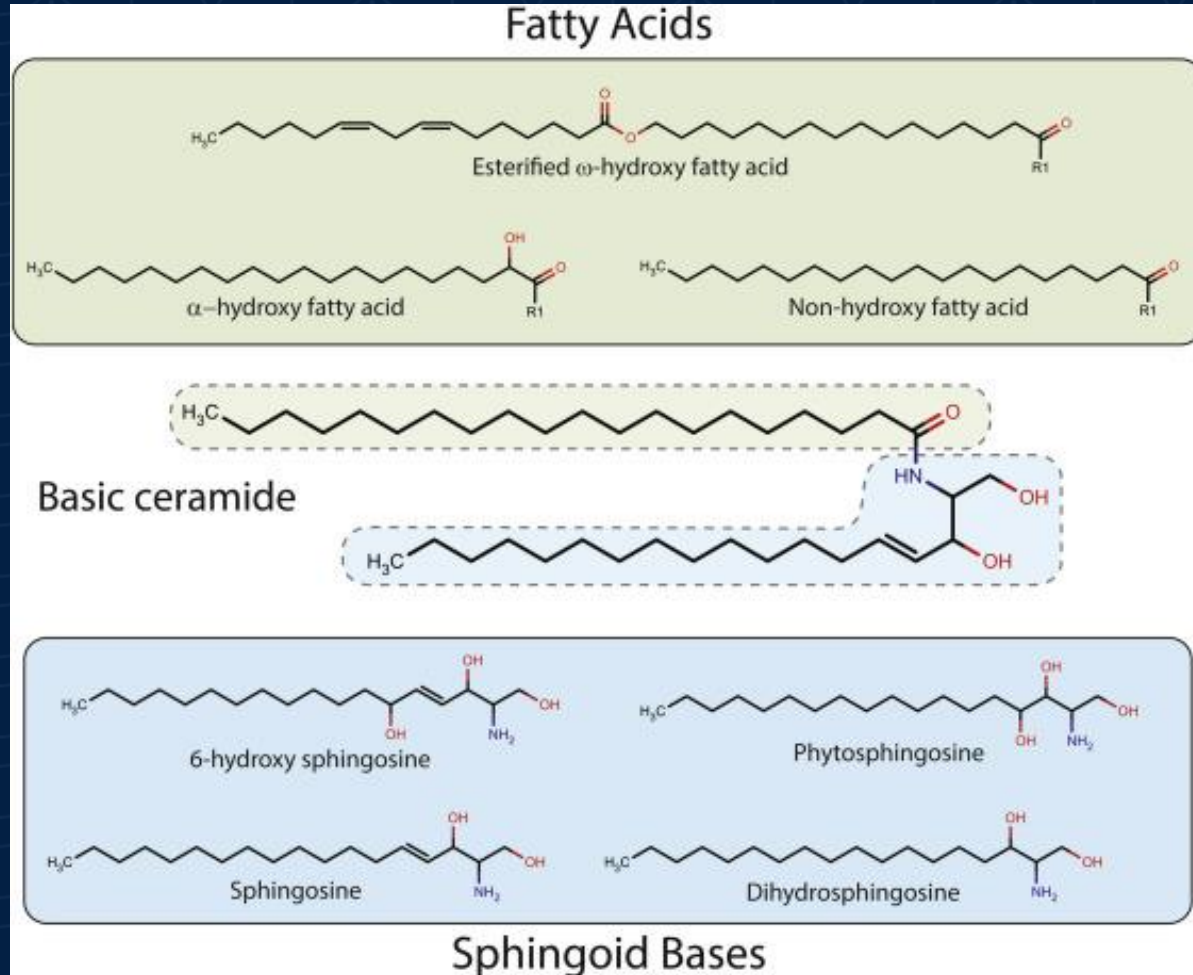
- More than 1 in 7 US adults have CKD
- Kidney diseases are a leading cause of death in the US
- **1.4 M Veterans** have CKD; prevalence ~34% higher than general population
- Annual cost for CKD: \$87.2 B; Additional \$37.3 B for ESKD
- No effective therapeutics for CKD



Changes to Podocytes in the Aged Human and Rodent Kidney



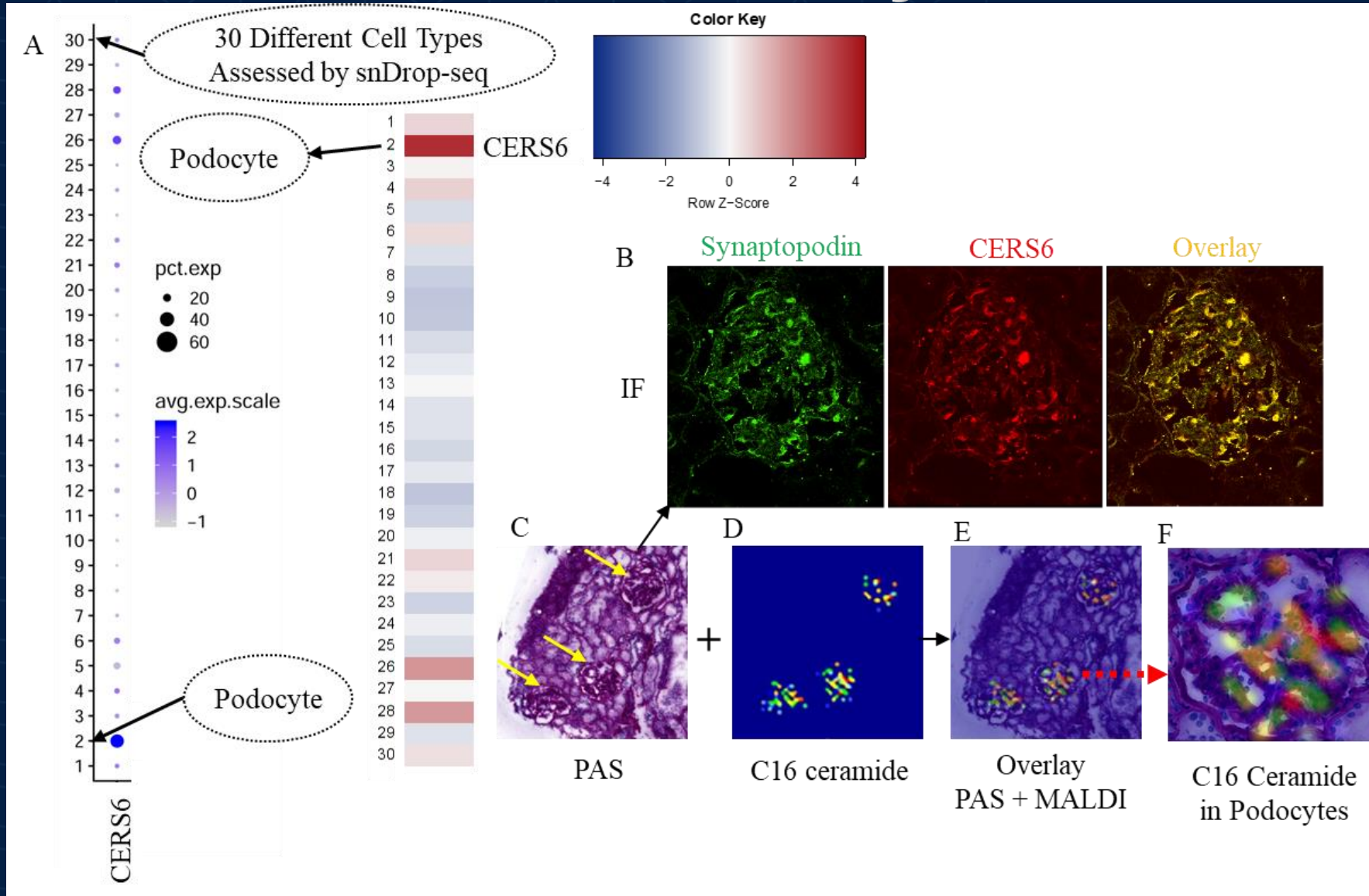
Ceramides and Ceramide Synthases (CerS) and Ceramide Metabolism



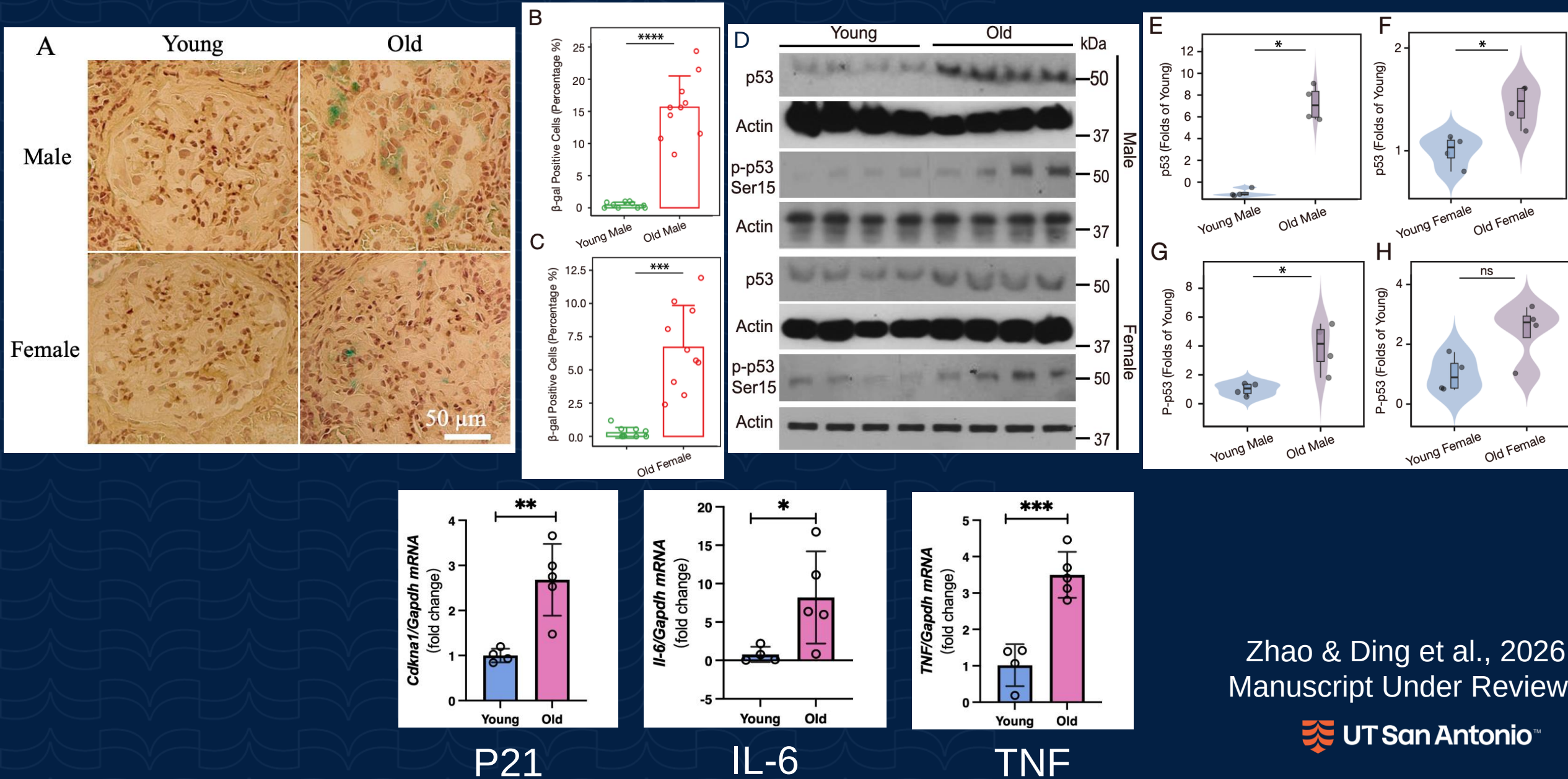
Hammerschmidt and Brüning. 2022. *Cell Mol. Life Sci.* 79:395.

Wilkerson et al. 2024. *Physiol Rev.* 104:1061-1119.

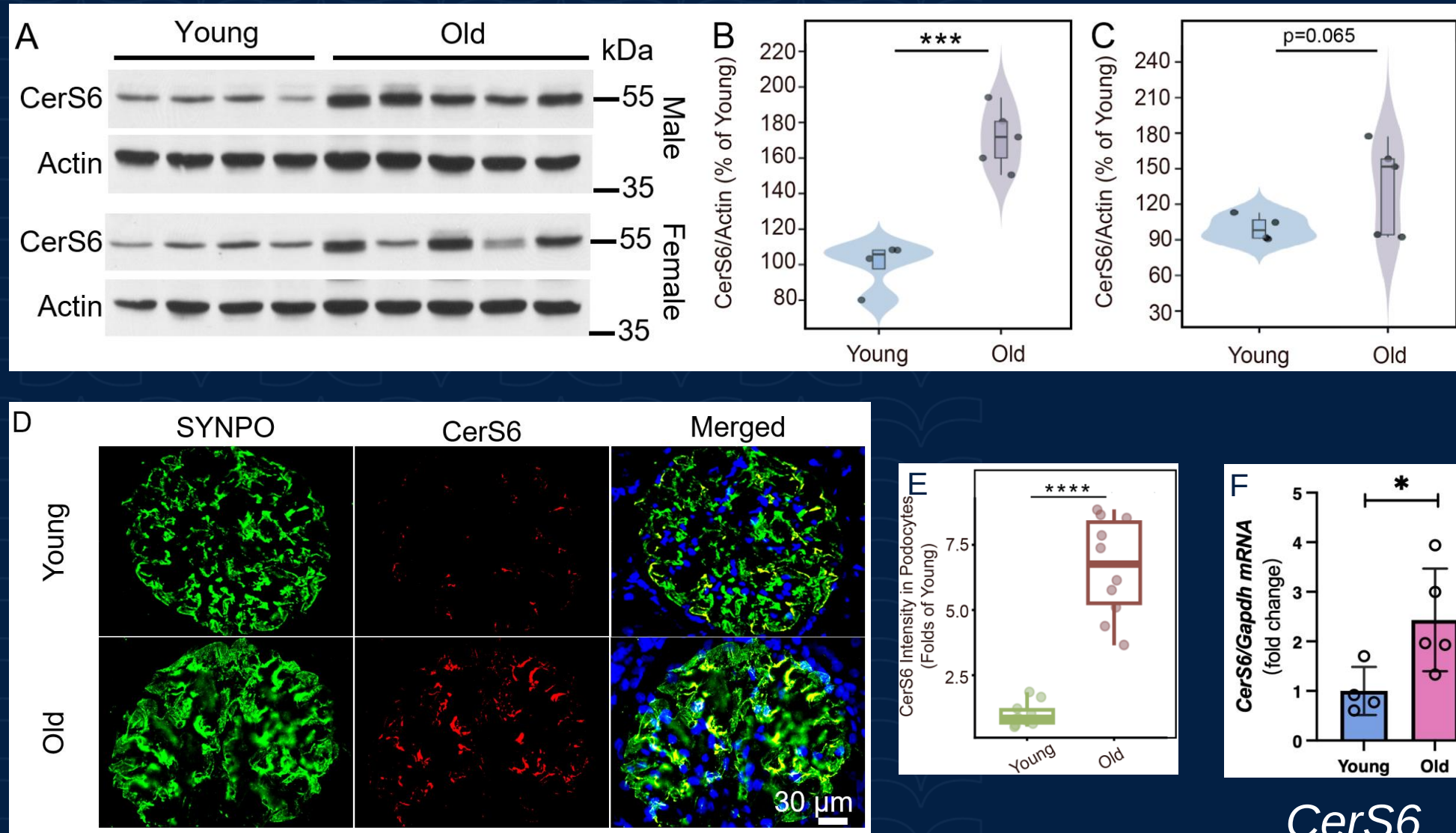
CerS6 and C16 Cer in Healthy Human Kidney



Senescence in Aged Marmoset Kidneys

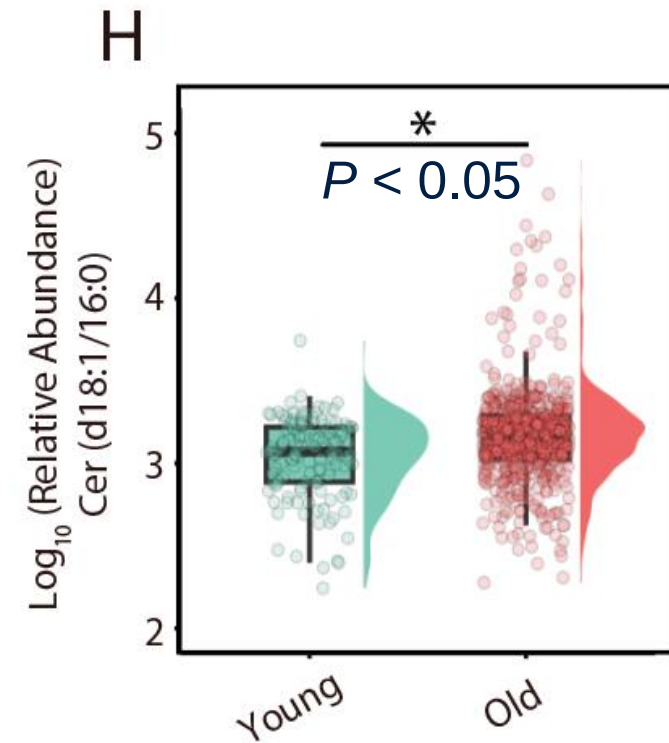
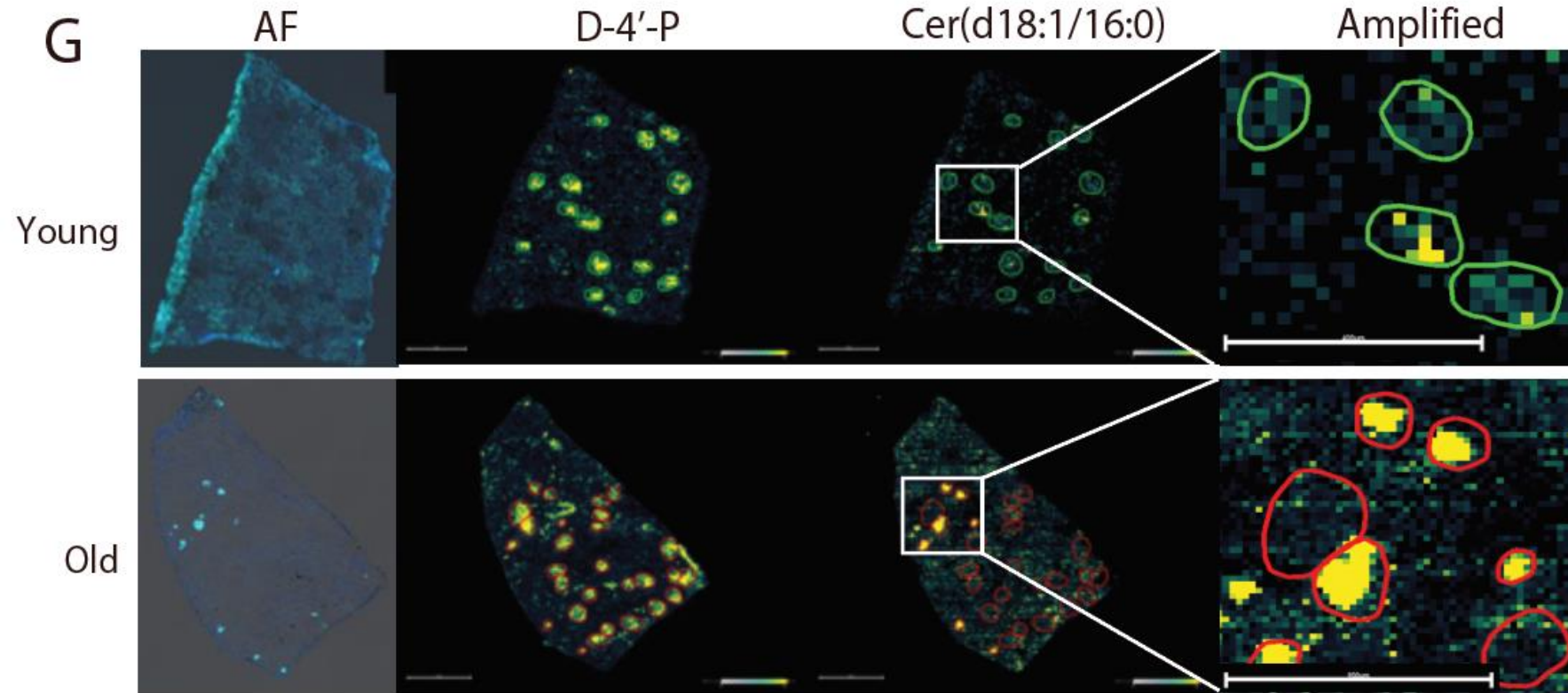


CerS6 is Elevated in Aged Marmoset Kidneys

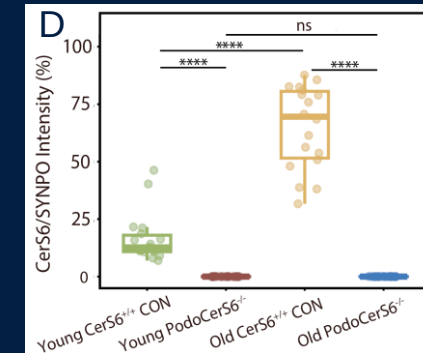
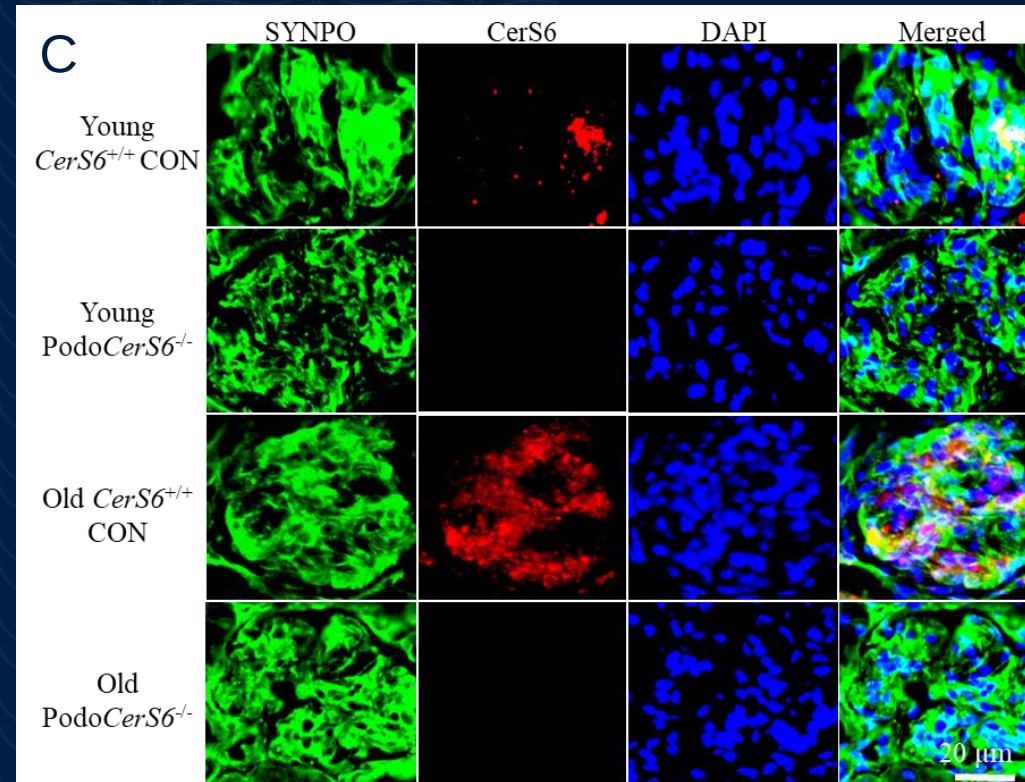
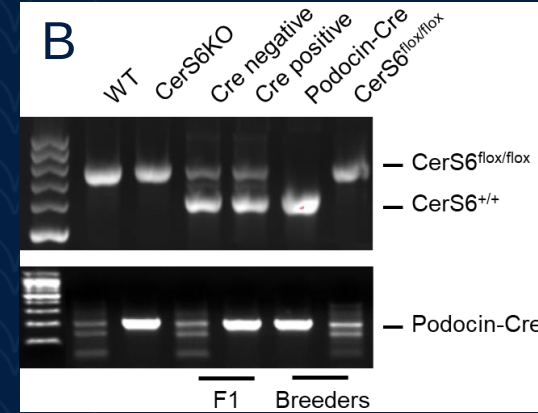
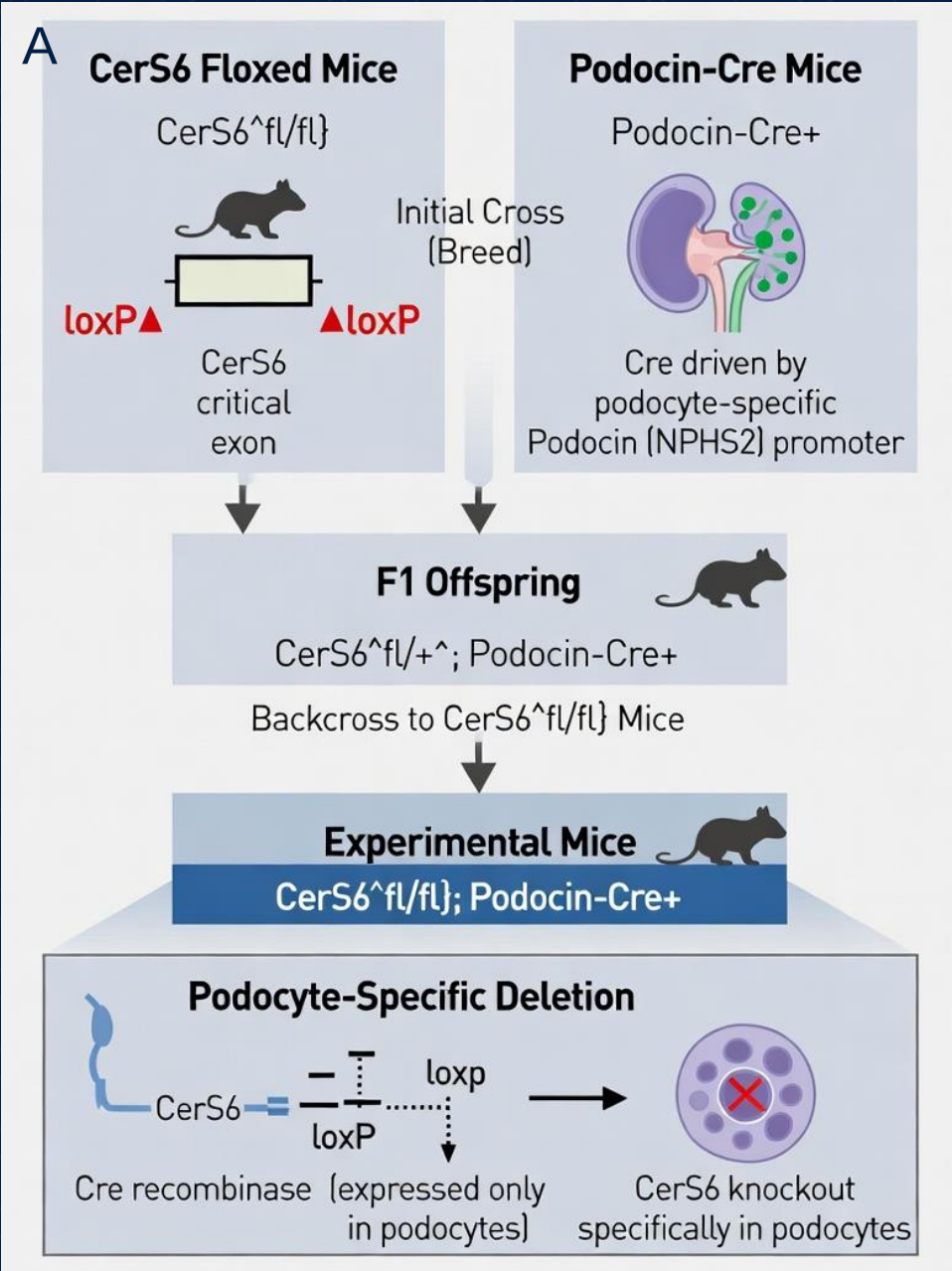


CerS6

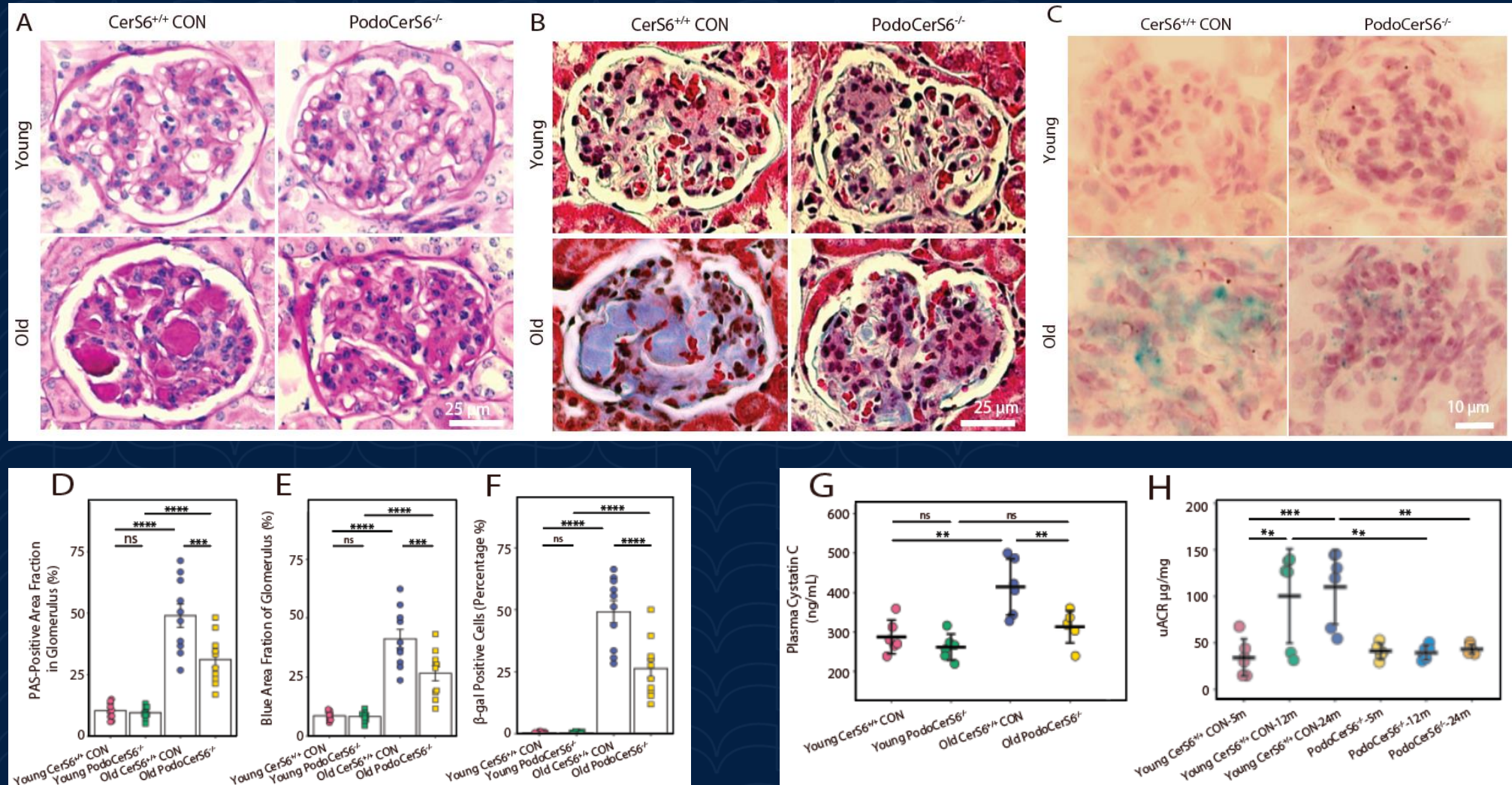
C16 Cer is Accumulated in Glomeruli of Aged Marmosets



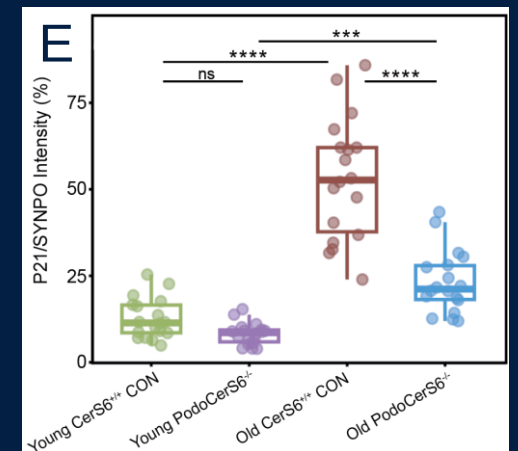
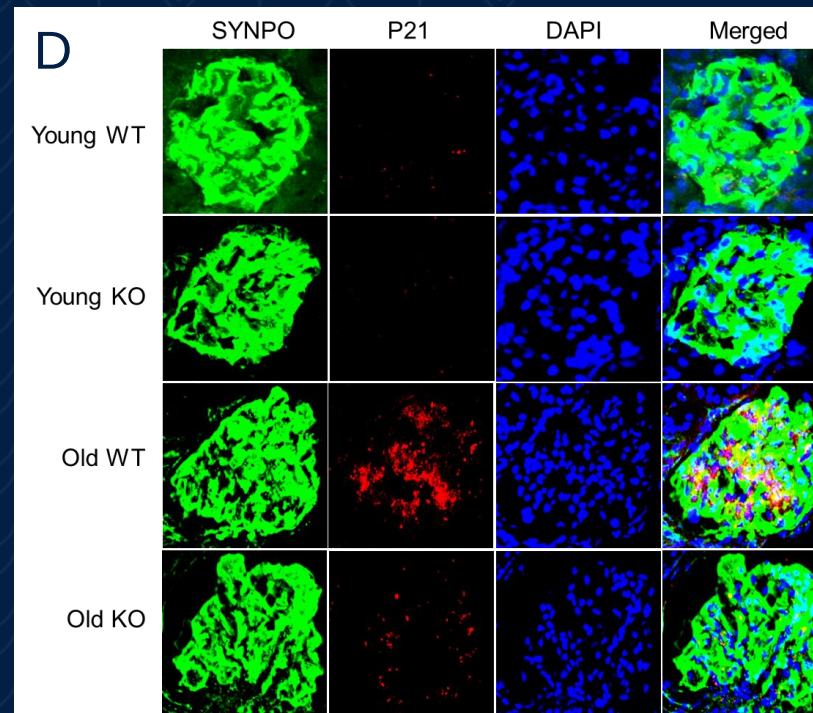
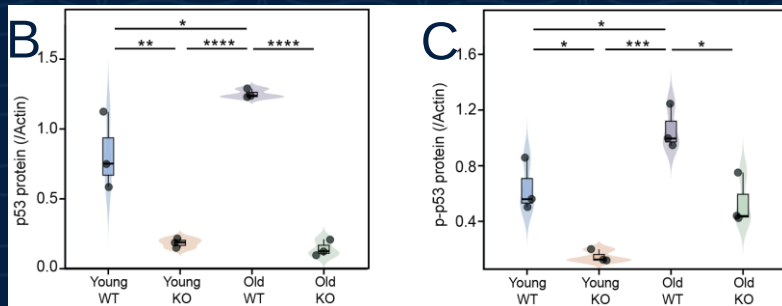
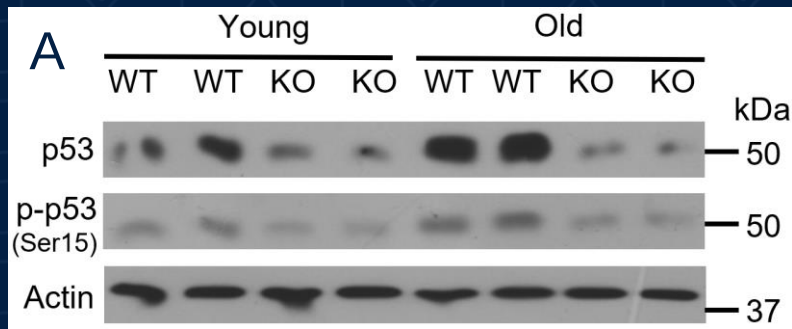
Generation of Podocyte-Specific CerS6 KO Mice



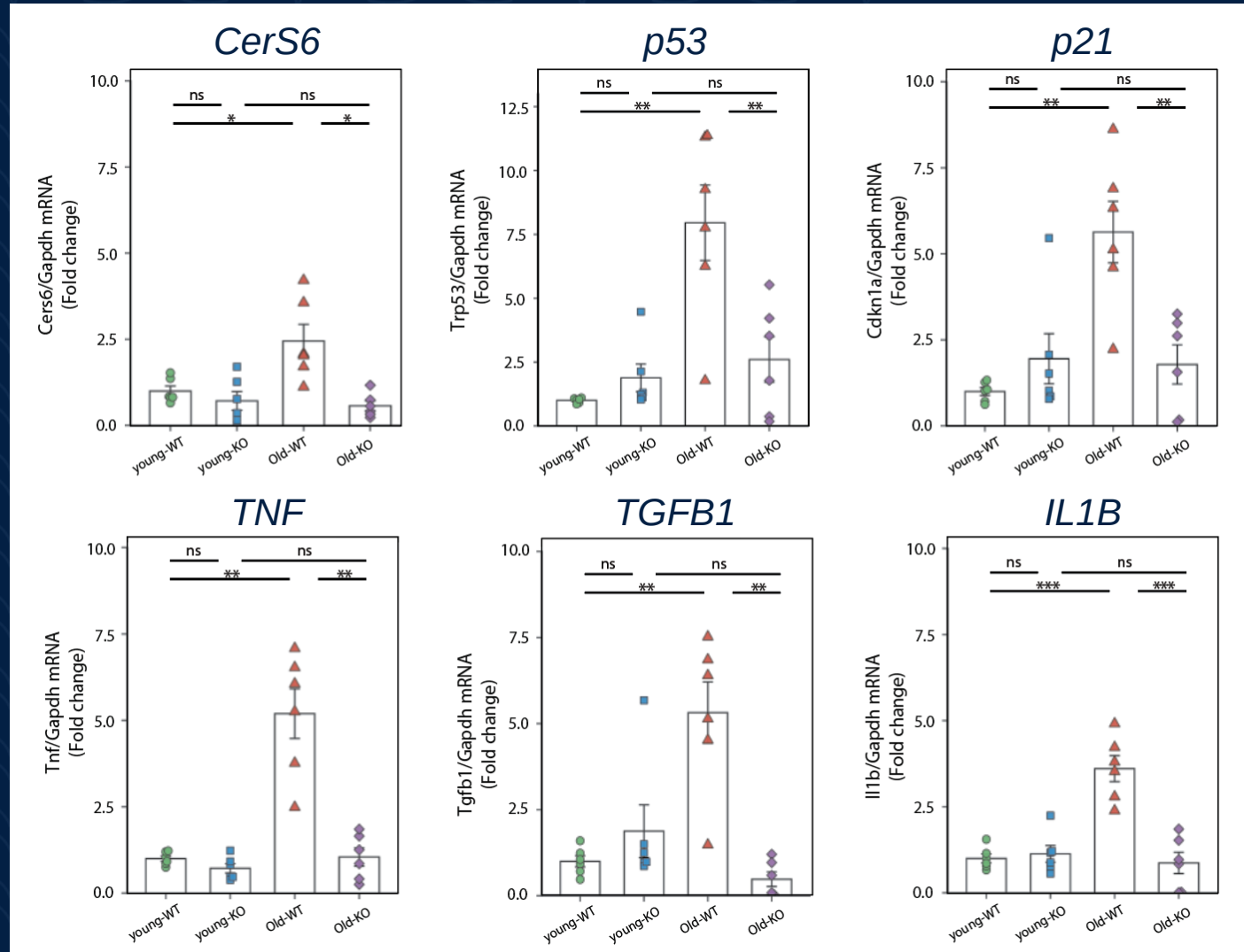
Podocyte-Specific CerS6 KO Protects Aging-related Glomerular Changes



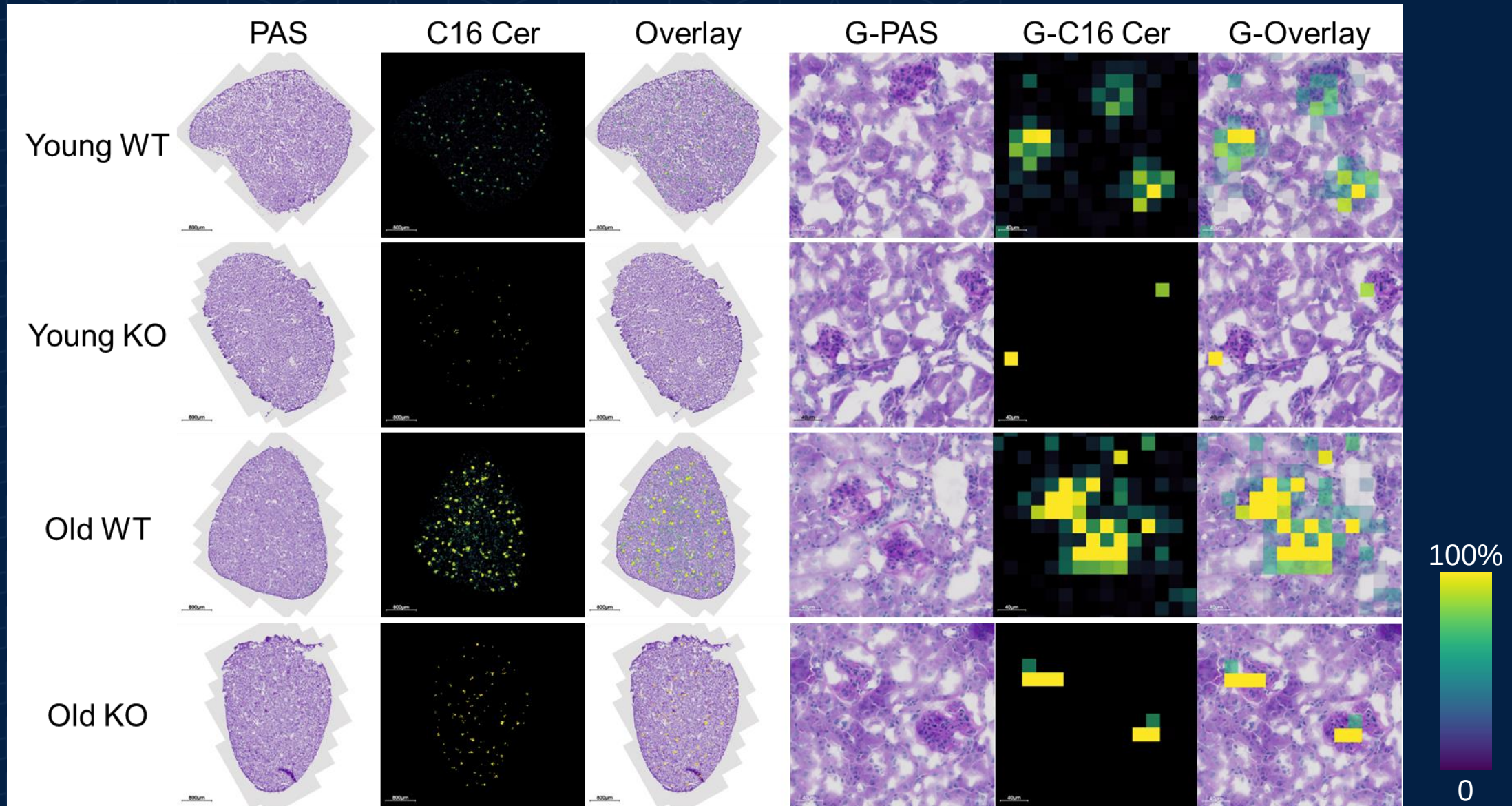
Podocyte-Specific CerS6 KO Suppresses p53/p21 Senescence Signaling



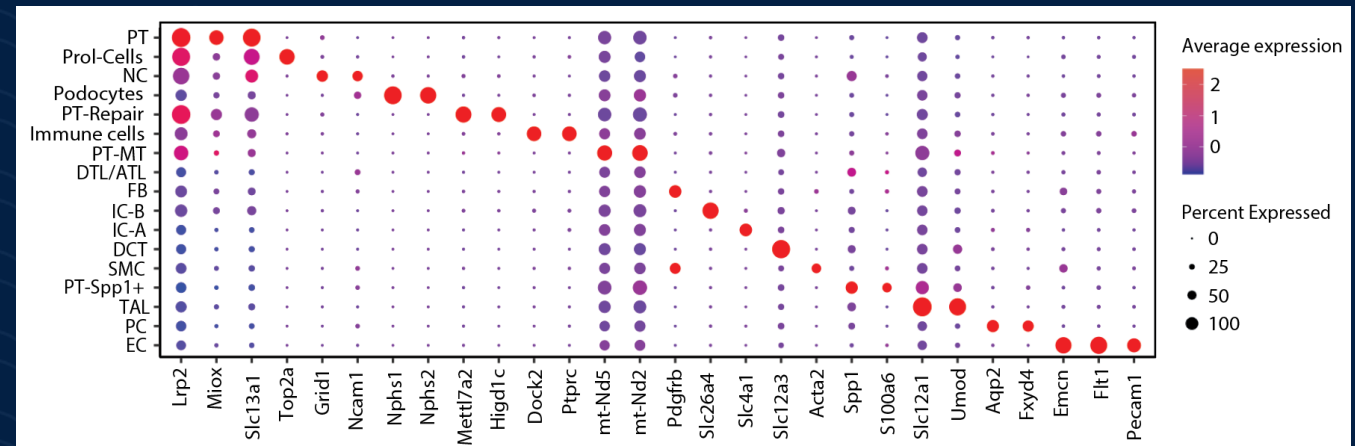
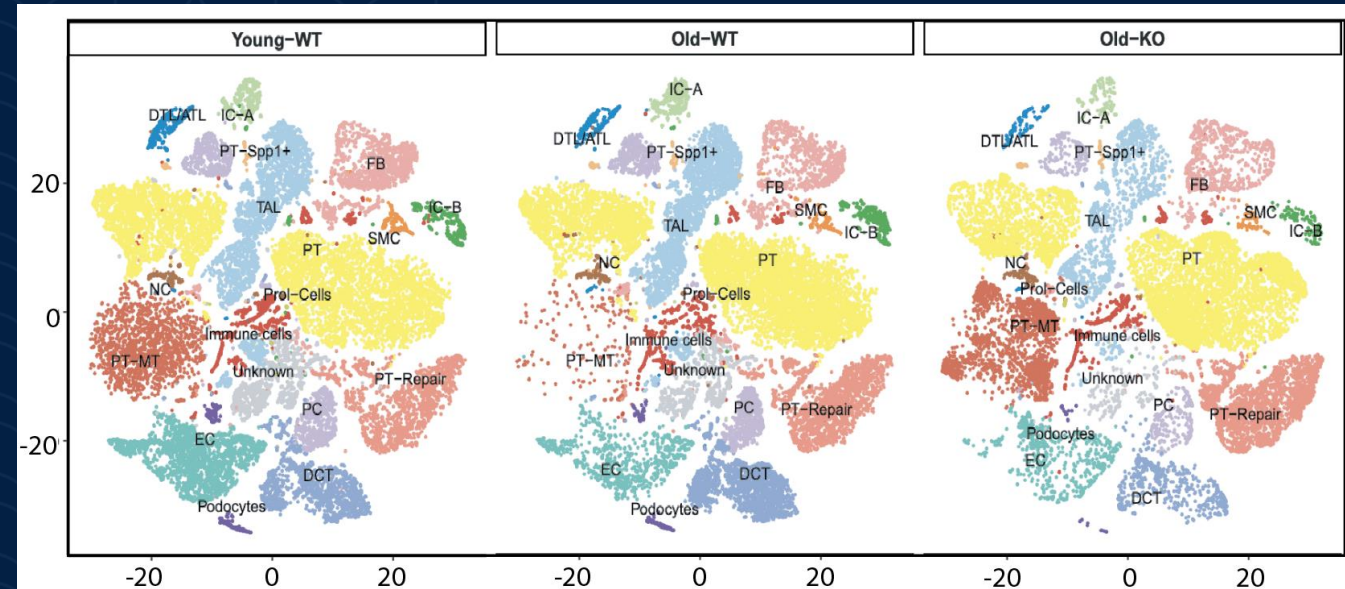
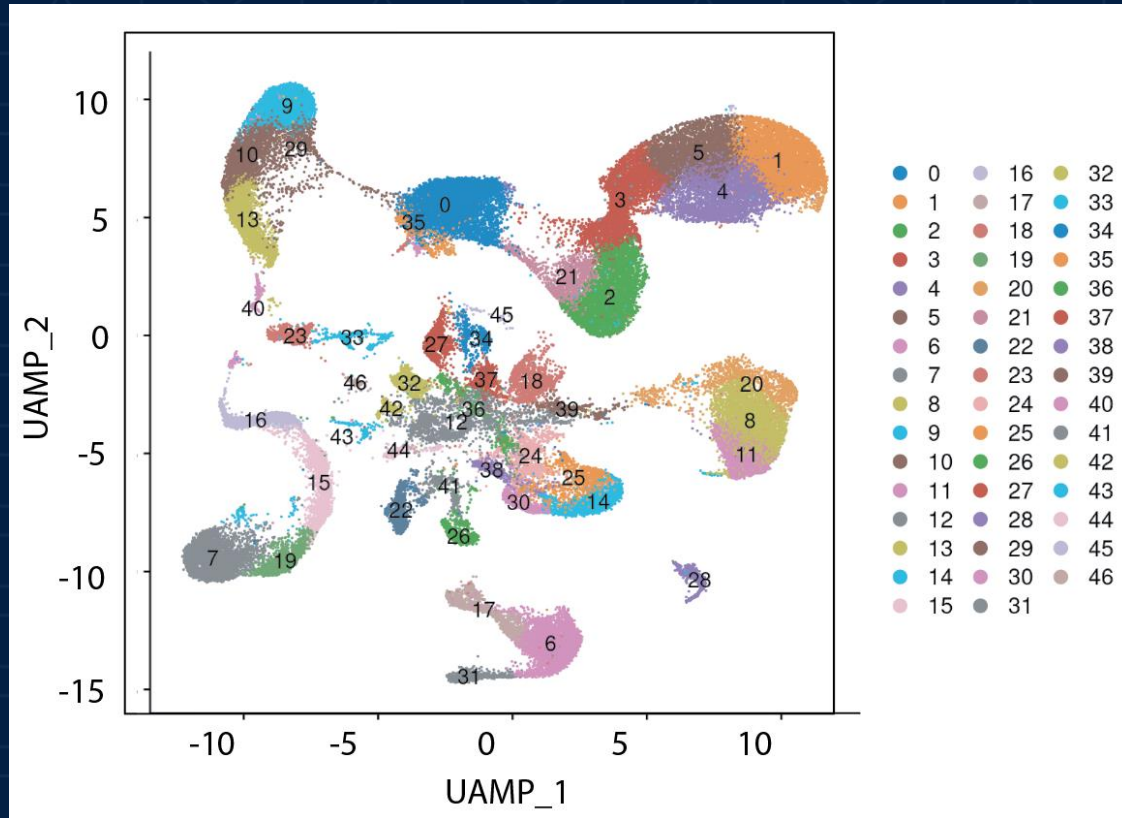
Podocyte-Specific CerS6 KO Suppresses p53/p21 Senescence Signaling



C16 Cer is Accumulated in Glomeruli of Aged Mice



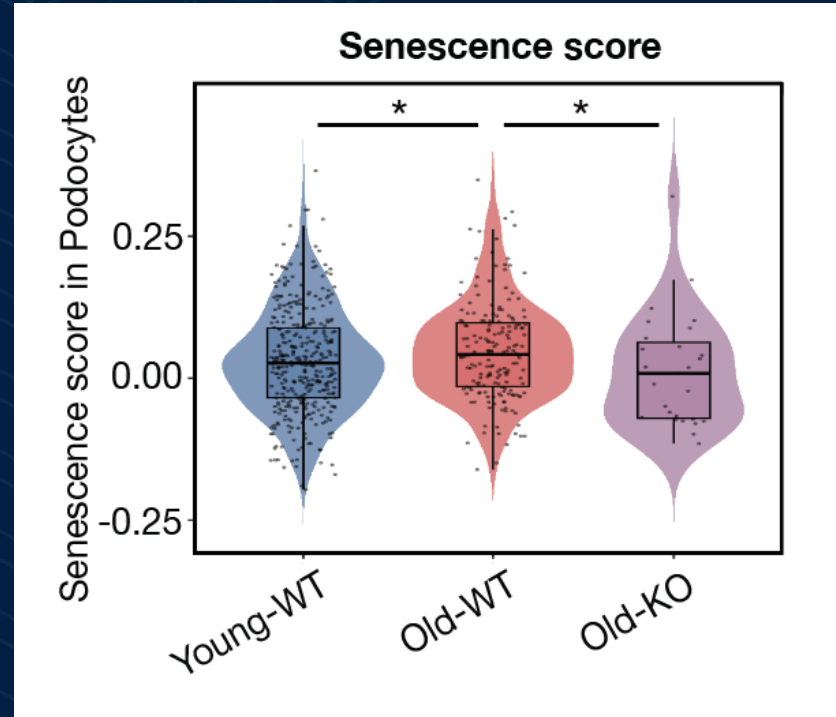
snRNA-seq of Aged Mouse Kidney - Cell Type



We use leiden with 1.0 resolution and get 46 clusters, and we finally annotated them as 17 different types in the first level.

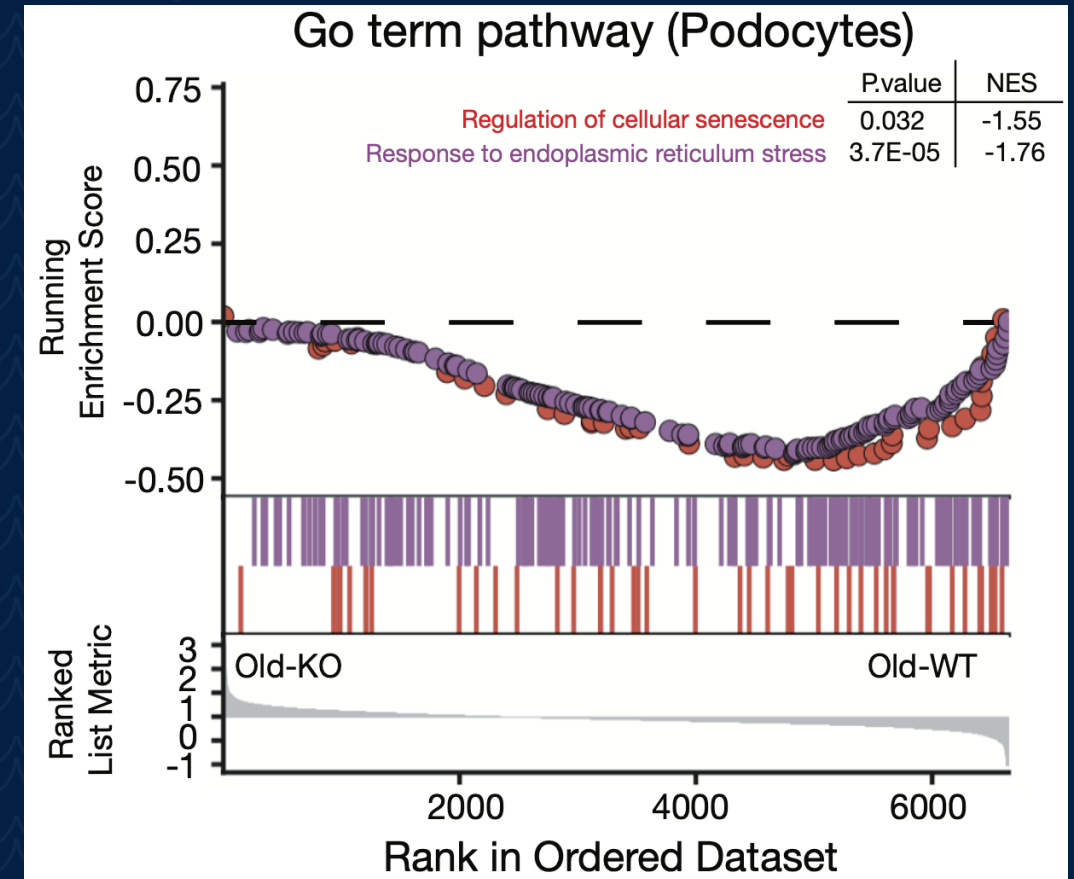
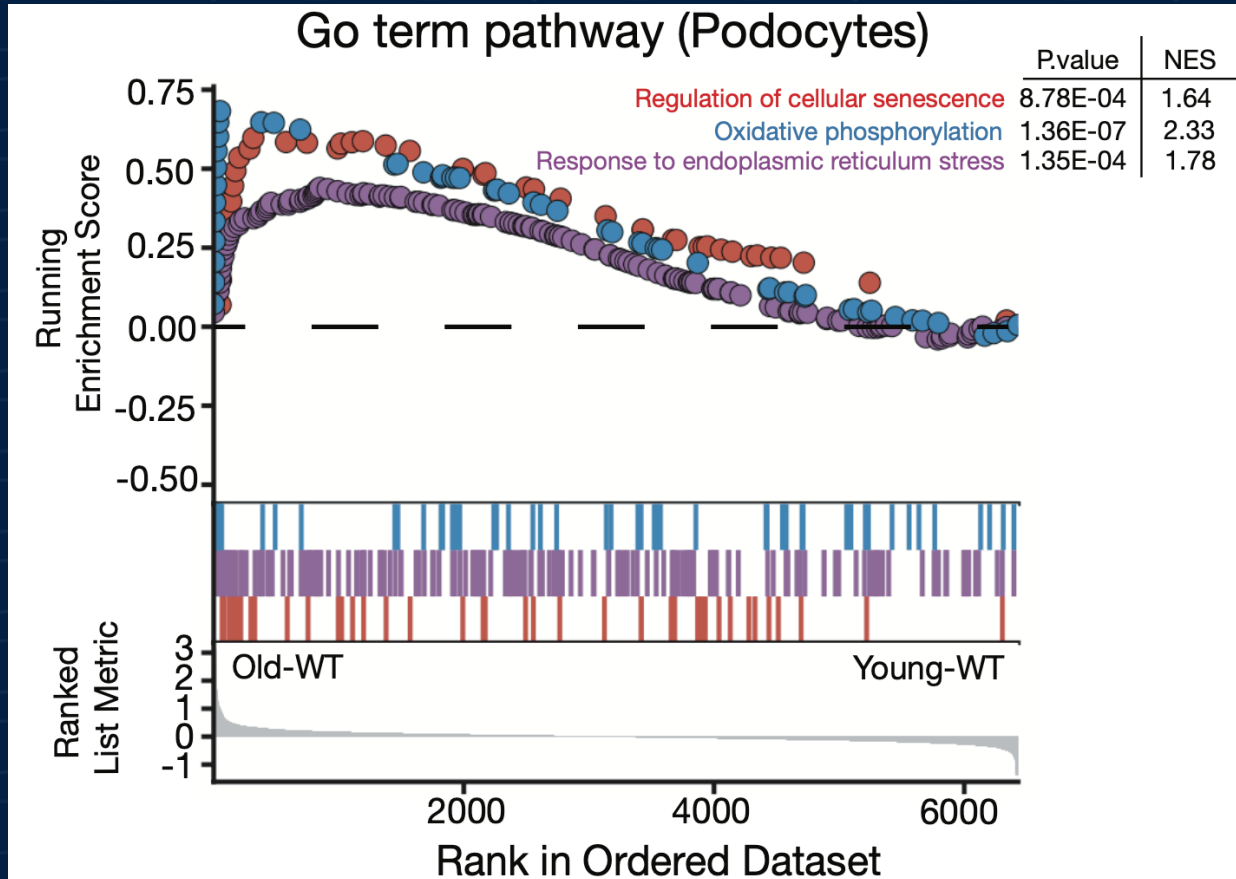
Podocyte-Specific CerS6 Knockout Reduces Senescence Score in Podocytes

```
senescence_genes <- c(  
  "Cdkn2a","Cdkn1a","Cdkn1b",  
  "Cdkn2b","Trp53",  
  "H2afx","Atm","Gadd45a",  
  "Lmnb1","Hmgb1",  
  "Glb1","Lamp1",  
  "Serpine1",  
  "Igfbp3","Igfbp5","Igfbp7",  
  "Sirt6","Nfkb1",  
  "Foxo1","Foxo4",  
  "Sirt1","Sirt2","Sirt7",  
  "Sod1","Cat")
```

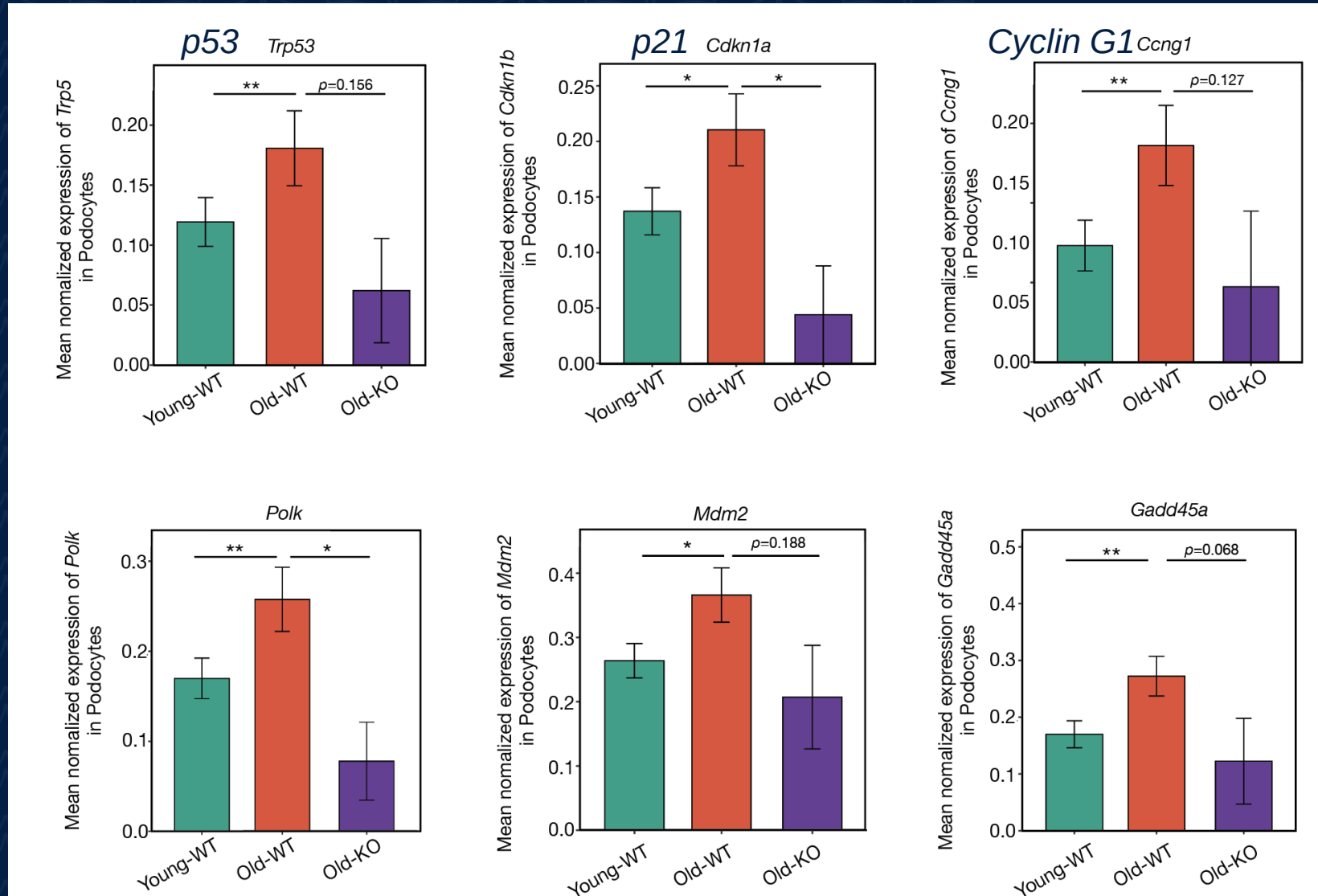


The senescence gene set was curated based on canonical regulators of cellular senescence, including genes involved in cell-cycle arrest (Cdkn2a, Cdkn1a), DNA damage response (H2afx, Atm), chromatin remodeling (Lmnb1, Hmgb1), lysosomal activity (Glb1, Lamp1), senescence-associated secretory phenotype (Serpine1, Igfbp family), oxidative stress (Sod1, Cat), and longevity pathways (Foxo and Sirtuin family members).

Podocyte-Specific CerS6 Knockout Suppresses P53-related Pathways in Podocytes



Podocyte-Specific CerS6 Knockout Suppresses P53-related Gene Expressions in Podocytes



Conclusion

- Podocyte CerS6 is a novel mediator of renal aging via C16-ceramide and p53-driven senescence
- Clinical implication: podocyte CerS6 is potential target to slow age-related kidney decline in Veterans and aging Service Members

Future Directions & Therapeutic Potential

- Human biopsy, urine, plasma/serum validation
- CerS6 inhibitors or podocyte-specific delivery
- Other ceramide species (e.g., C24 Cer) & SASP targeting
- Relevance to VA/DOD: address age-related CKD burden in Veterans via targeted therapies



Thank you for
your attention!



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