Is Diabetic Kidney Injury Accentuated in the Farnesoid X Receptor Knockout Mouse?

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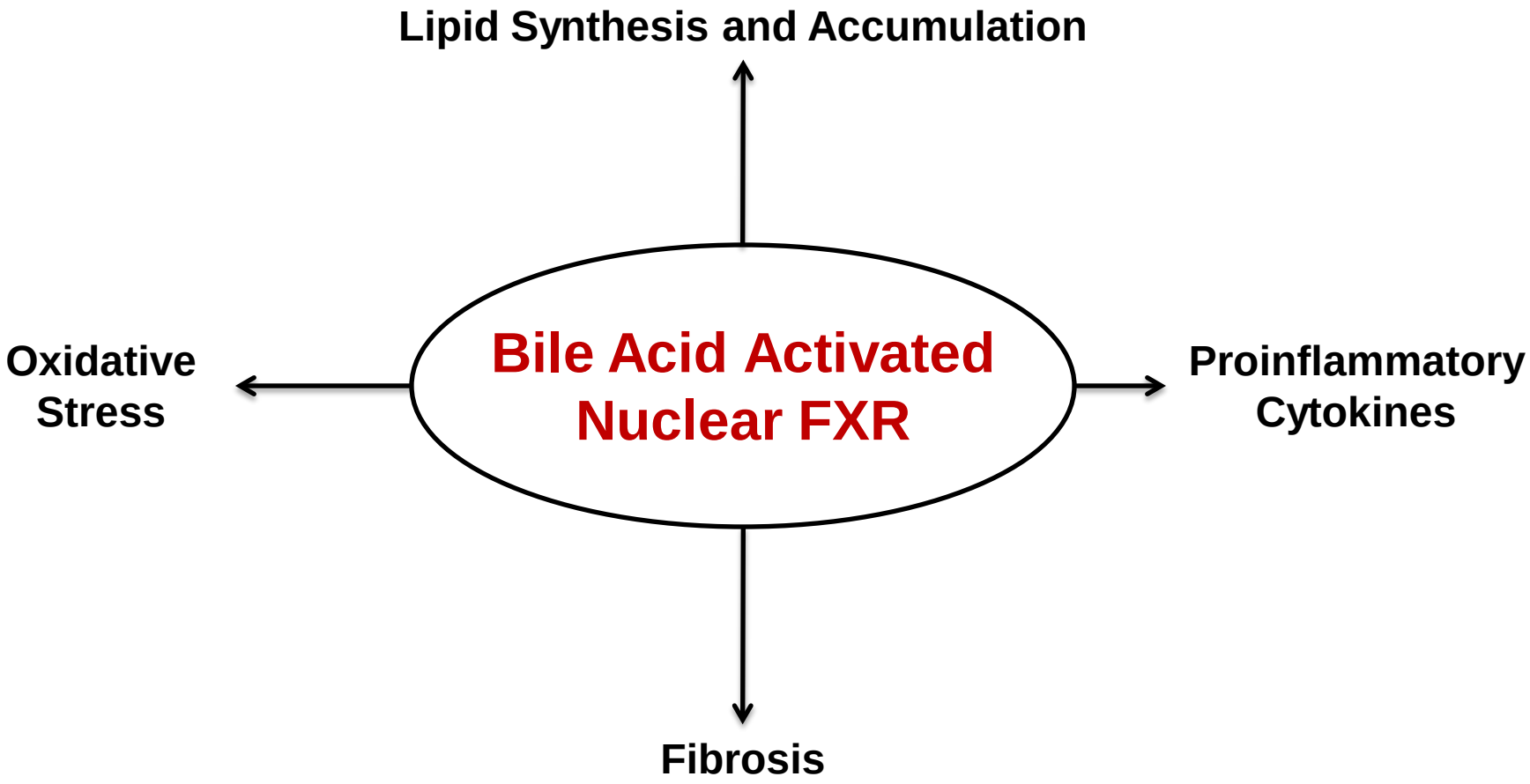
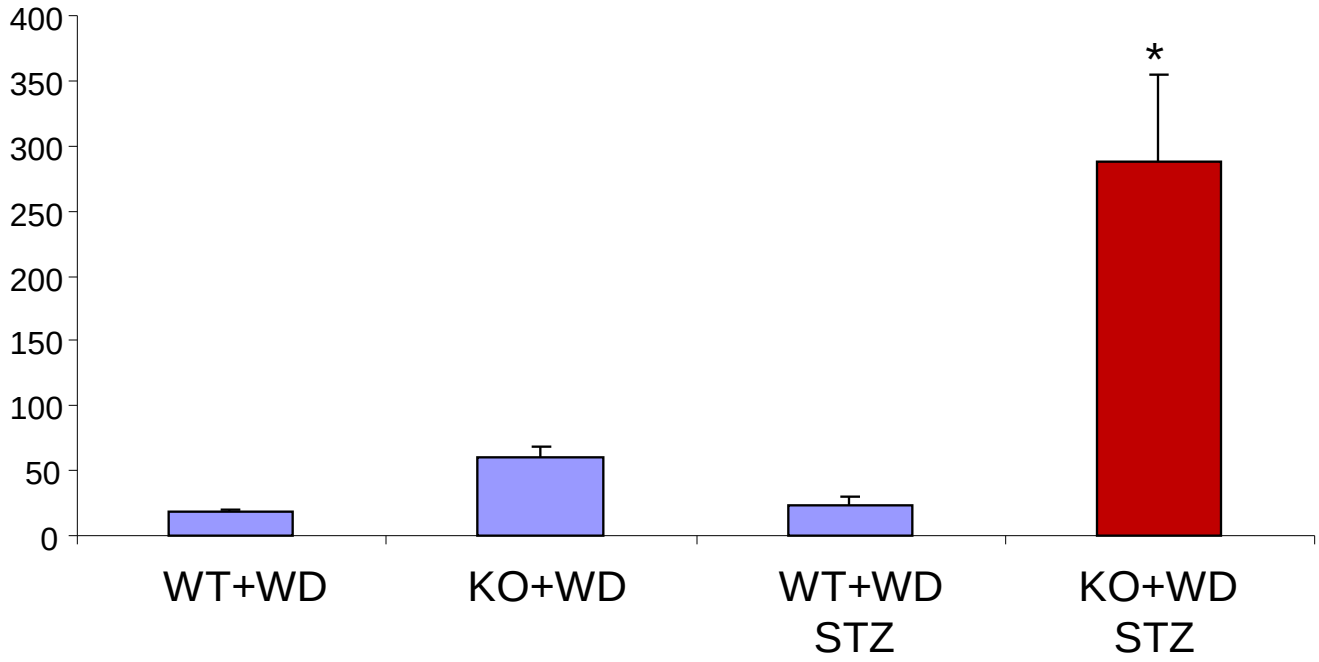
Why FXR in the kidney?



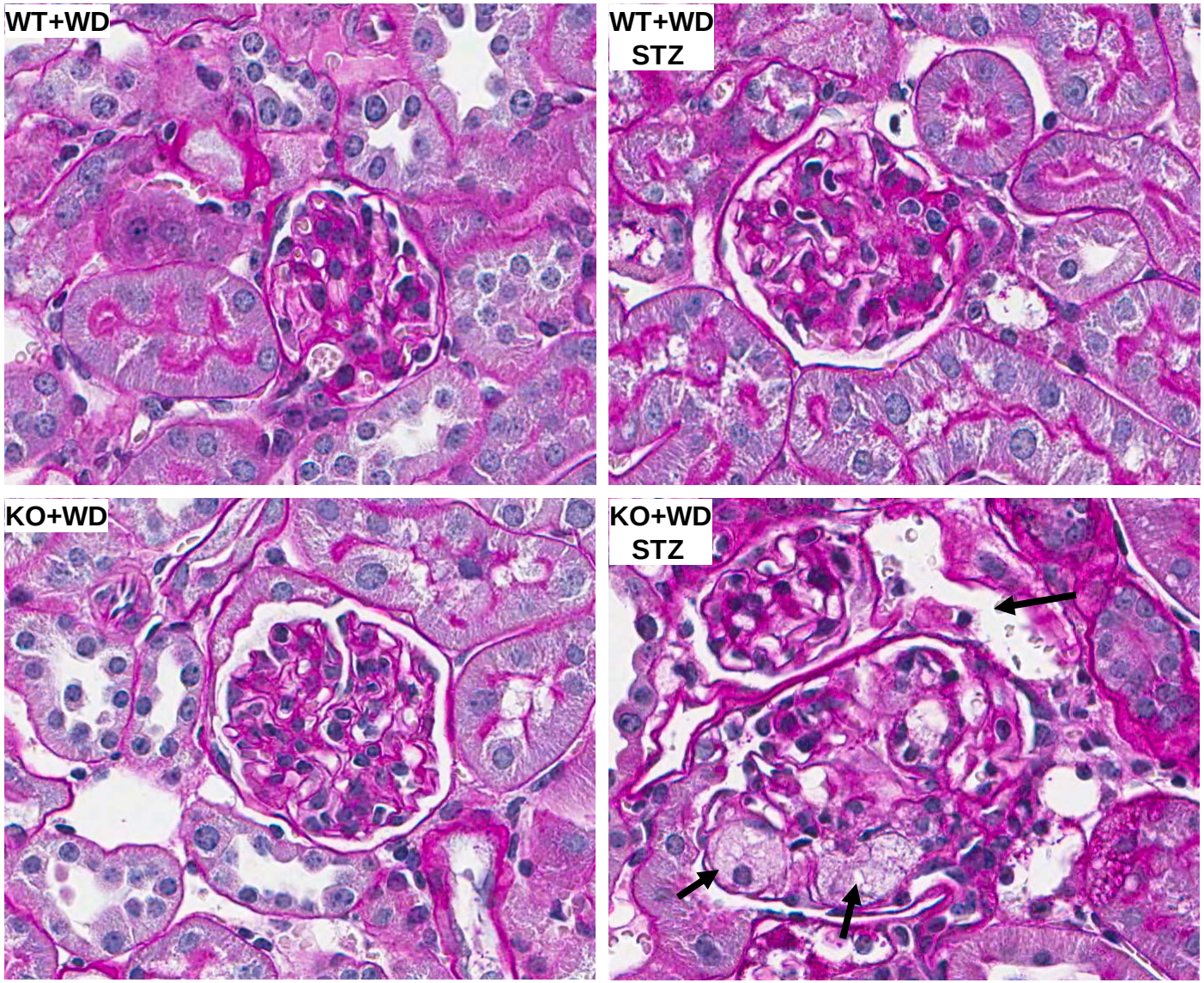
Experimental Design

6-month old FXR KO and wild type C57BL/6 male mice were treated with STZ (40mpk/d, 5 days) and fed a western diet for 2 months

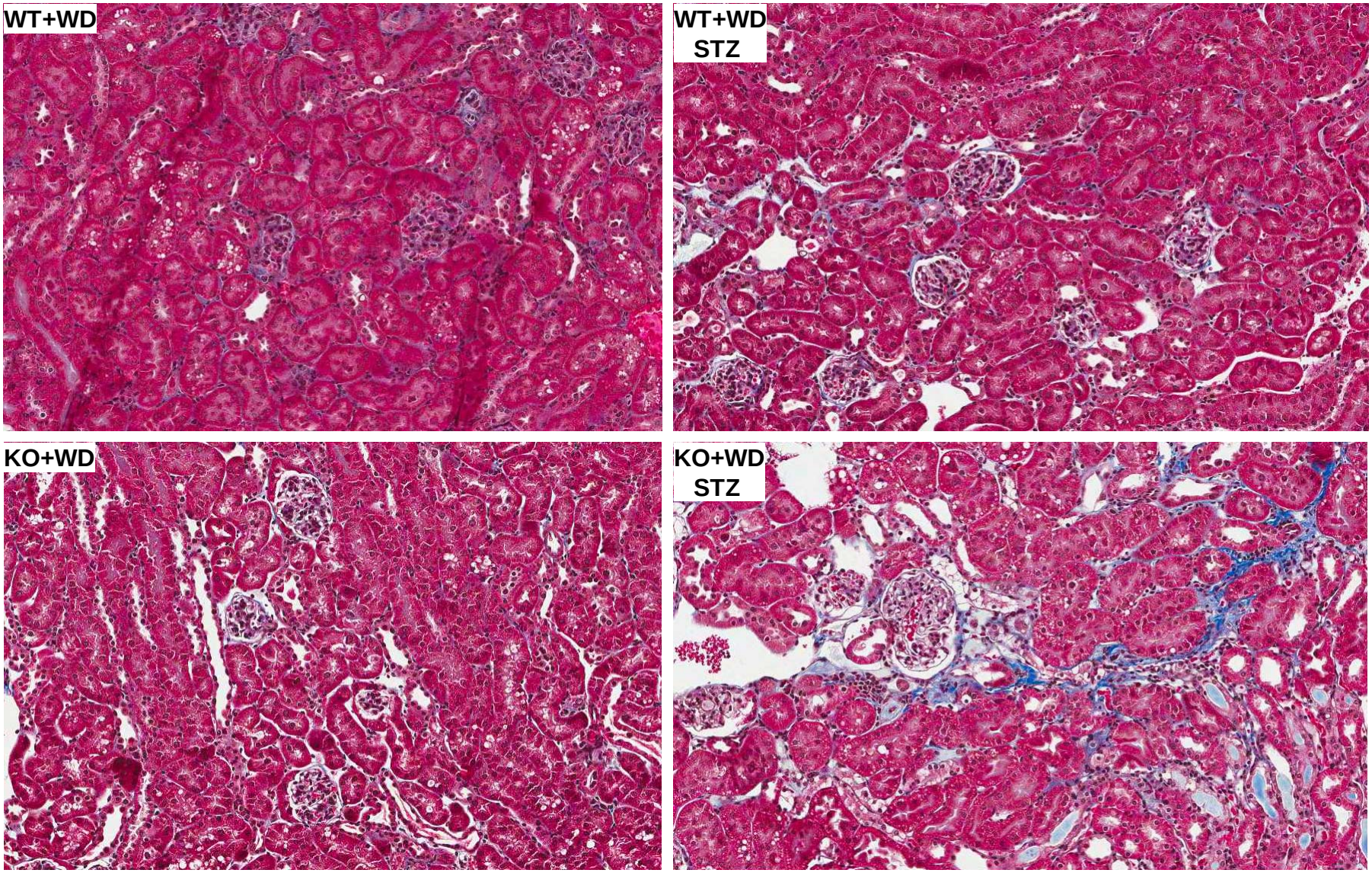
Diabetic FXR KO Mice Develop Significant Increase in Proteinuria



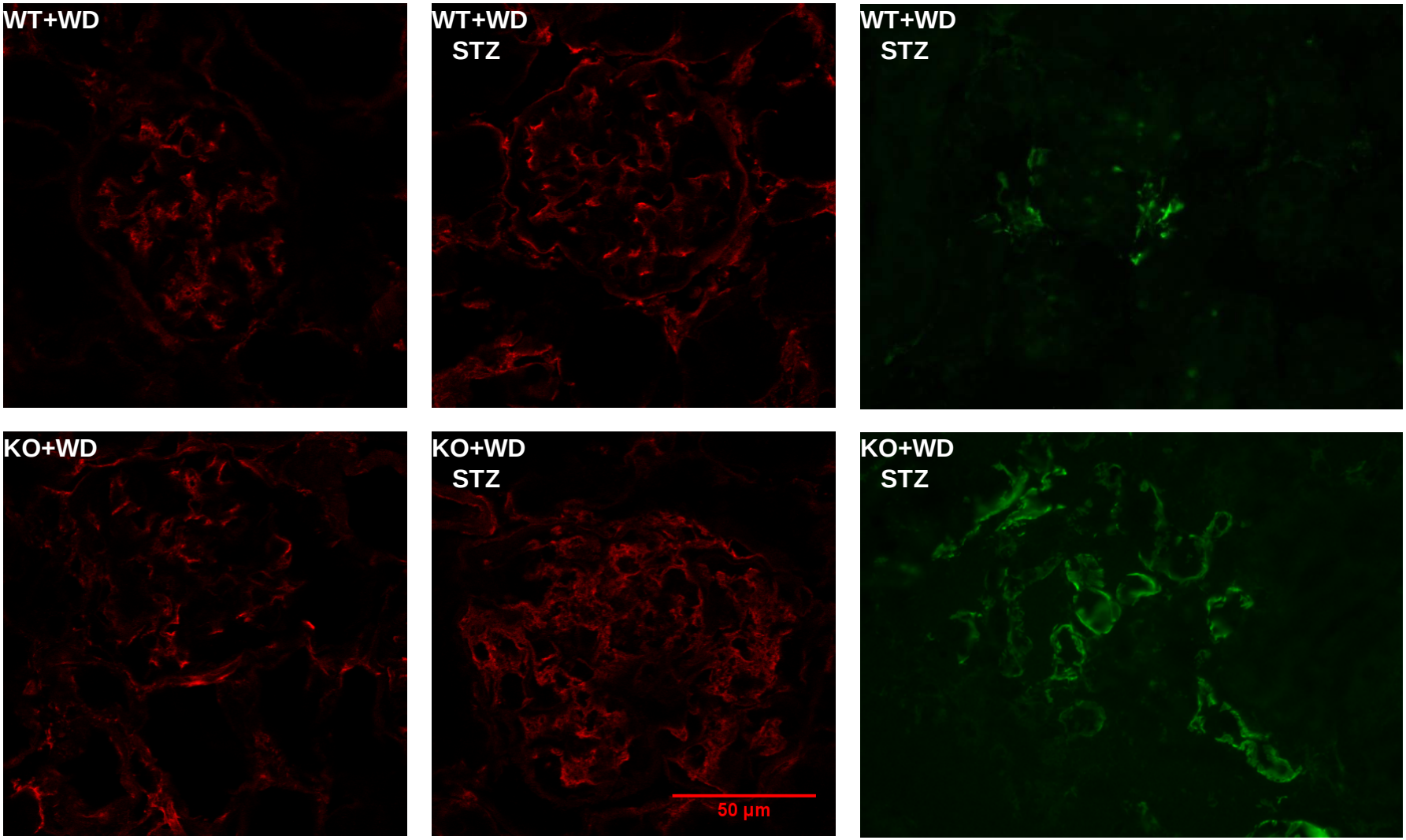
Diabetic FXR KO Mice Develop Hypertrophic Glomeruli with Lysis and Tubular Damage



Diabetic FXR KO Mice Develop Tubulointerstitial Fibrosis

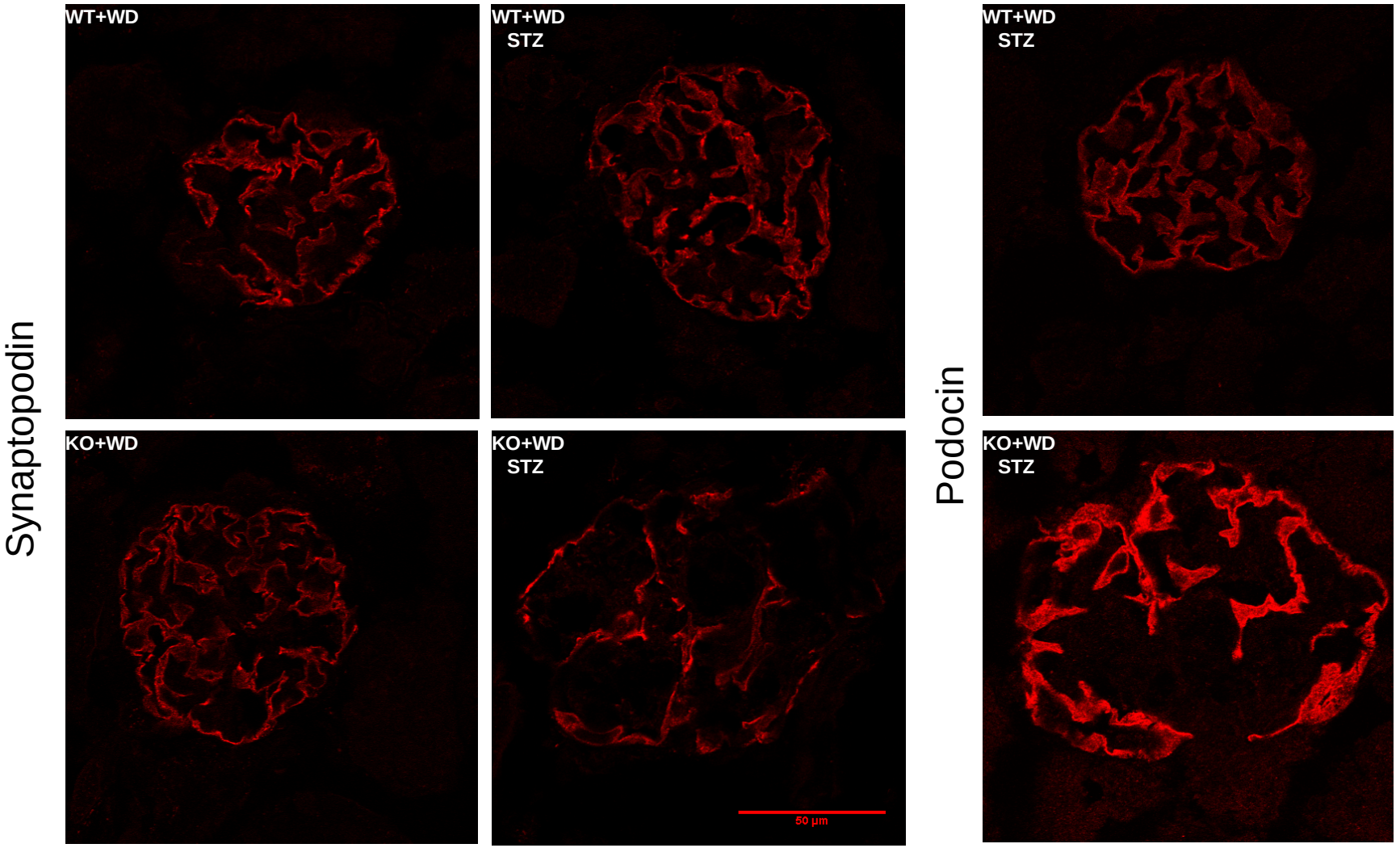


Diabetic FXR KO Mice Have Increased Expression of Matrix Proteins and Fibrosis Markers

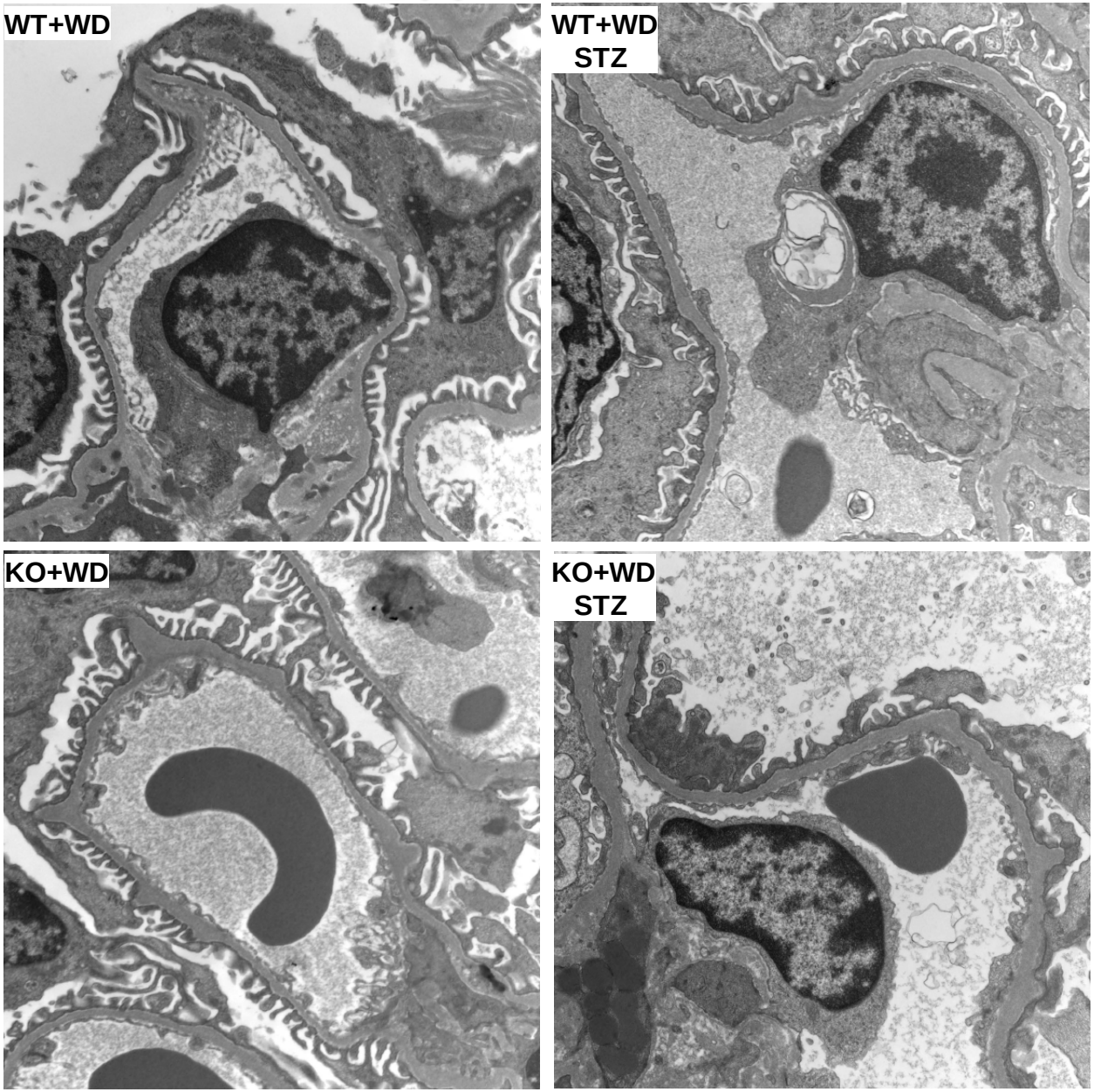


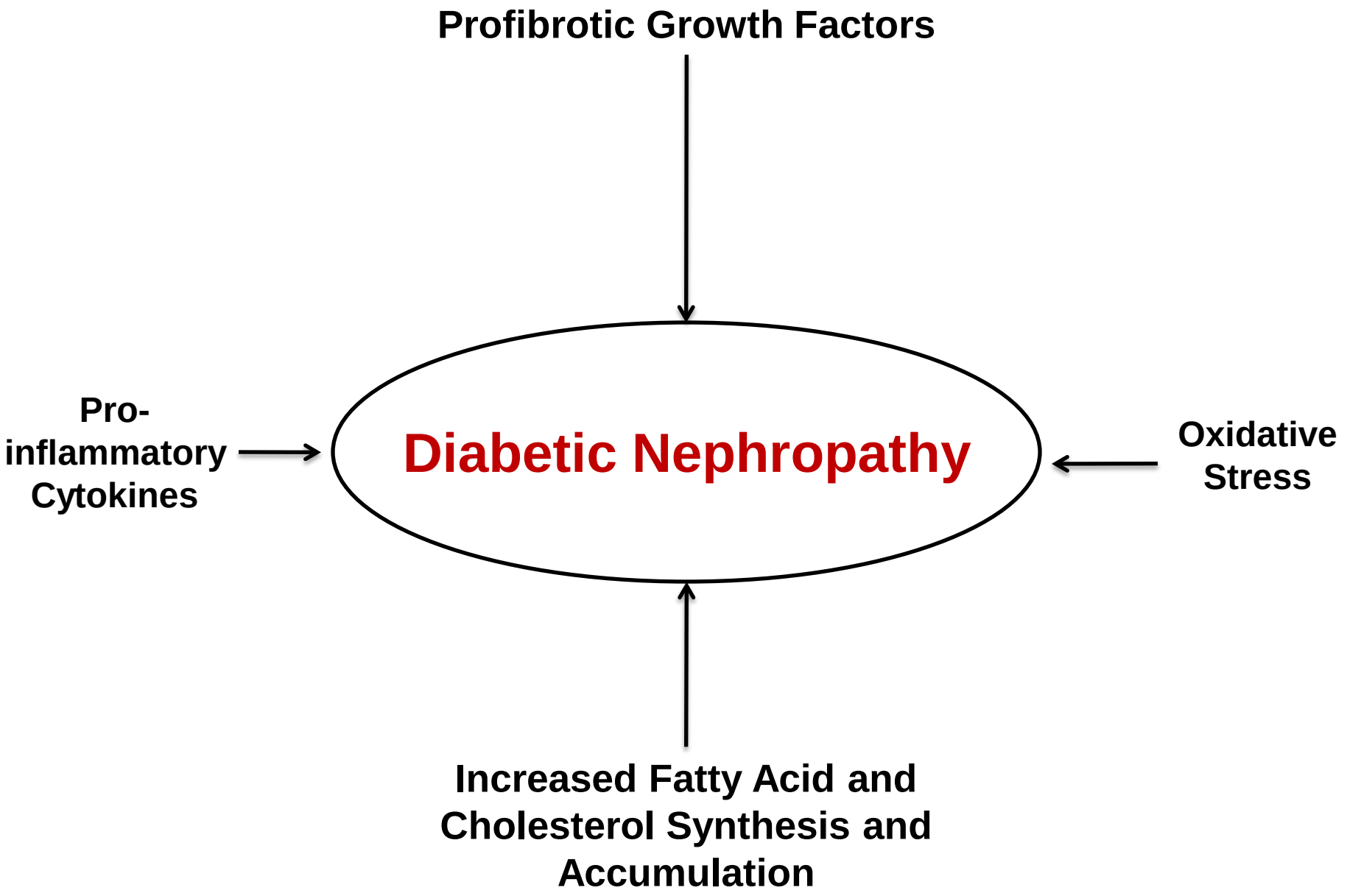
Fibronectin **α-SMA**

Diabetic FXR KO Mice Have Altered Podocyte Density

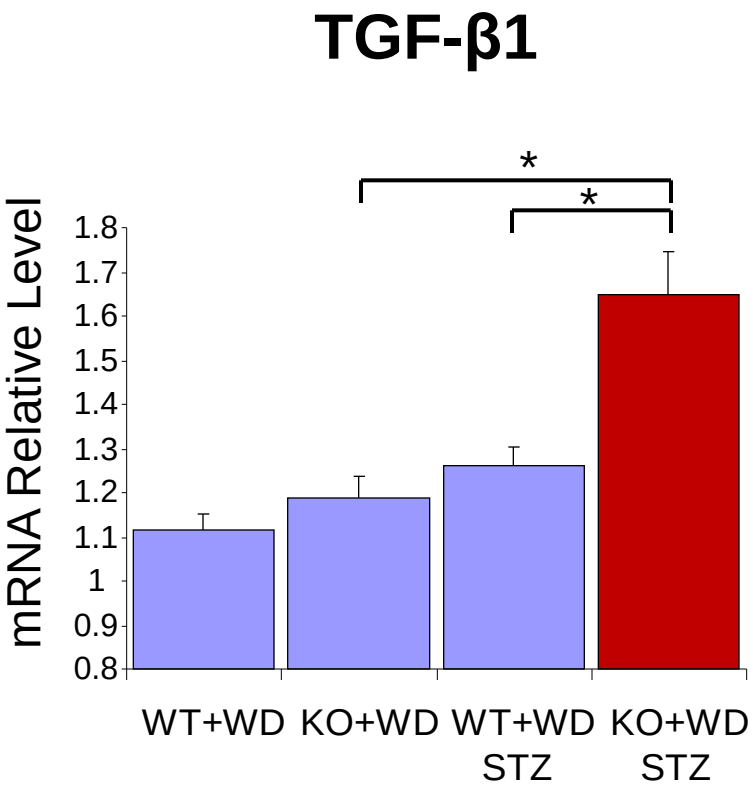


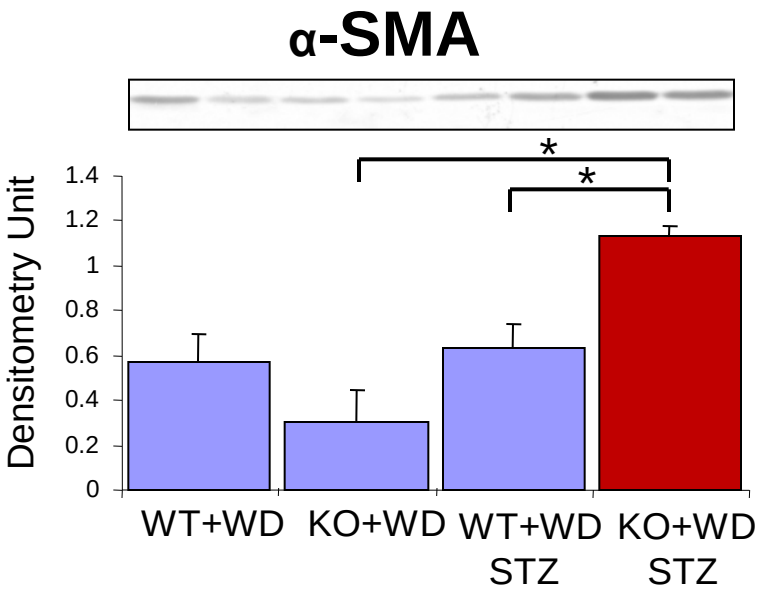
Diabetic FXR KO Mice Develop Foot Process Effacement

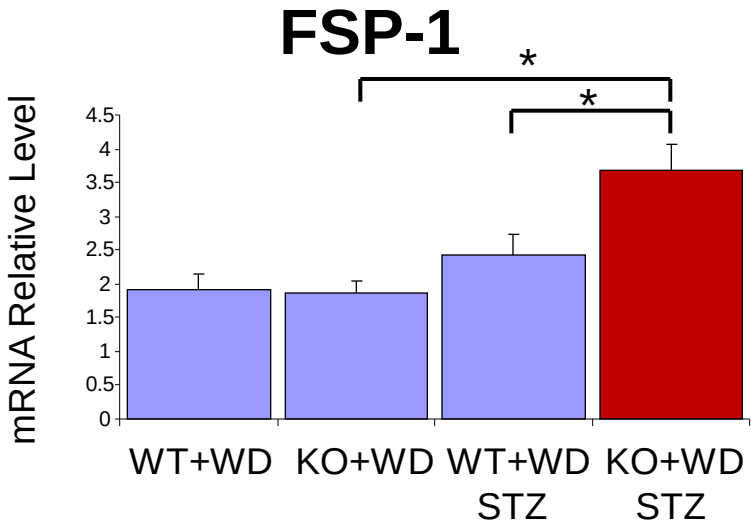



Profibrotic Growth Factors
Pro-
inflammatory
Cytokines
Diabetic Nephropathy
Oxidative
Stress
Increased Fatty Acid and
Cholesterol Synthesis and
Accumulation

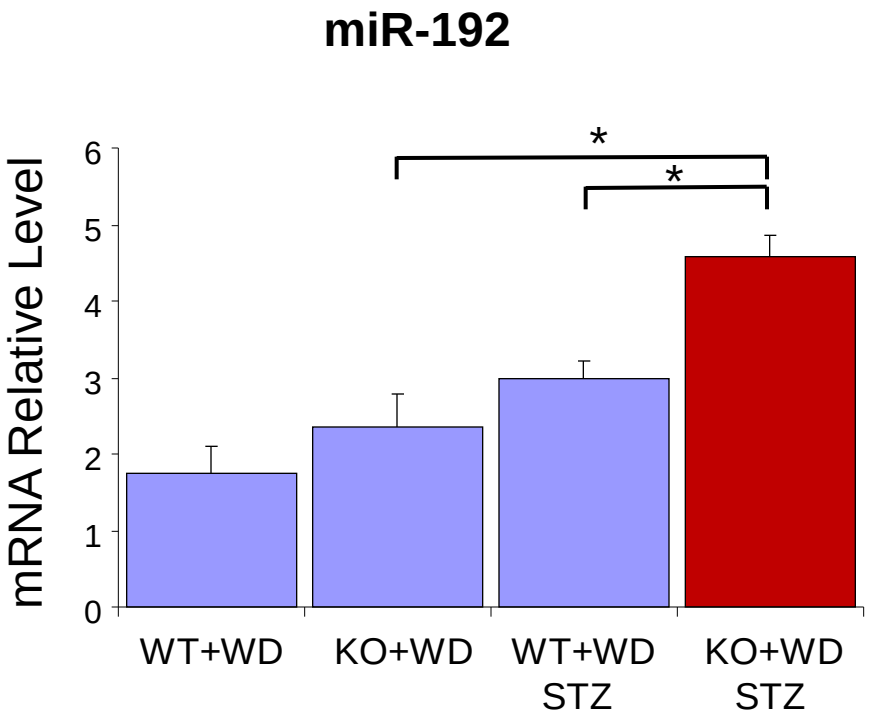
Diabetic FXR KO Mice Have Increased Expression of Profibrotic Growth Factor and Fibrosis Markers

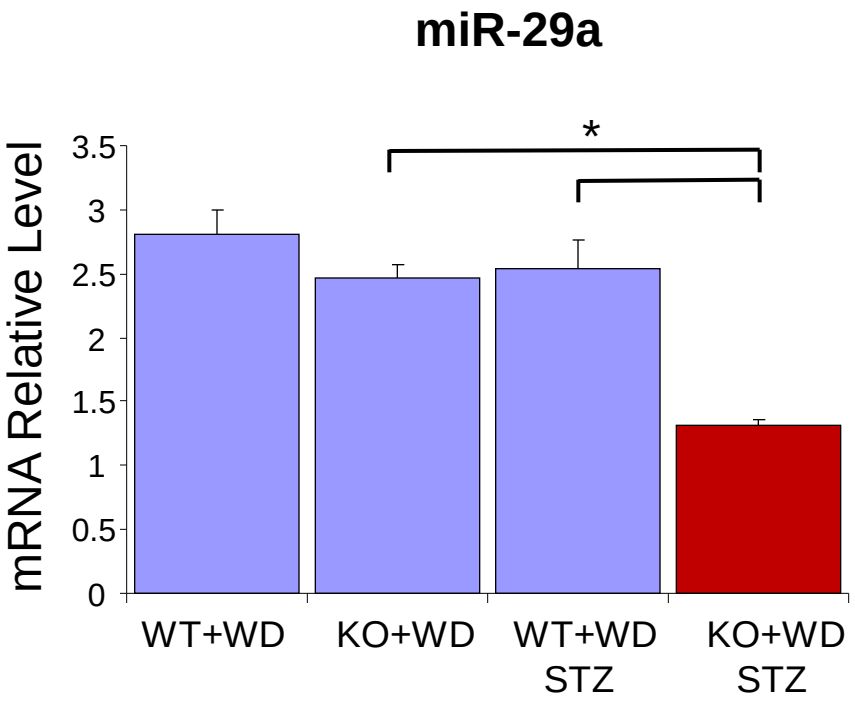






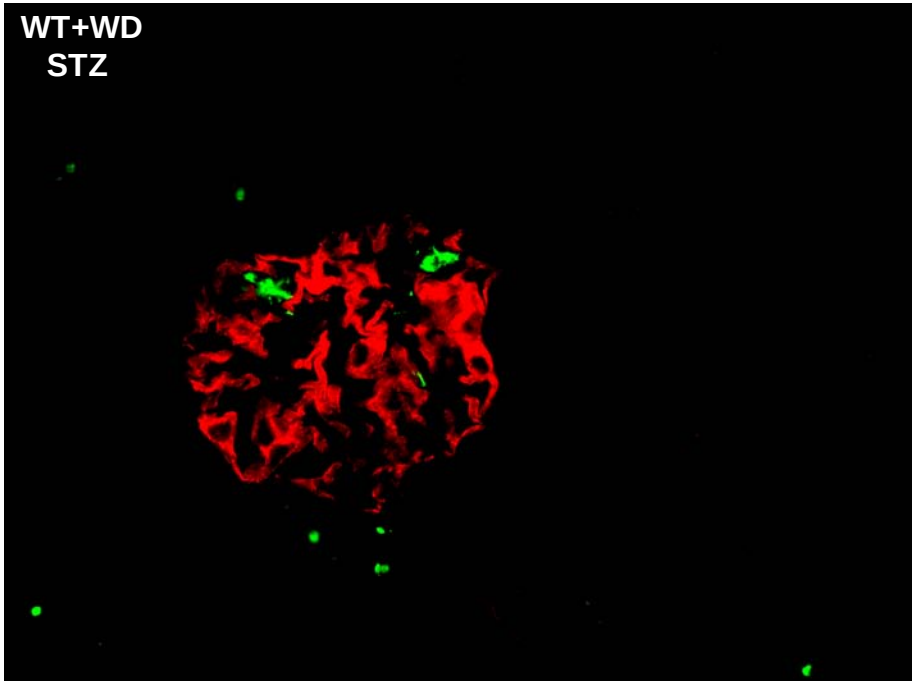
Diabetic FXR KO Mice Have Altered Expression of Micro RNA

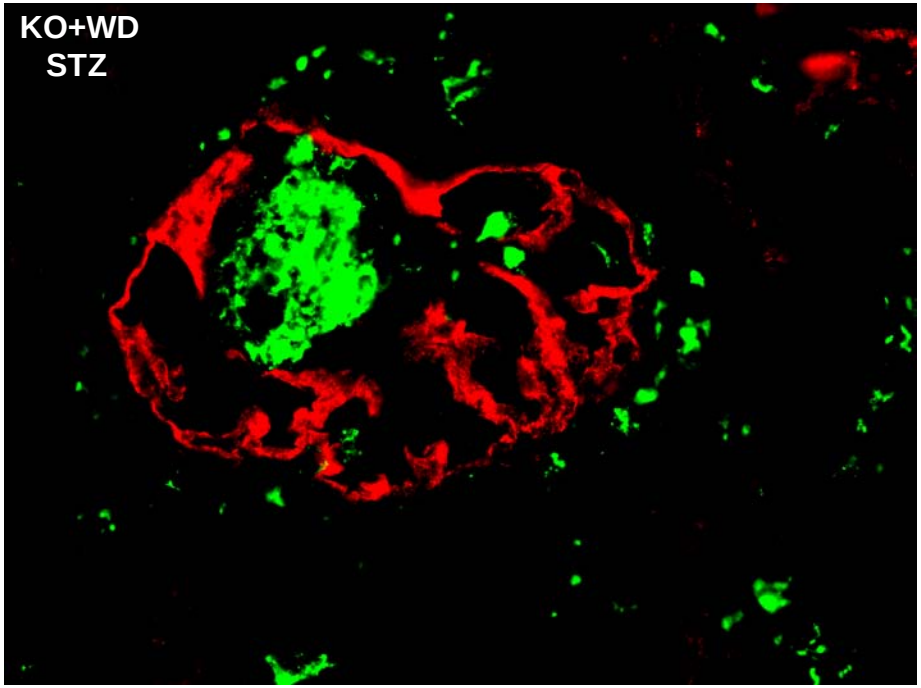




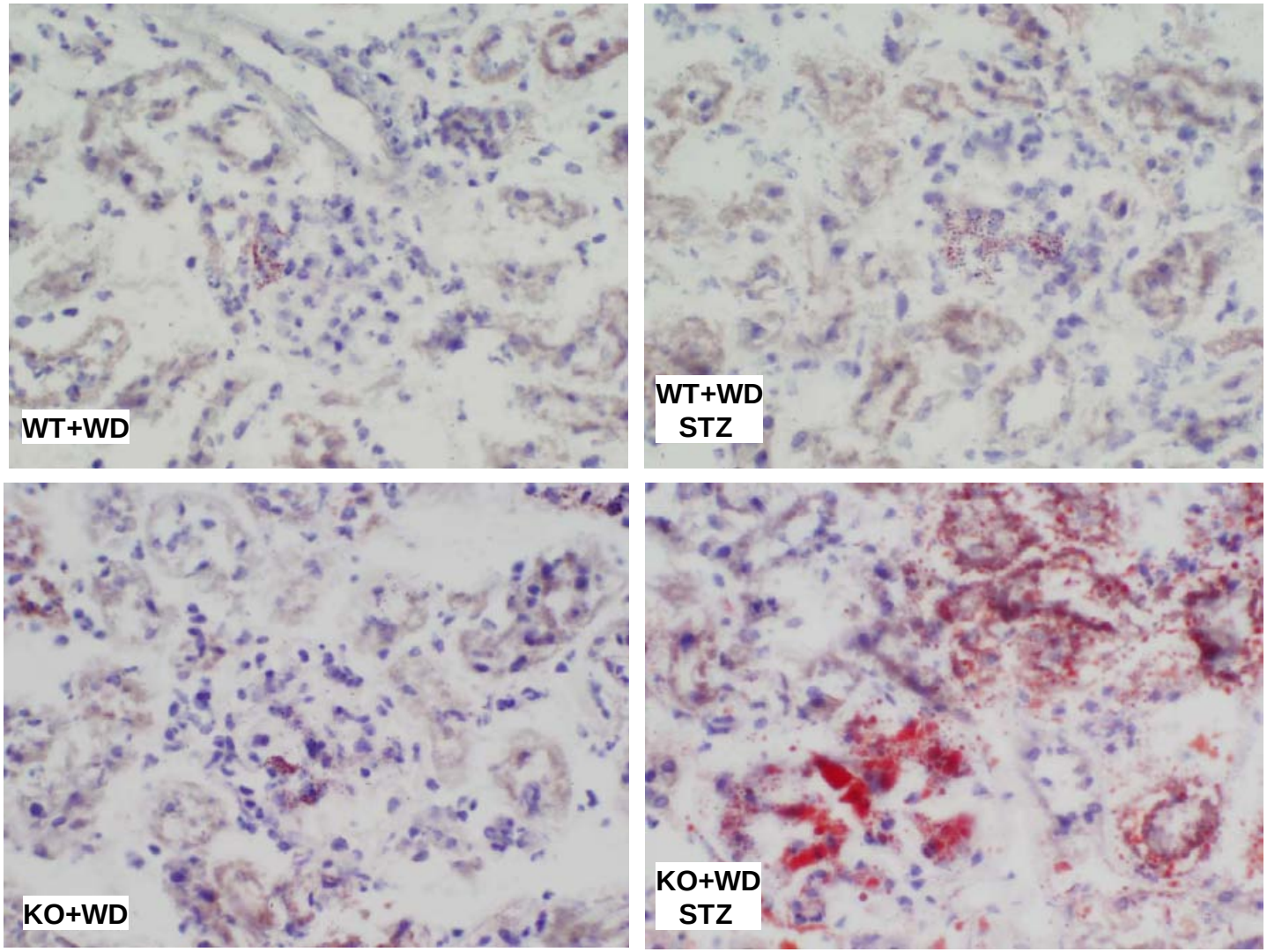
FXR KO Mice Have Increased Macrophage Infiltration

CD68/Podocin

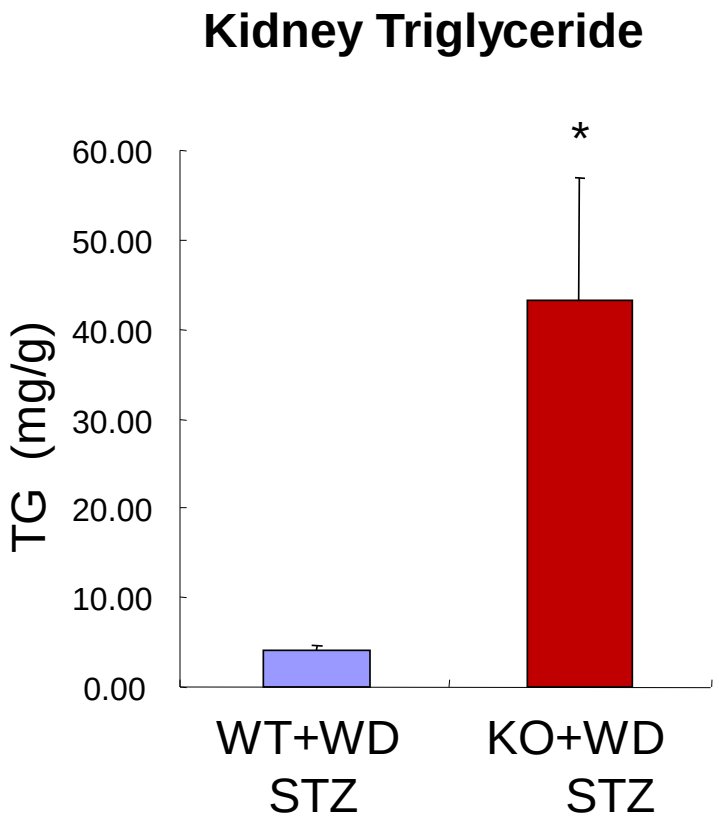


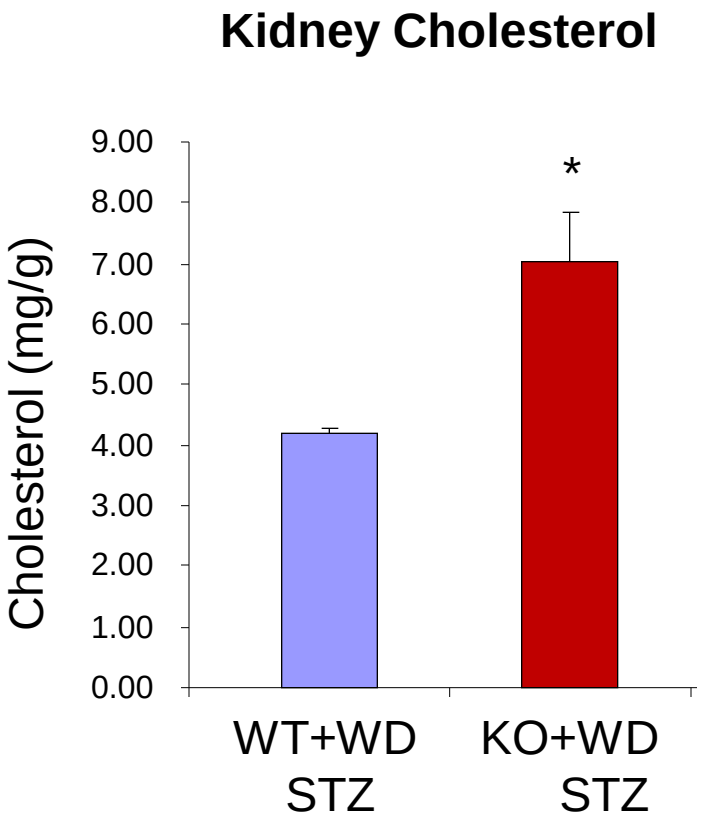


Diabetic FXR KO Mice Have Increased Lipid Deposits in Glomeruli and Tubular Cells

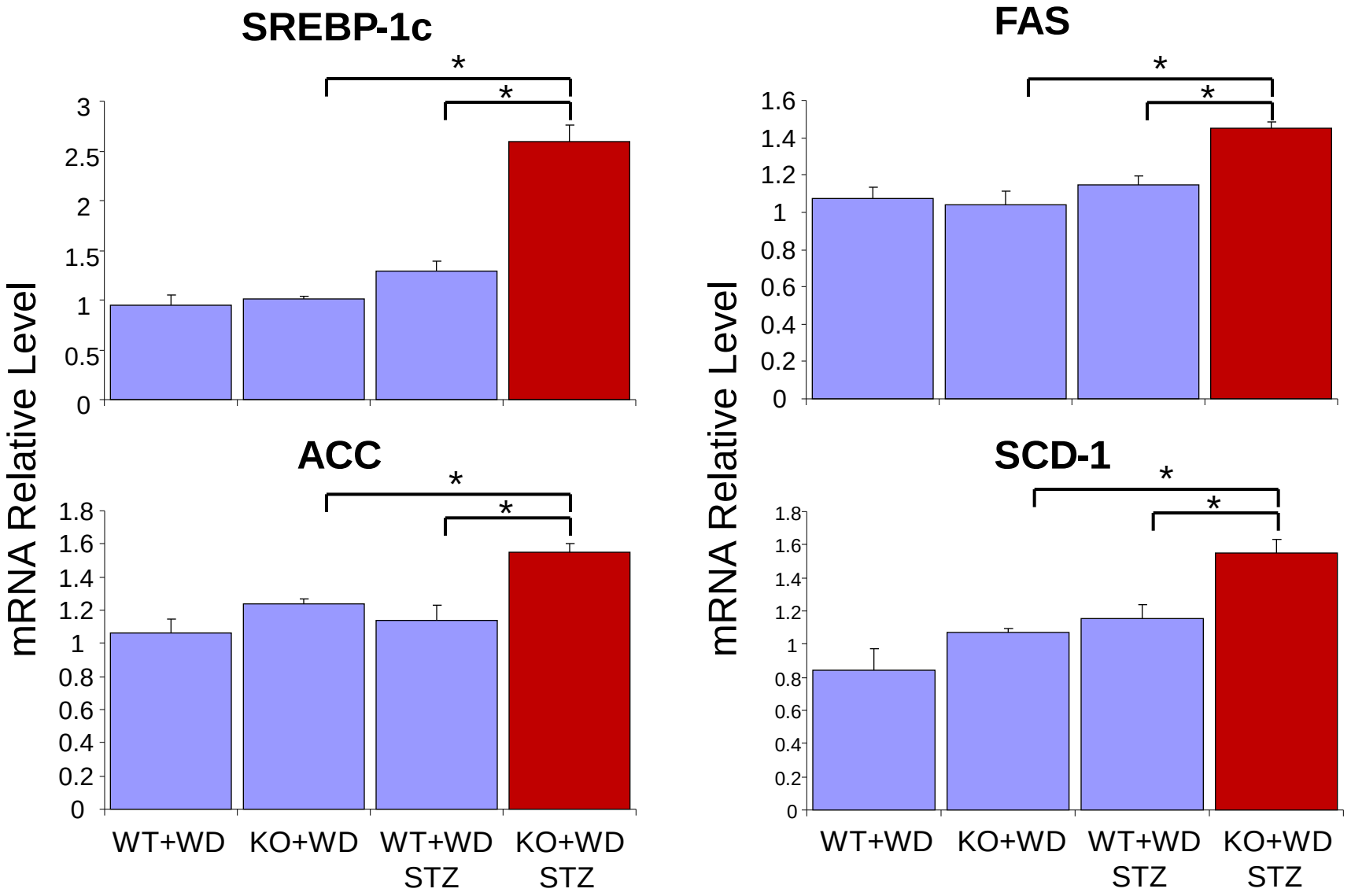


Diabetic FXR KO Mice Have Increased Kidney Triglyceride and Cholesterol Content

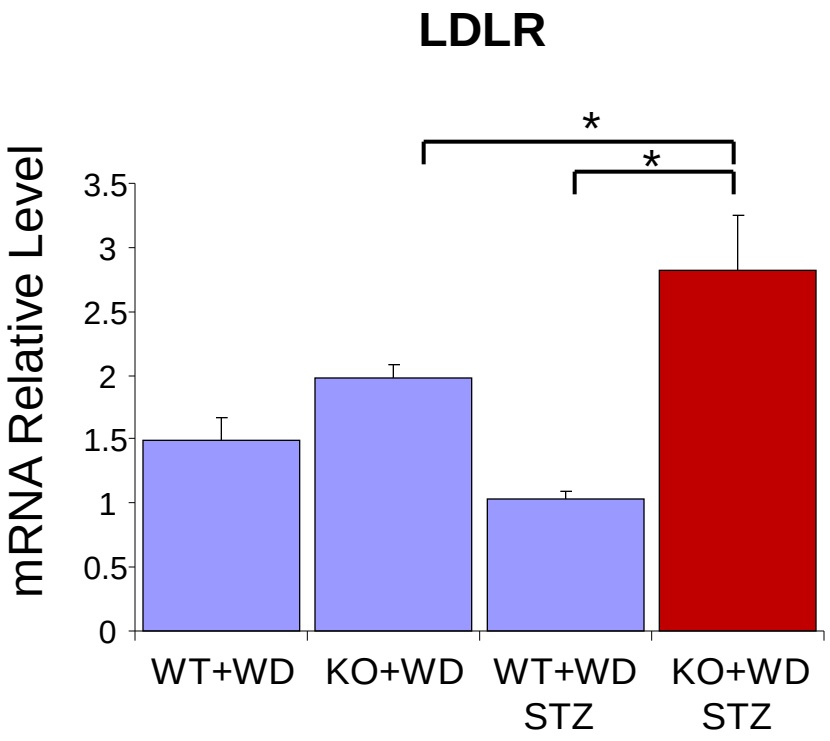


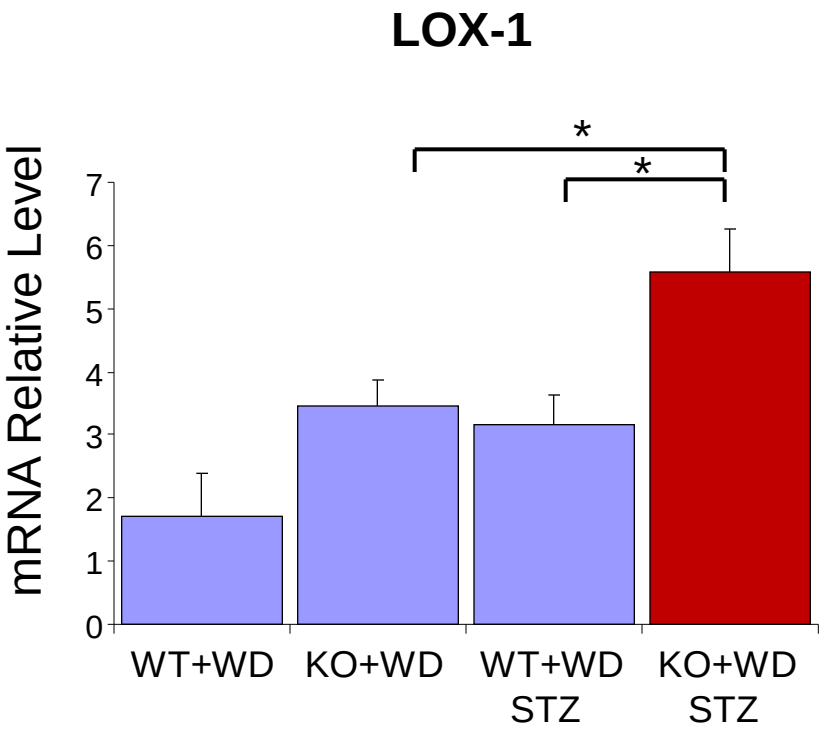


Diabetic FXR KO Mice Have Increased Kidney Expression of Fatty Acid Synthesis Genes



Diabetic FXR KO Mice Have Increased Kidney Expression of Cholesterol Uptake Genes





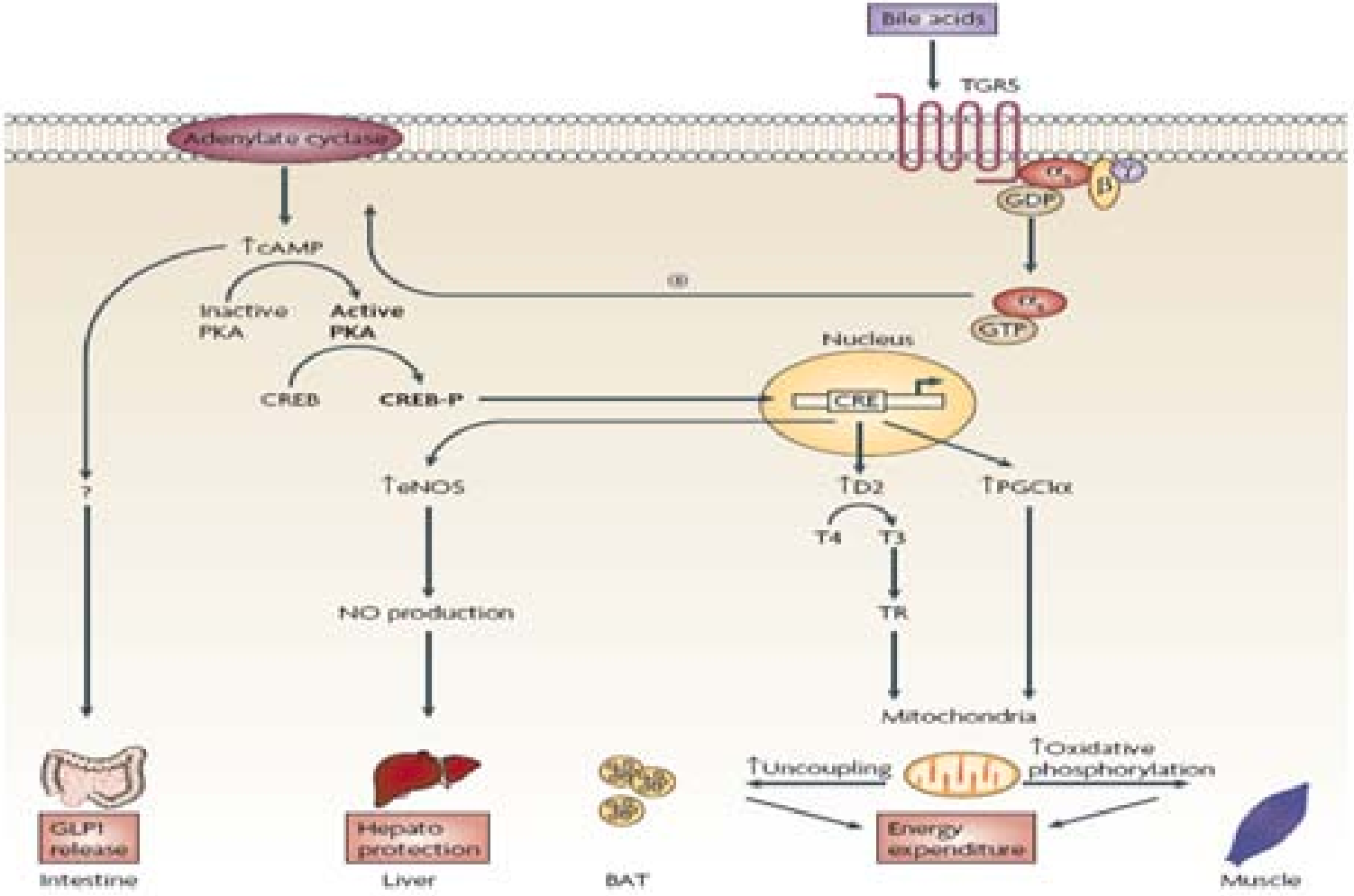
Studies in Progress

- **FXR KO Mice in C57Bl/6 or FVB or DBA/2J genetic backgrounds x Akita Mice**
- **FXR podocyte KO mice x STZ or FXR podocyte KO mice x Akita**

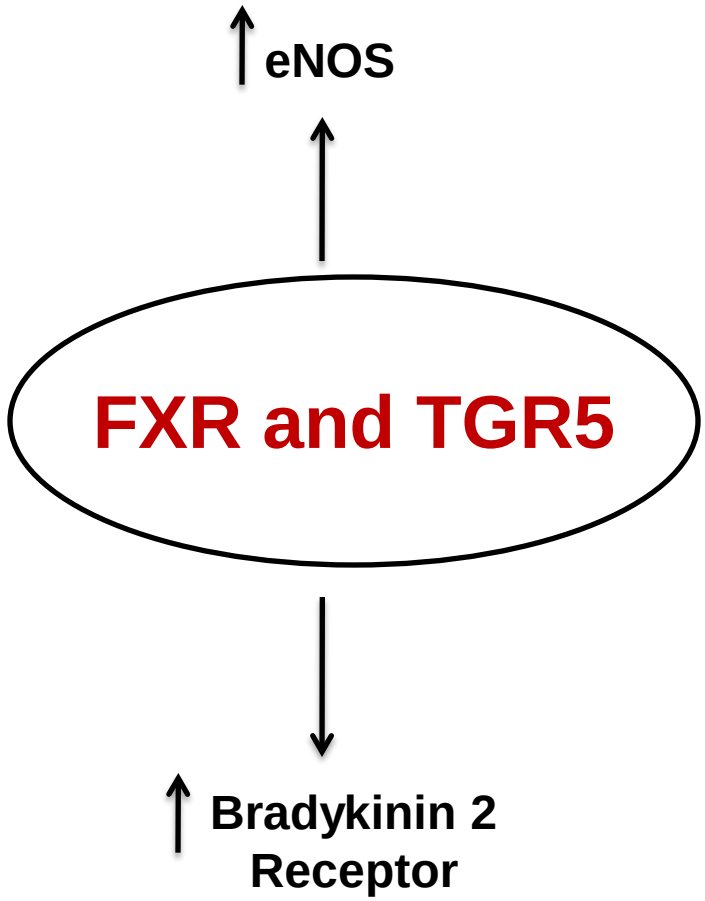
Future Studies

- **Diabetic FXR KO Mice versus TGR5 KO Mice versus FXRxTGR5 DKO Mice**

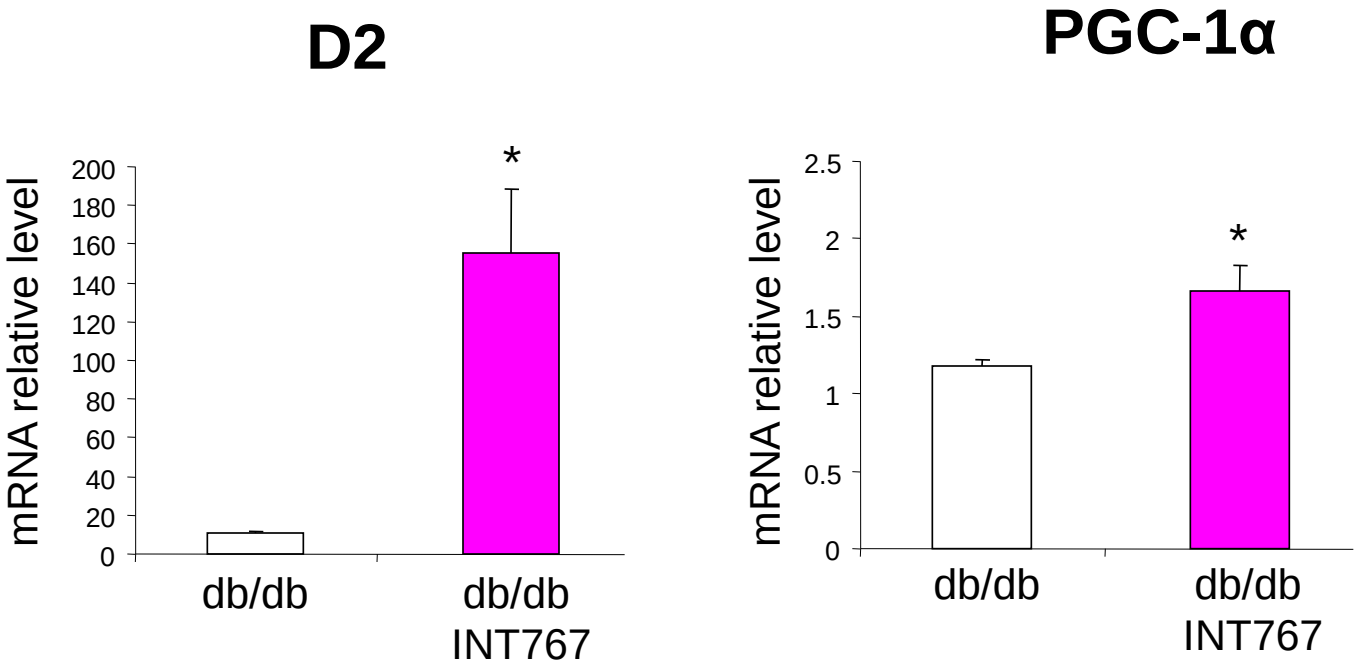
TGR5: A Bile Acid Activated GPCR



Why FXR and TGR5 in the kidney?



Treatment with the dual FXR-TGR5 agonist INT-767 Increases Expression of D2 and PGC-1 in db/db Mice



Treatment with the dual FXR-TGR5 agonist INT-767 Increases Expression of eNOS and Bradykinin B2 Receptor in db/db Mice