



肾脏病医学中心
南京医科大学第二附属医院

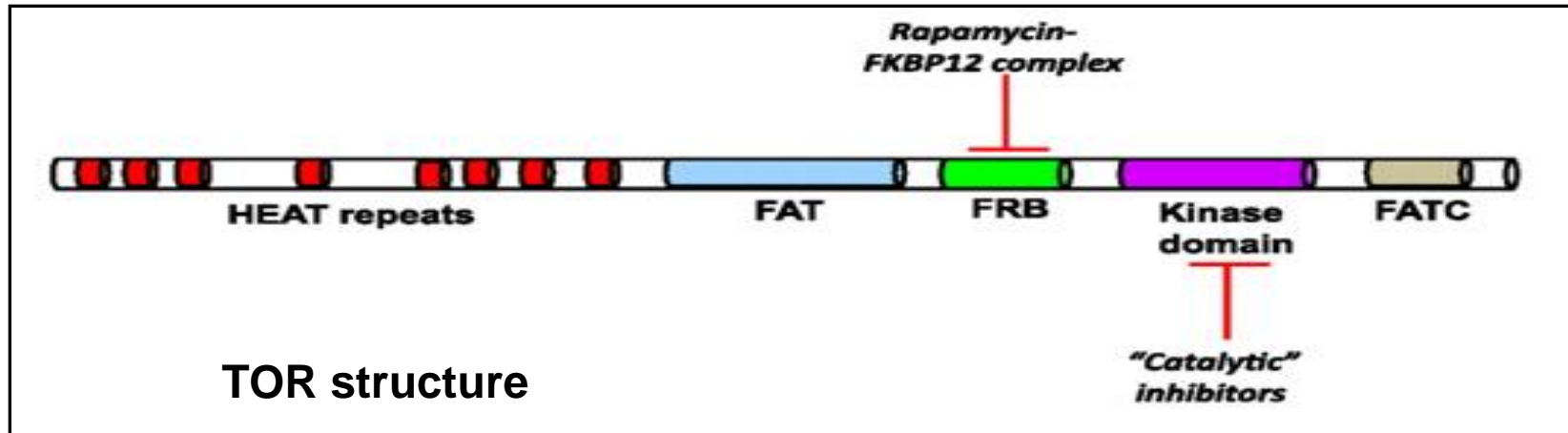
mTOR signaling in renal fibrosis: potential of novel therapeutic agents

Chunsun Dai, MD/PhD

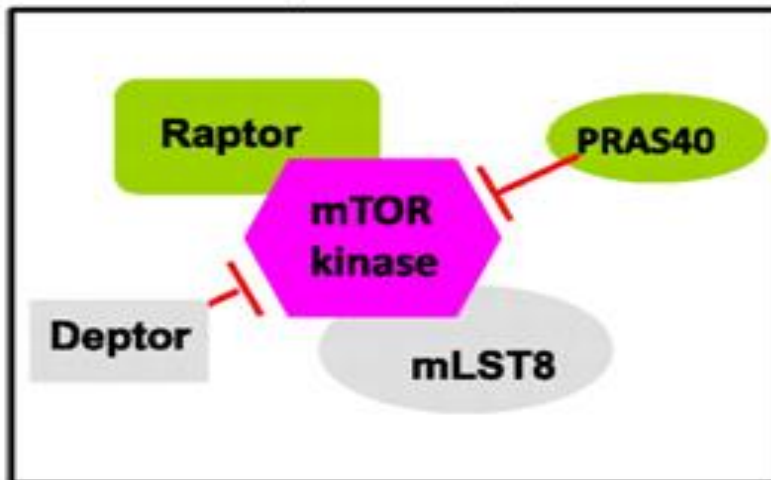
Center for Kidney Diseases, 2nd Affiliated Hospital,

Nanjing Medical University

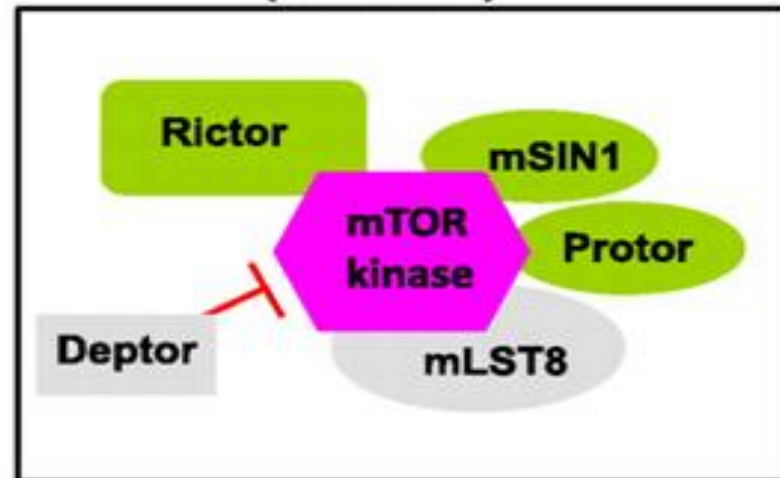
MTOR forming two complexes: mTORC1 and mTORC2



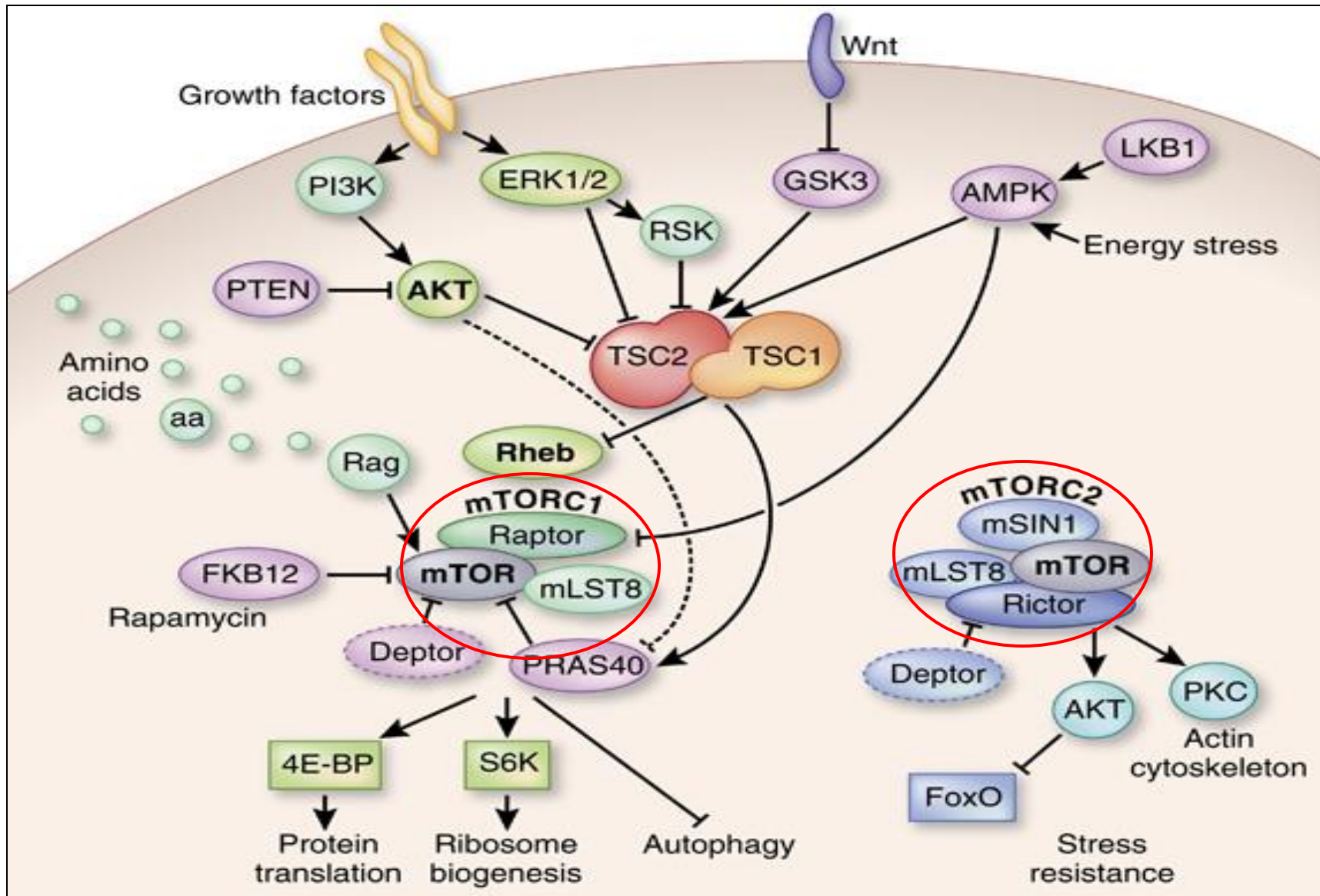
**mTOR complex 1
(mTORC1)**



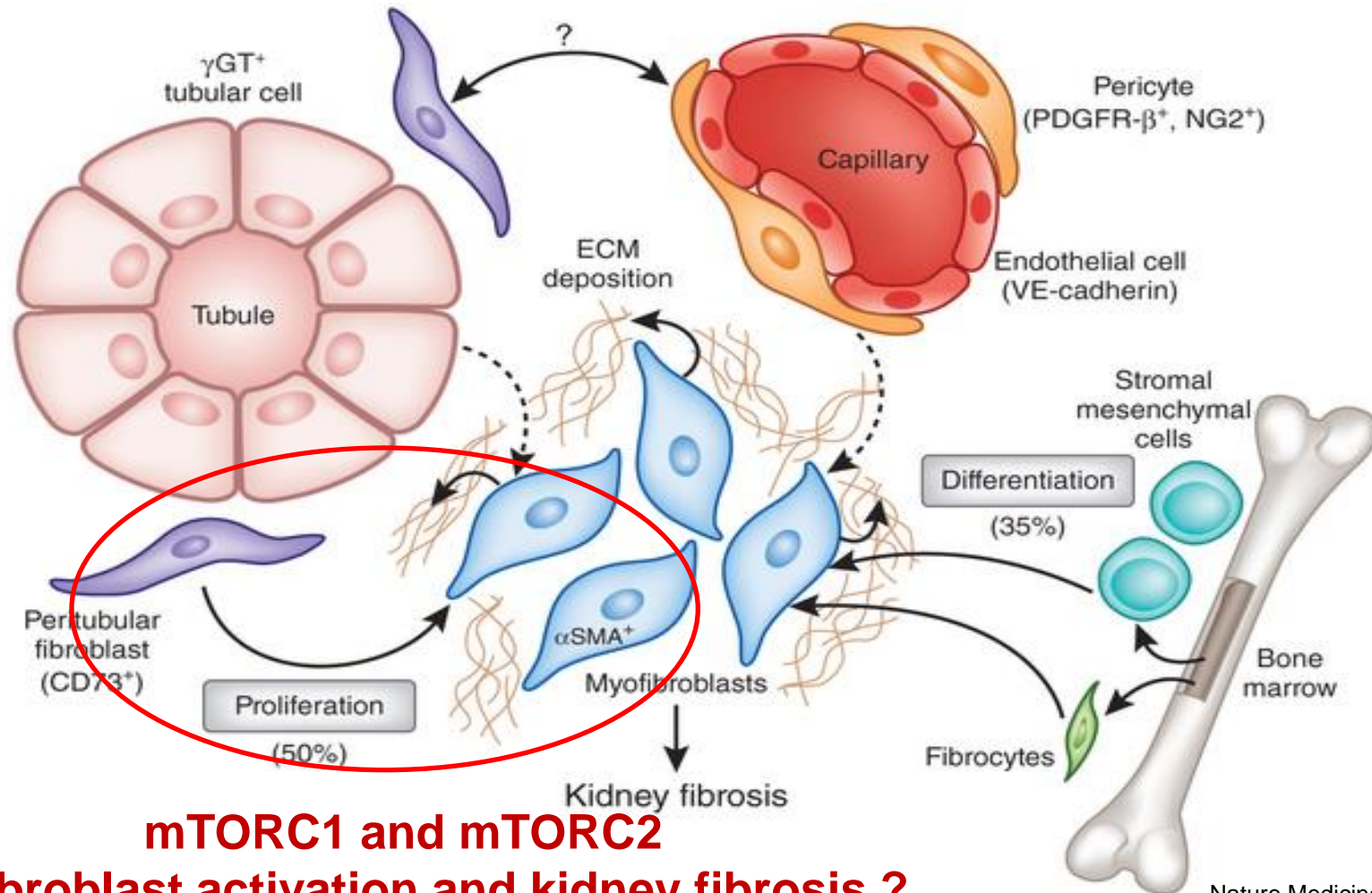
**mTOR complex 2
(mTORC2)**



MTOR signaling pathways



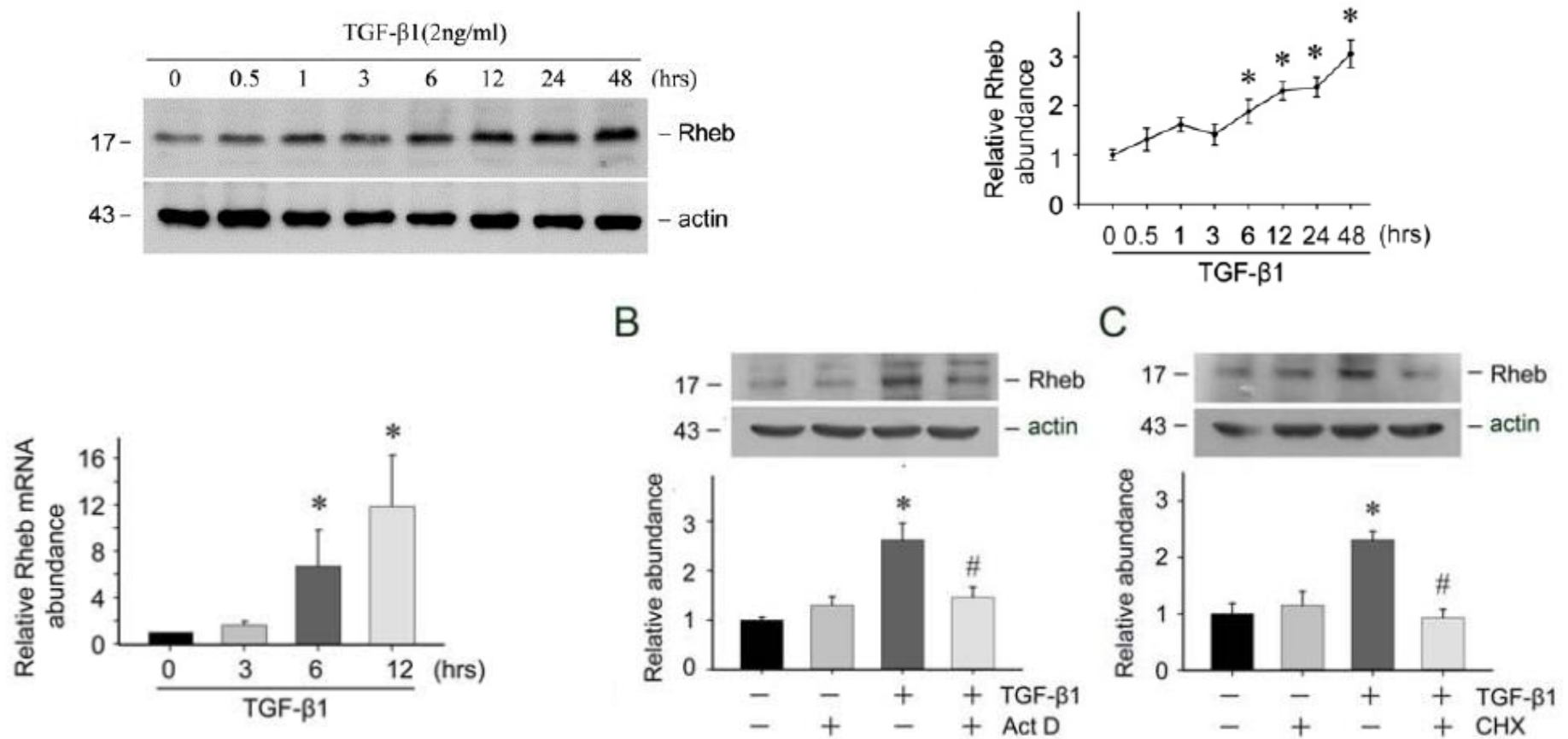
Origins and activation of myofibroblasts in the kidney



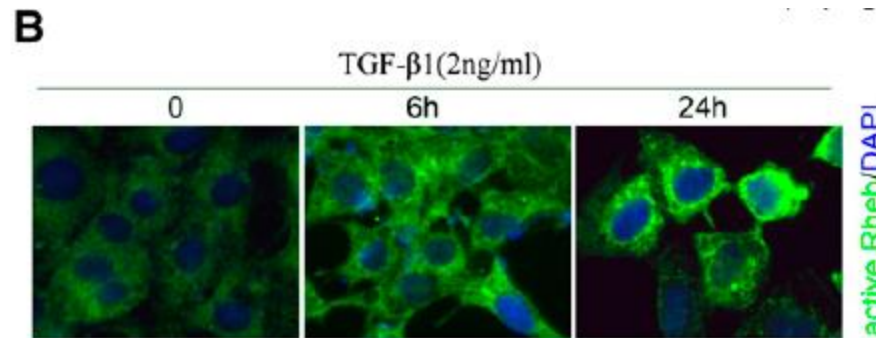
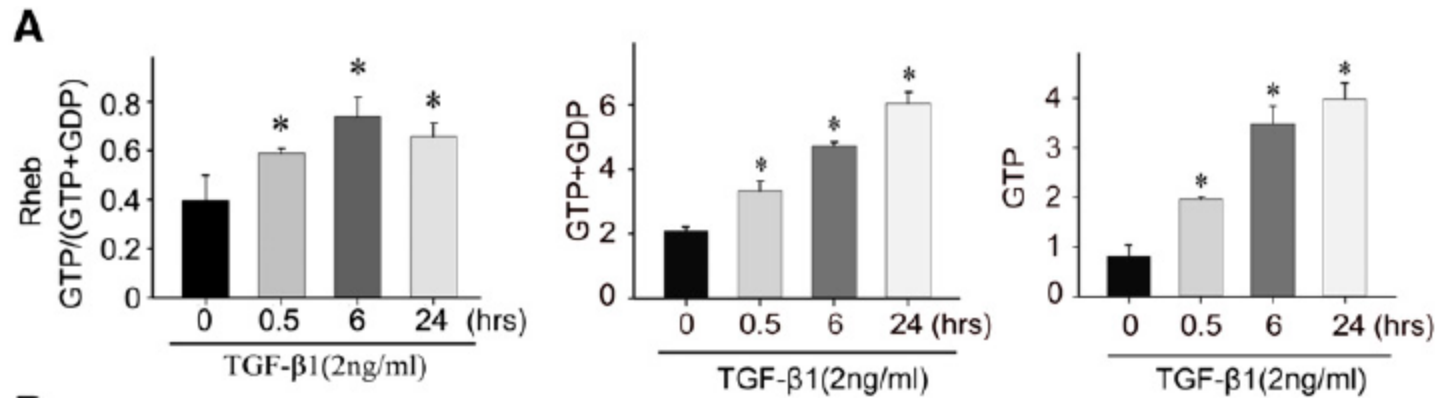
**mTORC1 and mTORC2
in fibroblast activation and kidney fibrosis ?**

- ❖ **Rheb/mTORC1 signaling activation promotes fibroblast activation and kidney fibrosis**
- ❖ **Rictor/mTORC2 signaling activation mediates TGF β 1-induced fibroblast activation and kidney fibrosis**
- ❖ **Targeting mTOR signaling in protecting against renal fibrosis**

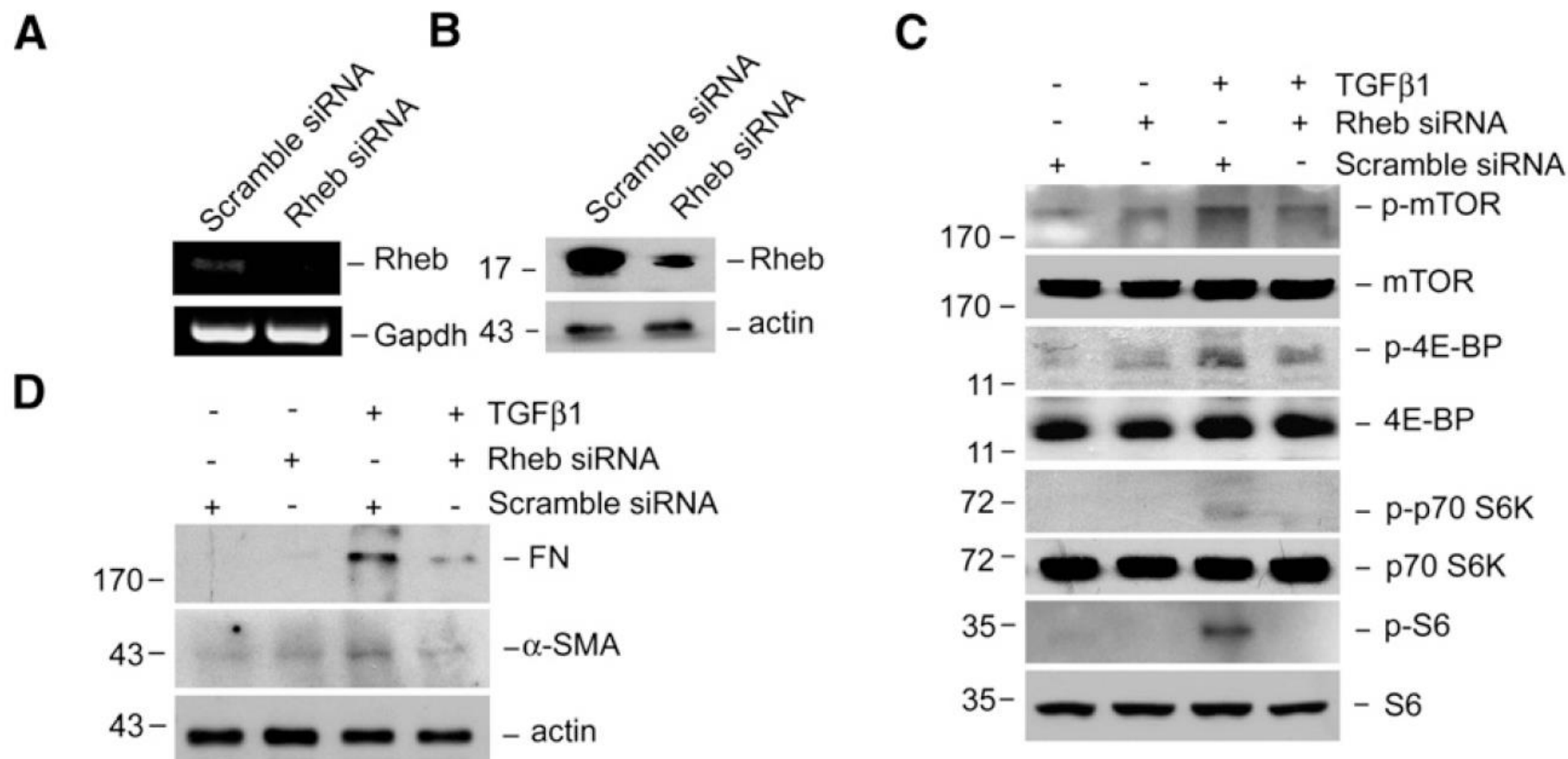
TGF- β 1 upregulates Rheb expression in NRK-49F cells



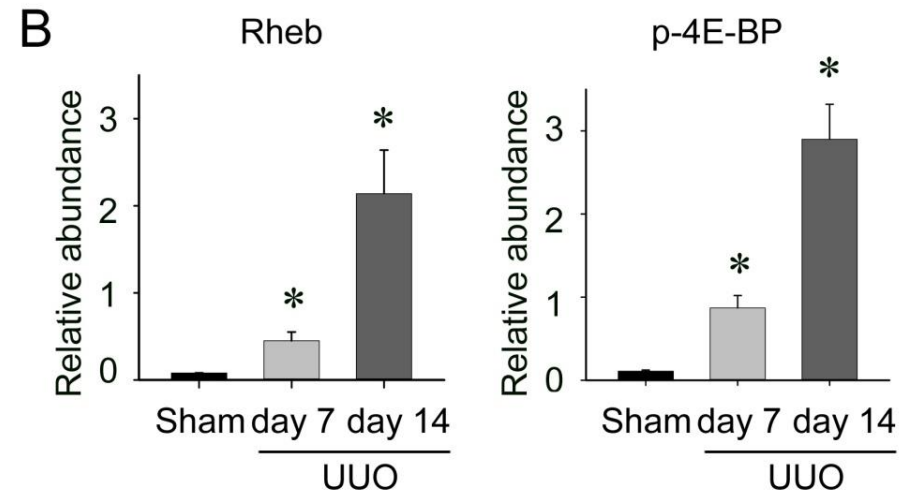
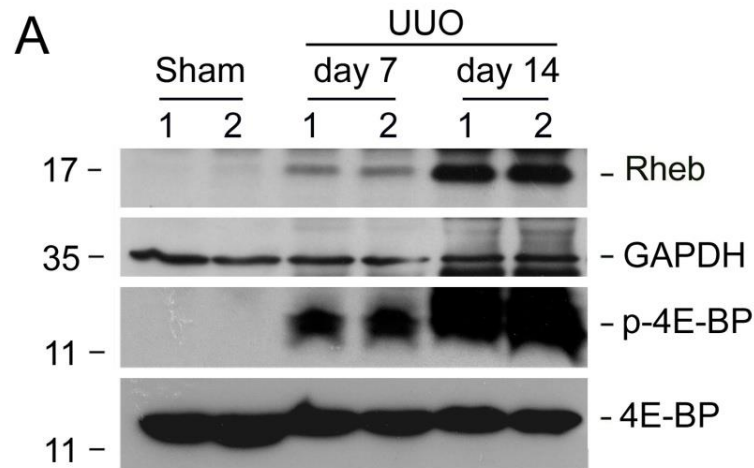
TGF- β 1 stimulates Rheb activation in NRK-49F cells



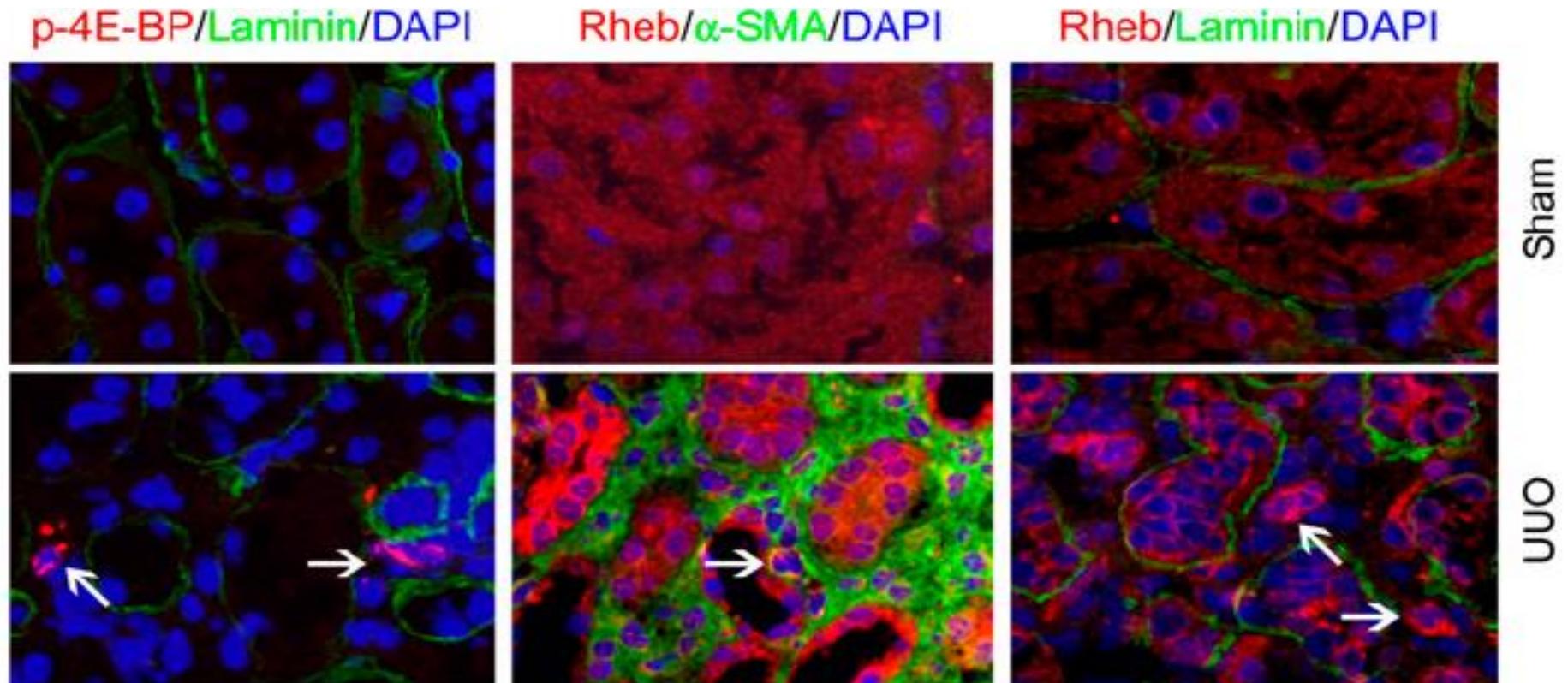
Down regulating Rheb expression inhibits TGFβ1-stimulated mTORC1 signaling and NRK-49F cell activation



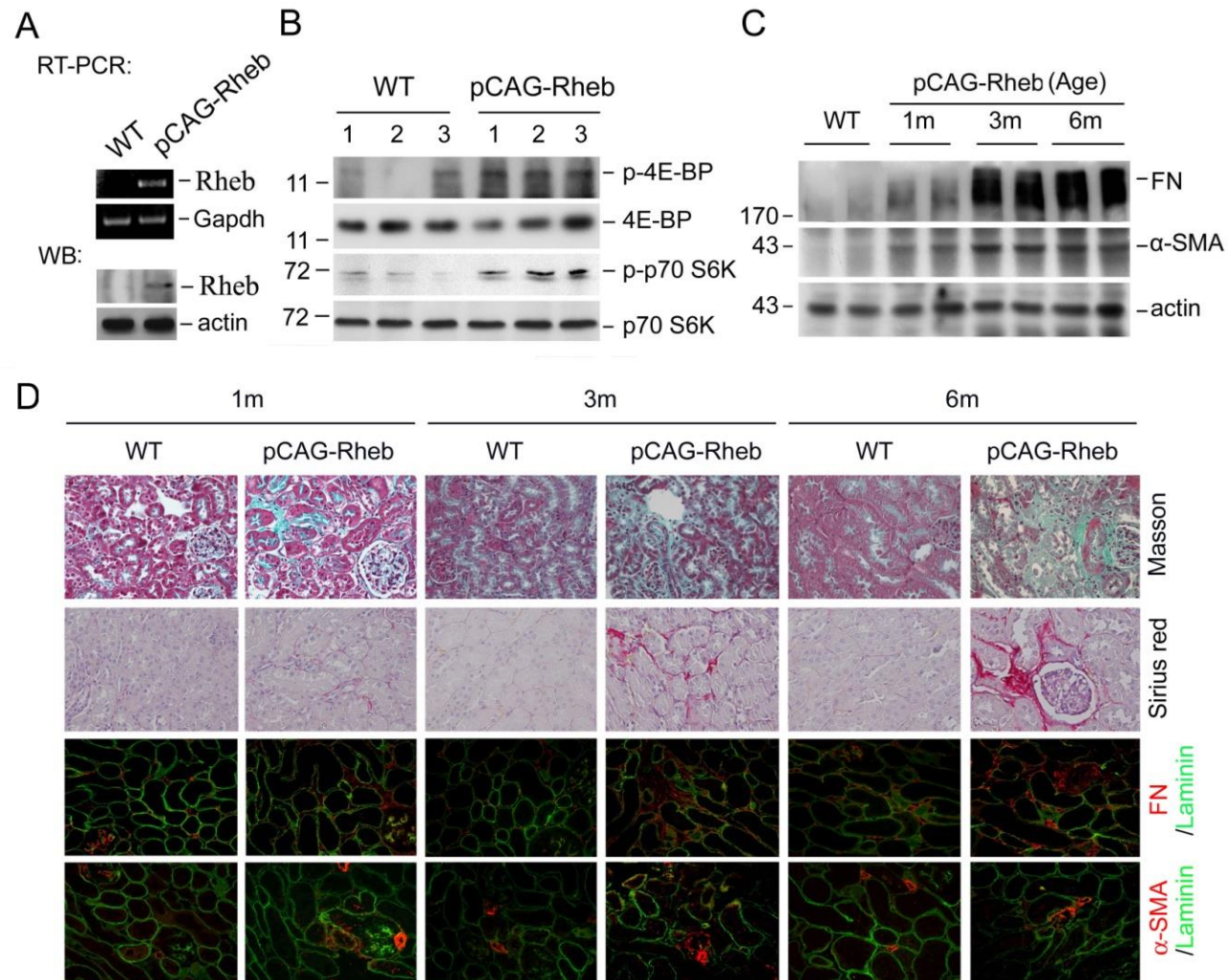
Rheb/mTORC1 signaling is activated in kidneys with UUO nephropathy



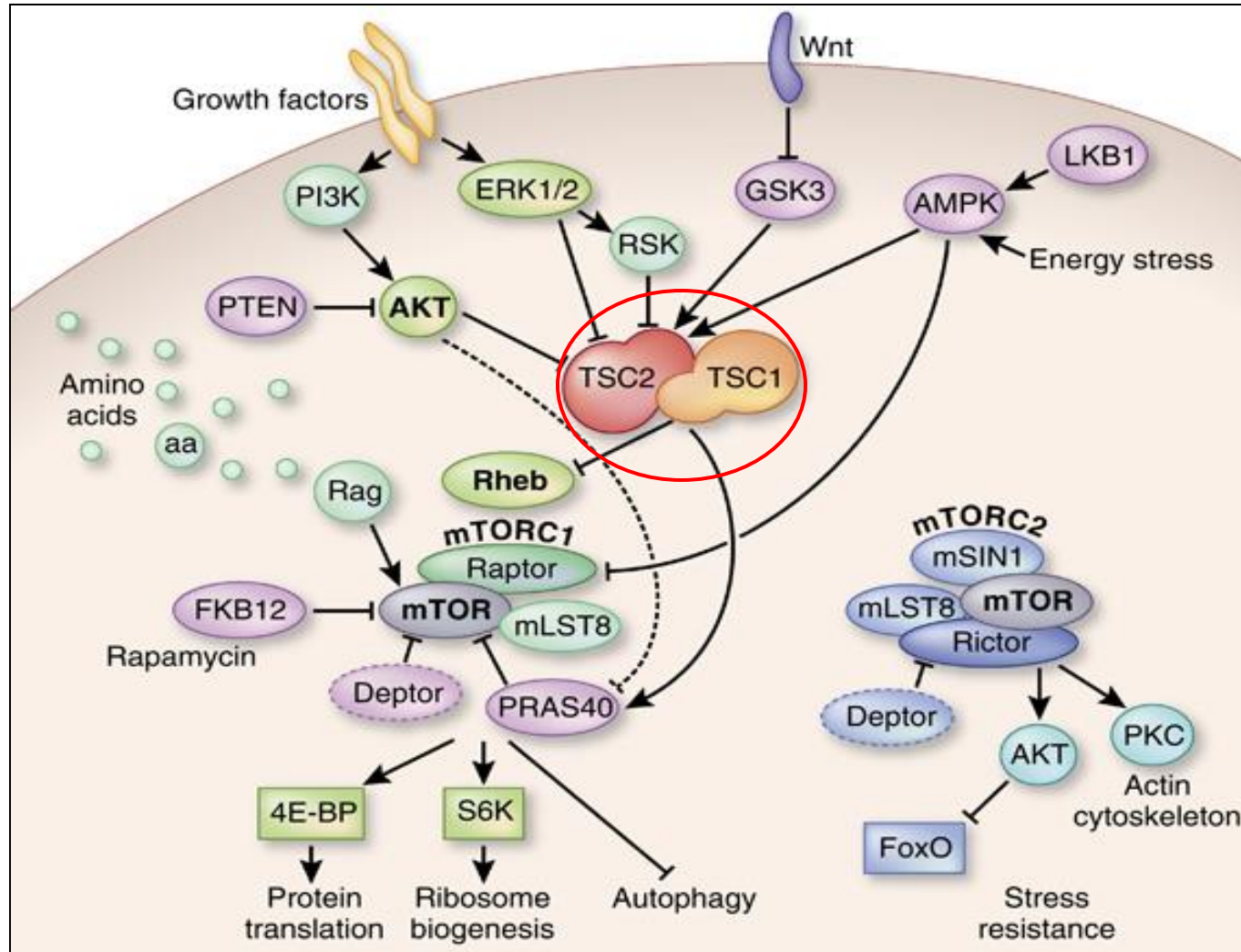
Rheb/mTORC1 is activated in myofibroblasts from the fibrotic kidneys



Rheb transgenic mice exhibit focal kidney interstitial fibrosis

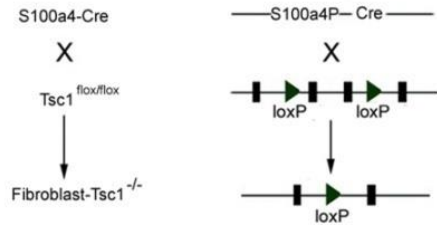


Tsc1/2 regulates Rheb activity

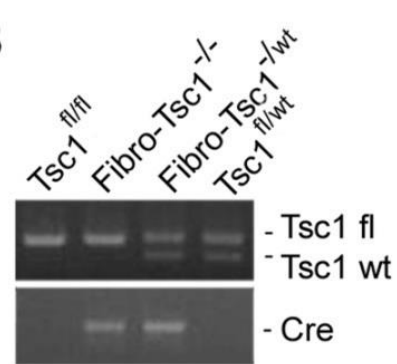


mTORC1 is activated in the kidney fibroblasts from Fibro-TSC1^{-/-} mice

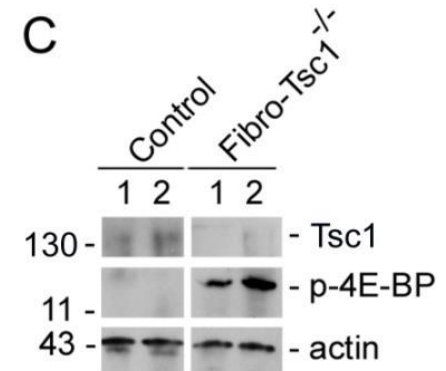
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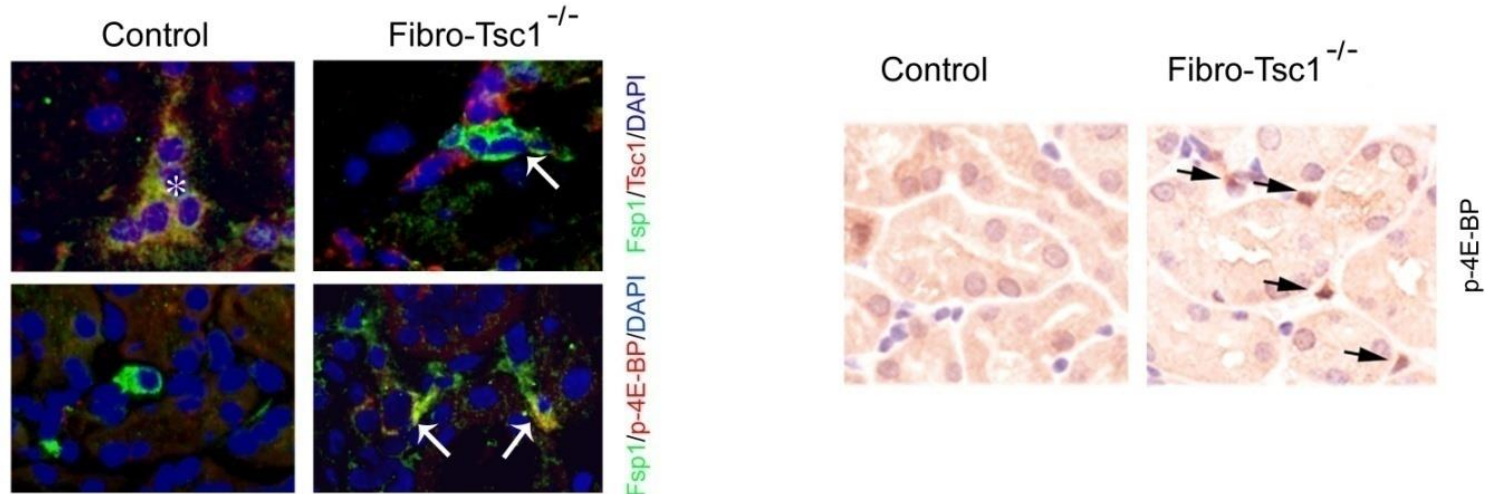
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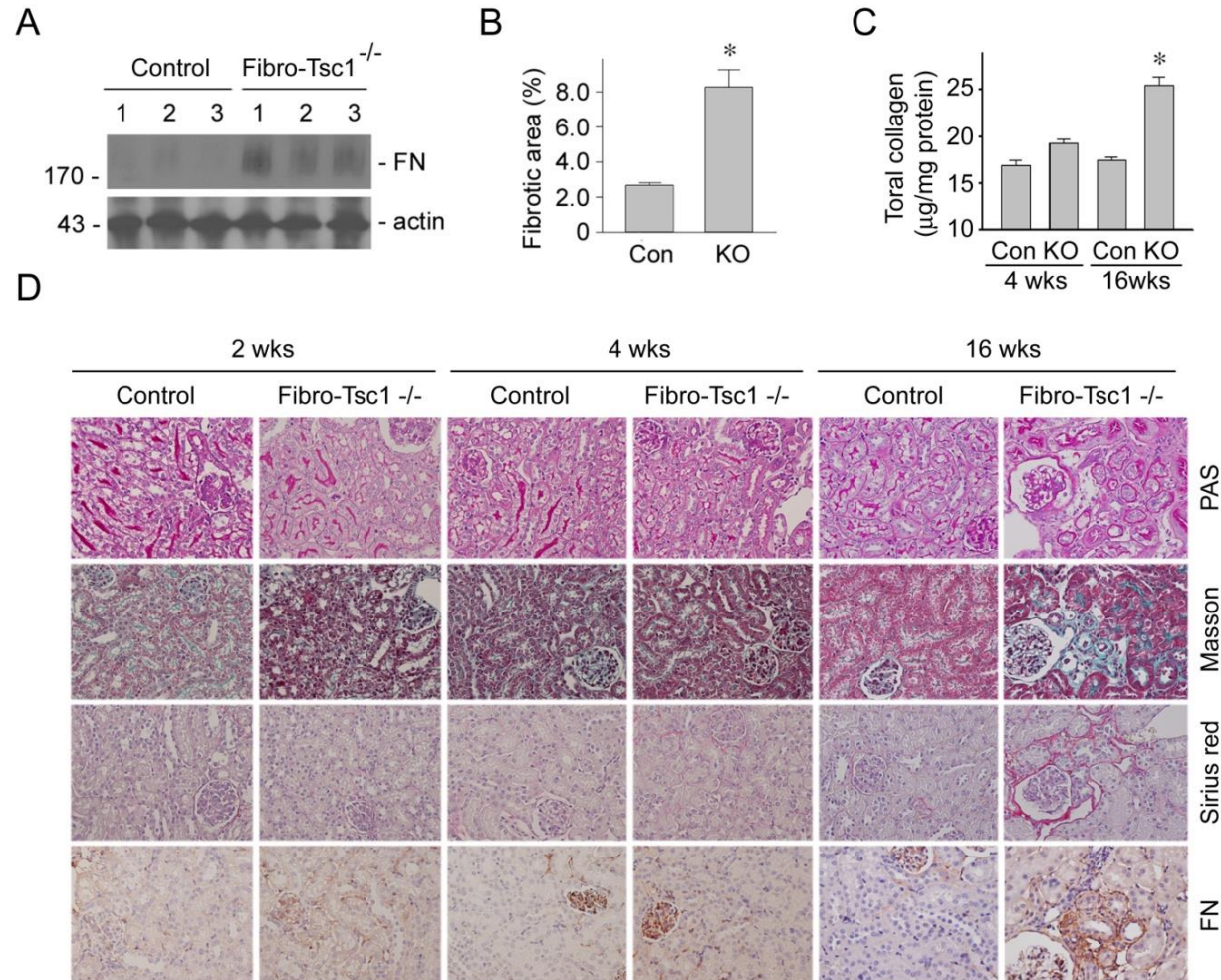
C



D



Fibro-TSC1^{-/-} mice exhibit focal kidney interstitial fibrosis



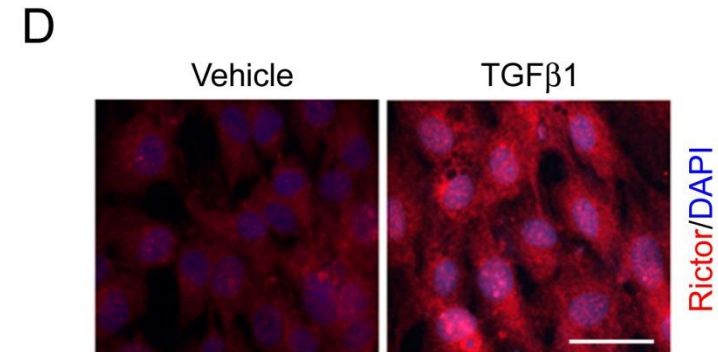
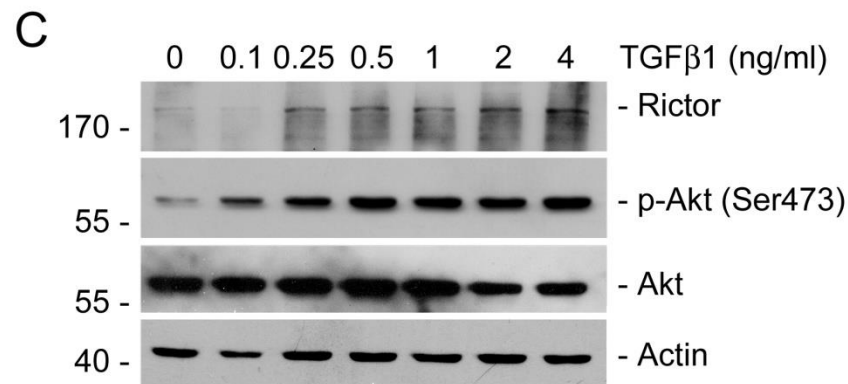
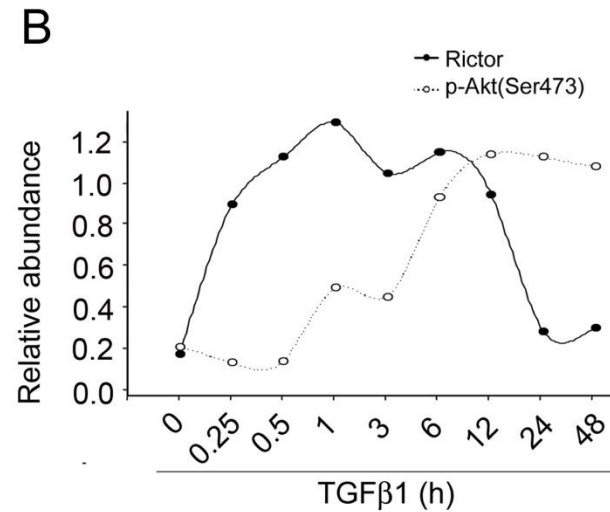
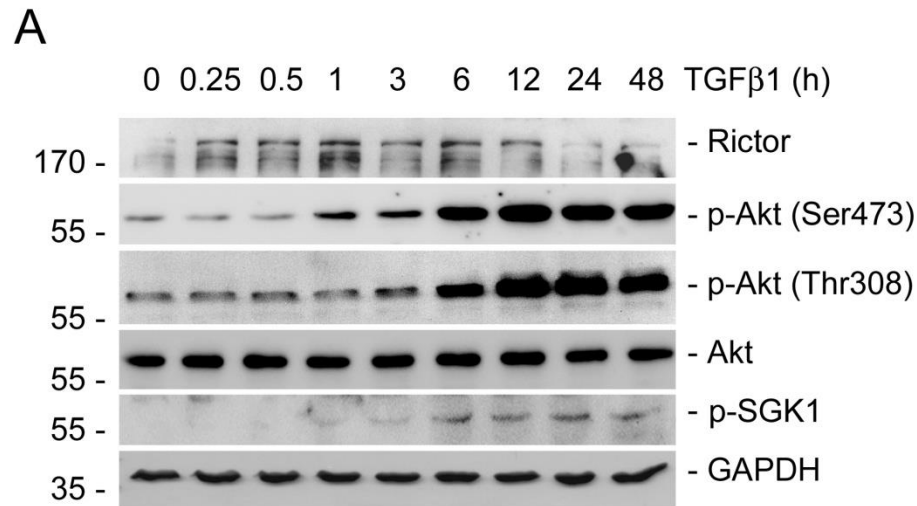


Summary (1)

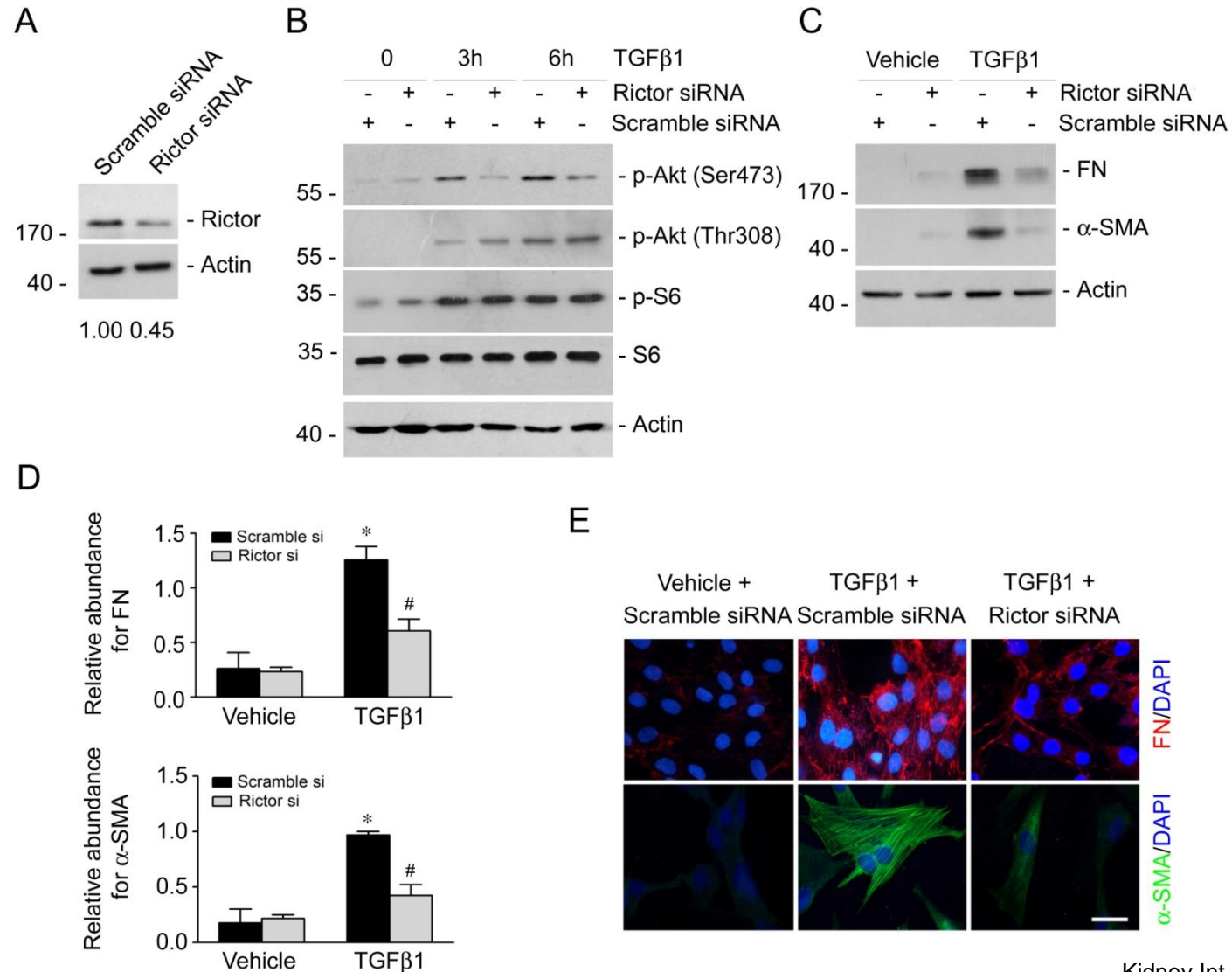
- ❖ **TGF β 1 treatment stimulates Rheb/mTORC1 signaling activation in cultured kidney fibroblasts.**
- ❖ **Activation of Rheb/mTORC1 in fibroblasts induces focal kidney interstitial fibrosis in mice.**

- ❖ Rheb/mTORC1 signaling activation promotes fibroblast activation and kidney fibrosis
- ❖ **Rictor/mTORC2 signaling activation mediates TGF β 1-induced fibroblast activation and kidney fibrosis**
- ❖ Targeting mTOR signaling in protecting against renal fibrosis

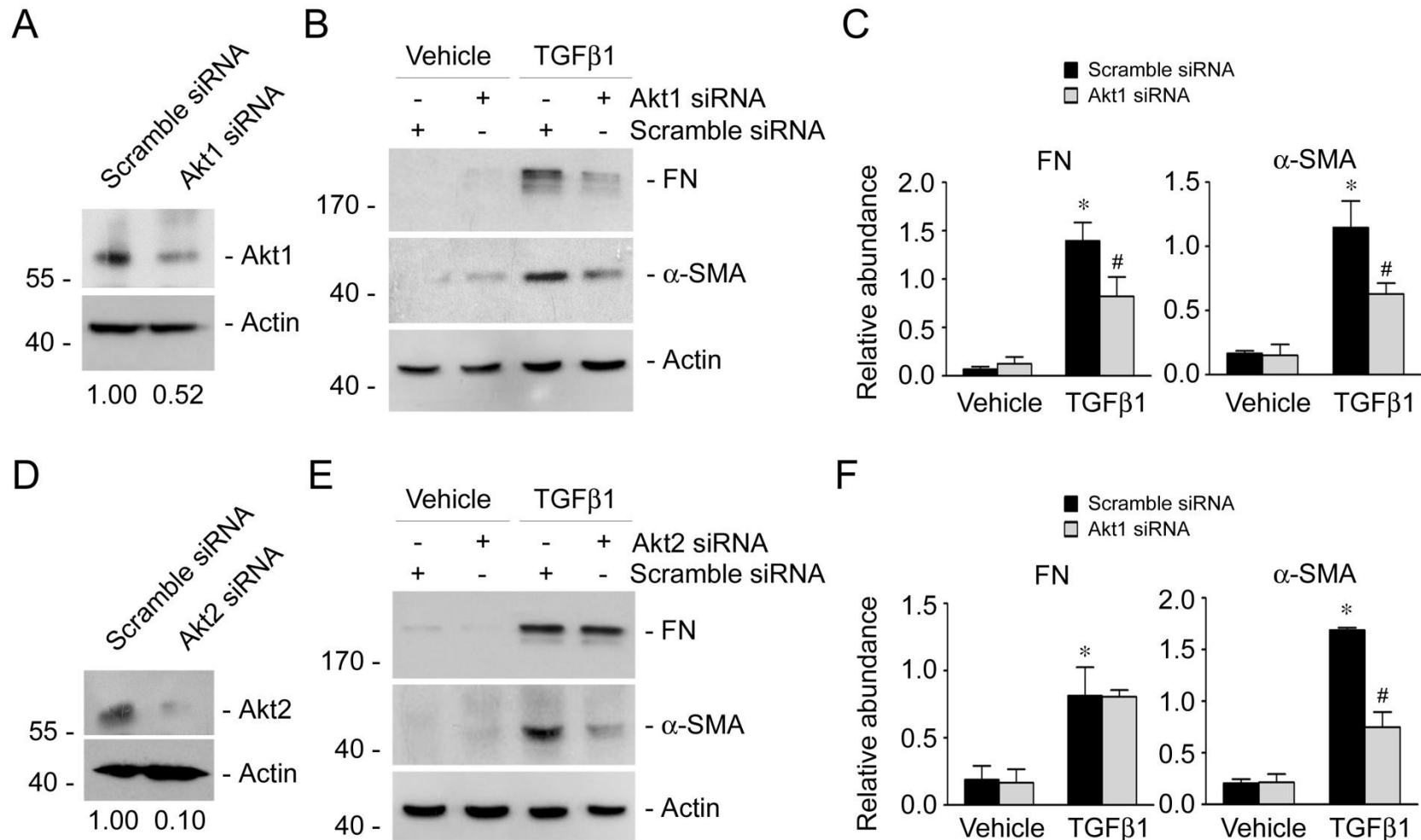
TGFβ1 induces Rictor/mTORC2 signaling activation in NRK-49F cells



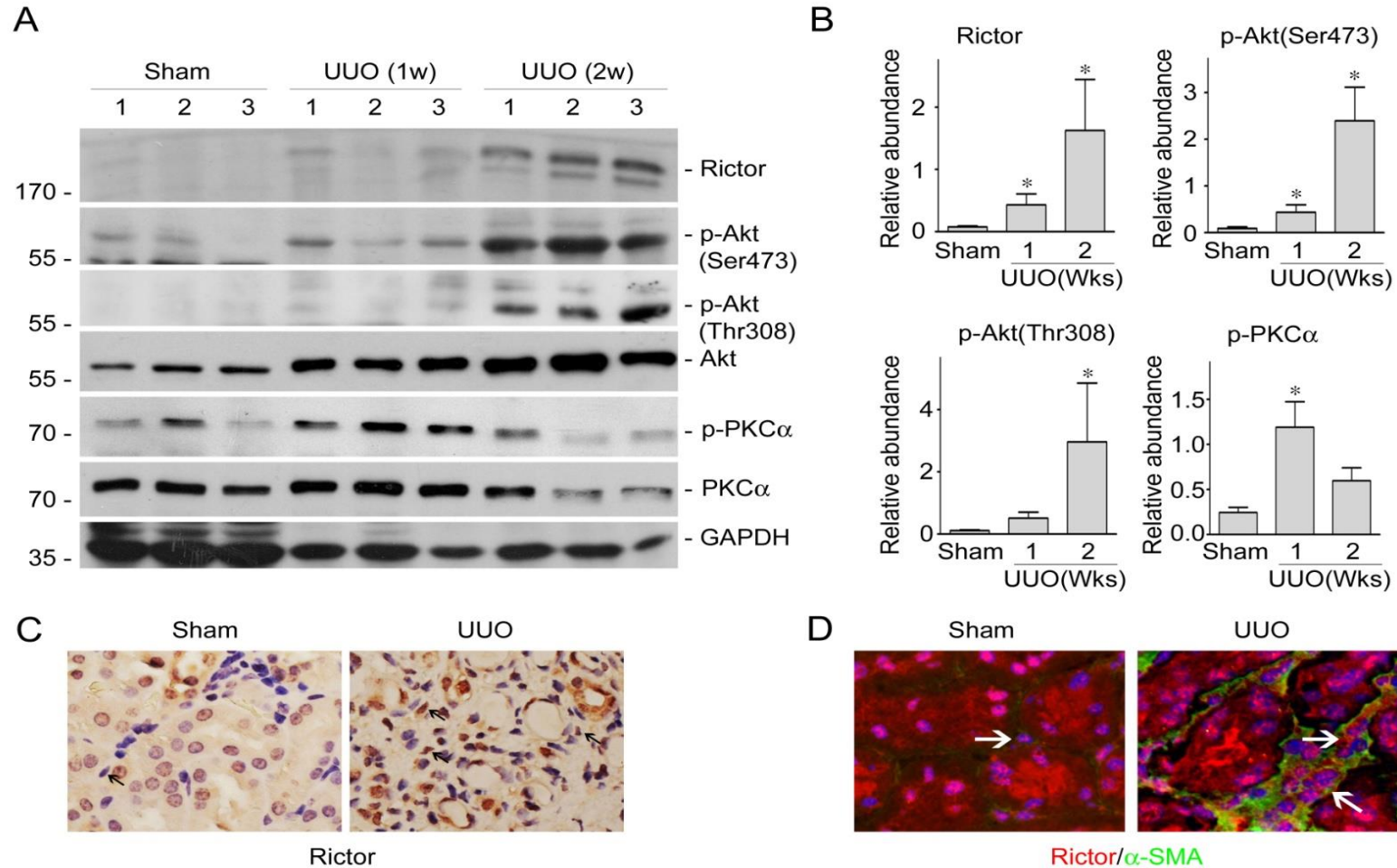
Knocking down Rictor expression diminishes TGF β 1-Induced Akt phosphorylation and fibroblast activation



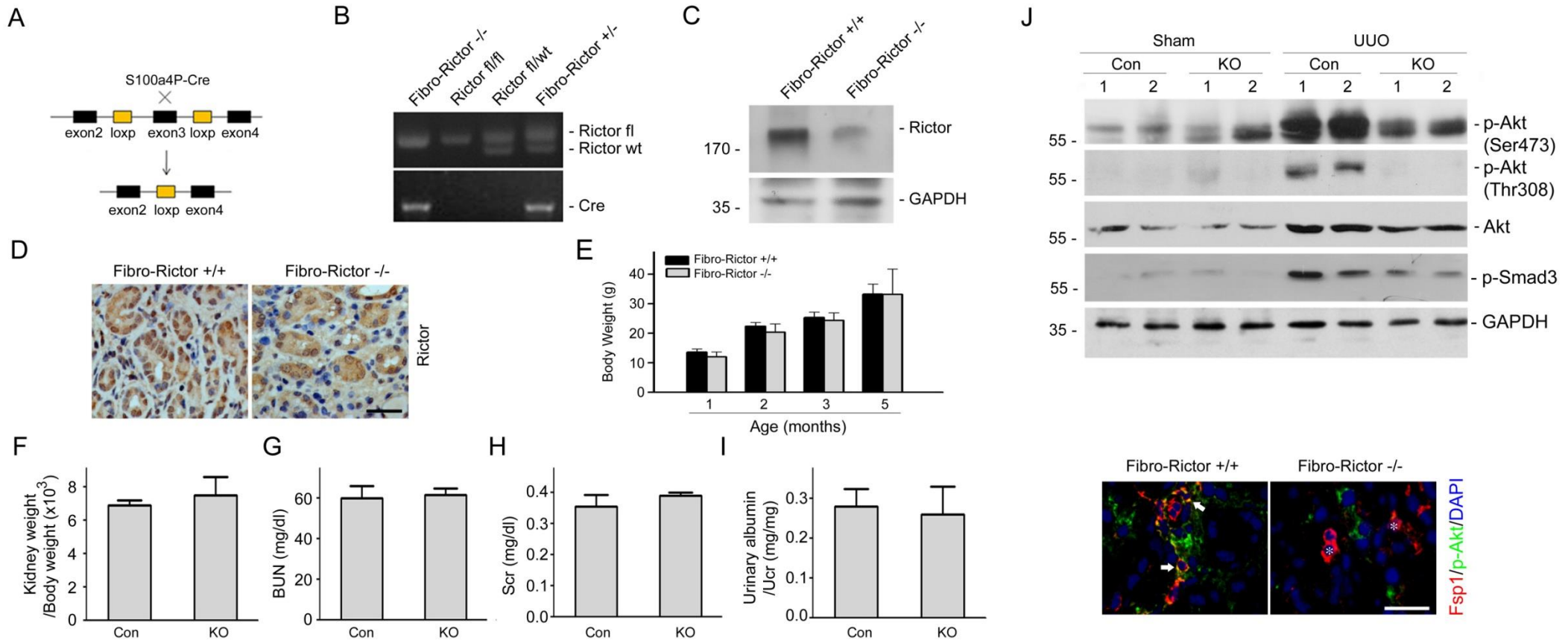
Knocking down Akt diminishes TGF β 1-induced fibroblast activation



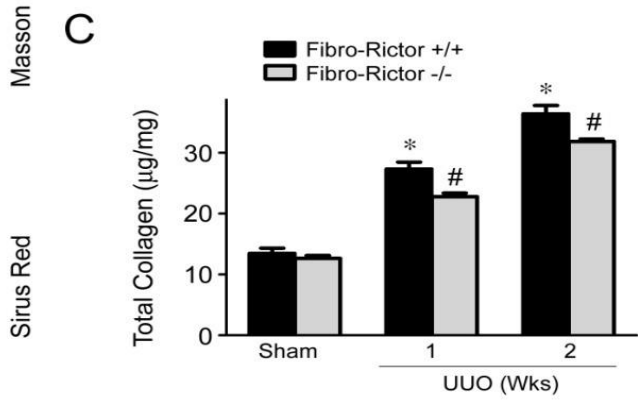
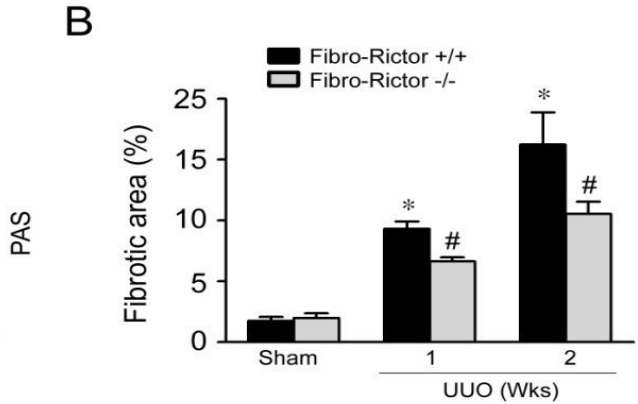
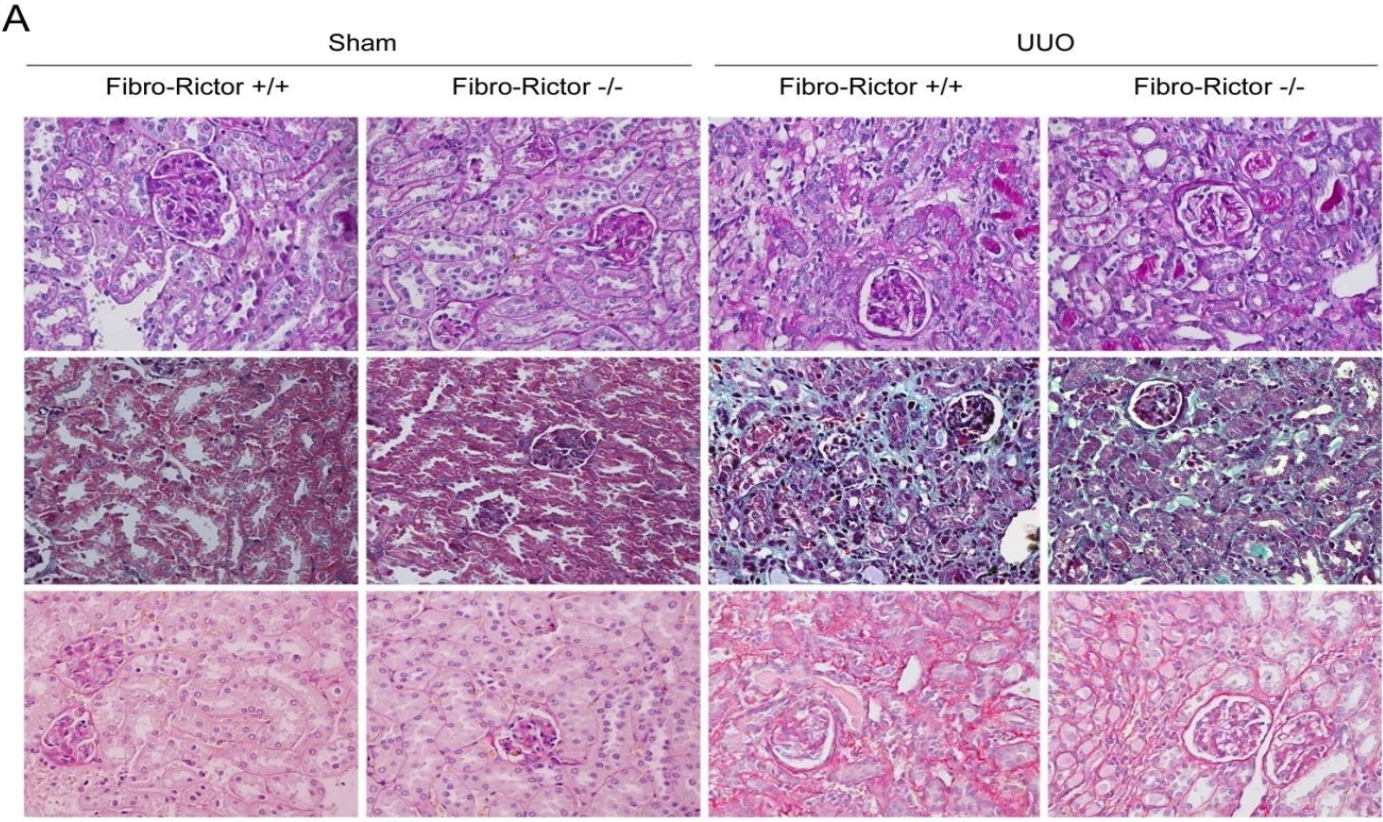
Activation of Rictor/mTORC2 signaling in the myofibroblasts in fibrotic kidneys



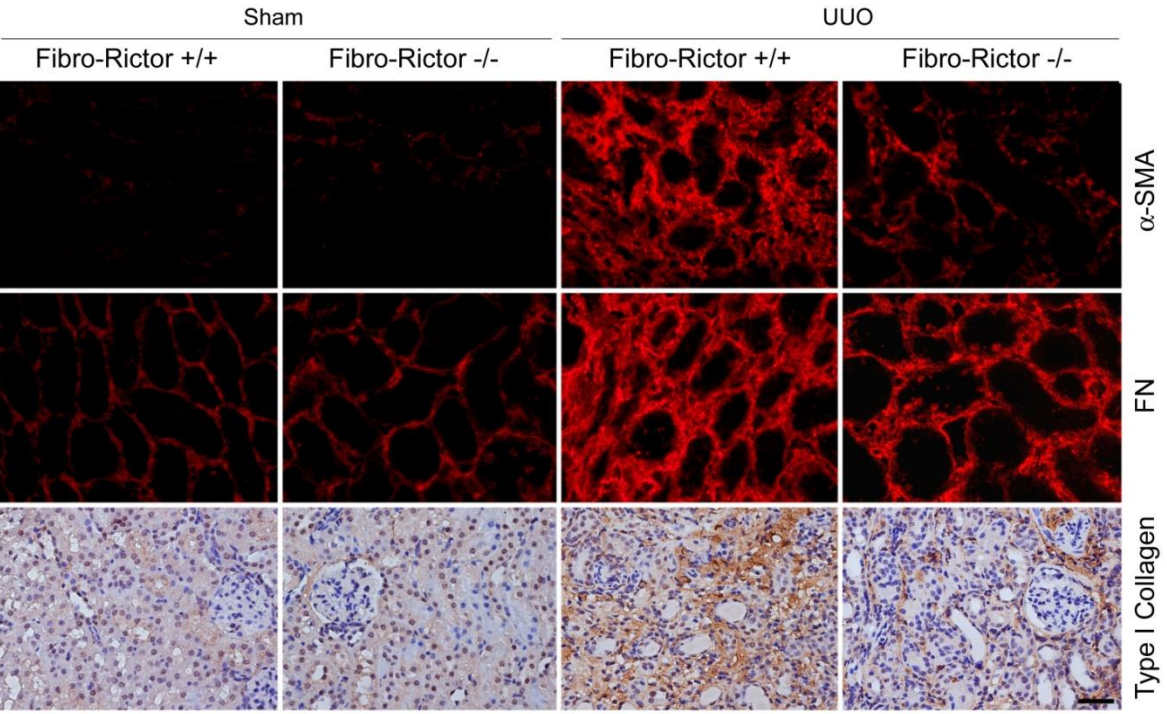
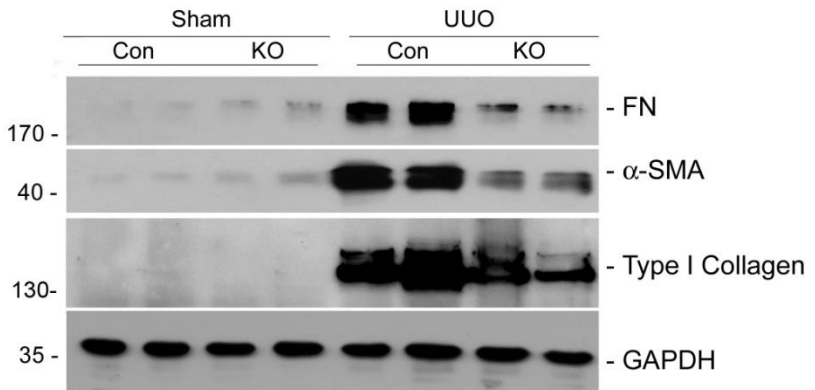
Generating the mice with fibroblast-specific ablation of Rictor



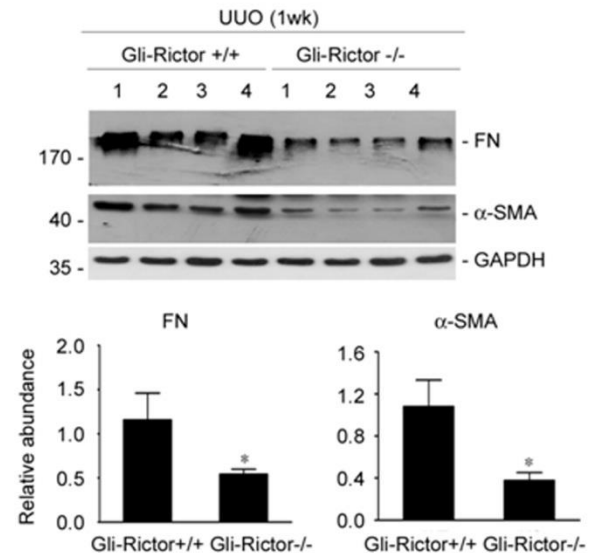
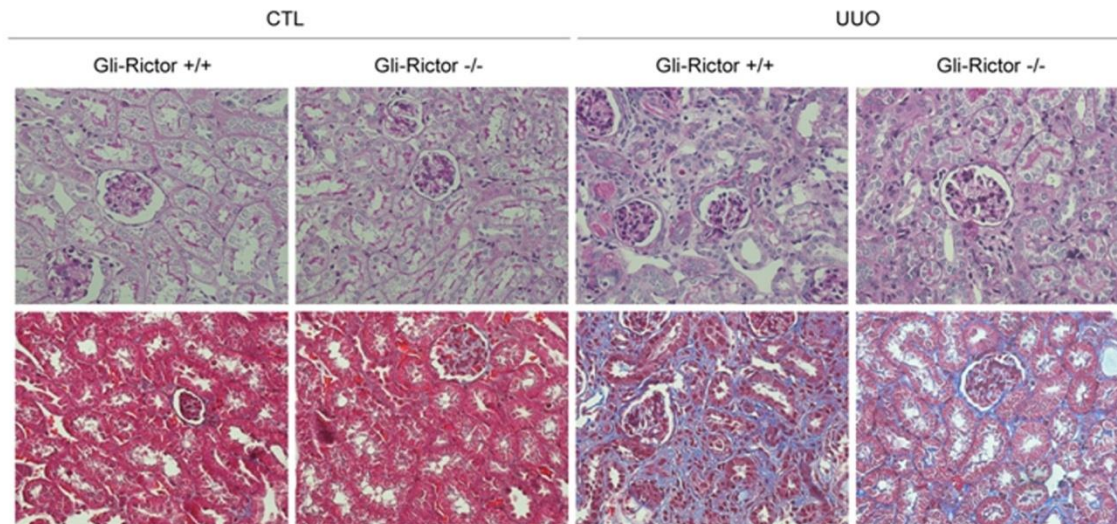
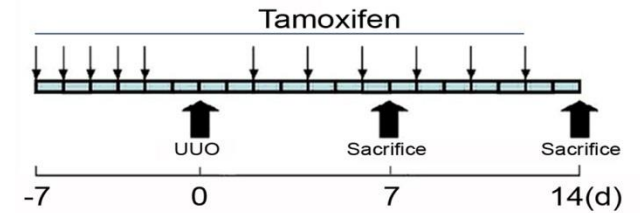
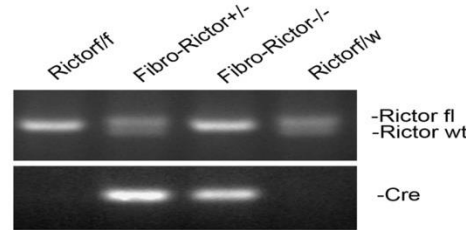
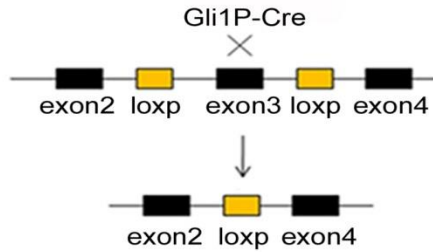
Specific deletion of Rictor in fibroblasts ameliorates kidney interstitial fibrosis in mice with UUO nephropathy



Deletion of Rictor in fibroblasts diminishes FN and α -SMA expression in the UUO kidneys



Induced deletion of Rictor in fibroblasts ameliorates UUO nephropathy in mice



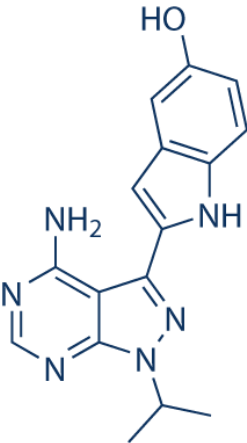


Summary (2)

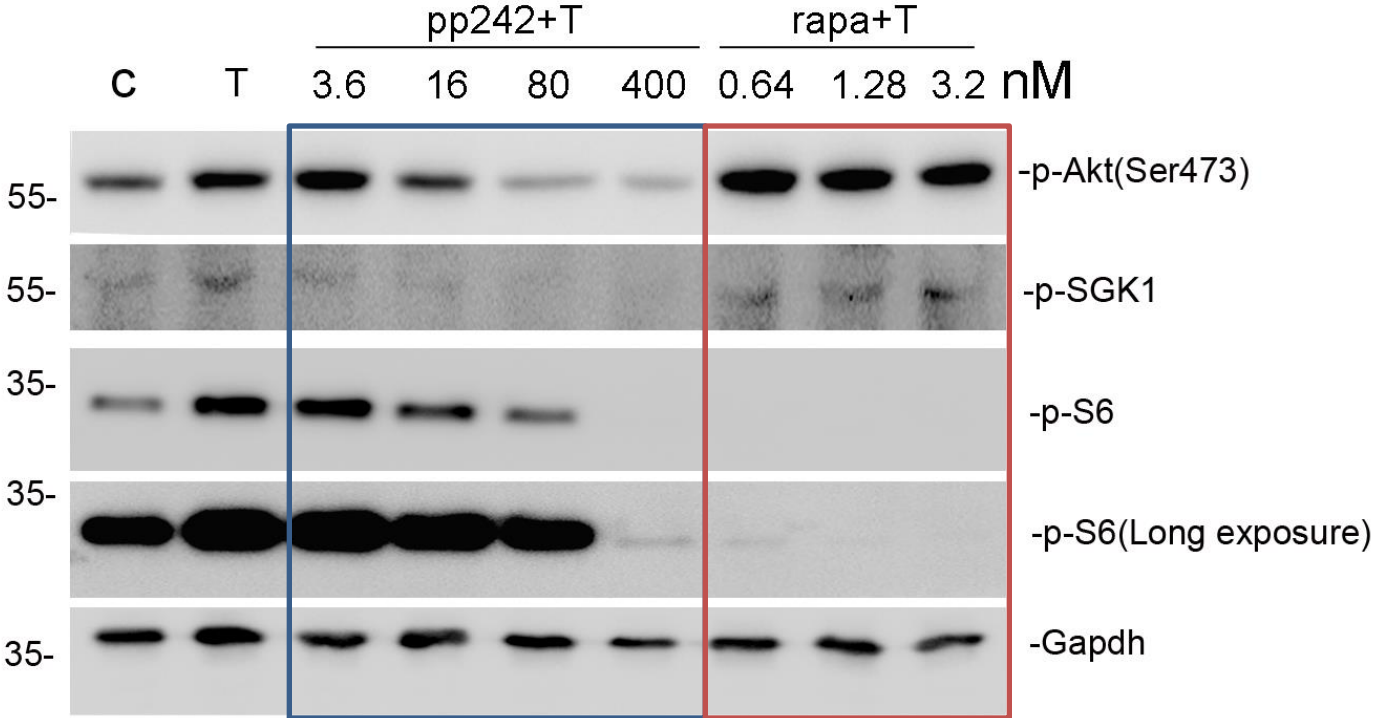
- ❖ **TGF β 1 treatment stimulates Rictor/mTORC2 signaling activation in cultured kidney fibroblasts.**
- ❖ **Blockade of Rictor/mTORC2 inhibits fibroblast activation and kidney fibrosis in mice with UUO nephropathy.**

- ❖ Rheb/mTORC1 signaling activation promotes fibroblast activation and kidney fibrosis
- ❖ Rictor/mTORC2 signaling activation mediates TGF β 1-induced fibroblast activation and kidney fibrosis
- ❖ **Targeting mTOR signaling in protecting against kidney fibrosis**

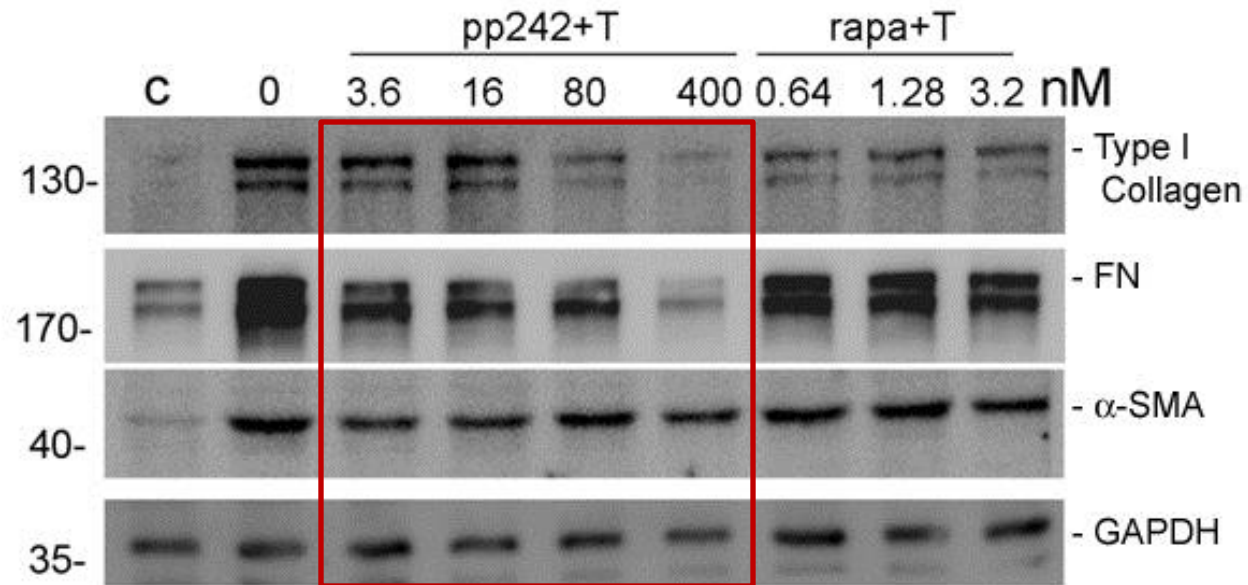
PP242 inhibits TGFβ1-stimulated mTOR signaling activation in NRK-49F cells



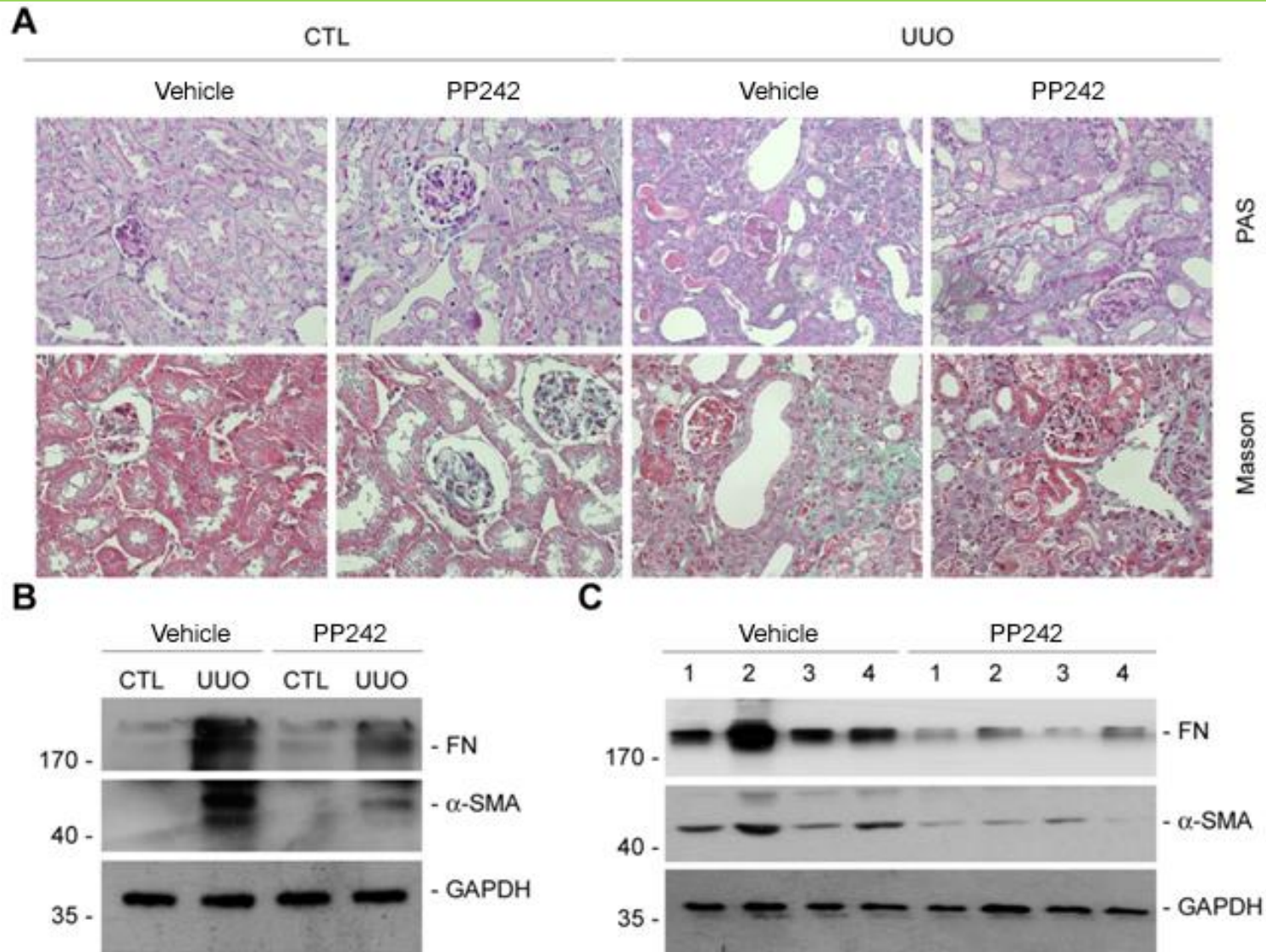
PP242



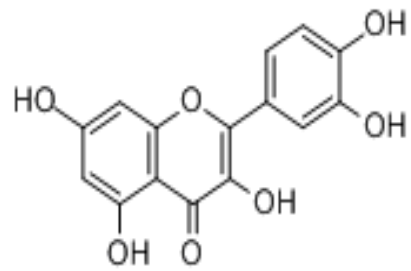
PP242 ameliorates TGF β 1-induced fibroblast activation



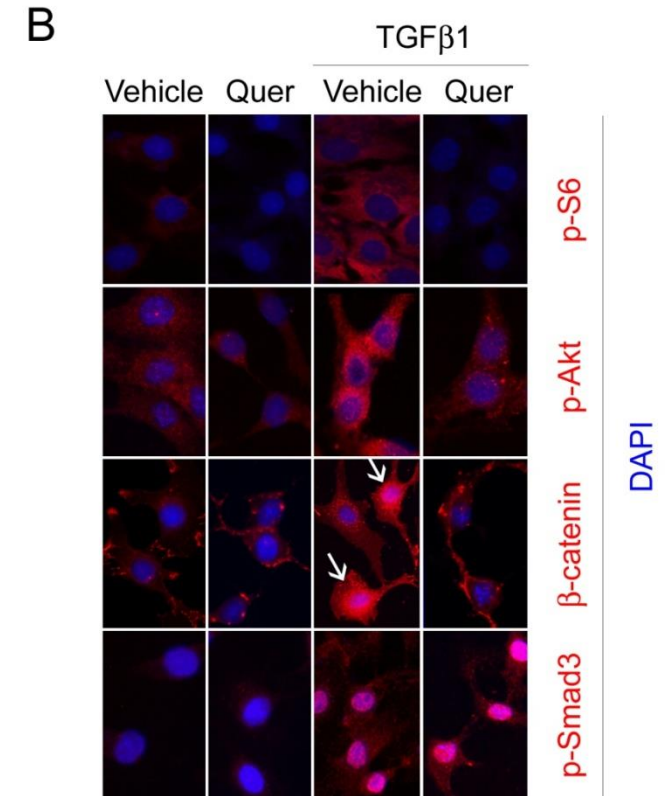
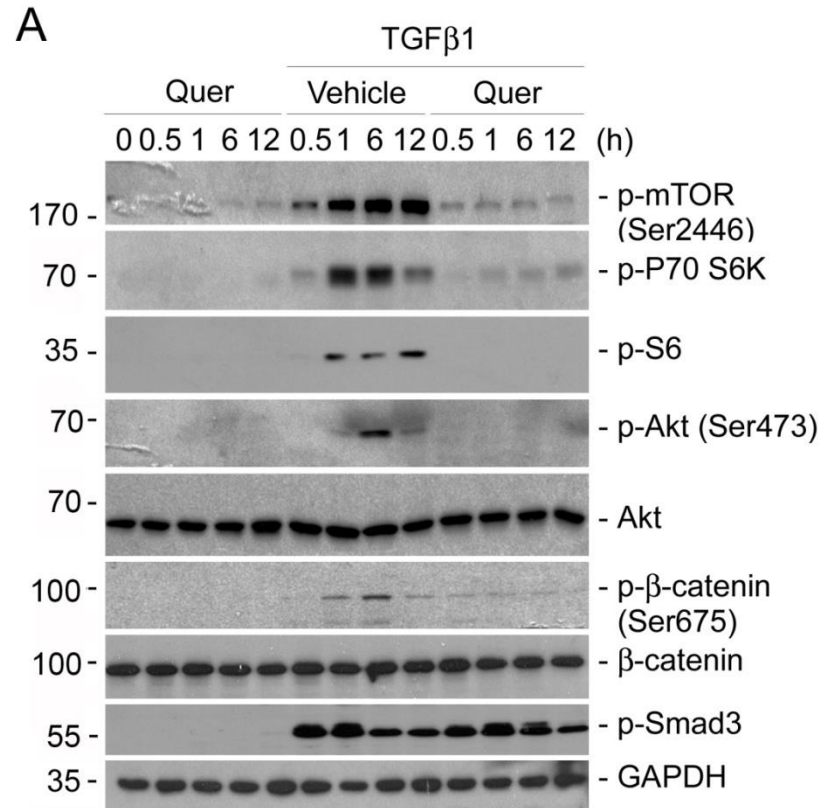
PP242 alleviates UUO nephropathy in mice



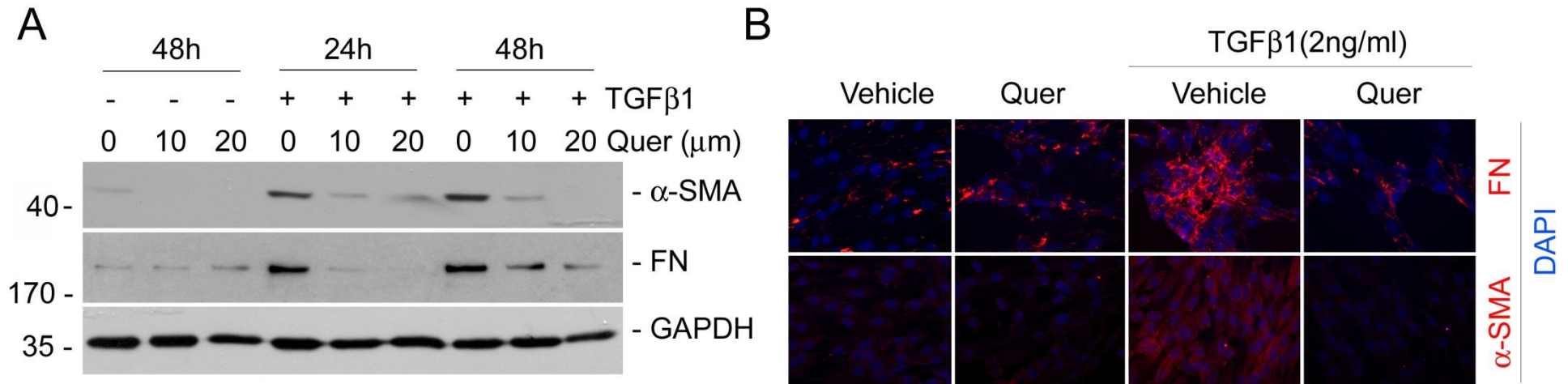
Quercetin inhibits mTOR and β -catenin but not Smad3 signaling activation stimulated by TGF β 1 in NRK-49F cells



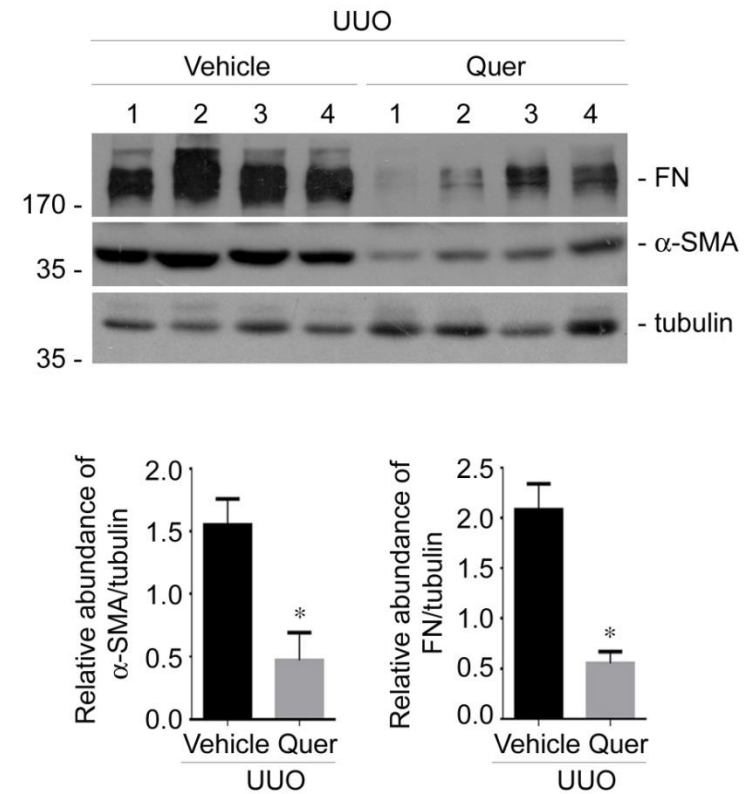
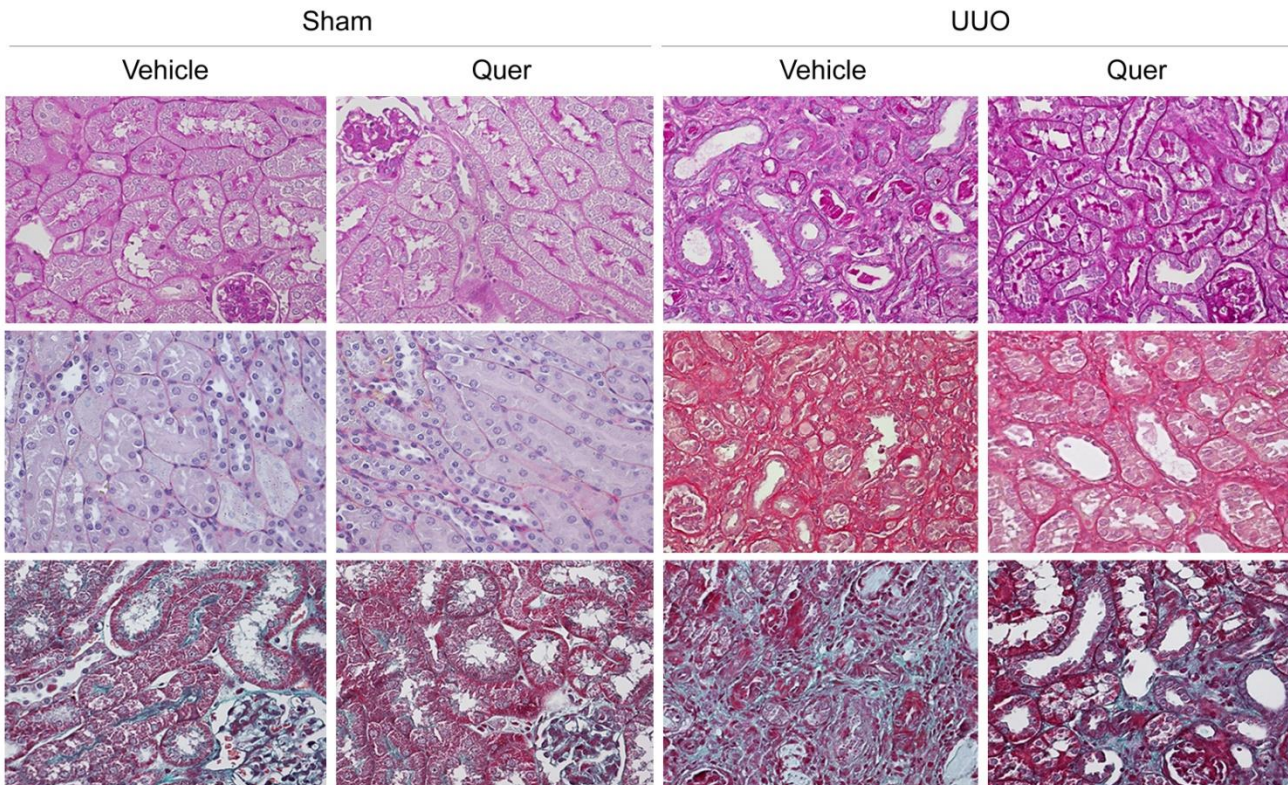
Quercetin



Quercetin diminishes TGFβ1-induced NRK-49F cell activation



Quercetin ameliorates UUO nephropathy in mice



Conclusions

- **Both mTORC1 and mTORC2 are involved in TGF β 1-induced fibroblast activation and kidney fibrosis.**
- **Targeting mTORC1 and mTORC2 signaling pathways may provide a new therapeutic strategy for protecting against kidney fibrosis.**

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Thank you !