



香港中文大學
The Chinese University of Hong Kong



香港中文大學醫學院
Faculty of Medicine
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Advances in Molecular Pathology of Hypertensive nephropathy: Role of TGF- β /Smads

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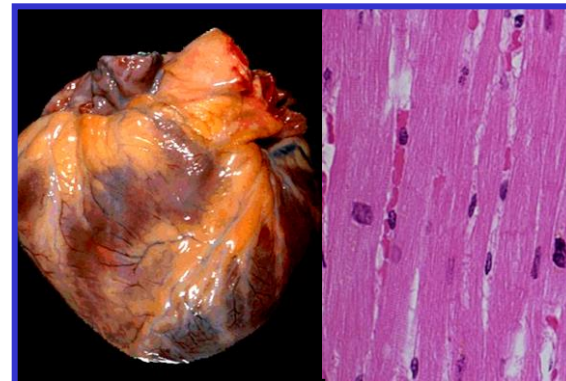
Hypertensive CKD and CVD

Fibrosis and **inflammation** are two key pathological features of CKD and CVD

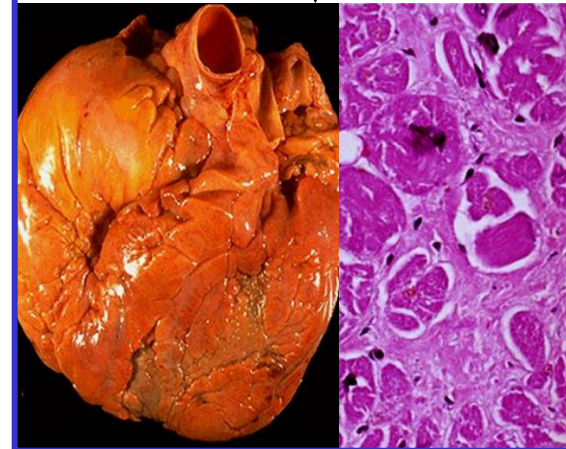
Kidney

Heart

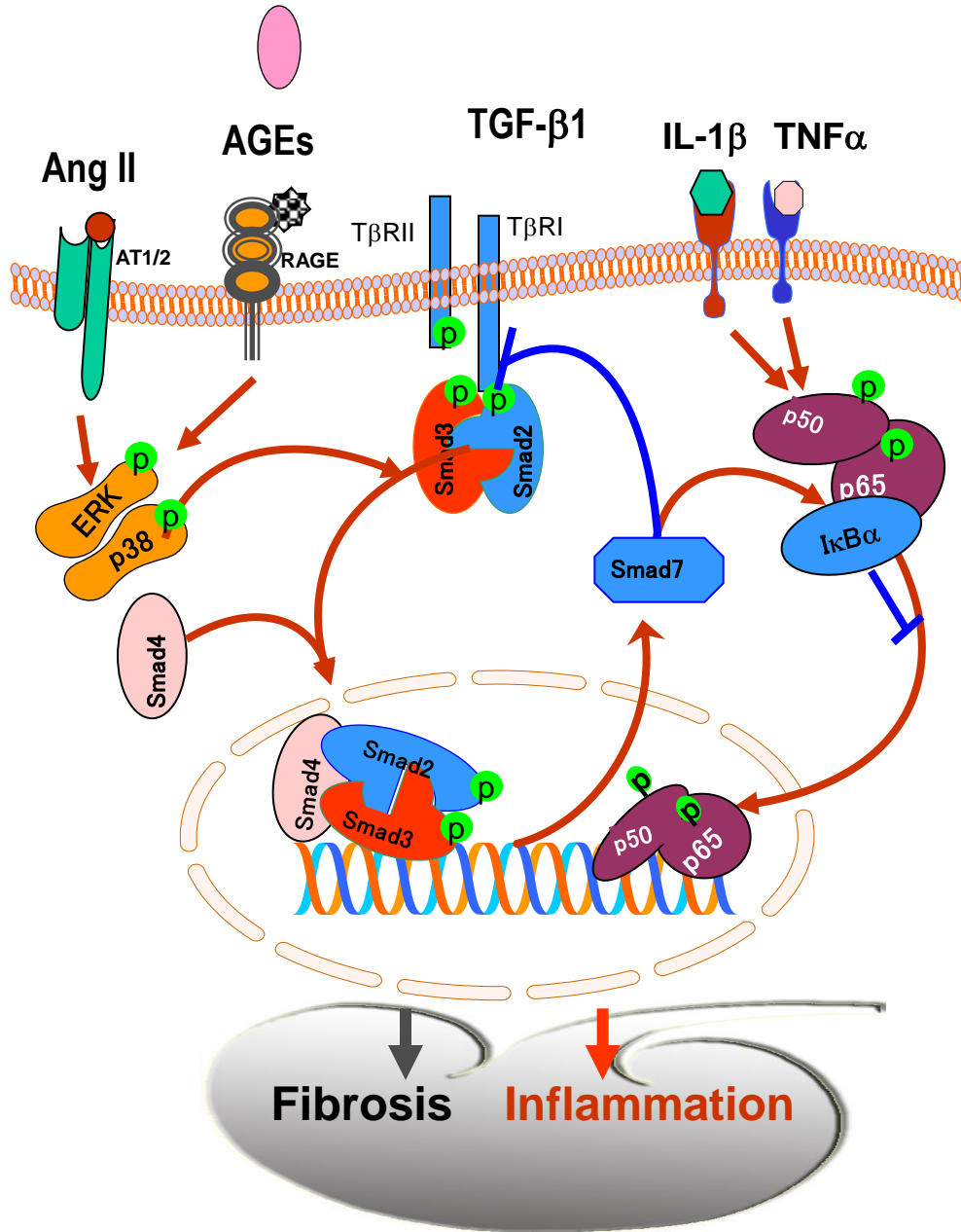
Normal



ESOD



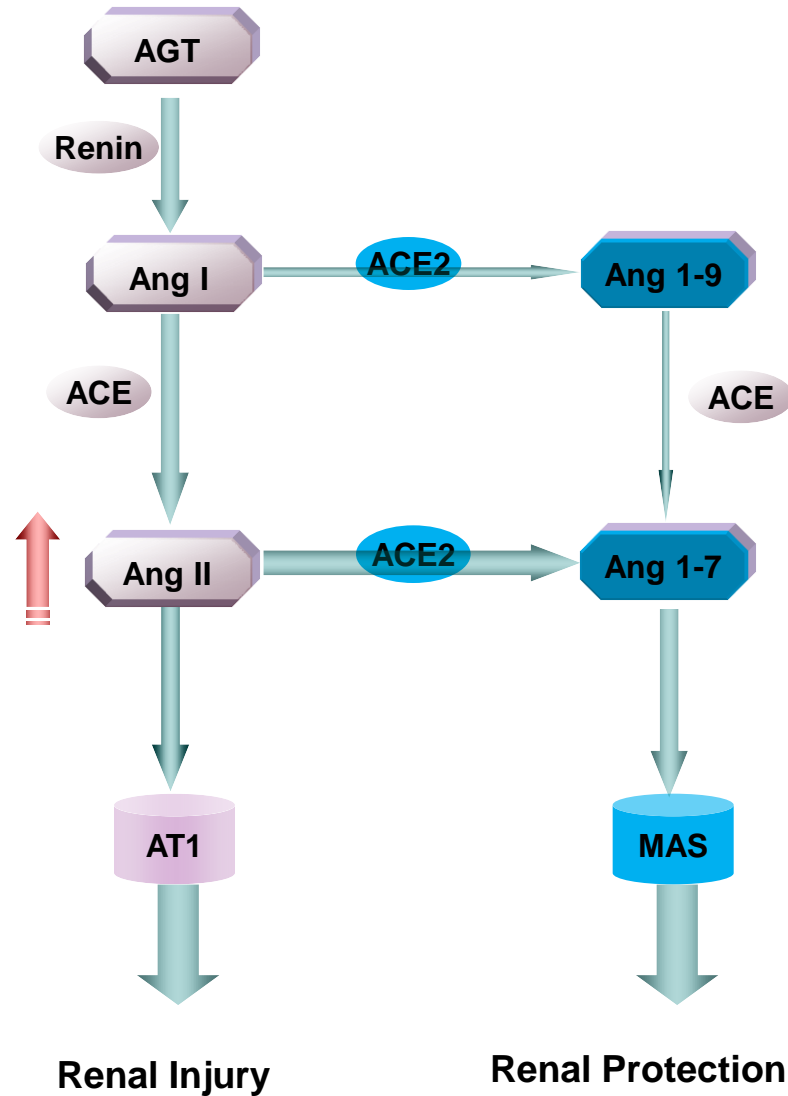
TGF- β /Smad signaling-crosstalk pathways in CKD/CVD



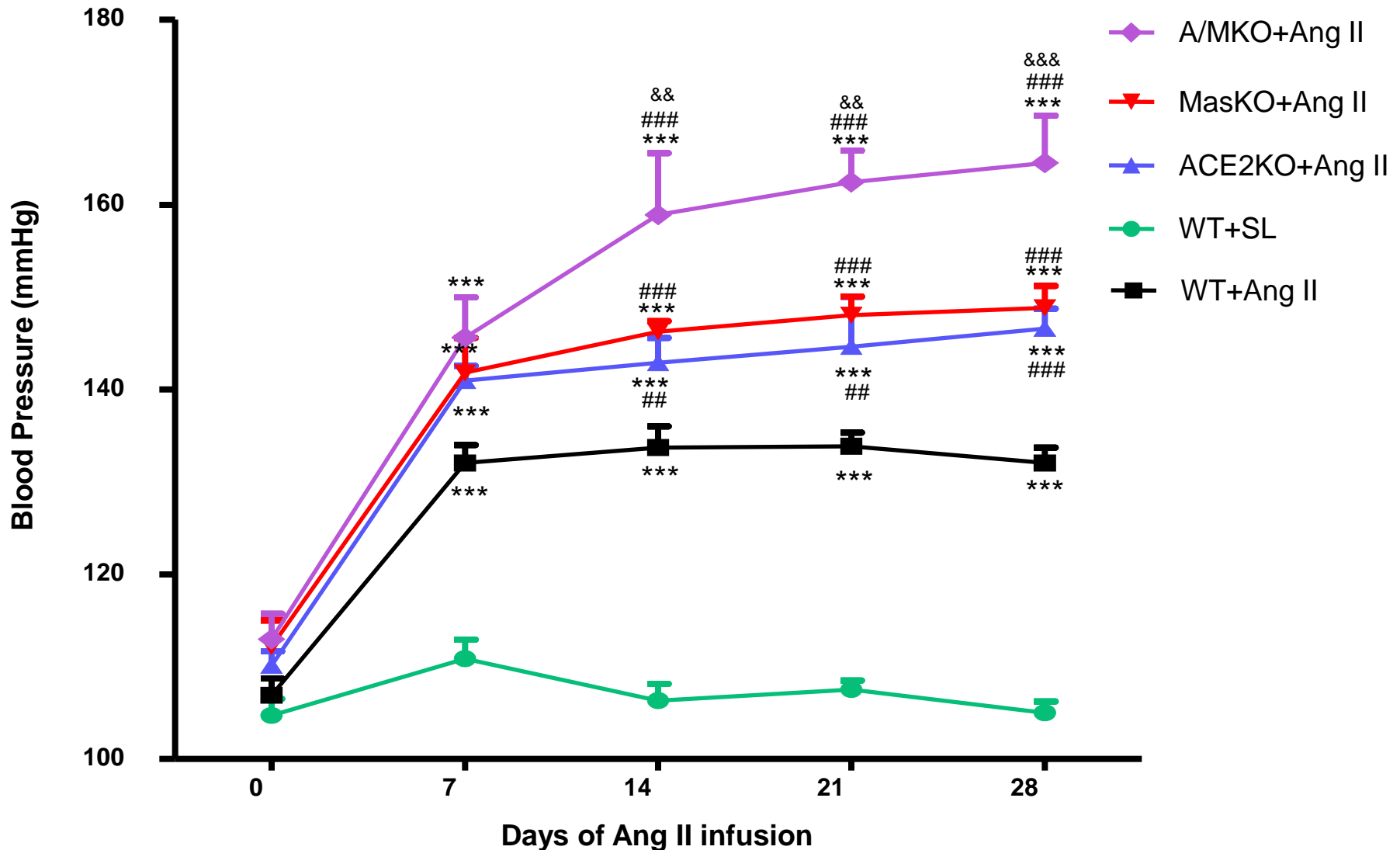
Relevant Publications

1. Li JH et al: *JASN* 13:1464-72, 2002
2. Li JH et al: *Kidney Int* 63:2010-19, 2003
3. Lan HY et al: *JASN* 14:1535-48, 2003
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5. Li JH et al: *Am J Pathol* 164:1389-97, 2004
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7. Hou CC et al: *Am J Pathol* 166:761-71, 2005
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30. Zhou L, et al: *AJP-Renal* 298:1006-17, 2010
31. Huang XR, et al: *Hypertension* 55:1165-71, 2010
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34. Meng X et al: *JASN* 21:1477-87, 2010
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38. Zhong X et al: *JASN* 22:1668-81, 2011
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40. Meng X et al: *J Pathol* 217:175-88, 2012

Imbalancing Ang II Signaling Mediates HTN

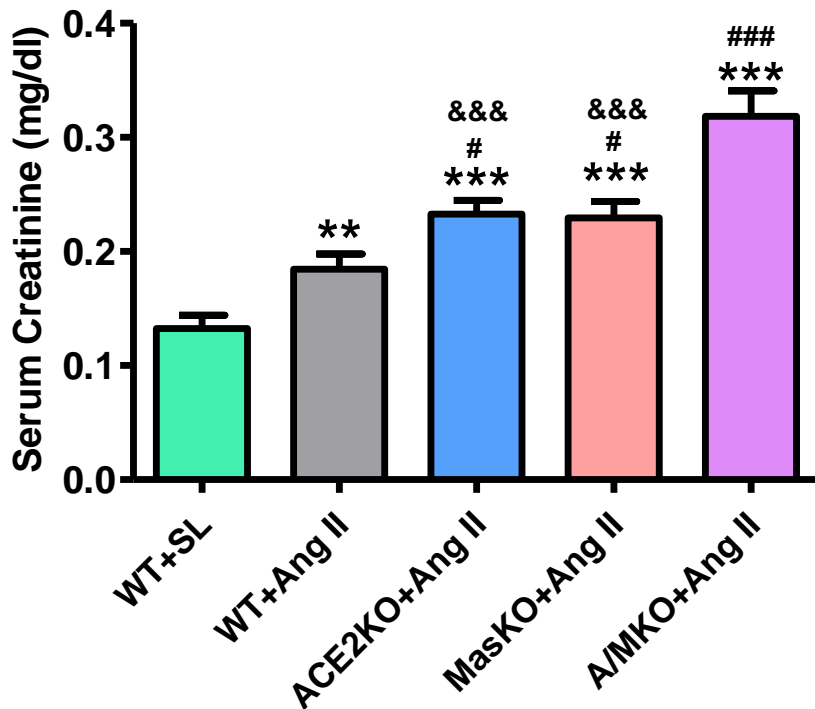


ACE2/Mas Double Deficiency Increases Blood Pressure With Ang II Infusion

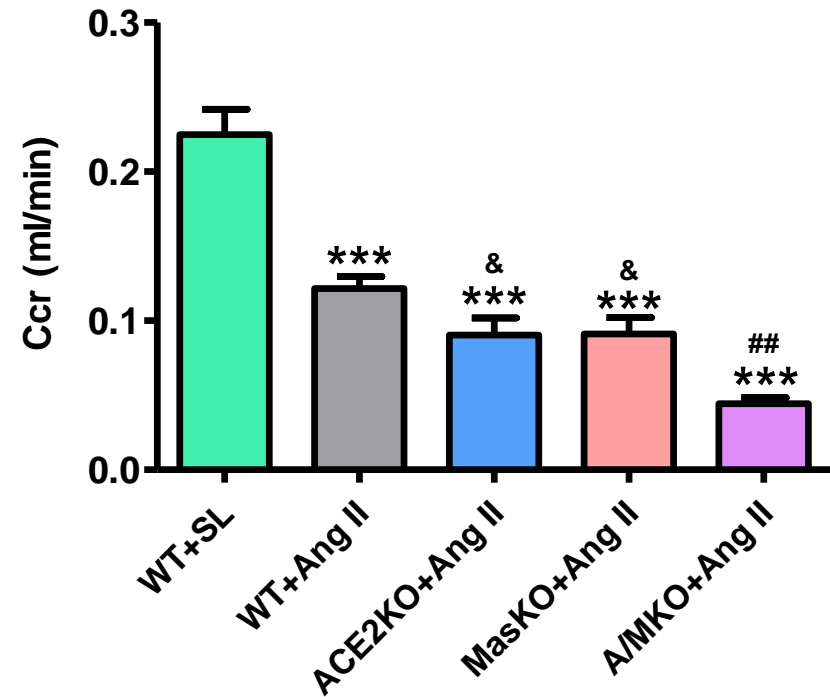


ACE2/Mas Double Deficiency Promotes Renal Injury in HTN

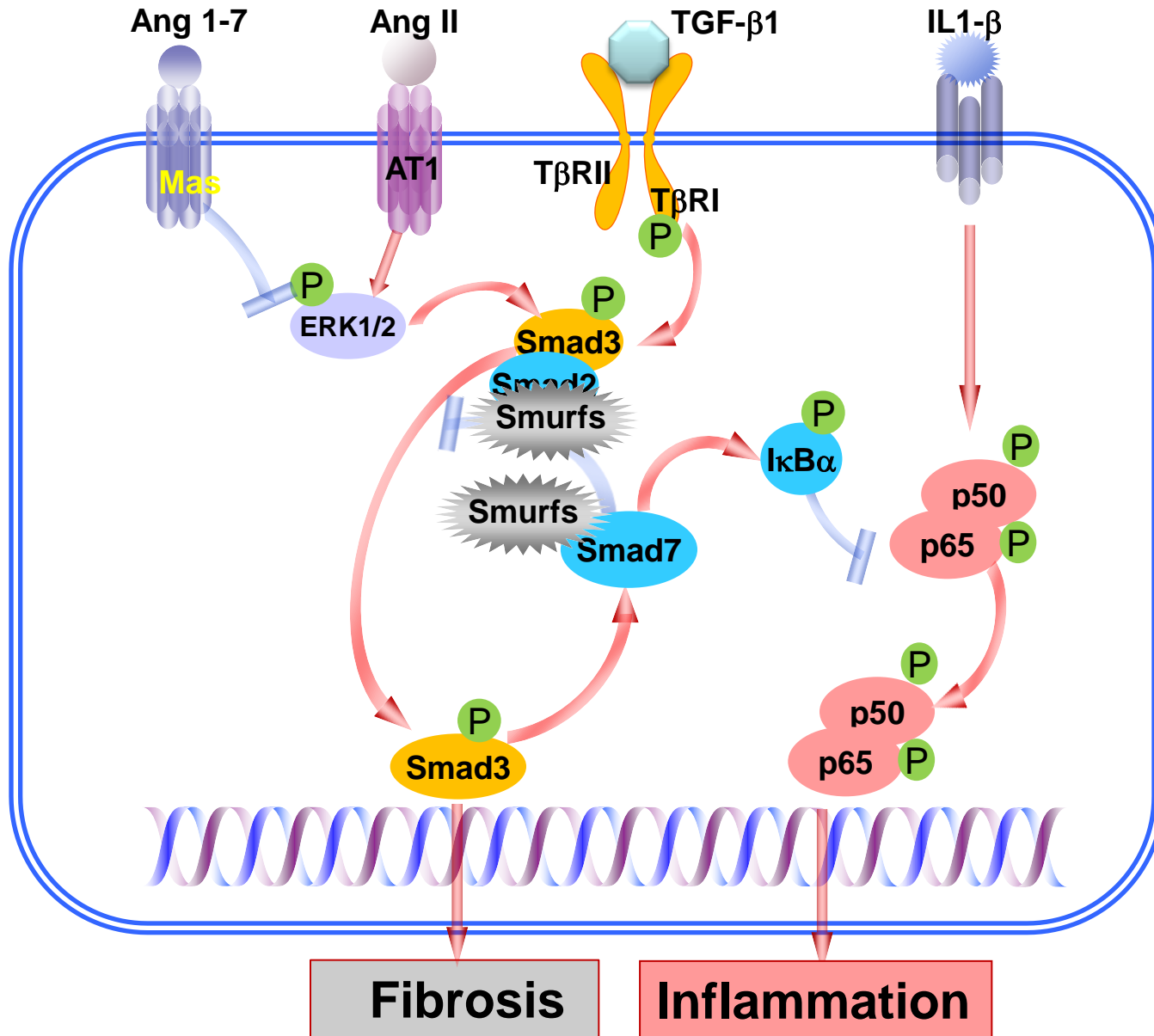
Serum Creatinine



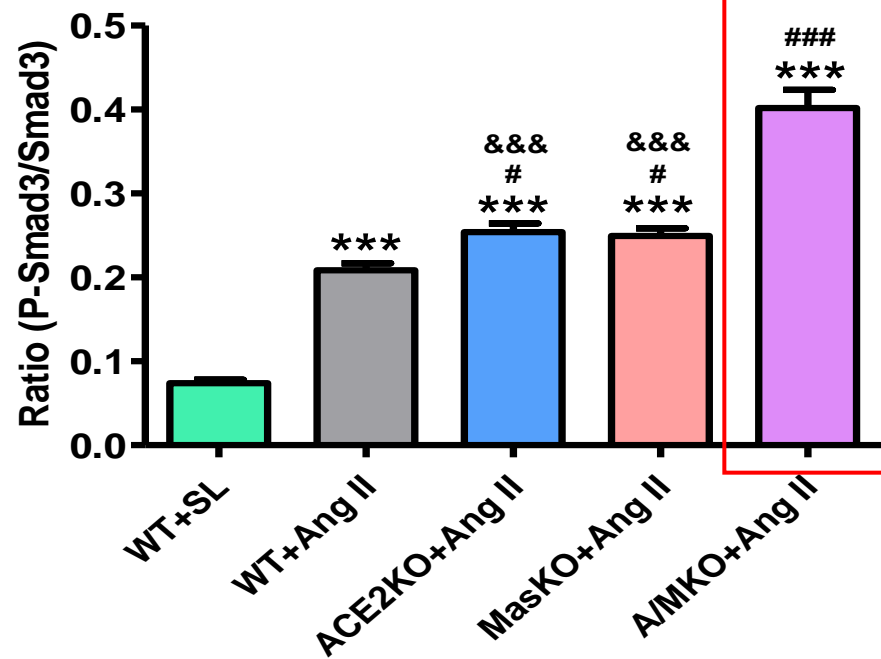
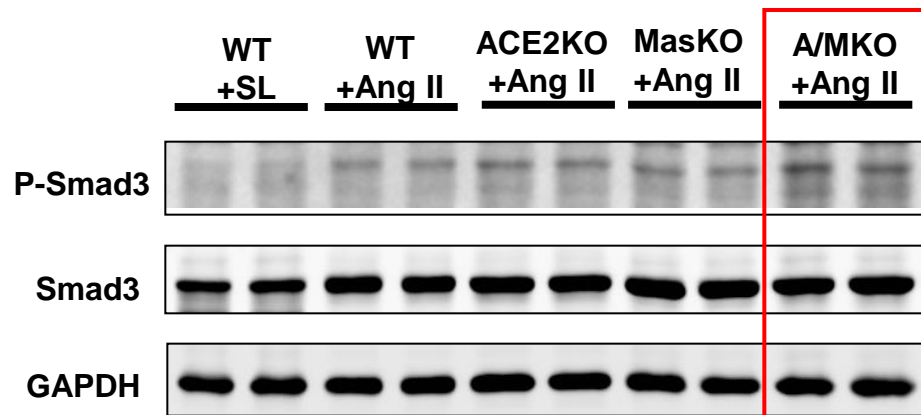
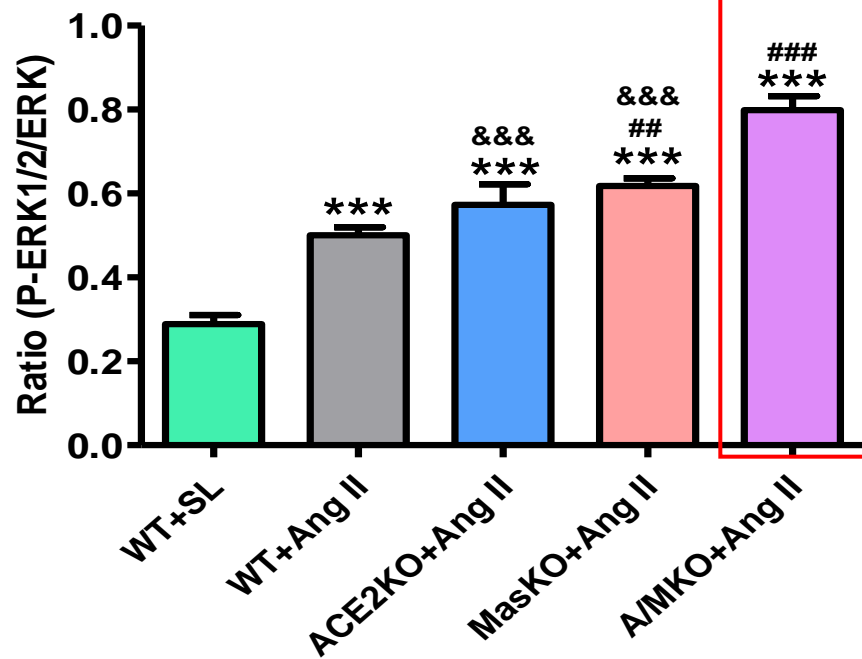
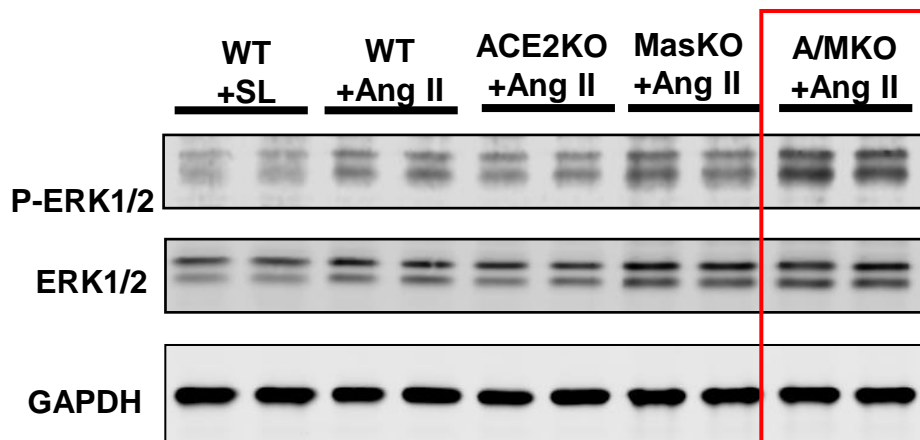
Creatinine Clearance



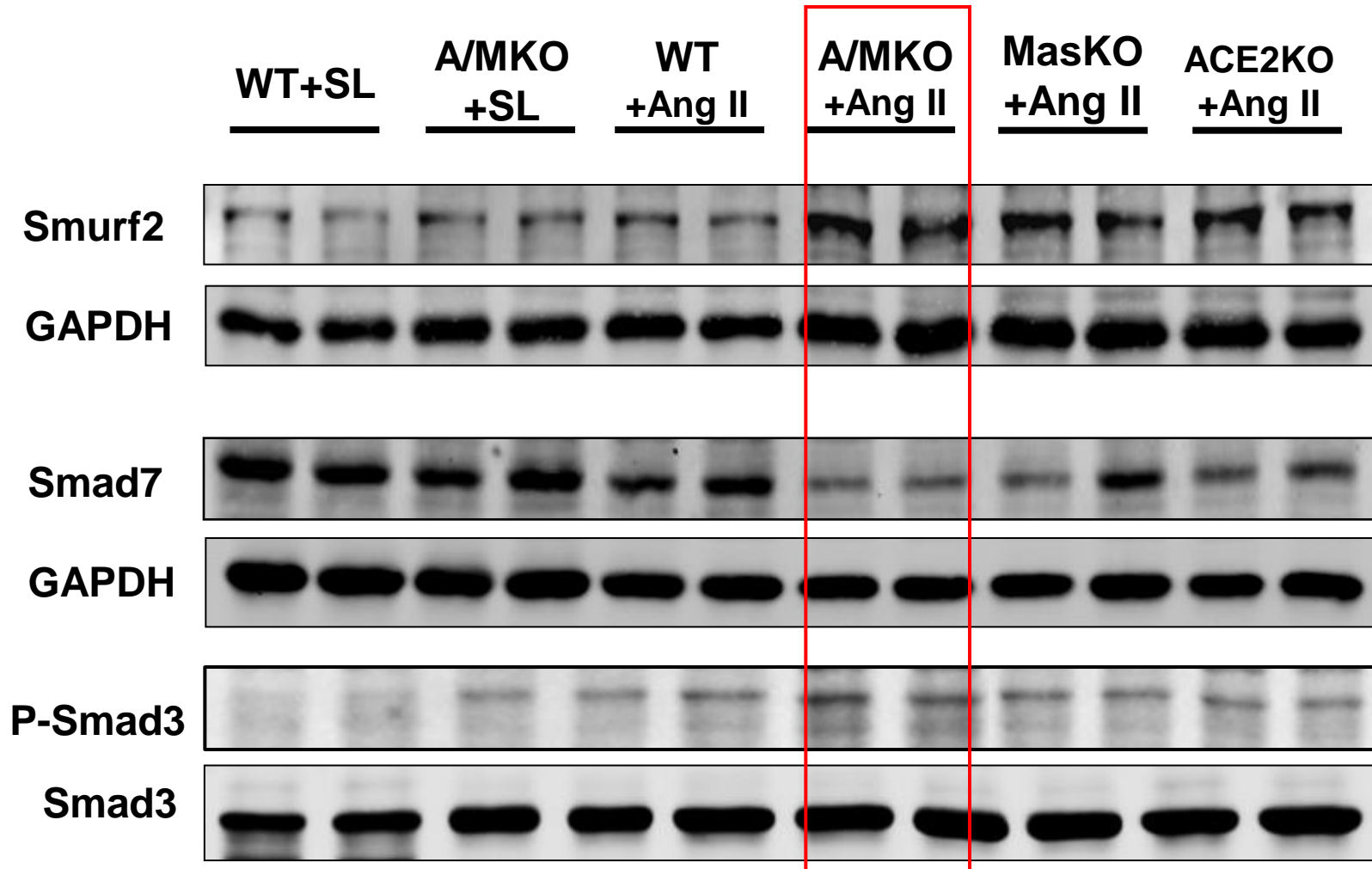
Disrupted AngII degradation pathway enhances TGF- β /Smad and NF- κ B Signaling



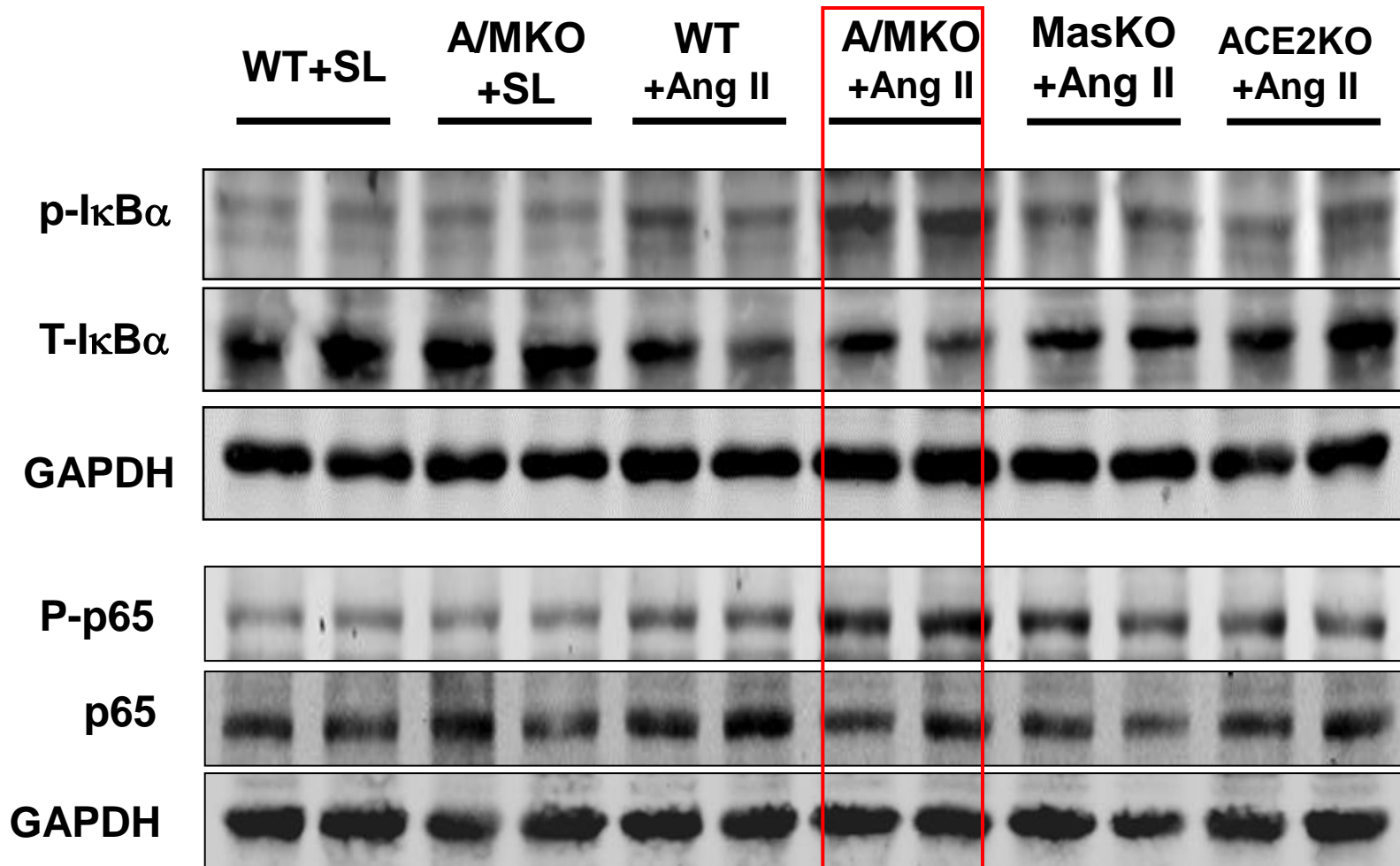
ACE2/Mas Double Deficiency Promotes ERK1/2 and P-Smad3 signaling in HTN



ACE2/Mas Double KO Promotes Smurf2-Smad7 Degradation and Smad3 Activation in HTN

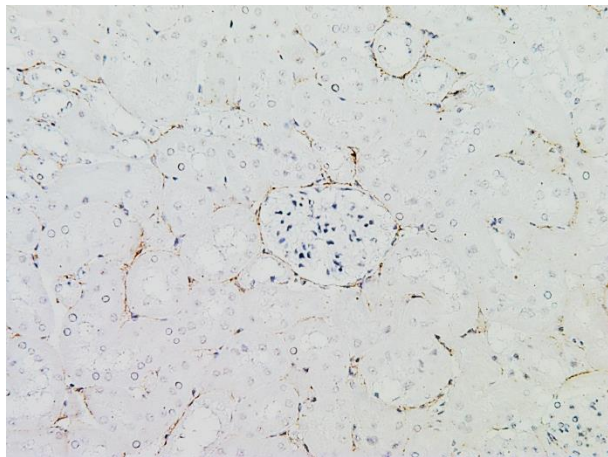


ACE2/Mas Double Deficiency Promotes NF κ B Signaling in HTN

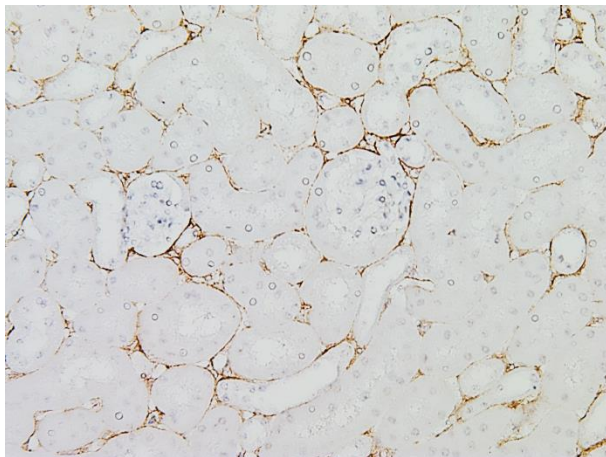


ACE2/Mas Double Deficiency Increases Collagen I Accumulation in Response to Ang II Infusion

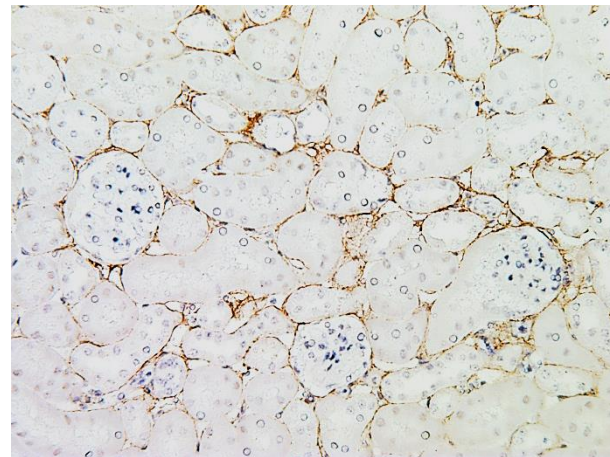
WT+SL



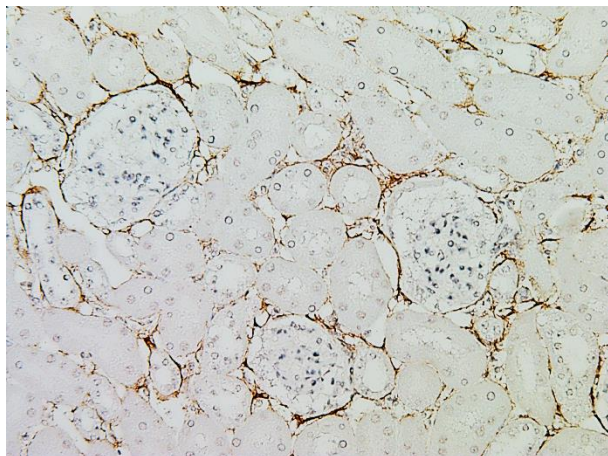
WT+AngII



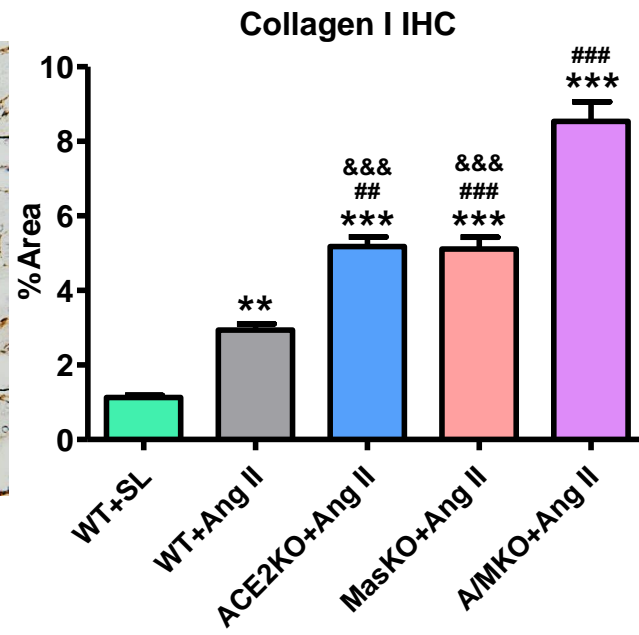
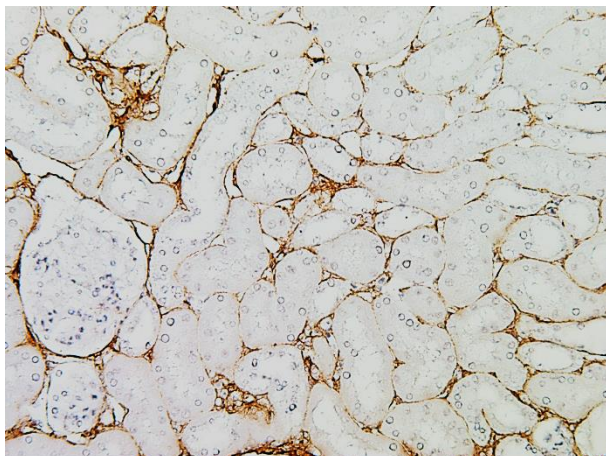
ACE2KO+AngII



MasKO+AngII

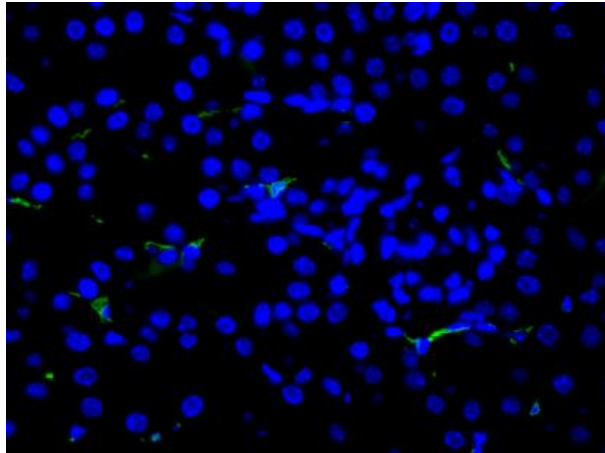


ACE2/MasKO+AngII

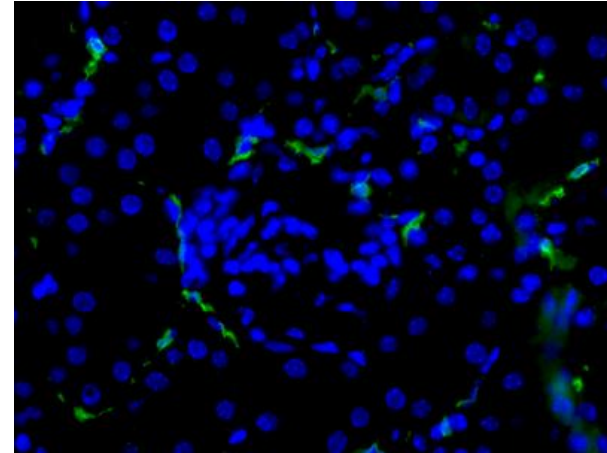


ACE2/Mas Double Deficiency Increases F4/80+ Macrophages in Response to Ang II Infusion

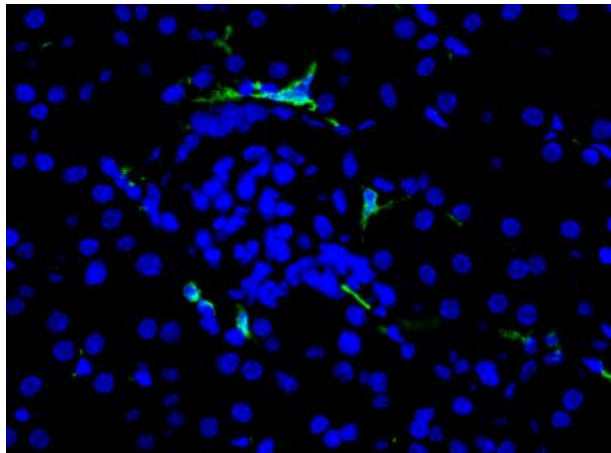
WT+SL



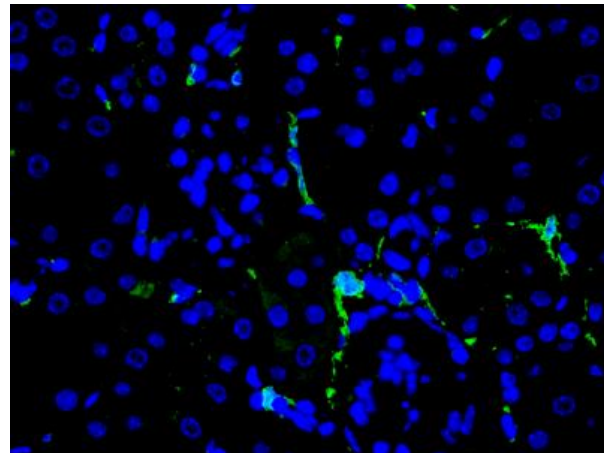
WT+AngII



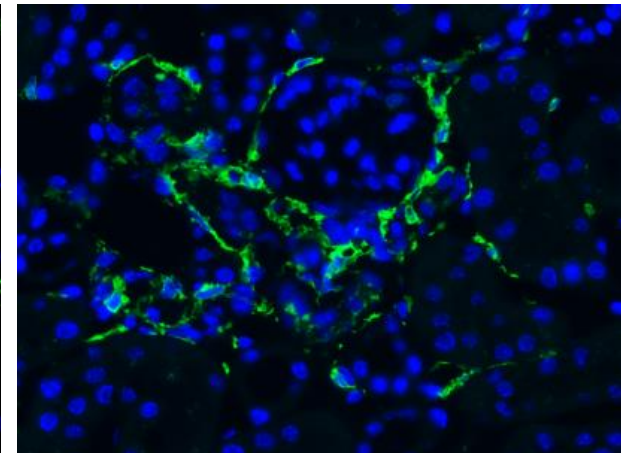
ACE2KO+AngII



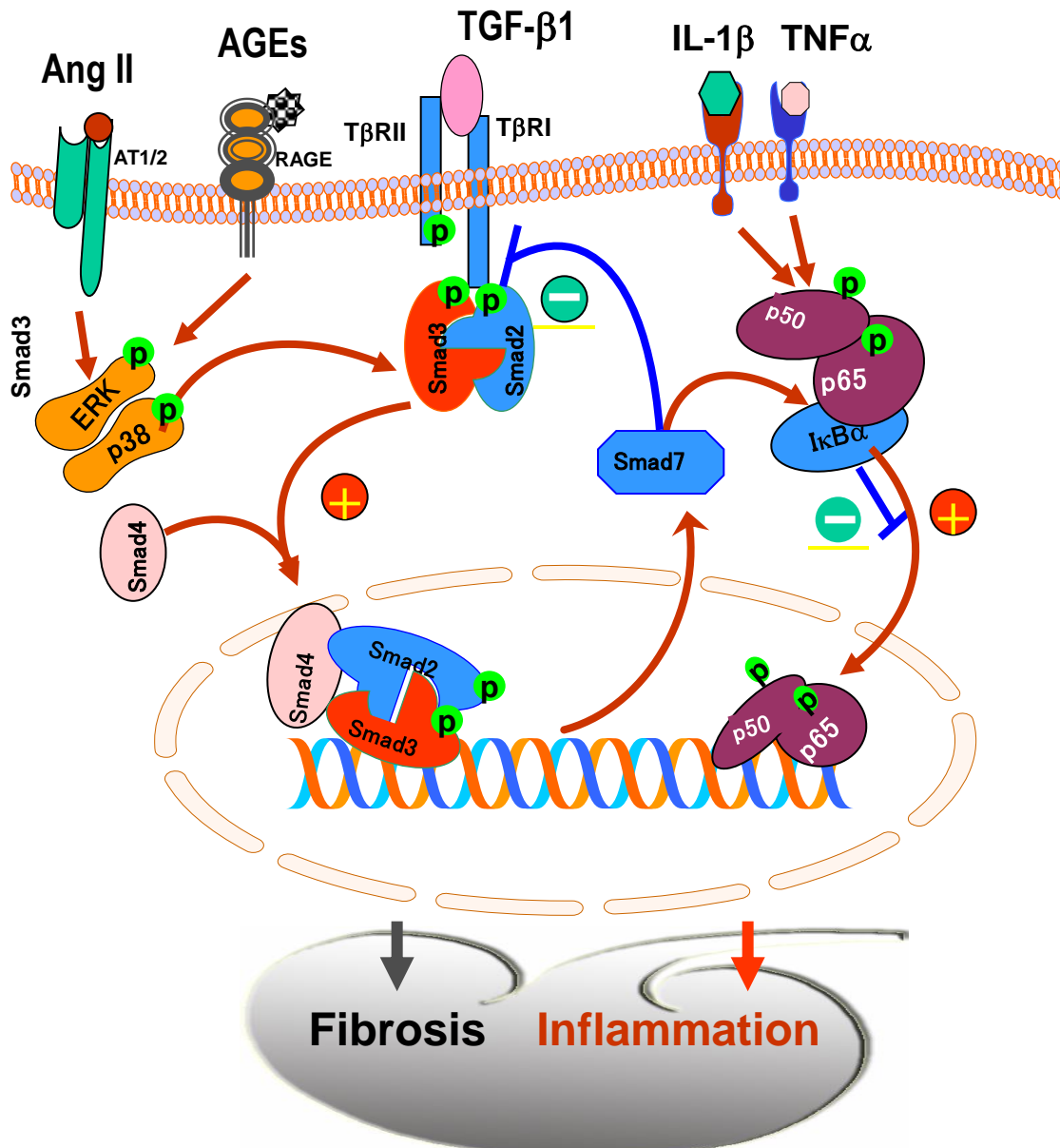
MasKO+AngII



ACE2/MasKO+AngII



Q1: Is Smad7 protective in HT CKD?

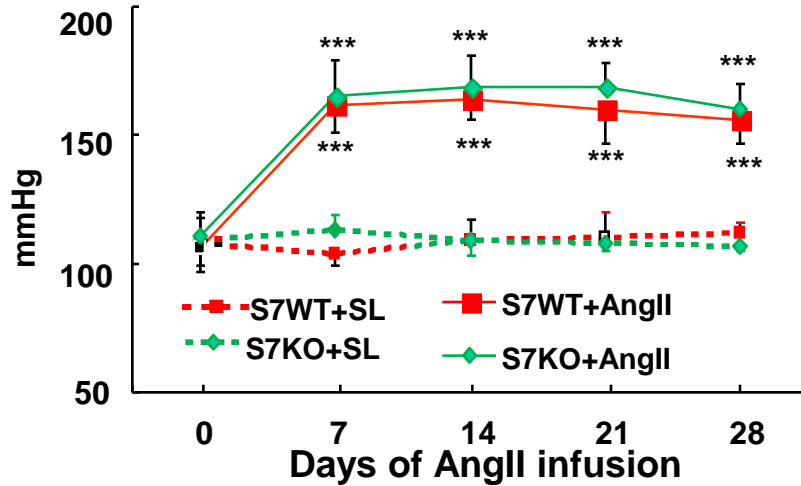


Relevant Publications

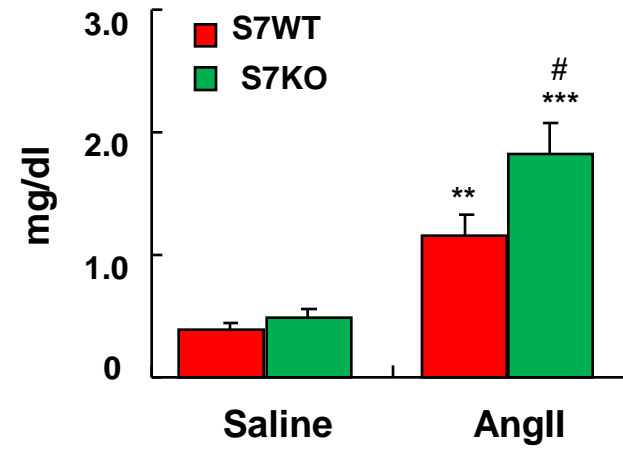
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39. Meng X et al: *Kidney Int* 81:266-79, 2012
40. Meng X et al: *J Pathol* 217:175-88, 2012

Deletion of Smad7 enhances hypertensive CKD in a mouse model of Ang II-induced hypertension

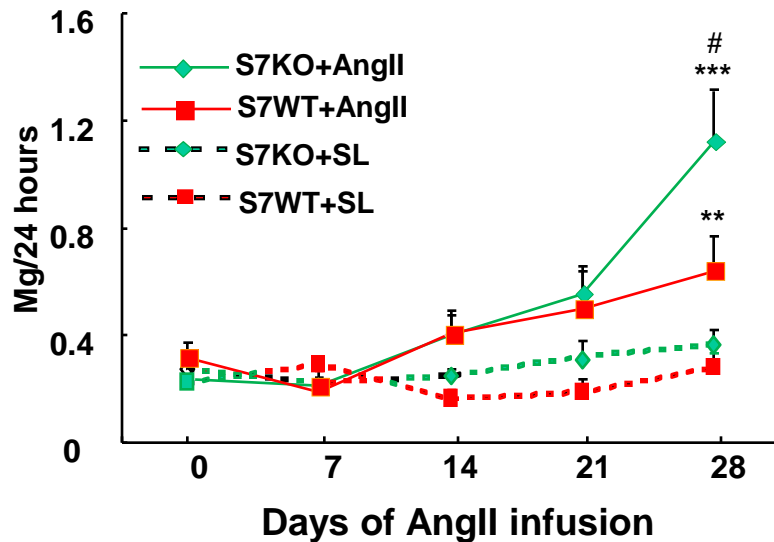
A. Blood Pressure



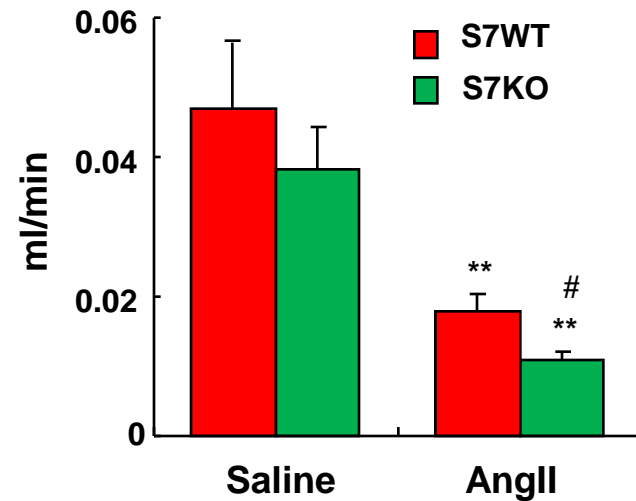
C. Serum Creatinine



B. Proteinuria

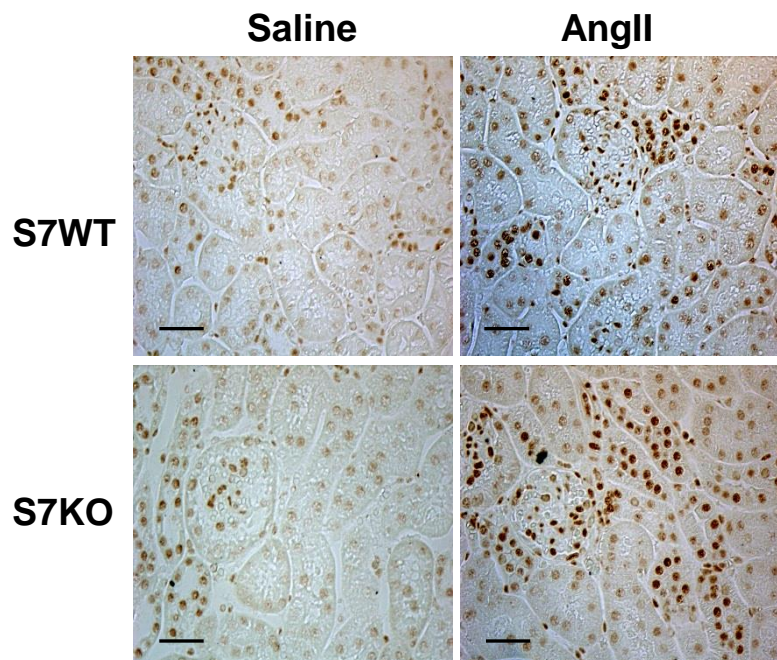


D. CCR

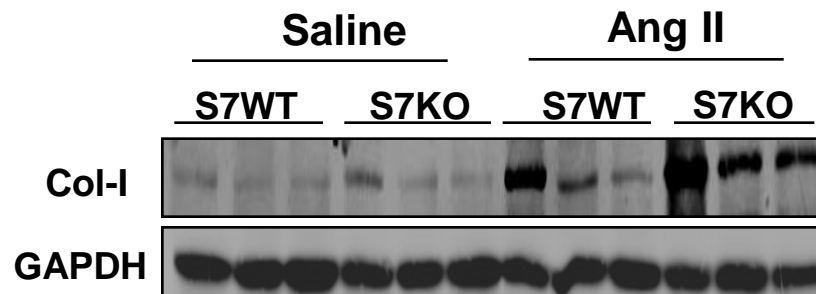
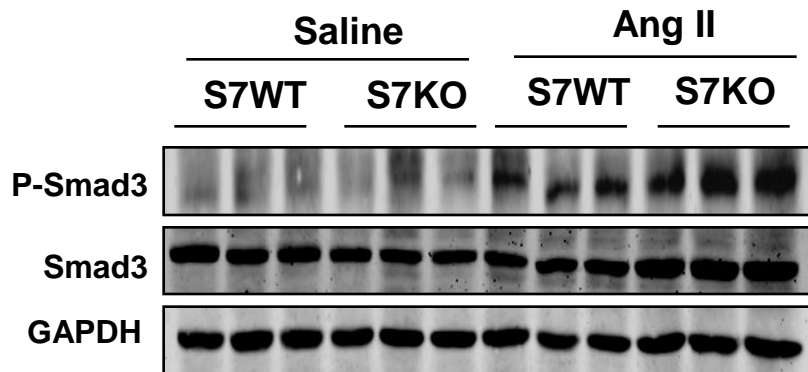
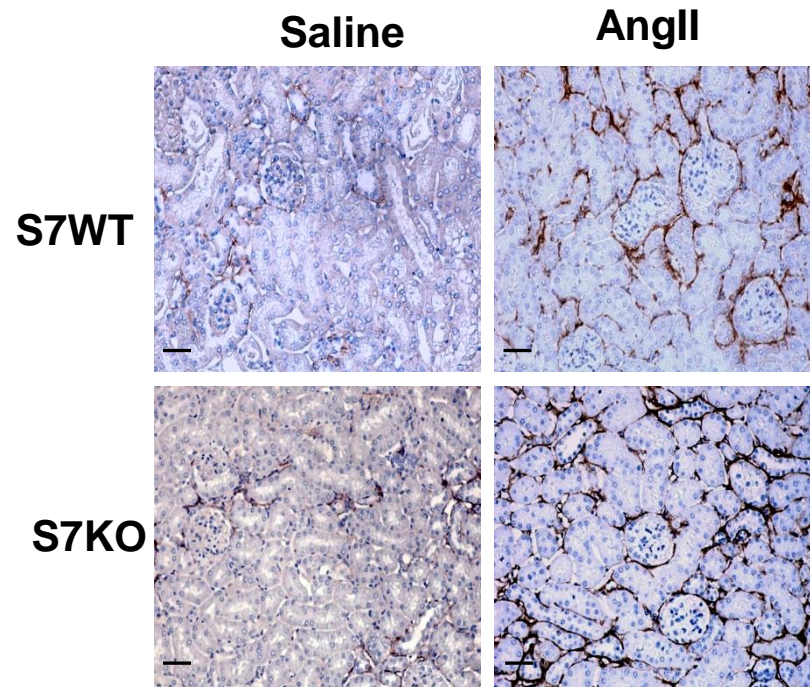


Disrupted Smad7 enhances AngII-induced Smad3 signaling and renal fibrosis in a mouse model of hypertension

Smad3 activation



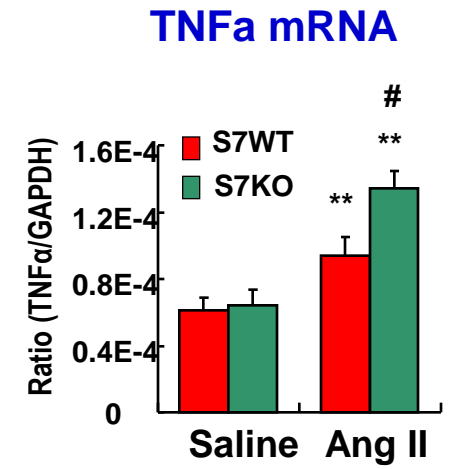
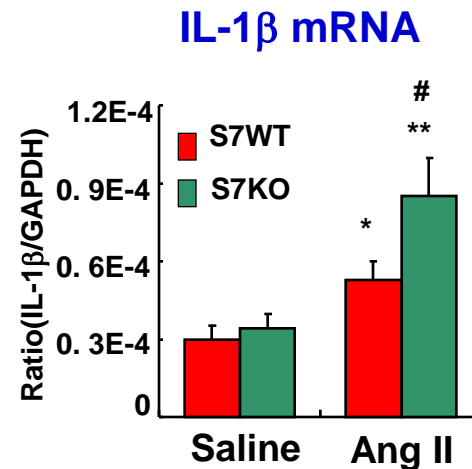
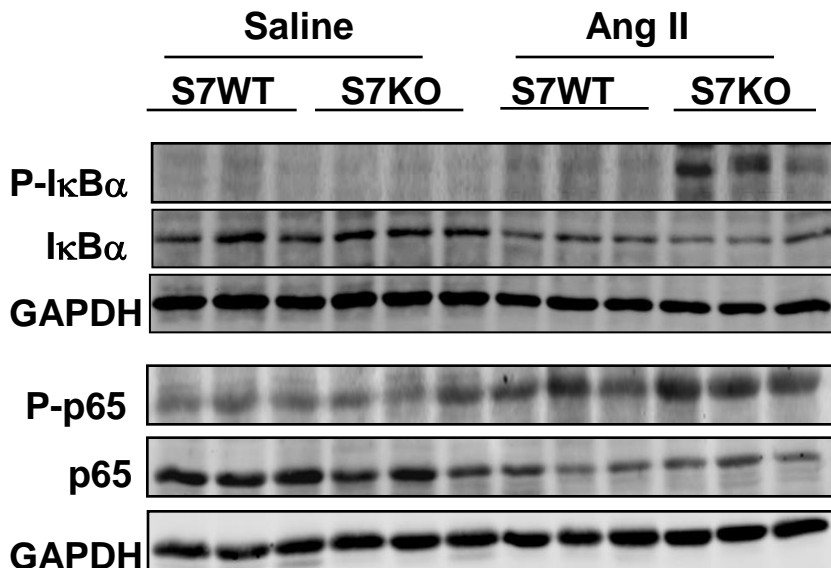
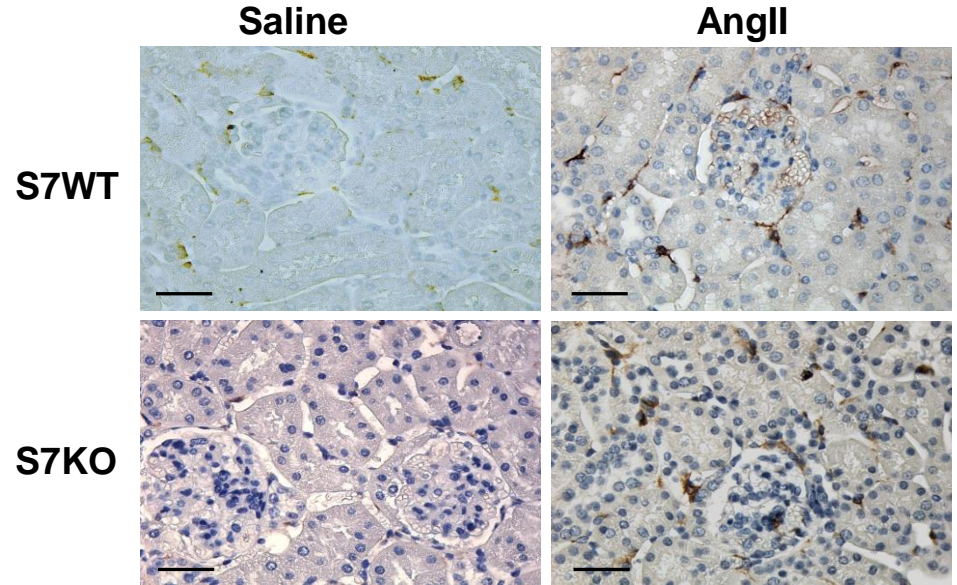
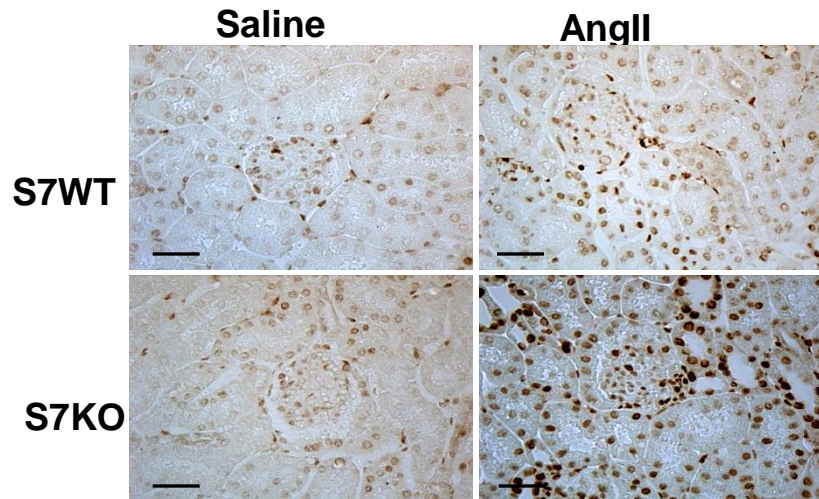
Collagen I expression



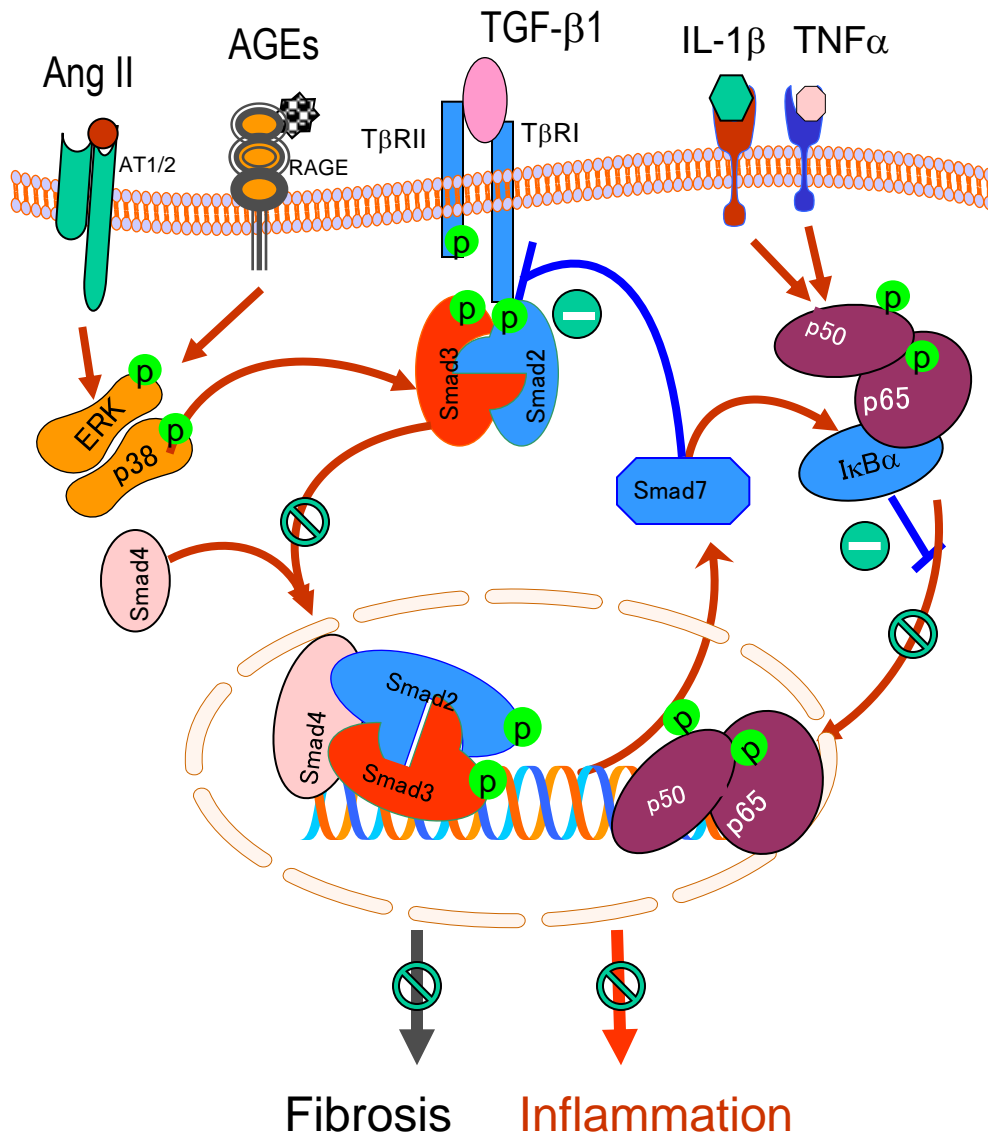
Disrupted Smad7 enhances AngII-induced NF- κ B signaling and renal inflammation in a mouse model of hypertension

NF- κ B Signaling

Macrophage infiltration



Q2: Can restored Smad7 inhibit hypertensive CKD and CVD?

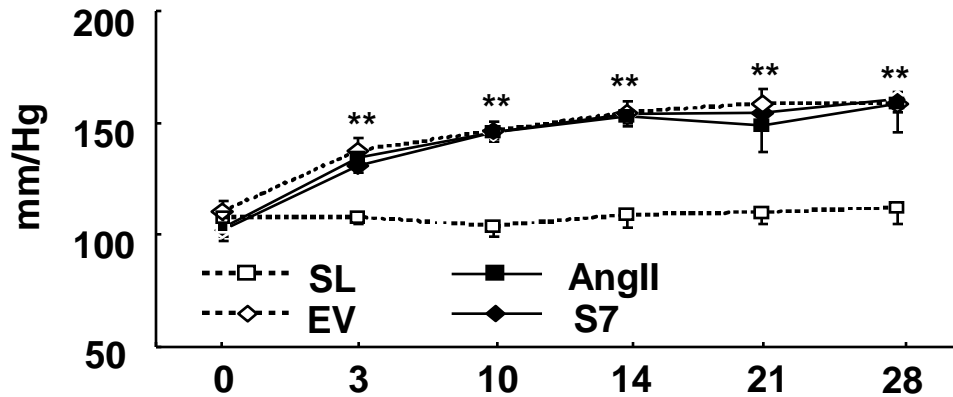


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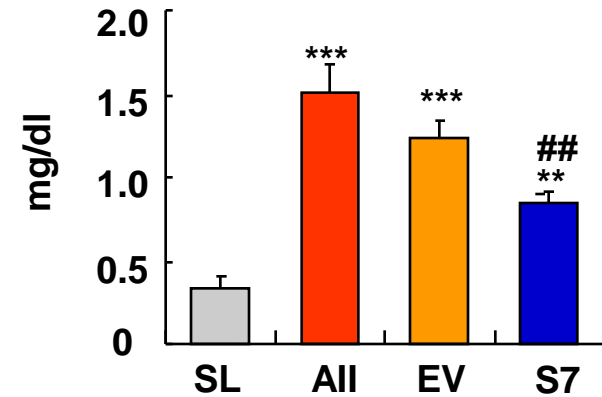
- ➔ 1. Li JH et al: *JASN* 13:1464-72, 2002
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Smad7 gene transfer inhibits hypertensive CKD in a mouse model of AngII-induced hypertension

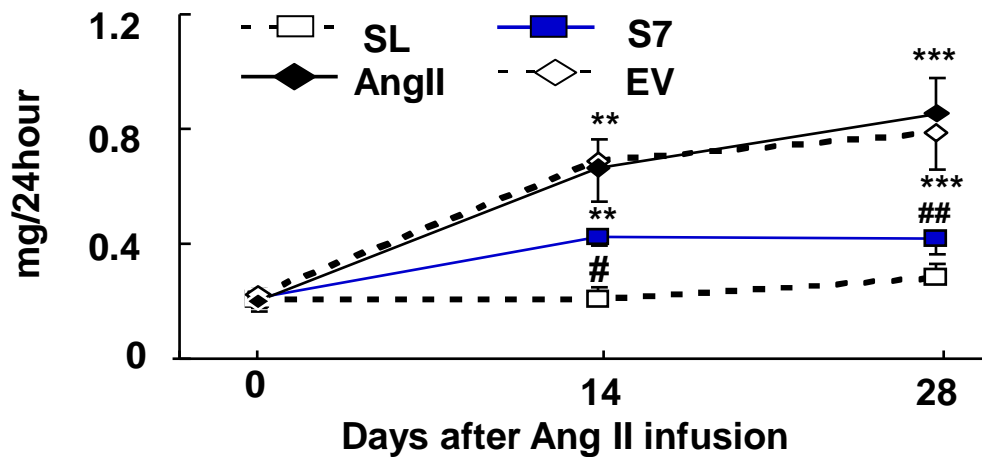
Blood Pressure



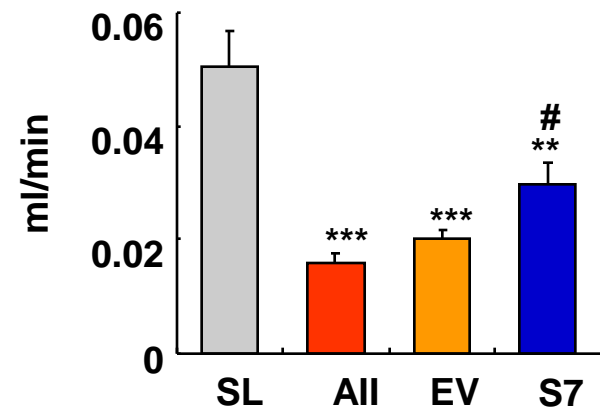
Serum creatinine



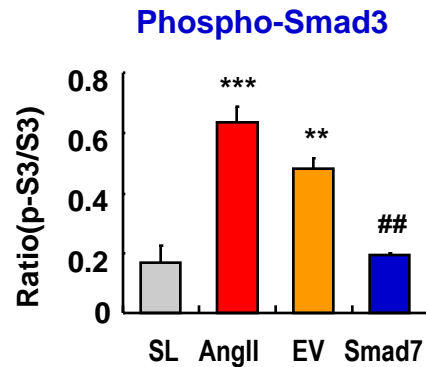
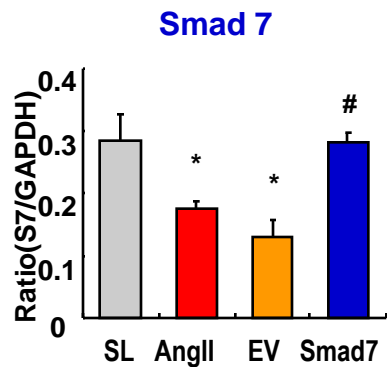
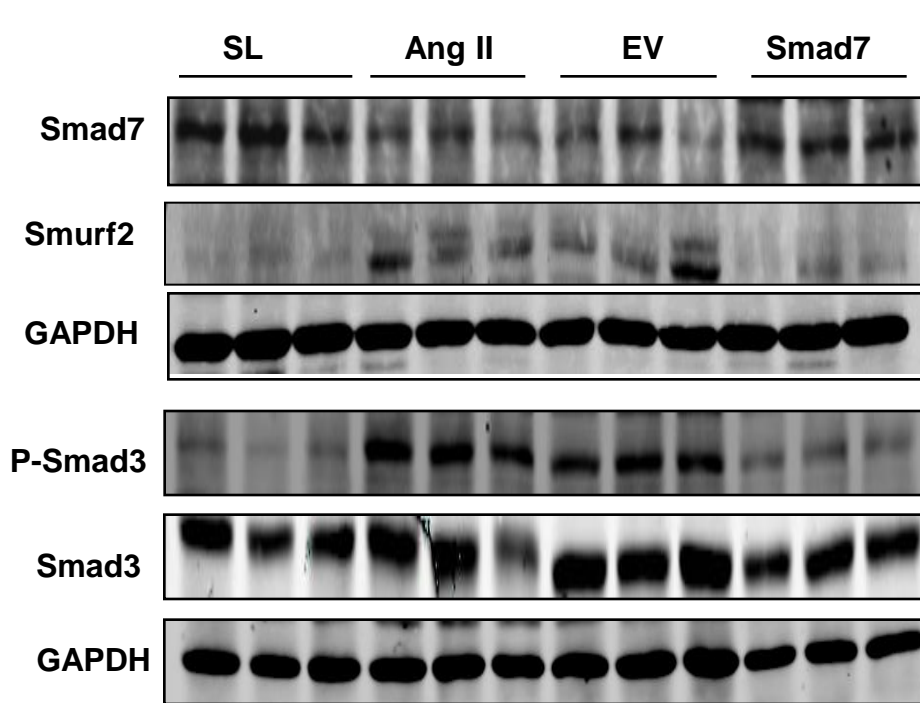
Proteinuria



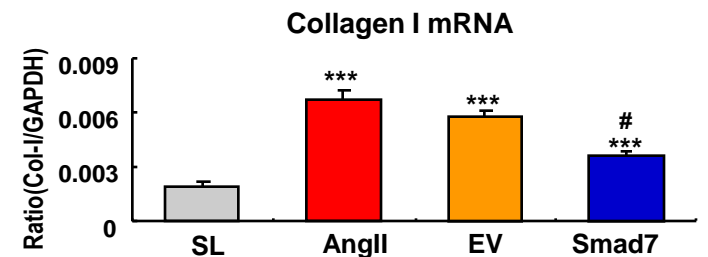
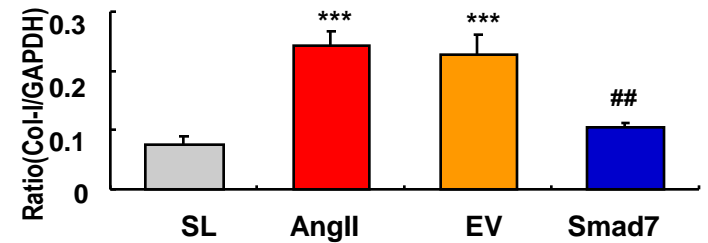
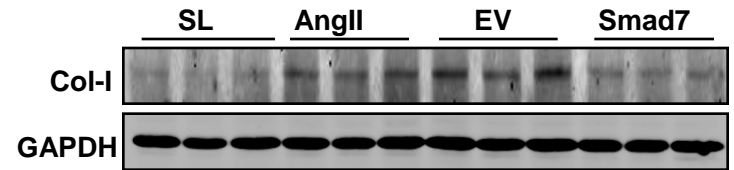
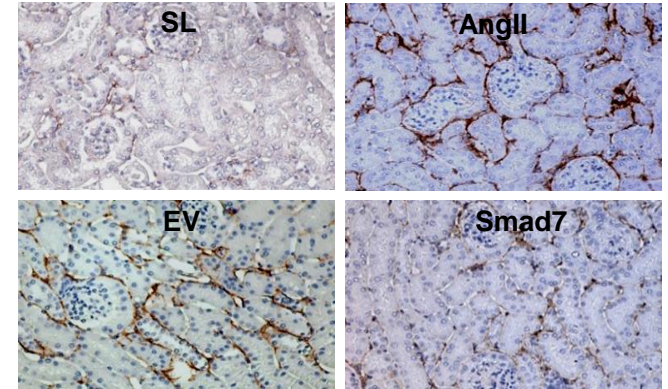
Creatinine clearance



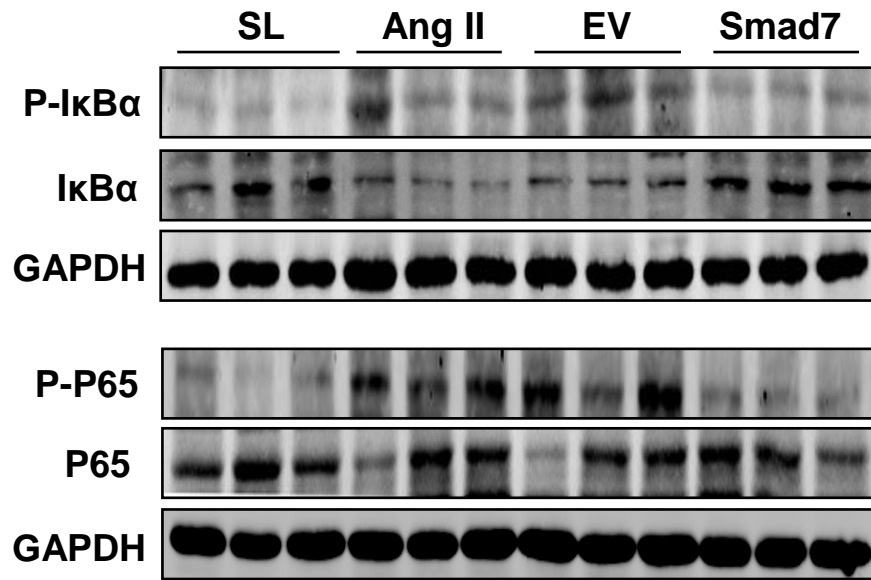
Overexpression of renal Smad7 blocks Smad3 signaling and fibrosis in a mouse model of AngII-induced hypertension



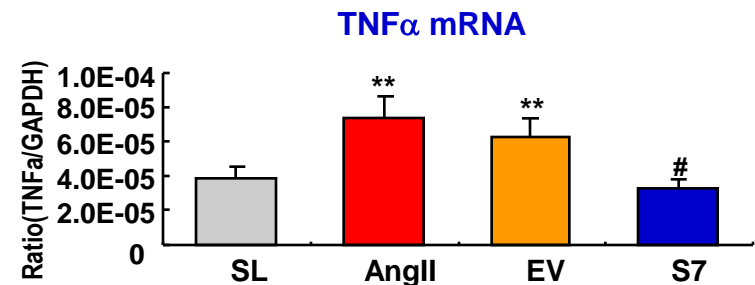
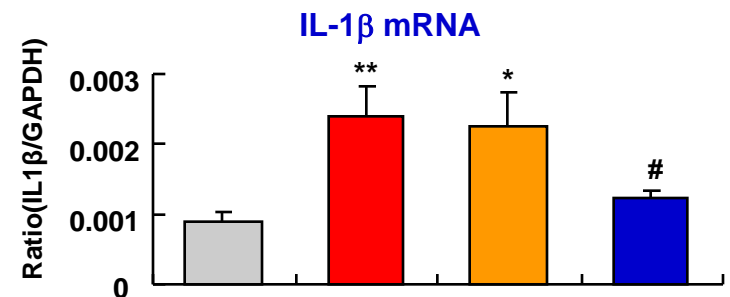
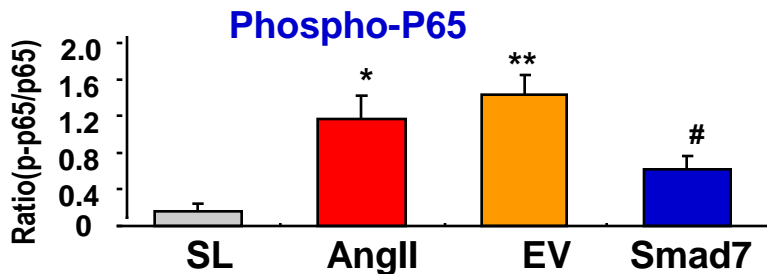
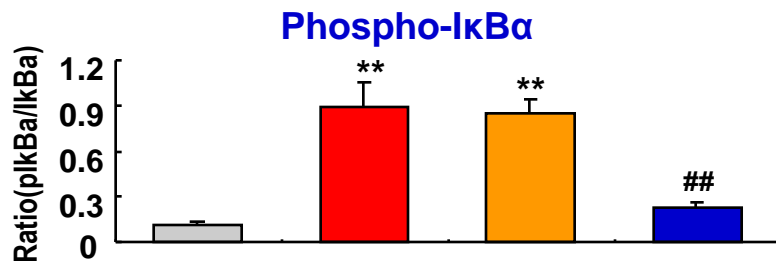
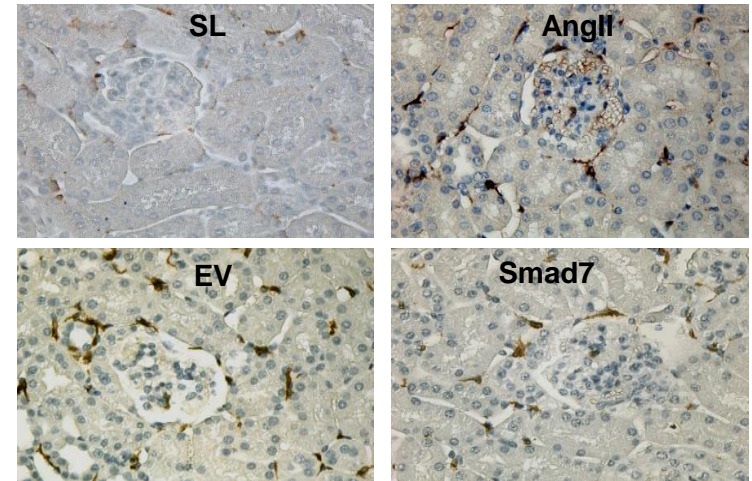
Collagen I expression



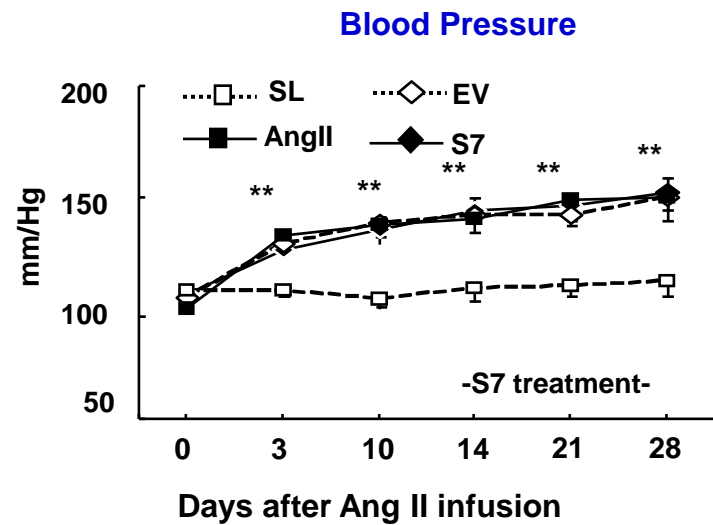
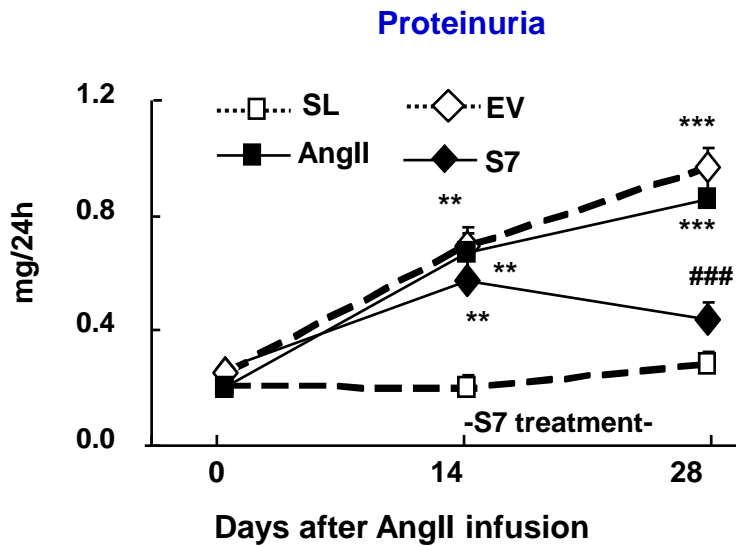
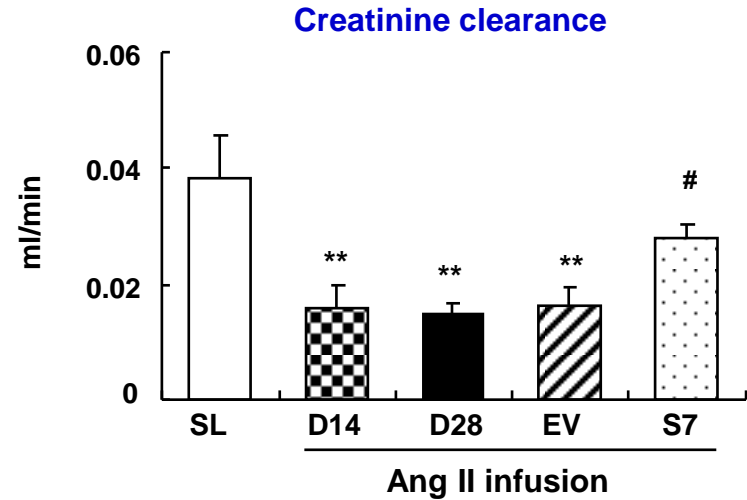
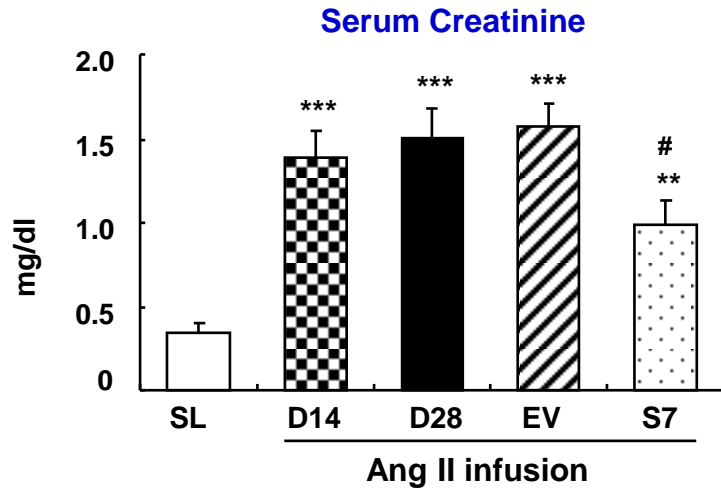
Overexpression of renal Smad7 blocks NF- κ B signaling pathways in a mouse model of hypertension



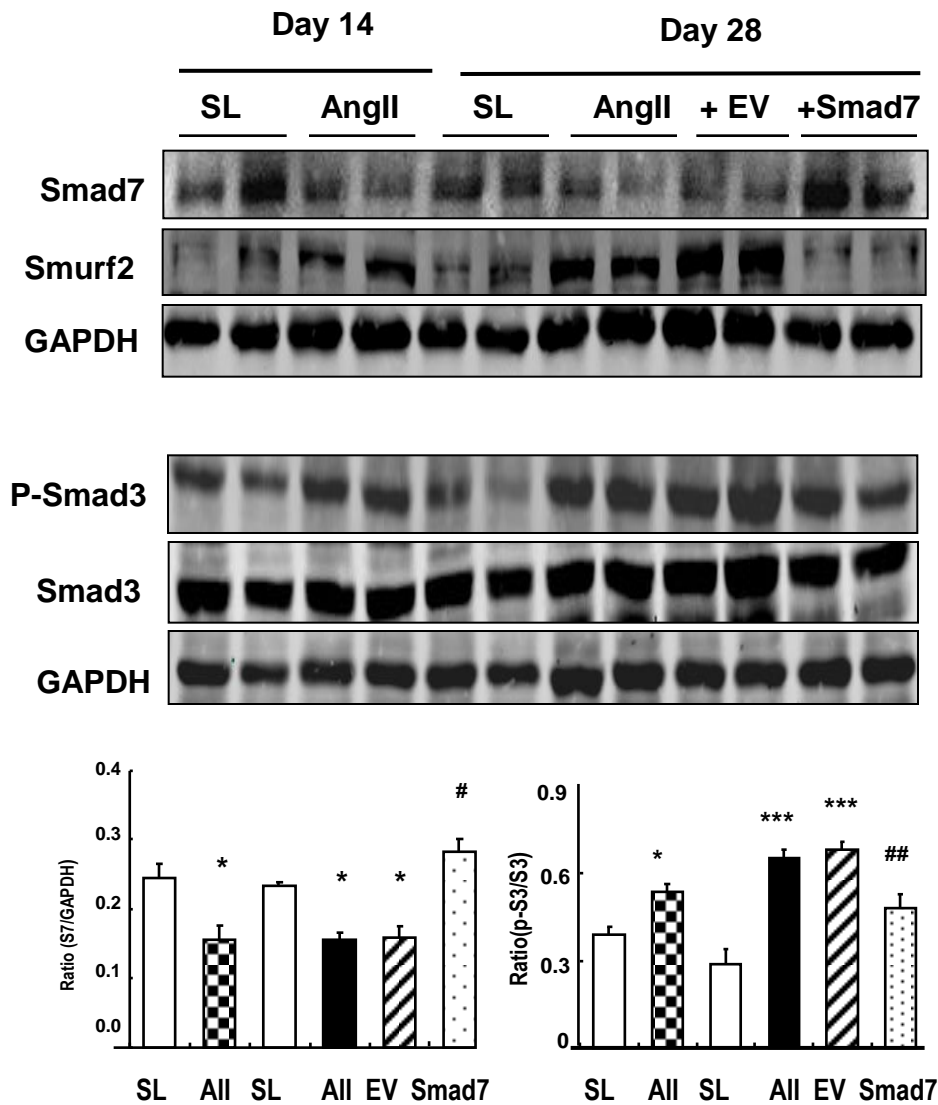
Macrophage infiltration



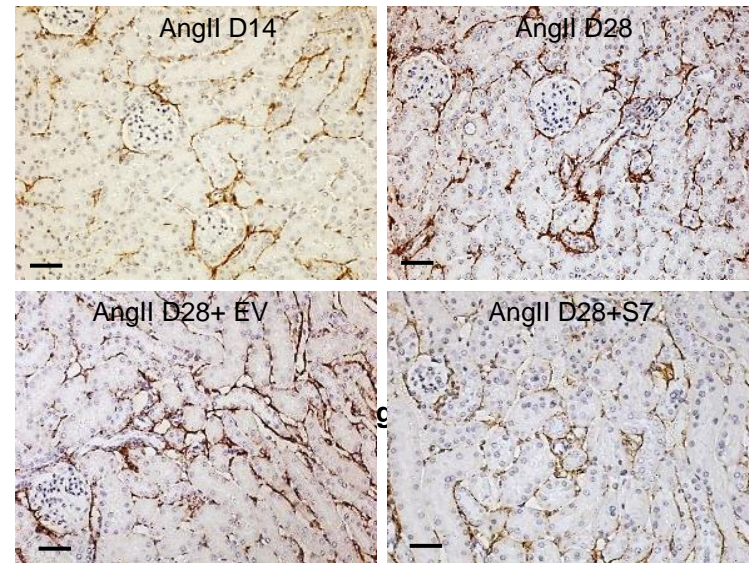
Smad7 treatment blocks progressive renal injury in established HTN



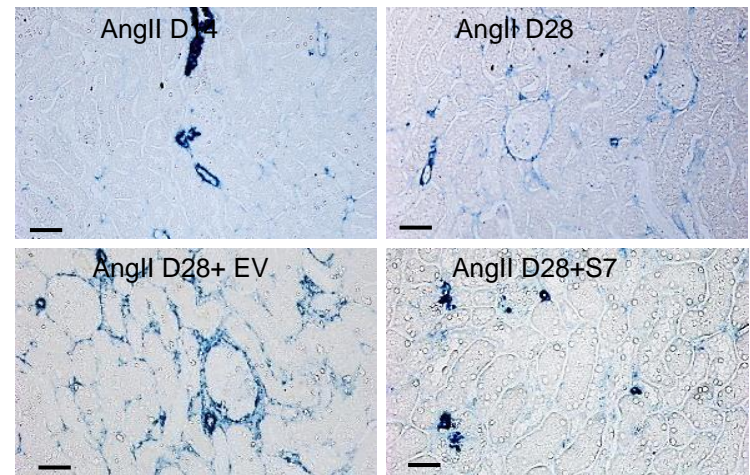
Smad7 treatment blocks Smad3-mediated renal fibrosis in established HTN



Collagen I expression



α -SMA+ myofibroblasts

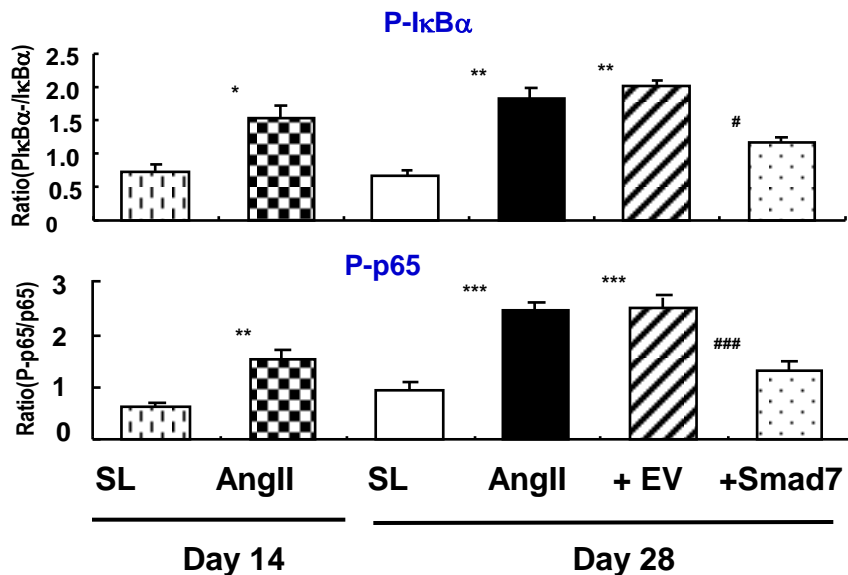
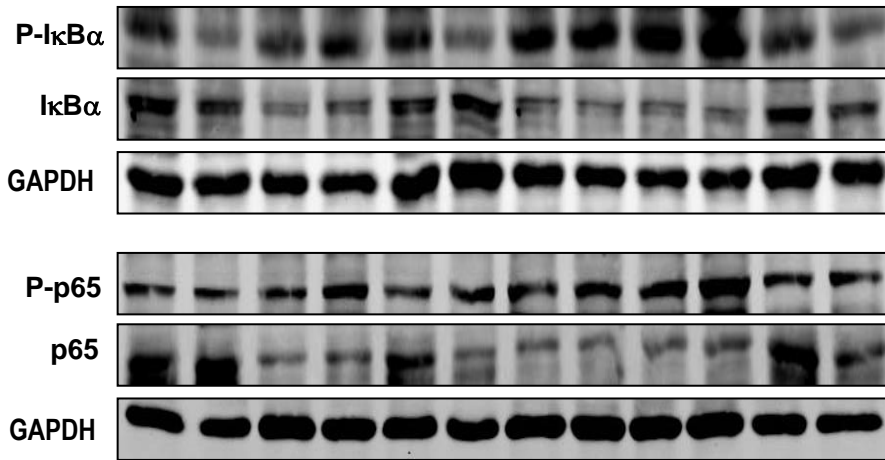


Smad7 treatment blocks NF- κ B-mediated renal inflammation in established HTN

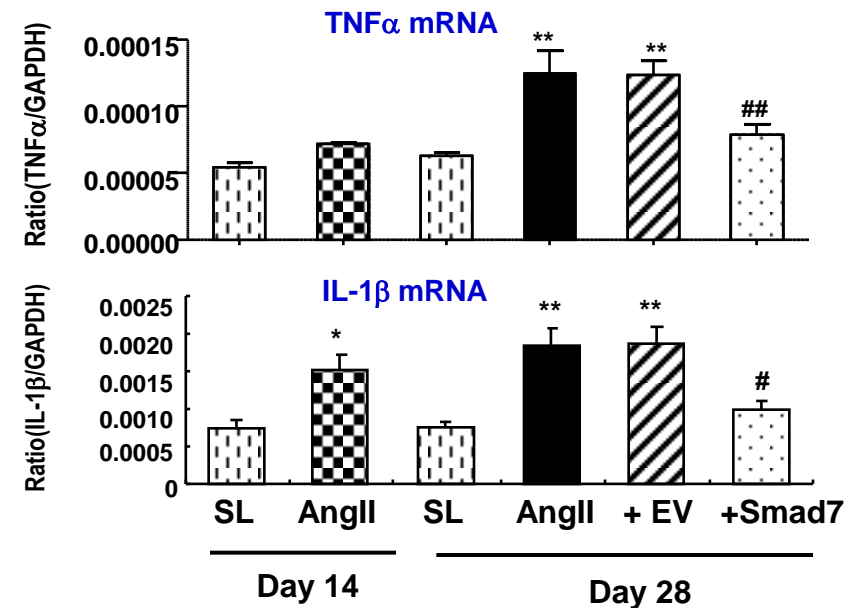
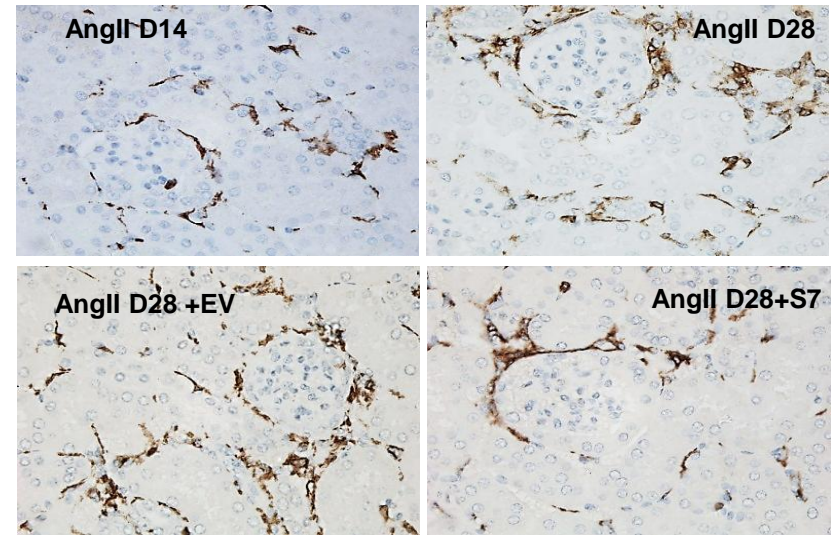
Day 14

Day 28

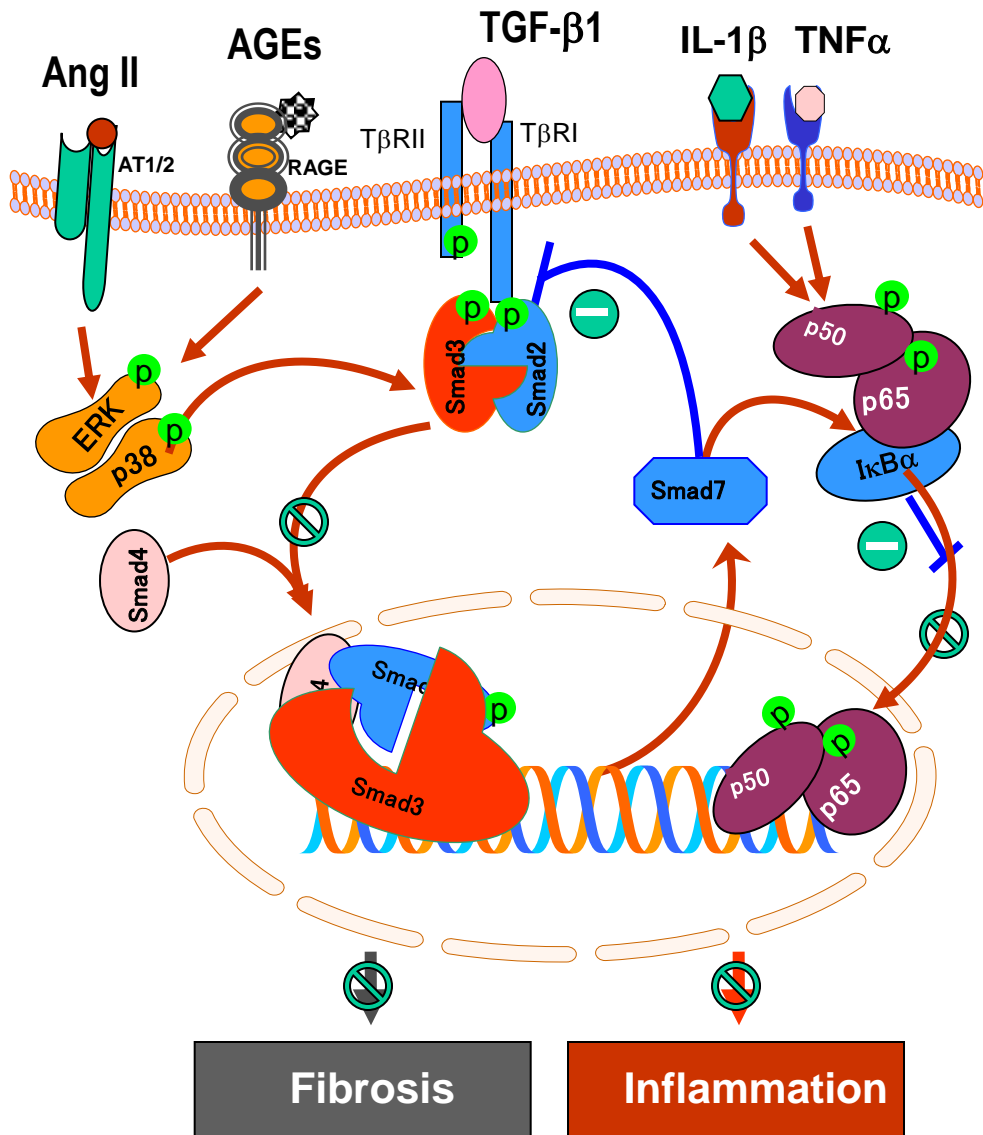
SL AngII SL AngII + EV +Smad7



Macrophage infiltration

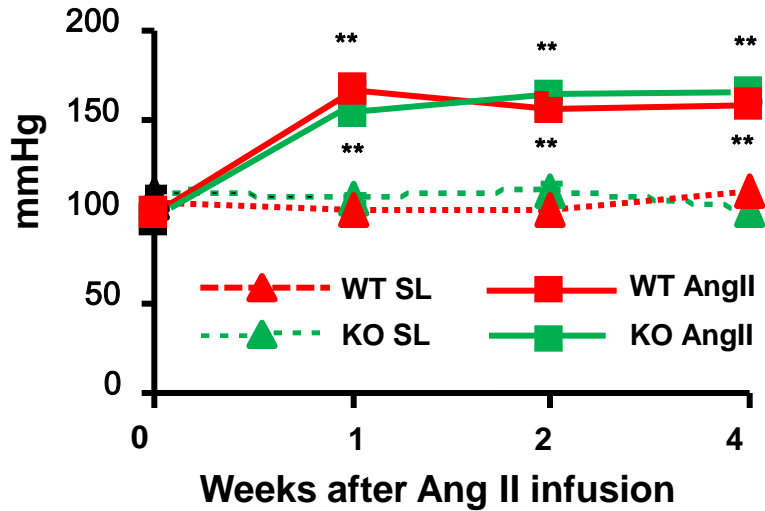


Q3. Is Smad3 a mediator in HTN?

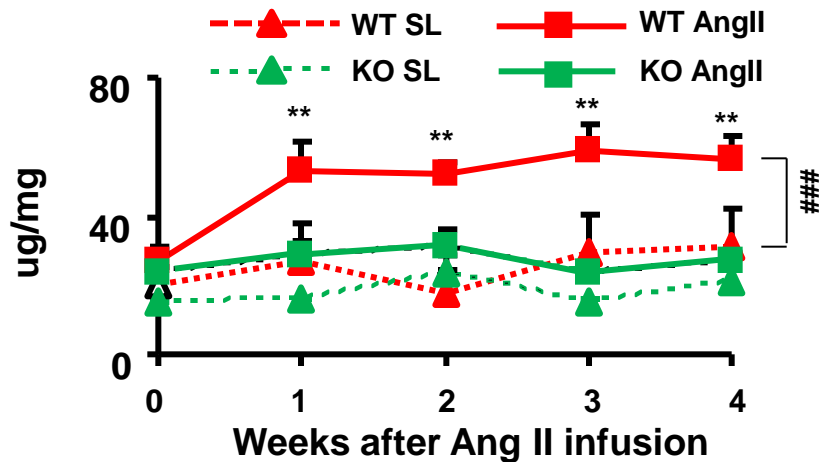


Disrupted Smad3 Prevents Ang II-induced HTN

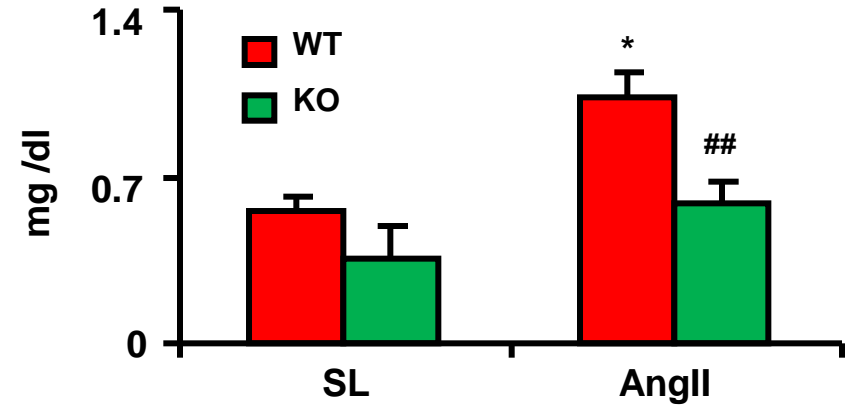
A. Blood pressure



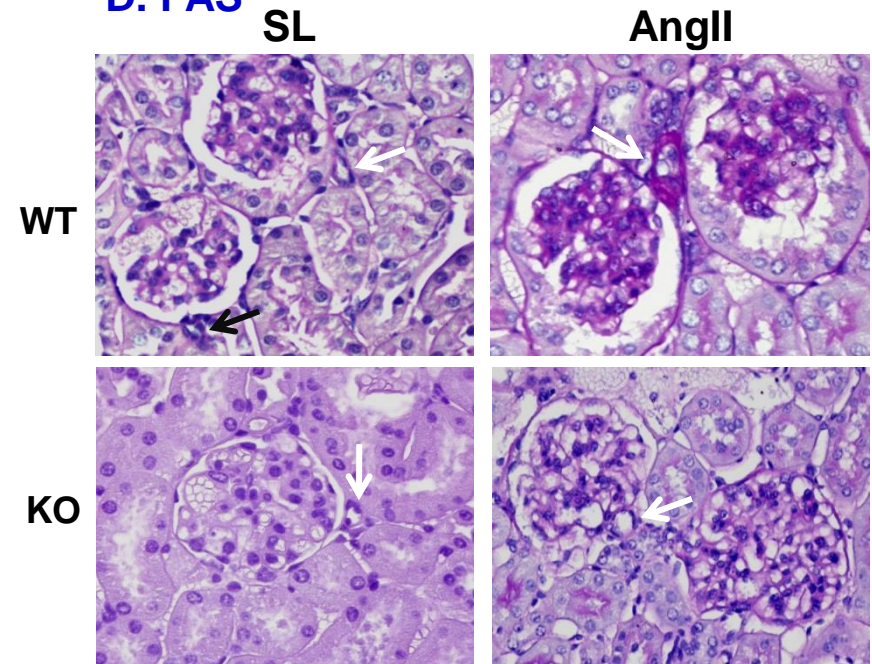
B. UAE



C. Serum creatinine

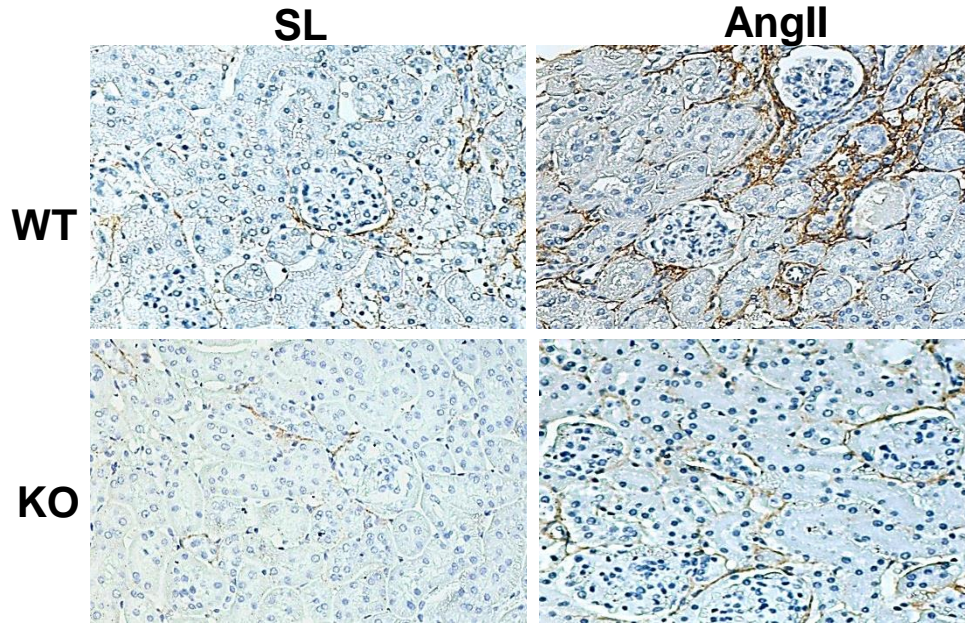


D. PAS

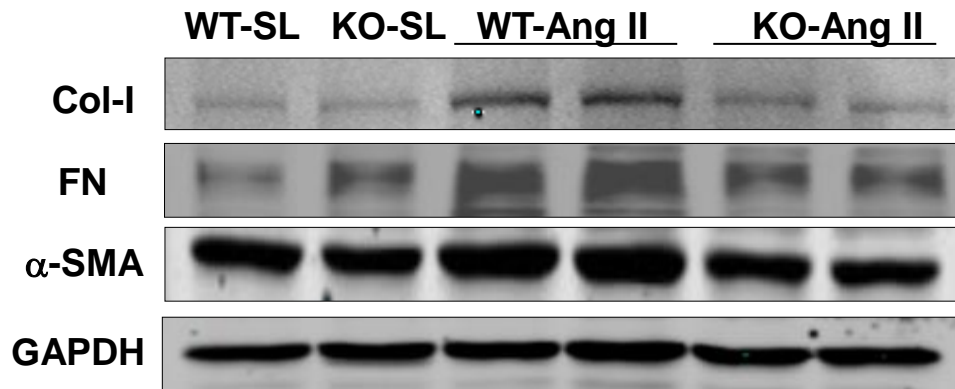


Disrupted Smad3 Prevents Ang II-Mediated renal fibrosis

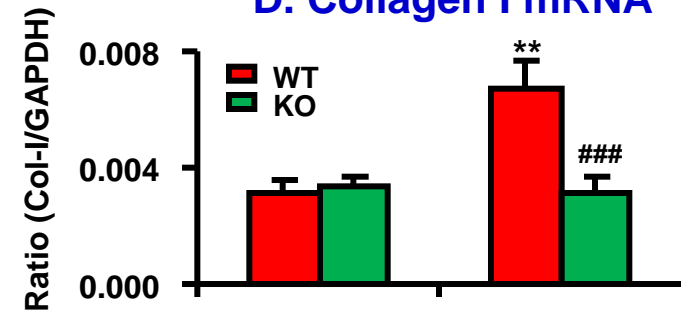
A. Collagen I immunohistochemistry



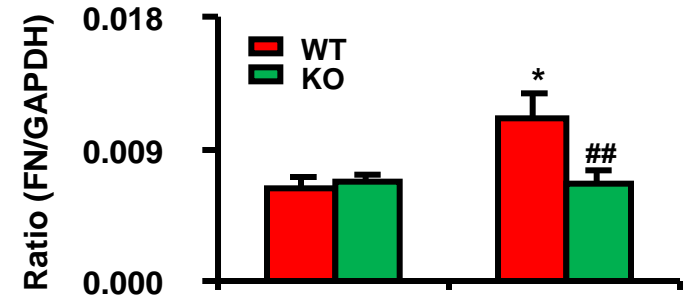
B. Western blots



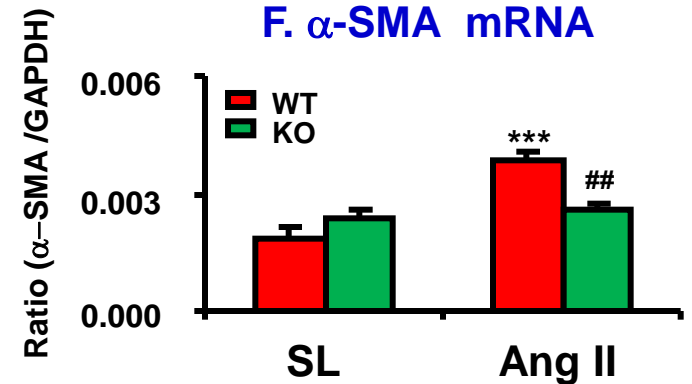
D. Collagen I mRNA



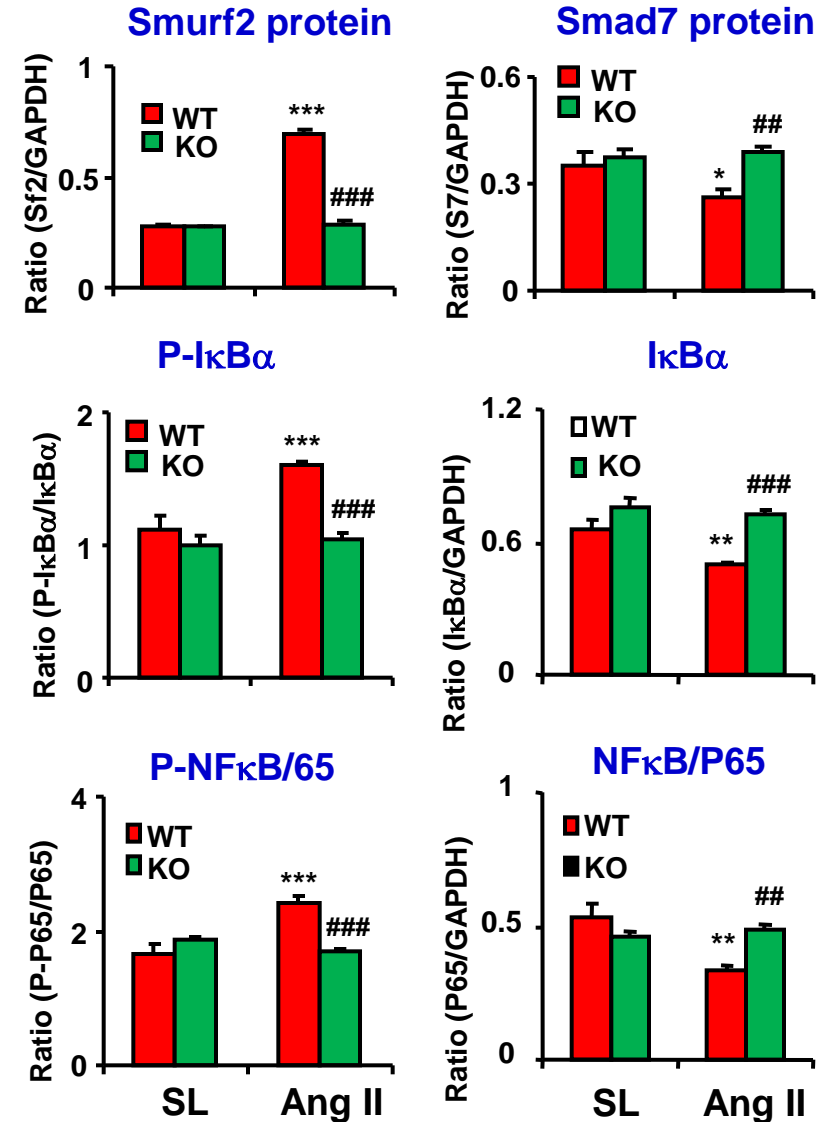
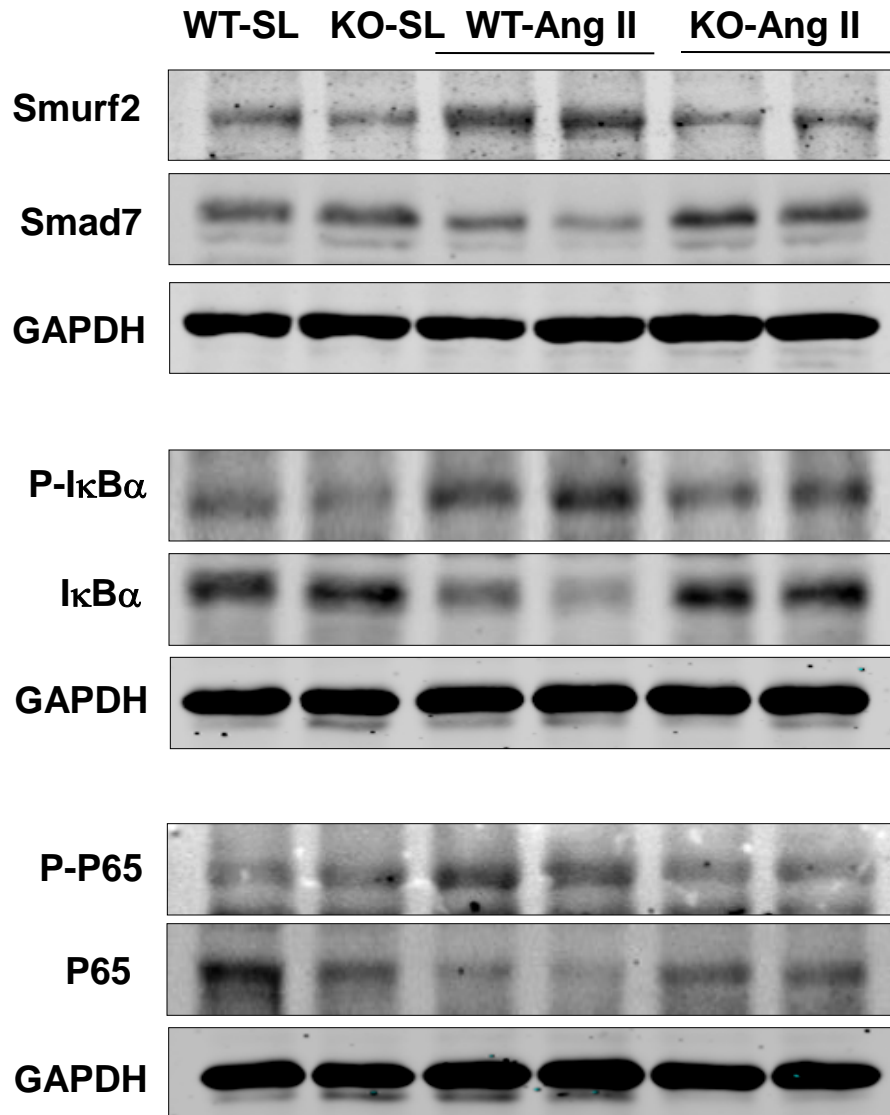
E. FN mRNA



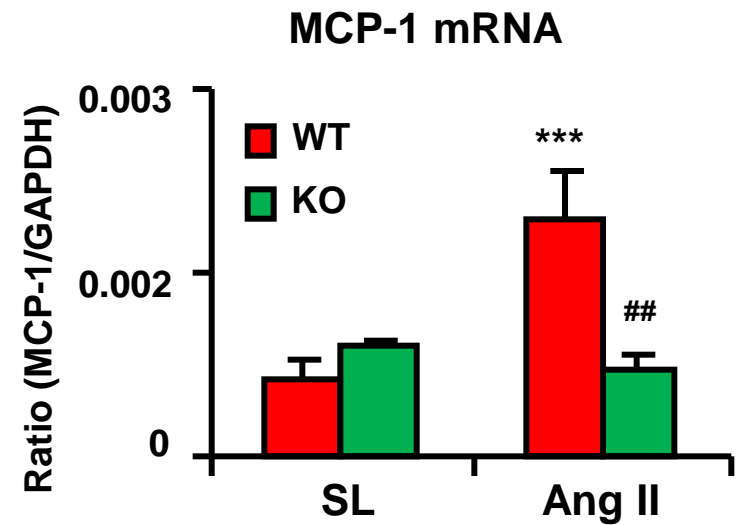
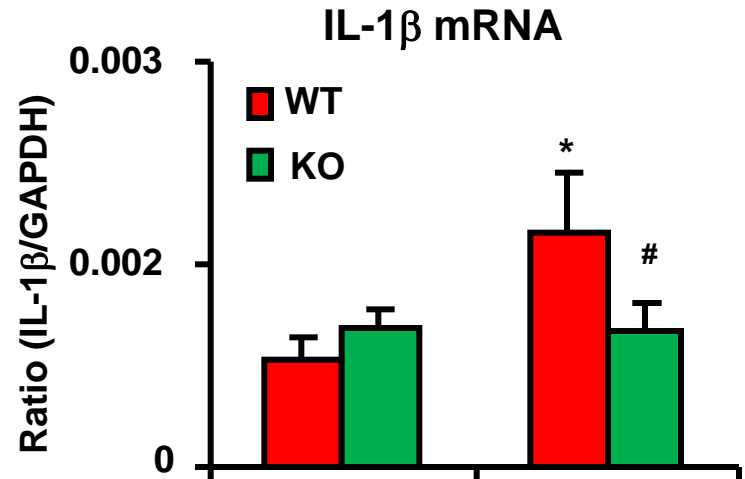
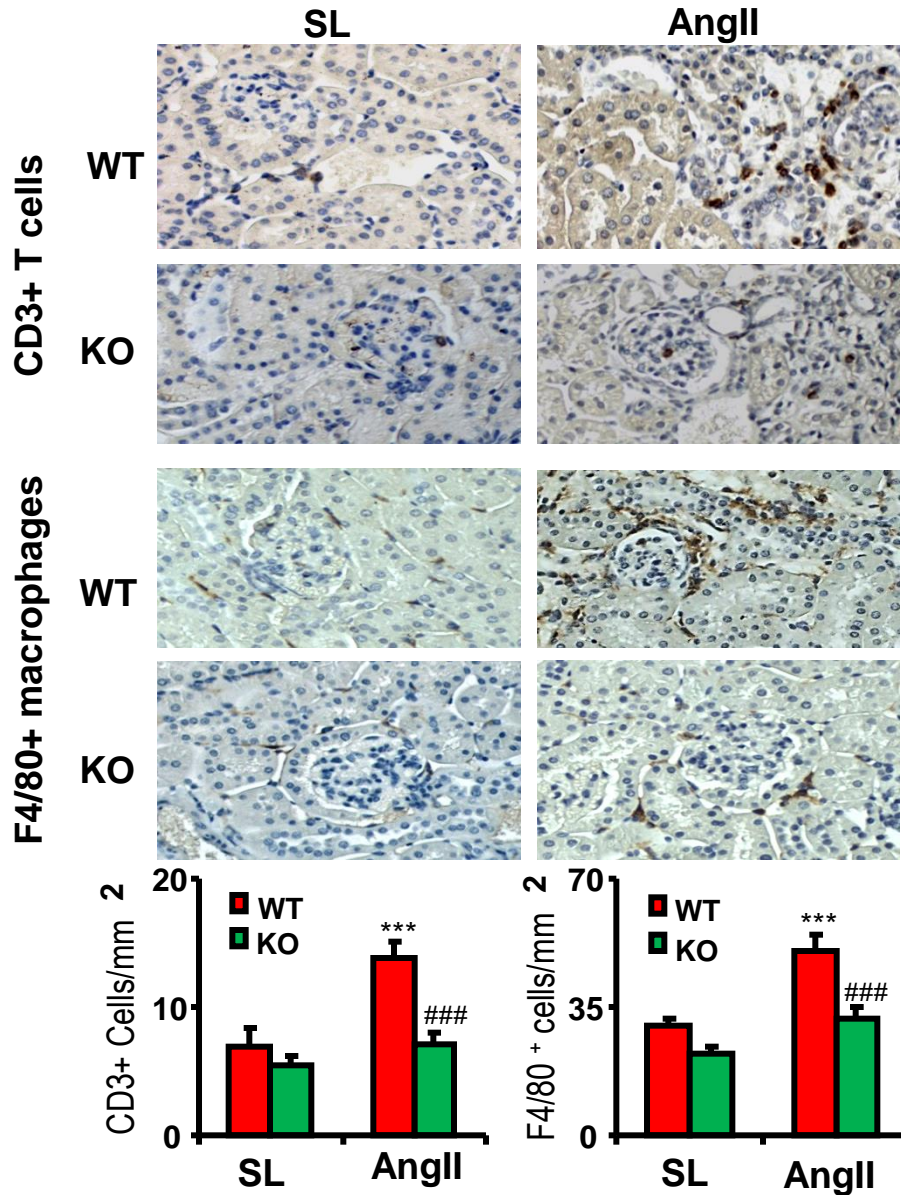
F. α -SMA mRNA



Disrupted Smad3 inhibits NF- κ B signaling by blocking Smurf2-mediated Smad7 degradation in HTN

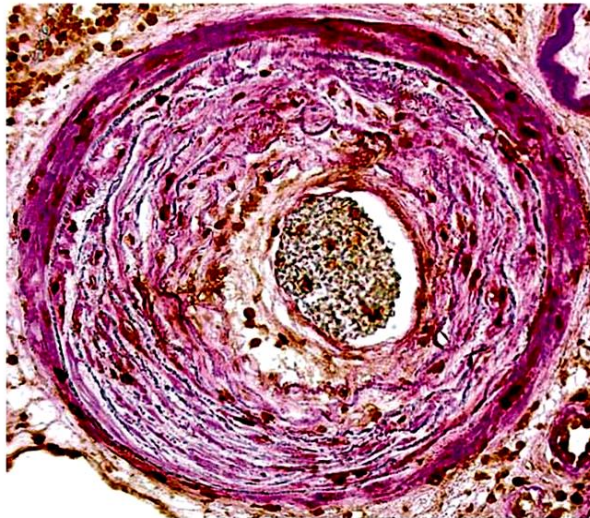


Disrupted Smad3 Prevents Renal Inflammation in HTN



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Essential Role of Smad3 in Angiotensin II–Induced Vascular Fibrosis

Wang, et al:

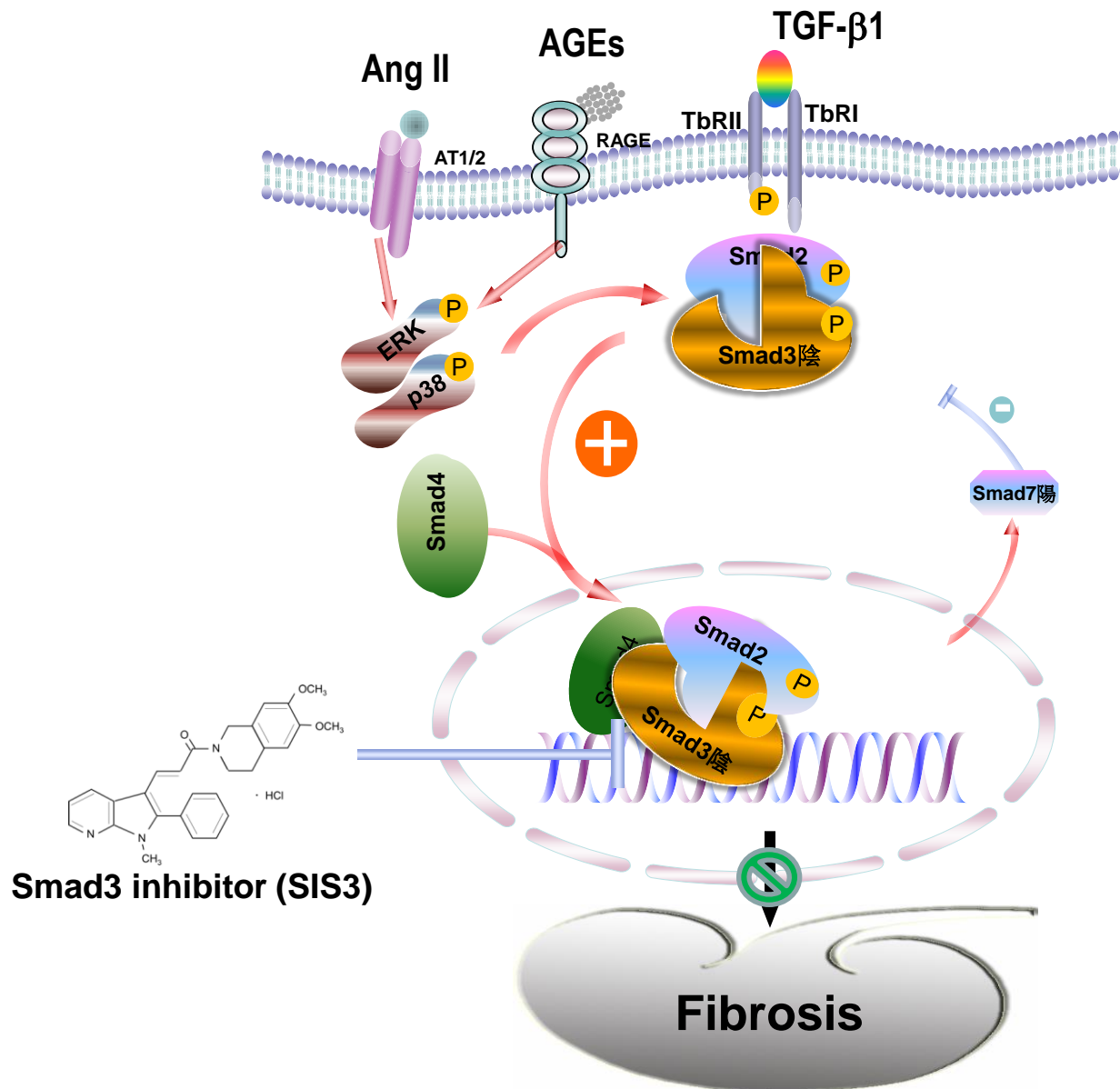
Circ. Res. 2006 April 28;98:1032-9

Editorial by: D. Sorescu

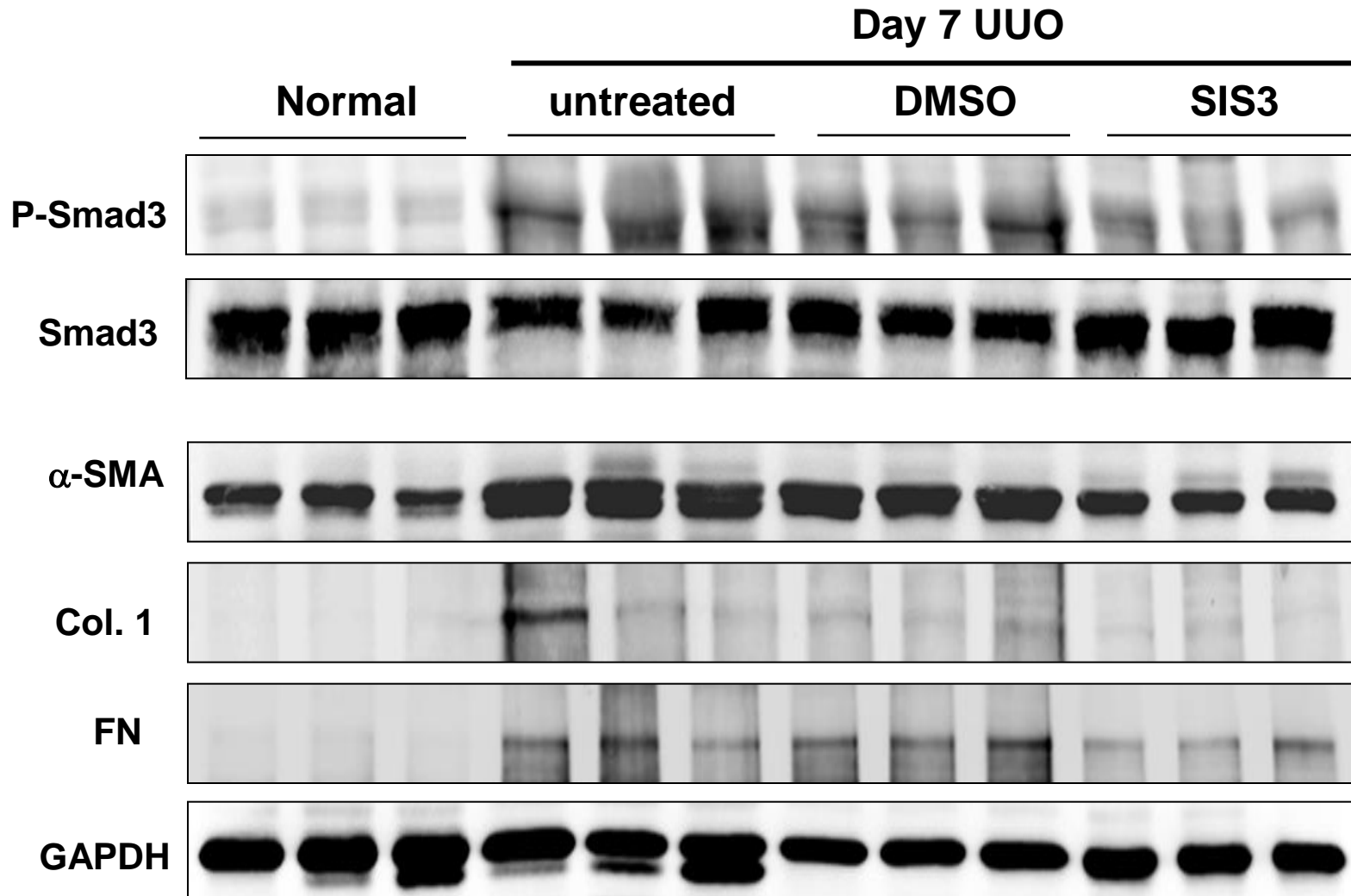
Smad3 Mediates Angiotensin II- and TGF- β 1-Induced Vascular Fibrosis: Smad3 Thickens the Plot

Circ. Res., April 28, 2006; 98(8): 988
- 989.

Q4: Can re-balancing Smad signaling by inactivating Smad3 signaling inhibit renal fibrosis?

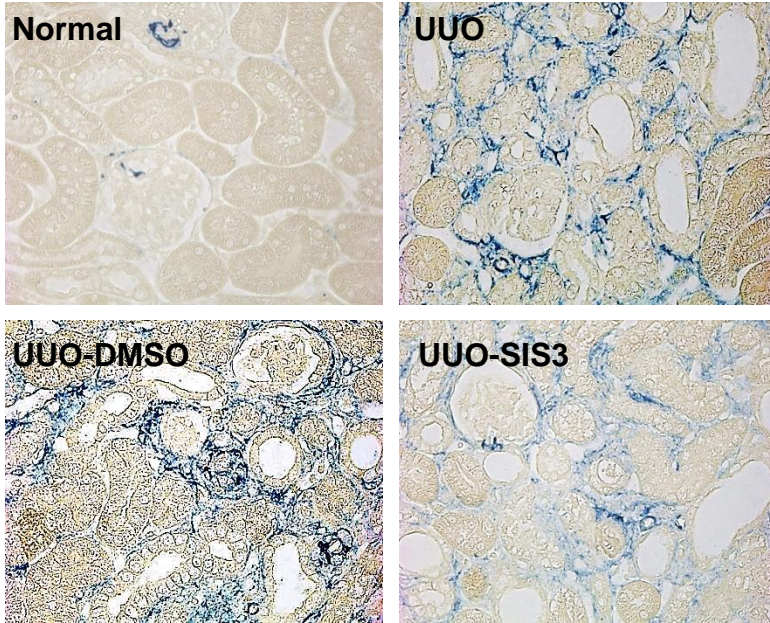


Smad3 inhibitor (SIS3) inhibits renal fibrosis in the UUO kidney

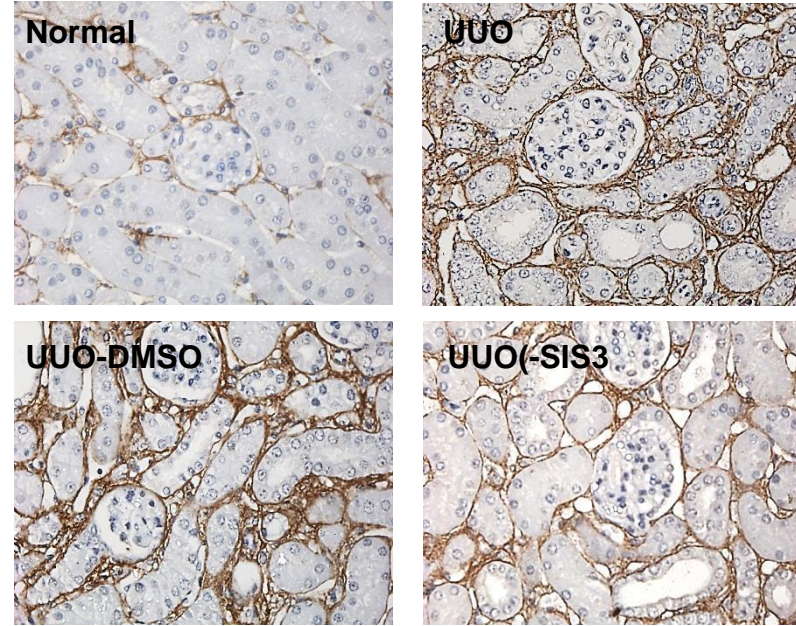


Smad3 inhibitor (SIS3) inhibits renal fibrosis in UUO

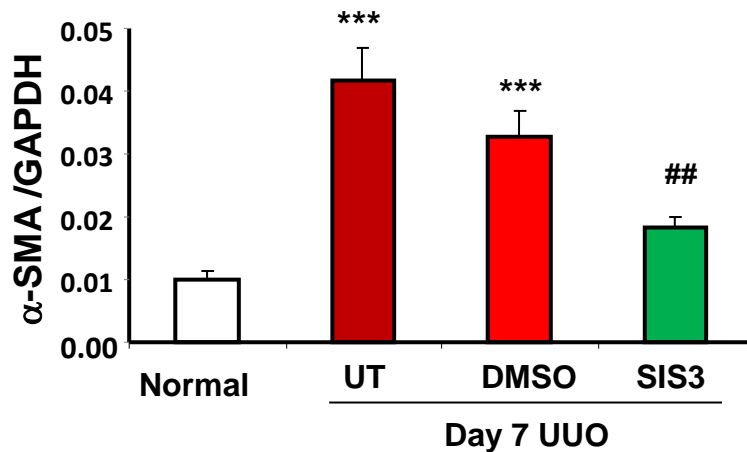
α -SMA



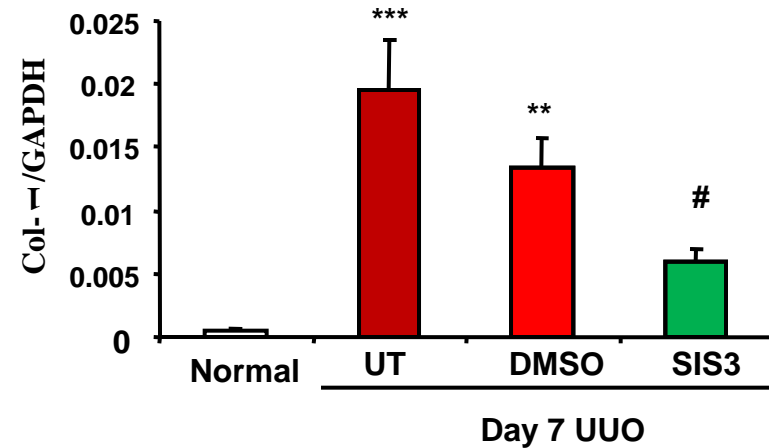
Collagen I



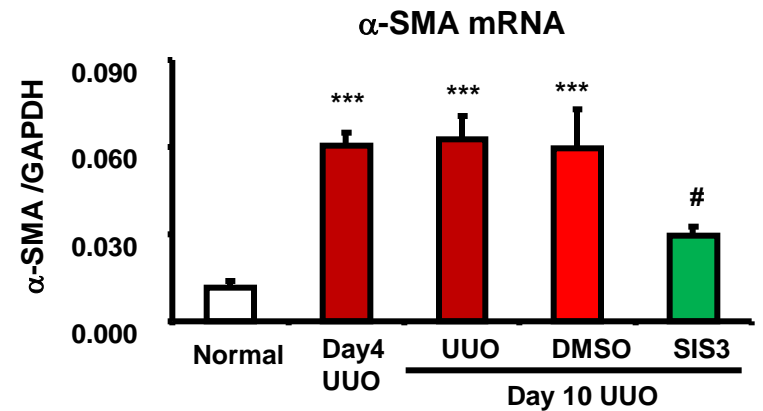
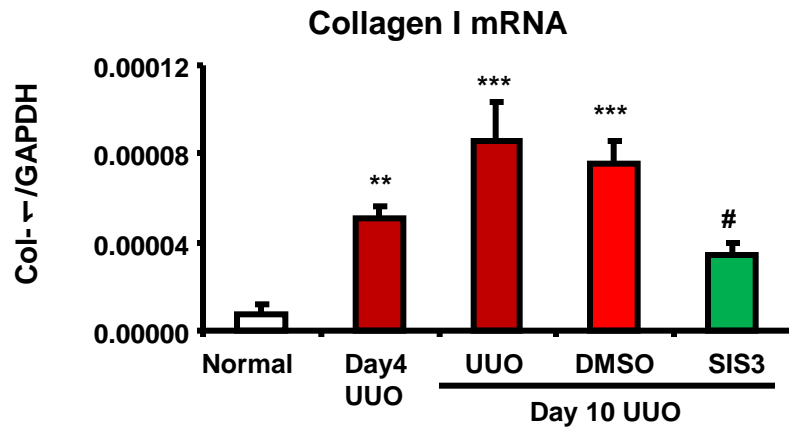
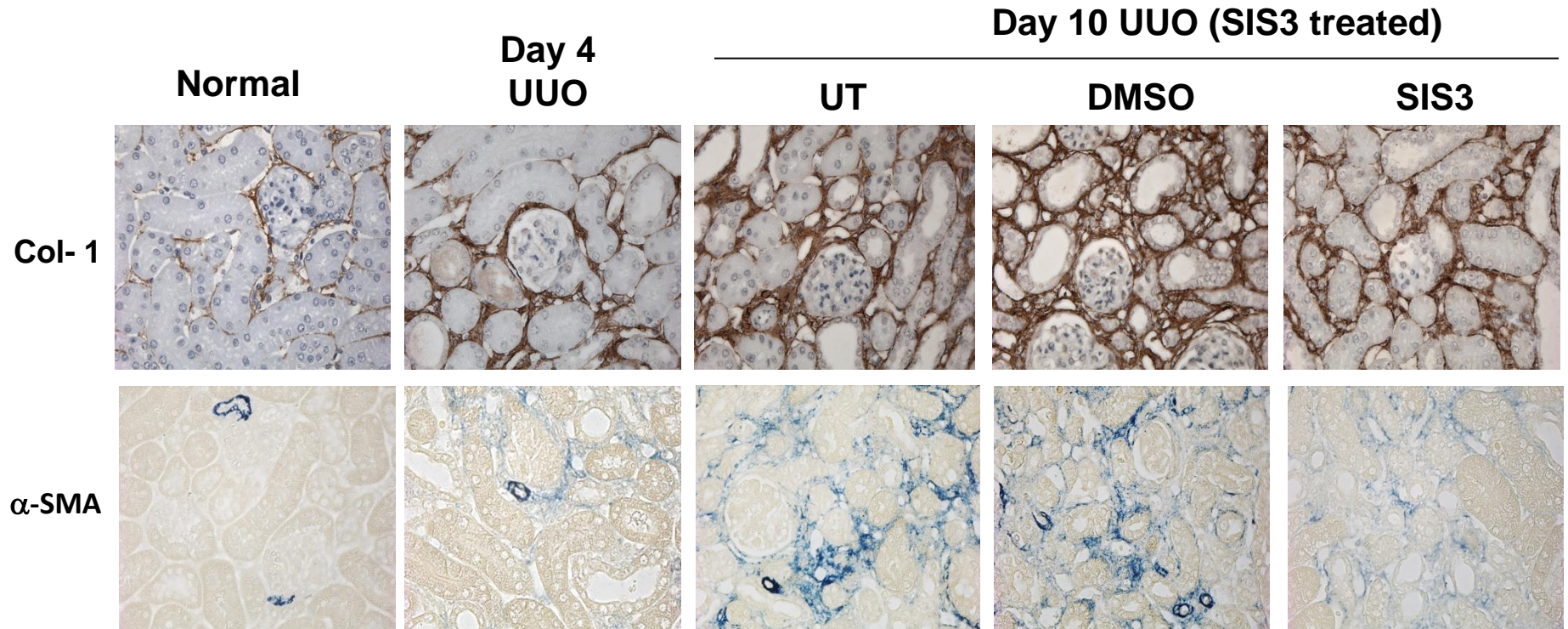
mRNA



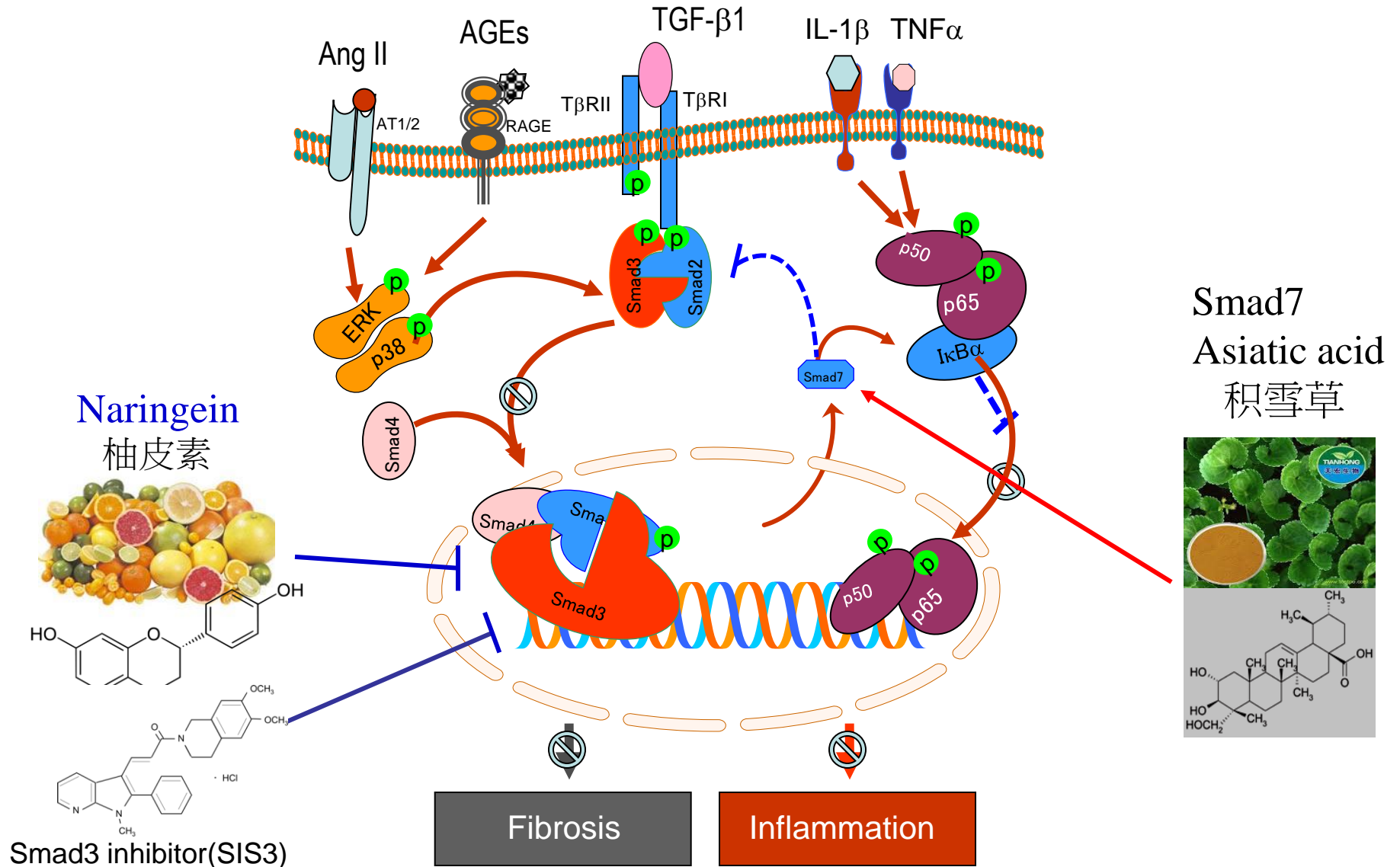
mRNA



Smad3 inhibitor halts renal fibrosis in the established UUO kidney



Rebalancing SMAD signaling by inhibiting Smad3 while activating Smad7 may be a new and specific treatment for CKD





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