Constitutive activation of PDGFR-β in renal mesenchymal cells drives renal fibrosis

Eva Miriam Buhl[1,2], Sonja Djudjaj[1], Barbara Mara Klinkhammer[1], Erawan Borkham-Kamphorst[3], Ralf Weiskirchen[3], Lorin E. Olson[4], Jürgen Floege[2], Peter Boor[1,2]

[1] Pathology, [2] Nephrology, [3] Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry, RWTH University of Aachen, Germany,
[4]Cardiovascular Biology Program, Oklahoma Medical Research Foundation, Oklahoma City, USA

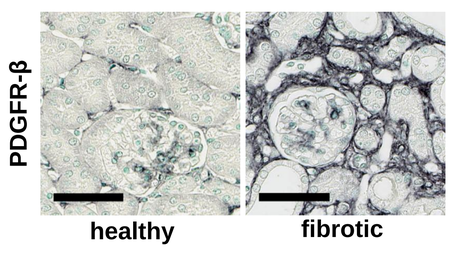
Introduction

- PDGFR-β is expressed on all renal mesenchymal cells
- PDGFR-β is upregulated in renal fibrosis

(reviewed in Boor et al., NDT 2014)

- FoxD1 is expressed in progenitors of renal mesenchymal cells

(reviewed in Gomez and Duffield, Kidney Int. 2014)



AIM: What is the consequence of PDGFR-β activation in the kidney?

Summary & Conclusion

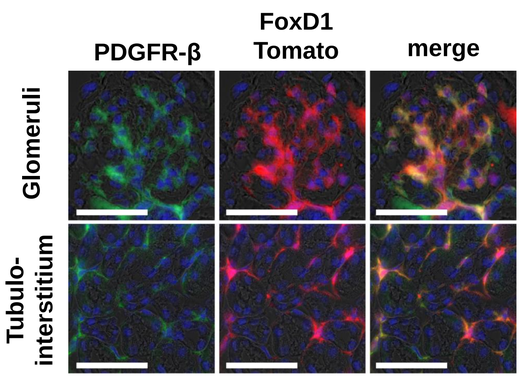
PDGFR-β activation in the FoxD1 lineage of renal mesenchymal cells leads to:

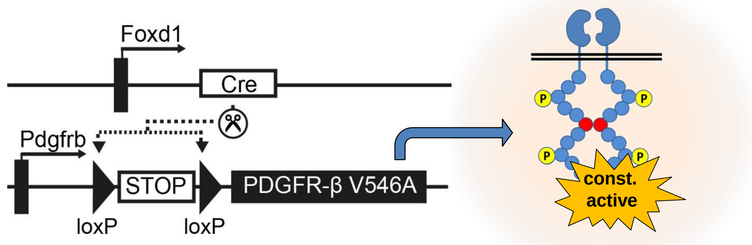
- mesenchymal proliferation & profibrotic activation
- mildly decreased kidney function and secondary tubular injury
- decreased EPO production and anemia
- aggravated fibrosis in injury models
- fibrosis, which is reversible using PDGFR-β inhibitor (TKI - imatinib)

Constitutive activation of PDGFR-β in renal mesenchymal cells is sufficient to drive progressive renal fibrosis.

Methods & Results

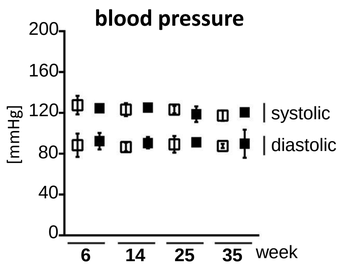
FoxD1-βJ mutant mouse

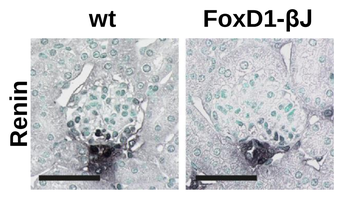




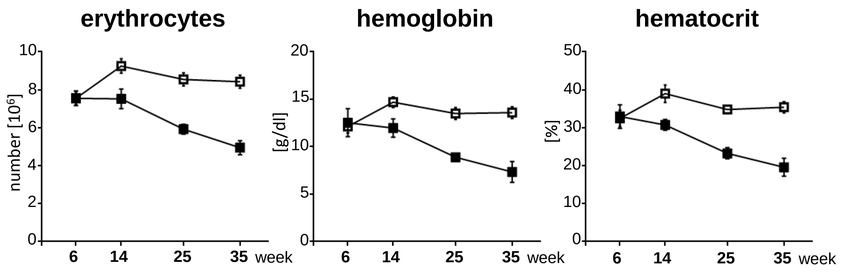
→ constitutively active PDGFR-β due to point mutation **V536A** in Foxd1 lineage cells

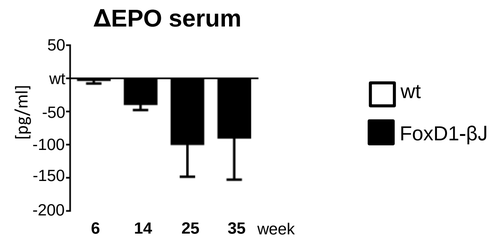
Blood pressure is not affected in FoxD1-βJ mice



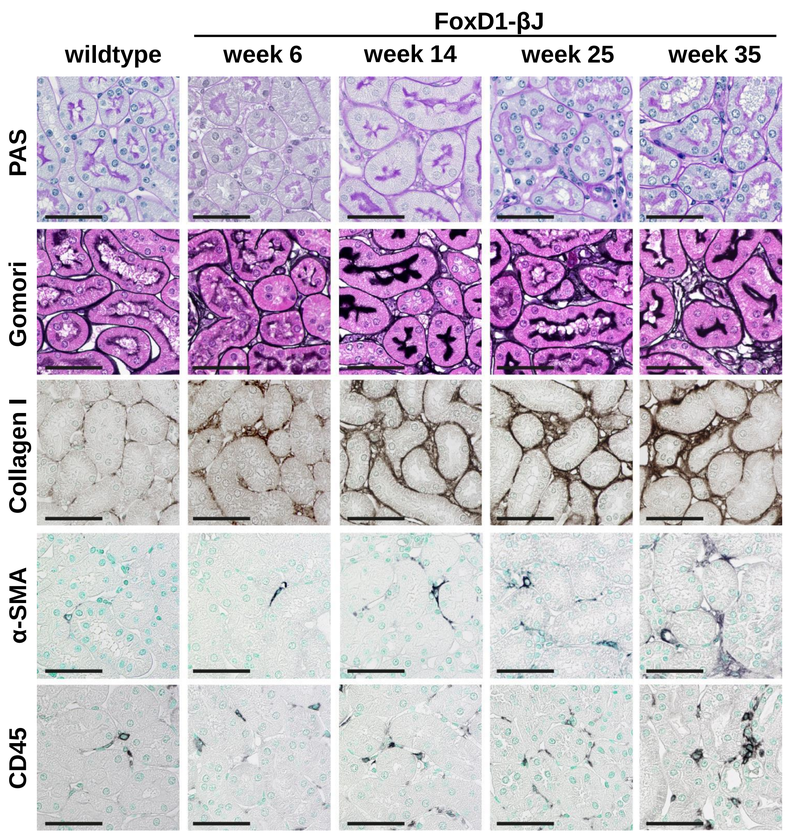


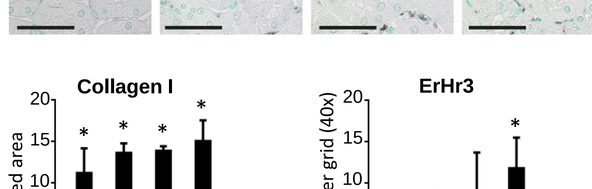
FoxD1-βJ mice develop anemia



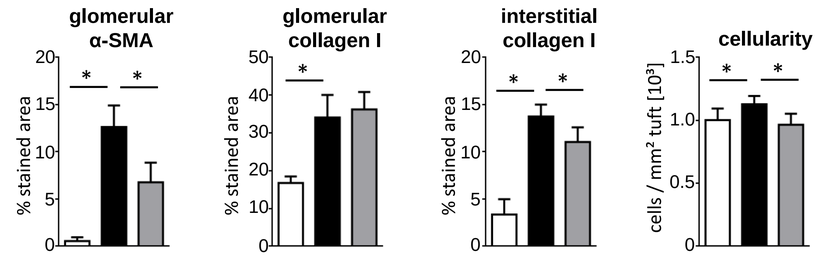


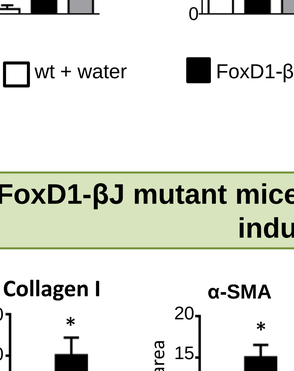
FoxD1-βJ mutant mice develop interstitial fibrosis

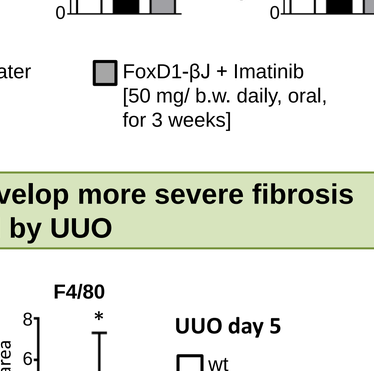




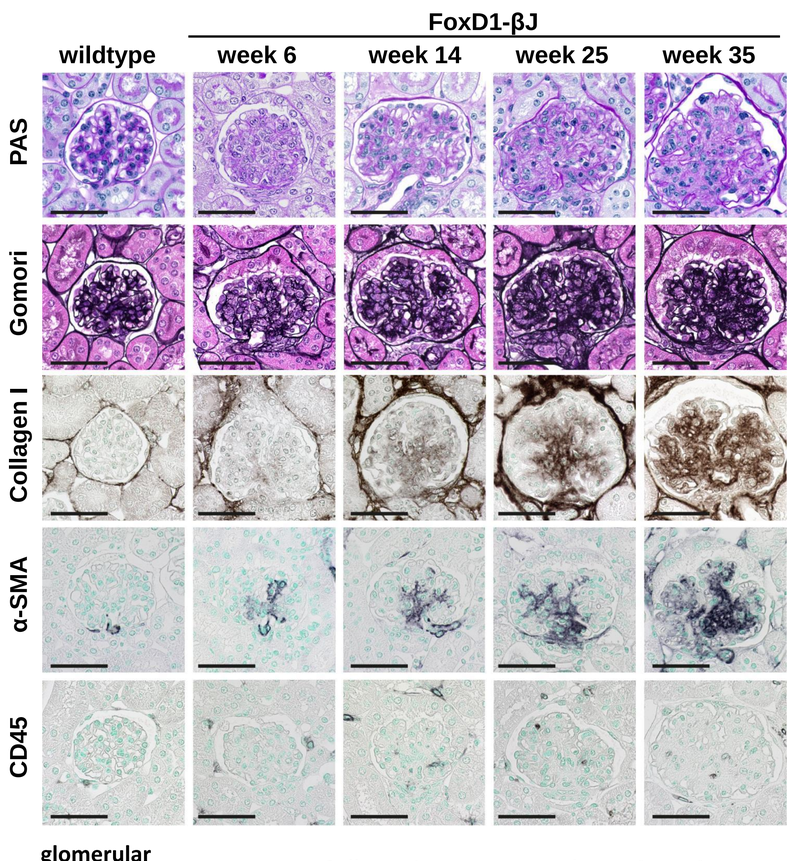
PDGFR-β activation promotes mesenchymal proliferation

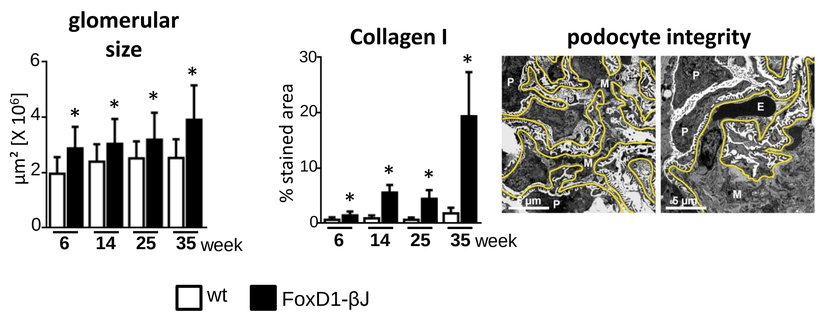




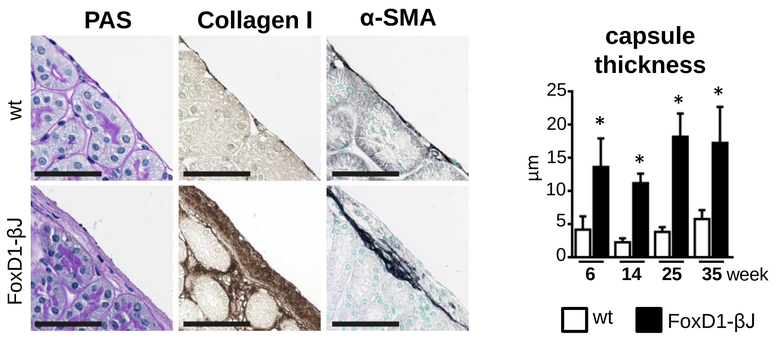


FoxD1-βJ mutant mice develop progressive mesangioproliferative and mesangiosclerotic glomerulopathy

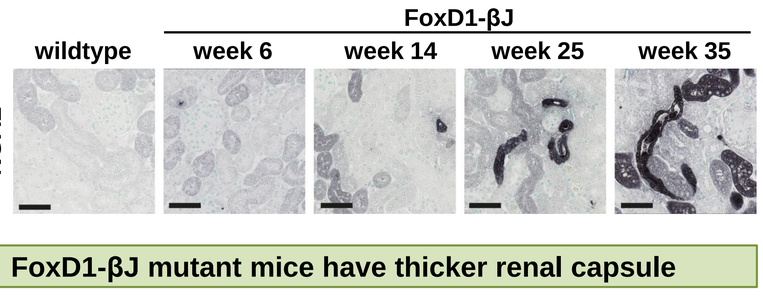




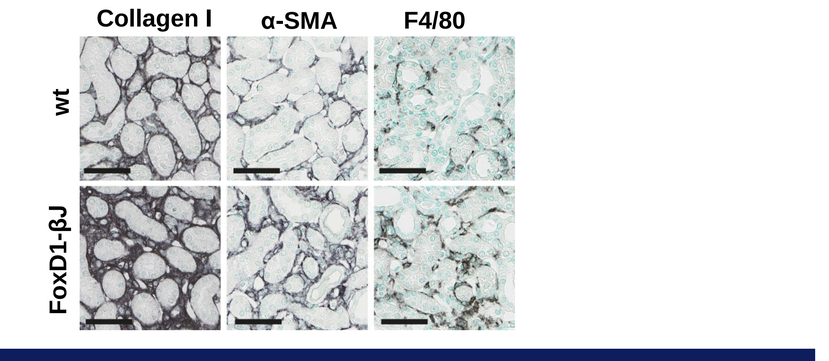
FoxD1-βJ mutant mice have thicker renal capsule



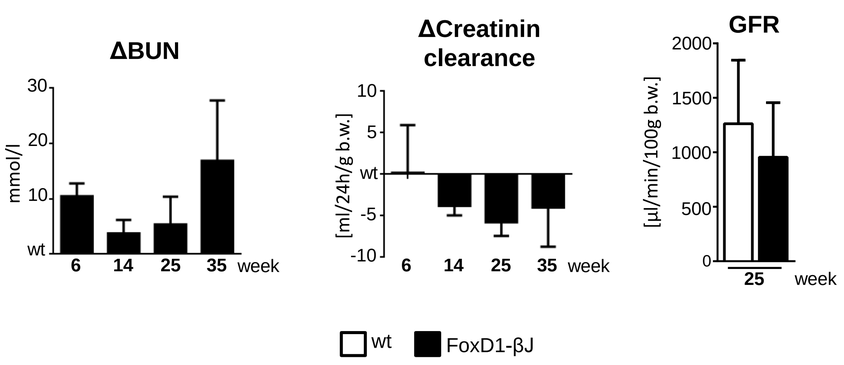
FoxD1-βJ mutant mice develop secondary tubuli injury



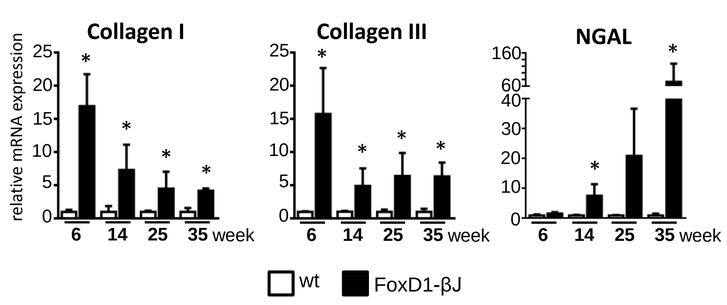
PDGFR-β inhibition by Imatinib reverses the effects



FoxD1-βJ mice show a mild decrease in kidney function



Gene expression in FoxD1-βJ mutant mice



FoxD1-βJ mutant mice develop more severe fibrosis induced by UUO

contact: pboor@ukaachen.de
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