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## Role of myeloid TGF- $\beta$ receptor in renal fibrosis after acute kidney injury

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I worked on the following experiment at Vanderbilt University, Nashville, USA: transforming growth factor- $\beta$  (TGF- $\beta$ ) is a central mediator of fibrosis. TGF- $\beta$  signals through a receptor complex composed of two type I and two type II transmembrane subunits. Renal macrophages are major producers of TGF- $\beta$ 1 and play important roles in the development of fibrosis after acute kidney injury (AKI). However, a previous study found that deletion of myeloid TGF- $\beta$ 1 did not prevent fibrosis after severe renal ischemia/reperfusion (I/R) or obstructive injury. This study examined whether deletion of myeloid type II TGF- $\beta$  receptors (Tgfbr2) affected development of fibrosis after AKI. Wild type or KO (CD11b-Cre;Tgfbr2<sup>f/f</sup> or LysM-Cre;Tgfbr2<sup>f/f</sup>) mice (male, 3 months old, C57BL/6) were used. For a severe I/R AKI model, the animals were uninephrectomized, immediately followed by unilateral I/R with renal pedicle clamping. Mice were sacrificed after 3 weeks. For an AKI to chronic kidney disease (CKD) model, unilateral I/R with renal pedicle clamping was performed, with contralateral uninephrectomy on the 8th day, and animal sacrifice on day 28. Deletion of macrophage/dendritic cell Tgfbr2 did not affect functional recovery from AKI, as indicated by similar rates of BUN and creatinine recovery. However, deletion of Tgfbr2 in macrophages/dendritic cells led to dramatic decreases in development of fibrosis at 3 weeks in the severe AKI model, as indicated by quantitative picro-sirius red staining and Masson's trichrome staining. Deletion of Tgfbr2 in macrophages/dendritic cells was associated with decreased expression levels of profibrotic and fibrotic components, including CTGF,  $\alpha$ -SMA and collagen I. In addition, macrophage/dendritic cell Tgfbr2 deletion led to marked decreases in macrophage and T cell infiltration and oxidative stress. Macrophage/dendritic cell Tgfbr2 deletion also markedly reduced development of fibrosis in the AKI-CKD model. In renal macrophages/dendritic cells isolated with CD11b microbeads, Tgfbr2 deletion led to decreased expression levels of M2 markers and increased M1 markers. The results indicate that myeloid Tgfbr2 promotes fibrosis after severe AKI at least in part by promotion of M2 polarization and suggest that activation of myeloid TGF- $\beta$  receptors by TGF- $\beta$  produced by non-myeloid cell types plays an important role in this process.