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Macrophage-specific deletion of transforming growth factor-β1 does not prevent renal fibrosis after severe ischemia-reperfusion or obstructive injury

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Submitted 5 November 2012; accepted in final form 3 June 2013

Huen SC, Moeckel GW, Cantley LG. Macrophage-specific deletion of transforming growth factor-β1 does not prevent renal fibrosis after severe ischemia-reperfusion or obstructive injury. Am J Physiol Renal Physiol 305: F477–F484, 2013. First published June 12, 2013; doi:10.1152/ajprenal.00624.2012.—Macrophage infiltration is a prominent feature of the innate immune response to kidney injury. The persistence of macrophages is associated with tubulointerstitial fibrosis and progression of chronic kidney disease. Macrophages are known to be major producers of transforming growth factor-β1 (TGF-β1), especially in the setting of phagocytosis of apoptotic cells. TGF-β1 has long been implicated as a central mediator of tissue scarring and fibrosis in many organ disease models, including kidney disease. In this study, we show that homozygous deletion of Tgfb1 in myeloid lineage cells in mice heterozygous for Tgfb1 significantly reduces kidney Tgfb1 mRNA expression and Smad activation at late time points after renal ischemia-reperfusion injury. However, this reduction in kidney Tgfb1 expression and signaling results in only a modest reduction of isolated fibrosis markers and does not lead to decreased interstitial fibrosis in either ischemic or obstructive injury models. Thus, targeting macrophage-derived TGF-β1 does not appear to be an effective therapy for attenuating progressive renal fibrosis after kidney injury.

macrophage; renal fibrosis; TGF-β1; ischemia-reperfusion

RECENT CLINICAL STUDIES SUGGEST THAT acute kidney injury is associated with the development of chronic kidney disease and progression to end-stage kidney disease (7). Data from animal studies support this association (30). Animal models have shown that despite initial functional renal recovery, an acute episode of ischemia-reperfusion (I/R) leads to long-term functional abnormality and interstitial scarring (2). Progressive chronic kidney disease is characterized by an inflammatory cellular infiltrate, increased extracellular matrix deposition, and fibrosis. The predominant immune cell of the cellular infiltrate is the macrophage, whose role in injury, repair, and fibrosis after renal ischemic injury appears to be multifaceted. Studies utilizing monocyte/macrophage depletion methods suggest that macrophages mediate the initial injury after reperfusion, promote tubular repair, and contribute to long-term kidney fibrosis after I/R injury (10, 14, 15, 17, 20, 22).

Activated macrophages within the injured kidney secrete many inflammatory cytokines and growth factors, such as transforming growth factor-β1 (TGF-β1) (27). TGF-β1 is considered a central mediator of fibrosis by promoting extracellular matrix production and proliferation of myofibroblasts and fibroblasts (3). Transgenic and renal injury animal models implicate TGF-β1 as a major player in the development of renal fibrosis (4, 12). Even in the absence of injury, overexpression of TGF-β1 by renal tubular epithelial cells alone results in renal fibrosis (18). Treatment with a neutralizing antibody against TGF-β attenuated late-stage interstitial cellularity and renal vascular density loss after renal I/R injury (29).

To determine the fibrogenic role of macrophage-derived TGF-β1, we deleted Tgfb1 from myeloid cells by establishing a LysM-Cre: Tgfb1f/n transgenic mouse and induced severe unilateral ischemic renal injury. At late time points after severe ischemic injury, LysM-Cre; Tgfb1f/n kidneys showed a trend toward less fibrosis that did not reach statistical significance. Gene expression analysis of profibrotic genes shows that despite significantly lower expression of Tgfb1 and decreased downstream Smad signaling in LysM-Cre;Tgfb1f/n kidneys, markers of extracellular matrix and fibrogenic genes remain elevated and were only modestly decreased compared with wild-type kidneys 28 days after ischemic injury. Similar findings were observed in the UUO model of kidney injury. Our data suggest that selective loss of macrophage-derived TGF-β1 is not sufficient to prevent fibrosis in the kidney after I/R or obstructive kidney injury.

MATERIALS AND METHODS

Animal models. Animal models were approved by the Yale University Institutional Animal Care and Use Committee. LysM-Cre mice (Jackson Laboratory, Bar Harbor, ME) were bred with Tgfb1f/n mice (gift from Dr. Richard Flavell) (21). Both mouse models were on C57BL/6 backgrounds.

Renal I/R model. Male 8- to 10-wk-old LysM-Cre; Tgfb1f/n, Tgfb1f/n, and Tgfb1f/f mice were anesthetized with intraperitoneal ketamine (100 mg/kg) and xylazine (10 mg/kg) and then subjected to renal I/R using a modified approach to that previously described (20). Briefly, to induce severe unilateral renal ischemia, the left renal pedicle was isolated via a midline abdominal incision and clamped for 35 min using a nontraumatic micro-aneurysm clip (Fine Science Tools, Foster City, CA). Mice were euthanized on day 14 and day 28 after reperfusion. Kidney tissue was harvested for histomoni-
tochemistry, and RNA isolation. Mice were kept at 37°C using a warming pad and reperfusion of the left kidney was confirmed after clamp release. Mice were given 1 ml of normal saline intraperitoneally to prevent dehydration. To assess functional injury after I/R, the left renal pedicle was clamped for 30 min and right nephrectomy was performed. Mild I/R injury experiments consisted of bilateral renal pedicle clamping for 20 min.

UUO model. Male 8- to 10-wk-old LysM-Cre;Tgfb1f/n and Tgfb1f/+ mice were anesthetized with intraperitoneal ketamine/xylazine and UUO was performed by ligation of the right ureter of each animal at the ureteropelvic junction using a 0.4 silk suture through a flank incision. Mice were euthanized on day 10 after ureter ligation and kidney tissue was harvested for histology and RNA isolation.

Renal histologic and morphologic analysis. Kidneys were perfusion fixed with 4% paraformaldehyde and processed for histology (H&E and trichrome in paraffin blocks). One renal pathologist, masked to the identity of the study animal, reviewed each kidney

Analysis of mRNA. Whole kidney RNA was extracted with TRIzol (Life Technologies, Grand Island, NY). RNA from cultured bone marrow-derived macrophages and isolated in vivo kidney macrophages was isolated using the RNeasy Mini and Micro kits, respectively (Qiagen, Valencia, CA). RNA was reverse transcribed to cDNA with iScript cDNA Synthesis kit (Bio-Rad, Hercules, CA). Gene expression analysis was determined by quantitative real-time PCR using a Bio-Rad CFX96 and normalized to Hprt1. The following primers were used: aSMA Fw: ACTGGGACGACATGGAAAAG; Rev: CATCCTCAGTTCAGGAAAG; CD11c- macrophages were isolated from kidneys at baseline (day 0) and compared with F4/80 CD11c-MR- macrophages 24 h after 30 min I/R injury as previously described (20). Kidney macrophage isolation at day 28 after 35 min of I/R injury was performed with kidney digestion as previously described (20), followed by staining of the single cell suspension with anti-F4/80 FITC (BM8, eBioscience), anti-CD11c-PE-Cy7 (HL3, BD Bioscience), and anti-CD45-PerCP (30F11, BD Bioscience). Stained cells were sorted by Beckman Coulter MoFlo (Beckman Coulter, Brea, CA). Total RNA was extracted from CD45+/F4/80+CD11c+ cells and reverse transcribed for real-time PCR analysis of gene expression as described above.

Statistical analysis. Statistical comparisons were made using unpaired t-tests or one-way ANOVA with Bonferroni multiple compar-

### Fig. 1. Macrophages upregulate Tgfb1 expression during the later phase of tubular recovery and persist in areas of focal fibrosis at late time points. A–B: mice were subjected to mild renal ischemia-reperfusion (I/R) injury (20-min bilateral renal pedicle clamping). Kidneys were harvested 14 days after I/R. A: kidney histology at 14 days after 20-min I/R injury shows focal areas of trichrome-positive staining around damaged tubules (area marked with * and outlined by dashed line). Original magnification x400. B: immunostaining for F4/80 (green) shows persistence of macrophages in focal areas of fibrosis. Original magnification x400. C: F4/80+/CD11c− macrophages were isolated from kidneys at baseline (day 0) and compared with F4/80+/CD11c+ macrophages 24 h after 30 min of I/R injury and F4/80+/CD11c+ macrophages 7 days after I/R injury. Real-time quantitative PCR for Tgfb1 relative to their expression in day 0 cells is shown and expression was normalized to Hprt1. Renal macrophages were obtained from 4 injured or uninjured kidneys per time point. Isolated renal macrophages from 2 kidneys were pooled for RNA isolation; data representative of 2 experiments.
RESULTS

Macrophage Tgfb1 expression in vivo after I/R injury. Analysis of kidneys from mice exposed to mild renal ischemia followed by 14 days of reperfusion reveals some tubules that have not fully regenerated, and instead are surrounded by a persistent F4/80+ macrophage infiltrate and focal fibrosis (Fig. 1, A and B). We previously demonstrated that the macrophages infiltrating the kidney after renal I/R injury are initially proinflammatory and then change toward an anti-inflammatory, reparative phenotype in which they express Arginase-1 and mannose receptor (MR) (20). MR-positive macrophages isolated from the kidney at day 7 after reperfusion also express high levels of Tgfb1 mRNA compared with macrophages at baseline and 1 day after injury (Fig. 1C). This suggests that during the latter phase of repair, when kidney function is recovering and tubular proliferation has declined, macrophages within the kidney continue to express high levels of TGF-β. Thus, we hypothesized that the persistence of macrophage-derived TGF-β1 adjacent to chronically damaged tubules might promote the late development of kidney fibrosis.

Macrophage-specific Tgfb1 deletion. To create a transgenic mouse model with macrophage-specific Tgfb1 deletion, LysM-Cre transgenic mice (6) with myeloid-specific expression of Cre recombinase were mated with Tgfb1f/n mice (21). The Tgfb1f/n mice have loxP sites flanking exon 1 of the Tgfb1 gene on one allele with the second allele being Tgfb1 null as described by Li et al. (21). Thus, LysM-Cre;Tgfb1f/n mice have heterozygous for Tgfb1 in all cells except myeloid macrophage and polymorphonuclear precursors that undergo homozygous deletion of Tgfb1. These mice were born in the expected Mendelian ratio and demonstrated no detectable abnormalities in kidney development, histology, or function (data not shown).

To assess the efficiency of macrophage Tgfb1 deletion, BMM were cultured from LysM-Cre;Tgfb1f/n mice as previously described and compared with BMM from wild-type littermates (Tgfb1f/n). In this primary culture, which consists of 98% macrophages based on prior FACS analysis (20), Tgfb1f/n

![Image](http://ajprenal.physiology.org/)

*Fig. 2. LysM-Cre;Tgfb1f/n mice exhibit decreased kidney Tgfb1 expression and Smad2/3 signaling after I/R injury. A: real-time quantitative PCR for Tgfb1, Tgfb2, and Tgfb3 relative to Hprt1 expression in bone marrow mononuclear macrophages (BMM) from wild-type Tgfb1f/n (open bars) and LysM-Cre; Tgfb1f/n (light gray bars) mice. Tgfb2 mRNA expression was undetectable and Tgfb3 mRNA expression was <0.001 in both Tgfb1f/n and LysM-Cre;Tgfb1f/n BMM, relative to Hprt1; n = 3, ****P < 0.0001. dc/HPRT. expression relative to Hprt1 as calculated by 2^(-dCt). B: serum blood urea nitrogen (BUN) at baseline and 24 h after 30 min of unilateral renal ischemia and contralateral nephrectomy was not different between the 2 genotypes (n = 4–5 animals/group). C–D: real-time quantitative PCR of Tgfb1 at day 14 (C) and day 28 (D) of whole kidney mRNA expression of I/R injured (35 min of unilateral ischemia) and contralateral uninjured kidneys. Wild-type Tgfb1f/n (open bars, n = 3 day 14, n = 13 day 28), whole body Tgfb1 heterozygous Tgfb1f/n (dark gray bars, n = 4 day 14, n = 5 day 28), and whole body Tgfb1 heterozygous with macrophage-specific Tgfb1 knockout LysM-Cre;Tgfb1f/n (light gray bars, n = 3 day 14, n = 13 day 28), expression shown relative to Hprt1, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001 vs. wild-type Tgfb1f/n postischemic kidney. Kidney Tgfb1 mRNA expression of injured kidneys from heterozygous and macrophage-specific Tgfb1 knockout LysM-Cre;Tgfb1f/n was not statistically different from injured kidneys from heterozygous Tgfb1f/n mice at day 14 or day 28 after I/R. E: real-time quantitative PCR of Tgfb1, Tgfb2, and Tgfb3 mRNA expression at day 28 after I/R of whole kidney and isolated CD45+F4/80+CD11c- kidney macrophages (Mφ). Expression shown relative to Hprt1, ****P < 0.0001, n = 10–13, total kidney samples, n = 3, isolated macrophages. Inset: same data with an expanded y-axis. F: whole kidney lysates of contralateral uninjured and injured kidneys 28 days after I/R injury immunoblotted for phosphorylated Smad2/3. Densitometry shown relative to GAPDH. *P < 0.05, n = 3 per group.
mRNA expression was markedly reduced by 92.9% in LysM-Cre;Tgfb1f/n-derived cells compared with Tgfb1f/+ derived cells, consistent with knockout of Tgfb1 in macrophages from LysM-Cre;Tgfb1f/n mice (Fig. 2A). There was no detectable increase in Tgfb2 or Tgfb3 in the Tgfb1-null cells. It has been suggested that TGF-β1 can be protective against ischemic kidney injury, suggesting that loss of macrophage-derived TGF-β1 could increase initial injury (13). Therefore, to determine whether LysM-Cre;Tgfb1f/n mice exhibited a different functional response to ischemic injury than Tgfb1f/+, both groups

**Fig. 3.** Macrophage-specific Tgfb1 deletion does not attenuate fibrosis, macrophage infiltration, or tubular injury at 14 or 28 days after renal I/R. A: trichrome-stained sections from representative wild-type (Tgfb1f+) mice and mice that are whole body Tgfb1 heterozygous with macrophage-specific Tgfb1 knockout (LysM-Cre;Tgfb1f/n) at day 14 and 28 after unilateral 35-min ischemia. Original magnification ×100. B: F4/80 immunostaining (green) of macrophage infiltration at day 14 and day 28 after unilateral ischemia. Original magnification ×400. C: blinded scoring shows no difference in interstitial fibrosis or tubular injury between wild-type and LysM-Cre;Tgfb1f/n postischemic kidneys (n = 6–8/group/time point).
were subjected to 30 min of unilateral I/R injury and contralateral nephrectomy to induce a reproducible loss of glomerular filtration rate (GFR). Assessment of serum blood urea nitrogen (BUN) at 24 h after I/R showed that serum BUN concentrations were elevated to a similar degree in both groups (Fig. 2B).

To determine the role of macrophage-derived TGF-β1 in the development of postischemic tubulointerstitial fibrosis, LysM-Cre;Tgfb1f/n and Tgfb1f0/n mice were subjected to severe renal I/R injury (35 min of unilateral renal ischemia) in the absence of contralateral nephrectomy. This degree of ischemia results in significant late fibrosis of the injured kidney while the intact contralateral kidney provides near normal GFR so that the animals can be followed long term. Analysis of whole kidney Tgfb1 mRNA expression revealed that Tgfb1 increases by sixfold 14 and 28 days after injury in wild-type mice, while kidneys from injured LysM-Cre;Tgfb1f0/n mice exhibit an overall reduction of Tgfb1 by 57.6% at 14 days and 75.5% at 28 days (Fig. 2, C and D). Tgfb1f0/n heterozygotes subjected to the same injury exhibited a reduction in Tgfb1 mRNA that was not statistically different from that seen in the injured LysM-Cre; Tgfb1f0/n kidneys. To determine the extent of reduction in macrophage Tgfb1 expression in the injured kidney, macrophages were isolated from wild-type (Tgfb1f+/+) and LysM-Cre;Tgfb1f0/n kidneys. CD45+ F4/80+ CD11c- macrophages isolated from LysM-Cre;Tgfb1f0/n kidneys at day 28 after I/R injury showed significantly decreased Tgfb1 expression compared with macrophages isolated from injured wild-type Tgfb1f+/+ kidneys (Fig. 2E). As with cultured BMM analysis, there was no detectable difference in Tgfb2 or Tgfb3 mRNA expression in the isolated LysM-Cre;Tgfb1f0/n macrophages or whole kidney compared with wild-type.

To reliably quantify functional TGF-β1 protein expression, we utilized an antibody that is specific for the activated forms of the TGF-β receptor signaling effectors, Smad2 and Smad3. Consistent with the sustained increase in Tgfb1 mRNA expression in wild-type kidneys, Smad2/3 remained highly activated in kidneys of contralateral nephrectomized mice compared with macrophages isolated from injured wild-type or Tgfb1f0/n kidneys. To determine the extent of reduction in macrophage Tgfb1 expression in the injured kidney, macrophages were isolated from wild-type (Tgfb1f+/+) and LysM-Cre;Tgfb1f0/n kidneys. CD45+ F4/80+ CD11c- macrophages isolated from LysM-Cre;Tgfb1f0/n kidneys at day 28 after I/R injury showed significantly decreased Tgfb1 expression compared with macrophages isolated from injured wild-type Tgfb1f+/+ kidneys (Fig. 2E).

Macrophage-specific deletion of Tgfb1 does not prevent fibrosis after I/R injury. The extent of fibrosis and tubular injury was then analyzed in kidneys from LysM-Cre;Tgfb1f0/n mice compared with Tgfb1f+/+ mice at 14 and 28 days after I/R injury. These studies revealed the expected areas of persistent tubular injury and peritubular fibrosis in Tgfb1f+/+ mice, with no difference detected in the LysM-Cre;Tgfb1f0/n mice (Fig. 3A, quantified in 3C). Macrophage infiltration assessed by F4/80 immunostaining was similar in both genotypes (Fig. 3B). At 28 days after reperfusion, LysM-Cre;Tgfb1f0/n kidneys showed a trend toward less fibrosis and tubular injury that did not reach statistical significance.

Consistent with the histologic findings, real-time quantitative PCR of whole kidney RNA revealed no difference in the upregulation of profibrotic genes α-smooth muscle actin, collagen I, collagen IV, connective tissue growth factor, fibroblast-specific protein 1, or fibronectin at day 14 (Fig. 4A) in wild-type Tgfb1f+/+, whole body Tgfb1 heterozygous Tgfb1f0/n, or LysM-Cre;Tgfb1f0/n mice after I/R injury. At day 28 after I/R injury, there was a modest decrease in collagen I and fibroblast-specific protein-1 expression in kidneys from LysM-Cre; Tgfb1f0/n mice compared with wild-type, although no difference was found in the other markers analyzed (Fig. 4B).

Macrophage-specific deletion of Tgfb1 does not attenuate fibrosis after UUO. UUO induces a mechanical obstructive injury to the kidney and is a model for severe progressive tubulointerstitial fibrosis. We therefore examined whether macrophage-derived TGF-β1 plays a more significant role in the development of renal fibrosis after obstructive nephropathy compared with ischemic injury. Similar to the result in I/R injury, whole kidney Tgfb1 mRNA levels were significantly reduced in kidneys from LysM-Cre;Tgfb1f0/n mice following UUO compared with kidneys from Tgfb1f+/+ mice (Fig. 5C).
Despite this overall reduction in Tgfb1, interstitial fibrosis and tubular injury were not significantly different 10 days after unilateral ureteral ligation of LysM-Cre;Tgfb1f/n and Tgfb1f/ H11001 kidneys (Fig. 5A, quantified in 5D). Macrophage infiltration was also similar between the two groups (Fig. 5B). The profibrotic gene expression profile in the obstructed kidney was not different between the two genotypes (Fig. 6).

**DISCUSSION**

Since macrophages are specifically enriched in regions where late fibrosis occurs, we originally postulated that the level of TGF-β1 would be highest in these regions, where it could promote focal fibrosis. Indeed, it is well-recognized that the level of TGF-β1 available for signaling is regulated locally by the balance between production and matrix binding (26). To study the macrophage-specific role of TGF-β1 in the development of renal fibrosis after renal injury, we developed the LysM-Cre;Tgfb1f/n mouse model. While it is known that the LysM-Cre model can be problematic due to its inefficiency in deletion of some floxed alleles and its mosaic-type expression (25), the alternative, Tie2-Cre, is expressed in endothelial cells in which deletion of Tgfb1 would be problematic both developmentally and after renal injury. Tgfb1 mRNA was effec-
tively reduced (92.9% decrease compared with control) in a purified population of in vitro bone marrow-derived macrophages from LysM-Cre;Tgfb1fl/fl mice. Isolated CD45+/F4/80+CD11c-kidney macrophages, which were 95–97% pure by postsort analysis, demonstrated a less efficient deletion of Tgfb1, as assessed by a 64.5% decrease in mRNA expression. This suggests that either contamination of nonmacrophage cells is contributing to the Tgfb1 expression or a subset of CD45+/F4/80+CD11c-cells never expressed Tgfb1 deletion and the contribution of each cell type to the overall expression of TGF-β1 in the fibrotic kidney.

Despite the limitations of this transgenic model, our data demonstrate several important findings for consideration as we develop therapeutic approaches to prevent kidney fibrosis after episodes of acute kidney injury. First, the LysM-Cre;Tgfb1fl/fl model resulted in a significant decrease in whole kidney Tgfb1 mRNA expression after ischemic and obstructive kidney injury. We confirmed that the 75% decrease in Tgfb1 mRNA seen on day 28 after I/R injury in LysM-Cre;Tgfb1fl/fl kidneys was sufficient to completely prevent downstream Smad activation. But despite this loss of canonical TGF-β1 receptor signaling, injured LysM-Cre;Tgfb1fl/fl mice exhibited only a modest decrease in two of the six profibrotic genes examined and had no clear difference in the development of histologic fibrosis.

It is worth noting that while the 75% reduction in Tgfb1 expression in LysM-Cre;Tgfb1fl/fl mice was sufficient to prevent Smad activation, the 51% reduction seen at the same time point in Tgfb1fl/+ heterozygotes had no impact on Smad activation. This observation is consistent with previous data demonstrating that the amount of bioavailable TGF-β1 present in the extracellular matrix is often in excess of that needed for efficient Smad-mediated signaling (1, 5) and that a substantial reduction in TGF-β1 is required to reach the threshold for inhibition of receptor activation. Thus it is conceivable that TGF-β1 from nonmyeloid sources present in the renal extracellular matrix is sufficient for early activation of TGF-β1-mediated profibrotic responses and that infiltrating macrophages serve to replace this supply of TGF-β1 at later time points. This possibility would be consistent with our observation that fibrosis and fibrogenic gene expression are indistinguishable in wild-type and LysM-Cre;Tgfb1fl/fl mice on day 10 after UUO and day 14 after I/R, whereas by day 28 after I/R there is a nonsignificant trend toward reduction of fibrosis and the emergence of a statistically significant decrease in Col1a1 and Fsp1 in the LysM-Cre;Tgfb1fl/fl mice.

An alternative explanation for the persistence of fibrosis despite the loss of macrophage-derived TGF-β1 is the potential role for TGF-β2 and/or TGF-β3 in the development of renal fibrosis. Earlier studies investigating the role of TGF-β in the development of renal fibrosis after ischemic or obstructive injuries utilized a pan-Tgfb-β neutralizing antibody capable of neutralizing all three isoforms (1D11) (9, 24, 29). In contrast, our model specifically reduced the expression of Tgfb1, whereas Tgfb2 and Tgfb3 were still expressed and upregulated in a normal fashion after I/R injury (Fig. 2E). The increase of total kidney Tgfb2 and Tgfb3 mRNA expression on day 28 after I/R injury in our model is comparable to the increase in a murine model of diabetic renal fibrosis reported by Juárez and colleagues (16). In their model of diabetic nephropathy, a soluble type III TGF-β receptor with TGF-β2>TGF-β3>TGF-β1 isomeric binding affinities (31) effectively lowered the expression of all three TGF-β isoforms, decreased renal fibrosis, and preserved renal function (16). The above studies (16, 24, 29) did not report the effect on Smad signaling. While the LysM-Cre;Tgfb1fl/fl model prevented pSmad2/3 signaling, fibrotic roles for TGF-β2 and TGF-β3 cannot be completely ruled out in our model as the TGF-β family is known to also activate non-Smad pathways (32). Further research is needed to determine the specific roles of TGF-β2 and TGF-β3 in the development of renal fibrosis.

Data from studies on transgenic models targeting specifically TGF-β1 provide a complex picture of the role TGF-β1 plays in mediating fibrogenesis and inflammation. Whole body Tgfb1 knockout mice develop lethal autoimmune inflammatory disease (19, 28), while tubular overexpression of TGF-β1 leads to renal fibrosis even in the absence of renal injury (18). Thus, TGF-β1 can play a role in suppressing inflammation and promoting fibrosis as part of a wound-healing response. Our current data suggest that although Tgfb1 is highly upregulated in renal macrophages following kidney injury, specifically targeting myeloid TGF-β1 may not be helpful clinically to combat the progression of renal fibrosis after acute kidney injury. Studies of transgenic models targeting the TGF-β signaling pathway have highlighted the complex role of TGF-β in both injury and wound repair and clearly show that further research is required to clarify the functional impact of manipulating this pathway in the prevention of renal fibrosis.

GRANTS

This work was funded by National Institutes of Health Awards DK65109 and DK93771 to L. G. Cantley. S. C. Huen was supported by National Institute of Diabetes and Digestive and Kidney Diseases Institutional Training Grant T32-DK007276.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES

MACROPHAGE-DERIVED TGF-β1 IS NOT REQUIRED FOR RENAL FIBROSIS


