Tgf-β, Notch, and HGF weave a tangled web of kidney repair

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ACUTE AND CHRONIC KIDNEY INJURY results from a variety of causes, and each may lead to the other. In either case, renal failure is a common outcome requiring renal replacement therapy. However, the kidney has endogenous repair mechanisms that are activated in response to injury. A better understanding of the molecular mechanisms of repair and how we might use them therapeutically to retain or restore kidney function following an insult could greatly improve patient outcomes. Accordingly, this has been the subject of both basic research and clinical trials.

A variety of animal models of chronic kidney injury, including subtotal nephrectomy, diabetic or obstructive nephropathy, and ischemia-reperfusion, have been developed. Studies using these models, as well as in vitro assays, have provided insight into the complex cascade of events that follows kidney injury, including inflammation, apoptosis, proliferation, epithelial-mesenchymal transition, fibrosis, and regeneration (1). Hepatocyte growth factor (HGF) and transforming growth factor-β (TGF-β) are induced with kidney injury and act as major regulators of these events.

Studies initially supported a generally reparative role for HGF and a damaging, profibrotic role for TGF-β. On the basis of these findings, clinical trials of anti-TGF-β treatments have been conducted but have yielded disappointing results (6). It seems that TGF-β may have greater signaling complexity and more beneficial effects than was initially appreciated. Accordingly, some studies have shown that TGF-β signaling is not necessarily positively linked with fibrosis, and TGF-β may be essential as a modulator of inflammation and autophagy.

In a recent issue of American Journal of Physiology-Renal Physiology, Nlandu Khodo et al. (5) report a novel interaction network in kidney injury in which TGF-β signaling, via Notch, positively regulates HGF signaling. Their previous work showed that inhibition of TGF-β signaling protects against HgCl2-induced acute kidney injury (2). This injury model induces HGF signaling; thus they hypothesize that inhibition of TGF-β protects against kidney injury by promoting HGF signaling. They tested this hypothesis in vivo using mice lacking the TGF-β receptor TβRII and in vitro using proximal tubule cells derived from these mice. However, instead of increased HGF signaling in cells lacking TβRII, they found the opposite. Cells lacking TβRII had impaired HGF signaling, including decreased expression of the HGF receptor c-Met, at both transcript and protein levels, and decreased activation of downstream signaling. Since Notch signaling is a target of TGF-β signaling (4), they assessed Notch signaling in cells lacking TβRII and also assessed effects of Notch inhibition. Their data show reduced Notch signaling in the absence of TβRII and reduced c-Met expression in response to γ-secretase inhibitor. Besides demonstrating biochemical evidence of a TGF-β-Notch-HGF signaling network, their data reveal corresponding biological effects. Stimulation of proximal tubule cells with HGF increased cell migration and proliferation, and these responses were attenuated in cells lacking TβRII. Additionally, γ-secretase inhibition reduced cell migration but did not further affect the lower migration level in cells lacking TβRII. Together, these data support a model whereby stimulation of migration by HGF is enhanced by TGF-β signaling through TβRII and Notch.

These studies add to our knowledge of TGF-β, Notch, and HGF signaling. TGF-β is known to regulate Notch signaling in kidney injury, and regulation of c-Met by Notch has been observed in other tissues (3, 7). A previous study using a human kidney cell line showed that TGF-β increased c-Met expression (8). The work of Nlandu Khodo et al. (5) showing loss of signaling in the absence of TβRII in vivo, as well as in vitro, supports the validity of this initial finding.

A noteworthy contribution of Nlandu Khodo et al. (5) is their finding that promotion of HGF signaling by TβRII is specific to proximal tubule cells. In contrast to the decreased expression of c-Met in proximal tubule cells lacking TβRII, c-Met expression was increased in cortical fibroblasts lacking TβRII. This cell type-specific response is an important finding that may explain at least some of the controversy regarding whether TGF-β is damaging or reparative following kidney injury.

An interesting question for future study is as follows: How would deletion of a single TGF-β isoform compare with the total loss of TGF-β shown here in the absence of TβRII? All three major TGF-β isoforms are expressed in the human kidney, and the isoforms differ in several of their downstream effects, including their effect on fibrosis (6). All isoforms bind TβRII, the receptor deleted here. Taken together, therefore, the effects of the individual TGF-β isoforms are unclear.

A better understanding of the kidney’s response to injury has great potential for improving treatment options for a wide variety of insults leading to renal failure. Effective research in this area should take into account both individual components of the response and interactions among pathways, as demonstrated elegantly by Nlandu Khodo et al. (5).

DISCLOSURES

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AUTHOR CONTRIBUTIONS

C.R.S. drafted the manuscript; C.R.S. edited and revised the manuscript; C.R.S. approved the final version of the manuscript.

REFERENCES


