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 have been developed, including subtotal nephrectomy, diabetic or obstructive nephropathy, and ischemia-reperfusion. 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 (EMT), 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, pro-fibrotic role for TGF-β. Based on these findings, clinical trials of anti-TGF-β treatments have been conducted, but have yielded disappointing results (6). It seems TGF-β may have greater signaling complexity and beneficial effects than was initially
appreciated. Accordingly, some studies have shown TGF-β signaling is not necessarily positively linked with fibrosis, and TGF-β may be essential as a modulator of inflammation and autophagy.

In this issue, Nlandu Khodo et al. report a novel interaction network in kidney injury in which TGF-β signaling, via Notch, positively regulates HGF signaling (5). Their previous work has shown that inhibiting TGF-β signaling protects against mercuric chloride-induced acute kidney injury (2). This injury model induces HGF signaling, thus they hypothesized in the current paper that inhibiting TGF-β protected against kidney injury by promoting HGF signaling. They tested this in vivo using mice lacking the TGF-β Receptor, TβRII, and in vitro using proximal tubule cells derived from these mice. However, instead of finding increased HGF signaling in cells lacking TβRII, they saw 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, they assessed Notch signaling in cells missing TβRII and also assessed effects of Notch inhibition (4). Their data showed reduced Notch signaling in the absence of TβRII, and reduced c-Met expression in response to gamma secretase inhibition. 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, gamma 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 what is known about 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). Nlandu Khodo and colleagues’ work showing loss of signaling in the absence of TβRII *in vivo*, as well as *in vitro*, support the validity of this initial finding.

A noteworthy contribution of Nlandu Khodo *et al.* is showing that the promotion of HGF signaling by TβRII is specific to proximal tubule cells. In contrast to the decreased expression of c-Met seen in proximal tubule cells lacking TβRII, cortical fibroblasts lacking TβRII had increased expression of c-Met. 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 how would deletion of a single TGF-β isoform compare to the total loss of TGF-β shown here in the absence of TβRII. All of the three major TGF-β isoforms are expressed in the human kidney, and the isoforms differ in several of their downstream effects, including 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 in this issue by Nlandu Khodo and coauthors.


