

# Tubule epithelial cells and fibroblasts communication: Vicious cycle of renal fibrosis

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Chronic kidney disease (CKD) has been recognized as a leading public health burden worldwide driven by the increasing prevalence of diabetes mellitus, hypertension, obesity, and aging, but effective treatment options are limited.<sup>1</sup> Renal fibrosis is the pathological feature of CKD regardless of underlying causes. Therefore, a clearer understanding of the mechanism is essential for defining potential therapeutic target for CKD.

Tubule epithelial cells are the most populous cell type which are vulnerable to a variety of injury stimuli. In recent years, the signals sending by injured tubules in the process of renal fibrosis has attracted increasing attention. Single-cell RNA-sequencing technologies have revealed the appearance of maladaptive or failed repaired proximal tubule clusters which express proinflammatory and profibrotic cytokines.<sup>2,3</sup> Those injured tubules secrete cytokines, such as CXCL1 which interacts with CXCR2+ basophils, contributing to the development of renal fibrosis.<sup>4</sup> Tubular cells undergoing autophagy release FGF2 as paracrine factor leading to fibroblast activation and renal fibrosis.<sup>5</sup> In addition to cytokines, tubules also communicate with macrophages or fibroblast via secreting extracellular vesicles carrying functional cargoes such as TGF- $\beta$ 1 mRNA, CCL2 mRNA and Osteopontin protein.<sup>6-8</sup> Therefore, the communication of altered renal tubules with interstitial cells indeed contributed to the process of kidney fibrosis.

In the recent issue of *eBiomedicine*, Xu and colleagues uncovered a previously unrecognized vicious cycle mediated by leukemia inhibitory factor (LIF)-Sonic Hedgehog (SHH) signaling between fibroblast and tubule epithelial cells, leading to the development of renal fibrosis<sup>9</sup> (Fig. 1). They observed that LIF was prominently increased among the IL6 family members in both kidneys of CKD patients and mouse models induced by ischemia-reperfusion injury (IRI) and unilateral ureteral obstruction (UUO). Importantly, LIF has the strongest association with the severity of

tubulointerstitial fibrosis and the decline of renal function. In a large prospective cohort of CKD patients, they found that baseline urine LIF levels predicted the risk of CKD progression to end stage renal disease.

In mechanism, Xu et al. demonstrated a pro-fibrotic role of LIF in myofibroblast activation via ERK and STAT3 pathway, and a similar fibrosis response was induced in tubules by LIF. Interestingly, fibroblasts-derived LIF augment SHH expression in renal tubules which in turn promoted LIF expression in fibroblasts. Therefore, fibroblasts and renal tubular cells communicated with LIF-SHH signaling which formed a vicious cycle in pro-fibrotic response. To confirm the pro-fibrotic role of LIF *in vivo*, lentiviral overexpression of LIF were introduced into renal parenchyma which accelerated renal fibrosis in UUO model. At the same time, they showed that renal fibrosis was alleviated significantly through knockdown of LIF receptor or by using LIF-neutralizing antibody in animal models. Thus, experiments with both gain- and loss-of-function *in vivo* strongly supported the pro-fibrotic role of LIF in renal fibrosis. Besides, LIF promoted macrophage phenotype transition toward pro-fibrotic phenotype. Taken together, LIF expression on fibroblasts contributes importantly to renal fibrosis, and its communication with tubules and macrophages accelerated pro-fibrotic responses.

Previous study showed that LIF was involved in tubular regeneration after acute kidney injury.<sup>10</sup> However, sustained activation of LIF signaling may contribute to the pathogenesis of renal fibrosis. Given the different roles of LIF in acute and chronic kidney injury, more refined studies are needed to establish the optimal strategies of targeting LIF considering the intervention dosage and stages after kidney injury. Nevertheless, this study demonstrated a new paracrine vicious cycle mediated by LIF-SHH signaling between tubules and fibroblasts in renal fibrosis. Therapeutically inhibiting LIF to disrupt this cycle may represent a novel approach of therapy, and urinary LIF may be a useful non-invasive biomarker for renal fibrosis with potential to monitor the progress of CKD.

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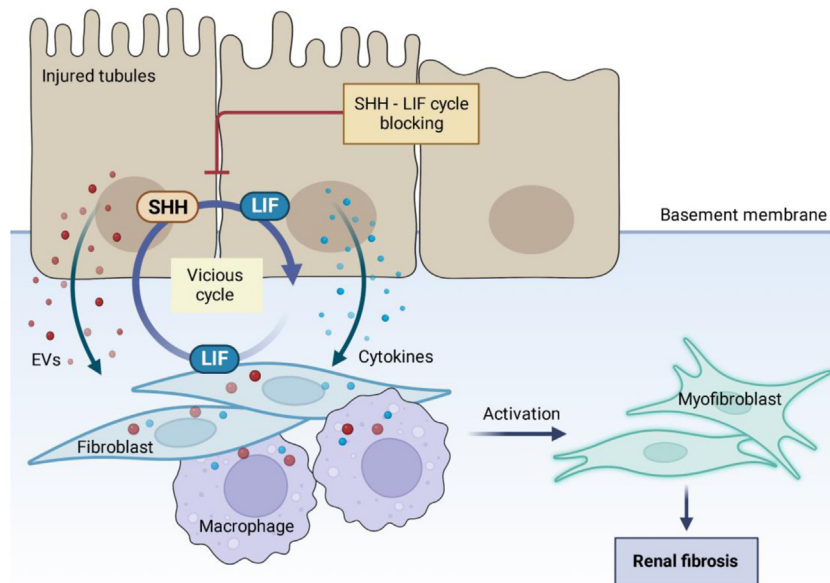
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## Contributors

Literature search: A.R.S. and L.L.L.; Graph preparation: A.R.S.; Data interpretation: L.L.L.; Writing: A.R.S. and L.L.L. Both authors read and approved the final version of the manuscript.



**Fig. 1: The communication of tubules and interstitial cell in kidney fibrosis.** Injured tubules communicate with interstitial fibroblast and immune cells with paracrine factors including cytokines, extracellular vesicles (EVs) to amplify the pro-fibrotic responses. Xu et al. identified a vicious cycle mediated by leukemia inhibitory factor (LIF)- Sonic Hedgehog (SHH) signaling between fibroblast and tubule epithelial cells. LIF elicits a pro-fibrotic response in both fibroblasts and renal tubular cells, which may represent a potential therapeutic target and biomarker for renal fibrosis.

#### Declaration of interests

The authors declare no conflict of interest.

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