# Renal tubule injury: a driving force toward chronic kidney disease

Bi-Cheng Liu[1], Tao-Tao Tang[1], Lin-Li Lv[1] and Hui-Yao Lan[2]

[1]Institute of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, Nanjing, China; and [2]Department of Medicine and Therapeutics, Li Ka Shing Institute of Health Sciences, Chinese University of Hong Kong, Hong Kong, China

**Renal tubules are the major component of the kidney and are vulnerable to a variety of injuries including hypoxia, proteinuria, toxins, metabolic disorders, and senescence. It has long been believed that tubules are the victim of injury. In this review, we shift this concept to renal tubules as a driving force in the progression of kidney diseases. In response to injury, tubular epithelial cells undergo changes and function as inflammatory and fibrogenic cells, with the consequent production of various bioactive molecules that drive interstitial inflammation and fibrosis. Innate immune-sensing receptors on the tubular epithelium also aggravate immune responses. Necroinflammation, an autoamplification loop between tubular cell death and interstitial inflammation, leads to the exacerbation of renal injury. Furthermore, tubular cells also play an active role in progressive renal injury via emerging mechanisms associated with a partial epithelial-mesenchymal transition, cell-cycle arrest at both G1/S and G2/M check points, and metabolic disorder. Thus, a better understanding the mechanisms by which tubular injury drives inflammation and fibrosis is necessary for the development of therapeutics to halt the progression of chronic kidney disease.**

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**Correspondence:** *Hui Y. Lan, Department of Medicine and Therapeutics, and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, China. E-mail: hylan@cuhk.edu.hk or Bi-Cheng Liu, Institute of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, Nanjing, China. E-mail: liubc64@163.com*

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The renal tubules and tubulointerstitium make up a significant portion of the kidney and are the major sites in response to injuries. Increasing evidence shows that tubular epithelial cells (TECs) play diverse roles in renal repair or progression to chronic kidney disease (CKD). The innate immune characteristics of TECs enable them to act as immune responders to a wide range of insults, with the consequent production and release of bioactive mediators that drive interstitial inflammation and fibrosis. Accumulating evidence shows that renal function decline correlates better with tubulointerstitial damage than that of glomerular injury.[1–3] Maladaptive repair of injured tubules after acute kidney injury (AKI) also leads to the progression of CKD.[4,5] Thus, TECs should be regarded not only as victims in the context of kidney diseases, but also as key inflammatory and fibrogenic cells that drive the progression from acute to chronic kidney disease. It should be noted that due to the length limitations, this review focuses on the emerging mechanisms by which TECs play a driving role in renal injury, whereas other potentially important factors/pathways not directly related to this topic are not discussed here.

## TECs as inflammatory cells: tubule-derived factors associated with tubulointerstitial inflammation

Researches have shown that tubulointerstitial inflammation can be observed in the early stage of many renal diseases,[6] and the response of TECs to injury is likely to be a key determinant in the development of interstitial inflammation. These damaged TECs can be transformed into a secretory phenotype and elicit proinflammatory mediators.

***Proinflammatory cytokines.*** Injured TECs can facilitate the immune response through induction of a variety of proinflammatory cytokines (e.g., interleukin, tumor necrosis factor, colony-stimulating factor, and growth factor). After the first report of tumor necrosis factor (TNF)-α and interleukin (IL)-6 produced by TECs.[7,8] As shown in Table 1, a variety of cytokines have been shown to be produced by activated TECs, including IL-1β,[9,10] IL-18,[9,11] IL-15,[12,13] IL-16,[14] TNF-α,[15] TWEAK,[16,17] Fas ligand,[18,19] connective tissue growth factor (CTGF),[20,21] and vascular endothelial growth factor.[22–24] Recently, emerging evidence indicates that the expression of colony-stimulating factor 1 is upregulated in TECs and may be responsible for the polarization of renal macrophages and recovery from AKI.[25–27] TEC-derived IL-34 also plays a key role in aggravating macrophage infiltration and tubular cell injury, leading to persistent ischemic AKI and subsequent

**Table 1 | List of proinflammatory cytokines produced by TECs**

| Cytokines | Effects | References |
|---|---|---|
| IL-1β | Triggers proinflammatory cytokines and initiates acute-phase responses | 9,10 |
| IL-18 | Triggers proinflammatory cytokines | 9,11 |
| IL-6 | Proinflammation | 7,8 |
| IL-15 | $CD103^+$ T-cell recruitment | 12,13 |
| IL-16 | $CD4^+$ T-cell recruitment | 14 |
| IL-34 | Neutrophil and macrophage recruitment | 28 |
| TNF-α | Triggers proinflammatory cytokines<br>Innate and adaptive immunity<br>Apoptosis | 15 |
| CSF-1 | Macrophage recruitment and adhesion<br>Polarization into an M2 phenotype | 25–27 |
| TWEAK | Cell death in the presence of TNF-α/IFN-γ<br>Proinflammation | 16,17 |
| Fas ligand | Apoptosis | 18,19 |
| CTGF | Triggers proinflammatory cytokines | 20,21 |
| VEGF | Macrophage recruitment | 22–24 |

CSF-1, colony-stimulating factor 1; CTGF, connective tissue growth factor; IL, interleukin; TECs, tubular epithelial cells; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

CKD.[28] These findings support the notion that activated TECs gain the inflammatory phenotype that drives the immune response by producing inflammatory cytokines directly in an autocrine manner or indirectly through the infiltrating leukocytes in a paracrine manner.

***Chemokines.*** Chemokines are a family of small molecular cytokines with chemotactic activity. TECs are rich sources of the CC chemokine ligand (CCL) subfamily including monocyte chemoattractant protein-1/CCL2, RANTES (regulated on activation, T-cell expressed, and secreted)/CCL5, and monocyte chemoattractant protein-1/CCL3, and CX3CL subfamily (fractalkine/CX3CL1).[29] Monocyte chemoattractant protein-1/CCL2 is one of the most widely studied chemokines in kidney injury.[30–32] Increased levels of monocyte chemoattractant protein-1/CCL2 are associated with progressive tubulointerstitial inflammation.[33,34] In addition, other chemokines such as CXC chemokine ligand 8/IL-8 and CXC chemokine ligand 12/SDF-1 are also overexpressed by injured TECs and are chemotactic to a number of leukocyte populations.[35–37] A recent study reported that CXC chemokine ligand 5 is increased in tubular cells following the induction of nephrotoxic nephritis and is responsible for neutrophil recruitment during acute renal tissue injury.[38] It is now clear that the induction of chemokines is regulated via several pathways including extracellular signal–regulated kinase 1/2, p38 mitogen-activated protein kinase, nuclear factor-κB (NF-κB), STAT (signal transducer and activator of transcription) signaling, and transforming growth factor (TGF)-β signaling.[39–43]

***Adhesion molecules.*** Cell adhesion molecules are integral cell-membrane proteins that maintain cell-cell and cell-substrate adhesion and, in some cases, act as regulators of intracellular signaling cascades.[44] In the kidney, cell adhesion molecules such as the cadherins, catenins, zonula occludens protein 1, occludin, and claudins are essential for maintaining the epithelial polarity and barrier integrity that are necessary for the normal absorption/excretion of fluid and solutes. Notably, it is now widely appreciated that intracellular adhesion molecule-1 and selectins derived from TECs represent relatively early events in the pathophysiology of renal injury by promoting leukocyte infiltration and inflammatory responses.[44] In addition, the CD40/CD154 ligation can induce mononuclear cell adhesion to PTECs via an intracellular adhesion molecule-1–dependent mechanism.[45] IL-8 amplifies CD40/CD154-mediated intracellular adhesion molecule-1 production via the CXC chemokine receptor 1 and p38 mitogen-activated protein kinase pathway.[36]

***Reactive oxygen species.*** It has become clear that oxidative stress contributes to CKD progression via myriad effects.[46–48] Oxidative stress implies an increased production of reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide, and hydroxyl anion. In response to multiple stimuli and agonists, mitochondrial dysfunction and reduced nicotinamide adenine dinucleotide phosphate oxidases have been recognized as the major contributors to ROS generation in TECs.[49,50] Angiotensin II (Ang II) can induce tubular hypertrophy and TEC apoptosis via ROS-dependent mechanisms.[51,52] Albumin acts through the epidermal growth factor receptor to stimulate reduced nicotinamide adenine dinucleotide phosphate oxidase and ROS production. ROS then activates NF-κB, which then ultimately leads to activation of extracellular signal–regulated kinase 1/extracellular signal–regulated kinase 2 pathway.[53] In addition, albumin has also been shown to stimulate tubulointerstitial inflammation via the mitochondrial ROS-mediated activation of NACHT, LRR, and PYD domains containing protein 3 (NLRP3) inflammasome.[54] Taken together, a surplus of ROS in TECs can result in various injurious consequences such as inflammation.

***C-reactive protein.*** C-reactive protein (CRP) is an acute-phase protein that is rapidly synthesized by the liver in response to infection, inflammation, and tissue damage. Besides its use as a biomarker of inflammation, CRP has been recognized as a pathogenic mediator in diabetic kidney disease,[55] obstructive nephropathy,[56] and AKI.[57–59] CRP is also inducible by high glucose in human TECs and promotes renal inflammation and fibrosis through activation of TGF-β/Smad and NF-κB signaling pathways under diabetic conditions and unilateral ureteral obstructive nephropathy.[55,56] Recent studies demonstrated that CRP promotes AKI by causing TEC G1 cell-cycle arrest via CD32-Smad3–dependent p27-driven inhibition of the cyclin-dependent kinase 2/cyclin E mechanism.[58,59]

## TECs as fibrogenic cells: tubule-derived factors associated with tubulointerstitial fibrosis

TECs often localize at the epicenter of kidney injury and are especially vulnerable to damage. After severe or recurrent injury, TECs undergo changes in structure and phenotype that are accompanied by altered expression and production of profibrotic factors. The main factors associated with tubulointerstitial fibrosis (TIF) are listed in Table 2.