Cellular and molecular pathways of renal repair after acute kidney injury

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The acutely injured mammalian kidney mounts a cellular and molecular response to repair itself. However, in patchy regions such intrinsic processes are impaired and dysregulated leading to chronic kidney disease. Currently, no therapy exists to treat established acute kidney injury *per se*. Strategies to augment human endogenous repair processes and retard associated profibrotic responses are urgently required. Recent studies have identified injury-induced activation of the intrinsic molecular driver of epithelial regeneration and induction of partial epithelial to the mesenchymal state, respectively. Activation of key developmental transcription factors drive such processes; however, whether these recruit comparable gene regulatory networks with target genes similar to those in nephrogenesis is unclear. Extensive complex molecular cross-talk between the nephron epithelia and immune, interstitial, and endothelial cells regulate renal recovery. *In vitro*–based M1/M2 macrophage subtypes have been increasingly linked to renal repair; however, the precise contribution of *in vivo* macrophage plasticity to repair responses is poorly understood. Endothelial cell–pericyte intimacy, balance of the angiocrine/antiangiocrine system, and endothelial cell–regulated inflammatory processes have an impact on renal recovery and fibrosis. Close scrutiny of cellular and molecular pathways in repairing human kidneys is imperative for the identification of promising therapeutic targets and biomarker of human renal repair processes.

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Despite advances in medical care, acute kidney injury (AKI) remains an independent predictor of in-hospital mortality. Depending on the clinical setting and underlying comorbidities, in-hospital mortality rates can approach 50% to 70%.[1,2] AKI frequently leads to chronic kidney disease (CKD),[3] with AKI survivors at ~9-fold, 3-fold, and 2-fold increased risk of progression to CKD, end-stage renal disease, and mortality, respectively, compared with patients without AKI.[4] Currently, no definite therapies exist to prevent or treat established AKI *per se*.

Proximal tubular epithelial cell (PTEC) death is the most common cause of AKI, and frequently occurs due to ischemic, toxic, septic, or obstructive insults.[5] PTECs are exquisitely sensitive to such insults, although distal tubular epithelial cells (TECs) also undergo apoptosis in human AKI.[6] The histologic features of human AKI include loss of brush border typical of PTECs, flattening and focal loss of renal TECs, and infiltration of inflammatory cells with the appearance of Tamm-Horsfall protein-rich urinary casts.[7] After injury, PTEC regeneration leads to the restoration of epithelial morphology and kidney function (Figure 1). However, particularly in regions of persistent or severe injury, the regenerative processes are frequently inefficient, impaired, and dysregulated, resulting in extensive tissue remodeling and fibrosis. These foci demonstrate persistently flattened tubular epithelium, chronic interstitial inflammation, microvascular dropout "capillary rarefaction," and the presence of α-smooth muscle actin–positive (α-SMA$^+$) myofibroblasts[8] (Figure 1). The injury-induced profibrotic milieu sets up a self-perpetuating vicious cycle of tubular atrophy, further nephron loss, and fibrosis, inexorably transforming AKI to CKD.

The *Oxford English Dictionary*'s definition of repair is to "restore (something damaged, faulty or worn) to a good condition." In contrast, regeneration is to generate again to its original form and function. Therefore, in this review, the word "regeneration" is used for the proximal tubular epithelium generated after injury, with complete restoration of basolateral polarity and acquisition of brush border. Of note, nephron epithelial regeneration can only be confirmed by genetic lineage tracing strategy, where progeny demarcating regenerated nephron epithelia display reattainment of the brush border and basolateral polarity. Harnessing and augmenting the human kidney's intrinsic regenerative processes and suppressing concomitant profibrotic responses is one of the approaches to treat established human AKI *per se*. To this end, deep critical understanding of the cellular and

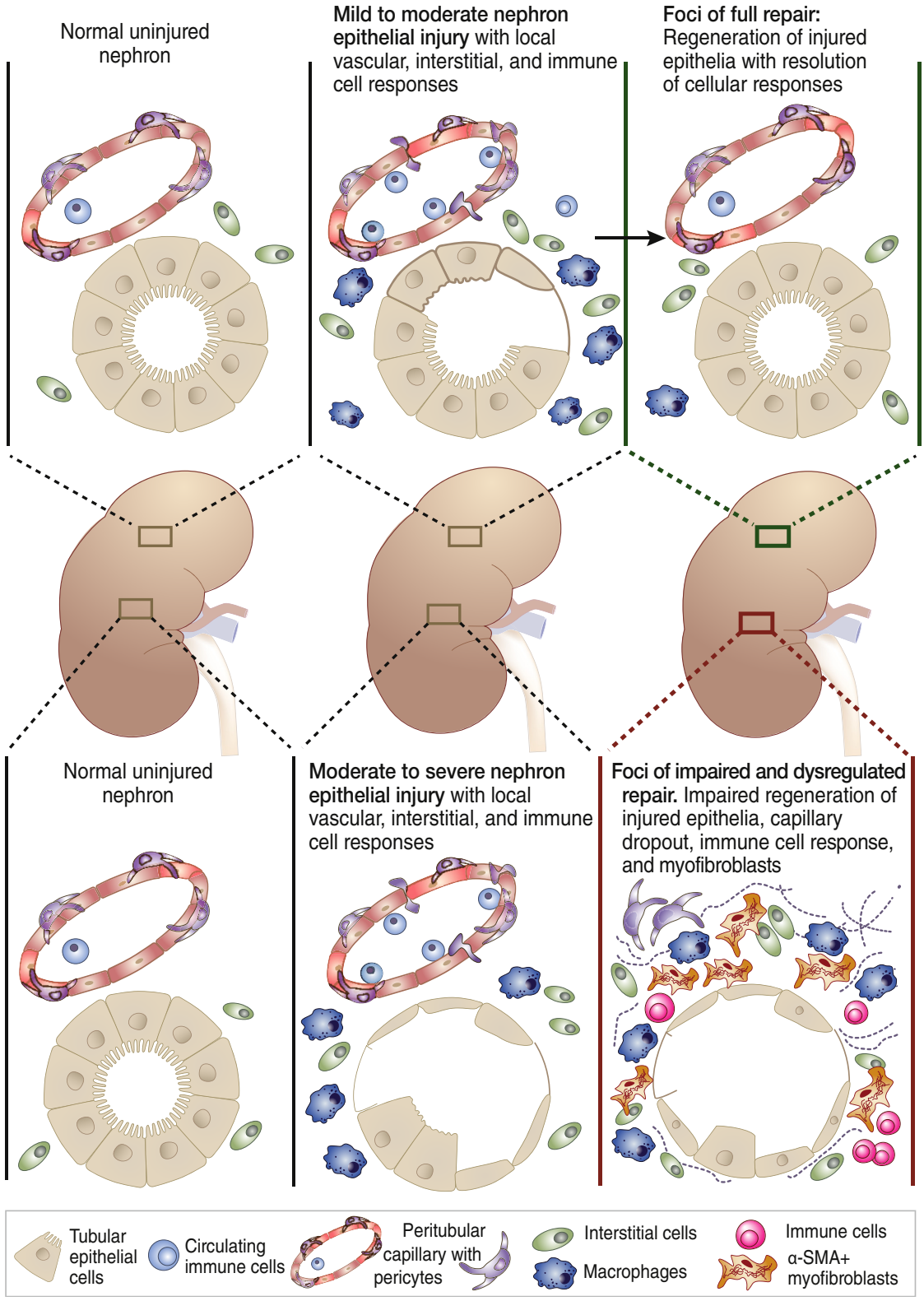

Figure 1 | Schematic illustration highlighting patchy regenerative/reparative processes after mammalian acute kidney injury. (Upper panels) Regions of mild to moderate acute nephron injury: the injured nephron epithelia regenerate, and such regions of full repair are restored to their previous morphology. (Lower panels) Nephrons with severe injury leading to extensive epithelial cell loss are less likely to regenerate the injured epithelia in its entirety. Such areas tend to be associated with peritubular capillary dropout with disruption of endothelial cell–pericyte organization, immune/inflammatory cell infiltration, fibroblasts, and α-SMA+ myofibroblasts, thereby highlighting foci of impaired and dysregulated repair processes with aberrant extracellular matrix remodeling. Such microdomains serve as a nidus of fibrosis. α-SMA, α-smooth muscle actin; IRI, ischemia reperfusion injury.