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A step towards understanding mechanisms of renal repair

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Abstract

In 2014, key articles in the field of acute kidney injury highlighted the importance of tubular homeostasis in renal regeneration. Cell cycle regulators, inflammatory signals and progenitors were identified as important factors that mediate the balance between inflammation and tubular regeneration necessary for renal repair.

“It is the fixity of the ‘*milieu interieur*’ which is the condition of free and independent life,” and “all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment,” wrote Claude Bernard in 1878,¹ introducing the concept of homeostasis. After a century of therapies that have focused on aggressively defeating disease, many human maladies remain beyond our ability to cure. Perhaps we may be returning to Bernard’s realization that the mastery of internal balance is as important as defeating ‘the enemy’ in complex medical conditions. Four publications from 2014 questioned current understanding of the sequelae of acute kidney injury (AKI) by offering an alternative view of the mechanisms that bring the acutely injured kidney back to homeostasis.

The kidney possesses the capacity to regenerate after injury but the origin of the progenitor cells that give rise to new tubular cells remains uncertain. Although cell lineage tracing has excluded extrinsic sources such as the bone marrow, whether tubules can regenerate from any surviving tubular cells or whether a specialized progenitor cell population exists, is unclear. Scattered tubular cells (STCs), which have high regenerative potential, have been characterized phenotypically using surface markers for dedifferentiation.² Their transcriptional profile is strikingly similar to that of glomerular parietal epithelial cells (PECs) but distinctly different from differentiated tubular cells. Berger *et al.* designed a series of cell lineage tracing experiments using PEC-specific, doxycycline-inducible

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Competing interests

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transgenic (PEC–rtTA) mice, to investigate the origin and functional role of STCs in experimental AKI.³ Upon administration of doxycycline to normal adult PEC–rtTA mice, transcriptional activity in the kidneys was induced in tubular cells with the STC phenotype but not in adjacent epithelial cells. Ischaemia–reperfusion (IR) injury resulted in upregulation of PEC–rtTA transcriptional activity in proximal tubules, where more than 80% of proliferating cells were PEC–rtTA-positive. Using lineage tracing, they determined that the PEC–rtTA transgene was induced during IR injury in previously unlabelled ‘normal’ tubular cells, indicating that STCs might arise from any surviving tubular cell. The notion that the STC phenotype could represent a transient regenerative phenotype or transcriptional programme in surviving tubular cells as a common response to injury, is supported by another 2014 study.⁴

Lech and colleagues tied the mechanism of tubular regeneration to the innate immune response in AKI, while questioning the common belief that macrophage-driven renal fibrosis is the main cause of progression to chronic kidney disease (CKD).⁵ During AKI, the necrotic tubules release molecules that activate Toll-like receptors (TLRs), trigger proinflammatory cytokines and recruit neutrophils and proinflammatory macrophages to the site of injury. Subsequent phagocytic uptake of apoptotic neutrophils induces a functional switch in the proinflammatory macrophages towards an immunoregulatory phenotype that promotes resolution of inflammation and fibrosis. IL-1 receptor–associated kinase-M (IRAK-M) is a macrophage-specific inhibitor of TLR signalling that prevents polarization towards a proinflammatory phenotype. Using IRAK-M-deficient mice Lech *et al.* demonstrated that IRAK-M-mediated deactivation of proinflammatory macrophages is required for resolution of renal inflammation and is a prerequisite for structural and functional tubular repair. IRAK-M-deficient macrophages produced significantly more TNF upon stimulation with lipopolysaccharide and had a greater potential to kill tubular cells than did wild-type macrophages. In contrast to the full recovery from AKI observed in wild-type mice, kidneys from IRAK-M-deficient mice displayed progressive shrinkage with predominantly tubular atrophy and degeneration of the glomerular–tubular junction rather than loss of glomeruli or excessive interstitial fibrosis as previously thought. Administration of a TNF antagonist to IRAK-M-deficient mice prevented loss of kidney mass, establishing the functional relevance of proinflammatory macrophages in mediating tubular injury and repair.

The above themes highlighting the importance of balanced pluripotency in AKI development and repair are reiterated in two clinical studies from 2014. Bihorac and colleagues validated tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) as risk markers for AKI.⁶ These are the first AKI biomarkers approved by the FDA for clinical use. The multicentre validation study, which involved 420 patients, found that the product obtained by multiplying urinary concentrations of TIMP-2 and IGFBP7 was predictive of moderate-to-severe AKI in critically ill patients within 12 h of obtaining a positive test. Unlike prior studies that evaluated these or other markers⁷ of AKI, the trial end point in this validation study was adjudicated by a committee of three independent experts who were blinded to the results of the test. The area under the receiver-operating-characteristic curve for this test was 0.82 (95% CI 0.76–0.88) and was

superior to simultaneously measured serum creatinine level for assessing the risk of imminent AKI. Patients with a urinary test result above a pre-specified high-sensitivity cutoff of 0.3 (ng/ml)²/1,000 had a 7-fold greater risk of AKI compared with individuals with normal test results and yet TIMP-2 and IGFBP7 are associated with G1 cell-cycle arrest, a protective mechanism against AKI. By virtue of their anatomical position, tubular cells are susceptible to multiple environmental stressors, including radiation, oxidative stress and inflammation. In order to avoid replicating with damaged DNA or when bioenergetic resources are scarce, epithelial cells enter cell-cycle arrest to protect themselves. Yet sustained cell-cycle arrest might result in cell senescence and lead to maladaptive repair. TIMP-2 and IGFBP7 are important components in the pathophysiology of injury with roles in both early tubular injury and tubular regeneration. Balance and timing are therefore key to understanding the effects of these signalling processes in providing renal protection, and when their activation can be used as an alarm signal to indicate an increased risk of renal injury.

Wald and colleagues examined recovery from severe AKI using a population-wide database from Ontario, Canada, to determine whether type of renal replacement therapy (continuous versus intermittent) is associated with the risk of chronic dialysis among survivors of AKI.⁸ The researchers followed 2,004 patients on continuous therapy and 2,004 matched patients on intermittent haemodialysis over 3 years. Risk of chronic dialysis was significantly lower among patients who initially received continuous therapy compared to those who initially received intermittent therapy (HR 0.75, 95% CI 0.65–0.87). The relationship was more prominent among those with pre-existing CKD and heart failure. Prior observational studies from around the world⁹ have suggested similar results, but randomized trials have found no such relationship. If such a relationship does exist it could reflect common anecdotal experience that continuous therapy enables a faster and more persistent resolution of disturbed homeostasis in AKI, associated with less haemodynamic instability, less fluid accumulation, improved nitrogen balance and more consistent drug dosing.

These studies have improved current understanding of how the kidney returns to homeostasis following injury. Rather than thinking of heroes and villains, we need to better understand the balance between inflammation, regeneration and repair and how this balance acts to restore homeostasis within the kidney. Factors that lead to a persistent predominance of proinflammatory macrophages, such as genetic deficiencies or bacterial DNA exposure, can prevent tubular regeneration, leading to tubular atrophy and mesenchymal scarring. The concept of persistent inflammation as a driver of failing homeostasis and chronic organ failure is increasingly recognized in complex human diseases linked to AKI, such as sepsis and trauma,¹⁰ and could underpin the observed differences related to dialysis modalities. The ability to recognize damage, or even stress to the kidneys before disruption of homeostatic balance occurs using validated biomarkers, and the development of novel interventions to promote homeostasis once injury occurs, are key tasks for the future of AKI clinical and translational research.

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Key advances

- Scattered tubular cells have regenerative potential and may represent a transient regenerative phenotype or transcriptional programme in surviving tubular cells following acute kidney injury (AKI)³
- Regulation of proinflammatory macrophages following injury is required for resolution of renal inflammation and structural and functional repair⁵
- The cell cycle arrest markers TIMP-2 and IGFBP7 can be used to predict the risk of AKI and indicate the importance of cell cycle regulation in injury and repair⁶
- Continuous renal replacement therapy might be associated with a lower risk of chronic dialysis than is intermittent haemodialysis, particularly among patients with pre-existing chronic kidney disease and heart failure⁸