McWilliam, S., Wright, R., Welsh, G. I., Tuffin, J., Budge, K., Swan, L., Will, T., Martinas, I-R., Littlewood, J., & Oni, L. (2020). The complex interplay between kidney injury and inflammation. Clinical Kidney Journal, [sfaa164]. https://doi.org/10.1093/ckj/sfaa164

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
10.1093/ckj/sfaa164

Link to publication record in Explore Bristol Research

PDF-document

This is the final published version of the article (version of record). It first appeared online via Oxford University Press at https://doi.org/10.1093/ckj/sfaa164. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/
The complex interplay between kidney injury and inflammation

Stephen J. McWilliam1,2, Rachael D. Wright2, Gavin I. Welsh3, Jack Tuffin3, Kelly L. Budge2, Laura Swan4, Thomas Wilm4, Ioana-Roxana Martinas4, James Littlewood4,5 and Louise Oni2,6

1Department of Paediatric Pharmacology, Alder Hey Children’s Hospital, Liverpool, UK, 2Department of Women and Children’s Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK, 3Bristol Renal, Bristol Medical School, University of Bristol, Bristol, UK, 4Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK, 5Department of Nephrology, Royal Liverpool University Hospital Hospital, Liverpool, UK and 6Department of Paediatric Nephrology, Alder Hey Children’s NHS Foundation Trust Hospital, Liverpool, UK

Correspondence to Louise Oni; E-mail: louise.oni@liverpool.ac.uk

ABSTRACT

Acute kidney injury (AKI) has gained significant attention following patient safety alerts about the increased risk of harm to patients, including increased mortality and hospitalization. Common causes of AKI include hypovolaemia, nephrotoxic medications, ischaemia and acute glomerulonephritis, although in reality it may be undetermined or multifactorial. A period of inflammation either as a contributor to the kidney injury or resulting from the injury is almost universally seen. This article was compiled following a workshop exploring the interplay between injury and inflammation. AKI is characterized by some degree of renal cell death through either apoptosis or necrosis, together with a strong inflammatory response. Studies interrogating the resolution of renal inflammation identify a whole range of molecules that are upregulated and confirm that the kidneys are able to intrinsically regenerate after an episode of AKI, provided the threshold of damage is not too high. Kidneys are unable to generate new nephrons, and dysfunctional or repeated episodes will lead to further nephron loss that is ultimately associated with the development of renal fibrosis and chronic kidney disease (CKD). The AKI to CKD transition is a complex process mainly facilitated by maladaptive repair mechanisms. Early biomarkers mapping out this process would allow a personalized approach to identifying patients with AKI who are at high risk of developing fibrosis and subsequent CKD. This review article highlights this process and explains how laboratory models of renal inflammation and injury assist with understanding the underlying disease process and allow interrogation of medications aimed at targeting the mechanistic interplay.

Keywords: acute kidney injury, glomerulonephritis, inflammation, renal fibrosis
INTRODUCTION

Over the past few years, acute kidney injury (AKI) has gained significant attention following patient safety alerts about the increased risks of harm to patients who experience an episode of AKI. It is estimated that one in five emergency admissions into hospital is associated with AKI [1] and that one in three patients in hospital with AKI develops it while in hospital [2]. AKI is responsible for prolonging inpatient care and contributing to ~100 000 deaths annually in the UK [3]. AKI is defined as a sudden alteration in the function of the kidney due to a variety of causes. It is typically reported in terms of measurable clinical outcomes, with an increase in the serum creatinine concentration and/or a reduction in the patient’s urine output being the most universally recognized definition [4]. These measurable outcomes define whether a patient has clinical features of AKI and they have improved standardization across clinical settings and research studies. However, they tell us very little about the underlying cause or mechanisms that have led to the injury itself. The most common causes of AKI include hypovolaemia, nephrotoxic medications, ischaemia and acute glomerulonephritis, although in reality it may be undetermined or multifactorial [5, 6]. Within the mechanisms of AKI, one likely area of consistency is a period of inflammation either as a contributor or as a consequence of the renal injury, for example, systemic lupus erythematosus as an inflammatory disease causing glomerulonephritis or nephrotoxic kidney injury causing local renal inflammation, respectively. This article was compiled as a result of a multispecialty kidney injury and inflammation event attended by the authors. The aim of this review is to discuss the complex interplay between kidney injury and inflammation with regard to its mechanisms, diagnosis and potential targets for treatment. It also aims to consider future directions for further research to help improve our understanding of this disease process and improve the clinical outcomes of our patients.

CELLULAR AND MOLECULAR MECHANISMS OF INFLAMMATION IN RESPONSE TO RENAL INJURY

Understanding the cellular and molecular mechanisms that lead to renal inflammation is one of the most promising ways to identify early targets for treatment or prevention of AKI (Figure 1). Inflammation is a physiological process designed to protect the body against an acute injurious stimulus, such as ischaemia, toxins or pathogens. In a healthy individual, these stimuli are initially detected by the kidney through immune cells that include not only tissue-resident dendritic cells and macrophages, but also native renal cells that are able to express receptors for sensing damage (for excellent recent reviews on the interactions between kidneys and the immune system, the reader is directed to Ernandez et al. [7] and Tecklenborg et al. [8]). These intrarenal immune cells respond to such stimuli by actively secreting cytokines such as interleukin (IL)-1 and IL-6 and chemokines such as monocyte chemoattractant protein-1,
which migrate to nearby blood vessels and recruit leucocytes from the circulation to the area of damage to destroy invading pathogens, repair damaged tissue and restore tissue homeostasis [9].

The recruitment of leucocytes to the kidney occurs in a sequential manner to efficiently repair damage and restore renal function. Neutrophils are usually the first to be recruited to the area, as these cells are non-specific and are able to release their toxic granule contents to destroy invading pathogens at the site of inflammation [10]. However, as this is non-specific, these cells are also able to induce tissue damage and thus a second phase of monocytes is recruited from the bloodstream. These cells are more specific and can be subdivided into two groups: M1 and M2 monocytes. M1 monocytes release cytokines to destroy any pathogens that were not destroyed by the neutrophils. M2 monocytes differentiate into macrophages and phagocytose damaged tissue and apoptotic neutrophils to restore homeostasis to the tissue [11].

Studies interrogating the resolution of renal inflammation in acute inflammatory models identified a whole range of molecules that are increased in the tissue during the resolution phase of inflammation [12]. These molecules are most commonly lipid mediators that are released by neutrophils and monocytes at the site of inflammation, where they act to reduce the infiltration of neutrophils and promote the phagocytic clearance of apoptotic cells by macrophages [13]. Many in vitro and in vivo studies have been performed assessing the role of these lipid mediators in preventing or treating AKI. They have been shown to mitigate sepsis-associated AKI [14], improve tubular function after kidney ischaemia–reperfusion (KIR) injury [15] and blunt the development of lupus nephritis in lupus-prone New Zealand Black × New Zealand White (NZB/W) F1 mice [16].

**AKI AND ITS PROGRESSION TO CHRONIC KIDNEY DISEASE (CKD)**

Irrespective of the underlying cause, AKI is characterized by some degree of renal cell death through either apoptosis or necrosis and a strong inflammatory response [17, 18]. More recent studies have demonstrated evidence of necroptosis, ferroptosis, parthanatos and mitochondrial permeability transition-induced regulated necrosis [19]. These all represent different pathways leading to an inflammatory response and thus different targets for potential AKI therapeutic development. While epithelial cells of the proximal tubule are mostly affected in the main causes of AKI, there is also significant damage to the endothelial and smooth muscle cells and obviously a predominance of glomerular damage in AKI due to glomerulonephritis [20, 21]. Studies have demonstrated that podocyte injury precedes tubular injury and can be seen as early as 30 min post-reperfusion in KIR injury in mice [22]. After the initial injury, surviving cells undergo a process of dedifferentiation and proliferation to replace damaged cells and restore integrity [23–25]. Previous studies have indicated that the kidneys are able to intrinsically regenerate after an episode of AKI provided that the threshold of damage is not too high [26, 27].

However, kidneys are unable to generate new nephrons, and maladaptive or repeated episodes of AKI will lead to further nephron loss and injury that is ultimately associated with CKD and end-stage renal disease (ESRD) [26–28]. In addition, a single episode of AKI puts patients at risk of future episodes of AKI, which, in combination with individual modifiers, increases the risk of developing CKD and ESRD [29, 30] (Figure 2). The AKI to CKD transition is a complex process that was reviewed recently by Sato and Yanagita [31]. The transition is mainly facilitated by maladaptive repair that facilitates fibrosis and CKD [32]: the

![Figure 2: A summary of the pathway determining an individual patient’s outcome of AKI. A patient experiences an episode of AKI following a certain stimuli, such as sepsis or ischaemia, resulting in an inflammatory process that can be modified by an individual’s genetic predisposition and may be further insulted by primary modifiers including age and pre-existing disease. Secondary modifiers include additional hits such as haemodynamic instability, nephrotoxic pharmacotherapy or other interventions (radiological investigations). These impact on the subsequent inflammatory response and the eventual AKI outcome.](https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfaa164/5934685)
process of dedifferentiation can lead to failed tubule recovery, a decrease in epithelial markers and an increase in mesenchymal markers [25, 33, 34]. Damaged tubules, as well as immune cell-derived myofibroblasts, are a source of pro-fibrotic factors and are associated with the subsequent development of fibrosis and scarring. Whereas the process of fibrosis is meant to prevent further damage, it also reduces renal function by promoting capillary rarefaction and exacerbating hypoxia and atrophy [32, 34, 35]. Currently >100 therapies have proven effective in animal models of AKI and yet none are effective in preventing AKI in people or preventing the transition from AKI to CKD [36]. Understanding the complex interaction between renal inflammation and injury may allow earlier identification and subsequent intervention to prevent the onset of irreversible fibrosis.

CLINICAL EXAMPLES OF AKI AND ITS INFLAMMATORY MECHANISMS

One must consider the clinical context in which kidney injury or inflammation has occurred: in several cases, the injury and/or inflammation may be sequelae of ongoing systematic disease or even due to genetic disorders or acquired injuries where inflammation may not classically be considered. Below we outline some clinical examples that either directly or indirectly affect kidney function and explore what factors may limit treatment options.

AKI following cardiac bypass surgery

The process of cardiopulmonary bypass is acknowledged to cause sudden alterations in renal perfusion, with consequent ischaemia and reperfusion cycles [37]. During ischaemia, aerobic respiration within mitochondria ceases. The metabolites of the citric acid cycle, required for aerobic respiration via electron transport, become depleted, except for succinate, which accumulates during ischaemia [38]. Upon reperfusion the accumulated succinate in mitochondria is rapidly oxidized, driving superoxide formation via reverse electron transport at complex 1 of the electron transport chain [38]. This burst of superoxide [39, 40] is then followed by further superoxide formation via the xanthine oxidase pathway and nicotinamide adenine dinucleotide phosphate oxidases [41]. Production of reactive oxygen species (ROS) activates a variety of pathways that lead to tissue injury. These include opening of the mitochondrial permeability transition pore, leading to apoptosis or necrosis, and induction of damage-associated molecular patterns, leading to activation of both innate and adaptive immune responses [42]. Production of ROS also induces pro-inflammatory transcription factors such as nuclear factor-κB [43], leading to recruitment of inflammatory cells to the renal parenchyma and the potential for fibrosis [44]. Clinically between 30 and 50% of patients develop AKI following cardiopulmonary bypass surgery [45] and strategies to ameliorate this in adults have included large randomized controlled trials to evaluate the use of perioperative methylprednisolone, but with little benefit [46]. Typically patients have a period of AKI spanning several days while the repair mechanisms restore renal function. Of those with AKI, many (~12% in congenital heart disease) will develop CKD within 5 years [45].

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease has traditionally been considered a disease of adulthood, however, chronic inflammation is observed early in this disorder, with M1 and M2 macrophages modulating fibrosis and increasing deposition of extracellular matrix to which inflammatory cells are recruited [47]. In mouse models, ablation of the adhesion molecule β1 integrin reduces both the formation of cysts and fibrosis [48], suggesting that crosstalk between extracellular matrix and inflammatory cytokines may be a fruitful approach to disease management. Likewise, the physical presence of cysts in these patients makes controlling infection and inflammation difficult; antibiotics have some difficulty in penetrating infected kidney cysts, which makes urinary tract infections more damaging [49]. A recent development in this condition has seen the introduction of an effective pharmacological treatment to suppress the growth of kidney cysts using the vasopressin inhibitor tolvaptan [50] and preclinical studies are evaluating adenosine monophosphate–activated protein kinase as a signalling target [51].

Low syndrome/Dent2 disease

These are rare multisystemic X-linked disorders affecting brain, kidney, eyes and bone. The kidney disorder manifests in defective resorption of metabolites in the proximal tubule, leading, if untreated, to rickets, aminoaciduria and disturbance of parathyroid hormone signalling [52]. Treatments are lifelong supplementation of metabolites and close management of symptoms. These patients frequently develop kidney stones due to excessive calcium loss [52], which then deposits in the kidney, causing a progressive process of kidney scarring and fibrosis leading to ESRD between the second and fourth decades of life. Work in model systems suggests that defects in the causative gene OCRLinositol polyphosphate-5-phosphatase (OCRL) also manifest as increased amplification of inflammatory immune signalling [53]. Interestingly, Lowe syndrome patients frequently exhibit tenosynovitis, joint swelling and arthritis [54], which may indicate immune misregulation. This has been reversed in animal models by injection of virally encoded OCRL to affected chondrocytes [55], although this is not yet a therapy that can be deployed in humans.

FUTURE DIRECTIONS

Earlier detection using biomarkers

Standard clinical practice continues to focus on changes in serum creatinine and urine output as markers of kidney injury despite research on novel biomarkers receiving increased attention over the last 15 years [56]. The ongoing success of creatinine as the biomarker of choice is derived from the fact that it is endogenous, easily measured, well-validated and used in formal staging criteria. Creatinine’s limitations are the relative requirement to have a comparative baseline value to aid interpretation, non-glomerular elimination via the proximal tubule and gastrointestinal tract and interference from commonly prescribed drugs [57]. A number of exogenous markers can be measured in the blood, urine and via nuclear imaging [58]. The use of exogenous markers of injury and function is much less frequently favoured due to the added technical complexity and additional expense. However, markers such as technetium-99m diethylenetriaminepentaacetate give useful additional information about the, for example, differential function between kidneys (split function).

Current clinical practice to measure renal inflammation remains limited. Renal histology remains the gold standard and
is usually required in the diagnosis of acute glomerulonephritis [59]. However, interobserver variability can be poor, as demonstrated in a study assessing renal histology slides from patients with lupus nephritis [60]. Examining the urine for sediment and casts seems to have fallen out of favour, but in trained hands it can provide a wealth of information [61]. Glomerular inflammation may be inferred from the degree of proteinuria and serological markers such as C-reactive protein, erythrocyte sedimentation rate and eosinophilia may be suggestive of inflammatory conditions but are not renal specific.

Novel markers can be categorized as endogenous or exogenous. They can be measured in the serum, urine or via imaging methods. A list of considered biomarkers for AKI is presented in Table 1. Criticisms of these markers include the limited clinical settings that these are tested in, their role when measured in isolation, as recent studies have suggested the need to develop an AKI panel to compensate for specificity and sensitivity deficiencies, and that some markers may be generated extrarenally (e.g. neutrophil gelatinase-associated lipocalin in states of infection or physiological stress [62, 75]). In a clinical setting, an endogenous marker would be preferable to simplify the technical process in large patient groups. Due to its obvious proximity, urine has been implicated as the best site for early detection of kidney injury [75], but despite many of these novel biomarkers appearing within the literature, none of these are in routine clinical use.

**Targets to modify AKI outcome**

Treatment options in AKI remain experimental and, aside from treating the underlying cause, current clinical management for AKI is conservative, with careful fluid and electrolyte control and supportive renal replacement therapy when indicated. Virtually all immune cells are implicated in the pathogenesis of AKI and blockade of several innate immune receptors (e.g. toll-like receptor 2) has been shown to ameliorate experimental AKI in animal models, although their translation into clinical practice is uncertain [36]. Targeting pro-fibrotic signalling cascades may be another useful way to modify AKI, for example, fibroblast growth factor 23 (FGF23) induces pro-fibrotic signalling via activation of the transforming growth factor (TGF)-β pathway in kidney cells primed with injury. Individual genetic variants may predispose patients to increased concentrations of FGF23 and modify the inflammatory response to acute injury stimuli [76]. Direct inhibitors specifically targeting FGF23 are not available. However, it may be indirectly reduced by inhibition of the renin-angiotensin- aldosterone system. Post-translational modification proteins called small ubiquitin-related modifiers are extensively expressed in eukaryotes and influence the individual response to the activation of the nuclear factor b inflammatory signalling pathway. Therefore they play a central regulatory role in the inflammatory response and may have a role in contributing to the TGF-β/Smad pathway, leading to fibrosis of the kidney [77].

**Preclinical modelling of AKI**

Part of the reason for the limited treatment options is the inability of existing preclinical disease models to accurately recapitulate kidney injury. Additionally, the lack of validated AKI biomarkers has resulted in a disconnect and ultimately poor translation between preclinical and clinical models [78]. Inflammation and kidney injury are tightly coupled and for a model to be useful for the study of mechanisms or to assist with drug discovery, it needs to incorporate this cyclical phenomenon. However, modelling of this complexity is difficult, with researchers subsequently forced to strike a balance between the scalability of an experimental model and the degree of disease homology (Figure 3).

The approach with the greatest scalability is in silico modelling, which uses bioinformatics and chemoinformatics to hypothesize and test during drug discovery [79]. These methods are capable of screening virtual compound libraries and simulating their binding using structural data. However, computational approaches are limited by our understanding of the binding targets in question [80] and are held back by biomarker discrepancies [78]. In addition, in silico models are often validated using poor in vitro models, thus reducing disease

| Table 1. A summary of the urine biomarkers implicated in renal injury and inflammation |
|---------------------------------|---------------------------------|
| **Biomarkers implicated in renal injury** | **Biomarkers implicated in renal inflammation** |
| [61–71] | [72–74] |
| Neutrophil gelatinase-associated lipocalin | Pentraxins |
| Kidney injury molecule-1 | IL-1-β |
| Cystatin C | Tumour necrosis factor-α |
| IL-6 and -18 | IL-8 |
| Retinol-binding protein | IL-12 |
| Glutathione S-transferase (x, n, η) | Interferon γ |
| Urinary insulin-like growth factor-binding protein 7 | Tissue inhibitor of metalloprotei-nases-2 |
| Micro-ribonucleic acids | Anti-inflammatory cytokines |
| Na⁺/H⁺ exchanger isofrom 3 | IL-1 receptor antagonist |
| Perforin | IL-4 |
| Granzyme B | TGF-β |
| Monocyte chemoattractant protein-1 (chemokine ligand 2) | Adipokines and related compounds |
| N-acetyl-β-D-glucosaminidase | Visfatin |
| Liver-type fatty acid-binding protein | Resistin |
| Nitrin-1 | Leptin |
| Clusterin | CD163 |
| β2-microglobulin | Vascular cell adhesion molecule-1 |
| Matrix metalloproteinases | E-selectin |
| Endogenous ouabain | Neopterin (monocyte/macrophage activator) |
| Selenium-binding protein 1 | N-acetyl-beta-D-glucosaminidase |
| BPI fold containing family A member 2 | Resistin |
| salivary protein | Leptin |
| Chromophores via multispectral optoacoustic tomography, e.g. IRDye 800CW carboxylate | CD163 |
| Fluorophores via transcutaneous detection, e.g. fluorescein isothiocyanate–sinistrin | Vascular cell adhesion molecule-1 |
| Dickkopf-3 | E-selectin |

Many urinary biomarkers have been evaluated to determine their role in the early identification of renal injury and inflammation within the literature, as demonstrated within this table. While many are implicated in isolation, their strength is evident once combined to produce a panel of biomarkers.
homology. Two-dimensional cell models are also highly scalable and conditionally immortalized human podocytes [81], glomerular endothelial cells [82] and mesangial cells [83] are used routinely to model kidney disease in vitro. For high-throughput assays, cells are often grown in monoculture on culture plastic in a way far removed from their in vivo niche. For podocytes, this has been shown to deleteriously affect proteome and transcriptome readouts, hampering their capacity for simulating disease [84].

It is apparent that co-culturing renal cells in three dimensions helps to better recapitulate the three-dimensional architecture and signalling environment of in vivo tissue [85, 86]. Moreover, these bioengineered models of acute and chronic injury offer superior toxicology sensitivity than their two-dimensional cultured counterparts [87]. However, models such as this are far less scalable and reproducible than two-dimensional cell models and as such are not suitable for high-throughput screening. Kidney-on-a-chip approaches seek to add flow to cultured cells and have successfully bioengineered a kidney tubule from conditionally immortalized human proximal tubule epithelial cells [88]. It is also possible for multiorgan systems to be established, including sequentially connected gut, liver and kidney cells [89]. These models have the potential to simulate the cyclical nature of kidney injury, although they are currently very low throughput, impeding their usefulness for screening.

The advent of kidney organoids from induced pluripotent stem cells represents a significant step in the right direction for improving disease homology of in vitro models [90]. These systems have the potential to model genetically acquired disease such as Alport syndrome [91]. Improving the scalability of these models is once again a challenge, however, if they are to be used for drug screening. In vivo animal disease models (despite modelling non-human disease) currently offer the greatest simulation of the many comorbidities that underpin kidney injury. Among these, rodent models of ischaemia-reperfusion [92] and uretic obstruction [93] are most ubiquitous. However, it is not possible to use animal models for the early stages of compound screening, which means that cell models must first be used.

There is a clear need for refinement in the high-throughput models used in the early stages of drug discovery. An in vitro model of kidney injury that is jointly scalable and representative of the disease, with transferable biomarker readouts, would drastically improve the translation between preclinical and clinical models.

CONCLUSIONS
Historically the lack of consensus definitions for AKI and a limited understanding of the pathophysiology of AKI has impeded advances in the management of these patients and the development of new treatments. The advent of a widely accepted definition of AKI has opened the way for more valuable research in this field. Here we have considered the role of inflammation within the mechanism of kidney injury and identified future directions for research that will translate into improved understanding of mechanisms to benefit patients.

FUNDING
This article was compiled as a result of a multispecialty kidney injury and inflammation event attended by the authors that was financially supported by an unrestricted educational grant from AOP Orphan Pharmaceuticals UK and a local institutional research development award.

CONFLICT OF INTEREST STATEMENT
None declared.

REFERENCES
1. Wang HE, Muntner P, Chertow GM et al. Acute kidney injury and mortality in hospitalized patients. *Am J Nephrol* 2012; 35: 349–355
2. Argyropoulos A, Townley S, Upton PM et al. Identifying on admission patients likely to develop acute kidney injury in hospital. *BMC Nephrol* 2019; 20: 1–11
3. Stewart JA. Adding insult to injury: care of patients with acute kidney injury. *Br J Hosp Med* 2009; 70: 372–373
4. Kidney Disease: Improving Global Outcomes Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2: 1–138
5. Uber AM, Sutherland SM. Nephrotoxins and nephrotoxic acute kidney injury. *Pediatr Nephrol* 2019; doi: 10.1007/s00467-019-04397-2
6. Fenoglio R, Sciascia S, Baldovino S et al. Acute kidney injury associated with glomerular diseases. *Curr Opin Crit Care* 2019; 25: 573–579
7. Fernandez T, Mayadas TN. The changing landscape of renal inflammation. *Trends Mol Med* 2016; 22: 151–163
8. Tecklenborg J, Clayton D, Siebert S et al. The role of the immune system in kidney disease. *Clin Exp Immunol* 2018; 192: 142–150
9. Rabb H, Griffin MD, McKay DB et al. Inflammation in AKI: current understanding, key questions, and knowledge gaps. *J Am Soc Nephrol* 2016; 27: 371–379
10. Faurchou M, Borregaard N. Neutrophil granules and secretory vesicles in inflammation. Microbes Infect 2003; 5: 1317–1327
11. Cao Q, Harris DC, Wang Y. Macrophages in kidney injury, inflammation, and fibrosis. Physiology (Bethesda) 2015; 30: 183–194
12. Serhan CN, Clish CB, Brannon J et al. Novel functional sets of lipid-derived mediators with anti-inflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing, J Exp Med 2000; 192: 1197–1204
13. Dalli J, Serhan CN. Specific lipid mediator signatures of human phagocytes: microparticles stimulate macrophage effectorcytosis and pro-resolving mediators. Blood 2012; 120: e60–e72
14. Sun S, Wang J, Wang JX et al. Maresin 1 mitigates sepsis-associated acute kidney injury in mice via inhibition of the NF-κB/STAT3/ MAPK pathways. Front Pharmacol 2019; 10: 1523
15. Rund KM, Peng S, Greite R et al. Dietary omega-3 PUFA improved tubular function after ischemia induced acute kidney injury in mice but did not attenuate impairment of renal function. Prostaglandins Other Lipid Mediat 2020; 146: 106386
16. Hye Khan MA, Stavniichuk A, Sattar MA et al. Epoxycisatrienoic acid analog EET-A blunts development of lupus nephritis in mice. Front Pharmacol 2019; 10: 512
17. Zhang M-Z, Yao B, Yang S et al. CSF-1 signaling mediates recovery from acute kidney injury. J Clin Invest 2012; 122: 4519–4532
18. Zager RA, Johnson ACM, Becker K. Acute unilateral ischemic renal injury induces progressive renal inflammation, lipid accumulation, histone modification, and "end-stage" kidney disease. Am J Physiol Renal Physiol 2011; 301: F1334–F1345
19. Linkermann A. Nonapoptotic cell death in acute kidney injury and transplantation. Kidney Int 2016; 89: 46–57
20. Tögel F, Weiss K, Yang Y et al. Vasculotropic, paracrine actions of infused mesenchymal stem cells are important to the recovery from acute kidney injury. Am J Physiol Renal Physiol 2007; 292: F1626–F1635
21. Basile DP. The endothelial cell in ischemic acute kidney injury: implications for acute and chronic kidney. Kidney Int 2007; 72: 151–156
22. Chen Y, Lin L, Tao X et al. The role of podocyte damage in the etiology of ischemia-reperfusion acute kidney injury and post-injury fibrosis. BMC Nephrol 2019; 20:106
23. Witzgall R, Brown D, Schwarz C et al. Localization of proliferating cell nuclear antigen, vimentin, c-Fos, and clusterin in the postischemic kidney. Evidence for a heterogenous gene expression among nephron segments, and a large pool of mitotically active and dedifferentiated cells. J Clin Investig 1994; 93: 2175–2188
24. Kusaba T, Lalli M, Kramann R et al. Differentiated kidney epithelial cells repair injured proximal tubule. Proc Natl Acad Sci USA 2014; 111: 1527–1532
25. Shu S, Zhu J, Liu Z et al. Endoplasmic reticulum stress is activated in post-ischemic kidneys to promote chronic kidney disease. EBioMedicine 2018; 37: 269–280
26. Humphreys BD, Valerius MT, Kobayashi A et al. Intrinsic epithelial cells repair the kidney after injury. Cell Stem Cell 2008; 2: 284–291
27. Anders HJ. Immune system modulation of kidney regeneration—mechanisms and implications. Nat Rev Nephrol 2014; 10: 347–358
28. Huen SC, Cantley LG. Macrophage-mediated injury and repair after ischemic kidney injury. Pediatr Nephrol 2015; 30: 199–209
29. John D, Imig MJR. Immune and inflammatory role in renal disease. Compr Physiol 2014; 3: 957–976
30. Jang HR, Rabb H. Immune cells in experimental acute kidney injury. Nat Rev Nephrol 2015; 11: 88–101
31. Sato Y, Yanagita M. Immune cells and inflammation in AKI to CKD progression. Am J Physiol Renal Physiol 2018; 315: F1501–F1512
32. Basile DP, Bonventre JV, Mehta R et al. Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. J Am Soc Nephrol 2016; 27: 687–697
33. Kang HM, Ahn SH, Choi P et al. Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development. Nat Med 2015; 21: 37–46
34. Venkatachalam MA, Weinberg JM, Kizr W et al. Failed tubule recovery. J Am Soc Nephrol 2015; 26: 1765–1776
35. Norman JT, Fine LG. Intra-renal oxygenation in chronic renal failure. Clin Exp Pharmacol Physiol 2006; 33: 989–996
36. Okusa MD, Rosner MH, Kellum JA et al. Therapeutic targets of human AKI: harmonizing human and animal AKI. J Am Soc Nephrol 2016; 27: 44–48
37. O’Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: current understanding and future directions. Crit Care 2016; 20: 187
38. Chouchani ET, Pell VR, Gaude E et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. Nature 2014; 515: 431–435
39. Chouchani ET, Pell VR, James AM et al. A unifying mechanism for mitochondrial superoxide production during ischemia-reperfusion injury. Cell Metab 2016; 23: 254–263
40. Jassem W, Fuggle SV, Rela M et al. The role of mitochondria in ischemia/reperfusion injury. Transplantation 2002; 73: 493–499
41. Kezic A, Stajic N, Thaiss F. Innate immune response in kidney ischemia/reperfusion injury: potential target for therapy. J Immunol Res 2017; 2017: 1–10
42. Martin JL, Gruszczczyk AV, Beach TE et al. Mitochondrial mechanisms and therapeutics in ischaemia reperfusion injury. Pediatr Nephrol 2019; 34: 1167–1174
43. Wei C, Li L, Kim IK et al. NF-κB mediated miR-21 regulation in cardiomyocytes apoptosis under oxidative stress. Free Radic Res 2014; 48: 282–291
44. Schrier RW. Diseases of the Kidney and Urinary Tract, 8th ed. Philadelphia: Lippincott, Williams and Wilkins, 2007
45. Madsen NL, Goldstein SL, Frøsløv T et al. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. Kidney Int 2017; 92: 751–756
46. Garg AX, Chan MT, Cuerden MS et al. Effect of methylprednisolone on acute kidney injury in patients undergoing cardiac surgery with a cardiopulmonary bypass pump: a randomized controlled trial. CMAJ 2019; 191: E247–E256
47. Bergmann C, Guay-Woodford LM, Harris PC et al. Polycystic kidney disease. Nat Rev Dis Primers 2018; 4: 51
48. Lee K, Boctor S, Barisoni LM et al. Inactivation of integrin-β1 prevents the development of polycystic kidney disease after the loss of polycystin-1. J Am Soc Nephrol 2015; 26: 888–895
49. Anselmo A, Iaria G, Pellicciaro M et al. Native nephrectomy in patients with autosomal dominant polycystic kidney disease.
p Missenden M, Ahmed FJ, Hardingham TE et al. The role of epithelial cell adhesion molecule in kidney disease. J Am Soc Nephrol 2019; 30: 162–174
90. Acton RJ, Tang HS, Zeisberg EM et al. Review of kidney mesenchymal cell signalling: a novel target for anti-fibrotic therapy. J Am Soc Nephrol 2019; 30: 175–185
91. Benett GD, O'Donnell N, Jacoby SJ et al. Urinary urinary insulin-like growth factor-1 measures renal injury in chronic kidney disease. Clin Chem Lab Med 2019; 57: 161–170
92. Blackley J, Drysdale M, Jablecki C et al. In vitro model for the evaluation of drug-induced kidney injury. Am J Kidney Dis 2019; 73: 652–662
93. Blind E, Benn TO, Henriksen L et al. Urinary acetylcholinesterase activities are associated with renal function in type 2 diabetes. Sci Rep 2019; 9: 18098
94. Boden C, Biermann P, Grötzinger J et al. Circulating des-OCRL maintains dOCRL maintaining dOCRL maintains immune cell quiescence by regulating endosomal traffic. PLoS Genet 2017; 13: e1007052
95. Bökenkamp A, Ludwig M. The oculocephalorrenal syndrome of Lowe: an update. Pediatr Nephrol 2016; 31: 2201–2212
96. Zhu S, Dai J, Liu H et al. Down-regulation of Rac GTPase-activating protein OCRL1 causes aberrant activation of rac1 in osteoarthrosis development. Arthritis Rheumatol 2015; 67: 2154–2163
97. Berli T. American Society of Nephrology Renal Research Report. J Am Soc Nephrol 2005; 16: 1886–1903
98. Steedon S, Chesser A, Cunningham J et al. Oxford Handbook of Nephrology and Hypertension. Oxford: Oxford University Press, 2014.
99. Soveri I, Berg UB, Björk J et al. Measuring GFR: a systematic review. Am J Kidney Dis 2014; 64: 411–424
100. Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2020; 2: 129–174
101. Oni L, Beresford MW, Witte D et al. Inter-observer variability of the histological classification of lupus glomerulonephritis in children. Lupus 2017; 26: 1205–1211
102. Perazella MA. The urine sediment as a biomarker of kidney disease. Am J Kidney Dis 2015; 66: 748–755
103. Beker BM, Corleto MG, Fieras C et al. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. Int Urol Nephrol 2018; 50: 705–713
104. Siew ED, Ware LB, Ikizler TA. Biological markers of acute kidney injury. J Am Soc Nephrol 2011; 22: 810–820
105. Beltrami C, Clayton A, Phillips AO et al. Analysis of urinary microRNAs in chronic kidney disease. Biochem Soc Trans 2012; 40: 875–879
106. Du Cheyron D, Daubin C, Poggiole J et al. Urinary measurement of Na+/H+ exchanger isoform 3 (NHE3) protein as a marker of tubule injury in critically ill patients with ARF. Am J Kidney Dis 2003; 42: 497–506
107. Li B, Hartono C, Ding R et al. Noninvasive diagnosis of renal-allograft rejection by measurement of messenger RNA for perforin and granzyme B in urine. N Engl J Med 2001; 344: 947–954
108. Skálová S. The diagnostic role of urinary N-acetyl-β-D-gluco-saminidase (NAG) activity in the detection of renal tubular impairment. Acta Med 2005; 48: 75–80
109. Dieterle F, Perentes E, Cordier A et al. Urinary clusterin, cystatin C, B2-microglobulin and total protein as markers to detect drug-induced kidney injury. Nat Biotechnol 2010; 28: 463–469
110. van der Zijl NJ, Hanemaaijer R, Tushuizen ME et al. Urinary matrix metalloproteinase-8 and -9 activities in type 2 diabetic subjects: a marker of incipient diabetic nephropathy? Clin Biochem 2010; 43: 635–639
111. Scarfe L, Rak-Raszewska A, Geraci S et al. Measures of kidney function by minimally invasive techniques correlate with histological glomerular damage in SCID mice with adriamycin-induced nephropathy. Sci Rep 2015; 5: 1–13
112. Schunk SJ, Zarbock A, Meersch M et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. Lancet 2019; 394: 488–496
113. Axelsson J, Bergsten A, Qureshi AR et al. Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. Kidney Int 2006; 69: 596–604
114. Hsu CY, Huang PH, Chen TH et al. Increased circulating visfatin is associated with progression of kidney disease in non-diabetic hypertensive patients. Am J Hypertens 2016; 29: 528–536
115. Sullivan ME, Yilmaz MI, Carrero JJ et al. Novel links between the long pentraxin 3, endothelial dysfunction, and albuminuria in early and advanced chronic kidney disease. Clin J Am Soc Nephrol 2008; 3: 976–985
116. Obermüller N, Geiger H, Weipert C et al. Current developments in early diagnosis of acute kidney injury. Int Urol Nephrol 2014; 46: 1–7
117. Robinson-Cohen C, Bartz TM, Lai D et al. Genetic variants associated with circulating fibroblast growth factor 23. J Am Soc Nephrol 2018; 29: 2583–2592
118. Li O, Ma Q, Li F et al. Progress of small ubiquitin-related modifiers in kidney diseases. Chin Med J 2019; 132: 466–473
119. Fiorentino M, Castellano G, Kellum JA. Differences in acute kidney injury ascertainment for clinical and preclinical studies. Nephrol. Dial. Transplant 2017; 32: 1789–1805
120. Ekins S, Mestres J, Testa B. In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. Br J Pharmacol 2007; 152: 9–20
121. Sacan A, Ekins S, Kortagere S. Applications and limitations of in silico models in drug discovery. Methods Mol Biol 2012; 910: 87–124
122. Saleem MA, O’Hare MJ, Reiser J et al. A conditionally immortalized human podocyte cell line demonstrating nephrin and podocin expression. J Am Soc Nephrol 2002; 13: 630–638
123. Satchell SC, Tasman CH, Singh A et al. Conditionally immortalized human glomerular endothelial cells expressing fenestrations in response to VEGF. Kidney Int 2006; 69: 1633–1640
124. Sarrab RM, Lennon R, Ni L et al. Establishment of conditionally immortalized human glomerular mesangial cells in culture, with unique migratory properties. Am J Physiol Renal Physiol 2011; 301: F1131–F1138
125. Rinschen MM, Gödel M, Grahammer F et al. A multi-layered quantitative in vivo expression atlas of the podocyte unravels kidney disease candidate genes. Cell Rep 2018; 23: 2495–2508
126. Des Rochers TM, Suter L, Roth A et al. Bioengineered 3D human kidney tissue, a platform for the determination of nephrotoxicity. PLoS One 2013; 8: e59219
127. Rinschen MM, Gödel M, Grahammer F et al. A multi-layered quantitative in vivo expression atlas of the podocyte unravels kidney disease candidate genes. Cell Rep 2018; 23: 2495–2508
128. Des Rochers TM, Suter L, Roth A et al. Bioengineered 3D human kidney tissue, a platform for the determination of nephrotoxicity. PLoS One 2013; 8: e59219
129. Rinschen MM, Gödel M, Grahammer F et al. A multi-layered quantitative in vivo expression atlas of the podocyte unravels kidney disease candidate genes. Cell Rep 2018; 23: 2495–2508
127. Des Rochers TM, Suter L, Roth A et al. Bioengineered 3D human kidney tissue, a platform for the determination of nephrotoxicity. PLoS One 2013; 8: e59219
membranes that actively transport organic cations. Sci Rep 2015; 5:16702
89. Vernetti L, Gough A, Baetz N et al. Corrigendum: functional coupling of human microphysiology systems: intestine, liver, kidney proximal tubule, blood-brain barrier and skeletal muscle. Sci Rep 2017; 7: 42296
90. Takasato M, Er PX, Chiu HS et al. Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. Nature 2015; 526: 564–568
91. Hale LJ, Howden SE, Phipson B et al. 3D organoid-derived human glomeruli for personalised podocyte disease modelling and drug screening. Nat Commun 2018; 9:5167
92. Hesketh EE, Czopek A, Clay M et al. Renal ischaemia reperfusion injury: a mouse model of injury and regeneration. J Vis Exp 2014; 88: 51816
93. Ucero AC, Benito-Martin A, Izquierdo MC et al. Unilateral ureteral obstruction: beyond obstruction. Int Urol Nephrol 2014; 46: 765–776