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Acute kidney injury and chronic kidney disease: from the laboratory to the clinic

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Abstract

Chronic Kidney Disease and Acute Kidney Injury have traditionally been considered as separate entities with different etiologies. This view has changed in recent years, with chronic kidney disease recognized as a major risk factor for the development of new acute kidney injury, and acute kidney injury now accepted to lead to *de novo* or accelerated chronic and end stage kidney diseases. Patients with existing chronic kidney disease appear to be less able to mount a complete 'adaptive' repair after acute insults, and instead repair maladaptively, with accelerated fibrosis and rates of renal functional decline. This article reviews the epidemiological studies in man that have demonstrated the links between these two processes. We also examine clinical and experimental research in areas of importance to both acute and chronic disease: acute and chronic renal injury to the vasculature, the pericyte and leukocyte populations, the signaling pathways implicated in injury and repair, and the impact of cellular stress and increased levels of growth arrested and senescent cells. The importance and therapeutic potential raised by these processes for acute and chronic injury are discussed.

Keywords

kidney microvasculature; senescence; cell cycle arrest; fibrosis; kidney repair

Introduction

Chronic kidney disease (CKD) and acute kidney injury (AKI) have been recognised as important but distinct pathologies since their original descriptions by physicians such as Bright (1), Heberden (2) and Abercrombie in the 19th century (3). Until recent years, convention held that oliguric AKI was often fatal if untreated (4), but with the advent of

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dialysis complete recovery was often possible (5). CKD was considered a separate, irreversible and often progressive entity leading to end-stage renal disease.

Linking the epidemiology of AKI and CKD

In recent years standardized criteria have been adopted to allow consistent assessment of degrees of AKI, and their impact on early mortality and subsequent renal function in survivors (6, 7). With improved sample size, assessment criteria and length of follow-up there are now strong data in support of three findings that: 1) pre-existing CKD is a major risk factor for the development of AKI (8-10); 2) patients with CKD who develop AKI often recover incompletely and experience worsened subsequent renal deterioration (8, 11, 12); and 3) the survivors of de novo AKI are more likely to develop proteinuria, increased cardiovascular disease risk and progressive CKD than matched non-AKI control patients (8, 12-14) (summarised in Table 1).

Hence AKI and CKD are interlinked, with complete recovery from AKI far less common than previously assumed, and pre-existing CKD priming the kidney for subsequent injury and maladaptive repair. In this review we will discuss functions of the kidney implicated in AKI and CKD, and examine the clinical and experimental evidence for their role in determining levels of acute renal injury and adaptive vs maladaptive renal repair.

Functional and structural changes of acute kidney injury

Although AKI is a common clinical problem with high levels of morbidity and mortality, renal biopsy is seldom undertaken in the acute phase of disease, and much of our understanding is based on studies undertaken in experimental animals (15). From rodent models such as ischemia-reperfusion injury (IRI) and the cecal ligation and puncture model of multi-organ failure it is understood that acute hypoperfusion and sepsis result in injury to multiple cell populations (16). Early endothelial injury occurs, with obstruction and paradoxical vasoconstriction potentiating reduced local oxygen delivery. In parallel with this ligands are expressed promoting platelet aggregation, complement deposition via the alternative pathway and the recruitment of inflammatory neutrophils and monocytes (17). Consequent to altered oxygen availability there is tubular injury and necrosis causing tubular dysfunction, oliguria and reduced glomerular filtration via tubulo-glomerular feedback.

Over subsequent days, a series of reparative steps ensue which if completed successfully result in adaptive repair and a fully functional kidney. Tubular replacement starts, with current data demonstrating a general dedifferentiation and proliferation of surviving mature cells as responsible for repair (18-20). Monocytes replace neutrophils as the predominant infiltrating leukocyte, and switch phenotype from M1 (pro-inflammatory) to M2 (pro-repair) to support the process of proliferation and regeneration, before exiting or undergoing apoptosis to leave resident cells at similar levels to pre-injury (17). For true adaptive repair to occur, after a period of several days kidney function should return to its previous level (although clinical tools such as creatinine measurement lack sensitivity to detect small changes). There should be no proteinuria and detailed histological assessment should show

preserved tubules, glomeruli and microvasculature with no fibrosis or change in pericyte location or markers (Figure 1). In practice, however, such assessment is seldom undertaken.

Functional and structural changes of chronic kidney disease

CKD can occur through diverse pathologic mechanisms injuring one or several of the compartments of the kidney: vasculature, the tubulointerstitium or the glomerulus. Several features are seen in the kidney regardless of the initiating insult and are known to be important for prognosis and progression to end stage renal disease. Microvascular loss occurs along with increased fibrosis, leading to increased relative hypoxia within the kidney and in particular within the outer medulla (21). This change is associated with and potentially related to a change in pericyte location and behavior, with a loss of pericyte-endothelial contact and pericyte migration to adopt a pro-fibrotic myofibroblast phenotype (22, 23), which then deposit interstitial collagen. With chronic renal injury, there is also a progressive increase in cells expressing markers of senescence and cell-cycle arrest (24-27). Irrespective of the initial insult, evidence of tubular cell loss and their replacement by collagen scars and density of chronically infiltrating macrophages are associated with further renal functional loss and progression towards end stage renal failure.

Changes to tubular cell survival and function, leukocyte and pericyte behaviour and microvascular integrity are all features seen in both AKI and CKD (Figure 2). Evidence for their involvement in the overlap between these two conditions will now be discussed.

Changes to the renal vasculature and oxygen delivery in acute kidney injury

A common feature of diverse processes causing AKI is a reduction in regional renal oxygen delivery leading to inflammation, ischemia and necrosis (28). These features reflect an imbalance between arterial pressure and vascular resistance, with areas of the kidney such as the outer stripe of the outer medulla particularly vulnerable (29). Experimental work in rats demonstrate that vascular function is abnormal for several days after IRI, with a failure of nitric oxide generation from the blood vessels (30, 31) and increased vascular permeability leading to tissue swelling (32). Concurrent with this the endothelium expresses adhesion molecules resulting in the adhesion and recruitment of platelets and leukocytes- both also capable of contributing to injury (33, 34). Studies using intra-vital microscopy have demonstrated that with renal ischemia there is sluggish and even reversed flow in the early phase after initial injury (35, 36).

The transition between acute and chronic vascular injury

Work in both rats and mice demonstrate that experimental IRI results in a reduction in the density of tubular capillaries even after apparently 'adaptive' complete repair (37, 38). It is possible that signalling in early recovery which promotes tubular regeneration such as increased TGF- β and reduced VEGF may oppose survival and recovery within the microvasculature. The renal pericyte is now recognized as a key contributor to vascular stability in development, in homeostasis and in response to kidney injury (22, 39). Defects in

pericyte function result in vascular rarefaction and increased fibrosis- features that are both seen in clinical CKD (23).

Altered ability to respond to acute hemodynamic changes with CKD

There is now accumulating evidence demonstrating that even in the context of a normal serum creatinine, changes persist in the kidney in the aftermath of AKI (11). Alterations within the chronically damaged kidney lead to a state of relative hypoxia even in baseline conditions, with reduced numbers of peritubular capillaries (40, 41) and increased deposition of collagen leading to increased distances between the vessels and tubular cells (42). Kidneys with CKD have increased activation of the renin-angiotensin system, and reduced numbers of glomeruli lead to hyperfiltration and increased tubular oxygen consumption of the corresponding tubules- further worsening imbalances between oxygen requirement and delivery (43). New technologies such as blood oxygen level dependent (BOLD) MRI scanning now allows the detection of renal hypoxia non-invasively in patients, and in a research setting has documented changes in response to blockers of the renin-angiotensin-aldosterone system (44-46). Such drugs have actions on renal hypoxia and are documented to improve outcome in CKD, though whether such effects contribute to protection remains unproven. Ischemia in the kidney results in stabilization of hypoxia inducible factor 1- α (HIF1 α) and there is considerable interest in the potential for HIF-stabilizing agents as therapeutic tools in renal injury (47, 48).

Altered tubular epithelial cell maturation in AKI and CKD

While evidence shows that tubular epithelial cells do not give rise to renal myofibroblasts in response to acute or chronic injuries (39, 49), studies have shown that epithelial cells can upregulate mesenchymal surface markers in the context of both acute and chronic renal injury (50). This is thought to be a transient upregulation, which in conjunction with expression of the proliferative marker suggests that this reflects a de-differentiation of cells undergoing active replication. (18, 51-53). The Wnt pathway is also induced in response to AKI, while it is usually expressed only in embryogenesis and suppressed in the adult kidney (54). There is evidence in both experimental models and in human disease implicating activity of Wnt signaling genes and their downstream pathways such as β -catenin as effectors of renal fibrosis (55, 56). Experimental IRI has been shown to result in Wnt4 induction, with return to baseline within 24h, contributing to de-differentiation of surviving epithelial cells capable of responding to the various proliferative cues present in the injured kidney (50, 57). There is also a burst of TGF β signaling at this point which, if maintained, may mediate later fibrosis. Studies, *in vitro*, have demonstrated a combination of Wnt downregulation and expression of matrix metalloproteinases as necessary for full differentiation of renal tubules- but whether this is the case *in vivo* requires further study (58, 59).

Altered behaviour of leukocytes

Macrophages

Macrophages have contrasting roles in renal injury and repair, augmenting early injury (60) as M1 polarized cells, then switching to an M2 phenotype, clearing debris and supporting epithelial cell repair (61, 62). Indeed whilst early depletion of macrophages is often protective, depletion of M2 macrophages in mice with established AKI results in prolongation of renal injury (63). While important in facilitating repair after AKI, the presence of macrophages is also correlated with fibrosis and adverse outcome in both humans and experimental models of renal disease (64, 65), with the persistence of M2 cells shown to be deleterious.

Lymphocytes

Studies in mice lacking lymphocyte subtypes support their involvement in the evolution of renal injury (66). B cell deficient (μ MT) and CD4/CD8 deficient mice are both protected from AKI, but the RAG-1 strain demonstrates no alteration in susceptibility to injury (67-69). Adding to the complexity of the field, in the RAG-1 strain, protection is restored by adoptive transfer of either B or T cells alone only. Regulatory T cells have been reported to limit tissue injury (70) with Treg depleted and deficient mice exhibiting worsened tissue damage after experimental IRI (70).

Studies on μ MT mice using bone marrow chimeras demonstrate that B cells appear to delay tissue repair after injury (71), and adoptive transfer of lymphocytes from animals previously exposed to severe IRI induce albuminuria in naïve recipients (72). If such findings are replicated in man then the adaptive immune system and immunological memory play a larger than expected role in the genesis of CKD and proteinuria after AKI.

Alterations in pericyte number and activation status

Pericytes sit in close proximity to the endothelial cells within many organs where they maintain vascular stability and release factors, including PDGF (73), angiopoietin (74), TGF- β (75), VEGF (76) and sphingosine-1-phosphate (77). There is now an increasing understanding of the role played by these cells in acute and chronic renal injury and fibrosis- where they leave their perivascular locations in response to injury and differentiate to become myofibroblasts (39, 78, 79). Thus in both AKI and CKD, injury activates pericytes and induces their migration- contributing both to microcirculatory instability and loss (23). Whether interventions targeting pericyte activation and survival could protect the renal microcirculation and prevent the post-AKI loss of kidney vasculature is an important unanswered question.

Processes contributing to the development of CKD post AKI

Recurrent tubular injury as a stimulus to renal scarring

As clinical AKI impacts on multiple cell types including the vascular, epithelial, mesenchymal and leukocyte lineages, it has been very difficult to establish which cell or cells are responsible or involved with the scarring process. The role of the tubular epithelial

cell on fibrosis has been investigated using a transgenic mouse expressing the simian diphtheria toxin receptor on the tubular epithelia, allowing their selective depletion *in vivo* without injury to other cell types (80). These studies showed that a single round of injury led to complete repair, but repeated sublethal injuries led to progressive fibrosis, loss of capillaries and glomerulosclerosis. Thus, injury to the tubule alone is sufficient to produce interstitial scarring and loss of glomeruli and capillaries- likely related to the release of proinflammatory and vasoconstrictive cytokines by the injured tubule.

KIM-1 as a potential surface receptor linking AKI to CKD

Kidney injury molecule 1 (KIM-1) is, an epithelial phagocytic receptor which is markedly upregulated on the proximal tubule in various forms of acute and chronic kidney injury in humans and many other species. Its ectodomain is released by metalloproteases and appears in the urine and blood, serving as an excellent sensitive biomarker of proximal tubule injury and predicting progression of CKD (81). Acute KIM-1 is adaptive and protective with anti-inflammatory effects (82-84). If expression of KIM-1 continues chronically it is possible that this results in progressive uptake of noxious compounds from the intratubular lumen and secondary cell injury over time with senescence, secretion of proinflammatory and profibrotic cytokines. A transgenic mouse expressing KIM-1 developed CKD (85) and zebrafish overexpressing KIM-1 have smaller kidneys and higher mortality rates (86).

Epigenetic Changes after AKI

The potential role for epigenetic changes in mediating the transition from AKI to CKD, and in altering the response of the chronically damaged kidney to further AKI insults is an area of active study (87),(88). Within clinical cohorts there is emerging evidence for alteration in histones, DNA methylation and miRNA molecules within scarred kidneys (89). Similarly, changes in histones and in patterns of methylation have also been noted in AKI, and have been reported to alter expression of pro-fibrotic genes such as MCP-1 and TNF α (90, 91). With our tools to investigate these alterations improving, so will our ability to probe for epigenetic cues which may prime 'adaptively repaired' kidneys to develop CKD or leave them susceptible to recurrent AKI.

Senescence and cell cycle arrest in the acutely and chronically injured kidney

While cellular senescence was first described as a feature of prolonged culture of cells *in vitro* it is now recognized as a key feature of aging *in vivo* and degeneration in organs including the kidney (92). With advancing age, with CKD or in response to interventions such as renal transplantation and immunosuppression there are increases in the numbers of senescent cells within the kidney, and it is plausible but unproven that these cells may contribute to the sensitivity of an aged or chronically damaged kidney to further acute injury. Studies in progeroid mice have shown that depletion of p16^{INK4a} expressing senescent cells can delay age-associated pathologies, but this remains to be tested in naturally aged animals to assess the importance of cells expressing p16^{INK4a} (93). Data from human kidney transplants demonstrates increased cellular senescence (94), with pre-implantation p16^{INK4a} levels predictive of graft survival (95, 96). Experimental murine transplantation of kidneys

lacking the senescence trigger gene p16^{INK4a} show increased survival rates and reduced fibrosis supporting a role for cellular senescence in the progression of renal fibrosis after acute or chronic injury (96). This protection may reflect reductions in levels of factors such as connective tissue growth factor (CTGF) and TGF- β which are both released from senescent cells and can contribute to inflammation, vascular loss and fibrosis (25, 97, 98). Senescent cells may also promote G2/M cell cycle arrest through release of the cytokine IL-8 (99).

Our laboratory has demonstrated an important role for mitotic arrest at the G2/M phase of the cell cycle in response to AKI, where it drives maladaptive repair and progressive fibrosis (25-27) (Figure 3). Supporting this finding, additional studies using pharmacological inhibition or potentiation of G2/M cell cycle arrest demonstrate reduced or increased levels of fibrosis respectively (26, 27, 100). With age, AKI and CKD all associated with increased levels of senescent cells (92), the potential for these cells to mediate crossover effects between chronic and acute renal pathologies merits further investigation.

Conclusions

Our understanding of the relationships between CKD and AKI remains incomplete, with new data demonstrating more areas of overlap and inter-dependence. Both processes are associated with major increases in patient morbidity and mortality, and new interventions to lessen AKI susceptibility and reduce maladaptive repair leading to new or worsened CKD are required. Our knowledge of the processes underlying vascular damage and loss, pericyte migration, leukocyte activation, acute and chronic cellular senescence and tubular hypoxia continues to advance. Increased understanding should lead to new, targeted therapies to protect kidneys from these interrelated forms of kidney injury in the future.

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Figure 1. Chronic kidney disease and maladaptive repair after acute kidney injury

A kidney with chronic kidney disease is less likely to undergo complete adaptive repair after an acute renal insult. In the context of pre-injury fibrosis, senescence and microvascular loss the kidney is more likely to repair maladaptively with increased tubular loss and scarring. While a normal kidney can respond to injury with adaptive repair it is also recognized that with greater levels of injury and increasing age maladaptive repair to CKD is more likely.

Figure 2. Inter-related features of chronic kidney disease and acute kidney injury

Features seen in chronic kidney disease are shown on the left and acute kidney injury on the right. Solid lines demonstrate well established connections between these features, with dotted lines indicating suspected or proposed connections.

Figure 3. Cell cycle progression in acute and chronic kidney disease

Studies of models of renal injury have detected cells arrested at the G2/M checkpoint that secrete pro-fibrotic factors promoting maladaptive repair and the transition from acute to chronic kidney disease. Cell cycle arrest can also occur in the G1/S phase resulting in p16^{INK4a} positive senescent cells which, via the senescence-associated secretory phenotype (SASP), also promote changes in aged and injured kidneys.

Table 1
Clinical studies of interactions between acute kidney injury and chronic kidney disease

Several studies and meta-analyses have been performed in the last 10 years examining the impact of chronic kidney disease in rates of acute kidney injury in hospital inpatients, and the impact of de novo acute kidney injury on subsequent kidney function and rates of end stage renal disease in survivors.

Study	Population Sample/size	Risk of AKI	Effects of CKD on AKI	Effects of AKI on CKD or ESRD	Comments
Ishani et al (8) JASN 2009	n=233,803 Inpatients aged>67yrs. Medicare in year 2000	3.1% in survivors	12% of total patients had CKD. 34.3% of AKI patients had CKD	5.3 per 1000 developed ESRD. 25% had prior AKI	Relative risk of ESRD was 41.2 in AKI+CKD patients, 13.0 in AKI only patients
Xue et al (9) JASN 2006	n=5,403,015 Medicare discharges 1992-2001	23.8 cases per 1000 discharges Age, male gender and black race associated with risk.	No data	No data	Risk of death at 90d was 13.1% without AKI, 34.5% with AKI as the principal diagnosis, and 48.6% with AKI as a secondary diagnosis
Coca et al (11) KI 2012	13 studies, >1,000,000 participants	No data	No data	AKI resulted in a pooled HR for new CKD of 8.82 and of ESRD of 3.1	Survivors of AKI had a pooled HR for death of 1.98.
Wald et al (12) JAMA 2009	3769 AKI patients, 13,598 controls (1996-2006)	No data	No data	Rate of ESRD in AKI patients of 2.63 per 100 person years, vs 0.9 in controls	An episode of AKI resulted in a HR for ESRD of 3.23.
Chawla et al (13) KI 2011	N=5351 AKI patients	No data	No data	13.6% of survivors developed CKD 4.	Age of patient and severity of AKI both predicted subsequent CKD
Chertow et al (101)	N=19,982 total patients 1997-1998	13.1% of inpatients had AKI (by AKIN1 criteria)	Pre-existing CKD was a significant risk factor for AKI	No data	
Coca et al (102) AJKD 2007	8 studies total n=78,855				Creatinine increases of 10-24% increased RR of 30d mortality by 1.8x, rises of >50% increased RR by 6.9x.
Liano et al (5) KI 2007	N=187 ATN patients. Mean follow up of 7.2 years	All patients had biopsy proven ATN	No previous nephropathies were seen	11/57 patients followed up had mild/moderate CKD	
Vikse et al (14) NEJM 2008	N=570,433 females (1967-1991)	3.7% of pregnant ladies developed pre-eclampsia		1x prior Preeclampsia resulted in RR of ESRD of 4.7. 2+ prior preeclampsias had a RR of ESRD of 15.5.	
James et al (10) AJKD 2015	8 control studies n=1,285,045 and 5 CKD studies n=79,519	In control patients, 0.2-6% developed AKI vs 2-25% In CKD studies	Lower eGFR and higher albumin:creatinine ratio conferred higher AKI risk	No Data	
Heung et al (103), AJKD 2015	VA inpatients n=17,049 with AKI, n=87,715 without AKI.		No patients had documented CKD prior to the study	Rate of recovery of AKI equated to a 2 year RR of new CKD3+/- <3	

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Study	Population Sample/size	Risk of AKI	Effects of CKD on AKI	Effects of AKI on CKD or ESRD days RR 1.43 3-10 days RR 2.0 >10 days RR 2.65	Comments