HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Kidney Int. 2017 November ; 92(5): 1071–1083. doi:10.1016/j.kint.2017.06.030.

AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms

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Abstract

Acute kidney injury (AKI) and chronic kidney disease (CKD) are inter-connected. While AKI-to-CKD transition has been intensively studied, the information of AKI on CKD is very limited. Nonetheless, AKI, when occurring in CKD patients, is known to be more severe and difficult to recover. CKD is associated with significant changes in cell signaling in kidney tissues, including the activation of TGF-β, p53, HIF, and major developmental pathways. At the cellular level, CKD is characterized by mitochondrial dysfunction, oxidative stress, and aberrant autophagy. At the tissue level, CKD is characterized by chronic inflammation and vascular dysfunction. These pathological changes may contribute to the heightened sensitivity of, and non-recovery from, AKI in CKD patients.

Keywords

acute kidney injury; chronic kidney disease; fibrosis; inflammation; mitochondria; cell signaling

I. Introduction

Chronic kidney disease (CKD) is characterized by the gradual loss of renal function over a period of months to years. In addition to renal deficiency, CKD is a major risk multiplier in patients with diabetes, hypertension, heart diseases, and stroke[1]. The prevalence of CKD has

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DISCLOSURE

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reached a staggering high level around the world. In the United Sates, across-sectional analysis of the National Health and Nutrition Examination Surveys shows that the prevalence of CKD stages 1 to 4 increased to 13.1% in 1999–2004[2]. In China, over 10% adults suffer from CKD according to the analysis of a nationwide representative sample of 47,024 adults[3]. Acute kidney injury (AKI), in contrast, is defined as a kidney disease with rapid loss of renal function. While previously thought to be two separate syndromes, AKI and CKD have been recognized to be closely associated or inter-connected by both clinical and experimental studies in the last decade[4–6]. On one hand, AKI may contribute to the development and progression of CKD. On the other hand, CKD is known to predispose or sensitize patients to AKI. While AKI-to-CKD transition has been intensively studied in recent years, very limited work has been directed to investigate how CKD affects AKI. In this review, we aim to briefly summarize the inter-relationship between AKI and CKD, and then focus on the potential mechanisms that underlie the poor prognosis of AKI in CKD patients.

II. The AKI-CKD connection

Despite some disputes, recent epidemiology and experimental studies have demonstrated that AKI contributes to the development and progression of CKD. AKI in both adults and children is closely associated with the increased risk of developing CKD and the risk of CKD incidence shows a dependence on the severity of AKI[7–10]. In a meta-analysis of 13 cohort studies, Cocaet al. showed that AKI patients had significantly higher risks of developing CKD and end stage renal disease (ESRD) and higher mortality as compared to the patients without AKI[11]. More recently, Kim et al. reported that persistent AKI (defined as incomplete reduction of serum creatinine at 7 days) after gastric surgery was associated with CKD progression 1 year later[12]. Similarly, the duration of AKI after cardiac surgery was also regarded as a strong independent risk factor for CKD development[13]. In addition, a recent retrospective study indicated that 29% of patients with elective cardiac surgery and cardiopulmonary bypass experienced AKI and notably, half of these AKI patient developed CKD[14]. In diabetic patients, Thakar et al. reported that AKI was a factor that doubled the risk of reaching stage 4 CKD and significantly reduced the survival of patients[15]. Comparing to the CKD patients who did not experience superimposed AKI, those who did also had 30% higher long-term risk of death or ESRD. Moreover, based on a large community-based cohort of patients with CKD, Hsu et al. showed that 49% of CKD patients who sustained severe AKI reached ESRD status within 30 days after discharge, while the percentage for CKD patients without severe AKI was only 1.5%[16]. Experimentally, severe and repeated episodes of AKI led to renal interstitial fibrosis that was associated with gradual loss of renal function over time, a characteristic of CKD[17–19]. These studies have provided compelling evidence for a role of AKI in the development and progression of CKD[11]. Mechanistically, AKI-CKD transition is related to a complex interplay between injured or stressed renal tubular cells with vasculature, immune system, and interstitial fibroblasts[4–6, 20, 21].

Conversely, CKD is also an important risk factor for the development of AKI. James et al. conducted a meta-analysis in 2015 showing that CKD was a risk factor of developing AKI in patients with diabetes or hypertension[22]. Consistently, CKD was shown to be an independent risk factor of AKI in patients of major cardiac surgery[23]. Similar results were shown in a

multicenter study of a large cohort of postoperative patients by The National Taiwan University Surgical ICU Associated Renal Failure group[24]. In this study, among the patients who survived to hospital discharge after major surgery, 46.8% patients without prior CKD experienced AKI, whereas significantly higher percentage (67.0%) of patients with prior CKD did. In addition, Wilson et al. conducted a systematic review of risk prediction models for AKI following major non-cardiac surgery and found that renal insufficiency was an important risk factor of AKI occurrence[25]. In animal models, there is evidence that ischemic AKI is significantly more severe in diabetic mice than in non-diabetic mice[26, 27]. Together, these studies indicate that CKD predisposes and sensitizes patients to AKI.

Furthermore, CKD may adversely affect kidney repair in, and the recovery from, AKI. In 2004, Go et al. showed that reduced baseline kidney function due to proteinuria, diabetes, hypertension or other diseases was a strong and independent risk factor for hospitalization, cardiovascular events, and death[28]. More recently, Zhou et al. showed that the pre-existence of CKD worsened renal function in AKI patients and delayed the renal function recovery after AKI; in fact, acute on chronic kidney injury (ACKI) was frequently associated with higher risk of mortality[29]. Findlayet al. further examined the information of patient with renal replacement therapy requiring AKI in Southwest Scotland between 1994 and 2005. The data from this study indicate that the underlying CKD rather than illness severity can predict the medium- to long-term mortality[30]. Macedoet al. followed 84 adult survivors of AKI for a median time of 4.1 years and showed that age and serum creatinine levels at hospital discharge were independent factors associated with non-recovery of renal function[31]. Consistently, a large cohort study of 43,008 hospitalized patients by Pannu et al. revealed that a lower baseline estimated glomerular filtration rate (eGFR) pre-AKI was associated with higher risk of ESRD and death[32]. These studies are consistent with the general observation in clinical practice that in young and otherwise healthy patients, AKI is mostly reversible or recoverable, whereas AKI in patients with CKD and related comorbid conditions (eg. diabetes, hypertension, aging) is severe and hard to recover (Figure 1). Experimentally, Polichnowski et al. demonstrated that kidney repair following ischemic AKI was impaired and renal fibrosis increased in rats with severe renal mass reduction or nephrectomy, a model of CKD[33]. Despite these clinical and experimental studies, the mechanism of non-recovery from AKI in CKD patients remains largely elusive.

III. Potential mechanisms underlying the susceptibility and non-recovery of AKI in CKD patients

a. CKD-associated changes in signaling pathways

Pathologically, AKI is characterized by cell injury and death in renal tubules[34]. Interestingly, CKD is also associated with tubular damage and dysfunction. It has been known for years that tubulointerstitial pathology is a defining feature of virtually all types of CKD[35]. Although abnormal glomerular filtration may impact on CKD progression, the tubulointerstitial pathology involving mainly tubular epithelial cells and interstitial fibroblasts, plays a major role in the initiation of CKD[36]. Drastic alterations of cell signaling in renal tubular cells during the initiation and progression of CKD may contribute to the susceptibility of CKD kidneys to AKI.

TGF-β—In CKD, TGF-β signaling pathway is activated and consequently induces renal cells to produce fibrotic extracellular matrix proteins, leading to glomerulosclerosis as well as tubulointerstitial fibrosis[37, 38]. However, the role of TGF-β signaling in AKI is paradoxical probably due to its multiple patho-physiological functions in different cells and at different stages of AKI. Some early studies reported the transient activation of TGF-β signaling in AKI that may promote kidney tubular cell proliferation and apoptosis[39, 40]. In sharp contrast, most recent studies suggested that TGF-β is an injurious factor and inhibition of TGF-β pathway may reduce renal tubular injury[41–44]. Using a mouse model of inducible TGF-β expression in kidney tubular cells, Koesters R et al demonstrated that tubular TGF-β activation may initially stimulate interstitial cell proliferation, but sustained TGF-β induction leads to tubular degeneration through autophagy-mediated tubular decomposition[45]. Therefore, the persistently elevated TGF-β signaling in CKD may have synergistic or additive injury effect at the acute phase of AKI. Furthermore, activated TGF-β signaling in CKD may prevent the recovery of AKI. In this regard, TGF-β is known to trigger fibrogenic foci and initiate progressive fibrogenesis in kidney injury[46]. In addition, the activation of TGF-β signaling in renal tubular cells may prevent their re-differentiation and ensuing regeneration of functional renal tubules after AKI[47].

P53—P53 is a major mediator of tubular cell injury and death in AKI[48–50]. More recent studies have further verified the role of p53 in AKI by testing renal tubule-specific p53 ablation mouse models[51, 52]. Interestingly, CKD may also be associated with the increase or activation of p53 as a consequence of TGF-β up-regulation or PTEN down-regulation[53, 54]. Such “pre-activation” of p53, though at low to moderate levels, may greatly enhance tubular damage upon AKI. In support, Peng et al. detected marginal p53 activation in hyperglycemic renal tubular cells and in diabetic kidneys, which was dramatically increased upon ischemic AKI; importantly, these cells and tissues showed significantly more injury that could be ameliorated by p53 inhibitors and genetic knockout[26]. However, p53 may also play a dual role in AKI as it may suppress renal inflammation and related inflammatory injury by increasing the infiltration of anti-inflammatory M2 macrophages[55]. Recent studies have further indicated the involvement of p53 in renal fibrosis. Pifithrin-α, a pharmacological inhibitor of p53, was shown to stimulate post-ischemia renal fibrosis[56], whereas targeted ablation of p53 from renal proximal tubules led to the suppression of renal fibrosis[52], suggesting that p53 in different renal cell types may contribute differently to kidney repair.

Developmental signaling pathways—Multiple signaling pathways in kidney development are activated in both CKD and AKI, and contribute to their pathogeneses. Especially, these pathways play an important role in kidney repair following injury, including fibrogenesis, as reviewed recently[57–59]. Briefly, Notch signaling pathway is known for its indispensable role in kidney development for long time[60]. Recently, Notch activation was detected in ischemic AKI and was shown to prevent renal tubular epithelial cells from proliferation and regeneration, resulting in a delay of the recovery from AKI[61, 62]. In addition, Notch activation was also reported to increase inflammation and apoptosis in ischemic AKI[63]. In CKD, Notch is also activated in renal tubular cells where it may promote renal fibrosis and inflammation[64–66]. The elevated Notch signaling in CKD may therefore

exaggerate tubular damage upon AKI and delay kidney repair or recovery, contributing to the susceptibility of, and non-recovery from, AKI in CKD patients.

The Hedgehog signaling is also a critical pathway in kidney development that promotes renal fibrosis in AKI and CKD-related conditions. Specifically, Liu and colleagues demonstrated that Sonic Hedgehog from injured renal tubular cells may activate fibroblasts for proliferation, suggesting a model of epithelial-mesenchymal communication[67, 68]. The recent studies by Kramann, Humphreys and colleagues have further pinpointed the critical role of the Hedgehog transcriptional activator Gli1 in specifying perivascular mesenchymal stem cells in kidneys as the main origin of myofibroblasts in renal fibrosis[69]. Moreover, Gli2 is a key to myofibroblast proliferation by driving cell cycle progression, further supporting a pivotal role of Hedgehog signaling in renal fibrosis[70]. In contrast, less is known about Hedgehog signaling in the acute phase of AKI. Nonetheless, inhibition of Hedgehog signaling in obstructively injured kidneys promoted renal tubular cell apoptosis and inhibited tubular cell proliferation[71], suggesting a cytoprotective function of this pathway. Thus, Hedgehog signaling in CKD and associated fibrosis may antagonize AKI acutely, but it may prevent kidney repair and enhance fibrosis in the long term.

Other kidney developmental signaling pathways that are activated in various CKD conditions include the canonical WNT/β-catenin pathway, which also promotes renal fibrosis[72–77]. Interestingly, this pathway is also activated during and following AKI. While WNT/β-catenin signaling protects renal tubular cells and promotes their proliferation[78, 79], sustained WNT/β-catenin activation contributes to renal fibrosis during the recovery or repair phase of AKI[80, 81]. Thus, CKD-associated WNT/β-catenin signaling may have paradoxical effects on AKI: protecting against acute injury initially but enhancing renal fibrosis thereafter.

HIF—Kidney tissues, especially renal tubules, are highly oxygen demanding and susceptible to hypoxic injury. In both AKI and CKD conditions, hypoxia is an important pathogenic factor that is accompanied with the activation of HIF (including HIF-1, -2, -3) to modulate gene expression[82]. In AKI, HIF activation in renal proximal tubules does not have a major protective role[83, 84]; however, global stabilization of HIF or selective regulation of HIF in other kidney cell types may reduce AKI[85–87], suggesting that HIF activation in other cells may have renoprotective effects. In the repair phase of AKI, HIF may also play a perplexing role, likely depending on the expressing cell types. While HIF-1 activation did not significantly improve wound healing in renal tubular cells in some studies[81, 88], there is evidence that HIF-1 may enhance renal tubular cell migration after wounding[89, 90]. HIF signaling was also shown to promote renal fibrosis by trans-activating genes for ECM turnover, co-operating with TGF-β1, and by promoting the change of tubular cells to a pro-fibrotic phenotype[91]. As HIF is activated in CKD, it is important to understand whether HIF protects CKD patients from AKI and/or further promotes fibrosis following AKI for accelerated progression of CKD.

b. Mitochondrial dysfunction and oxidative stress

Mitochondria are the main energy source in kidney cells, especially renal tubule cells. However, after damage, mitochondria may turn into active “killer” of these cells. In this regard, permeabilization of mitochondrial outer membrane by pro-apoptotic Bcl-2 family proteins can directly activate the intrinsic pathway of apoptosis. Ablation of these pro-apoptotic genes, such as Bax and Bak, results in the amelioration of ischemic as well as cisplatin nephrotoxic AKI[50, 92, 93]. Interestingly, prior to membrane permeabilization, mitochondria experience a dramatic change in morphology and become fragmented. Now it is clear that mitochondria are dynamic organelles that constantly undergo fission and fusion, and during cell stress mitochondrial fusion is arrested while fission activated, culminating in mitochondrial fragmentation[94]. Fragmented mitochondria are highly susceptible to Bax insertion and consequent outer membrane permeabilization[95]. Thus, mitochondrial fragmentation and outer membrane permeabilization are considered to be two critical events in triggering the intrinsic pathway of apoptosis[96]. In ischemic and nephrotoxic models of AKI, inhibition of mitochondrial fragmentation pharmacologically or genetically has significant renoprotective effects[93, 97, 98], further verifying the pathogenic role of mitochondrial fragmentation. Cell death can also be triggered by damages at the mitochondrial inner membrane. In this case, a well-documented phenomenon is mitochondrial permeability transition (MPT) that leads to necrosis in a variety of cell types. MPT has been implicated in tubular necrosis in AKI for a long time, which has been verified recently by using gene knockout mouse models[99–101]. Mitochondrial dysfunction occurs in kidney tissues and cells during the development and progression of CKD[102, 103]. Both high glucose and albumin overload can stimulate mitochondria-mediated intrinsic pathway of apoptosis, which may result from the activation of p53, PKC-δ, and oxidative stress under CKD condition[104]. Mitochondrial fragmentation, as a result of pathological alterations in mitochondrial dynamics, has also been detected in experimental models of diabetic kidney disease[105, 106]. Fragmented mitochondria are more vulnerable to damage, including Bax attack[95]. Indeed, the severity of ischemic AKI in diabetic mice is associated with heightened activation of the mitochondrial pathway of apoptosis. Thus, the loss of mitochondrial dynamics in diabetic kidneys and other CKD conditions is expected to contribute to the AKI sensitivity in CKD.

Mitochondria in CKD kidneys are also low in function. For example, Sharma and colleagues[107] analyzed the metabolites in urine from diabetic patients with or without CKD. Interestingly, the diabetic patients with CKD had less water-soluble organic anions in urine that are related to kidney mitochondrial function. Moreover, these patients had less mitochondrial protein and DNA, and lower levels of PGC1α (key transcription factor for mitochondrial biogenesis) in kidneys. Together, these data indicate an overall down-regulation of mitochondrial function and biogenesis in kidneys during diabetic nephropathy. Interestingly, kidney repair or recovery from AKI is associated with and may depend on mitochondrial biogenesis. In this regard, Schnellmann and colleagues demonstrated that pharmacological stimulation of mitochondrial biogenesis may promote kidney recovery from AKI[108–111]. In addition, Parikh and colleagues demonstrated worsened septic AKI in PGC1α-knockout mice[112], providing further support for the beneficial effect of PGC1α and associated mitochondrial biogenesis in AKI and its recovery. In view of these studies, it is

concluded that CKD-associated suppression of mitochondrial function and biogenesis would sensitize kidney cells and tissues to AKI and prevent kidney repair or recovery from AKI.

Oxidative stress is a common feature of CKD. By comparing CKD patients with healthy people, Oberg et al. revealed significantly elevated oxidative stress in stage 3–5 CKD patient blood samples by measuring oxidative stress biomarkers, including increases in plasma levels of protein-associated carbonyl content and decreases in plasma protein–reduced thiol content[113]. Similar increases of oxidative stress were shown in CKD patient blood samples by Ramos et al, who further reported an interesting correlation of oxidative stress with body fat deposition[114]. The oxidative stress in CKD may have multiple origins including, but not limited to, dysfunctional mitochondria[102, 103, 115]. For example, it may also involve the down-regulation of Nrf2 in CKD, a key transcriptional factor of anti-oxidant genes[116].

The oxidative status in CKD may adversely affect AKI because oxidative stress is a well-known pathogenic factor in AKI. In critically ill patients with AKI, Himmelfarb J et al. showed that plasma protein oxidation is significantly increased and it cannot be substantially improved by hemodialysis[117]. In an orthopedic trauma-induced model, obese rats with higher oxidative stress developed more severe AKI[118]. In addition, the pre-existing CKD, such as diabetic nephropathy, is the most prominent risk factor of contrast medium-induced AKI[119, 120]. A major factor in the susceptibility of the CKD patients to contrast medium-induced AKI is considered to be oxidative stress in kidney tissues, which may result in enzymatic and vascular/endothelial dysfunction to markedly increase the incidence of AKI[121]. Altogether, these studies implicate that existing oxidative stress, such as that in obesity and CKD, may exacerbate AKI.

c. Changes of autophagy

Autophagy is a cellular process of degradation of cytoplasmic contents, including protein aggregates and dysfunctional organelles. Functionally, autophagy is an important mechanism for the maintenance of cellular homeostasis by removing potentially toxic components and recycling degraded substances. In AKI, autophagy is rapidly activated in renal tubular cells. Blockade of autophagy pharmacologically or genetically results in more severe AKI while induction of autophagy protects kidneys, supporting a protective role of autophagy in AKI[122–127]. After AKI, autophagy decreases in some renal tubular cells but it is still maintained at high levels in other cells[128]; however, the role of autophagy in kidney repair following AKI remains unclear. Baisantryet al. reported that specific ablation of Atg5 from renal proximal tubules increased ischemic AKI at earlier time-points, but suppressed renal fibrosis during kidney recovery or repair[129]. Consistently, Livingston et al. showed that renal fibrosis in obstructed kidneys was ameliorated in renal proximal tubule Atg7-knockout mice and interesting, this was associated with decreased production of specific pro-fibrotic factors[130]. However, Li et al. reported higher levels of renal fibrosis in obstructed kidneys of proximal tubule Atg5-knockout mice[131]. Thus, while the protective role of autophagy in AKI is well-established, it is inconclusive whether autophagy is beneficial or detrimental to kidney repair.

Currently, the information of autophagy regulation in CKD is limited and sometimes controversial, likely due to the complexity of the etiologies of CKD. In this regard,

autophagy in diabetic nephropathy has received much attention as it is considered a metabolic disorder. The accumulating evidence indicates that the nutrient-sensing pathways in kidneys are altered under diabetic conditions, including particularly the activation of mTOR and the inhibition of SIRT1 and AMPK[132–134]. Changes of these nutrient-sensing pathways may further impair the autophagic response in kidneys[135]. For example, accumulation of the autophagy substrate p62 in kidneys has been shown in both STZ-induced type 1 diabetic mice[136] and Wistar fatty type 2 diabetic rats[137]. Moreover,p62 accumulation has also been observed in renal tubules of kidney biopsy samples from patients with type 2 diabetes, suggesting the inhibition of autophagy[138]. In addition, autophagy reduction occurs in the kidney biopsies from patients with focal segmental glomerulosclerosis (FSGS), although the main affected cells are glomerular podocytes[139]. Autophagy regulation in other CKD models or conditions is less clear. In the 5/6th nephrectomy model of CKD, Li H et al. showed evidence of autophagy suppression in kidneys, including decreases in LC3II and accumulation of P62[140]. However, in the same model Fedorova et al. detected the up-regulation of autophagy genes (eg. beclin 1 and BNIP3)[115]. In Leishmania infantum-associated glomerulonephritis, Eschet al. showed autophagy induction in both glomeruli and renal tubules with induction[141].

Would the autophagy changes in CKD affect AKI and kidney repair? In other words, does autophagy contribute to the AKI sensitivity and non-recovery in CKD? Based on the protective role of autophagy in AKI, it is predicted that autophagy inhibition in some CKD conditions, such as diabetic nephropathy and FSGS, would sensitize kidney cells and tissues to AKI. However, in other CKD conditions where autophagy is induced, autophagy may have an opposite role. It is more difficult to predict the effect on kidney repair, because, as presented above, the role of autophagy in kidney repair and fibrosis remains elusive. Again, it is important to emphasize that this depends on the etiology of CKD, which not only determines if autophagy is up- or down-regulated but also the repair response after AKI: normal vs. maladaptive repair. Normal repair fully restores tubular structure and function, whereas maladaptive repair includes a series of pathological changes including tubular atrophy, persistent inflammation, capillary rarefaction, expansion of myofibroblasts, and development of fibrosis that prevent the recovery of AKI[142–144]. Thus, the changes of autophagy in CKD likely contribute to the AKI sensitivity and non-recovery/repair in CKD patients. However, the effects may largely depend on the etiology or types of CKD.

d. Chronic inflammation

Chronic inflammation is a common feature in CKD patients due to multiple factors such as the induction of pro-inflammatory cytokines, oxidative stress, uremia, and high chances of infection. In a study of 687 patients with myocardial infarction-induced CKD, Tonelli M et al. showed the significant induction of two inflammatory biomarkers (C-reactive protein and soluble tumor necrosis factor receptor II) and its association with the progression of CKD[145]. More recently, AmdurRL et al. examined the association of inflammatory biomarkers and the progression of CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study, which enrolled 3430 adults with a wide range of kidney function, and found that elevated plasma levels of TNF-α was closely related to the rapid loss of kidney function in patients with CKD[146]. CKD patients are also more susceptible to infection and related

inflammation. In fact, pre-operative CKD was shown to a strong predictor of post-operative infection, AKI, and in-hospital death[147].

Importantly, the pro-inflammatory cytokines that are up-regulated in CKD also play critical roles in the induction and progression of AKI. Firstly, the cardiovascular events in CKD patients are closely related to proinflammatory cytokine induction[148–151]. As such, the CKD patients with chronic inflammation have high rates of cardiovascular problems, which lead to decreased blood supply to kidneys resulting in ischemic AKI. Among the various cytokines up-regulated in CKD, IL-10 is closely associated with and has been suggested to be responsible for the risk of cardiovascular events in CKD[151]. CKD is also accompanied with the induction of other major cytokines, such as TNF-α, TNF-like weak inducer of apoptosis (TWEAK) and IL-6[152–156]. TNF-α and TWEAK can reduce Kotho expression through the activation of NF-kB pathway, which may contribute to kidney functional loss in folic acid-induced AKI[157]. TNF-α is also important to the increased severity of ischemic AKI in diabetic mice[158]. In addition, the activation of fibroblast growth factor-inducible 14 (Fn14) by TWEAK in pericytes may further promote the release of inflammatory cytokines and capillary vasoconstriction, contributing to AKI[159]. In AKI, IL-6 can activate STAT3 pathway, which not only induces more tubular cell death but also increases renal fibrosis and glomerulosclerosis in post-AKI kidneys[160, 161]. Notably, CKD is associated with high levels of IL-6, which is a critical risk factor of AKI in sepsis patients[154, 162].

There is also an increase of High-mobility group box1 (HMGB1) in CKD. For example, in a cross-sectional study Bruchfeld et al. analyzed 177 CKD patients to reveal the significant increase of serum HMGB1. In this study, HMGB1 showed a correlation with the decline of renal function or glomerular filtration rate and increases in markers of inflammation and malnutrition[163]. Interestingly, HMGB1 may also be a major player in the inflammatory response and associated tissue damage in AKI[164]. In AKI patients, there is a marked increase in HMGB1 that correlates with inflammation[165]. In animal models, neutralizing antibodies of HMGB1 protect against ischemic AKI and reduced renal inflammation, whereas recombinant HMGB1 have opposite effects[166, 167]. Quite relevant to the focus of our discussion, Star and colleagues demonstrated the release of HMGB1 from apoptotic cells in spleen in the 5/6th nephrectomy mouse model of progressive CKD, and notably, cecal ligation and puncture-induced AKI in this model was attenuated by anti-HMGB1 antibodies, suggesting a critical role of HMGB1 in septic AKI under CKD conditions[168].

Of note, increases of other inflammatory cytokines (eg. IL-8) and interferons have also been reported in CKD patients, although less is clear about their involvement in AKI[169–171]. Also, in addition to induced expression, renal clearance of cytokines is decreased in CKD, which may contributes to the accumulation of pro-inflammatory cytokines in kidney tissues and the susceptibility of and non-recovery from AKI[168].

The increases of chemokines and cytokines in CKD are often associated with the infiltration of inflammatory cells into kidneys. The infiltration of these cells is generally believed to predispose the kidneys to AKI. In this regard, macrophages have received much attention. Due to the differences in surface antigens and polarization status, macrophages may present as M1, M2, and various subtypes inbetween that may react differently to stimuli [172, 173]. M1

macrophages are pro-inflammatory and mediate kidney damage during the early phase of AKI. In contrast, M2 macrophages generally contribute to kidney tissue remodeling following AKI by enhancing tubular cell proliferation and repair as well as inducing maladaptive repair of fibrosis[174]. Macrophage infiltration occurs in CKD in both human patients and animal models[175–177], and notably, the infiltration is followed by M1 macrophage polarization whereas M2 polarization is impaired[177], predisposing the kidneys to inflammation and tissue damage in AKI.

e. Vascular dysfunction

Depending on its progression, CKD is associated with various degrees of vascular dysfunction that occurs in both renal vasculature and other peripheral vasculature. In kidneys, CKD induces alterations in the tissue microenvironment that may directly induce vascular pathology. The dysfunction of endothelial cells as well as vascular calcification in kidneys during CKD have been noticed for long time[178–180]. In fact, the extent and histoanatomic type of vascular calcification are good predictors of subsequent cardiovascular mortality in CKD patients[181]. The endothelial dysfunction in CKD leads to changes in microcirculation, adhesion of inflammatory cells for inflammation, vascular permeability, and abnormal glomerular leakage. Especially at late stages of CKD when patients are experiencing proteinuria, renal vasculature damage and changes of glomerular architecture can adversely affect the blood supply to renal tubular cells and result in further reduction of GFR. Such loss of renal function leads to the accumulation of multiple pathogenic factors, such as uremic toxins, oxidized proteins, and advanced glycation end products (AGE), to name just a few[182–186]. Those injurious factors are delivered through blood to all over the body to cause further peripheral vasculature damage and major cardiovascular defects, which may directly decrease blood support to kidneys to induce ischemic AKI[28, 187, 188].

In addition, vasculature damage may significantly enhance the risk of AKI. A good example in this aspect is contrast medium-induced AKI[189]. Pre-existence of CKD is known to significantly increase the incidence of AKI following the administration of contrast medium in patients[190]. Though the detailed mechanism of contrast medium-induced AKI is not fully understood, it is closely related to the vascular dysfunction in addition to the direct toxic effect in renal tubular cells. Contrast medium has been reported to have vasoconstriction effect, resulting in the reduction of vasa recta blood supply and decreases in the blood flow rate in afferent arteriole, which further lead to renal tubular damage and decline of glomerular filtration[191–193]. The pre-existence of vascular dysfunction in CKD can certainly augment these pathological changes, inducing more severe AKI.

In 2001, Basile and colleagues demonstrated the loss of peritubular capillary or vascular rarefaction within weeks after ischemic AKI in rats[194]. Subsequent studies further established a role of vascular rarefaction in the development of renal fibrosis and chronic kidney problems after AKI[18]. Remarkably, Polichnowski et al. recently demonstrated that kidney repair and recovery after ischemic AKI was disproportionately impaired in rats with severe (75%) renal mass reduction (RMR) compared to rats without RMR[33]. In these animals, renal function remained lower and greater numbers of renal tubules failed to differentiate after 4 weeks of recovery, which was associated with more severe

tubulointerstitial fibrosis and capillary rarefaction, with development of hypertension and proteinuria. The most hypertensive rats showed the most proteinuria and in addition, had glomerulosclerosis. The findings indicate that pre-existing CKD may compromise tubule repair, induce greater capillary dropout, and promote fibrosis with hypertension development after superimposed AKI. In a later study[195], Polichnowski and coworkers quantified tubulointerstitial fibrosis and glomerulosclerosis at 4 weeks and at a later time-point of 16 weeks after IRI in rats with 50% RMR. Whereas averaged tubulointerstitial fibrosis early after AKI at 4 weeks decreased with time, averaged glomerulosclerosis scores were increased. Plotted as a function of systolic blood pressure measured by radio telemetry in conscious rats, severe tubulointerstitial fibrosis was observed only in animals exhibiting marked glomerulosclerosis, proteinuria and kidney hypertrophy as well as systolic blood pressures in excess of 127 mm3Hg. The strong association of tubulointerstitial fibrosis and glomerulosclerosis with modest blood pressure increase over time when AKI is superimposed upon CKD (in the RMR model), together with impaired autoregulation of pre-glomerular arterioles known to occur after RMR suggests that increased transmission of even small increases of arterial pressure through less responsive pre-glomerular arterioles is sufficient to cause progression of renal disease after AKI in settings of preexisting CKD[6,195]. Therefore, fibrosis associated with tubule atrophy may actually decrease at the late phase of AKI recovery unless vascular pathologies and associated tubule dysfunction cause sufficient increase of arterial pressure that is transmitted directly to glomeruli because of impaired glomerular arteriolar autoregulation. Of note, and relevant to human disease, in a large retrospective cohort study, elevated blood pressure was observed in patients with preexisting CKD recovering from AKI and even after AKI alone[196].

Mechanistically, post-AKI vascular defects may involve the impairment of proliferation and phenotypic change in endothelial cells[18]. As discussed above, CKD is associated with vascular dysfunction, which may further prevent vascular repair and regeneration in post-AKI kidneys, resulting in worsened vascular defects, the suppression of normal kidney repair, and the induction of maladaptive repair or renal fibrosis.

f. Epigenetic regulation

CKD is frequently associated with significant changes in epigenetics in kidneys, such as DNA methylation, histone acetylation, and expression of non-coding RNAs[197, 198]. DNA methylation changes in CKD are characterized by hypermethylation and hypomethylation of different genes. Smyth LJ et al identified different loci of genes either hypermethylated or hypomethylated in CKD by genome-wide profiling[199]. The development of diabetic nephropathy is also associated with DNA methylation changes in specific genes[200]. Interestingly, significant changes in DNA methylation occurs cisplatin-induced AKI and blockade of DNA methylation sensitizes kidney injury, suggesting a protective role of DNA methylation in AKI[201]. In terms of specific genes, the hypermethylation of klotho gene promoter in CKD conditions has been reported by several laboratories[202–207]. The suppression of klotho by hypermethylation is a potential risk factor for AKI development since klotho plays a protective role in AKI[208–210]. Chromatin modifications, especially histone acetylation, may also contribute to AKI sensitivity of CKD patients because inhibition of histone deacetylases showed beneficial effects in both CKD and AKI

conditions[211–214]. As to the regulation of non-coding RNAs, genomic wide profiling has identified the dysregulation of multiple microRNAs in CKD, although the information about long non-coding RNAs is still limited[215–217]. The roles of specific microRNAs, such as mir-21, −192, and −29, have been delineated in CKD[218–223], providing a foundation for further investigation of their involvement in AKI susceptibility of CKD patients.

IV. Conclusions and Perspectives

AKI and CKD are interconnected syndromes. On one hand, AKI contributes to the initiation and progression of CKD; on the other hand, CKD predisposes patients to AKI, and AKI on CKD has a poor prognosis. While much has learned about AKI-CKD transition, the underlying mechanism of AKI on CKD remains largely elusive. In this review, we have analyzed the major changes in CKD that may increase the sensitivity or susceptibility of AKI and suppress kidney repair or recovery from AKI in CKD patients (Figure 2). Although the molecular, cellular and tissue alterations in CKD are discussed separately, they are related and most likely cooperate to result in a pro-AKI condition. In addition, other pathological changes in CKD may be involved as well. For example, the kidney is a production site of several growth factors, such as epidermal growth factor, hepatocyte growth factor, and insulin-like growth factor I[224]. These growth factors not only affect the severity of AKI but also play important roles in the regulation of kidney repair and fibrosis[225]. In CKD, the production and function of these growth factors may be altered. Thus, AKI sensitivity, severity and non-recovery in CKD may involve multiple mechanisms at epigenetic, gene expression, signaling, organellar, cellular and tissue levels. Elucidation of these mechanisms may identify effective therapeutic targets to reduce AKI and promote kidney repair and recovery in CKD patients.

Acknowledgments

This work was supported in part by grants from the National Natural Science Foundation of China (81430017, 81370791), and the National Institutes of Health and Department of Veterans Administration of USA.

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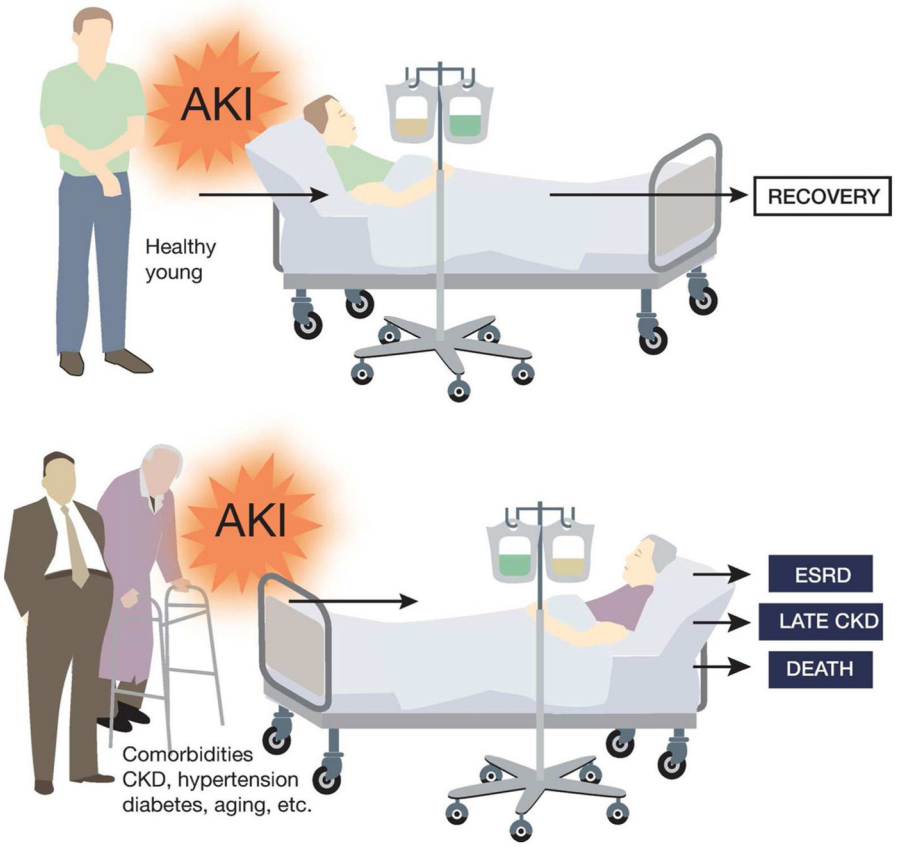

Figure 1.
Poor prognosis of AKI in patients with CKD and related co-morbidities.

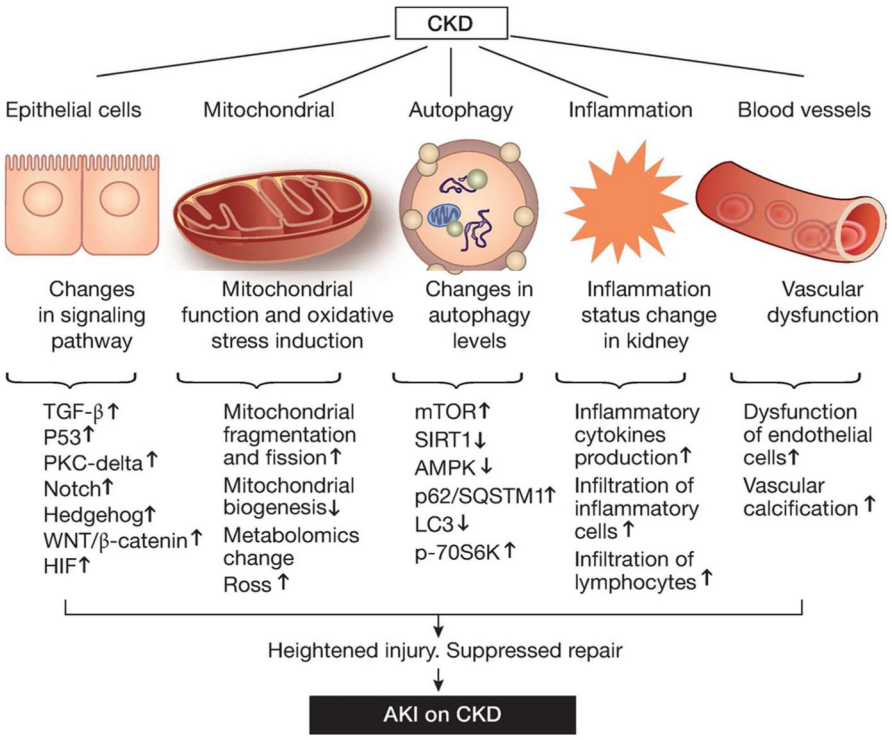

Figure 2.
Potential mechanisms underlying AKI sensitivity and non-recovery in CKD patients.