Published in final edited form as:

Clin Nephrol. 2008 December ; 70(6): 453–463.

Therapeutic and predictive targets of AKI

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Abstract

Acute kidney injury (AKI) is a very common condition encountered in a hospital setting. AKI is an independent risk factor for in-hospital mortality. In this review, we discuss in detail about the tubular, inflammatory and vascular molecular targets of AKI which may result in therapies to improve mortality and biomarkers for earlier diagnosis of AKI.

Keywords

biomarkers; interleukin-18; NGAL; fractalkine; mesenchymal stem cells

Introduction

Acute kidney injury (AKI) is a very common condition encountered in a hospital setting. The incidence of hospital-acquired AKI is 7.2% [Lameire et al. 2006]. In a multicenter and multinational observational study done by the BEST (beginning and ending supportive therapy for the kidney) study investigators, the period prevalence of AKI during the ICU stay is about 5.7% and close to 2/3 of these patients needed renal replacement therapy (RRT) [Uchino et al. 2005].

Common causes of AKI in various settings are listed in Table 1. The definition of AKI has been varied. Presently, the commonly used definition and classification of AKI is based on the RIFLE criteria (Table 2). The RIFLE criteria use the relative increase in serum creatinine and decrease in urine output as the criteria to classify the severity of AKI [Bellomo et al. 2007]. Another definition of AKI has emerged from the acute kidney injury network (AKIN) in 2005: an absolute increase in serum creatinine of either ≥ 0.3 mg/dl or a percentage increase of 50%, or a reduction in urine output to < 0.5 ml/kg/h for > 6 h [Van Biesen et al. 2006]. The term AKI as used here will not include prerenal azotemia or renal failure secondary to obstruction.

Multiple studies have addressed the relationship between AKI and mortality and have demonstrated that AKI is an independent risk factor for in-hospital mortality (Table 3). In different clinical settings even a small increase in serum creatinine was associated with increased mortality after adjusting for various comorbidities. Table 3 shows the adjusted odds ratio (OR) for mortality in patients with AKI in various settings. In the BEST study, severe AKI in the ICU was associated with an in-hospital mortality rate of 60.3% [Uchino et al. 2005]. The exact reasons for increased mortality in patients with AKI is unknown and the mortality rate has not changed significantly in the last 2 decades. The reasons for the high mortality might be the delay in the diagnosis of AKI as serum creatinine is not a specific or

sensitive test for the diagnosis of AKI. In addition, there are no specific therapies available for AKI. Renal replacement therapies (hemodialysis, continuous renal replacement therapies) are the only FDA-approved therapies for AKI [Star 1998]. A better understanding of tubular, inflammatory and vascular molecular targets in AKI may result in therapies to improve mortality and the development of biomarkers for earlier diagnosis of AKI.

Tubular targets

Table 4 shows the various therapeutic tubular targets of AKI and Table 5 shows the tubular targets that may be predictive of AKI. Here we discuss some of them.

Caspase-1 and interleukin-18 (IL-18)

Cysteine proteases are the group of enzymes that are mainly involved in both necrotic and apoptotic cell death. There are 3 major groups of cysteine proteases. These include: caspases, calpains and cathepsins [Edelstein et al. 1999]. Calpains are calcium-dependent cytosolic proteases. Caspase-1 is a proinflammatory caspase that activates IL-1 and IL-18. Caspase-3 is a mediator of apoptotic and necrotic cell death. The role of caspases, calpain and lysosomal cathepsins in hypoxia-induced tubular injury was studied in freshly isolated proximal tubules in vitro. Cathepsin activity did not increase with hypoxia but calpain activity increased and inhibiting calpain activity caused a marked decrease in the LDH release, which is a marker of tubular injury. This study supported a role of calpain in the hypoxic tubular injury [Edelstein et al. 1995]. The protective effects of low pH and low calcium on hypoxia-induced tubular injury are in part mediated by inhibition of calpains [Edelstein et al. 1996]. In rat proximal tubule cells, a specific caspase inhibitor not only inhibited the hypoxia-induced increased activity of caspases but also inhibited the hypoxia-induced increase of calpain activity and protected against hypoxic damage [Edelstein et al. 1999]. In summary, calpain and caspases play a role in hypoxia-induced injury in proximal tubules.

Because of the role of caspases in both necrotic and apoptotic cell death in hypoxic proximal tubules in vitro, the role of caspases in vivo in mouse models of AKI was studied. In ischemic AKI in mice, caspase-1 converts pro-IL-18 into the active form and both caspase-1 inhibition and IL-18 antiserum protect against ischemic AKI [Melnikov et al. 2001]. In summary, a pathogenetic role of caspase-1-mediated conversion of pro to active IL-18 was demonstrated in ischemic AKI in vivo. Caspase inhibitors and IL-18 inhibitors are potential new therapies for AKI (Table 4).

In mice, urinary IL-18 was increased in ischemic AKI when compared to controls [Melnikov et al. 2001]. Thus, we tested the hypothesis that urine IL-18 is a marker of proximal tubular injury in humans. In an initial study, urine IL-18 levels were found to be elevated in patients with acute tubular necrosis (ATN) and delayed graft function (DGF) after kidney transplantation but not in patients with urinary tract infections, chronic kidney disease, and in patients with nephrotic syndrome (Figure 1) [Parikh et al. 2004].

In a subsequent nested case control study performed within the acute respiratory distress syndrome (ARDS) network trial, urine samples were collected on Days 0, 1 and 3 after patients were randomized in the ARDS studies. Patients with baseline creatinine greater than 1.2 mg/dl were excluded. A total of 52 patients developed AKI 1 – 6 days after enrollment into the ARDS study. AKI was defined as increase of serum creatinine by 50%. On multivariate analysis, urine IL-18 predicted development of AKI in the next 24–48 h. In this study, urine IL-18 values above 100 pg/ml were associated with increased odds of 6.5 for AKI development in the next 24 h. As shown in Figure 2, IL-18 was also higher in nonsurvivors than survivors with ARDS [Parikh et al. 2005].

AKI is also a frequent complication of cardiopulmonary bypass (CPB). In a recent study, 55 children undergoing CPB were studied. Out of the 55, 20 developed AKI and 35 were controls. Using serum creatinine, AKI was detected 48 – 72 h after CPB. In contrast, IL-18 increased at 4 – 6 h, peaked at 12 h and stayed elevated at 48 h after CPB [Parikh et al. 2006 ■■■ a or b?]. The area under the receiver operated characteristic (ROC) curve for IL-18 to diagnose AKI 12 and 24 h after CPB was 75 and 73%, respectively.

IL-18 is also a biomarker of kidney DGF. Urine samples were collected within 24 h after renal transplantation in patients who received deceased donor kidneys and IL-18 levels were compared between those with prompt graft function and delayed graft function. IL-18 predicted subsequent development of DGF with an area under the ROC curve of 0.9 [Parikh et al. 2006 ■■■ a or b?].

In a recent study, 137 critically ill children (on mechanical ventilation) were studied. Urine samples were collected daily for 4 days after enrollment. In this study, a urinary IL-18 level more than 100 pg/ml predicted the development of AKI in the next 24 h with a specificity of 81%. In the same study in children, higher urinary IL-18 levels predicted longer duration of AKI and increased levels of urinary IL-18 were associated with higher mortality [Washburn et al. 2007].

In summary, urinary IL-18 is a biomarker of AKI in humans in the following conditions:

- critically ill adult patients in the ICU,
- post cardiopulmonary bypass in children,
- in kidney transplants with DGF, and
- in critically ill children in the ICU.

Early diagnosis of AKI may lead to earlier therapies which in turn may improve outcomes. Presently, a NIH-funded prospective multicenter trial is in progress to validate serum and urinary biomarkers in patients undergoing cardiac surgery. This study is being performed by the TRIBE-AKI (Translational Research to Investigate Biomarkers of AKI) consortium.

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a 25 kDa iron-transporting protein that is covalently bound to gelatinase from neutrophils. NGAL is expressed at very low levels in several human tissues. NGAL expression is markedly induced in injured epithelia. Recently, by screening ischemic mouse kidneys with cDNA microarrays, NGAL was found to be up-regulated greater than 10-fold within few hours after ischemia [Mishra et al. 2003]. NGAL has been studied in detail both in mice and humans with AKI. In postischemic kidney, NGAL is expressed predominantly in proximal tubules and is involved in renal tubular epithelial regeneration. As NGAL expression dramatically increases in kidney and urine after ischemic injury, it was postulated that NGAL may be involved in repair and regeneration of tubular epithelium [Mishra et al. 2004]. In mice, intravenous administration of 250µg of NGAL either before, during, or after ischemia offered functional and histological protection against AKI [Mishra et al. 2004].

In addition to offering protection against AKI in mice, NGAL is also a biomarker of tubular injury in AKI. NGAL was prospectively studied in AKI following CPB in a pediatric population. Of the 71 children studied, 20 developed AKI. Both serum and urine NGAL were markedly increased within 2 h after CPB. The area under the ROC curve for urine NGAL at 2 h to predict AKI was 0.99. For a cut-off value of urine NGAL at 2 h after CPB of 50 µg/l, specificity was 0.98 and sensitivity was 1 [Mishra et al. 2005]. IL-18 levels were also measured on the same urine samples and as shown in Figure 3. IL-18 and NGAL are sequential

biomarkers of AKI. Both NGAL and IL-18 are promising candidates for a urine panel of biomarkers to diagnose AKI early after the insult and before the increase in serum creatinine.

NGAL was studied in adult cardiac surgery. 81 cardiac surgery patients were prospectively studied. 16 patients developed AKI postoperatively. Urine NGAL levels 18 h after the surgery had an area under the ROC curve of 0.8 and for a level of 213 ng/ml at 18 h after the surgery had a sensitivity of 0.7, specificity of 0.78, and negative predictive value of 0.91 for the prediction of AKI [Wagener et al. 2006].

NGAL is also a biomarker of AKI in other settings of AKI. Nickolas et al. [2008] studied sensitivity and specificity of single emergency department measurement of urinary NGAL for diagnosing AKI as defined by RIFLE criteria. At a cut-off level of urine NGAL of 130 µg/g of creatinine, sensitivity and specificity for diagnosing AKI were 0.90 and 0.995, respectively. The area under the ROC curve for urinary NGAL for diagnosing AKI in this study was 0.948. A urinary NGAL level of more than 130 µg/g of creatinine predicted clinical outcomes (including nephrology consultation, dialysis initiation or ICU admission) better than other biomarkers (NAG, microglobulin, acid glycoprotein).

In a small cohort of patients undergoing coronary angiography, a 25% increase in urine NGAL was found to be predictive of contrast nephropathy (contrast nephropathy as defined as a 25% increase in serum cystatin C) with a sensitivity of 80% and specificity of 83%. Serum creatinine did not change significantly after the angiography [Bachorzewska-Gajewska et al. 2007].

Urine NGAL is also a biomarker of AKI in the pediatric ICU. Urine NGAL increased 48 h before serum creatinine. The area under the ROC curve for urine NGAL for predicting AKI in ICU was 0.78 [Zappitelli et al. 2007].

Urine NGAL levels also predicted subsequent development of delayed graft function in both adults and children who were cadaveric kidney transplant recipients [Mishra et al. 2006].

Urine NGAL has also been shown to predict the severity of AKI and dialysis requirement in a multicenter study of children with diarrhea-associated hemolytic uremic syndrome [Trachtman et al. 2006].

In summary, urinary NGAL is a biomarker of AKI in humans in the following conditions:

- post cardiopulmonary bypass in children and adults,
- in the emergency department,
- contrast nephropathy,
- children in the ICU,
- DGF of transplanted kidneys,
- hemolytic uremic syndrome.

Kidney injury molecule-1 (KIM-1)

KIM-1 is a transmembrane protein with unknown function [Ichimura et al. 1998]. The following studies demonstrate that KIM-1 is a biomarker of AKI in rat and mouse models of AKI. In a rat ischemia model, KIM-1 was found to be up-regulated in the regenerating proximal tubules. KIM-1 expression is also increased in 3 nephrotoxic rat models [Ichimura et al. 2004]. The toxins used were TFEC, folic acid and cisplatin. KIM-1 is localized to proximal tubule cells and KIM-1 is also detected in the urine of toxin-treated rats [Ichimura et al. 2004]. Vaidya et al. [2006] developed a sandwich ELISA for the KIM-1 ectodomain and

hypothesized that urinary excretion of KIM-1 increases with kidney injury. Urinary KIM-1 ectodomain excretion increased 3- to 5-fold at Day 1 after rats were exposed to cisplatin. Vaidya et al. [2006] also found increasing amount of urinary KIM-1 ectodomain levels with increasing periods of bilateral ischemia in the rat model.

KIM-1 has also been extensively studied as a biomarker of AKI in humans. Han et al. [2002] studied the expression of KIM-1 in human biopsy sections from 6 patients with a confirmed pathological diagnosis of acute tubular necrosis. KIM-1 was markedly induced in proximal tubules in kidney biopsies of these patients. The authors also studied urine samples of 40 patients with various renal diagnoses and found that the amount of KIM-1 was greatest in urines from patients with ischemic AKI.

Liagos et al. [2007] studied the relationship between the adverse events and the levels of KIM-1 and N-acetyl- β glucosaminidase (NAG) activity in the urine in 201 hospitalized patients with AKI. Patients were divided into 4 quartiles depending on the level of KIM-1 and NAG. Patients in the higher quartiles of the KIM-1 and NAG levels are at high risk of a getting dialysis or have higher mortality than patients in lower quartiles on univariate analysis. For the composite outcome of dialysis or death, APACHE II score provided an area under the ROC curve of 0.78 which only improved slightly by combining this score with urinary NAG (area under the ROC curve 0.79) and KIM-1 (area under the ROC curve 0.8). Han et al. [2002] reported the results of 2 studies, 1 cross-sectional study and a case-control study. In the cross-sectional study, urinary levels of matrix metalloproteinase-9 (MMP-9), N-acetylglucosaminidase (NAG) and KIM-1 were measured for the detection of AKI. The area under the ROC curve for diagnosis of AKI for MMP-6, KIM-1 and NAG were 0.74, 0.90 and 0.97, respectively. In the case-control study MMP-9, NAG and KIM-1 were analyzed at various time points (6, 12, and 24 h) after CPB. AKI was defined as 50% postoperative increase in serum creatinine. KIM-1 was better than NAG at all time points and MMP-9 was not a sensitive biomarker for early detection of AKI.

Van Timmeren et al. [2007] studied the expression of KIM-1 in various human kidney diseases and analyzed whether urinary KIM-1 is related to renal KIM-1 expression, renal histologic injury, renal function and proteinuria. KIM-1 expression was increased in all renal diseases except in minimal-change disease. KIM-1 expression correlated positively with serum creatinine and negatively with creatinine clearance. There was no correlation between KIM-1 expression and proteinuria. Urinary KIM-1 was significantly associated with tissue KIM-1 ($p = 0.002$).

In summary, KIM-1 appears to be a promising biomarker of AKI. Larger studies need to be done to further characterize the specificity and sensitivity of KIM-1 for the early diagnosis of AKI. KIM-1 expression is not specific for ischemic AKI.

Other tubular targets in AKI

Another potential target in AKI is erythropoietin (EPO). Recently, considerable interest has been shown in the role of EPO in protection against AKI in various rodent models (Table 6).

Vaziri et al. [1994] studied the effects of EPO on cisplatin-induced AKI in a rat model. There was a significantly improved functional recovery in animals that received EPO when compared to controls and enhanced recovery was secondary to increased regeneration of tubules as shown by increased uptake of radioactive thymidine. In another study, EPO-pretreated rats with ischemic AKI had a lower serum creatinine and decreased apoptosis when compared to controls [Yang et al. 2003]. Vesey et al. [2004] studied both in vivo and in vitro models. EPO offered significant protection from ischemia/reperfusion injury by inhibiting apoptosis and increasing tubular cell regeneration. EPO was also shown to be protective against AKI in rat cyclosporine

and contrast nephropathy models [Goldfarb et al. 2006, Lee et al. 2005]. Kolyada et al. [2007] studied the effect of iohexol on the renal tubular epithelial cells and demonstrated that EPO decreased iohexol-induced activation of caspase-3 and caspase-8 and subsequent apoptosis. EPO and α -MSH also decreased the ischemic AKI in mice [Gong et al. 2004]. Sepsis is a common cause of AKI and has a high mortality when associated with AKI. Wild-type mice were given lipopolysaccharide to induce a drop in GFR. EPO significantly attenuated the renal dysfunction as assessed by GFR and was associated with a decrease in renal superoxide dismutase [Mitra et al. 2007].

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study demonstrated that a target level of hemoglobin of 13.5 g/dl was associated with increased risk (death, myocardial infarction, stroke and hospitalization for congestive heart failure) and no incremental improvement in quality of life in chronic kidney disease patients [Singh et al. 2006]. Thus, the use of high doses of EPO, as used in animal studies, in humans with AKI may be problematic with regard to increased side effects.

Inflammatory targets

In this section, adhesion molecules, chemokines and inflammatory cells (neutrophils, lymphocytes and macrophages) will be discussed.

Ischemia/reperfusion (I/R) injury causes endothelial damage and up-regulates adhesion molecules, e.g ICAM-1 (intercellular adhesion molecule-1), that recruit leukocytes into the area of injury. Kelly et al. [1994] showed that administering ICAM-1 antibodies at the time of I/R injury in rats protected from AKI. In another study, mice deficient in ICAM-1 were protected against renal I/R injury [Kelly et al. 1996]. Leukocytes express the adhesion molecules CD11/CD18 on their cell surface. Sprague Dawley rats pretreated with monoclonal antibodies against CD11a and CD11b before induction of renal failure had improved renal function and renal histology compared to control rats [Rabb et al. 1994]. Neutrophil recruitment into the kidney depends on other adhesion molecules including P-selectin and E-selectin. Both P-selectin or E-selectin-deficient mice and postischemic injection of P-selectin or E-selectin antibodies protects against ischemic AKI in mice [Singbartl et al. 2000, Singbartl and Ley 2000].

The chemokines are small chemotactic cytokines, that were originally described to attract specific subsets of leukocytes to sites of inflammation via specific chemokine receptors. Chemokines can be divided into 4 groups depending on a 4-cysteine motif close to the N terminus. Some important chemokines include monocyte chemoattractant protein (MCP), monocyte inflammatory protein (MIP), regulated upon activation, normal T cell expressed and secreted (RANTES), fractalkine (CX3CL1) and IL-8 (also known as KC or CXCL1). Chemokines can be constitutively expressed or induced during inflammatory responses. Chemokines play a major role in inflammation and regulate all important steps of inflammation including recruiting, adhesion of leukocytes, migration and activation. Chemokines can also cause cell proliferation, apoptosis, angiogenesis and fibrosis [Segeer and Alpers 2003].

Fiorina et al. [2006] showed that when exposed to ischemic injury, mice deficient in CXCR3 (chemokine receptor 3) were protected both functionally and histologically when compared to the wild-type mice.

Fractalkine (CX3CL1) acts as both a chemokine and adhesion molecule. Fractalkine inhibition is protective against ischemic AKI in mice, partly by decreasing macrophage infiltration [Oh et al. 2008].

In the initial phases of AKI neutrophil infiltration predominates and in later phases macrophage and lymphocyte infiltration predominates. As discussed above, the proinflammatory cytokine IL-18 is involved in the pathogenesis of AKI. The mechanism of IL-18 causing AKI was further investigated. The caspase inhibitor, OPH-001, protected against the ischemic injury in mice. OPH-001 reduced the surge in caspase-1, IL-18 and decreased neutrophil infiltration [Melnikov et al. 2002]. So, it was postulated that IL-18 may be mediating AKI by stimulating and recruiting neutrophils. To test whether neutrophils were the mediators, a neutrophil depletion model using rat IgG_{2b} mAb RB6-8C5 was developed [Melnikov et al. 2002]. Mice were injected with rat IgG_{2b} mAb RB6-8C5 intraperitoneally 24 h before bilateral renal pedicle clamp. Core body temperature was maintained at 37 °C. Neutrophil-depleted mice had a small reduction in serum creatinine but no reduction in ATN score despite lack of neutrophil infiltration in the kidney [Melnikov et al. 2002].

CD4 cells were postulated to be a source of inflammatory mediators of AKI. Burne et al. [2001] demonstrated that athymic mice were protected from ischemia reperfusion (I/R) injury and the protection was lost with the adoptive transfer of T cells. In addition, CD4 T-cell-deficient mice were protected from I/R injury when compared to CD8 T cell-deficient mice.

In another experiment addressing the same issue, Faubel et al. [2005] showed that CD4 depletion with the antibody GK 1.5 as well as mice deficient in both CD4 and CD8 T cells (T cell receptor α $-/-$ mice) were not protected from ischemic ATN.

The role of T cells in ischemic AKI is complex and may depend on T cell phenotypes (Th1, Th2), early transient increases in T cells in the kidney, the presence of IFN- γ and the costimulatory pathway. In summary, the CD4 T cell, working both via interferon- γ (IFN- γ) and costimulatory molecules appears to be an important modulator of AKI [Friedwald and Rabb 2004].

Liposome encapsulated clodronate (LEC) that depletes macrophages is protective against ischemic AKI [Day et al. 2005, Jo et al. 2006, Oh et al. 2008]. The mechanism by which macrophage depletion protects against ischemic AKI is presently unknown. The production of proinflammatory cytokines for example, IL-18, by macrophages is being investigated as a mechanism of the injurious effect of macrophages in AKI.

Blockade of the costimulatory pathway by administration of CTLA-4 immunoglobulin or blockade of B7-1 and B7-2 costimulatory molecules decreases accumulation of T cells and monocytes/macrophages in the kidney and protects against ischemic AKI [De Greef et al. 2001].

Statins protect against sepsis-induced AKI [Yasuda et al. 2006] and ischemic AKI [Yokota et al. 2003] by an anti-inflammatory effect. Mycophenolic acid (MMF) decreases CD4 T cells during the later stages of ischemic AKI [Ysebaert et al. 2003]. Administration of IL-10 or α -MSH inhibits both ischemic and cisplatin-induced AKI by decreasing leukocyte activation and adhesion and by the induction of inducible nitric oxide synthase (iNOS) [Deng et al. 2001]. The ω_3 fatty acid, docosahexanoic acid, is converted to resolvins and protectin D1 which are naturally occurring inhibitors of inflammation. Administration of resolvins and protectin D1 is functionally and histologically protective against ischemic AKI [Duffield et al. 2006].

In summary, adhesion molecules, chemokines and inflammatory cells (neutrophils, lymphocytes and macrophages) represent inflammatory targets in AKI. Potential new therapies against inflammatory targets for prevention and treatment of AKI are summarized in Table 7.

Vascular targets

Recent evidence suggests that injury to the renal vasculature may play an important role in the pathogenesis of AKI. Thus, endothelial cells are a potential site of injury that leads to AKI.

In 1972, Flores et al. proposed a “no-reflow” hypothesis after demonstrating in rats that ischemia is associated with endothelial cell swelling and decreased blood flow. In addition, no-reflow and renal dysfunction can be prevented by the infusion of hypertonic solutions like mannitol [Flores et al. 1972]. Sutton et al. [2003] hypothesized that ischemic injury leads to alterations of endothelial cytoskeleton and permeability. In FVB-TIE2/ GFP mice, which express GFP (green fluorescent protein) in endothelial cells under the direction of TIE2 promoter, there was alteration in F-actin aggregation in endothelial cells after ischemia. In addition, VE cadherin that is present in the endothelial junctions disappeared 24 h after ischemic injury and returned to baseline 72 h after the ischemia. In the same study, fluorescent microscopy demonstrated that high-molecular weight dextran leaked into interstitium after ischemic injury. Circulating von Willebrand factor (vWf), which is a marker of endothelial injury, was elevated to maximum at about 24 h after ischemic injury.

Brodsky et al. [2002] studied the effect of ischemia on endothelial cells using male athymic nude rats and human umbilical vein endothelial cells (HUVEC). Intravital microscopy demonstrated the phenomenon of no-reflow after ischemic injury. Infusion of HUVEC or their surrogates expressing eNOS, after the ischemic injury resulted in functional protection against ischemic AKI suggesting that endothelial cell dysfunction is the primary cause of no-reflow phenomena.

The role of endothelial cell loss via apoptosis on microvascular permeability was examined in a mouse model of ischemic AKI. After 24 h of postischemic reperfusion, an intact endothelial monolayer without morphological evidence of apoptosis was demonstrated in areas of increased microvascular permeability. At 4 weeks after ischemic AKI, a 45% decrease in microvascular density was observed [Horbelt et al. 2007].

In a lipopolysaccharide (LPS) model of AKI, capillary perfusion, measured by intravital video microscopy, was severely compromised as early as 2 h after LPS administration and returned to normal at 48 h after LPS administration [Wu et al. 2007].

In summary, evidence suggests that injury to the renal vasculature and loss of endothelial function may play a role in the pathogenesis of early ischemic AKI and chronic changes in the kidney after AKI [Basile 2007].

Stem cells are being investigated as a potential therapy for AKI. Reyes et al. [2002] showed that multipotent adult progenitor cells (MAPC) copurify with mesenchymal stem cells (MSCs) from human bone marrow and are progenitors for angioblasts. These MAPCs may be an important source of endothelial cells for cellular proliferation and targets for antiangiogenic therapies. Nagaya et al. [2004] showed that intravenous administration of MSCs in a rat myocardial infarction model resulted in angiogenesis and myogenesis and improved cardiac function. Lange et al. [2005] did a similar experiment in a renal ischemia model. In this study, rats were given iron dextran-treated MSCs i.v. immediately after ischemic injury. MSC-treated rats were functionally and histologically (less injury score and better tubular brush border preservation) protected against AKI by Day 3. Iron-labeled MSCs were found in glomerular capillaries by Day 3.

In summary, preclinical studies demonstrate that MSCs play an important role in improving renal injury and stimulating repair in AKI. Besides direct engraftment into areas of injury, MSCs also have paracrine and endocrine effects including antiapoptotic and antiinflammatory

effects. In the future, MSC-based therapies may be used for the treatment of human AKI [Humphreys and Bonventre 2008].

The origin of the regenerating cells in ischemic AKI has been studied. It has been demonstrated that cells from the adult mouse bone marrow are mobilized into the circulation by transient renal ischemia and are found specifically in injured regions of the renal tubule. In the injured kidney, these bone marrow-derived cells make up the majority of the cells present in the previously necrotic tubules. Bone marrow ablation causing loss of stem cells results in worse AKI, while stem cell infusion after bone marrow ablation reverses this effect [Kale et al. 2003].

Another study demonstrated that regeneration by surviving tubular epithelial cells is the predominant mechanism of repair after ischemic AKI in the mouse kidney [Humphreys et al. 2008]. Using genetic fate mapping techniques, transgenic mice were generated in which 94 – 95% of tubular epithelial cells, but no interstitial cells, were labeled with either β -galactosidase (lacZ) or red fluorescent protein (RFP). 2 days after induction of AKI, the majority of the outer medullary epithelial cells coexpressed Ki67, a marker of proliferation, and RFP, indicating that differentiated epithelial cells that survived injury undergo proliferative expansion. There was extensive cell proliferation in AKI without dilution of the cell fate markers.

In summary, the origin of the regenerating cells in ischemic AKI is controversial. It is also controversial whether adult stem cells or progenitor cells contribute to epithelial cell repair after AKI.

Conclusion

We have reviewed potential therapeutic targets of AKI involving the tubules, in inflammatory cells and renal vasculature. Renal tubular studies have resulted in the development of predictive targets of AKI, e.g. biomarkers of tubular injury. Some of these biomarkers, e.g. IL-18, NGAL, KIM-1 and tubular enzymes, increase early in the urine in AKI before serum creatinine.

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Figure 1. Urinary IL-18 levels in patients with various kidney diseases. Urinary IL-18 levels in patients with ATN is several 100-fold higher when compared to other kidney diseases [Parikh et al. 2004].

Figure 2. Urinary IL-18 levels are significantly higher in non-survivors in critically ill patients [Parikh et al. 2005].

Figure 3. NGAL and IL-18 levels after cardiopulmonary bypass. Both biomarkers increased several hundred fold within few hours after CPB and predicted AKI much earlier than serum creatinine [Parikh et al. 2006].

Table 1

Causes of AKI.

–	Community acquired AKI: prerenal azotemia (e.g dehydration, ACE inhibitors), congestive heart failure, rhabdomyolysis, drugs (e.g. nonsteroidal anti-inflammatory drugs), hemolytic uremic syndrome (HUS) in children
–	Asia and Africa: infections (e.g. malaria), snake bites, poisons
–	Hospital acquired AKI: prerenal azotemia, ischemia, nephrotoxins and contrast media
–	AKI in the ICU: sepsis

Table 2

RIFLE criteria for acute kidney injury.

	GFR criteria	Urine output criteria	
Risk	SCr $\times$ 1.5 GFR decrease $>$ 25%	UO $<$ 0.5 ml/h/kg $\times$ 6 h	High sensitivity
Injury	SCr $\times$ 2 GFR decrease $>$ 50%	UO $<$ 0.5 ml/h/kg $\times$ 12 h	High sensitivity
Failure	SCr $\times$ 3 GFR decrease $>$ 75% SCr $>$ 4 mg/dl	UO $<$ 0.3 ml/h/kg $\times$ 24 h (= oliguria) Anuria $\times$ 12 h	High specificity
Loss	Persistent AKI	Loss of function $>$ 4 w	High specificity
ESKD	End-stage	$>$ 3 months	

Table 3

Studies demonstrating that AKI is an independent risk factor for death.

AKI characteristics	Adjusted OR	Study
Hospital acquired	6.2	Shusterman et al. [1987]
Radiocontrast	5.5	Levy et al. [1996]
Aortic surgery	9.1	Kashyap et al. [1997]
Cardiac surgery	7.9	Chertow et al. [1998]
ICU	1.6	de Mendonca et al. [2000]
Hospital acquired	2.5	Obialo et al. [2000]
Amphotericin B	6.6	Bates et al. [2001]
Liver cirrhosis	4.3	Aggarwal et al. [2001]
Bone marrow transplant	6.8	Parikh et al. [2002]

Table 4

New therapies for prevention and treatment of AKI that act on the tubular targets based on recent animal studies.

–	Caspase-inhibitors
–	Interleukin-18 antiserum
–	Interleukin-18 receptor binding protein
–	NGAL
–	EPO
–	EPO receptor agonist

Table 5

Predictive biomarkers of established AKI in human studies.

–	Urinary IL-18
–	Urinary NGAL
–	Urinary kidney injury molecule-1 (KIM-1)
–	Urinary IL-6 and IL-8
–	Urinary tubular enzyme, e.g. γ -GT, alk. phos., NAG

Table 6

Role of erythropoietin in protection against AKI.

Model	Outcome	Reference
Rat cisplatin	Less AKI	Vaziri et al. [1994]
Rat AKI	Functional protection, less apoptosis	Yang et al. [2003]
Rat AKI	Less apoptosis and necrosis	Vesey et al. [2004]
Rat AKI	Functional protection, less apoptosis	Sharples et al. [2004]
Rat shock	Less AKI, decreased caspase-3	Abdelrahman et al. [2004]
Rat cyclosporine nephrotoxicity	Less inflammation, less apoptosis	Lee et al. [2005]
Rat contrast nephropathy	Less AKI	Goldfarb et al. [2006]
Mouse endotoxemia	Less renal dysfunction	Mitra et al. [2007]

Table 7

New therapies against inflammatory targets for prevention and treatment of AKI based on recent animal studies.

–	Lymphocyte or macrophage depletion
–	Mycophenolate mofetil (MMF)
–	α -MSH
–	Statins
–	IL-10, anti-IL-6, anti-IL-18
–	CTLA-4 Ig
–	Fractalkine receptor (CX3CR1) inhibition
–	Resolvins and protectin D1