Chapter 23
Acute Kidney Injury and Cytokines

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Abstract Cytokines and chemokines are potential signaling molecules that maintain homeostasis by activating intracellular communication. Cytokines orchestrate various processes, ranging from cellular survival, proliferation, and chemotaxis for tissue repair to regulation of inflammation. Extracellular vesicles (EVs), which are cell-derived membrane particles such as exosomes and microvesicles, may also play crucial roles similar to cytokines. The kidneys are highly susceptible to intrinsic oxidative stress resulting from ischemia and to the excessive inflammatory response resulting from systemic autoimmunity. These types of stress may eventually result in the development of acute kidney injury (AKI). In this setting, the skewed cytokine profile produced by macrophages and lymphocytes disrupts the reciprocal relationship for regulating tissue repair and remodeling due to amplification of a physiological vicious loop. We have so far shown that AKI induces the secretion of midkine (MK) and CD147/basigin, which are responsible for skewed cytokine production. MK and CD147/basigin secreted by tubular epithelial cells promote the recruitment of macrophages and neutrophils, respectively, which are accompanied by monocyte chemotactic protein-1, transforming growth factor-β, E cadherin, and extracellular matrix metalloproteinase inducer.

This chapter will present the functions of macrophage-related cytokines and EVs and summarize our findings on how MK and CD147/basigin are involved in the pathogenesis of AKI.

Keywords Inflammation · Renal ischemia · Macrophage · Midkine · CD147/Basigin · Extracellular vesicles

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23.1 Introduction

Ischemia, loss of self-tolerance, and bacterial infection induce white blood cells to enter various organs due to activation of chemotactic cytokines and adhesion molecules, eventually resulting in systemic inflammation [1, 2]. Because the kidneys are highly sensitive to intrinsic oxidative stress caused by systemic ischemia and systemic autoimmunity, various stresses can lead to acute kidney injury (AKI) [3]. Renal tubular epithelial cells (TECs) are the antigen-presenting cells in the kidneys. Following activation of cell adhesion molecules resulting from injury to tubules, TECs interact directly with various immune cells such as neutrophils, monocytes, and T lymphocytes [4]. Maintenance of an anti-inflammatory and anti-thrombotic environment and prevention of renal fibrosis require homeostasis of renal endothelial cells [5]. AKI and the immune system show bidirectional cross-talk [6, 7]. Renal damage can result from both adaptive and innate immune cells and recovery from AKI. The etiology of AKI involves dendritic cells (DCs), monocytes/macrophages, neutrophils, T lymphocytes, and B lymphocytes. In addition, M2 macrophages and regulatory T cells mediate inflammatory processes, tissue remodeling, and repair after AKI. Higher levels of cytokines and immune cell dysfunction, especially dysfunctional neutrophils, may exacerbate immune dysfunction and block removal of bacteria during AKI.

A vicious cycle of injury after acute or subacute kidney injury may spread to distant organs, such as the heart, liver, and lungs. Multiple cytokines and chemokines expressed by circulating inflammatory cells and damaged organs may mediate the cross-talk between distant organs and the kidneys. Ischemia-induced AKI may be followed by impaired function of distant organs [8, 9]. Renal inflammation prophylaxis is necessary for reduced mortality and morbidity after kidney injury. Although mediated by different primary disease processes, long-term injury to the kidney leads to permanent abnormalities such as glomerular obsolescence and interstitial fibrosis; these conditions may eventually develop into chronic kidney disease (CKD). Patients with moderate renal dysfunction usually do not show symptoms. Thus, early identification of susceptible patients and increased understanding of mechanisms that induce inflammation may be important for determining therapeutic strategies for treatment of kidney diseases. Studies of cytokines, chemokines, and extracellular vesicles (EVs), as well as their associated mRNAs and miRNAs, are critical for preventing death and improving the health of patients with AKI. Here, we describe in vivo studies of various promising molecules.

23.2 Macrophage-Related Cytokine and Chemokine Portfolio

When cells are damaged and damage-associated molecular patterns are triggered and released from the damaged cells themselves, an inflammatory response is formed around the damaged cells. Next, chemokines (CXCL1, CXCL8, CCL2,

CCL5) are secreted from epithelial cells and resident DCs/macrophages, which recruits neutrophils and monocytes to the sites of inflammation in AKI [3]. At the same time, inflammatory cytokines (tumor necrosis factor-α, interferon-γ, interleukin (IL)-6, IL-1β, IL-23, IL-17) and anti-inflammatory cytokines (IL-4, IL-10, transforming growth factor (TGF)-β, hepatocyte growth factor, resolvins) are secreted from resident and recruited cells at the sites of inflammation [3]. The balance between inflammatory cytokines and anti-inflammatory cytokines are important determinants of when inflammation leads to injury and injury to regeneration.

Macrophages are present in healthy and diseased kidneys where they perform critical roles in maintenance, the immune response, tissue injury, and tissue repair. Macrophages are highly heterogeneous cells and exhibit distinct functions depending on their local microenvironment, which includes cytokines. This macrophage heterogeneity allows the cells to respond to changes in various cytokines. Macrophages are classified into two broad subsets, pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages (Fig. 23.1). At the time of initial

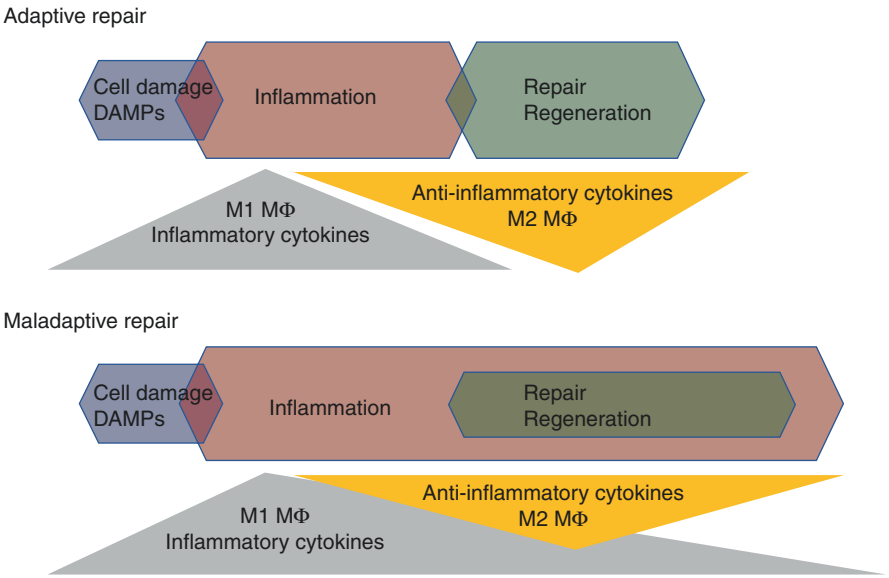

Fig. 23.1 Inflammation and regeneration. Once cells are damaged, they produce damage-associated molecular patterns (DAMPs) and danger signals, leading to activation and recruitment of leukocytes (M1 macrophages). This phase is known as inflammation. The inflammatory signals induce stem cells from dormancy to proliferative state, and the proliferated stem cells differentiate to compensate for the tissue defect. At the peak of inflammation, anti-inflammatory cells (M2 macrophages) begin to appear in the inflamed sites. In the case of adaptive repair, the inflammation is terminated by the increase of anti-inflammatory cells and the concomitant increase of anti-inflammatory cytokines. Anti-inflammatory cytokines restore stem cells from proliferation to dormancy to prevent stem cell exhaustion. In the case of maladaptive repair, the sustained inflammation continues to induce stem cell proliferation and differentiation, and eventually stem cells are exhausted. Tissue repair cannot be achieved due to stem cell exhaustion and persistent attack on differentiated cells by immune cells

injury in AKI, the kidney is protected from ischemic injury by depletion of kidney macrophages [10, 11]. Furthermore, if M1 macrophages induced in vitro are transferred back into mice with ischemic kidney injury, kidney damage is worsened. These observations indicate that M1 macrophages play pathogenic roles in ischemic kidney injury [12]. On the other hand, recovery from ischemic kidney injury is impaired when macrophages are removed after the onset of ischemic AKI [13]. Administration of macrophages during the recovery phase from ischemic AKI induces TEC proliferation and promotes recovery of renal function [14]. These results suggest that M2 macrophages mediate kidney repair and regeneration. M1 macrophages injected during the regeneration phase change their phenotype from M1 to M2 within the kidney [12]. This indicates that macrophages switch from an inflammatory (M1 macrophage) to an anti-inflammatory (M2 macrophage) state as the cytokines change from inflammatory to anti-inflammatory in the inflammatory sites. In other words, macrophages function as effector cells that converge inflammation at the injured site and convert the environment towards a regenerative state by recognizing changes in the surrounding environment. In vitro stimulation or administration of lipopolysaccharide or interferon-γ induces M1 macrophages, whereas M2 macrophages are induced by Th2 cytokines such as IL-4 and IL-10. However, the mechanisms by which in vivo macrophages switch to M2 macrophages in ischemic AKI remains poorly understood.

Apoptotic cells, anti-inflammatory cytokines, and growth factors are important factors in the induction of M2 macrophages. Macrophages take up apoptotic bodies, and sphingosine-1-phosphate from apoptotic cells in mice after ischemic reperfusion promotes induction of M2 macrophages, leading to production of TGF-β and IL-10 [15]. Production of anti-inflammatory cytokines by M2 macrophages enhances M2 polarization at inflamed sites. IL-10 derived from regulatory T cells also plays a partial role in M2 polarization [16]. Steroid treatment increases M2 macrophage numbers in vivo, leading to a reduction in inflammation and injury in the inflamed kidney [17]. Colony stimulating factor-1 derived from TECs in ischemic reperfusion-induced mice polarizes resident macrophages towards M2 macrophages, enhancing regeneration following ischemic renal damage [18]. Once M2 macrophages are induced in inflammatory and damaged lesions, these cells reduce inflammation by removal of cell debris and production of protective mediators such as heme-oxygenase-1 (HO-1) and IL-10. HO-1 is an anti-inflammatory enzyme. HO-1-expressing M2 macrophages promote phagocytosis of apoptotic cells and production of IL-10 [19], which is a strong anti-inflammatory cytokine that blocks inflammatory pathways. Systemic administration of IL-10 protects against ischemic AKI and cisplatin-induced AKI by inhibiting intercellular adhesion molecule-1 and granulocyte activation [20]. Moreover, by secreting angiogenic factors and growth factors, macrophages establish an environment that is necessary for organ regeneration. M2 macrophages locally support vascularization by secreting vascular endothelial growth factor to restore the energy and oxygen that are necessary for organ regeneration. The reparative potentials of M2 macrophages appear to be mediated

by Wnt7b, which leads to cell-cycle progression of renal TECs after ischemic AKI [21]. Further research is needed to investigate the mechanism by which M2 macrophages promote regeneration.

Based on these findings, two therapeutic strategies have been considered for acute renal failure. The first is direct administration of cultured macrophages into the body. Administration of induced pluripotent stem cell-derived M2 macrophages ameliorates nephritis in mice [22]. HO-1-overexpressing macrophages show an anti-inflammatory phenotype with increased IL-10 production [19]. These reports suggest that direct administration of M2 macrophages may be a new treatment strategy for kidney injury.

The second strategy is to induce a change in the inflammatory environment by administering a drug or growth factor that will lead to promotion of regeneration and induction of M2 macrophages. Administration of mesenchymal stem cells (MSCs) can change the inflammatory environment, leading to induction of M2 macrophages and kidney regeneration.

MSCs can differentiate into bone, cartilage, and adipose tissue. Although MSCs are rare populations in bone marrow and adipose tissue, MSCs show excellent growth ability in culture while retaining their growth and multilineage potential. Thus, MSCs may be ideal candidates for cell therapy, and many researchers have examined the therapeutic effects of MSCs in various animal models. MSCs show pleiotropic effects in damaged sites by producing various growth factors and immunoregulatory factors, depending on signals in the inflammatory milieu. In the area of kidney research, administration of cultured MSCs protects against AKI and nephritis via production of hepatocyte growth factor and M2 induction, respectively [23, 24]. Recently, phase 1 and 2 clinical trials using bone marrow- or adipose-derived MSCs have begun to target AKI.

Adenosine may be a therapeutically useful molecule because it alters the inflammatory environment. Adenosine is a purine nucleoside found in many living systems, and it is also a medication. In the clinic, adenosine is used to treat supraventricular tachycardia. Adenosine is constitutively present in physiological conditions at a very low concentration, but its concentration increases in pathological conditions such as hypoxic and inflammatory conditions. CD39 is an extracellular enzyme that catalyzes the conversion of adenosine triphosphate (ATP) and adenosine diphosphate to adenosine monophosphate. CD73 rapidly converts adenosine monophosphate into adenosine. Of the four different types of adenosine receptors (adenosine A_1, A_{2A}, A_{2B}, and A_3 receptors), the A2A adenosine receptor (A2AR) is predominantly expressed in immune cells. Activation of A2AR generally produces immunosuppressive signals, which inhibit activities of T cells, natural killer cells, macrophages, DCs, and neutrophils. An A2AR agonist also induces conversion of macrophages to an M2 phenotype, an activity that is independent of IL-4/IL-4Rα signaling [25]. In A2AR-deficient mice, tissue damage due to inflammation is exacerbated compared to wild-type mice. Some reports show that administration of an A2AR agonist strongly inhibits the induction of inflammatory

diseases. In the area of kidney research, increasing the adenosine concentration reduces the severity of ischemic kidney injuries [26]. Another article indicated that a nonspecific adenosine receptor inhibitor prevents the reduction in renal blood flow following ischemic renal injury [27]. Therefore, whether adenosine in inflamed sites shows protective effects or not in ischemic kidney injuries is still controversial. This discrepancy may be related to expression levels and subtypes of adenosine receptors and may depend on the disease model and injury severity.

By decreasing inflammatory cytokines, decreasing M1 macrophages, and increasing M2 macrophages, dysfunctional organs can shift to a phase of regeneration and repair, eventually leading to adaptive repair. If the transition from inflammation to regeneration is minimal and inflammation remains, chronic inflammation and fibrosis may result. Cellular therapy, cytokine therapy, and growth factor therapy may be new treatment options for patients with acute renal disorders following increased understanding of microenvironmental changes and factors that determine the function and subtype of macrophages in the kidney. Many factors related to inflammation have been identified, and new drugs are being developed as a result. In addition, as the mechanisms of development of inflammation and organ regeneration are elucidated, new therapeutic applications for existing drugs have attracted attention as treatment for acute renal disorder.

23.3 Cytokines and Chemokines Derived from Infiltrating Inflammatory Cells and TECs

23.3.1 Midkine

Midkine (MK; gene, *Mdk*) is a 13-kDa growth factor that contains multiple basic amino acids and cysteines and binds heparin. MK was first identified as a transcript of a retinoic acid-responsive gene. MK plays a role in kidney development, increases cell growth, enhances cell survival, increases cell migration, is anti-apoptotic, and is involved in fibrinolysis and development of cancer [28, 29]. In the normal kidney, MK is expressed in proximal and distal TECs and at lower levels in endothelial cells [5, 30]. MK receptors may form a complex that also includes proteoglycans such as low density lipoprotein receptor-related proteins [28, 31, 32]. MK signaling involves mitogen-activated protein kinase and phosphatidylinositol 3-kinase. The pro-inflammatory role of MK has been shown in various in vivo studies of arterial restenosis [33], rheumatoid arthritis [34], ischemic renal injury [35–37], cisplatin-induced tubulointerstitial injury [38], diabetic nephropathy [39, 40], and endothelial dysfunction [41]. MK has various pathophysiological effects on disorders such as AKI, CKD, high blood pressure, ischemia, and type 2 diabetes.

Renal ischemia is a primary cause of AKI and is related to injury to various organs via organ–organ interactions including the kidney. Renal ischemia also involves several chemokines, with the end result of multiple organ failure [1, 42]. In this setting, TECs become energy deprived, and various beneficial and harmful

systems are activated. This causes direct disruption of the cytoskeleton, aberrant cell polarity, and cell death. Indirect effects that induce chemotaxis are seen including activation of different types of cells such as endothelial cells and leukocytes [5]. Severe depletion of ATP leads to necrosis, whereas GTP depletion tends to promote apoptosis [43]. Necrosis and autophagy are both observed after ischemic reperfusion injury. In this condition, disrupted vascular endothelial cells lead to vascular congestion, edema, decreased blood flow, and migration of neutrophils and macrophages. When these inflammatory cells enter the injured kidney, cytokines are secreted, and the presence of reactive oxygen species (ROS), proteases, myeloperoxidase, and other chemokines can lead to additional injury. These processes have been repeatedly demonstrated in both humans and animal models of renal reperfusion. After ischemic reperfusion in vivo, MK is quickly upregulated in the proximal tubules, which increases macrophage inflammatory protein for neutrophils and monocyte chemotactic protein-1 for macrophages [35, 37]. The inflammatory cells induce severe tubulointerstitial damage. Blocking MK inhibits inflammatory cell movement to the damaged epithelial layer and decreases the severity of kidney injury. Thus, MK increases movement of inflammatory cells into the kidney following ischemic injury and also induces chemokines, thus playing a role in worsening ischemic tissue damage.

Patients with acute or subacute kidney injury should not experience death or complications due to pulmonary dysfunction [44]. Most kidney–lung interactions are accompanied by secretion of cytokines, including TGF-β, IL-1β, IL-6, IL-18, nuclear factor kappa-light-chain enhancer of activated B cells, and tumor necrosis factor-α, as well as MK and induction of renin-angiotensin system (RAS) [44, 45]. Factors that are upstream of the MK-RAS system have been investigated. Our group showed that oxidative stress induces expression of MK [39]. Another group showed that hypoxia increases MK via hypoxia-inducible factor-1α and induces pulmonary vascular remodeling [46]. We hypothesized that NADPH oxidases (Nox), which are enzymes that generate and release superoxide by electron transfer from NADPH to oxygen, are important in *MK induction*. Pulmonary Nox1, 2, and 4 expression in wild-type ($Mdk^{+/+}$) mice is significantly upregulated following kidney ablation, but Nox expression is not affected by ablation in MK-deficient ($Mdk^{-/-}$) mice [47]. Nox-mediated ROS induces pulmonary MK expression. The membrane-permeable radical scavenger, 4-hydroxy-2,2,6,6- tetramethylpiperidine-N-oxyl (Tempol), decreases MK induction and returns plasma Angiotensin (Ang) II to normal levels in the lungs. Tempol also improves blood pressure and decreases kidney damage including glomerular sclerosis and tubular interstitial injury. ROS are unlikely to be transported between the kidney and lung due to their short half-life. Ang II induces Nox expression [48]. Thus, we conclude that the oxidative stress-induced initial increase in MK in the endothelium increases ACE expression in the lung, and the end result is a vicious cycle of Ang II overexpression. The RAS may strongly drive positive feedback induced by oxidative stress.

Segmental breaks in the glomerular basement membrane (GBM) may lead to formation of crescents in the glomerulus, and are often accompanied by fibrinoid necrosis [49]. These phenomena induce deposits of fibrin, infiltration of inflammatory cells, and accumulation of the extracellular matrix. Fibrin deposits disrupt

glomerular blood flow, lead to irreversible ischemia and glomerular obsolescence, and promote entrance of inflammatory cells and cell division by epithelial cells in Bowman's space [50]. Macrophage and neutrophil recruitment is induced by inflammatory mediators such as fibrin, oxidative stress, and different chemokines. The end result is induction of coagulation during crescentic glomerulonephritis (GN), thrombotic microangiopathy, and severe endothelial dysfunction. This vicious cycle must be inhibited to decrease deaths associated with aggressive kidney diseases.

The glycoprotein plasminogen activator inhibitor (PAI)-1, an inhibitor of serine proteases, is the major endogenous inhibitor of plasminogen activators such as tissue-type plasminogen activator and urokinase-type plasminogen activator [51]. Concentrations of PAI-1 in tissues and plasma are extremely low in normal physiological states, but are upregulated in abnormal conditions. PAI-I has multiple effects, including induction of thrombotic disorders and a role in ischemic diseases, fibrotic disorders, metabolic syndrome, type 2 diabetes, and cancer [49, 51, 52]. Increased levels of PAI-1 induced by various factors such as high ambient glucose exposure [53], TGF-β [54], oxidative stress [55], and Ang II [56, 57] lead to recruitment of interstitial macrophages and direct effects of cells following urokinase-type plasminogen activator receptor binding. Reduced PAI-1 decreases the severity of anti-GBM-induced nephritis [58]. Elucidation of signaling induced by PAI-1 may lead to development of novel therapeutic strategies for rapidly progressive GN.

MK is induced by an inflammatory microenvironment, followed by direct and indirect recruitment of macrophages through activation of monocyte chemotactic protein-1. Induction of PAI-1 in both normal and pathological states has been extensively studied. However, the endogenous systems that block induction of PAI-1 are not known. MK increases fibrinolysis by decreasing PAI-1 in vascular endothelial cells [59, 60]. Our group performed in vivo studies and showed that MK has harmful effects on both glomerular damage and tubulointerstitial injury due to its ability to recruit inflammatory cells in mice with accelerated Masugi nephritis [61]. Several studies have shown that MK may protect against crescentic GN, and that the pathological features of this condition may be due to an imbalance in the coagulation-fibrinolysis system.

Capillary endothelial dysfunction and subsequent intravascular fibrin lead to macrophage infiltration, disruption of the GBM, and leakage of its contents, such as fibrin, red blood cells, extracellular matrix, and inflammatory cells. Macrophage recruitment in this condition may be the first step in a critical series of cellular events that lead to crescent formation. Consistent with this idea, deletion of macrophages stops the progression of crescentic GN [62]. PAI-1 both stabilizes the fibrin net and is a chemoattractant for monocytes and leukocytes [50, 63]. Macrophages and PAI-1 increase fibrin formation, and fibrin induces macrophage infiltration and endothelial dysfunction. Consistent with this idea, a study of experimental models of anti-GBM crescentic GN showed that compared to PAI-1-deficient mice, more crescents were formed, more fibrin deposits were seen, and greater macrophage infiltration was present in PAI-1-overexpressing mice [58]. High levels of PAI-1 are observed both in regions with glomerular necrosis and in crescents in progressive GN [64, 65]. Parietal epithelial cells and glomerular endothelial cells preferentially

express PAI-1. Consistent with these in vivo data, our group showed that primary cultured endothelial cells from $Mdk^{-/-}$ mice have higher levels of PAI-1 mRNA after a fibrin challenge, and they also show less fibrinolysis than cells from $Mdk^{+/+}$ mice. PAI-1 is also induced by factors such as high ambient glucose, TGF-β, oxidative stress, and Ang II.

23.3.2 CD147/Basigin

CD147/Basigin, an extracellular matrix metalloproteinase inducer, is a highly glycosylated transmembrane protein that is a member of the immunoglobulin superfamily [66]. CD147 includes a 185-amino acid (aa) extracellular domain with two immunoglobulin domains, a 24-aa transmembrane domain, and a 39-aa cytoplasmic domain [67, 68]. The extracellular domain harbors three N-linked glycosylation sites. Glycosylation is different depending on the organ, and these glycosylation differences may explain the variety of physiological roles of CD147. CD147 is expressed by many cell types including hematopoietic, epithelial, and endothelial cells and leukocytes. This protein is important in oncogenesis and cancer progression due to its ability to induce matrix metalloproteinases and monocarboxylate transporters. CD147 was first discovered in embryonal carcinoma cells where it functions as a receptor for Lotus tetragonolobus agglutinin. This protein has the Lewis X structure: Galβ1→4(Fucα1→3) GlcNAc [69]. CD147 binds to multiple molecules such as caveolin, cyclophilin, monocarboxylate transporter (MCT), and CD147 itself [4, 70]. The extracellular domain of CD147 binds to caveolin-1, β1 integrin, cyclophilin, and CD147 itself, whereas the transmembrane domain is necessary for the association with MCT, CD43, and syndecan [71–74]. Similar to MK, mitogen-activated protein kinase and phosphatidylinositol 3-kinase are involved in CD147 downstream signaling. Normal kidneys, especially the basolateral side of TECs, express high levels of CD147 [75]. In contrast, CD147 expression in glomerular structures and vascular endothelial cells is very low, perhaps explaining the inability of many antibody clones to detect low levels of CD147 with western blotting or immunohistochemistry. Increased CD147 is observed with immunohistochemistry in glomeruli and vessels injured by inflammation, as well as in glomerular adhesions to Bowman's capsule, endocapillary proliferation, and crescent formation. Inflammatory cells that show CD147 induction infiltrate strongly into damaged regions [76]. On the other hand, clearly reduced CD147 expression is observed in the damaged tubulointerstitium in patients with AKI and diabetic nephropathy [77]. CD147 expression does not occur in patients with diabetic nephropathy and nodular glomerulosclerosis.

Short-term harmful events such as ischemia, kidney-specific auto-antigens, and activation of the immune system interact over a period of minutes to days, resulting in AKI. Early in AKI, inflammatory cell infiltration increases disease activity via secretion of chemotactic cytokines and ROS [3]. Increased interactions between leukocytes and endothelial cells due to increased cell–cell adhesion greatly decrease

peritubular capillary blood flow, which leads to oxidative injury to renal tubules and subsequent depletion of ATP [2, 76]. These events lead to cytoskeletal and cell polarity abnormalities, culminating in cell death. A vicious cycle involving multiple cytokines and adhesion molecules ensues. Compared to expression in other organs, CD147 is very highly expressed in the tubules of normal kidneys, suggesting important roles for CD147 in the above events [75]. Insufficient levels of CD147 lead to ATP depletion in ischemia-induced AKI, and hypoxia depletes ATP in primary cultured $Bsg^{-/-}$ TECs. Thus, in normal conditions, CD147 may increase the activity of lactate metabolism via MCT, which induces ATP in renal tubules.

In vivo studies using $Bsg^{-/-}$ mice were performed to confirm in vitro data and increase our understanding of the functions of CD147. $Bsg^{-/-}$ mice with renal ischemic reperfusion show a marked decrease in recruitment of neutrophils and macrophages, resulting in a reduction in tubulointerstitial damage [78]. Thus, CD147 appears to be important for recruitment of inflammatory cells in this type of injury. The CXC chemokines, keratinocyte-derived chemokine and macrophage inflammatory protein-2, attract neutrophils following ischemic injury. However, wild-type and $Bsg^{-/-}$ mice show similar expression levels of these molecules. The role of CD147 in the pathogenesis of ischemia-induced AKI remains unknown. Blocking CD147 pharmacologically inhibits the migration of neutrophils and monocytes/macrophages after myocardial ischemia and reperfusion, and subsequently protects left ventricular function and myocardial tissues [79]. The interaction between CD147 and its ligand cyclophilin A (CyPA) is crucial for regulation of leukocyte recruitment. Results from in vivo studies of conditions such as sepsis-induced AKI, bronchial asthma, lipopolysaccharide-induced lung injury, and collagen-induced arthritis, are consistent with this idea [80–83]. However, wild-type and $Bsg^{-/-}$ mice show similar levels of CyPA expression, and therefore, CD147-CyPA binding may not be involved in the etiology of ischemic AKI. Further studies of this interaction are needed. The infiltration of massive numbers of neutrophils into damaged regions is due to CD147 expression on neutrophils, and not on other cell types such as TECs. In addition, CD147 expressed on neutrophils is a critical physiological ligand for E-selectin; CD147-E-selectin binding mediates adhesion of neutrophils to vascular endothelial cells. Inflammatory stimuli induce selectin specifically in endothelial cells [84, 85]. Consistent with this observation, mice deficient in E-selectin show greatly reduced myeloperoxidase activity, which is an indicator of active neutrophils. CD147 includes a sialyl Lewis X structure, which is necessary for E-selectin recognition [69]. In addition to CD147, other glycoproteins including P-selectin glycoprotein ligand-1 and CD44 bind to E-selectin. The primary interaction between neutrophils and endothelial cells occurs in parallel with P-selectin glycoprotein ligand-1 expression at the tip of neutrophil microvilli. The steady, slow rolling of leukocytes is regulated by CD44, which is expressed on the planar surface of neutrophils [86, 87]. Thus, chemotactic cytokines and adhesion-related molecules may be necessary for leukocyte recruitment. Highly glycosylated CD147 expressed on the planar surfaces and the microvilli of neutrophils binds E-selectin early during formation of leukocyte-endothelial contact, increasing recruitment of neutrophils into the ischemic kidney.

23.4 Extracellular Vesicles (EVs)

EVs are the generic term for cell-derived membrane particles including exosomes, microvesicles, and apoptotic bodies. Exosomes originate from endosomes and are the smallest vesicles (30–100 nm in diameter) among EVs. Microvesicles and apoptotic bodies are derived directly from the plasma membrane and are 0.1–1.0 μm and 1.0–5.0 μm in diameter, respectively. These EVs are sometimes difficult to distinguish from each other. These vesicles do not contain a functional nucleus, but do contain mRNA, microRNA (miRNA), and protein from their parental cells. They transfer their contents to or stimulate cell surface receptors on recipient cells in an autocrine and paracrine manner. In particular, the transfer of mRNA and miRNA can genetically reprogram the phenotypes of recipient cells. EVs have been intensively explored in immunology, oncology, and cardiology research fields. They play roles in intracellular communication such as antigen presentation, distant organ metastasis, and atherosclerosis [88, 89]. Compared with these other research fields, little is known about the contribution of EVs to the pathogenesis of kidney disease. A body of evidence is gradually accumulating that demonstrates the involvement of EVs in disease processes of the kidney, including IgA nephropathy, renal transplantation, thrombotic microangiopathies, nephrotic syndrome, urinary tract infection, cystic kidney disease, CKD, and AKI [90–95]. EVs are not only involved in pathogenesis, but have attracted a great deal of attention as a new class of disease biomarkers. In addition, some basic studies have suggested that exosomes from MSCs or progenitor cells protect against ischemic kidney injury. Below, we discuss the current knowledge regarding the association of EVs with pathogenesis, as a biomarker, and as potential therapy for AKI.

23.4.1 EV-Related Pathogenesis of AKI

Plasma from patients with sepsis-associated AKI induces granulocyte adhesion, apoptosis, and altered polarity in cultured tubular cells [96]. Thus, researchers have speculated that some soluble factors in plasma directly cause AKI. In the lipopolysaccharide-induced AKI mouse model, the amounts of exosomes in urine and kidney are increased and contain higher levels of CCL2 mRNA compared with control mice. An in vitro experiment revealed that BSA-stimulated TECs contain a high level of CCL2 mRNA, and exosomes derived from TECs were directly transferred into macrophages. Combined with these data, intracellular communication between TECs and macrophages through exosomes exists and causes tubulointerstitial inflammation [97].

Necroptosis is a programmed cell death process that is mediated by mixed lineage kinase domain-like protein, and growing evidence has revealed the importance of tubular necroptosis in causing AKI [98]. From that point of view, serum-derived

exosomes from AKI patients increase mixed lineage kinase domain-like protein-mediated necroptosis in cultured HK2 cells via a reduction in miR-500a-3p expression [99]. Further studies are needed to increase the knowledge of the role of exosomes in AKI.

23.4.2 EVs as a Promising Biomarker of AKI

Urinary EVs may be useful as biomarkers of AKI. The level of Na^+/H^+ exchanger isoform 3 is elevated in the urinary membrane fraction of patients with acute tubular necrosis compared with patients with prerenal azotemia and controls [100]. At that time, the contribution of EVs was not mentioned, but the molecules from renal parenchymal cells in urine were proposed to serve as markers of damaged tubules. Studies of animal disease models and human samples have shown that activating transcription factor 3 may serve as a biomarker of tubular injury. On the other hand, Wilms tumor 1 was proposed as an early podocyte injury marker. Both molecules are present in the concentrated exosomal fraction, but not in whole urine [101]. A proteomics study of an animal disease model identified urinary exosomal fetuin A as an AKI biomarker, and the presence of this protein was confirmed in urine samples from ICU patients with AKI [102]. Usually, EVs contain the parental cell's surface proteins. As biomarkers, the strong point of evaluating EVs rather than blood or urine is that the source of the EVs is detectable. Thus, to evaluate tubular damage, tubular EVs should be collected and analyzed intensively.

23.4.3 The Utility of EVs for AKI Therapy

EVs secreted from MSCs or progenitor cells have beneficial effects for many kinds of organ injury by transferring mRNAs, miRNAs, growth factors, and cytokines. Focusing on AKI, single administration of microvesicles secreted from MSCs immediately after rat ischemia/reperfusion injury protects the rats from AKI by inhibiting apoptosis and stimulating TEC proliferation [103]. Another report revealed that MSC-derived exosomes express high levels of C-C motif chemokine receptor 2, and injected MSC-derived exosomes reduce the levels of its ligand, CCL2, in an ischemia/reperfusion injury model. That process attenuates inflammation of the injured kidney [104]. Therapy with a combination of adipose-derived MSCs and exosomes derived from these cells showed a renoprotective effect in the rat ischemia/reperfusion injury model [105]. Exosomes from human cord blood endothelial colony-forming cells are enriched in miR-486-5p, which targets phosphatase and tensin homolog and the Akt pathway. When EVs from endothelial colony-forming cells are given to mice with ischemic kidney injury, renal function was preserved, the kidney miR-486-5p level was increased, phosphatase and tensin homolog expression was decreased, and Akt was activated [106]. Not only EVs derived from MSCs and progenitor cells, but also EVs from renal tubular cells, have

therapeutic potential against established rat ischemia/reperfusion AKI. Furthermore, EVs from hypoxia preconditioned tubular cells show greater improvement of the renal phenotype than EVs from normoxic tubular cells [107].

In addition, several attempts have been made to use EVs as a drug delivery system. A growing concept is that EVs have a preference regarding which organ or cell type will take them up, according to the type of integrins on the EVs. For example, the preference of tumor-derived exosomes explains the pathogenesis of metastatic organotropism due to establishment of a pre-metastatic niche before cancer metastasis [108]. Furthermore, by genetically modifying the expression of membrane proteins on parental cells, secreted EVs can be designed to target specific recipient cells. Surface proteins of the parental cells are usually contained within secreted EVs, and work as ligands for the receptors of EV recipient cells [109]. Thus, EVs can be loaded with therapeutic materials and administered to specific, intended organs. These EV-based medicines are generating a lot of attention and will be used in future clinical trials.

23.5 Conclusion

Following the initiation of AKI, a vicious cycle of injury often spreads to distant organs through activation of various cytokines and chemokines derived from circulating inflammatory cells and damaged organs. Elucidation of the molecular mechanisms underlying AKI from a variety of perspectives is essential for improving mortality and morbidity rates.

References

1. Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med. 2007;357:797–805.
2. Cantaluppi V, Quercia AD, Dellepiane S, Ferrario S, Camussi G, Biancone L. Interaction between systemic inflammation and renal tubular epithelial cells. Nephrol Dial Transplant. 2014;29(11):2004–11.
3. Kurts C, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol. 2013;13:738–53.
4. Kosugi T, Maeda K, Sato W, Maruyama S, Kadomatsu K. CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint. Nephrol Dial Transplant. 2015;30:1097–103.
5. Kosugi T, Sato W. Midkine and the kidney: health and diseases. Nephrol Dial Transplant. 2012;27:16–21.
6. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol. 2014;5:491.
7. Singbartl K, Formeck CL, Kellum JA. Kidney-immune system crosstalk in AKI. Semin Nephrol. 2019;39:96–106.
8. Andres-Hernando A, Altmann C, Ahuja N, Lanaspa MA, Nemenoff R, He Z, Ishimoto T, Simpson PA, Weiser-Evans MC, Bacalja J, Faubel S. Splenectomy exacerbates lung injury after ischemic acute kidney injury in mice. Am J Physiol Renal Physiol. 2011;301:F907–16.
9. Brochner AC, Dagnaes-Hansen F, Hojberg-Holm J, Toft P. The inflammatory response in blood and in remote organs following acute kidney injury. APMIS. 2014;122:399–404.

10. Jo SK, Sung SA, Cho WY, Go KJ, Kim HK. Macrophages contribute to the initiation of ischaemic acute renal failure in rats. Nephrol Dial Transplant. 2006;21:1231–9.
11. Cho WY, Choi HM, Lee SY, Kim MG, Kim HK, Jo SK. The role of Tregs and CD11c(+) macrophages/dendritic cells in ischemic preconditioning of the kidney. Kidney Int. 2010;78:981–92.
12. Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi BS, Ruhrberg C, Cantley LG. Distinct macrophage phenotypes contribute to kidney injury and repair. J Am Soc Nephrol. 2011;22:317–26.
13. Jang HS, Kim J, Park YK, Park KM. Infiltrated macrophages contribute to recovery after ischemic injury but not to ischemic preconditioning in kidneys. Transplantation. 2008;85:447–55.
14. Vinuesa E, Hotter G, Jung M, Herrero-Fresneda I, Torras J, Sola A. Macrophage involvement in the kidney repair phase after ischaemia/reperfusion injury. J Pathol. 2008;214:104–13.
15. Sola A, Weigert A, Jung M, Vinuesa E, Brecht K, Weis N, Brune B, Borregaard N, Hotter G. Sphingosine-1-phosphate signalling induces the production of Lcn-2 by macrophages to promote kidney regeneration. J Pathol. 2011;225:597–608.
16. Liu G, Ma H, Qiu L, Li L, Cao Y, Ma J, Zhao Y. Phenotypic and functional switch of macrophages induced by regulatory CD4+CD25+ T cells in mice. Immunol Cell Biol. 2011;89:130–42.
17. Ikezumi Y, Suzuki T, Karasawa T, Hasegawa H, Kawachi H, Nikolic-Paterson DJ, Uchiyama M. Contrasting effects of steroids and mizoribine on macrophage activation and glomerular lesions in rat thy-1 mesangial proliferative glomerulonephritis. Am J Nephrol. 2010;31:273–82.
18. Zhang MZ, Yao B, Yang S, Jiang L, Wang S, Fan X, Yin H, Wong K, Miyazawa T, Chen J, Chang I, Singh A, Harris RC. CSF-1 signaling mediates recovery from acute kidney injury. J Clin Invest. 2012;122:4519–32.
19. Ferenbach DA, Ramdas V, Spencer N, Marson L, Anegon I, Hughes J, Kluth DC. Macrophages expressing heme oxygenase-1 improve renal function in ischemia/reperfusion injury. Mol Ther. 2010;18:1706–13.
20. Deng J, Kohda Y, Chiao H, Wang Y, Hu X, Hewitt SM, Miyaji T, McLeroy P, Nibhanupudy B, Li S, Star RA. Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. Kidney Int. 2001;60:2118–28.
21. Lin SL, Li B, Rao S, Yeo EJ, Hudson TE, Nowlin BT, Pei H, Chen L, Zheng JJ, Carroll TJ, Pollard JW, McMahon AP, Lang RA, Duffield JS. Macrophage Wnt7b is critical for kidney repair and regeneration. Proc Natl Acad Sci U S A. 2010;107:4194–9.
22. Du Q, Tsuboi N, Shi Y, Ito S, Sugiyama Y, Furuhashi K, Endo N, Kim H, Katsuno T, Akiyama S, Matsuo S, Isobe KI, Maruyama S. Transfusion of CD206(+) M2 macrophages ameliorates antibody-mediated glomerulonephritis in mice. Am J Pathol. 2016;186:3176–88.
23. Katsuno T, Ozaki T, Saka Y, Furuhashi K, Kim H, Yasuda K, Yamamoto T, Sato W, Tsuboi N, Mizuno M, Ito Y, Imai E, Matsuo S, Maruyama S. Low serum cultured adipose tissue-derived stromal cells ameliorate acute kidney injury in rats. Cell Transplant. 2013;22:287–97.
24. Furuhashi K, Tsuboi N, Shimizu A, Katsuno T, Kim H, Saka Y, Ozaki T, Sado Y, Imai E, Matsuo S, Maruyama S. Serum-starved adipose-derived stromal cells ameliorate crescentic GN by promoting immunoregulatory macrophages. J Am Soc Nephrol. 2013;24:587–603.
25. Ferrante CJ, Pinhal-Enfield G, Elson G, Cronstein BN, Hasko G, Outram S, Leibovich SJ. The adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor alpha (IL-4Ralpha) signaling. Inflammation. 2013;36:921–31.
26. Bor MV, Durmus O, Bilgihan A, Cevik C, Turkozkan N. The beneficial effect of 2′-deoxycoformycin in renal ischemia-reperfusion is mediated both by preservation of tissue ATP and inhibition of lipid peroxidation. Int J Clin Lab Res. 1999;29:75–9.
27. Lin JJ, Churchill PC, Bidani AK. Theophylline in rats during maintenance phase of post-ischemic acute renal failure. Kidney Int. 1988;33:24–8.
28. Muramatsu T. Midkine and pleiotrophin: two related proteins involved in development, survival, inflammation and tumorigenesis. J Biochem. 2002;132:359–71.

29. Kadomatsu K, Muramatsu T. Midkine and pleiotrophin in neural development and cancer. Cancer Lett. 2004;204:127–43.
30. Hayashi H, Sato W, Kosugi T, Nishimura K, Sugiyama D, Asano N, Ikematsu S, Komori K, Nishiwaki K, Kadomatsu K, Matsuo S, Maruyama S, Yuzawa Y. Efficacy of urinary midkine as a biomarker in patients with acute kidney injury. Clin Exp Nephrol. 2017;21:597–607.
31. Chen S, Bu G, Takei Y, Sakamoto K, Ikematsu S, Muramatsu T, Kadomatsu K. Midkine and LDL-receptor-related protein 1 contribute to the anchorage-independent cell growth of cancer cells. J Cell Sci. 2007;120:4009–15.
32. Sakamoto K, Bu G, Chen S, Takei Y, Hibi K, Kodera Y, McCormick LM, Nakao A, Noda M, Muramatsu T, Kadomatsu K. Premature ligand-receptor interaction during biosynthesis limits the production of growth factor midkine and its receptor LDL receptor-related protein 1. J Biol Chem. 2011;286:8405–13.
33. Horiba M, Kadomatsu K, Nakamura E, Muramatsu H, Ikematsu S, Sakuma S, Hayashi K, Yuzawa Y, Matsuo S, Kuzuya M, Kaname T, Hirai M, Saito H, Muramatsu T. Neointima formation in a restenosis model is suppressed in midkine-deficient mice. J Clin Invest. 2000;105:489–95.
34. Maruyama K, Muramatsu H, Ishiguro N, Muramatsu T. Midkine, a heparin-binding growth factor, is fundamentally involved in the pathogenesis of rheumatoid arthritis. Arthritis Rheum. 2004;50:1420–9.
35. Sato W, Kadomatsu K, Yuzawa Y, Muramatsu H, Hotta N, Matsuo S, Muramatsu T. Midkine is involved in neutrophil infiltration into the tubulointerstitium in ischemic renal injury. J Immunol. 2001;167:3463–9.
36. Sato W, Yuzawa Y, Kadomatsu K, Tayasu T, Muramatsu H, Muramatsu T, Matsuo S. Midkine expression in the course of nephrogenesis and its role in ischaemic reperfusion injury. Nephrol Dial Transplant. 2002;17(Suppl 9):52–4.
37. Sato W, Takei Y, Yuzawa Y, Matsuo S, Kadomatsu K, Muramatsu T. Midkine antisense oligodeoxyribonucleotide inhibits renal damage induced by ischemic reperfusion. Kidney Int. 2005;67:1330–9.
38. Kawai H, Sato W, Yuzawa Y, Kosugi T, Matsuo S, Takei Y, Kadomatsu K, Muramatsu T. Lack of the growth factor midkine enhances survival against cisplatin-induced renal damage. Am J Pathol. 2004;165:1603–12.
39. Kosugi T, Yuzawa Y, Sato W, Kawai H, Matsuo S, Takei Y, Muramatsu T, Kadomatsu K. Growth factor midkine is involved in the pathogenesis of diabetic nephropathy. Am J Pathol. 2006;168:9–19.
40. Kosugi T, Yuzawa Y, Sato W, Arata-Kawai H, Suzuki N, Kato N, Matsuo S, Kadomatsu K. Midkine is involved in tubulointerstitial inflammation associated with diabetic nephropathy. Lab Investig. 2007;87:903–13.
41. Sato Y, Sato W, Maruyama S, Wilcox CS, Falck JR, Masuda T, Kosugi T, Kojima H, Maeda K, Furuhashi K, Ando M, Imai E, Matsuo S, Kadomatsu K. Midkine regulates BP through cytochrome P450-derived eicosanoids. J Am Soc Nephrol. 2015;26:1806–15.
42. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380:756–66.
43. Padanilam BJ. Cell death induced by acute renal injury: a perspective on the contributions of apoptosis and necrosis. Am J Physiol Renal Physiol. 2003;284:F608–27.
44. Klein CL, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Faubel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. Kidney Int. 2008;74:901–9.
45. Hoke TS, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, Tao Y, Dursun B, Voelkel NF, Edelstein CL, Faubel S. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. J Am Soc Nephrol. 2007;18:155–64.
46. Reynolds PR, Mucenski ML, Le Cras TD, Nichols WC, Whitsett JA. Midkine is regulated by hypoxia and causes pulmonary vascular remodeling. J Biol Chem. 2004;279:37124–32.
47. Hobo A, Yuzawa Y, Kosugi T, Kato N, Asai N, Sato W, Maruyama S, Ito Y, Kobori H, Ikematsu S, Nishiyama A, Matsuo S, Kadomatsu K. The growth factor midkine regulates the renin-angiotensin system in mice. J Clin Invest. 2009;119:1616–25.

48. Mollnau H, Wendt M, Szocs K, Lassegue B, Schulz E, Oelze M, Li H, Bodenschatz M, August M, Kleschyov AL, Tsilimingas N, Walter U, Forstermann U, Meinertz T, Griendling K, Munzel T. Effects of angiotensin II infusion on the expression and function of NAD(P)H oxidase and components of nitric oxide/cGMP signaling. Circ Res. 2002;90:E58–65.
49. Eddy AA, Fogo AB. Plasminogen activator inhibitor-1 in chronic kidney disease: evidence and mechanisms of action. J Am Soc Nephrol. 2006;17:2999–3012.
50. Hertig A, Rondeau E. Role of the coagulation/fibrinolysis system in fibrin-associated glomerular injury. J Am Soc Nephrol. 2004;15:844–53.
51. Ha H, Oh EY, Lee HB. The role of plasminogen activator inhibitor 1 in renal and cardiovascular diseases. Nat Rev Nephrol. 2009;5:203–11.
52. Roelofs JJ, Teske GJ, Bonta PI, de Vries CJ, Meijers JC, Weening JJ, van der Poll T, Florquin S. Plasminogen activator inhibitor-1 regulates neutrophil influx during acute pyelonephritis. Kidney Int. 2009;75:52–9.
53. Lee EA, Seo JY, Jiang Z, Yu MR, Kwon MK, Ha H, Lee HB. Reactive oxygen species mediate high glucose-induced plasminogen activator inhibitor-1 up-regulation in mesangial cells and in diabetic kidney. Kidney Int. 2005;67:1762–71.
54. Jiang Z, Seo JY, Ha H, Lee EA, Kim YS, Han DC, Uh ST, Park CS, Lee HB. Reactive oxygen species mediate TGF-beta1-induced plasminogen activator inhibitor-1 upregulation in mesangial cells. Biochem Biophys Res Commun. 2003;309:961–6.
55. Liao H, Hyman MC, Lawrence DA, Pinsky DJ. Molecular regulation of the PAI-1 gene by hypoxia: contributions of Egr-1, HIF-1alpha, and C/EBPalpha. FASEB J. 2007;21:935–49.
56. Yoshimoto T, Fukai N, Sato R, Sugiyama T, Ozawa N, Shichiri M, Hirata Y. Antioxidant effect of adrenomedullin on angiotensin II-induced reactive oxygen species generation in vascular smooth muscle cells. Endocrinology. 2004;145:3331–7.
57. Yoshimoto T, Gochou N, Fukai N, Sugiyama T, Shichiri M, Hirata Y. Adrenomedullin inhibits angiotensin II-induced oxidative stress and gene expression in rat endothelial cells. Hypertens Res. 2005;28:165–72.
58. Kitching AR, Kong YZ, Huang XR, Davenport P, Edgtton KL, Carmeliet P, Holdsworth SR, Tipping PG. Plasminogen activator inhibitor-1 is a significant determinant of renal injury in experimental crescentic glomerulonephritis. J Am Soc Nephrol. 2003;14:1487–95.
59. Kojima S, Soga W, Hagiwara H, Shimonaka M, Saito Y, Inada Y. Visible fibrinolysis by endothelial cells: effect of vitamins and sterols. Biosci Rep. 1986;6:1029–33.
60. Kojima S, Muramatsu H, Amanuma H, Muramatsu T. Midkine enhances fibrinolytic activity of bovine endothelial cells. J Biol Chem. 1995;270:9590–6.
61. Kojima H, Kosugi T, Sato W, Sato Y, Maeda K, Kato N, Kato K, Inaba S, Ishimoto T, Tsuboi N, Matsuo S, Maruyama S, Yuzawa Y, Kadomatsu K. Deficiency of growth factor midkine exacerbates necrotizing glomerular injuries in progressive glomerulonephritis. Am J Pathol. 2013;182:410–9.
62. Duffield JS, Tipping PG, Kipari T, Cailhier JF, Clay S, Lang R, Bonventre JV, Hughes J. Conditional ablation of macrophages halts progression of crescentic glomerulonephritis. Am J Pathol. 2005;167:1207–19.
63. Oda T, Jung YO, Kim HS, Cai X, Lopez-Guisa JM, Ikeda Y, Eddy AA. PAI-1 deficiency attenuates the fibrogenic response to ureteral obstruction. Kidney Int. 2001;60:587–96.
64. Rondeau E, Mougenot B, Lacave R, Peraldi MN, Kruithof EK, Sraer JD. Plasminogen activator inhibitor 1 in renal fibrin deposits of human nephropathies. Clin Nephrol. 1990;33:55–60.
65. Grandaliano G, Gesualdo L, Ranieri E, Monno R, Schena FP. Tissue factor, plasminogen activator inhibitor-1, and thrombin receptor expression in human crescentic glomerulonephritis. Am J Kidney Dis. 2000;35:726–38.
66. Muramatsu T, Miyauchi T. Basigin (CD147): a multifunctional transmembrane protein involved in reproduction, neural function, inflammation and tumor invasion. Histol Histopathol. 2003;18:981–7.
67. Yoshida S, Shibata M, Yamamoto S, Hagihara M, Asai N, Takahashi M, Mizutani S, Muramatsu T, Kadomatsu K. Homo-oligomer formation by basigin, an immunoglobulin superfamily member, via its N-terminal immunoglobulin domain. Eur J Biochem. 2000;267:4372–80.

68. Nabeshima K, Iwasaki H, Koga K, Hojo H, Suzumiya J, Kikuchi M. Emmprin (basigin/CD147): matrix metalloproteinase modulator and multifunctional cell recognition molecule that plays a critical role in cancer progression. Pathol Int. 2006;56:359–67.
69. Miyauchi T, Kanekura T, Yamaoka A, Ozawa M, Miyazawa S, Muramatsu T. Basigin, a new, broadly distributed member of the immunoglobulin superfamily, has strong homology with both the immunoglobulin V domain and the beta-chain of major histocompatibility complex class II antigen. J Biochem. 1990;107:316–23.
70. Yurchenko V, Constant S, Eisenmesser E, Bukrinsky M. Cyclophilin-CD147 interactions: a new target for anti-inflammatory therapeutics. Clin Exp Immunol. 2010;160:305–17.
71. Cho JY, Fox DA, Horejsi V, Sagawa K, Skubitz KM, Katz DR, Chain B. The functional interactions between CD98, beta1-integrins, and CD147 in the induction of U937 homotypic aggregation. Blood. 2001;98:374–82.
72. Sun J, Hemler ME. Regulation of MMP-1 and MMP-2 production through CD147/extracellular matrix metalloproteinase inducer interactions. Cancer Res. 2001;61:2276–81.
73. Pakula R, Melchior A, Denys A, Vanpouille C, Mazurier J, Allain F. Syndecan-1/CD147 association is essential for cyclophilin B-induced activation of p44/42 mitogen-activated protein kinases and promotion of cell adhesion and chemotaxis. Glycobiology. 2007;17:492–503.
74. Khunkaewla P, Schiller HB, Paster W, Leksa V, Cermak L, Andera L, Horejsi V, Stockinger H. LFA-1-mediated leukocyte adhesion regulated by interaction of CD43 with LFA-1 and CD147. Mol Immunol. 2008;45:1703–11.
75. Maeda-Hori M, Kosugi T, Kojima H, Sato W, Inaba S, Maeda K, Nagaya H, Sato Y, Ishimoto T, Ozaki T, Tsuboi N, Muro Y, Yuzawa Y, Imai E, Johnson R, Matsuo S, Kadomatsu K, Maruyama S. Plasma CD147 reflects histological features in patients with lupus nephritis. Lupus. 2014;23:342.
76. Nagaya H, Kosugi T, Maeda-Hori M, Maeda K, Sato Y, Kojima H, Hayashi H, Kato N, Ishimoto T, Sato W, Yuzawa Y, Matsuo S, Kadomatsu K, Maruyama S. CD147/basigin reflects renal dysfunction in patients with acute kidney injury. Clin Exp Nephrol. 2014;18:746–54.
77. Mori Y, Masuda T, Kosugi T, Yoshioka T, Hori M, Nagaya H, Maeda K, Sato Y, Kojima H, Kato N, Ishimoto T, Katsuno T, Yuzawa Y, Kadomatsu K, Maruyama S. The clinical relevance of plasma CD147/basigin in biopsy-proven kidney diseases. Clin Exp Nephrol. 2018;22(4):815–24.
78. Kato N, Yuzawa Y, Kosugi T, Hobo A, Sato W, Miwa Y, Sakamoto K, Matsuo S, Kadomatsu K. The E-selectin ligand basigin/CD147 is responsible for neutrophil recruitment in renal ischemia/reperfusion. J Am Soc Nephrol. 2009;20:1565–76.
79. Seizer P, Ochmann C, Schonberger T, Zach S, Rose M, Borst O, Klingel K, Kandolf R, MacDonald HR, Nowak RA, Engelhardt S, Lang F, Gawaz M, May AE. Disrupting the EMMPRIN (CD147)-cyclophilin a interaction reduces infarct size and preserves systolic function after myocardial ischemia and reperfusion. Arterioscler Thromb Vasc Biol. 2011;31:1377–86.
80. Gwinn WM, Damsker JM, Falahati R, Okwumabua I, Kelly-Welch A, Keegan AD, Vanpouille C, Lee JJ, Dent LA, Leitenberg D, Bukrinsky MI, Constant SL. Novel approach to inhibit asthma-mediated lung inflammation using anti-CD147 intervention. J Immunol. 2006;177:4870–9.
81. Dear JW, Leelahavanichkul A, Aponte A, Hu X, Constant SL, Hewitt SM, Yuen PS, Star RA. Liver proteomics for therapeutic drug discovery: inhibition of the cyclophilin receptor CD147 attenuates sepsis-induced acute renal failure. Crit Care Med. 2007;35:2319–28.
82. Arora K, Gwinn WM, Bower MA, Watson A, Okwumabua I, MacDonald HR, Bukrinsky MI, Constant SL. Extracellular cyclophilins contribute to the regulation of inflammatory responses. J Immunol. 2005;175:517–22.
83. Damsker JM, Okwumabua I, Pushkarsky T, Arora K, Bukrinsky MI, Constant SL. Targeting the chemotactic function of CD147 reduces collagen-induced arthritis. Immunology. 2009;126:55–62.
84. Ley K, Allietta M, Bullard DC, Morgan S. Importance of E-selectin for firm leukocyte adhesion in vivo. Circ Res. 1998;83:287–94.

85. Zarbock A, Ley K. Mechanisms and consequences of neutrophil interaction with the endothelium. Am J Pathol. 2008;172:1–7.
86. Moore KL, Patel KD, Bruehl RE, Li F, Johnson DA, Lichenstein HS, Cummings RD, Bainton DF, McEver RP. P-selectin glycoprotein ligand-1 mediates rolling of human neutrophils on P-selectin. J Cell Biol. 1995;128:661–71.
87. von Andrian UH, Hasslen SR, Nelson RD, Erlandsen SL, Butcher EC. A central role for microvillous receptor presentation in leukocyte adhesion under flow. Cell. 1995;82:989–99.
88. Witwer KW, Soekmadji C, Hill AF, Wauben MH, Buzas EI, Di Vizio D, Falcon-Perez JM, Gardiner C, Hochberg F, Kurochkin IV, Lotvall J, Mathivanan S, Nieuwland R, Sahoo S, Tahara H, Torrecilhas AC, Weaver AM, Yin H, Zheng L, Gho YS, Quesenberry P, Thery C. Updating the MISEV minimal requirements for extracellular vesicle studies: building bridges to reproducibility. J Extracell Vesicles. 2017;6:1396823.
89. Stahl AL, Johansson K, Mossberg M, Kahn R, Karpman D. Exosomes and microvesicles in normal physiology, pathophysiology, and renal diseases. Pediatr Nephrol. 2019;34:11–30.
90. Lv LL, Cao YH, Ni HF, Xu M, Liu D, Liu H, Chen PS, Liu BC. MicroRNA-29c in urinary exosome/microvesicle as a biomarker of renal fibrosis. Am J Physiol Renal Physiol. 2013;305:F1220–7.
91. Zhou H, Kajiyama H, Tsuji T, Hu X, Leelahavanichkul A, Vento S, Frank R, Kopp JB, Trachtman H, Star RA, Yuen PS. Urinary exosomal Wilms' tumor-1 as a potential biomarker for podocyte injury. Am J Physiol Renal Physiol. 2013;305:F553–9.
92. Dimuccio V, Ranghino A, Pratico Barbato L, Fop F, Biancone L, Camussi G, Bussolati B. Urinary CD133+ extracellular vesicles are decreased in kidney transplanted patients with slow graft function and vascular damage. PLoS One. 2014;9:e104490.
93. Duan ZY, Cai GY, Bu R, Lu Y, Hou K, Chen XM. Selection of urinary sediment miRNAs as specific biomarkers of IgA nephropathy. Sci Rep. 2016;6:23498.
94. Karpman D, Loos S, Tati R, Arvidsson I. Haemolytic uraemic syndrome. J Intern Med. 2017;281:123–48.
95. Karpman D, Stahl AL, Arvidsson I. Extracellular vesicles in renal disease. Nat Rev Nephrol. 2017;13:545–62.
96. Cantaluppi V, Weber V, Lauritano C, Figliolini F, Beltramo S, Biancone L, De Cal M, Cruz D, Ronco C, Segoloni GP, Tetta C, Camussi G. Protective effect of resin adsorption on septic plasma-induced tubular injury. Crit Care. 2010;14:R4.
97. Lv LL, Feng Y, Wen Y, Wu WJ, Ni HF, Li ZL, Zhou LT, Wang B, Zhang JD, Crowley SD, Liu BC. Exosomal CCL2 from tubular epithelial cells is critical for albumin-induced tubulointerstitial inflammation. J Am Soc Nephrol. 2018;29:919–35.
98. Wang S, Zhang C, Hu L, Yang C. Necroptosis in acute kidney injury: a shedding light. Cell Death Dis. 2016;7:e2125.
99. Jiang L, Liu XQ, Ma Q, Yang Q, Gao L, Li HD, Wang JN, Wei B, Wen J, Li J, Wu YG, Meng XM. hsa-miR-500a-3P alleviates kidney injury by targeting MLKL-mediated necroptosis in renal epithelial cells. FASEB J. 2019;33(3):3523–35.
100. du Cheyron D, Daubin C, Poggioli J, Ramakers M, Houillier P, Charbonneau P, Paillard M. Urinary measurement of Na+/H+ exchanger isoform 3 (NHE3) protein as new marker of tubule injury in critically ill patients with ARF. Am J Kidney Dis. 2003;42:497–506.
101. Zhou H, Cheruvanky A, Hu X, Matsumoto T, Hiramatsu N, Cho ME, Berger A, Leelahavanichkul A, Doi K, Chawla LS, Illei GG, Kopp JB, Balow JE, Austin HA 3rd, Yuen PS, Star RA. Urinary exosomal transcription factors, a new class of biomarkers for renal disease. Kidney Int. 2008;74:613–21.
102. Zhou H, Pisitkun T, Aponte A, Yuen PS, Hoffert JD, Yasuda H, Hu X, Chawla L, Shen RF, Knepper MA, Star RA. Exosomal Fetuin-A identified by proteomics: a novel urinary biomarker for detecting acute kidney injury. Kidney Int. 2006;70:1847–57.
103. Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, Camussi G. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. Nephrol Dial Transplant. 2011;26:1474–83.

104. Farzamfar S, Hasanpour A, Nazeri N, Razavi H, Salehi M, Shafei S, Nooshabadi VT, Vaez A, Ehterami A, Sahrapeyma H, Ai J. Extracellular micro/nanovesicles rescue kidney from ischemia-reperfusion injury. J Cell Physiol. 2019;234(8):12290–300.
105. Lin KC, Yip HK, Shao PL, Wu SC, Chen KH, Chen YT, Yang CC, Sun CK, Kao GS, Chen SY, Chai HT, Chang CL, Chen CH, Lee MS. Combination of adipose-derived mesenchymal stem cells (ADMSC) and ADMSC-derived exosomes for protecting kidney from acute ischemia-reperfusion injury. Int J Cardiol. 2016;216:173–85.
106. Vinas JL, Burger D, Zimpelmann J, Haneef R, Knoll W, Campbell P, Gutsol A, Carter A, Allan DS, Burns KD. Transfer of microRNA-486-5p from human endothelial colony forming cell-derived exosomes reduces ischemic kidney injury. Kidney Int. 2016;90:1238–50.
107. Dominguez JH, Liu Y, Gao H, Dominguez JM 2nd, Xie D, Kelly KJ. Renal tubular cell-derived extracellular vesicles accelerate the recovery of established renal ischemia reperfusion injury. J Am Soc Nephrol. 2017;28:3533–44.
108. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, Di Giannatale A, Ceder S, Singh S, Williams C, Soplop N, Uryu K, Pharmer L, King T, Bojmar L, Davies AE, Ararso Y, Zhang T, Zhang H, Hernandez J, Weiss JM, Dumont-Cole VD, Kramer K, Wexler LH, Narendran A, Schwartz GK, Healey JH, Sandstrom P, Labori KJ, Kure EH, Grandgenett PM, Hollingsworth MA, de Sousa M, Kaur S, Jain M, Mallya K, Batra SK, Jarnagin WR, Brady MS, Fodstad O, Muller V, Pantel K, Minn AJ, Bissell MJ, Garcia BA, Kang Y, Rajasekhar VK, Ghajar CM, Matei I, Peinado H, Bromberg J, Lyden D. Tumour exosome integrins determine organotropic metastasis. Nature. 2015;527:329–35.
109. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol. 2011;29:341–5.