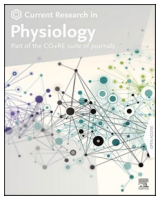
Current Research in Physiology 8 (2025) 100152

Contents lists available at ScienceDirect

Current Research in Physiology

journal homepage: www.sciencedirect.com/journal/current-research-in-physiology



From acute tubular injury to tubular repair and chronic kidney diseases – KIM-1 as a promising biomarker for predicting renal tubular pathology

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ARTICLE INFO

Keywords:
Acute kidney injury
Tubular repair
Kidney injury molecule-1
Tubular dedifferentiation
Chronic kidney disease

ABSTRACT

Kidney Injury Molecule-1 (KIM-1) has emerged as a significant biomarker and mechanistic player in kidney pathology, particularly in acute kidney injury (AKI). Normally absent in healthy kidney proximal tubules, KIM-1 becomes upregulated specifically along the proximal tubule cells' surface in response to acute injury, reflecting the differential vulnerability of convoluted versus straight proximal tubules. Functionally, KIM-1 aids proximal tubules in clearing apoptotic cells and moderating inflammatory responses, thereby helping to prevent excessive immune activation during the early stages of injury. Clinically, KIM-1 is a sensitive, non-invasive biomarker for detecting proximal tubular injury, allowing for assessment in urine, plasma samples, and tissue biopsies in AKI. However, if tubular injury persists without repair, prolonged KIM-1 expression can drive chronic inflammatory responses and interstitial fibrosis, leading to chronic kidney disease (CKD). In addition, KIM-1's role may extend further into promoting tubular dedifferentiation, potentially contributing to renal cell carcinoma under certain conditions. Over the past two decades, KIM-1 research has reshaped our understanding of kidney pathophysiology and immunology, spanning acute injury responses to chronic disease progression. This review aims to provide an updated synthesis of recent findings, highlighting KIM-1's role across the spectrum of renal injury and repair.

1. Introduction

The kidneys contain over one million functional nephrons, which consists of a glomerulus and its associated renal tubules. However, the glomeruli and renal tubules have a limited capacity for self-repair following injury. Significant damage to any part of the nephron—whether to the glomerulus, the renal tubules, or both—there is a substantial risk of developing interstitial fibrosis, which can progressively impair kidney function by interfering with normal blood filtration and or renal tubular reabsorption, and subsequently leading to chronic kidney disease (CKD).

Landmark studies led by Dr. Berry M. Brenner and colleagues examined specific effects of hyperfiltration on glomerular health. Hyperfiltration occurs when there is an increased pressure within the glomeruli. In their studies using animal models with focal segmental glomerulosclerosis (FSGS) or diabetic nephropathy, they found that hyperfiltration within the glomeruli led to further glomerular damage (Brenner et al., 1996). This excessive filtration process contributed to global glomerulosclerosis, a condition where larger portions of the glomerulus develop scarring. This scarring process, in turn, promoted interstitial fibrosis and tubular atrophy, as the affected parts of the nephron could no longer function properly. These cumulative changes cause progressive decline in kidney function, leading to CKD and, ultimately, end-stage renal disease (ESRD).

Dr. Brenner's studies identified that angiotensin-converting enzyme (ACE) inhibitors could reduce hyperfiltration in the glomeruli (Brenner, 2002) by selectively dilating the efferent arterioles, the blood vessels that exit the glomerulus. By dilating these arterioles, ACE inhibitors

This article is part of a special issue entitled: Mechanisms-CKD progression published in Current Research in Physiology.

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https://doi.org/10.1016/j.crphys.2025.100152
Received 3 December 2024; Received in revised form 13 May 2025; Accepted 12 June 2025
Available online 13 June 2025

lowers pressure within the glomeruli, thereby reducing hyperfiltration independently of the drug's ability to control blood pressure. This mechanism effectively reduces glomerular stress and slows the progression of nephron damage in animal models with FSGS or diabetic nephropathy. Following these promising animal studies, clinical trials demonstrated that ACE inhibitors and angiotensin-2 receptor blockers (ARBs) significantly delay the progression of CKD in patients with diabetic nephropathy and other renal diseases (Brenner et al., 2001). The trials provided evidence that inhibition of angiotensin-2 by ACE inhibitors or ARBs could slow the path to ESRD by mitigating glomerular hyperfiltration and reducing interstitial fibrosis and tubular atrophy, thus preserving kidney function. Dr. Brenner's pioneering work established that targeting nephron hyperfiltration could slow disease progression, validating ACE inhibitors or ARBs as essential treatment for CKD, particularly in patients with diabetes and other glomerular/renal vascular diseases (Taal and Brenner, 2000; Brenner, 2002).

Beyond traditional treatment, recent advances highlight two promising drug classes for addressing glomerular hyperfiltration, including sodium-glucose cotransporter-2 (SGLT2) inhibitors (Wada et al., 2024; Vallon and Verma, 2021) and glucagon-like peptide-1 (GLP-1) receptor agonists (Bjornstad et al., 2024). SGLT2 inhibitors decrease glomerular hyperfiltration by blocking sodium-glucose reabsorption in the proximal tubule, which increases sodium delivery to the macula densa and activates tubuloglomerular feedback, which constricts the afferent arteriole. As a result, intraglomerular pressure decreases, protecting the kidneys from hyperfiltration-induced damage (Vallon and Verma, 2021), and slowing progression of kidney disease (Kalantar-Zadeh et al., 2021). This mechanism of SGLT2 is independent of glycemic control (Vallon and Verma, 2021). Notably, GLP-1 receptor agonists also reduce glomerular hyperfiltration through multiple mechanisms (Bjornstad et al., 2024). The systemic effects of GLP-1 include improved glycemic control, weight loss, and blood pressure reduction, contributing to decreased renal workload (Hti Lar Seng et al., 2023). Additionally, preclinical studies suggest that GLP-1 exerts direct renal actions, including reduced afferent arteriolar tone and anti-inflammatory effects, which may provide protection against hyperfiltration-induced kidney damage (Bjornstad et al., 2024), and slow the progression of chronic kidney disease (Kalantar-Zadeh et al., 2021). However, their exact nephroprotective mechanisms remain under investigation.

The current review will shift focus to how renal tubular injury contributes to kidney repair and CKD, particularly following acute kidney injury (AKI). a common clinical issue (Bonventre, 2010). Many AKIs result from acute tubular injury to the proximal tubules due to their chief role in the active transportation of reabsorbing electrolytes, thus being vulnerable to hypoxic insult. Whereas distal nephron tubules are relatively resistant to ischemic or toxic injury because of their main role in passive electrolyte and water transportation (Rosen and Stillman, 2008). Traditionally, the proximal tubules are divided into three segments based on their morphologic differences in rat kidneys (Maunsbach, 1966). Segment 1 (S1) includes the main portion of the convoluted proximal tubules. Segment 2 (S2) is composed of a portion of distal convoluted proximal tubules and straight proximal tubules mainly in the medullary rays. Segment 3 (S3) is composed of straight proximal tubules in the outer stripe of the outer medulla. Major portion of the S2 proximal tubules is located in the medullary ray, whereas S3 proximal tubules locate in medulla and receive venous blood. S3 segments appear more vulnerable to ischemic insults than cortical S1 segments that receive highly oxygenated blood (Brezis and Rosen, 1995). Since the 1970s, this classification of the proximal tubules has been widely used animal and human studies. The S3 proximal tubules are composed of a large zone in rat kidneys; it is, therefore, convenient to focus on this zone for ischemic analysis in rodents (Zhang et al., 2008a,b). However, most morphologic studies of renal tubular injury in humans were based on light microscopy. This limitation makes it difficult to accurately separate the convoluted proximal tubules in S1 from the distal portion of the convoluted tubules in S2.

Obvious acute tubular injury (or acute tubular necrosis) is identifiable in human renal biopsies when injured proximal tubules are dilated and flattened with diminished brush borders on Periodic acid-Schiff (PAS) stained sections (Parasuraman et al., 2013). However, the morphologic changes in mild acute tubular injury are difficult to ascertain. This challenge led to the investigation of biomarkers, such as tumor suppression gene p53 and proliferative marker Ki-67, which confirmed subtle acute tubular injury. In 1998, kidney injury molecule-1 (KIM-1) was discovered for investigating the acute injury of proximal tubules in rats (Ichimura et al., 1998). KIM-1 is typically absent in healthy kidneys but becomes specifically upregulated in injured proximal tubular cells, and such upregulation can persist until the damaged cells completely recovered (Huo et al., 2010). Therefore, KIM-1 has emerged as a specific marker for proximal tubular injury, enabling critical advances in renal pathology through urine and serum analysis, genetic studies, and mechanistic investigations (Bonventre and Yang, 2010; Bonventre, 2014). The KIM-1's functions include its role in acute tubular injury, its potential role in generating interstitial fibrosis, and its use as a urinary biomarker for analysis of renal function. This review summarizes the morphologic expression of KIM-1 in acute tubular injury, its implications for proximal tubule physiology, its links to CKD progression, and its association with de-differentiated renal tissue and malignant transformation.

2. KIM-1 and its pathophysiological functions in renal diseases

KIM-1, also named T cell immunoglobulin mucin domains-1 (TIM-1) and hepatitis A virus cellular receptor-1 (HAVCR-1), was first identified in injured proximal tubules of rat kidneys following acute ischemic injury (Ichimura et al., 1998). KIM-1 expression can be induced by tubular stress of damaging compensatory hyperfiltration, which occurs in remaining tubules after nephron loss. KIM-1 is the most highly upregulated protein in the proximal tubule of the injured kidneys, but also expressed in other organs or tissues, including immune cells and the liver (Ichimura et al., 1998). KIM-1 is a type I transmembrane protein with an extracellular domain, a transmembrane domain, and an intracellular domain (Ichimura et al., 1998). The extracellular domain of KIM-1 contains a mucin domain and six-cysteine immunoglobulin-like domains, which are involved in protein-protein interactions and binding to extracellular matrix components (Ichimura et al., 1998; Bailly et al., 2002). Later studies revealed that ADAM 10/17 cleaves the extracellular domains of KIM-1, releasing a soluble form in the urine or blood (Schweigert et al., 2014; Zhang et al., 2019; Schmidt et al., 2022). Soluble KIM-1 is a promising biomarker for diagnosing various renal diseases, including acute and chronic renal diseases (Bonventre et al., 2013).

There are two populations of proximal tubular epithelium including regular tubular epithelial cells with brush borders and scattered progenitor cells without brush borders (Lazzeri et al., 2018). It is well known that hypoxia-inducible factors (HIFs) are the master transcription factors regulating hypoxia-associated transcription response (Schodel and Ratcliffe, 2019; Shu et al., 2019). With normal oxygen, HIF-1α is degraded. In contrast, hypoxia results in a retention of HIF-1α that activates many genes such as erythropoietin and CD133 to deal with the hypoxic challenge. Without oxygen, the tubular progenitor cells undergo cellular proliferation with mitosis and the remaining tubular epithelial cells undergo endoreplication cycles leading to tubular epithelial hypertrophy without mitosis (endocycle) (Lazzeri et al., 2018). In the meantime, in response to severe insults from ischemia, injured proximal tubules release apoptotic bodies with phosphatidylserine (PS) on their surface, which activate KIM-1 as PS receptor along the proximal tubules (Ichimura et al., 2008; Yang et al., 2015; Brooks et al., 2015) (Fig. 1). KIM-1's extracellular six-cysteine immunoglobulin-like domains enable its binding to PS, a natural ligand exposed on the surface of apoptotic cells or membrane extracellular vesicles (EVs) (Zhang and Liu, 2021). KIM-1 is a type 1

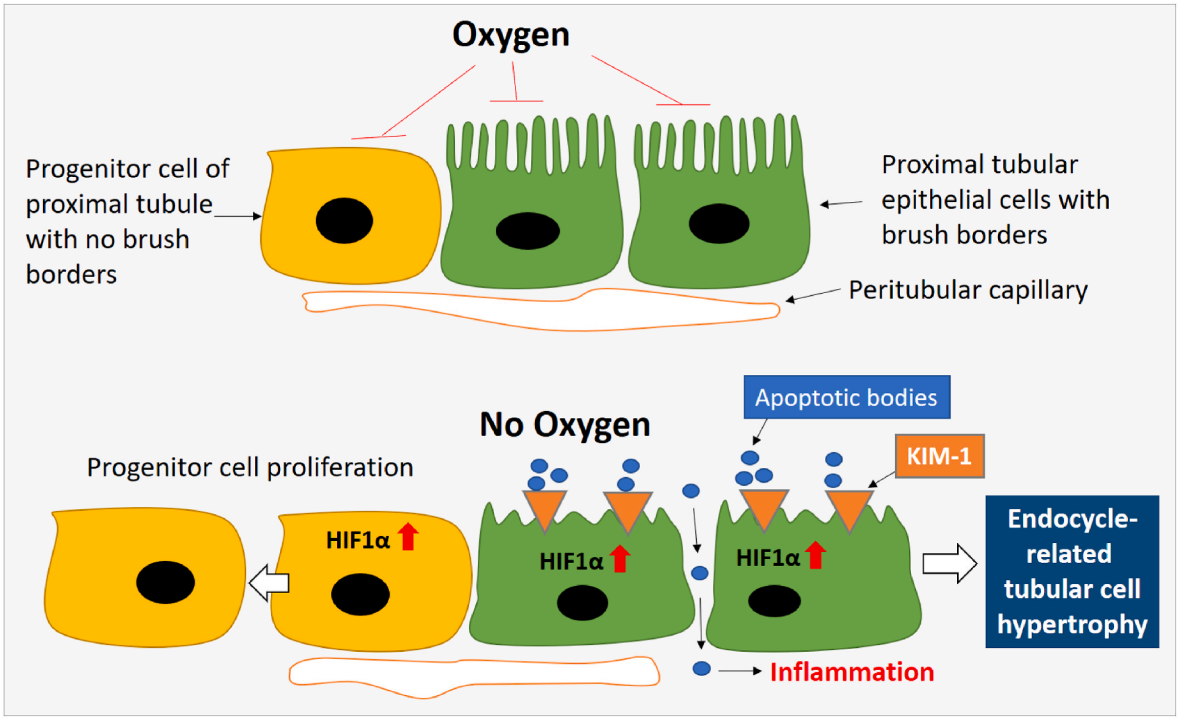

Fig. 1. Schematic illustration of proximal tubules under normal and hypoxic conditions. The top panel shows normal proximal tubules composed of progenitor cells (yellow without brush borders) and regular epithelial cells (green color with brush borders). Oxygen permeates to individual epithelial cells and inhibits the production of hypoxia-inducible factor 1-alpha (HIF1a). The lower panel illustrates a scenario in the absence of oxygen. To repair the tubular injury, the progenitor cell undergoes mitosis-related cell proliferation leading to the growth of additional cells (yellow cells from the left side) and other epithelial cells enter endocycles for tubular epithelial hypertrophy (enlarged cells without additional cell number growth, green cells on the right side). Meanwhile, kidney injury molecule-1 (KIM-1) as a phagocytotic receptor binds to the apoptotic bodies and prevents them from leaking into the peritubular capillary for induction of inflammation.

transmembranous glycoprotein located along the luminal surface of proximal tubules, and is only up-regulated during acute tubular injury (Ichimura et al., 1998). Notably, KIM-1 is also a phagocytosis and scavenger receptor for sensing dying cells in health and disease (Tutunea-Fatan et al., 2024; Ichimura et al., 2008). KIM-1 plays a phagocytic role in engulfing the apoptotic bodies or EVs into the residual proximal tubules, and subsequently delivering the apoptotic bodies or EVs from the phagosomes to lysosomes for autophagy-mediated clearance (Brooks et al., 2015). The process of phagocytosis/endocytosis and autophagy-mediated clearance serve as an immune surveillance mechanism to prevent apoptotic bodies from triggering innate inflammatory responses, thus helping avoid further kidney damage and maintains self-tolerance in proximal tubules (Ichimura et al., 2012; Yang et al., 2015; Brooks et al., 2015; Tutunea-Fatan et al., 2024). Without clearance of dying cells or apoptotic EVs by KIM-1's protective phagocytosis, the kidneys would demonstrate more harmful over-reactive inflammation and subsequent interstitial fibrosis in various renal diseases, including CKD (Zhang and Liu, 2021; Tutunea-Fatan et al., 2024). However, Chen et al. reported that KIM-1 expressed by injured renal tubules can mediate EV uptake by recognizing PS, which participated in the amplification of tubule inflammation induced by hypoxia, leading to the development of tubulointerstitial inflammation in ischemic kidney injury (Chen et al., 2023).

Interestingly, KIM-1/TIM-1 is also expressed in T cells (Angiari et al., 2014) and B cells (Bod et al., 2023), where it modulates immune and autoimmune responses. Angiari et al. reported that TIM-1 is a major P-selectin ligand with a specialized role in T cell trafficking during inflammatory responses and the induction of autoimmune disease (Angiari and Constantin, 2014; Angiari et al., 2014). In addition, Nozaki and colleagues demonstrate that endogenous KIM-1/TIM-1 can promote Th1 and Th17 nephritogenic immune responses, and its neutralization can reduce renal injury by limiting cell-mediated injury and inflammation in experimental glomerulonephritis (Nozaki et al., 2012). Furthermore, inhibition of KIM-1/TIM-1 protects against kidney or cerebral ischemia-reperfusion injury (Rong et al., 2011; Zheng et al., 2019). Notably, a recent study demonstrated that engineered red blood cell-derived EVs equipped with KIM-1 binding peptides effectively delivered P65 and Snai1 siRNAs to the injured tubules, leading to reduced expression of P-p65 and Snai1, which inhibits renal inflammation and fibrosis in mice subjected to ischemia/reperfusion injury, thus blunting the chronic progression of ischemic AKI (Tang et al., 2021).

If an acute tubular injury fails to heal, the damaged proximal tubules become flat and shrink into a small gland appearance, called atrophic renal tubules. Interstitial fibrosis often develops around these atrophic renal tubules. KIM-1 staining is usually found within the lumens of atrophic proximal tubules. However, this should not be confused with acute injury as only KIM-1 expression in non-atrophic proximal tubules should be counted as ongoing acute tubular injury. Bonventre and colleagues found that transgenic mice with turned-on KIM-1 develop more fibrosis in the interstitium, implying that KIM-1 may play a maladaptive role in interstitial fibrosis during CKD development (Humphreys et al., 2013; Yin et al., 2016).

Therefore, KIM-1 is a multifunctional protein with complex roles in renal pathophysiology. It promotes renal repair during acute renal injury, mediates phagocytosis and endocytosis, modulates inflammatory and immune responses, and contributes to renal fibrosis and the transition from AKI to CKD, and the progression of CKD. A better understanding of KIM-1's dual functions could help to develop innovative strategies for the diagnosis and treatment of kidney diseases.

3. KIM-1 in acute tubular injury during AKI

From the embryology point of view, glomeruli and proximal tubules

are derived from the cap mesenchyme of metanephros, whereas distal tubules and collecting ducts are derived from the ureteric bud (Moritz and Wintour, 1999). They fuse together to form a nephron system. Because the proximal tubules carry out 80 % of the nephron's reabsorptive activity, mostly through active electrolyte transportations, the nature of this high energy-dependent status in the proximal tubules makes the proximal tubules vulnerable to an ischemic injury, especially when compared to distal tubular resistance to ischemic insults (Brezis and Rosen, 1995). Since Ichimura and colleagues first described KIM-1 in 1998 for its role in repairing acute proximal tubule damage in post-ischemic kidneys (Ichimura et al., 1998), our understanding of KIM-1 has evolved to a range of pathological conditions related to AKI.

3.1. KIM-1 expression in animal models with AKI

Ichimura et al. found that KIM-1 expression was significantly upregulated in rat kidneys following acute tubular injury, suggesting its involvement in the healing process (Ichimura et al., 1998; Bonventre and Yang, 2010). As early as 3 h following reperfusion after an ischemic insult, rat kidneys show a 7.8 fold increase in the gene up-regulation of KIM-1 (Zhang et al., 2008a,b). Several other studies also demonstrate the rapid upregulated KIM-1 protein expression of KIM-1 as early as 6 h following ischemia-reperfusion injury (Ichimura et al. 1998, 2004; Vaidya et al., 2009). In the ischemic-reperfusion model of rodents, KIM-1 is up-regulated in the injured proximal tubules of rat kidneys following ischemic or cytotoxic challenges (Fig. 2). The injury pattern is typically more prominent in S3 proximal tubules, followed by S2 proximal tubules, whereas S1 proximal tubules demonstrated relatively mild injury (Fig. 2). As the area of S3 proximal tubules is obviously large in rats, the injured S3 proximal tubules stained positively by KIM-1 can be readily identified.

3.2. KIM-1 expression in acute tubular injury of human renal grafts

Interestingly, AKG7 monoclonal antibody against KIM-1 is a unique antibody that is only overexpressed in the injured human proximal tubules by immunohistochemical staining (Bailly et al., 2002). Notably, there is no KIM-1 staining in normal proximal tubules, glomeruli, distal nephron tubules, and other internal organs (Zhang et al., 2008a,b). Protocol biopsies from early renal transplant grafts with healthy renal parenchyma were negative for KIM-1 staining, while study groups with transplant biopsies were KIM-1 positive in injured proximal tubules as acute tubular injury or following acute cellular rejection (Zhang et al., 2008a,b). In addition, stronger KIM-1 immuno-staining is correlated with increased serum creatinine levels secondary to either ischemic or rejection insults, suggesting that KIM-1 is a reliable marker for assessing renal dysfunction in transplant recipients (Zhang et al., 2008a,b). Interestingly, the higher levels of KIM-1 detected in the injured proximal tubules have better recovery in the transplant grafts over one and a half years (Zhang et al., 2008a,b). These findings imply that acutely injured proximal tubules possess a strong capacity for repair and recovery, potentially linked to the degree of KIM-1 expression. In accordance with the Banff criteria, type 1 acute antibody-mediated rejection is characterized by an "acute tubular necrosis (ATN)-like" injury with positive donor-specific antibody, positive C4d staining, and the absence of neutrophil infiltration of peritubular capillaries or thrombotic microangiopathy. To validate this "ATN-like" injury as a true acute tubular injury, we compared it to negative controls, renal transplant biopsies with ischemia-associated acute tubular injury, and biopsies diagnosed with "ATN-like" type 1 acute antibody-mediated rejection (Johnson et al., 2013). KIM-1 staining consistently identified acute tubular injury in type 1 acute antibody-mediated rejection, highlighting its crucial role in the renal dysfunction associated with this condition. Furthermore, KIM-1 is useful for differential diagnosis in renal transplant biopsies, especially in ruling out acute cellular rejection. In two patients with sickle cell disease (Wang et al., 2015), one biopsy showed positive

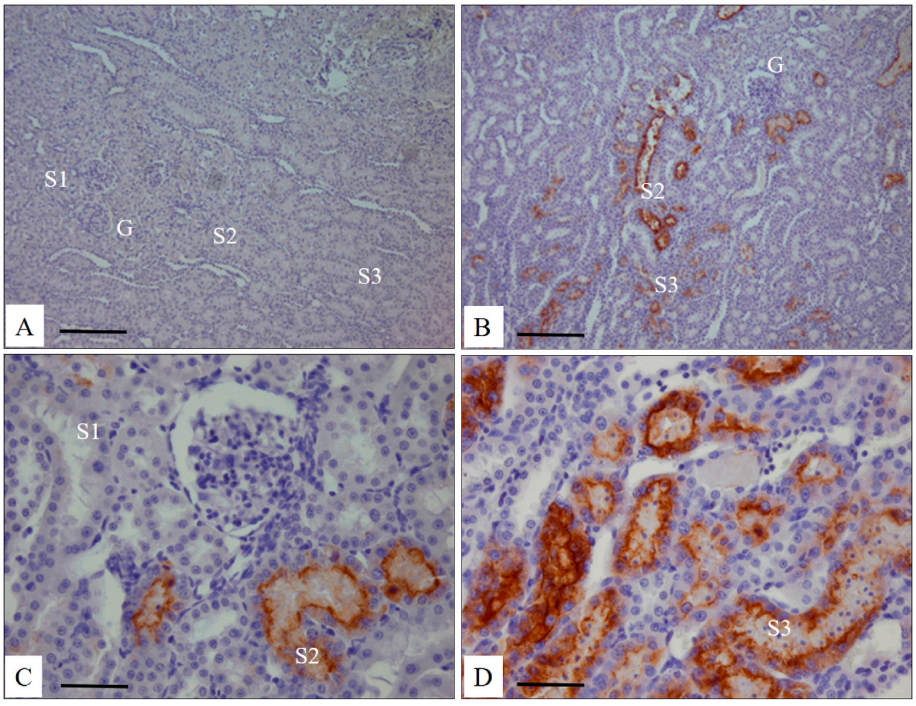

Fig. 2. KIM-1 expression in renal ischemic model. A. In the normal kidney of a rat, there is no expression of kidney injury molecule-1 (KIM-1) in any renal tubules. B-D. After ischemic and reperfusion injury, the proximal tubules in medullary rays (S2 segment) and the outer stripe of the inner medulla (S3 segment) show much stronger KIM-1 staining (brown color staining) than proximal tubules around glomeruli (S1 segment). This finding indicates that the S1 segment of proximal tubules is more resistant to an ischemic insult when compared to the S2 and S3 segments of proximal tubules. G – glomerulus. (Scale Bars: 1 mm on A-B and 0.25 mm on C-D) (Magnifications ×100 in A-B and x400 in C-D).

staining for both KIM-1 and iron in the proximal tubules, implying acute tubular injury was due to recurrent sickle cell nephropathy. The other demonstrated thrombotic microangiopathy with positive KIM-1 staining but negative iron staining, indicating a more likely cause of thrombotic microangiopathy for acute tubular injury (Wang et al., 2015). Therefore, KIM-1 expression has been used as a useful biomarker to detect acute tubular injury of human renal grafts in patients with renal transplantation.

3.3. KIM-1 expression in human native kidneys

In adult kidneys, there is no KIM-1 expression in normal renal parenchyma on renal biopsy, but KIM-1 immuno-staining has been used to identify acute tubular injury secondary to using nephrotoxic drug, as well as many types of glomerulonephritis, acute tubular injury, acute interstitial nephritis and tubular obstruction associated tubular injury (Han et al., 2002; van Timmeren et al., 2007). In a patient with end-stage liver disease who underwent a liver transplant and received Tacrolimus (Cosner et al., 2015), his serum creatinine elevated after the transplant. A renal biopsy with KIM-1 staining of proximal tubules in medullary rays but not in those proximal tubules around the glomeruli suggested acute tubular injury due to acute Tacrolimus nephrotoxicity (Cosner et al., 2015). Stopping Tacrolimus restored normal renal function, which has been maintained normal since. Moreover, renal biopsies reveal that acute tubular injury in proximal tubules is often present in various glomerular, renal tubular, and vascular diseases. In adult patients, 80 %–92 % of renal biopsies are KIM-1 positive while only 82 % of pediatric biopsies are positive for KIM-1 expression (Yin et al., 2019). In adults, a receiver operating characteristic (ROC) curve between KIM-1 expression and serum creatinine levels shows a good under-curve area (UCA) at 0.87 (Yin et al., 2019), indicating that KIM-1 staining is a "good" predictor of acute renal tubular injury in correlating to serum creatinine. In the pediatric population, KIM-1 also demonstrates a great correlation with serum creatinine as well with a fair UCA at 0.74 (Yin et al., 2019). In addition, we find that a higher KIM-1/serum creatinine ratio is associated with better renal functional recovery, implying that stronger KIM-1 responses may represent greater proximal tubule repair activity.

On the other hand, KIM-1 staining often correlates well with other biomarkers of acute proximal tubule injury. Since PAS staining, a marker of brush borders, is diminished in acute tubular injury (Parasuraman et al., 2013), dual staining reveals a reciprocal relationship between reduced PAS staining and upregulated KIM-1 staining (Yin et al., 2019). As KIM-1 is a phagocytotic factor, early upregulation of KIM-1 often coincides with increased CD68 expression, a lysosomal biomarker, suggesting proximal tubule phagocytic capacity. In severe acute tubular injury with strong KIM-1 expression in the proximal tubules, CD68 expression decreases, implying a potential loss of proximal tubular repairing capability (unpublished observation). Several mechanisms have been proposed for how injured renal tubules are repaired following an acute tubular injury. It is believed that either intratubular progenitor cells or residual tubular epithelial cells play a critical role in repairing the damaged renal tubules by restoring new epithelial cells (Humphreys et al., 2008; Lazzeri et al., 2019). CD133, a progenitor cell marker normally expressed in the parietal epithelium and scattered in proximal tubules (Lasagni and Romagnani, 2010; Romagnani, 2011), is co-expressed with KIM-1 in injured proximal tubules during acute tubular injury, indicating the activation of multiple repair and regenerative mechanisms (Zhang and Hafron, 2014).

Furthermore, KIM-1 staining has been used to understand acute tubular injury patterns of different renal diseases. In acute calcium phosphate nephropathy with distal nephron tubule calcium phosphate deposition, KIM-1 staining can highlight proximal tubule acute tubular injury without calcium phosphate, indicating secondary acute tubular injury due to distal tubular obstruction (Hayek et al., 2013). In contrast to calcium phosphate nephropathy, polarizable calcium oxalate nephropathy shows KIM-1 staining in proximal tubules containing calcium oxalate crystals, suggesting direct obstruction as the potential cause of acute tubular injury (Hayek et al., 2013). In acute tubular injury due to ischemia, KIM-1 expression is dominantly seen in the medullary rays. However, in renal biopsies with thrombotic microangiopathy, KIM-1 staining is predominantly in the convoluted proximal tubules around the glomeruli, reflecting the immediate ischemic insult caused by thrombotic glomeruli (unpublished data).

3.4. KIM-1 expression in autopsy kidneys in human

Using full sections of kidneys from adult autopsy cases, the striking finding of KIM-1 immuno-staining is that KIM-1 staining highlights more acute tubular injury in straight proximal tubules located in medullary rays and the outer stripe of outer medulla than that in the convoluted proximal tubules due to ischemic injury (Fig. 3A–C) (Yin et al., 2018). Using light microscopy, proximal tubules can be divided into three zones based on their vulnerability to ischemic insults (Fig. 3D): Zone 1 (convoluted proximal tubules), Zone 2 (straight proximal tubules in the medullary rays), and Zone 3 (straight proximal tubules in the outer stripe of the outer medulla (lower than arcuate artery) (Yin et al., 2018). This concept is also partially supported by our biopsy study that Zone 2 proximal tubules showed more KIM-1 expression than Zone 1 proximal tubules due to Tacrolimus nephrotoxicity (Cosner et al., 2015). Similarly, KIM-1 staining is useful in identifying acute tubular injury in pediatric autopsy kidneys as well (Yin et al., 2018). KIM-1 staining is essentially not affected by the autolysis of autopsies, indicating the durability of KIM-1 protein. This durable character of KIM-1 in autopsy kidneys supports that this biomarker can be reliably measured in urine analysis for renal dysfunction in animal models and human studies (Zhou et al., 2008; Vaidya et al., 2009; Hsu et al., 2017; Park et al., 2017).

Since the beginning of 2020, the coronavirus disease 19 (COVID19) has infected billions of people and caused millions of deaths worldwide. The SARS-CoV-2 is known to cause lung infection with subsequent infection of other organs, including the kidneys through viral interaction with cell surface receptors, angiotensin-converting enzyme 2, and subsequent endocytosis (Luan et al., 2020; Zhou et al., 2020; Tan et al., 2004). Among our autopsy cases, we found that two patients died of COVID19 infection-associated complications. The kidneys of both patients demonstrated extensively positive staining of KIM-1 despite their normal levels of pre-mortem serum creatinine, implying serum creatinine can underestimate renal dysfunction (Fig. 4A and B) (Zhang et al., 2020). The direct infection of COVID-19 in renal tissue causes acute tubular injury and collapsing focal segmental glomerulosclerosis (Su et al., 2020; Farkash et al., 2020; Kissling et al., 2020; Braun et al., 2020; Puelles et al., 2020). However, several recent studies report no definite SARS-CoV-2 detected in the renal biopsies or autopsy kidneys from COVID-19-positive patients by RNA in situ hybridization techniques (Wu et al., 2020; Sharma et al., 2020; Santoriello et al., 2020; Kudose et al., 2020).

3.5. Discrepancies in acute kidney injury studies between humans vs animals

In recent years, multiple review articles indicate that animal models of human acute kidney injury (AKI) do not generate specific therapies that benefit the disease in humans, in terms of preventing its occurrence, ameliorating its severity, hastening its recovery, or delaying a potential transformation from AKI to CKD (Nath, 2015; de Caestecker et al., 2015; Agarwal et al., 2016; Liu et al., 2017). There are several possibilities for the discrepancy in studies with humans versus animals. The first is that rodents and humans have different renal anatomic structures with different renal responses to ischemic injury. But KIM-1 up-regulation after ischemic injury appears to have similar response patterns between animal models (Fig. 2) and human kidneys (Fig. 3), both of which show more prominent expression of KIM-1 in Zone 2 (S2 segment) and Zone 3

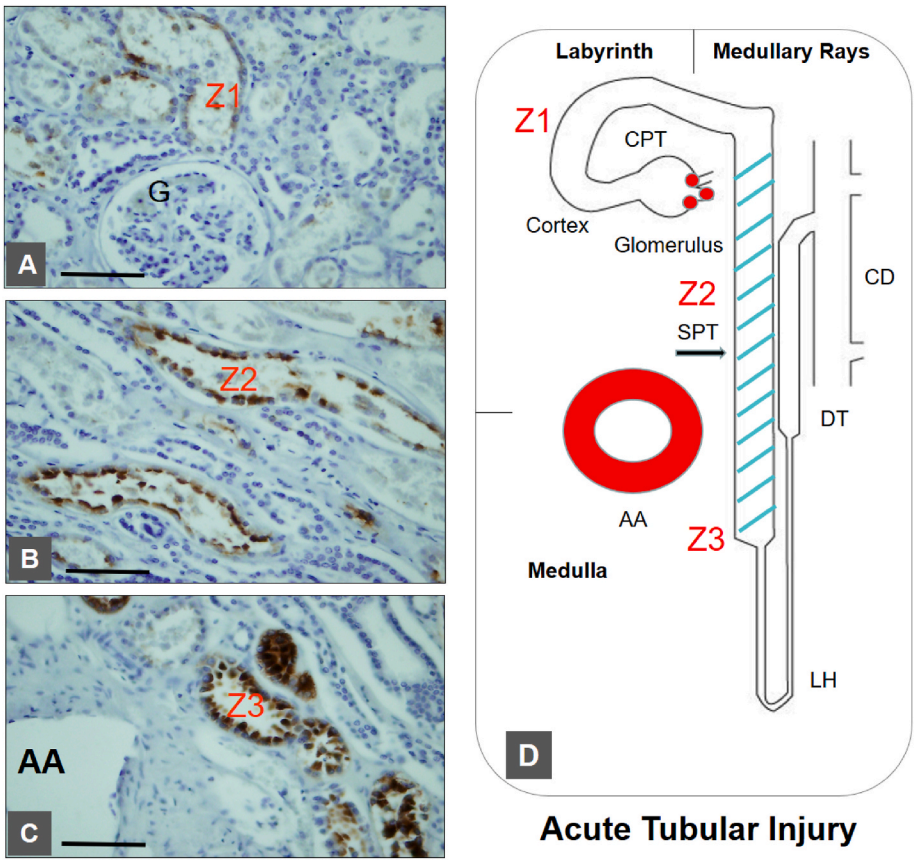

Fig. 3. KIM-1 expression in human autopsy kidneys. On full sections of human kidney, KIM-1 immuno-staining in the modified zone 1 (Z1 of proximal tubules around glomeruli) (A) is weaker than that in modified zone 2 (Z2 of proximal tubules in medullary rays) (B) and modified zone 3 (Z3 of proximal tubules in the outer stripe of inner medulla) (C), compatible with ischemic renal injury model in rats (Fig. 1, using conventional concept of S1 to S3 proximal tubules). Schematic illustration of Z1 to Z3, highlighting the vulnerable Z2 and Z3 when compared to Z1 (D). Note. Z1, Z2, and Z3 of proximal tubules are modified from the previous S1-S3 proximal tubular system for the light microscopic identification of different zones of proximal tubules easily (see text for details). AA – arcuate artery, G – glomerulus, CPT – convoluted proximal tubules, SPT – straight proximal tubules, LH – loop of Henle, DT – distal tubule, CD – collecting duct. (Scale Bars: 0.25 mm on A-C) (Magnification ×400 in A-C).

(S3 segment) than in Zone 1 (S1 segment). The second possibility is that the design and statistical analysis of these studies may be suboptimal and require more careful consideration and optimal scrutiny. A third possibility is that there are differences in disease progression between animal models and injured human kidneys. As our current population becomes older, many elderly patients with AKIs often have underlying kidney disease due to hypertension, diabetes, or both. Once their kidneys develop AKI in addition to kidney disease, their chance of renal recovery is low. However, animals used for generating AKI models are usually young and healthy, and their kidneys have a robust recovery capacity in response to a variety of treatments. Therefore, different scenarios of disease progression between animal models and humans may be the key issue for the failed goals of some preclinical AKI studies. However, KIM-1 is a valuable biomarker for studying acute tubular injury in both human diseases and animal models.

4. KIM-1 in the transition from AKI to CKD and the development of CKD

In addition to its role in AKI, emerging evidence indicates that KIM-1 is also involved in various pathophysiological conditions in CKD. Increasing evidence indicates that AKI and CKD are interconnected conditions with overlapping pathophysiological mechanisms (Zhang et al., 2024). AKI frequently progresses to CKD due to inadequate repair mechanisms, ongoing inflammatory and immune responses, and fibrosis, with both conditions sharing common signaling pathways involving cell death, immune responses, and the accumulation of extracellular matrix (ECM) (Zhang et al., 2024).

4.1. KIM-1 in the transition from AKI to CKD

KIM-1 is typically absent from healthy kidneys, while acute kidney injury results in KIM-1 initial upregulation and exhibits anti-inflammatory and protective functions by facilitating the clearance of damaged and apoptotic cells. However, persistent upregulation of KIM-1 expression following AKI is associated with the development of CKD (Ko et al., 2010), and prolonged overexpression of KIM-1 contributes to inflammatory damage and interstitial fibrosis of the kidneys (Humphreys et al., 2013). Xu and colleagues reported that KIM-1 expression was upregulated in the proximal tubules of mice with AKI on day 1 following renal ischemia-reperfusion, and remained at substantially higher levels in the kidneys on days 7 and 14 (Xu et al., 2022). This initial acute tubule injury, with KIM-1 upregulation, was followed by increased expression of vascular cell adhesion molecule 1 (VCAM1) and a second wave of immune activation with infiltration of T cells and neutrophils, as well as proximal tubule cell loss, tubule atrophy, and the development of CKD by days 30 (Xu et al., 2022). In another study, Holderied et al. investigated the impact of varying durations of unilateral ischemia/reperfusion injury to explore the critical threshold beyond which the renal tissue damage becomes irreversible, with the “point of no return” ischemia time of 35 min (Holderied et al., 2020). Prolonged ischemia of 35 or 45 min resulted in persistent upregulation of inflammation, injury, cell

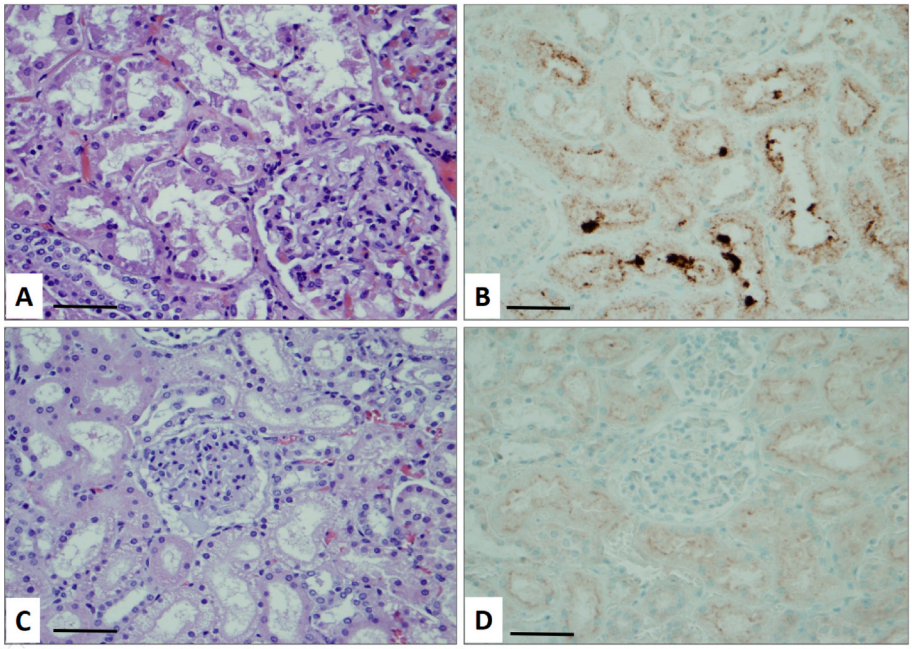

Fig. 4. Morphologic changes by routine hematoxylin/eosin staining and KIM-1 expression in autopsy kidneys from patients complicated by COVID19 infection. A-B. Morphologic changes and KIM-1 expression in adult kidneys (autopsy). Although this 53 Asian man with COVID19 had pre-mortem serum creatinine level at 0.63 mg/dl, light microscopy showed dilated proximal tubules (A) and diffuse and strong KIM-1 staining (brown color) in proximal tubules, consistent with moderate acute tubular injury (B). C-D. Morphologic changes and KIM-1 expression in pediatric kidneys (autopsy). A 5-year-old African-American girl with COVID19 infection had a pre-mortem serum creatinine of 0.17 mg/dl, but light microscopy revealed flattened proximal tubules epithelium with cytoplasmic vacuolization (C) and diffuse and moderate KIM-1 expression (brown color) along the luminal surface of proximal tubules (D), consistent with mild acute tubular injury (Scale Bars: 0.25 mm on A-D) (Magnifications ×400 in A-D).

death, and fibrosis markers, including KIM-1, leading to atrophy of the ischemic kidney and compensatory hypertrophy of the contralateral kidney (Holderied et al., 2020). These interesting findings indicate a potential transition from acute to chronic kidney disease (Holderied et al., 2020). Therefore, KIM-1 serves as a valuable biomarker for AKI and CKD, as well as the transition between these pathological conditions (Ko et al., 2010; Zhang et al., 2024). By monitoring KIM-1 levels, clinicians may assess kidney injury severity, identify patients at risk for developing CKD, and implement timely interventions.

4.2. KIM-1 in chronic kidney diseases

Notably, elevated circulating levels of KIM-1 have been linked to both acute and chronic kidney damage (Sabbisetti et al., 2014). Additionally, elevated levels of KIM-1 in the blood or urine are often associated with the progression of CKD. In the Boston Kidney Biopsy Cohort and Chronic Renal Insufficiency Cohort Studies, patients with diabetic nephropathy, glomerulopathies, and tubulointerstitial disease have significantly higher plasma levels of KIM-1, indicating a prognostic value of plasma KIM-1 across a spectrum of kidney diseases (Schmidt et al., 2022). Therefore, plasma KIM-1 may serve as a tool in the non-invasive assessment of kidney tubular injury, and higher plasma KIM-1 levels are independently associated with progression to kidney failure (Schmidt et al., 2022). Sabbisetti and colleagues found that KIM-1 levels elevated in both blood and urine in mice with unilateral ureteral obstruction, even when plasma creatinine levels remained unchanged (Sabbisetti et al., 2014), suggesting that KIM-1 might be a more sensitive biomarker for kidney damage than traditional markers like creatinine (Sabbisetti et al., 2014).

Lupus nephritis is a renal complication of systemic lupus erythematosus (SLE), a prototype autoimmune disease characterized by the immune system attacking its organs/tissues, including the kidneys. Lupus nephritis causes permanent kidney damage, gradually leading to CKD, which is a major cause of death in patients with SLE. Nozaki and colleagues found that urinary KIM-1 levels can be used to screen active lupus nephritis (LN) and estimate tubular KIM-1 tissue expression in renal biopsies from patients with active lupus nephritis, predicting renal damage, ongoing glomerular nephritis, tubulointerstitial inflammation, and tubular atrophy in patients with LN (Nozaki et al., 2014). Nozaki et al. also found that urinary KIM-1 correlates with LN disease activity and renal histopathology findings, serving as a predicting biomarker for monitoring treatment responses in patients with LN (Nozaki et al., 2023). In addition, Ding et al. demonstrated that urinary KIM-1, together with neutrophil gelatinase-associated lipocalin (NGAL), and monocyte chemoattractant protein-1 (MCP-1) were associated with kidney injury, and a combination of these three biomarkers showed increased power in predicting tubulointerstitial lesions and renal outcomes in patients with LN (Ding et al., 2018). Furthermore, the Renal Activity Index for Lupus (RAIL), a composite biomarker incorporating urinary KIM-1, NGAL, MCP-1, adiponectin, hemopexin, and ceruloplasmin, is a valuable and accurate non-invasive tool for assessing LN activity and monitoring response to LN therapy (Cody et al., 2023).

In addition, KIM-1 contributes to kidney damage during CKD development by promoting inflammation, fibrosis, ECM deposition, and epithelial-to-mesenchymal transition (EMT) (Huang et al., 2023). Thus, it serves as a potent biomarker in the non-invasive assessment of kidney tubular injury and disease activities in CKD development and monitoring therapeutic responses during LN therapy (Nozaki et al., 2014; Schmidt et al., 2022; Cody et al., 2023). Additionally, KIM-1 may play a role in regulating proteinuria (Karmakova capital Te et al., 2021), a common symptom of CKD. All of the above indicated the potential of KIM-1, either alone or in combination with other biomarkers, to serve as valuable biomarkers for the diagnosis, prognosis, and monitoring of CKD progression and therapeutics. A comprehensive understanding of the functions of KIM-1 can help us to develop new therapeutic strategies to slow the progression of CKD and improve patient outcomes. Therefore, recent research efforts have been shifted towards developing KIM-1 inhibitors, such as TW-37, a small molecule inhibitor that can block

KIM-1-mediated uptake of palmitic acid-albumin in vivo in a mouse kidney injury model (Mori et al., 2021). This inhibitor has shown promise in alleviating renal inflammation and fibrosis, ultimately delaying the progression of CKD (Mori et al., 2021).

5. KIM-1 expression during renal tubular dedifferentiation to renal neoplasm

There is a significant chance for the development of various renal cell carcinomas in the end stage of kidney disease (Tickoo et al., 2006; El-Zaatari and Truong, 2022; Al-Othman et al., 2024). In addition to clear cell renal cell carcinoma (RCC) and papillary RCC, acquired cystic kidney disease-associated RCC and clear cell papillary RCC can be seen as well (Tickoo et al., 2006; Al-Othman et al., 2024). During the embryonic development of the kidney, a critical change is the mesenchyme to epithelial transition (MET). When developed kidneys are injured, there is a trend of epithelium to mesenchyme transition (EMT) for tubular repair (Zeisberg and Kalluri, 2004). The EMT process can lead to aberrant pathways in renal tubules, contributing to tumorigenesis (Chuang et al., 2008). This may explain why patients with chronic kidney disease have a higher risk of developing RCC compared to the general population (Denton et al., 2002). From the pathologic point of view, normal proximal tubules are negative for the mesenchymal marker vimentin but injured proximal tubules and RCCs derived from proximal tubules, including clear cell RCC and papillary RCC, stain positive for vimentin, indicating that they have undergone an EMT process.

KIM-1 is up-regulated in clear cell RCC and papillary RCC, but stains negatively in the renal neoplasms from distal nephron tubules, namely chromophobe RCC and oncocytoma (Han et al., 2005; Lin et al., 2007; Zhang et al., 2019). KIM-1 does not show expression in many types of carcinomas except for a small percentage of colonic carcinomas and 40 % of clear cell carcinomas of the ovary (Lin et al., 2007). Colonic carcinomas may have an overlapping mucinous component of the extra-cellular KIM-1 domain in clear cell RCC. The clear cell carcinoma of the ovary may reserve some overlapping KIM-1 component from the mesonephros, which may be similar to that of the clear cell RCC which has a metanephros origin. The DNA sequences of KIM-1 in clear cell RCC and papillary RCC remain intact (Zhang et al., 2014), implying that KIM-1 may have certain functions in RCC. Furthermore, KIM-1 and a phagocytic biomarker CD68 co-express in clear cell RCC and papillary RCC but not in chromophobe RCC and oncocytoma, implying that KIM-1 may play a role in the phagocytosis of apoptotic debris in RCC cells as well (Zhang et al., 2014). This potential scavenging role of KIM-1 may contribute to a “self-cleaning” of tumor cells to promote tumor spread.

Due to its upregulation in clear cell and papillary renal cell RCC, KIM-1 has been used as a valuable urinary biomarker to detect RCC (Morrissey et al., 2011; Zhang et al., 2014; Mijuskovic et al., 2018). Several studies have shown that the urine assay of KIM-1 in RCC appears to be very useful in early detection of RCC, mainly because clear cell RCC and papillary RCC represent the vast majority (approximately 90 %) of RCC (Zhang et al., 2014; Morrissey et al., 2011; Mijuskovic et al., 2018). In 2018, a multicenter study using plasma samples from the European Prospective Investigation into Cancer and Nutrition (EPIC) confirmed that positive KIM-1 serology testing is correlated with the detection of RCC by imaging study and higher serology values of KIM-1 are associated with poorer outcomes of RCC (Scelo et al., 2018). Recently, another international study based on two independent cohorts, the WHO/International Agency for Research on Cancer (IARC) K2 multinational prospective study and Johns Hopkins Brady Urological Institute Biorepository, demonstrated that plasma KIM-1 was associated with malignant renal pathology, worse metastasis-free survival, and increased risk of death in patients with RCC (Xu et al., 2024). Therefore, the accumulated clinical evidence suggests that KIM-1 could be a valuable biomarker for screening RCC in the future.

6. Conclusions

KIM-1, initially linked to acute tubular injury during AKI, is increasingly demonstrated its role in AKI to CKD transition and CKD development. Renal pathology using KIM-1 staining helps identify injured proximal tubules, particularly in medullary rays and inner medulla, and reveals a complex immune system involved in injured proximal tubules, interstitial inflammatory reaction, and interstitial fibrosis, leading to CKD development. The role of KIM-1 in AKI to CKD transition and CKD development deserves extensive investigations in the future. Furthermore, KIM-1 is valuable to differentiate RCC subtypes as clear cell RCC and papillary RCC is from proximal tubules while chromophobe RCC is from distal nephron tubules. This capability of KIM-1 raises the question of whether the existing RCC classification needs to be revised to reflect their different tubular origins. KIM-1 immuno-staining is also useful in confirming metastasis of either clear cell RCC or papillary RCC. Finally, urine and serologic KIM-1 analysis shows promise as a non-invasive biomarker for screening early RCC and confirmation before invasive procedures. In summary, KIM-1 is a specific and sensitive biomarker to identify and monitor acute tubular injury, AKI to CKD transition, and CKD development, as well as screening and confirming RCC.

CRediT authorship contribution statement

Ping L. Zhang: conceived the concepts and designed the study, drafted the first manuscript, and made critical revision of the manuscript, and finalized the article, All authors critically contributed to the manuscript for important intellectual content. **Ming-Lin Liu:** conceived the concepts and designed the study, drafted the first manuscript, and made critical revision of the manuscript, and finalized the article, All authors critically contributed to the manuscript for important intellectual content.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Author PLZ thanks his former mentor Dr. Barry M. Brenner (Emeritus Director of the Renal Division of Brigham and Women’s Hospital, Boston) for his teaching, inspiration, and pioneering role in understanding how controlling glomerular hyperfiltration can delay the progression of CKD in animal models and humans. Author PLZ also appreciates the long-term collaboration of Dr. Joseph V. Bonventre, Renal Division, Brigham and Women’s Hospital, Boston, for the KIM studies and congratulates him for his receiving the Homer W. Smith Award of the American Society of Nephrology on October 26, 2024, mainly for his outstanding contribution in understanding acute kidney injury, repairing and generation of kidney tissue. The authors also thank Dr. Olaf Kroneman, Division of Nephrology, Corewell Health (East), Royal Oak, Michigan, for his critical review of this manuscript. This work was supported by Lupus Research Alliance (416805) and NIH R21AI144838 (to MLL).

Data availability

No data was used for the research described in the article.

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