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Review Article

Understanding kidney injury molecule 1: a novel immune factor in kidney pathophysiology

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Abstract: Kidney injury molecule 1 (KIM-1) is a type I membrane protein, comprising an extracellular portion and a cytoplasmic portion. It is also named as HAVCR1 (Hepatitis A virus cellular receptor 1) or TIM1 (T-cell immunoglobulin mucin receptor 1), and is expressed in the kidney, liver, and spleen. KIM-1 plays different roles via various molecular targets in immune diseases and kidney injury. KIM-1 is involved in HAV infections, autoimmunity, immune tolerance, and atopic diseases. The urinary KIM-1 level is closely related to its tissue level, and correspondingly related to kidney tissue damage. KIM-1 is not only an early biomarker of acute kidney injury (AKI), but also has a potential role in predicting the long-term renal outcome. In this review, we provide a summary of KIM-1's activities, focusing on the latest studies concerning the important roles of KIM-1 in the immune system and kidney diseases.

Keywords: KIM-1, immune, kidney diseases, acute kidney injury, chronic kidney disease

Introduction

The protein encoded by the *KIM-1* gene is a membrane receptor for both human hepatitis A virus (HHAV) and T cell immunoglobulin and mucin domain containing 4 (TIMD4). Alternative splicing of this gene results in multiple transcript variants that are also known as *HAVCR1* (Hepatitis A virus cellular receptor 1) and *TIM1* (T-cell immunoglobulin mucin receptor 1) [1, 2]. HAVCR1 was first reported by Kaplan [3], and recognized as the receptor for hepatitis A virus (HAV) on the surface of the monkey's kidney that promotes cellular entry of the virus under certain conditions. TIM1 is a co-stimulator of T cell activation that regulates the innate and adaptive immune system via related molecular mechanisms [4]. Thus there is a potential link between HAVCR1/TIM1 and immune susceptibility.

Ichimura first reported that KIM-1, which is shed into urine after acute kidney damage, is a marker of renal tubular injury. Whereafter, their lab identified that KIM-1 overexpression also is a marker for the long-term prognosis of chronic kidney diseases [5-7].

Here, we first briefly review the comprehensive roles of HAVCR1/TIM1/KIM-1 in immune and kidney diseases. We then present a map of the potential relationships among them to aid future research.

The structure of KIM-1

The human *KIM-1* gene maps to chromosome 5p33.3 and comprises 14 exons. The length of its mRNA is 1095 bp, encoding a 39 kDa type I membrane glycoprotein [7]. KIM-1 has signal peptide before the N-terminal domain, which may be directly responsible for KIM-1's location on the cell surface. However, some studies showed that endogenous KIM-1 clusters mostly in the cytoplasm, and does not localize to the cell surface except under sustained cell activation. The cell-specific location of KIM-1 could affect its diverse cell functions [8, 9]. For example, in kidney cells, KIM-1 trafficking to lysosomes can promote nuclear hormone receptor

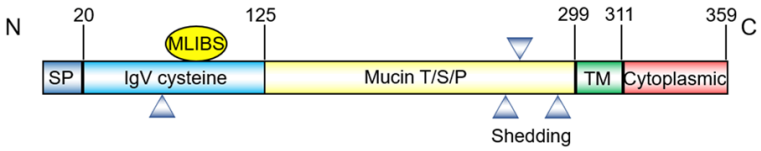

Figure 1. Structure of the Human KIM-1 protein. Schematic representation of KIM-1, showing the signal peptide, IgV, mucin, transmembrane, and cytoplasmic domains. The triangles are the predicted location of N-linked glycosylation sites. KIM-1, kidney injury molecule-1; MLIBS, metal ion-dependent ligand binding site; T/S/P, threonine/serine/proline; TM, transmembrane.

NUR/77 (NUR77) degradation. In lymphoid cells, KIM-1 in endosomes is required to sense enveloped viruses. Whereas in Jurkat T cells, intracellular KIM-1 may modulate antigen-driven immune responses by locating to the immune synapse rather than the cell surface (**Figure 1**).

Its extracellular segment comprises a six-cysteine immunoglobulin variable (IgV) domain and a threonine/serine/proline (TSP) rich mucin region, which is characteristic of mucin-like glycosylated proteins [10, 11]. Considering the many glycosylation sites on the extracellular domain, including one putative N-glycosylation in IgV region, along with three putative N-glycosylation and multiple O-glycosylation sites in mucin region, the molecular mass of the mature form of KIM-1 is 104 kDa, containing a 90 kDa soluble portion and a 14 kDa membrane-bound fragment [12]. The IgV domain has a unique metal ion-dependent ligand binding site (MILIBS). MILIBS can recognize phosphatidylserine (PtdSer) that is exposed on the outer leaflet of the apoptotic cell membrane [11]. Thus, cells expressing KIM-1 can engulf and eliminate apoptotic cells [13], which is an essential process for cell homeostasis and immune responses [14, 15]. Recent data suggested that the mucin domain on the cell surface participates in intracellular calcium release [16]. During calcium stone formation, urinary mucin is decreased, which further enhances transient receptor potential cation channel subfamily V member 5 (TRPV5) channel activity to protect against kidney stones.

A short cytoplasmic tail with a conservative tyrosine phosphorylation motif follows the transmembrane segment. Tyrosine phosphorylation of this tail may be related to the activation of downstream signaling pathways by engaging several protein kinases [17]. The cytoplasmic portion has two splice variants, KIM-1a and KIM-1b. KIM-1a is mainly expressed in the liver and lacks the tyrosine kinase phosphorylation motif. KIM-1b, which contains two conserved tyrosine residues and a tyrosine kinase phosphorylation motif, is mainly expressed in the kidney [16].

Kim-1 and immune diseases

Numerous studies have shown that KIM-1 is associated with control of viral infections, autoimmunity, immune tolerance, and atopic diseases [18-20]; which indicate that KIM-1 plays a major role in the immune system.

Initially, KIM-1 was identified as an entry receptor for HAV and is expressed on the surface of different epithelial cells. It also promotes the entry of a wide range of viruses such as Zaire Ebola virus (EBOV), Lake Victoria Marburg virus, Plasmodium berghei ANKA, Dengue virus (DV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) [21-25]. A recent report suggests that KIM-1 participates in the identification of alternative virus receptors. The interaction between a virus and KIM-1 indicates the entrance pathway for the virus [26]. Evidence for the HAV/KIM-1 interaction implies that both the IgV and mucin domains, especially the first N-glycosylation site, are required for HAV uncoating and subsequent cell infectivity [27, 28]. Other studies revealed that KIM-1 is incorporated into HIV virions and retains particles on the cell plasma membrane by interacting with the virion-associated PtdSer [29, 30]. KIM-1 acts as a dual-attachment receptor for EBOV by interacting directly with viral glycoprotein (GP) and PtdSer on the viral envelope [31], inducing a cytokine storm phenomenon [32].

Kim-1 is also linked with many immune dysfunction diseases, including allergies, asthma, ectopic dermatitis, rheumatoid arthritis, and systemic lupus erythematosus (SLE) [2, 33-36].

KIM-1, previously named TIM-1, is expressed on CD4(+) T cells. In patients with SLE, the expression of interleukin (IL)10, which is a Th2 immuno-modulatory cytokine, correlated positively with the increase in KIM-1 expression

[37]. In patients with allergic rhinitis, after stimulation by dust or lipopolysaccharide, The cells expressing KIM-1 differentiated into Th2 cells, suggesting that KIM-1 plays an important role in regulating the Th2 immune response [38-40].

In asthma, TIM4 binding to KIM-1 increases the expression of silent information regulator 1 (SIRT1) on CD4(+) T cells via the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT kinase (AKT) signaling pathway and promotes the proliferation of Th2 cells [41]. Their combination could also trigger T cells activation via linker for activation of T cells (LAT), AKT, and extracellular regulated protein kinases (ERK1/2) signaling pathways and mediates T cell trafficking [40, 42], which was predominant in inducing the Th2 immune response by increasing cell differentiation and decreasing apoptosis [11, 43-45]. Some reports indicated that KIM-1 acts as a costimulatory molecule during antigen presentation, amplifying T cell receptor (TCR) signaling with TCR complex components zeta chain of T cell receptor associated protein kinase 70 (ZAP-70) and CD3 (T-cell receptor T3) [46]. KIM-1 combined with CD3 can be recruited to the TCR complex, thus increasing the activation signal of T cells, aided by activation of the PI3K pathway [47]. In a mouse transplantation experiment, KIM-1 regulated the endogenous Th2-immune response, which provided new insights for the clinical treatment of graft rejection [48]. These reports showed that KIM-1 is predominantly associated with the Th2 immune response. However, in asthma, KIM-1 also serves as a pattern recognition receptor on invariant natural killer cells (iNKTs), where it mediates cell activation when iNKT cells bind to PtdSer on the surface of cells undergoing apoptosis [49]. KIM-1 is also a marker of regulatory B cells [50] and its signaling is required for B cells to augment antibody or IL10 production by enhancing B cell proliferation and differentiation [51-53]. KIM-1 on immune cells may be a useful therapeutic target to treat immune diseases.

By contrast, in allergic inflammation, application of an anti-KIM-1 antibody induced T cells that markedly increased the production of proinflammatory IL4. This indicated that immunotherapies that regulate KIM-1 might inhibit immune tolerance [54]. KIM-1 on NKT cells and mast cells also enhanced Th2-type cytokine production of IL-4, IL-5, and IL-13 [37, 55]. Moreover, in a mouse model of asthma, the production of IL4 induced by KIM-1 might have resulted from the elevation of Th2 transcription factor GATA binding protein 3 (GATA3) [39]. KIM-1 can promote macrophages to produce a dramatic increase of proinflammatory cytokines, including tumor necrosis factor alpha (TNFα) and IL6 [56]. KIM-1 is a major P-selectin ligand and is involved in a pivotal trafficking mechanism for Th1 and Th17 cells during inflammation, which are potent inducers of inflammation and autoimmunity. These observations suggested that interference with KIM-1 activity might provide a therapeutic approach in T cell-mediated diseases [57]. KIM-1 is also constitutively expressed on dendritic cells (DCs), where it confers pro-inflammatory properties [58]. In a DC-induced allergy model, disruption of the KIM-1/TIM4 interaction was promoted as a therapeutic strategy [59].

Patterns of variation in *KIM-1* have been shaped by both positive and balancing natural selection in the course of primate evolution [60]. For example, the levels of polymorphisms in exon 4 of *KIM-1* are unusually high in humans or among human, chimp, and gorilla, which represents evidence that natural selection may have applied to preserve functional variation in exon 4, suggesting that *KIM-1* can adapt to a continually changing environment under long-range pressure. Several studies have shown that cells containing polymorphic *KIM-1* are susceptible to HAV infection and immune diseases [34, 35, 61-65]. For example, a 6-amino-acid-encoding insertion in *KIM-1* (157insMTTTVP) is associated with HAV-induced severe liver disease [61]. Moreover, *KIM-1* gene polymorphisms (-416G>C and -1454G>A) were observed to be related to allergic rhinitis susceptibility in a Han Chinese population [63]. However, HAV infection induces the production of the short-form KIM-1 protein, which has the low efficiency to combine with HAV and limits its entry into cells [66, 67]. In acquired immunodeficiency syndrome (AIDS), patients carrying the *KIM-1* D3-A haplotype have lower expression levels of KIM-1, resulting in better survival rates compared with other patients because of their higher CD4 cell count [68]. These data prove a correlation between KIM-1 and immune-related diseases, confirming that

both genetic and environmental factors play a role in such pathologies.

Expression and secretion of KIM-1 in the kidney

Normal kidney tissues rarely express KIM-1, except in the acute injury resulting from ischemia, hypoxia, toxicity, or some renal tubular interstitial, and polycystic kidney disease [69-71]. Under conditions of acute kidney injury, urinary and renal KIM-1 levels are significantly elevated in a short period of time, and correlate with the extent of kidney damage. KIM-1 is mainly expressed in differentiated proximal renal tubular epithelial cells, which can regenerate after injury, especially in the proximal tubule S3 outer medulla area because of its sensitivity to ischemia, hypoxia, and toxicity.

After injury to renal tubular cells, the extracellular section of KIM-1 is released into the renal tube cavity and is further shed into the urine, mediated by mitogen-activated protein kinase (MAPK) signaling pathways [72]. This shedding of KIM-1 is also based on the activation of type I and III membrane matrix metalloproteinases (MT-MMPS) [73, 74] and a disintegrin and metalloprotease (ADAM) [75], which lead to its detection in urine. Measuring the expression level of KIM-1 in urine is sensitive for the early diagnosis of acute kidney disease (AKI) and chronic kidney diseases (CKD) [76], as well as useful to effectively assess renal pathological damage and disease progression [77].

KIM-1 and acute kidney injury

In patients with acute renal tubular injury, the KIM-1 expression level in the kidney is significantly elevated compare with that in the healthy population. The proposed mechanism is that acute renal damage initiates ERK1/2 and signal transducer and activator of transcription 3 (STAT3) phosphorylation. Then, nuclear STAT3 binds to the *KIM-1* promoter and increases its mRNA and protein levels [78, 79]. Shedding of the extracellular domain leads to greatly increased levels of KIM-1 in blood and urine, which can be used to diagnose acute renal tubular dysfunction after renal transplant [80]. The KIM-1 level is also significantly correlated with the decline of the estimated glomerular filtration rate (eGFR) and kidney damage [81].

Acute overexpression of KIM-1 in proximal renal tubular epithelial cells after ischemia, hypoxia, and toxicity promotes transformation of the cells into “semi-professional” phagocytic cells, with the help of KIM-1’s mucin domain. KIM-1 is a phosphatidylserine receptor on the surface of the liposome that can identify the apoptosis body and phosphatidylserine, which mediates further phagocytosis [82].

Thus, KIM-1 plays a role in the removal of apoptotic cells and necrotic tissue fragments. Furthermore, KIM-1 phosphorylation, and its interaction with p85, enhance cell autophagy to degrade KIM-1 phagosomes relying on Unc-51 like autophagy activating kinase 1 (ULK1, also known as ATG1) phosphorylation and maintain self-tolerance by the presentation of antigens on the proximal tubule cell [83]. In kidney diseases of protein overload, KIM-1 can be used to increase the phagocytosis of albumin by renal tubular epithelial cells, which alleviates the tubular damage [84].

In addition to its role in mediating phagocytosis, KIM-1 is also involved in the repair process after injury to renal tubular epithelial cells. *In vitro*, transient KIM-1 overexpression can promote the migration and proliferation of renal tubular epithelial cells by activation of the ERK/MAPK signaling pathway. KIM-1 serves as a therapeutic target to facilitate the renal repair process after AKI [85]. Other studies have reported that after the acute kidney ischemia injury in mice, KIM-1 and G Protein Alpha 12 (Gα12) interact directly. At the same time, Gα12 can inhibit the activation of downstream Ras homolog gene family, member A (RhoA). Through these signaling events, endocytosis is negatively regulated by Gα12 in acute renal ischemic injury [86]. Upregulation of KIM-1 can protect against kidney ischemia damage by suppressing Gα12 activation and blocking GTP loading [87]. Thus, accumulated evidence has demonstrated the beneficial effects of the KIM-1-related renal tubular protection mechanism in the early stages of kidney injury.

KIM-1 and chronic kidney disease

KIM-1 also is a sensitive biomarker for chronic proximal tubular injury [88]. Studies showed that in urine samples from adults and children, the level of KIM-1 correlates highly with the inci-

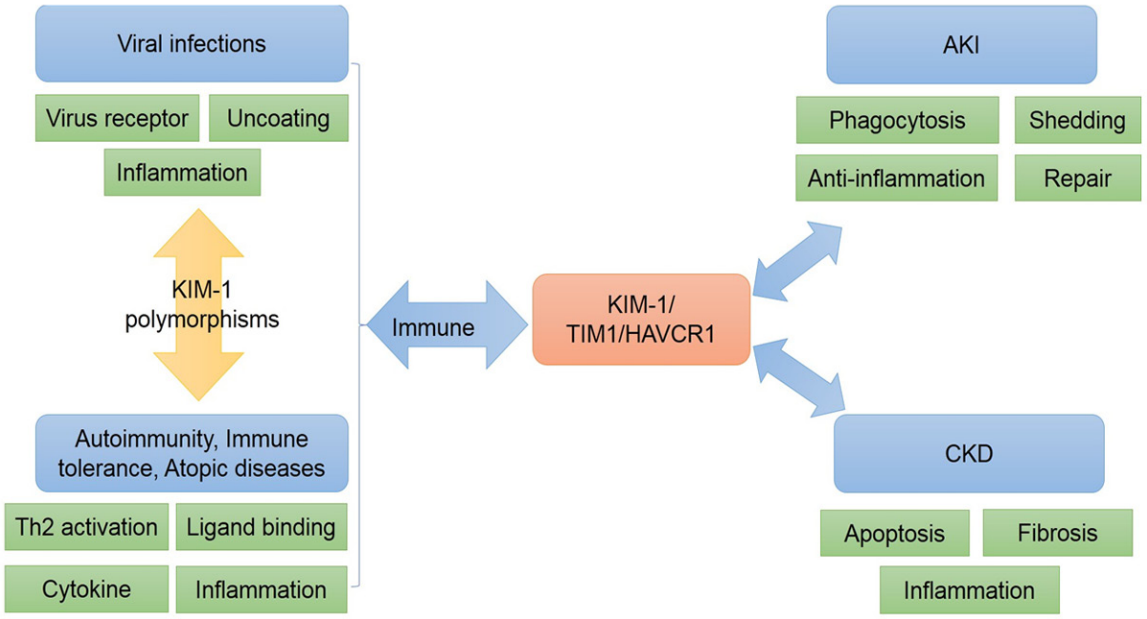

Figure 2. The role of KIM-1 in different diseases. In the immune system, KIM-1 is related to viral infections and autoimmunity. In acute kidney injury (AKI), KIM-1 is involved in cell phagocytosis, repair processes, and anti-inflamation, and is shed into urine. However, KIM-1 can promote renal fibrosis, tubular apotosis, and inflammatory response in chronic kidney disease (CKD). KIM-1, kidney injury molecule-1; TIM-1, T-cell immunoglobulin mucin receptor 1.

dence and prognosis of CKD [89-91]. In the progression of IgA nephropathy, a higher level of KIM-1 in urine leads to more serious and rapid disease progression [92]. In protein-overload nephropathy, increasing KIM-1 levels are associated with inflammation of the renal tubules [93]. KIM-1 is the only effective clinical biomarker for CKD associated with hypertension [94]. In more severe CKD, KIM-1 is an independent risk factor for progression to end-stage renal disease (ESRD) [95].

In vivo animal models of unilateral ureteral obstruction (UUO) showed that continued chronic expression of KIM-1 in renal tubular promoted the secretion of monocyte chemotactic protein 1 (MCP-1), which enhanced macrophage chemotaxis, thus further promoting the occurrence of fibrosis [5]. In addition to these rodent models, the expression level of KIM-1 was also increased in human renal proximal tubule epithelial cells (HK2) under conditions of chronic hypoxia. This led to activation of mononuclear macrophages and the occurrence of renal tubule interstitial inflammation [96]. Moreover, KIM-1 plays a crucial role in macrophage activation via the MAPK signaling pathway in kidney disease, inducing macrophages to differentiate into the M1 type. The renal mRNA expression levels of the M1-dependent genes *IFNG* (interferon gamma) and *INOS* (nitric oxide synthase 2) markedly increased. This was consistent with the increases of proinflammatory macrophage cytokines in blood, such as TNF-α and IL-6. In contrast, the expression levels of M2-dependent genes (*MR* (mineralocorticoid receptor) and *Arg1* (arginase 1)) and cytokines (IL-4 and IL-10) decreased [97].

In addition, when HK2 cells were cultured in high glucose, the expression levels of KIM-1 and LC3II (microtubule associated protein 1 light chain 3 alpha, a marker of autophagy) increased. Autophagy and apoptosis are initiated in high glucose at the same time, which leads to cell death. Meanwhile, silencing of *KIM-1* resulted in the inhibition of the glucose-induced production of LC3II, autophagy, and apoptosis, followed by a reduction in cell death. This indicated that blocking KIM-1 in a high glucose environment helps to maintain cellular homeostasis via autophagy and apoptosis [98]. Observation of kidney pathological sections revealed a more severe extent of renal tubular injury, inflammation reaction, and fibrosis in the area where KIM-1 was markedly expressed [99]. These findings indicated that KIM-1 is involved in regulating the development of CKD and renal fibrosis.

In the early stage of diabetic kidney disease (DKD), the expression of KIM-1 in the glomeruli is significantly elevated, mainly in the proliferative parietal epithelium of the capsule. The expression of KIM-1 increases along with the development of the disease and correlates with decreased numbers of podocytes [100]. Moreover, glomerular KIM-1 expression was elevated in proportion to the extent of proteinuria and podocytopenia in diabetic animals; supporting the view that it could be used as a potential biomarker for glomerular injury in proteinuria kidney disease. In anti-neutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis, the levels of both KIM-1 and MCP-1 in the urine can reflect inflammation and are related to prognosis evaluation of the glomeruli [101].

Conclusions

In summary, KIM-1 has a wide variety of physiological and pathological functions in different diseases (**Figure 2**). The earliest identified homolog of KIM-1, HAVCR1, which is the receptor for HAV, is involved in cell entry and pathogenesis of HAV, as well as other viruses. In immune system related diseases, TIM1 (a variant of KIM-1) is a co-stimulator of T cell activation and plays an important role in regulating the Th2 reaction. TIM4 and CD3 as ligands can promote the proliferation and activation of Th2 cells, as well as inducing the production of cytokines IL4, IL5, IL-10, and IL13, which play important roles in immune system activation. With the help of metalloproteinases, the ectodomain of KIM-1 is shed into the renal tube cavity and is excreted in the urine and blood, acting as an indicator of kidney injury. Furthermore, the function of KIM-1 in AKI and CKD is different. In the early stage of renal tubular damage, the increased expression of KIM-1 promotes cell phagocytosis, repairs tubular injury, and inhibits the renal inflammatory response. By contrast, the continuous increase in KIM-1 levels is not a protective factor in CKD, which in turn promotes the occurrence and development of renal fibrosis.

In this review, we provided an overview of KIM-1. Further studies are required to determine its function to develop effective and suitable therapeutic methods to treat immune and renal diseases by directly targeting KIM-1.

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Disclosure of conflict of interest

None.

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