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Abstract

Kidney injury molecule-1 (KIM-1), a recently discovered transmembrane protein, is expressed in dedifferentiated proximal renal tubular epithelial cells in damaged regions. It may participate in the progress of renal injury or repair. Many studies have illustrated the different functions of KIM-1 in various renal diseases including protective functions in acute kidney injury and damaging functions in chronic kidney disease. Although, the exact functions of KIM-1 still remain unclear, some scientists speculate that KIM-1 is expected to be a therapeutic target for kidney injury. In this review, some of the known features and functions of KIM-1 are highlighted.

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1. Introduction

Renal epithelial cell injury is the feature of many acute and chronic renal diseases. Kidney injury molecule-1 (KIM-1), a recently discovered transmembrane tubular protein, is undetectable in normal kidneys, but it is markedly induced in renal injury including acute kidney injury (AKI) and chronic kidney disease (CKD) [1-3]. Many studies indicate that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis [4,5]. In fact, KIM-1 is more than a noninvasive marker for kidney injury. A number of studies have demonstrated that KIM-1 may play a role in kidney injury and repair, although very little is known about the precise molecular mechanism that regulates these events [6,7].

2. Structure of KIM-1

KIM-1 (also known as TIM-1—T-cell immunoglobulin and mucin-containing molecule) was originally discovered in a screen for molecules involved in the pathogenesis of AKI. Ichimura et al [1] first identified the complementary DNA for a type 1 membrane protein from postischemic rat kidney by representational difference analysis and called it kidney injury molecule-1. This gene encodes a type I cell membrane glycoprotein containing in its extracellular portion a 6-cysteine immunoglobulin-like domain and a Thr/Ser-Pro rich domain characteristic of mucinlike O-glycosylated proteins. Immunoglobulin-like domains have been widely implicated in mediating protein-protein interaction in particular at the cell surface. Kidney injury molecule-1 also has a transmembrane domain and a cytoplasmic domain, and the latter contains a conservative tyrosine phosphorylation site that can be phosphorylated by tyrosine, indicating that KIM-1 may be a signaling molecule [8]. The ectodomain of KIM-1 can be shed into the tubular lumen, and this ectodomain shedding is mediated by matrix metalloproteinases possibly involving mitogen-activated protein (MAP) kinase activation [9]. Human KIM-1 exhibits homology to a monkey gene, hepatitis virus cell receptor 1, which was identified recently as a receptor for the hepatitis A virus. Structurally, KIM-1 closely resembles mucosal addressin cell adhesion molecule 1, and it is a member of the immunoglobulin gene superfamily [10] (Fig. 1).

3. KIM expression location

The KIM-1 gene or protein expression is undetectable in normal kidney. In the injured kidney, KIM-1 messenger RNA is rapidly duplicated and protein is generated and
localized at very high levels on the apical membrane of proximal tubule in the region where the tubule is most affected. The KIM-1 expression is absent in the glomerulus, peritubular interstitial cells, or inner medullary cells [1,2]. In the experiment of kidney ischemia in rodents, KIM-1 was expressed predominantly in the S3 segment of the proximal tubule that was highly susceptible to ischemic insult, but in human ischemic and toxic kidney injury, it was found in 3 segments of the proximal tubule [11,12]. Kidney injury molecule-1 was usually present in damaged tubular epithelial cells undergoing dedifferentiation and replication. However, in severely damaged tubule cells, such as completely flattening or atrophic cells, it was not easy to detect KIM-1 [13].

4. KIM-1 as a specific biomarker for kidney injury

In renal patients, KIM-1 is up-regulated in a variety of conditions including ischemia, nephrotoxic drugs, CKD, and acute/chronic renal transplant dysfunction. There are a growing number of studies that demonstrate the use of KIM-1 as a marker for kidney injury including AKI and chronic kidney injury. There are many characteristics of KIM-1 making it an ideal biomarker for kidney injury. For example, KIM-1 is not expressed in normal kidney but specifically expressed in injured proximal tubular cells, and such an expression can persist until the damaged cells have completely recovered. Moreover, the rapid and integrated cleavage of its ectodomain into the lumens of kidney tubules can make it detectable in urine [14]. Urinary KIM-1 level is closely related to tissue KIM-1 and correlates with the severity of renal damage, so quantitation of urinary KIM-1 is likely to be a noninvasive and sensitive method for the evaluation of kidney injury and even for monitoring the therapeutic effects of kidney injury [15]. In the study of nephrotoxicity, urinary KIM-1 levels increased severely earlier than the increases of blood urea nitrogen and plasma creatinine [16]. Similar results were obtained in the ischemia-reperfusion (I/R) injury model because 10-minute I/R injury caused a significant increase of urinary KIM-1 without any changes in plasma creatinine, creatinine clearance, or proteinuria [2,17]. In the transplant biopsies, KIM-1 expression was reported being able to diagnose early tubular that was not detectable by histologic examination, and KIM-1 also helped distinguish acute tubular necrosis from other allograft dysfunction [18]. Thus, KIM-1, as a specific and early marker of tubular injury, may be used to guide and individualize renoprotective intervention.

5. Double-edged functions of KIM-1 in kidney injury

5.1. KIM-1 and AKI

In situ hybridization and immunohistochemistry revealed that KIM-1 was expressed in dedifferentiated and regenerative proximal tubular epithelial cells in damaged regions after toxic or ischemic injury, and KIM-1 colocalized with bromodeoxyuridine (a marker of proliferation) and elastin (a marker of dedifferentiation). Therefore, KIM-1 may play a role in the regeneration process of tubular epithelial cells, through which it can help reconstitute a continuous epithelial layer [1,7,8]. Structurally, KIM-1 is an adhesion molecule that may have multiple roles in epithelial function. In addition to tethering cells to the extracellular matrix and interconnecting cells to each another, it is also involved in cell locomotion, proliferation, and dedifferentiation. It is known that dedifferentiation of tubular epithelial cells is necessary for the regeneration, and such a transition from normal epithelial cells to dedifferentiated cells is associated with a dramatic up-regulation of KIM-1 expression [1,8].

Bailly et al [8] described the constitutive release of the ectodomain of KIM-1 by a metalloproteinase-dependent cleavage from cells, and they observed that the shed soluble form was bound to extracellular matrix and could support integrin-mediated cell adhesion and migration. Such a process was proved to be regulated by the MAP kinase signaling pathways activated by cell stress. The released ectodomain of KIM-1 containing Ig domain could combine the integrin located in the apical membrane of proximal tubule and restrained the depolarization of the integrin, which helped to avoid the undesirable attachment of exfoliated cells to one another or fibronectin so as to reduce cast formation and tubular obstruction [9].

In addition, recent findings by Ichimura et al demonstrated that KIM-1 was a phosphatidylserine receptor that conferred on epithelial cells the properties of highly phagocytic cells [19]. Kidney injury molecule-1 was able to specifically bind phosphatidylserine on the apoptotic cell surface and transform tubular epithelial cells into semiprofessional phagocytes, which enhanced the clearance of apoptotic and necrotic cell debris [19]. Functionally, the ability of KIM-1 to phagocytose apoptotic and necrotic cells in the tubule of the kidney may be critical for remodeling after injury because it is important that the lumen of the epithelial tubule be cleared of dead cell debris to relieve intratubular obstruction. In fact, in addition to the facilitation of clearance of the apoptotic debris from the tubular lumen,
KIM-1 may play an important role in limiting the autoimmune response to injury because phagocytosis of apoptotic cells mediated by KIM-1 may result in the generation of antiinflammatory cytokines and restrain the activation of proinflammatory cytokines [19,20]. Interestingly, hepatocyte growth factor, a well-known renal repair factor was reported to be up-regulated in epithelial cells that phagocytosed apoptotic cells [19,21]. Therefore, although speculative, KIM-1 may contribute to the regenerative mechanism that works in the replacement and restoration of the epithelium.

5.2. KIM-1 and CKD

In spite of the reported protective functions of KIM-1 in AKI, there are a number of evidences for its roles of being involved in the chronic injury in CKD. Kidney injury molecule-1 was expressed in dedifferentiated tubular epithelium in CKD similar to in AKI, which also suggested a role for KIM-1 in tubular fibrosis for some chronic renal diseases. The level of KIM-1 expression in tubular epithelial cells correlated with the level of tissue osteopontin and α-smooth muscle actin expression and colocalized with these 2 markers of tubulointerstitial damage [12,22,23]. Kuehn et al [22] observed the expression of KIM-1 in murine autosomal dominant polycystic kidney disease, and the interstitium surrounding KIM-1-positive tubules showed high proliferative activity and were stained of α-smooth muscle actin t was a characteristic of myofibroblasts, so they proposed that KIM-1 expression in tubules was strongly associated with dedifferentiation of epithelial cells and might play a role in the development of interstitial fibrosis.

In addition, a study in homozygous rennin Transgene (Ren2) rats demonstrated that KIM-1 was associated with the development of renin-angiotensin system (RAS)–mediated renal damage, for renal KIM-1 expression correlated with tubulointerstitial fibrosis and interstitial collagen III deposition. Moreover, antifibrotic treatment through RAS blockade or p38 MAP kinase inhibition could inhibit the KIM-1 expression in the Ren2 model and at the same time reduced the interstitial fibrosis, and such a result was also observed in the treatment of adriamycin nephrosis by RAS blockade [12,24].

Furthermore, in the study of biopsy specimens from 102 cases of various renal diseases, van Timmeren et al [13] found that KIM-1 was significantly induced and localized to the apical side of dilated tubules in fibrotic areas in all renal diseases except for minimal change disease, and KIM-1 expression was significantly associated with glomerular pathologic condition and glomerular influx of macrophages. In addition, double labeling immunohistochemistry for KIM-1 showed that KIM-1 was primarily present in regions with interstitial macrophages and prefibrotic lesions, and KIM-1 positive tubular cells possessed a dedifferentiated phenotype, which suggested a role of KIM-1 in tubular fibrosis [25].

5.3. KIM-1 and kidney transplantation

As to kidney transplantation, it is well-known that I/R is an inevitable event that induces acute tubular injury and increases the risk of acute rejection. It is well-known that I/R has a profound influence on not only the early graft function but also the long-term allograft survival [26]. Repair and regeneration processes occur together with apoptosis and necrosis of renal tubular epithelial cells during the progress of I/R injury. Therefore, KIM-1, as an important molecule involved in renal injury and regeneration may also be induced in renal graft and have some certain functions. In fact, in the prophase of kidney transplantation, KIM-1 was not found to be an accurate marker for predicting DGF because KIM-1 maintained a high level in patients with both delayed graft function and normal graft function [27]. So we will speculate that KIM-1 is more than a marker of acute tubular necrosis, and the increased KIM-1 expression may potentially enhance renal protection from I/R injury. In the animal experiment of autotransplanted graft, some evidences have showed the expression of KIM-1 in renal grafts and its regenerative functions for the graft recovery [28]. Zhang et al [18] investigated the usefulness KIM-1 for the early diagnosis of tubular injury in renal graft biopsy specimens and found that KIM-1 expression could identify proximal tubular injury sensitively and specifically. Their study showed that KIM-1+–positive staining was present before the occurrence of morphological pathology and KIM-1 levels significantly correlated with the degree of graft dysfunction. However, they also reported that higher KIM-1 expression was found to predict a better prognostic sign, given an equivalent level of level of renal graft dysfunction. Therefore, the data suggested that KIM-1 was not only a biomarker of tubular injury but also a potential repair marker joining in the regeneration process of tubular epithelial cells. van Timmeren et al [29] evaluated the baseline urinary kidney injury molecule-1 excretion of 145 patients with chronic allograft nephropathy (CAN) and found that high KIM-1 levels were associated with low creatinine clearance, proteinuria, and high donor age and could be an independent predictor of graft loss. Furthermore, KIM-1 may play a possible role in the progress of CAN that is characteristic of tubular fibrosis because KIM-1 is believed to be related to tubulointerstitial renal damage caused by various diseases [13,30].

6. Summary and prospect

Kidney injury molecule-1 is an epithelial cell adhesion molecule that is induced in damaged tubular epithelial cells undergoing dedifferentiation and proliferation, and the role of KIM-1 as a biomarker has a robust future. Although the exact function of KIM-1 still remains unclear, the protective function of KIM-1 was reported mainly in AKI such as ischemic or toxic injury and the damaging function of KIM-1 was reported mainly in chronic renal diseases. So, we can
hypothesize that KIM-1 may play a protective role in the initial stage of kidney injury, and in the later stage, it may play a damaging role due to the excessive cell proliferation caused by the KIM-1-induced renal repair. For kidney transplantation, AKI and CAN are almost destined injuries for the renal graft recipients, so it will be particularly interesting to explore the roles of KIM-1 during the different courses of transplantation. Maybe gene knockout animal models can clarify the issue, and KIM-1 may someday become a novel therapeutic target for kidney injury of various stages.

The authors report no conflict of interest.

References


