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Review

Urinary kidney injury molecule-1 in renal disease

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ABSTRACT

Kidney injury molecule-1 (KIM-1), a type l transmembrane glycoprotein, is recognized as a potential biomarker for detection of tubular injury in the main renal diseases. Urinary KIM-1 increases rapidly upon the tubular injury, and its levels are associated with the degree of tubular injury, interstitial fibrosis, and inflammation in the injured kidney. Currently, the investigation of kidney diseases is usually performed through the assessment of serum creatinine and urinary albumin. However, these biomarkers are limited for the early detection of changes in renal function. Besides, the tubular injury appears to precede glomerular damage in the pathophysiology of renal diseases. For these reasons, the search for sensitive, specific and non-invasive biomarkers is of interest. Therefore, the purpose of this article is to review the physiological mechanisms of KIM-1, as well to present clinical evidence about the association between elevated urinary KIM-1 levels and the main renal diseases such as chronic kidney disease, diabetic kidney disease, acute kidney injury, and IgA nephropathy.

1. Introduction

The investigation of early biomarkers to detect renal damage seems to be a primordial point for the management of the major renal clinical conditions, such as chronic kidney disease (CKD), diabetic kidney disease (DKD), acute kidney injury (AKI), among other pathologies. Additionally, the early detection of kidney injury is the main diagnostic factor as treatment can be started as soon as possible, well before the onset of renal function decline [1]. For these reasons, a simple, sensitive, specific, non-invasive biomarker for the early detection of kidney injury would is essential. Several promising biomarkers of kidney injury have been investigated to facilitate early detection, differential diagnosis, and prognosis of kidney diseases, including neutrophil gelatinase-associated lipocalin (NGAL) [2], interleukin 18 (IL-18) [3], liver-type fatty acid-binding protein (L-FABP) [4], and tubular enzymes, such as *N*-acetyl-β-D glucosaminidase (NAG) [5] and γ-glutamyltransferase [6]. Among the potential biomarkers, kidney injury molecule-1 (KIM-1) appears to be one of the most promising [7]. In a study performed in rats exposed to nephrotoxic agents as gentamicin, mercury, and chromium, urinary KIM-1was more sensitive for detecting acute kidney injury following exposure to nephrotoxic chemicals and drugs when compared to blood urea nitrogen, serum creatinine, and urinary NAG [8]. In some preclinical and clinical studies, urinary KIM-1 presented encouraging results as an early indicator of tubular injury [9,10]. However, the data available comparing the performance of KIM-1 to other biomarkers in AKI are still limited.

The decline of renal function during kidney disease may occur rapidly and reversibly, as in the case of AKI. In contrast, the renal function may decline slowly with no prominent symptoms in the early stages, as it happens in CKD. Both AKI and CKD may progress to end-stage renal disease (ESRD) [11]. Currently, the diagnosis of renal diseases including AKI and CKD is mainly based on the evaluation of serum creatinine. However, serum creatinine is a limited biomarker for the early detection of changes in renal function, and its concentration is not able to differentiate structural kidney damage and functional hemodynamic changes [12–14]. Diabetic kidney disease (DKD), a frequent complication of diabetes, is the leading cause of CKD and ESRD [15]. The early and accurate identification of DKD is of critical importance to

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ERK, extracellular signal-regulated kinase; ESRD, end-stage renal disease; FcαRI/CD89, myeloid IgA Fc alpha receptor; Gα12, alpha subunit of heterotrimeric G12 protein; HF, heart failure; HSA, human serum albumin; IgAN, IgA nephropathy; KIM-1, kidney injury molecule-1; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species; TG2, transglutaminase-2; TNF-α, tumor necrosis factor-alpha; TfR/CD71, transferrin receptor; UTI, urinary tract infection

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improve clinical outcomes. Currently, diagnosis of DKD is established through the evaluation of estimated glomerular filtration rate (eGFR) and albuminuria. However, a significant proportion of renal impairment occurs among normoalbuminuric diabetic patients [16].

Despite these efforts and the consensus that specific measures must be undertaken to identify patients with subclinical kidney diseases to protect them from poor long-term outcomes, there is still a little implementation of this knowledge in daily clinical practice. Therefore, the purpose of this article is to review physiological and clinical data on KIM-1, as well to present clinical evidence about the association between elevated urinary KIM-1 levels and the main renal diseases.

2. Physiological aspects of KIM-1

KIM-1 is a type l transmembrane glycoprotein with an extracellular immunoglobulin-like domain (IgV) topping a long mucin domain [17]. It has a transmembrane domain (membrane-bound domain) and a relatively short intracellular domain (cytoplasmic domain). Two human homologs of KIM-1 have been identified, known as KIM-1a and KIM-1b (structurally identical except the cytoplasmic domain) [18]. The KIM-1b (359 amino acids) contains a signaling protein for tyrosine phosphorylation [14] and the KIM-1a variant (334 amino acids) lacks this phosphorylation site, and it is mainly expressed in the liver [1]. On the other hand, the KIM-1b variant is predominantly expressed in the kidney [19].

The membrane-bound domain of KIM-1b is a 104 kDa. After a kidney injury, the membrane-bound domain is shed from the cell surface into extracellular space (by a metalloproteinase-dependent process) and a 90 kDa peptide appears in urine (Fig. 1) [20,21]. Indeed, the expression of KIM-1 is co-localized with the type 3 metalloproteinase (MMP-3) in the S3 segment of the tubules after kidney injury [22]. Since the phosphorylation sites in the cytoplasmic domain may provide signaling function [23], it was demonstrated that KIM-1 shedding was mediated by extracellular signal-regulated kinase (ERK) activation and p38 mitogen-activated protein kinase (MAPKs) activation [19]. Interestingly, human serum albumin (HSA), the pro-inflammatory cytokine tumor necrosis factor (TNF)-α and reactive oxygen species (ROS) were identified as stimuli to up-regulated the constitutive KIM-1 shedding [21].

In a healthy kidney, KIM-1 is expressed at low levels. Physiologically, urinary KIM-1 levels linearly increase with age in healthy human individuals, and higher KIM-1 values are noted in males than in females [24], but this is still contradictory [25]. However, its expression is significantly upregulated in the kidney after ischemia-reperfusion injury [17] and toxic insults as the drug-induced nephrotoxicity [26,27]. Thus, briefly, following tubular damage, the injured kidney cells have deranged expression and secretion of KIM-1, which has been suggested as a potential biomarker for monitoring the degree of tubular epithelial cell injury. Furthermore, the expression of KIM-1 is associated with the degree of interstitial fibrosis and inflammation in the injured kidney [17,28,29]. The assessment of the levels of KIM-1 is now recognized as a potential biomarker for early detection of kidney tubular injury [7,28]. The possible sources of the increase of KIM-1 levels in the urine after kidney injury are due to rising of shedding by a metalloproteinase-dependent process together with an increased intrarenal synthesis of KIM-1 [9,30]. Therefore, upon kidney injury, the KIM-1 expression is induced in the affected tubular epithelial cells, which release abundant amounts of soluble KIM-1 into extracellular spaces and excreted in the urine [31].

Although the exact role of the released soluble KIM-1 remains unknown, it has been suggested that KIM-1 may participate in both kidney healing and injury processes [20]. It has been indicated that KIM-1 plays an important role in the proliferation and regeneration processes in proximal tubules [1,32]. After kidney injury, the proximal tubule epithelium would regenerate, and this process involves differentiation and proliferation of several cells bordering the damaged areas. This transition from normal epithelial cells to differentiated cells is associated with a dramatic up-regulation of KIM-1 expression [17]. Besides, it was shown that KIM-1 acts as an epithelial phosphatidylserine receptor and mediates the phagocytosis of apoptotic bodies and cell debris in tubule epithelial cells, through a process known as efferocytosis [33–35]. The clearance of apoptotic and necrotic cells by KIM-1 seems to be necessary for the mitigation of inflammation and to promote tissue repair [36]. This process appears to be modulated by the alpha subunit of heterotrimeric G12 protein (Gα12) [20]. Since the activation of Gα12 (stimulated by ROS, for example) had been shown to be enrolled in the downstream injury pathways [37], it was speculated that KIM-1 may directly inhibit the Gα12 in tubular kidney and act as a renal protection mediator [20].

In addition to the knowledge about the pathophysiological role of KIM-1, it is important to highlight the main characteristics which contribute to its utility as a biomarker of kidney injury, including: the absence of KIM-1 expression in normal kidney, the markedly

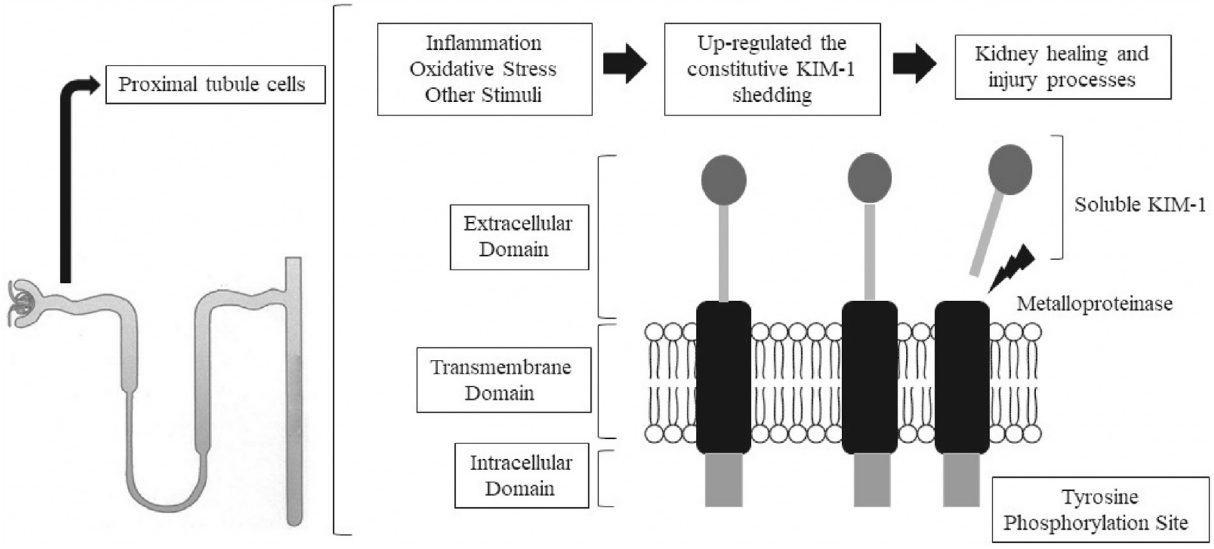

Fig. 1. Structure of KIM-1. KIM-1 is mainly expressed in the apical membrane of tubular epithelial kidney cells after kidney injury (induced by stimuli, such as inflammation and oxidative stress). The extracellular domain ok KIM-1 is shed from the cell surface into extracellular space by a metalloproteinase-dependent process from injured kidney, which releases the soluble KIM-1 and it is excreted in the urine.