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An Overview on Kidney Injury Molecule -1

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Abstract:

Kidney injury molecule 1 (KIM-1), also known as T-cell immunoglobulin mucin 1 (TIM-1), is a transmembrane glycoprotein mostly expressed by renal proximal tubular cells. The extracellular domain of KIM-1 is cleaved by matrix metalloproteinases and is present in the urine of rodents and humans after proximal tubular injury. It has been recognized as an early, sensitive and specific urinary biomarker for kidney injury, in both rodent models and in humans. In an acute setting, KIM-1 has anti-inflammatory and protective properties as it can transform epithelial cells into semiprofessional phagocytes by linking phosphatidylserine on dead cells. However, chronic overexpression in tubular cells can lead to inflammation and interstitial fibrosis. More recently, elevated circulating levels of KIM-1 in blood were associated with acute and chronic kidney damage. Beyond its capacity to serve as a receptor for virus entry (hence its other name, Hepatitis A virus cellular receptor 1), KIM-1 is also involved in immune response. Indeed, KIM-1 acts as: (i) a co-stimulatory molecule for T-cell activation, especially implicated in Th2 polarization; (ii) a pattern recognition receptor on invariant natural killer cells (iNKTs); and (iii) a regulator of B-cell proliferation and differentiation.

Keywords: Kidney Injury Molecule -1, kidney damage, inflammation.

Introduction:

Kidney injury molecule 1 (KIM-1), also known as T-cell immunoglobulin mucin 1 (TIM-1), is a transmembrane glycoprotein mostly expressed by renal proximal tubular cells. The extracellular domain of KIM-1 is cleaved by matrix metalloproteinases and is present in the urine of humans after proximal tubular injury. It has been recognized as an early, sensitive, and specific urinary biomarker for kidney injury**.** KIM-1 can be found on the apical surface of renal proximal TECs, however, a healthy kidney does not express KIM-1 but transiently upregulates its expression following an injury to the kidney **[1]**.

One of the major advantages of KIM-1 is its ability to be detected in the urine soon after kidney injury occurs. Unlike serum creatinine, which is influenced by factors such as hydration status and muscle mass, KIM-1 levels correlate more closely with tubular injury, making it a more specific and sensitive marker for AKI. Numerous studies have demonstrated that elevated urinary KIM-1 levels can be detected in both human and animal models of kidney injury well before changes in conventional clinical markers like serum creatinine or blood urea nitrogen (BUN) become evident. The early detection of kidney injury through KIM-1 is crucial, especially in settings like intensive care units (ICUs) or during surgeries that may predispose patients to ischemic or nephrotoxic injury. Identifying AKI in its initial stages allows clinicians to initiate prompt interventions, potentially preventing further renal damage and improving patient outcomes**[2].**

In addition to its role in early detection, KIM-1 has shown promise as a prognostic biomarker. Elevated levels of KIM-1 have been associated with more severe kidney damage, including progression to chronic kidney disease (CKD) in some patients. Studies have suggested that the persistence of high urinary KIM-1 levels following AKI could predict long-term renal dysfunction or even the need for renal replacement therapy. This

makes KIM-1 not only useful for acute diagnosis but also valuable in assessing the long-term prognosis of kidney injury **[2].**

STRUCTURE OF KIM-1:

KIM-1 is a type-1 membrane glycoprotein with a molecular weight of 104kDa and consists of:

•An extracellular part, containing a novel six-cysteine immunoglobulin domain, two putative sites of N-glycosylation, and a mucin domain that is rich in Threonine/Serine-Proline, where O-glycosylation of the polypeptide chain can occur **[3].**

•A transmembrane domain and A cytoplasmic domain, which is relatively short and contains a highly conserved tyrosine kinase phosphorylation site that is phosphorylated by tyrosine. This indicates that KIM-1 could act as a signaling molecule **[4]**.

The Ig-like domains mediate cell surface protein interactions, which are responsible for interactions between cells to cells and cell to matrix**.** It proposed the "lollipop on a stick" model, which states that the mucin domain functions as a configurational domain that extends the Ig-like domain sufficiently above the plasma membrane like a stalk. Mucins could be involved in cell adhesion and also protect the epithelial cellular surface **[5]**.

Molecular Structure of KIM-1 The open reading frame of KIM-1 consists of 307 amino acids. The signal sequence is of 21 amino acids, the trans-membrane spanning domain of 23 amino acids from 235 to 257, and the cytoplasmic portion consists of 50 amino acids.

The extracellular domain consists of 213 amino acids. It contains two distinct domains. Within its amino terminal is a region that is homologous to the variable regions of IgSF with respect to two cysteine residues (Cys37 and Cys108). In addition to these two residues, KIM stands unique due to the presence of four additional cysteine residues in its Ig domain. The mucin domain is from amino acids 131-201. The two putative N-glycosylation sites are found between the mucin domain and transmembrane domain **[6].**

Detection of urinary KIM-1

Two different methods for detecting urinary concentrations of KIM-1 in humans after kidney injury. One is a microbead-based enzyme-linked immunosorbent assay, which is very sensitive and specific. It requires only three 10 μl samples of urine to measure KIM-1 concentration, with an assay range of 12.21 pg/mL to 50 ng/mL. The other method is a laminar-flow dipstick assay, which is very rapid. It can provide a quantitative assessment of urinary KIM-1 concentration within 15 min, with an assay range of 195 pg/mL to 50 ng/mL **[7]** also found that increased levels of KIM-1 could be detected in the blood and serve as a biomarker of kidney injury that was not affected by liver toxicity. The size of the KIM-1 fragment in plasma and urine was similar (∼90kD) in patients with acute kidney injury and chronic kidney disease.

urinary KIM-1 concentrations were stable in urine for up to 48 h when stored at 4 °C and for up to 6 months when stored at −80 °C, independent of the addition of protease inhibitors. the concentrations of urinary KIM-1 were related to the pre-freezing and thawing time. An increasing number of freeze-thaw cycles adversely affected KIM-1 measurement. Urinary KIM-1 concentrations had no relationship with the addition of protease inhibitors and centrifugation before freezing. **Pennemans et al.2011 [4]** suggested that urine samples should be frozen within 3 h after collection and only defrosted immediately before measurement.

TYPES OF KIM-1:

KIM-1 was first identified in African green monkeys as the cellular receptor for hepatitis A virus (HAVcr-1).

Subsequently two homologs of KIM-1 were cloned in humans.

a) KIM-1a (hepatic form): cloned from liver as the homolog of KIM-

b) KIM-1b (renal form): cloned from the kidney as the homolog of HAVcr-1 These two homologs are splice variants which differ in their C-terminal part of the cytoplasmic domain. KIM-1 was recently discovered to be expressed also in activated Th-1 and Th-2 lymphocytes. Hence, it is also called Tim-1 (T-cell immunoglobulin

and mucin-containing molecule). Tim-1 is a member of closely related molecules, with 8 types found in mice (Tims1-8) and 3 in humans (Tims1, 3 and 4). Tim-1 is mainly expressed in Th-2 cells and is involved in airway hyper-responsiveness and atopic disease, whereas Tim-4 is in dendritic cells and macrophages. They act as co-stimulating molecules and positive regulators of the activity of T-cells **[8].**

Shedding of the ectodomain:

1. KIM-1 is dramatically upregulated in the dedifferentiated epithelium of proximal tubules of the kidney as an early response to injury**.** Subsequently, the heavily glycosylated ectodomain of KIM-1 is shed from the surface of the cells into the tubular lumen. This surface proteolytic cleavage of the transmembrane glycoprotein leads to the release of a soluble form of 90 kDa into the extracellular matrix, leaving a C-terminal stalk associated with the cell **[5].**

2. This process is found to be regulated by mitogen-activated protein kinase (MAPK) signaling pathway, which is induced by cell stress. The enzymes that participate in cleavage are matrix metalloproteinases (MMPs) or members of the ADAM family (a desintegrin and metalloproteinase)**.** The ectodomain that is shed in the urine is sufficiently stable for a prolonged period of time **[9].**

This adds to the value of KIM-1 as a biomarker because the expression of KIM-1 in the tissue is closely correlated with its excretion in the urine**.** The function of the ectodomain is that it interacts with integrins in the apical membrane of tubular cells, restraining their depolarization. This prevents the exfoliated cells from getting attached, producing tubular obstruction by forming casts **[10].**

KIM-1 IN KIDNEY INJURY KIM-1 has been discovered as the most highly expressed proximal tubular protein in response to renal injury. Following an acute insult, KIM-1 mRNA rapidly translates to generate massive amounts of the protein, which localizes on the proximal tubular apical membrane. In humans following ischemia or toxic renal injury, all three segments of proximal tubule show increased KIM-1 expression, although it is most prominently expressed in the S3 segment, being most susceptible to injury due to ischemia or toxins. The expression of the KIM-1 gene in the kidney correlates with the expression of the KIM-1 protein in the kidney as well as urine **[11].** The concentration of KIM-1 in the urine of healthy humans is less than 1ng/ml.

FUNCTIONAL ROLE OF KIM-1:

a) Role as a scavenger receptor: KIM-1 has been established as a functional phosphatidylserine receptor, which confers the properties of phagocytosis on the epithelial cells in the post-ischemic kidney. KIM-1 transforms the epithelial cells of the tubule into semiprofessional phagocytes. This involves not only binding to the cell surface but also triggering internalization**.** These transformed cells clear off the necrotic and apoptotic cell debris from the tubular lumen, which is critical for remodeling following injury, hence relieving intratubular obstruction. KIM-1 has been found to be the first epithelial cell scavenger receptor, which is found in non-myeloid cells. KIM-1 also has the properties of macrophage scavenger receptor type B that binds oxidized LDL **[12].**

b) Anti-inflammatory role: KIM-1 has an anti-inflammatory role by mediating phagocytosis. This protective effect is mucin domain-dependent. KIM-1 interacts with p85, and subsequently, PI3K mediates the downregulation of NFkB. This culminates in a decline in the TLR-4 expression, reduced pro-inflammatory cytokines, and macrophage activity. This protects the kidney by dampening inflammation and innate immunity **[13].**

c) Role in immunity: In the immune system, KIM-1/TIM-1 mediates the activation of Th1, Th2, and Th17 differentiation by acting as a surface receptor on T-cells, interacting with antigen-presenting cells. It also functions as a receptor that activates the natural killer T-cells, dendritic cells and B-cells **[14].**

d) Adhesion molecule: KIM-1 has many roles in epithelial function. It interconnects the cells to one another and also tethers the epithelial cells to the extracellular matrix **[10].**

e) Role in regeneration and repair: Following an acute insult, KIM-1 plays an important role in maintaining the morphological and functional integrity of the kidney **[15].**

The surviving epithelial cells undergo cell locomotion, proliferation, and dedifferentiation mediated by KIM-1, which is necessary for the regeneration and repair of the injured epithelium. KIM-1 is involved in the migration of dedifferentiated cells, hence facilitating the reconstitution of continuity of the epithelial layer **[10]**.

KIM-1 IN KIDNEY INJURY

Acute kidney injury (AKI) may be the result of shock conditions and acute cardiovascular insufficiency, toxic or septic injury, or urinary duct obstruction **[16]**. The most common cause of AKI is ischemia, which leads to the death and exfoliation of tubular epithelial cells from the basement membrane. AKI is a potentially reversible disorder since the kidney tubule epithelium possesses high regeneration ability. The cells with preserved viability undergo epithelial-mesenchymal transition, proliferate, and migrate to the areas of the exposed basement membrane, where they return to the differentiated epithelial phenotype **[17].**

Following an acute insult, KIM-1 mRNA rapidly translates to generate massive amounts of the protein, which localizes on the proximal tubular apical membrane. In humans following ischemia or toxic renal injury, all three segments of the proximal tubule show increased KIM-1 expression, although it is most prominently expressed in the S3 segment, being most susceptible to injury due to ischemia or toxins. **[10].**

In AKI, KIM-1 is directly involved in the processes of preservation and restoration of the structural and functional integrity of the epithelium of proximal nephron compartments. KIM-1 may induce phagocytosis of dying cell residues, thereby cleaning the proximal tubular lumen from cellular debris and decreasing the probability of filtrate flow impairment **[18].** An increase in KIM-1 expression on the surface of the proximal tubular epithelial cells is induced by the presence of albumin in the glomerular filtrate **[19]**. In this case, KIM-1 can capture albumin from the primary urine and carry it into the cell, which supplements the main receptor mechanisms of protein reabsorption in the kidneys in severe proteinuria **[19]**

KIM-1 possesses the properties of an ideal marker of renal proximal tubule epithelium injury **[3]** in the normal kidney, KIM-1 expression is determined in trace quantities; in ischemic or toxic kidney injury, activation of KIM-1 synthesis in the cells of the damaged tubules and its increased expression on the apical cell membrane is observed; shedding of KIM-1 from the cell surface results in a considerable increase of its content in urine and/or in the circulating blood. The expression of the KIM-1 gene in the kidney correlates with the expression of the KIM-1 protein in the kidney as well as urine. **[11].**

KIM-1 expression in the epithelial cells of the renal proximal tubules and its concentration in urine and blood plasma correlate with the severity of the pathological process in the kidneys **[3].** Elevation of KIM-1 level in urine (uKIM-1) is a more sensitive indicator of AKI than the reduction of creatinine clearance or albuminuria. It is underlined that enhanced excretion of KIM-1 in urine is highly specific for the conditions caused by kidney injury since, due to a large molecular mass, free KIM-1 entering the blood from extrarenal sources is not filtered through the glomerular barrier **[20]**

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