Kim-1/Tim-1: from biomarker to therapeutic target?*

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The best biomarkers turn out to be important in pathogenesis and some become therapeutic targets—a paradigm illustrated beautifully by the herceptin receptor in breast cancer [1]. A paper in the May issue of the Journal of Clinical Investigation raises the exciting possibility that the renal biomarker, kidney injury molecule-1 (Kim-1), may become an equally important example [2].

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 acute kidney injury (AKI) [3]. Although undetectable in normal rat kidney, Kim-1 is abundantly expressed by proliferating and dedifferentiated renal proximal tubular epithelial cells 48 h after acute ischaemic injury in kidneys examined by in situ hybridization and immunohistochemistry. The human orthologue was also identified and behaved identically. The authors concluded that ‘Kim-1 may play an important role in the restoration of the morphological integrity and function to post-ischaemic kidney’. However, subsequent data demonstrating Kim-1’s exceptional promise as a urinary biomarker for proximal tubular injury diverted much attention from its pathophysiological role.

The selective expression by injured proximal tubular cells provides the foundation for Kim-1’s use as a biomarker. Furthermore, it is cleaved from the surface of activated tubular cells and released into the urine by a metalloproteinase [4]—a process regulated by the MAP kinase signalling pathways activated by cell stress [5]. This results in a close correlation between Kim-1 expression in the tissue and its excretion in urine [6], adding to its value as a biomarker. The development of sensitive immunoassays for urinary Kim-1 [6,7] prompted an avalanche of studies over the past 2 years that confirm its effectiveness as a biomarker for AKI in both rodents [6,8–10] and in man [7,11–14], regardless of whether precipitated by ischaemia, nephrotoxic drugs or even renal transplantation [13]. Kim-1 excretion may even predict the severity and outcome of AKI [14]. Rats with heavy proteinuria induced by protein overload nephropathy have increased urinary Kim-1 excretion [15] as do some patients with chronic kidney disease who may be at risk of progressive renal failure [16]. In the face of these data, it is not surprising that nephrological interest has focussed mainly on the practical use of Kim-1 rather than its function, but this should change following the recent report by Ichimura et al. [2].

This report addressed the question of how cells that had undergone death by apoptosis and other debris are cleared from the lumen of renal tubules in AKI—a process essential for tissue remodelling and restoring normal tissue integrity in other settings [17]. In solid tissues, this is achieved by macrophages that recognize phosphidylserine (PS) on the surface of apoptotic cells where it provides an ‘eat me’ signal that ensures that apoptotic cells are phagocytosed without inducing inflammation [18]. The absence of macrophages means that other mechanisms are required to deal with the removal of apoptotic cells from epithelial surfaces such as renal tubules, bronchial airways, etc., but these are far from clear. One possible mechanism for the epithelial cells themselves would be to have evolved specific high-capacity mechanisms for the uptake of apoptotic cells as an alternative to macrophages. Indeed, one such system has been described for the specific removal of apoptotic cosinophils by airway epithelium [19]. Ichimura et al. [2] now provide a compelling case that activated renal proximal tubular epithelial cells also phagocytose apoptotic cells utilizing Kim-1 as a critical receptor.

The authors make four key observations: firstly, they show that surviving proximal tubular cells ingest apoptotic cells that can be seen within Kim-1 lined phagosomes 24 and 48 h after acute ischaemic injury to the kidney. Secondly, they demonstrate that Kim-1 expression is heterogeneous in this model and that the uptake of apoptotic cells is substantially greater in tubules that express Kim-1 than in those that do not. Next, they analyse the role of Kim-1 in phagocytosis of apoptotic cells by renal tubular epithelium; these experiments confirm previous reports that Kim-1 is a functional phosphidylserine receptor that induces
phagocytosis of apoptotic cells [20–22], and they demonstrate Kim-1’s predominant role in the uptake of apoptotic cells by renal tubular epithelium. Finally, they show that Kim-1 also binds oxidized LDL and has the properties of a Type B macrophage scavenger receptor. Taken together, these results provide a compelling case that Kim-1 has a central role in the removal of dying cells and other debris from the injured tubule, thus facilitating repair. This of course remains to be proved, but it raises the exciting prospect of novel treatment strategies for AKI targeted at Kim-1. Studies designed to explore the consequences of manipulating tubular expression of Kim-1 would need to be based on a more general knowledge of its function.

Kim-1 has been discovered three times in different contexts: first as the hepatitis-A cellular receptor (HAVCR) in green monkeys (and subsequently in man) that facilitated the cellular entry of the virus [23]. HAVCR corresponds to the hepatic form of Kim-1 (Kim-1a) that is one of the splice variants that differ only in the cytoplasmic tail. Specifically, Kim-1a lacks the conserved tyrosine-phosphorylation signalling motif found in the renal form (Kim-1b). Neither the significance of this difference nor Kim-1b’s role is known. Kim-1 was subsequently discovered independently during a search for molecules differentially expressed on Th1 and Th2 lymphocytes and given the name T-cell immunoglobulin and mucin-containing molecule or Tim-1 [24]. Tim-1 has been subjected to intense studies by immunologists, and their results have important implications for nephrologists studying Kim-1 in the kidney (reviewed in [25,26]).

Tim-1 is one of the members of a family of related molecules with eight members in mice (Tim-1–8) and three in men (Tim-1, 3 and 4) encoded by genes adjacent to the IL4, IL5 and IL13 cluster, respectively, on mouse chromosome 11B1.1 and human chromosome 5q33.2 [24]. They function as T-cell co-stimulatory molecules that have powerful effects in the balance between helper and regulatory T-cells and the bias towards either Th1 or Th2 responses (reviewed in [25,26]). Tim-1 is expressed predominantly on Th2 cells and Tim-4—a natural ligand for Tim-1—is expressed on macrophages and dendritic cells [27]. Detailed structure and function studies published last year provide information directly relevant to understanding how Kim-1/Tim-1 functions in the kidney, by demonstrating that Tim-1/Kim-1 is a PS receptor responsible for the uptake of apoptotic cells and exosomes [20–22]. They also showed that a narrow groove in the immunoglobulin domain facilitates homophilic interactions with other Tim-1/Kim-1 molecules [28] and with PS [22], thus explaining its action as a PS receptor. Two other insights from lymphocyte studies are relevant to understanding Kim-1’s function in the renal tubule: first, monoclonal antibodies to Tim-1 can either be stimulatory or inhibitory depending on which parts of the molecule they recognize [29], and second, the concentration of Tim-1 ligand determines whether the effect is stimulatory or inhibitory [25]. This knowledge will have to be considered when designing experiments or therapeutic strategies to manipulate Kim-1 function in the kidneys that are now inevitable.

The real importance of the Ichimura paper is to demonstrate Kim-1’s role in the clearance of debris from the damaged renal tubule. This opens new avenues for research that might provide the foundations for novel treatments to protect the kidney from acute injury or to promote its repair. More needs to be known about the precise Kim-1/Tim-1 in renal injury and repair. An obvious question is: would increased Kim-1/Tim-1 expression enhance renal protection from nephrotoxic insult? It is equally important to understand more about the function of soluble Kim-1/Tim-1—for example, would inhibiting its release or neutralizing its activity in urine be beneficial or harmful. More speculatively, it will be important to know whether Kim-1/Tim-1 gains access to the interstitial space and modulates macrophage or T-cell function. Lastly, genetic polymorphisms of Kim-1/Tim-1 have major effects on their function in the immune system and specifically in determining susceptibility to autoimmune and allergic diseases [25,30]. It will now be important to know whether these polymorphisms also affect susceptibility to Kim-1/Tim-1 activity in the kidney, perhaps by influencing susceptibility to AKI or to progressive renal injury. Answers to these questions will emerge over the next few years, and it will be exciting to find out whether they lead on to novel therapeutic strategies.

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References


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