Kim-1/Tim-1 and Immune Cells: Shifting Sands

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Kim-1/Tim-1 and Immune cells: Shifting Sands

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Abstract

Kim-1/Tim-1 is an apoptotic-cell phagocytosis and scavenger receptor that is most highly upregulated in proximal tubular epithelium in acute and chronic kidney injury. While Kim-1/Tim-1 has been proposed to be a costimulatory molecule for immune cells, its potential immunological role has been controversial. In the presence of very high epithelial cell expression understanding the influence of immune cell Kim-1/Tim-1 expression in kidney injury relies on a better definition of its functional significance in immune cells and better characterization of antibodies used to probe function.

Kidney <3> (Figure 1) injury <4> molecule-1/T-cell immunoglobulin and mucin domain-containing protein-1 <5> (KIM-1/TIM-1 in humans, Kim-1/Tim-1 in rodents) is a type 1 membrane receptor1,2 that is the most highly upregulated protein in the proximal tubule of the injured kidney (Figure 1) [1]. It has also, to varying degrees, been reported to be expressed on immune cells. [2, 3]. In the kidney Kim-1 is upregulated in a wide variety of human diseases and in various animal models [1]. A large amount of KIM-1 protein is also shed into the urine, making it a useful urinary biomarker for kidney injury [1]. Kim-1 functions as a phosphatidylserine (PS) receptor which recognizes and internalizes apoptotic cells [4]. Kim-1 also functions as a scavenger receptor, mediating the uptake of modified low density lipoprotein and necrotic cell debris [4]. Kim-1 expression transforms proximal tubular epithelial cells into semiprofessional phagocytes. In the immune system, Kim-1/Tim-1 has been implicated in activation of Th2, Th1 and Th17 differentiation [2]. It has also been proposed to be an activating receptor in B cells, dendritic cells and natural killer T cells [2, 3, 5, 6]. Many of the experiments leading to these conclusions have relied on antibodies against Kim-1/Tim-1, which have been presumed to be agonists or antagonists, or Kim-1/Tim1-Fc fusion proteins as key reagents [2].

In this issue of Kidney International, Nozaki and colleagues report that a low avidity anti-Tim-1 antibody RMT1-10* , used as an antagonist of Kim-1/Tim-1, suppressed T cell immune responses and glomerular/tubulointerstitial changes in a model of disease induced by anti-glomerular basement membrane globulin [7]. Treatment with RMT1-10 reduced crescentic glomerulonephritis and Th1/Th17 cellular responses in both systemic immune cells and within the kidney while increasing renal foxp3+ cell and interleukin-10 mRNA, characteristics of regulatory T cells and Th2 cells, respectively. Two other studies have recently demonstrated a partial protection of kidneys by the same RMT1-10 antibody in acute kidney injury (AKI) induced by cisplatin or ischemia reperfusion [8, 9]. The authors of

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Disclosure: Takaharu Ichimura and Joseph V. Bonventre are co-inventors of KIM-1 patents that are assigned to Partners Healtcare and licensed by Partners to J and J, Sekisui, BiogenIdec and a number of research reagent companies. JVB is a consultant for Sekisui.

*This antibody may not be identical to the commercially available antibody with the same name (Kane L: T cell Ig and mucin domain proteins and immunity. *J Immunol* 184:2743-2749, 2010).

these studies also concluded that Kim-1/Tim-1 mediated activation of detrimental T cell and/or innate immune responses [8, 9]. Activation of injurious T helper 1 (Th1) cells was inhibited or Th1-related cytokines were diminished by RMT1-10. In the study by Nozaki and colleagues, however, a significant portion of the injected RMT1-10 antibody was shown to accumulate at proximal tubules where Kim-1 is expressed [7]. Given the very high expression of Kim-1/Tim-1 in the kidney relative to its expression in immune cells, care must be taken to interpret the results achieved with the antibody (Figure 1).

Questions have also been raised concerning the RMT1-10 antibody. RMT1-10 was shown to stimulate (not antagonize) Tim-1 on regulatory B cells, a newly identified population whose function in kidney injury is not clear [6]. In addition, RMT1-10 has been reported to be an antagonist of Th1/17 activation and also induced Th2 cytokine expression [2], indicating that the mechanism by which RMT1-10 affects T cell activation is not well defined. Conversely, 3B3 antibody stimulates Th1 activation, even though it binds to the same domain of Tim-1 as RMT1-10 [2]. Recently, using Tim-1 knockout and transgenic mice it was reported that RMT1-4 is the only commercially available Tim-1 specific monoclonal antibody (RMT1-10 was not mentioned) [5]. These studies suggest that the current model for the role of Tim-1 in T cell activation may require revision and the antibody approach requires better definition of mechanism of action.

Several recent findings have suggested that the widely held notion that Tim-1 is a Th2 regulator, requires reconsideration [2]. In studies using Kim-1/Tim-1 knockout mice, Tim-1 expression was very low (or nonexistent) in activated T cells or Th2 cells [2, 5]. Additionally, the Tim-1 knockout study demonstrated that Tim-1 may weakly contribute to inflammatory lung injury but not to Th2 cell activation [2, 5]. Transgenic expression of Tim-1 in T cells did not stimulate Th2 differentiation [2, 5]. Rather, Tim-1 expression was proposed to be present in subsets of activated B cells, dendritic cells and invariant NKT cells [2, 3, 5], each of which have been implicated in the pathophysiology of kidney injury [10]. The potential function of Tim-1 in renal dendritic cells has not been well characterized [3]. To test the specificity of Tim-1 function in T cells, Rag-1-/- mice were used to evaluate T cell function in cisplatin and ischemia induced kidney injury [8, 9]. However, these mice lack both T and B cells. Splenocytes (which contain both T cells and B cells) were used for the adaptive transfer in the ischemia study [9]. Therefore, cells other than T cells might be contributing to the observed effects in Rag-1-/- mice.

Following kidney injury, numerous proximal tubules become KIM-1 positive and copious amounts (nanogram levels) of soluble KIM-1 protein are shed into extracellular spaces, including the urine [1, 4, 7]. In contrast, few T cells are present in the injured kidney [7-9] and a very small portion of the activated T cells have been proposed to be Kim-1/Tim-1 positive [7]. For instance, in the report by Nozaki and colleagues Kim-1/Tim-1 positive T cells account for only 2% of all activated CD4+ cells, and very few interstitial CD4+ T cells (1.3 cells/hpf) are found in the GN kidney model [7]. Additionally, immunostaining of Kim-1 in rodent AKI showed an absence of interstitial Kim-1, suggesting Kim-1/Tim-1 expression is predominantly restricted to the tubules [4]. Consequently, there is a dramatic imbalance between nominal Tim-1 expression on a minority of T cells and abundant kidney tubular Kim-1 expression. The abundant amount of tubule and soluble Kim-1/Tim-1 may potentially sequestrate administrated anti-Kim-1/Tim-1 blocking antibodies, as evident in binding of the injected RMT1-10 antibody to the apical side of tubules in the GN model [7]. Thus, inhibitory antibodies may not be the most efficient means of manipulating Kim-1/Tim-1 function on immune cells and T cells may not express very much Kim-1/Tim-1.

Thus, there remain many caveats in interpreting data using antibodies against Kim-1/Tim-1. Antibody blocking experiments will require a standardized antibody with well characterized

functional properties and high specificity to Kim-1/Tim-1. In addition Kim-1/Tim-1 cell type specific knockout or transgenic mice, such as CD3 derived T cell or B cell specific transgenic mice and Kim-1/Tim-1 knockout mice [5] can be used to assess the role of Kim-1/Tim-1 in immune cells during kidney injury. Cells isolated from Tim-1 knockout or transgenic mice can also increase the specificity of adaptive transfer experiments. It is likely that Kim-1/Tim-1's phagocytosis/endocytosis function is crucial in tubular injury and repair. Therefore phagocytosis specific functional knockout (mutant) mice and/or Kim-1 specific conditional knockout/transgenic mice should be utilized to evaluate Kim-1's function in the proximal tubule and the immune system. Even though obstacles remain, studies such as those of Nozaki et al using reagents that interfere with or activate Kim-1/Tim-1 should give us important insights into disease mechanisms and potentially lead to specific Kim-1/Tim-1 targeted therapies in humans.

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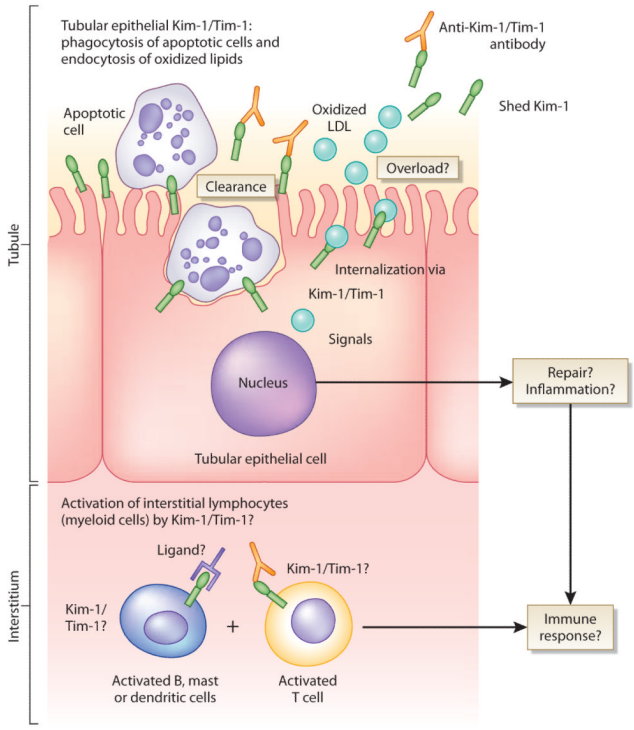

Figure 1.

Kim-1/Tim-1 is expressed in injured proximal tubule epithelium and shed but may also be expressed in activated lymphocytes and/or myeloid cells in injured kidney. Tubular Kim-1/Tim-1 promotes clearance of apoptotic and necrotic cells but may also contribute to uptake of oxidized lipids if its expression is prolonged. A large amount of Kim-1/Tim-1 is shed to extracellular spaces. It has been proposed that Kim-1/Tim-1 may also be expressed, albeit at much lower levels, by activated lymphocytes and/or myeloid cells in injury-induced immune response. Antibodies can activate cells or prevent ligand binding to Kim-1/Tim-1. They also may interact with shed Kim-1/Tim-1.