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VISTA-dependent role of resident macrophages in kidney homeostasis and inflammation

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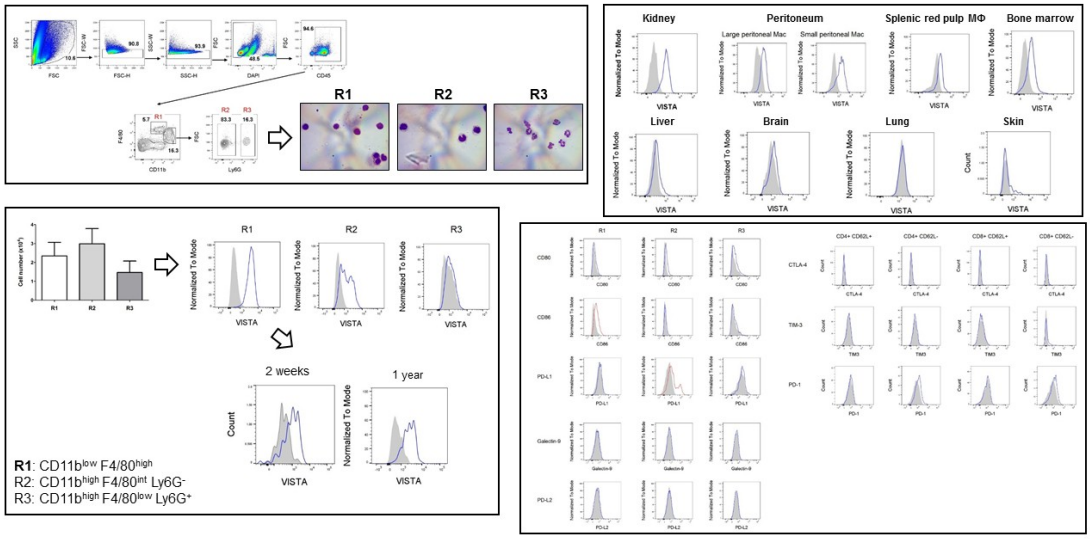
Objectives: V-domain Ig suppressor of T cell activation (VISTA), expressed primarily on antigen-presenting cells, has been known to participate in the progression of cancer through an immune checkpoint. Nevertheless, both the expression pattern and role of VISTA within kidney environment remain unresolved.

Methods: .

Results: Mouse kidney myeloid cells were categorized based on the expression of CD11b and F4/80 as follows: kidney resident macrophage (rMΦ) ($CD11b^{int}$ $F4/80^{high}$), bone marrow-derived MΦ ($CD11b^{high}$ $F4/80^{int}$ $Ly6G^{-}$), and neutrophils ($CD11b^{high}$ $F4/80^{low}$ $Ly6G^{+}$). Kidney rMΦ expressed CD11c, MHC II, CD86, and CX3CR1 together, but did not express CD80, Ly6C, Ly6G, CD115, or CCR2. When rMΦ was predominantly depleted by clodronate liposome, the degree of ischemic renal injury (IRI) was reduced. Intriguingly, all rMΦs expressed VISTA in normal kidneys, but not other immune checkpoints, including CD273, CD274, or galectin-9. The VISTA expression of rMΦ differed between organs: high expression was found only in the kidneys and peritoneum. The high VISTA expression in kidney rMΦ was retained throughout the life and even after IRI. In the VISTA overexpression experiments, using bone marrow-derived MΦ and dendritic cells, VISTA increased the efferocytotic efficacy against apoptotic cells and conferred negative signals to antigen-presented T cells. It has been known that the kidney rMΦ is scarcely replaced by the bone marrow-derived cells in adulthood. When this issue was addressed in the post-inflammatory environment using parabiosis mouse model (parabionts were harvested after 1 month of unilateral IRI), the proportion of rMΦ originated from paired parabionts was higher in injured kidneys than in counterpart non-injured kidneys, and their VISTA expressions were high irrespective of origins.

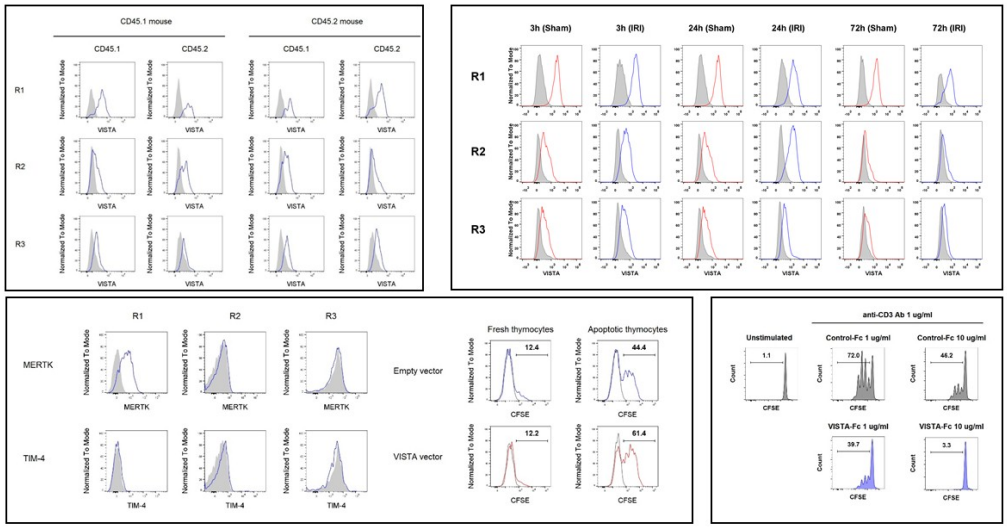
Conclusions: These data indicate that VISTA, distinctively shown in kidney rMΦ and highly maintained within kidney environment, functions via phagocytosis and crosstalk with lymphocytes in both homeostatic and inflammatory status.

Figure 1. Characterization of kidney resident macrophages



Kidney resident macrophages highly express VISTA, which is a distinctive pattern compared to other resident or infiltrating leukocytes

Figure 2. Functional assay depending on the VISTA expression in kidney resident macrophages



Kidney environment determines the expression of VISTA, and its role includes phagocytosis and negative regulating of T cell activation.