Renal Dendritic Cells: An Update

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Key Words

Renal dendritic cells · Renal parenchyma · Immunology

Abstract

Discovery into the role of renal dendritic cells (rDCs) in health and disease of the kidney is rapidly accelerating. Progress in deciphering DC precursors and the heterogeneity of monocyte subsets in mice and humans is providing insight into the biology of rDCs. Recent findings have extended knowledge of the origins, anatomy and function of the rDC network at steady state and during periods of injury to the renal parenchyma. This brief review highlights these new findings and provides an update on the study of rDCs.

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Steady-State Anatomic and Functional Relationships

Renal dendritic cells (rDCs) are major constituents of the mononuclear phagocytic system (MPS) within normal kidneys [1, 2], but the formation and maintenance of the rDC network is not yet fully understood. rDCs derive from a common bone marrow macrophage and DC precursor, which also gives rise to circulating and patrolling $\text{Csflr}^+\text{Gr1}^+$ and $\text{Csflr}^+\text{Gr1}^-$ blood monocytes [3, 4]. Although yet poorly understood for the kidney, studies in other nonlymphoid and lymphoid organs suggest that $\text{Csflr}^+\text{Gr1}^-$ or $\text{Csflr}^+\text{Gr1}^+$ blood monocytes or perhaps nonmonocyte ‘pre-DCs’ may serve as precursors for rDCs

during cellular turnover within the renal MPS [3–6]. Recent characterizations of the renal MPS suggest that rDCs, phenotyped as Gr1^- , may derive from ‘noninflammatory’ $\text{Csflr}^+\text{Gr1}^-$ blood monocytes [7, 8]; however, speculation remains that rDCs at steady state might also convert or mature from ‘inflammatory’ $\text{Csflr}^+\text{Gr1}^+$ blood monocytes, particularly following resolution of renal inflammation [4]. Intriguingly, studies utilizing Csflr-EGFP mice have shown that the renal MPS begins to form in the renal interstitium prior to nephrogenesis [9], raising the possibility that vestigial niches of intrarenal ‘pre-DCs’ might reside within the mature kidney as well. Further research is needed to determine the contribution of these potential intrarenal and circulating sources towards maintenance of the rDC network at steady state.

Wherever the precursors for the mature rDC network reside anatomically, the major ligand for Csflr , macrophage colony-stimulating factor, and for Flt3 , Flt3 ligand (Flt3L), are emerging as two of its central poietins. Several groups have now demonstrated that granulocyte macrophage colony-stimulating factor-derived DCs, whether propagated from bone marrow cultures *ex vivo* or detected *in vivo*, represent inflammatory DCs, not DCs at steady state as originally conceived [3]. Flt3L -derived DCs are phenotypically similar to DCs at steady state [3], however, and recent studies in nonhuman primates recapitulate murine studies which showed transient increases in all rDC subsets with administration of Flt3L [10]. Similar to the requirement for ligation of Flt3 for homeostatic DC development in peripheral lymphoid tissues [11], disruption of the Flt3-Flt3L interaction in

Fig. 1. Trophic interactions between rDCs and renal epithelial cells cocultured in 3-dimensional collagen matrices. **a** The fecundity of rDCs ex vivo is captured by measuring over a 5-day period the morphologic area of spreading and number of GFP⁺ rDCs isolated from CX₃CR1^{GFP/+} mice by confocal microscopy. rDCs cultured alone (○) do not spread, whereas rDCs cocultured with mouse IMCD-3 renal epithelial cells (●) survive, proliferate and spread, suggesting trophic, paracrine interactions between rDCs and renal epithelial cells. **b** Images captured by confocal microscopy at day 5 showing the following: GFP⁺ rDCs cultured alone [left panel: small green cells (white in the printed version) in the low-power tile scan (2.2 × 2.2 mm)]; mouse IMCD-3 cells cocultured with GFP⁺ rDCs (middle panel: larger, stellate-shaped green cells (white in the printed version) in the low-power tile scan (2.2 × 2.2 mm)), and a high-power view of branching mouse IMCD-3 tubules (right panel; arrows show the upper border of a tubule; high-power ×63 objective) intimately associated in coculture with GFP⁺ rDCs. Unlike rDCs cultured alone (left panel), rDCs cocultured with renal epithelial cells survive, proliferate and morphologically differentiate (middle panel).

vivo may cause a severe deficiency in rDCs [A. Thomson, pers. commun.]. While it is yet unclear whether Flt3L is produced by the renal parenchyma as a trophic factor for rDCs, macrophage colony-stimulating factor is known to be expressed by renal epithelial cells [1] and to maintain conventional and plasmacytoid DCs [12]. In support of this, we have found that tissue-resident mouse rDCs isolated from normal kidneys of adult CX₃CR1^{GFP/+} mice survive and proliferate rather than die when cocultured with mouse renal epithelial cells ex vivo (fig. 1). This con-

served ability to proliferate ex vivo suggests that at least a subset of rDCs is not terminally differentiated in vivo.

Experimental evidence is mounting that rDCs help to maintain peripheral tolerance in the kidney at steady state [1]. Exogenous, nonself antigen introduced into normal kidneys is captured by rDCs and presented in draining renal lymph nodes, leading to immune activation and proliferation of antigen-specific CD4⁺ T lymphocytes [13]. Notwithstanding, normal kidneys must also continually process glomerular ultrafiltrates of blood along the

course of nephrons that may contain otherwise harmless endogenous antigens without loss of tolerance to these potential urinary antigens. This was discovered to occur in part through rDC-independent cross-tolerance of CD8⁺ lymphocytes to these soluble filtrated antigens after bulk transport of the antigens to renal lymph nodes [14]. Any additional role of major histocompatibility complex transfer between rDCs and extrarenal DCs [15] in generating this renal immunity to exogenous antigens versus renal tolerance to endogenous antigens is unclear.

rDCs in Renal Inflammation

Using specific markers to localize rDCs in human biopsy specimens, several new studies have demonstrated renal compartment-specific accumulation of rDC subsets during renal inflammation; however, the pathogenic role of this unique rDC traffic is poorly understood. BDCA1⁺ conventional and BDCA4⁺ plasmacytoid rDCs accumulate in the renal interstitium [16], whereas BDCA2⁺ plasmacytoid rDCs preferentially accumulate in glomeruli [17], in patients with active lupus nephritis. Likewise, DC-SIGN⁺ conventional rDCs are not readily detected in diseased glomeruli in other nonproliferative and proliferative glomerular diseases, whereas they occur in abundance, along with BDCA2⁺ plasmacytoid rDCs, in the renal interstitium [18]. In some cases, tertiary lymphoid aggregates composed of CD21⁺ follicular rDCs and CD20⁺ B lymphocytes have been detected in the renal interstitium [19, 20]. Of note, these aggregates have been observed in other nonrenal inflammatory diseases, suggesting a conserved immunologic program executed by DCs, whether resident or recruited [20]. Interestingly, paracrine communications at previously unrecognized renal neuron-rDC interfaces may be an important factor in rDC-mediated inflammation [21].

While these reports posit a positive correlation suggesting causality between the extent of inflammatory rDC accumulation and renal parenchymal injury, preliminary studies in animal models suggest a more complex role. After sequentially ablating accumulating inflammatory CD11c⁺ rDCs and all other intrarenal and extrarenal CD11c⁺ DC subsets in mice with experimental nephrotoxic nephritis, tubulointerstitial and glomerular injury was observed to be aggravated, not ameliorated [22]. This may be due to a need for inflammatory CD11c⁺ rDCs to induce intrarenal CD4⁺ T lymphocytes to produce IL-10 that may attenuate other proinflammatory cy-

tokines [22, 23]; however, given the simultaneous ablation of all other intrarenal and extrarenal CD11c⁺ DC subsets in these studies, several other compensatory immunocytoprotective mechanisms may have been disrupted [24, 25]. In contrast with these potential anti-inflammatory mechanisms is the recent finding that rDCs facilitate the recruitment of detrimental CD4⁺ T lymphocytes secreting IL-17 following experimental acute urinary obstruction [26]. One possibility that may explain this dichotomy is the dual role of TGF- β , which can be produced by DCs and drives the development of regulatory T lymphocytes or Th17 effector T lymphocytes depending on additional cues [27]. Further research is needed to determine the dynamic pathogenic roles of steady-state and inflammatory rDCs during injury to the renal parenchyma, inquiries that will be aided by the development of specific rDC subset ablation systems limited to the kidney [24, 25].

rDC Surveillance in Acute Kidney Injury

Experimental acute kidney injury models are providing insights into the complexity of immunologic surveillance by rDCs [1]. Recent reports suggest that endogenously expressed ligands for Toll-like receptors contribute to activation of rDCs during renal ischemia-reperfusion injury [28]. In contrast, local and systemic inflammation during lipopolysaccharide-induced acute kidney injury may not be sufficient to activate rDCs [29]. Likewise, the acute hypoxia of renal ischemia-reperfusion injury is a presumed stimulus favoring maturation of rDCs via hypoxia-inducible factor-1 α activation [30], but the contribution of hypoxia as compared to that from other stimuli towards further pro- versus anti-inflammatory activation of rDCs is unclear [31]. For example, hypoxic preconditioning before renal ischemia-reperfusion can also be cytoprotective, marked by the induction of heme oxygenase-1, which may contribute to suppressed maturation of rDCs [32] and their functional role via regulatory T lymphocytes [33]. These paradoxical findings are also exemplified by the recent speculation that Tamm-Horsfall protein, an endogenous renal ligand for Toll-like receptor-4, is protective in renal ischemia-reperfusion injury via rDCs [34]. Together, these studies indicate that much remains to be learned about the integration and timing of various environmental cues in the sentinel priming of tissue-resident rDCs towards immunity and tolerance [35].

Conclusion

Recent research supports the paradigm that rDCs function at the nexus of innate and adaptive immunity, self-tolerance and tissue homeostasis within the kidney. It is clear that studying the communication between rDCs and other renal parenchymal cell types promises to yield insights into the maintenance and immune modulation of rDCs by homeostatic and environmental cues. While advances have been made in characterizing subsets of tissue-resident and infiltrating rDCs at steady state and during renal injury, further research is needed to determine the surveillance and effector function of these

subsets, both within the kidney and after their egress to secondary lymphoid organs. Together, these future inquiries should uncover strategies towards modulating rDCs for therapeutic benefit in various kidney diseases.

Acknowledgments

We thank Angus Thomson for helpful discussions on the development of rDCs and Lloyd Cantley for helpful discussions on IMCD-3 cells. This work was supported by the National Institutes of Health grants DK078153 (P.V.), AI055037 (M.L.D.), DK065498 (P.J.N.) and DK079498 (P.J.N.).

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