Dendritic Cells in the Kidney

Rohan John† and Peter J. Nelson†
†Division of Nephrology, New York University School of Medicine, New York, New York

ABSTRACT
Dendritic cells (DC) in nonlymphoid organs function at the crossroads of innate and adaptive immunity, self-tolerance, and tissue homeostasis. This review provides an overview of the study of DC in the kidney, tracing its history leading to the current knowledge of the origins, migration, and function of renal DC. Together, these studies suggest that renal DC play a critical role in the health and disease of the kidney, opening the way to direct targeting of renal DC for therapeutic benefit.

Dendritic cells (DC) have been extensively studied in lymphoid and many nonlymphoid organs in the past three decades but have received comparatively little attention in the kidney. One reason for this disparity has been an apparent difficulty in identifying, isolating, and manipulating renal DC (rDC) in vitro and in vivo to gain a better understanding of their function in the kidney. These barriers to the study of rDC have fallen in recent years, and it is now clear that rDC exist in intimate communication with the entire renal parenchyma, constantly surveying for and responding to local environmental cues. Here, we review the history of the identification of the rDC network; the origins and migration of rDC at steady state; and the function of rDC in innate and adaptive immunity, self-tolerance, and homeostasis of the renal parenchyma.

IDENTIFICATION OF THE RDC NETWORK

Ground-breaking studies in the 1970s by Steinman and colleagues1,2 identified and functionally segregated “dendritic cells” from other immunocytes in lymphoid organs. This led to the discovery that splenic DC potently stimulated the proliferation of T lymphocytes in mixed leukocyte reactions and expressed surface Ia antigens,3 identifying DC as MHC class II+ rDC in rat kidney were subsequently recognized in 1981 by the existence of resident MHC class II+ cells with stellate and “mononuclear phagocyte” morphology in the renal interstitium4,5 and mesangium.6 These anatomic locations were subsequently confirmed by electron microscopy7,8; however, proof that rDC alloactivate T lymphocytes, similar to DC isolated from lymphoid tissues, was not reported until 19949 or substantiated until more recent-ly,10–12 after the ability to isolate rDC via CD11c (the integrin α chain) expressed by differentiated mouse DC.13 Similar to other DC, differentiated rDC were also characterized as “immature” versus “mature” on the basis of their low versus high expression of co-stimulatory molecules, respectively.

Several functional subsets of DC have now been phenotyped,13–18 and some of these subsets have been identified in the kidney using defined markers (Table 1). Within normal mouse kidneys, >90 to 95% of CD11c+ rDC are negative for CD8α and CD45RA (B220),10,12,19 indicating that the majority of mouse rDC are of the myeloid lineage and major constituents of the mononuclear phagocyte system within the kidney.19,20 Small numbers of lymphoid (CD11c+CD8α–B220+) rDC have also been detected within mouse kidneys.10,19

Within normal human kidneys, myeloid (BDCA-1+DC-SIGN+ and BDCA-1+DC-SIGN+) and preplasmacytoid (BDCA-2+DC-SIGN+) rDC were recently identified, and on the basis of the quantitative area of positive staining for BDCA-1 versus BDCA-2 in thin sections, preplasmacytoid rDC represent a greater fraction of total rDC in normal human kidneys as compared with normal mouse kidneys (up to 20% versus <10%, respectively).10,19,21 Whether mouse or human kidneys harbor or recruit any of the most recently defined functional DC, such as IFN-producing killer DC,22,23 inflammatory TNF-α-inducible nitric oxide synthase–producing DC,24,25 and tolerogenic IDO-expressing DC,26–31 is unclear.

Unequivocal evidence that rDC form a true anatomic surveillance network within the renal parenchyma, rather than a random dispersion at steady state, was determined by examination of rDC in situ in the kidneys of CX3CR1GFP+/+ mice (Figure 1).18 Under intravital and confo
cal microscopy from the capsule to the papilla of kidneys in CX3CR1<sup>GFP/+</sup> mice, stellate-shaped myeloid rDC form a contiguous network throughout the entire interstitium, encompassing all nephrons.19 Confirming previous studies,6,7 myeloid rDC that resemble pre-DC (analogous to the globular shape of resident plasmacytoid DC15) are also present at low density within the mesangium of normal kidneys.21 Similar studies indicated that a similar anacytoid DC15) are also present at low density within the renal parenchyma, whether derived from self or nonself sources.

**ORIGINS AND MIGRATION OF RDC AT STEADY STATE**

Similar to DC in other nonlymphoid organs,13–35 rDC constitute a heterogeneous population of bone marrow–derived hematopoietic cells that, unlike DC that function solely within lymphoid tissues (most of the DC in the thymus and spleen and approximately half of the DC in lymph nodes), serve as sentinels within the kidney before trafficking to lymphoid organs.13–18 Because of the plasticity of FLT3<sup>+</sup> common myeloid and common lymphoid DC precursors to generate all DC subsets,16 local trophic cues rather than the availability of DC precursors probably determine the constituency of rDC at steady state. Notably, although administration of the ligand for FLT3 to mice can mobilize rDC precursors and transiently increase the total number of rDC, as it does for DC in other tissues,36 the proportion of each rDC subset is not significantly altered when compared with the normal steady state.10 Recent studies of myeloid rDC suggest a probable role of the renal microenvironment in stipulating the heterogeneity of rDC. Deriving from a shared clonal progenitor of the mononuclear phagocyte system37 along the long-lived “noninflammatory” CX3CR1<sup>high</sup>CCR2<sup>-</sup> monocyte lineage (also Ly6C<sup>+</sup> GR1<sup>−</sup> in mice; CD14<sup>+</sup> CD16<sup>-</sup> in humans),19,38–41 myeloid rDC can express markers conventionally assigned to macrophages (F4/80, CD68),10–12,19,42 This phenotypic overlap between myeloid rDC and macrophages20 is differential within normal kidneys; stellate-shaped CD11c<sup>+</sup> F4/80<sup>+</sup> rDC, for example, predominate in the medulla, whereas globular-shaped MHC class II<sup>+</sup> pre-rDC reside in the mesangium.6,7,19,43 This finding suggests that regional inductive factors shape the repertoirre of rDC. It is interesting that engagement of the CSF-1 receptor is required for the differentiation and survival of myeloid DC,44 and constitutive expression of CSF-1 (i.e., M-CSF, a major chemoattractant and growth factor for mononuclear phagocytes45) by renal epithelial cells seems to be more prominent in the medulla than in the cortex at steady state.46,47 Whether this alone explains the heterogeneity of rDC is unclear. More likely, other differentially expressed trophic ligands (thymic stromal lymphopoietin-like factors that may be elaborated by renal epithelial cells or interstitial stromal cell populations48,49) and extracellular matrices within the kidney also contribute to the specification of rDC.

**Trafficking rDC precursors express several chemokine receptors (CCR)50–53 that are also involved in establishing and maintaining the rDC network. Circulating immature mouse DC mobilized by FLT3 ligand migrate in vitro to CCR ligands expressed at basal levels within normal kidneys and, after adoptive transfer, traffic into the renal interstitium and mesangium in vivo.54 In contrast, isolated immature mouse rDC fail to demonstrate similar migration behavior despite expression of the same CCR.53 This suggests that renal-derived chemoines recruit trafficking rDC precursors at steady state, but once in residence, differentiating rDC precursors undergo CCR desensitization, possibly by molecules other than chemokines.50,53–55 In addition, the lack of redundant cellularity within the contiguous rDC network19 suggests exquisite, reciprocal downregulation or sequestration of chemotractants directly at sites of occupancy by individual rDC.50

It is intriguing that self-renewal of rDC within the kidney may also occur (analogous to DC in the skin56 and ovaries57), a possibility hinted at by the small population (<3%) of resident CX3CR1<sup>high</sup>GR1<sup>−</sup> leukocytes in normal mouse kidneys that lack phenotypic
Figure 1. Surveillance of the renal parenchyma by the rDC network. The three panels shown are high-power views of the same location in the outer medulla of a normal kidney from a CX3CR1GFP+/H2A1001 mouse captured by confocal microscopy. The resident rDC network (A) is an anatomically separate cellular compartment from the renal parenchyma that it surveys (B). This affords rDC the ability to respond rapidly to local environmental cues, to migrate apart from nephrons, and to communicate with other components of the immune system both within and outside the kidney. (C) Merge of A and B demonstrates the intimate relationship that exists between rDC and the renal parenchyma.
markers of differentiated DC.19 Because preliminary bromodeoxyuridine-labeling experiments in normal mice58 suggest an average half-life across all rDC subsets of approximately 35 d12 (Matthew Griffin, personal communication; Matthew Griffin, MD Associate Professor Mayo Clinic, Rochester, Minnesota, USA, Date of communication: 2/22/07), this latter possibility, if true, will require innovative long-term studies to capture. Approaches such as total body irradiation, long known to be insufficient at fully ablating rDC,59,60 followed by bone marrow transplantation to reform the rDC network does not recapitulate normal rDC homeostasis and can lead to chimerism between donor and recipient rDC56

FUNCTION OF RDC

**Innate Immunity**

As sentinels of the immune system, rDC are positioned to integrate environmental cues and influence innate immune responses anywhere within the kidney.19 This functional plasticity rests in the intrinsic ability of tissue-resident, surveying DC such as immature rDC to sense and sample continually their immediate environment. This surveillance by rDC occurs by multiple mechanisms and includes the following: Engagement of a broad repertoire of surface receptors such as Toll-like receptors,61,62 receptors for alarmins,63 Fc receptors,64,65 complement receptors,66–68 C-type lectin receptors,68–71 scavenger receptors,72,73 and cytokine and CCR; contact or paracrine-mediated signals from trafficking innate immune cells such as neutrophils,74 natural killer cells,75,76 natural killer T lymphocytes,75,77 and γδ T lymphocytes75,78; contact or paracrine-mediated signals from trafficking adaptive immune cells79; and contact (e.g., via tunneling nanotubes19,80) or paracrine-mediated signals from adjacent resident rDC.81

In turn, the rapid integration of these external stimuli by rDC and their subsequent proinflammatory activation (if the stimuli are not tolerogenic) can prime and amplify innate immune responses. This occurs mainly through the secretion of cytokines (e.g., TNF-α, type I IFN, IL-1β, IL-2, IL-6, IL-12, IL-15) and chemokines by rDC that act on adjacent renal parenchymal cells and innate immune cells,50,75,82 which includes resident plasmacytoid DC as “professional type I IFN–producing” leukocytes.15 For example, resident myeloid rDC were recently identified as the predominant source of intrarenal TNF-α produced during the early “sterile” innate immune response to renal ischemia-reperfusion injury,42 an insult that also induces the maturation and migration of these resident myeloid rDC to lymphoid tissues.12 This initial cytokine response by resident rDC is separate from the cytokines subsequently released by recruited “inflammatory” CX3CR1<sup>+</sup>,CCR2<sup>+</sup> rDC precursors (also Ly6C<sup>+</sup>,GR1<sup>+</sup> in mice; CD14<sup>+</sup>,CD16<sup>+</sup> in humans).19,38–41 These latter cytokines contribute to sequelae of renal ischemia-reperfusion injury such as interstitial fibrosis,83 analogous to the cytokine response and egress versus influx of rDC12,53,84 versus rDC precursors,85 respectively, in response to LPS.

**Adaptive Immunity**

Not unexpected, rDC exhibit the hallmarks of well-equipped antigen-presenting cells of the adaptive immune system. Resident rDC at steady state express MHC class I and class II molecules but bear low levels of co-stimulatory molecules (e.g., CD80, CD86, CD40).9–12,19 Resident rDC probe their immediate environment (which may include the lumens of the nephron)19 and capture self- and nonself molecules, whether derived from within or outside the kidney, via phagocytosis, pinocytosis, and receptor-mediated endocytosis.12,18 In response to the same “danger” signals that invoke innate immune responses, rDC also up-regulate the expression of co-stimulatory molecules and CCR7 (the CCR for ligands, CCL19, and CCL21, expressed by stromal cells in T lymphocyte–rich areas of lymph nodes86,87) and migrate to secondary lymphoid tissues bearing any molecules captured within the kidney (or generated within rDC) for processing and presentation to adaptive immune cells.9,10,12,53

These mature rDC potently stimulate T lymphocyte proliferation9–12 and, depending on the nature of maturing stimuli,61,62,88 presumably secrete cytokines that promote the differentiation of naive T lymphocytes toward specific T helper (Th) effectors such as Th1, Th2, or Th17 lymphocytes89 (this has yet to be formally reported). It is unclear, however, the degree to which environmental cues that are unique to the kidney (e.g., Toll-like receptor recognition of the kidney-restricted protein, Tamm-Horsfall glycoprotein90) “imprint” rDC to polarize preferentially naive T lymphocytes and generate kidney-tropic Th effectors.91 Moreover, little is known regarding environmental cues that may retard the egress of mature, antigen-presenting rDC out of the kidney (as recently shown in the bowel92), a recipe for inducing adaptive immune responses within the kidney itself and subsequently organizing pathogenic “nephron-associated lymphoid tissue.”

**Self-Tolerance**

DC in peripheral tissues contribute to self-tolerance by supplementing central tolerance.93–96 Preliminary studies indicate that rDC also play an important role in maintaining self-tolerance within the kidney. Immature rDC induce the expansion of T regulatory lymphocytes (Treg) in mixed leukocyte reactions and suppress allorecognition in vivo.10 These findings suggest that rDC may be tolerogenic if engaged by T lymphocytes that have escaped thymic selection and are reactive to self-antigens within the kidney. Moreover, cross-presentation of self-antigens derived within the kidney by rDC deletes autoreactive T lymphocytes in vivo by a Fas-mediated mechanism.97–99 These observations are intriguing because several tissue-specific self-antigens demonstrate low or no expression in the thymus and, thus, rely on peripheral mechanisms to help maintain tolerance.100 This is a potential confounder of many experimental kidney-restricted promoter systems that is often ignored.
For example, failure to regulate or delete autoreactive T lymphocytes generated during accelerated apoptosis of renal parenchyma, an instigator of autoimmune-ty,101,102 may explain why CD8+ T lymphocytes directed against kidney antigens, presumably presented by rDC, can develop in kd/kd mice.103,104 The ability of DC to process and present antigen can also be suppressed after contact with Treg105,106 raising the possibility that resident rDC themselves are targets for trafficking Treg. Notably, Treg ameliorate both the acute and chronic phases of renal disease in disparate models of immune-mediated renal injury,107–109 although rDC–Treg interactions have not been studied in these experiments. This possible interaction is an exciting area of future inquiry, as is the potential to manipulate the reciprocal relationship between rDC and Treg to suppress immune responses that may be coordinated by rDC.110

Immunologic Homeostasis of the Renal Parenchyma
Surveillance by DC resident in tissues may mediate self-tolerance to and regeneration of dying parenchymal cells.102,111,112 There is mounting evidence that the rDC network may fulfill this crucial role within the kidney. In mice, “alternatively” activated mononuclear phagocytes (i.e., an anti-inflammatory tolerogenic state in contrast to the “classically” activated proinflammatory state113) clear apoptotic cells within the kidney. rDC migrate and communicate these cues to both arms of the immune system and to the renal parenchyma and renew to maintain a contiguous network. In many respects, our understanding of rDC in the health and disease of the kidney is very rudimentary, spawned in part by the considerable lag in research on rDC compared with DC in other organs and tissues. Fortuitously, much is now known about the biology of DC in general. Application of this knowledge should yield rapid and important advances in deciphering the contribution of rDC to the pathogenesis, such as their role in HIV infection in the kidney,120,121 and treatment, such as their targeting by CDK/GSK-3 inhibitors,122,123 of many renal diseases. This inquiry promises to be revealing in the years immediately ahead.

CONCLUSIONS
In this brief review, we have discussed the current knowledge surrounding rDC. rDC function in the fundamental immunologic paradigm of continual surveillance. This is evidenced by the anatomic availability and intrinsic ability of rDC to respond rapidly to environmental cues anywhere within the kidney. rDC migrate and communicate these cues to both arms of the immune system and to the renal parenchyma and renew to maintain a contiguous network. In many respects, our understanding of rDC in the health and disease of the kidney is very rudimentary, spawned in part by the considerable lag in research on rDC compared with DC in other organs and tissues. Fortuitously, much is now known about the biology of DC in general. Application of this knowledge should yield rapid and important advances in deciphering the contribution of rDC to the pathogenesis, such as their role in HIV infection in the kidney,120,121 and treatment, such as their targeting by CDK/GSK-3 inhibitors,122,123 of many renal diseases. This inquiry promises to be revealing in the years immediately ahead.

ACKNOWLEDGMENTS
P.J.N. is supported by National Institutes of Health grants DK065498 and DK079498.

We thank Matthew Griffin for critical reading of the manuscript and David Hume for helpful discussions on the role of mononuclear phagocytes in nephrogenesis. Rohan John was a visiting fellow at the NYU School of Medicine.

DISCLOSURES
None.

REFERENCES
alpha-and inducible nitric oxide synthase-producing dendritic cells are rapidly recruited to the bladder in urinary tract infection but are dispensable for bacterial clearance. Infect Immun 74: 6100–6107, 2006


Liu YJ, Soumelis V, Watanabe N, Ito T, 2007

RENAL DENDRITIC CELLS
control of the adaptive immune responses. 

Net Immunol 5: 987–995, 2004

62. Mazzoni A, Segal DM: Controlling the Toll road to dendritic cell polarization. 
J Leukoc Biol 75: 721–730, 2004

63. Oppenheim JJ, Yang D: Alarmins: Chemo-
tactic activators of immune responses. 
Curr Opin Immunol 17: 359–365, 2005

64. Nimmerjahn F, Ravetch JV: Fcgamma re-
ceptors: Old friends and new family mem-

65. Bajtaz Z, Csomor E, Sandor N, Erdei A: 
Expression and role of Fc- and comple-
ment-receptors on human dendritic cells. 

66. Kohl J: The role of complement in danger 
sensing and transmission. Immun Res 34: 
157–176, 2006

67. Zhou W, Peng Q, Li K, Sacks SH: Role of 
dendritic cell synthesis of complement in 
the allospecific T cell response. Mol Immunol 
44: 57–63, 2007

68. Apostolopolou V, McKenzie IF: Role of 
the mannose receptor in the immune re-

69. Allavena P, Chiappa M, Monti P, Piemonti 
L: From pattern recognition receptor to 
regulator of homeostasis: the double-faced 
macrophage mannose receptor. Crit Rev 
Immunol 24: 179–192, 2004

70. Gijzen K, Cambi A, Torensma R, Figdor 
GJ: C-type lectins on dendritic cells and 
cells in innate responses. 
Curr Mol Med 
14: 123–128, 2002

71. Kanazawa N: Dendritic cell immunorecep-
tors: C-type lectin receptors for pattern-
recognition and signaling on antigen-pre-

72. Peiser L, Mukhopadhyay S, Gordon S: 
Scavenger receptors in innate immunity. 

73. Becker M, Cottaen A, Gordon S, Platt N: 
Expression of the class A macrophage 
scavenger receptor on specific subpopula-
tions of murine dendritic cells limits their 
edtoxin response. Eur J Immunol 36: 
950–960, 2006

74. Ludwig IS, Geijtenbeek TB, van Kooij Y: 
Two way communication between neutro-
phils and dendritic cells. Curr Opin Phar-
macol 6: 408–413, 2006

75. Munz C, Steinman RM, Fujii S: Dendritic 
cell maturation by innate lymphocytes. 
Co-
ordinated stimulation of innate and adap-
2005

76. Walzer T, Dalod M, Vivier E, Zitvogel L: 
Natural killer cell-dendritic cell crosstalk in 
the initiation of immune responses. 

77. Monyota CJ, Jie HB, Al-Harthi L, Mulder C, 
Patino PJ, Rugeles MT, Krieg AM, Landay 
AL, Wilson SB: Activation of plasmacytoid 
dendritic cells with TLR9 agonists initiates 
invariant NKT cell-mediated cross-talk with 
myeloid dendritic cells. J Immunol 177: 
1028–1039, 2006

78. Born WK, Reardon CL, O’Brien RL: The 
function of gammadelta T cells in innate 
immunity. Curr Opin Immunol 18: 31–38, 
2006

79. So T, Lee SW, Croft M: Tumor necrosis 
factor/tumor necrosis factor receptor family 
members that positively regulate immu-

80. Watkins SC, Saltor RD: Functional connec-
tivity between immune cells mediated by 
tunneling nanotubules. Immunity 23: 309– 
318, 2005

81. Fonteneau JE, Larsson M, Beignon AS, 
McKenna K, Dasilva I, Amara A, Liu YJ, 
Lifson JD, Littman DR, Bhardawj N: Human 
immune-deficiency virus type 1 activates 
plasmacytoid dendritic cells and concomi-
tantly induces the bystander maturation of 
5232, 2004

82. Foti M, Granucci F, Ricciardi-Castagnoli P: 
A central role for tissue-resident dendritic 
cells in innate responses. Trends Immunol 
25: 650–654, 2004

83. Furuchi K, Gao JL, Murphy PM: Chemo-
kine receptor CX3CR1 regulates renal in-
testinal fibrosis after ischemia-reperfusion 

84. Roake JA, Rao AS, Morris PJ, Larsen CP, 
Hanks DF, Austyn JM: Dendritic cell loss 
from nonlymphoid tissues after systemic 
administration of lipopolysaccharide, tu-
mor necrosis factor, and interleukin 1. 

85. Roake JA, Rao AS, Morris PJ, Larsen CP, 
Hanks DF, Austyn JM: Systemic lipopolysac-
charide recruits dendritic cell progeni-
tors to nonlymphoid tissues. Transplanta-
tion 59: 1319–1324, 1995

86. Sanchez-Sanchez N, Riol-Blanco L, Rodri-
guez-Fernandez JL: The multiple personal-
alties of the chemokine receptor CCR7 in 
dendritic cells. J Immunol 176: 5153–5159, 
2006

87. Ziegler E, Gueller F, Rong S, Mengel M, 
Witzke O, Kribben A, Haller H, Kunzendorf 
U, Krautwald S: CCL19-IgG prevents allo-
graft rejection by impairment of immune 
cell trafficking. J Am Soc Nephrol 17: 
2521–2532, 2006

88. Vieira PL, de Jong EC, Wierenga EA, 
Kapsenberg ML, Kalinski P: Development of 
Th1-inducing capacity in myeloid den-
dritic cells requires environmental instruc-

89. Weaver CT, Hatton RD, Mangan PR, Harrin-
geon LE: IL-17 family cytokines and the 
expanding diversity of effector T cell lin-
2007

90. Saemann MD, Weichhart T, Zeyda M, 
Stafferl G, Schunn M, Stuhlmeier KM, So-
banov Y, Stulnig TM, Akira S, von Gabain

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006

157–176, 2006


